Lab-in-Silico
https://lab-in-silico.com
eISSN: 2717-1922

ORIGINAL RESEARCH

Lab-in-Silico. 2021;2(1):3-8. DOI: 10.22034/labinsilico21021003

Loading Tacrine Alzheimer's Drug at the Carbon Nanotube: DFT Approach

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Received: 14 January 2021 / *Accepted*: 17 January 2021 / *Published Online*: 30 June 2021

ABSTRACT. Density functional theory (DFT) calculations were performed to investigate complex formation of loaded tacrine (TAC) Alzheimer's drug at carbon nanotube (CNT) to make such TAC@CNT complex. To this aim, each of singular TAC and CNT molecular systems were first optimized to achieve the minimum energy structures. Next, the complex formation of TAC@CNT was investigated by performing further optimization of interacting counterparts. The results were obtained to analyze the systems regarding quantitative and qualitative aspects, in which the main goal was to investigate features of such TAC@CNT complex system. It was indicated that TAC could be loaded at CNT and it could remain safe from interactions with other substances as the frontier molecular orbital distributions were moved from TAC to CNT in the complex of TAC@CNT. Finally, such complex formation of TAC@CNT could be proposes for applications regarding the purposes of targeted drug delivery systems.

KEYWORDS. Tacrine; Nanotube; Alzheimer; Drug delivery; DFT.

INTRODUCTION. The carbon nanotube (CNT) innovation in 1991 has raised considerable interest of researchers to put efforts on determining various characteristics of the novel material.[1] The efforts has led to generation of huge amount of information on the characterization of properties of nanostructures up to now.[2-10] The applications of CNTs in living system has been always an important goal for using this novel material to improve the quality of human life.[11] Among the research results, investigating possible applications of CNTs for drug delivery purposes has been seen very much important regarding the necessity of targeted drug delivery processes.[12] Covalent and non-covalent loading of different drugs on different nanostructures have been investigated to show the effects of such combination on the properties of each counterpart.[13] All procedures of *in silico*, *in vitro* and *in vivo* have been examined for the purpose.[14] Indeed, nanostructure have been expected as vehicles for medicinal compounds inside the living systems but with so many restricting factors.[15] Therefore, details for such topic of applications in living systems has been always an

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important task for the researchers of corresponding fields. To this aim, computer-based *in silico* works could very well generate insightful information for the investigated materials at the lowest atomic scale.[16-23] Non-covalent loading of drugs at CNTs have been investigated earlier employing such computer-based works, in which the results approved the significant roles of nanostructure for drug delivery purposes.[24, 25] Tacrine (TAC) is a drug for medication of Alzheimer's disease.[26] Several attempts have been dedicated to characterize the features of TAC to increase its efficacy for the patients.[27] Applications of nanostructures for drug delivery of TAC have been also investigated.[28] To this point, this work was performed to investigate the features of loading TAC at CNT (TAC@CNT) employing the computer-based *in silico* methodology. A representative model structure of CNT was chosen to provide a nanostructure-based surface for TAC to be loaded non-covalently on it (Fig. 1). Quantum chemical calculations were performed to achieve optimized geometries for the investigated model and the corresponding descriptors for such optimized model. The major goal of this work was to examine possibility of loading TAC@CNT and to evaluate atomic and molecular scale descriptors for describing such system by the advantage of computer-based works. Avoiding existence of any external interferer is the main advantage of such computational techniques, which isolate the investigated system to be pure as much as possible.[29-34]

METHODOLOGY. In this work, a representative (6,0) model of CNT was chosen for providing nanostructure-based surface for loading TAC (Fig. 1). Each of singular molecule of CNT and TAC were first optimized to have the single-standing structures with minimized energy level. Afterwards, combination of already optimized CNT and TAC was created to optimize the relaxation of TAC at the surface of CNT. By doing such optimizations, the model of loaded TAC at CNT (TAC@CNT) was obtained for further investigations. In addition to the optimized geometers and interacting distance, other parameters including binding energy (BE), dipole moment (DM), molecular orbitals energy levels (HOMO and LUMO), and energy gap (EG) were evaluated for the investigated models. Moreover, distribution patterns for HOMO and LUMO and electrostatic potential (ESP) surfaces were evaluated for better representing electronic properties for the investigated models. Density functional theory (DFT) approach was employed to perform computations of this work using the B3LYP exchange-correlation functional and the 6-31G* standard basis set as implemented in the Gaussian program.[35] All the obtained results of this work were exhibited in Table 1 and Fig. 1 to be discussed in details by the following text.

Table 1: Optimized features.*

Property	TAC	TAC@CNT	CNT
BE	N/A	0.50	N/A
DM	3.89	5.89	0
HOMO	-5.29	-4.03	-3.67
LUMO	-0.78	-3.09	-2.96
EG	4.51	0.94	0.71

*See Fig. 1 for models. DM is in Debye, others are in eV.

RESULTS & DISCUSSION. Within this work, loading TAC Alzheimer's drug on CNT was studied employing DFT calculations. To this aim, each of singular molecular models of TAC and CNT were first optimized to reach the minimum energy structures. Subsequently, complex formation of TAC@CNT was investigated by performing further optimization to reach the most stable conformational structures of the interacting counterparts (Fig. 1). The results of this work included the obtained values of energies for binding process of molecules in addition to energies of molecular orbital levels and dipole moments (Table 1). By such obtained results, the main achievements of this work were evaluated regarding the goal of this work to load TAC on CNT for such drug delivery purposes. This work was done at the molecular scale to show clearly the effects of such complex formation on the properties of each counterpart, especially for TAC. Indeed, targeted drug delivery systems are mainly involved with choosing proper carriers for drugs to deliver them safe up to the specific target. However, such goal could not be followed in conventional drug delivery processes. Nanostructures have been seen to have significant advantages for such purpose, as investigated in this work. Indeed, innovation of nanotechnology has raised hopes for providing more powerful devices and processes in the living systems to lead to higher quality of life.

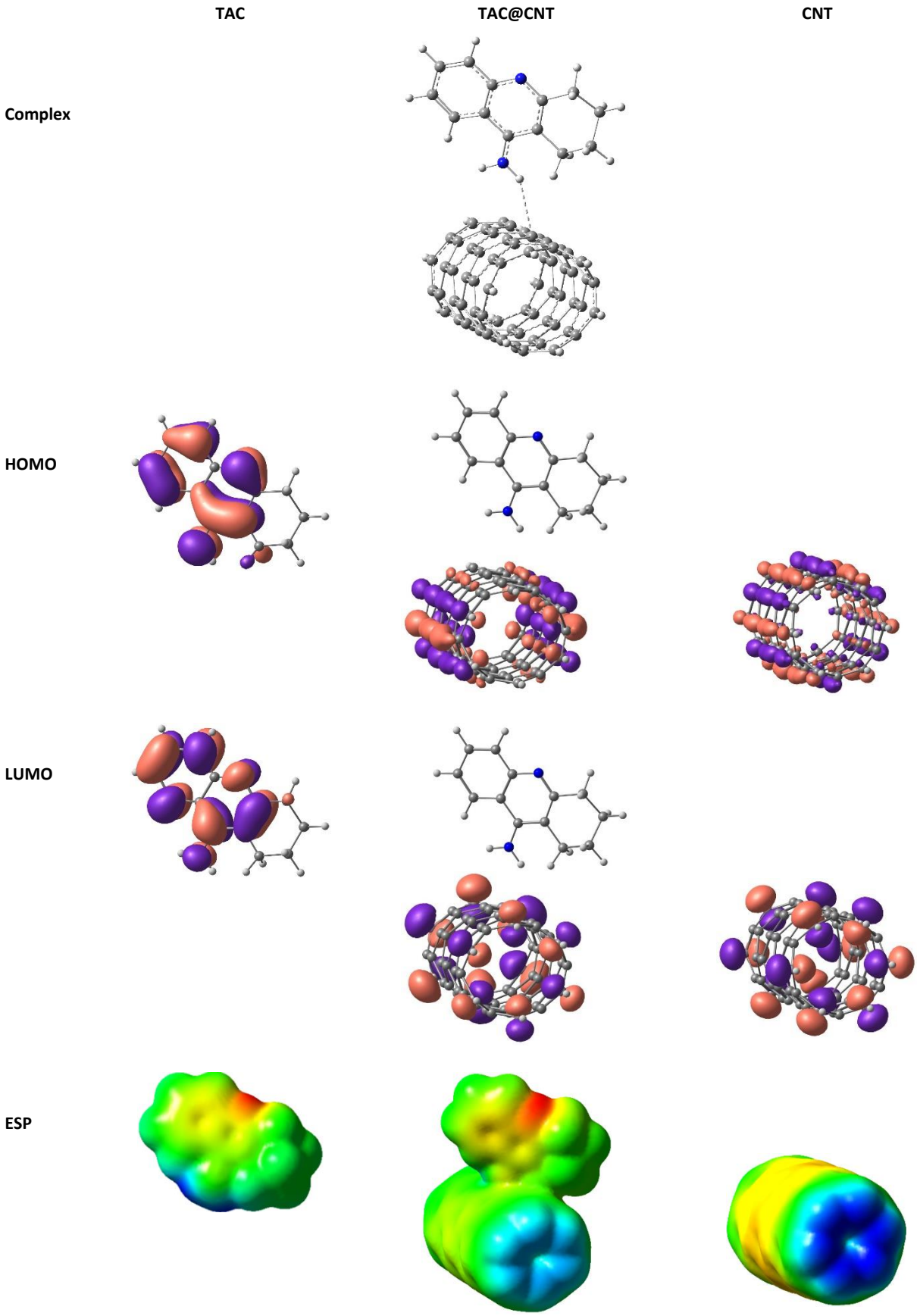

Fig. 1: Molecular, molecular orbital and ESP representations.

At the first step of this work, 3D molecular models of TAC and a representative CNT were optimized to reach the minimum energy structures. As could be seen by Fig. 1, HOMO and LUMO distribution patterns were located at both of individual molecules. Moreover, ESP surfaces could show the localization of charge at the investigated molecules. After such singular molecule analyses, the complex formation of TAC@CNT was

investigated by further optimization of interacting molecular system. Interestingly, HOMO and LUMO distributions were localized only on the CNT counterpart of TAC@CNT complex not at all at the TAC counterpart. This is an important achievement showing the dominant role of CNT for proper carrying the loaded TAC drug. More clarifying, it means that by loading the drug at the CNT, the drug losses its reactivity by localizing the HOMO and LUMO distributions only at the CNT. It is noted that the complex formation was approved by the continuous representation of ESP surface for TAC@CNT. In this case, CNT could work as a biosensor in addition to its carrier role for detecting the specific target to deliver the loaded drug. Indeed, such applications were always expected for the nanostructures to work great functions in biological systems to save human life. In this regards, the obtained graphical results showed that the singular TAC was an active molecule to react with other substances, but its reactivity was reduced when loading at the CNT counterpart. Therefore, it could be expected that such system could be delivered more specifically avoiding the unwanted side effects.

Quantitative analyses of content of Table 1 could reveal helpful information for the purpose of this work to load TAC drug at CNT. The values of binding energy approved the formation of TAC@CNT complex, in which it was approved by ESP surface also. This is an important point of agreement for quantitative and qualitative analyses of the obtained results. The structure of CNT was symmetric yielding the zero-value for dipole moment; however, such symmetry was broken in the complex of TAC@CNT. The results indicated that the value of dipole moment for TAC@CNT was larger than each of singular TAC and CNT counterparts. Contributing to such interacting complex formation, the levels of HOMO and LUMO detected the effects of such perturbation to molecular orbital systems yielding different values in complex of TAC@CNT regarding those of singular counterparts. Correspondingly, the values of energy gaps showed such changes because of effects of HOMO and LUMO frontier levels. As a result, new environment was arisen for the complex of TAC@CNT in comparison with each of singular TAC and CNT to reveal the importance of such complex formation for defining functions of the structures. Such results are actually remembering the trend of SAR meaning the relationship between structure and activity. Hence, it could be concluded here that TAC@CNT complex formation could help for the purposes of targeted drug delivery by highlighted role of CNT for achieving such purpose. This is important to mention that the molecular scale studies could reveal the information avoiding the effects of external interferers, in which the pure materials could be recognized and characterized for the purposes. Additionally, detailed information could be found with such works, in which the mechanism of interaction of TAC with CNT was carefully examined here using the computed molecular-scale parameters. To this point, TAC@CNT was seen as a stable complex for further investigations regarding the drug delivery purposes.

CONCLUSION. This computer-based *in silico* work was done to load TAC drug at CNT to investigate TAC@CNT complex formation for the purposes of targeted drug delivery systems. The work was done at the molecular scale to significantly recognize the properties of materials avoiding the existence of external interferers. The results of singular and complex models indicated that the CNT could attract the TAC drug at the surface by analyzing quantitative and qualitative results. Moreover, such processes yielded remarkable electronic environment for the complex of TAC@CNT by localizing the HOMO and LUMO distribution patterns mainly at the CNT counterpart not at all at the TAC counterpart of complex. Hence, the reactivity of TAC was reduced in the complex to put the role of biosensor for CNT in addition to its carrier role. As a concluding remark of this work, the complex of TAC@CNT could work for the purpose of targeted drug delivery systems by the advantage of employing CNT carrier. Therefore, such complex system could be proposed for further investigation of features for TAC@CNT applications.

DISCLOSURE STATEMENT. The author(s) did not report any potential conflict of interest.

ACKNOWLEDGEMENTS. This work was evaluated from a part of master thesis of M. Mirali granted by the research council of Tehran Medical Sciences, Islamic Azad University, which is acknowledged.

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How to Cite: Mirali M, Jafariazar Z, Mirzaei M. Loading Tacrine Alzheimer's Drug at the Carbon Nanotube: DFT Approach. Lab-in-Silico. 2021;2(1):3-8.
DOI: https://doi.org/10.22034/labinsilico21021003
URL: https://sciengpub.com/lab-in-silico/article/view/labinsilico21021003