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Benchmark investigation of diamondoid-functionalized electrodes for nanopore DNA sequencing

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Abstract
Small diamond-like particles, diamondoids, have been shown to effectively functionalize gold electrodes in order to sense DNA units passing between the nanopore-embedded electrodes. In this work, we present a comparative study of Au(111) electrodes functionalized with different derivatives of lower diamondoids. Focus is put on the electronic and transport properties of such electrodes for different DNA nucleotides placed within the electrode gap. The functionalization promotes a specific binding to DNA leading to different properties for the system, which provides a tool set to systematically improve the signal-to-noise ratio of the electronic measurements across the electrodes. Using quantum transport calculations, we compare the effectiveness of the different functionalized electrodes in distinguishing the four DNA nucleotides. Our results point to the most effective diamondoid functionalization of gold electrodes in view of biosensing applications.

Keywords: DNA sequencing, quantum transport, density functional theory, diamondoids, nanopore, nanogap

1. Introduction
Diamondoids are tiny diamond caged molecules with hydrogen terminations [1, 2] which occur in small amounts in petroleum as well as in rock crystals [3]. These small diamond-like cages form a family of nanoscale building blocks [4, 5] of which the smallest is known as adamantane. By modifying diamondoids with synthetic techniques, they can be selectively functionalized on surfaces [6]. The electronic, optical, mechanical and thermal properties of these diamondoid surfaces exhibit features of both single-crystal diamond and nanomaterials [7, 8]. It is also possible to tune the optical gap of these cages by functionalization and doping [9–11]. Diamondoids and their functional derivatives [12] have been proposed for applications such as opto-electronic devices including high-efficiency field emitters [12, 13, 17], single molecule biosensors [14], and as pharmaceutical agents [15]. Diamondoids can self assemble [16] and form self assembled layers on surfaces [17, 18] and ordered phases in carbon nanotubes [19].

Derivatives of diamondoids have been shown to form hydrogen bonds to DNA nucleobases [20, 35] and efficiently functionalize gold electrodes to sense DNA nucleobases and their mutations [14, 21]. These functionalized electrodes can be embedded into nanopores in order to produce DNA sequencing devices [22–24]. DNA molecules can be electrophoretically driven through such nanopores giving rise to nucleobase transverse current signals across the nanopores.
Using a functionalization in the nanopore has the potential to enhance these transverse signals. It is crucial to find small molecules of the size of the nucleobases, which can functionalize nanopores and indeed increase the signal-to-noise ratio in the electronic current measurements. Such an increase is required to facilitate an almost error-free reading-out of the DNA nucleotides and promote sequencing.

Work along these lines is carried out in view of choosing a molecule for efficient functionalization of electrodes embedded in nanopores. The term ‘efficient’ is here meant as enabling a selective read-out of the nucleotides through these electrodes which lead to distinguishable electronic signals for each nucleotide. To this aim, lower amine-doped diamondoids are scanned and are attached to gold electrodes, which are in turn investigated for their biosensing properties.

In this work, we perform a detailed comparative investigation of different diamondoid-functionalized electrodes in order to point to the functionalizing molecule with the most efficient sensing properties. The remainder of this paper is organized as follows: the methodology and set-up of the functionalized sensing electrodes is first presented, followed by the comparative analysis of the results for different electrode functionalizations. Finally, we discuss the impact of these results and conclude.

2. Methodology

In order to assess the sensing efficiency of diamondoid-functionalized gold electrodes such as the ones shown in figure 1 (top row) we examine their electronic and transport properties when DNA nucleobases are placed in the gap between them. The three different amine-modified diamondoid derivatives are shown in figure 1 (middle row), rimantadine, amantadine, memantine are used for the functionalization of the electrodes. These will be referred to as ‘rim’, ‘ama’, and ‘mem’, respectively, in the following text. The four DNA nucleotides shown in figure 1 (bottom row), deoxyadenosine monophosphate, deoxythymidine monophosphate, deoxyctydine monophosphate, and deoxyguanosine monophosphate are placed in the electrode gap. We will refer to these simply as ‘A’, ‘T’, ‘C’, and ‘G’, respectively. Each nucleotide interacts with the functionalized electrodes through hydrogen bonds with the functionalizing diamondoid. An extensive analysis of amantadine-functionalized gold electrodes was carried out and presented elsewhere and is therefore not included here. Results for the amine-modified electrodes will only be used for comparison whenever applicable.

The systems modeled include two Au(111) electrodes, left and right, and the scattering region of gold. The three outer layers of Au(111) on either side of the electrodes form the semi-infinite lead. The ten inner layers of Au(111) along with the embedded molecules form the device region as sketched in figure 1 (top row). A gap of a fixed distance d separates the two electrodes. This gap is sufficiently large to include the functionalizing diamondoid and a nucleotide. We have tested that for distances d > 4 Å, no tunneling current exists [14]. Note, that we investigate only the single-functionalized case, in which the diamondoid is chosen to functionalize only the left electrode. The right electrode remains unmodified. The transport direction occurs from the left electrode to the right one in the positive z-direction as shown in figure 1 (top row). The nucleotides are initially placed close to the diamondoid at distances which would lead to the formation of hydrogen bonds [14]. The functionalizing diamondoid and the nucleotide interact through hydrogen bonds. In this binding, amantadine and memantine are always donors. In the rimantadine case, though, the diamondoid can be a donor or an acceptor in the hydrogen bonding to the nucleotides depending on the relative arrangements of these two molecules. For the rimantadine case, then, we need to account for the two different arrangements in which rimantadine acts as (a) an acceptor (‘rim-1’) or (b) a donor (‘rim-2’) to the hydrogen bonding. These two configurations are depicted in figure 2.

A density functional theory scheme as implemented in SIESTA was used to investigate the systems. The electronic transport calculations were carried out using the non-equilibrium Green’s functions approach within TranSIESTA. The transport setup can be seen in figure 1. The zero-bias Green’s function can be written as:

$$\mathcal{G}(E) = [E \times S_S - H_S[\rho] - \Sigma_L(E) - \Sigma_R(E)]^{-1},$$

where $S_S$ and $H_S$ are the overlap matrices and the Hamiltonian for the scattering region, respectively. The terms $\Sigma_L(R)$ are self-energies to account for the semi-infinite leads. $E$ and $\rho$ are the energy and charge density, respectively. Consequently, the transmission $T(E)$ can be written as:

$$T(E) = \text{Tr}[\Gamma_L(E)\mathcal{G}(E)\Gamma_R(E)\mathcal{G}^\dagger(E)].$$

The generalized gradient approximation of Perdew–Burke–Erzernhof (PBE-GGA) and the norm-conserving Troullier–Martins pseudopotentials were used. For the expansion of the Kohn–Sham states, a double-$\zeta$ polarized basis-set (DZP) for the nucleotides, diamondoid derivatives and a single-$\zeta$ with polarized (SZP), with $(5d^{10}, 6s^1)$ orbital states for the gold atoms were considered. These basis sets have been proven efficient in simulating similar systems. An energy shift of 0.01 Ry with a real space sampling grid (mesh cutoff) of 200 Ry, and 5 × 5 × 1 k-points using the Monkhorst–Pack scheme were also used. The ionic relaxations were performed until the net atomic forces are smaller than 0.01 eV Å$^{-1}$. For the device functionalization, a supercell of 14.8 × 14.8 × 40.8 Å (14.8 × 14.8 × 39.8 Å) for rimantadine (memantine) was used. Five unit cells in the x and y directions and ten along the z direction with a gap of 19 Å (18 Å) for rimantadine (memantine) were repeated to build the supercell.

For the two semi-infinite gold electrodes, the (111) surface was taken and structurally relaxed. A lattice constant of 4.186 Å was obtained from the relaxation and compares well with literature data. In the second step, a thiolated amine-modified diamondoid (figure 1 (middle row)) is placed close to the left gold layers and relaxed until the thiol group of the matrix...
diamondoid was bonded to the gold surface. Finally, a nucleotide was added close to the diamondoid with an orientation favoring the formation of hydrogen bonds with the diamondoid. The sugar-phosphate group is pointing towards the right inner gold layer. The choice of the distance between the gold layers is based on the condition that even the largest two nucleotides (A and G) could fit inside the electrode gap. These specific conformations are chosen for consistency to our earlier studies [20].

3. Results and discussion

We begin our analysis with the electronic transmission curves for all cases. The calculated transmission for the rimantadine- (both acceptor and donor conformations) and the memantine-functionalized electrodes are summarized in figure 3. The data for all four nucleotides are included in the graphs. In these, the shaded areas correspond to a region including the most prominent peaks for the nucleotides. These areas are considered as the energy window for scanning the sensing properties of the diamondoid-functionalized electrodes and will be used for the comparison of the efficiency of each diamondoid.

Inspection of figure 3 reveals that the transmission hierarchy at the Fermi energy, $T(E_F)$, for rim-1 follows the trend $G > A > C > T$. The respective peaks are found in the range $10^{-2}–10^0$. On the other hand, rim-2 and mem exhibit different $T(E_F)$ hierarchy, including a much wider spread, namely $C \gg G \gg T \gg A$ and $C \gg G > T \gg A$, respectively. For rim-2 the values of the $T(E)$ peaks differ and lie in the range $10^{-3}–10^{-1}$. For mem, the $T(E)$ peaks differ by one order of magnitude, but the T and G peaks have similar values (figure 3(c)). Note that the relevant hierarchy for amantadine was found $G \gg C \gg A > T$ with values for the peaks in $T(E)$ in the range $10^{-3}–10^{-1}$ [14]. The fact that the peaks for all nucleotides in all functionalization cases are clearly distinguishable points to efficient and device-specific sensing of the nucleotides.

The zero bias conductance, which is the transmission at the Fermi energy, could give another indication of whether sensing is efficient or not. It is necessary for the discrimination of the nucleotides that the zero bias conductance for all cases is distinguishable. The results in figure 3 show that
these are indeed distinguishable at the Fermi energy. There is an overlap of the zero bias conductance values for T and G and the memantine functionalization, as well as A and C in the rim-1 functionalization. In the amantadine functionalization, the curves at the Fermi level for A and T are very close together, while those for C and G are clearly distinguishable \[14\]. In order to deal with similar or overlapping signals for the zero bias conductance at the Fermi energy, we turn to gating sensing. Accordingly, the resonant peaks for each nucleotide and the different functionalizations were sampled. This is similar to the experimental case of tuning the Fermi energy through gating in a specific energy region (the shaded regions in figure 3) where resonances arising from the different nucleotides occur. Nucleotide-specific transmission peaks are evident in the gating windows in all functionalized electrodes studied here. Our results suggest that it is possible to identify the nucleotides with the functionalization diamondoids by tuning the Fermi energy in a nucleotide-specific way. Overall, the memantine-functionalized electrodes seem to have the best potential for sensing as the transmission peaks for the four nucleotides are clearly distinguishable compared to the rim-1, rim-2, and ama cases. In the the rim-1, rim-2, and ama cases, some peaks are very close to each other and would not allow a clear identification of the respective nucleotides. In the following discussion, we focus on the analysis of the mem-functionalization.

As discussed before, the transmission peaks in the mem case in figure 3(c), are clearly distinguishable. In the following, we illustrate the protocol to identify one particular nucleotide of the four types, which we call the reference
nucleotide, and distinguish it from the other possible three nucleotides, which we refer to as non-reference nucleotides. Accordingly, in order to identify for example G, which corresponds to the first peak below the Fermi energy in the shaded region, a gating voltage of \( V_g = -0.46 \) V would need to be applied in order to shift the Fermi level to that energy. In order to understand the electronic characteristics of the mem-functionalized gold electrodes, we turn to the zero-bias scattering state eigenchannel wavefunctions (EWF) \[33\]. At \( V_g = -0.46 \) V these are shown in figure 4.

For the reference nucleotide G, the real part of the EWF is delocalized over the whole scattering region. For the non-reference nucleotides (A, T, and C), the EWF are mainly located at the diamondoid site and the functionalized side of the electrodes. In those cases, only a small contribution on the nucleotides sites is seen. Accordingly, for G, there is a clear and enhanced strong coupling of the left and right electrodes, memantine, and the G nucleotide indicating higher probability of electrons flowing at this referred gate voltage. For A, T, and C, though the EWFs clearly decay as we move from the left electrode to the right, resulting in negligible transmission.

This qualitative analysis can be quantified through the concept of sensitivity \[14\], which reveals how well resolved the conductance of a reference nucleotide will be with respect to other nucleotides:

\[
S(V_g) \% = \left| \frac{g_{\text{ref}} - g_x}{g_{\text{ref}}} \right| \times 100,
\]

where \( g_{\text{ref}} \) is the reference zero-bias conductance under application of a given gating voltage, which corresponds to the transmission peak of a specific nucleotide at a gating voltage \( V_g \), and \( g_x \) is the gating conductance, at the same gate voltage for any other nucleotide (excluding the reference nucleotide). Following the discussion on the electronic wavefunctions and the mem case, we begin the analysis with the sensitivity \( S(V_g) \) for recognizing G. This was found to be at least six orders of magnitude higher than A, T, and C as long as the gating voltage is very close to \( V_g = -0.46 \) V (the energy corresponding to the first peak for G in the transmission graph in figure 3(c)). The other two nucleotides, T and C, would easily be recognized as long as the device is tuned at the correct gating voltage. Within the same context and for the same device, using a gating voltage of \( V_g = -1.12 \) V which corresponds to the transmission peak of A in figure 3(c) would resolve A by at least two orders of magnitude more than the other nucleotides T, C, and G. Overall, the sensitivity of a memantine-functionalized nanogap was found to be higher than the nanogap functionalized by other diamondoids investigated as part of this study.

The results for all diamondoid functionalizations are summarized in figure 5. The best and worst identified nucleotide from our analysis are taken as examples (see figure 3). These are G and T, respectively. G has in all cases a well defined transmission peak, while the peak for T is often almost overlapping with the peak of another nucleotide. In figure 5, the gate voltage corresponding to the transmission peak of T or G for each of the diamondoid cases is shown. It becomes clear from the figure, that T is least distinguishable with the ama-functionalized electrodes, as it is less than 2 orders of magnitude better resolved than C (top panel in figure 5(c)). Also, using the rim-2 setup, T can be 3 orders of magnitude better resolved than A, C, and G, which at this gate voltage have a very similar conductance and their peaks cannot be separated (top panel in figure 5(b)). On the other hand, G can be best identified with a mem-functionalized device and up to 8 orders of magnitude better than A, 7 orders of magnitude better than T, and about 6 orders of magnitude better than C (bottom panel in figure 5(d)). With the ama-functionalization, which was not very efficient for T \[14\], G can be six orders of magnitude better identified than T at the gating voltage corresponding to the transmission peak of G. Overall, the sensitivity analysis in figure 5 clearly underlines the differences in an efficient identification of the DNA.

**Figure 4.** Eigenchannel plot for memantine functionalized gold(111) for the four nucleotides at \( V_g = -0.46 \) V corresponding to the first transmission peak of G below the Fermi level. For clarity all wavefunctions are plotted for the same isovalue, with positive values of the wavefunctions in red and negative in blue. Both the real and imaginary contributions to the EWFs are shown, but the imaginary part is either too small or below the cutoff and is not clearly visible in most of the panels. For the color coding of the atoms, the reader should refer to the color bar in figure 1.
nucleotides with the different diamondoid-based gold electrodes. A good choice of the diamondoid is essential for a clear identification of the nucleotides.

4. Conclusions

In this work, we have presented a comparative analysis of diamondoid-functionalized Au(111) electrodes. Specifically, we investigated different diamondoids functionalizing the electrodes between which the four canonical nucleotides are inserted. In these setups, the diamondoids act either as donors or acceptors in their binding to the nucleotides. The choice of the diamondoids is based on the variability in sizes and modifications these can assume. Chemical modification of the electrodes is expected to increase the capture time of the nucleotides in the nanogap due to the formation of hydrogen bond bridges of the nucleotides with the functionalized electrodes. Stabilizing the DNA within the functionalized gold nanogap is expected to also reduce noise in the electrical measurements. Note, that stabilization is needed as the DNA is very flexible and is fluctuating in the nanogap. This work, though, has not accounted for these fluctuations as the main focus has been the comparison of different functionalizations of gold nanogaps based on the most prominent hydrogen bond bridges between the nucleotide and the functionalizing diamondoid. It is also expected that the surrounding environment should influence the transmission spectra. This aqueous environment was not considered here, but will be the subject of a separate study. Note, that our work is based on the suggestion that functionalized electrodes [22, 23] have a high potential to improve the read-out signal for DNA. Such electrodes can be efficiently embedded in a silicon nitride nanopore. These kinds of nanopores are one among a variety of possible approaches to electrical DNA sequencing.

The electronic transmission of the different diamondoid-functionalized gold nanogaps were compared here. The diamondoid derivative known as ‘memantine’ has shown a higher nucleobase-specific hydrogen bonding, which lead to a better read-out of the DNA nucleobases with the mem-functionalized device. The sensitivity of such a device was also analyzed and revealed that a careful choice of the functionalizing diamondoid can resolve by up to eight orders of magnitude a specific nucleotide with respect to the other nucleotides. This is possible as long as the device operates at the respective gating voltage for a given reference nucleotide. This voltage enhances significantly the coupling of the left and right electrodes allowing the generation of a large transverse tunneling current across the nanogap. This strong coupling was found in all devices studied here, whenever the gating voltage corresponds to a transmission peak. It remains to be shown in which way the observations made here will be altered when the memantine-functionalized electrodes are inserted into a nanopore containing a salt solution. Specifically, the longitudinal electric field which drags the DNA through such a nanopore [34] and the transverse electric field for measuring the transverse tunneling current will introduce additional complex features into the read-out device. These factors should be further probed in order to realize a diamondoid-functionalized nanopore for biosensing applications.

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