Studies on mono- and polynuclear metal tetrazolato complexes synthesized *via* 1,3-dipolar cycloaddition

Ph.D. Thesis

By MANIDEEPA SAHA



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Studies on mono- and polynuclear metal tetrazolato complexes synthesized *via* 1,3-dipolar cycloaddition

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Submitted in partial fulfillment of the requirements for the award of the degree of DOCTOR OF PHILOSOPHY

> By MANIDEEPA SAHA



DISCIPLINE OF CHEMISTRY INDIAN INSTITUTE OF TECHNOLOGY INDORE JUNE, 2016



INDIAN INSTITUTE OF TECHNOLOGY INDORE

CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **Studies on mono- and polynuclear metal tetrazolato complexes synthesized** *via* **1,3-dipolar cycloaddition** in the partial fulfillment of the requirements for the award of the degree of **DOCTOR OF PHILOSOPHY** and submitted in the **DISCIPLINE OF CHEMISTRY, Indian Institute of Technology Indore**, is an authentic record of my own work carried out during the time period from July, 2011 to May, 2016 under the supervision of Dr. Suman Mukhopadhyay, Associate Professor.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

Signature of the student with date (MANIDEEPA SAHA)

This is to certify that the above statement made by the candidate is correct to the best of my/our knowledge.

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ABSTRACT

Over the last decades, design and synthesis of metal-tetrazole complexes (MTCs) have aroused considerable attention, emerging not only from their potential applications in many areas but also as a result of their chemical and structural diversities. It has gained significant attention of the scientific community due to their applications as energetic materials, ligands in coordination chemistry, intermediates in organic synthesis, and drugs in pharmaceuticals. A tetrazole is a five membered ring containing four nitrogen and one carbon atom (Figure 1). Due to its energetic potential and structural similarity to carboxylic acids, this ring system has a wide number of applications. In this thesis, a sustainable process to produce metal-tetrazolato complexes has been employed that achieved high yields under relatively milder conditions. Synthesized complexes have shown interesting properties in terms of geometrical isomerism, magnetism, interaction with biomolecules and bioinspired catalysis.



Figure 1. Molecular structure and numbering system of tetrazole (Tz).

As tetrazole based ligands are in prime focus in last few years because of their rich coordination chemistry that leads to great variety of interesting structures, various methods have been reported to generate tetrazole ligands in presence of different catalysts (Figure 2). Among them, one environmentally friendly approach has been recently reported. However, there are many other reports where substituted tetrazoles have been generated mostly by energy demanding pathways. Furthermore, *in-situ* generation of tetrazole ligands to generate metal complexes are also reported which are mainly achieved through uncontrolled solvothermal pathways. Controlled production of tetrazolato-metal complexes through cycloaddition of metal ligated azide and organonitriles are relatively unexplored and rare.

$$R - CN \xrightarrow{\text{NaN}_3, \text{ZnBr}_2}_{\text{H}_2\text{O}, \text{ reflux}} R \xrightarrow{\text{N}}_{\text{N}} N$$

Figure 2. Synthesis of tetrazole by environmentally friendly procedure.

With the above scenario of tetrazolato based metal complexes, the main objectives for this particular work are as follows:

> To generate tetrazole ligands by cycloaddition of organonitriles through 1,3 dipolar cycloaddition to cobalt ligated azide and to study the influence of cycloaddition on preference of geometry (if any) of metal complexes with the formation of preferential isomer. Also to explore the possible role of different substituent at 5-position of tetrazole ring.

> To design polynuclear metal complexes through bridging tetrazolato ligand by limiting the nuclearity in the presence of another ligand [tridentate (N,N,O) type] under relatively milder conditions and explore their magnetic properties.

> To target formation of water soluble copper-tetrazolato complexes under controlled and environmentally friendly conditions and to study their interactions with biomolecules like DNA and serum albumin. The biomimetic catecholase like ability of the synthesized complex to act as a catalyst to oxidize 3,5-di-*tert*-butylcatechol (3,5-DTBC) to 3,5-di-*tert*-butylbenzoquinone (3,5-DTBQ) is also explored.

➤ To study the structural effect of substituent at 5-position of tetrazolato ring in a metal complex and the choice of metal ion on the catecholase like activity of the metal complexes with oxidation of 3,5-DTBC to 3,5-DTBQ which may provide the control to synthesize more active metal complexes.

> To study the effect of mono- and dinuclear copper-tetrazolato complexes as homogeneous catalysts for the oxidation of cyclohexane to cyclohexanol and cyclohexanone. These complexes were also explored for having protein binding ability and catecholase like properties.

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Chapter 1: General introduction

This chapter describes the current status regarding the synthesis and functionalization strategies of metal-tetrazolate derivatives, and their applications in diverse fields.

Chapter 2: The effect of remote substitution on the formation of preferential isomers of cobalt(III)-tetrazolato complexes by microwave assisted cycloaddition

Chapter 2 describes the [2+3] cycloaddition reaction between cobalt coordinated diazide *cis*- $[Co(N_3)_2(en)_2](NO_3)$ and *trans*- $[Co(N_3)_2(en)_2](ClO_4)$ with different organonitriles in a controlled and systematic manner under relatively milder reaction conditions (Figure 3). It has been observed that the remote substitution at 4-position of 5-substituted phenyl group of tetrazolato ring has an influence on formation of preferred geometrical isomers. Furthermore, the counterion and solvent of crystallization also have shown some roles to dictate the formation of one isomer over another. DFT study indicates some isomers are thermodynamically preferred product whereas the rest of the products are kinetic in nature.



Figure 3. Reaction of cobalt diazide complexes with organonitriles.

Chapter 3: Limiting nuclearity in formation of polynuclear metal complexes through [2 + 3] cycloaddition: synthesis and magnetic properties of tri- and pentanuclear metal complexes

Chapter 3 describes the generation of polynuclear compounds with limiting nuclearity *via* [2 + 3] cycloaddition reactions between metal coordinated azide [Ni(L¹)(N₃)] where [HL¹ = *p*-chloro-2-{(2-(dimethylamino)ethylimino)methyl} phenol] and different organonitriles to afford tetrazolato bridged tri- and pentanuclear nickel(II) complexes under relatively milder conditions (Figure 4). The magnetic susceptibility data shows dominant antiferromagnetic interactions between the nickel centers for all the complexes. DFT calculations were performed to investigate the magnetic parameter of the complexes by broken symmetry approach.



Figure 4. Synthesis of tetrazolato bridged tri- and pentanuclear nickel (II) complexes.

Chapter 4: Targeted water soluble copper-tetrazolato complexes: interactions with biomolecules and catecholase like activities

This chapter describes work on the design and synthesis of two new water soluble copper-tetrazolato complexes [Cu{(5-pyrazinyl)tetrazolato}₂(1,10-phenanthroline)]

and $[Cu\{(5-pyrazinyl)tetrazolato\}(1,10-phenanthroline)_2](NO_3)_{0.5}$ (N₃)_{0.5} by metal mediated [2+3] cycloaddition reaction between copper bound azide and pyrazinecarbonitrile (Figure 5). Their interaction with DNA, bovine serum albumin (BSA) and catecholase like activity are explored. Interaction of the complexes with DNA are further investigated with density functional theory.



Figure 5. Interaction of copper-tetrazolato complex with DNA, BSA and showing oxidation of 3,5-DTBC.

Chapter 5: Effect on catecholase activity and interaction with biomolecules of metal complexes containing differently tuned 5- substituted ancillary tetrazolato ligands

Chapter 5 describes, formation of four new mono/di-nuclear nickel(II) and copper(II) complexes in presence of a Schiff-base ligand with an N,N,O-donor set containing a phenol group and different tetrazoles (Figure 6). Catechol oxidase-like activity of the synthesized compound have been examined and compared subsequently indicating the role of ligand strength of tetrazolato ion and metal center influencing the activity. Mechanism of the oxidation process is investigated

through mass studies and density functional theory. Interaction of the complexes with biomolecules like DNA and serum albumin protein have also been investigated.



Figure 6. Ancillary ligand based catecholase activity of copper complexes.

Chapter 6: Oxidative functionalization of C-H bonds under mild conditions catalyzed by copper tetrazolate complexes

Chapter 6 reports the design and synthesis of mono and dinuclear coppertetrazolato complexes which can act as homogeneous catalysts in functionalization of C-H bond for the oxidation of cyclohexane to cyclohexanol and cyclohexanone (Figure 7). These complexes also show interactions with the serum albumin proteins and their catecholase like properties are also explored. Finally, the molecular docking studies were performed to obtain detailed binding information of the Cu(II) complexes with BSA.



Figure 7. Dinuclear copper-tetrazolato complex act as homogeneous catalysts and its interaction with BSA along with oxidation of 3,5-DTBC.

Chapter 7: Conclusions and future scope.

Chapter 7 summarizes the salient features of the work and its future prospects.

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- Saha M., Das M., Nasani R., Choudhuri I., Mobin S.M., Pathak B., Mukhopadhyay S.* (2015), Targeted water soluble copper-tetrazolato complexes: interactions with biomolecules and catecholase like activities, *Dalton Trans.*, 44, 20154–20167 (DOI: 10.1039/c5dt01471a).
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| 50110110 0.2. | where wave-assisted heat exitation of eyelenexane to eyelenexy. | |
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ACRONYMS

| BSA | Bovine serum albumin |
|-------------------|--|
| CPs | Coordination Polymers |
| Calcd. | Calculated |
| CDCl ₃ | Chloroform-d |
| DMSO- d_6 | Dimethyl sulfoxide- d_6 |
| DCM | Dichloromethane |
| DMF | Dimethylformamide |
| DFT | density functional theory |
| DNA | Deoxyribonucleic acid |
| 3,5-DTBC | 3,5-di-tert-butylcatechol |
| 3,5-DTBQ | 3,5-di-tert-butylbenzoquinone |
| DAPI | 4',6-diamidino-2-phenylindole |
| en | ethylene diamine |
| EtBr | ethidium bromide |
| ESI-MS | Electrospray Ionization- Mass Spectrometry |
| GOF | Goodness of Fitting |
| GC | Gas Chromatography |
| IR | Infrared |
| LMCT | Ligand to Metal Charge Transfer |
| MLCT | Metal to Ligand Charge Transfer |
| MW | Microwave |
| MOFs | Metal-organic Frameworks |
| MeOH | Methanol |
| μ | Represents bridging |
| NLO | Nonlinear Optical |
| NMR | Nuclear Magnetic Resonance |
| Ph | phenyl |
| PXRD | Powder X-ray diffraction |
| рН | The negative logarithm of hydronium-ion concentration (- |
| | $\log_{10}[H_3O^+])$ |

| 2-ptz | 2-(tetrazol-5-yl)-pyridine |
|------------------|---|
| 3-ptz | 3-(tetrazol-5-yl)-pyridine |
| 4-ptz | 4-(tetrazol-5-yl)-pyridine |
| pzta | 5-pyrazinyltetrazolate |
| pytz | 5-(2-pyridyl)tetrazolate |
| pmtz | 5-pyrimidyltetrazolate |
| phen | 1,10-phenanthroline |
| pzta | 5-pyrazinyltetrazolate |
| PPh ₃ | Triphenylphosphine |
| SCXRD | Single Crystal X-ray diffraction |
| SOD | superoxide dismutase |
| tta | tetrazole |
| TGA | Thermogravimetric Analysis |
| TOF | Turnover Frequency |
| TON | Turnover Number |
| TBHP | tert-Butyl hydroperoxide |
| TEMPO | 2,2,6,6-Tetramethylpiperidine 1-oxyl |
| Tris-HCl | Tris(hydroxymethyl)aminomethane-hydrochloride |
| UV-Vis | UV-Visible Spectroscopy |
| | Represents interaction |

NOMENCLATURE

| λ | Wavelength | |
|-------------------|------------------------|--|
| 3 | Extinction coefficient | |
| α | Alfa | |
| β | Beta | |
| γ | Gamma | |
| π | Pi | |
| Å | Angstrom | |
| nm | Nanometer | |
| cm | Centimeter | |
| 0 | Degree | |
| °C | Degree Centigrade | |
| mmol | Millimol | |
| mL | Milliliter | |
| μL | Microliter | |
| μΜ | Micromolar | |
| a. u. | Arbitrary Unit | |
| $	ilde{\upsilon}$ | Wave number | |
| δ | Chemical shift (NMR) | |

Chapter 1 General introduction

1.1 Background

Research on coordination chemistry is gradually taking a turn from understanding the mode of interaction between ligands and metal ions towards the application of the generated compounds in the field of material science and biology. Among the numerous areas on which coordination chemists are working on, generation of novel complexes to provide solutions for many contemporary problems are of highest interests. Among the various classes of ligand molecules which are creating a lot of interests, organic heterocycles with many potential applications in different fields are on priority in the domain of coordination chemistry because of their versatility to develop novel coordination complexes.^[1] In the kingdom of heterocycles, tetrazoles are very much significant as they find use *e.g.* in material science,^[2,3] pharmaceutical chemistry,^[4,5] photography and information recording systems.^[5] Apart from those, tetrazole ligands have generated a great interest owing to their ability to contribute to synthesize mono- and polymeric metal complexes (Figure 1.1) with an exceptional combination of stability and reactivity which has been evident through their interesting properties in the field of magnetism, [6,7,8]catalysis,^[9] photoluminescence ^[6,10] or in gas absorption.^[11,12]



Figure 1.1. Structure of small molecule (SM) and coordination polymer (CP).

Furthermore, they can be also utilized in several other functional applications *viz*. sensors and in biological applications. Following is a brief about the current status of applications of tetrazole based metal complexes in various fields.

1.1.1 Metal-tetrazolato complexes in catalysis

The catalytic activity of a complex essentially depends on its ability to provide microporous frameworks bearing coordinatively unsaturated metal centers towards interaction with reaction components. Such crystalline solids with well-defined pores and surface-isolated Lewis acid sites could also potentially serve as size- or shape-selective heterogeneous catalysts, in a manner similar to zeolites. Tetrazoles have a natural tendency to generate metal based frameworks with exposed metal centers.

Long et al. (2008) prepared a tetrazole containing manganese frame work with 1,3,5-benzene-tristetrazol-5-yl, which is porous and coordinatively unsaturated where metal centers are found to be exposed towards the inner surface of the pores (Figure 1.2) and being used for size-selective Lewis acid catalysis for the cyanosilylation of carbonyl substrates in microporous metal-organic framework (Scheme 1.1).^[13]



Figure 1.2. A portion of the crystal structure of Mn-1,3,5-benzene-tristetrazol-5-yl frame work showing the two different types of Mn(II) sites exposed within its three-dimensional pore system of 10 Å wide channels. Orange, green, gray, and blue spheres represent Mn, Cl, C, and N atoms, respectively; H atoms and bound MeOH molecules are omitted for clarity. Site I is five-coordinate, while site II is only two-coordinate; the separation between them is 3.420(8) Å.

$$Ar \stackrel{O}{\underset{R}{\leftarrow}} + Me_{3}SiCN \xrightarrow{Mn_{3}[(Mn_{4}Cl)_{3}(BTT)_{8}(CH_{3}OH)_{10}]_{2}} \xrightarrow{Me_{3}SiO} \xrightarrow{CN} Ar \xrightarrow{R}$$

Scheme 1.1. Size-selective cyanosilylation of carbonyl compounds by Mn_3 [$(Mn_4Cl)_3(BTT)_8(CH_3OH)_{10}$]_{2.}

1.1.2 Tetrazolate frameworks in gas storage applications

Zeolitic Tetrazolate Frameworks (ZTFs), that mimic the zeolite type structure but possess larger and more modifiable pores, has received considerable attention as materials for strategic gases such as CO_2 and H_2 sorbents.^[14,15,16,17,18] A three dimensional –NH₂ functionalized Zeolitic Tetrazolate Framework (ZTF-1) has been reported (Figure 1.3). ZTF-1 shows high CO_2 (273 K) and H_2 (77 K) uptake due to the presence of the free –NH₂ group and uncoordinated tetrazolate nitrogen.^[19]



Figure 1.3. Gas adsorption isotherms of ZTF-1. (a) Nitrogen adsorption isotherm (77) K. (b) Adsorption isotherms for CO_2 (red circles) and N_2 (black triangles) at 273K. (c) Hydrogen adsorption isotherms at 77K. The filled and open circles represent adsorption and desorption, respectively. (d) Distances between CO_2 molecule and different N atoms in ZTF-1.

1.1.3 Tetrazolato ligand based magnetic materials

The magnetic properties of linear trinuclear Cu(II) complexes, in which the metal ions are bridged by *N*,*N* linkages derived from *N*-heterocyclic ligands, have received much attention. Most studies are focused on tris-triazole systems.^[20–26] As there is no magnetic data for the tris-tetrazole analogues, it was interesting to carry out temperature-dependent magnetic susceptibility measurements for Cu(II) tristetrazole complex (Figure 1.4). This complex shows a $\chi_M T$ value of 1.258 cm³ mol⁻¹ K at 300 K which is close to the expected value for three uncoupled Cu(II) ions with S = 1/2 (1.125 cm³ mol⁻¹ K, for g = 2). By decreasing the temperature to ~150 K, the $\chi_M T$ value remains constant and further cooling leads to the increase of $\chi_M T$. At a temperature of 2 K, the $\chi_M T$ value reaches 1.459 cm³ mol⁻¹ K. This behaviour indicates a weak ferromagnetic interaction between adjacent Cu(II) ions.^[27]



Figure 1.4. Plots of $\chi_M T$ versus T for the Cu(II) complex. The solid line is the best fit to the experimental data.

1.1.4 Tetrazole based luminescent materials

Recently, lanthanide metal chemistry has shown great importance in the field of luminescence, offering a wide range of applications in lasers and photochemistry.^[28] For examples, the Eu(III) and Tb(III) ions, which exhibit intense emission in the visible region of the spectrum which can be used in fluorescent lighting and color displays. Other lanthanide-metal ions, such as the Nd(III) and Yb(III) ions, which produce near-infrared (NIR) emission, are useful for biological imaging and telecommunication applications. These trivalent lanthanide ions notably present weak emission as a result of forbidden f-f transitions.^[29] An excellent approach to increase the luminescence of lanthanide-based complexes involves introduction of suitable π -conjugated ligands, which can absorb ultraviolet light and offer electronic transfer interactions between the Ln(III) ions (the so-called "antenna effect").^[30,31] Despite their potential benefits, however, investigations on near-infrared luminescent Ln-based complexes such as the Yb(III) ion are rare because of organic molecular vibrations, such as the C–H and

O–H stretching modes, which easily quench these lanthanide excited states.^[32,33] Therefore, exploration of appropriate organic ligands, which can act as antennae to sensitize otherwise weakly luminescent metal centers and give lanthanide complexes with strong visible and near-infrared region emissions, is an important task (Figure 1.5).^[34]



Figure 1.5: Solid-state excitation spectra measured at room temperature for $[Ln_2(1-tza)_4(NO_3)_2(2,2'-bipy)_2]$ (Ln = Sm (1), Eu (2), (1-tza = tetrazole-1-acetate and 2,2'-bipy = 2,2'-bipyridine).

1.1.5 Metal-tetrazolato complexes with biological applications

Seiji Komeda et al. (2012) have reported anti-tumor properties of di-nuclear Pttetrazolate complexes $[\{cis-Pt(NH_3)_2\}_2(\mu-OH)(\mu-tetrazolato-N1,N2)]^{2+}$ (**a**) and $[\{cis-Pt(NH_3)_2\}_2(\mu-OH)(\mu-tetrazolato-N2,N3)]^{2+}$ (**b**). The investigation revealed that the reactions of the tetrazolato-bridged complexes **a** and **b** with 9EtG (9ethylguanine) yielded an identical product, $[\{cis-Pt(NH_3)_2(9EtG-N7)\}_2(\mu$ tetrazolato-N1,N3)]^{3+} (**c**). The mechanism (Scheme 1.2) involves linkage isomerization through Pt(II) migration. Interestingly, two different types of Pt(II) migration, N2 to N3 and N3 to N4 (N2 to N1), were observed on the tetrazolate ring. This finding indicates that a Pt(II) ion bound to the N2 of (**a**) can migrate to N4 via N3 without breaking the coordination bond, as long as there is a driving force. As for the Pt–DNA interactions of **a** and **b**, the Pt(II) migration may enable these compounds to provide not only intrastrand cross-links but also other Pt–DNA

adducts (e.g. interstrand cross-links) with higher frequency than that provided by *cis*-platin.^[35]



Scheme 1.2. Mechanism involving in anti-tumor properties of $[{cis-Pt(NH_3)_2}_2(\mu-OH)(\mu-tetrazolato-N1,N2)]^{2+}$.

Considerable attention has also been diverted towards the synthesis of pyrimidines and related *N*-containing heterocyclic derivatives such as tetrazolopyrimidines. Pyrimidines and fused pyrimidines are an integral part of DNA and RNA, and thus, play an essential role in several biological and pharmacological agents such as antibiotics, antibacterial, antitumor and cardiovascular drugs and so on.^[36, 37] The formation of tetrazolopyrimidines derived from the condensation of β -diketones and β -ketoesters with 5-aminotetrazole was first described by Bulow.^[38] The tetrazolopyrimidines have been reported to be used in the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hyperlipidemia, hypercholesterolemia, thyroid cancer, hypothyroidism, depression, glaucoma, cardiac arrhythmias and congestive heart failure. In addition to this, the interaction of tetrazolato metal complexes with DNA has been extensively studied because of their site specific binding properties and many applications in cancer therapy. These coordination compounds are suitable for DNA secondary structure probes, photo cleavers and antitumor drugs.^[39] DNA binding studies of complexes with calf-thymus DNA suggest that the copper complexes bind in the grooves of the DNA. These results were further supported by molecular docking studies. In vitro cytotoxic activities of the ligands and complexes against human cancer cell lines such as lung (A549), cervical (HeLa), colon (HCT-15) and a non-cancer human embryonic kidney cell line revealed that the complexes selectively inhibit the growth of cancer cells and are inactive against non-cancer cell lines, whereas the ligands were found to be inactive with both cancer and non-cancer cell lines. The IC_{50} values (The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a substance in inhibiting a specific biological or biochemical function) of the complexes revealed that the copper (II) complexes (Scheme 1.3) exhibit high cytotoxic activity against colon (HCT-15) cells when compared to the standard drug cisplatin. Furthermore, the live cell and fluorescent imaging of cancer cells show that complexes induce cell death through apoptosis (Figure 1.6).^[40]



Scheme 1.3. Schematic route for synthesis of ligands and metal(II) complexes.



Figure 1.6. Live cell imaging of lung (A549), cervical (HeLa) and colon (HCT-15) cancer cells treated with IC_{50} concentrations of complex **A** (Ethyl 5-methyl-7-pyridine-2-yl-4,7-dihydrotetrazolo[1,5-a]-pyrimidine-6-carboxylato)dichlorocopper (II) complex and Bis(ethyl 5-methyl-7-pyridine-4-yl-4,7-dihydrotetrazolo[1,5-a]-pyrimidine-6-carboxylato)dichlorocopper(II) complex **B**.

1.2 Preparation of the tetrazoles

The Swedish chemist Bladin and co-workers in 1885, established the first most widely used synthetic route to prepare tetrazoles by the [2+3] cycloaddition of an azide to a nitrile. Addition of hydrazoic acid to the cyanide group which results in the formation of 5-substituted tetrazole derivatives was first reported by Hantzsch and Vagt^[41] and it led to the birth of [2+3] cycloaddition as the procedure of choice for the synthesis of tetrazoles. However, these traditional cycloaddition reactions have many drawbacks. It needs expensive and toxic metal–organic azide complexes such as tin or silicon organic azides. The reaction conditions are highly moisture-sensitive and there is use of hydrazoic acid, which is extremely toxic, volatile, and explosive.

In 2001, Demko and Sharpless^[42] established that, in the presence of a zinc salt as a catalyst, the cycloaddition reaction was facilitated and the tetrazole moiety was obtained at 100 °C in high yields, with reaction times from 6 to 48 h (Scheme 1.4). Other metal-assisted cycloadditions have also been reported to afford various 5-substituted tetrazoles.^[43]

$$R-CN \xrightarrow{NaN_3, ZnBr_2} R \xrightarrow{N \approx N} N \xrightarrow{I} NH$$

Scheme 1.4. Synthesis of tetrazole by environmentally friendly procedure.^[44]

The [3+2]-cycloaddition of azides with C=N bond is the most significant heterocyclisation reaction for the synthesis of tetrazoles.^[45, 46, 47] Both 5-substituted tetrazoles and their metal derivatives^[48] can be prepared by this method using nitriles and organic or inorganic azides, in particular, sodium or ammonium azide. Sodium azide, like other alkali metal azides, is less reactive than ammonium azide and reacts only with activated nitriles containing electron-withdrawing substituents. The reaction occurs efficiently at room temperature or on moderate heating to give 5-R-tetrazolates in quantitative yields^[49, 50, 51, 52] (Scheme 1.5).

Scheme 1.5. Synthesis of metal derivatives of tetrazoles by heterocyclization.

The reaction of sodium cyanide and azide with manganese dioxide in the presence of copper(II) salts^[53] gives 5,5'-bitetrazole sodium salts (Scheme 1.6).



Scheme 1.6. Synthesis of 5,5'-Bitetrazole sodium salts.

1.3 Coordination modes of tetrazoles

Tetrazoles have attracted a growing attention in recent years in coordination chemistry due to the exceptional coordination capacity of the four nitrogen atoms of the functional group to act as either a multidentate or a bridging building block in supramolecular assemblies. It has been found that tetrazole ligands are able to participate in at least nine distinct types of coordination modes with metal ions in production of metal–organic frameworks (Figure 1.7).^[54]



Figure 1.7. Nine different types of coordination modes of tetrazole with metal ions.

1.4 Tetrazoles as ligands

Tetrazoles can be utilized as ligands starting from the organic molecule itself or by generating the ligand *in situ* by cycloaddition.

1.4.1 Direct utilization of the tetrazole molecule as ligand

1.4.1.1 <u>Reactions of N¹-substituted tetrazoles with metal salts</u>

The N^1 -Substituted tetrazoles do not have the labile hydrogen atom in the ring (unlike the NH-unsubstituted tetrazoles) and therefore do not exhibit acidic properties, being only weak bases. So, the N^1 - and N^2 - substituted tetrazoles are involved into the formation of metal derivatives completely in the neutral form.^[55-61] The metal ions binds to the nitrogen atoms of the tetrazole ring by the covalent or coordination bonds. It is well known that in the N^1 - substituted tetrazoles the highest basicity is at the N4 atom so in most cases this atom takes part in the formation of the coordination bond.

The N^1 -Substituted tetrazoles can readily react with transition metal halides (Scheme 1.7) giving adducts which can be polymers and can precipitate from solutions forming insoluble substances.^[62] The choice of the solvent for such reactions is based on its electron-donor activity, the ability to dissolve the initial components, and the medium for crystallization of the final products. However, at room temperature in presence of weakly coordinating solvents (alcohols, acetone, diethyl ether, acetonitrile, etc.) the complex formation with N^1 substituted tetrazoles proceeds easily with the formation of a solid compound.^[1]



Scheme 1.7. Synthesis of transition metal based tetrazolate.

For the first time in 1982, Franke described the magnetic properties of Fe(II) tetrazole-containing complexes with respect to the temperature. It was revealed that the reaction of iron(II) tetrafluoroborate with 1-alkyltetrazoles furnished octahedral iron complexes which suffered a reversible transition from a white high-spin form $({}^{5}T_{2g})$ to a violet low-spin form $({}^{1}A_{1g})$ at the temperature variation from 140 to 80 K.^[63] The hexacoordinated iron(II) complexes are studied that possess extremely high sensitivity of electronic characteristics to relatively weak external effects of the temperature, pressure or irradiation at a definite wave length.^[11] Presently the

properties of Fe(II) complexes with tetrazoles are widely investigated (Scheme 1.8).^[64-70]



Scheme 1.8. Synthesis of Fe(II) complexes with tetrazoles.

1.4.1.2 <u>Reactions of N^2 -substituted tetrazoles with metal salts</u>

The synthesis of N^2 -substituted tetrazole complexes requires high concentration of reagents and dry solvents; in some cases the reaction mixture should be heated and then concentrated. When the N^2 -substituted tetrazoles are liquid it is possible to carry out the synthesis of the metal complexes by the reaction of the starting components without solvent.^[1]

In the N^2 -substituted tetrazoles, the most basic atom is the nitrogen in the 4 position of the heterocycle (the basicity of the N^2 -substituted tetrazoles is somewhat lower than that of the corresponding N^1 -isomers). So during complex formation the coordination bond exists mainly with the N4 nitrogen atom of the heterocycle. For example, the reaction between copper(II) chloride dihydrate and 2-methyltetrazole furnished bis-(2-methyltetrazole)dichlorocopper(II) (Scheme 1.9).^[71]

$$\bigwedge_{N \searrow N^{-}CH_{3}}^{N} \frac{CuCl_{2}}{\text{methanol/diethyl ether}} \left[Cu \left(\bigvee_{N \searrow N^{-}CH_{3}}^{N} \right)_{2}^{Cl_{2}} \right]$$

Scheme 1.9. Synthesis of bis-(2-methyltetrazole)dichlorocopper(II).



Figure 1.8. Coordination environment of the copper atom in the bis-(2-methyltetrazole)dichloro copper(II) structure.

The crystallographic data showed that the Cu atom is present in an octahedral environment with two 2-methyltetrazole ligands (*N*4- bounded) and two Cl atoms in equatorial positions (Figure 1.8).

1.4.1.3 Reactions of 5-substituted tetrazoles with metal salts

5-substituted tetrazolato ion can also act as a prospective ligand to fulfill the coordination environment surrounding the metal center. More often, the tetrazolato anion acts as a bidentate bridging ligand or a monodentate ligand. In one such example, the X-ray diffraction data shows that both types of coordination exist in a mixed-ligand copper (II) complex (Figure 1.9), prepared by the reaction of 5-phenyltetrazole with copper acetate in aqueous ethanol in the presence of 2,2'-bipyridine.^[72]



Figure 1.9. The tetrazolate anion acts as a bidentate bridging ligand.

However, 5-substituted tetrazoles on reaction with bases like alkali, alkaline earth metal hydroxides,^[73-77] alkoxides ^[78-84] or hydrides ^[85] afford tetrazolates . Mostly, the reaction is carried out in water, ethanol or acetonitrile, and the resulting salts are often used for subsequent transformations without isolation from the reaction medium (Scheme 1.10).



X=H, OH, OAlk; M is alkali or alkaline earth metal

Scheme 1.10. Synthesis of metal tetrazolate.

1.4.2 In-situ generation of tetrazole ligand

In the last two decades it has been revealed that the formation of substituted tetrazoles can be achieved by using a transition metal coordinated azide and free organonitriles ^[86, 87, 88] or isonitriles.^[89, 90] The *in situ* synthesis of tetrazole-based ligands to generate coordination polymers by a hydrothermal process has been also studied.^[91,92,93] The advantage of the *in situ* method (meaning "in the original position" in Latin), making all the reactions take place just in one step from the reactants. In addition, the *in situ* method was shown to be: (1) highly efficient because there was no need for ligand synthesis; (2) it is able to produce sufficient amount of large single crystals; and (3) environmentally friendly.^[94] It is broadly classified into two ways: (1) generation of tetrazole based complexes in classical controlled synthesis and (2) uncontrolled generation of tetrazole based complexes by solvothermal, microwave or refluxing methods.

1.4.2.1 Classical controlled synthesis

1.4.2.1.1 Generation of tetrazole at ambient temperature

The reaction of equimolar amounts of NaN_3 and cyanopyridines in the presence of Mn(II) salt^[95] in water-methanol mixture at ambient temperature led to the formation of the corresponding 5-(pyridyl)-1H-tetrazolato complexes with a highly efficient yield (Scheme 1.11).



Scheme 1.11. Synthesis of 5-(pyridyl)-1H-tetrazoles of Mn(II).

In another example the cycloaddition reaction of the nickel azide complex were carried out at room temperature (Scheme 1.12) by simply stirring a methanolic solution of the corresponding complex with an equivalent amount of 2-cyanopyridine, to furnish the dinuclear nickel tetrazolato complex $[Ni(L)(pytz)]_2$ where $[pytz = 5-(2-pyridyl)tetrazolate].^{[96]}$



Scheme 1.12. Synthesis of $[Ni(L)(pytz)]_2$ where $[HL= 2-\{(2-(dimethylamino) ethylimino)methyl\}$ phenol and $pytz = N_4C(2-NC_6H_4)]$.

1.4.2.1.2 <u>Generation of tetrazole based complexes by focused microwave</u> irradiation

The most direct method to form tetrazole is *via* the concerted and highly regioselective [2 + 3] cycloaddition between an organic azide (RN₃) and an organic nitrile (RCN) or isonitrile (RNC).^[97, 98] However, this cycloaddition is too slow to be synthetically useful except when a potent electron-withdrawing group activates the nitrile moiety. However, the reaction can be accelerated by using microwave irradiation, as observed for the conversion of nitriles into aryl and vinyl tetrazoles upon reaction with sodium azides.^[99] Moreover, the formation of substituted tetrazoles can be achieved by using a transition metal coordinated azide and free organonitriles.^[88]The controlled cycloaddition reactions between metal coordinated azide and organonitriles have been explored in the last few decades but mostly centered around group 10 metals, particularly platinum and palladium (Scheme 1.13).^[100]



Scheme 1.13. Synthesis of *trans*-[Pt(N₄CR)₂(PPh₃)₂].

The reaction is undertaken under microwave (M.W.) irradiation (100 °C, 300 Watt). This method greatly accelerates the reactions, leading to the products only in 1 h to give the comparable yield which can be obtained after 12 h under conventional heating. The tetrazolato complexes are formed *via* [2 + 3] cycloaddition of the organonitriles with the ligated azides.

1.4.2.1.3 Generation of tetrazole by refluxing method

cis-[Pt(N₃)₂(2,2'-bipy)] with different organonitriles in DMF yielded tetrazolato complexes *cis*-[Pt(N₄CR)₂(2,2'-bipy)] (Scheme 1.14).^[100]



Scheme 1.14. Synthesis of cis-[Pt(N₄CR)₂(2,2'-bipy)].

Zinc^[101] and manganese^[95] salts react with 2-cyanopyridine to produce 5-(2-pyridyl)tetrazolate dihydrate complex which are linked to one another by hydrogen bonds to form a 2D framework (Scheme 1.15).^[102]



Scheme 1.15. Synthesis of 5-(2-pyridyl)tetrazolate dihydrate complexes.

1.4.2.2 Generation of tetrazolato complexes without much control on system

1.4.2.2.1 Generation of tetrazolato complexes by solvothermal method

Solvothermal synthesis is a method of producing chemical compounds. It is very similar to the hydrothermal route where the synthesis is conducted in a stainless steel autoclave. Using the solvothermal route gains one the benefits of both the solgel and hydrothermal routes. Thus solvothermal synthesis can lead to diversity depending upon the condition in terms of size, shape distribution, and crystallinity of the synthesized complexes. These characteristics can be altered by changing certain experimental parameters, including reaction temperature, reaction time, solvent type, surfactant type, and precursor type.

Use of hydrothermal or solvothermal methods many time induce uncontrolled cycloaddition reaction leading to formation of polymeric structures of various dimensions (Scheme 1.16).



Scheme 1.16. Synthesis of 2D coordination polymers of Zn.

The solid state structure of complex revealed that the Zn atom coordinates only to four of the N atoms from the tetrazoles of the 3-PTZ ligands to give a polymeric structure. (Mode III).^[54]

Further, under hydrothermal conditions, 5-(4-pyridyl)tetrazole anion acts as a bridging ligand forming two-dimensional coordination polymers (Figure 1.10) upon reaction with $Cd^{[103]}$ and $Cu^{[104]}$ ions. The products were characterized by X-ray diffraction. The high thermal stability, insolubility in most of solvents and photophysical properties of these complexes encourage interest in these compounds as promising fluorescent materials.^[103-105]



Figure 1.10. Structures of 2D coordination polymers of Cd and Cu.

A remarkable method for the preparation of coordinated tetrazoles starting from the inorganic complex, bis(3-cyanopyridine)copper(II)azide , in the presence of Lewis acids $CuCl_2$ and $CdCl_2$ has been reported.^[106] As a result of these reactions homometallic and heterometallic complexes were obtained (Scheme 1.17). X-ray analysis shows that these coordination polymers have three-dimensional structures.



Scheme 1.17. Synthesis of homometallic and heterometallic tetrazole complexes.

Further, it is observed that the multidentate ligands coordinated to metal atoms through different nitrogen atoms (N1, N2, N3, N4) of tetrazolyl groups (Scheme 1.18) can lead to formation of polymeric structures as shown by X-ray diffraction. The composition and the structure of obtained complexes can be varied depending on the reagent ratio and also on the acidity of the reaction mixture. Through the metal-promoted azidation of nitriles, the arising complexes are one-, two-, and three-dimensional coordination polymers.^[101, 107-109]

$$CH_{3}CN \xrightarrow{NaN_{3}, Zn(ClO_{4})_{2}}_{H_{2}O/C_{2}H_{5}OH} \left[Zn_{3} \left(H_{3}C \xrightarrow{N}_{N} \right)_{I} \\ N \xrightarrow{N}_{6} \right] H_{2}O$$

Scheme 1.18. Synthesis of metal tetrazole complex by hydrothermal conditions.
Moreover, in presence of zinc chloride and 1,10-phenanthroline, 4,5dicyanoimidazole is converted into crystals of one-dimensional polymeric complex of 4,5-di(tetrazol-5-yl)imidazole after 24 h at 160 °C (yield 53%).^[109] A parallel treatment of 1,2-dicyanohydrazine is accompanied by cleavage of the N-N bond to give (5-aminotetrazolato)hydroxyzinc (Figure 1.11).^[110]



Figure 1.11. Polymeric structures of 4,5-di(tetrazol-5-yl)imidazole and (5-amino tetrazolato)hydroxyzinc.

1.4.2.2.2 By refluxing method

Zinc chloride reacts with 3-cyano-pyridine and forms zinc 5-(3-pyridyl)tetrazolate ^[101] or hydroxyl complex^[92] under refluxing condition (Scheme 1.19). According to X-ray diffraction data the compounds are polymeric in nature. The Lewis acid zinc chloride acts as a catalyst for cycloaddition.



Scheme 1.19. Synthesis of Zn-tetrazolate complexes under reflux.

1.4.2.2.3 By microwave irradiation method

A mixture containing copper(II) chloride, sodium azide and 4-cyanopyridine in a 1 : 2 : 4 molar ratio using a water–DMF mixture was reacted in a microwave reactor at 85 °C for 30 min. The obtained mixture was filtered and the filtrate was left in air for 3 d, resulting in blue coloured cubic crystals of $\{[Cu(\mu_2-4-ptz)_2(H_2O)_2]\}_n$ (Scheme 1.20). Single crystal X-ray diffraction data revealed that the structure has 2D coordination framework assembled from the Cu(II) centres and μ_2 -4-ptz linkers.^[9]



Scheme 1.20. Synthesis of $\{[Cu(\mu_2-4-ptz)_2(H_2O)_2]\}_n$.

1.5. Purpose and span of present investigation

Owing to the ability of tetrazole derivatives to be coordinated through different nitrogen atoms of the ring and donor atoms of substituents and to the structural, chemical and functional diversity of the metal tetrazolate formed, these compounds present considerable interest for the study of geometrical isomerism, magnetism, interaction with biomolecules, bio-inspired catalysis and in C-H bond activation reactions.

Chapter 2: Examples of generation of metal-tetrazole complexes in a systematic way by conventional thermal or microwave irradiation method using cycloaddition as a tool are relatively scarce and discrete. Though there are few examples of *insitu* generation of tetrazolato ligands *via* cycloaddition using cobalt ion by thermal methods or hydrothermal reactions, however no such study has been ever reported regarding the synthesis of tetrazolato-cobalt complexes in a controlled and systematic manner for a series of compounds. Moreover the tendency of cobalt(III) ion to form different geometrical isomers depending upon various conditions incites more interest to investigate such cycloaddition in order to find out that if any structural correlation exists between the employed organonitrile and geometrical preferences.

Chapter 3: Limiting nuclearity to a finite level is a challenging task from the synthetic viewpoint as polynuclear complexes can many times show unusual magnetic or catalytic properties. Only a handful polynuclear complexes have been synthesized under different reaction conditions where tetrazoles act as bridging ligands. To further explore the metal mediated cycloaddition reactions involving organonitriles and coordinated azides for the synthesis of novel 5-substituted tetrazole complexes, preferably under mild conditions, interest have been focused to generate polynuclear compounds with limiting nuclearity in the presence of an additional tridentate ligand. Two of the reported compounds exhibit a linear trinuclear structure while the other compound shows a pentanuclear structure. The magnetic susceptibility data shows dominant antiferromagnetic interactions between the nickel centers for all the complexes. Furthermore DFT calculations were performed to investigate the magnetic parameter by broken symmetry approach.

Chapter 4: Binding of DNA with tetrazolato metal complexes has attracted much attention recently because of their site specific binding properties and wide range of applications. The interactions between DNA and copper tetrazolate complexes are relatively rare in the literature; however, to the best of knowledge, interactions of copper–tetrazolate complexes with bovine serum albumin (BSA) or any kind of bioinspired catalytic activities of these complexes have not been explored yet. A rational explanation might be that the solvothermally generated uncontrolled copper–tetrazolate frameworks are mostly insoluble in nature, which makes them unsuitable for this kind of investigation. However, in the continuous endeavor to generate metal tetrazolate complexes under more controlled and environmentally friendly conditions, herein two new mononuclear copper tetrazolato complexes have been synthesized and structurally characterized. The interactions of these complexes with biomolecules like DNA and bovine serum albumin (BSA) were studied and the catecholase like catalytic activity of the compounds are also explored.

Chapter 5: Four new metal complexes (one mononuclear and three dinuclear) *viz*. [NiL²(5-phenyltetrazolato)], [Ni₂L²₂{5-(2-cyanophenyl)-tetrazolato}₂], [Cu₂L²₂{5-(2-cyanophenyl)-tetrazolato}₂] and [Cu₂L²₂{5-phenyltetrazolato}₂]·C₆H₅CN [HL² = 3-(2-dimethylamino-ethylimino)-1-phenyl-butan-1-one] have been synthesized by *in-situ* generation of tetrazolato ligands and characterized by X-ray crystallography, different spectroscopic techniques and elemental analyses. Introduction of one nitrile group in the 5-substituted phenyl ring makes the tetrazolato ligand comparatively weaker donor leading the complex to be more vulnerable towards dissociation facilitating subsequent substrate binding for catecholase oxidation study. Copper complex [Cu₂L²₂{5-(2-cyanophenyl)-tetrazolato}₂] has been found to be more active with respect to analogous nickel complexes as it provides the metal centered oxidation route rather than ligand centered oxidation in nickel complex. The comparative catalytic activities of all complexes were further explored by DFT calculations which also support the experimental results.

Chapter 6: The development of more efficient catalysts for C-H bond activation under milder conditions using low toxicity media and benign oxidizing agents is an important area of current research. Herein, three tetrazolato copper(II) compounds were explored for use as catalyst for selective oxidation of cyclohexane (to cyclohexanol and cyclohexanone) under very mild and green (solvent- and additive-free) conditions toward the protection of environment and quality of life. In addition, interaction of synthesized complexes with bovine serum albumin (BSA) has also been studied. Finally, the molecular docking studies were performed to obtain detailed binding information of the Cu(II) complexes with BSA.

In the present study few compounds have been prepared by stirring or conventional refluxing at elevated temperatures and most of the complexes were prepared by microwave irradiation at elevated temperature. All of the compounds have been characterized by single crystal X-ray crystallography, IR, Elemental analyses. ESI-

MS and ¹H NMR spectroscopy was employed wherever required. DFT and molecular docking studies have also been carried out to support the experimental results.

In the metallosupramolecular structure different functionalities can be readily introduced by employing functional tetrazoles in the assembly processes. However, in comparison to metal-free tetrazole molecules, tetrazole coordination polymers containing metal ions are generally more sensitive and responsive to electro- and photochemical stimuli. Therefore, the development of highly stable tetrazole coordination polymers may increase new opportunities to build up novel molecular switches and devices.

Future research will certainly focus more on developing new applications in catalysis, adsorption, magnetic and optical materials. Improving the performance of either already mentioned or newly designed metal tetrazole system. Some intriguing approaches such as the use of mixed ligands and tetrazolates deserve further attention. Novel heterometal tetrazole complexes can show even more fascinating properties.

1.6 <u>References</u>

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Chapter-2

The effect of remote substitution on the formation of preferential isomers of cobalt(III)-tetrazolate complexes by microwave assisted cycloaddition

PART A

2.1A Introduction

Metal-promoted azidation of nitriles provides an easy and convenient method to synthesize metal tetrazolate complexes. Tetrazole behaves as an interesting ligand as it can act in a unidentate or polydentate fashion, furnishing mono- and polynuclear compounds with interesting topologies.^[1] Moreover, tetrazole-based complexes have evoked much interest because of their utility in organic synthesis, ^[2] gas generating agents, ^[3] medicinal chemistry^[4] and anti-corrosion species.^[5] In recent years many metal tetrazolate complexes have been synthesized using the [2+3] cycloadditions of metal ligated azides and nitriles. However, most of them are associated with group 10 transition metals,^[6] apart from some limited examples of some other transition metal elements.^[7,8] There are few examples of cobalt tetrazolate complexes, however in most of these cases the tetrazole itself has been used as the ligand $^{[9,10]}$ or it has been generated by *in situ* [2+3] cycloaddition of an azide and a nitrile in a hydrothermal process.^[11] To the best of our knowledge there are very few examples where the *in situ* generation of a tetrazolate ligand has been reported using cobalt ions in a controlled and systematic manner.^[12,13] Moreover, as cobalt(III) ions tend to form different geometrical isomers it was also interesting to investigate if there is any influence of the counter-ions used and the remote substitution of the 5-tetrazole ligands on the overall preferential geometry adopted by the cobalt center.

In the first part, the synthesis, characterization and spectroscopic properties of two cobalt(III) complexes *cis*-[Co(5-phenyltetrazolato)₂(en)₂](NO₃) (1) and *trans*-[Co{5-(4-chlorophenyl)-tetrazolato}₂(en)₂](NO₃) (2) is reported, both of which have been prepared by [2+3] cycloaddition of solid cobalt diazide complex *cis*-

 $[Co(N_3)_2(en)_2](NO_3)$ (3) with benzonitrile and 4-chlorobenzonitrile respectively (Scheme 2.1). The cycloaddition has been carried out by irradiating the solution of metal complex in the presence of organonitriles by microwave reactor. In the first case benzonitrile itself has been used as a reaction medium and it gets completed in 1 h at 110 °C whereas for compound 2, DMF has been used as reaction medium and it takes about 3 h at 130 °C for the reaction to be completed. The solvent was removed from the solution mixture by driving off the excess solvent at lower pressure. The residue upon treatment with diethyl ether forms a reddish brown powder which was further recrystallized from methanol-ether mixture.



Scheme 2.1. Schematic presentation for the formation of two different geometrical isomers of cobalt(III)-tetrazolato complexes.

2.2A Experimental section

2.2A.1 Materials and instrumentation

All the chemical reagents required were purchased from sigma and used without further purification. *cis*- $[Co(N_3)_2(en)_2](NO_3)$ (3)^[14] was prepared according to reported methods. Infrared spectra (4000–500 cm⁻¹) were recorded with a Bio-Rad FTS 3000MX instrument in KBr pellets. Mass spectrometric analyses had done on Bruker-Daltonics, microTOF-Q II mass spectrometer and the microwave irradiation experiments were done in focused microwave CEM discover reactor 300W and the reaction tube used was with 10mL capacity and 13mm internal diameter. Elemental

analyses were carried out with a ThermoFlash 2000 elemental analyzer. UV-visible absorption spectra of both the compounds in methanol were recorded on a Carry-100 Bio UV-Visible spectrophotometer. ¹H and ¹³C NMR in DMSO- d_6 were measured on an AVANCE III 400 Ascend Bruker BioSpin machine at ambient temperature.

X-ray structure determination: Single crystal X-ray structural studies of compounds **1** and **2** were performed on a CCD Agilent Technologies (Oxford Diffraction) SUPER NOVA diffractometer. Data for compound **1** was collected at 293(2) K whereas for **2** it was collected at 150(2) K using graphitemonochromoated MoK α radiation ($\lambda_{\alpha} = 0.71073$ Å). The strategy for the Data collection was evaluated by using the CrysAlisPro CCD software. The data were collected by the standard 'phi-omega scan techniques and were scaled and reduced using CrysAlisPro RED software. The structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares with SHELXL-97, refining on F².^[15]

The positions of all the atoms were obtained by direct methods. All non-hydrogen atoms were refined anisotropically. The remaining hydrogen atoms were placed in geometrically constrained positions and refined with isotropic temperature factors, generally 1.2Ueq of their parent atoms. The crystal and refinement data are summarized in Table 2.1. Selected bond lengths (Å), bond angles (°) and hydrogen bonding interactions for **1** and **2** are shown in Table 2.2, Table 2.3, Table 2.4 and Table 2.5 respectively.

| | 1 | 2 |
|---|---|--|
| Empirical formula | C ₁₉ H ₃₀ N ₁₃ O ₄ Co | C ₁₈ H ₂₄ N ₁₃ O ₃ CoCl ₂ |
| Formula weight | 563.49 | 600.33 |
| Wavelength(A) | 0.71073 | 0.71073 |
| Temperature(K) | 293(2) | 150(2) |
| Crystal system | Triclinic | Triclinic |
| Color and shape | Yellow needle | Yellow needle |
| Space group | <i>P</i> -1 | <i>P</i> -1 |
| a/Å | 7.8757(15) | 7.8730(4) |
| b/Å | 13.489(2) | 12.5588(10) |
| c/Å | 14.084(3) | 13.0611(9) |
| α/degree | 109.620(16) | 73.982(6) |
| β/degree | 101.219(16) | 82.489(5) |
| γ/degree | 102.116(16) | 83.409(5) |
| Volume(Å ³) | 1319.7(4) | 1226.43(14) |
| Ζ | 2 | 2 |
| $D_{\rm calcd}/{ m mg}~{ m m}^{-3}$ | 1.418 | 1.626 |
| μ (Mo K α)/mm ⁻¹ | 0.702 | 0.969 |
| F(000) | 588 | 616 |
| Crystal size/mm | $0.21 \times 0.17 \times 0.13$ | $0.23 \times 0.18 \times 0.11$ |
| θ range(°) | 2.98 to 25.00 | 3.00 to 25.00 |
| Limiting indices | $-9 \le h \le 9$ | $-9 \le h \le 9$ |
| | $-16 \le k \le 16$ | $-14 \le k \le 14$ |
| | $-16 \le l \le 15$ | $-15 \le l \le 15$ |
| Total/ unique no. of reflns. | 12099 / 4641 | 9642 / 4327 |
| R _{int} | 0.0955 | 0.0423 |
| Data/restr./params. | 4641/0/339 | 4327 / 0 / 369 |
| $GOF(F^2)$ | 0.996 | 1.052 |
| R1, wR2 | 0.0873, 0.1883 | 0.0403, 0.0300 |
| R1, wR2 (all data) | 0.1475, 0.2251 | 0.0003, 0.1020 0.445 and 0.334 |
| Peak and hole (e $Å^{-3n}$) | 1.064 and -0.327 | 0.445 allu -0.554 |

 Table 2.1: Crystallographic data and structure refinement of complexes 1 and 2

2.2A.2 Synthesis of compounds 1-2

2.2A.2.1 Synthesis of cis-[Co(5-phenyl-tetrazolato)₂(en)₂](NO₃) (1):

Solid cobalt diazide complex cis-[Co(N₃)₂(en)₂](NO₃) (0.12 g, 0.37 mmol) and 2 mL of benzonitrile were added to a cylindrical pyrex tube and 3 mL of DMF was

also added into it. The system was placed in the focused microwave reactor. The reaction mixture was left under irradiation for 1 h at 110 °C. The solvent was then removed *in vacuo* and the resulting residue was treated with diethyl ether to obtain a reddish-brown powder which was then recrystallized from methanol/ether mixture. Benzonitrile has been used as nitrile source and along with DMF it also acts as reaction medium.

cis-[Co(5-phenyl-tetrazolato)₂(en)₂](NO₃)·MeOH (1·MeOH): Yield: 48%. IR (KBr, selected bands, cm⁻¹): 1611 (C=N stretch), 1384 (NO₃). Anal. Calc. for $C_{19}H_{30}N_{13}O_4Co$ (563.49): C 40.48; H 5.37; N 32.32. Found: C 40.15; H 5.04; N 31.44; MS (ESI): m/z = 469.16 [M]⁺ (Figure A1).

2.2A.2.2 <u>Synthesis of trans-[Co{5-(4-chlorophenyl)-tetrazolato}_2(en)_2](NO_3)</u> (2):

A solution of 0.12 g (0.37 mmol) of cobalt diazide complex *cis*- $[Co(N_3)_2(en)_2]NO_3$ and 0.54 (3 mmol) of 4-chlorobenzonitrile in 5 mL of DMF was taken in a cylindrical pyrex tube and it was irradiated for 3 h at 130° C. The solvent was then removed *in vacuo* and the resulting reddish-brown residue was washed several times with diethyl ether to obtain a brown powder which was then recrystallized from DMF/ether mixture.

trans-[Co{5-(4-cholorophenyl)-tetrazolato}₂(en)₂](NO₃) (2): Yield: 50%. IR (KBr, cm⁻¹): 1665 (C=N stretch), 1384 (NO₃). Anal. Calc. for C₁₈H₂₄N₁₃O₃Cl₂Co (600.05): C 36.00; H 4.03; N 30.34. Found: C 34.79; H 5.11; N 22.40; MS (ESI): $m/z = 537.09 \text{ [M]}^+$ (Figure A2).

2.2A.3 Liberation of 5-substituted tetrazoles from cobalt-complex

Liberation of 5-substituted tertrazole from bis(tetrazolate) complexes was carried out by treating the precursor tetrazolate–metal complexes with excess of sodium azide in methanol. After refluxing the mixture for 2 h the filtrate was evaporated to dryness and the residue was washed with diethyl ether which upon concentration provides respective 5-substituted tetrazoles in its neutral form rather than the sodium salt as it is evident by the presence of protonated form of molecular ion peak [MH]⁺ in ESI-MS spectroscopy. Both the liberated tetrazoles have been also identified using ¹H and ¹³C NMR which corresponds well with earlier reports.^[16]

2.3A Results and discussions

2.3A.1 <u>Crystal structures</u>

The nature of both the complexes has been unambiguously established by singlecrystal X-ray crystallography.

2.3A.1.1 Crystal structure of cis-[Co(5-phenyl-tetrazolato)₂(en)₂](NO₃) (1):

Complex 1 crystallizes in triclinic space group $P\bar{1}$. The structure consists of [Co(5phenyl-tetrazolato)₂(en)₂]⁺ cations and NO₃⁻ anions. In the complex cation the central metal cobalt is surrounded by six nitrogen atoms originating from two coordinated ethylenediamines and two substituted tetrazolato ligands, resulting in the expected octahedral geometry. Two tetrazolato groups occupy cis positions and are coordinated to the metal center through N^2 -atoms (Figure 2.1.a). Bond lengths and angles for complex 1 are comparable with those similar compounds reported earlier in literature for Co(III) complexes (Table 2.2).^[17] Interestingly the two tetrazolato ligands bound to metal center are twisted by an angle of 9.0° and 28.3° with respect to the phenyl rings. The methanol molecules which are present as solvent of crystallization get attached to the main complex through N2-H2B···O101 and N3-H3B···O101 hydrogen bonding interaction (Figure 2.1.b). The counter nitrate ions are helping to hold the two ethylenediamine ligands surrounding one metal center by the formation of N1-H1B····O222 and N4-H4B...O222 (Figure 2.1.b) hydrogen bonds to two different ethylenediamine ligands. Along with that there are further hydrogen bonded intermolecular interaction involving nitrate ion [N3-H3A···O111, C4-H4A···O333, N3-H3A···O333, C4-H4B···O222] and methanol molecule [O101-H101···N11] which induce the formation of a molecular chain structure along *a*-axis (Figure 2.1.c). This chains are further interconnected between themselves via hydrogen bonding N1-H1A···O333, N1-H1B···O222, N4-H4B···O222 to form a 2D structure along yz plane (Figure 2.1.d). Selected internal hydrogen bonding interactions for **1** are summarized in Table 2.4.

Table 2.2: Selected bond lengths (Å) and bond angles (°) for **1** are compared with the calculated (in the parenthesis) bond lengths and bond angles from DFT

| Co(1)-N(9) | 1.913(4) [1.903] | N(1)-Co(1)-N(4) | 92.0(2) [92.018] |
|------------|------------------|-----------------|--------------------|
| Co(1)-N(5) | 1.902(6) [1.908] | N(5)-Co(1)-N(9) | 89.7(2) [91.540] |
| Co(1)-N(1) | 1.943(4) [1.975] | N(2)-Co(1)-N(4) | 176.4(2) [176.391] |
| Co(1)-N(3) | 1.947(6) [1.962] | N(9)-Co(1)-N(1) | 176.1(2) [176.140] |
| Co(1)-N(2) | 1.948(6) [1.962] | N(5)-Co(1)-N(2) | 92.4(2) [91.847] |
| Co(1)-N(4) | 1.955(6) [1.970] | N(1)-Co(1)-N(2) | 85.5(2) [86.598] |
| | | N(1)-Co(1)-N(3) | 92.7(2) [91.377] |
| | | N(1)-Co(1)-N(5) | 88.3(2) [88.058] |
| | | N(2)-Co(1)-N(3) | 91.6(2) [90.678] |
| | | N(2)-Co(1)-N(9) | 91.3(2) [89.829] |
| | | N(3)-Co(1)-N(4) | 86.0(2) [85.750] |
| | | N(3)-Co(1)-N(5) | 176.0(2) [177.374] |
| | | N(3)-Co(1)-N(9) | 89.5(2) [89.183] |
| | | N(4)-Co(1)-N(5) | 90.1(2) [91.705] |
| | | N(4)-Co(1)-N(9) | 91.3(2) [91.578] |



Figure 2.1. (a) Showing local coordination environment of Co (III) atom (hydrogen atoms omitted for clarity) in **1**; (b) showing hydrogen bonding interaction from both the en molecules towards one of the oxygen atom of nitrate ion and to one methanol molecule; (c) showing hydrogen bonded molecular chain structure of **1**; (d) showing supramolecular interactions through hydrogen bonds, to form 2D polymer structure along *yz* plane.

2.3A.1.2 <u>Crystal structure of *trans*-[Co{5-(4-chlorophenyl)-tetrazolato}₂(en)₂]</u> (NO₃) (2):

Compound **2** also crystallizes in space group $P_{\overline{1}}$. There are two crystallographically independent complex molecules which exist with very similar geometries and the two tetrazolato groups occupy *trans* positions and are coordinated to the metal center through N2-atoms (Figure 2.2.a). Bond lengths and angles for complex **2** are indicated in Table 2.3. The dihedral angles between tetrazole and phenyl ring are found to be 25.02° and 7.53°, respectively. Each nitrate ion is found to be connected with three molecules *via* N12-H4N···O222, N12-H3N···O333 and N6-

H7N···O333 interaction (Figure 2.2.b). Further each individual molecule has been found interacting to the adjacent molecules along *c*-axis *via* N6-H8N···N10 and N11-H1N···N3 (Figure 2.2.c). However in this case the independent molecules are packed along *c*-axis and *a*-axis through H-bonding between different molecules and the nitrate counter ions help in forming a hydrogen bonded 2D polymer in *ac*-plane (Figure 2.2.d). All these network which are running in the direction of *ac*-plane orients in such a way that the para substituted chlorine atoms get stacked one upon another along *c*-axis with a distance in the range of 6.433–6.645 Å. However long distance Cl···Cl interactions between the chlorine atom of one molecule and two other chlorine atoms of adjacent network [Cl3–Cl4 3.762 Å; Cl3–Cl3 4.144 Å; Cl4–Cl4 4.597 Å] may also contribute for the preferential *trans*-geometry of complex **2**. Selected internal hydrogen bonding interactions for **2** are summarized in Table 2.5.

| Co(1)-N(1) | 1.923(3) [1.917] | N(1)-Co(1)-N(5) | 89.1(1) [88.562] |
|-------------|------------------|-----------------|-------------------|
| Co(1)-N(5) | 1.950(3) [1.969] | N(1)-Co(1)-N(6) | 91.7(1) [89.182] |
| Co(1)-N(6) | 1.948(2)[1.965] | N(1)-Co(1)-N(1) | 180.0(1) [180.0] |
| Co(1)-N(1) | 1.923(3) [1.917] | N(1)-Co(1)-N(5) | 90.9(1) [91.437] |
| Co(1)-N(5) | 1.950(3) [1.969] | N(1)-Co(1)-N(6) | 88.3(1) [89.182] |
| Co(1)-N(6) | 1.948(2) [1.965] | N(5)-Co(1)-N(6) | 86.2(1) [88.562] |
| Co(2)-N(7) | 1.916(3) [1.912] | N(5)-Co(1)-N(1) | 90.9(1) [93.847] |
| Co(2)-N(11) | 1.929(2) [1.947] | N(5)-Co(1)-N(5) | 180.0(1) [180.00] |
| Co(2)-N(12) | 1.946(3) [1.962] | N(5)-Co(1)-N(6) | 93.8(1) [93.847] |
| Co(2)-N(7) | 1.916(3) [1.912] | N(6)-Co(1)-N(1) | 88.3(1) [89.182] |
| Co(2)-N(11) | 1.929(2) [1.947] | N(6)-Co(1)-N(5) | 93.8(1) [93.847] |
| Co(2)-N(12) | 1.946(3) [1.962] | N(6)-Co(1)-N(6) | 180.0(1) [180.00] |
| | | N(1)-Co(1)-N(5) | 89.1(1) [91.437] |
| | | | |

Table 2.3: Selected bond lengths (Å) and bond angles (°) for **2** are compared with the calculated (in the parenthesis) bond lengths and bond angles from DFT

| N(1)-Co(1)-N(6) | 91.7(1) [89.182] |
|-------------------|-------------------|
| N(5)-Co(1)-N(6) | 86.2(1) [93.847] |
| N(7)-Co(2)-N(11) | 90.1(1) [90.294] |
| N(7)-Co(2)-N(12) | 88.8(1) [88.917] |
| N(7)-Co(2)-N(7) | 180.0(1) [180.00] |
| N(7)-Co(2)-N(11) | 89.9(1) [89.706] |
| N(7)-Co(2)-N(12) | 91.2(1) [91.008] |
| N(11)-Co(2)-N(12) | 86.9(1) [87.042] |
| N(11)-Co(2)-N(11) | 180.0(1) [180.00] |



Figure 2.2. (a) Showing local coordination environment of Co(III) atom (hydrogen atoms omitted for clarity) in 2; (b) showing hydrogen bonding interaction from nitrate ion with three different molecules; (c) showing hydrogen bonded structure of 2 along *c*-axis; (d) showing supramolecular interactions hydrogen bonds, helping to form a stacked like structure along *c*-axis.

| D-H····A | d(D-H) / Å | d(H····A)∕ Å | d(D····A)/Å | $\angle D$ -H····A/° |
|----------------------|------------|--------------|-------------|----------------------|
| | | | | |
| N(2)-H(2B)····O(111) | 0.901 | 2.187 | 3.032 | 155.87 |
| N(4)-H(4B)····O(222) | 0.900 | 2.369 | 3.183 | 150.35 |
| N(1)-H(1B)····O(222) | 0.900 | 2.351 | 3.116 | 142.81 |
| N(2)-H(2B)····O(101) | 0.901 | 2.187 | 3.032 | 155.87 |
| N(4)-H(4A)····O(111) | 0.900 | 2.343 | 3.059 | 136.50 |
| N(3)-H(3A)····O(111) | 0.900 | 2.159 | 3.053 | 172.61 |
| N(3)-H(3A)O(333) | 0.900 | 2.525 | 3.233 | 136.00 |
| N(3)-H(3B)····O(101) | 0.901 | 2.144 | 2.973 | 152.71 |

 Table 2.4: Geometric features of internal hydrogen bonding interactions for 1

Table 2.5: Geometric features of internal hydrogen bonding interactions for 2

| D-H····A | d(D-H) / Å | d(H····A) / Å | d(D····A) / Å | ∠D-H····A/° |
|----------------------|------------|---------------|---------------|-------------|
| N(12)-H4N····O(222) | 0.904 | 2.110 | 2.919 | 148.24 |
| N(12)-H3N·····O(333) | 0.918 | 2.077 | 2.972 | 164.57 |
| N(6)-H7NO(333) | 0.784 | 2.161 | 2.905 | 158.90 |
| N(6)-H8NN(10) | 0.940 | 2.334 | 3.092 | 137.30 |
| N(11)-H1N····N(3) | 0.887 | 2.337 | 3.021 | 133.92 |

Both compounds **1** and **2** have been characterized by elemental analyses, IR, ESI-MS spectroscopy, ¹H, ¹³CNMR and X-ray crystallography. The IR spectra do not show the typical azide band at *ca*. 2086 and 2019 cm⁻¹ of the starting diazide complex and display a new strong band within the 1603–1665 cm⁻¹ range due to the tetrazole ring.^[18] The typical bands for nitrate ion are also observable in the vicinity of 1350 cm⁻¹.^[19] In ESI-MS for both the bis(tetrazolato) complexes, the molecular ion peaks have been observed confirming the presence of bistetrazolato moiety.

The ¹H NMR and ¹³C NMR spectra of the cobalt complexes are in agreement with similar types of (ethylenediamine)cobalt complexes reported earlier.^[20] Complex 1 has shown fractured peaks for the methylene protons in the range 2.07–3.19 ppm, typical for cobalt(III) coordination compound with ethylenediamine ligand. Several fractured peaks can also be observed in the range 4.22-6.31 ppm for nitrogen protons of ethylenediamine. In compound 2 the same set of signals is obtained in the range of 2.32-3.16 ppm and 4.56-6.28 ppm, respectively. The ¹³C NMR of compound 1 reveals four different resonance signals in the range of 44.13–48.59 ppm for the ethylenic carbon indicating the nonsymmetric nature of two coordinated tetrazolato groups which may arise out of their difference in internal twist between the phenyl and tetrazolato rings which have been indicated in crystal structure discussion. Whereas, in case of compound 2 it shows two ¹³C resonance signals at 44.40 and at 44.94 ppm for the ethylenic carbon corroborating the nonequivalent nature of tetrazolato ligands. The presence of two tetrazolato species of non-symmetric nature in compounds 1 and 2 is further confirmed by the presence of a pair of signals in the range of 163–165 ppm in the ¹³C NMR spectrum.^[18]

2.3A.2 <u>UV-Visible spectroscopy</u>

The solution state electronic spectra of the isolated cobalt(III) complex in the near UV–Vis region exhibits the presence of one absorption band due to the d–d transitions in the octahedral CoN₆ crystal field. The transition which is observed in the range of 445-455 nm can be assigned due to ${}^{1}A_{1g} \rightarrow {}^{1}T_{1g}$ transition.^[21] The absorption due to ${}^{1}A_{1g} \rightarrow {}^{1}T_{2g}$ transition is masked (observed as very weak shoulder) because of the presence of long tail of the charge-transfer peaks. The other electronic transition which were observed in the UV region can be assigned as $\pi \rightarrow \pi^*$ electronic transition in the ligand.

2.3A.3 DFT study

The density functional calculations (DFT) were carried out to understand the driving force for the formation of complexes 1 and 2 as preferential isomers (Scheme 2.1). This has been directed to obtain a clear picture whether the *cis*- and *trans*- geometries are kinetically or thermodynamically controlled. To comprehend this detailed theoretically studies of the respective cations in the molecular level have been considered. Moreover, the *trans* geometry of complex 1 and *cis* geometry of complex 2 was also modelled to understand their thermodynamical stabilities.

All the calculations were carried out using the B3LYP/6-311++G** level of theory^[22] as implemented in the Gaussian 09 suit of programs.^[23] Vibrational frequency calculations were carried out to confirm their nature of stationary points. All structures are calculated to be minimum on their potential energy surfaces. The calculated geometrical parameters (Table 2.2 and Table 2.3) of the compounds **1** and **2** are in very much agreement with their experimental data. Our relative energetic calculations show that both the complexes (**1** and **2**) are more stable (by ~13 Kcal/mole) in their *trans* geometries than their respective *cis* geometries which is differing for the complex **1** from our experimental findings.

To obtain a greater insight, as calculating only the thermodynamically stabilities are not good enough because it does not include the Van der Waals interactions between the metal complexes as we have studied them in their solid state structures retaining their space group geometry. So, periodic boundary conditions are used for the three dimensional structure modelling. The first-principles calculations are used using projected augmented wave (PAW) method as implemented in the Vienna abinitio simulation package (VASP) for their structural relaxations.^[24] The exchange-correlation interaction was treated in the level of the GGA using Perdew-Burke-Ernzerhof (GGA-PBE).^[25] Moreover, the van der Waals corrected interaction energies was calculated using the semi-empirical correction of Grimme^[26] as available with VASP for the accurate treatment of the weak interactions. The calculations show both the complexes (**1** and **2**) are stable within their geometry. The *trans* geometry of complex 1 and the *cis* geometry of complex 2 was optimized but it was seen that the *cis* geometry of the complex 2 was not relaxed where as *trans* geometry of complex 1 was found to be a minimum in the potential energy surface. More importantly, *trans* geometry of complex 1 is thermodynamically more stable (by ~19 Kcal/mole) than the respective *cis* geometry. The calculated van der Waals interaction energies for complex 2 is 21.96 Kcal/mol which is more than the complex 1.It was found that the van der Waals interaction energies are maximum in the chloro substituted complex 2 which might be playing a major role in crystallizing the complex in *trans*- form. Therefore the theoretical study suggests the formation of complex 1 is kinetically controlled whereas complex 2 is thermodynamically controlled.

PART B

2.1B Background

Based on the outcome of the first part, the investigation was continued for the reactions of different organonitriles with cobalt(III) coordinated azides in presence of varying counterions. It has been observed that reactions of *cis*- $[Co(N_3)_2(en)_2](NO_3)$ (**3**) and *trans*- $[Co(N_3)_2(en)_2](ClO_4)$ (**3a**) with various aryl nitrile furnished corresponding *cis*- or *trans*-bis(tetrazolato) complexes or their mixtures depending upon various factors like remote substitution, counter-anion used or solvent of crystallization in the cycloadded tetrazolato ligand.

The diazidocobalt (III) complex cis-[Co(N₃)₂(en)₂](NO₃) (**3**) reacts with the respective organonitriles RCN [R= 3-NC₅H₄, 4-NC₅H₄ and 4-BrC₆H₄] under microwave irradiation and gives the corresponding bis(tetrazolato) complexes [Co(N₄CR)₂(en)₂](NO₃) (Scheme 2.2). But reaction with 3-cyanopyridine shows a mixture of *cis*- and *trans*- isomers of tetrazolato complex (*cis*-4 & *trans*-4).



Scheme 2.2. The reaction of cobalt diazide complex 3 with different organonitriles.

Further, upon reaction of *trans*- $[Co(N_3)_2(en)_2](ClO_4)$ **3a** with 4-cyanopyridine, 4bromobenzonitrile and benzonitrile, a mixture of *cis*- and *trans*- isomers of bis(tetrazolate)complexes $[Co(N_4CR)_2(en)_2](ClO_4)$ was obtained respectively (Scheme 2.3).



Scheme 2.3. The reaction of cobalt diazide complex 3a with various organonitriles.

2.2B Experimental section

2.2B.1 Materials and instrumentations

All the chemical reagents required were purchased from sigma and used without further purification. *cis*-[Co(N₃)₂(en)₂](NO₃) (**3**) and *trans*-[Co(N₃)₂(en)₂](ClO₄) (**3a**) were prepared according to reported methods.^[277] Infrared spectra (4000–500 cm⁻¹) were recorded with a BRUKER TENSOR 27 instrument in KBr pellets. Mass spectrometric analyses was done on Bruker-Daltonics, microTOF-Q II mass spectrometer and the microwave irradiation experiments had done in focused microwave CEM discover reactor 300W and the reaction tube used was with 10mL capacity and 13mm internal diameter. Elemental analyses were carried out with a ThermoFlash 2000 elemental analyzer. UV-visible absorption spectra of all the compounds in Methanol were recorded on a Carry-100 Bio UV-Visible spectrophotometer. ¹H NMR (400 MHz) in DMSO-*d*₆ were measured on an AVANCE III 400 Ascend Bruker BioSpin machine at ambient temperature.

Caution! *Azide, tetrazolate and perchlorate compounds are potentially explosive. Only a small amount of material should be prepared and handled with care.*
X-ray crystallography: Single crystal X-ray structural studies of (*cis-4*), (*cis-5*), (*trans-6*), **7** and **9** were performed on a CCD Agilent Technologies (Oxford Diffraction) SUPER NOVA diffractometer. Data for all the complexes were collected at 293(2) K except for (*cis-5*), **7** and **9** for which it was at 150(2) K using graphite-monochromated MoK α radiation ($\lambda_{\alpha} = 0.71073$ Å). The strategy for the Data collection was evaluated by using the CrysAlisPro CCD software. The data were collected by the standard phi-omega scan techniques and were scaled and reduced using CrysAlisPro RED software. The structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares with SHELXL-97, refining on F^{2} .^[28]

The positions of all the atoms were obtained by direct methods. All non-hydrogen atoms were refined anisotropically. The remaining hydrogen atoms were placed in geometrically constrained positions and refined with isotropic temperature factors, generally $1.2U_{eq}$ of their parent atoms. The crystal and refinement data are summarized in Table 2.6, selected bond distances, bond angles for *cis*-4, *cis*-5, *cis*-7, *cis*-8, *cis*-9, and *trans*-6 and are shown in Table 2.8-2.13 respectively.

However, the single crystal X-ray diffraction data collections for the compound *cis*-**8** was performed using Bruker-APEX-II CCD diffractometer with graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å). The structure was solved by SIR-92^[29] available in WinGX, which successfully located most of the nonhydrogen atoms. Subsequently, least square refinements were carried out on F² using SHELXL-97 (WinGX version)^[28] to locate the remaining non-hydrogen atoms. All non-hydrogen atoms were refined anisotropically and most of the hydrogen atoms were refined isotropically on calculated positions using a riding model.

| | cis-4 | cis-5 | trans-6 |
|---|--|---|--|
| Empirical formula | C ₃₈ H ₄₈ N ₃₂ O ₈ Co ₂ | C ₂₀ H ₂₄ N ₁₅ O ₄ Co | C ₂₁ H ₃₁ N ₁₄ O ₄ CoBr ₂ |
| Formula weight | 1198.94 | 597.47 | 762.35 |
| Wavelength (A) | 0.71073 | 0.71073 | 0.71073 |
| Temperature (K) | 293(2) | 150(2) | 293(2) |
| Crystal system | Monoclinic | Monoclinic | Triclinic |
| Colour and shape | Yellow needle | Yellow needle | Yellow needle |
| Space group | <i>P</i> 2 ₁ /c | $P 2_1/c$ | <i>P</i> -1 |
| a/Å | 18.5537(5) | 11.6957(6) | 8.5104(7) |
| b/Å | 20.4481(7) | 18.9480(6) | 12.417(2) |
| c/Å | 14.4208(5) | 12.5618(3) | 16.104(2) |
| α/degree | 90 | 90 | 109.442(14) |
| β/degree | 91.001(3) | 92.388(4) | 100.647(9) |
| γ/degree | 90 | 90 | 95.584(10) |
| Volume (Å ³) | 5470.2(3) | 2781.40(18) | 1553.7(4) |
| Z | 4 | 4 | 2 |
| $D_{\rm calcd}/{ m mg}~{ m m}^{-3}$ | 1.456 | 1.427 | 1.672 |
| μ (Mo K α)/mm ⁻¹ | 0.685 | 0.673 | 3.193 |
| F(000) | 2472 | 1232 | 788 |
| Crystal size/mm | 0.32×0.28×0.24 | 0.33×0.26×0.21 | 0.38×0.34×0.29 |
| θ range (°) | 3.00 to 25.00 | 3.17 to 25.00 | 3.05 to 25.00 |
| Limiting indices | $-22 \le h \le 22$ | $-13 \le h \le 11$ | $-10 \le h \le 10$ |
| | $-24 \le k \le 24$ | $-22 \le k \le 22$ | $-14 \leq k \leq 12$ |
| | $-17 \le l \le 17$ | $-14 \leq 1 \leq 14$ | $-19 \le l \le 19$ |
| Total/ unique no. of reflns. | 31738 / 9616 | 15822 / 4888 | 10996 / 5454 |
| R _{int} | 0.0629 | 0.0387 | 0.0545 |
| Data/restr./params. | 9616/0/721 | 4888 / 25 / 361 | 5454 / 0 / 384 |
| $GOF(F^2)$ | 1.026 | 1.034 | 1.057 |
| R1, wR2 | 0.0589, 0.1390 | 0.0502, 0.1328 | 0.0751, 0.2081 |
| R1, wR2 (all data) | 0.1020, 0.1721 | 0.0676, 0.1467 | 0.1078, 0.2381 |
| Peak and hole (e $Å^{-3n}$) | 0.729 and -0.449 | 0.587 and -0.316 | 0.907 and -0.719 |

Table 2.6: Crystal data and structure refinement of complexes cis-4, cis-5, trans-6,cis-7, cis-8 and cis-9

| | cis-7 | cis-8 | cis-9 |
|---|---------------------------------|---------------------------------|---|
| Empirical formula | $C_{32}H_{50}N_{28}O_9Co_2Cl_2$ | $C_{18}H_{24}N_{12}O_4Br_2CoCl$ | C ₁₉ H ₂₆ N ₁₂ O ₅ CoCl |
| Formula weight | 1159.76 | 726.65 | 596.9 |
| Wavelength(A) | 0.71073 | 0.71073 | 0.71073 |
| Temperature(K) | 150(2) | 293(2) | 150(2) |
| Crystal system | Monoclinic | Trigonal | Orthorhombic |
| Color and shape | Yellow needle | Yellow needle | Yellow needle |
| Space group | $P2_{1}/c$ | P3c1 | $P2_{1}2_{1}2_{1}$ |
| a/Å | 11.6499(7) | 12.545(3) | 13.0541(4) |
| b/Å | 16.1363(13) | 12.545(3) | 13.3594(7) |
| c/Å | 13.5916(11) | 32.893(16) | 14.8320(4) |
| α/degree | 90.00 | 90.00 | 90 |
| β/degree | 95.163(6) | 90.00 | 90 |
| γ/degree | 90.00 | 120.00 | 90 |
| Volume(Å ³) | 2544.7(3) | 4483(3) | 2586.63(17) |
| Z | 4 | 6 | 10 |
| $D_{ m calcd}/ m mg~m^{-3}$ | 1.511 | 1.585 | 1.533 |
| μ (Mo K α)/mm ⁻¹ | 0.834 | 3.381 | 0.823 |
| F(000) | 1192 | 2108 | 1232 |
| Crystal size/mm | 0.26×0.21×0.18 | 0.33×0.25×0.08 | 0.23×0.1×0.13 |
| θ range(°) | 2.94 to 25.00 | 1.24 to 20.92 | 3.14 to 24.99 |
| Limiting indices | $-13 \le h \le 13$ | $-12 \leq h \leq 12$ | $-15 \le h \le 15$ |
| | $-19 \le k \le 19$ | $-12 \leq k \leq 12$ | $-12 \le k \le 15$ |
| | $-16 \le l \le 14$ | $-33 \le l \le 32$ | $-17 \le l \le 17$ |
| Total/ unique no. of reflns. | 21371 / 4471 | 33225 / 1589 | 18243 / 4554 |
| R _{int} | 0.0740 | 0.1818 | 0.0367 |
| Data/restr./params. | 4471 / 0 / 334 | 1589 / 0 / 164 | 4554 / 0 / 343 |
| $GOF(F^2)$ | 1.067 | 1.156 | 1.104 |
| R1, wR2 | 0.0678, 0.1706 | 0.0896, 0.2471 | 0.0418, 0.1103 |
| R1, wR2 (all data) | 0.0908, 0.1951 | 0.1374, 0.3084 | 0.0451, 0.1131 |
| Peak and hole (e $Å^{-3n}$) | 0.820 and -0.715 | 1.762 and -0.819 | 0.524 and -0.474 |
| | | | |

2.2B.2 Synthesis

2.2B.2.1 Synthesis of cis-[Co{5-(3-pyridyl)-tetrazolato}₂(en)₂](NO₃)·DMF (cis-4) and trans-[Co{5-(3-pyridyl)-tetrazolato}₂(en)₂](NO₃) (trans-4):

0.12 g (0.37 mmol) of cobalt diazide complex **3** was dissolved in 5 mL of DMF in a cylindrical pyrex tube and 0.31 g (3 mmol) of 3-cyanopyridine was added to that solution. The system was irradiated for 1 h at 130 °C in microwave reactor. The solvent was then removed *in vacuo* and the resulting reddish-brown residue was washed several times with diethyl ether to obtain a brown powder. The presence of both *cis*- and *trans*-isomer was detected in the resultant compound by ¹H NMR spectroscopy which are formed tentatively in 1:2 ratio (Figure 2.3).



Figure 2.3. ¹H NMR Spectrum of mixture containing both *cis*-4 and *trans*-4.

The mixture was separated by ion-exchange chromatography using SP-Sephadex C-25 which is a strongly acidic $(-SO_3^-Na^+)$ cation exchanger based on cross-linked dextran. 0.1 (M) NaNO₃ solution was used as the elution solvent to run the column. Both the isomers were further recrystallized from DMF-diethyl ether mixture. Although it was possible to grow suitable X-ray diffraction quality crystals for compound *cis-4* during recrystallization, no single crystal was obtained for the corresponding *trans* isomer.

cis-[Co{5-(3-pyridyl)-tetrazolato}₂(en)₂](NO₃)·DMF (*cis*-4): Yield: 11%. IR (KBr, selected bands, cm⁻¹): 1640 (C=N stretch), 1384 (NO₃). Anal. Calc. for C₁₉H₂₄N₁₆O₄Co (599.43): C 38.03; H 4.00; N 37.36. Found: C 37.92; H 3.89; N 37.20. MS (ESI): m/z = 471.15 [M]⁺ (Figure A3). ¹H NMR (400 MHz, DMSO-*d*₆, Me₄Si): δ 2.29-2.90 (m, 8H, CH₂), 4.73 (s, 2H, NH₂), 5.04 (s, 2H, NH₂), 5.81 (s, 2H, NH₂), 6.29 (s, 2H, NH₂), 6.60 (s, 2H, aromatic), 7.50 (s, 2H, aromatic), 8.30 (s, 2H, aromatic), 8.58 (s, 2H, aromatic) (See figure 2.4 for ¹H NMR spectra).



Figure 2.4. ¹H NMR Spectrum of compound *cis*-4

trans-[Co{5-(3-pyridyl)-tetrazolato}₂(en)₂](NO₃)·DMF (*trans*-4): Yield: 38%. IR (KBr, selected bands, cm⁻¹): 1617 (C=N stretch), 1384 (NO₃). Anal. Calc. for C₁₉H₂₄N₁₆O₄Co (599.43): C 38.03; H 4.00; N 37.36. Found: C 37.83, H 3.82, N 37.03. MS (ESI): m/z = 471.15 [M]⁺ (Figure A4). ¹H NMR (400 MHz, DMSO-*d*₆, Me₄Si): δ 2.06-2.26 (m, 8H, CH₂), 4.55 (s, 8H, NH₂), 6.78-7.55 (m, 8H, aromatic) (See figure 2.5 for ¹H NMR spectra)



Figure 2.5. ¹H NMR Spectra of compound *trans*-4.

2.2B.2.2 Synthesis of *cis*-[Co{5-(4-pyridyl)-tetrazolato}₂(en)₂](NO₃)·Et₂O (*cis*-5):

This compound was prepared in an identical manner which has been followed for compound *cis-4*. However, in this case the only pure *cis*-compound has been isolated instead of a mixture and it was recrystallized from methanol/diethyl ether mixture which produced some single crystals for X-ray diffraction analysis.

cis-[Co{5-(4-pyridyl)-tetrazolato}₂(en)₂](NO₃)-Et₂O (*cis*-5): Yield: 58%. IR (KBr, selected band, cm⁻¹): 1614 (C=N stretch), 1384 (NO₃). Anal. Calc. for C₂₀H₂₄N₁₅O₄Co (597.47): C 40.16; H 4.01; N 35.14. Found: C 39.94; H 3.89; N 35.04. MS (ESI): $m/z = 471.20 \text{ [M]}^+$ (Figure A5). ¹H NMR (400 MHz, DMSO- *d*₆, Me₄Si): δ 2.34-2.83 (m, 8H, CH₂), 4.60 (s, 2H, NH₂), 4.85 (s, 2H, NH₂), 5.82 (s, 2H, NH₂), 6.31 (s, 2H, NH₂), 7.91 (d, 4H, aromatic), 8.87 (d, 4H, aromatic) (See figure 2.6 for ¹H NMR spectra).



Figure 2.6. ¹H NMR Spectra of compound *cis*-5.

2.2B.2.3 <u>Synthesis of trans-[Co{5-(4-bromophenyl)tetrazolato}₂(en)₂](NO₃)·</u> DMF (trans-6):

A solution of 0.12 g (0.37 mmol) of cobalt diazide complex **3** and 0.54 (3 mmol) of 4-bromobenzonitrile in 5 mL of DMF was taken in a cylindrical pyrex tube and it was irradiated for 3 h at 130 °C. The solvent was then removed *in vacuo* and the resulting reddish-brown residue was washed several times with diethyl ether to obtain a brown powder which was then recrystallized from DMF-ether mixture to obtain reddish-brown crystalline compound along with single crystals suitable for X-ray diffraction studies.

trans-[Co{5-(4-bromophenyl)-tetrazolato}₂(en)₂](NO₃)·DMF (*trans*-6): Yield: 56%. IR (KBr, cm⁻¹): 1665 (C=N stretch), 1384 (NO₃). Anal. Calc. for C₂₁H₃₁N₁₄O₄ Br₂Co (762.35): C 33.05; H 4.06; N 25.70. Found: C 32.85; H 3.90; N 25.31. MS (ESI): m/z = 626.99 [M]⁺ (Figure A6). ¹H NMR (400 MHz, DMSO-*d*₆, Me₄Si): δ

2.45 (s, 8H, CH₂), 5.41 (s, 8H, NH₂), 7.73 (d, 4H, aromatic), 8.08 (d, 4H, aromatic). See figure 2.7 for ¹H NMR spectra.



Figure 2.7. ¹H NMR Spectra of compound *trans-4*.

2.2B.2.4 Synthesis of cis-[Co{5-(4-pyridyl)-tetrazolato}2(en)2](ClO4)·H2O (cis-

<u>**7**</u>): 0.12 g (0.33 mmol) of *trans*- cobalt diazide complex **3a** was dissolved in 5 mL of DMF in a cylindrical pyrex tube and 0.31 g (3 mmol) of 4-cyanopyridine was added to that solution. The system was irradiated for 1 h at 130 °C in microwave reactor. The solvent was then removed *in vacuo* and the resulting reddish-brown residue was washed several times with diethyl ether to obtain a brown powder. This brown powder was found to be a mixture of *cis*- and *trans*-[Co{5-(4-pyridyl)-tetrazolato}₂(en)₂]ClO₄ (*cis*-7 and *trans*-7) which was formed tentatively in 5:2 ratio (Figure 2.8 for ¹H NMR spectra). The mixture was tried to be separated by ion-exchange method through SP-Sephadex C-25. However, only *cis*- compound could have been isolated upon elution with NaNO₃ whereas the *trans*-compound gets decomposed in ion-exchange resin column. The resultant *cis*-compound was then recrystallized from methanol-diethyl ether mixture which furnished some X-ray diffraction quality crystals.



Figure 2.8. ¹H NMR Spectrum of mixture containing both *cis*-7 and *trans*-7.

cis-[Co{5-(4-pyridyl)-tetrazolato}₂(en)₂](ClO₄)·H₂O (*cis*-7): Yield: 56%. IR (KBr, selected bands, cm⁻¹): 1612 (C=N stretch), 1096 (ClO₄). Anal. Calc. for C₁₆H₂₆N₁₄O₅ CoCl (588.85): C 32.60; H 4.41; N 33.28. Found: C 32.06; H 4.10; N 33.07; MS (ESI): m/z = 471.15 [M]⁺ (Figure A7). ¹H NMR (400 MHz, DMSO-*d*₆, Me₄Si): δ 1.91-2.82 (m, 8H, CH₂), 4.57 (s, 2H, NH₂), 4.84 (s, 2H, NH₂), 5.82 (s, 2H, NH₂), 6.30 (s, 2H, NH₂), 7.91 (d, 4H, aromatic), 8.67 (d, 4H, aromatic). See figure 2.9 for ¹H NMR spectra.



Figure 2.9. ¹H NMR Spectra of compound *cis*-7.

2.2B.2.5 Synthesis of *cis*-[Co{5-(4-bromophenyl)-tetrazolato}₂(en)₂](ClO₄) (*cis*-8) and *trans*-[Co{5-(4-bromophenyl)-tetrazolato}₂(en)₂](ClO₄) (*trans*-8):

Solid cobalt diazide complex *trans*- $[Co(N_3)_2(en)_2]ClO_4$ (0.12 g, 0. 33 mmol) **3a** and 0.54 (3 mmol) of 4-bromobenzonitrile in 5 mL of DMF was taken in a cylindrical

pyrex tube and it was irradiated for 3 hrs at 130 °C. After removing the solvent *in vacuo* the resulting reddish-brown residue was washed several times with diethyl ether. The brown powder yielded was found to be a mixture of *cis*- and *trans*-compound in a tentatively ratio of 1:1 (Figure 2.10 for ¹H NMR spectra).



Figure 2.10. ¹H NMR Spectra of mixture containing both *cis*-8 and *trans*-8.

However the mixtures could not be separated by ion-exchange method as both the compound is getting decomposed in column. Recrystallization of the brown powder from methanol-diethyl ether mixtures provides crystalline compound which has been found to be mixture again. However, it was possible to grow the single crystals of *cis*-variety only by this method.

cis- and *trans*-[Co{5-(4-bromophenyl)-tetrazolato}₂(en)₂](ClO₄) (*cis*- and *trans*-8): Yield: 54%. IR (KBr, selected bands, cm⁻¹): 1666 (C=N stretch), 1126 (ClO₄). Anal. Calc. for C₁₈H₂₄N₁₂O₄Br₂CoCl (726.65): C 29.72; H 3.30; N 23.11. Found: C 30.00; H 3.62; N 22.98. MS (ESI): m/z = 627.18 [M]⁺ (Figure A8). ¹H NMR (400 MHz, DMSO-*d*₆, Me₄Si): δ 2.32-2.88 (m, 8H, CH₂), 4.52, 4.91, 5.80, & 6.27 (all singlet, 8H, from *cis* isomer), 5.41 (s, 8H, from the *trans* isomer), 7.66-8.10 (m, 8H, aromatic). See figure 2.11 for ¹H NMR spectra.



Figure 2.11. ¹H NMR Spectra of mixture containing both *cis*-8 and *trans*-8.

2.2B.2.6 <u>Synthesis of cis-[Co(5-phenyltetrazolato)₂(en)₂](ClO₄) (cis-9) and <u>trans-[Co(5-phenyltetrazolato)₂(en)₂](ClO₄) (trans-9):</u></u>

Solid cobalt diazide complex $[Co(N_3)_2(en)_2](ClO_4)$ (0.12 g, 0.33 mmol) **3a** and 2 mL of benzonitrile were added to a cylindrical pyrex tube and 3 mL of DMF was also added into it. The system was placed in the focused microwave reactor. The reaction mixture was left under irradiation for 1 h at 130 °C. The solvent was then removed *in vacuo* and the resulting residue was treated with diethyl ether to obtain a reddish-brown powder which was found to be a mixture of *cis*- and *trans*- variety tentatively in 9:1 ratio (Figure 2.12 for ¹H NMR spectra).



Figure 2.12. ¹H NMR Spectrum of mixture containing both *cis-9* and *trans-9*.

The mixture was separated by ion-exchange method as previously described for other compounds and then separately recrystallized from methanol/ether mixture. However, only the *cis*-variety produced some crystals suitable for X-ray analysis.

cis-[Co(5-phenyl-tetrazolato)₂(en)₂](ClO₄)·MeOH (*cis*-9): Yield: 28%. IR (KBr, selected bands, cm⁻¹): 1640 (C=N stretch), 1048 (ClO₄). Anal. Calc. for C₁₉H₂₆N₁₂ClCoO₅ (596.9): C 38; H 4.61; N 29.55. Found: C 37.56; H 4.92; N 28.72. MS (ESI): $m/z = 469.16 [M]^+$ (Figure A9). ¹H NMR (400 MHz, DMSO-*d*₆, Me₄Si): δ 2.27-2.89 (m, 8H, CH₂), 4.63 (s, 2H, NH₂), 4.99 (s, 2H, NH₂), 5.79 (s, 2H, NH₂), 6.27 (s, 2H, NH₂), 7.42-7.98 (m, 10H, aromatic). See figure 2.13 for ¹H NMR spectra.



Figure 2.13. ¹H NMR Spectrum of *cis-9*.

trans-[Co(5-phenyl-tetrazolato)₂(en)₂](ClO₄)·MeOH·4C₆H₅CN (*trans*-9): Yield : 6%. IR (KBr, selected bands, cm⁻¹): 2230 (C=N stretch), 1637 (C=N stretch), 1046 (ClO₄). Anal. Calc. For C₄₇H₄₆N₁₆ClCoO₅ (1009.35): C 55.87; H 4.55; N 22.19. Found: C 55.56; H 4.25; N 22.02. MS (ESI): m/z = 469.16 [M]⁺ (Figure A10). ¹H NMR (400 MHz, DMSO-*d*₆, Me₄Si): δ 2.01 (s, 4H, CH₂), 2.26 (s, 4H, CH₂), 4.47 (s, 8H, NH₂), 6.49-7.18 (m, 10H + 20H, 5-phenyltetrazole + benzonitrile). See figure 2.14 for ¹H NMR spectra.



Figure 2.14. ¹H NMR Spectra of *trans-9*.

2.2B.2.7 Liberation of 5-substituted tetrazoles from cobalt-complex:

The following method has been adopted for the release of the pure tetrazoles from the corresponding cobalt-tetrazolato complexes. In a typical example 0.1 g (0.164 mmol) of complex *cis-4* was taken in 10 mL of methanol and about 0.069 g (1.064 mmol) of NaN₃ dissolved in 10 mL of methanol was added into it. The reaction mixture was refluxed for 2 hrs. It gives no precipitate. The solution was filtered. The filtrate was evaporated to dryness under reduced pressure. The solid obtained was washed several times with diethyl ether and the washing was concentrated to obtain a colorless solid which was identified as 5-Phenyl-1*H*-tetrazole. Different tetrazoles were isolated in moderate to good yields (40 to 60%) and characterized by ESI mass spectroscopy furnishing similar data reported elsewhere.^[30-38] All the tetrazoles were identified in their molecular protonated form [MH]⁺ in ESI-MS spectra.

2.3B Results and discussion

2.3B.1 <u>Synthesis and isolation of metal complexes and 5-substituted</u> <u>tetrazoles</u>

Treatment of the diazidocobalt (III) complex cis-[Co(N₃)₂(en)₂](NO₃) **3** under microwave irradiation with the respective organonitriles RCN [R= 3-NC₅H₄, 4- NC_5H_4 and $4-BrC_6H_4$] gives the corresponding bis(tetrazolato) complexes $[Co(N_4CR)_2(en)_2](NO_3)$ (Scheme 2.2). Use of microwave technique in metal assisted cycloaddition reaction is well known as it can drive the reaction much faster than the conventional refluxing method.^[18] The reaction with 3cyanopyridine furnished a mixture of *cis*- and *trans*-isomers of tetrazolato complex (cis-4 & trans-4) tentatively in 1:4 ratio (In absence of any other clear cut demarcation between both isomers, calculations are based on the integration of ¹H NMR peak observed due to nitrogen protons in ethylenediamine for *cis*- and *trans*isomers). However, the reaction with 4-cyanopyridine yielded purely cis- isomer (cis-5) as reddish-brown product. A similar reaction with 4-bromobenzonitrile furnished exclusively *trans*- isomer of bis(tetrazolato) complex (*trans*-6) indicating a possible role of remote substitution at 5-position of phenyl ring for the formation of preferential geometric isomer of the cycloadded complex. In all the reactions DMF was used as the solvent because of poor solubility of the precursor complexes in other common organic solvents. In view of the above findings, now the interest was to check the outcome when the starting material is in *trans*-configuration. As the compound *trans*- $[Co(N_3)_2(en)_2]NO_3$ is not reported so far, therefore a known compound *trans*- $[Co(N_3)_2(en)_2]ClO_4$ **3a** was synthesized as per literature procedure.^[27] Upon reaction of **3a** with 4-cyanopyridine, 4-bromobenzonitrile and benzonitrile, a mixture of *cis*- and *trans*- isomers of bis(tetrazolate)complexes $[Co(N_4CR)_2(en)_2](ClO_4)$ in tentatively 5:2, 1:1 and 9:1 ratio, respectively was obtained(Scheme 2.3). This result indicates a possible role of counter-anion to dictate the preferential isomer for the tetrazolate complexes. However only cisisomer of tetrazolate complex synthesized from 4-cyanopyridine which has been separated by ion-exchange chromatographic method (*cis-7*). A similar effort to separate the isomers of bromo-substituted tetrazolato complexes (*cis-8* and *trans-8*) remained futile as both the compounds decomposed in the ion-exchanged column. However, both the geometrical isomers (cis-9 & trans-9) of [Co(5phenyltetrazolato) $_2(en)_2](ClO_4)$ can be separated by ion-exchange column chromatography.

All the reactions were carried out by focused microwave radiation at 130 °C for 1-3h. Most of the complexes are soluble in methanol, dichloromethane and DMF.

All the complexes (except for *trans-7, cis-8 & trans-8*) have been characterized by elemental analyses, IR, ESI-MS and ¹H NMR spectroscopy. As *cis-8* and *trans-8* could not be separated from the mixture therefore it was characterized as a whole by IR, elemental analysis, ESI-MS and ¹H NMR spectroscopy. The IR spectra of all the compounds do not show the typical azide bands at *ca*. 2078 and 2019 cm⁻¹ for complex **3** and 2016 cm⁻¹ for complex **3a** and display a new strong band within the 1612–1665 cm⁻¹ range due to the tetrazole ring, in agreement with the literature.^[7,8,39,40] In ESI-MS in all bis(tetrazolate) complexes the molecular ion peaks have been observed confirming the presence of bistetrazolate ligand in the metal complex.

The ¹H NMR spectroscopy was used to determine the relevant ratio of the geometrical isomers that have been obtained as a result of cycloaddition reactions. In absence of any other clear cut distinguishable protons between *cis*- and *trans*isomers, integration of NH₂ protons have been used to calculate a tentative ratio of geometrical isomers generated in the solution state. Each individual isomers have been further characterized with the help of the ¹H NMR spectroscopy. All the *cis*isomers show four signals within the range 4.51-6.37 ppm typical for nitrogen protons of ethylenediamine characteristic of cis-[Co(en)₂]³⁺ group,^[41] while CH₂ groups of ethylenediamine show a more complex multiplet within the range 1.91-2.90 as reported elsewhere.^[42] The results obtained are in good agreement with similar types of (ethylenediamine)cobalt complexes reported earlier.^[43-45] All the trans- isomers show a single peak in the range of 4.47-5.41 ppm attributed to nitrogen protons of ethylenediamine while the CH₂ protons are observed in the range of 2.01-2.45 ppm. Some additional protons in the aromatic region are observed for compound *trans-9* may be attributed to the presence of free benzonitrile which might have been entrapped during the crystallization of the

compound. This fact is also further supported by the presence of a small nitrile peak at 2130 cm^{-1} in the IR spectrum of the compound and elemental analysis result.

Liberation of 5-substituted tetrazole from bis(tetrazolato) complexes were carried out by treating precursor tetrazolato-metal complexes with excess of sodium azide in methanol. After refluxing the mixture for 2 hours the filtrate was evaporated to dryness and the residue was washed with diethyl ether which upon concentration provides respective 5-substituted tetrazoles in its neutral form rather than the sodium salt as it is evident by the presence of protonated form of molecular ion peak [MH]⁺ in ESI-MS spectroscopy. In all probability the tetrazolate ion picks up one proton from the water present in the solvent. Apart from ESI-MS, all these tetrazoles have been identified using ¹H and ¹³C NMR which corresponds well with the earlier reports.^[30-38]

2.3B.2 UV-Visible spectroscopy

The Co⁺³ ion with d⁶ configuration in an octahedral crystal field, in the solution state shows the presence of mostly one absorption band due to the d–d transitions in the octahedral CoN₆ crystal field. The strong bands which is observed in the range of 443.7-450.9 nm is assigned to the ${}^{1}A_{1g} \rightarrow {}^{1}T_{1g}$ transition while the absorptions due to the transition ${}^{1}A_{1g} \rightarrow {}^{1}T_{2g}$ are mostly masked (correlated as very weak shoulder) due to the presence of long tail of the charge-transfer peaks.^[46,47] The presence of other electronic transitions which appear in the UV region can be correlated to the $\pi \rightarrow \pi^*$ transition in the ligand (Table 2.7). One thing to be noted here is that although not much difference has been observed in the absorption spectra of different isomers, it should be mentioned that they are not totally identical (figure 2.15).



Figure 2.15. UV-vis spectra of compound *cis-4* and *trans-4*.

Table 2.7: Absorption Spectra of compounds *cis*-4, *trans*-4, *cis*-5, *trans*-6, *cis*-7, *cis*-8 and *cis*-9 in methanol.

| compound no. | λ nm , (ϵ , M ⁻¹ cm ⁻¹) | |
|--|--|--|
| cis-4 | 446.8 (180) | |
| trans-4 | 447.5 (171) | |
| cis-5 | 445.1 (147), 249.8 (22400), 202.5 (42200) | |
| trans-6 | 443.7 (174), 252.9 (47000), 203.5 (71300) | |
| cis-7 | 446.7 (165) | |
| trans-7 | cannot be separated | |
| mixture of <i>cis</i> -8 and <i>trans</i> -8 | 447.6 (72), 242 (137000), 204.6 (120900) | |
| cis-9 | 450.86 (72) | |
| trans-9 | 446.27 (91) | |

2.3B.3 Crystal structures

2.3B.3.1 <u>Crystal structures of cis-[Co{5-(3-pyridyl)-tetrazolato}₂(en)₂](NO₃)·</u> <u>DMF (cis-4), cis-[Co{5-(4-pyridyl)-tetrazolato}₂(en)₂](NO₃)·Et₂O (cis-5), cis-[Co{5-(4-pyridyl)tetrazolato}₂(en)₂](ClO₄)·H₂O (cis-7), cis-[Co{5-(4-bromo phenyl)-tetrazolato}₂ (en)₂](ClO₄) (cis-8) and cis-[Co(5-phenyl-tetrazolato)₂ (en)₂](ClO₄) (cis-9):</u>

The nature of all the above complexes has been established by single-crystal X-ray crystallography. The corresponding crystallographic data are given in table 2.6 and selected bond distances and angles in table 2.8-2.13. X-ray structure determination of *cis*-4 compound revealed that there are two crystallographically independent complex molecules exist with very similar geometries in the unit cell (figure 2.16).



Figure 2.16. View of two crystallographically independent complex molecules of compound *cis*-4.

The central ion is situated in a distorted octahedral environment. Both the tetrazolate anions coordinate in a monodentate fashion and their disposition around the metal center is *cis*. The dihedral angle between the coordinated tetrazoles and substituted pyridyl rings are found to be 7.96° and 10.44° , respectively for first cobalt center.



Figure 2.17. Hydrogen-bonded interaction between complex molecule and nitrate ions in *cis*-4.

However, for the second cobalt center they are 3.40° and 3.73°, respectively. The complex cation and non-coordinated anion are associated in ionic pairs through very close hydrogen bonding interaction from both the ethylenediamine molecules towards the oxygen atoms of nitrate ion. The first type of molecules are coordinated to different surrounding nitrate ions through N2-H2B···O555, N4-H4B···O555, C1-H1C···O111, N1-H1B···O111, N1-H1B···O222 and C16-H16···O222 (figure 2.17).

The second independent molecule is also connected to the counter-ions by several similar hydrogen bonding connections. Further these molecules are interconnected through pyridyl nitrogen [N3-H3B····N23 and N4-H4A····N28] to form two strands of one-dimensional chain structure interconnected through hydrogen bonding *via* nitrate anions along *a*-axis (figure 2.18). (N2-H2B···O555, N4-H4B···O555, N1-H1B···O111, C1-H1C···O111, N16-H16···O011, N17-H17A···O011, N15-H15B···O666, N17-H17B···O666).



Figure 2.18. Hydrogen bonding interaction between the ethylenediamine molecules and surrounding nitrate ions in *cis-4*.

One of the independent molecule is further stabilized by hydrogen bond formation between DMF and one of the en molecules attached to the metal centre (N1-H1A-O888). There are two types of nitrate ions. One is forming a hydrogen bonded 1D polymer by forming bridges between the two crystallographically independent molecules and the other is helping to join the two strands together by hydrogen bond formation (figure 2.19). Compound *cis-5* which crystallizes in the monoclinic space group $P2_1/c$, shows crystallographically one independent structure. The *cis* configuration of the compound has been enforced by weak H-bonded interaction between one nitrate ion and two en molecules attached to the same metal center (N1-H1A…O111, N4-H4B…O111, N1-H1A…O333) (figure 2.20).



Figure 2.19. Formation of hydrogen-bonded 1D polymer through the nitrate ions which bridges between the two crystallographically independent molecules in *cis-4*.



Figure 2.20. View of weak H-bonded interaction between nitrate ion and two ethylenediamine molecules attached to the same metal center in *cis*-5.

Two such molecules are hydrogen bonded with each other *via* mutual interaction through N4-H4A…N14 involving pyridyl nitrogen atom and one of the hydrogen of en ligand (figure 2.21).



Figure 2.21. Hydrogen bonded interaction between two molecules through pyridyl nitrogen in *cis-5*.

These dimers are further mutually interconnected *via* C16-H16...N9 forming a ladder type of structure along *c*-axis (figure 2.22). These strand type ladder structures are interconnected by hydrogen bonded nitrate structure N3-H3B...O222, N2-H2B...O222, N4-H4B...O111 in a three dimensional way to form hydrogen bonded framework (figure 2.23).



Figure 2.22. Compound *cis*-5 forms a ladder type of structure through hydrogen bonding along *c*-axis.



Figure 2.23. Hydrogen bonded 3D structure of compound *cis*-5.

Diethylether molecule has been also observed as the solvent of crystallization which is also associated with one of the ethylene diamine hydrogen *via* hydrogen bonding (N1-H1B····O101). The single crystal X-ray structure of *cis*-7 confirms the formation of *cis* configuration of the compound. It crystallizes in monoclinic space group $P \ 2_1/c$ and exhibit 3D supramolecular arrays formed by hydrogen bond interactions. In *cis*-7, the Co(III) resides in an octahedral co-ordination geometry (figure 2.24).



Figure 2.24. View of local co-ordination geometry at the Co(III) centre in *cis*-7 where tetrazolato ligands are *cis* to each other.

Each cationic unit is connected to three neighboring oxygen atoms of the perchlorate anion *via* N1-H1B····O333, N1-H1B····O444, C2-H2A····O333, N4-H4A····O333, N2-H2A····O111, C3-H3A····O111 and N3-H3A····O444 interactions (figure 2.25). Furthermore, in this network each unit is connected to two adjacent units through the pyridyl nitrogen atom and hydrogens of en ligand *via* N3-H3B····N14, C2-H2B····N13 and N2-H2B····N13 interactions along *b*-axis (figure 2.26). All of these H-bonds altogether form a 3D supramolecular framework structure.



Figure 2.25. The hydrogen bonded interactions between the complex and the surrounding perchlorate ions in *cis*-7.



Figure 2.26. Hydrogen bonded interaction between molecules through pyridyl nitrogen and ethylenediamine hydrogens in *cis*-7.

Although the refinement factor for the crystal structure of compound *cis*-8 is on high side, it unequivocally indicates that the two tetrazolate ions coordinate the metal ion in *cis*- fashion through N^2 -atoms (figure 2.27).



Figure 2.27. Molecular structure of compound *cis*-8.

The dihedral angle between tetrazole and phenyl ring is found to be 22.73° for both the ligands. Each perchlorate ions is found to be connected with three molecules through three equivalent oxygen atom C1-H1A····O1 and C9-H9····O1. This is further supported by N1-H1B····O2 hydrogen bonding (figure 2.28) and may be helping to enforce the *cis*-geometry within the molecule.



Figure 2.28. Each perchlorate ions are connected with three molecules through three equivalent oxygen atom *via* hydrogen bonding interactions in compound *cis*-8.

The independent molecules are packed along *a*-axis and *b*-axis through H-bonding between different molecules and the perchlorate counter ions helps in forming a hydrogen bonded 2D polymer in *ab*-plane. All these network which are running in the direction of *ab*-plane, orients in such a way that due to the complexes being in the *cis* conformation, the *para*-substituted bromine atoms get stacked one upon another along *b*-axis as well as *a*-axis (figure 2.29).

However, long distance $Br \cdots Br$ interactions between the bromine atom of one molecule and two other bromine atoms of neighboring molecules [Br-Br 4.969 Å] may also contribute for the preferential *cis*- geometry of complex *cis*-8.



Figure 2.29. 2D H-bonded packing network of compound *cis*-8.

Compound *cis-9* crystallizes in space group $P2_12_12_1$ and the metal nitrogen distances are found to be in the range of 1.906-1.972 Å, typical for the Co³⁺ ion. The tetrazolato ligands are *cis* to each other (figure 2.30).



Figure 2.30. View of local co-ordination geometry at the Co(III) centre in *cis*-9.

The counter perchlorate ions are found to be connecting different molecules *via* hydrogen bonding *viz.* N1-H1A····O222, C3-H3D····O222, N3-H3B····O333, N3-H3B····O555, N4-H4B····O555, C3-H3C····O444, N4-H4B····O444 and N2-H2B····O444 (figure 2.31) leading to the formation of a hydrogen bonded 3D network (figure 2.32).



Figure 2.31. Interactions between perchlorate ions with different molecules via hydrogen bonding in compound *cis-9*.



Figure 2.32. Hydrogen bonded 3D network of compound *cis*-9.

| Co(1)-N(5) | 1.904(4) | N(5)-Co(1)-N(10) | 91.90(16) |
|-----------------|----------|------------------|------------|
| Co(1)-N(10) | 1.907(4) | N(1)-Co(1)-N(4) | 178.46(16) |
| Co(1)-N(1) | 1.955(4) | N(5)-Co(1)-N(3) | 174.28(16) |
| Co(1)-N(3) | 1.958(4) | N(5)-Co(1)-N(2) | 87.56(15) |
| Co(1)-N(2) | 1.958(3) | N(10)-Co(1)-N(1) | 90.31(16) |
| $C_{0}(1)-N(4)$ | 1.952(4) | | |
| N(5)-N(7) | 1.305(5) | | |
| N(7)-N(8) | 1.341(5) | | |

 Table 2.8: Selected bond lengths (Å) and bond angles (°) for cis-4

Table 2.9: Selected bond lengths (Å) and bond angles (°) for cis-5

| Co(01)-N(10) | 1.919(2) | N(10)-Co(01)-N(5) | 87.98(12) |
|--------------|----------|-------------------|------------|
| Co(01)-N(5) | 1.919(3) | N(10)-Co(01)-N(2) | 174.76(13) |
| Co(01)-N(4) | 1.953(3) | N(10)-Co(01)-N(4) | 91.38(11) |
| Co(01)-N(3) | 1.953(3) | N(3)-Co(01)-N(1) | 176.90(11) |
| Co(01)-N(1) | 1.956(3) | N(4)-Co(01)-N(1) | 92.42(12) |
| Co(01)-N(2) | 1.956(3) | | |
| N(5)-N(6) | 1.314(4) | | |
| N(6)-N(7) | 1.340(4) | | |

Table 2.10: Selected bond lengths (Å) and bond angles (°) for *cis-*7

| Co(1)-N(9) | 1.902(4) | N(9)-Co(1)-N(5) | 92.38(17) |
|------------|----------|-----------------|-----------|
| Co(1)-N(4) | 1.960(4) | N(9)-Co(1)-N(3) | 90.79(17) |
| Co(1)-N(5) | 1.913(4) | N(5)-Co(1)-N(3) | 89.99(17) |
| Co(1)-N(3) | 1.942(4) | N(9)-Co(1)-N(1) | 90.19(17) |

| Co(1)-N(1) | 1.949(4) | N(5)-Co(1)-N(1) | 90.12(18) |
|-------------|----------|-----------------|------------|
| Co(1)-N(2) | 1.955(4) | N(3)-Co(1)-N(1) | 179.01(17) |
| N(5)-N(6) | 1.311(6) | N(9)-Co(1)-N(2) | 175.50(17) |
| N(5)-N(8) | 1.341(6) | N(5)-Co(1)-N(2) | 89.40(17) |
| N(6)-N(7) | 1.345(6) | N(3)-Co(1)-N(2) | 93.34(17) |
| N(9)-N(10) | 1.321(6) | N(1)-Co(1)-N(2) | 85.67(17) |
| N(9)-N(12) | 1.339(5) | N(9)-Co(1)-N(4) | 86.82(18) |
| N(10)-N(11) | 1.344(6) | N(5)-Co(1)-N(4) | 175.79(18) |
| | | N(3)-Co(1)-N(4) | 85.89(18) |
| | | N(1)-Co(1)-N(4) | 94.02(19) |
| | | N(2)-Co(1)-N(4) | 91.70(18) |

 Table 2.11: Selected bond lengths (Å) and bond angles (°) for *cis*-8

| Co(1)-N(4) | 1.936(11) | N(4)-Co(1)-N(4)#3 | 90.9(6) |
|--------------|-----------|---------------------|----------|
| Co(1)-N(4)#3 | 1.936(11) | N(4)-Co(1)-N(1) | 91.6(4) |
| Co(1)-N(1) | 1.935(9) | N(4)#3-Co(1)-N(1) | 91.1(4) |
| Co(1)-N(1)#3 | 1.935(9) | N(4)-Co(1)-N(1)#3 | 91.1(4) |
| Co(1)-N(2)#3 | 1.943(10) | N(4)#3-Co(1)-N(1)#3 | 91.6(4) |
| Co(1)-N(2) | 1.943(10) | N(1)-Co(1)-N(1)#3 | 176.1(6) |
| N(4)-N(5) | 1.312(13) | N(4)-Co(1)-N(2)#3 | 175.7(4) |
| N(4)-N(3) | 1.328(13) | N(4)#3-Co(1)-N(2)#3 | 89.2(4) |
| N(6)-N(5) | 1.321(14) | N(1)-Co(1)-N(2)#3 | 92.8(4) |
| | | N(1)#3-Co(1)-N(2)#3 | 84.5(4) |
| | | N(4)-Co(1)-N(2) | 89.2(4) |

| N(4)#3-Co(1)-N(2) | 175.7(4) |
|-------------------|----------|
| N(1)-Co(1)-N(2) | 84.5(4) |
| N(1)#3-Co(1)-N(2) | 92.8(4) |
| N(2)#3-Co(1)-N(2) | 91.1(6) |

Symmetry transformations used to generate equivalent atoms:

#1 -x+y+2, -x+1, z #2 -y+1, x-y-1, z #3 y+1, x-1, -z+1/2

#4 -x+y+1, -x+1, z #5 -y+1, x-y, z

Table 2.12: Selected bond lengths (Å) and bond angles (°) for *cis-9*

| Co(01)-N(1) | 1.935(4) | N(1)-Co(01)-N(2) | 86.0(1) |
|-------------|----------|------------------|----------|
| Co(01)-N(2) | 1.972(3) | N(1)-Co(01)-N(3) | 91.5(1) |
| Co(01)-N(3) | 1.947(3) | N(1)-Co(01)-N(4) | 177.5(1) |
| Co(01)-N(4) | 1.962(4) | N(1)-Co(01)-N(5) | 90.8(1) |
| Co(01)-N(5) | 1.920(3) | N(1)-Co(01)-N(9) | 92.1(1) |
| Co(01)-N(9) | 1.906(3) | N(2)-Co(01)-N(3) | 92.7(1) |
| N(5)-N(6) | 1.343(4) | N(2)-Co(01)-N(4) | 94.0(1) |
| N(5)-N(7) | 1.310(6) | N(2)-Co(01)-N(5) | 175.7(1) |
| N(7)-N(8) | 1.339(5) | N(2)-Co(01)-N(9) | 86.9(1) |
| N(9)-N(10) | 1.327(5) | N(3)-Co(01)-N(4) | 85.9(1) |
| N(9)-N(12) | 1.345(4) | N(3)-Co(01)-N(5) | 90.2(1) |
| N(10)-N(11) | 1.345(4) | N(3)-Co(01)-N(9) | 176.3(1) |
| | | N(4)-Co(01)-N(5) | 89.4(1) |
| | | N(4)-Co(01)-N(9) | 90.4(1) |
| | | N(5)-Co(01)-N(9) | 90.4(1) |

2.3B.3.2 Crystal structure of *trans*-[Co{5-(4-bromophenyl)-tetrazolato}₂(en)₂]

(NO₃)(trans-6):

Compound *trans*-6 has crystallized in space group *P*-1 having two crystallographically independent complex molecules with very similar geometries (figure 2.33).



Figure 2.33. View of compound *trans-6* having two crystallographically independent unit.





Two tetrazolato ligands coordinate in a *trans* fashion and the twist of phenyl ring with respect to coordinated tetrazole rings are different for two independent

molecule. The dihedral angle has been found to be 4.74° for the first type where as for the second type this is about 25.02° for both the 5-substituted tetrazole ligands. The twist in the ring can be attributed because of the H-bond formation between ethylenic hydrogen of one molecule and tetrazolyl nitrogen of the adjacent complex (N5-H5B···N11) (figure 2.34). These molecules are further interconnected with different ethylenic hydrogen and tetrazolyl nitrogen (N5-H5B···N11, N8-H8A···N1) to form a 1D-chain along *b*-axis (figure 2.35).



Figure 2.35. View of 1D-chain along *b*-axis through H-bonding of *trans-6*.

This chain is further supported by nitrate ions which connects four different molecules surrounding it by hydrogen bonds (C7-H7…O111, N8-H8B…O111, N8-H8B…O333, N6-H6B…O333, C9-H9A…O222) which altogether forms a 2D-network in *ab*-plane (figure 2.36). Furthermore one DMF molecules has been found hydrogen bonded to the first type of cobalt center *via* N5-H5A…O101 hydrogen bond. The consequence is that all 5-substituting bromine atoms are found to be aligning in a single line when viewed along *a*- or *b*-axis (figure 2.37). The nearest Br…Br [Br(1)…Br(2)] contact has been found to be 4.082 Å slightly larger than the sum of the van der Waals radii sum. However, the formation of long distance

Br \cdots Br interaction could be one of the driving force for the crystallization of the molecule in *trans*- geometry.



Figure 2.36. Formation of 2D-network in *ab*-plane where nitrate ions connects with different molecules by hydrogen bonds in compound *trans-6*.

Figure 2.37. Stacking of 5-substituted bromine atoms in compound *trans*-6.

| Co(1)-N(3) | 1.915(6) | N(3)#1-Co(1)-N(3) | 180.0(3) |
|------------|----------|-------------------|----------|
| Co(1)-N(5) | 1.956(5) | N(3)-Co(1)-N(6) | 89.5(2) |
| Co(1)-N(6) | 1.951(5) | N(6)-Co(1)-N(6)#1 | 180.0(3) |
| N(3)-N(2) | 1.297(7) | | |
| N(2)-N(1) | 1.350(8) | | |

Table 2.13: Selected bond lengths (Å) and bond angles (°) for *trans-6*

2.3B.4 Computational studies

Density functional calculations (DFT) are carried out to understand the driving force behind the crystallization of complex *trans-6* in the preferred geometry. Interestingly, reaction of 4-bromobenzonitrile with *trans*-[Co(N₃)₂(en)₂](ClO₄) produced predominantly *cis*- isomer (*cis-8*). These two complexes (*trans-6* and *cis-*8) are considered for our calculations as both the complexes having same set of ligands (R=4-BrC₆H₄) though different counter anions. Therefore to understand the

factors which may be playing a role in preferred geometry, these two complexes (*trans-6* and *cis-8*) were modelled for our comparative study.

These complexes were studied in their solid state structures retaining their space group geometry. Periodic boundary conditions are used for the three dimensional structure modelling. The first-principles calculations are used using projected augmented wave (PAW) method as implemented in the Vienna ab-initio simulation package (VASP) for their structural relaxation.^[24] The exchange-correlation interaction is treated in the level of the GGA using Perdew-Burke-Ernzerhof (GGA-PBE).^[25] The van der Waals corrected interaction energies was calculated using the semi-empirical correction of Grimme^[26] as available with VASP for the accurate treatment of the weak intermolecular interactions between the metal complexes. The calculations showed that both the complexes (*trans*-6 and *cis*-8) are minima in their potential energy surfaces. The calculated van der Waals interaction energies for the complexes *trans*-6 and *cis*-8 are 4.90 and 4.30 eV (per molecular unit) respectively. Therefore, the van der Waals interaction energy is more for the trans geometry. Interestingly, in the trans (trans-6) geometry, it was found that one solvent molecule (DMF) was trapped for each molecular units. To understand the possible role of solvent for preferred geometry, the solvent was removed from the crystal structure of trans-6 complex and the structure was relaxed retaining in the same space group geometry. It was found that the calculated van der Waals interaction energies reduced from 4.90 eV to 3.99 eV per molecular unit. Therefore each solvent molecule is contributing around 20.98 kcal (0.91 eV) towards the total van der Waals interaction energies. Therefore the weak interaction directed by the solvent molecule is possibly playing a major role in crystallizing the complex *trans*-6 in *trans* geometry.

2.4 <u>Conclusions</u>

The part A concludes that the [2+3] cycloaddition induces the formation of bistetrazolato complexes *cis*-[Co(5-phenyl-tetrazolato)₂(en)₂](NO₃) (1) and *trans*-[Co{5-(4-chlorophenyl)-tetrazolato}₂(en)₂](NO₃) (2) from diazide cobalt complex *cis*-[Co(N₃)₂(en)₂](NO₃) with benzonitrile and 4-chlorobenzonitrile, respectively.

The remote substitution in 4-position of phenyl ring of organonitrile has an influence on the preferential formation of a geometrical isomer. DFT reveals that the formation of compound **1** is kinetically driven whereas formation of compound **2** is associated with extra thermodynamical stability out of additional distant halogen–halogen interaction.

The conclusion of the part B indicates the interaction of diazido complex cis- $[Co(N_3)_2(en)_2](NO_3)$ (3) and trans- $[Co(N_3)_2(en)_2](ClO_4)$ (3a) with various organonitriles under focussed microwave irradiation. Interaction of 3 with 3cyanopyridine forms cis- and trans- isomers of cycloadded bis-tetrazolato complexes tentatively in 1:2 ratio. However interaction with 4-cyanopyridine produced exclusive cis-isomer of bis(tetrazolate) complex and reaction with 4bromobenzonitrile produced bis(tetrazolate) complex in *trans* disposition indicating the role of remote substitution in phenyl ring in formation of the preferential isomer. The interaction of *trans*- $[Co(N_3)_2(en)_2]ClO_4$ under similar condition with 4cyanopyridine, 4-bromobenzonitrile and benzonitrile furnished mixture of cis- and trans- isomers of bis(tetrazolate) complexes where the cis-geometry predominates. It has been assumed possibly the counter-anion which is helping the compound to crystallize and also interacting with the complex in solution state is also contributing to preferential geometrical isomer formation upon cycloaddition. Further, a DFT calculation study indicates that the *trans* isomer *trans*-6 is being further stabilized by means of van der Waals interactions through an extra DMF molecule (compared to *cis-8*), which is present as solvent of crystallization along with some Br....Br halogen interaction. Furthermore 5-substituted tetrazole can be isolated from the bis(tetrazolate) complex by treating it with excess sodium azide.

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Chapter-3

Limiting nuclearity in formation of polynuclear metal complexes through [2 + 3] cycloaddition: synthesis and magnetic properties of tri- and pentanuclear metal complexes

3.1 Introduction

Generation of coordination polymers using tetrazole ligands is now a popular method as tetrazoles can act as a very good bridging ligand for the formation of multidimensional coordination polymers exhibiting great structural diversity sometimes with interesting catalytic, optical, magnetic, membrane and absorption properties.^[1] However, the synthetic procedure largely depends upon solvothermal synthesis, which generates polymers in an uncontrolled way irrespective of whether the tetrazoles were used as a starting material or generated *in situ* by cycloaddition between azide and organonitriles in the presence or absence of supporting ligands.^[2] Limiting nuclearity to a finite level is a challenging task from the synthetic viewpoint as polynuclear complexes can many times show unusual magnetic or catalytic properties.^[3] Only a handful polynuclear complexes have been synthesized under different reaction conditions where tetrazoles act as bridging ligands.^[4] To further explore the metal mediated cycloaddition reactions involving organonitriles and coordinated azides^[5] for the synthesis of novel 5substituted tetrazole complexes, preferably under mild conditions, the interest was focused to generate polynuclear compounds with limiting nuclearity in the presence of an additional tridentate ligand. Herein, the reaction of a monoazido nickel $[Ni(L^{1})(N_{3})]$ $[HL^1]$ compound (11) *p*-chloro-2-{(2-(dimethyl = amino)ethylimino)methyl phenol] was investigated with various organonitriles. The precursor **11** was easily synthesized from chloro-diaquo-complex $[Ni(L^{1})(Cl)(H_{2}O)_{2}]$ (10) by ligand displacement reaction with azide. Two of the reported nickel tetrazole compounds exhibit a linear trinuclear structure while the other compound interestingly shows a pentanuclear structure.

3.2 Experimental section

3.2.1 Materials and physical measurements

All the chemical reagents required were purchased from Sigma and used without further purification. The ligand *p*-chloro-2-{(2-(dimethylamino)ethylimino)methyl}phenol (HL¹) was prepared according to the reported method.^[6] Infrared spectra (4000–500 cm^{-1}) were recorded with a BRUKER TENSOR 27 instrument in KBr pellets. Mass spectrometric analyses had been done on a Bruker-Daltonics, microTOF-Q II mass spectrometer and microwave irradiation experiments had been done in a focused microwave CEM discover reactor 300 W and the reaction tube used was of 10 mL capacity and 13 mm internal diameter. Elemental analyses were carried out with a Thermo- Flash 2000 elemental analyzer. TGA measurements were performed by heating the crystalline samples from 20 to 300 °C at a rate of 5 °C min⁻¹ in air on a Metler Toledo TGA/DSC 1 STAR^e System thermal analyzer. The magnetic susceptibility data were collected in a temperature range of 2–300 K under an applied field of 0.1 Tesla on powdered samples with a SQUID magnetometer (MPMS-7, Quantum Design). Experimental susceptibility data were corrected for the underlying diamagnetism using Pascal's constants. The temperature dependent magnetic contribution of the holder was experimentally determined and subtracted from the measured susceptibility data. The resulting molar susceptibility data were plotted in $\chi_{\rm M}$ T vs. T. The program julX^[7] was used for spin Hamiltonian simulations of the data for some compounds whereas the program clumag^[8] was used for spin Hamiltonian simulations of the other compound.

X-ray crystallography: Single crystal X-ray structural studies of compounds $[Ni(L^1)(N_3)]$ (11), $[Ni_3L^1_2(5\text{-phenyltetrazolato})_4(DMF)_2]$ (12), $[Ni_3L^1_2\{5-(3\text{-pyridyl})-\text{tetrazolato}\}_4(DMF)_2]\cdot 2H_2O$ (13) and $[Ni_5L^1_4\{5-(2\text{-cyanophenyl})-\text{tetrazolato}\}_4(OH)_2(H_2O)_2]\cdot 3H_2O\cdot DMF$ (14) were performed on a CCD Agilent Technologies (Oxford Diffraction) SUPER NOVA diffractometer. Data for all the complexes were collected at 150(2) K using graphite-monochromated MoK α radiation ($\lambda_{\alpha} = 0.71073$ Å). The strategy for the data collection was evaluated using

the CrysAlisPro CCD software. The data were collected by the standard phi-omega scan techniques and were scaled and reduced using the CrysAlisPro RED software. The structures were solved by direct methods using the SHELXS-97 and refined by full matrix least-squares with the SHELXL-97, refining on $F^{2,[9]}$ The positions of all the atoms were obtained by direct methods. All non-hydrogen atoms were refined anisotropically. The remaining hydrogen atoms were placed in geometrically constrained positions and refined with isotropic temperature factors, generally 1.2Ueq of their parent atoms. It should be noted that solvent molecules in the structure of $[Ni_3L_2^1{5-(3-pyridyl)-tetrazolato}_4(DMF)_2]\cdot 2H_2O$ (13) and $[Ni_5L_4^1 \{ 5-(2-cyanophenyl)-tetrazolato \}_4(OH)_2(H_2O)_2] \cdot 3H_2O \cdot DMF$ (14)were randomly dispersed and thus difficult to refine using conventional discrete-atom models. To resolve this issue, the contribution of the solvent electron density was removed by the SQUEEZE routine in PLATON.^[10] The crystal and refinement data are summarized in Table 3.1.

Table 3.1: Crystal data and structure refinement information for compounds $[Ni(L^1)(N_3)]$ (11), $[Ni_3L^1_2(5-Phenyltetrazolato)_4(DMF)_2]$ (12), $[Ni_3L^1_2\{5-(3-pyridyl)-tetrazolato\}_4(DMF)_2]\cdot 2H_2O$ (13) and $[Ni_5L^1_4\{5-(2-cyanophenyl)-tetrazolato\}_4(OH)_2(H_2O)_2]\cdot 3H_2O\cdot DMF$ (14).

| | 11 | 12 | 13 ^a | 14 ^a |
|---|--|---|--|---|
| | | | | |
| Empirical formula | C ₁₁ H ₁₄ N ₅ ONiCl | C ₂₈ H ₃₁ N ₁₁ O ₂ Ni _{1.5} Cl | C ₅₂ H ₆₂ N ₂₆ O ₂ Ni ₃ Cl ₂ | C ₇₉ H ₈₅ N ₂₉ O ₁₂ Ni ₅ Cl ₄ |
| Formula weight | 326.43 | 677.15 | 1394.27 | 2067.95 |
| Wavelength(A) | 0.71073 | 0.71073 | 0.71073 | 0.71073 |
| Temperature(K) | 150(2) | 150(2) | 150(2) | 150(2) |
| Crystal system | Monoclinic | Triclinic | Triclinic | Monoclinic |
| Color and shape | Brown needle | Green needle | Green needle | Green needle |
| Space group | $P 2_1 / c$ | <i>P</i> -1 | $P 2_1/c$ | $P 2_1 / c$ |
| a/Å | 9.4997(3) | 11.0194(11) | 15.6896(18) | 10.5420(10) |
| b/Å | 12.1258(4) | 12.2772(12) | 15.8934(17) | 22.598(3) |
| c/Å | 11.8494(4) | 12.3400(13) | 16.5290(15) | 21.861(2) |
| α/degree | 90 | 79.470(8) | 76.751(9) | 90 |
| β/degree | 100.933(3) | 76.251(9) | 89.705(9) | 91.357(9) |
| γ/degree | 90 | 79.852(8) | 69.725(10) | 90 |
| Volume(Å ³) | 1340.18(8) | 1578.8(3) | 3750.9(7) | 5206.5(10) |
| Z | 4 | 2 | 2 | 2 |
| $D_{\rm calcd}/{ m mg}~{ m m}^{-3}$ | 1.618 | 1.424 | 1.231 | 1.384 |
| μ (Mo K α)/mm ⁻¹ | 1.646 | 1.033 | 0.875 | 1.062 |
| F(000) | 672 | 702 | 1436 | 2220 |
| Crystal size/mm | 0.32×0.28×0.22 | 0.32 0.26×0.21 | 0.23×0.16×0.13 | 0.26 	imes 0.21 	imes 0.18 |
| θ range(°) | 3.03 to 25.00 | 3.15 to 25.00 | 3.15 to 25.00 | 2.94 to 25.00 |
| Limiting indices | $-11 \leq h \leq 9$ | $-12 \le h \le 13$ | $-18 \le h \le 18$ | $-11 \leq h \leq 12$ |
| | $-14 \le k \le 12$ | $-14 \le k \le 14$ | $-18 \le k \le 18$ | $-26 \le k \le 23$ |
| | $-14 \le l \le 14$ | $-14 \le l \le 14$ | $-19 \le l \le 18$ | $-25 \le l \le 25$ |
| Total/ unique no. of reflns. | 8391 / 2357 | 10777 / 5547 | 30207 / 13183 | 41030 / 9170 |
| R _{int} | 0.0214 | 0.0533 | 0.0866 | 0.1220 |
| Data/restr./params. | 2357 / 0 / 174 | 5547 / 0 / 398 | 13183/0/813 | 9170/0/623 |
| $GOF(F^2)$ | 1.153 | 1.038 | 1.142 | 1.041 |
| R1, wR2 | 0.0478.0.1408 | 0.0563. 0.1516 | 0.1086. 0.3015 | 0.0837. 0.2231 |
| R1, wR2 (all data) | 0.0492, 0.1416 | 0.0733, 0.1743 | 0.1491, 0.3507 | 0.1318, 0.2817 |
| Peak and hole (e $Å^{-3n}$) | 2.069 and -0.498 | 0.925 and -0.886 | 2.160 and -0.889 | 1.120 and -0.663 |

^a The "SQUEEZE" software was applied to subtract the contribution of disordered solvent from diffraction data of **13** (two water molecules) and **14** (one DMF and three water molecules). Refinement was carried out after the solvent electron density was removed by the SQUEEZE routine in PLATON.

3.2.2 Synthesis

3.2.2.1 [Ni(L¹)Cl(H₂O)₂] (10)

A methanolic solution (10 mL) of NiCl₂·6H₂O (0.25 g, 1.04 mmol) was added dropwise to a solution of HL¹ (0.23 g, 1.04 mmol) in methanol (10mL). The resultant green solution was stirred for *ca*. 3 h and filtered. The filtrate was concentrated up to 10 mL under reduced pressure and filtered again. The resultant solution was kept at room temperature for slow evaporation to obtain a green crystalline precipitate of compound **10**. The solid was isolated by filtration and washed with ether and dried *in vacuo* (70% yield based on Ni). Anal. Calc. for C₁₁H₁₈Cl₂N₂NiO₃ (355.87): C 37.09; H 5.05; N 7.86%. Found: C 37.82; H 5.25; N 7.33%. IR (cm⁻¹, KBr): 3384, 1650, 1466. MS (ESI): *m/z* = 284.37 [M–Cl–2H₂O]⁺.

3.2.2.2 [Ni(L^1)(N_3)] (11)

To a solution (10 mL) of complex **10** (0.35 g, 1.0 mmol) in methanol, a methanolic solution (10 mL) of NaN₃ (0.08 g, 1.2 mmol) was added dropwise. The solution colour turned from green to red, and the solution was stirred for further 2 h, where after it was filtered. The red crystalline compound **11**, with some suitable crystals for X-ray diffraction, was obtained by concentration of the filtrate and keeping it at room temperature for several days. Compound **11** was isolated by filtration and dried *in vacuo* (67% yield based on Ni). Anal. Calc. for $C_{11}H_{14}CIN_5NiO$ (326.43) : C 40.43; H 4.28; N 21.44%. Found: C 40.35; H 4.26; N 21.32%. IR (cm⁻¹, KBr): 2051, 1647, 1464, 1461, 1385.

3.2.2.3 [Ni₃L¹₂(5-Phenyltetrazolato)₄(DMF)₂] (12)

A mixture of $[Ni(L^1)(N_3)]$ (11) (0.12 g, 0.37 mmol), 2 mL of benzonitrile and 3 mL of DMF were added to a cylindrical pyrex tube. The system was placed in the focused microwave reactor. The reaction mixture was left under irradiation for 2 hrs at 130 °C. The solvent was then removed *in vacuo* and the resulting residue was treated with diethyl ether to obtain a reddish-brown powder which was then recrystallized from methanol/ether mixture. Anal. Calc. for C₂₈H₃₁ClN₁₁Ni_{1.50}O₂

(677.15): C 49.61; H 4.57; N 22.74%. Found: C 49.16; H 4.45; N 22.45%. IR (cm⁻¹, KBr): 1650, 1529, 1464, 1387, 1171.

3.2.2.4 [Ni₃L¹₂{5-(3-pyridyl)-tetrazolato}₄(DMF)₂]·2H₂O (13)

Monoazide nickel complex $[Ni(L^1)(N_3)]$ (**11**) (0.12 g, 0.37 mmol) and 0.15 g (1.5 mmol) of 3-cyanopyridine in 5 mL of DMF was taken in a cylindrical pyrex tube and it was irradiated for 2 hrs at 130 °C. After removing the solvent *in vacuo* the resulting reddish-brown residue was washed several times with diethyl ether. The brown powder yielded was recrystallized from DMF/ether mixture. Anal. Calc. for $C_{52}H_{62}Cl_2N_{26}Ni_3O_6$ (1394.27): C 44.75; H 4.44; N 26.10%. Found: C 44.11; H 4.43; N, 26.05%. IR (cm⁻¹, KBr): 3416, 1646, 1463, 1421, 1172.

3.2.2.5 $[Ni_5L_4^1 \{5-(2-cyanophenyl)-tetrazolato\}_4(OH)_2(H_2O)_2] \cdot 3H_2O \cdot DMF(14)$

A solution of 0.12 g (0.37 mmol) of $[Ni(L^1)(N_3)]$ complex (**11**) and 0.26 g (2 mmol) of 1,2-dicyanobenzene in 5 mL of DMF was taken in a cylindrical pyrex tube and it was irradiated for 2 hrs at 130 °C. The solvent was then removed *in vacuo* and the resulting reddish-brown residue was washed several times with diethyl ether to obtain a brown powder which was then recrystallized from chloroform/hexane mixture. Anal. Calc. for $C_{79}H_{85}Cl_4N_{29}Ni_5O_{12}$ (2067.98): C 45.84; H 4.11; N 19.63 %. Found: C 44.60; H 3.83; N 18.89 % IR (cm⁻¹, KBr): 3422, 2229, 1649, 1463, 1296.

3.3 <u>Results and discussion</u>

3.3.1 Synthesis and isolation of metal azide complex

To target the formation of polynuclear compounds a square-planar monoazido nickel complex **11** has been synthesized. This complex with a limited number of coordinated ligands demonstrates a natural tendency to expand its coordination number when more prospective coordination sites have been supplied through formation of polydentate tetrazole ligand by *in situ*-cycloaddition of coordinated azide and nitrile.



Scheme 3.1. Schematic representation for the synthesis of the complex $[Ni(L^1)(N_3)]$ (11).

A methanolic solution of the iminophenol $[HL^{1}= p$ -chloro-2-{(2-(dimethyl amino)ethylimino) methyl}phenol] was treated with nickel chloride (1 eq), at room temperature for 3 h to furnish a chloro-diaquo-complex $[Ni(L^{1})Cl(H_{2}O)_{2}]$ (10). Subsequent treatment of complex 10 with NaN₃ at room temperature replaces the chloride ligand with azide and liberates the coordinated water molecules to yield $[Ni(L^{1})(N_{3})]$ (11) (Scheme 3.1).^[11] Compound 10 and 11 were isolated in good yields. Treatment of the monoazido complex 11 under microwave irradiation with different organonitriles RCN [R = C₆H₅ (a), 3-NC₅H₄ (b), 2CN-C₅H₄ (c)] gives the corresponding polynuclear complexes $[Ni_{3}L^{1}_{2}(5-Phenyltetrazolato)_{4}(DMF)_{2}]$ (12), $[Ni_{3}L^{1}_{2}\{5-(3-pyridyl)-tetrazolato\}_{4}(DMF)_{2}]\cdot 2H_{2}O$ (13) and $[Ni_{5}L^{1}_{4}\{5-(2-cyanophenyl)-tetrazolato]_{4}(OH)_{2}(H_{2}O)_{2}]\cdot 3H_{2}O\cdot DMF$ (14), respectively (Scheme 3.2). In all the cases the compounds were isolated as reddish-brown powder which has been further recrystallized from suitable solvents.



Scheme 3.2. Synthetic route of the complexes 12-14.

All the complexes (10-14) have been characterized by elemental analyses, IR and TGA analyses (except 11). Complex 10 is further characterized by ESI-MS spectroscopy and the complexes 11,12,13,14 by single crystal X-ray crystallography. IR spectra of all the compounds have a couple of prominent bands at *ca*. 1635 and 1535 cm⁻¹ region assignable to v(C=N) and v(C-O/phenolate)

stretching modes, respectively.^[12] In the high frequency region, a broad band of medium intensity around 3420-3500 cm⁻¹ indicates the presence of coordinated water molecule in complex **10** and **14**.^[12] The IR spectrum of compound **11** displays a strong band at 2051 cm⁻¹ due to the asymmetric stretching vibration of coordinated azido group. ^[13] Complexes **12–14** show a strong band *ca*. 1650 cm⁻¹, attributed to the coordinated tetrazolate group.^[5] Moreover, complex **14** exhibits a band at 2229 cm⁻¹ indicating the presence of free nitrile group which is not involved in the cycloaddition. In conclusion, the infrared spectral data of the complexes **11** and **12–14** are found to be consistent with crystal structure analyses.

3.3.2 Thermogravimetric Analyses (TGA)

The thermal stabilities of complexes **10** and **12-14** were examined by thermogravimetric analysis. For complex **10** weight loss of 10.11% is observed in the temperature range 30-100 °C which corresponds to the loss of two coordinated water molecules. Further heating to 700 °C results in the slow decomposition of the sample.



Figure 3.1. Thermogravimetric curve of compound 10. Plot of weight loss/% against temperature/°C.

The polycrystalline complex 12 shows a rapid decomposition in the temperature range 30-300 °C (Figure 3.2). The complex 13 exhibits two thermal steps which were followed by a continuous weight loss above 270 °C (Figure 3.3). The first

weight loss of 2.72 % in the temperature range 40-120 °C corresponds to the loss of two water of crystallization. The anhydrous complex further undergoes weight loss of 10.29 % in the range 150-190 °C which corresponds to the loss of two coordinated *N*,*N*-Dimethylformamide (DMF) molecules.



Figure 3.2. Thermogravimetric curve of compound 12. Plot of weight loss/ % against temperature/°C.



Figure 3.3. Thermogravimetric curve of compound 13. Plot of weight loss/ % against temperature/°C.

The TGA graph of complex **14** shows a two step weight loss. The initial weight loss of 4.26 % in the temperature range 60-130 °C, corresponds to the loss of five water molecules (three water of crystallization and two coordinated water molecule) which is followed by the weight loss of 3.56 % due to loss of one DMF molecule in the temperature range of 140-200 °C (Figure 3.4). A continuous weight loss was recorded above 270 °C for complex **14**.



Figure 3.4. Thermogravimetric curve of compound 14. Plot of weight loss/ % against temperature/°C.

3.3.3 Crystal structure

3.3.3.1 <u>Crystal structures of [Ni(L¹)(N₃)] (11), [Ni₃L¹₂(5-Phenyltetrazolato)₄</u> (DMF)₂] (12), [Ni₃L¹₂{5-(3-pyridyl)-tetrazolato}₄(DMF)₂]·2H₂O (13) and [Ni₅L¹₄{5-(2-cyanophenyl)-tetrazolato}₄(OH)₂(H₂O)₂]·3H₂O·DMF (14):



Figure 3.5. Molecular structure of $[Ni(L^1)(N_3)]$ (11) with atomic numbering scheme.

The monoazide compound **11** crystallizes in space group $P2_{1/C}$ (Table 3.1). In $[Ni(L^1)(N_3)]$ (**11**), the central metal ion is coordinated to the tridentate Schiff-base ligand L¹ and one azide ion to give a distorted square planar geometry (Figure 3.5). The Ni-N bond lengths range from 1.856(4) to 1.955(4) Å and together with the Ni-O distance (1.837(3) Å) (Table 3.2) are well within the ranges of related square planar nickel complexes.^[11,14] The N₃ group is almost linear [N5-N4-N3 175.9(5)°] and is not coaxial with the Ni1-N3 bond as shown by the Ni1-N3-N4 angle [122.1(3)°] and lies in the same plane as the O1, N1 and N2 atoms.

Complex **12** crystallizes in space group *P*-1 (Table 3.1). It comprises of discrete centrosymmetric trinuclear units of the neutral compound $[Ni_3L_2^1(5-Phenyltetrazolato)_4(DMF)_2]$ (Figure 3.6). The three nickel atoms are found to be in linear disposition. The central nickel atom Ni(2) has a coordination number of six, being bonded to the four nitrogen atoms of the bridging tetrazolato group (2,3-bridged) at distances ranging 2.067(3)–2.077(3) Å (Table 3.3) that form the square plane of the Ni(II) while the axial positions are occupied by bridging oxygen atoms O1 of phenoxo groups. The two terminal nickel atoms are bonded to three atoms of ligand L¹ in the equatorial plane where as the fourth position of the plane has been

taken up by bridging tetrazole nitrogen atom N3. The coordination environment surrounding the terminal nickel atoms are also distorted octahedral and the axial positions are taken up by another nitrogen N8 atom of bridging tetrazolate group and one DMF molecule, respectively. The Ni-N bond distances are found to be in the range 1.997(4)-2.151(3) Å, whereas the Ni-O distances remain in the range 2.056(2)-2.169(3) Å. The central nickel atom has been found to be bridged to the terminal nickels atoms through phenoxo-group of tridentate ligand and two bridging tetrazolato groups. The central nickel- terminal nickel distance was found to be 3.327(6) Å.



Figure 3.6. Molecular structure of $[Ni_3L_2^1(5-Phenyltetrazolato)_4(DMF)_2]$ (12) with atomic numbering scheme.

Compound 13, $[Ni_3L_2^1{5-(3-pyridyl)-tetrazolato}_4(DMF)_2]\cdot 2H_2O$ has a similar structure like compound 12. However, there are two crystallographically independent molecules in the unit cell (Figure 3.7). For both the molecules the three nickel centers are linearly arranged. For the central nickel atom the Ni-N bond

distances are found to be in the range of 2.071(7)-2.107(7) Å, whereas the Ni-O_{phenoxo} bonds are found in the range of 2.106(4)-2.117(5) Å (Table 3.4). Regarding the terminal nickel centers the Ni-N bond distances were found to be in the range of 1.970(6)-2.161(9) Å and Ni-O_{phenoxo} and Ni-O_{DMF} are 2.057(5) Å and in the range of 2.136(6)-2.143(7) Å, respectively. The central nickel- terminal nickel distances were found to be in the range of 3.333(1)-3.336(1) Å.



Figure 3.7. Molecular structure of $[Ni_3L_2^1\{5-(3-pyridyl)-tetrazolato\}_4(DMF)_2]$ '2H₂O (**13**) with atomic numbering scheme. Solvent of crystallization is omitted for clarity.

Discrete homopentanuclear nickel(II) clusters are relatively rare.^[15] However there are many nickel (II) complexes which have been reported bearing a μ_3 -OH ligand. ^[16] The pentanuclear structure of complex **14** comprises of two dinuclear [Ni₂L¹₂{5-(2-cyanophenyl)-tetrazolato}] units which are each linked to the central nickel atom by bridging μ_3 -hydroxo groups and also through another tetrazolate moiety which also connects two dimeric units through 1,2,3-tetrazolate bridge (Figure 3.8).



Figure 3.8. Molecular structure of $[Ni_5L_4^1{5-(2-cyanophenyl)-tetrazolato}_4(OH)_2(H_2O)_2]^3H_2O^{-}$ DMF (**14**) with atomic numbering scheme. Solvent of crystallization is omitted for clarity.

The central nickel atom is six coordinated with {N₂O₄} donor set. Two nitrogen atoms come from two bridging tetrazolate group and two oxygen donor is comprised of two μ_3 -OH ligand to complete the equatorial positions. The apical positions have been taken up by water molecules. The Ni-N bond distance are found to be 2.044(5) Å, whereas the Ni-O_{hydroxo} bond distance is 2.050(4) Å and Ni-O_{water} bond distance is found to 2.117(4) Å (Table 3.5). The Ni-O_{hydroxo} bond length is quite indicative that the μ_3 -bridging ligand is hydroxo- but not oxo- where the expected bond length is in the range of 1.8-1.9 Å.^[17] The terminal nickel atoms are also having octahedral geometry with {N₄O₂} environment. The ligand L¹ provides the {N₂O} donor set where the other positions are taken up by two bridging tetrazolate group (2,3-bridged and 1,2,3-bridged) and another μ_3 -hydroxo group. The Ni-N bond distances are found to be in the range 2.023(7) to 2.230(5) Å whereas the Ni-O bond distances remains within the expected range of 2.023(4) to 2.146 (4) Å. The central nickel atom and terminal nickel atoms are found to be separated to each other by 3.460 to 3.589 Å, whereas the distance between two nickel centers of terminal dimer is 3.687 Å. Moreover, the crystal structure of complex **13** (two water molecules) and **14** contains disordered solvent molecules (probably water and DMF), which could not be modeled by discrete atoms. Its contribution was subtracted from the diffraction pattern by the "SQUEEZE" method.

| Ni(1)-O(1) | 1.836(3) | O(1)-Ni(1)-N(2) | 94.55(16) |
|------------|----------|------------------|------------|
| Ni(1)-N(2) | 1.855(4) | O(1)-Ni(1)-N(3) | 89.08(16) |
| Ni(1)-N(3) | 1.900(4) | N(2)-Ni(1)-N(3) | 175.39(17) |
| Ni(1)-N(1) | 1.955(4) | O(1)-Ni(1)-N(1) | 176.99(15) |
| Cl(1)-C(4) | 1.751(5) | N(2)-Ni(1)-N(1) | 87.28(17) |
| O(1)-C(1) | 1.318(6) | N(3)-Ni(1)-N(1) | 89.21(17) |
| N(1)-C(11) | 1.485(6) | C(1)-O(1)-Ni(1) | 126.2(3) |
| N(1)-C(9) | 1.493(6) | C(11)-N(1)-C(9) | 110.4(4) |
| N(1)-C(10) | 1.495(6) | C(11)-N(1)-C(10) | 108.8(4) |
| N(2)-C(7) | 1.288(6) | C(9)-N(1)-C(10) | 108.3(4) |
| N(2)-C(8) | 1.479(6) | C(11)-N(1)-Ni(1) | 108.9(3) |
| N(3)-N(4) | 1.206(6) | C(9)-N(1)-Ni(1) | 106.9(3) |
| N(4)-N(5) | 1.154(6) | C(10)-N(1)-Ni(1) | 113.5(3) |
| | | C(7)-N(2)-C(8) | 119.2(4) |
| | | C(7)-N(2)-Ni(1) | 127.6(3) |
| | | C(8)-N(2)-Ni(1) | 113.2(3) |
| | | N(4)-N(3)-Ni(1) | 122.1(3) |
| | | N(5)-N(4)-N(3) | 175.9(5) |
| | | | |

 Table 3.2: Selected bond lengths (Å) and bond angles (°) for 11

| Ni(1)-N(1) | 1.997(3) | N(1)-Ni(1)-N(3) | 175.71(14) |
|--------------|----------|---------------------|------------|
| Ni(1)-N(3) | 2.035(3) | N(1)-Ni(1)-O(1) | 90.55(13) |
| Ni(1)-O(1) | 2.056(3) | N(3)-Ni(1)-O(1) | 88.38(12) |
| Ni(1)-N(7) | 2.141(3) | N(1)-Ni(1)-N(7) | 94.06(13) |
| Ni(1)-N(2) | 2.151(4) | O(1)-Ni(1)-N(7) | 84.42(12) |
| Ni(1)-O(2) | 2.170(3) | N(1)-Ni(1)-N(2) | 82.63(14) |
| Ni(2)-N(8)#1 | 2.067(3) | N(3)-Ni(1)-N(2) | 98.40(13) |
| Ni(2)-N(8) | 2.067(3) | N(7)-Ni(1)-N(2) | 96.31(13) |
| Ni(2)-N(4) | 2.077(3) | N(1)-Ni(1)-O(2) | 85.96(13) |
| Ni(2)-N(4)#1 | 2.077(3) | N(3)-Ni(1)-O(2) | 89.84(12) |
| Ni(2)-O(1)#1 | 2.103(2) | O(1)-Ni(1)-O(2) | 87.10(11) |
| Ni(2)-O(1) | 2.103(2) | N(2)-Ni(1)-O(2) | 92.11(13) |
| | | N(8)#1-Ni(2)-N(8) | 180.0 |
| | | N(8)#1-Ni(2)-N(4) | 88.86(13) |
| | | N(8)#1-Ni(2)-N(4)#1 | 91.14(13) |
| | | N(4)-Ni(2)-N(4)#1 | 180.0(2) |
| | | N(8)#1-Ni(2)-O(1)#1 | 82.17(11) |
| | | N(8)-Ni(2)-O(1)#1 | 97.83(11) |
| | | N(4)-Ni(2)-O(1)#1 | 94.30(11) |
| | | O(1)#1-Ni(2)-O(1) | 180.00(13) |

Table 3.3: Selected bond lengths (Å) and bond angles (°) for 12

Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y+1,-z

Table 3.4: Selected bond lengths (Å) and bond angles (°) for 13^a .

| Ni(1)-N(1) | 1.970(7) | N(1)-Ni(1)-N(3) | 178.6(3) |
|------------|----------|-----------------|----------|
| Ni(1)-N(3) | 2.037(7) | N(1)-Ni(1)-O(1) | 90.4(2) |
| Ni(1)-O(1) | 2.057(5) | N(3)-Ni(1)-O(1) | 88.7(2) |
| Ni(1)-N(8) | 2.118(6) | N(1)-Ni(1)-N(8) | 89.8(3) |
| Ni(1)-O(2) | 2.135(6) | N(3)-Ni(1)-N(8) | 89.0(3) |

| Ni(1)-N(2) | 2.161(6) | O(1)-Ni(1)-N(8) | 84.4(2) |
|---------------|----------|---------------------|------------|
| Ni(2)-N(4) | 2.072(6) | N(1)-Ni(1)-O(2) | 89.9(3) |
| Ni(2)-O(1)#1 | 2.107(5) | N(3)-Ni(1)-O(2) | 91.1(3) |
| Ni(2)-O(1) | 2.107(5) | O(1)-Ni(1)-O(2) | 87.0(2) |
| Ni(2)-N(9)#1 | 2.107(6) | N(8)-Ni(1)-O(2) | 171.3(2) |
| Ni(2)-N(9) | 2.107(6) | N(1)-Ni(1)-N(2) | 83.0(3) |
| Ni(3)-N(21)#2 | 2.071(6) | N(3)-Ni(1)-N(2) | 97.9(3) |
| Ni(3)-N(16) | 2.081(6) | O(1)-Ni(1)-N(2) | 172.8(3) |
| Ni(3)-N(16)#2 | 2.081(6) | N(8)-Ni(1)-N(2) | 98.6(3) |
| Ni(3)-O(3) | 2.117(5) | O(2)-Ni(1)-N(2) | 90.0(3) |
| Ni(3)-O(3)#2 | 2.117(5) | N(4)# -Ni(2)-N(4) | 180.00(14) |
| Ni(4)-N(14) | 1.994(7) | N(4)#1-Ni(2)-O(1)#1 | 85.7(2) |
| Ni(4)-N(22)#2 | 2.037(6) | N(4)-Ni(2)-O(1)#1 | 94.3(2) |
| Ni(4)-O(3) | 2.057(5) | N(4)#1-Ni(2)-O(1) | 94.3(2) |
| Ni(4)-N(17)#2 | 2.115(7) | N(4)-Ni(2)-O(1) | 85.7(2) |
| Ni(4)-O(4) | 2.143(6) | O(1)#1-Ni(2)-O(1) | 180.0(3) |
| Ni(4)-N(15) | 2.151(6) | N(4)#1-Ni(2)-N(9)#1 | 90.4(2) |
| | | | |

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y+2,-z #2 -x+1,-y,-z+1

^a Refinement was carried out after solvent electron density was removed by the SQUEEZE routine in PLATON.

 Table 3.5: Selected bond lengths (Å) and bond angles (°) for 14^a.

| Ni(1)-N(1) | 2.044(5) | N(1)-Ni(1)-N(1)#1 | 180.0(3) |
|--------------|----------|---------------------|-----------|
| Ni(1)-N(1)#1 | 2.044(5) | N(1)-Ni(1)-O(3)#1 | 91.87(19) |
| Ni(1)-O(3)#1 | 2.051(4) | N(1)#1-Ni(1)-O(3)#1 | 88.13(19) |
| Ni(1)-O(3) | 2.051(4) | N(1)-Ni(1)-O(3) | 88.13(19) |
| Ni(1)-O(4) | 2.116(5) | N(1)#1-Ni(1)-O(3) | 91.87(19) |
| Ni(1)-O(4)#1 | 2.116(5) | O(3)#1-Ni(1)-O(3) | 180.0(2) |
| Ni(2)-N(7) | 2.030(6) | N(1)-Ni(1)-O(4) | 88.4(2) |
| Ni(2)-N(2) | 2.170(6) | N(1)#1-Ni(1)-O(4) | 91.6(2) |

| Ni(2)-N(6) | 2.280(6) | O(3)#1-Ni(1)-O(4) | 86.6(2) |
|--------------|----------|---------------------|----------|
| Ni(2)-O(1) | 2.044(5) | O(3)-Ni(1)-O(4) | 93.4(2) |
| Ni(2)-N(8) | 2.092(6) | N(1)-Ni(1)-O(4)#1 | 91.6(2) |
| Ni(2)-O(3) | 2.146(4) | N(1)#1-Ni(1)-O(4)#1 | 88.4(2) |
| Ni(3)-O(2) | 2.023(5) | O(3)#1-Ni(1)-O(4)#1 | 93.4(2) |
| Ni(3)-N(14) | 2.024(6) | O(3)-Ni(1)-O(4)#1 | 86.6(2) |
| Ni(3)-N(9) | 2.069(6) | O(4)-Ni(1)-O(4)#1 | 180.0(2) |
| Ni(3)-O(3) | 2.083(5) | N(7)-Ni(2)-O(1) | 88.6(2) |
| Ni(3)-N(3)#1 | 2.128(6) | N(7)-Ni(2)-N(8) | 91.4(2) |
| Ni(3)-N(13) | 2.230(6) | O(1)-Ni(2)-N(8) | 92.4(2) |

Symmetry transformations used to generate equivalent atoms: #1 -x,-y+1,-z

^a Refinement was carried out after solvent electron density was removed by the SQUEEZE routine in PLATON.

3.3.4 Magnetic property study:

The magnetic properties of compounds **12**, **13** and **14** were studied on powdered samples by variable temperature susceptibility measurements. The susceptibility data were collected in a temperature range of 2 -300 K in an applied field of 0.1 Tesla and are shown as $\chi_M T$ vs. T (Figure 3.9 and Figure 3.10 respectively). The red lines correspond to the best simulation for **13** and **14**.



Figure 3.9. The resulting molar susceptibility data were plotted in $\chi_M T vs$. T in blue line for complex **12** and in black line for complex **13**. The red line corresponds to the best simulation for **13**.



Figure 3.10. The resulting molar susceptibility data were plotted in $\chi_M T vs$. T for complex **14**. The red line corresponds to the best simulation for **14**.

For compound **12** at room temperature no meaningful simulation could be obtained due to underlying impurities. The χ_M T-value for **13** at room temperature is with 3.41 cm³ K mol⁻¹ slightly higher than the expected one of 3.00 cm³ K mol⁻¹ for three uncoupled spins with $S_1 = S_2 = S_3 = 1$ but perfectly in agreement with the expected value considering g-values of 2.15 for the three nickel ions. Only a small decrease of the χ_M T-value can be observed by lowering the temperature up to 70 K. Further cooling leads to a sharper decrease reaching a χ_M T-value of 0.94 cm³ K mol⁻¹ at 2 K, indicating dominant antiferromagnetic interactions between the nickel centers.

For 13 the magnetic data can be simulated satisfactorily by applying the isotropic exchange Hamilton operator: $\hat{H} = -2J (\hat{S}_1 \hat{S}_2 \cdot \hat{S}_2 \hat{S}_3)$. The best simulation is obtained with J = -4.93 cm⁻¹ and $g_1 = g_2 = g_3 = 2.156$. A temperature independent paramagnetism, TIP, of 300×10^{-6} was included to obtain a good simulation.

DFT calculations are carried out to understand the anti-ferromagnetic interactions between the three Ni centers on complex **13**. The magnetic behavior of polynuclear transition metal complexes have been studied by evaluating their magnetic exchange coupling constants. Several standard theoretical approaches are reported in literatures^[18] but among all these, Broken Symmetry (BS) is the most popular one.^[19] The BS approach uses unrestricted Hartree-Fock (UHF) or density

functional theory (DFT) calculations for low spin molecular systems in which α and β spin densities are allowed to localize on their respective atomic centers. Generally, the calculated exchange coupling (*J*) constant differs very much from the experimental value due to the complexity of such problems and the limitation of DFT theory. Moreover, in the weakly coupled magnetic system, the *J* values even differ in both sign and magnitude from the experimental one.^[20] In spite of all these, BS approach is very useful for understanding the mechanism of spin exchange in polynuclear complexes.^[21] In the present study, DFT calculations were performed with BS approach to evaluate the magnetic exchange coupling constant using the Hamiltonian H= -2JS₁S₂ on Yamaguchi formalism,^[22]

$$J = -\frac{E_{HS} - E_{BS}}{\langle S^2 \rangle_{HS} - \langle S^2 \rangle_{BS}}$$

Where, E_{HS} and E_{BS} are the energies of the high spin state and broken symmetry state (low spin state) respectively, and $S^2 = S(S+1)$. The positive and negative value of *J* indicates ferromagnetic and antiferromagnetic interaction respectively.

The complexity of the magnetic systems increases if it has more than two magnetic centers. Therefore, such problems can be simplified if one of the magnetic centers can be substituted by a non-magnetic one.^[23] As Fe(II) has two electrons less than Ni(II) therefore one of Ni(II) is substituted by Fe(II) and then the three center magnetic problem can be simplified into a two center magnetic problem. Similarly in the present study, one of the Ni(II) atom was substituted by a Fe(II) atom.

DFT calculations were performed using Gaussian 09 program.^[24] The X-ray coordinates of the complex were used for all the calculation. The unrestricted B3LYP functional and $6-31G^{*/25/}$ basis set were used for all the atoms.

The calculated exchange coupling value of complex **13** is found to be -5.78 cm^{-1} . Therefore the calculated value is in very good agreement with the experimental value of $J = -4.93 \text{ cm}^{-1}$. To understand the magnetic exchange behaviour of complex **13** it is important to note that Ni(1) and Ni(2) are bridged by one μ -phenoxo and two tetrazolate group in N(2)N(3) mode. There are few trinuclear nickel(II) complexes reported so far with μ -phenoxo bridge and it is also reported that the magnetic properties of such complexes are mostly governed by bridging Ni-O-Ni angles. For trinuclear Ni(II) complexes, ferromagnetic interaction is observed for Ni-O-Ni angles that are less than 93.5° while the magnetic coupling is antiferromagnetic for greater values.^[26]

In the present case the bond angles of Ni(1)-O(1)-Ni(2) is 106.50° and Ni(3)-O(3)-Ni(4) is 105.97°, respectively indicative of possible antiferromagnetic coupling as reported earlier.^[26] Moreover from the Ni-O-Ni angle observed in this complex, the J value was expected in more lower range than the observed value. However, it should be also noted that there are reports where second bridging ligand can play counter complementary effect leading to the decrease of antiferromagnetic coupling by formation of ferromagnetic exchange.^[27] So far there are only few reports available where nickel centers are bridged by tetrazolate group in N(2)N(3) mode in presence of other bridging centers and most of the compounds reported are showing weak ferromagnetic interaction.^[28] Considering the above facts it may be proposed that though there is weak ferromagnetic coupling between the nickel centers through tetrazole bridge however antiferromagnetic nature of the compound dominates because of the presence of more stronger exchange through phenoxo bridged ligand.

For compound **14** (Figure 3.10) at room temperature a χ_M T-value of 5.51 cm³ Kmol⁻¹ is observed, which is slightly higher than the theoretical value of 5.00 cm³ K mol⁻¹ for five uncoupled spins with $S_1 = S_2 = S_3 = S_4 = S_5 = 1$, as expected for nickel(II) ions with *g*-values larger than 2.0. With lowering temperature a decrease of the χ_M T-value is observed reaching a χ_M T-value of 1.01 cm³ K mol⁻¹ at 2 K indicative for dominant antiferromagnetic interactions between the nickel centers.



Figure 3.11. The magnetic data of **14** can be simulated satisfactorily by applying the isotropic exchange Hamilton operator: $\hat{H} = -2J \Sigma \hat{S}_i \hat{S}_j$ and the exchange model.

The magnetic data of **14** can be simulated satisfactorily applying the isotropic exchange Hamilton operator: $\hat{H} = -2J_{ij}\Sigma \hat{S}_i \hat{S}_j$ and the exchange model, shown in figure 3.11. The best simulation is obtained with $J_1 = -5.84 \text{ cm}^{-1}$, $J_2 = -6.94 \text{ cm}^{-1}$ and $g_{all} = 2.20$. A temperature independent paramagnetism, TIP, of 600×10^{-6} was included to obtain a good simulation.

It has been reported earlier the magnetic exchange properties for μ_3 - or μ_2 -hydroxo bridge depends upon the Ni-O-Ni angle and it has shown that generally angles with more than 97° inducts antiferromagnetic nature in the compounds whereas angle less than that usually leads to the formation of ferromagnetic exchange.^[29] For complex **14** the average Ni-O-Ni angles are found to be in the range of 117° which predicts the magnetic exchange between nickel centers should be highly antiferromagnetic. Relatively higher value of *J* obtained for complex **14** may be because of the counter complementary effect from bridging tetrazolate groups in N(1)N(2)N(3) mode and N(2)N(3) mode. However, because of lack of more magnetic data regarding tetrazolate bridged nickel complexes it is difficult to elucidate the *J* value obtained for complex **13** and **14** in conclusive manner.

3.4 Conclusion

tridentate ligand *p*-chloro-2-{(2-(dimethylamino)ethylimino)methyl}phenol Α (HL^1) and [2 + 3] cycloaddition between metal coordinated azide and different organonitriles have been used to limit the nuclearity of the isolated compound as tri- and pentanuclear nickel (II) complex. The nuclearity of the product depends on the nature of organonitrile used for cycloaddition. Thus when the organonitrile used is benzonitrile or 3-cyanopyridine trinuclear species 12 and 13 were obtained, respectively, formed by tetrazolate bridge (via N(2)N(3) mode) and a phenoxo bridge between central and terminal nickel centers. The nickel centers are found to be linearly disposed. The separation between metal centers are found to be in the range of 3.327-3.336 Å. Upon reaction with 1,2-dicyanobenzene, complex 11 furnished a pentanuclear complex 14. The structure can be described as a central nickel center is connected to two nickel dimers by means of µ₃-hydroxo bridge apart from bridging tetrazole ligand which operates through 1,2,3-bridging mode. The distance between the central nickel atom and terminal nickel atoms are found to be in the range of 3.460-3.589 Å, whereas the distances between two nickel centers of terminal dimer are 3.687 Å. The number of metal bound solvent molecules and solvent of crystallization in 13 and 14 were also confirmed by thermo-gravimetric analysis. The magnetic susceptibility data for compound 12-14 in the temperature range of 2-300 K shows dominant antiferromagnetic interactions between the nickel centres for all the complexes. The magnetic exchange parameters of one of the compound 13 has been investigated by DFT in broken-symmetry approach.

3.5 <u>References</u>

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Chapter-4

Targeted water soluble copper-tetrazolate complexes: interactions with biomolecules and catecholase like activities

4.1 Introduction

Interactions of various 5-substituted tetrazoles with copper ions have been widely investigated by different researchers in the past few years.^[1-14] However, the prime focus of these kinds of studies remain limited to generation of metal-organic frameworks, where the tetrazole ligand is able to participate in nine different types of coordination, with a vast array of structural diversities having various topologies. Solvothermal synthesis of copper-tetrazolate complexes mostly have taken control in the arena of generation of polymeric materials.^[1,4,6,7] Some of these synthesized frameworks or mononuclear compounds have shown interesting magnetic,^[1,6,7,11,13] catalytic,^[2] photoluminescence^[5,6] or gas absorption^[3,8,12] properties

The binding of DNA with tetrazolo metal complexes has attracted much attention recently because of their site specific binding properties and wide range of applications. The interaction between DNA and copper tetrazolate complex are relatively rare in literature,^[15] however to the best of our knowledge the interaction of copper-tetrazolate complexes with bovine serum albumin (BSA) or any kind of bioinspired catalytic activities of these complexes have not been explored yet. The rational reasoning might be lying in the fact that the solvothermally generated uncontrolled copper-tetrazolate frameworks are mostly insoluble in nature that make them unsuitable for this kind of investigation. However, as per the continuous endeavor to generate metal tetrazolate complexes in a more controlled and environmental friendly condition, herein the synthesis and structural characterization has been reported for the mononuclear copper tetrazolate complexes $[Cu{(5-pyrazinyl)tetrazolate}_2(1,10-phenanthroline)]$ (15) and $[Cu{(5-pyrazinyl)tetrazolate}_2(1,10-phenanthroline)]$ pyrazinyl)tetrazolate $\{(1,10\text{-phenanthroline})_2\}(NO_3)_{0.5}(N_3)_{0.5}$ (16). Both the

complexes **15** and **16** exhibit interesting interactions with biomolecules like DNA and serum albumin protein. Furthermore, compound **16** has shown interesting catecholase like activity which is also reported here. Interaction of the complexes with DNA are further investigated with Density functional theory.

4.2 Experimental section

4.2.1 Materials and physical measurements

Reagents and Materials: All reagents and solvents were purchased commercially and were used as received. Copper(II) nitrate trihydrate, 1,10-phenanthroline monohydrate, sodium azide and pyrazine carbonitrile were purchased from Merck-India Chemical Company. Calf thymus DNA, bovine serum albumin (BSA, fraction V powder), ethidium bromide (EB), Agarose Low EEO Superior grade type II gel, supercoiled plasmid pBR322 DNA, DAPI dihydrochloride (4',6diamidino-2-phenylindole dihydrochloride), methyl green and superoxide SRL dismutase (SOD) were purchased from (India). Tris(hydroxymethyl)aminomethane-hydrochloride (Tris-HCl) buffer was prepared using distilled water.

Methods and Instrumentation: Infrared spectra (4000 to 500 cm⁻¹) were recorded with a BRUKER TENSOR 27 instrument in KBr pellets. Mass spectrometric analyses were done on Bruker-Daltonics, microTOF-Q II mass spectrometer and elemental analyses were carried out with a Thermo Flash 2000 elemental analyzer. Spectrophotometric measurements were performed on a Varian UV-Vis spectrophotometer (Model: Cary100) (for absorption) and a Fluoromax-4p spectrofluorometer from Horiba JobinYvon (Model: FM-100) (for emission) using a quartz cuvette with path length of 1 cm.

Caution! Azide and tetrazolate compounds are potentially explosive. Only a small amount of material should be prepared and handled with care.

X-ray crystallography: Single crystal X-ray structural studies of compound **15** and **16** were performed on a CCD Agilent Technologies (Oxford Diffraction) SUPER NOVA diffractometer. Data for both the complexes **15** and **16** were collected at

150(2) K using graphite-monochromatic MoK_a radiation ($\lambda_{\alpha} = 0.71073$ Å) and Cu K_a radiation ($\lambda_{\alpha} = 1.54184$ Å) respectively. The strategy for the data collection was evaluated using the CrysAlisPro CCD software. The data were collected by the standard phi-omega scan techniques and were scaled and reduced using the CrysAlisPro RED software. The structure was solved by direct methods using the SHELXS-97 and refined by full matrix least-squares with the SHELXL-97 for compound **15** and SHELX-2014 for compound **16**, refining on F^{2.[16]} The positions of all the atoms were obtained by direct methods. All non-hydrogen atoms were refined anisotropically. The remaining hydrogen atoms were placed in geometrically constrained positions and refined with isotropic temperature factors, generally 1.2*U*_{eq} of their parent atoms. The contribution of solvent electron density was removed by the SQUEEZE routine in PLATON.^[177] The crystal and refinement data are summarized in Table 4.1, and selected bond distances and bond angles for **15** and **16** are shown in Table 4.3 and Table 4.4.

| | 15 | 16 ^a |
|---|-----------------------------|-----------------------------------|
| Empirical formula | $C_{44}H_{32}Cu_2N_{28}O_2$ | $C_{29} H_{23} Cu N_{12} O_{3.5}$ |
| Formula weight | 1112.02 | 659.13 |
| Wavelength (Å) | 0.71073 | 1.54184 |
| Temperature (K) | 150(2) | 150(2) |
| Crystal system | Triclinic | Triclinic |
| Colour and shape | Blue block | Green block |
| Space group | <i>P</i> -1 | <i>P</i> -1 |
| a/Å | 12.3344(8) | 11.9248(10) |
| b/Å | 14.2954(9) | 11.9276(12) |
| c/Å | 15.4511(5) | 13.4576(11) |
| α/degree | 95.631(4) | 71.600(8) |
| β/degree | 107.583(4) | 68.381(8) |
| γ/degree | 108.242(6) | 70.668(8) |
| Volume (Å ³) | 2410.1(2) | 1637.7(3) |
| Z | 2 | 2 |
| $D_{ m calcd}/ m mg~m^{-3}$ | 1.527 | 1.337 |
| μ (Mo K α)/mm ⁻¹ | 0.954 | 1.372 |
| F(000) | 1124 | 676 |

 Table 4.1: Crystal data and structure refinement of complexes 15 and 16

| Crystal size/mm | 0.33×0.26×0.21 | 0.21×0.18×0.13 |
|------------------------------|--------------------|--------------------|
| θ range(°) | 2.96 to 25.00 | 3.622 to 71.321 |
| Limiting indices | $-14 \le h \le 14$ | $-14 \le h \le 9$ |
| | $-16 \le k \le 16$ | $-14 \le k \le 13$ |
| | $-18 \le l \le 15$ | $-16 \le l \le 14$ |
| Total/ unique no. of | 18321 / 8470 | 10588 / 6179 |
| reflns. | | |
| R _{int} | 0.0473 | 0.0275 |
| Data/restr./params. | 8470 / 0 / 685 | 6179 / 30 / 404 |
| $GOF(F^2)$ | 1.057 | 1.254 |
| R1, wR2 | 0.0442, 0.1054 | 0.0909, 0.2831 |
| R1, wR2 (all data) | 0.0593, 0.1198 | 0.0963, 0.2987 |
| Peak and hole (e $Å^{-3n}$) | 0.396 and -0.521 | 1.110 and -0.620 |
| | | |

^aThe "SQUEEZE" program was applied to subtract the contribution of the disordered solvent from diffraction data of complex **16** (water molecules). Refinement was carried out after the solvent electron density was removed by the SQUEEZE routine in PLATON.

4.2.2 Synthesis

 $[Cu(phen)(N_3)_2]_n$ and $[Cu(phen)_2N_3](NO_3) \cdot H_2O$ was synthesized according to the literature procedure.^[18,19]

4.2.2.1 [Cu(phen)(pzta)₂]·H₂O (15·H₂O) and [Cu(phen)₂(pzta)](NO₃)_{0.5}(N₃)_{0.5}·2H₂O (16·2H₂O):

A mixture of $[Cu(phen)(N_3)_2]_n$ (120 mg, 0.37 mmol), 2 mL of pyrazine carbonitrile and 3 mL of DMF was refluxed for 12 hrs. 30 mg of NaNO₃ was added and the reaction mixture was stirred for 30 mins at room temperature. The solvent was then removed in vacuo and the resulting residue was dissolved in methanol and filtered. The filtrate was concentrated to 2-3 mL. This greenish brown compound was found to be mixture of two compounds viz. $[Cu(phen)(pzta)_2]$ а and $[Cu(phen)_2(pzta)](NO_3)_{0.5}(N_3)_{0.5}$. The mixture was separated by ion-exchange chromatography using SP-Sephadex C-25, which is a strongly acidic $(-SO_3^Na+)$ cation exchanger based on cross-linked dextran. Methanol was used to elute the

neutral complex $[Cu(phen)(pzta)_2]$ (15) and 0.1 M NaNO₃ solution was used as the elution solvent to run the column for the elution of the charged complex $[Cu(phen)_2(pzta)](NO_3)_{0.5}(N_3)_{0.5}$ (16). Complex 15·H₂O was recrystallized from methanol-diethyl ether mixture to get suitable X-ray diffraction-quality crystals. Yield 42%. Anal. Calc. for compound **15**•**H**₂**O**: C₄₄H₃₂Cu₂N₂₈O₂ (1112.02): C 47.52; H 2.90; N 35.27%. Found: C 46.89; H 2.45; N 34.95%. ESI-MS (positive ion, CH₃OH) m/z: 537.7552 [Cu(phen)(pzta)₂]⁺ (calcd 537.0822). IR (cm⁻¹, KBr): 3426, 1681, 1642, 1523, 1023. Complex 16·2H₂O was recrystallized from acetonitrile-diethyl ether mixture to get suitable X-ray diffraction-quality crystals. Yield 38%. Anal. Calc. for compound **16·2H**₂**O**: [C₂₉H₁₉N₁₀Cu](NO₃)_{0.5}(N₃)_{0.5}•2(H₂O) (659.13): C 52.79; H 3.48; N 25.48%. Found: C 52.38; H 3.25; N 24.96%. ESI-MS (positive ion, CH₃OH) m/z: 570.1 [M–NO₃]⁺ (calcd 570.109). IR (cm⁻¹, KBr, selected peak): 3414, 1624, 1385. IR (cm⁻¹, CH₂Cl₂, selected peak): 3424, 2111, 1628, 1377.

4.2.2.2 <u>Synthesis of exclusive $[Cu(phen)_2(pzta)](NO_3)_{0.5}(N_3)_{0.5} \cdot 2H_2O$ (16·2H₂O):</u>

A mixture of $[Cu(phen)_2N_3](NO_3) \cdot (H_2O)$ (120 mg, 0.37 mmol), 2 mL of Pyrazine carbonitrile and 3 mL of DMF was refluxed for 12 hrs to get a clear green colour solution. The solvent was then removed in vacuo to obtain green colour residue upon concentration. This residue was dissolved in acetonitrile and layered with diethylether to obtain a relatively small amount of green coloured crystals, which were physically separated. Those crystals were then dissolved in acetonitrile and layered with ether. This procedure was repeated thrice to obtain an increasingly more pure compound **16** and the remaining mother solution was rejected. Yield 46 %. Anal. Calc. for compound **16** ·2**H**₂**O**: $[C_{29}H_{19}N_{10}Cu](NO_3)_{0.5}(N_3)_{0.5} ·2(H_2O)$ (659.13): C 52.79; H 3.48; N 25.48%. Found: C 52.38; H 3.25; N 24.96%. ESI-MS (positive ion, CH₃OH) *m*/*z*: 570.1 [M–NO₃]⁺ (calcd 570.109). IR (cm⁻¹, KBr, selected peak): 3414, 1624, 1385. IR (cm⁻¹, CH₂Cl₂, selected peak): 3424, 2111, 1628, 1377.

Solubility and Stability: The complexes are highly soluble in H_2O and MeOH. They were stable in the solid and solution phases.

4.3 <u>Results and discussion</u>

4.3.1 Synthesis and isolation of metal tetrazolate complex

To tackle the problem of lower solubility of copper-tetrazolate complex and to explore the possibilities in the domain of interaction with biomolecules, pyrazinecarbonitrile was chosen as a prospective precursor of tetrazolate ligand with extra hydrogen bonding site in the form of pyrazinyl nitrogen. A copper azide polymer complex $[Cu(phen)(N_3)_2]_n$ was chosen as the starting material where the ratio between copper to azide was 1:2 inducing the possibility for cycloaddition with two molecules to pyrazine nitrile to generate two chelating bidentate 5pyrazinyltetrazole ligands which along with one ancilliary 1,10-phenanthroline ligand completes the octahedral geometry surrounding the copper center and helps to break down the polymeric complex to a monomeric entity. Reaction between $[Cu(phen)(N_3)_2]_n$ and excess of pyrazine carbonitrile in DMF at refluxing condition provides a mixture of compound 15 and 16 upon addition of NaNO₃. ESI-MS indicates the presence of two separate species viz. [Cu(phen)(pzta)₂] 15 and $[Cu(phen)_2(pzta)]^+$ 16 [phen = 1,10-phenanthroline and pzta = 5pyrazinyltetrazolate] (Scheme 4.1 & Figure 4.1). The cationic complex 16 was solidified upon addition of NaNO₃ as $[Cu{(5-pyrazinyl)tetrazolate}(1,10$ phenanthroline)₂](NO₃)_{0.5}(N₃)_{0.5} (16) (Scheme 4.1). The mixture of compounds 15 and 16 were further separated by cation-exchange chromatography using SP-Sephadex C25. The neutral complex 15 was obtained by eluting with methanol where as the cationic complex 16 was isolated by elution with aqueous 0.1 M NaNO₃ solution. The compound 16 was also prepared through different method which provides $[Cu{(5-pyrazinyl)tetrazolate}(1,10-phenanthroline)_2](NO_3)_{0.5}(N_3)_{0.5}$ 16 as the exclusive product only. The [2+3] dipolar cycloaddition reaction between copper ligated azide $[Cu(phen)_2N_3](NO_3)$ with pyrazine carbonitrile under refluxing condition in DMF yielded a green residue upon concentration. This residue was dissolved in acetonitrile and layered with diethylether to obtain a relatively small amount of green coloured crystals, which were physically separated. Those crystals were then dissolved in acetonitrile and layered with ether. This procedure was repeated several times to obtain an increasingly more pure compound **16** and the remaining mother solution was rejected. Both the compounds (**15** and **16**) were characterized by IR, ESI-MS spectroscopy, elemental analyses and single crystal X-ray diffraction method.



Scheme 4.1. Schematic representation for the synthesis of complex $[Cu(phen) (pzta)_2]$ (15) and $[Cu{(5-pyrazinyl)tetrazolate}(1,10-phenanthroline)_2]$ (NO₃)_{0.5}(N₃)_{0.5}(16).



Figure 4.1. ESI-MS shows the presence of two separate species viz. $[Cu(phen)(pzta)_2 + Na]^+$ (15) and $[Cu(phen)_2(pzta)]^+$ (16).

Compound **15** shows a typical band at 1681 cm⁻¹ for tetrazolate ligand instead of two bands around 2057 cm⁻¹ for ligated azide in starting compound.^[20] Compound **16** also confirms the presence of free azide, tetrazolate and nitrate ion through their signature bands at 2111 cm⁻¹, 1628 cm⁻¹ and 1377 cm⁻¹ in IR spectrum, respectively.^[21] The ESI-MS spectrum for the mixture of compounds shows two main peaks at 570.116 and 560.0786 corresponding to the cationic complex of $[Cu(phen)_2(pzta)]^+$ **16** and molecular ion peak of $[Cu(phen)(pzta)_2 + Na]^+$ **15**, respectively (Figure 4.1). However after separation of the mixtures, the respective pure compounds were further characterized through ESI-MS spectra (as shown in Figure 4.2 for complex **15** and Figure 4.3 for complex **16**).



Figure 4.2. ESI-Mass spectrum of complex 15.

As the compounds **15** and **16** obtained show good solubility in common polar solvents including water, so their interaction with different biomolecules was

checked and the catecholase like activity was explored since these areas are relatively unexplored for copper tetrazolate complexes.



Figure 4.3. ESI- Mass spectrum of complex 16.

4.3.2 Thermogravimetric Analyses (TGA)

To ascertain the number of water molecules in the complex thermogravimetric analysis was carried out. Complex **16** shows first weight loss of 5% within the range of 25-70 $^{\circ}$ C (Figure 4.4). This corresponds to the loss of four molecules of water of crystallization for one unit cell.



Figure 4.4. Thermogravimetric curve of compound 16. Plot of weight loss/ % against temperature / °C.

4.3.3 UV-Visible spectroscopy

The electronic absorption spectra for both the complexes were recorded in methanol. Complex **15** reveals a shoulder around 660 nm and a low intensity peak for complex **16** was observed at 662 nm, characteristic of d-d transition band arising due to ${}^{2}B_{1g} \rightarrow {}^{2}E_{g}$ transition of tetragonally distorted octahedral geometry.^[22] The presence of other electronic transitions which appear in the UV region can be correlated to the $\pi \rightarrow \pi^*$ transition in the ligand (Table 4.2).^[23]

Table 4.2: Absorption spectra peaks of compounds 15 and 16 in methanol

| Compound no. | λ , nm (ε, M ⁻¹ cm ⁻¹) | |
|--------------|---|--|
| 15 | 270 (72500), 618 (38) | |
| 16 | 269 (76500), 669 (54) | |

4.3.4 Crystal structure

4.3.4.1 <u>Crystal structures of $[Cu(phen)(pzta)_2] \cdot H_2O$ (15·H₂O) and $[Cu(phen)_2$ (pzta)](NO₃)_{0.5} (N₃)_{0.5}(16·2H₂O):</u>

The exact structures of the copper complexes were determined by single crystal Xray crystallographic study. Compound **15·H**₂**O** crystallizes in the space group *P*-1 (Table 4.1) and displays two molecules with very similar geometries (Figure 4.5). The central ion is situated in the distorted octahedral environment where both the tetrazole ligands act as chelating bidentate fashion (Figure 4.5). The N-Cu-N bond angle in tetrazole ligands are found to be in the range of 72-74° (Table 4.3), because of the very small bite. The Cu-N bond distances are found to be within the expected range except the pyrazinyl nitrogen which are coordinated axially and making distance around 2.4-2.5 Å, because of Jahn-Teller distortion.^[24]



Figure 4.5. Molecular structure of $[Cu(phen)(pzta)_2] \cdot H_2O$ (15·H₂O) with the atomic numbering scheme.

Compound **16** crystallizes in the space group *P*-1 (Table 4.1) with one Cu complex, one-half azide, and one-half nitrate in the asymmetric unit for a Z value of 2 (Figure 4.6). The azide and nitrate sit on inversion centers and are disordered. The disorder was treated with ISOR restraints. The central atom exists in the center of a highly distorted octahedral geometry. The pyrazine nitrogen is found to be coordinated to the metal center at a distance of 2.678 Å generating a semi-coordinated bond (Table 4.4).^[25] Moreover, the small bite angle of the tetrazole ligand (70.8°) makes the molecule further distorted (Table 4.4). The nitrate and azide counterion are further enjoined with each other through complicated hydrogen bonding to form a three dimensional hydrogen bonded network (Figure 4.7).

The crystal structure of complex $16\cdot 2H_2O$ contains two disordered water molecules which could not be modeled by discrete atoms. Their contribution was subtracted from the diffraction pattern by the "SQUEEZE" method.



Figure 4.6. Molecular structure of $[Cu(phen)_2(pzta)](NO_3)_{0.5}(N_3)_{0.5}$ (16) with the atomic numbering scheme. The azide and nitrate ions are omitted for clarity.



Figure 4.7. Three dimensional hydrogen bonded network for complex 16.

| Cu(1)-N(9) | 1.985(2) | N(9)-Cu(1)-N(2) | 167.25(11) |
|------------|----------|-----------------|------------|
| Cu(1)-N(2) | 2.012(2) | N(9)-Cu(1)-N(3) | 92.94(10) |
| Cu(1)-N(3) | 2.012(2) | N(2)-Cu(1)-N(3) | 95.04(10) |

Table 4.3: Selected bond lengths (Å) and bond angles (°) for complex 15

| Cu(1)-N(1) | 2.037(2) | N(9)-Cu(1)-N(1) | 93.45(9) |
|-------------|----------|-------------------|------------|
| Cu(1)-N(13) | 2.401(3) | N(2)-Cu(1)-N(1) | 81.68(9) |
| Cu(2)-N(23) | 1.991(3) | N(3)-Cu(1)-N(1) | 163.00(11) |
| Cu(2)-N(17) | 2.002(3) | N(9)-Cu(1)-N(13) | 74.80(10) |
| Cu(2)-N(16) | 2.022(3) | N(2)-Cu(1)-N(13) | 93.96(10) |
| Cu(2)-N(15) | 2.030(3) | N(3)-Cu(1)-N(13) | 100.43(10) |
| N(3)-N(4) | 1.347(3) | N(1)-Cu(1)-N(13) | 96.44(10) |
| N(4)-N(5) | 1.313(4) | N(23)-Cu(2)-N(17) | 93.24(12) |
| N(5)-N(6) | 1.342(4) | N(17)-Cu(2)-N(16) | 94.95(11) |

Table 4.4: Selected bond lengths (Å) and bond angles (°) for complex 16

| Cu1-N5 | 2.003(4) | N5-Cu1-N9 | 70.9(1) |
|-----------|----------|-------------------|----------|
| Cu1-N3 | 2.015(4) | N5-Cu1-N1 93.0(2) | |
| Cu1-N1 | 2.026(3) | N3-Cu1-N1 | 171.2(2) |
| Cu1-N4 | 2.069(3) | N5-Cu1-N4 | 160.0(2) |
| Cu1-N2 | 2.231(4) | N3-Cu1-N4 | 80.9(2) |
| N(5)-N(6) | 1.312(5) | N1-Cu1-N4 | 94.9(2) |
| N(6)-N(7) | 1.302(7) | N5-Cu1-N2 | 99.8(1) |
| N(7)-N(8) | 1.335(8) | N3-Cu1-N2 | 94.7(1) |
| | | N1-Cu1-N2 | 78.2(1) |
| | | N(4)-Cu(1)-N(2) | 99.7(2) |

4.3.5 DNA Binding property

To explore the possibility of these copper complexes binding with CT-DNA, (which has been found to be a critical step for the chemical nuclease activities of metal complexes) DNA was added over several steps with increasing amounts while changes in the absorption spectrum of the metal complex were monitored. It has been reported that interaction between metal complexes and DNA bases may lead to intercalation where hypochromic shift in the UV region was found to be a manifestation of that phenomena.^[26,27] Furthermore a bathochromic shift indicates the decrease in the energy gap between the highest occupied and lowest unoccupied molecular orbital when the complex binds to DNA.^[28] Absorption spectral titration carried out for compounds **15** and **16** reveals a decrease in molar absorptivity with a slight bathochromic shift indicating a possible interaction between aromatic moieties of the complex with DNA base pairs and stabilization of CT-DNA duplex. In the presence of DNA, complex **15** exhibited hypochromism of 10% at 275 nm (Figure 4.8) whereas for complex **16** it increased to 20% (Figure 4.9), revealing considerable interaction between complexes and DNA. These interactions are attributed to $\pi \rightarrow \pi^*$ transition of the complex. The hypochromicity and bathochromic shift indicates the intercalative mode of binding and considerable stacking interaction between aromatic chromophore and base pairs of DNA.



Figure 4.8. Absorption titration spectra of fixed concentration (12 μ M) of complex **15** with increasing concentrations (0–200 μ M) of CT-DNA.



Figure 4.9. Absorption titration spectra of fixed concentration (10 μ M) of complex **16** with increasing concentrations (0–200 μ M) of CT-DNA.

The plot of [DNA]/[$\varepsilon_a - \varepsilon_f$] versus [DNA] (where $\varepsilon_a = A_{obs}$ /[compound] and ε_f is the extinction coefficient of the free compound) gives a straight line and the ratio of the slope to the intercept gives the intrinsic binding constant K_b. The values of the intrinsic binding constant for **15** and **16** were found to be 2.02×10^4 M⁻¹ and 2.88×10^4 M⁻¹ respectively (Figure 4.10). These values are moderate in nature with respect to the other ternary copper complexes reported so far.^[29]



Figure 4.10. Plot of [DNA]/(ϵ_{α} - ϵ_{f}) vs. [DNA] for complex 15 (left) and 16 (right).

In order to obtain further information and investigate the interaction mode between the complex and CT-DNA, fluorescence titration experiments were carried out using ethidium bromide (EB) as a spectral probe. EB shows reduced emission intensity in buffer because of significant solvent quenching, however in presence of CT-DNA the emission intensity gets enhanced because of intercalative binding of EB to DNA. In presence of metal complex which competes with EB to bind the DNA a noteworthy reduction of emission intensity are generally observed.^[28]

In our experiment the fluorescence intensity at 607 nm showed significant decreasing trend with increasing concentration of complex **15** and **16** due to the displacement of DNA bound EB by copper complex (Figure 4.11). The K_q value which was obtained from Stern-Volmer plot was found to be 4.18×10^3 M⁻¹ and 3.30×10^4 M⁻¹ for complex **15** and **16**, respectively (Figure 4.12).



Figure 4.11. ETBr displacement assay by change in fluorescent intensity of EB with respect to conc. of complex **15** (left) and **16** (right).



Figure 4.12. Stern-Volmer plot for complex 15 (left) and 16 (right).

This shows a greater interaction for compound **16** over compound **15**. The corresponding K_b values obtained from the Scatchard plot where found to be $1.27 \times 10^4 \text{ M}^{-1}$ and $1.73 \times 10^5 \text{ M}^{-1}$, respectively (Figure 4.13). The values obtained are consistent with other values reported for similar copper complexes.^[30,31]



Figure 4.13. Scatchard plot for the complex 15 (left) and 16 (right).

4.3.6 DFT Studies

In order to understand the DNA binding with the octahedral Cu-complexes (**15** and **16**), the density functional theory (DFT) study was performed to investigate the role of the frontier orbitals towards such binding. The DNA structure is modelled as a deoxy-guanosine monophosphate $(dGMP)^{[32]}$ unit where one of the phosphate

oxygen is methylated. Therefore, the total charge of the dGMP unit is negative. All the calculations are carried out in water solvent using B3LYP level of theory as implemented in the Gaussians 09 package.^[33] The 6-311++G** basis set is used for the main group elements (C, N, O, P, and H) and LANL2DZ ECP basis set is used for Cu.^[34,35] The solvent calculations are carried out using the polarizable continuum model^[36] as implemented in the Gaussian 09.

The optimized Cu complexes (**15**, **16**) and dGMP structures are presented in figure 4.14. The time dependent density functional theory (TDDFT) study^[37-43] was carried out on the Cu complexes to understand their absorption spectrum. The calculated results (Figure 4.15) show that the complex **15** and **16** absorbs at 288.38 nm and 296.31 nm respectively. The oscillator strength and expansion coefficients calculated for these two transitions are 0.057 and 0.68 for complex **15** and 0.031 and 0.36 for complex **16** respectively. The calculated values are very much in agreement with the experimental absorption spectra of the metal complexes. Our molecular orbital study shows that such transition corresponds to the ligand to metal charge transfer (LMCT) transition (Figure 4.15), which agrees well with the experimental findings.



Figure 4.14. Optimized structure of Cu-complexes (**15-16**) and dGMP fragment. Here orange, grey, blue, red, green and pink colour ball denotes the copper, carbon, nitrogen, oxygen, phosphorous and hydrogen atom respectively.



Figure 4.15. The calculated absorption (λ_{max}) corresponds to the LMCT of the Cucomplexes (15 and 16).

The frontier orbitals (Figure 4.16) of the dGMP and the Cu-complexes (**15** and **16**) was studied to understand their role towards the binding. It is well established that the HOMO of the DNA fragments donate electron to the LUMO of the metal complexes.^[44,45] So, the HOMO energy of the dGMP structure was calculated and presented (Figure 4.16) with respect to the LUMO energies of the Cu-complexes (**15-16**). The HOMO orbital energy of the dGMP fragment is -3.66 eV and LUMO energies of the **15** and **16** are -3.26 eV and -3.65 eV respectively. Therefore the HOMO orbital energy of the dGMP fragment (-3.66 eV) is very close to the LUMO energy of **16** (-3.65 eV) than **15** (-3.26 eV). So the electron transfer from dGMP fragment to metal complexes is easier for **16** than **15**. Such finding agrees well with the experimental DNA binding constant of complexes **15** and **16**.



Figure 4.16. The position of the frontier orbitals of dGMP fragment and Cucomplexes (15 and 16).

The complexes (**15** and **16**) bonded to the dGMP fragment (Figure 4.17) was also modelled. Here it was considered, that the dGMP fragment attacks the metal centre *via* the negatively charged O atom of the PO_4^- group as shown in figure 4.17. Both the dGMP-bonded Cu-complexes are relaxed and found to be minima in their potential energy surfaces. It was found that the Cu-dGMP complex **16** is more distorted than complex **15**. The binding energy of the Cu complexes with dGMP fragments was calculated using the following equation.

$$E_{B} = E_{(Cu-dGMP)} - (E_{dGMP} + E_{Cu-complex})$$

The energy of the $E_{(Cu-dGMP)}$ is taken from the energy of the optimized structure of Cu- dGMP complex and the energy of the E_{dGMP} and $E_{Cu-complex}$ are taken from the single point energy of the fragments within the geometry of the Cu-dGMP complex. Hence the single point energy is calculated by deleting the fragments one by one from the optimized geometry of the Cu-dGMP complexes.

The calculated binding energy between the dGMP and complex 15 and 16 are - 0.59 Kcal/mol and -2.51 Kcal/mol respectively. Therefore the binding energy of the complexes (15 and 16) show similar trend as it was found through the frontier

orbitals study, which in turn agrees well with the experimental trend of the DNA binding constant.



Figure 4.17. Optimized geometry of the Cu-dGMP complexes (15 and 16).

As both the complexes have shown considerable DNA binding ability therefore, the DNA cleavage activities for both the Cu tetrazolate complexes 15 and 16 was also explored. Plasmid pBR322 DNA was taken as the substrate in a medium of 50 mM Tris-HCl buffer (pH=7.2) and the DNA cleavage activity was studied under physiological conditions. It is well known that circular plasmid DNA under conduction by electrophoresis splits into several bands. Fastest migration happens for supercoiled form (Form I). If one strand gets cleaved then nicked circular form is produced which moves in a slower manner with respect to supercoiled form (Form II). A linear form (Form III) is obtained when both strands are cleaved and it migrates between Form I and Form II.^[46] Cleavage of supercoiled (SC) DNA (Form I) to nicked circular (NC) DNA (Form II) was observed for both the complexes by varying the concentration of the test solutions. The experiments were carried out in the concentration range of 50 μ M-400 μ M for the complexes 15 and 16 and the results obtained after 1 hour of incubation at a temperature of 40 °C are displayed in figure 4.18 and figure 4.19 respectively. Examination of these figures revealed that in control experiment no measurable DNA cleavage occurred when supercoiled pBR322 plasmid DNA was incubated whereas in presence of copper complex substantial cleavage of DNA was observed even in the absence of any coreagents.



Figure 4.18. Agarose gel electrophoresis cleavage showing cleavage of pBR322 supercoiled DNA by complex **15** after 1 hr of incubation at different concentration; Lane 1: DNA control; Lane 2: DNA+ H_2O_2 ; Lane 3: DNA + $H_2O_2 + 15(50 \ \mu\text{M})$; Lane 4: DNA+ $H_2O_2 + 15(100 \ \mu\text{M})$; Lane 5: DNA + $H_2O_2 + 15(200 \ \mu\text{M})$; Lane 6: DNA+ $H_2O_2 + 15(400 \ \mu\text{M})$; Lane 7: DNA+ $15(50 \ \mu\text{M})$.



Figure 4.19. Agarose gel electrophoresis cleavage showing cleavage of pBR322 supercoiled DNA by complex **16** after 1 hr of incubation at different concentration; Lane 1: DNA control; Lane 2: DNA + H_2O_2 ; Lane 3: DNA + H_2O_2 + **16** (50 μ M); Lane 4: DNA + H_2O_2 + **16** (200 μ M); Lane 5: DNA+ H_2O_2 + **16**(400 μ M); Lane 6: DNA + **16** (50 μ M).

This cleavage is more prominent in the case of complex **16** (Figure 4.19) where almost 91% of the DNA is cleaved to form nicked circular strands even in the absence of oxidizing agent H_2O_2 at 1 μ M concentration. With increasing concentration of copper complexes an enhanced DNA cleavage was observed. This

cleavage may be due to the increased reaction of copper ions with H_2O_2 , thereby producing diffusible hydroxyl radicals or molecular oxygen, both of which are capable of damaging DNA by Fenton-type mechanism.^[47] In the range of 50µM complex concentration, complex **16** possesses a superior DNA cleavage capability than complex **15** where the percentage of nicked circular is 46.2 for complex **15** (Table 4.5) and 94.8 in case of complex **16** (Table 4.6). It was also observed that higher concentration range of metal complexes **15** and **16**, promotes depletion of the supercoiled DNA form, with the consequent formation of linear DNA as a result of double stranded breaks.

Serial **Reaction conditions** Form % No. % Linear % Nicked % Circular Supercoiled 1 **DNA** Control 5.3 94.7 0 2 $DNA + H_2O_2$ 5.5 94.5 0 3 $DNA + H_2O_2 + 15 (50 \ \mu M)$ 0 46.2 53.8 4 $DNA + H_2O_2 + 15 (100 \ \mu M)$ 93.3 6.7 0 5 $DNA + H_2O_2 + 15 (200 \mu M)$ 94.5 0 5.5 $DNA + H_2O_2 + 15 (400 \ \mu M)$ 74.3 0 25.7 6 7 DNA+15 (50 µM) 41.4 0 58.6

 Table 4.5. pBR322 SC DNA cleavage data for complex 15

To explore the cleavage mechanism, DNA cleavage was investigated with different potential radical scavangers to find out the intermediate which are possible reactive oxygen species (ROS) in presence and absence of external cofactors. DMSO and ethanol were used as a hydroxyl radical (HO⁻) scavenger and sodium azide was used as a singlet oxygen ($^{1}O_{2}$) scavenger and SOD was used as a Superoxide radical Scavenger. The results indicate that NaN₃ inhibits more than the other two scavengers to cleave DNA from SC form to NC form (Figure 4.20). This noticeable

inhibition was observed with NaN₃, indicating the involvement of the Cu(II) complexes to cleave the SC form of pBR322 DNA by producing singlet molecular oxygen.^[48] The groove binding ability of complex **16** was studied in the presence of minor groove binder DAPI and major groove binder methyl green. As shown in figure 4.20, in presence of methyl green the band darkness for nicked circular DNA is very less. So it may be concluded that methyl green inhibits the cleavage of SC DNA to NC DNA, suggesting that the Cu complex **16** preferentially interacts through the major groove of the DNA helix.

| Serial No. | Reaction conditions | Form % | | |
|---------------|--|-------------------------|---------------|-------------|
| | | % Nicked Circular | % Supercoiled | % Linear |
| 1 | DNA Control | 8.9 | 91.1 | 0 |
| 2 | $DNA + H_2O_2$ | 7.3 | 92.7 | 0 |
| 3 | $DNA + H_2O_2 + 16 (50 \ \mu M)$ | 94.8 | 0 | 5.2 |
| 4 | DNA+ H_2O_2 + 16 (200 μ M) | 48.9 | 0 | 51.1 |
| 5 | DNA + H_2O_2 + 16 (400 μ M) | 34.5 | 0 | 65.5 |
| 6 | DNA + 16 (50 µM) | 91.4 | 0 | 8.6 |

 Table 4.6: pBR322 SC DNA cleavage data for complex 16



Figure 4.20. Agarose gel electrophoresis cleavage showing cleavage of pBR322 supercoiled DNA by complex **16** after 1 hr of incubation at different concentration; Lane 1: **16** + DNA; Lane 2: **16** + DMSO + DNA; Lane 3: **16** + EtOH + DNA; Lane 4: **16** + NaN₃ + DNA; Lane 5: **16** + SOD+ DNA; Lane 6: **16** + DAPI + DNA; Lane 7: **16** + methyl green + DNA.

4.3.7 Interaction with bovine serum albumin (BSA)

Interactions of bovine serum albumin (BSA) with copper complexes were studied through spectroscopic methods. It is well known that the interaction between metal complex and protein leads to the quenching of the fluorescence of the BSA protein and it may happen because of dynamic or static interaction.^[49] In a dynamic mechanism the fluorescent molecule undergoes change only in the excited state whereas in a static quenching mechanism the interaction takes place at the ground state leading to considerable change in the absorption in UV-vis spectroscopy. The absorption peak for BSA is visible at 278 nm arising from the presence of aromatic amino acids (Trp, Tyr and Phe),^[50] while with addition of both the complexes **15** and **16**, individually the absorption increases with a concomitant slight blue shift accompanied by it (Figure 4.21 and Figure 4.22). This is an indication of the interaction between BSA and the complex at ground state. This leads to

conformational changes in BSA and induces a change in the polarity of the microenvironment around Tyr and Trp residues of BSA.^[51]



Figure 4.21. UV-Vis Absorption titration of BSA (10 μ M) by successive addition of complex 15.



Figure 4.22. UV-Vis Absorption titration of BSA (10 μ M) by successive addition of Complex 16.

To investigate further Trp-emission quenching experiments were carried out using BSA in the presence of increasing amounts of complexes **15** and **16**. A fixed amount of BSA solution was titrated with an increasing concentration of each complex. A continuous decrease of fluorescence intensity for the fluorophore was observed accompanied with a red shift (Figure 4.23 and Figure 4.24). The fluorescence emission was observed at 340 nm upon excitation at 290 nm. To get more insight concerning the interaction between complex and BSA the obtained result was analysed by the Stern-Volmer equation:^[52]

$$\frac{F_0}{F} = 1 + k_q \tau_0[Q] = 1 + K_{SV}[Q]$$

where F_0 and F are the fluorescence intensities in the absence and the presence of a quencher, k_q is the bimolecular quenching rate constant, τ_0 is the average lifetime of fluorophore in the absence of a quencher and [Q] is the concentration of a quencher (metal complexes). In this case a non-linear plot with an increasingly upward trend was obtained (Figure 4.23 and Figure 4.24).



Figure 4.23. Fluorescence quenching of BSA by complex **15**. Stern–Volmer plot is in the inset.

This positive deviation indicates a probable two way quenching by collision and as well as by complex formation with the same quencher.^[52] K_{SV} is the Stern–Volmer

quenching constant in M^{-1} which can be determined by linear regression of F_0/F against [Q]. The calculated value of the Stern–Volmer quenching constant (K_{SV}), the bimolecular quenching rate constant (k_q), and the number of binding sites (n) for both the complexes **15** and **16** are listed in Table 4.7. The values of the quenching constant from Stern–Volmer plot were found to be in the order of 10^{13} .



Figure 4.24. Fluorescence quenching of BSA by complex **16**. Stern–Volmer plot is in the inset.

This value also indicates that there is a larger possibility that the quenching mechanism of fluorescence of BSA by two different complexes is initiated by static quenching process.^[51] The binding constant value (K_a) and the number of binding sites (n) from Scatchard plot were obtained from the equation:

$$\log\left[\frac{F_0 - F}{F}\right] = \log K_a + n \log[Q]$$

The value of n was found to be more than 2 indicating that there might be two probable binding sites available in BSA for all the complexes (Figure 4.25). The value of K_a indicates a very strong interaction between copper complexes and BSA.

| System | $K_{SV}(M^{-1})$ | $K_q (M^{-1} S^{-1})$ | $K_a (M^{-1})$ | n |
|----------------|--------------------|------------------------|-------------------------|-------|
| Complex 15-BSA | 1.95×10^5 | 3.155×10^{13} | 2.1647×10^{10} | 2.158 |
| Complex 16-BSA | 4.62×10^5 | 7.499×10 ¹³ | 6.1573×10 ¹² | 2.623 |

Table 4.7: Table for Stern–Volmer quenching constant, binding constant and binding site



Figure 4.25. Scatchard plot for complex 15 (left) and 16 (right).

4.3.8 Catalytic oxidation of 3,5-DTBC

To explore the possible catecholase like activity of the copper complex 3,5-di-*tert*butylcatechol (3,5-DTBC) was taken as the prospective substrate as the compound shows a low quinone-catechol reduction potential.^[52] The reactions were carried out at 25 °C in presence of air and monitoring was done by UV-vis spectroscopy. The experiments revealed that whereas complex **16** is quite active towards catalytic oxidation of 3,5-DTBC, complex **15** has not shown any such tendency. In case of complex **16** appearance of a new band at 440 nm occurred instantaneously upon addition of catechol which obscures the peak which is supposed to be observed at around 400 nm for the formation of benzoquinone. The peak observed at 440 nm may be attributed to ligand to metal charge transfer band because of the binding of phenoxo moiety to copper ion (Figure 4.26).^[23] However, the reaction was monitored for 90 minutes and a hint of another peak gradually appears at 402 nm with time.

To obtain the rate constant for the catalyst complex traditional initial rate method was employed and on the basis of the Michaelis–Menten approach of enzymatic kinetics, the observed rate versus substrate concentration data were then analyzed. Linearization of Lineweaver–Burk plot (Figure 4.27) provides the value of Michaelis–Menten constant (K_M) and maximum initial rate (V_{max}) which were found to be 0.00367 (M) and 0.0022 M min⁻¹.



Figure 4.26. Spectral pattern of catecholase activity over time for complex **16** after addition of 3,5-DTBC.


Figure 4.27. Michaelis-Menten plot for complex 16. Inset- lineweaver burk plot.

The turnover number values (k_{cat}) obtained was 1.32×10^4 h⁻¹. These results clearly show the ability of complex **16** to effectively catalyse the oxidation of 3,5-DTBC. All the obtained kinetic parameters are presented in Table 4.8.

Table 4.8: Table for various kinetic parameters of catecholase activity

| Complex /Catalyst | Fixed Complex/ Catalyst Conc. (M) | V _{max} (M min ⁻¹) | Std. Error | K _M (M) | Std. Error | K _{cat} / T.O.N (h ⁻¹) |
|----------------------|--|--|------------------------|------------------------------------|---------------|---|
| Complex 16 | 0.00001 | 0.0022 | 5.022×10 ⁻⁴ | 0.00367 | 0.00133 | 1.32×10^4 |

To look further into the probable mechanism, compound **16** was subjected to electrospray ionization mass spectrum in methanol solution which exhibits three assignable peaks at 570.45, 423.36 and 390.32 arising out of $[Cu(phen)_2(pzta)]^+$, $[Cu(phen)_2]^+$ (copper (II) gets reduced to copper (I) at ESI-mass spectroscopy condition) and $[Cu(phen)(pzta)]^+$ (Figure 4.28). To find out the possible complex-substrate intermediate ESI-MS positive spectrum was taken for a mixture of complex **16** and 3,5-DTBC in 1:100 molar ratio and recorded in 5 minutes interval. The spectra obtained was having lot of peaks indicating extensive fragmentation of

the complex, substrate or complex-substrate intermediate. However, the peak at 243.1 is assigned as quinone-sodium aggregate $[(3,5-DTBQ)Na]^+$. Among the remaining peaks the peak at 301.1 could be assigned for {[(phen)₂Cu-(OH)₂- $Cu(phen)_2|^{2+} + Na^+\}$ and 339.2 could be for $[Cu(phen)_2(3,5-DTBCH)(O_2)-H]^{2+}$ (Figure 4.28). Dimeric species similar to $[(phen)_2Cu-(OH)_2-Cu(phen)_2]^{2+}$ are also reported elsewhere as a probable intermediate for catcholase mimicking activity.^[53] Identification of these two probable species helps us to understand and propose a possible mechanism for the catalytic process. To get further insight into the probable mechanism, the qualitative as well as quantitative detection of I_3 band (~353nm) by UV-Vis spectroscopy was carried out, for indication of formation of H₂O₂ during catalytic oxidation procedure. The experiment indicates the oxidation of I to I_2 followed by the generation of I_3 , which was qualitatively detected by UV-Vis spectral study of solution which is the outcome of the reduction of dioxygen to H_2O_2 as reported before (Figure 4.29).^[52] Quantitative analysis of H_2O_2 indicates that 0.85 mol (\approx 1) of H₂O₂ was shown to be produced per mol of 3,5 DTBC along with formation of 1 mol 3,5 DTBQ, which strongly supports the mechanism of reaction involving a two electron reduction process of areal oxygen.



Figure 4.28. Electrospray mass spectrum (ESI-MS positive) of a 1:100 16/3,5-DTBC mixture in methanol, recorded within 10 min of mixing.



Figure 4.29. Characterized peak for I_3 for qualitative detection of H_2O_2 during catalytic oxidation process.

Taking account of all the above experimental results a reaction mechanism is proposed (Scheme 4.2) in which the oxidation process occurs through catecholate bound copper(I) center (A) which gets generated by elimination of tetrazolate ion from the copper center and subsequent coordination by catechol in an unidentate manner keeping the option open for aerial oxygen to get attached to the copper(I) center to reoxidize it to copper (II) superoxide intermediate (B). The next step involves the intramolecular proton transfer process from oxygen atom of catechol moiety to the superoxide oxygen atom to produce a peroxo-intermediate (C) which upon reacting with moisture of the solvent molecule is generating the dihydroxo bridged copper (II) intermediate [(bipy)₂Cu-(OH)₂-Cu(bipy)₂]²⁺ (D) as evidenced by ESI-MS spectroscopy. Intermediate (D) upon further reaction with DTBC regenerates the copper (I) center (A) to complete the catalytic cycle.



Scheme 4.2. Probable catalytic cycle of oxidation of 3,5-DTBC by Cu(II) octahedral complex 16.

4.3.9 DNA binding experiments

The experiments involving the interaction of the complexes with calf thymus (CT) DNA were carried out in Tris-HCl buffer (50 mM Tris-HCl, pH 7.4). A solution of calf thymus DNA dissolved in this buffer gave a ratio of UV absorbance at 260 and 280 nm of about 1.8:1, suggesting the CT-DNA are sufficiently free from protein. The concentration of CT-DNA was estimated from its absorption intensity at 260 nm with a known molar extinction coefficient value (ϵ) of 6600 M⁻¹cm⁻¹ after 1:

100 dilution. The stock solution of CT-DNA in buffer was stored at 4 °C and used within 4 days. Absorption titration experiments were carried out by varying the concentration of CT-DNA from 0-200 µM while keeping the metal complex concentration constant at 10 μ M. Due correction were made for the absorbance of CT-DNA by adding an equal quantity of CT-DNA to both the complex solution and reference solution during titration. Moreover, DNA binding for both the complexes was measured by a special fluorescence spectral technique; ETBr displacement assay from ETBr bound CT-DNA in Tris-HCl buffer at biological pH 7.4. The fluorescence intensities of ethidium bromide (20 μ M) at 605 nm (520 nm excitation) bound to DNA were measured with respect to concentration of the complex (0 to 100 µM). There was no apparent emission of Ethidium bromide in Tris-buffer medium (pH 7.4) because of fluorescence quenching of the free ethidium bromide by the solvent molecules. But in the presence of CT- DNA, ethidium bromide shows appreciably improved emission intensity due to its intercalative binding to DNA. The competitive binding of the copper complexes to CT-DNA resulted the displacement of the bound EtBr which was manifested in decreasing its emission intensity.

Interaction between DNA and complexes: Absorption titration method has been used to monitor the mode of interaction of the complexes with CT-DNA. The intrinsic equilibrium DNA binding constants (K_b) of the complexes with DNA are determined by monitoring the change in the absorption intensity of the charge-transfer spectral bands of the compounds with increasing concentration of the DNA. In the experiment, there is addition of CT-DNA from 0-200 μ M to the aqueous solution of complex **15** (12 μ M) and complex **16** (10 μ M) respectively. An intercalative binding of the complexes to DNA normally leads to hypochromism along with a bathochromic (red) shift of the electronic spectral bands. From the changing tendency of UV spectras and the binding constants, it was concluded that the intercalative binding of complex **16** is more than complex **15**.

4.3.10 BSA Interaction Studies

The protein interaction study was performed by tryptophan fluorescence quenching experiments using BSA in TRIS-HCl buffer (pH ~ 7.4) with excitation at 295 nm and the corresponding emission at 340 nm, using a Fluoromax-4p spectrofluorometer [from Horiba JobinYvon (Model: FM-100)] with a rectangular quartz cuvette of 1 cm path length. Concentrated stock solutions of complexes **15** and **16** were prepared by dissolving them separately in TRIS-HCl buffer and diluted suitably with TRIS-HCl buffer to get the required concentrations. Quenching of the emission intensity of tryptophan residue of BSA (2 ml, 10 μ M) was monitored using complexes **15** and **16** (0-100 μ M) as quenchers with increasing complex concentration. Furthermore, the interaction with proteins was also studied by measuring the increment in the absorption band at 278 nm in UV-Vis spectroscopy through successive addition of 0 to 100 μ M of complex **15** and **16** in 10 μ M protein solution.

4.3.11 <u>Catecholase activity study</u>

In order to study the ability of the Cu(II) complexes to oxidize 3,5-DTBC, 2×10^{-5} M methanolic solutions of complexes **15** and **16** were treated with 2×10^{-3} M (100 equiv) of 3,5-DTBC under aerobic conditions at room temperature. In the UV–vis spectroscopy, where the absorbance of the resultant reaction mixture was plotted with respect to wavelength 300-500 nm, the time-dependent spectral scans for the complex **16** is plotted in Figure 4.26. From the figure, it is apparent that a band ~398 nm is observed to increase with time after the addition of 3,5-DTBC because of the gradual increment of the concentration of 3,5-DTBQ (3,5-DTBQ exhibits $\lambda_{max} \sim 400$ nm in methanol) while no change is noticed in the spectral pattern with complex **15**. These data definitely reveal that complex **16** is an active catalysts for the aerial oxidation of 3,5-DTBC to 3,5-DTBQ, whereas complex **15** turns out to be inactive.

For the complex **16**, the kinetics for the oxidation of the substrate 3,5-DTBC was determined by the initial rate method at 25 °C. The substrate solutions of

concentration ranging from 0.002 to 0.01 mol dm⁻³ were prepared in methanol from a concentrated stock solution. A total of 2 mL of the substrate solution was poured into a 1 cm spectrophotometer quartz cell thermostatted at 25 °C. Then 1 mL of a 0.00002 M methanolic solution of complex **16** was quickly added to it so that the ultimate concentration of the complex became 1×10^{-5} mol dm⁻³. The dependence of the initial rate on the concentration of the substrate was spectrophotometrically monitored at the respective wavelength. Furthermore, the initial rate method display a first-order kinetics on the complex concentration and shows a saturation kinetics at higher substrate concentrations based on Michaelis–Menten model. The binding constant (K_M), maximum velocity (V_{max}), and rate constant for dissociation of the substrates (i.e., turnover number, k_{cat}) were calculated for the complex **16** using the Lineweaver–Burk graph of 1/V versus 1/[S], (Figure 4.27, left), with the equation $1/V = (K_M/V_{max})(1/[S]) + 1/V_{max}$, and all the obtained kinetic parameters are presented in Table 4.8.

Iodometric method was followed to detect the formation of hydrogen peroxide during the catalytic reaction. The reaction mixtures were used as it was prepared in the kinetic experiments. After 45 mins of the reaction, an equal amount of water was added, to prevent further oxidation. Then the formed quinone was extracted three times with dichloromethane and the solution was acidified to pH = 2 with H₂SO₄. To the aqueous layer, 1 mL of 10% KI solution and two drops of 3% ammonium molybdate solution was added. The formation of I₃⁻ was monitored by UV-Visible spectrophotometer due to the formation of the characteristic I₃⁻ band at $\lambda = 353$ nm. ($\epsilon = 14100$ M⁻¹ cm⁻¹).

4.4 <u>Conclusion</u>

In conclusion two new octahedral water soluble copper complexes [Cu{(5pyrazinyl)tetrazolate $_{2}(1,10-phenanthroline)$] (15)and [Cu{(5pyrazinyl)tetrazolate(1,10-phenanthroline)₂](NO₃)_{0.5}(N₃)_{0.5} (16) were synthesized cycloaddition between by [2+3]dipolar copper ligated azide and pyrazinecarbonitrile. Single crystal X-ray diffraction (XRD) results for the complexes **15** and **16** revealed distorted octahedral geometry around the metal ion. Interaction with DNA and BSA binding studies of water soluble copper tetrazolate compounds has been explored. Both the complexes have shown binding ability to CT-DNA where compound 16 was found to be a stronger binder. DFT studies indicated that a lower HOMO-LUMO energy gap between DNA fragment and metal complexes might be the reason behind this kind of stronger interaction. Furthermore both the complexes 15 and 16 have shown DNA nuclease property in presence and absence of additional co-reagents. Inhibitation of DNA cleavage activity in presence of sodium azide indicates the involvement of singlet molecular oxygen in mechanistic pathway. The interaction of compounds 15 and 16 with albumin protein show intense interaction between metal complex and protein with very high fluorescence quenching. The Stern-Volmer quenching constant value obtained was to the tune of 10^{13} M⁻¹ showing that both static and dynamic quenching occurring simultaneously. Apart from the above mentioned interaction with biomolecules complex 16 exhibited promising catecholase like activity with TON value to the order of 10^4 h^{-1} . ESI-MS study indicates the mechanistic pathway of the reaction probably involves a dimeric copper intermediate [(phen)₂Cu-(OH)₂- $Cu(phen)_2$ ²⁺ as cited in various previous reports.

4.5 <u>References</u>

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Chapter-5

Effect on catecholase activity and interaction with biomolecules of metal complexes containing differently tuned 5- substituted ancillary tetrazolato ligands

5.1 Introduction

Tetrazole based metal complexes are gaining importance in coordination chemistry because of the versatile coordination of tetrazole moiety with the ability to induce plethora of metal complexes with diverse structural features.^[1] Researchers have also tried to explore the application of tetrazolato complexes in various fields like gas absorption, catalysis, luminescence, magnetic properties etc.^[2] However, application of tetrazole based complexes in the field of bioinspired catalysis remained almost unexplored though there are lot of potentials. The literature reveals that type-3 dicopper enzyme catechol oxidase process atmospheric dioxygen to achieve selective oxidation of catechols to orthoquinones.^[3] It is interesting to note that the catecholase like activities of the dinuclear tetrazole based copper and nickel complexes have never been reported. In the continuous endeavor to generate tetrazole based complexes through 1,3-dipolar cycloaddition of metal ligated azides and organonitriles^[4] in much energy efficient approach and more controlled manner and to explore various bioinspired catalytic activities of the synthesized complexes. Herein, the synthesis, characterization and structure has been reported for one mononuclear and three dinuclear di-tetrazolato bridged nickel and copper complexes with the general formula $[ML^2(N_4CR)]$ (17) and $[M_2(L^2)_2(N_4CR)_2]$ (18-20) $[HL^2 = 3-(2-dimethylamino-ethylimino)-1-phenyl$ butan-1-one; $R = C_6H_5$ [M= Ni] (17), 2-NCC₆H₄ [M= Ni] (18), 2-NCC₆H₄ [M = Cu] (19) and C_6H_5 [M=Cu] (20).

It is reported that nickel and copper based binuclear model complexes have shown various structural factors which may affect their catalytic activity namely the metal-metal distance, type of exogenous bridging ligand, coordination geometry around the metal ion, and flexibility of the ligand used.^[5] In this particular work, the opportunity to use 5-substituted tetrazoles has been taken as a co/bridgingligand while keeping tridentate Schiff bases containing N,N,O donor ligand as the back bone as similar ligands have been widely used to generate nickel (II) and copper (II) complexes mimicking the active site of catechol oxidase. Furthermore tuning of the substitution at 5-position of the tetrazole and choice of metal ion provides the control to synthesize more active metal complexes towards catecholase like activity.

Apart from that, development of DNA binding ability of transition metal complexes has been an active area of research due to their potential applications as metallo-drugs, tools for molecular biology and others.^[6] However, there are not many reports where metal tetrazolato complexes have been studied for such kind of interaction.^[7] Furthermore in the context of therapeutic applications of a potential drug, it is relevant to investigate the protein binding levels of the drug, especially to serum albumins, as these proteins may influence the metallo-pharmaceutical relationships.^[8] Bovine serum albumin (BSA) has been widely used as a model protein to study drug interactions due to its structural resemblance to human serum albumin (HSA). Similar study with metal tetrazolato complexes with CT-DNA and bovine serum albumin (BSA) are also explored and it was found that some of the complexes are active towards both types of biomolecules.

5.2 Experimental section

5.2.1 Materials and physical measurements

Reagents and Materials: Nickel chloride, copper (II) acetate, phenyl acetone, *N*,*N*-Dimethylethylenediamine and sodium azide were purchased from Merck-India chemical company. Calf thymus DNA, bovine serum albumin (BSA, fraction V powder), ethidium bromide (EB) were purchased from SRL (India). 3,5-di-*tert*-butylcatechol (3,5-DTBC) was purchased from Sigma. Tris(hydroxymethyl) aminomethane-hydrochloride (Tris-HCl) buffer was prepared using distilled water.

Methods and Instrumentation: Infrared spectra (4000–500 cm⁻¹) were recorded with a BRUKER TENSOR 27 instrument in KBr pellets. Mass spectrometric analyses were carried out on Bruker-Daltonics, microTOF-Q II mass spectrometer. Microwave irradiation experiments were executed in focused microwave CEM discover reactor at 300W and the reaction tube used was with 10 mL capacity and 13mm internal diameter. Elemental analyses were carried out with a ThermoFlash 2000 elemental analyzer. Spectrophotometric measurements were performed on a Varian UV-Vis spectrophotometer (Model: Cary100) (for absorption) and a Fluoromax-4p spectrofluorometer from Horiba JobinYvon (Model: FM-100) (for emission) using a quartz cuvette with path length of 1 cm.

Caution! Azide and tetrazolato compounds are potentially explosive. Only a small amount of material should be prepared and handled with care.

X-ray crystallography: Single crystal X-ray structural studies of all the compounds **17-20** were performed on a CCD Agilent Technologies (Oxford Diffraction) SUPER NOVA diffractometer. Data for the complexes **17** and **18** were collected at 150(2) K using graphite-monochromated Mo K α radiation ($\lambda_{\alpha} = 0.71073$ Å) whereas for the complexes **19** and **20** it was collected by Cu K α radiation (Table 5.1). The strategy for the data collection was evaluated by using the CrysAlisPro CCD software. The data were collected by the standard 'phi-omega scan techniques and were scaled and reduced using CrysAlisPro RED software. The structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares with SHELXL-97, refining on $F^{2,[10]}$

The positions of all the atoms were obtained by direct methods. All non-hydrogen atoms were refined anisotropically. The remaining hydrogen atoms were placed in geometrically constrained positions and refined with isotropic temperature factors, generally $1.2U_{eq}$ of their parent atoms. The crystal and refinement data are summarized in Table 5.1, and selected bond distances and bond angles for **17-20** are shown in Table 5.2-Table 5.5.

| | 17 | 18 | 19 | 20 |
|---|----------------------|-------------------------------|-----------------------------|-----------------------------|
| | | | | |
| Empirical formula | $C_{21}H_{24}N_6ONi$ | $C_{44}H_{46}N_{14}O_2N_{12}$ | $C_{44}H_{46}N_{14}O_2Cu_2$ | $C_{56}H_{58}N_{14}O_2Cu_2$ |
| Formula weight | 435.17 | 920.33 | 930.02 | 1086.24 |
| Wavelength (Å) | 0.71073 | 0.71073 | 1.5418 | 1.5418 |
| Temperature (K) | 150(2) | 150(2) | 150(2) | 150(2) |
| Crystal system | Monoclinic | Triclinic | Triclinic | Triclinic |
| Colour and shape | Green block | Blue block | Green block | Green Block |
| Space group | $P 2_1/c$ | <i>P</i> -1 | <i>P</i> -1 | <i>P</i> -1 |
| a/Å | 12.8261(3) | 8.6466(6) | 8.7471(5) | 9.1958(10) |
| b/Å | 10.8109(2) | 10.5605(6) | 10.5465(7) | 10.5453(16) |
| c/Å | 15.0517(3) | 12.2048(8) | 12.3693(9) | 13.8981(14) |
| α/degree | 90.00 | 93.627(5) | 86.933(5) | 95.257(10) |
| β/degree | 101.962(2) | 109.579(6) | 69.718(6) | 90.501(8) |
| γ/degree | 90.00 | 90.210(5) | 89.880(5) | 90.198(10) |
| Volume(Å ³) | 2041.77(7) | 1047.54(12) | 1068.64(13) | 1342.0(3) |
| Ζ | 4 | 2 | 2 | 1 |
| $D_{\rm calcd}/{\rm mg}~{\rm m}^{-3}$ | 1.416 | 1.459 | 1.445 | 1.344 |
| μ (Mo K α)/mm ⁻¹ | 0.975 | 0.956 | 1.680 | 1.419 |
| F(000) | 912 | 480 | 482 | 566 |
| Crystal size/mm | 0.33×0.25×0.18 | 0.09×0.06×0.04 | 0.33×0.21×0.18 | 0.33×0.23×0.18 |
| θ range(°) | 2.90 to 25.00 | 3.12 to 24.99 | 3.81 to 71.87 | 3.19 to 73.42 |
| Limiting indices | $-15 \le h \le 14$ | -8 < h < 10 | -10 < h < 8 | -11 < h < 8 |
| 6 | $-12 \le k \le 12$ | -12 < k < 12 | -12 < k < 13 | $-12 \le k \le 12$ |
| | -17 < 1 < 17 | -14 < 1 < 14 | -14 < 1 < 15 | -16<1<17 |
| | | | | |
| Total/ unique no. | 16365 / 3579 | 7657 / 3685 | 6818 / 4089 | 8929 / 5156 |
| of reflns. | | | | |
| Rint | 0.0362 | 0.0411 | 0.0165 | 0.0393 |
| Data/restr./params | 3579 / 0 / 265 | 3685 / 0 / 283 | 4089 / 0 / 283 | 5156/0/337 |
| $.GOF(F^2)$ | 1.067 | 1.041 | 1.050 | 1.008 |
| R1. wR2 | 0.0314, 0.0734 | 0.0498 0.1247 | 0.0413 0.1090 | 0.0534 0.1496 |
| R1. wR2 | 0.0416, 0.0788 | 0.0627, 0.1354 | 0.0490. 0.1155 | 0.0691, 0.1712 |
| (all data) | | 0.0027, 0.1001 | | 0.00071, 0.1712 |
| Peak and hole | 0.196 and -0.208 | 1 123 and -0 403 | 0 721 and -0 274 | 0 515 and -0 3777 |
| $(e Å^{-3n})$ | | 1.125 und 0.105 | 0.721 und 0.274 | 0.010 und 0.0777 |

Table 5.1: Crystal data and structure refinement of complexes 17-20.

5.2.2 Synthesis

5.2.2.1[NiL²(5-Phenyltetrazolato)](17)

A mixture of [Ni(L²)(N₃)] (0.12 g, 0.36 mmol), 2 mL of benzonitrile and 3 mL of DMF were added to a cylindrical pyrex tube. The system was placed in the focused microwave reactor. The reaction mixture was left under irradiation for 4 h at 130 °C. The solvent was then removed *in vacuo* and the resulting residue was treated with diethyl ether to obtain a green powder which was then recrystallized from

methanol/ether mixture. Yield 79%. Anal. Calc. for $C_{21}H_{24}NiN_6O$ (435.17): C 57.90; H 5.51; N 19.30%. Found: C 58.07; H 5.58; N 19.76%. IR (cm⁻¹, KBr): v(C=N) 1595, v(C=C) 1569, 1510, 1487, 1445, v(C-H) 1011, 733. MS (ESI): m/z = 435.5 [NiL(5-phenyltetrazole)]⁺, Melting Point > 300 °C.

5.2.2.2 [Ni₂ L^2_2 {5-(2-cyanophenyl)-tetrazolato}₂] (18)

A solution of $[Ni(L^2)(N_3)]$ (0.12 g, 0.36 mmol) complex and 0.26 g (2 mmol) of 1,2-dicyanobenzene in 5 mL of DMF was taken in a cylindrical pyrex tube and was irradiated in microwave reactor for 4 h at 130 °C. The solvent was then removed *in vacuo* and the resulting greenish residue was washed several times with diethyl ether to obtain a green powder which was then recrystallized from chloroform/hexane mixture to give blue crystals. Yield 82%. Anal. Calc. for C₄₄H₄₆Ni₂N₁₄O₂ (920.33): C 57.24; H 5.20; N 21.24 %. Found: C 56.89; H 5.34; N 21.04%. IR (cm⁻¹, KBr): v(C=N) 2225, v(C=N) 1652, 1594, v(C=C) 1571, 1459. MS (ESI): m/z = 460.5 [NiL{5-(2-cyanophenyltetrazole)}]⁺, melting point > 300 °C.

5.2.2.3 [$Cu_2L_2^2$ {5-(2-cyanophenyl)-tetrazolato}₂] (19)

A solution of $[Cu(L^2)(N_3)]$ (0.12 g, 0.36 mmol) complex and 0.26 g (2 mmol) of 1,2-dicyanobenzene in 5 mL of DMF was taken in a cylindrical pyrex tube and was irradiated for 4 h at 130 °C. The solvent was then removed *in vacuo* and the resulting greenish residue was washed several times with diethyl ether to obtain a green powder which was then recrystallized from chloroform/hexane mixture. Yield 81%. Anal. Calc. for C₄₄H₄₆Cu₂N₁₄O₂ (930.02): C 56.77; H 4.94; N 21.07 %. Found: C 55.31; H 4.34; N 20.49%. IR (cm⁻¹, KBr): v(C=N) 2224, v(C=N) 1598, v(C=C) 1461, 1296. MS (ESI): m/z = 953.23 [Cu₂L₂{5-(2-cyanophenyl)-tetrazolato}₂ + Na]⁺, melting point > 300 °C.

5.2.2.4 [Cu₂L²₂{5-phenyltetrazolato}₂]·C₆H₅CN (20)

A solution of $[Cu(L^2)(N_3)]$ (0.12 g, 0.36 mmol) complex and 2 mL of benzonitrile and 3 mL of DMF was taken in a cylindrical pyrex tube and was irradiated for 4 h at 130 °C. The solvent was then removed *in vacuo* and the resulting greenish residue was washed several times with diethyl ether to obtain a green powder which was then recrystallized from methanol/ether mixture. Yield 80%. Anal. Calc. for C₄₉H₅₃Cu₂N₁₃O₂ (983.12): C 59.80; H 5.39; N 18.51%. Found: C 58.91; H 5.34; N 18.49%. IR (cm⁻¹, KBr): v(C=N) 2224, v(C=N) 1658, 1595, v(C=C) 1461, 1296. MS (ESI): m/z = 903.2 [Cu₂L₂{5-phenyltetrazolato}₂ + Na]⁺, Melting point : no sharp melting point was observed but starts to melt around 200 °C.

5.2.3 Catechol oxidation studies

To study the ability of the complexes **17**, **18** and **19** to oxidize 3,5-DTBC, 2×10^{-5} M methanolic solutions of complexes **17**, **18** and **19** were treated with 2×10^{-3} M (100 equiv) of 3,5-DTBC under aerobic conditions at room temperature. In the UV–vis spectroscopy, the absorbance of the resultant reaction mixture was plotted with respect to the wavelength of 300-500 nm. The kinetics for the oxidation of the substrate 3,5-DTBC was determined by the initial rate method at 25 °C for the complexes **17-19**. The substrate solutions of concentration ranging from 0.002 to 0.01 mol dm⁻³ were prepared in methanol from a concentrated stock solution. A total of 2 mL of the substrate solution was poured into a 1 cm spectrophotometer quartz cell thermostatted at 25 °C. Then 1 mL of a 0.00002 M methanolic solution of complexes **17-19** were quickly added to it so that the ultimate concentration of the concentration of the substrate was spectrophotometrically monitored at the respective wavelength.

5.2.4 <u>Detection of hydrogen peroxide in the catalytic reactions</u>

The reaction between ferrous sulphate and 1,10-phenanthroline which formed a red-orange coloured Fe^{+2} -tri-phenanthroline complex that absorbed at 509 nm was followed to detect the formation of hydrogen peroxide during the catalytic reaction. A 1:3 ratio between Fe^{+2} and 1,10-phenanthroline was prepared for the experiment. When a 10^{-3} (M) solution of each individual complexes **17-19** was mixed with FeSO₄ and 1,10-phenanthroline, there is formation of an absorption band at 509 nm

in the UV visible spectrum. With the addition of an equal amount of DTBC to the above solution, the intensity of the band at 509 nm decreases after 10 mins. When the reaction mixture was kept for 25 min, there was no absorption band at 509 nm which clearly indicates that the entire ferrous ion has been converted to ferric ion due to the formation of H_2O_2 in the reaction mixture.

5.2.5 DNA binding experiments

The experiments involving the interaction of the complexes 17 and 19 with calf thymus (CT) DNA were carried out in EtOH/Tris-HCl buffer, 1:1, v/v. A solution of calf thymus DNA dissolved in 50 mM Tris-HCl buffer (pH 7.4) gave a ratio of UV absorbance at 260 and 280 nm of about 1.8 : 1, suggesting the CT-DNA are sufficiently free from protein. The concentration of CT-DNA was estimated from its absorption intensity at 260 nm with a known molar extinction coefficient value (ϵ) of 6600 M⁻¹cm⁻¹ after 1:100 dilution. The stock solution of CT-DNA in buffer was stored at 4 °C and used within 4 days. Absorption titration experiments were carried out by varying the concentration of CT-DNA from 0-200 µM while keeping the metal complex concentration constant at 10 µM. Due correction were made for the absorbance of CT-DNA by adding an equal quantity of CT-DNA to both the complex solution and reference solution during titration. Moreover, DNA binding for both the complexes was measured by the fluorescence spectral technique; ETBr displacement assay from ETBr bound CT-DNA in Tris-HCl buffer at biological pH 7.4. The fluorescence intensities of ethidium bromide (20 μ M) at 606 nm (520 nm excitation) bound to DNA were measured with respect to concentration of the complex (0 to 100 μ M). There was no apparent emission of Ethidium bromide in Tris-buffer medium (pH 7.4) because of fluorescence quenching of the free ethidium bromide by the solvent molecules. But in the presence of CT- DNA, ethidium bromide shows appreciably improved emission intensity due to its intercalative binding to DNA. The competitive binding of the nickel and copper complexes to CT-DNA resulted the displacement of the bound EtBr which was evident in decreasing its emission intensity.

5.2.6 Interaction between DNA and complexes

Absorption titration method has been used to monitor the method of interaction of the complexes with CT-DNA. The intrinsic equilibrium DNA binding constants (K_b) of the complexes with DNA are determined by monitoring the change in the absorption intensity of the charge-transfer spectral bands of the compounds with increasing concentration of the DNA. In the experiment, there is addition of CT-DNA from 0-200 μ M to the aqueous solution of complex **17** (150 μ M) and complex **19** (150 μ M) respectively. An intercalative binding of the complexes to DNA normally leads to hypochromism along with a bathochromic (red) shift of the electronic spectral bands.

5.2.7 <u>BSA interaction studies</u>

The protein interaction study was performed by tryptophan fluorescence quenching experiments using BSA in TRIS-HCl buffer (pH ~ 7.4) with excitation at 290 nm and the corresponding emission at 340 nm, using a Fluoromax-4p spectrofluorometer [from Horiba JobinYvon (Model: FM-100)] with a rectangular quartz cuvette of 1 cm path length. Concentrated stock solutions of complexes **17** and **19** were prepared by dissolving them separately in EtOH/Tris-HCl buffer, 1:1, v/v and diluted them suitably with TRIS-HCl buffer to get the required concentrations. Quenching of the emission intensity of tryptophan residue of BSA (2 mL, 10µM) was monitored using complexes **17** and **19** (0-100 µM) as quenchers with increasing complex concentration. Furthermore, the interaction with proteins was also studied by measuring the increment in the absorption band at 278 nm in UV-Vis spectroscopy through successive addition of 0 to 100 µM of complex **17** and **19** in 10 µM protein solution.

5.3 <u>Results and discussion</u>

5.3.1 Synthesis and isolation of metal tetrazolate complexes

The ligand HL^2 was prepared according to the reported method^[11] by refluxing 1phenyl-1,3-butanedione (0.81 g, 5 mmol) and N,N-Dimethylethylenediamine (0.54 mL, 5 mmol) in 30 mL of methanol for half an hour. The resulting mixture gave a yellow solution containing the tridentate ligand (HL^2). This methanolic solution was evaporated to dryness to obtain a yellow oil which was used without further purification. Complex [$ML^2(N_3)$] [M = Cu or Ni] were also prepared as per reported methods.^[11,12] All the tetrazolato complexes were synthesized by microwave irradiation of a solution of precursor metal azide complex [$ML^2(N_3)$], where M = Ni (for complex **17** and **18**), M = Cu (for complex **19** and **20**), with appropriate organonitriles (Scheme 5.1).



Scheme 5.1. Schematic representation for the synthesis of complexes $[NiL^2(5-phenyltetrazolato)]$ (17), $[Ni_2L^2_2\{5-(2-cyanophenyl)-tetrazolato\}_2]$ (18), $[Cu_2L^2_2\{5-(2-cyanophenyl)-tetrazolato\}_2]$ (19) and $[Cu_2L^2_2\{5-phenyltetrazolato\}_2] \cdot C_6H_5CN$ (20).

In all the cases DMF was used as solvent. The obtained compounds were isolated as green powders which have been further recrystallized from suitable solvents to give $[NiL^{2}(5-phenyltetrazolato)]$ (17), $[Ni_{2}L^{2}_{2}\{5-(2-cyanophenyl)-tetrazolato\}_{2}]$ (18), $[Cu_{2}L^{2}_{2}\{5-(2-cyanophenyl)-tetrazolato\}_{2}]$ (19) and $[Cu_{2}L^{2}_{2}\{5-phenyltetrazolato\}_{2}]\cdot C_{6}H_{5}CN$ (20). All the complexes (17, 18, 19 and 20) have been characterized by elemental analyses, IR, ESI-MS spectroscopy and single crystal X-ray crystallography.

About two hours of irradiation were found to be enough at 130 °C for the completion of reactions as indicated by the disappearance of azide stretching band at around 2043 cm⁻¹. Compounds **17** and **20** are recrystallised from methanol/ether mixture and compounds **18** and **19** are recrystallised from chloroform/hexane. All the compounds have shown a new band at around 1600-1660 cm⁻¹ in IR spectra indicating the formation of tetrazolato moiety.^[13,14] Apart from that compounds **18** and **19** have shown moderate band in the range of 2220 cm⁻¹ to 2230 cm⁻¹ representing the presence of unreacted nitrile groups. The ESI-MS spectra of complex **17** (Figure 5.1) show molecular ion peak of [NiL²(5-phenyltetrazole)]⁺ at 435.5; whereas compound **18** (Figure 5.2) has shown the fragmented peak of [NiL²{5-(2-cyanophenyltetrazole)]]⁺ at 460.1. The ESI-MS spectrums for the complex **19** and **20** (Figure 5.3 and Figure 5.4) shows the main peak at 953.2 and at 903.2 which corresponds to the molecular ion peak of [$\{Cu_2L^2_2\{5-(2-cyanophenyl)-tetrazolato\}_2\} + Na$]⁺ and [$Cu_2L^2_2\{5-phenyltetrazolato\}_2 + Na$]⁺ respectively.



Figure 5.1. The ESI-MS Spectrum of complex 17.



Figure 5.2. The ESI-MS spectrum of complex 18.



Figure 5.3: The ESI-MS spectra of complex 19.



Figure 5.4. The ESI-MS spectrum of complex 20.

5.3.2 Crystal structure

5.3.2.1 <u>Crystal structures of [NiL²(5-Phenyltetrazolato)]</u> (17), [Ni₂L²₂{5-(2cyanophenyl)-tetrazolato]₂] (18), [Cu₂L²₂{5-(2-cyanophenyl)-tetrazolato]₂] (19) and [Cu₂L²₂{5-phenyltetrazolato}₂]·C₆H₅CN (20): While complex **17** has shown a mononuclear square-planar structure, all the other three structures are found to be centrosymmetric dimers; either of nickel (**18**) or of copper ions (**19** and **20**). The geometry for compound **18-20** surrounding the metal ions are distorted square pyramidal in nature with penta-coordinated metal ion through N/O donor sets. Selected bond distances and bond angles for **17-20** are shown in Table 5.2-Table 5.5.

Complex 17 is monomeric in nature and crystallizes in the monoclinic space group $P2_1/c$ (Table 5.1) with square planar environment surrounding the nickel ion. The ligand HL² acting in tridentate fashion while one tetrazolato group completes the square base (Figure 5.5). The tetrazolato moiety has been found to get attached to the nickel center through N^2 -atom. The bond lengths between Ni atom and N/O-donor centers are within the range of 1.828 to 1.944 Å (Table 5.2), quite similar to those which have been reported earlier.^[15] The average co-ordination bond angle around the Ni center of square planar geometry is around 91.42° (Table 5.2).



Figure 5.5. Molecular structure of $[NiL^2(5-phenyltetrazolato)]$ (17) with the atomic numbering scheme.

Single-crystal X-ray studies revealed that 18 crystallizes in the triclinic space group P-1(Table 5.1). The molecular structure of 18 is shown in figure 5.6 together with its atomic-numbering scheme. The bond distances and angles are provided in Table 5.3. The nickel atoms are five-coordinated where the ligand provides three coordinating centers and two tetrazolato ions are found to be bridging between two

nickel centers. The distortion of the coordination geometry of penta-coordinated system can be calculated by the τ_5 value, a reference to describe the degree of distortion for square-pyramid and trigonal-bipyramid [square pyramid, $\tau_5 = 0$; trigonal-bipyramid, $\tau_5 = 1$; $\tau = (\beta - \alpha)/60^\circ$, α and β are the two largest angles around the central atom]. The τ_5 value for complex **18** is 0.28, indicating a distorted square-pyramidal geometry adopted by nickel center where the axial positions is occupied by the nitrogen atom N(5) of one tetrazolato ion with a distance of 2.035 Å.



Figure 5.6. Molecular structure of $[Ni_2L_2^2{5-(2-cyanophenyl)-tetrazolato}_2]$ (18) with the atomic numbering scheme.

Tridentate Schiff-base ligand and another N-atom form tetrazolato ligand completes the square base. Interestingly, the free nitrile group in 5-substituted phenyl ring of tetrazolato ion adjust itself in an axial position with respect to the nickel ion at a distance of 5.09 Å and with N(5)-Ni(1)-N(7) angle of 156.5° giving an impression of some kind of interaction between free nitrile group and nickel center. The Ni…Ni separation distance was found to be 4.016 Å and in the crystal lattice, the di-nickel units are interconnected connected by hydrogen bonds, namely

C22-N(7)···H(8B) (Table 5.3), giving rise to a 1-D polymeric structure (Figure 5.7).

This is interesting to note that although 5-phenyl tetrazolato ion can stabilize the square planar geometry in complex **17**, however, owing to the electron withdrawing nature of nitrile group, 5-(2-cyanophenyl)-tetrazolato ion act as a weaker ligand and it fails to create the necessary ligand field splitting to stabilize the square planar system with nickel center and two such square-planar system takes the advantage of bridging nature of tetrazolato ion to stabilize them as pentacoordinated dimeric moiety. This observation is also explored in DFT section (*vide infra*).



Figure 5.7. 1-D polymeric structure for complex 18.

The crystal structures of **19** and **20** (Table 5.1) are shown in Figure 5.8 and 5.9, respectively together with the atom numbering scheme. The copper ions are found to be forming dimeric compounds with pentacoordinated geometry surrounding the metal center, which is expected as copper(II) is comparatively resistive to form square planar complexes because of its ninth electron going to the higher energy orbitals. The τ_5 values are found to be 0.28 and 0.3, respectively. In an analogous manner to compound **18** the tridentate Schiff-base ligand coordinates to the copper centers in equatorial plane whereas two tetrazolato ligand make bridge between the

copper centers through N^2N^3 mode. One of the tetrazolato nitrogen coordinates to the basal plane whereas another nitrogen from other tetrazole ligand coordinates axially to fulfil the square pyramidal geometry. Like compound **18**, complex **19** also show the positioning of free nitrile group in an axial mode with respect to copper ion and the Cu(1)-N(7) distance was found to be 5.08 Å.



Figure 5.8. Molecular structure of $[Cu_2L_2^2{5-(2-cyanophenyl)-tetrazolato}_2]$ (19) with the atomic numbering scheme.



Figure 5.9. Molecular structure of $[Cu_2L_2^2{5-phenyltetrazolato}_2] \cdot C_6H_5CN$ (20) with the atomic numbering scheme.

Interestingly for both the compounds **18** and **19** the substituted phenyl ring is found to be almost coplanar with tetrazolato moiety. However, for compound **20** it makes a dihedral angle of 28.95°. Compound **19** has been also found to be forming 1D chain with the help of hydrogen bonds between free nitriles and C-H proton of ligand L^2 , along *b*-axis (C5-H5...N7) (Figure 5.10).



Figure 5.10. 1-D chain polymeric structure for complex 19.

In complex **20** there is one benzonitrile molecule present as solvent of crystallization. The presence of this molecule helps compound **20** to grow as hydrogen bonded one dimensional chain along *a*-axis through C21-H21····C24 and C23-H23····N4. Two such adjacent molecules are further interconnected through C1-H1A····C18 and C18-H18····C13. These 1D chains are found to be further interconnected through C6-H6B····N6 along *b*-axis to afford a 2D-hydrogen bonded network in *ab*-plane (Figure 5.11). The Cu····Cu separations are found to be 4.20 Å and 4.25 Å, respectively for compounds **19** and **20**. Selected bond distances and angles for complexes **19** and **20** are given in Table 5.4 and 5.5, respectively.



Figure 5.11. 1D chains along *b*-axis to afford a 2D-hydrogen bonded network for complex **20**.

Table 5.2: Selected bond lengths (Å) and bond angles (°) for complex 17

| Ni(1)-O(1) | 1.8282(15) | O(1)-Ni(1)-N(2) | 95.11(8) |
|------------|------------|-----------------|------------|
| Ni(1)-N(2) | 1.8597(19) | O(1)-Ni(1)-N(3) | 86.24(7) |
| Ni(1)-N(3) | 1.8997(19) | N(2)-Ni(1)-N(3) | 178.62(8) |
| Ni(1)-N(1) | 1.9436(19) | O(1)-Ni(1)-N(1) | 176.02(8) |
| N(3)-N(5) | 1.318(3) | N(2)-Ni(1)-N(1) | 87.21(8) |
| N(3)-N(4) | 1.340(3) | N(3)-Ni(1)-N(1) | 91.42(8) |
| N(5)-N(6) | 1.336(3) | C(8)-O(1)-Ni(1) | 126.91(15) |
| N(6)-C(15) | 1.339(3) | C(1)-N(1)-C(2) | 108.9(2) |
| N(5)-N(6) | 1.332(3) | C(1)-N(1)-Ni(1) | 115.71(16) |

| N(1)-C(1) | 1.488(3) | C(2)-N(1)-Ni(1) | 107.72(16) |
|-----------|----------|-----------------|------------|
| N(1)-C(2) | 1.490(3) | C(3)-N(1)-Ni(1) | 106.03(15) |
| N(1)-C(3) | 1.492(3) | C(5)-N(2)-Ni(1) | 126.30(16) |
| N(2)-C(4) | 1.475(3) | C(4)-N(2)-Ni(1) | 113.83(15) |

Table 5.3: Selected bond lengths (Å) and bond angles (°) for complex 18

| Ni(1)-O(1) | 1.964(3) | O(1)-Ni(1)-N(2) | 92.04(11) |
|------------|----------|-----------------|------------|
| Ni(1)-N(1) | 2.148(3) | O(1)-Ni(1)-N(5) | 94.48(12) |
| Ni(1)-N(5) | 2.031(3) | N(2)-Ni(1)-N(5) | 109.64(12) |
| Ni(1)-N(3) | 2.064(3) | O(1)-Ni(1)-N(3) | 89.19(11) |
| Ni(1)-N(2) | 1.978(3) | N(2)-Ni(1)-N(3) | 152.52(13) |
| N(1)-C(1) | 1.494(5) | N(5)-Ni(1)-N(3) | 97.62(12) |
| N(2)-C(3) | 1.314(5) | O(1)-Ni(1)-N(1) | 169.57(11) |
| N(2)-C(2) | 1.469(5) | N(2)-Ni(1)-N(1) | 82.59(12) |
| O(1)-C(6) | 1.292(4) | N(5)-Ni(1)-N(1) | 95.74(13) |
| N(3)-N(4) | 1.333(4) | N(3)-Ni(1)-N(1) | 91.49(12) |

 Table 5.4: Selected bond lengths (Å) and bond angles (°) for complex 19

| Cu(1)-O(1) | 1.922(18) | O(1)-Cu(1)-N(2) | 92.82(8) |
|------------|-----------|-----------------|-----------|
| Cu(1)-N(2) | 1.949(2) | O(1)-Cu(1)-N(3) | 89.14(8) |
| Cu(1)-N(3) | 2.027(2) | N(2)-Cu(1)-N(3) | 156.60(9) |
| Cu(1)-N(1) | 2.083(2) | O(1)-Cu(1)-N(1) | 174.14(9) |
| | | | |

| Cu(1)-N(5)#1 | 2.344(2) | N(2)-Cu(1)-N(1) | 83.61(9) |
|--------------|----------|-------------------------|------------|
| O(1) C(6) | 1 202(2) | $N(2) \subset (1) N(1)$ | 02 20(0) |
| U(1)-C(6) | 1.292(3) | N(3)-Cu(1)-N(1) | 92.30(9) |
| N(3)-N(5) | 1.307(3) | O(1)-Cu(1)-N(5)#1 | 91.08(8) |
| | | | |
| N(3)-N(4) | 1.336(3) | C(6)-O(1)-Cu(1) | 126.38(17) |

Table 5.5: Selected bond lengths (Å) and bond angles (°) for complex 20

| Cu(1)-O(1) | 1.921(2) | O(1)-Cu(1)-N(2) | 93.27(10) |
|-------------|----------|-----------------|------------|
| Cu(1)-N(2) | 1.950(2) | O(1)-Cu(1)-N(7) | 87.86(10) |
| Cu(1)-N(7) | 2.034(2) | N(2)-Cu(1)-N(7) | 157.04(12) |
| Cu(1)-N(1) | 2.071(3) | O(1)-Cu(1)-N(1) | 173.74(10) |
| Cu(1)-N(3) | 2.316(3) | N(2)-Cu(1)-N(1) | 83.75(10) |
| N(1)-C(1) | 1.471(4) | N(7)-Cu(1)-N(1) | 92.74(11) |
| N(1)-C(3) | 1.478(5) | O(1)-Cu(1)-N(3) | 93.06(10) |
| N(1)-C(2) | 1.487(5) | N(2)-Cu(1)-N(3) | 107.67(10) |
| N(2)-C(5) | 1.304(4) | N(7)-Cu(1)-N(3) | 95.15(10) |
| N(2)-C(4) | 1.468(4) | N(1)-Cu(1)-N(3) | 93.08(11) |
| N(3)-N(7)#1 | 1.318(3) | C(1)-N(1)-Cu(1) | 114.6(2) |
| N(3)-N(4) | 1.341(4) | C(3)-N(1)-Cu(1) | 103.7(2) |

5.3.3 <u>UV-visible spectroscopy</u>

The electronic spectra of these four compounds were recorded in methanolic solution. Compound **17** shows a band at 453 nm which correspond to the d-d transition in square planer Ni(II) complex along with one metal to ligand charge

transfer band at 350 nm.^[11] The electronic spectrum for a five coordinated Ni(II) compound **18** with a square pyramidal geometry exhibits absorption bands near 455 nm which corresponds to spin allowed *d*-*d* transitions.^[11] Moreover compound **18** also exhibits weak band centered at 918 nm which can be attributed to another spin allowed *d*-*d* transitions ${}^{3}A_{2g} \rightarrow {}^{3}T_{1g}(F)$.^[16] Furthermore, the electronic spectra for complexes **19** and **20** exhibits single absorption bands at 590 and 668 nm respectively due to *d*-*d* transition.^[12] In higher energy region, the ligand to metal charge transfer bands for compounds **19** and **20** were located in the range of 240-350 nm.

5.3.4 <u>Catecholase activity study</u>

The catecholase oxidation reaction were explored utilizing the synthesized complexes as probable catalyst as no such studies have been reported so far with tetrazolato bridged dimeric metal complexes to the best of our knowledge. As it was found that 5-(2-cyanophenyl)-tetrazolato moiety act as a weaker ligand with respect to 5-phenyl-tetrazolato ion, it was expected that quicker dissociation of 5-(2-cyanophenyl)-tetrazolato ligand will pave the way of faster binding of the substrate to the metal center and will show subsequent enhanced catalytic rate. Furthermore, it was also speculated that as metal complexes can show two different pathways for catechol oxidation *viz.* ligand centered and metal centered, changing metal ion from nickel(II) to copper(II) may increase the rate as it may facilitate a combined pathway or metal centric pathway for catalytic oxidation.

In order to evaluate the catecholase activity (scheme 5.2) of the synthesized complexes 3,5-di-*tert*-butylcatchol (3,5-DTBC) was taken as the substrate as it shows a low quinone-catechol reduction potential.



Scheme 5.2. Schematic representation of catecholase activity.
The reactions were carried out under aerobic condition and monitored by UV-vis spectroscopic technique. In an experimental set up, a 10^{-5} M solutions of the complexes were prepared in methanol and were treated with 100 equiv of 3,5-DTBC in methanol. Generally for the oxidation of 3,5-DTBC after addition of the substrate into the complex, a new band gradually starts to appear at about 400 nm with time due to the formation of the oxidize product 3,5-DTBQ. However, for these complexes the observation was something different. The time-dependent spectral scans for the complexes **17** and **18** are plotted in Figure 5.12 and 5.13 respectively. In case of complex **17** (Figure 5.12) and **18** (Figure 5.13), time dependent UV-vis spectra up to 3 h revealed substantial increment in the CT band of the complex at 350 nm. The observed bands gradually shift with time to stabilize at 340 nm and 342 nm for complex **17** and **18**, respectively, indicating formation of new complex-substrate aggregate.



Figure 5.12. (a) Catecholase activity by change in time spectral pattern of complex 17 after addition of 3,5-DTBC and (b) Michael-Menten plot for complex 17. Insetlineweaver burk plot.

As the peaks around 340 nm does not correspond to 3,5-DTBQ therefore to ensure that 3,5-DTBQ is really the ultimate product, spectral scan was conducted in every 30 minutes up to 6 hours with addition of 100 equivalent of extra 3,5-DTBC in each interval. The spectra show generation of a new band around 405 nm unambiguously indicating the gradual formation of 3,5-DTBQ in solution (Figure

5.14 and 5.15). A similar kind of observations are also previously reported.^[17] Obtained results clearly proves that initially formed complex-substrate aggregate is getting oxidised in presence of aerial oxygen to form the quinone.



Figure 5.13. Catecholase activity by change in time spectral pattern of complex **18** after addition of 3,5-DTBC.



Figure 5.14. The variation of the spectral behavior for complex **17** in methanolic solution followed up for 6 h after the addition of 3,5-DTBC in each 30 minutes interval.



Figure 5.15. The variation of the spectral behavior for complex **18** in methanolic solution followed up for 6 h after the addition of 3,5-DTBC.



Figure 5.16. Increase of the quinine band at 402 nm after the addition of 100 equiv of 3,5-DTBC to the methanolic solution of complex **19**. The spectra were recorded at 5 min intervals.

In the case of complex **19** with addition of 3,5-DTBC a new band starts to appear around 402 nm indicating the formation of DTBQ (Figure 5.16). The ligand to

metal charge transfer band around 350 nm also found to be gradually increasing with time and shifting towards lower wavelength. This indicates the formation of a complex-substrate aggregate as the intermediate. However, complex **20** was found to be unresponsive towards catechol oxidation reactions.

To understand the kinetic aspects of catalysis for **17-19** the rate constant for a catalyst complex was determined by traditional initial rate methods. Michaelis-Menten approach of enzyme kinetics was employed to derive the kinetic parameters from observed rate *vs* substrate concentration data (Figure 5.17). Linearization by using Lineweaver-Burk plot of 1/V versus 1/[S], (Figure 5.12b and 5.18 respectively), with the equation $1/V = (K_M/V_{max})(1/[S]) + 1/V_{max}$, provides the Michaelis-Menten constant (K_M) and maximum initial rate (V_{max}). The turnover number values (k_{cat}) was obtained by dividing the V_{max} values by the concentration of the corresponding complexes.



Figure 5.17. Michael-Menten plot for complex 18. Inset- lineweaver burk plot.

All the obtained kinetic parameters are presented in Table 5.6. These data unambiguously demonstrate that except complex 20, other complexes are quite active and the reactivity order was found to be 19 > 18 > 17. The probable reason for complex 20 not to be reactive may lie in the fact that 5-phenyl tetrazolato ion being a comparatively stronger ligand, do not dissociate easily in the reaction condition to provide necessary unsaturation for the metal-substrate binding. Copper complex **19** was found to be more reactive with respect to the corresponding nickel complex **18**, which might be attributed to the fact that copper is more prone to provide the more efficient metal centric oxidation process rather than ligand centric oxidation process observed for nickel ion as per DFT calculation (*vide infra*).



Figure 5.18. Michael-Menten plot for complex 19. Inset- lineweaver burk plot.

Among complex **18** and complex **17** comparatively weaker ligand 5-(2cyanophenyl)-tetrazolato ion ensures ready dissociation to make the complex **18** more vulnerable towards substrate. All the kinetic data are represented in Table 5.6.

Table 5.6: Table for various kinetic parameters of catecholase activity forcompounds 17-19.

| Complex /Catalyst | Fixed Complex/ Catalyst | Vmax (M min ⁻¹) | Std. Error | $\mathbf{K}_{\mathbf{M}}\left(\mathbf{M} ight)$ | Std. Error | Kcat / T.O.N (h ⁻¹) |
|----------------------|-------------------------------|--------------------------------|---|---|--|---|
| 17 18 | 0.00001 | 0.00067 0.00083 | $\begin{array}{c} 2.56 \times 10^{\text{-5}} \\ 3.35 \times 10^{\text{-5}} \end{array}$ | 0.00019 0.00026 | 3.13×10^{-5} 2.45×10^{-5} | $\begin{array}{c} 4.02\times10^3\\ 4.98\times10^3\end{array}$ |
| 19 | 0.00001 | 0.00692 | 0.0016 | 0.0057 | 0.0021 | $4.15 	imes 10^4$ |

To obtain a mechanistic inference of the catecholase activity and to investigate possible complex-substrate intermediates, the ESI-MS spectra was recorded for the complexes **17**, **18** and **19** with 3,5-DTBC in methanol solvent. The ESI-MS positive spectrum of a 1:100 mixture of the proportionate complex **17** and 3,5-DTBC, recorded after 10-20 min of mixing exhibits two peaks at m/z = 243 and

464, respectively which can be assigned as $[(3,5-DTBQ)Na]^+$ and $[(3,5-DTBQ)_2Na]^+$. Apart from that a major peak was observed at 723.7 which may be due to the formation of $[L^2Ni(5-phenyltetrazolato)NiL^2]^+$, a dimeric catalyst originated by dissociation of one tetrazolato ligand and reassociation of the remaining complex with another molecule through tetrazolato bridge (complex "**A**" in scheme 5.3). Another smaller peak at 968.1 indicates the formation of complex-substrate aggregate $[L^2Ni(5-phenyltetrazolato)(3,5-DTBC)NiL^2]$ ("**B**" in scheme 5.3) (Figure 5.19).



Figure 5.19. Electrospray mass spectrum (ESI-MS positive) of a 1:100 **17**/3,5-DTBC mixture in methanol, recorded within 10 min of mixing.



Scheme 5.3. Possible catalytic cycle of oxidation of 3,5-DTBC by complex 17.

Monitoring the catalytic reaction by UV-Vis spectroscopy reveals the gradual formation of very broad d-d transition bands (possibly a combination of many bands) in the region of 650 to 900 nm (Figure 5.20). This result indicates the change of the coordination environment of the Ni(II) center from tetra-coordinated

to penta- or hexa-coordinated during substrate binding.^[18] After binding of the substrate simultaneously to two nickel centers dissociation of phenolic proton and transfer of electron to ligand center *via* metal ion produced a *ortho*-quinone intermediate ("C" in scheme 5.3) which is coordinated to the two nickel centers.



Figure 5.20. Change in *d*-*d* transition band of Ni(II) with time upon reaction with 3,5 DTBC.

It is also important to note that the dioxygen of the atmosphere is reduced to H_2O_2 during the oxidation process along with the liberation of DTBQ. Finally, liberation of quinone and the binding of another catechol moiety with the intermediate ("C" in scheme 5.3) regenerates the intermediate ("A" in scheme 5.3) and completes the catalytic cycle. To find out the fate of the oxygen after reduction, the possible oxidation of Fe⁺² to Fe⁺³ was explored, with the disappearance of a characteristic band of Fe⁺²-phenanthroline complex at 509 nm in reaction mixture because of formation of H₂O₂ during oxidation reaction (Figure 5.21). The details of the method is discussed at the end of results and discussions section.

A similar delocalization mechanism is also proposed for complex 18 with theoretical support (*vide infra*) indicates the probable delocalization of the transferred electrons over ligands. In case of complex 18 the ESI-MS positive

spectrum of a 1:100 mixture of the proportionate complex **18** and 3,5-DTBC, recorded after 10-20 min of mixing exhibits two major peaks at m/z = 243 and 464, respectively, for [3,5-DTBQ)Na]⁺ and [(3,5-DTBQ)₂Na]⁺ as expected (Figure 5.22). Among the remaining peaks, the peak at 972.1 could be assigned to complex-substrate aggregate {[(L²)₂(Ni)₂(tet)(DTBC)]}⁺ (Figure 5.23). The preorganized dinickel(II) complex upon elimination of a tetrazolato ions from the dinickel(II) center, binds the catechol which acts as a bridge between two metal centers (scheme 5.4). The next steps involve similar kind of mechanism as for complex **17** to complete the catalytic cycles (scheme 5.3) with concomitant formation of H₂O₂ (Figure 5.21). To understand that if the oxidation of catechol is ligand centric or metal centric, detailed DFT calculations were carried out (*vide infra*) which indicates electron transfer is facilitated by metal center and the received electron is further delocalized *via* C=N bond of metal Schiff-base complex to the adjacent conjugate system.



Scheme 5.4. Possible catalytic cycle of oxidation of 3,5-DTBC by complex 18.



Figure 5.21. Change in the absorption band for the complexes 17-19 due to formation of H_2O_2 .



Figure 5.22. Electrospray mass spectrum (ESI-MS positive) of a 1:100 **18**/3,5-DTBC mixture in methanol, recorded within 10 min of mixing.



Figure 5.23. Electrospray mass spectrum (ESI-MS positive) of a 1:100 **18**/3,5-DTBC mixture in methanol, recorded within 20 min of mixing.

The mechanism of oxidation of 3,5-DTBC by complex **19** is represented in scheme 5.5. The ESI-MS positive spectrum of a 1:100 mixture of the proportionate complex **19** and 3,5- DTBC, recorded after 10 min of mixing exhibits major peaks for $[(3,5-DTBQ)Na]^+$ and $[(3,5-DTBQ)_2Na]^+$ apart from another significant assignable peak at 809.2 (Figure 5.24). The later peak can be assigned to the formation of $[Cu_2L^2_2(DTBC)]^+$ ("A" in scheme 5.5). From ESI-MS data it seems the dinuclear complex easily looses two bridging tetrazolato ligand to form a catechol bridged dinuclear species. Catechol moiety transfers two electron *via* two copper center to aerial oxygen to get oxidized to quinone. The metal centric oxidation mechanism is further supported by DFT calculations.



Figure 5.24. Electrospray mass spectrum (ESI-MS positive) of a 1:100 **19**/3,5-DTBC mixture in methanol, recorded within 10 min of mixing.



Scheme 5.5. Possible catalytic cycle of oxidation of 3,5-DTBC by complex 19.

5.3.5 <u>Study of detection of H₂O₂ from DTBC using UV absorption</u> <u>method</u>

The experiment is based on the reaction between the ferrous ion (Fe^{+2}) and 1,10phenanthroline in presence of complex and 3,5-DTBC.^[14] Ferrous ion specifically forms red-orange tri-phenanthroline complex which absorbs maximally at 509 nm. It is known that if hydrogen peroxide is added to the ferrous ion before addition of 1,10-phenanthroline, then H₂O₂ will oxidize all the ferrous ion to ferric ion which is incapable of forming red-orange complex with 1,10-phenanthroline and a sharp reduction in 509 can be seen. This concept has been exploited for determination of H₂O₂ in the samples.

Herein, the advantage of this experiment was further taken in a way that after adding ferrous ion and 1,10-phenanthroline to the complex solution, its UV spectrum is recorded which shows an absorption band at 509 nm. However, when DTBC solution is added to the complex solution along with ferrous ion and 1,10-phenanthroline, a sharp decrease in absorbance spectra can be seen after 10 mins. Moreover, the absorption band at 509 nm completely vanishes after 25 mins. This reduction trend clearly indicates the absence of Fe⁺²-tri-phenanthroline complex. This is because of the formation of H₂O₂ in catechol oxidation as it converts all the ferrous ion to ferric ion leading to the disappearance of the characteristic band at 509 nm.

5.3.6 Computational study

Density functional theoretical (DFT) study is performed to understand the catechol oxidation reaction catalysed by dinuclear tetrazole based nickel (**18**) and copper (**19**) complexes.^[19] All the calculations are carried out using UB3LYP level of theory as implemented in the Gaussians 09 package.^[20] The 6-31G** basis set is used for all the elements.^[21] The solvent calculations are carried out in methanol solvent using the polarizable continuum model,^[22] as the catechol oxidation reaction experiments are performed in methanol solvent. The vibrational frequency

calculations are performed for all the complexes (Figure 5.25a-b) and intermediates (Figure 5.26a-b) to confirm the nature of the stationary points.



Figure 5.25. Optimized structures of (a) **18** and (b) **19** using UB3LYP/6-31+G** level of theory. Here green, sea-green, grey, blue, red, pink colour balls denote the nickel, copper, carbon, nitrogen, oxygen, and hydrogen atoms respectively.

The ground state structures of **18** (di-nuclear Ni complex) and **19** (di-nuclear Cu complex) are shown in figure 5.25a and 5.25b respectively. Complex **18** has an open-shell quintet (S = 2) structure in its most stable ground state, whereas open-shell triplet (S = 1) is the ground state structure of complex **19**.

It was assumed that the catechol first binds to the metal complex for the oxidation reaction. It was found that complex **18** binds to the catechol substrate in a bridging manner (Scheme 5.4) followed by the elimination of tetrazolato ions from the dinickel(II) center and subsequent coordination by the catechol in a bidentate manner. Thus, the intermediate **18C** was modelled (Scheme 5.4) by substituting one of the tetrazole ligands of complex **18** with the catechol (3,5-di*tert*butylcatechol) molecule (Figure 5.26a). Whereas, catechol oxidation in complex **19** goes *via* the formation of a bridging catecholate dicopper intermediate (B or C) (Scheme 5.5). So, here the catechol ligand binds to complex **19** as shown in Figure 5.26b.



Figure 5.26. Optimized structures of intermediates (a) **18C** and (b) **19C** during the catechol oxidation. Here green, sea-green, grey, blue, red, pink colour balls denote the nickel, copper, carbon, nitrogen, oxygen, and hydrogen atoms respectively.

During the catechol oxidation, the bi-nuclear metal complex will be reduced by two electrons.^[23] The catechol coordinated intermediate **18C** (Scheme 5.4) is most stable with an open-shell septet (S=3) state, where as intermediate **19C** (Scheme 4) has an open shell singlet (S=0) ground state.^[24]

The frontier orbitals and spin density difference of **18** and **18C** (Figure 5.27a-b) are plotted to understand the change in frontier orbitals and spin density differences (SDD) (Figure 5.27c-d) during the catechol oxidation reaction. One of the singly occupied molecular orbitals (SOMO) of complex **18** (Figure 5.27a) shows the π -bonding nature of the C=N bond. But, the antibonding nature (π *) of the SOMO of **18C** (Figure 5.27b) gives a clear indication of the CN· radical formation after two-electron reduction. This is even reflected in the C=N bond distance, which is elongated by 0.04 Å, suggesting that the CN· radical formation after the two electron reduction.

This is further confirmed from the projected SDD of complex **18**, which is mainly localized on the metal centres (Figure 5.27c). But the projected SDD (Figure 5.27d) of **18C** is concentrated on the ligands too. Hence, DFT study confirms the

generation of ligand-centered free radicals, which agrees well with the experimental finding too.



Figure 5.27. Singly occupied molecular orbital (SOMO) of (a) **18** and (b) **18C** and spin density differences (SDD) of (c) **18** and (d) **18C** (Isosurface value $0.03 \text{ e.}\text{Å}^{-3}$).

The frontier orbitals and SDD of **19** and **19C** (Figure 5.28a-b) are also plotted to understand (Figure 5.28c-d) the catechol oxidation mechanism. Here, Cu(II) is reduced to Cu(I) after the catechol oxidation. On the other hand, C=N bonding (Figure 5.28) does not change during the course of the reaction.

This is further confirmed from the projected SDD of **19** and **19C**. The spin density is mainly localized on the metal centres of complex **19** (Figure 5.28c) whereas absent in the **19C** after two electrons reduction. As here, Cu(II) is reduced to Cu(I). Thus, the DFT study confirms that this is a metal centered reduction, which is again very much in agreement with the experimental finding.

The SOMO-LUMO gap of **18** and **19** are also investigated to find out their reactivity towards the catechol oxidation reaction. It was found that complex **19** (1.03 eV) has lower SOMO-LUMO gap compared to complex **18** (1.59 eV). It proves that complex **19** is more reactive towards the catechol oxidation compared to complex **18**. On the other hand, the calculated SOMO energies are -3.60, -5.30 eV for complex **18** and **19** respectively. It shows that the SOMO is highly stabilized in **19** and ready to accept an electron, which in turn facilitates the catechol oxidation reaction. Thus, the catechol oxidation trend (**19**>**18**) is very much in agreement with the experimental finding.



Figure 5.28. SOMO of (a) 19 and (b) 19C and SDD of (c) 19 and (d) 19C (Isosurface value 0.03 e.Å^{-3}).

Interestingly, it is seen that CN substituted Ni-complex crystallizes into a dinuclear complex rather than monomer. To understand this, a nitrile (–CN) substitute monomer (**17-CN**) has been modelled, where one of the phenyl hydrogen atoms of phenyl tetrazolato moiety (complex **17**) is substituted by a –CN ligand. The 1-CN

structure calculated to be minima in the potential energy surface. The d-orbital splitting energy diagram (Figure 5.29) has been plotted to understand the reason behind this. It is found that complex **17-CN** has a less HOMO-LUMO gap (Figure 5.29, 4.03 eV) compared to complex **17** (4.11 eV), which suggests that complex **17** is more stable than complex **17-CN**. The energy gap between the d_z^2 and d_{xy} orbitals decreases from complex **17** (0.59 eV) to complex **17-CN** (0.46 eV) and lowest in complex **18** (0.18 eV). This indicates that CN substitution favours the dinuclear complex to crystallize into a square pyramidal geometry.



Figure 5.29. The d-orbital splitting energy (eV) diagram for square planar (monomer 17 and CN substituted monomer 17-CN) to dinuclear Ni complexes (complex 18).

5.3.7 Interaction with biomolecules

To investigate the possibility of these nickel and copper tetrazolato complexes to bind with CT-DNA (which has been found to be a critical step for the chemical nuclease activities of metal complexes)^[25,26] DNA was added step by step with increasing amounts and the changes in the absorption spectrum of the metal complex were monitored. The literature study shows that the interaction between metal complexes and DNA bases may lead to intercalation where hypochromic shift in the UV region was found to be an evidence of that phenomena.^[27] Furthermore, when the complex binds to DNA,^[28] the bathochromic shift suggests a decrease in the energy gap between the highest occupied and lowest unoccupied molecular orbital of DNA and metal complex. Absorption spectral titration carried out for compounds **17** and **19** display a decrease in molar absorptivity with a slight bathochromic shift indicating a possible interaction between aromatic moieties of the complex with DNA base pairs and stabilization of CT-DNA duplex. In the presence of DNA, complex **19** shows 5% (Figure 5.31a), showing considerable interaction between complexes and DNA.



Figure 5.30. (a) Absorption titration spectra of fixed concentration of complex 17 with increasing concentrations of CT-DNA and (b) Plot of $[DNA]/(\epsilon_{\alpha}-\epsilon_{f})$ vs. [DNA] for the titration of the complex 17 with CTDNA.

The hypochromicity and bathochromic shift indicates the intercalative mode of binding and considerable stacking interaction between aromatic chromophore and base pairs of DNA.^[29] The plot of [DNA]/[$\varepsilon_a - \varepsilon_f$] versus [DNA] (where $\varepsilon_a = A_{obs}$ /[compound] and ε_f is the extinction coefficient of the free compound) gives a straight line and the ratio of the slope to the intercept gives the intrinsic binding constant K_b. The values of the intrinsic binding constant for **17** (Figure 5.30b) and

19 (Figure 5.31b) were found to be 2.47×10^4 M⁻¹ and 2.32×10^4 M⁻¹ respectively. These values are average in nature with respect to the other nickel and copper complexes reported so far.^[30]



Figure 5.31. (a) Absorption titration spectra of fixed concentration of complex 19 with increasing concentrations of CT-DNA and (b) Plot of $[DNA]/(\epsilon_{\alpha}-\epsilon_{f})$ vs. [DNA] for the titration of the complex 19 with CTDNA.



Figure 5.32. ETBr displacement assay by change in fluorescent intensity of EB with respect to conc.of complex **17**.

To further study the interaction mode between the complexes and CT-DNA, fluorescence titration experiments were carried out using ethidium bromide (EB) as a spectral probe. EB shows reduced emission intensity in buffer because of significant solvent quenching, however in presence of CT-DNA the emission intensity gets enhanced because of intercalative binding of EB to DNA. In presence of metal complex which competes with EB to bind the DNA a significant reduction of emission intensity are generally observed.^[28] In our experiment the fluorescence intensity at 607 nm showed remarkable decreasing trend with increasing concentration of complex **17** (Figure 5.32) and **19** (Figure 5.33) due to the displacement of DNA bound EB by the metal complexes.



Figure 5.33. ETBr displacement assay by change in fluorescent intensity of EB with respect to conc. of complex **19**.

The K_q value which was obtained from Stern-Volmer plot was found to be 2.13×10^3 M⁻¹ and 1.45×10^3 M⁻¹ for complex **17** (Figure 5.34a) and **19** (Figure 5.35a), respectively. This shows a greater interaction for nickel tetrazolate complex **17** over the copper complex **19**. The corresponding K_b values obtained from the Scatchard plot (Figure 5.34b and Figure 5.35b) where found to be 7.42×10^5 M⁻¹ and 2.45×10^3 M⁻¹, respectively for the complex **17** and **19**. The values obtained are

consistent with other values reported for similar nickel and copper complexes.^[31] However, it is noted that compounds **18** and **20** were non-responsive towards DNA binding study.



Figure 5.34. (a) Stern-Volmer plot of fluorescence titration of the complex **17** with CTDNA and (b) Scatchard plot of fluorescence titration of the complex **17** with CTDNA



Figure 5.35. (a) Stern-Volmer plot of fluorescence titration of the complex **19** with CTDNA and (b) Scatchard plot of fluorescence titration of the complex **19** with CTDNA.

The interactions of bovine serum albumin (BSA) with these nickel and copper tetrazolato complexes was also explored through spectroscopic methods. The literature reveals that the interaction between metal complex and protein leads to the quenching of the fluorescence of the BSA protein and it may happen because of dynamic or static interaction.^[32] Dynamic quenching is a process in which a fluorophore and a quencher come into contact during the transient existence of an excited state, whereas static quenching refers to the formation of a fluorophore–quencher complex in the ground state leading to considerable change in the UV-vis absorption spectroscopy. The absorption peak for BSA is visible at 278 nm arising from the presence of aromatic amino acids (Trp, Tyr and Phe),^[33] while with addition of both the complexes **17** and **19**, individually the absorption increases with a concomitant slight blue shift accompanied by it (Figure 5.36 and Figure 5.37). The band in the range of 330-350 nm is due to internal charge transfer band of the complexes in both the case.



Figure 5.36. UV-VIS Absorption titration of BSA by successive addition of complex **17**.



Figure 5.37. UV-VIS Absorption titration of BSA by successive addition of Complex 19.

The study shows an indication of the interaction between BSA and the complex at ground state. This leads to conformational changes in BSA and induces a change in the polarity of the microenvironment around Tyr and Trp residues of BSA.^[34]



Figure 5.38. Fluorescence quenching of BSA by complex **17**. Stern–Volmer plot is in the inset.

To explore further, Trp-emission quenching experiments were carried out using BSA in the presence of increasing amounts of complexes **17** and **19**. A constant amount of BSA solution was titrated with an increasing concentration of each complex. A continuous decrease of fluorescence intensity for the fluorophore was observed which was accompanied with a red shift (Figure 5.38 and Figure 5.39). The fluorescence emission was observed at 345 nm upon excitation at 290 nm. To know the interaction between complexes and BSA, the obtained results were analysed by the Stern-Volmer equation:^[10]

$$\frac{F_0}{F} = 1 + k_q \tau_0[Q] = 1 + K_{SV}[Q]$$

where F_0 and F are the fluorescence intensities in the absence and the presence of a quencher, k_q is the bimolecular quenching rate constant, τ_0 is the average lifetime of fluorophore in the absence of a quencher and [Q] is the concentration of a quencher (metal complexes). Here, a linear plot was obtained for both the complexes (Figure 5.38 and Figure 5.39).



Figure 5.39. Fluorescence quenching of BSA by complex **19**. Stern–Volmer plot is in the inset.

This positive deviation specify a possible two way quenching by collision and as well as by complex formation with the same quencher.^[18] Here, K_{SV} is the Stern–

Volmer quenching constant in M^{-1} which can be determined by linear regression of F_o/F against [Q]. The calculated value of the Stern–Volmer quenching constant (K_{SV}), the bimolecular quenching rate constant (k_q), and the number of binding sites (n) for both the complexes **17** and **19** are listed in Table 5.7. The quenching constant values from Stern–Volmer plot were found to be in the order of 10^{12} . This value also indicates that there is a larger possibility that the quenching mechanism of fluorescence of BSA by two different complexes is initiated by static quenching process.^[34]

 Table 5.7: Table for Stern–Volmer quenching constant, binding constant and binding site

| System | $K_{SV}(M^{-1})$ | $K_q (M^{-1} S^{-1})$ | $K_a (M^{-1})$ | n |
|----------------|--------------------|------------------------|-----------------------|------|
| Complex 17-BSA | 7.81×10^3 | 1.264×10^{12} | 7.926×10 ³ | 1 |
| Complex 19-BSA | 1.55×10^4 | 2.516×10^{12} | $1.074 \ge 10^5$ | 1.22 |

The binding constant value (K_a) and the number of binding sites (n) from Scatchard plot were obtained from the equation:

$$\log\left[\frac{F_0 - F}{F}\right] = \log K_a + n \log[Q]$$

The study shows that the value of n was found to be 1 indicating probability of presence of one binding site in BSA (Figure 5.40). The binding constant K_a indicates a very strong interaction between the di-nuclear copper-tetrazolato complex **19** and BSA.



Figure 5.40. Scatchard plot of the fluorescence titration of the complex **17** with BSA (left) and complex **19** with BSA (right).

5.4 Conclusions

1,3-dipolar cycloaddition between metal ligated azide and organonitriles has been $[NiL^2(5$ utilized to synthesize four new tetrazolato complexes viz. phenyltetrazolato)] (17), $[Ni_2L_2^2 \{5-(2-cyanophenyl)-tetrazolato\}_2]$ (18), $[Cu_2L_2^2 \{5-(2-cyanophenyl)-tetrazolato]_2]$ (18), $[Cu_2L_2^2 \{5-(2-cyanophenyl)-tetrazolato]_2]$ (2-cyanophenyl)-tetrazolato $_{2}$ (19) and $[Cu_{2}L^{2}_{2}\{5-phenyltetrazolato\}_{2}]\cdot C_{6}H_{5}CN$ (20). All the complexes have been characterized by various spectroscopic tools, Xray crystallography and elemental analyses. Tuning at the 5-position of the tetrazolato ligand with a nitrile substituted phenyl group provides a weaker ligand, leading to an enhanced catecholase activity of the metal complexes through easier dissociation and in turn providing the vacant coordination site for the substrate. Copper complex 19 has shown much superior activity than the analogous nickel complex 18. This factor may be attributed to the fact that the oxidation process for copper system is routed through metal center instead of preferential ligand centered oxidation in case of nickel complex. The comparative catalytic activity of complex **18** and **19** is further investigated by DFT calculations supporting the relative order of activity among the various complexes. The DNA and protein binding of the complexes (17 and 19) were investigated using absorbance and fluorescence spectroscopic techniques. The results of DNA binding experiments revealed that the square planer Ni(II)-tetrazolate complex **17** significantly bind to double stranded DNA, possibly by intercalation and having binding constant in the order of 10^5 M^{-1} . The experimental results suggested that the complex **17** can bind to DNA more strongly than the complex **19**. The protein binding studies of the compounds suggested a strong interaction with BSA for the dinuclear Cu(II)-tetrazolate complex **19** than complex **17**. The Stern–Volmer quenching constant value obtained in the order of 10^{12} M^{-1} shows that both static and dynamic quenching are occurring simultaneously.

5.5 <u>References</u>

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Chapter-6

Oxidative functionalization of C-H bonds under mild conditions catalyzed by copper tetrazolato complexes

6.1 Introduction

The controlled partial oxidation of hydrocarbons is the key reaction for the conversion of oil and gas feedstock to industrial organic chemicals.^[1] One of the hurdles towards oxidation of hydrocarbons is the inertness of C-H bonds, especially in saturated hydrocarbons, where the bond energy amounts to 400 kJ mol⁻¹.^[2] Moreover, the formed product needs to be stabilized as it is often more reactive than the starting material.^[3] Thus, the formed alcohols can be further oxidized to e.g. the aldehyde, acid and even CO₂.^[4]

The use of molecular oxygen as the primary oxidant is desirable from economic and environmental points of view. However, the ground state of the dioxygen contains two unpaired electrons (triplet ³O₂), and therefore is spin forbidden to react with spin-paired singlet C-H bonds.^[4,5] Hence, catalysts are needed to activate molecular oxygen and to direct the selectivity of the reaction. Transition metals containing unpaired electrons are able to react directly with the triplet state of oxygen, forming dioxygen adducts, which can incorporate an oxygen into the C-H bond or oxidize an organic substrate.^[5]

Different catalytic methods using transition metals have been developed for the oxidation of organic compounds. Among numerous types of transition metal catalyzed oxidations, copper- mediated reactions are of great interest due to their low toxicity, environmental abundance and effectiveness as a catalyst. Different oxidation states of copper contributes in the mechanism and thus make it easier for one-electron and two-electron pathways in oxidation process. This allows copper to be an effective catalyst in a broad range of oxidation reactions including reactions in living organisms.^[6] Copper enzymes have been observed in catalyzing oxidation reactions in biological systems, such as in methane monooxygenase (pMMO)

(which is composed of tri or multinuclear cluster of copper) which is responsible for the C-H activation in methane to methanol.^[7]

As selective partial oxidation of alkanes is an important topic with great potential in terms of economic and ecological perspectives of sustainable chemistry, copper based metal complexes as catalysts for hydrocarbon oxidation have been studied in detail for the last few years with diverse ligand systems.^[8-12] A relevant example of selective alkane oxidation^[8,13-17] with industrial significance concerns the oxidation of cyclohexane to cyclohexanol and cyclohexanone that are important reagents for the production of adipic acid and caprolactam used for the manufacture of nylon.^[13-14,17] The current industrial route uses a homogeneous cobalt species as catalyst, dioxygen as oxidant and requires considerably harsh conditions (150 °C), forming the oxidation products in low yields (ca. 5%) to achieve a good selectivity (ca. 85%).^[13,14] The development of more efficient catalysts, under milder conditions, at

room temperature and in low toxicity media and benign oxidizing agents is current interest of research.^[13,14,17] Besides O₂, tert-butyl hydroperoxide is the preferred oxidant since it simply produces tert-butanol as a side product, but the conversions and turnovers of the cyclohexane oxidation are still commonly low.^[17] In the current study, we have utilized peroxidative (with ${}^{t}BuOOH$) alkane oxidation with selected metal tetrazolato complexes under microwave irradiation. Use of microwave irradiation in this kind of catalysis is relatively rare and less explored.^[18] Herein, the use of tetrazolato copper(II) compounds [Cu₂(phen)₂(5-[Cu(phen)(5-pyrimidyltetrazolate)₂] phenyltetrazolato)₄] (21),(22)and $[Cu(phen){5-(2-pyridyl)tetrazolate}_2]$ (23) was explored as catalyst for selective oxidation of cyclohexane (to cyclohexanol and cyclohexanone) under very mild and green (solvent- and additive-free) conditions toward the protection of environment.

Encouraged by the successfully application of tetrazolato copper(II) complexes^[19] as catalyst in the oxidation of 3,5-di-*tert*-butylcatechol (to *tert*-butylquinone), the catalytic activity of such kind of compounds in the oxidation of hydrocarbons have been also explored. In addition, interaction of synthesized complexes with bovine serum albumin (BSA) have also been studied. Finally, the molecular docking
studies were performed to obtain detailed binding information of the Cu(II) complexes with BSA.

6.2 Experimental section

6.2.1 Materials and physical measurements

Reagents and Materials: All reagents and solvents were purchased commercially and were used as received. Copper(II) nitrate trihydrate, 1,10-phenanthroline mono hydrate, sodium azide, benzonitrile, pyrimidine carbonitrile and 2-cyano pyridine were purchased from Merck-India Chemical Company. Bovine serum albumin (BSA, fraction V powder) was purchased from SRL (India). 3,5-di-*tert*butylcatechol (3,5-DTBC) was purchased from Sigma. Tris(hydroxymethyl) aminomethane-hydrochloride (Tris-HCl) buffer was prepared using distilled water.

Methods and Instrumentation: Infrared spectra (4000 to 500 cm⁻¹) were recorded with a BRUKER TENSOR 27 instrument in KBr pellets. Mass spectrometric analyses were done on Bruker-Daltonics, microTOF-Q II mass spectrometer and elemental analyses were carried out with a Thermo Flash 2000 elemental analyzer. Spectrophotometric measurements were performed on a Varian UV-Vis spectrophotometer (Model: Cary100) (for absorption) and a Fluoromax-4p spectrofluorometer from Horiba JobinYvon (Model: FM-100) (for emission) using a quartz cuvette with path length of 1 cm.

Caution! Azide and tetrazolate compounds are potentially explosive. Only a small amount of material should be prepared and handled with care.

X-ray crystallography: Single crystal X-ray structural studies of compounds **21**, **22** and **23** were performed on a CCD Agilent Technologies (Oxford Diffraction) SUPER NOVA diffractometer. Data for the complexes **21** and **23** were collected at 150(2) K and for the complex **22**, the data was collected at 293(2) using graphite-monochromatic MoK_{α} radiation (λ_{α} = 0.71073 Å). The strategy for the data collection was evaluated using the CrysAlisPro CCD software. The data were collected by the standard phi-omega scan techniques and were scaled and reduced

using the CrysAlisPro RED software. The structures were solved by direct methods using the SHELXS-97 and refined by full matrix least-squares with the SHELXL-97 refining on F^{2} .^[20]

The positions of all the atoms were obtained by direct methods. All non-hydrogen atoms were refined anisotropically. The remaining hydrogen atoms were placed in geometrically constrained positions and refined with isotropic temperature factors, generally $1.2U_{eq}$ of their parent atoms. The contribution of solvent electron density was removed by the SQUEEZE routine in PLATON.^[21] The crystal and refinement data are summarized in Table 6.1, and selected bond distances and bond angles for **21**, **22** and **23** are shown in Table 6.3 -Table 6.5.

| | 21 | 22 | 23 |
|---|--------------------------|------------------------|------------------------|
| | | | |
| Empirical formula | $C_{52}H_{36}N_{20}Cu_2$ | $C_{22}H_{14}CuN_{14}$ | $C_{24}H_{16}N_{12}Cu$ |
| Formula weight | 1068.07 | 538.01 | 536.03 |
| Wavelength (Å) | 0.71069 | 0.71073 | 0.71069 |
| Temperature (K) | 150(2) | 293(2) | 150(2) |
| Crystal system | Triclinic | Triclinic | Orthorhombic |
| Colour and shape | Blue block | Green needle | Blue plate |
| Space group | <i>P</i> -1 | <i>P</i> -1 | P_{bcn} |
| a/Å | 8.6135(17) | 11.411(7) | 14.2473(8) |
| b/Å | 11.038(2) | 11.992(2) | 10.1063(6) |
| c/Å | 12.681(2) | 12.146(3) | 15.7715(9) |
| α/degree | 76.353(4) | 67.80(2) | 90 |
| β/degree | 87.643(5) | 87.75(4) | 90 |
| γ/degree | 77.866(3) | 78.39(3) | 90 |
| Volume(Å ³) | 1145.4 | 1506.2(11) | 2270.9(2) |
| Z | 1 | 2 | 4 |
| $D_{ m calcd}/ m mg~m^{-3}$ | 1.548 | 1.186 | 1.568 |
| μ (Mo K α)/mm ⁻¹ | 0.993 | 0.759 | 1.004 |
| F(000) | 546 | 546 | 1092 |
| Crystal size/mm | 0.30×0.21×0.11 | 0.23×0.18×0.13 | 0.28×0.18×0.09 |
| θ range(°) | 2.41 to 25.57 | 3.323 to 32.229 | 2.47 to 34.70 |
| Limiting indices | $-10 \le h \le 10$ | $-14 \le h \le 16$ | $-22 \leq h \leq 22$ |
| | $-13 \le k \le 13$ | $-17 \le k \le 17$ | $-16 \le k \le 9$ |
| | $-15 \le 1 \le 15$ | $-18 \le l \le 18$ | $-25 \le 1 \le 25$ |
| Total/ unique no. of reflns. | 4272 / 2889 | 17206 / 9611 | 4920 / 3551 |
| Data/restr./params. | 1272 / 0 / 334 | 9611 / 0 / 334 | /1920 / 0 / 168 |
| $GOF(F^2)$ | 0.928 | 0 573 | 1 060 |
| R1. wR2 | 0.0465 0.0922 | 0.0998, 0.2304 | 0.0314, 0.0813 |
| R1. wR2 (all data) | 0.0970, 0.1055 | 0.2695, 0.2710 | 0.0957, 0.0869 |
| Peak and hole (e Å ⁻ | 0.408 and -0.312 | 0.40 and -0.35 | 0.589 and -0.430 |
| ³ⁿ) | | | |

Table 6.1: Crystal data and structure refinement of complexes 21, 22 and 23

6.2.2 Synthesis

 $[Cu(phen)(N_3)_2]_n$ was synthesized according to the literature procedure.^[22]

6.2.2.1 $[Cu_2(phen)_2 \{5-phenyltetrazolato\}_4]$ (21)

A mixture of $[Cu(phen)(N_3)_2]_n$ (0.12 g, 0.367 mmol), 2 mL of benzonitrile and 10 mL of DMF was refluxed for 12 hrs to obtain a clear green coloured solution. The solvent was then removed in *vacuo* and the resulting residue was treated with diethyl ether to obtain a green powder which was then recrystallized from methanol–diethyl ether mixture to get suitable X-ray diffraction-quality crystals. Anal. Calcd. for compound **21**: C₅₂H₃₆Cu₂N₂₀ (1068.07): C 58.48; H 3.40; N 26.23%. Found: C 58.23; H 3.12; N 26.04%. ESI-MS (positive ion, CH₃OH) *m/z*: 568.1 [Cu(phen)₂(5-phenyltetrazolato)]⁺ (calcd 568.12). IR (cm⁻¹, KBr, selected peak): 3419, 1630, 1606, 1429, 1020.

6.2.2.2 [Cu(phen)(5-pyrimidyltetrazolato)₂] (22)

A mixture of $[Cu(phen)(N_3)_2]_n$ (0.12 g, 0.367 mmol), 0.29 g (2.7 mmol) of pyrimidine carbonitrile and 10 mL of DMF was refluxed for 12 hrs to get a clear green coloured solution. The solvent was then removed in *vacuo* to obtain green coloured residue upon concentration. The resulting residue was washed several times with diethyl ether. Then the residue was dissolved in methanol and layered with diethyl ether to obtain green coloured crystals of compound **22**. Anal. Calcd. for compound **22**: C₂₂H₁₄N₁₄Cu (537.99): C 49.12; H 2.62; N 36.45%. Found: C 49.02; H 2.12; N 36.04%. ESI-MS (positive ion, CH₃OH) *m/z*: 560.06 [M+Na]⁺ (calcd 560.07). IR (cm⁻¹, KBr, selected peak): 1630, 1392, 1142, 1054.

6.2.2.3[Cu(phen){5-(2-pyridyl)tetrazolato}₂](23)

0.12 g (0.37 mmol) of $[Cu(phen)(N_3)_2]_n$ was dissolved in 10 mL of DMF and 2 ml (20.8 mmol) of 2-cyanopyridine was added to that solution. The mixture was refluxed for 12 hrs to get a clear green solution. The solvent was then removed *in vacuo* and the resulting oily residue was treated with diethyl ether to obtain a green powder which was then recrystallized by layering a solution of methanol with CH_2Cl_2 to afford large green crystals of compound **23**. Anal. Calcd. for compound **23**: $C_{24}H_{16}CuN_{12}$ (536.01): C 53.78; H 3.01; N 31.36%. Found: C 53.34; H 3.45; N 30.89%. ESI-MS (positive ion, CH₃OH) *m/z*: 558.08 [M+Na]⁺ (calcd 558.08). IR (cm⁻¹, KBr, selected peak): 1678, 1425, 1124, 1038.

6.2.3 Microwave-assisted oxidation of cyclohexane

The catalytic oxidations of cyclohexane were carried out in an Anton Paar Microwave 300 reactor fitted with a rotational system and an IR temperature detector. Gas chromatographic (GC) measurements were carried out using a FISONS Instruments GC 8000 series gas chromatograph with a FID detector and a capillary column (DB-WAX, column length: 30 m; internal diameter: 0.32 mm) and the Jasco-Borwin v.1.50 software. The temperature of injection was 240 °C. The initial temperature was maintained at 100 °C for 1 min, then raised 10 °C/min to 180 °C and held at this temperature for 1 min. Helium was used as the carrier gas. GC-MS analyses were performed using a Perkin Elmer Clarus 600 C instrument (He as the carrier gas). The ionisation voltage was 70 eV. Gas chromatography was conducted in the temperature-programming mode, using a SGE BPX5 column (30 m×0.25 mm×0.25 μ m).

The oxidations of cyclohexane were carried out in sealed cylindrical Pyrex tubes (5 mL capacity with a 10 mm internal diameter) under focused microwave irradiation (MW) as follows: 1–5 μ mol of the catalyst was added to 2.50 mmol of cyclohexane, whereafter 5.00 mmol of 70% aqueous *tert*-butyl hydroperoxide (TBHP) were introduced in the tube. Nitromethane, as the internal standard compound, was also added. When used, the 2,2,6,6-tetramethylpiperidyl-1-oxyl radical (TEMPO), was used in an amount of 2.5 mol% relative to the substrate. The tube was then placed in the microwave reactor and the system was stirred (800 - 1000 rpm) and irradiated (5 - 7 W) for 0.5–3 h at 60-100 °C. Solution aliquots were taken and analysed by GC. Subsequently, an excess of solid triphenylphosphine was added to each aliquot (to reduce the cyclohexyl hydroperoxide to cyclohexanol, and hydrogen peroxide to water) and the mixture was analysed again to estimate the amount of cyclohexyl hydroperoxide, following the method developed by Shul'pin.^[23-25]

For precise determination of the product concentrations only data obtained after the reduction of the reaction sample with triphenylphosphine were typically used, taking into account that the original reaction mixture contained cyclohexyl hydroperoxide, cyclohexanol and cyclohexanone. Reaction products were identified by comparison of their retention times with known reference compounds, and by comparing their mass spectra to fragmentation patterns obtained from the NIST spectral library stored in the computer software of the mass spectrometer. Blank experiments, in the absence of any catalyst, were performed under the studied reaction conditions and no significant conversion was observed.

6.2.4 <u>Catechol oxidation studies</u>

To explore the ability of the three Cu(II) complexes to oxidize 3,5-DTBC, a 2×10^{-5} M methanolic solutions of complexes **21**, **22** and **23** were treated with 2×10^{-3} M (100 equiv.) of 3,5-DTBC under aerobic conditions at room temperature. In the UV-vis spectroscopy, the absorbance of the resultant reaction mixture was plotted with respect to wavelengths of 300–500 nm. From the figures, it is observed that a band at ~400 nm increases with time after the addition of 3,5-DTBC because of the gradual increment of the concentration of 3,5-DTBQ (3,5-DTBQ exhibits $\lambda_{max} \sim$ 400 nm in methanol). These data definitely display that all the complexes act as active catalysts for the aerial oxidation of 3,5-DTBC to 3,5-DTBQ.

Substrate solutions of concentrations ranging from 0.002 to 0.01 mol dm⁻³ were prepared in methanol from a concentrated stock solution. A total of 2 mL of the substrate solution was poured into a 1 cm spectrophotometer quartz cell thermostated at 25 °C. Then 1 mL of a 0.00002 M methanolic solution of the complexes **21**, **22** and **23** were quickly added to it, respectively, so that the ultimate concentration of the complex became 1×10^{-5} mol dm⁻³. The dependence of the initial rate on the concentration of the substrate was spectrophotometrically monitored at the respective wavelength. Furthermore, the initial rate method displays a first-order kinetics on the complex concentration and shows a saturation kinetics at higher substrate concentrations based on the Michaelis–Menten model. The binding constant (K_M), maximum velocity (V_{max}), and rate constant for dissociation of the substrates (i.e., turnover number, k_{cat}) were calculated for the three complexes using the Lineweaver–Burk graph of 1/V versus 1/[S], with the

equation $1/V = (K_M/V_{max})(1/[S]) + 1/V_{max}$, and all the obtained kinetic parameters have been recorded.

6.2.5 BSA Interaction studies

The binding of copper (II) complexes (**21** and **22**) with BSA was studied using fluorescence spectra recorded at a fixed excitation wavelength of 290 nm and the emission was monitored at 340 nm. The excitation and emission slit widths and scan rates were constantly maintained for all the experiments. Stock solution of BSA was prepared in 50 mM Tris-HCl buffer (pH 7.2) and stored in the dark at 4 °C for further use. Concentrated stock solutions of each test compound were prepared by dissolving them in EtOH/Tris-HCl buffer, 1:1, v/v and diluted with Tris-HCl buffer to obtain required concentrations. 2 mL of BSA solution was titrated by successive additions of a 5 mM stock solution of the complexes using a micropipette.

6.3 Results and Discussion

6.3.1 Synthesis and isolation of metal tetrazolato complexes

A copper azide polymer complex $[Cu(phen)(N_3)_2]_n$ (phen = 1,10-phenanthroline) was chosen as the starting material where the ratio between copper to azide was 1:2 inducing the possibility for cycloaddition with different organonitriles to generate chelating bidentate tetrazole ligands which along with one ancilliary 1,10phenanthroline ligand completes the octahedral geometry surrounding the copper center and helps to break down the polymeric complex to a monomeric entity. Reaction between $[Cu(phen)(N_3)_2]_n$ and excess of benzonitrile in DMF at refluxing condition provides a tetrazolato bridged dimeric metal complex [Cu₂(phen)₂(5phenyltetrazolato)₄] (21). However, the reaction of $[Cu(phen)(N_3)_2]_n$ with pyrimidine carbonitrile and 2-cyanopyridine, respectively furnished the mononuclear copper tetrazolate complexes $[Cu(phen)(pmtz)_2]$ (22) and [pmtz = 5-pyrimidyltetrazolato, pytz = 5-(2- $[Cu(phen)(pytz)_2]$ (23)pyridyl)tetrazolato] (Scheme 6.1). These compounds are well soluble in methanol, CH₂Cl₂ and DMF. All the three compounds were characterized by IR, ESI-MS spectroscopy, elemental analyses and single crystal X-ray diffraction technique.



Scheme 6.1. Schematic representation for the synthesis of complexes $[Cu_2(phen)_2(5-phenyltetrazolato)_4]$ (21), $[Cu(phen)(pmtz)_2]$ (22) and $[Cu(phen)(pytz)_2]$ (23).

Compounds **21**, **22** and **23** show typical band in the range of 1630-1678 cm⁻¹ for tetrazolate ligand instead of two bands around 2057 cm⁻¹ for ligated azide in starting compound. The ESI-MS spectrum for the compounds $[Cu_2(phen)_2(5-phenyltetrazolato)_4]$ (**21**), $Cu(phen)(pmtz)_2]$ (**22**) and $[Cu(phen)(pytz)_2]$ (**23**) shows peaks at 568.1, 560.06 and at 558.08 which corresponds to the cationic complex of $[Cu(phen)_2\{5-phenyltetrazolato\}]^+$, molecular ion peak of $[Cu(phen)(pmtz)_2 + Na]^+$ and $[Cu(phen)(pytz)_2+Na]^+$, respectively (Figure 6.1, 6.2 and 6.3).



Figure 6.1. ESI-MS spectrum of [Cu(phen)₂(5-phenyltetrazolato)] (21).



Figure 6.2. ESI-MS spectrum of [Cu(phen)(pmtz)₂] (22).



Figure 6.3. ESI-MS spectrum of [Cu(phen)(pytz)₂] (23).

These were stable in the solid and solution phases. Herein, the effect of mono- and dinuclear copper-tetrazolato complexes as homogeneous catalysts for the oxidation of cyclohexane have been studied. These complexes were further explored for protein binding ability and catecholase like properties.

6.3.2 UV-Visible spectroscopy

The electronic absorption spectra for all the complexes were recorded in methanol. The electronic spectra for complex **21** exhibits single absorption band at 655 nm due to *d*-*d* transition and in higher energy region, the ligand to metal charge transfer band is located in the range of 240-350 nm. Compounds **22** and **23** reveal a low intensity peak in the range 600-700 nm, characteristic of *d*-*d* transition band arising due to ${}^{2}B_{1g} \rightarrow {}^{2}E_{g}$ transition of tetragonally distorted octahedral geometry^[26,27] (Table 6.2).

| Compound no. | λ , nm (ϵ , M ⁻¹ cm ⁻¹) |
|--------------|--|
| 21 | 270 (176200), 655 (438) |
| 22 | 257 (138000), 644 (1370) |
| 23 | 265 (130100), 650 (599) |

Table 6.2: Absorption spectra of compounds 21, 22 and 23 in methanol

6.3.3 Crystal structure

6.3.3.1 Crystal structures of $[Cu_2(phen)_2[5-phenyltetrazolato]_4]$ (21), [Cu(phen) (pmtz)_2](22) and [Cu(phen)(pytz)_2] (23)

The accurate structures of the three copper-tetrazolate complexes were determined by single crystal X-ray crystallographic study. The crystal structure of **21** is shown in Figure 6.4 together with the atomic numbering scheme. It crystallizes in space group P-1 (Table 6.1). The copper ions are found to be forming dimeric compounds with pentacoordinated geometry surrounding the metal center (Table 6.3). The bidentate phenanthroline moiety coordinates the copper centers in equatorial plane whereas two tetrazolato ligand make bridge between the copper centers through N^2N^3 mode. One of the tetrazolato nitrogen coordinates to the basal plane whereas nitrogen from other tetrazole ligand coordinates axially to fulfill the square pyramidal geometry. The fifth position is again occupied by the tetrazolato nitrogen in a monodentate fashion for both the copper centers. Compound **21** has been found to be forming a hydrogen bonded 1D chain along *b*-axis through C17-H17...N3, C19-H19...N4 and C20-H20...N8 (Figure A11).

Compound **22** and **23** crystallizes in the space group C2/c and P_{bcn} respectively (Table 6.1). The central ion is situated in the distorted octahedral environment where both the tetrazole ligands can coordinate the metal in chelating bidentate fashion (Figure 6.5 and 6.6).



Figure 6.4. Molecular structure of $[Cu_2(phen)_2\{5-phenyltetrazolato\}_4]$ (21) with the atomic numbering scheme.



Figure 6.5. Molecular structure of $[Cu(phen)(pmtz)_2]$ (22) with the atomic numbering scheme.

The N-Cu-N bond angles in tetrazole ligands are found to be in the range of 73-75° for both complexes (Table 6.4 and Table 6.5), observed a small bite angle compared to phenanthroline moiety at the metal center. The Cu-N bond distances are found to be within the expected range except the pyrimidine nitrogen which are coordinated axially and making distance around 2.41-2.49 Å, because of Jahn-Teller distortion.^[28]



Figure 6.6. Molecular structure of $[Cu(phen)(pytz)_2]$ (23) with the atomic numbering scheme.

| N(2)-Cu(1) | 2.001(3) | N(1)-C(1)-N(4) | 111.7(3) |
|-------------|----------|-----------------|------------|
| N(6)-Cu(1) | 1.984(3) | N(3)-N(2)-Cu(1) | 119.3(2) |
| N(7)-Cu(1) | 2.237(3) | N(1)-N(2)-Cu(1) | 129.2(2) |
| N(9)-Cu(1) | 2.036(3) | N(5)-N(6)-Cu(1) | 120.4(2) |
| N(10)-Cu(1) | 2.036(3) | N(7)-N(6)-Cu(1) | 128.9(2) |
| Cu(1)-N(7) | 2.237(3) | N(8)-N(7)-Cu(1) | 123.0(2) |
| N(1)-N(2) | 1.343(4) | N(6)-Cu(1)-N(2) | 88.98(11) |
| N(2)-N(3) | 1.331(4) | N(6)-Cu(1)-N(7) | 103.10(10) |

Table 6.3: Selected bond lengths (Å) and bond angles (°) for Complex 21

Table 6.4: Selected bond lengths (Å) and bond angles (°) for complex 22

| | | | - |
|-------------|----------|------------------|-----------|
| Cu(1)-N(5) | 1.971(5) | N(5)-Cu(1)-N(2) | 166.2(3) |
| Cu(1)-N(2) | 2.011(5) | N(5)-Cu(1)-N(1) | 94.7(2) |
| Cu(1)-N(1) | 2.045(4) | N(2)-Cu(1)-N(1) | 81.21(19) |
| Cu(1)-N(9) | 2.062(5) | N(5)-Cu(1)-N(9) | 93.72(19) |
| Cu(1)-N(13) | 2.408(7) | N(2)-Cu(1)-N(9) | 95.01(19) |
| Cu(1)-N(3) | 2.446(7) | N(1)-Cu(1)-N(9) | 157.3(2) |
| N(5)-N(6) | 1.339(7) | N(5)-Cu(1)-N(13) | 90.3(2) |
| N(6)-N(7) | 1.282(7) | N(2)-Cu(1)-N(13) | 102.5(2) |

| Cu(1)-N(1) | 2.0114(10) | N(1)-Cu(1)-N(1) | 97.05(6) |
|------------|------------|-----------------|------------|
| Cu(1)-N(1) | 2.0114(10) | N(1)-Cu(1)-N(6) | 92.72(4) |
| Cu(1)-N(6) | 2.0429(10) | N(1)-Cu(1)-N(5) | 74.53(4) |
| Cu(1)-N(5) | 2.4119(11) | N(6)-Cu(1)-N(5) | 106.55(4) |
| N(2)-N(3) | 1.3224(17) | N(1)-Cu(1)-N(5) | 88.61(4) |
| N(2)-N(1) | 1.3458(14) | N(6)-Cu(1)-N(5) | 92.82(4) |
| N(3)-N(4) | 1.3524(19) | N(5)-Cu(1)-N(5) | 154.62(5) |
| N(1)-C(1) | 1.3381(16) | N(2)-N(3)-N(4) | 110.44(10) |

Table 6.5: Selected bond lengths (Å) and bond angles (°) for complex 23

6.3.4 <u>Catalytic activity for the oxidation of cyclohexane under mild</u> conditions

Encouraged by the promising activity of copper-tetrazolato complexes as catalyst for the oxidation of 3,5-di-*tert*-butylcatechol (to *tert*-butylquinone) in previous chapters 4 and 5, herein the catalytic oxidation activity of inert substrate was investigated, such as alkanes by synthesized copper(II) complexes. The selected model reaction was the oxidation of cyclohexane in view of its industrial and economic significance and the recognized need to find new catalytic systems with improved efficiency.^[17]

Thus, compounds **21–23** were tested as catalysts for the microwave (MW) assisted peroxidative (with aq. *tert*-butyl hydroperoxide, TBHP) oxidation of cyclohexane to cyclohexanol and cyclohexanone. The primary product formed is the cyclohexyl hydroperoxide (CyOOH) which further decomposes in cyclohexanol and cyclohexanone (Scheme 6.2). The formation of CyOOH was proved by using the method proposed by Shul'pin^[23-25] where the addition of PPh₃ prior to the GC analysis of the products resulted in the reduction of CyOOH by PPh₃ (with formation of phosphane oxide) detected by a marked increase of the amount of cyclohexanol and a corresponding decrease of cyclohexanone.



Scheme 6.2. Microwave-assisted neat oxidation of cyclohexane to cyclohexyl hydroperoxide, cyclohexanol and cyclohexanone with *tert*-butylhydroperoxide catalysed by the copper complexes **21–23**.

Under optimized (100 °C and 2 h of low power (7 W) microwave irradiation, 0.1% molar ratio of Cu catalyst relatively to cyclohexane) conditions, these solvent- and additive-free MW-assisted catalytic systems lead to good yields of the oxygenated products: up to 21% for 22 and 23 (see Figure 6.7), *ca*. 5 times higher than those reported for the industrial aerobic process to guarantee a good selectivity. Cyclohexanol and cyclohexanone were the only products detected by GC-MS analysis under the assayed conditions, thus revealing a very selective process.



Figure 6.7. Effect of the reaction time on the yield of cyclohexanol and cyclohexanone obtained by microwave-assisted (7 W) neat oxidation of

cyclohexane with THBP, at 100 °C, catalyzed by 21 - 23 (0.1% molar ratio relatively to cyclohexane).

Interestingly, the activity of the dinuclear complex **21** is much less sensitive to the MW irradiation exposure time than the mononuclear compounds **22** and **23**, as depicted in Figure 6.7. Moreover, whereas for **22** and **23** cyclohexanone is obtained in a larger amount than cyclohexanol (ratio ketone /alcohol of *ca.* 1.6), the ratio cyclohexanone / cyclohexanol is 0.7 for the cyclohexane oxidations catalyzed by **21**. The presence of the carbon radical trap 2,2,6,6-tetramethyl-piperidinyloxyl (TEMPO) in the reaction medium strongly inhibits the formation of the oxygenates (total, cyclohexanol and cyclohexanone, yield decreases to 1.7% under optimized conditions for *e.g.*, compound **21** when TEMPO, 2.5 mol% *vs.* cyclohexane is added). Such an inhibiting effect, along with the formation of the cyclohexyl hydroperoxide (typical intermediate product in free-radical type reactions) and the obtained cyclohexanol/cyclohexanone ratios, supports the hypothesis of a free-radical mechanism for the cyclohexane oxidation carried out in this study.^[29]

Thus, the following mechanism can be proposed:

| $Cu^{2+} + t$ -BuOOH $\rightarrow t$ -BuOO' + H ⁺ + Cu ⁺ | (1) |
|--|-----|
| $Cu^+ + t$ -BuOOH $\rightarrow t$ -BuO' + Cu^{2+} + HO ⁻ | (2) |
| t -BuO [•] + CyH \rightarrow t -BuOH + Cy [•] | (3) |
| $Cy' + O_2 \rightarrow CyOO'$ | (4) |
| $CyOO^{\bullet} + t-BuOOH \rightarrow CyOOH + t-BuOO^{\bullet}$ | (5) |
| $CyOOH + Cu^{+} \rightarrow CyO' + Cu^{2+} + HO^{-}$ | (6) |
| $CyOOH + Cu^{2+} \rightarrow CyOO^{\bullet} + H^{+} + Cu^{+}$ | (7) |
| $CyO' + CyH \rightarrow CyOH + Cy'$ | (8) |
| $2CyOO' \rightarrow CyOH + Cy_{-H} = O + O_2$ | (9) |

6.3.5 Catalytic oxidation of 3,5-DTBC

To investigate the possible catecholase like activity of the three copper complexes, 3,5-di-*tert*-butylcatechol (3,5-DTBC) was taken as the prospective substrate as the compounds shows a low quinone-catechol reduction potential (Scheme 6.3).^[30]



Scheme 6.3. Schematic representation of catecholase activity.

The oxidation product 3,5-di-*tert*-butylquinone (3,5-DTBQ) is very much stable and exhibits a maximum absorption at 400 nm in pure methanol (Scheme 6.3). Prior to a detailed kinetic study, it is necessary to check the ability of the mono and dinuclear complexes to oxidize 3,5-DTBC. For this purpose, 10^{-5} M solutions of complexes **21**, **22** and **23** were treated with 100 equiv of 3,5-DTBC under aerobic conditions in a methanol solution. Immediately after the addition of substrate 3,5-DTBC to the complex solution, the absorption peak at 400 nm is observed, which is due to the oxidation from 3,5- DTBC to quinone (3,5-DTBQ). The reaction was monitored for 90 minutes and the band at 400 nm increases in size, thus showing considerable catecholase activity, as shown in Figure 6.8 (for complex **21**). All complexes were quite active towards catalytic oxidation of 3,5-DTBC.

Linearization of Lineweaver–Burk plot (Figure 6.9) provides the value of Michaelis–Menten constant (K_M) and maximum initial rate (V_{max}). The k_{cat} values can be calculated by dividing the V_{max} values by the concentration of the corresponding complexes. These results clearly show the ability of complex **21** to effectively catalyse the oxidation of 3,5-DTBC. The data obtained from the Lineweaver–Burk plot model are used for a comparison of the catalytic activity of the complexes toward the oxidation of 3,5-DTBC, as shown in Table 6.6. It is significant to note that compound **21** showed higher catecholase activity (k_{cat} =

 2.76×10^4 h⁻¹) than compounds **22** and **23** (k_{cat} = 1.12×10^4 and 4.25×10^3 h⁻¹, respectively). Michaelis–Menten and Lineweaver–Burk plot for the complexes **22** and **23** are not shown as these are very similar with the work reported in previous chapters (see in chapter 4.3.8, 5.2.3 and 5.3.4).



Figure 6.8. Spectral pattern of catecholase activity over time for complex **21** after addition of 3,5-DTBC.



Figure 6.9. Michael-Menten plot for complex 21. Inset: Lineweaver–Burk plot.

| Complex /Catalyst | V _{max} (M min ⁻¹) | Std. Error | K _M (M) | Std. Error | K _{cat} / T.O.N (h ⁻¹) |
|----------------------|--|------------------------|------------------------------------|-------------------------|--|
| Complex 21 | 0.00461 | 6.554×10 ⁻⁴ | 1.2780×10^{-4} | 5.9816×10 ⁻⁵ | 2.766×10^4 |
| Complex 22 | 0.00187 | 3.382×10 ⁻⁴ | 6.4980×10 ⁻⁴ | 3.8160×10 ⁻⁴ | 1.122×10^4 |
| Complex 23 | 0.00070 | 5.204×10 ⁻⁴ | 0.00349 | 0.00627 | 4.254×10^{3} |

Table 6.6: Table for selected kinetic parameters of catecholase activity exhibited by complexes 21-23.^{*a*}

^aCatalyst concentration: 0.00001(M)

6.3.6 Interaction with bovine serum albumin (BSA)

Absorbance and fluorescence studies: The interaction of complexes 21 and 22 with BSA was investigated using fluorescence studies. BSA (1 μ M) was titrated with various concentrations of the complexes ($0-100 \mu M$). Fluorescence spectra were recorded in the range of 300-550 nm upon excitation at 290 nm. The changes observed in the fluorescence emission spectra of BSA on the addition of increasing concentrations of the copper(II) complexes are shown in Figure 6.10. On the addition of complexes 21 and 22 to BSA, there is a significant decrease in the fluorescence intensity of BSA at 340 nm up to 88 and 84 % with a blue shift of 29 and 5 nm respectively. The decrease in fluorescence intensity with the blue shift shows the interaction between the complexes and BSA.^[31] The fluorescence quenching is described by the Stern–Volmer relationship $F_0/F = 1 + K_a[Q]$ where F_o and F demonstrate the fluorescence intensities in the absence and presence of a quencher, respectively, Kq is a linear Stern–Volmer quenching constant, and [Q] is the quencher concentration. The quenching constant (K_q) can be calculated from the plot of F_0/F versus [Q] (Figure 6.10) for the complexes 21 and 22, respectively. When small molecules bind independently to a set of equivalent sites, on a macromolecule, the equilibrium between free and bound molecules is represented by the Scatchard equation^[32] $\log[(F_o - F)/F] = \log K_b + n \log[Q]$ where K_b is the binding constant of the complex with BSA and n is the number of binding sites. From the plot of $\log[(F_0 - F)/F]$ versus $\log[Q]$ (Figure 6.11), the number of binding sites (n) and the binding constant (K_b) values have been obtained for both the compounds **21** and **22** respectively. K_q , K_b and n values for the interaction of the copper(II) complexes with BSA are provided in Table 6.7. The calculated value of n is around 1–1.4 for the complexes, proving the existence of a single binding site in BSA for both the complexes. From the values of K_q and K_b , it is proved that complex **21** interacts with BSA more strongly than the complex **22**. Quenching usually occurs either by dynamic or static mode.^[32] UV-Visible absorption spectroscopy is the tool to determine the type of quenching involved. Addition of the complexes to BSA leads to an increase in BSA absorption intensity without affecting the position of the absorption band. It showed the existence of static interactions between BSA and the complexes. Fluorescence quenching and Scatchard plots for complex **22** is not shown as they are very similar with our previous work. It should be noted that the interaction of complex **23** with BSA was not discussed here as the compound was not soluble in EtOH/Tris-HCl buffer.



Figure 6.10. Fluorescence quenching of BSA by complex **21**. Stern–Volmer plot is in the inset.



Figure 6.11. Scatchard plot of the fluorescence titration of the complex 21 with BSA.

Table 6.7: Protein binding constant (K_a), quenching constant (K_q) and number of binding sites (n) values

| System | $K_{SV}(M^{-1})$ | $K_q (M^{-1} S^{-1})$ | $K_a (M^{-1})$ | n |
|------------------------|---------------------|------------------------|-----------------------|------|
| Complex 21 -BSA | 4.045×10^4 | 6.545×10 ¹² | 1.255×10^{6} | 1.38 |
| Complex 22-BSA | 2.875×10^4 | 4.652×10^{12} | 1.190×10^{6} | 1.34 |

6.3.7 Docking analysis

The experimental observation on the quenching of bovine serum albumin (BSA) by three copper(II) complexes were validated using computational approach. Molecular docking studies is widely accepted approach for understanding the interaction of small-molecules to proteins. In the present study, the single crystal X-ray structures of Cu(II) complexes were considered as the input conformations for possible interaction with BSA whose crystal structure is reported recently (PDB: 4F5S). In this study, molecular docking simulation was employed as a complementary way to identify the possible binding sites of the protein with the dinuclear and mono-nuclear copper complexes. It is well documented that the fluorescence of BSA arises mainly due to the presence of tryptophan (Trp) residues. Eventually in BSA two Trp residues were identified such as Trp134 (Hydrophilic region or domain I) and Trp213 (Hydrophobic region or Domain II). ^[33] Additionally, BSA has allosteric binding sites, indicating compounds can bind in different sites depending on their nature and sizes. In this present study, we have found that the two complexes have significant binding interactions with BSA at domain I (Trp134) region (Figure 6.12).



Figure 6.12. Molecular docking of the complexes 21(left) and 22 (right) with BSA.

Among the two complexes, compound **21** exhibited highest binding affinity with a binding energy of -8.95 kcal/mol. The negative value is the indicative of a stable and favorable protein-ligand interaction. The other compound **22** also showed reasonably good affinity (-5.15 kcal/mol) (see Table 6.8). The favorable binding of complexes in the present study with BSA was supported by the H-bonding interactions of N-atoms of the complexes with side-chain residue of Lysine 114 (Lys114). Additionally, while compound **21** do not show any affinity at another binding site (domain II), compound **22** found to have moderate binding affinity to both the sites. The difference in their selectivity is probably due to the difference in their sizes.

| Lig code | Binding Energy (Kcal/mol) | Hydrogen bonding |
|----------|---------------------------|------------------|
| Lig 21 | -8.95 | LYS114 |
| Lig 22 | -5.15 | LYS114 |

Table 6.8: Docking data for the compounds **21** and **22** with BSA (PDB: 4f5)

6.4 Conclusion

In conclusion two new mononuclear and one dimeric copper tetrazolato complexes were prepared by [2+3] dipolar cycloaddition between copper ligated azide and different organonitriles. Single crystal X-ray diffraction (XRD) results revealed that complex 21 has a distorted square pyramidal geometry whereas complexes 22 and 23 are having octahedral geometry around the metal ion. The three compounds exhibited good catalytic activity concomitant with a high selectivity for the oxidation of cyclohexane to the cyclohexanol and cyclohexanone mixture. Although the obtained yields are comparable to other catalysts previously reported however these catalytic systems present several advantages in terms of sustainability: they are solvent-and additive-free, fast, use of alternative green energy source (MW), availability of facile work-up process and use of non-toxic and cheap metal as catalyst. Furthermore, all compounds exhibited promising catecholase like activity with TON value to the order of 10^4 h^{-1} and showed high fluorescence quenching while interacting with BSA. The Stern–Volmer quenching constant value of 10^4 M^{-1} shows that both static and dynamic quenching occurring simultaneously. Molecular docking studies indicated that dinuclear copper complex 21 has comparatively higher affinity towards BSA protein.

6.5 <u>References</u>

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Chapter-7 Conclusions and future scope of work

7.1 Conclusion

Tetrazoles are important class of compound due to their wide range of applications as energetic materials,^[1] ligands in coordination chemistry,^[2] intermediates in organic synthesis,^[3] and drugs in pharmaceuticals.^[4] A tetrazole is a five membered ring containing four nitrogen and one carbon atom. Due to its energetic potential and structural similarity to carboxylic acids, this ring system has a wide number of applications. In the last few years, design and synthesis of metal–tetrazole complexes (MTCs) have gained considerable attention, emerging not only from their potential applications in many areas but also as a result of their chemical and structural diversities.^[5] A sustainable process to produce metal-tetrazolato complexes has been employed in this thesis that can achieved high yields under relatively milder conditions. The synthesized complexes have shown interesting properties in terms of geometrical isomerism, magnetism, interaction with biomolecules, bioinspired catalysis and C-H bond activation.

As tetrazole based ligands are in major focus in last few years because of their wealthy coordination chemistry that leads to great variety of interesting structures,^[6] various methods have been reported to generate tetrazole ligands in presence of different catalysts. Among them, in 2001, one environmentally friendly approach has been reported.^[7] However, there are many other reports where substituted tetrazoles have been generated mostly by energy demanding pathways. Furthermore, *in-situ* generation of tetrazole ligands to generate metal complexes are also reported which are mainly achieved through uncontrolled solvothermal pathways. Controlled production of tetrazolato-metal complexes through cycloaddition of metal ligated azide and organonitriles are relatively unexplored and rare.^[8] In this thesis *in situ* production of tetrazole based ligands and their application in various field of chemistry have been explored as discussed below.

Chapter 2 describes the synthesis of new bistetrazolato complexes $[Co(N_4CR)_2(en)_2]NO_3$ via 1,3-dipolar cycloaddition between diazide cobalt complex cis-[Co(N₃)₂(en)₂]NO₃ and different organonitriles (NCR) under focused microwave irradiation. Interaction of cis-[Co(N₃)₂(en)₂]NO₃ with benzonitrile yielded cis-[Co(5-phenyl-tetrazolato)₂(en)₂](NO₃) (1), while reaction with 4chlorobenzonitrile afforded *trans*- $[Co{5-(4-chlorophenyl)-tetrazolato}_2(en)_2]NO_3$ (2). Interestingly, in the case of 3-cyanopyridine the reaction produced both cisand *trans*-isomers $(cis-[Co{5-(3-pyridy])-tetrazolato}_2(en)_2]NO_3 \cdot DMF$ (cis-4), *trans*- $[Co{5-(3-pyridyl)-tetrazolato}_2 (en)_2]NO_3$ (*trans*-4), whereas for 4cyanopyridine, exclusively cis-[Co{5-(4-pyridy])-tetrazolato}₂(en)₂]NO₃·Et₂O (cis-5) isomer was obtained and for 4-bromobenzonitrile, only the trans-[Co{5-(4bromophenyl)-tetrazolato $_2(en)_2$ NO₃·DMF (*trans-6*) compound was isolated. These suggested a probable role of remote substitution of the phenyl ring indicating the formation of the preferential isomer. The interaction of trans- $[Co(N_3)_2(en)_2]ClO_4$ under similar condition with 4-cyanopyridine, 4bromobenzonitrile and benzonitrile furnished mixture of cis- and trans- isomers of bis(tetrazolate) [R = $4-NC_5H_4$ complexes (cis-[Co{5-(4-pyridyl)tetrazolato $\frac{1}{2}(en)_{2}ClO_{4}\cdot H_{2}O$ (*cis*-7) and trans-[Co{5-(4-pyridyl)tetrazolato $_{2}(en)_{2}$ ClO₄·H₂O (*trans*-7), 4-BrC₆H₄ (*cis*-[Co{5-(4-bromophenyl)tetrazolato $_2(en)_2$]ClO₄ (*cis-8*), trans-[Co{5-(4-bromophenyl)-(*trans*-8) and C_6H_5 $(cis-[Co(5-phenyltetrazolato)_2$ tetrazolato $_2(en)_2$ ClO₄ $(en)_2$]ClO₄ (*cis*-9), *trans*-[Co(5-phenyltetrazolato)₂(en)₂]ClO₄ (*trans*-9) where the *cis*-geometry predominates. It has been assumed possibly the counter-anion which was helping the compound to crystallize and also interacting with the complex in solution state was also contributing to preferential geometrical isomer formation upon cycloaddition. Further, a DFT calculation study revealed that the *trans* isomer trans-6 was being further stabilized by means of van der Waals interactions through an extra DMF molecule (compared to *cis-8*), which was present as solvent of crystallization along with some Br....Br halogen interaction.

Chapter 3 reported the formation of polynuclear Ni(II) compounds by *in situ* generated tetrazolato ligands from nickel based azide precursors upon treatment

with different nitrile sources. The nuclearity of the product depends on the nature of organonitrile used for cycloaddition. Thus when the organonitrile used is benzonitrile 3-cyanopyridine trinuclear species $[Ni_3L_2^1(5$ or $[Ni_3L_2^1\{5-(3-pyridyl)-tetrazolato\}_4]$ (12)and phenyltetrazolato)₄(DMF)₂] (DMF)₂]·2H₂O (13) were obtained, respectively, formed by tetrazolato bridge (via N(2)N(3) mode) and a phenoxo bridge between central and terminal nickel centers. For both the molecules the three nickel centers were linearly arranged. The separation between metal centers are found to be in the range of 3.327-3.336 Å. Treatment with 1,2-dicyanobenzene complex **11** afforded a pentanuclear complex $[Ni_5L_4^1 \{5-(2-cyanophenyl)-tetrazolato\}_4(OH)_2(H_2O)_2]\cdot 3H_2O\cdot DMF$ (14). In this pentanuclear compound two dimeric nickel units were connected to the central nickel center by a μ_3 -hydroxo bridge and a tetrazolate ligand operating via a relatively rare 1,2,3-bridging mode. The distance between the central nickel atom and terminal nickel atoms are found to be in the range of 3.460-3.589 Å, whereas the distances between two nickel centers of terminal dimer are 3.687 Å. The number of metal bound solvent molecules and solvent of crystallization in 13 and 14 were also confirmed by thermo-gravimetric analysis. The magnetic susceptibility data for compound 12-14 in the temperature range of 2-300 K showed dominant antiferromagnetic interactions between the nickel centres for all the complexes. The magnetic exchange parameters of one of the compound 13 has been investigated by DFT in broken-symmetry approach.

Chapter 4 introduced rationally designed two new water soluble copper-tetrazolato complexes [Cu{(5-pyrazinyl)tetrazolato}₂(1,10-phenanthroline)] (**15**) and [Cu{(5-pyrazinyl)tetrazolato}(1,10-phenanthroline)₂](NO₃)_{0.5}(N₃)_{0.5} (**16**) by metal mediated cycloaddition reaction. Structural determination revealed that both compounds **15** and **16** were octahedral in nature. The interactions of these water soluble copper tetrazolate compounds with biomolecules like DNA and bovine serum albumin (BSA) were studied. Both the complexes have shown binding ability to CT-DNA where compound **16** was found to be a stronger binder. DFT studies indicated that a lower HOMO-LUMO energy gap between DNA fragment and metal complexes

might be the reason behind this kind of stronger interaction. Furthermore both the complexes **15** and **16** have shown DNA nuclease property in presence and absence of additional co-reagents. Inhibitation of DNA cleavage activity in presence of sodium azide indicates the involvement of singlet molecular oxygen in mechanistic pathway. The interaction of compounds **15** and **16** with albumin protein show intense interaction between metal complex and protein with very high fluorescence quenching. The Stern–Volmer quenching constant value obtained was to the tune of 10^{13} M⁻¹ showing that both static and dynamic quenching occurring simultaneously. Besides this, compound complex **16** exhibited pronounce catecholase like activity with TON value to the order of 10^4 h⁻¹. An ESI-MS spectral study indicated the probable involvement of dimeric species [(phen)₂Cu–(OH)₂–Cu(phen)₂]²⁺ in the catalytic cycle.

In chapter 5, a series of mono- and binuclear nickel(II) and copper(II) tetrazolate NiL²(5-phenyltetrazolato)] (17), $[Ni_2L^2_2\{5-(2-cyanophenyl)$ complexes tetrazolato $_{2}$ (18), [Cu₂L²₂{5-(2-cyanophenyl)-tetrazolato}₂] (19) and [Cu₂L²₂{5phenyltetrazolato $_{2}$]·C₆H₅CN (**20**) synthesized by 1,3-dipolar cycloaddition between metal ligated azide and organonitriles have been reported. All the complexes were characterized by X-ray crystallography, elemental analyses, and different spectroscopic techniques. Tuning at the 5-position of the tetrazolato ligand with a nitrile substituted phenyl group provided a weaker ligand, leading to an enhanced catecholase activity of the metal complexes through easier dissociation and in turn providing the vacant coordination site for the substrate. Copper complex 19 has shown much superior activity than the analogous nickel complex 18. This result implied that the oxidation process occurred through metal centered for copper complex, rather than preferential ligand centered oxidation for nickel system. The comparative catalytic activity of both the compounds was further investigated by DFT calculations supporting the relative order of activity among the various complexes. The DNA and protein binding of the complexes (17 and 19) were investigated using absorbance and fluorescence spectroscopic techniques. The results of DNA binding experiments revealed that the square planer Ni(II)-

tetrazolato complex 17 significantly bind to double stranded DNA, possibly by intercalation and having binding constant in the order of 10^5 M⁻¹. The experimental results suggested that the complex 17 can bind to DNA more strongly than the complex 19. The protein binding studies of the compounds suggested a strong interaction with BSA for the dinuclear Cu(II)-tetrazolate complex 19 than complex 17.

Chapter 6 disclosed the synthesis of new copper tetrazolato complexes $[Cu_2(phen)_2(5-phenyltetrazolato)_4]$ (21), $[Cu(phen)(5-pyrimidyltetrazolate)_2]$ (22) and $[Cu(phen){5-(2-pyridyl) tetrazolate}_2]$ (23). The structure characterization of these compounds were achieved with X-ray diffraction (XRD), infrared spectrophotometer, elemental analyzer and mass spectrometry. XRD results revealed that complex 21 is having distorted square pyramidal geometry and complexes 22 and 23 have shown octahedral geometry around the metal ion. These complexes exhibited a promising catalytic activity concomitant with a very high selectivity for the oxidation of cyclohexane to the cyclohexanol and cyclohexanone mixture. Although the obtained yields were comparable to others previously reported catalytic systems, however these compounds have shown several advantages in terms of sustainability: they were solvent-and additive-free, fast, utilize an alternative green energy source (MW), allow a facile work-up process and use a non-toxic, biologic and cheap metal copper as catalyst. Further optimization on the design of 21-23, based on the present results, towards more effective (in particular, recyclable) catalysts deserves to be developed. Furthermore, all compounds display catecholase like activity with TON value to the order of 10^4 h^{-1} and show high fluorescence quenching while interacting with metal complexes and BSA. The Stern–Volmer quenching constant value of 10⁴ M⁻¹ suggested that both static and dynamic quenching occurred simultaneously. Molecular docking studies indicated that dinuclear copper complex 21 has the highest binding energy with the protein BSA.

7.2 <u>Scope for Future Work</u>

A majority of compounds in this work have been prepared by microwave assisted method which proved to be an excellent tool for generation of tetrazolato ligand *in situ*. It is relatively a cleaner method, reducing waste since it requires very small amounts of solvent (or no solvent) and a simple filtration as the isolation process, reducing the use of time and solvent consuming purification techniques such as chromatography or crystallization. Microwave assisted synthesis in addition of being clean, economic and efficient offers access to new species that are sometime difficult or impossible to attain using conventional synthetic methods. Hence it opens up great and yet unexplored possibilities to chemists.

Conventional synthetic procedure for tetrazolato ligand largely depends upon hydrothermal/solvothermal process, which generates metal-tetrazolate polymers in an uncontrolled way irrespective of whether the tetrazoles were used as a starting material or generated in situ by the cycloaddition pathway between azide and organonitriles in the presence or absence of supporting ligands.^[9,10,11] Limiting nuclearity to a finite level is a challenging task from the synthetic viewpoint as polynuclear complexes can many times show unusual magnetic or catalytic properties.^[12,13,14] There are a few literature reports which proved that preparation of metal-tetrazolate compounds by cycloaddition under microwave irradiation in a controlled and systematic manner. In this direction, there is successful generation of polynuclear compounds with limiting nuclearity in presence of additional ligand under mild condition.^[15] This methodology can be explored and the metaltetrazolate polymers can be generated in environment friendly way. Some intriguing approaches such as the use of mixed ligands and tetrazolates deserve further attention. Novel heterometal tetrazole compounds can show even more fascinating properties towards bioinspired catalysis and C-H bond activation reactions. Future research will certainly focus more on developing new applications in catalysis, adsorption, magnetic and optical materials. Improving the performance of either already mentioned or newly designed metal tetrazole system.

7.3 References

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APPENDIX-A



Figure A1: ESI-mass spectrum indicating molecular fragment peak of complex cis-[Co(5-phenyl-tetrazolato)₂(en)₂]NO₃·MeOH (1), m/z = 469.16 [M]⁺.



Figure A2: ESI-mass spectrum indicating molecular fragment peak of complex trans- $[Co{5-(4-cholorophenyl)-tetrazolato}_2(en)_2]NO_3(2), m/z = 537.09[M]^+$.



Figure A3: ESI-mass spectrum indicating molecular fragment peak of complex cis- $[Co{5-(3-pyridyl)-tetrazolato}_2(en)_2]NO_3 \cdot DMF$ (*cis-4*), $m/z = 471.15 [M]^+$.



Figure A4: ESI-mass spectrum indicating molecular fragment peak of complex trans- $[Co{5-(3-pyridyl)-tetrazolato}_2(en)_2]NO_3 \cdot DMF$ (*trans-4*), $m/z = 471.15 \text{ [M]}^+$.



Figure A5: ESI-mass spectrum indicating molecular fragment peak of complex cis- $[Co{5-(4-pyridyl)-tetrazolato}_2(en)_2]NO_3 \cdot Et_2O$ (*cis-5*), $m/z = 471.20 [M]^+$.



Figure A6: ESI-mass spectrum indicating molecular fragment peak of complex trans-[Co{5-(4-bromophenyl)-tetrazolato}₂(en)₂]NO₃·DMF (**trans-6**), m/z = 626.99 [M]⁺.



Figure A7: ESI-mass spectrum indicating molecular fragment peak of complex cis-[Co{5-(4-pyridyl)-tetrazolato}₂(en)₂]ClO₄·H₂O (*cis-7*), m/z = 471.15 [M]⁺.



Figure A8: ESI-mass spectrum indicating molecular fragment peak of complex cis-[Co{5-(4-bromophenyl)-tetrazolato}₂(en)₂]ClO₄ (*cis-8*), m/z = 627.18 [M]⁺.



Figure A9: ESI-mass spectrum indicating molecular fragment peak of complex cis-[Co(5-phenyl-tetrazolato)₂(en)₂]ClO₄·MeOH (*cis-9*), m/z = 469.16 [M]⁺.



Figure A10: ESI-mass spectrum indicating molecular fragment peak of complex trans- $[Co(5-phenyl-tetrazolato)_2(en)_2]ClO_4\cdot MeOH\cdot 4C_6H_5CN$ (trans-9), $m/z = 469.16 [M]^+$.



Figure A11: Hydrogen bonded 1D chain formation along *b*-axis for compound 21.