

NANOMATERIALS AND BIOLOGICALLY ACTIVE COMPOUNDS: IN SILICO CHARACTERIZATION AND EVALUATION OF THEIR USE IN THE PHARMACEUTICAL FIELD

ABSTRACT

The present work is structured in three parts that include (1) the main scientific achievements of the author elaborated after the defense of the doctoral thesis, (2) the didactic activity carried out within the department of General and Inorganic Chemistry and (3) the proposal for the development of the university career. Scientific activity includes the following research areas: the study of carbon-based nanomaterials and their precursors; the study of various antioxidants with polyphenolic structure; assessment of chemical reactivity. The research is mainly conducted on computational chemistry methods, but also relies on experimental methods such as extraction with different solvents or analysis of compounds by means physico-chemical analysis methods.

An important part of the research activity is represented by the characterization of nanomaterials and their precursors, as well as their use in the pharmaceutical field. Thus, the stability of five circulenes was evaluated according to the total energy and HOMO-LUMO gap, calculated for structures optimized with HF and DFT methods. The local aromatic character of the polycyclic aromatic hydrocarbons was quantified by means of the magnetic and geometric criterion, namely the NICS and HOMA indices. The properties of circulenes like coronene and sumanene, part of two tessellated fullerenes, were calculated; the results were compared to those obtained for the isolated circulenes. The assessment of aromaticity can be helpful in explaining various aspects related to the stability/reactivity of these molecules. The data obtained suggested that the fullerenes tessellated by coronene and sumanene may be potential candidates for laboratory synthesis.

Another study aimed to evaluate the properties of three nonplanar circulenes [4:6₄], [7:6₇] and [8:5₈] at the B3LYP/6-311+G(d,p) level of theory. Due to the lack of a universal definition of aromatic character, magnetic, energetic and geometric criteria were used. Global descriptors such as HOMO-LUMO gap, exaltation of magnetic susceptibility and ASE index conclude that the "most aromatic" of the three compounds is circulene [4:6₄], followed by [7:6₇]. In contrast, the enthalpies of formation show a higher stability of the circulene [7:6₇], while the local aromaticity descriptors lead to only insignificant differences between the outer rings of the circulene [4:6₄] and [7:6₇]. All the criteria that were used within the study suggest the antiaromaticity of circulene [8:5₈].

The properties of nanomaterials can be adjusted by doping with heteroatoms. Thus, the effects of substituting one (or more) carbon atoms with group 15 elements were studied. The possible aromatic character of a new series of heterobenzenes substituted with N, P, As, Sb and Bi atoms was investigated. The singlet-triplet difference values show that heterobenzenes containing Sb and Bi and their compounds with As are less stable, namely (CH-Sb)₃, (CH-Bi)₃, (As-Sb)₃, (As-Bi)₃ and (Sb-Bi)₃, together with the heterobenzenes (N-P)₃ and (N-As)₃. Among all, (N-P)₃ and (N-As)₃ were classified as having the weakest aromatic character.

Also, a correlation is observed between the HOMO-LUMO gap and the global electrophilicity index (smaller HOMO-LUMO gap, higher electrophilicity values). The calculation of the global reactivity descriptors showed that, as expected, a possible reaction of electrophilic substitution occurs at the most electronegative heteroatom. NBO analysis shows that the stabilization energy due to donor-acceptor interactions decreases as the size of the heteroatoms increases.

Another study investigated the effects of substituting carbon atoms with nitrogen on the stability and properties of some aza-fullerenes. Thus, a series of diaza-derivatives of coronene, an aromatic circulene, were studied and some structures of new aza-fullerenes were proposed. Based on previous results regarding the stability and aromaticity of heterobenzenes substituted with group 15 elements, the three types of diaza-substitutions -namely 1,2; 1,3; and 1,4- were considered. Evaluation of the aromaticity of nanomaterial precursors (namely, polycyclic aromatic hydrocarbons and heterofullerenes) provides good characterization regarding their stability and magnetic and geometrical properties. The influence of the position of the heteroatoms in the polycyclic structures, which can be evaluated by theoretical methods, is valuable information for the future synthesis of these compounds. Geometrical, energetic and magnetic aspects regarding the aromaticity of diaza-coronenes and derived aza-fullerenes were investigated. According to geometrical criteria, the most pronounced aromatic character is attributed to 1,3-substituted and 1,4-substituted aza-derivatives. Also, the substitution pattern strongly influences the stability and properties of these compounds. The presence of nitrogen atoms only in the outer rings seems to lead to a better conservation of coronene aromaticity (1,2-aza-substitution and 1,3-aza-substitution).

Nanomaterials can be used as effective delivery systems of various biologic active compounds. Another study investigated the capacity of rhombellanes, a new class of nanostructures, to be used as delivery systems for indomethacin and its derivatives. Computational chemistry methods were used to analyze the interactions between the nanostructures and biologic active compounds. A docking study of five ligands (indomethacin and four of its derivatives) on 13 new structures of rhombellanes was performed, in order to determine their possible use as drug delivery systems. According to the calculated binding affinities for the ligand-rhombellanes complexes, there are four structures that gave similar results to those obtained for the reference ligand-fullerene complex C_{60} . For the first ligand, indomethacin, the highest rhombellane/ C_{60} ratio is 0.89 and is assigned to a rhombellane structure containing 360 atoms. Regarding the second ligand (derivative I1), an improved ratio of 0.96 was obtained for both rhombellanes with 360 and 420 atoms, respectively. The results suggest that rhombellanes structures that are characterized by a smaller HOMO-LUMO gap are the most favored for higher values of binding affinity to indomethacin derivatives.

Another study investigated the properties of five porphyrins substituted with amino, hydroxyl, fluorine, aminoethyl, and hydroxyethyl groups for their use in photodynamic therapy as photosensitizers. In this regard, a number of properties such as the singlet-triplet gap, polarizability, dipole moment, partition coefficient and steric parameters were calculated. Then, a series of rhombellanes were investigated as possible delivery systems for these substituted porphyrins. The lowest values of binding energies were obtained for the fluoro-substituted porphyrin, which is most likely due to its hydrophobic character. The best results were obtained for porphyrins characterized by hydrophobic character, lower values of the surface accessible to the solvent and lower values of ovality. As a result, our future studies will be directed towards the design and investigation of porphyrins exhibiting the aforementioned characteristics. Regarding the rhombellanes, the compounds that gave the best results in the interaction with porphyrins are

characterized by the highest values of the LUMO energy. It should be noted that six of the seven investigated rhombellanes gave better results than fullerene C₆₀.

In another study, several fullerenes doped with nitrogen atoms, derived from the C₂₄ structure, were characterized. The properties of seven compounds of general formula C₂₂N₂ and C₂₀N₄ were investigated and compared with the corresponding ones for fullerene C₂₄. The results showed that the substitution pattern significantly influences the energetic, geometric and magnetic properties of fullerenes. Calculations were performed using the 6-311G+ basis set, using both Hartree-Fock and DFT (B3LYP functional) methods. The analysis of frontier molecular orbitals can be considered a good indicator of the general reactivity of a compound. One of these descriptors is the HOMO-LUMO gap, which can be tuned by means of dopant atoms or functional groups. The present study aimed to investigate the influence of the number and position of nitrogen atoms on the HOMO-LUMO gap values. The results show that larger HOMO-LUMO differences, associated with lower reactivity and higher stability, were obtained for fullerenes C₂₄, two fullerenes C₂₂N₂ and one fullerene C₂₀N₄. It was demonstrated that the values calculated by the HF method are significantly higher than those obtained with the DFT method. The difference is a consequence of the LUMO energies calculated at the B3LYP/6-311G+ level of theory. The same hierarchy was obtained for the chemical potential. The energies of the frontier molecular orbitals show that the presence of nitrogen atoms leads to a decrease in the energy of the HOMO orbitals and an increase in the energy of the LUMO orbitals, compared to C₂₄. Also, the singlet-triplet difference was calculated as part of the study of the general properties of fullerenes, in order to evaluate all possible influences of substitution with nitrogen atoms and to take them into account for the design of new nanomaterials.

Molecular docking studies were also performed to verify the possible use of nitrogen-doped C₂₄ fullerenes as delivery systems for two antiviral drugs with adamantane structure. Several steric parameters of fullerenes were also calculated. C₂₂N₂ fullerenes are characterized by similar values of ovality and solvent accessible surface area, regardless of the substitution pattern. The major influence of the number and position of nitrogen atoms was observed on the partition coefficient values. The calculated binding affinities show that the best results were obtained for the three hydrophobic fullerenes. The ligand-receptor interactions were of "atoms-in close-contact" type, with the ligand (the adamantane-derived drug) oriented towards the fullerene side consisting of carbon atoms. According to the results, higher or equal binding affinities (compared to C₂₄) were obtained for two of the studied aza-fullerenes. The best affinities for adamantane-derived drugs were obtained for hydrophobic fullerenes, substituted with two nitrogen atoms and a larger HOMO-LUMO gap. Among the two investigated ligands, better results were obtained for rimantadine, a compound characterized by higher values of the surface accessible to solvent and a more pronounced hydrophobic character than amantadine.

Another study investigated the photosensitizing properties of some iron, nickel and zinc phthalocyanines. This way, several properties such as the HOMO-LUMO gap, the dipole moment, the maximum wavelength were calculated, the results suggesting that all the investigated compounds have the properties of a good photosensitizer. Regarding the influence of the central metal on the properties of the studied compounds, it can be stated that the energies of the HOMO and LUMO frontier molecular orbitals are only slightly influenced by the central metal type; as a result, the overall global reactivity parameters have similar values for the same type of substitution, regardless of the metal. The central metal has also been observed to influence the steric parameters of phthalocyanines; a longer N-Fe bond length (1.97 Å, compared to 1.88 Å for Ni-N and Zn-N) led to different values of Connolly accessible surface area and solvent excluded Connolly volume for Fe-phthalocyanines compared to Ni- and Zn-phthalocyanines. The main

influence on the properties of metal-phthalocyanines results from the presence of substituents. The differences are highlighted in the calculated values of the reactivity descriptors. The presence of methyl groups leads to higher energies for the HOMO and LUMO orbitals, while amino-substituted compounds are characterized by lower energies (both compared to unsubstituted metal-phthalocyanines). Another part of the study dealt with the interactions between each metal-phthalocyanine and four fullerenes consisting of 52 atoms (fullerene C₅₂ and three fullerenes doped with isovalent nitrogen and phosphorus atoms) as possible delivery systems. All four studied fullerenes led to the best affinities for Ni- and Zn-phthalocyanines substituted with methyl groups.

Another research area is represented by the study of natural compounds with an antioxidant character. Thus, an *ab initio* study (HF/6-31G) was performed to evaluate the antioxidant capacity of cyanidin, delphinidin and malvidin. The thermodynamic parameters (BDE, IP, PA, ETE) characterizing the three possible radical scavenging mechanisms were calculated for each of the hydroxyl groups of the anthocyanidins. The calculated electronic properties of anthocyanidins show a more pronounced antioxidant character of the –OH groups in the phenolic B ring of cyanidin, delphinidin and malvidin.

Also, the antioxidant properties of six flavonols were investigated at the theoretical HF/6-311+G(d,p) level, using ethanol as solvent. All three antioxidant mechanisms HAT, SET-PT and SPLET were considered, and the corresponding thermodynamic parameters BDE (bond dissociation enthalpy), IP (ionization potential), PA (proton affinity) and ETE (electron transfer enthalpy) were calculated. According to the obtained results for the thermodynamic parameter BDE, an improved antioxidant character is presented by the 3-OH groups, followed by the phenolic hydroxyl groups on the ring B. Similar results were obtained for the condensed Fukui functions, calculated for a radical attack. The results suggest the increased reactivity of both the 3-OH groups and the OH groups on ring B in the case of a radical mechanism (especially of flavonols exhibiting a catechol-type configuration). Regarding the calculated ionization potential values, the presence of a larger number of OH groups on ring B leads to increased antioxidant activity. Regarding the proton affinity values, when there are two OH groups in the catechol position (fisetin, gossypetin and myricetin), one of them is characterized by a low proton affinity value, while the other OH group shows the character the least acidic of the flavonol hydroxyl groups.

Another study dealt with the characterization of six anthocyanins in various pH-influenced forms: flavylum cations, hemiketals and quinoidal bases. Also, their interactions with alpha-, beta- and gamma-cyclodextrins were analyzed, in order to evaluate the possibility of encapsulation. Regarding the influence of molecular shape descriptors, the results showed that three anthocyanins are favored: cyanidin-3-O-rutinoside, malvidin-3-O-glucoside, and delphinidin-3-O-rutinoside. All these structures are characterized by a larger number of acceptor and donor atoms in the formation of hydrogen bonds. Another specific property of these three compounds is the Connolly solvent accessible surface within the range of 700-750 Å², while the solvent-excluded volume has values in the range of 390-460 Å³. The ovality has similar values for the three aforementioned compounds: 1.498, 1.505 and 1.526, respectively. Molecular docking results show that the affinity of the investigated anthocyanins for α-cyclodextrin is much lower than those corresponding to β-cyclodextrins and γ-cyclodextrins. This is due to the relatively large size of the six anthocyanins, which allows only the partial inclusion in the host molecule in the case of α-cyclodextrin. It can also be observed that anthocyanidin-3-rutinosides are favored for the formation of inclusion complexes with cyclodextrins. Only two anthocyanidin-3-O-glucosides, namely oenin and myricetin, have higher binding affinities to β-cyclodextrin. The computation of

Mulliken atomic charges showed that the formation of hydrogen bonds is mostly influenced by geometrical aspects, and not by atomic charges. There are no significant differences in the values obtained for beta- and gamma-cyclodextrins, respectively. Taking into account the fact that beta-cyclodextrins are less expensive than their gamma derivatives, it can be said that beta-cyclodextrins represent an optimal choice as a host molecule for these compounds.

Another chapter presents the study of chemical reactivity, especially of the heterocyclic compounds. One of these studies investigated the thiol-thione tautomerism in 2-(5-mercapto-1,3,4-thiadiazol-2-yl)thioacetic acid. The acidity constant was calculated by means of two theoretical methods: one based on isodesmic reactions and the other using two thermodynamic cycles. The results lead to the conclusion that, in aqueous solution, the dominant tautomer is the thiol form of 2-(5-mercapto-1,3,4-thiadiazol-2-yl)thioacetic acid. Another series of thermodynamic cycles was employed to calculate the electrode potential of cyanidin. A value of 0.414 V was determined for the electrode potential of the most stable conformer of cyanidin. The comparison with the experimental results leads to a calculation error of 0.1 V, which is attributed to the underestimation of the calculated free energies within the computational model.

Another study aimed to evaluate the reactivity of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone, a compound used as a ligand in various metal complexes. It is well known that a metal complex results from the interactions between the frontier HOMO orbitals of the ligand and the LUMO orbitals of the metal. The frontier molecular orbitals HOMO appear mainly located at the sulfur atom, the results being also confirmed by the values of the Fukui function, which indicate the sulfur atom as the atom with the most important electron-donating character of the investigated compound. Another study aimed to investigate the electron-donating character of ten bis-benzazole-pyridine and bis-benzazole-triazine derivatives and their possible use as ligands. Fukui functions (calculated for an electrophilic attack) showed that the sp^2 nitrogen atom (or the "pyridinic" nitrogen atom) of benzimidazole and benzothiazole, respectively, have higher reactivity. Global reactivity descriptors led to the conclusion that the most effective ligands are bis-benzimidazole-pyridine derivatives.

In addition to the scientific activity, the thesis presents the teaching and professional activity of the author. The teaching activity is centered on the presentation of the materials prepared for the students, the coordination of the volunteer students' activity within the discipline, as well as the activity of guiding the students to specific scientific events and the elaboration of the bachelor's theses. The professional activity presents the academic course of the author, together with the summarization of the research results. The university career development plan is also presented, which also includes the new research directions proposed by the author.