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STRUCTURAL AND ELECTRONIC PROPERTIES OF FULEROL FUNCIONALIZED WITH RADIOPHARMACEUTICALS[1]

PROPRIEDADES ESTRUTURAIS E ELETRÔNICAS DO FULEROL FUNCIONALIZADO COM RADIOFÁRMACOS

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ABSTRACT

The blood-brain barrier is one of the most difficult barriers to permeate of the organism, allowing only the passage of nutrients necessary for brain function. However, nanostructures, such as fullerol, have gained prominence by being able to cross this barrier. In parallel, fluorescent radiopharmaceuticals have been used in the diagnosis of different diseases that affect the central nervous system, also having affinity with one of the biomarker proteins of Azheimer's disease: the phosphorylated tau protein. In an unprecedented, this work aimed to verify the electronic and structural properties of functionalized fullerol with different radiopharmaceuticals via ab initio computational simulation, in order to use this system as a marker for Alzheimer's disease. The results demonstrated that the complexes formed a chemical bond without changing the properties of the isolated structures. Therefore, those systems can be considered stable for the intended application.

Keywords: ab initio, binder, Density Functional Theory, nanocarrier.

RESUMO

A barreira sangue-cérebro é umas das barreiras mais difíceis de permear do organismo, permitindo somente a passagem de nutrientes necessários para o funcionamento cerebral. Entretanto, nanoestruturas, como o fulerol, têm ganhado destaque por conseguirem permear nessa barreira. Paralelamente, radiofármacos fluorescentes vêm sendo utilizados no diagnóstico de diferentes doenças que acometem o sistema nervoso central, possuindo também afinidade com uma das proteínas biomarcadoras da doença de Azheimer: a proteína tau fosforilada. De forma inédita, esse trabalho teve como objetivo verificar as propriedades eletrônicas e estruturais do fulerol funcionalizado com diferentes radiofármacos via simulação computacional ab initio, a fim de utilizar esse sistema como um marcador para a doença de Alzheimer. Os resultados demonstraram que os complexos formam uma ligação química sem alterar as propriedades das estruturas isoladas. Portanto, esses sistemas podem ser considerados estáveis para a aplicação pretendida.

Palavras-chaves: *ab initio, ligante, nanocarreador, Teoria do Funcional da Densidade.*

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INTRODUCTION

The targeting of substances to the brain is a major challenge because the barrier between the circulatory system and the brain, the blood-brain barrier (BBB), is one of the most difficult barriers to permeate of the organism. This barrier only allows the passage of nutrients necessary for brain functioning, severely restricting the permeability of potentially toxic substances, such as medicines (POLLAK et al., 2018; SERLIN et al., 2015). With this, the treatment of diseases that affect the central nervous system, as well as possible systems for the diagnosis, are compromised.

Fullerol ($C_{60}(OH)_{24}$) is a spherical nanostructure belonging to the family of fullerenes. Due to the presence of hydroxyls in its structure, fullerol has solubility in aqueous medium and, therefore, has a higher bioavailability (BAKRY et al., 2007). This nanostructure has been suggested as a promising nanocarrier with respect to the passage of molecules through the blood-brain barrier (HSIEH et al., 2017; SANTOS et al., 2010). In addition, as it is a great electron acceptor, fullerol has excellent antioxidant and neuroprotective activity due to the ability to capture free radicals in the biological environment, also decreasing apoptosis in neurons (CHAWLA et al., 2010).

Furthermore, a series of fluorescent radiopharmaceuticals have been studied experimentally for the diagnosis of pathophysiological processes in the brain (BENADIBA et al., 2012; VILLEMAGNE et al., 2015) and affinity for the phosphorylated tau protein, which is one of the biomarkers of Alzheimer's disease (MASTERS et al., 2015; VILLEMAGNE et al., 2015).

In this context, the main objective of this study was to evaluate the electronic and structural properties of fullerol functionalized with different radiopharmaceuticals through *ab initio* computational simulations, in order to use this system as possible markers for Alzheimer's disease.

MATERIAL AND METHODS

The radiopharmaceuticals used in the study were ^{18}F-FDDNP, ^{18}F-T807, ^{18}F-T808, ^{18}F-THK523, ^{18}F-THK5105, ^{18}F-THK5117, ^{18}F-THK5351, ^{11}C-*N*-methyl lansoprazole and ^{11}C-PBB3. The choice of these radiopharmaceuticals occurred because they were fluorescent structures and showed to have affinity for the phosphorylated tau protein, which is a biomarker of Alzheimer's disease (BENADIBA et al., 2012; VILLEMAGNE et al., 2015). The models of radiopharmaceutical molecules were obtained from the PubChem database (WANG et al., 2016). The immobilization of the radiopharmaceuticals in fullerol occurred through covalent bonds from the removal of water molecules from the system. Different configurations were analyzed, varying the position of the radiopharmaceutical binding to the fullerol, and choosing the configuration of the highest final energy in the module.

To evaluate the electronic and structural properties of fullerol and isolated radiopharmaceuticals, as well as the binding between them, *ab initio* calculations based on DFT (Density Functional Theory)

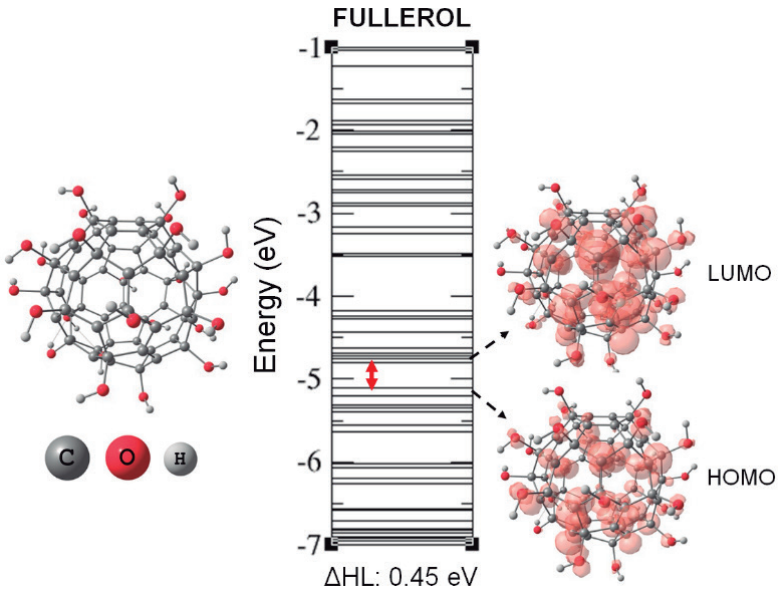
were developed using SIESTA computational code (SOLER et al., 2002). The DFT describes the properties of the system based on its electronic density (HOHENBERG; KOHN, 1964). The exchange-correlation term in the SIESTA code was reproduced using the Local Density Approximation (LDA) (CEPERLEY; ALDER, 1980).

RESULTS AND DISCUSSION

LIGANTS

The electronic and structural properties of radiopharmaceuticals and fullerol separately were studied. As can be seen in figure 1, the difference between the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) (ΔHL) found for fullerol was 0.45 eV. Conceptually, as the lower the ΔHL, than more susceptible the molecule will be in accepting or donating charges. Thus, fullerol is a molecule suitable for the exchange of charges. Observing the charge density for this structure we can observe that the molecule presented a homogeneous distribution throughout its surface for both HOMO and LUMO, that is, all sites present practically the same reactivity - with negligible spin, being also favorable for possible interactions with other molecules.

Figure 1 - Optimized structure, energy levels and charge density for isolated fullerol
The value of the isosurface plot for LUMO and for HOMO was 0.001 e-/Bohr³.

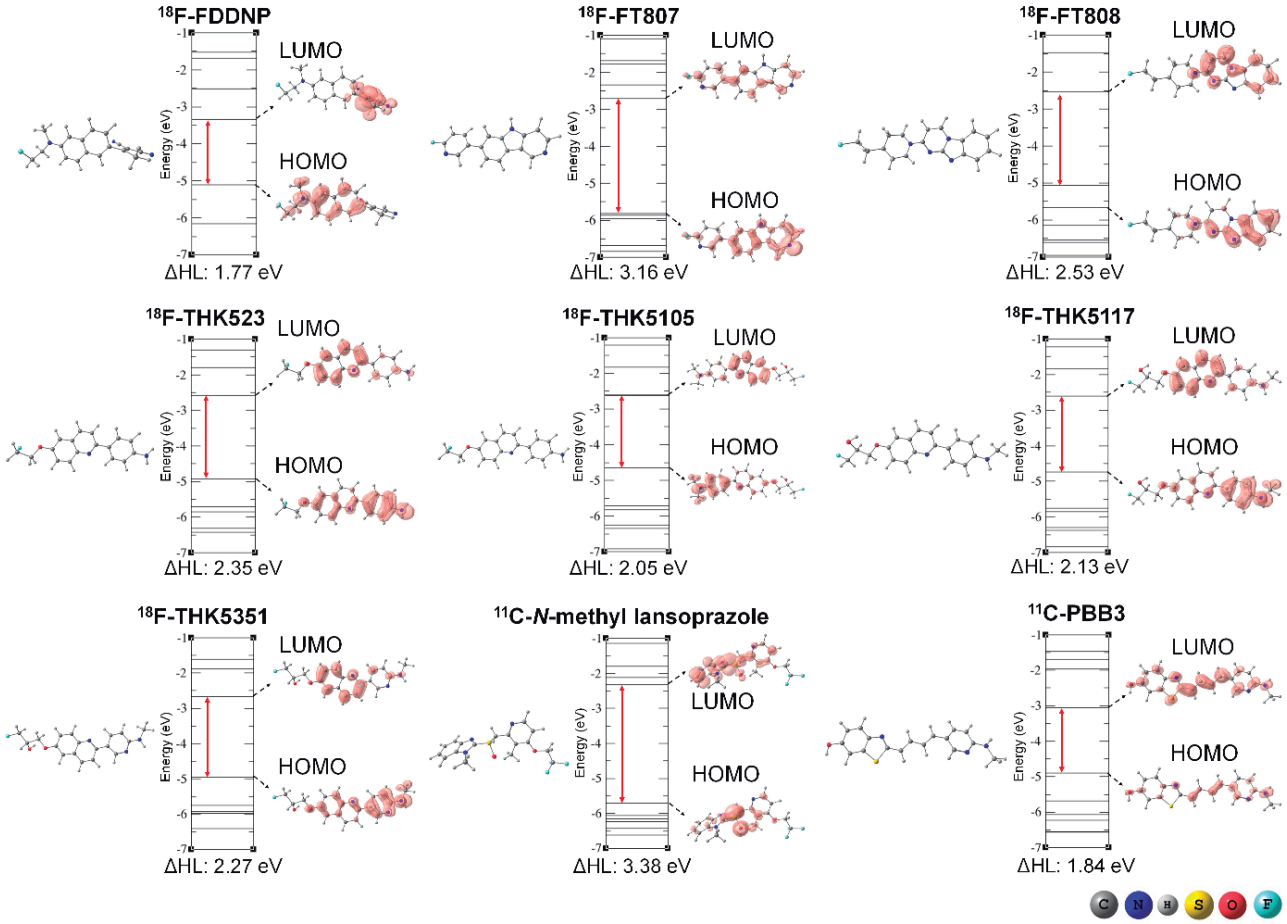


Source: author.

For the analysis of the radiopharmaceuticals (Figure 2), we can see that the ΔHL for all the structures is relatively high, ranging from 1.77 eV (^{18}F-FDDNP) to 3.38 eV (^{11}C-N-methyl lansoprazole), conferring great stability. Regarding the distribution of charges, all radiopharmaceutical structures

presented contributions in LUMO and HOMO, demonstrating the capacity for covalent and non-covalent interactions.

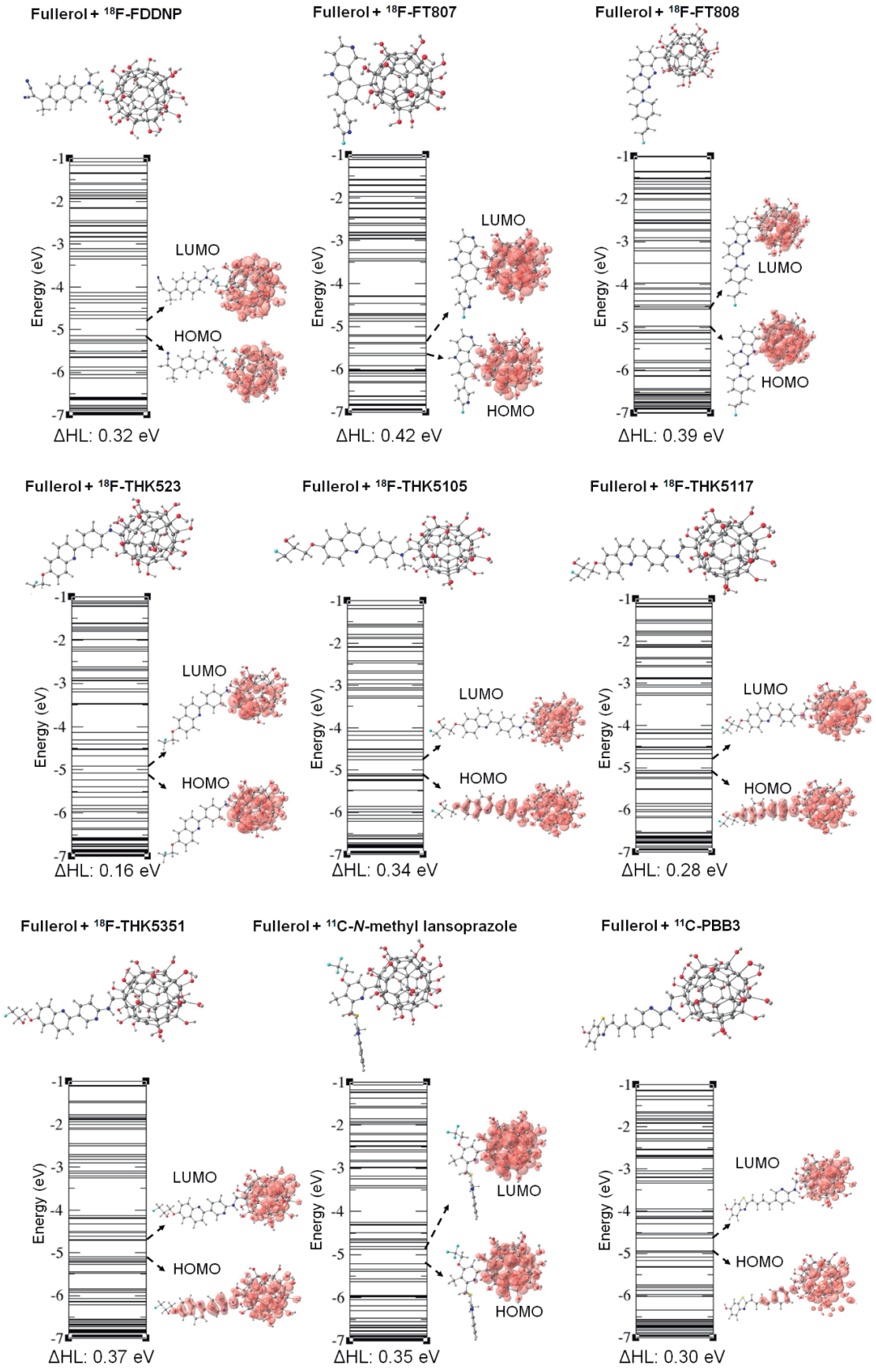
Figure 2 - Optimized structures, energy levels and charge density for isolated radiopharmaceuticals. The value of the isosurface plot for LUMO and for HOMO was 0.001 e-/Bohr³.



Source: author.

From the isolated structures, the systems composed of radiopharmaceuticals bounded to fullerol were modeled. Different configurations were constructed by varying the position of the covalent attachment of each radiopharmaceutical to the fullerol. This bond was was made from a reaction, where there was the elimination of a water molecule from the system. The choice of bonding positions was based on the load distribution of the isolated structures, and the lower energy conformations in the module were chosen from among the conformations analyzed to compose the new systems. In this way, the electronic and structural properties of these complexes were studied. Figure 3 shows the optimized energy levels and load distribution for each functionalization and table 1 shows the values for the initial and final bond distances, binding energy and ΔHL.

Figure 3 - Optimized structures of functionalization of fullerol with radiopharmaceuticals. The value of the isosurface plot for LUMO and for HOMO was 0.001 e-/Bohr³.



Source: author.

Table 1 - Initial and final binding distance, binding energy and ΔHL for fullerol functionalized with the radiopharmaceuticals.

System	Initial Distance (Å)	Final Distance (Å)	Bond energy (eV)	ΔHL (eV)
Fulerol+^{18}F-FDDNP	1.50 (C-C)	1.54 (C-C)	-3.67	0.32
Fulerol+^{18}F-T807	1.47 (C-C)	1.54 (C-C)	-5.85	0.42
Fulerol+^{18}F-T808	1.48 (C-C)	1.52 (C-C)	-4.77	0.39
Fulerol+^{18}F-THK523	1.48 (N-C)	1.47 (N-C)	-5.53	0.16
Fulerol+^{18}F-THK5105	1.48 (C-C)	1.54 (C-C)	-5.80	0.34
Fulerol+^{18}F-THK5117	1.48 (C-C)	1.52 (C-C)	-5.36	0.28
Fulerol+^{18}F-THK5351	1.48 (C-C)	1.53 (C-C)	-5.30	0.37
Fulerol+^{11}C-*N*-methyl lansoprazole	1.48 (C-C)	1.54 (C-C)	-5.03	0.35
Fulerol+^{11}C-PBB3	1.48 (C-C)	1.54 (C-C)	-4.58	0.30

Source: author.

Observing figure 3, we can notice that by connecting the fullerol and the radiopharmaceuticals there is an overlap of the energy levels of the nanostructure with the levels of the radiopharmaceuticals, indicating that there are no changes in the electronic properties with respect to the isolated structures. We can also see that in the plots of charge density for the HOMO region of all systems there was contribution in both the fullerol molecule and in the region of the covalent bond with the radiopharmaceutical, indicating a strong bond. In the fullerol + ^{18}F-THK51, fullerol + ^{18}F-THK5351 and fullerol + ^{11}C-PBB3 complexes it can be seen that there was distribution of charges throughout the full length of the fullerol + radiopharmaceutical system. For LUMO, the charges became more concentrated only in the region of the fullerol molecule.

As can be seen in table 1, all binding energies were high, configuring stability and chemical bonding between the structures. The formation of the covalent bond is also indicated by the low distances between the atoms. Values for ΔHL remained similar to the value found for fullerol isolated. The structures of fullerol and radiopharmaceuticals did not undergo significant changes in their structural and electronic parts, demonstrating that even after the structures were bonded, the intrinsic properties of each one remained.

CONCLUSION

For the first time, functionalization of fullerol with radiopharmaceuticals was performed through simulations of first principles. The results indicated that all systems studied had a strong attraction among their precursor structures. The analyzes confirmed the occurrence of a chemical bond, however, the properties of each of the structures remained according to their isolated structures. The system proved stable and can be used for applications in biological systems, mainly as a possible marker for the phosphorylated tau biomarker protein in systems for the diagnosis of Alzheimer's disease.

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