CHAPTER 1

INTRODUCTION

1.1 Background

Cyclic Compounds play a crucial role in Organic Chemistry, and their unique properties always offer an interesting subject. Numerous heterocycles are now identified as key compounds in most biological systems, and meanwhile they constitute a vast family of well-known compounds in chemical science. Among the heterocycles, nitrogen based 5-membered cyclic compound commonly known as 'Azoles' are now identified as extremely useful and promising energetic organic compounds in modern chemistry. Experimental and theoretical studies of azoles contributes tremendous researches at various disciplines from the late twentieth century. The 5-Membered N-Heterocycles are found to present in significant number of biologically important molecules and play indispensable role in pharmaceuticals, agro-chemicals, electro-active polymers, and many of biologically important natural product (e.g. vitamins) [Bruckner, R., 2002; Balaban *et al*., 2004; Petersen and Kiener, 1999; Ivashkevitch *et al.*, 2009; Zhao-Zu *et al*., 1999]. Since they are high energy-density materials, there is also interest as having applications as explosives material in combustion chemistry and also as propellant [Silva *et al*., 2006; Klapotke and Piercey, 2011; Ichino *et al*., 2008; Zhu and Xiao, 2010; Galvez-Ruiz *et al*., 2005; Chen *et al*., 1999; Halauko *et al*., 2010; Wang and Tian, 2002; Nathan and Lammerstma, 1996].

5-Membered heterocycles with two or more nitrogen atoms and their derivatives are well known compounds, but having distinct properties in the gas phase and in solvent in the study of cyclic chemistry. The nitrogen based 5-membered heterocycles, commonly termed as azoles are reported to show high thermodynamic stability and possess a complete aromatic nature from delocalized π-electron and their unique property is accompanied by the possibility of existence of tautomers. Azoles are nitrogen-containing

five-membered ring heteroaromatic compounds whose structures are analogous to cyclopentadiene, C_5H_6, where N atom has replaced one or more C-H groups. These compounds constitute an important class of heterocycles whose structures appear as fundamental units in biomolecules, pharmaceuticals, ionic liquids, dyes, explosives, and fuels [Jiang *et al*., 2011; Shalini *et al*., 2010]. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures and in particular, Nitrogen containing polycyclic structures has been reported to be associated with a wide range of biological activity [Thomas, 2003]. Five-member nitrogen heterocycles are structural fragments of a series of biologically active compounds where their derivatives are found to provide wide applications as plant growth regulator, pesticides, insecticides, herbicides, fungicides, antibacterial, antiviral, anti-inflammatory, antiulcer, analgesic, antihypertensive, anti-allergic, antibiotic, anticonvulsant, antagonist and useful industrial reagent such as corrosion inhibitors, stabilizer in photography and photo-imaging, gas generating agent, pigments and in petroleum refinery [Chen *et al*., 1999; Kiselev *et al*., 2011; Varadaraji *et al*., 2010; Jeyachandran and Shriram, 2011; Fang-Fang *et al*., 2005; Thomas, 2007; Avendano and Menendez, 2008; Lokesh *et al*., 2010; Li *et al*., 2011; Huang *et al*., 2005; Monajjemi *et al*., 2006; Zavaglia *et al*., 2005; Xu *et al*., 2006; Bisht *et al*., 2007; Wang *et al*., 2009; Mensah *et al*., 2009; Kiselev and Gritsan, 2009; Ogretir *et al*., 2010; Dimova and Perisic-Janjic, 2009; Frijia *et al*., 2008; Mohite *et al*., 2009].

N-Heterocycles are found in different classes of valuable natural compounds like amino acids, nucleosides, vitamins, and alkaloids; they are produced by nature, and are of interest due to their bio-activity [Petersen and Kiener, 1999]. The high-temperature reactions of five membered nitrogen-containing heterocycles are also of interest in

atmospheric and combustion chemistry, due to the role of these compounds in the production of the pollutants NO and NO_2 (NO_x) during combustion processes. Heterocyclic nitrogen compounds containing functional groups are prominent in organic fuels such as coal and biomass; in most coals, nitrogen is predominantly present in the pyrrolic form [Silva *et al*., 2006].

The most important breakthrough and highly interesting improvement in recent year is the substitution of bioactive site with nitrogen based 5-membered heterocycles as a non-classical bioisosteres in pharmacology [Ichino *et al*., 2008]. For example, when tetrazole moiety is used to replaced carboxylic, the bioisosteric substitution bring forth additional advantages such as prolonged half-life for the drug molecules to get to the target site and thus, render the molecule less susceptible and metabolically more stable [Jeyachandran and Shriram, 2011; Nogrady and Weaver, 2005; Himo *et al*., 2003; Massi *et al*., 2010; Balabin, 2010; Yoo *et al*., 1999]. Many biological systems are unable to differentiate between these two distinctive functional groups. We suspect stereo structures and thermo-chemical stability is responsible for such biological activity besides acidity.

Recent growth of patent claims and publications relating to theoretical and experimental works on azole derivatives are deeply associated with its potency for the treatment of cancer and AIDS [Shalini *et al*., 2010; Jeyachandran and Shriram, 2011; Avendano and Menendez, 2008; Huang *et al*., 2005; Zavaglia *et al*., 2005; Massi *et al*., 2010; Bugalho *et al*., 2002; Jochim *et al*., 2009; Islamoglu *et al*., 2010; Koldobskii and Ostrovskii, 1994]. Some of the specific antimetabolites possess nature to interfere with enzymatic reaction and cause inhibition of essential metabolic route. This action can be specifically directed towards cancer cells. For example, ZD-9331 is a potent inhibitor of

TS (Thymidylate Synthase), which has been under advanced clinical evaluation interestingly feature isosteric γ-carboxyl-tetrazole replacement at the glutamic portion for the prevention of polyglutamation. Hormones and their activities in certain biological system are highly responsible in cancer therapies. Particular steroid hormones are the main determinants in case of induction and growth of several types of tumors (malignant cells) through enzymatic reaction in living systems. Non-steroidal aromatase inhibitor comprises structurally varied compounds, which are able to bind to the active site of aromatase through the coordination of heterocyclic nitrogen atom, usually an imidazole or triazole rings to the iron atom of the heme group of the enzyme [Thomas, 2007; Avendano and Menendez, 2008]. Among this class of drugs, triazole derivatives - anastrozole, vorozole and letrozole are found to have high potency and specific aromatase inhibitors that allow estrogen suppression [Nogrady and Weaver, 2005].

1.2 Review of Literature

Investigations on 5-membered nitrogen heterocycles started from the past decades, though results from these far-reaching studies were reported only recently. With the fast growing technique of computational method, theoretical studies in terms of different scientific indexes from various disciplines concerning chemical, physical and biological properties of the azoles as a whole has now drawn considerable amount of interests. Chemical properties of azoles and their derivatives are now the most precious and highly valued informations in organic chemistry, and there is intense development in the chemistry of azoles from the areas of experimental and theoretical researches. This is mainly because a large number of azole families are considered promising compounds for the near future with wide applications.

Annular tautomerism in tetrazoles was reported by Charton [Charton, 1969] where values of the macroscopic ionization constant, pK_M, of 5-substituted tetrazoles have been calculated from the values of microconstants which were obtained from the extended Hammett equation by comparison with suitable model systems. From his report of substituted tetrazole, N2 protonated tautomer appears to be predominant. In 1973, C-NMR spectra of 1-substituted 1,2,3-triazoles and 1-phenyl tetrazoles have been obtained by Mikael Begtrup [Begtrup, 1973] where effect of substitution with methyl, chlorine or bromine on δ-values and coupling constant were measured and the data indicate that interannular conjugation is extensive in simple N-substituted azoles. Experimental evidences and theoretical considerations of gas phase mass spectrometer study of prototropic equilibria in 5-substituted tetrazoles was reported by Razynska and co-workers [Razynska *et al* 1983]. Their work evaluates the fragmentation pattern of tautomerism in 5-methyltetrazole and its isotopically labelled derivatives through LCAO-MO method using quantum chemical calculation. The results include displacement of equilibrium constant in the gas phase toward the 2H-tautomer and randomization of hydrogen between -CH_3 and –NH groups from the mass spectra of 5-methyl tetrazole.

Experimental and theoretical studies on proton affinities of azoles including 1,2,4-triazole was done by Meot-Ner and co-workers [Meot-Ner *et al.*, 1985] having a report on pulsed high pressure mass spectrometry and *ab initio* calculation of protonation enthalpies at the MP2/6-31G(d,p) level of theory and their calculations showed the protonation site favoring N4 in 1,2,4-triazole where the N2 less favored by 13 kcal/mol.

A detailed account on systematic study of tetrazole on account of method of synthesis, physicochemical properties and applications including electronic structures, acid-base properties, tautomerisms, reactivities and thermal stabilities was published

[Koldobskii and Ostrovskii, 1994] by Koldobskii and Ostrovskii, and they mentioned that systematic analysis of tetrazole involving the examination of 700 patents published in 20 countries at that time. Polarizabilities of aromatic 5-membered rings of azoles, including triazoles and tetrazoles tautomers from ab initio electron correlation calculations were reported by Kassimi and co-workers [Kassimi *et al*., 1995]. Their study showed that structural isomerism affects the dipole moments strongly but the dipole polarizabilities were rather insensitive to it, and their results from HF calculation indicate that only about half the polarizability comes from the π-electrons. They also pointed out that simple empirical formulas correlate the calculated polarizabilities quite well.

Experimental and theoretical study on the aromaticity variation with environment of 1H-1,2,4- triazole was reported by Katritzky and co-workers having a result of significant increase in aromaticity with the polarity of the medium [Katritzky, *et al*., 1996]. Theoretical study on chlorotetrazole isomers was reported by Heming and co-workers [Heming *et al*., 1998]. They calculated molecular geometries and electronic structures with *ab initio* method at MP2/6-311G** level. Their results showed planar structure and aromatic nature with uniform bond length, and 5-substituted tetrazole was more acidic as compare to the 1- and 2-substituted isomers [Hemming *et al*., 1998]. They predicted 5-Chloro-2H-Tetrazole as the most stable and lowest in energy.

A study of solvent polarity and hydrogen bonding effects on the nitrogen NMR shielding of isomeric tetrazoles and *ab initio* calculation of nitrogen shielding of azoles was carried out by Witanowski and co-workers. Using RHF and CHF approach combined with 6-31++G** basis set and GIAO method, they reported that the solvent effect concerned on NMR shielding were quite significant where pyridine-type nitrogens exhibit deshielding effect with increasing polarity while pyrrole-type nitrogen atoms

exhibit increase in the magnetic shielding [Witanowski *et al*., 1998]. A triazole ligand, 2,6-bis (5-butyl-1,2,4-triazol-3-yl)-pyridine was studied experimentally and theoretically by Drew and co-workers in 1999. Their theoretical result indicate three possible conformation characterized by the N(4)-C-C-N(py) torsion angles as trans-trans, cis-trans and cis-cis [Drew *et al*., 1999].

Results from the study on heat of formation for 49 tetrazole derivatives with Density Functional Theory B3lyp method was reported by Chen and co-workers. Their report on calculated heat of formation indicated that most neutral 2H-isomers are more stable than the corresponding 1H-isomers, whereas the 1-substituted tetrazole anions are more stable than the 2-substituted anions [Chen *et al*., 1999]. Furthermore, their results consistently showed that C-substituted tetrazoles are more stable than the corresponding N-substituted isomers.

Again, Chen and co-workers reported results from theoretical study on tetrazole and its derivative and thermodynamic calculations of amino derivatives of tetrazoles at MP2/6-31G* level of *ab initio* theory. Their results indicated planar ring structure with aromatic amino derivatives of tetrazole though the conformation of the amino group was mainly depend on the electronic repulsion between the substituent and the ring [Zhao-Xu *et al*., 1999]. They also reported that the energy gap between the LUMOs and HOMOs of 2H-aminotetrazoles and ground state C-aminotetrazole are smaller than those of the corresponding 1H-isomers and ground state N-aminotetrazole respectively.

Report from quantum-chemical study of the relative stability of N-substituted tetrazole isomers in the gas phase and in solution, carried out by Ivashkevitch and co-workers indicated that 2-substituted tetrazoles are more stable in the gas phase and the solvent nature forms an important factor in isomerization of N-substituted tetrazoles and

also rise in the solvent polarity leads to displacement of the equilibrium toward 1-substituted isomers [Ivashkevitch *et al*., 2000]. Investigation of low temperature matrix-isolation and solid state vibrational spectra of tetrazole revealed that in the crystalline phase, tetrazole exist in its 1H-tautomeric form (triclinic α-form) [Bugalho *et al*., 2001]. In gaseous phase, 2H-tetrazole is more stable than the 1H-tautomer by 6.95 kJ/mol. According to Bugalho and co-worker, the experimental value of $\Delta E_{1H\text{-}2H}$=6.95±1.50 kJmol^{-1} compares fairly well with theoretical prediction of 9.96 kJmol^{-1} enthalpy differences.

Ab initio MD and quantum chemistry study on the mechanism of thermal decomposition of 5-nitro-1-H-tetrazole performed by Wang and co-worker [Wang *et al*., 2002] predicted that reaction channel by direct ring rapture of N1-N2 has the lowest energy barrier for the first step followed by higher energy in the succeeding step. Their study suggested that the thermal decomposition of 5-nitro-1H-tetrazole should be the main contribution to the N_2 unit releasing process of the decomposition of 5-nitro-tetrazole. Astakhov and co-worker obtained crystal and molecular structure of nitramino derivatives of tetrazole and 1,2,4-triazole by single X-ray diffraction. They reported monoclinic crystal structure with planar tetrazole fragment [Astakhov *et al*., 2004]. Review paper on aromaticity as a corner stone of heterocyclic chemistry featured higher aromatic property of 2H-1,2,3-triazole over 1H-isomer, and less aromaticity of tetrazoles than diazoles [Balaban *et al*., 2004].

In 2005, experimental and theoretical study of 1,5-diamino-4-H-1,2,3,4-tetrazolium perchlorate by Drake and co-workers strongly support protonation of tetrazole ring at N4, and their calculation at CCSD(T)/6-311G(2df,p)//MP2/6-311G(d,p) predict protonation at N4 to be the lowest in energy [Drake *et al*., 2005]. In 2005, Raczynska and co-workers

presented that 2H-tautomer is the most stable form in the gas phase whereas more polar 1H-tautomer is the most stable species in solution, and in the solid state, 1,2,3-triazole exists as 1:1 mixture of 1H- and 2H-tautomers [Raczynska *et al*., 2005]. Theoretical studies of tautomeric equilibria for 5-membered N-heterocycles in gas phase and in solution predicted that the 2H-tautomer is the most stable for 4-methyl-1,2,3-triazole and even for aqueous solution despite the small dipole moment, whereas the 4H-tautomer of 3-Methyl-1,2,4-triazole is unstable in any solvent within the ϵ = 4.7-78.4 range, and for 5-methyl-tetrazole, the population of 1H-from increase with increasing dielectric constant [Nagy *et al*., 2005]. A DFT investigation of NQR parameters (quadrupole coupling constant, asymmetry factor) on tetrazole-azide tautomeric equilibria by revealed that nitrogen atom of the compound is highly sensitive to substituent effects [Monajjemi *et al*., 2006], and N1 and N2 atoms showed similar behavior as well as N3 and N4.

Quantum chemical study on the Structure and thermochemistry of five-membered nitrogen-containing heterocycles and their anions and radicals was reported on the evolution of unwanted NO and NO_2 from organic fuels such as coal and biomass [Silva *et al*., 2006]. Using the theoretical methods CBS-APNO, G3, and G3B3, calculated enthalpies of formation were 63.7, 46.8, 81.0, and 79.0 kcal mol-1 for 1,2,3-triazole, 1,2,4-triazole, 1*H*-tetrazole, and 2*H*-tetrazole. Enthalpies of formation of 1,2,3-triazole, 1,2,4-triazole, 1*H*-tetrazole, and 2*H*-tetrazole were 63.7, 46.8, 81.0, and 79.0 kcal mol-1 via atomization work reactions. A computational study on π and σ modes of metal binding to heteroaromatics reported that the 4H-1,2,4-triazole as the strongest σ complex among the 29 five-membered and six-membered heteroaromatic systems considered [Vijay and Sastry, 2006], and the complexation energy of the π and σ complexes was

found to decrease with the increase in the heteroatom substitution in the ring where the metal binds away from the σ complexes of electron deficient nitrogen.

Experimental, theoretical and biological study on 1-(4,5-dihydro-3-arylpyrazol-1-yl)-2-(1H-1,2,4-triazol-1-yl)-ethanone, a triazole derivative [Xu *et al*., 2006] revealed a moderate fungicidal activities. Experimental study on the nitration products of 5-amino-1H-tetrazole and methyl-5-amino-1H-tetrazole [Klapotke and Stierstorfer, 2007] revealed that the compound was stabilized in the crystalline state by strong intermolecular H-bonds, and the nitration products were promising energetic materials, showing increased in sensitivity towards friction and impact.

From the mass spectrometry and theoretical study on tautomeric equilibria of tetrazole and 5-methyltetrazole and its isotopically substituted derivatives [Allegretti *et al*., 2007], the equilibrium in the gas phase was found to be displaced towards the 2H-tautomer. Also, for tetrazolate anions, a shortening of the 1-2 bond and simultaneous elongation of the 2-3 bond was observed. According to this study, the relative thermodynamic stability of the 2H-forms as compared to the 1H-tautomers did not practically depend on the nature of the substituents. A combination of experimental methods, photoelectron-imaging spectroscopy, flowing afterglow-photoelectron spectroscopy and the flowing afterglow-selected ion flow tube technique, and the electronic structure calculations at the B3lyp/6-311++G(d,p) level of DFT [Ichino *et al*., 2008] studies on ion chemistry of 1,2,3-triazole suggested that deprotonation by –OH at all sites of the triazole takes place to yield products, and the N-H bond dissociation energy of 1H-1,2,3- and 2H-1,2,3 tautomers were determined to be 108.0 kcal mol^{-1} and 112.2±0.6 kcal mol^{-1} respectively. Although 2H-form is predominant in the gas phase

from microwave study, their experiments revealed the predominance of 1H-tautomer in liquid phase.

A review paper on therapeutic drug monitoring for triazole [Hope *et al*., 2008] summarized the application of triazole for the prevention and treatment of invasive fungal infections and suggested a routine monitoring should be considered for intraconazole and voriconazole, which are derivatives of azole. An experimental and computational study in the gaseous and crystalline phases of asymmetric coordination of trimethylsilyl groups to tetrazole and triazole rings [Wann *et al*., 2008] demonstrated that a weak C-H---N hydrogen bond can lead to subtle changes in the conformations of molecular compounds, while leaving other secondary interaction almost unaffected. A comparative X-ray crystallographic study on triazoles systemic fungicides [Chauhan, 2009] provided molecular structures of Tridymenol, Tricyclazole and Tridimefon, which are known inhibitors of fungal sterol biosynthesis regarding C-C, C-H and N-H bond distances.

QSAR study of 1,2,4-triazole using physico-chemical descriptor such as correlation coefficients, Q^2 and PRESS/SSY ratio for the bacterial inhibitory activity [Dimova and Perisic-Janjic, 2009] suggested that physico-chemical properties such as Surface Tension (ST), Molar Refraction (MR), Molar Volume (MV), Parachor (Pc), Index of Refractivity (η), Density (D) and Polarizability (α) can successfully be used for modelling growth inhibition activity of triazole derivatives against *Bacillus subtilis*. These results suggested a propound assistance for medical and agricultural scientists in view of designing and prediction of compounds with increased activity, thus putting forward the synthesis of new triazoles to exhibit better activities.

Quantum chemical studies on the standard enthalpies of formation in the gas phase and relative stability of tautomers of C-nitro-1,2,4-triazole and isomers of N-alkyl-C-

nitro-1,2,4-triazole [Ivashkevitch *et al*., 2009] provide an information on the relative Gibb's free energies of the tautomers and isomers in aqueous solution. They estimated structural indexes of aromaticity (HOMA and Bird indexes) and also analyzed electron population density of the natural bond orbital. In 2009, Balabin performed high level ab initio calculations and focal point analysis of tautomeric equilibrium and hydrogen shifts in tetrazole and triazole [Balabin, 2009]. He obtained an accuracy of 0.10-0.25 kcal mol^{-1} for comparison of tautomeric energy differences. The relative CCSD(T)/CBS energies calculated were 2.07, 3.98 and 6.25 kcal mol^{-1} for 1H-tetrazole, 1H-1,2,3-triazole and 4H-1,2,4-triazole respectively. He also predicted acyclic structure for 5H-tetrazole in MP2 method and the used of electron correlation methods resulted in markedly different convergence behavior for triazole and tetrazole tautomers along with their transition states with respect to corresponding minima structures. Theoretical approach of the catalytic hydrochlorination of 3-amino-2H-1,2,4-triazole (amitrol, a weed-killer) [Mensah *et al*., 2009] showed a selective protonation on the same nitrogen of the cycle for both $MoS_3H_3^+$ and $ZnCl_2$ hydrochlorination and the reaction was predicted as exothermic on $MoS_3H_3^+$ catalytic sites and endothermic for $ZnCl_2$ sites.

According to the theoretical study [Kiselev and Gritsan, 2009] on the thermal decomposition of 5-aminotetrazole, it was found that the imino form undergoes fast isomerization to the amino form in the H-bonded dimers and does not participate in the 5-ATZ thermolysis. On the contrary, amino and, probably, the 2H isomer are the main isomers of 5-ATZ in the melt and gas phase. The N2 elimination reaction was found to be the dominant unimolecular channel of the amino and 2H isomer decompositions in both the gas phase and melt. The significant lowering of the activation barriers of decomposition reactions in H-bonded dimers was found. In agreement with the existing

experimental data, HN3 elimination dominates for some of the considered complexes. It was concluded that the initial stages of thermolysis of 5-ATZ cannot be satisfactory described by the simple unimolecular reactions proposed in the literature.

A computational approach for the study of heterocyclic concluded that due to the lability of the azole, the most stable tautomer among 1,2,4-triazole isomers is the 1H, and the 4H-tautomers are much less stable than 1H-form. For C-halogen substituted 1,2,4-triazole series, 1H-3-substituted tautomer is the most stable while 4-substituted is the least. Gas-phase and aqueous basicities of 1H-1,2,3-triazoles, 1-methyl-1,2,3-triazole, 2-methyl-1,2,3-triazole, 1H-4-phenyl-1,2,3-triazole, 1-methyl-4-phenyl-1,2,3-triazole and 5-phenyl-1,2,3-triazole, have been determined, the former by FTICR and the latter by spectrophotometry and 1H NMR. The gas-phase experiments are in good agreement with the Gibbs free energies calculated at the B3LYP/6-31G* level aromaticity [Alkorta and Elguero, 2008].

Unimolecular decomposition of 5-aminotetrazole and its tautomer 5-iminotetrazole from isopotential search [Paul *et al*., 2009] predicted the initial gaseous products of 5-iminotetrazole (5-ITZ) unimolecular decomposition are HN3 and NH2CN (calculated activation barrier equal to 199.5 kJ/mol). On the other hand, the initial gaseous products of 1*H*-5-ATZ and 2*H*-5-ATZ unimolecular decomposition are predicted to be N2 and metastable CH3N3 (calculated activation barriers equal to 169.2 and 153.7 kJ/mol, respectively).

Investigation of aza-substitution on azole aromaticity [Ramsden, 2010] from microwave and photoelectron spectroscopy revealed that the 2H-tautomers strongly dominates over the 1H-tautomer for 1,2,3-triazole in the gas phase, and the ratio estimated from the microwave spectrum of the triple ^{15}N species is 4:5≈1:1000. For

1,2,4-triazoles, the 1H-tautomer is more stable than the 4H-tautomer by ~7 kcal mol^{-1}. UV-photoelectron spectroscopy investigation confirmed that tetrazole in the gas phase exists predominantly as the 2H-tautomer. A minor contribution (10%) of the 1H-form is also present in low-temperature inert matrices. A gas phase DFT calculations of CH acidity of substituted triazoles [Halauko *et al*., 2010] showed that 2H-isomers have considerably lower CH acidity than 1H-isomers.

Investigation on electrochemical behavior of 1,2,4-triazole at glassy carbon electrode (by Cyclic Voltammetric measurement) in acidic medium [Lokesh *et al*., 2010] detected a single reduction wave was observed for 1,2,4-triazole due to the reduction of N=N moiety and no oxidation peak was observed in the reverse scan. Peak potential was found to shift to more positive value with increase in the acidity of the medium, indicating easier reduction due to the involvement of proton in the reduction process. A paper featuring tetrazole as crystallization modification [Massi *et al*., 2010] stated that tetrazoles are a new class of compound as carboxylic acid analogues that tetrazoles are able to influence crystal growth and morphology although in a different manner to their carboxylate counterparts with tetrazoles showing impact on barium sulfate and calcium carbonate crystallization to varying degrees. Thus, the tetrazoles represent a new class of crystal modifier and it can be conclusively stated that the tetrazole functionality has an effect on crystallization.

Quantum chemical studies on tautomerism and basicity behavior of some 1,2,4-triazole derivatives predicted that the 4H-1,2,4 triazole form for all studied molecules was favored over the 1H-1,2,4 triazole form and the protonation processes indicated the predominance of the 1H-1,2,4 triazole form over the 2H-1,2,4 triazole form [Ogretir *et al*., 2010]. The correlation attempt between the experimental and the calculated acidity

constants, p*Ka* values, revealed that they are quite close to the experimental values and they correlate well with a regression of around unity (R2 = 1). A computational study for the comparisons of substituent effects in tetrazole and benzene was performed by Oziminski and Krygowski in 2011. The individual occupancies of 2pz orbitals at all atoms of the tetrazole and benzene derivatives were correlated with the sum of occupation overall $2p_z$ orbitals, named pEDA(A) or pEDA(B), respectively [Oziminski and Krygowski, 2011] . These characteristics correlate well with the Hammett-like substituent constants. Acceptable correlations between the individual atom occupancies at the $2p_z$ orbital and pEDA were found for all atoms except for N4.

Tautomerism in drug discovery was discussed from thermodynamic and kinetic aspects [Katritzky *et al*., 2010]. In this, types of tautomerism encountered in the structure of drugs in current use were surveyed together with the effect of pH, solvent polarity, and temperature. They mentioned that the tetrazole ring appears in a number of drugs affording N1 to N2 tautomerism, including Diovan, Benicar, Avapro, Atacand and Hyzaar ^{15}N CPMAS experiments showed that at room temperature (295 K), the four tetrazole nitrogen atoms gave a very broad signal compared to the imidazole signals, but became sharp at 253 K. These finding are consistent with fast prototropic exchange [Harris and Lammertsma, 1996]. These tetrazoles are generally used as cardiovascular or hypertension drugs and the acidity of the tetrazole ring system (pKa~4.8) means they exist largely as anions in biological systems which effectively eliminates the relevance of tautomerism. Lonsartan potassium salt or Hyzaar, the parent drug was approved by FDA 1995 under the commercial name COZAAR. Early studies showed that lonsartan degrades by dimerisation and the drugs act on very specific targets such as cell receptors of Angiotensin II.

Study of tetrazole as high energetic nitrogen-rich compound with a N_{10} chain was carried by Klapotke and Piercey, where the reaction of 1-aminotetrazole with acidic sodium dichloroisocyanurate allowed isolation of tetrazole (1,1'-azobis). The rare chain of 10 nitrogen atoms in this compound was confirmed by X-ray crystallography, and the physical and explosive properties of the azo compound were characterized [Klapotke and Piercey, 2011]. The tetrazole chain possesses both exceedingly high explosive performance and sensitivity and possesses explosive performances comparable to those of the most powerful energetic materials in common use. Unfortunately, it is both thermally and physically unstable with a decomposition temperature of 80^0C and undergoes violent explosion when subjected to mild stimuli. Proof of the existence of this N10 compound opens the possibility for the discovery of even longer chain nitrogen compounds, although the trend in increasing sensitivity from N8 to N10 compounds may present challenges for isolation.

High level *ab initio* study on the tautomerism and thermal decomposition of tetrazole performed [Kiselev *et al.*, 2011] featured mutual interconversion and decomposition reactions of four tetrazole isomers (1H-TZ, 2H-TZ, 5H-TZ, and an N-heterocyclic carbene 14H) calculations using the W1 high-level procedure. The tautomeric equilibria between 1H-TZ, 2H-TZ, and 14H from their theoretical studies turned out to play a very important role in the mechanism of thermal decomposition. Although the barriers of monomolecular tautomeric transformations were found to be high (~50-70 kcal/mol), the concerted double H atom transfer reactions in the H-bonded complexes of TZ tautomers have profoundly lower barriers (~18-28 kcal/mol). These reactions lead to fast interconversion between 1H-TZ, 2H-TZ, and 14H. The carbene 14H was predicted to be a key intermediate in the mechanism of thermal decomposition of

TZ. For all species considered, the unimolecular reactions of N2 elimination were predicted to dominate over the elimination of hydrazoic acid. In agreement with existing experimental data, the effective activation energy of thermolysis was predicted as 36.2 kcal mol^{-1}.

1.3 Aromaticity of Azoles

Azoles are undoubtedly known to possess certain degree of aromaticity to some extent. The delocalized π-electron from nitrogen atoms within the rings are seems to be highly responsible for the ring current, which rendered the azoles energetically very persistent aromatic compounds. Moreover, from geometric and magnetic criteria, azoles are always found to show aromatic characters.

Aromaticity has been known for many years as a basic concept and common feature for defining the properties of cyclic compounds. Aromatic compounds are mainly understood as those unsaturated cyclic molecules that possess extra stability as a result of the arrangement of π-electrons associated with the unsaturation of the ring systems. In other words, a cyclic π-electron compound is aromatic if there is a measurable π-electron delocalization in the ground state of the molecule [Portella *et al*., 2005]. This phenomenon is generally accepted to be associate with :- (a) an increase of stability related to the system without cyclic π-electron delocalization, (b) intermediate and unaltered bond length that are close to the mean value of the length for the typical single and double bond, and (c) inducing π-electron ring current when the molecule is exposed to the external magnetic field. Since its isolation in 1825 by Faraday, Benzene has been used as a paradigm for aromatic compounds. Kekule first suggested the cyclic structure of Benzene in 1865 and applied the term aromatic to compounds containing Benzene. But later studies from certain pioneer revealed aromatic character can exist in some cyclic

compounds other than Benzene. For example, the 19th century concept of the oscillation of double and single bond in benzene was replaced by the concept of resonance between canonical structures. 'Aromatic sextet' was followed by MO calculations, and the Huckel's 4n+2 rule [Krygowski and Cyranski, 2009; Ciesielski *et al*., 2011]. It is well known that aromatic stability depends on the number of canonical structures that might suggest relative equal stability from all of them [Matito *et al*., 2005]. It is also generally accepted that the particular stability of aromatic hydrocarbon depends upon the presence of a π-electron system and that each carbon atom contributes one electron to the system, i.e. the number of π-electrons in an aromatic hydrocarbon is equal to the number of carbon atoms (4N+2). Therefore, aromaticity has been recognised as multidimensional phenomenon for a cyclic system, and the quantum mechanical description of the electron confined to move on a ring and provides a basis for Huckel's rule for aromatic hydrocarbon [Grinter, 2005]. For all modern chemists, definition from Krygowsky, Katritzky *et al* must be taken into account which proposed that – *those cyclic π-electron systems which follow all the features of aromatic character are aromatic, while those which follow some but not all are partly aromatic*. Also Schleyer et al proposed that - *Aromaticity is a manifestation of electron delocalization in closed circuits, either in two or in three dimensions. This results in energy lowering, often quite substantial, and a variety of unusual chemical and physical properties. These include a tendency toward bond length equalization, unusual reactivity, and characteristic spectroscopic features. Since aromaticity is related to induced ring currents, magnetic properties are particularly important for its detection and* evaluation [Portella *et al*., 2005]. There has been a recent development in defining rules and measuring the degree of aromaticity because multiple definitions of aromaticity are possible and necessary for the elucidations

of phenomena such as stability/reactivity, magnetic shielding/deshielding and bond equalization/alternation [Cioslowski, 2007]. There are various indices for the study of the degree of aromaticity in cyclic compounds. Some of these are Resonance energy per electron (REPE), Para-delocalization index (PDI), the aromatic fluctuation index (FLU), ring current (I_{ring}), the multicenter index (MCI), Bird index (I_5 or I_6), the harmonic oscillator model of aromaticity (HOMA) and nuclear independent chemical shift (NICS). Among these, HOMA, NICS and Bird (I_5) indices are included for the titled compounds.

There are three major principles relating to the properties of cyclic compounds, that are use to define criteria of aromaticity: (1) Energetic criteria (2) Structural or Geometric criteria, and (3) Magnetic criteria. All these originated from the properties of Benzene and Huckel's treatment of Benzene [Stanger, 2009]. Energetic criteria is associated with kinetic and thermodynamic stability and different methods like Heat of hydrogenation, Aromatic stabilization energy (ASE) and Relative energy are often used for the assessment of aromaticity with appropriate references. Benzene always offers the best reference for a variety of systems. Structural or geometric criteria mainly based on the concept of optimal interatomic bond distances. Experimental data available from X-ray measurement support the advantages of using bond length as a criterion of aromaticity. Magnetic criteria of aromaticity depend on two magnetic properties, viz., diamagnetic susceptibility under external magnetic field and proton NMR chemical shift due to the induction of ring current in a cyclic π-system [Stanger, 2009; Krygowski *et al*., 2000]. All these three criteria are possible to investigate computationally.

1.4 Tautomerism in Azoles

The importance in the possibilities and existence of tautomerism in organic compounds has long been recognised for the understanding of chemical processes in

chemistry and biochemistry. The tautomerism of organic compounds has been the subject of extensive theoretical studies using various quantum mechanical approaches [Karelson *et al.*,1996]. The correct geometry, conformation, and stereochemistry of a molecule permit it to gain access to the molecular environment. However, it is the electronic structure of the molecule that enables to predict its chemical behavior.

Tautomerism, a particular case of isomerism, plays an important role in modern organic chemistry, biochemistry, medicinal chemistry, pharmacology, molecular biology, and life itself [Raczynska *et al*., 2005]. Understanding the mechanisms of the many organic reactions and biochemical processes, including those involving specific interactions with proteins, enzymes, and receptors, in which a substrate or an active intermediate requires an understanding of tautomerization. Tautomerism partially explains the structure of nucleic acids and their mutations. It can also be applied in computer-aided drug design. Although tautomerism is exceptionally difficult to study because tautomeric interconversions are usually very fast processes, the variety and importance of applications continuously encourage researchers to undertake investigations on tautomerism.

The term ‘tautomerism’ (Gr., *tauto* - same, and *meros* - part) refers to a compound existing in equilibrium between two or more labile isomeric forms called the tautomers. Tautomers are interconverted in this reversible process, and the molecular rearrangement is intra-, or more frequently, intermolecular. Tautomeric interconversion consists in a heterolytic splitting of the molecule followed by recombination of the fragments formed. Such isomerism can be accompanied by migration of one or more double bonds and atoms or groups in so-called prototropic, cationotropic, or anionotropic tautomerism or by the opening of a ring in one direction of isomerization and cyclization in the opposite

direction in the so-called ring-chain tautomerism. Another type of isomerism, called valence tautomerism, proceeds without migration of atoms or groups but involves only the formation and breaking of bonds, either single or double. Interconversion between thermodynamically stable tautomers is possible in action of various influences such as light, temperature, acid, base, solvent, electron solvation, or ionization). Electron delocalization is a concept originally introduced to explain the exceptional stability of benzene. According to the Ingold theory of mesomerism, in which electron delocalization was even initially called 'intra-annular tautomerism', benzene was represented by a few dynamically interchanging Lewis electronic structures. With the development of quantum theory, the term 'resonance hybrid', corresponding to a complete electron delocalization, was introduced, and a distinction was made between tautomerism and electron delocalization, also called resonance. The relation between the phenomena of tautomerism and that of resonance was also formulated [Raczynska *et al*., 2005].

In the crystalline phase, tetrazole exists exclusively as its 1H-tautomer, and, on the other hand, in solution, 1H- and 2H-tautomer co-exist, and the relative proportion of the more polar 1H-form increases with increasing solvent polarity. In the gas phase, the existence of 1H-tetrazole has been suggested by microwave spectroscopy [Balabin, 2009]. Therefore, we suspect there can be a possibility for 1H- and 2H-tetrazole to co-exist under the influence of suitable substituents even in the gas phase. As a rule, 2-substituted isomers are more stable than 1-substituted tetrazoles in the gas phase, and the stability of 1-substituted tetrazoles relative to the corresponding 2-substituted isomers increase in going to condensed state [Ivashkevich, 2003]. Also, the existence of a Hammett correlation for a set of potentially tautomeric compounds in nitrogen heterocycles does not show that they exist predominantly in one of the possible

tautomeric forms [Charton, 1969]. Tautomeric equilibrium in 5-substituted tetrazoles is strongly dependent on the phase, nature of the substituents and its position [Kiselev *et al*., 2009]. But our study focused only 5-substituted tetrazoles in the gas phase. We expect the introduction of substituents to the ring Nitrogen atom stabilizes the corresponding 1H- or 2H-isomers. Early investigation of five membered heteroaromatic compounds were mostly examined using IR, UV, NMR spectra and p*K* values, and the results are always discussed using a combination of physical methods [Charton, 1969; Katrytzki and Maine, 1964]. But, most studies provide inadequate information especially for our compound of interest. Some of the theoretical investigation mainly based on *ab initio* calculations where the results were discussed in reference to the characteristic dipole moment, stability, existing spectroscopy and crystallographic data. Some predictions of tautomeric preferences were reported to deeply influence by the basis sets and the degree of correlation included in the computational methods [Shcherbakova *et al*.,2007]. Also, gas phase investigation of tautomeric preference show strong dependent on aromatic character and intramolecular electron delocalization [Perez-Lustres *et al*., 2001]. The tautomerism of 5-methyltetrazole and its isotopically substituted derivatives has been discussed on the basis of their fragmentation patterns and of quantum-chemical calculations by the LCAO MO method in the CNDO/2 approximation. The equilibrium of these compounds in the gas phase was found to be displaced towards the 2H-tautomer [Allegretti *et al*., 2007]. Recently, microwave and photoelectron spectroscopy revealed that the 2H-tautomers strongly dominates over the 1H-tautomer for 1,2,3-triazole in the gas phase, and the ratio estimated from the microwave spectrum of the triple ^{15}N species is 4:5≈1:1000. For 1,2,4-triazoles, the 1H-tautomer is more stable than the 4H-tautomer by ~7 kcal mol^{-1}, and UV-photoelectron spectroscopy investigation also confirmed that

tetrazole in the gas phase exists predominantly as the 2H-tautomer. A minor contribution (10%) of the 1H-form is also present in low-temperature inert matrices [Ramsden, 2010].

Tautomerism in drug molecules almost invariably involves prototropy but in all cases the influence of a single tautomer on therapeutic activity depends on the time scale of the tautomeric equilibrium relative to that of the biological process in question. Thus in judging the influence of tautomerism on biological activity, it is essential to consider both thermodynamic and kinetic factors. Fast interconversion of tautomers relative to a specific biological process means that both tautomers may be consumed. Conversely, slow interconversion relative to the biological process may result in one tautomer being the only active species [Katritzky *et al*., 2010]. Triazoles are more acidic than pyrazoles because they can undergo tautomerism. In effect, optimised structures of azoles show that the proximity of the nitrogen lone-pair reduces the maximum electrostatic potential value of the H-donor [Lamarche and Platts, 2003]. However, in the case of triazoles, tautomerism allows migration of the H-donor to escape this constraint so its electrostatic potential value can increase. Some experimental study indicates that both tautomers may exist in solution.

1.5 Aim and significant of the study

The main purpose of this work is to provide sufficient and reliable computational data concerning tautomeric interconversion, intrinsic reaction coordinate, electronic structures of ground state and transition state geometry, aromatic properties and NMR spectroscopy of Nitrogen based 5-membered substituted heterocycles in the gas phase. Quantum mechanical approach will be incorporated for the systematic investigation of the influence of different substituents on the electronic structure of azole system. Comparisons with existing theoretical data and experimental results were carried out as

far as possible in order to predict electronic properties and geometries for all the species under consideration. This study focuses towards the influence of substituents on the electronic structures of the azoles. Therefore, *Ab initio* Hartree-Fock (HF) and Density functional theory (DFT) of computational methods were incorporated in order to redefine the chemical behavior of the selected azoles and, ONIOM, a hybrid method for large molecule, was also incorporated for the azole derivatives.

Computational chemistry methods offered a unique ability to study from the simplest atoms to most complicated compounds, or even large molecular systems. Although the possibility is still limited in some areas, development and refinement of the methods and software packages over the past decades enable theoretical study to accomplish what should have been considered impossible for a chemist a few years back. The greatest advantage of computational method lies within recent development in the method itself and computational technique, and, the machine itself. The development of powerful desk top and larger computers has enabled chemists to predict the structures and the values of properties of known, unknown, stable and unstable molecular species using mathematical equations. Modern fast performing computer are now to be seen available for researcher in most well-equipped theoretical laboratory, and personal computer with lower or medium performance are everywhere at a good price. This situation made computational study a great success in 21st century, and the best friend for experimentalist, we can say. Since theoretical predictions are now always correlated well with experimental results from any kind of computational work, no one can completely ignore computational results at all level. Therefore, the major task is to perform detail calculations on the structure of the selected azoles in order to analyze the chemical behavior and for the interpretation of Physico-chemical and biological properties in terms of different

parameters. The vast industrial and agricultural applications, interesting chemical properties and biological activity of the azole is the main reason as to why we chose the subject for the research.

Chemical compounds are the basic building blocks of all biological structures and processes that are the basis of life as we know it [Thomas, 2003]. Organic chemistry in particular, is a very broad subject that bears a profound relationship with all phases of drug discovery, design, and development [Avendano and Menendez, 2008]. In modern science, heterocyclic chemistry is a key to the understanding of life processes and to improve the quality of life for humankind. The knowledge of chemical structure is the basis of understanding physical, chemical, biological, and technical properties of compounds in relation to living systems. Therefore, we can state that the study of aromaticity in organic chemistry is a cornerstone to rationalize and understand the structure and thus the behavior of heterocyclic compounds. Among approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic, and approximately half are heteroaromatic [Balaban, 2004].

Heterocycles play a major part in biochemical processes. The side groups of the most typical and essential constituents of living cells, DNA and RNA, are based on pyrimidine (cytosine, uracil and thymine) and purine (adenine and guanine) which are all aromatic heterocycles. Hydrolyses of DNA and RNA produce five nucleosides, each being composed of an aromatic heterocyclic base, a phosphate, and a ribose moiety, the latter two form the backbones of the polymer, and in the DNA's double helix the C-G and A-T base pairs form the rungs of the ladder. They participate along with other amino acids in protein constitution through amide linkages. A practically infinite number of proteins can

be synthesized from the 20 naturally occurring amino acids with the aid of DNA via translation into RNA messenger and transcription according to the universal genetic code. Most coenzymes have aromatic heterocycles as major constituents. While enzymes possess purely protein structures, coenzymes incorporate non-amino acid moieties, most of them aromatic nitrogen heterocycles. Coenzymes are essential for the redox biochemical transformations, e.g., nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD). Both are hydrogen transporters through their tautomeric forms that allow hydrogen uptake at the termini of the quinonoid chain [Balaban, 2004].

Numerous plant and animal hormones have aromatic heterocycles as a major component. Observations of life in nature by primitive communities led humans to the discovery of many healing materials. Very many pharmaceutical products are mimics of natural products with biological activity, which include many heterocycles. In the fight against disease, some of the most significant advances have been and are being made by designing and testing new structures, many of which are heteroaromatic derivatives. The same is true for many pesticides.

Antibiotics such as penicillins and cephalosporins, alkaloids such as vinblastine, ellipticine, morphine, and reserpine, and cardiac glycosides such as the class of digitalis are heterocyclic natural products of significance for human and animal health. Inspired by them, pharmaceutical researchers have constantly designed and produced better pharmaceuticals for a better living. In the same light, pesticides, insecticides, rodenticides, and weed killers followed natural models, and a significant part of such biologically active compounds are heterocycles. Modern life and civilization opened the way to other important practical applications of heterocycles, for example dyestuffs, copolymers, solvents, photographic sensitizers and developers, and in the rubber industry

antioxidants and vulcanization accelerators. Some of the sturdiest polymers, such as Kevlar, have aromatic rings [Balaban, 2004].

A book on the importance of heterocycles in biochemistry and everyday life has been published. Apart from all the above reasons underlying the importance of heterocyclic chemistry as an applied science, it has much fascination as a subject for study in its own right. Heterocyclic chemistry is an inexhaustible resource of novel compounds. Almost unlimited combinations of carbon, hydrogen, and heteroatoms can be designed, making available compounds with the most diverse physical, chemical, and biological properties. Heterocycles provide the main source of new aromatic compounds.

The investigation of the microscopic properties of energetic materials remains to be a challenging task. Theoretical calculations are an effective way to model the physical and chemical properties of complex solids at the atomic level as a complement to experimental work. As the electronic structure, absorption spectra, and thermodynamic properties of the tetrazole derivatives are not always systematically investigated, there is a clear need to gain an understanding of those at the computational levels.

1.6 Objective of the study

The main objective of this theoretical investigation was to perform computational task on ground states and transition states species of triazoles and tetrazoles to gain access for understanding their general electronic properties governing the chemical and physical behavior through the interpretation of obtained results in the gas phase. Substitution was made at carbon atom (C_5) of the heterocyles with –OH, -CH_3, -C_2H_5, -NO_2, -NH_2, -COOH and –C_6H_5 respectively. All the geometries were fully optimised with ab initio Hartree-Fock and Density Functional Theory of quantum mechanical descriptors with different selected basis sets. Influences of substituents on the cyclic

geometries and aromaticity were compared with the unsubstituted parent compound mostly in relation to their bond length. Degree of aromaticity was discussed on the base of structure and magnetic properties of the cyclic systems and stability of the compounds and nature of tautomerism, which involve intramolecular hydrogen shift of the azole rings, was predicted from the energetic properties of ground state and transition state species respectively.

Computational QM/MM (the ONIOM) study on the chemistry of azole derivative, viz., letrozole and vorozole, which were important drug molecules under clinical test, was also conducted in these studies addition to the study of the parent azoles. This was purely the subject of today's most advance medicinal chemistry for expert researchers in the field of experimental and theoretical Bio-Chemistry. The reason for including this topic was mainly due to the hope for providing general chemistry on drug related azole derivatives, and also for the benefit of computational study on medicinal chemistry.

Computational investigations were carried out in the following manners:-

(a) Optimizations on the ground state geometries of unsubstituted and substituted tetrazole isomers at DFT levels of theory with 6-31G, 6-31+G*, 6-311++G** and cc-pVTZ basis sets were performed. Calculations on transition state energies and geometries were also done at the same levels of theories with the same basis sets. Results were discussed according to the energetic properties, tautomeric equilibria and aromaticity indices respectively.

(b) Optimizations on the ground state geometries of unsubstituted and substituted isomers of 1,2,3-triazole and 1,2,4-triazole at HF and DFT levels of theory with 6-31G(d), 6-311G(d), 6-311++G(d,p), cc-pVDZ, cc-pVTZ, aug-cc-pVDZ and aug-cc-pVTZ basis sets were performed. Calculations on the transition state geometries were done at the same

levels of theories with the same basis sets and transition state species were investigated through intrinsic reaction coordinate (IRC) along the potential energy Results were discussed according to the singlet-triplet energy differences, HOMO-LUMO energy gap and magnetic shielding respectively.

(c) The azole derivatives Letrozole and Vorozole were investigated computationally using ONIOM calculation where calculations was carried out by assigning the molecules into two or three layers and were treated at different levels of accuracy with the selected model chemistries. Results were discussed according to the predicted energies and geometries.