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In silico Complexes of Amino Acids and Diamondoids

Pouya Partovi-Azar,*[a] Chandra Shekar Sarap,[b] and Maria Fyta[c]

We report on the specific interaction of a small diamond-like molecule, known as diamondoid, with single amino-acids forming nano/bio molecular complexes. Using time-dependent density-functional theory calculations we have studied two different relative configurations of three prototypical amino acids, phenylalanine, tyrosine, and tryptophan, with the diamondoid. The optical and charge-transfer properties of these complexes exhibit amino acid and topology specific features which can be directly utilized for in the direction of novel biomolecule detection schemes.

1. Introduction

The influence of nanostructures on physical and chemical properties of biomolecules plays a key role in understanding their biocompatibility. Understanding and controlling such interactions facilitate their application in various fields such as biosensing, drug delivery, and molecular recognition.[1,2,3] Among other materials, carbon-based nanostructures, such as fullerenes, carbon nanotubes, graphene, etc., have attracted much attention due to their distinct optical, electronic, and mechanical properties.[4,5,6] These materials have diverse applications, for example in self-assembly, catalysis, hydrogen production, energy storage, and in photonic devices.[7,8] It has been demonstrated that these nanostructures are also effective sensing devices for bio-molecular detection.[9,10,11,12] In view of biosensing, the high potential of small nanometer-sized hydrogen-terminated hydrocarbon cages, the diamondoids, as probes for distinguishing the DNA nucleotides has been recently explored.[13] Modification of small diamondoids with specific functional groups has opened up their use in drug development,[14] specifically in chemotherapeutics against many infectious diseases including Herpes Simplex, Hepatitis C, HIV and Malaria,[15] and as a well known drug for Alzheimer's disease,[16] etc. Numerous bio-related experiments as well as theoretical studies have been carried out on carbon-based materials and have proved them to be excellent templates for DNA hybridization and DNA sequencing.[17,12,18,19,20]

Additionally, other biosensing applications involve the detection of amino acids, which are organic compounds and molecular components of proteins. The amino acids and the nucleic acids form the building blocks of life. In that respect, amino acids are significantly involved in a vast number of biological processes. Accordingly, any changes in the amino acids could be related to cardiovascular diseases, metabolic disorders, abnormal neurological conditions, etc. It is thus evident, why a quantitative and qualitative determination of amino acids has formed a large field of research since decades.[21] Throughout the years, different analytical tools for amino acids have been developed, ranging from mass spectroscopy[22] and chromatography[23] to optical[24] and calorimetric[25,26] sensors, nanorods,[27] etc. Moreover, other types of biomedical applications propose the utilization of nanodiamonds and amino acid derivatives.[28] Aligned with the above lines, we explore the performance of a small diamondoid derivative as a probe for identifying amino acids. This will be achieved through an investigation of the properties of certain diamondoid/amino acid complexes.

2. Methodology

This study has been carried out using quantum mechanical calculations within the density functional theory (DFT)[29,30] using the code Gamess-US.[31] All geometry optimizations were performed using the Pople-type polarized basis functions and the M06-2X functional,[32] accounting for long-range dispersion interactions. The initial geometry optimizations were performed using the 6-31G(d,p) basis set, followed by single-point energy calculations at the 6-311+G(d,p) level. A vibrational frequency analysis was carried out to ensure that the obtained geometries represent the minimum energy configuration on the potential energy surface. All optical and charge-transfer properties were investigated using the linear-response time-dependent DFT (LR-TDDFT) using the CAM-B3LYP functional[33] with the 6-31+G(d) basis set. The CAM-B3LYP hybrid, range-separated functional ensures the correct asymptotic behavior of the exchange energy and has been successfully applied to study long-range charge transfer processes between neighboring molecules.[34–38] Particularly, the empirical parameters in CAM-B3LYP have been originally optimized to predict, among other properties, correct charge-transfer excited state energies.[33] Additionally, to correctly account for charge transfer processes in anions, it is generally important to use diffuse functions in the employed basis sets, like the one used in this work for optical and charge transfer calculations, i.e. 6-31+G(d). Charge transfer dynamics were studied using a real-time approach TDDFT (RT-TDDFT)[36] as implemented in NWCHEM.[39] The Ahlrichs Coulomb fitting

[a] Dr. P. Partovi-Azar
Institute of Chemistry, Martin Luther University Halle-Wittenberg, Von-Danckelmann-Platz 4, 06120 Halle (Saale), Germany
E-mail: pouya.partovi-azar@chemie.uni-halle.de
[b] Dr. C. S. Sarap
Institute for Computational Physics, Universität Stuttgart, Allmandring 3, 70569 Stuttgart, Germany
[c] Prof. Dr. M. Fyta
Institute for Computational Physics, Universität Stuttgart, Allmandring 3, 70569 Stuttgart, Germany

basis set was used in the RT-TDDFT simulations to compute the Coulomb part of the Fock matrix.[40] The interaction energy of the nano/bio complexes are calculated through $E_{int} = E_{complex} \; E_{diamondoid} \; E_{amino\ acid}$, where $E_{complex}$, $E_{diamondoid}$ and $E_{amino\ acid}$ are the energies of the diamondoid/amino acid complex, isolated diamondoid, and isolated amino acids, respectively in their optimized geometries. All energy terms have been corrected for the basis set superposition error.[41]

3. Results and Discussion

In this study, we focus on nano/bio complexes made of a small adamantane derivative known as memantine.[16] This molecule differs from the native adamantane by an additional amine group. We further functionalize this molecule with a thiol group and use in the following for this the notation 'memS'. The reason behind this is the need of an additional atomic group that would graft the molecule on a carrier. The aim is to find amino acid specificity in the electronic and charge transfer dynamics of these nano/bio complexes. As representative amino acids, we focus on aromatic aminoacids, phenylalanine, tyrosine, and tryptophan. The optimized geometries of these amino acids in gas-phase are depicted in Figure 1 (top panel). For their interaction with the memS nanoparticle, we consider the most stable configurations as representatives in which memS serves as a hydrogen bond donor or acceptor towards the amino acid. These are of course a very small fraction of the possible configurations, serve though as a proof of principle towards our aim.

To obtain the geometries of memS-amino acid complexes, first the three amino acids are each placed at a different orientation with respect to the diamondoid. These correspond to the memS being either a donor or an acceptor to the respective hydrogen bond. The optimized gas-phase geometries of the corresponding complexes are depicted in Figure 1 (middle and bottom panels). This indeed reveals one or two hydrogen bonds between the nanoparticle and the biomolecule, mostly governed by NH···NH and CH···OH interactions. An energy decomposition analysis of all the configurations clearly shows a large contribution of the dispersion interactions to the total interaction energies of the complexes. In the hydrogen bond donor configurations, the dispersion interactions are slightly larger than the electrostatic and polarization energies. In the hydrogen bond acceptor configurations these are considerably larger. This results in an overall stronger interaction in memS-phenylalanine and memS-tyrosine in the hydrogen bond acceptor configurations. The memS-tryptophan complex is found to be slightly more bound to the memS in the hydrogen bond donor configuration. Inspection of these interaction energies already reveals distinct features depending on the amino acid identity.

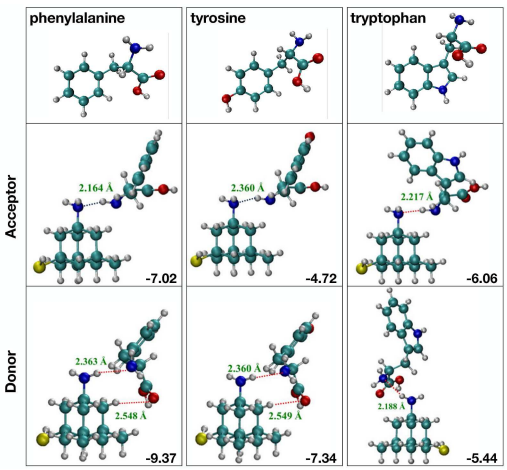

Figure 1. Top: Optimized *in vacuo* geometries of isolated aromatic amino acids, phenylalanine, tyrosine and tryptophane. Middle and bottom: optimized geometries of the respective nano/bio complexes, memS-phenylalanine, memS-tyrosine, and memS-tryptophan, in which memS is a hydrogen bond acceptor and donor in the complex, as denoted by the labels. The dotted lines denote the two distinct types of hydrogen bonds, the length of which is also shown in Å. The interaction energies are shown on the bottom of each panel in kcal/mol.

The absorption spectra of the isolated amino acids also show very distinct features as evident from Figure 2. These features remain amino acid-specific while showing additional configuration dependence in amino acids-diamondoid complexes. The absorption of the memS-complexes in both configurations are mostly governed by that of the isolated amino acids, emphasizing the minimal effect of the memS probe on the optical properties of the amino acid targets. In the energies below 6 eV, there is a shift observed in the absorption spectrum of the memS-tyrosine compared to the that of the isolated tyrosine. This results in a more profound difference between the optical activity of tyrosine and that of phenylalanine and tryptophan in the energies below 6 eV when using a memS probe. Note that, in this energy range, memS has no contribution and, thereby, the optical activities in this range come solely from tyrosine in the tyrosine-memS complex. The optical activity of tryptophan dominates in the 6–7 eV energy range, but is negligible in 7–8 eV. Although, the optical activity of the isolated phenylalanine and tyrosine are almost indistinguishable in the same energy range, their complexes with memS show different features in the same energy range. The memS-phenylalanine complex reveals an excitation at a ~200 meV higher energy (~7.2 eV) compared to the memS-tyrosine (~7.0 eV), as well as higher oscillator strengths. These findings demonstrate the ability of memS in enhancing the differences in the optical activities of amino acids. Overall, the results clearly show that tryptophan can be detected at lower energies than the other two amino acids. In the lower energy range, no optical activity is observed in the phenylalanine-memS complex, whereas there is a rather detectable optical activity in the tyrosine-containing complex in both hydrogen bonded configurations.

The amino acid-specific optical activity in the complex indicates possible differences in the charge-transfer characteristics within the complexes. In order to evaluate this, we follow the time evolution of an additional electron on the memS in the complexes for about 15 fs. The resulting charge dynamics for all H-bond configurations are summarized in Figure 3.

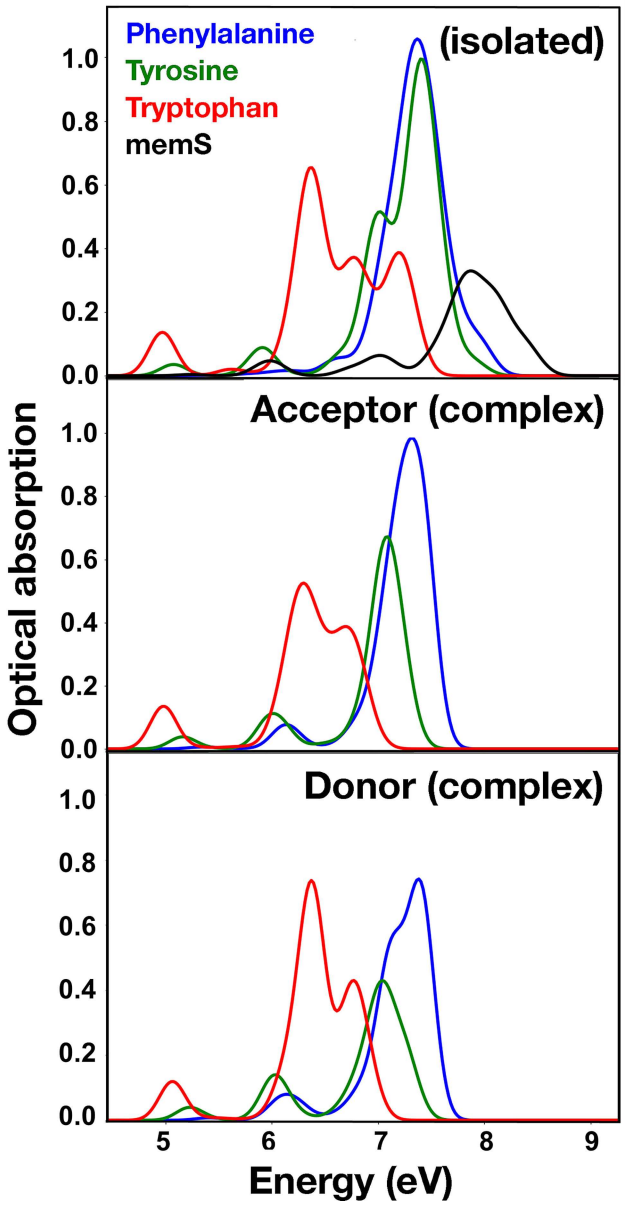

Figure 2. Absorption spectra of the isolated diamondoid and amino acids and the memS/amino acid complexes in which memS is a hydrogen bond acceptor and donor, as denoted by the legends „isolated", „Acceptor (complex)", and „Donor (complex)", respectively. The line coloring indicates the different molecules in their isolated form (top) or in the complex (middle, bottom).

Interestingly, distinct configuration-dependent dynamics are observed. For the configuration with the memS being the hydrogen-bond acceptor (upper panel of Figure 3), though the net charge strongly oscillates with periods of ~9–~14 fs, there is no complete charge transfer from the memS to the amino acid. In the hydrogen-bond donor case (lower panel of Figure 3), a charge transfer is visible for all amino acids. A comparison of the complex geometries in the two H-bond configurations in Figure 1 indicates the importance of the NH_2 group of the memS in donor configurations in triggering a charge transfer between the probe and the amino acids. A comparison between memS-tryptophan and the other complexes in the donor configuration shows that the carboxyl group from the amino acid (which connects to C H from the memS via a hydrogen bond) appears to hinder the charge oscillations between the memS and the amino acids. For example, in both memS-tyrosine and memS-phenylalanine complexes in the donor configurations, the charge oscillations seem to occur on a very long time scale compared to the memS-tryptophan. The difference in the charge dynamics between memS-phenylalanine and memS-tyrosine in the donor configurations is related to the high electronegativity of the hydroxyl group connected to the aromatic ring in tyrosine. This appears to act against the flow of the additional electron back to the memS and thus results in a longer charge transfer time scale. The hydroxyl group should also be responsible for a small difference in the charge oscillations in memS-phenylalanine and memS-tyrosine in the acceptor configurations. Based on these observations, one can conclude that the most important role in the charge transfer between the probe and the amino acids is played by the amine group of the memS. This, when acting as a H-bond donor facilitates the charge transfer. The hydroxyl and carboxyl groups seem to have smaller effects on the charge transfer processes and only modify their time scales. As a test case, we have considered the interaction of memS-NH_2 with the carboxylic group of tryptophan. Interestingly, our computations show a reduced time scale charge oscillation along the N···HO bond validating the role of carboxylic group in the charge dynamics time scale.

Overall, based on the amino acid and configuration specificity in the charge dynamics, the memS probe shows a high potential not only in detecting different amino acids, but also revealing their topology with respect to the probe. The typical time scales for the charge transfer processes observed here are comparable to typical N H and C H stretching vibrations, i.e. ~10 fs (3000–3500 cm ^{1}). In principle, the former vibration at finite temperatures can affect the charge dynamics in both acceptor and donor configurations, while the latter should only affect the donor complexes (see Figure 1). Moreover, the longer charge transfer time scales observed in the phenylalanine- and tyrosine-memS complexes in the donor configurations (lower panel of Figure 3) might be comparable to that of a C=O stretching vibration, i.e. ~20 fs (1700–1750 cm ^{1}). All other vibrations in the complexes have longer time scales and should have a minimal effect on the observed charge dynamics. It can be expected that N H, C H, and C=O stretching modes modify the zero-temperature charge dynamics observed in this work. However, as discussed above, the CH···COOH part in phenylalanine-memS and tyrosine-memS seem to have only a secondary effect on the occurrence of charge transfer processes. Therefore, among the vibrations mentioned above, only the N H vibration of the amine group, either that of the memS or that of the amino acid can have an effect on the charge dynamics of the memS-amino acid complexes. The N H stretching vibration is common in all complexes with almost the same weight (there is only one amine group in the memS and only one in the amino acids). Accordingly, ultra-fast measurements at finite temperatures are

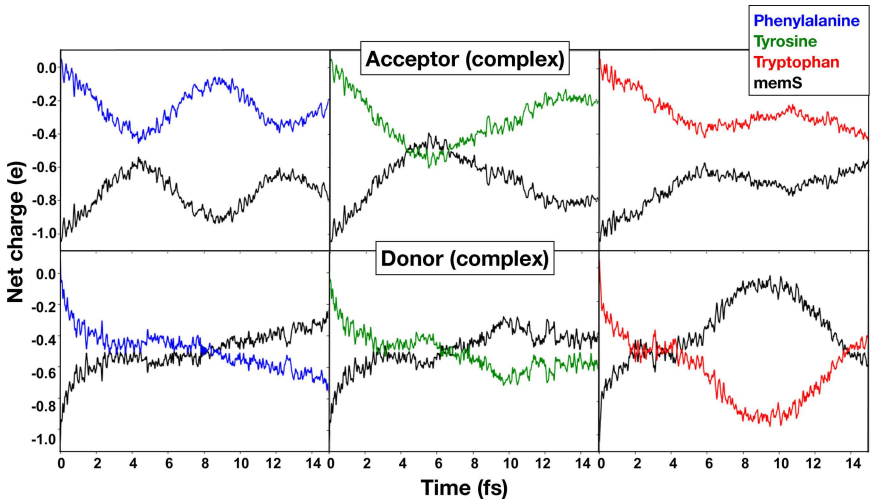

Figure 3. Electron transfer dynamics of an additional electron on memS within the complexes. The diamondoid acts as a hydrogen-bond acceptor (top) and donor (bottom) in its complex with an amino acid. The line coloring indicates the different amino acids in the complexes according to the legend.

expected to detect – on average – more transfer of charge from the probe to the amino acids in the donor configurations compared to the acceptor configurations.

4. Conclusions

In summary, we report on novel bio/nano molecular complexes made of a tiny modified diamond-like nanoparticle, memantine-thiol, and an amino acid, such as phenylalanine, tyrosine, and tryptophan. With the aid of *first-principles* density-functional theory calculations, we could unravel the structural, optical, and charge transfer properties of these complexes. The results are discussed for two distinct configurations, in which the probe (memS) acts either as a hydrogen-bond acceptor or a donor. We have found amino acid and configuration dependent characteristics in all cases. The single-molecule properties are enhanced through probing with the diamondoid and allow for a clear distinction of the biomolecule identity and topology with respect to the probe. In this respect, we provide a proof-of-principles study on nano/bio complexes in which the nano part acts as a probe for identifying the bio part. At a next step other factors, such as temperature, dynamics, and ionic/solvent effects need to be accounted for. One can expect that such factors would smear out the amino acid specific differences found here. However, it was recently shown that biomolecule specific signals still exist in the presence of a fluidic environment.[42] It remains to evaluate these effects also in the case of amino acids. In any case, though the influence of all these other factors is missing, this work contributes new ideas towards utilizing novel nanomaterials for efficient biosensing applications and can initiate further investigations along these directions.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: amino-acids · charge dynamics · computational chemistry · diamondoids · TDDFT

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