Chapter 5

Concluding Remarks

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The work described in this thesis is mostly related with the reactivity of derivatives of tetrazole. Along with the practical applications of tetrazoles, it is known that these compounds are also particularly notable compounds because they exhibit a very rich photochemistry.

Results obtained during part of this work, concerning the study of structural effects on the photoreactivity of a series of tetrazolyl derivatives, enabled the clarification of important mechanistic questions concerning the photodecomposition of these molecules submitted to different chemical environments. Accordingly, it was shown clearly that the properties of the substituents on the tetrazole ring are very relevant in determining the precise nature and relative amount of the final photoproducts, then making tetrazoles a permanent challenge to investigation.

Irradiation (λ = 254 nm) of 4-allyl-tetrazolones in methanol, 1-propanol and 1-hexanol solutions, generates 3,4-dihydro-6-substituted-3-phenylpyrimidin-2(1*H*)-ones as sole products. These pyrimidinones are easily isolated from the alcoholic medium as stable compounds in excellent yields, providing an alternative and attractive synthetic methodology for this class of compounds. The observed photostability of pyrimidinones in alcohols is ascribed to a very efficient solvation, with formation of hydrogen bonds, leading to deactivation of the excited state by reversible proton transfer, facilitated by stable solvent cages that enclose the pyrimidinone molecules and prevent their photodecomposition.

Additionally, the study of photolysis (λ = 254 nm) of 5-allyloxy-tetrazoles in methanol, acetonitrile and cyclohexane solutions, has permitted to design a new synthetic procedure for the preparation of *N*-phenyl-1,3-oxazines, via molecular nitrogen elimination from the tetrazole ring. In preparative-scale experiments, oxazines

were isolated from the reaction medium and fully characterized. DFT(B3LYP)/6-31G(d,p) calculations predict that, in the gaseous phase, oxazines should mostly exist in the tautomeric form where the NH group is the bridge connecting the oxazine and phenyl rings (the lowest-energy structures). The tautomers of oxazines with the NH function included in the oxazine ring are higher in energy, with the differences exceeding 7.5 kJ mol^{-1}, and have higher dipole moments. Accordingly, it is expected that, in the polar media, the higher-energy forms of oxazines will undergo additional stabilization with respect to the lowest-energy structures, and the relative population of the minor conformer will increase. In fact, secondary photoproduct analysis supports this interpretation. Mechanistically, primary photoexcitation of 5-allyloxy-tetrazoles involves formation of a triplet 1,3-biradical, observed by laser flash-photolysis, with a lifetime of *ca.* 10^{-6} s, which subsequently isomerizes to form a triplet 1,6-biradical. After intersystem crossing, the 1,6-biradical decays to the ground state to form the products.

Furthermore, it was shown that the matrix isolation technique also represents a powerful approach to investigate the photochemistry of tetrazole derivatives. The use of matrix isolation technique coupled to a suitable probing method, such as FT-IR spectroscopy, represents an accurate strategy to understand the mechanisms involved in photochemical reactions, its main advantage being the simplification of the photochemical processes due to cage confinement of the reactions and the possibility to achieve a high spectroscopic resolution, increasing the probability to detect chemical species produced in low amounts during photolysis or those with intrinsically low intensity IR absorptions.

According to the results obtained during this investigation, the fundamental photochemistry of matrix-isolated tetrazoles in solid argon involves fragmentation of

the tetrazole ring. The chemical nature of the substituents present in the ring determines in large amount the relative prevalence of the different available primary photochemical reaction channels and strongly determine secondary processes in which the primary photoproducts participate. As a general rule, the tetrazole ring can undergo photolytic cleavage in three different ways: *a)* through the $N_{(1)}$–$N_{(2)}$ and $N_{(3)}$–$N_{(4)}$ bonds, releasing molecular nitrogen and forming a diazirine derivative; *b)* through the $N_{(1)}$–$C_{(5)}$ and $N_{(3)}$–$N_{(4)}$ bonds and *c)* through $N_{(1)}$–$N_{(2)}$ and $N_{(4)}$–$C_{(5)}$ bonds. In the two latter cases, the precise nature of the photoproducts varies depending on the substituents present in the tetrazole ring, but one of the products is always an azide, which then can undergo subsequent reactions, most of times eliminating N_2 to form the nitrene that then can further react to form the final product (*e.g.*, 1-aza-1,2,4,6-cycloheptatetraene, produced by ring expansion of phenyl nitrene).

The number of available reaction channels correlates with the number of formally single bonds in the tetrazole ring. When four single bonds are present (like in tetrazolones), the 3 photochemical fundamental types of reaction can take place, a fourth reaction path being sometimes also activated, corresponding to cleavage through the $N_{(1)}$–$C_{(5)}$ and $N_{(4)}$–$C_{(5)}$ bonds. For all the investigated molecules exhibiting only three formally single bonds in the tetrazole ring, only two reaction channels were found to be active, with that corresponding to direct N_2 elimination always playing the most important role.

The presence in the ring or in the substituents of labile hydrogen atoms always increases the complexity of the photochemistry, mainly due to the occurrence of different tautomeric forms, whereas the conformational flexibility of the substituent may have effects difficult to predict *a priori*. These are strongly determined by the

number and relative energies of the possible conformers and conformational interconversion barriers.

The presence of a phenyl substituent at $N_{(1)}$ (or $N_{(4)}$) in alkoxy tetrazoles results in strong activation of the channel leading to production of phenylazide and the corresponding alkyl-cyanate (that undergoes major isomerization to the isocyanate). In tetrazolones, a phenyl or alkyl substituent at $N_{(1)}$ (or $N_{(4)}$) favors the pathway leading to direct production of the corresponding isocyanate, which is in general inhibited in the alkoxy tetrazoles.

The mechanism for direct elimination of molecular nitrogen from the tetrazole ring in solid argon was not yet fully explained, but it seems that it occurs mainly through the biradical intermediate, that subsequently undergoes cyclization and forms diazirine. The biradical has been observed during the investigation of 5-allyloxy-tetrazoles in solution. The mechanisms for the remaining two prototype primary ring-cleavage photochemical reactions of the tetrazole ring are still to be investigated.

It is fortunate that most of the prevalent photoproducts of the photochemistry of matrix-isolated tetrazoles can be easily identified by IR spectroscopy. In fact, three groups of bands, occurring in the usually clean spectral regions allow easy identification of the main products resulting from the three fundamental paths in tetrazoles' photochemistry: diazirines and diaziridinones give rise to characteristic bands in the 1800-1900 cm^{-1} spectral region, azides have their most intense band around 2100 cm^{-1} ($\nu N=N^{+}=N^{-}$ antisymmetric stretching) and isocyanates strongly absorb in the 2290–2300 cm^{-1} range ($\nu N=C=O$ antisymmetric stretching).

A final note shall be made regarding the possibility of using the *in situ* photolysis of matrix-isolated tetrazoles to produce novel molecular species, like for example antiaromatic diazirines or reactive isocyanates and azides *e.g.*, 3-methoxy-1-

phenyl-1*H*-diazirine, 3-ethoxy-1-phenyl-1*H*-diazirine, 1-phenyl-diaziridin-3-one, 1-allyl-2-phenyldiaziridin-3-one, allylisocyanate, allylazide.

Additionally, new derivatives of tetrazole and benzisothiazole have been synthesised and successfully applied in catalytic processes. Experimental conditions for palladium-catalysed hydrogenolysis of tetrazolyl and benzisothiazolyl naphthylmethylic ethers were developed. It was shown that reductive C–O cleavage of ethers over Pd/C can be achieved using sodium hypophosphite or molecular hydrogen as source of hydrogen. Under the reaction conditions tested, hydrogenolysis is generally faster and higher yielding for tetrazolyl than for benzisothiazolyl derivatives. From the results obtained, it is clear that the heteroaromatics tetrazole and benzisothiazole behave differently as derivatizing agents in the hydrogenolysis of naphthyl methanols, in sharp contrast to what was observed with other hydroxylic compounds.

Finally, procedures for the formation of a variety of novel molecules incorporating the tetrazole and benzisothiazole units linked by a spacer-group, have been designed. Three new benzisothiazole-tetrazolyl derivatives differing on the spacer-group used for linkage of the two heterocycles were prepared. Preliminary tests, involving these molecules as multidentate ligands in reactions with manganese(II) and iron(II) complexes, point clearly for their potential applicability in coordination chemistry.

The knowledge of the characteristic reactivity of heterocycles studied in the course of this investigation, when submitted to different conditions, should be of considerable value for a better understanding the reactivity of tetrazole and benzisothiazole derivatives in crucial fields, such as medicinal chemistry, synthetic enzyme mimetics or agriculture.