Chem Rev Lett 8 (2025) 547-554

Research Article

Chemical Review and Letters
journal homepage: www.chemrevlett.com
ISSN (online): 2645-4947 (print): 2676-7279

Computational assessments of 5-Fluorocytosine (Flucytosine) antifungal adsorption onto a fullerene oxide nanocage for engineering a potential drug delivery platform

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ARTICLE INFO

Article history:
Received: 14 March 2025
Received in revised form 14 April 2025
Accepted 15 April 2025
Available online 30 April 2025

Keywords:
Adsorption
Antifungal
Conjugation formation
Drug interaction
Fullerene

ABSTRACT

Computational assessments of 5-Fluorocytosine (Flucytosine); so called FLUC, antifungal adsorption onto a fullerene oxide (FO) nanocage was done in this work for engineering a potential drug delivery platform. The formation of interacting FLUC@FO conjugated systems yielded two conformations and the structural and electronic features were evaluated to discuss the adsorption processes. Density functional theory (DFT) computations were done to obtain the required information. The results indicated that the idea of FLUC@FO conjugated system formation could be accessible with enhanced electronic features for the adsorbed FLUC antifungal substance. Additionally, the involving interactions showed significant roles for the formation of conjugated systems during the optimization processes. As a result, the achievements indicated favorable formations of FLUC@FO conjugations with enhanced electronic specifications of FLUC antifungal agent for engineering a potential drug delivery platform. In this regard, values of adsorption strengths and electronic specifications showed the benefits of employing the investigated system in a monitorable reversible drug delivery purpose.

1. Introduction

The innovation of nanotechnology has encouraged researches to focus on various aspects of this novel technology for employing them in the specific functions and applications in all areas of science and engineering since their first announcement [1]. In this regard, considerable research works have been done up to now to recognize the role of nanotechnology in dealing with the biological living systems for repairing and medications of living organs [2-4]. However, the targeted topic of bio-functionality of nanotechnology is a complicated system requiring many more studies to understand details and architectures of nano-based therapeutics [5]. Accordingly, the current work was focused on the engineering a potential drug delivery platform for the 5-Fluorocytosine (Flucytosine) antifungal along with its adsorption onto a fullerene oxide nanocage as a representative work of employing nano-based therapeutics. A drug delivery platform is consisting of two main species including adsorbent scaffold and uploaded drug, in which learning details of interactions between them is crucial to achieve a customized drug carrier [6, 7]. For the cases of nano-based materials, such a carrier role was expected to work in the specific purposes as a complementary role to the medication [8, 9]. To this aim, details of interactions

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https://doi.org/10.22034/crl.2025.512441.1561

between FULC antifungal; standing for the 5-Fluorocytosine adsorbate, and FO nanocage; standing for the fullerene oxide adsorbent, were investigated within this work by performing density functional theory (DFT) based computational assessments to analyze the FLUC@FO conjugated systems as represented in Figure 1. Earlier works indicated benefits of DFT computations for exploring the adsorption process of nano-based molecular systems [10, 11].

FLUC; 5-Fluorocytosine or Flucytosine, is a heterocyclic compound and a 5-fluoro derivative of the well-known cytosine nucleobase, which works as an antifungal drug against *Candida* infection, cryptococcosis, and chromomycosis [12-14]. Although FLUC has been found with useful therapeutics impacts against fungal infections, but there are still deficiencies and side effects to approach a certain success of medication [15]. Hence, considerable efforts have been dedicated to recognize the ways of enhancing the efficiency of FLUC for approaching better treatments [16]. Indeed, dealing with the microbial and fungal infections is an important issue to be considered for the survival of living systems [17, 18]. As expected by the therapeutic role of nano-based structures, employing them as a carrier scaffold for specific drugs has been found as a potential way of enhancing medications along with engineering a drug delivery platform [19]. In this regard, formations of drug-nano conjugations could lead to the generation of a new system of delivery during an engineered platform [20]. Fullerenes are among the well-known nano-based structures, in which their spherical architecture gives them a single-standing chance of existence in a nanocage form among the nano-based structures [21]. However, the hydrophobic carbon composition is still a restricting factor for employing the fullerene based structures in the water media and biological systems [22]. Hence, oxidizing them could provide a fullerene oxide (FO) nanocage with better possibility of involving in water media in comparison with the pure carbon nanocage [23]. Accordingly, such a modified FO nanocage was employed in this research work to be assessed as a potential carrier of FLUC antifungal drug.

The FO nanocage was assigned as an adsorbent and the FLUC drug was assigned as an adsorbate to proceed an adsorption process for the formation of FLUC@FO conjugated systems. DFT based computations were performed to obtain the optimized structures and their corresponding structural and electronic features for assessing details of interactions between FLUC and FO of conjugated systems. The obtained results of this work for the investigated systems (Figure 1) were summarized in Tables 1 and 2 and Figure 2 to be used for initially assessing the idea of formation of FLUC@FO conjugated systems for engineering a potential drug delivery platform.

Regarding the results of earlier works, nano-based materials showed excellent behaviors of adsorbing other substances and also drug substances [24-26]. However, the strength of formations and details of interactions should be known for each system to have appropriate information for engineering a targeted platform [27]. Especially in the case of drug delivery, desorption is also a very important issue in addition the adsorption, in which the strength of adsorbate-adsorbent conjugated system could reveal a clue for how to deal with the system. Additionally, possibility of formations of conjugations with different architectures should be also know, in which the computer-based works could reveal details of such issues for examining the formation of all possible conformations. The investigation of pure substances and learning their own natures is an advantage of performing computer-based assessments of chemical systems [28-31]. Based on such mentioned issues, the current work was carried out to assess details of FLUC@FO conjugations for engineering a potential drug delivery platform. It should be noted that the current research is indeed a type of basically investigation of complicated systems for specifying their features and expected functions to predict the benefits of engineering such a complicated system for a desired function based on their characteristic features.

2. Computational Details

First, the single models of FLUC ($C_4H_4FN_3O$) and FO ($C_{24}O$) were optimized to generate the stabilized parental models of this work. Next, possibilities of FLUC@FO conjugations formations were examined by performing additional optimization calculations on two-species models resulting F1 and F2 conjugations. The strength of adsorption process was defined by adsorption energy (E_A) as the energy differences of conjugated systems and parental counterparts; the results were included in Table 1. Additionally, the effect of basis set superposition error (BSSE) was included in the calculation of EA based on counterpoise method [32]. The stabilized architectures of parental models and conjugations were shown in Figure 1 after relaxing the FLUC counterpart at the FO nanocage scaffold during the optimization processes. The global minimization process was confirmed based on the vibrational frequency calculations. At this step, the structural features could be learned for the optimized systems. After carefully investigation of structural features of models, the electronic features were investigated based on the nature of dominant frontier molecular orbitals including the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO). The electronic

based features were listed in Table 2 regarding energies of HOMO and LUMO (E_H and E_L), energy gap (E_G), chemical potential (μ), chemical hardness (η), chemical softness (σ), and transferred charge (Q_{NBO}) were evaluated for the optimized structures to assess the electronic based features of parental models and conjugations. The natural bond orbital (NBO) charges were calculated for obtaining the values of Q_{NBO}. Besides, distribution patterns of HOMO and LUMO, surfaces of molecular electrostatic potential (ESP), and spectra of density of states (DOS) were exhibited in Figure 2. DFT based computations were performed using the popular B3LYP/6-31G* level of theory as implemented in the Gaussian program [33-35]. However, the values of E_G were recalculated using the PBE0/6-31G* level of theory for making a confirmation of results [36, 37]. GaussView [38], ChemCraft [39], and GaussSum [40] programs were used to extract the required features from the computational outputs.

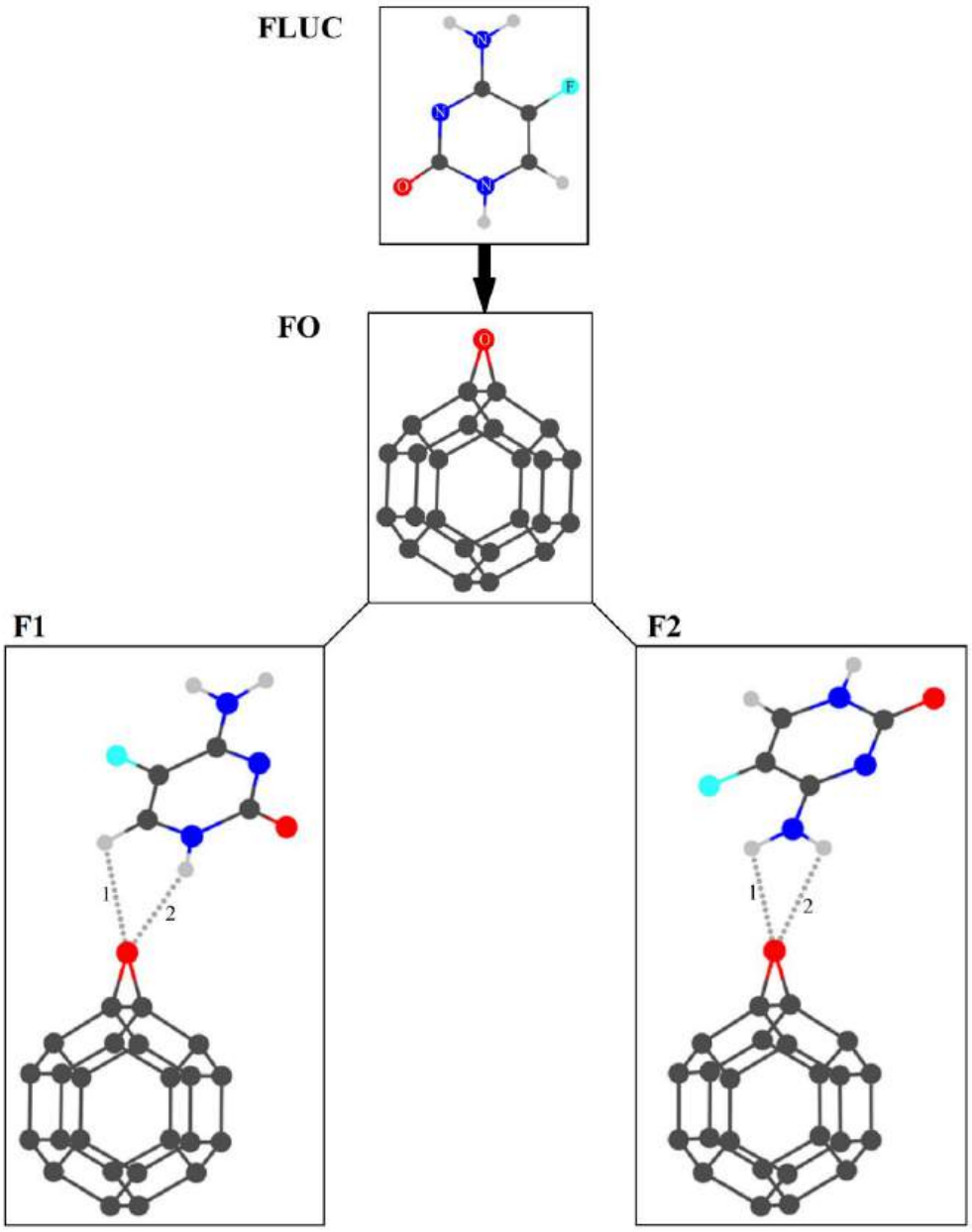

Fig. 1. The structural representations of parental FLUC and FO models and F1 and F2 conformations of FLUC@FO conjugations. The dashed lines represent the involving interactions in the conjugations; details were listed in Table 1.

Table 1. The calculated values of structural features of FLUC@FO conjugations.*

FLUC@FO	E_A (kcal/mol)	E_A + BSSE (kcal/mol)	Interaction-1	Distance-1 (Å)	Interaction-2	Distance-2 (Å)
F1	-3.89	-2.65	C-H…O	2.92	N-H…O	2.27
F2	-2.43	-1.48	N-H…O	2.66	N-H…O	2.60

* $E_A = E_{FLUC@FO} - E_{FLUC} - E_{FO}$.

3. Results and Discussion

Regarding the main aim of this work to approach an engineered drug delivery platform for the FLUC antifungal agent using the FO nanocage, DFT calculations were performed to provide the structural and electronic features for the targeted systems. As shown in Figure 1, the models were represented in both of parental and conjugation states to declare the schematic view of the whole process of this work. In this case, the models were divided into their original single forms or in the interacting conjugated form, in which the formation of FLUC@FO was investigated. As could be learned by these results, the conjugated models were in two conformational forms of F1 and F2 based on the involving sites of FLUC in interactions with the FO nanocage. Accordingly, the models were investigated by their calculated structural and electronic features in the optimized states. To further declare the aim of this work, it is worth to mention that the investigation of formations of conjugations could be known as initial steps of engineering a complicated drug delivery platform with a critical role of carrier for uploading the drug, carrying it, and delivering it to the specified target. To these issues, the models of molecular systems could be investigated in the computer media to assess the benefits of employing material substances towards each other in the interaction states and adsorption processes. In the case of drug delivery platforms, the carrier plays an adsorbent role and the drug plays an adsorbate role for the occurrence of adsorption process for the formation of drug…carrier conjugated system. In this regard, exploring the stabilized models and characterizing their details could enhance the understanding about the possibility of formation of such conjugations for expanding their further applications and investigations. In the case of current research work, such mentioned issues were investigated for the FO adsorbent and FLUC adsorbate for the formation of FLUC@FO conjugations through the relaxation of FLUC drug towards the FO nanocage. Accordingly, the structural and electronic based features were calculated for examining the hypothesized aim of this work for engineering a potential drug delivery platform.

The calculated structural features of models were listed in Table 1 including the values of adsorption energy (E_A) and details of interactions. Returning to Figure 1, the FLUC@FO conjugated models were optimized in two conformations including F1 and F2, in which their stabilizations were found through the relaxation of FLUC counterpart towards the FO nanocage. In this case, the involving interactions were predicted based on the distances of atoms for the formation of conjugations revealing two interactions for each conformation system. However, distances of interactions were different in the conjugations showing different roles of interactions and stabilities for the systems. For F1, C-H…O and N-H…O interactions were identified from the FLUC counterpart to the FO counterpart with 2.92 Å and 2.27 Å, respectively. Accordingly, -3.89 kcal/mol was found for E_A of F1 formation. For F2, two N-H…O interactions were identified from the FLUC counterpart to the FO counterpart with 2.66 Å and 2.60 Å, respectively. Accordingly, -2.43 kcal/mol was found for E_A of F2 formation. Besides, the values of BSSE were also calculated not to overestimate the values of EA, in which the values of E_A+BSSE were also in agreement with the results of E_A to emphasize on the strength level of interacting systems. As listed in Table 1, the values of -2.65 and -1.48 kcal/mol were found for E_A+BSSE of F1 and F2 formations. The interactions were shown in Figure 1 by the dashed lines. As could be learned by these results, the counterparts of F1 were relaxed in a closer distance to each other in comparison with the counterparts of F2; hence, the obtained values of E_A were different and showing a higher strength for the formation of F1 than that of F2. It should be mentioned here that the formation of both of F1 and F2 conjugations were found in a weak level of strength; however, their formations were still meaningful because of the strength of adsorption and the interaction distances. Since the FO has still the characteristic feature of pure carbon systems but with a little modification, the strength of this system may not be predicted to be in a high level, but exceptions could be expected. As a result of structural characterizations, formations of FLUC@FO conjugations were found and their structural features indicated the important roles of involving interactions for the relaxation of conformations. Additionally, formations of both of F1 and F2 conformations could be expected to be obtained based on the structural features and representations. By the results of this part, the main idea of FLUC@FO formation was achieved for the adsorbent role of FO towards the FLUC drug. It is also worthy to mention that the exploration of

such interacting FLUC@FO systems could reveal insightful information at the lowest scale of molecules and atoms to recognize the features of pure systems for assigning their specifications for future developments. To this aim, the idea of engineering drug delivery platforms could be approached based on these detailed results. Additionally, the obtained values of E_A and details of interactions indicated a possibility of approaching a reversible drug delivery platform for the FLUC@FO system. In this regard, a desorption process could be expected for the adsorbed drug.

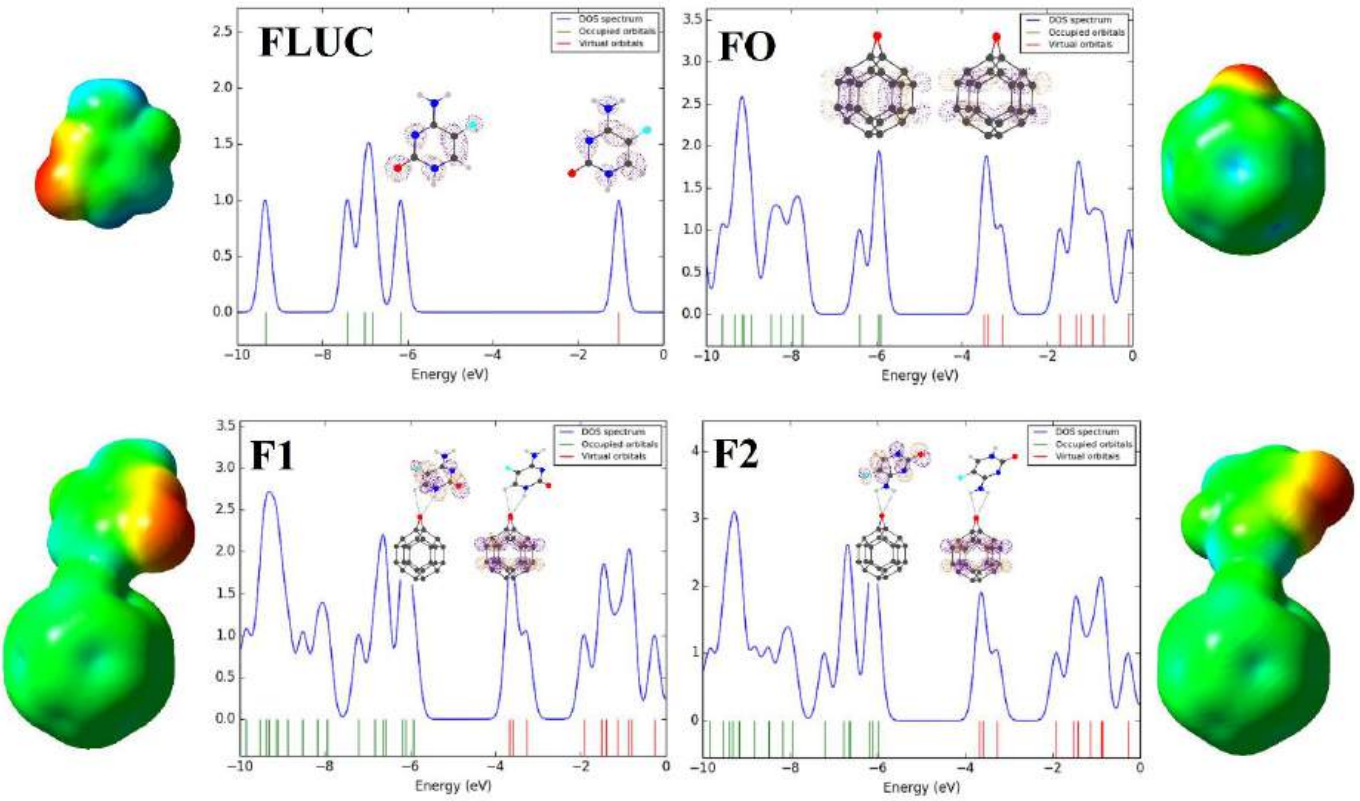

Fig. 2. The electronic representations of parental FLUC and FO models and F1 and F2 conformations of FLUC@FO conjugations including HOMO-LUMO distribution patterns (HOMO in the left and LUMO in the right at each panel), DOS spectrum, and ESP surfaces; details were listed in Table 2. It is noted that the vertical line of DOS spectra was numbered by the GaussSum software.

Table 2. The calculated values of electronic features of parental FLUC and FO models and FLUC@FO conjugations.*

CYS@BeO	E_H (eV)	E_L (eV)	E_G (eV)	μ (eV)	η (eV)	σ (eV)	Q_{NBO} |e|
FLUC	-6.16	-1.04	5.12 [5.53]	-3.60	2.56	0.39	n/a
FO	-5.92	-3.48	2.44 [2.71]	-4.70	1.22	0.82	n/a
F1	-5.91	-3.67	2.24 [2.51]	-4.79	1.12	0.89	0.009
F2	-6.00	-3.68	2.32 [2.59]	-4.84	1.16	0.86	0.003

* $E_G = E_L - E_H$, $\mu = (E_L + E_H)/2$, $\eta = (E_L - E_H)/2$, and $\sigma = 1/\eta$. The values of E_G in brackets were calculated using the PBE0/6-31G* level.

The obtained results of electronic features were represented in Figure 2 and Table 2 for the parental models and conjugations. After optimizing the molecular models and obtaining the stabilized conformations of interacting FLUC and FO counterparts, their electronic features were investigated. For this case, the dominant electronic molecular orbital levels including HOMO and LUMO were employed to find the electronic features of investigated molecular models. Indeed, the frontier HOMO and LUMO levels have significant roles for defining the electronic behaviors of molecular systems in terms of electron transactions inside and outside the molecules. To this importance, studying the HOMO-LUMO based features could reveal insightful information for the electronic

features of molecules. Within this work, these features were evaluated to examine the electronic properties of models in different states of parental and conjugations. As shown in Figure 2, DOS spectra, distribution patterns and ESP surfaces were exhibited for the models. Comparing the parental models and conjugations shows the changes of electronic features for the molecular systems. In the case of HOMO and LUMO patterns, the HOMO part was located at the adsorbed FLUC and the LUMO part was located at the adsorbent FO indicating a role of adsorbent for enhancing the electronic feature of adsorbed drug by inducing the HOMO part to its side. In the case of antifungals, the resistance to treatment may be considered as a preventing factor of achieving a successful treatment which could be resolved for the FLUC antifungal agent by the help of conjugation with the FO nanocage. Examining the DOS spectra show slight changes for F1 and F2 meaning a similar behavior for both of them as it was already expected by the values of E_A. However, changes of spectra from the parental models to conjugations indicated the impact of FLUC@FO formations on the electronic features of models. The evaluated ESP surfaces also approve the formation of FLUC@FO conjugations, in which the narrow neck of these surfaces indicates the formation of weak conjugations. However, the continuous feature is indeed an evidence of formation of meaningful conjugations. Hence, the models were found to be electronically reactive and meaningful based on changes of HOMO-LUMO distribution patterns, DOS spectra, and ESP surfaces from the parental state to the conjugation state and also between F1 and F2 conformations.

In addition to the graphical representations of electronic features, the calculated quantities were summarized in Table 2. Based on the energies of HOMO and LUMO (E_H and E_L), other related quantities including energy gap (E_G), chemical potential (μ), chemical hardness (η), and chemical softness (σ) were evaluated for the optimized structures. Comparing the results could show the significance of employing FO nanocage as an enhancing counterpart of FLUC antifungal agent. In this case, the distance of HOMO and LUMO levels were decreased in the conjugations in comparison with the parental models, in which the values of E_G were reduced for the conjugations. As F1 was found stronger than F2, a smaller value of E_G could approve this observation emphasizing on a lower activity for F1 in comparisons with F2. This issue could be approved by the values of (μ), chemical hardness (η), and chemical softness (σ), in which a higher softness was found for F1 than all other models. It is very important that the softness of F1 is even better than the parental FLUC agent remembering the enhancing role of FO for the function of FLUC antifungal agent. Additionally, the models were distinguishable from each other by comparing the HOMO-LUMO related quantities as found by their electronic representations. For making a confirmation for the values of E_G, the results of PBE0/6-31G* were also evaluated, in which the results indicated a meaningful achievement for the calculations by obtaining close values to each other using both of B3LYP and PBE0 functionals. The values of Q_{NBO} were also calculated for the models to show directions of charge transferees between the counterparts, in which a direction from the FO to the FLUC was found for the models as found previously by the localization of HOMO at the FLUC side and the localization of LUMO at the FO side in both of F1 and F2 conformations. Hence, a role of electronic enhancement for the FLUC drug could be considered for the formation of FLUC@FO systems. As a result, in terms of structural and electronic specifications, the formation of FLUC@FO conjugations could be known as useful models for engineering a potential drug delivery platform; however, further investigations are still required to recognize various aspects of such a basic suggestion. Besides obtaining a reversible drug delivery platform for the FLUC@FO system, the variations of electronic features could be also monitorable to recognize changes of investigated systems in different states.

4. Conclusion

Summarizing the achievements of this work could reveal some insightful comments about the investigated models. The first one is about the formation of FLUC@FO conjugations, in which F1 and F2 conformations were found for this system by the result of optimization calculations. Although the strengths of complexes were among the weak complexes, but the structural features approved the meaningful formation of FLUC@FO conjugations introducing a reversible drug delivery platform. The second one is about the enhancing role of FO nanocage for the function of FLUC antifungal agent, in which the localization of HOMO pattern was centralized at the FLUC side instead of FO side. This is very important for recognizing the FLUC part of conjugations as a stronger substance for involving in reactions and interactions with other substances. The third one is about the softness of conjugations in comparison with the parental FLUC substance, in which the electronic enhancement yielded to a better softness of FLUC@FO system for involving in chemical transactions. Such an enhanced electronic feature was seen by the charge transfer from the FO counterpart to the FLUC counterpart in the formation of FLUC@FO systems besides the localization of HOMO pattern at the FLUC side and the localization of LUMO pattern at the FO side. The final one is about the possibility of formation of

FLUC@FO conjugations for engineering a potential drug delivery platform, in which both of structural and electronic features indicated the advantage of employing FO nanocage as an adsorbent of FLUC antifungal agent to be considered as a possible carrier for approaching an engineered drug delivery platform. As a result, the hypothesized aim of this work was approached for providing a reversible and monitorable FLUC@FO platform, in which such obtained results could be considered for further investigations of features and applications regarding the drug delivery purpose.

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