The role of a diamondoid as a hydrogen donor or acceptor in probing DNA nucleobases

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Received 14 July 2014
Published online: 24 October 2014 – © EDP Sciences / Società Italiana di Fisica / Springer-Verlag 2014

Abstract. It has been shown that diamondoids can interact with DNA by forming relatively strong hydrogen bonds to DNA units, such as nucleobases. For this interaction to occur the diamondoids must be chemically modified in order to provide donor/acceptor groups for the hydrogen bond. We show here that the exact arrangement of an amine-modified adamantane with respect to a neighboring nucleobase has a significant influence on the strength of the hydrogen bond. Whether the diamondoid acts as a hydrogen donor or acceptor in the hydrogen binding to the nucleobase affects the electronic structure and thereby the electronic band-gaps of the diamondoid-nucleobase complex. In a donor arrangement of the diamondoid close to a nucleobase, the interaction energies are weak, but the electronic band-gaps differ significantly. Exactly the opposite trend is observed in an acceptor arrangement of the diamondoid. In each of these cases the frontier orbitals of the diamondoid and the nucleobase play a different role in the binding. The results are discussed in view of a diamondoid-based biosensing device.

1 Introduction

Diamondoids are nanoscale hydrogen-terminated carbon cages [1], which have very recently attracted a lot of attention [2,3]. These nanostructures have shown strong potential for nanotechnological [4–7] applications and are believed to be suitable building blocks for functional nanostructures [8]. Amine-derivatives [9] of the lower diamondoid, adamantane, are already in use in pharmaceutical applications [10–12] as anti-viral [13] and anti-Parkinsons agents [14]. These derivatives have also been found to have good conductance properties depending on their relative orientation between two metallic electrodes [15]. Diamondoids also show a strong monochromatic emission [4,16], while self-assembled layers of these nanoblocks have negative electron affinity [17] and are promising for electronics applications. These small carbon clusters can be synthesized in different sizes and can be chemically modified. The optical and electronic properties of diamondoids can be tuned according to their size [18], doping [19,20], and functionalization [21,22]. In view of novel applications, diamondoids can be easily attached through thiol groups on nanoscale devices, such as gold electrode-surfaces [23,24]. Lower diamondoids and their derivatives have also been theoretically found to self-assemble into larger interlinked nanostructures [25].

A use of diamondoids in biotechnological applications is also currently being investigated. For this, their interaction with biomolecules, such as DNA, as well as the binding to these has been studied both theoretically and experimentally. A diamondoid-modified DNA in which a diamondoid is functionally linked to a nucleobase has also been synthesized without significantly affecting the double helical conformation of the biomolecule [26]. A synthetic method for a site-specific incorporation of diamondoids on DNA has been developed, showing an effect on characteristics such as the melting temperature of the modified DNA [27]. Diamondoid-based DNA assemblies have also the potential to act as 3-D scaffolds for novel nanotechnologies [28]. Recently, it was proposed, that small amine-modified diamondoids can potentially be used to sense DNA molecules through the nucleobase-specific hydrogen bonding that occurs between the two entities [29].

Motivated by some of the above diamondoid-DNA studies, we further investigate the non-covalent binding characteristics between small diamondoids and DNA molecules. These will be important in novel applications in which diamondoids are used as sensors of biomolecules. In order to be sensed, i.e. have its nucleotides be read-out, DNA should be single-stranded being thereby very flexible. In this respect in a sensing device it will assume many different conformations (either acting as a hydrogen donor or acceptor) which will affect its binding to a probe diamondoid. Along these lines, we investigate here the effect of the arrangement of a small probe diamondoid close
to a nucleobase. The study will be carried out on a small scale where we consider only single nucleobases. Our aim is to provide a proof of principles of the influence of these conformations on the binding characteristics of the two molecules at a quantum-mechanical level. For an exhaustive conformational scan a more classical method would be needed. In this work, we are mainly interested in the binding energies and the band-gap characteristics. We do not get into the detail of how charge is transferred along the hydrogen bond; this can be tackled in its full detail in a separate study.

2 Methodology

In this work, quantum-mechanical simulations within the density-functional-theory (DFT) scheme were performed to study the influence of the different arrangements of a small amine-modified diamondoid with respect to adjacent DNA nucleobases. All simulations were performed using the code SIESTA [30]. For the exchange and correlation functional, we use the VDW-DF2 functional [31] which includes a non-local correlation term and can better describe dispersion interactions compared to a semi-local generalized-gradient-approximation (GGA) functional [32]. A split valence triple zeta polarized basis set [33] was chosen to be accurate enough together with norm-conserving Troullier-Martin pseudopotentials [34]. The mesh cutoff parameter was 350 Ry. All geometries were optimized using a conjugate gradient algorithm and the structure was relaxed until the forces acting on the atoms were lower than 0.015 eV/Å. We have initially performed benchmark simulations for the Adenine-Thymine Watson-Crick base-pair. For this base-pair the interaction energy with the VDW-DF2 functional was found to be $-17.60$ kcal/mol compared to the value of $-16.37$ kcal/mol obtained in the literature [35]. The strength of the hydrogen bond is determined through the interaction energy of the diamondoid/nucleobase complex. This is obtained from the total DFT energy of the complex from which the total energies of the two units, diamondoid and nucleobase, when these are isolated have been subtracted. The basis set superposition error (BSSE) [36] was taken into account to correct for the fact that a finite basis set was used in our calculations. The interaction energy corresponds to the average of the BSSE-corrected energy without including deformations and the cohesive energy of the complex.

We consider the smallest amine-modified diamondoid, amantadine, which can provide additional acceptor/donor sites for its binding to the nucleobase. Amantadine is placed at approximately 3 Å close to a nucleobase. We have considered all four nucleobases, Adenine(A), Thymine(T), Cytosine(C), and Guanine(G) in the diamondoid/nucleobase complex. All complexes are structurally optimized. The notation we will use for the cases which correspond to amantadine being an acceptor or a donor in the following will be $X(B) - H$ or $X(B)$, respectively. The atomic labelling $X$ refers to the numbering in fig. 1. In order to implicitly model the presence of a stiff backbone in a single-stranded DNA molecule, we have added constraints to the N9 atoms of A and G and the N1 atoms of T and C. These are the atoms which should attach to a backbone (not included in the simulations) in a longer DNA strand. The configurations with constraints are in the following denoted as “fixed”. We have also repeated the simulations without imposing any constraints. The corresponding conformations are labeled as “free” in the analysis. For the bonding to an adjacent amantadine all atoms of the nucleobases which are involved in the hydrogen bonding in the Watson-Crick base-pairs A-T and C-G were considered. This choice does not exclude that other atoms of the nucleobases could hydrogen-bond to amantadine. Note, though, that it is not possible to scan all the different conformations that two molecules, amantadine and nucleobase, assume when they are close. We chose the physically most intuitive conformations.

3 Results-discussion

The specific characteristics of the diamondoid-DNA complex are next analyzed through the interaction energy and the electronic properties of the complex. For the latter, focus is given on the electronic density of states (eDOS), as well as the frontier orbitals, namely the highest occupied and the lowest unoccupied molecular orbitals, HOMO and

Fig. 1. Adenine-Thymine (A-T) and Guanine-Cytosine (G-C) Watson-Crick base-pairs. The atoms which will be involved in the different hydrogen bonding arrangements with amantadine and the atoms which are virtually connected to a backbone are labelled.
LUMO, respectively. After structural relaxation, all hydrogen bonds were in the range of 3 Å and the respective angles are relatively close to planar as will be revealed in the following. All structural details are given in figs. 2–10 for the “fixed” complexes and are compared to the “free” ones. In these figures it is also easily visible that in the “starred” (denoted as a “*”) conformations the same atoms are involved in the hydrogen bond, but in a different orientation as in the “un-starred” conformations. All results will be presented for the “fixed” conformations, unless otherwise stated.

## 3.1 Amantadine as an acceptor

We first focus on the binding features of amantadine with all four nucleobases in the case where the former acts as a hydrogen acceptor in the bonding. The hydrogen bond distance varies from 3.00(3.00) Å to 3.32(3.41) Å for the fixed/free nucleobases. The bond-angles are in the range 152.72–178.56° and 163.18–177.03° for the fixed and free nucleobases, respectively. The fact that in some cases the deviation from a planar bond is not negligible denotes that there must be an additional repulsion or attraction between the two molecules. For example in the C2(A)-H...
Fig. 5. Acceptor arrangements of amantadine with respect to a Guanine nucleobase.

<table>
<thead>
<tr>
<th></th>
<th>N1(G)-H</th>
<th>N1(G)-H*</th>
<th>N2(G)-H</th>
<th>N2(G)-H*</th>
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<td>3.07</td>
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<tr>
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<td>3.01</td>
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<tr>
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<td>172.06</td>
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</tr>
<tr>
<td></td>
<td>167.87</td>
<td>171.32</td>
<td>166.59</td>
<td>163.18</td>
</tr>
</tbody>
</table>

Fig. 6. Interaction energies and electronic band-gaps when amantadine acts as an acceptor in the hydrogen bonding with the various nucleobases. Relative band-gaps are shown with respect to the band-gap of an isolated amantadine molecule.
case the hydrogen atom which is bonded to C2 and is involved in the hydrogen bond is also slightly repelled by the closest to the hydrogen bond H atom of the diamondoid. In general also atoms of the cyclohexane rings of the nucleobases can interact with the donor/acceptor atoms of the diamondoid which is involved in the hydrogen bond, causing more complex multi-furcated hydrogen bonds.

A comparison between the “fixed” and “free” arrangements shows no specific trend. In some conformations, such as in C2(A)-H the differences are negligible, while in other these are significant. The largest differences were found in C2(A)-H and N2(G)-H*. In the C2(A)-H arrangement, the bond length/bond-angle in the fixed and free cases were 3.32 Å (167.57°) and 3.41 Å (175.04°), respectively. In N2(G)-H* the corresponding values were 3.16 Å (171.29°) and 3.08 Å (163.18°), respectively. No robust conclusion can be drawn from this comparison, as in C2(A)-H the hydrogen bond-length increases and becomes more planar in the free case, while in N2(G)-H* the bond decreases and becomes less planar. The flexibility of the nucleobase in the free case results in a reversed behavior.

Bifurcated hydrogen bonds, meaning that the single hydrogen atom participates in two, rather than one hydrogen bonds have been observed. Bifurcated hydrogen bonds were found in the N1(G)–H, N1(G)–H*, and N2(G)–H cases. In these, the two entities, amantadine and G are less co-planar as expected and as compared to the complexes in which amantadine acts as an acceptor. The bifurcated hydrogen bond was present in both the fixed and free cases. It is also not a single hydrogen bond in N3(T)–H, but at least an additional bifurcated hydrogen bond. All bifurcated bonds contribute to the interaction energy. It is, though, difficult to extract the contribution from each single hydrogen bond, as the hydrogen bond energies are not additive in such networks [37].

An additional interesting feature of the hydrogen bonding between amantadine and the nucleobases is related to the electronic properties of the complexes. The frontier orbitals, HOMO and LUMO, of all the “fixed” complexes in the cases in which amantadine acts as an acceptor, are sketched in figs. 2–5. It is interesting to observe that both the HOMO and LUMO levels of the complexes are controlled by the nucleobases. This is directly visible since both levels are only located on the nucleobases. The only deviation from this observation was found in the “fixed” N3(T)–H case. We do not see this deviation, rather the HOMO and LUMO levels are again located only on T in the N3(T)–H free case. This deviation for the N3(T)–H fixed case might be an artifact of the constraints imposed on the nucleobase, which, though, do not seem to affect significantly the structural properties, as the bond-length has the expected value of 3.04 Å and the bond is almost planar.

The HOMO and LUMO levels of the amantadine/nucleobase complexes also define their electronic band-gaps. These are summarized together with the interaction energies for all the amantadine acceptor cases in fig. 6. In this figure the relative values for the complexes with respect to the electronic band-gap of an isolated amantadine are given. In a sensing device, the diamondoid will be the probe, thus we take this as a reference for the comparison. According to our calculations, the electronic band-gap of an isolated amantadine is 5.35 eV. All interaction energies were obtained after an energy minimization of the
complexes and are in the range of $\approx (-4)\,(-14)$ kcal/mol. These correspond to hydrogen bonds of weak up to moderate strengths. It can also be observed that for the N3(T)–H fixed conformation which shows a deviation in the HOMO/LUMO features as mentioned earlier, the strength of the hydrogen bond is moderate and not weak. This denotes again that the deviation which might be based on the application of the constraints does not affect significantly the strength of the bonding.

Comparison of complexes in which the same atoms are forming the hydrogen bond, but in different conformations (“starred” and “un-starred”) shows that these have very similar electronic band-gaps, but the strength of the hydrogen bond might differ considerably. For example, the N2(G)–H and N2(G)–H* cases have interaction energies of $-10.58$ kcal/mol and $-5.61$ kcal/mol, respectively. These also lie in different ranges, as the former corresponds to a moderate hydrogen bond, while the latter to a weak bond. Accordingly, the N2(G)–H* is a less favorable arrangement in view of sensing applications, as in this case the hydrogen bond might be too weak to measure or similarly its life-time might be too short. On the other hand, the interaction energies of the N1(G)–H and N1(G)–H* complexes are similar and equal to $-12.54$ kcal/mol and $11.37$ kcal/mol, respectively. Their band-gaps are also almost identical, 3.82 eV and 3.83 eV, respectively. For the N2(G)–H and N2(G)–H* conformations, the band-gaps are identical and equal to 3.78 eV. Overall, though as mentioned before, the strengths of the hydrogen bonds differ for the various arrangements of amantadine as an acceptor, the electronic band-gaps are very close (between 3.63 and 3.83 eV) and only slightly dependent on the bond strength and orientation.

### 3.2 Amantadine as a donor

Next, we turn to arrangements in which amantadine acts as a donor to the hydrogen bond with the neighboring nucleobase. The results are summarized in figs. 7–10. In these cases, we observe a smaller deviation from planar bonds compared to the acceptor arrangements of the amantadine, as all the bond-angles were in the range of $174.21^\circ$–$179.50^\circ$. The hydrogen bond-lengths lie in the range of 3.07–3.19 Å. The dispersion of these bonds is also smaller than the one in the acceptor arrangements. A comparison of different arrangements for the same nucleobase reveals also some interesting features. As an example, though the bond length of the O4(T) conformation is larger (3.19 Å) than that of O2(T) (3.10 Å), the bonding in the former case is stronger as it is less bent. The bond-angle is $179.50^\circ$ in O4(T) and $174.99^\circ$ in O2(T), while the interaction energy in O4(T) is slightly larger than in O2(T) ($-3.94$ eV compared to $-3.56$ eV, respectively).

Comparison of the same hydrogen bonded complex in different arrangements, such as in O2(C) and O2*(C) reveals that the structural properties of the bond vary. The bond-length and bond-angle were found to be 3.07 Å and 178.87° in O2(C) and 3.16 Å and 174.91° in O2*(C). Hence, in the former case the bond is shorter and slightly
Fig. 11. Interaction energies and electronic band-gaps when amantadine acts as a donor in the hydrogen bonding with the various nucleobases. Relative band-gaps are shown with respect to the band-gap of an isolated amantadine molecule.

more planar than in the latter case. Imposing the constraints on the nucleobases in some conformations shows variations with respect to the free case, while in others the differences are almost negligible. The largest differences were found in N1(A) and O6(G). In the N1(A) arrangement, the bond length (bond-angle) in the fixed and free cases were 3.13 Å (176.91°) and 3.23 Å (173.03°), respectively. In O6(G) the corresponding values were 3.11 Å (175.12°) and 3.17 Å (171.85°), respectively. In both cases (N1(A) and O6(G)) the bond in the free case was increased by almost 0.1 Å, while it became about 3° less planar with respect to the fixed conformations. This trend is directly related to the higher flexibility of the nucleobase in the free case. It is interesting to observe that in both acceptor and donor arrangements of the diamondoid the largest deviations between the fixed and free cases were found in the complexes including the largest nucleobases, A and G, the purines. These differences link to a slightly different level of flexibility of these with respect to the smaller nucleobases, T and C, the pyrimidines.

Inspection of the frontier orbitals for the “fixed” complexes in figs. 7–10 shows a completely different picture compared to the arrangements of the diamondoid as an acceptor in the hydrogen bond. In all cases we have studied here, in which amantadine acts as a donor, the frontier orbitals are separated. The HOMO state is always associated with the diamondoid, while the LUMO resides on the nucleobases. No deviation from this observation was found. The difference in the distribution of the frontier orbitals between the acceptor and donor cases strongly implies that the underlying mechanisms in forming the hydrogen bonds differ. When amantadine acts as a hydrogen acceptor, the electronic properties and characteristics of the hydrogen bond are defined mainly by the nucleobases, implicitly taking into account the diamondoid. In the opposite case when amantadine acts as a donor, the separate electronic features of both units, amantadine and nucleobase directly map on the common features of the complex.

The interaction energies and electronic band-gaps of all the cases we have studied in which amantadine acts as a donor depicted in fig. 11 also show significantly different trends than in the acceptor conformations. The electronic band-gaps are again all shown relative to the band-gap of an isolated amantadine molecule. The two main striking differences are that the interaction energies in this figure are in the weak range, between −3.56 kcal/mol and −7.01 kcal/mol, while the variations in the electronic band-gaps are larger and lie in the range 2.15–3.07 eV. This picture is qualitatively and quantitatively very different from the data shown in fig. 6. Comparison again of the “starred” and “un-starred” conformations, O2(C) and O2(C)*, reveals a large difference in the interaction energies, which are −4.59 kcal/mol and −7.01 kcal/mol, respectively. The variation in the electronic band-gaps which are 2.23 eV and 2.15 eV, respectively is smaller. These differences can be again associated with the different level of planarity of the hydrogen bond, as the respective bond-angle is 178.87° and 174.91°, respectively.

Finally, the electronic density of states (eDOS) of different arrangements of representative diamondoid/nucleobase complexes are compared. The results are depicted in fig. 12. In this figure, all results are shifted with respect to the LUMO state of the reference, an isolated amantadine. The LUMO state of this reference is set at zero energy. The binding of amantadine to a nucleobase shrinks the electronic band-gap by introducing states into the band-gap of the isolated amantadine. In the N3(T)-H acceptor conformation the HOMO level is more populated than the HOMO levels of the other conformations shown in the figure. This is in agreement with our finding that in the acceptor conformation of the diamondoid, the HOMO levels
that the HOMO and LUMO levels of the complex are associated solely with the amantadine and the nucleobase, respectively. In the acceptor arrangements, the hydrogen bonding imposes states only in the band-gap of the isolated amantadine and not in that of the isolated nucleobase. This feature is in turn associated with the HOMO and LUMO levels of the complex being solely assigned to the nucleobase.

4 Summary

Using quantum-mechanical simulations we were able to reveal the characteristics of binding, through hydrogen bonds, a small diamondoid to DNA nucleobases. Specifically, we have focused on the different arrangements of a diamondoid next to a nucleobase. In order to provide donor/acceptor sites for the hydrogen bonding, the diamondoid had to be modified with an amine group. We have observed that the use of a diamondoid as an acceptor or a donor in the hydrogen binding to the nucleobase leads to qualitatively very different binding characteristics. We have quantified these differences showing that when a diamondoid acts as an acceptor, the binding is 2-3 times stronger than in the donor case. On the other hand, in the former case no significant differences were found in the electronic band-gaps, which are in the range 1.49–1.73 eV. The distribution of the band-gaps is broader, 2.18–3.21 eV, when amantadine acts as a donor.

In the acceptor arrangement of the diamondoid, both the HOMO and LUMO levels of the diamondoid/nucleobase complex reside on the nucleobase. The picture changes in the donor arrangement of the diamondoid, in which the HOMO is associated with amantadine and the LUMO with the nucleobase. We have revealed the qualitatively different electronic features of the binding to a nucleobase when the diamondoid acts as a hydrogen donor or an acceptor. According to this analysis, though the interaction energies are lower when the diamondoid acts as a donor (i.e., the nucleobase is the hydrogen acceptor) the electronic features such as the band-gaps are more distinct, implying a higher sensing possibility through electronic means.

The results presented in this work have a high impact on novel diamondoid-based biosensing devices. In such devices, a diamondoid can be attached and increases the sensing ability of biomolecules in the near vicinity of the diamondoid. As evident in the previous analysis, the arrangement of the biomolecule units, i.e., the nucleobases, close to the diamondoid is crucial in order for the diamondoid-sensing device to electrically read these out. In this respect, it is important to control the biomolecules in the device so that they can arrange themselves in such a way to act as a hydrogen acceptor in their binding to the probe-diamondoid. For this an electric field would be needed. The strength of this field and the way it can Indeed control the biomolecule’s conformation needs to be still investigated. In addition, an open question would be in which way the results presented here would be affected by...
a fluidic environment as the one in which a biosensing device would operate in. The interaction of the diamondoid with other units (neighboring nucleobases, backbone) of a larger flexible single DNA strand would also alter the binding characteristics of the diamondoid/nucleobase complex. The presence of a material surface (e.g. gold electrodes) on which the diamondoid would be attached in such a device needs also to be taken into account in evaluating the electronic properties of the probe-diamondoid/DNA complexes studied here. The life-times of the hydrogen bonds are also of high importance, as low interaction energies could imply a short life-time of the bond not allowing it to be efficiently sensed. Nevertheless, the importance of the arrangement of the probe molecule and the biomolecule to be sensed is of crucial importance and should be further investigated in view of the above points.

The authors acknowledge support from the German Funding Agency (Deutsche Forschungsgemeinschaft-DFG) as part of the collaborative network SFB 716 “Dynamic simulation of systems with large particle numbers” (“Dynamische Simulation von Systemen mit großen Teilchenzahlen”).

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