Chapter 1

Introduction and Background

1. Introduction and Background

All the impressive advances on the comprehension of biological chemistry, genetic manipulation, enzymatic activity and antibody recognition at the molecular level, rely on basic principles of *Heterocyclic Chemistry*. It is commonplace to hear that upon recruitment of organic chemists into pharmaceutical and biotechnological companies, a first need for the new recruit is to familiarize him/herself with some basic heterocyclic chemistry concepts. Heterocyclic chemistry is the largest branch of organic chemistry in terms of the numbers of new compounds synthesised, and is an area of special interest to medicinal chemists.

Knowledge of the reactivity of heterocycles is of vital importance in the fight to improve our understanding of the basic chemistry underlying nearly all of the important life-processes. Furthermore, heterocyclic systems take part in most of the increasingly sophisticated products, that enhance the standards of living in our society and there is a social request for the pursuit of this tendency.

The research presented in this thesis was focused on understanding structure-reactivity relationships in several potential biologically active derivatives of two important classes of heterocyclic compounds: tetrazoles and benzisothiazoles. The mechanisms of selected reactions involving tetrazolyl and benzisothiazolyl derivatives were investigated. These investigations led to the development of new synthetic methodologies.

In Chapter one, a description of the physico-chemical characteristics and major applications of tetrazoles and benzisothiazoles that were most relevant to the investigation will be presented. Also, some of the theoretical and experimental techniques used will be described.

Chapter two discusses the photochemistry of a series of allyl-tetrazoles in solution, addressing several important mechanistic questions concerning the photofragmentation of these derivatives in diverse liquid environments. This investigation led to the development of synthetic methodologies for the preparation of 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones and *N*-phenyl-1,3-oxazines.

In Chapter three, we outline a general overview of the photochemistry of several representative tetrazoles trapped in a matrix of solidified argon, at cryogenic temperatures (typically 10 K). UV-excitation in this rigid environment resulted in photofragmentation of the monomeric tetrazoles, with a wide range of decomposition channels. FT-IR spectroscopy provided experimental frequencies and intensities of characteristic absorptions of the matrix-isolated chemical species, both for reagents and photoproducts. The analysis of experimental data was assisted by direct comparison with the vibrational spectra theoretically calculated for the single molecule in vacuum. A number of relatively unusual or highly reactive molecules, such as antiaromatic azirines, azides or isocyanates, may be formed from photolysis of tetrazoles in a matrix. In some of the examples described in Chapter three, the spectroscopic characterization of these molecular species was presented for the first time.

Chapter four addresses the synthesis of a range of new tetrazolyl and benzisothiazolyl naphthylmethylic ethers and the development of experimental conditions for palladium-catalysed hydrogenolysis of these ethers, using a hydrogen donor or molecular hydrogen. Structural effects on the reactivity of these ethers were investigated, and will also be discussed. The second part of Chapter four describes research inspired by the desire to find a route to the synthesis of a variety of novel molecules incorporating the tetrazole and benzisothiazole units, linked by a spacer-group. New benzisothiazole-tetrazolyl derivatives differing on the spacer-group used for

linkage of the two heterocycles, were produced and tested as multidentate ligands in coordination reactions with manganese (II) and iron (II) complexes.

1.1. Tetrazoles

The structure of the tetrazole ring may be considered unusual. The nitrogen content in an unsubstituted tetrazole (CN_4H_2) is 80% of the total weight of the molecule, the largest percentage among the stable unsubstituted heterocyclic systems. In this feature, tetrazole (**1**) surpasses tetrazine (**2**) and is inferior only to some unstable heterocyclic systems practically nonexistent in the free state, such as pentazoles (**3**) and pentazines (**4**) (see structures in Figure 1).

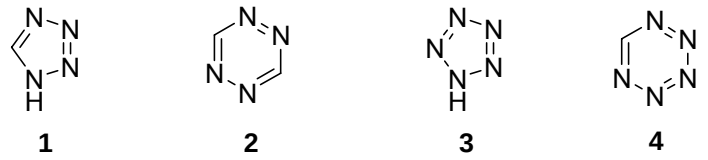


Figure 1. Structures of *1H*-tetrazole (**1**), 1,2,4,5-tetrazine (**2**), *1H*-pentazole (**3**) and pentazine (**4**).

Despite the extremely high nitrogen content in the ring, the unsubstituted tetrazole and most of its derivatives are relatively stable on heating or under microwave irradiation, and also in the presence of various chemical reagents (oxidants, acids, bases, alkylating agents, dienophiles, etc). In naturally occurring molecules, the tetrazole fragment is virtually lacking. Yet its presence in metabolic products of some protozoa was reported.[1] It is postulated that tetrazole, alongside other unusual polynitrogen heterocycles, may be formed under the natural conditions of other planets of the Solar system or their satellites, provided that they contain hydrocarbons and nitrogen in the

composition of the atmosphere or on the surface.[1] If this theory will be confirmed, tetrazoles will no longer be a natural rarity.

Tetrazole (CN_4H_2) and its derivatives have attracted much attention due to their practical applications. The tetrazolic acid fragment, $–CN_4H$, has similar acidity to the carboxylic acid group, $–CO_2H$, and is almost allosteric with it, but is metabolically more stable at the physiologic pH.[2] Hence, synthetic methodologies leading to the replacement of $–CO_2H$ groups by $–CN_4H$ groups in biologically active molecules are of major relevance.[3] Indeed, the number of patent claims and publications related with medicinal uses of tetrazolyl derivatives continues to grow rapidly and cover a wide range of applications: tetrazoles are found in compounds with antihypertensive, antiallergic and antibiotic activity.[4-6] Tetrazole derivatives are currently used as anticonvulsants[7] and in cancer and AIDS treatments.[8,9] Tetrazoles also show important applications in agriculture, as plant growth regulators, herbicides and fungicides,[10] as stabilizers in photography and in photoimaging.[11] Due to the high enthalpy of formation, tetrazole decomposition results in the liberation of two nitrogen molecules and a significant amount of energy. Therefore, several tetrazole derivatives are explored as explosives, propellant components for missiles and gas generators for air-bags applicable in the automobile industry.[12,13] In addition, various tetrazole-based compounds have good coordination properties and are able to form stable complexes with several metal ions. This ability is successfully used in analytical chemistry for the removal of heavy metal ions from liquids, and in chemical systems formulated for metal protection against corrosion.[14-16] Many physical, chemical, physico-chemical, and biological properties of tetrazoles are closely related to their ability to behave as acids and bases. In the tetrazole ring, the four nitrogen atoms connected in succession are able to be involved in protolytic processes. This heterocyclic system is to the same extent

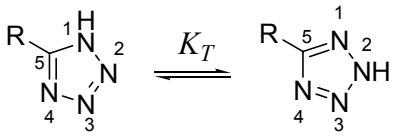
unusual in the structure and unique in acid-base characteristics. For instance, compared with other thermally and chemically stable azoles, tetrazoles possess abnormally high acidity and very weak basicity. Since the second half of 20th century until now, the acidity, basicity and prototropic tautomerism of tetrazoles were the subject of intensive research in various research groups. A considerable contribution to the investigation of protolytic equilibria involving tetrazoles was made by Russian (ex-USSR) chemists. Some of these studies were compiled in reviews and monographs dedicated to tetrazoles or protolytic equilibria of the nitrogen-containing heterocycles.[1, 17-28] In the last decade, new original investigations appeared in this field, extending and providing better insight on protolytic equilibria of tetrazoles. Among these studies, especially important is the research carried out with the use of modern theoretical methods that provided an understanding of many features of the protolytic equilibria involving the compounds of this series, and revealed some general trends.

1.1.1. Physico-chemical Properties

▪ Tautomerism of Neutral *NH*-Unsubstituted Tetrazoles

Neutral NH-tetrazoles, with no functional substituents at the carbon atom of the heterocyclic ring, can exist as 1*H*- or 2*H*-tautomers (**5** and **6**, Scheme 1).

Scheme 1.



5 *(1H)* **6** *(2H)*

Theoretically, it is presumable that a hypothetical non-aromatic 5*H*-form also exists. However, to the best of our knowledge this species was never experimentally

detected. Thermodynamically, the existence of the 5*H*-form of unsubstituted tetrazole is improbable due to its very high energy of formation.[32,33] Nevertheless, these species may be presumed as highly reactive short-lived intermediates in some chemical transformations of nitrogen-containing heterocycles.[34,35] 1*H*/2*H*-Tautomerism of tetrazoles has been the subject of detailed experimental and theoretical studies. The early experimental results in this field were carefully addressed in several reviews and monographs.[1,17,18,20,28,29-31] This type of protolytic equilibria of tetrazoles was experimentally investigated in solution and in the gas phase. The prevailing tautomers of 5-substituted tetrazoles were established also in the solid-state. Results from X-ray diffraction analysis, vibrational spectroscopy and ^{13}C NMR spectroscopy indicate that 1*H*-tetrazole and its derivatives exist predominantly as individual 1*H*-tautomers in the crystalline state.[1,18,30,36-41] However, some 5-substituted tetrazoles are likely to form hybrid crystals containing both 1*H*- and 2*H*-tautomers. The 1*H*-form is additionally stabilized in the crystal by hydrogen bonds N–H·····N, resulting in dimers, trimers, and other aglomerates.[1,18,20,36,40] In solution, the more polar 1*H*-tautomer also prevails (Table 1).[1,17,18,20] It was shown that, in several 5-substituted tetrazoles, the contribution of the 2*H*-tautomer in solution may reach 15–20%.[1,18,22,42] The percentage of the 2*H*-form in solution can increase in the following conditions: (*i*) reducing the dielectric permittivity of the medium (in solvents of low polarity the solvation of more polar 1*H*-form is less effective[43-44]); (*ii*) increasing the electron-withdrawing properties of substituents in the 5-position of the tetrazole ring; (*iii*) changing the size of the substituent attached to the carbon of the heterocycle (for instance, the introduction of bulky substituents into the *ortho*-position of the benzene ring in 5-aryltetrazoles increase the percentage of the 2*H*-tautomer in solution[1,18]) (Table 1). The tautomeric equilibrium represented in Scheme 1 can be considerably affected by formation of intra-

or intermolecular hydrogen bonds involving the protons of NH groups of the heterocyclic ring.[1,18] The most important and reproducible results in solution were obtained by dipole moment methods and by ^{13}C and ^{15}N NMR spectroscopy.[1,17,18,42,45,46] Indeed, it was shown that NMR signals and dipole moments of the different tautomeric forms of NH-unsubstituted tetrazoles are particularly specific, allowing their distinction.

Table 1. Data on tautomer composition of NH-unsubstituted 5-R-tetrazoles in solution.

R-substituent group	**Fraction of 1*H*-tautomer**	**Analytical method**	**Solvent**
H	78-85	Dipole moments	Dioxane
H	85	^{1}H NMR	Acetone
H	100	^{13}C NMR	DMF
	100	"	DMSO
	100	"	Acetone
	100	"	Water
H	90-99	^{15}N NMR	DMSO
MeS	85-87	^{13}C, ^{15}N, ^{1}H NMR	DMSO
2-tolyl	86	^{13}C NMR	DMSO
	73	"	Dioxane
2,6-dichloro-phenyl	91	^{13}C NMR	DMSO
	68	"	Dioxane

1*H*-Tetrazoles possess, as a rule, a larger dipole moment than the 2*H*-forms. For instance, the values of dipole moments (μ) of some N-alkyltetrazoles in benzene and dioxane were 5.46 D (1-ethyltetrazole), 2.46 D (2-ethyltetrazole),[47] 5.88 D (1-methyl-5-phenyltetrazole), and 2.52 D (2-methyl-5-phenyltetrazole).[45] According to the experimental results, the dipole moments of NH unsubstituted tetrazoles and 1-alkyl-tetrazoles in solutions have close values (for tetrazole $\mu = 5.14$ D).[45] The proton signals from α-methylene groups of 2-alkyltetrazoles in the ^{1}H NMR spectra are observed downfield, compared with the corresponding signals of the 1*H*-isomers.[1,18] Even more spectacular is the difference between these isomers in the ^{13}C NMR spectra. The

chemical shift of the heterocyclic carbon is 143-144 and 153-154 ppm for 1-alkyl- and 2-alkyltetrazoles respectively, 153.2 and 63.8 ppm for 1- and 2-methyl-5-phenyltetrazole respectively.[48,49] Chemical shifts of nitrogen atoms in the ^{14}N and ^{15}N NMR spectra of 1*H*- and 2*H*-tetrazoles are also considerably different[1,50] and dissimilarly sensitive to solvent.[51] The NMR spectra of NH-unsubstituted tetrazoles in solution are mostly similar to the spectra of 1-alkylisomers, confirming the prevalence of the 1*H*-form.

According to the data provided by photoelectronic, mass and microwave spectroscopy, the 2*H*-tautomer prevails in the gas phase.[22,24,29,30,35,52-54] However, some studies revealed the simultaneous presence in the gas phase of the 1*H*- and 2*H*-forms of 5-R-tetrazoles (R = H, CH_3, CD_3, CF_3, NH_2).[22,24,30]

Starting from the seventies of last century, the annular tautomerism of tetrazoles became the object of numerous theoretical studies. Versatile semi-empirical methods of quantum chemistry were exploited: CNDO, MNDO, MNDO/M, AM1, PM3.[55-60] It was shown that semi-empirical methods could not adequately describe tautomerism in tetrazoles: the results of these calculations were found to disagree with experimental findings. The reason for the divergence is due to the underestimation of the mutual repulsion of the unshared electron pairs of vicinal nitrogen atoms of the heterocyclic ring, that finally leads to a wrong estimation of the tautomer energy.[60] In 1*H*-tetrazoles, two interactions of the unshared electron pairs are probable, whereas in 2*H*-tetrazoles, only one is possible (see Figure 2).

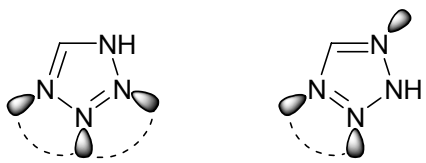


Figure 2. Mutual repulsion of unshared electron pairs in the 1*H*- and 2*H*-tautomers of tetrazole.

Besides, semi-empirical methods AM1, PM3, and MNDO describe poorly the electron density distribution and dipole moments of tetrazoles.[59] In describing the tautomerism of tetrazoles, a better agreement with the experiment was obtained by *ab initio* calculations.[32,43,44,54,60-69] However, the results obtained using these procedures depend essentially on the choice of the basis set.[54] The results of calculations carried out with HF, DFT, and MP methods are in fair agreement.[32,43,63,65,67] Thermodynamic parameters of tetrazole, calculated by MP2 method, showed that, although the 2*H*-form is more favoured in the gas phase, at higher temperature the thermodynamic stability of the 1*H*-tautomer increased.[67] The influence of solvation effects on the tautomeric equilibrium of tetrazole (Scheme 1) was also studied by HF, DFT, and MP methods.[32,43,44,70] A high degree of solvation decreases the energy of the 1*H*-tautomer comparatively to the 2*H*-form, and this effect is more pronounced, the greater the dielectric permittivity of the medium. In low-polarity media, like in the gas phase, the thermodynamic stability of the 2*H*-form of unsubstituted tetrazole is higher than that of the 1*H*-form. In calculations of energy of solvation of tetrazole tautomers, extended basis sets including polarization and diffuse functions, *e.g.*, 6-31++G**, are preferable.[43,67] A deeper description of the relative versatility of the various computational methods will be provided towards the end of this Chapter.

Yet, theoretical calculations on the tautomerism of some 5-substituted tetrazoles[44,61,64-66,69] has shown that, for all the derivatives studied in the gas phase (R = Alkyl, Ph, NH_2, N_3, NO_2, OMe), the 2*H*-tautomer is thermodynamically more stable than the 1*H*-form[65,69] and the nature of the substituent on the ring only slightly affects the energy difference. In contrast to the relative energy, the dipole moments of 1*H*- and 2*H*-tautomers of 5-substituted-tetrazoles significantly depend on the nature of the substituent in the 5-position and correlate with their Hammett σ_p constants [linear eq.(s)

(1.1) and (1.2) with parameters showing the correlation of calculated (B3LYP/6-31G*) dipole moments, μ, of different tautomeric forms of 5-substituted-tetrazoles (R= H, Me, *t*-Bu, Ph, Cl, CF_3, NO_2) with the σ_p constants of substituents].

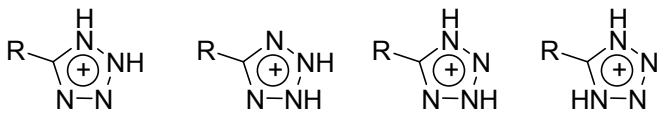
$$\mu_{1H} = 5.40 - 2.56\ \sigma_p \qquad (r=0.968,\ s=0.27,\ n=7) \qquad (1.1)$$

$$\mu_{2H} = 2.33 + 2.72\ \sigma_p \qquad (r=0.962,\ s=0.31,\ n=7) \qquad (1.2)$$

Particularly large differences in dipole moments between 1*H* and 2*H*-forms were found for electron-donating substituents. On increasing the electron-withdrawing character of the substituent, the dipole moment of the 2*H*-form grows, whereas that of the 1*H*-tautomer decreases. Based on these results, we can expect that in polar media the 1*H*-forms of 5-substituted-tetrazoles containing electron-donating substituents should be better solvated. From the above reasoning it is also possible to infer that only the solvation effects govern the different reactivity and selectivity of certain chemical reactions of 5-substituted-*NH*-tetrazoles containing substituents of different nature at the carbon atom of the heterocycle. The above mentioned experimental findings on the growing fraction of 2*H*-tautomer in solution, at increased electron-withdrawing character of the substituent in the 5-position, is obviously due only to the effect of the medium.

▪ Tautomerism of Tetrazolium Ions

The existence of four tautomeric forms of the tetrazolium aromatic cation is theoretically predictable (Figure 3).

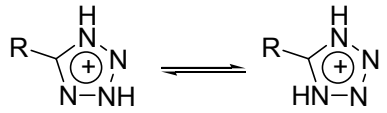


7 **8** **9** **10**

Figure 3. Tautomeric forms of tetrazolium aromatic cations.

Theoretical *ab initio* calculations have shown that 1*H*,2H^+ (**7)** and 2*H*,3H^+ (**8)** tetrazolium forms are thermodynamically less stable (about 15–20 kcal mol^{-1}) than 1*H*,3H^+ (**9**) and 1*H*,4H^+ (**10**) forms. The considerable destabilization of the 1*H*,2H^+ and 2*H*,3H^+ forms is due to the effect of mutual repulsion of vicinal NH-fragments in the heterocyclic system. This effect exists also in other azoles. Both experimental and theoretical methods demonstrated that the protonation of 1*H*- and 2*H*-tetrazoles occurs at the nitrogen atom in position 4 and results in the formation of 1*H*,3H^+ and 1*H*,4H^+ tetrazolium ions respectively.[22,29,56,57,71-75] Thus, a tautomeric equilibrium is possible involving just these two forms (Scheme 2).

Scheme 2.



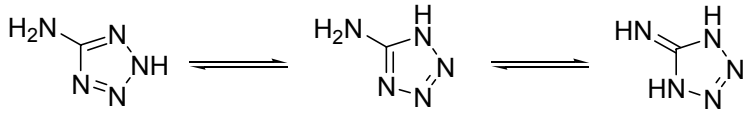
9 **10**

The thermodynamic stability of the two tautomeric forms of the tetrazolium cation presented in Scheme 2 is similar. Total energy and thermodynamic parameters of different prototropic forms of tetrazolium cations were calculated both by semi-empirical[56,57,72,76] and *ab initio* methods.[62,69,77-79,80] In keeping with previous considerations regarding the neutral 1*H*/2*H*-forms of tetrazole, non-empirical methods applying extended basis sets, proved to be the most appropriate for calculations involving tetrazolium cations.

▪ Tautomerism of 5-Aminotetrazole and its Derivatives

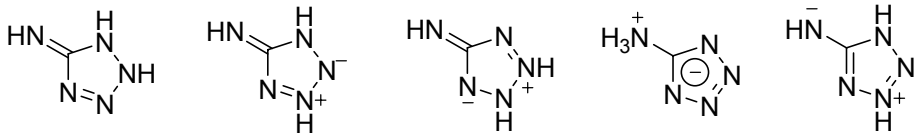
The protolytic equilibria of 5-aminotetrazole and its derivatives are complicated by the amino-imino tautomerism (Scheme 3).

Scheme 3.



11 **12** **13**

Accordingly, both amino and imino forms can exist as different annular tautomers, with the possibility of formation of various mesoionic and zwitterionic structures. Some of these structures are presented in Figure 4.



14 **15** **16** **17** **18**

Figure 4. Mesoionic and zwitterionic structures of 5-aminotetrazole.

Some of the mesoionic and zwitterionic forms of 5-aminotetrazole and its derivatives, although not observed experimentally, may be regarded as intermediates in different chemical reactions.[74,81,82] Quantum-chemical calculations (MP2/6- 31G*) have shown that the mesoionic forms and structures possessing the NH group in vicinal position are thermodynamically less stable (about 18 kcal mol^{-1}) than the forms presented in Scheme 3.[81,83] Therefore, investigations on the prototropic tautomerism in 5-aminotetrazoles are only based upon the equilibrium exposed in this Scheme .

For a long time, it remained unclear which would be the predominant form (amino or imino) of 5-aminotetrazole. Subsequently, it was shown by X-ray diffraction that this compound in the crystalline state exists exclusively as the amino-1*H*-form.[1,18,20] Later, it was confirmed by NMR, Raman and IR spectroscopy that 5-aminotetrazole and many if its derivatives, both in the crystalline state and in solution, exist predominantly in the amino form.[1,82,84]

Some compounds containing substituents at the nitrogen of the amino group capable of specific intramolecular or intermolecular interactions may be exceptions to the rule.[30] For instance, in 5-nitro-aminotetrazole, the imino form prevails due to the additional stabilization induced by formation of an intramolecular hydrogen bond involving the nitro group (see Figure 5).[1]

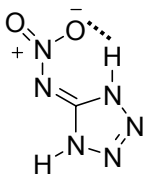


Figure 5. Intramolecular hydrogen bond formation in 5-nitro-aminotetrazole.

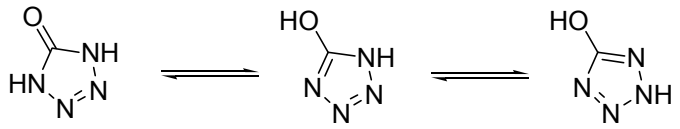
Results from molecular orbital calculations are in keeping with those obtained experimentally. According to MP2/6-31G* calculations, the amino form of 5-aminotetrazole in the gas phase is more stable than the corresponding imino tautomer.[83,84] The same qualitative result was obtained when solvation effects were considered.[84] The trend of annular tautomerism evidenced by 5-aminotetrazole is analogous to that described above for tautomerism of neutral NH-unsubstituted tetrazoles: the 2*H*-form prevails in the gas phase, whereas the 1*H*-tautomer possessing the largest dipole moment becomes the most favourable in solution.[44, 65, 84]

▪ Tautomerism of 5-Hydroxytetrazoles

5-Hydroxytetrazoles and their $N_{(1)}$-alkyl(aryl) derivatives can participate in keto-enol tautomeric equilibria (see Scheme 4). This ability results in major differences between the chemical and physico-chemical properties of these compounds and other 5-R-tetrazoles. This prototropic tautomerism of 5-hydroxytetrazoles was studied experimentally in sufficient detail. In contrast to the amino-imino tautomerism,

practically all the researchers who investigated the equilibrium presented in Scheme 4 reached the unique conclusion that 5-hydroxy-tetrazoles exist predominantly as the 1,4-dihydro-tetrazol-5-one tautomer (**19**) either in the solid state, in solution or in the gas phase. [1,17,18,20,30,85–89]

Scheme 4.

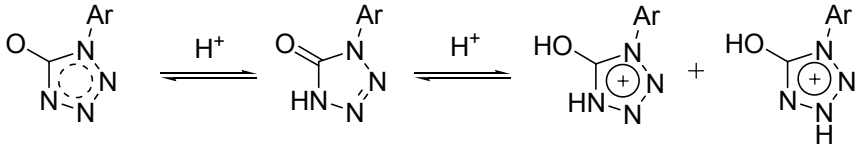


19 **20** **21**

Theoretical studies involving 5-tetrazolones were focused on the calculation of energy, geometry and electronic structure of their tautomeric forms (Scheme 4). The first publication under this topic describes the work of Postovskii and Kovalev, based on calculations performed by the Hückel method.[90] Later, non-empirical calculations of enthalpy of formation of neutral 1*H*- and 2*H*-5-hydroxytetrazoles demonstrated that the energy of the 2*H*-form is slightly smaller than that for the 1*H*-form.[61]

The prototropic tautomerism of 5-tetrazolone and 1-aryl-5-tetrazolones and of their conjugate acids, in the gas phase, was also investigated by *ab initio* (HF/6-31G**) and semi-empirical (AM1) methods. The results obtained by AM1 calculations are in total agreement with the experimental findings. In contrast, for the data extracted from *ab initio* calculations we need to include a correction to the mutual repulsion of the unshared electron pairs on the vicinal nitrogens in the heterocyclic ring. These data also confirm that the most favorable forms in the gas phase are those corresponding to 5-tetrazolones that undergo protonation at the exocyclic heteroatom, leading to the formation of 1*H*,3H^+ and 1*H*,4H^+ tetrazolium cations of similar energy (Scheme 5).

Scheme 5.



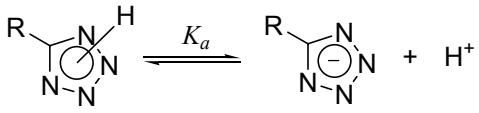
22 **23** **24** **25**

It is predicted that in the condensed phase the structures with an aromatic tetrazole ring should be more stabilized by intermolecular interactions and therefore their relative population may increase.

▪ *NH*-Acidity of Mononuclear Tetrazoles

NH-Unsubstituted tetrazoles possess acidic properties, whose strength depends on the electronic effect of the substituent in the 5-position.[22–25] The tetrazolate anion (tetrazolide **26**, Scheme 6), formed by proton exclusion, is endowed with a high stability and aromaticity, characterized by a high delocalization of the negative charge over the heterocyclic ring.[69]

Scheme 6.



5 *(1H)*
6 *(2H)*

26

Tetrazolides are efficient nucleophilic agents. They easily react with alkylating and acylating agents and with other electrophilic species. Also, many of these anionic derivatives, effectively coordinate with metal ions.[1,26,91] Unsubstituted tetrazole exhibits the properties of an organic acid similar in acidity to acetic acid (Table 2).

Comprehensive studies of NH-acidity of 5-substituted tetrazoles have been performed since the second half of 20th century. The pK_a values for a large number of 5-

R-tetrazoles were established in aqueous solutions[19,25] and in diverse organic solvent–water systems.[92,93] The quantitative measurement of the acidity constants in solutions was performed by using different physicochemical methods. However, the most precise proved to be potentiometric titration[80,94] and UV spectrophotometry.[95] NH-acidity values of 5-substituted tetrazoles in water, measured experimentally, are presented in Table 2.[1,18,19,80,95–98] In general, the discrepancies in pK_a values obtained by different authors upon the use of various experimental methods are insignificant.

Table 2. NH-Acidity constants of 5-R-tetrazoles in water at 25°C.

R-substituent group	**pK_a**
H	4.86[a]
	5.00[b]
Me	5.50[a]
	5.63[a]
Et	5.59[a]
i-Pr	5.53[a]
NH2	6.00[a]
	5.93[a]
AcNH	4.49[a]
NNO_2^-	1.0[a]
CF_3	1.7[a]
	1.14[a]
Ph	4.83[a]
Cl	2.07[a]
Br	2.13[a]
I	2.85[a]
NO_2	– 0.83[b,c]
2-$MeOC_6H_4$	6.99[b]
4-$MeOC_6H_4$	4.75[b]
4-$NO_2C_6H_4$	3.45[b]
2-$NO_2C_6H_4$	3.22[b]
COO^-	5.32[a]

[a] Determined by potentiometric titration.
[b] Determined by UV spectroscopy.
[c] In water solutions of sulfuric acid using H_0 acidity function.

The pK_a values of 5-R-tetrazoles (R = CH_3, H, Br, CF_3, NO_2) containing the substituent directly attached to the heterocycle correlate well with the σ_p constants for

the substituents (see linear eq. (1.3)).[80] The high slope value in this equation reveals the significant electronic effect of the substituent on the heterocycle.

$$pK_a = -6.65\ \sigma_p + 4.46 \qquad (r=0.98,\ s=0.5,\ n=6) \qquad (1.3)$$

A rigorous linear relationship between the acidity constants and the substituents constants is also observed when the dissociating tetrazole ring is connected to the substituent through a benzene ring.[95] Thus, the pK_a values of 5-aryltetrazoles correlate well with the σ_p constants of substituents:

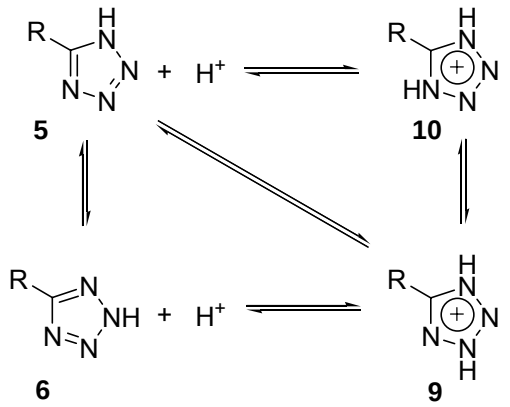
$$pK_a = -1.27\ \sigma_p + 4.40 \qquad (r=0.99,\ s=0.09,\ n=6) \qquad (1.4)$$

For several tetrazoles, the pK_a values were measured in organic solvent–water mixtures and in neat organic solvents.[19,92,93,99-103] As expected, the pK_a values of tetrazoles in mixed solvents (water mixtures with methanol, ethanol, DMSO, DMF and acetone) grew due to the increase of the organic solvent fraction and consequently, with the reduction of dielectric permitivity of the medium.[93,99,100] For instance, the pK_a value of the unsubstituted tetrazole obtained in DMSO was 8.23.[19] In many studies it was shown that the pK_a values of 5-R-tetrazoles correlate with various physico-chemical and spectral parameters of these heterocycles.[13,22,74,104-106] The value of Gibbs free energy (ΔG^0), determined by ion cyclotron resonance, for deprotonation of unsubstituted tetrazole, in the gas phase, was 326.7 kcal mol^{-1}.[107] This value is in agreement with the theoretical value (324.6 kcal mol^{-1}) obtained by DFT(B3LYP)/6-31G* calculations and fits to the general trend of variation of acid-base properties of azoles depending on their structure.

▪ Basicity of 5-R-NH-Unsubstituted Tetrazoles

The protonation of 5-R-NH-unsubstituted tetrazoles may be summarized by Scheme 7.

Scheme 7.



Effectively, all quantitative data on the basicity of tetrazole derivatives in solution were obtained by the Soviet researchers during the seventies and eighties of the 20th century. In these studies it was shown that tetrazoles behave as weak bases: these compounds are protonated only in the media whose acidity can be described by the empiric scales of acidity function. In the case of weak bases, the selection of the calculation method for final pK_{BH^+} values is crucially important. The application of different procedures to estimate the medium acidity and to calculate the ionization ratios, can give incomparable results.

Therefore, it is very important to stress that all basicity constants used for calculation of pK_{BH^+} values (eq. (1.5)), were obtained under the same standard conditions. The calculation of basicity constants of tetrazole derivatives was carried out by the Yates and McClelland method.[108] For the large majority of compounds under study the Hammett acidity function H_0 was used.

$$\log I = -m \cdot H_0 + pK'_{BH^+} \qquad (1.5)$$

$$pK_{BH^+} = pK'_{BH^+} / m \qquad (1.6)$$

In equation (1.5), I represents the ionization ratios determined by the Stewart–Granger rule[109] and m is the slope (solvation factor) of the linear dependence of log$I$ on the acidity of medium H_0. To exclude the influence of the solvation factor on the exponent of basicity constant pK_{BH^+}, the same technique was used in all cases: the ratio of the absolute term pK'_{BH^+} to the slope m, was regarded as the resulting pK_{BH^+} value (see eq. (1.6)). In many cases tetrazoles possess typical properties of Hammett bases, *i.e.*, the values of m factors in equation (1.5) are close to unity.

Presently, basicity constants are known for numerous tetrazoles derivatives. Table 3 shows the basicity constants exponents of a series of 5-R-NH-unsubstituted tetrazoles. As follows, the protonation of 5R-NH-unsubstituted tetrazoles can occur in a wide range of acidity function values H_0, from –1 to –10.

The basicity constants of unsubstituted tetrazole, measured by different methods are in good agreement.[110,111] The use of Raman spectroscopy in determination of pK_{BH^+} permitted establishing that protonation of the tetrazole ring occurred at the nitrogen in position 4.[110] This conclusion was confirmed by the fair agreement between the calculated and experimental vibrational spectra of compounds measured in concentrated sulfuric acid. A similar conclusion was made based on the results of ^{15}N NMR spectroscopy.[112,113]

Table 3. Basicity constants exponents of 5-R-NH-unsubstituted tetrazoles in aqueous solutions of sulfuric acid at 25°C, determined by UV spectroscopy, ^{1}H NMR spectroscopy, Raman spectroscopy and potentiometric titration.

R-substituent group	pK_{BH}^+	Method
H	–2.68	^{1}H NMR
	–3.01	Raman
Tetrazol-5-yl	–5.47	UV
4-$MeOC_6H_4$	–1.88	UV
Ph	–2.28	UV
	–2.45[a]	
	–2.32[b]	
4-ClC_6H_4	–2.51	UV
	–2.60[b]	
4-BrC_6H_4	–2.56	UV
4-IC_6H_4	–2.66	UV
3-ClC_6H_4	–2.94	UV
2-$NO_2C_6H_4$	–3.30	UV
3-$NO_2C_6H_4$	–3.38	UV
4-$NO_2C_6H_4$	–4.19	UV
	–3.40[b]	
COOH	–2.99	^{1}H NMR
$Me_2NCH_2CH_2$	–9.39[c]	PT [d]
$Me_2N^+HCH_2CH_2$	–2.78	^{1}H NMR
Me	–1.83	^{1}H NMR
Br	–5.20	UV
I	–4.40	UV
CF_3	–7.00	UV
NO_2	–9.26	UV

[a] At 60°C;
[b] In a system perchloric acid–water;
[c] For protonation at the dimethylamino group in water;
[d] Potentiometric titration.

1.1.2. Pharmacological Properties

At the beginning of this Chapter it was stated that the tetrazolic acid fragment, –CN_4H, has comparable acidity to the carboxylic acid group, –CO_2H, and is almost allosteric with it, but is metabolically more stable at physiologic pH.[2] In fact, from a pharmacologic point-of-view, the main interest for the inclusion of the tetrazole unit in the structure of several drugs and drug-candidates is due to the higher metabolic stability of this heterocycle comparatively to the carboxylic acid group.

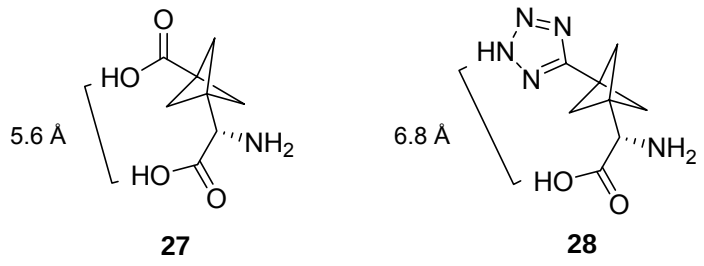
It has been held for long that 5-R-NH-unsubstituted tetrazoles (RCN_4H) may serve as non-classical isosteres for the carboxylic acid moiety (RCO_2H) in biologically active molecules.[1,2,17,114-117] The designation "non-classical isosterism", used interchangeably with the term bioisosterism, refers to the concept in which functional groups that have similar physico-chemical properties may be interchangeable, resulting in similar biological properties. Furthermore, a non-classical isostere may or may not have the same steric or electronic characteristics, nor even the number of atoms, of the substituent for which it is used as a replacement.[116-119]

5-R-NH-unsubstituted tetrazoles, which contain a free N–H bond, are also frequently referred to as tetrazolic acids. In general, these derivatives exhibit physical characteristics similar to carboxylic acids, but are strongly influenced by the effect of substituents at the 5-position. For example, many 5-aryl tetrazoles are highly soluble in water and are best crystallized from aqueous alcoholic solvents. However 5-aliphatic analogues, while often still soluble in water, are best crystallized from solvents such as ethyl acetate or toluene/pentane mixtures.[1] The corresponding tetrazolate anionic species (RCN_4Na or CN_4Li), which have a higher capacity for hydrogen bonding than the protic species,[52] are easily generated in hot alcohol or aqueous solutions and these intermediates are more reactive than the corresponding neutral species toward a variety of electrophiles and alkylating agents.

Like their carboxylic acid equivalents, tetrazoles are ionized at physiological pH (7.4), and both exhibit a planar structure. However, anionic tetrazoles are almost 10 times more lipophilic than the corresponding carboxylates,[120] which is an important factor to bear in mind when designing a drug molecule to pass through cell membranes. Another important factor when considering a tetrazole as a replacement is the effect of delocalization of the negative charge around the tetrazole ring. The distribution of

charge over a greater molecular surface area may be favorable for a receptor–substrate interaction, or may complicate the contact, depending on the local charge density available at the interface.[121] The larger size of the tetrazole ring, comparatively to a carboxyl group, may also reduce the binding affinity at the active site, either by a less favourable orientation of functional groups, or by steric hindrance of an active conformational change of the receptor complex.[122]

An interesting comparison between the effective length of carboxylic acid versus tetrazole pharmacophores was recently reported by Pellicciari and co-workers (see Figure 6).[123] In a study designed to explore the SAR (Structure Activity Relationship) of propellane-derived analogues of L-glutamic acid as mGlu1 receptor agonists, the authors prepared the amino acids **27** and **28**, which contained distal carboxylic acid and tetrazole units, respectively. Models suggested that the distance between the acidic functional groups were such that the 2*H*-tetrazole moiety increases the distance between the pharmacophores by about 1Å . In vitro evaluation revealed that the tetrazole **28** was 2.5-fold less potent than **27**, which was attributed to the increased distance between the two acidic sites, indicating an unfavorable fit between two important synergistic positions.

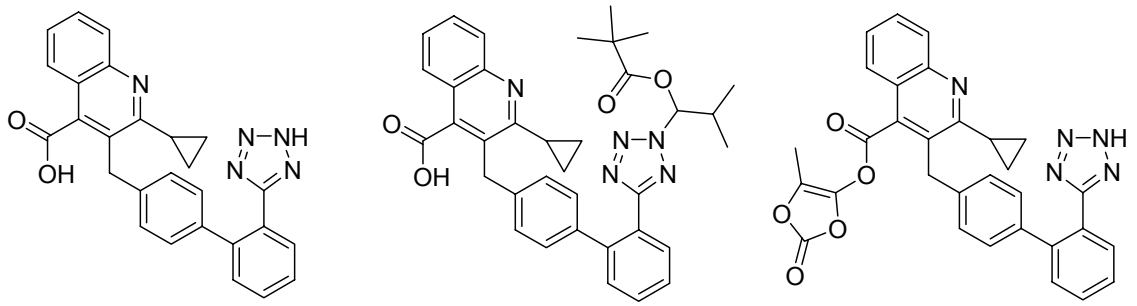


27 **28**

Figure 6. The size of the tetrazole ring in **28** extends the distance between the two acidic pharmacophores relative to the analogous dicarboxylic acid **27**.

In the design of drug molecules, one advantage of tetrazolic acids over carboxylic acids is that they are resistant to many biological metabolic degradation pathways. Some of the earliest findings showed that tetrazole-derived nicotinic acid analogues that were administered to dogs were excreted essentially unchanged over a 24h period, whereas nicotinic acid itself was rapidly metabolized.[124] As in these cases, it is often seen that the resistance of tetrazolic drug substances to metabolism may result in a longer duration of action versus carboxylic acids, although just as often a corresponding lack of potency is also observed.

Tetrazole compounds which contain an additional basic functionality in the molecule may exist as zwitterions, which can result in poor absorption properties for a potential drug candidate. In some cases a prodrug approach has been developed, similar to the strategy developed for carboxylic acids to enhance oral bioavailability.[125] Derivatization of polar molecules into compounds in which the acidic tetrazole N–H bond has been masked (protected by a moiety that can be removed under physiological conditions) results in a more lipophilic molecule of neutral charge that can exhibit greater biomembrane transport ability. This approach has been used to improve the physico-chemical properties of the angiotensin II receptor antagonist BMS-183920 (diacidic structure **29**) as the prodrug **30** (Figure 7).[126] By protection of the poorly absorbed tetrazole with a pivaloylisobutyl moiety, the bioavailability in rats was increased from 11% in **29** to 37% in **30**. Interestingly, prodrug protection of the carboxylic acid instead of the tetrazole moiety (**31**) did not increase oral availability to better than 26%.

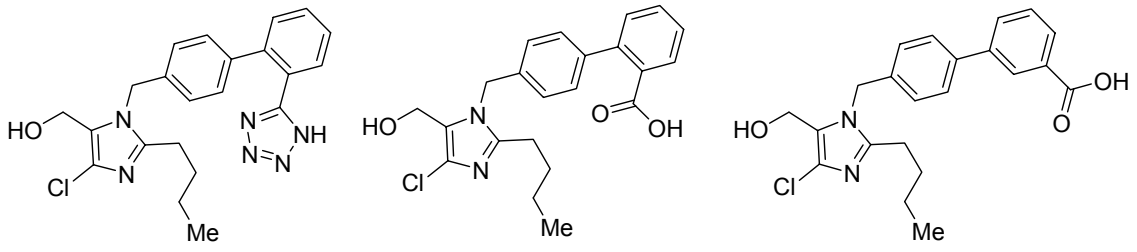


29 (BMS-183920), 11% F **30**, 37% F **31**, 26% F

Figure 7. A tetrazole prodrug approach to mask BMS-183920 (**29**) as **30** increased bioavailability (% F) by more than 3-fold.

A complete search of the literature shows that the majority of tetrazolic acid-based drug substances are aryl tetrazoles. In fact, a great part of these structures contain the biphenyl tetrazole function (such as structures **29-31**), many of which are analogues of DuPont's non-peptidic selective angiotensin II receptor antagonist Losartan (**32**, Figure 8), a drug launched in 1994 to treat hypertension.[127-130]

During an investigation involving a new series of analogues derived from a biphenyl base, it was found that isomers **33** and **34** (Figure 8) were both active by intravenous injection into renal hypertensive rats. Unfortunately, the effect was minimized upon oral administration.



32 (Losartan) **33** **34**

Figure 8. Structures of Losartan and 2- and 3-carboxybiphenyl analogues.

In an attempt by the same research team to find compounds of greater potency and bioavailability, a series of carboxylic acid isosteres were prepared. Interestingly, no

carboxamide or sulfonamide compounds were found to improve the oral activity, but when tetrazole was introduced at the $C_{(2)}$-position a remarkable enhancement in binding affinity and oral potency was observed. The authors postulated that the increase in receptor binding was due to the greater ability of the heterocycle to distribute a negative charge at physiological pH, allowing for better interaction (vs. carboxylate) with the positive charge at the receptor.[131] This early hypothesis has more recently been recognized by conformational analysis, using theoretical calculations and NMR spectroscopy.[4] Furthermore, the longer spatial distance of the N–H bond into the receptor may be the optimal depth for receptor binding. Better oral bioavailability (33% for Losartan) may be due to the greater lipophilicity of tetrazole **32** versus carboxybiphenyl analogues **33** and **34**. Since the introduction of Losartan (**32**) into the literature, a huge number of papers have been published related to potential analogues of this compound, as well as a variety of other biphenyl tetrazolic acid structures, proposed for other clinical uses.[131,132]

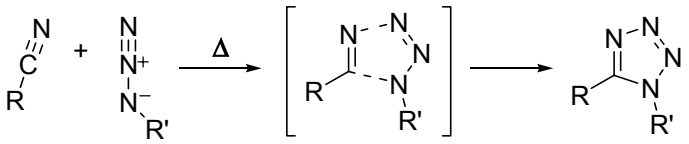
A word of good sense: the pharmacological effects resulting from the bioisosteric replacement of carboxylates with tetrazoles in a potential drug candidate are not necessarily predictable, as the wealth of medicinal chemistry literature points out. In fact, diverse examples from the literature show that the pharmacological effects can be improved, reduced or eliminated completely, when compared to carboxylic acid analogues. [133-136]

1.1.3. Synthetic Methods

Throughout this section, the text will attempt to provide a representative survey of the most widely literature procedures for the preparation of tetrazoles.

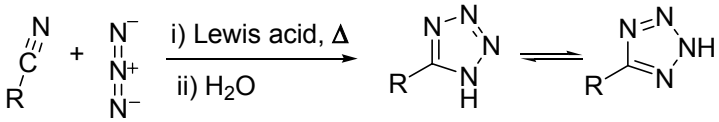
The most direct method to form tetrazoles is by the concerted and highly regioselective [2 + 3] cycloaddition between an organic azide ($R–N_3$) and an organic nitrile (R–CN) as shown in Scheme 8. However, this cycloaddition is too slow to be synthetically useful, except when potent electron-withdrawing groups activate the nitrile (dipolarophile) component.

Scheme 8.



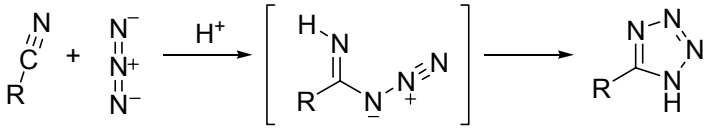
Of greater importance, is the synthetic method used to form 1*H*-tetrazoles, following the formally similar addition of azide salts and nitriles (Scheme 9).

Scheme 9.



This variant is of major synthetic interest, since the range of nitriles which are able dipolarophiles is much broader and a wide variety of metal-azide complexes can serve as azide donors.[137-140] Mechanistically, however, these transformations are less straightforward. In the case where hydrazoic acid or an amine salt of hydrazoic acid acts as the dipole, both an anionic two step mechanism[141,142] and a concerted [2 + 3] cycloaddition[143] have been proposed. More recently, a different mechanism was suggested,[144] proceeding through a previously unsuspected imidoyl azide intermediate (**35**, Scheme 10) that involves the activation of the nitrile by protonation.

Scheme 10.

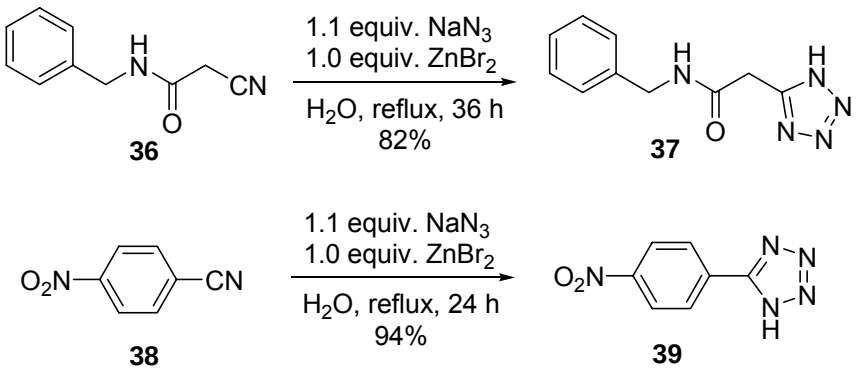


35

This pathway is computed to be some 10 kcal/mol lower in energy than the concerted [2 + 3] mechanism. Presently, there are no reports concerning the mechanistic details for the cases where nonprotic Lewis acids are employed as catalysts for the addition of an azide ion to a nitrile.

It has been recently shown that zinc salts are excellent catalysts for this reaction.[145,146] One of the most notable contemporary advances in tetrazolic acid synthesis was published by Demko and Sharpless at the end of 2001, in which a method was described for the assembly of tetrazoles from nitriles in water as a solvent (Scheme 11).[147] This method utilizes a 1:1 ratio of sodium azide and zinc(II) bromide as reagents, and reactions are carried out at temperatures ranging from reflux to 170 °C.

Scheme 11.

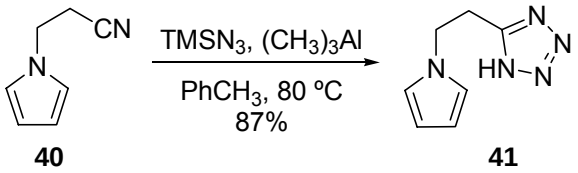


Electron-poor aromatic nitriles react entirely at reflux after a few days, whereas electron-rich aromatic species and unactivated aliphatic nitriles require higher temperatures with the use of a sealed glass pressure reactor. Nevertheless, the protocol minimizes the risk of liberating hydrazoic acid, and usually a simple acidification is all

that is necessary to provide the pure tetrazole products. The authors are hopeful that the ease of use will make this method amenable to both laboratory and industrial scales.

Some of the new methods for the preparation of 5-substituted tetrazolic acids involve the reaction of alkyl- or arylnitriles with safer organic soluble azide reagents, such as trialkyltin azide or trimethylsilyl azide.[1,115] A method using trimethylsilyl azide was recently described by Huff and Staszak, who showed that an equimolar mixture of trimethylaluminum and trimethylsilyl azide in hot toluene was very effective at producing 5-substituted tetrazole **41** from nitrile **40** in a yield comparable to the sodium azide phase-transfer method (Scheme 12).[138]

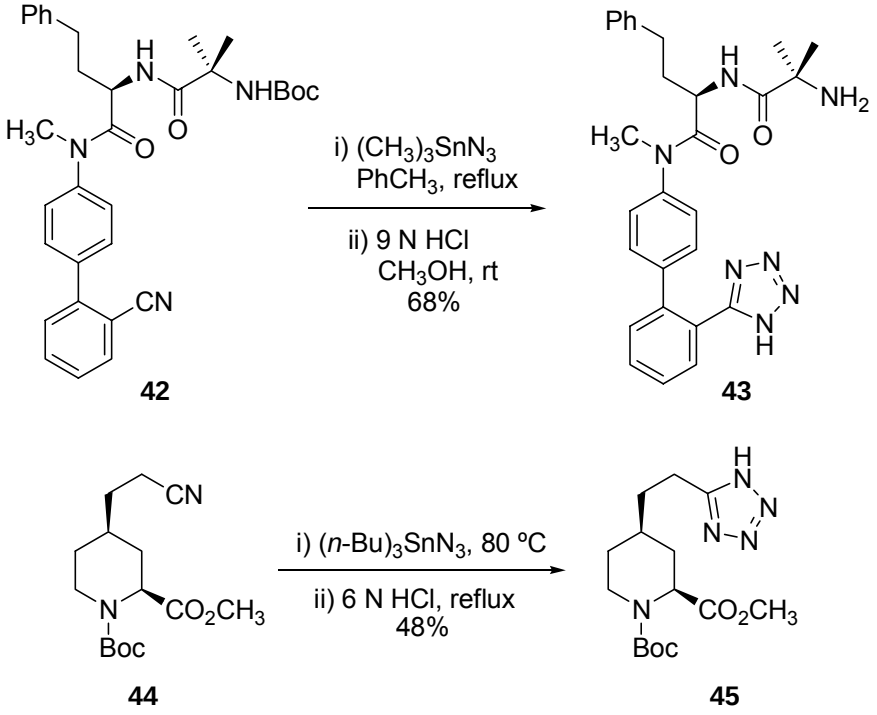
Scheme 12.



Methods for tetrazole formation from organic nitriles using the organic-soluble reagents trimethylstannyl azide[148,149] or tri-n-butylstannyl azide[150-153] seem to be more commonly used than the sodium azide/amine salt protocols (Scheme 13).

While this procedure generates one molar equivalent of hazardous tin by-product (which may present purification problems later), better yields are generally found when directly compared to silicon-based azide reagents. These conditions typically require the use of one equivalent of trialkyltin azide in refluxing THF, toluene, 1,4-dioxane or xylenes. A separate acidic hydrolysis step is then required to remove the tin group from the tetrazole ring.

Scheme 13.



Several reports have appeared which make use of precursors other than nitriles to prepare 5-substituted-1*H*-tetrazoles. The methods offered in these communications for preparation of various tetrazole derivatives have a minor impact from a synthetic viewpoint and, for this reason, will not be presented in this manuscript.

1.1.4. Tetrazoles as Metal Complexation Agents; Some Catalytic Applications

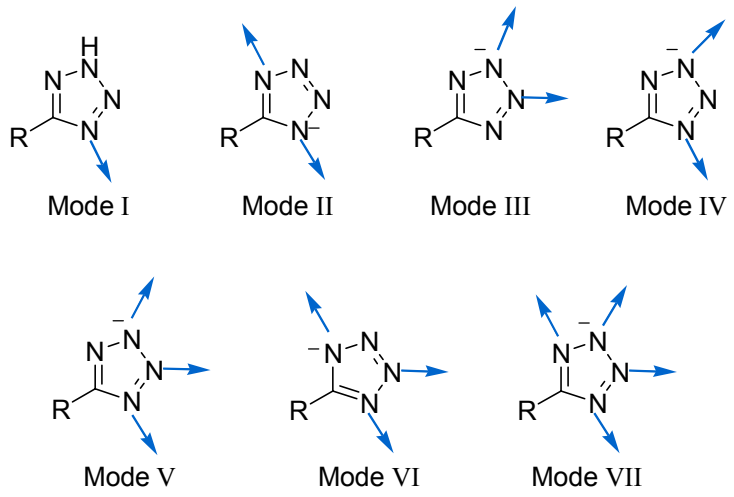
Dinuclear and polynuclear metal complexes bridged by polydentate ligands have received great attention in recent years in connection with the design of molecular electronic devices. In particular, dinuclear complexes bridged by conjugated ligands have been extensively studied because they can have interesting nonlinear optical (NLO) applications[154-156] or behave as molecular chains[157] or molecular switches.[158]

The tetrazole functional group has found a wide range of applications in coordination chemistry as ligand.[159-163] Of interest to supramolecular chemists is the

coordination ability of the tetrazolyl ligand through the four nitrogen electron-donating atoms that allows it to serve as either a multidentate or a bridging building block in supramolecular assemblies. Indeed, the tetrazole ligand has been shown to be able to participate in at least seven distinct types of coordination modes with metal ions in the construction of novel metal-organic frameworks.

As shown in Scheme 14, the nitrogen-containing heterocycle can either coordinate in a μ_1-tetrazolyl mode (*Mode* I); μ_2-tetrazolyl mode, which in itself has three different modes of coordination (*Modes* II-IV); adopt two different μ_3-tetrazolyl modes (*Modes* V-VI); or act in a μ_4-tetrazolyl mode (*Mode* VII).

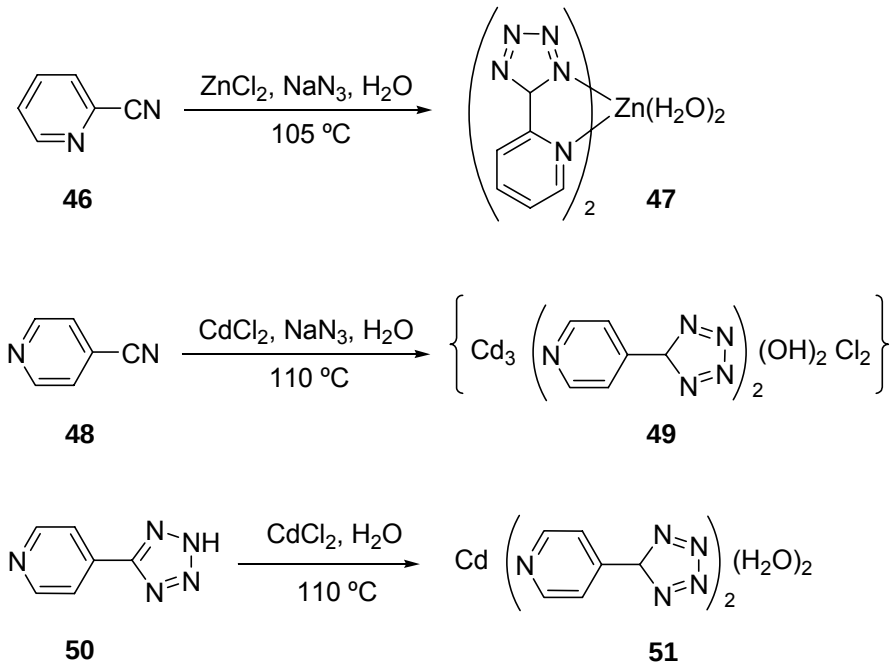
Scheme 14.



The study of complexes containing substituted tetrazole ligands is of interest to delineate the ways in which tetrazoles bind to metal centres. In recent studies, a series of 5-(pyridyl)tetrazole complexes as "metal organic frameworks" with Zn(II) and Cd(II) have been prepared under hydrothermal conditions (see Scheme 15 for three examples of complexes) in which a range of coordination modes for the tetrazoles were observed, and extended 2D and 3D structures were identified, indicating hydrogen storage properties.[161-166] Surprisingly, the composition and solid state structures of isolated

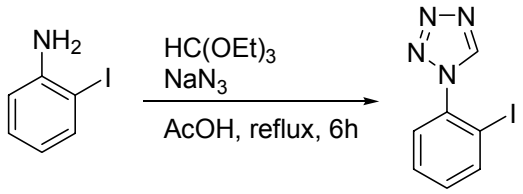
products (**47**, **50** and **51**, Scheme 15) are quite different, and depend on the complexing ability of the metal ions toward tetrazole and hydroxy groups. Some of the novel supramolecular motifs formed *in situ* under the hydrothermal conditions are not accessible by direct preparation from ZnX_2 and tetrazoles in solution under ambient conditions.

Scheme 15.



Besides, numerous tetrazolyl ligands have been tested in catalyzed reactions coordinated with different metal centres, such as niquel, ruthenium, palladium or platinum.[167-173] For instance, the synthesis of the new ligand 1-(2-iodo-phenyl)-1*H*-tetrazole (**53**) was recently reported and it was demonstrated that combination of the ligand with $Pd(OAc)_2$ could be an effective catalyst for Heck reactions.[172] Ligand **53** was prepared in one step from 2-iodo aniline, triethyl orthoformate and sodium azide in acetic acid (Scheme 16).

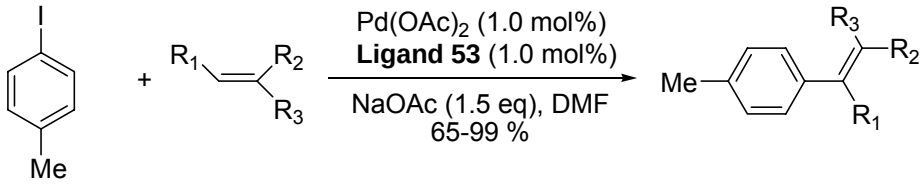
Scheme 16.



52 **53**

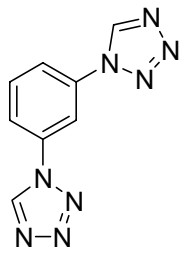
The activity of ligand **53** in the Heck methodology was assessed using combinations of 4-iodotoluene (**54**) with various α,β-unsaturated carbonyl compounds (**55**). These Heck reactions catalyzed by the tetrazole–Pd complex afforded the products (**56**) stereoselectively, in good to excellent yields (Scheme 17).[172]

Scheme 17.



54 **55** **56**

Additionally, during the same period, another tetrazolyl derivative, 1,3-bis(tetrazol-1-yl)benzene (**57**, Figure 9), has been proposed as a promising pincer ligand for the Suzuki cross-coupling, ensuring satisfactory yields of the target products even from non-activated aryl chlorides. This ligand is easy to prepare, is stable in air, and can form catalytically active metal complexes with palladium acetate *in situ*.[174]

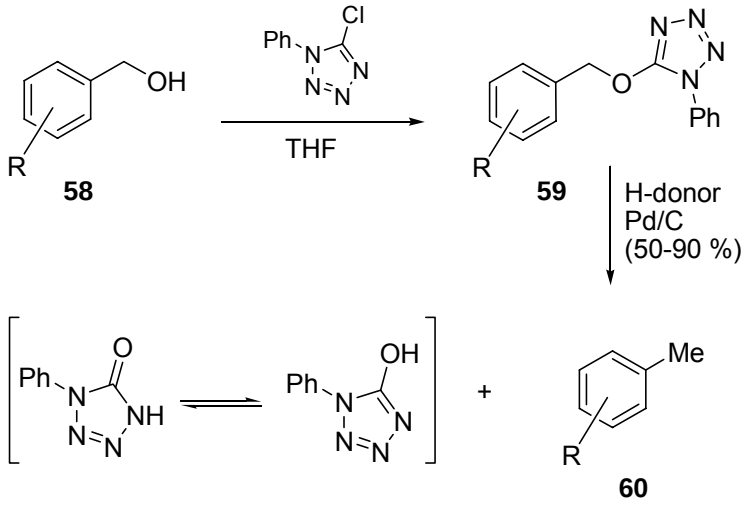


57

Figure 9. Structure of ligand 1,3-bis(tetrazol-1-yl)benzene.

Moreover, tetrazoles are also applied in heterogeneous catalytic reductive cleavage reactions. Heterogeneous catalytic transfer hydrogenolysis of aryloxy- and allyloxy-tetrazoles has been used in the hydrogenolysis of phenols and allylic alcohols, and presents a practical and selective synthetic alternative to other methods.[175-178] The hydrogenolysis of the C–OH bond can be achieved after conversion of the original alcohol or phenol into a tetrazolyl ether. Derivatization weakens the original C–O bond and increases the nucleophilic susceptibility of the carbon atom. The effect of the electron-withdrawing heterocyclic part of these ethers on the C–O bond strength has been clarified through X-ray studies.[179-181] The extent of cleavage and selectivity depends on the nature of the catalyst. Experimental conditions were also devised for selective conversion of benzyl alcohols (**58**) to toluenes (**60**) in good yields, over Pd/C, *via* transfer hydrogenolysis of the corresponding benzyl tetrazolyl ethers (**59**), using hydrogen donors (see Scheme 18).[182] This reductive methodology has been further extended to selective C–O cleavage in naphthyl methylic alcohols.

Scheme 18.



Palladium is normally used in these systems because it is known as a good catalyst for hydrogenolysis and, unlike rhodium or platinum catalysts, does not

dearomatise the ring.[183,184] The advances made throughout our investigation will be discussed later in this thesis.

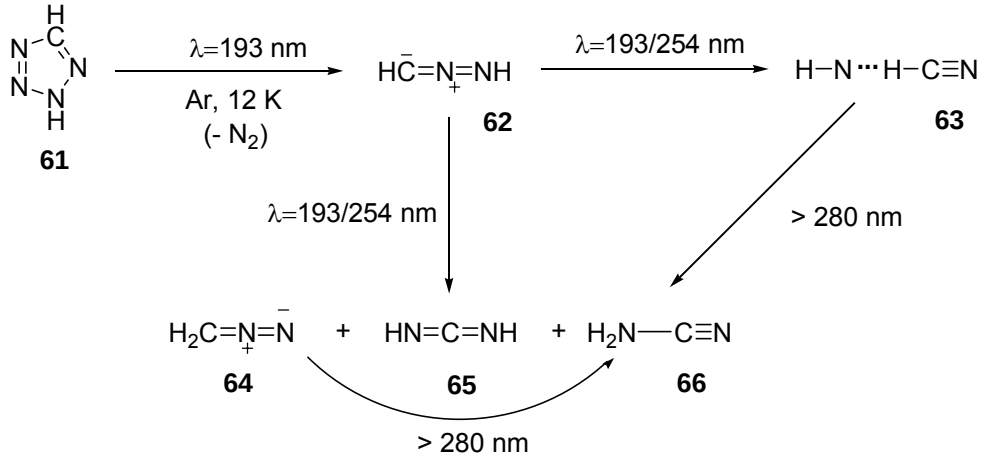
As exposed above, the tetrazole functional group possesses a wide range of potential applications in coordination chemistry. Accordingly, some exploratory research was carried out during the PhD program that is the object of the present thesis. Although the amount of results obtained is relatively modest, their nature is considered to be promising in terms of novelty, applications and scope. A detailed discussion on this field will be presented in Chapter four of this thesis.

1.1.5. Photochemistry

Along with the practical applications of tetrazoles, these heterocycles are also particularly interesting compounds because they exhibit a very rich photochemistry.[82,185-191] Two main factors contribute to enrich the photochemistry of tetrazoles: the possibility of tautomerism (which is associated with the presence in the molecule of labile hydrogen atoms) and the conformational flexibility of the substituents.

Effectively, most of the quantitative data on the photochemistry of tetrazole derivatives, matrix-isolated or in solution, results from the work of German researchers during the eighties of the 20th century.[192-197] A decade later, the photochemistry of matrix-isolated unsubstituted tetrazole was studied for the first time by Maier and co-workers.[198] Upon photolysis with the 193 nm emission line of an ArF laser, rapid photocleavage of tetrazole was observed, leading to extrusion of N_2 and formation of several different photoproducts, including nitrilimine (**62**), an HCN···NH complex (**63**), diazomethane (**64**), carbodiimide (**65**) and cyanamide (**66**) (Scheme 19).

Scheme 19.



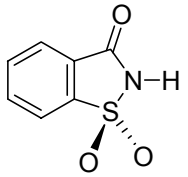
By use of different excitation wavelengths, cyanamide and carbodiimide could be accumulated as final products. Maier's group investigation also revealed, for the first time, the vibrational signature of matrix-isolated nitrilimine.[198]

Several substituted tetrazoles have been studied regarding their photochemical fragmentation reactions. For these compounds, the nature of the substituents present in the tetrazole ring was found to strongly determine the final photoproducts.[86,192,199] In the case of substituted tetrazoles, tautomerism may also involve substituent groups.[82,185] In general, the presence of labile hydrogen atoms (either directly linked to the tetrazole ring or belonging to the tetrazole substituents) is a source of complexity in photochemical reactions that opens additional reaction channels or allows for secondary photochemical reactions to take place concomitantly with the main primary photoprocesses.[82,86,185,192,198,200] When substituents are linked to the tetrazole ring, the photochemistry of the molecule can also be influenced by the conformational flexibility of the substituents, which may favor or exclude certain reaction channels.[82,187] Thus, it has been shown clearly that the properties of the substituents are very relevant in determining the precise nature and relative amount of the final photoproducts, then making tetrazoles a permanent challenge to investigation.

Recent studies on a series of tetrazole derivatives, in solution and matrix-isolated, will be presented in Chapters 2 and 3 respectively, where a general pattern of photofragmentation for these compounds upon UV-excitation can be defined. Besides, the observation of a number of relatively unusual or highly reactive molecules, formed from photolysis of the studied tetrazoles, such as antiaromatic azirines, azides, isocyanates, isothiocyanates, pyrimidinones or oxazines, led, in some cases, also to the first spectroscopic characterization of these species.[82,186-191]

1.2. Benzisothiazoles (Saccharin Derivatives)

1,2-Benzisothiazole-3-one 1,1-dioxide or saccharin (**67**, Figure 10) was discovered accidentally by Fahlberg in 1878 during an investigation of the oxidation of *o*-toluenesulfonamide[201,202] and published by Remsen and Fahlberg, 1 year later.[203]



67

Figure 10. Structure of 1,2-benzisothiazole-3-one 1,1-dioxide (saccharin).

For more than a century, saccharin has been commonly used as a non-caloric artificial sweetener in the form of its water-soluble salts (mainly the sodium, ammonium and calcium), being the principal sweetening component of diabetic diets. For about three decades, the debate on its toxicity to humans has not reached a consensus, since reports on the carcinogenicity in laboratory animals were published.[204-206] Numerous *N*-substituted derivatives of saccharin have recently been assessed for *in vitro* biological activity;[207-209] first-row transition metal saccharinates as well as the dioxovanadium(VI), dioxouranium(VI) and cerium(IV) saccharinates are protease inhibitors,[210,211] and

several metal(II) saccharinates display superoxide dismutase-like activity.[212] Furthermore, benzisothiazolyl and isothiazolyl derivatives have been used in agriculture, as herbicides, fungicides and pesticides.[213] The first non-benzoannelated 4-amino-2,3-dihydroisothiazole 1,1-dioxide, lacking a 3-oxo group, has recently been described and shows anti-HIV-1 activity.[214,215]

Aside from its relevance in biological systems, saccharin has been exploited as an excellent model system for investigating the structural preferences of small heterocycles containing conjugated CO/NH or NH/SO_2 groups. The diversity of bonding modes adopted by the 1,2-benzisothiazole-3-one 1,1-dioxide anion and the fortuitous crystalline nature of the resulting complexes are excellent reasons to scrutinize this system. Over 60 structures of metal saccharinates have been reported up to date. As a polyfunctional ligand, deprotonated saccharin can exist as an ion or it can be incorporated into a complex as a ligand, and it can also exist simultaneously as ionic and coordinated species in the same structure. As ligand, it can be engaged in N, O_{CO} or O_{OSO}-coordination,[216,217] but can also act as a bidentate amidato-like bridging agent.[218–221] The structural literature on metal saccharinates reveals larger population of coordinated than non-coordinated saccharinato residues. Thus, the saccharinate anion interacts with metal centres in very different ways, generating relatively strong interactions in crystalline environments, mostly through hydrogen bonding. Diverse forms of ligand-to-metal and molecular interactions of saccharinate anion (**68**) are briefly summarized in Figure 11.

Earlier infrared studies[201] and a recent comprehensive two-dimensional structure-infrared analysis[222] have demonstrated that the frequency shift of the ν(CO) mode of saccharinates from the average value of the ν(CO) doublet of solid saccharin can be used as a reliable spectroscopic criterion for estimating the metal-saccharinato

bond character. Several factors, such as the averaging undertaken to rationalize the inconsistency among spectroscopic and structural data, vibrational interactions as well as the environment of the saccharin, are attributed to the low correlation between the CO stretching frequency and the C–O and M–N bond orders.[222]

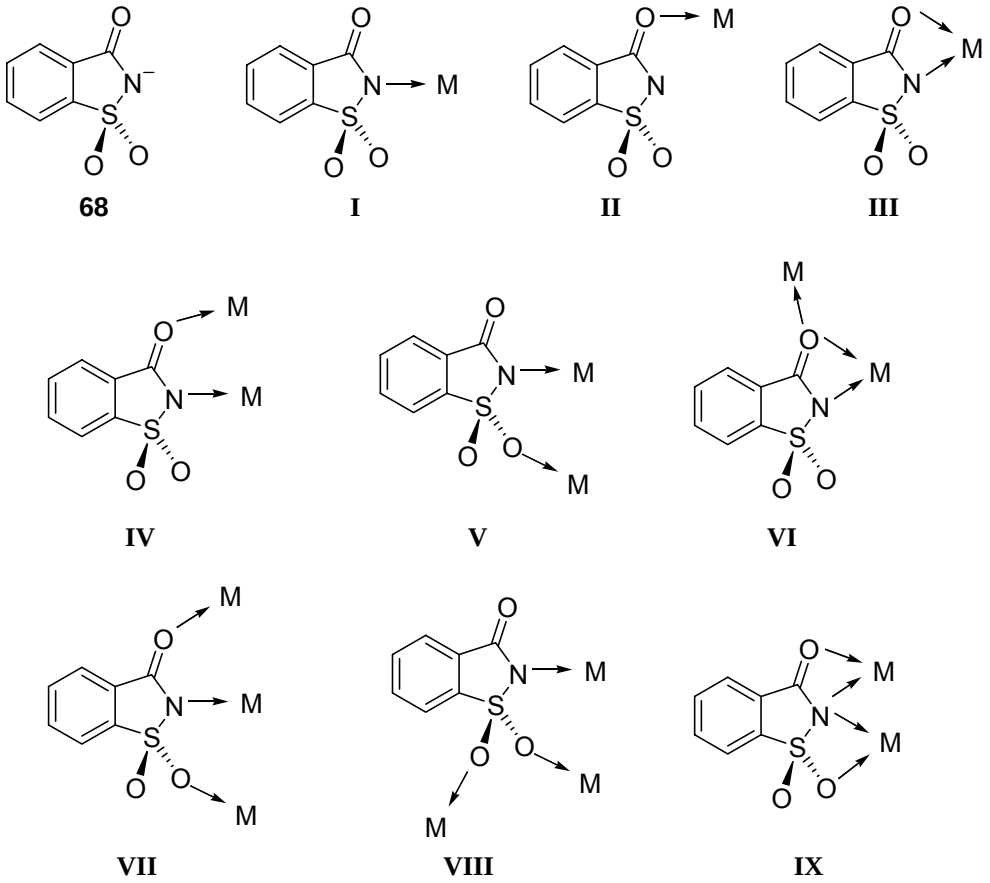


Figure 11. Coordination modes of the saccharinate ligand.

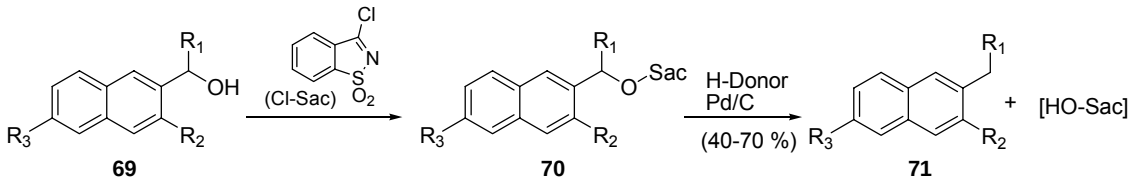
As a cheap and versatile starting material, saccharin is used as a building block for the synthesis of related heterocyclic derivatives. Among these, the 3-substituted ones are accessible through direct nucleophilic additions to the carbonyl carbon by strong nucleophiles such as alkyl- and aryl-lithium reagents.[223-225] Substitution of the carbonylic oxygen by a halogen facilitates nucleophilic addition of week nucleophiles, such as alcohols or amines, to the carbon atom in position 3.[226-228] In the last decade, special attention has been devoted to ethers derived from benzisothiazole, with

important synthetic uses as intermediate compounds in the transformation of alcohols.[182,229]

As described for tetrazoles, in Section 1.1.4 of this text, benzisothiazoles are also applied in reductive cleavage of C–O bonds catalysed by transition metals. Heterogeneous catalytic transfer hydrogenolysis of aryloxy- and benzyloxy-benzisothiazoles has been used in the hydrogenolysis of phenols and benzylic alcohols. The hydrogenolysis of the C–OH bond can be achieved after conversion of the hydroxyl group into an ether with an electron-withdrawing group, such as benzisothiazole. Derivatization weakens the original C–O bond and increases the nucleophilic susceptibility of the carbon atom.

In addition, experimental conditions were developed for selective conversion of naphthyl methanols (**69**) to methyl-naphthalenes (**71**) in moderate to good yields, over Pd/C, *via* transfer hydrogenolysis of the corresponding methyl-naphthyl benzisothiazolyl ethers (**70**), using hydrogen donors (see Scheme 20).[182]

Scheme 20.



In Chapter 4 of this thesis, original applications of some benzisothiazolyl derivatives in coordination chemistry and heterogeneous catalysis will be discussed.

1.3. Matrix Isolation / FT-IR Spectroscopy

Studies in the gas phase offer the potential for most precise and detailed measurements. However, because of the high chemical reactivity of transient molecules, it is difficult to obtain gas-phase infrared spectra of them. Nevertheless, the well known

advantages of Fourier transform infrared measurements, coupled with sophisticated digital data handling procedures, have permitted the acquisition of gas-phase survey spectra for a number of transient molecules. Diode lasers and other laser-based techniques with limited tunability have been used, and high resolution spectra of individual vibrational transitions of these species could be obtained.

The application of matrix isolation sampling for the stabilization and spectroscopic study of reaction intermediates has recently been reviewed.[230] Matrix isolation is an experimental technique used in chemistry and physics which requires that the material to be analysed is trapped within an unreactive matrix. The *host* matrix is a continuous solid phase in which *guest* particles (atoms, molecules, ions, etc.) are embedded. Matrix isolation has its origins in the first half of the 20th century with the experiments by photochemists and photophysicists using freezed samples in liquefied gases. The earliest isolation experiments involved the freezing of species in transparent, low temperature organic glasses. The modern matrix isolation technique was developed extensively during the 1950s, in particular by George C. Pimentel. He initially used higher-boiling inert gases like argon and nitrogen as the *host* material and, due to these huge advances, Professor Pimentel is often said to be the "father of matrix isolation".

Because nitrogen and the rare gases are transparent through the entire infrared spectral region, matrix isolation measurements provide a potentially valuable survey tool. In these matrices, infrared absorptions are typically sharp, with half band widths between 0.1 cm^{-1} and 1 cm^{-1}. The rotational structure is, with few exceptions, quenched. Multiple trapping sites occur, often resulting in the appearance of several absorption maxima - usually one or two of which predominate - over a range of a few cm^{-1}.

Matrix shifts for covalently "bound" molecules trapped in solid neon or argon are often quite small. A comparison of positions of the ground-state vibrational fundamentals of over two hundred diatomic molecules observed in the gas phase and in nitrogen and rare-gas matrices has shown that, typically, the smallest matrix shift occurs for neon matrix observations, with successively greater matrix shifts for the heavier rare gases and for nitrogen. The generalization that matrix interactions are minimal for neon and that they increase as the mass of the rare gas is increased and become even more important for nitrogen and most other small molecule matrices is also supported by experimental observations on larger molecules.

One of the most important advantages of matrix isolation spectroscopy is the possibility to follow photochemical reactions unambiguously. For a matrix isolated compound, *in situ* photolysis enables selective introduction of energy in the molecule under study, controlling the range of possible rearrangements of the isolated species. Thus, a wide range of intramolecular changes, up to molecule decomposition and formation of new entities, can be studied. In addition, contrarily to what occurs in the gaseous phase or in solution, where a multitude of possible photochemical reaction pathways leading to different products can be observed, in a matrix the processes are cage-confined (molecular diffusion is inhibited) and therefore a useful simplification to the photochemical reactivity is obtained. For example, if photofragmentation of a matrix-isolated species occurs, very frequently the obtained fragments stay in the matrix cage where they are formed. Then, no subsequent cross-reactions involving species resulting from photolysis of different reactant molecules can occur, strongly reducing the number of possible photoproducts in comparison with gas phase or solution studies. This fact may considerably facilitate the interpretation of the reaction mechanisms.

In Chapter 3 of this thesis, a general overview of the photochemistry, molecular structure and vibrational spectra of a series of matrix-isolated tetrazole derivatives is presented. The matrix isolation setup used in the course of these studies is depicted below (see Figure 12).

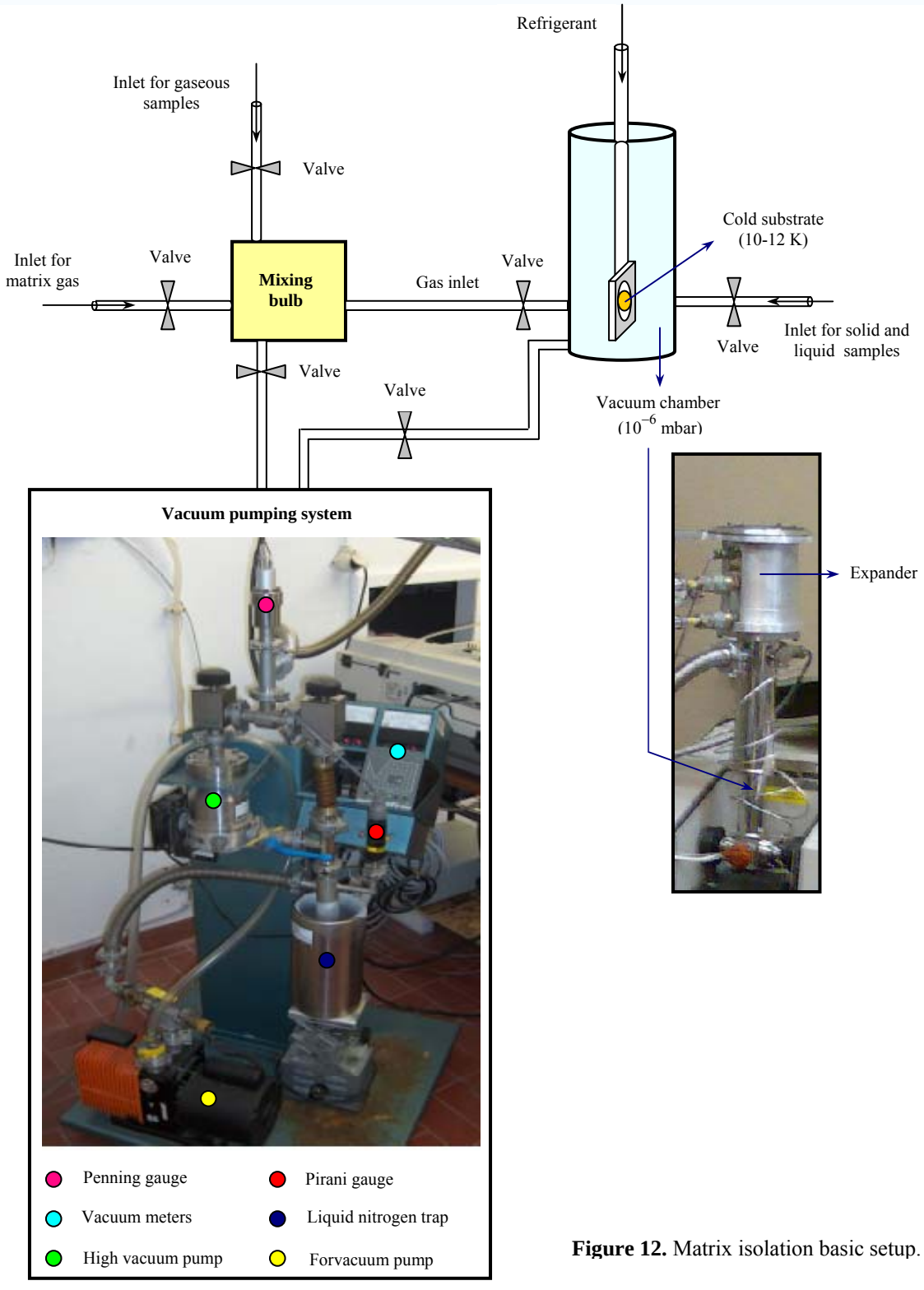


Figure 12. Matrix isolation basic setup.

1.4. Computational Chemistry: Molecular Modelling

Computational chemistry may be defined as the application of mathematical and theoretical principles to the resolution of chemical problems. Molecular modelling, a subset of computational chemistry, concentrates on predicting the behaviour of individual molecules within a chemical system. The most accurate molecular models use *ab initio* (or 'first principles') electronic structure methods, based upon the principles of quantum mechanics, and are generally very computer-intensive. However, due to advances in computer storage capacity and processor performance, molecular modelling has been a rapidly evolving and expanding field, to the point that it is now possible to solve relevant problems in an acceptable amount of time.

The types of predictions possible for molecules and reactions include:[231]

- Heats of formation;
- Bond and reaction energies;
- Molecular energies and structures (thermochemical stability);
- Energies and structures of transition states (activation energies);
- Charge distribution in molecules (reactive sites);
- Substituent effects;
- Electron affinities and ionisation potentials;
- Reaction pathways, kinetics and mechanisms;
- Vibrational frequencies (IR and Raman spectra);
- Electronic transitions (UV/Visible spectra);
- Magnetic shielding effects (NMR spectra);

Prediction of these properties and trends in reactivity has many applications in the general field of organic chemistry, including organic synthesis, the development of new synthetic methodologies and mechanistic studies.

All molecular modelling techniques can be classified under three major categories: *ab initio* electronic structure calculations, semi-empirical methods and molecular mechanics. Of the three, *ab initio* molecular orbital methods are the most accurate and consistent because they provide the best mathematical approximation to the real system (these calculations are capable of consistent predictions with high accuracy (± 20 kJ/mol) over a wide range of systems). Since a considerable part of the research presented in this thesis integrates *ab initio* electronic structure calculations, in particular, Density Functional Theory (DFT) calculations, a general overview covering the principles of these calculation techniques will be presented.

1.4.1. *Ab initio* Molecular Orbital Theory

The term *ab initio* implies that the computations are based only on the laws of quantum mechanics, the masses and charges of electrons and atomic nuclei, and the values of fundamental physical constants, such as the speed of light ($c = 2.998\times10^{8}$ m/s) or Planck's constant ($h = 6.626\times10^{-34}$ J s), and contain no approximations. Molecular orbital methods solve Schrödinger's equation for the chemical system using a basis set of functions that complies with a series of rigorous mathematical approximations.

Ab initio molecular orbital calculations are specified by a 'model chemistry', which includes the choice of method and basis set, the general structure and electronic state of the molecular system under study (for instance, charge and spin states), and the treatment of electron spin. Molecular properties can be assessed from a user-specified

input (single-point energy calculation), or the molecule can be allowed to relax to a minimum energy configuration (geometry optimisation).

Ab initio molecular orbital computations can provide accurate quantitative predictions of chemical properties for a wide range of molecular systems. However, they place a considerable demand on computer resources. The choice of theoretical method and basis set determines the duration of the calculation; thus, a sophisticated method and a large basis set will provide more accurate results, but will also require more computer resources.

- Hartree-Fock Theory

The simplest treatment of *ab initio* electronic structure theory offers is the Hartree-Fock (HF), independent-particle theory,[232,233] often called self-consistent-field (SCF) theory.[234,235]

The quantum mechanical description of chemical bonds is given by a space- and time-dependent probability distribution: the molecular wavefunction, $\Psi_{mol}(t)$. The molecular wavefunction is defined by the Schrödinger equation

$$\hat{H}_{mol}\,\Psi_{mol}(t) = i\hbar\frac{\partial\Psi(t)}{\partial t}. \qquad (1.7)$$

If the potential energy operator is time-independent, then the solution obtained by separation of variables, leads to the molecular wavefunction

$$\Psi_{mol}(t) = \psi_{mol}e^{-iE_{mol}t/\hbar}, \qquad (1.8)$$

where ψ_{mol} satisfies the time-independent Schrödinger equation

$$\hat{H}_{mol}\,\psi_{mol} = E_{mol}\psi_{mol}, \qquad (1.9)$$

and E_{mol} is the total energy of the molecule. Solutions of the time-independent Schrödinger equation represent various stationary states of the molecule (corresponding to stable or meta-stable electronic configurations). The set of wavefunctions ψ which satisfy equation (1.9) are its eigenfunctions, and the energies of the molecule, E_{mol}, in each stationary state are its eigenvalues. The stationary state with the lowest energy is called the 'ground state'.

Standard electronic structure methods assume that the molecular wavefunction describing several electrons can be written as a product of single-electron wavefunctions called 'orbitals'; that is, for a molecule containing *n* electrons,

$$\psi_{mol}(1,2,...n) = \psi(1)\psi(2)...\psi(n). \qquad (1.10)$$

Electrons possess an intrinsic angular momentum or 'spin' with a value of ±1/2. A half-integer spin quantum number implies that electrons are antisymmetric with respect to exchange - in other words, a wavefunction describing a pair of electrons *i* and *j* must change sign when the electrons are interchanged:

$$\psi(i,j) = -\psi(j,i). \qquad (1.11)$$

The simplest antisymmetric combination of molecular orbitals (MO's) is a matrix determinant. A Hartree-Fock wavefunction is constructed by assigning electrons to molecular orbitals $\phi(\mathbf{r})$ in pairs of opposite spin, and then forming a determinant using two spin functions α and β, where

$$\alpha(\uparrow) = 1 \qquad \alpha(\downarrow) = 0 \qquad (1.12)$$

$$\beta(\uparrow) = 0 \qquad \beta(\downarrow) = 1. \qquad (1.13)$$

For two electrons *i* and *j*, the total wavefunction takes the form:

$$\psi(i,j) = \phi(\mathbf{r}) \begin{vmatrix} \alpha(i) & \beta(i) \\ \alpha(j) & \beta(j) \end{vmatrix} \qquad (1.14)$$

with a determinant

$$\psi(i,j) = \frac{\phi(\mathbf{r})}{\sqrt{2}} \left[\alpha(i)\beta(j) - \beta(i)\alpha(j) \right] \qquad (1.15)$$

which satisfies the antisymmetrisation condition of equation (1.10). For a molecule containing *n* electrons, the wavefunction is referred to as a 'Slater determinant', and takes the form:

$$\psi_{mol} = \frac{1}{\sqrt{n!}} \begin{vmatrix} \phi_1(1)\alpha(1) & \phi_1(1)\beta(1) & \phi_2(1)\alpha(1) & \phi_2(1)\beta(1) & \cdots & \phi_{n/2}(1)\alpha(1) & \phi_{n/2}(1)\beta(1) \\ \phi_1(2)\alpha(2) & \phi_1(2)\beta(2) & \phi_2(2)\alpha(2) & \phi_2(2)\beta(2) & \cdots & \phi_{n/2}(2)\alpha(2) & \phi_{n/2}(2)\beta(2) \\ \vdots & \vdots & \vdots & \vdots & & \vdots & \vdots \\ \phi_1(n)\alpha(n) & \phi_1(n)\beta(n) & \phi_2(n)\alpha(n) & \phi_2(n)\beta(n) & \cdots & \phi_{n/2}(n)\alpha(n) & \phi_{n/2}(n)\beta(n) \end{vmatrix}$$

The application of the variational principle to a 'Slater determinant' wavefunction type leads to the Roothaan-Hall equations, which can be expressed in the matrix form as follows:

$$FC = SC\varepsilon \qquad (1.16)$$

where *F* is the so-called Fock matrix, *C* is a matrix of coefficients, *S* is the overlap matrix of the basis functions, and ε is the matrix of orbital energies. The energies extracted from the Hartree-Fock method have always an associated error, which is inherent to the SCF approximation, because the instantaneous correlation of the motions of electrons is neglected, and the method only treats it in an average way.[235] This error

is called correlation energy, which is not an experimentally accessible quantity. The correlation energy (E_{cor}) is defined as the difference between the energy in the Hartree-Fock limit (E_{HF}) and the exact non-relativistic energy of a system (E_{NR}):

$$E_{cor} = E_{NR} - E_{HF} . \qquad (1.17)$$

This energy will always be negative because the Hartree-Fock energy is an upper bound to the exact energy. The non inclusion of the electronic correlation in the Hartree-Fock calculations can be overcome in the so-called correlated methods (post Hartree-Fock). Hartree-Fock theory often provides a good starting point for these more elaborate theoretical methods, which are better approximations to the electronic Schrödinger equation [*e.g.*, density functional theory (DFT)].

- Electronic Correlation; Density Functional Theory

The neglect of electronic correlation has been blamed for systematic HF errors such as underestimated bond lengths and overestimated vibrational frequencies. Calculations added to HF-SCF theory to remedy these errors are termed 'electronic correlation' or 'post-HF' methods. There are three general types of electron correlation treatments: configuration-interaction (CI) methods, Møller-Plesset (MP) perturbation theory, and density functional theory (DFT). In this thesis, only one of these treatments is presented, the density functional theory.

Density functional theory models electronic correlation as a functional of the electron density, ρ. The functional employed by current DFT methods partitions the electronic energy *via* the Kohn-Sham equations[236,237] into several terms:

$$E(\rho) = E^{T}(\rho) + E^{V}(\rho) + E^{J}(\rho) + E^{XC}(\rho), \qquad (1.18)$$

where $E^T(\rho)$ is the kinetic energy term (arising from the motion of the electrons), $E^V(\rho)$ is the potential energy term that includes nuclear-electron and nuclear-nuclear interactions, $E^J(\rho)$ is the electron-electron repulsion term and $E^{XC}(\rho)$ is the electron correlation term. All terms except nuclear-nuclear repulsions are functions of the electron density. The terms $E^T(\rho) + E^V(\rho) + E^J(\rho)$ represent the classical energy of the electron distribution, while $E^{XC}(\rho)$ represents both the quantum mechanical exchange energy, which accounts for electron spin, and the dynamic correlation energy due to the concerted motion of individual electrons. Pure DFT methods calculate $E^{XC}(\rho)$ by pairing an exchange functional with a correlation functional and so are designated by the choice of combination. For example, BLYP combines Becke's gradient-corrected exchange functional with the gradient-corrected correlation functional of Lee, Yang and Parr.[238]

DFT calculations fall into three general categories: local density approximations (LDA), generalised gradient approximations (GGA), and 'hybrid' combinations of DFT and Hartree-Fock terms. LDA exchange and correlation functionals only contain terms related to electron density - an approach that works for some bulk materials, but fails to accurately predict properties in isolated molecules. GGA ('nonlocal') functionals contain terms that depend upon both the electron density and the density gradients.

The gradient-corrected density functional method BLYP is capable of predicting intramolecular bond dissociation energies to within a few kJ/mol.[239] However, the generalised gradient approximation severely underestimates activation barriers for some reactions due to neglect of Coulomb 'self-interaction' of the electrons.[240] This problem is solved with hybrid methods that combine Hartree-Fock self-interaction corrections with density functional exchange and correlation. Examples of hybrid methods are B3LYP and B3PW91, where B3 denotes Becke's three-parameter hybrid

functional,[241,242] while 'PW91' and 'LYP' are gradient-corrected correlation functionals of Perdew and Wang[243] and, as above, Lee, Yang and Parr.

Although even simple DFT methods have been employed successfully for the calculation of a number of properties, correct treatment of weak inter- and/or intramolecular interactions, abundant in heteroatomic compounds, such as tetrazoles and benzisothiazoles, provides great challenge for the functionals to be employed. For a successful conformational analysis, the application of some computational techniques should be taken into consideration whenever it is viable. Theoretical energies usually give better agreement with experiment if calculated at the MP2 level, while experimental vibrational spectra are well reproduced by the DFT calculations, which are generally much more efficient in terms of required computer resources.

- Basis Sets

In general, a basis set is an assortment of mathematical functions used to solve a differential equation. In quantum chemical calculations, the term 'basis set' is applied to a collection of contracted gaussians representing atomic orbitals, which are optimised to reproduce the desired chemical properties of a system.

Standard *ab initio* software packages generally provide a choice of basis sets that vary both in size and in their description of the electrons in different atomic orbitals. Larger basis sets include more and a greater range of basis functions. Therefore, larger basis sets can better refine the approximation to the 'true' molecular wavefunction, but require correspondingly more computer resources. Alternatively, accurate wavefunctions may be obtained from different treatments of electrons in atoms. For instance, molecules containing large atoms ($Z > 30$) are often modelled using

basis sets incorporating approximate treatments of inner-shell electrons which account for relativistic phenomena.

Minimal basis sets contain the minimum number of atomic orbitals (AO) basis functions needed to describe each atom (*e.g.*, 1s for H and He; 1s, 2s, 2px, 2py, 2pz for Li to Ne). Although minimal basis sets are not recommended for consistent and accurate predictions of molecular energies, their simple structure provides a good tool for visualising qualitative aspects of chemical bonding. Improvements on minimal basis sets are described below and illustrated in Figure 13.[244]

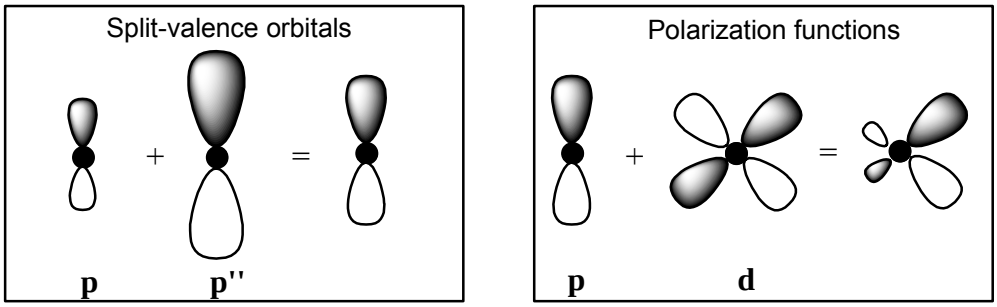


Figure 13. Basis set improvements.

- Polarized basis sets

Polarization functions can be added to basis sets to allow for non-uniform displacement of charge away from atomic nuclei, thereby improving descriptions of chemical bonding. Polarization functions describe orbitals of higher angular momentum quantum number than those required for the isolated atom (*e.g.*, *p*-type functions for H and He, and *d*-type functions for atoms with $Z > 2$), and are added to the valence electron shells. For instance, the 6-31G(d) basis set is constructed by adding six *d*-type gaussian primitives to the 6-31G description of each non-hydrogen atom. The 6-31G(d,p) is identical to 6-31G(d) for heavy atoms, but adds a set of gaussian *p*-type functions to hydrogen and helium atoms. The addition of *p*-orbitals to hydrogen is particularly important in systems where hydrogen is a bridging atom.

- Diffuse basis sets

Species with significant electron density far removed from the nuclear centres (*e.g.*, anions, lone pairs and excited states) require diffuse functions to account for the outermost weakly bound electrons. Diffuse basis sets are recommended for calculations of electron affinities, proton affinities, inversion barriers and bond angles in anions. The addition of diffuse *s*- and *p*-type gaussian functions to non-hydrogen atoms is denoted by a plus sign - as in 3-21+G. Further addition of diffuse functions to both hydrogen and larger atoms is indicated by a double plus.

- High angular momentum basis sets

Basis sets with multiple polarization functions are now practical for many systems and, although not generally required for Hartree-Fock calculations, are useful for describing the interactions between electrons in electron correlation methods.

Examples of high angular momentum basis sets include:

- 6-31G(d, p) - one *d*-function is added to heavy atoms and one *p*-function to hydrogens;
- 6-311G(2df, pd) - besides the (311) valence functions, two *d*-functions and one *f*-function are added to heavy atoms, and *p*- and *d*-functions to hydrogen;
- 6-311G(3df, 2df, p) - three *d*-functions and one *f*-function are added to atoms with $Z > 11$, two *d* functions and one *f* function to first-row atoms (Li to Ne) and one *p* function to hydrogens.

High angular momentum basis sets augmented with diffuse functions represent the most sophisticated basis sets available. For the molecules with a complicated electronic structure, the most accurate *ab initio* studies would be produced by reasonably sophisticated polarized split-valence basis sets augmented with high angular

momentum and diffuse atomic orbitals (*e.g.*, 6-311++G(d,p)). However, the size of the optimum basis set, especially when used with electron correlation methods will ultimately be determined by the size of the molecule, the amount of computing power available, and the time fixed for the studies.

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