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Benzo-homologated nucleobases in a nanotube-electrode set-up for DNA sequencing

Miguel Fuentes-Cabrera, Vincent Meunier and Bobby G Sumpter

Center for Nanophase Materials Sciences, Oak Ridge National Laboratory, PO Box 2008,
Oak Ridge, TN 37831-6494, USA

and

Computer Science and Mathematics Division, Oak Ridge National Laboratory, PO Box 2008,
Oak Ridge, TN 37831-6494, USA

E-mail: fuentescabma@ornl.gov

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Abstract

Motivated by the possibility that the conductivity signatures of benzo-homologated DNA bases could be used to sequence DNA, we have investigated the conductivity properties of these bases when they are non-covalently sandwiched between two (5, 5) nanotube electrodes. It is found that these bases conduct poorly, making it very difficult to distinguish them. An analysis of the changes in the conductivity of benzo-adenine as a function of the distance between the tips of the nanotubes revealed that, even though the conductance increases by four orders of magnitude when the electrodes are brought closer together, the net conductance remains rather small. These results suggest that benzo-homologated bases, despite having smaller HOMO–LUMO gaps than their natural counterparts, when non-covalently bound to the electrodes cannot be used to sequence DNA by means of conductivity measurements.

1. Introduction

The need for sequencing DNA in a timely and economical manner has recently led to the consideration of whether DNA could be sequenced in a set-up that measures the transversal conductivity of a single-stranded DNA (ssDNA) that is threaded in between two gold nano-electrodes [1a, 2]. The basic concept is that the DNA bases, adenine (A), cytosine (C), guanine (G) and thymine (T), could be distinguished in terms of their conductivity properties. This seems reasonable, for the bases have different HOMO–LUMO gaps, which in principle should lead to different conductivities. However, Zikic *et al* [2] have shown that in this set-up, having different electronic properties does not guarantee distinguishable conductivity signatures. Instead, the flexibility of the ssDNA makes it very difficult to control the geometry of the bases when they are positioned between the nano-electrodes, and this geometrical uncertainty ends up making the bases indistinguishable.

This problem could be solved in two ways. First, one can suggest a new set-up in which the geometrical uncertainty is

reduced. For example, Meng *et al* [3] have recently proposed anchoring the ssDNA by attaching it to a carbon nanotube (CNT) and then sequencing the polymer by probing the electronic structure of the CNT/ssDNA system with scanning tunneling microscopy. Second, one could still use the same set-up, but thread not a natural ssDNA but a molecule with the same sequence information and better transversal conductivity. For example, one could map a natural-ssDNA into an artificial-ssDNA that is made up of artificial bases whose HOMO–LUMO gaps are smaller than those of the natural ones. The main idea is that the smaller HOMO–LUMO gaps could increase the transversal conductance, offsetting the geometrical uncertainty. Here we focus on this second option, in particular in the benzo-homologated bases and the artificial duplexes they make up [4].

Figure 1(a) shows the DNA bases and figure 1(b) shows the corresponding benzo-homologated bases xA, xC, xG and xT; we refer to the latter as x-bases. An x-base is larger than its natural counterpart, ca. 2.4 Å, due to the lateral extension introduced by the benzene ring. By means of a

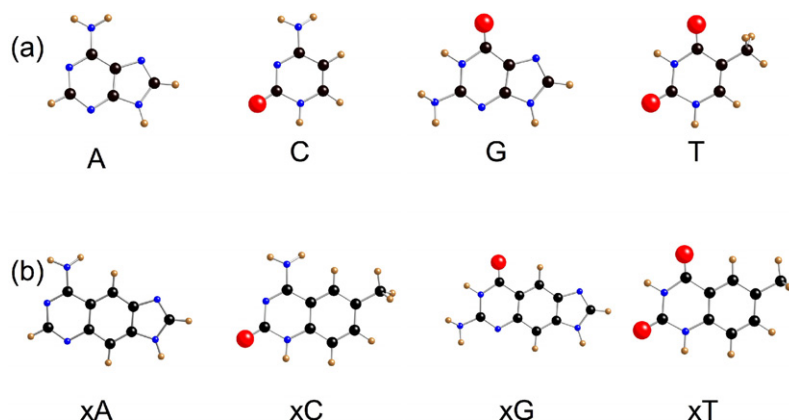


Figure 1. Natural and benzo-homologated DNA bases. (a) The natural bases; (b) the benzo-homologated bases, referred to here as x-bases. Color code: oxygen, red; carbon, black; nitrogen, blue; hydrogen, maroon.

Table 1. HOMO and LUMO orbital energies and HOMO–LUMO gap for the x- and natural bases as calculated with LDA and the basis set 6-31G**. The energies are given as relative to T's HOMO. All the energies are in eV. xA, xC, xG and xT stand for benzo-adenine, benzo-cytosine, benzo-guanine and benzo-thymine.

Base	HOMO	LUMO	Gap
A	0.4612	4.345	3.88
C	0.4022	4.0364	3.63
G	0.710	4.708	4.00
T	0.000	3.87	3.87
xA	0.616	3.518	2.90
xC	0.478	3.518	3.04
xG	0.790	3.949	3.16
xT	0.119	3.523	3.40

DNA synthesizer, the x- and natural bases have been combined to form different xDNAs. For example, an xDNA has been made that contains all 8 bases, i.e. A, C, G, T, and xA, xC, xG, xT [4j]. In this xDNA, the x-bases are placed either on one strand alone or alternate from one strand to the other, but regardless of their position they always pair with a natural base in a Watson–Crick-like arrangement, i.e. xA only pairs with T, xT with A, xC with G, and xG with C.

The reason why we consider the benzo-homologated bases is twofold. First, it has been shown that extending the DNA bases by fusing them to benzene is an efficient way of reducing the HOMO–LUMO gaps [5a, 6–8]. Table 1 shows that the HOMO–LUMO gap of the x-bases can be as much as 1 eV smaller than those of the natural counterparts (see xA and A in table 1). Second, because x- and natural bases pair up in a Watson–Crick-like scheme and in xDNA duplexes all the x-bases can be placed in the same strand, one could map the sequence of a natural ssDNA into that of a complementary single-stranded xDNA (ssxDNA). The overall implication is that one could try sequencing a natural ssDNA by measuring the transverse conductivity of a complementary ssxDNA that is threaded between two nano-electrodes.

Here we probe this hypothesis by computing the conductivity of the four x-nucleotides when placed in between two nano-electrodes made up of capped (5, 5) CNTs. We considered electrodes made of capped (5, 5) CNTs instead of Au for three reasons. First, these nanotubes are metallic,

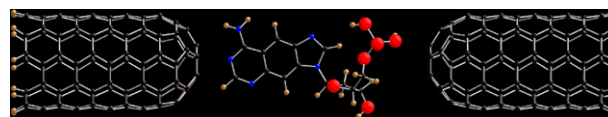


Figure 2. CNT/xA/CNT system when the CNT tips are 17.402 Å apart. The xA base is relaxed.

which is a necessary requirement for performing conductivity calculations. Second, in a localized-atom-centered all-electron basis set approach, such as the one used here, C is currently far better represented than Au. And third, we are investigating whether the x-nucleotides are distinguishable in terms of their conductivity properties, and this should not depend on the type of electrodes used to probe them. A representation of the CNT/x-nucleotide/CNT set-up used here is shown in figure 2 for the xA-nucleotide. An x-nucleotide denotes a system that is composed of an x-base and the sugar and phosphate motif. Two O atoms in the phosphate were saturated with H so as to insure charge neutrality. It should be noted that, in the xT- and xC-nucleotides, the sugar and the base are not bound by a N–C bond, as in their natural counterparts, but by a C–C bond; in the xA- and xG-nucleotides, the sugar and the base are bound by a N–C bond, as in their natural counterparts. We also investigated changes in the conductivity of the xA-nucleotide as a function of the electrodes separation. For simplicity, from now on we will use the term ‘x-base’ in place of ‘x-nucleotide’.

2. Methods

The optimized structures and Hamiltonian matrices were obtained with the NWChem suite of programs [9]. The quantum conductance was computed using the Green function formalism of the Landauer–Buttiker theory [10] following the method described in [11].

We considered 10 configurations of the system CNT/x-base/CNT. In each one of these, the base is not covalently inserted between two CNT electrodes. The distance between the tips of the CNTs is $17.402 - n \times 0.2$ Å, where $n = 0, 2, 3, 4, 5, 6, 7, 8, 9, 10$. We optimized each configuration allowing only the base to relax; the CNTs' structures were kept

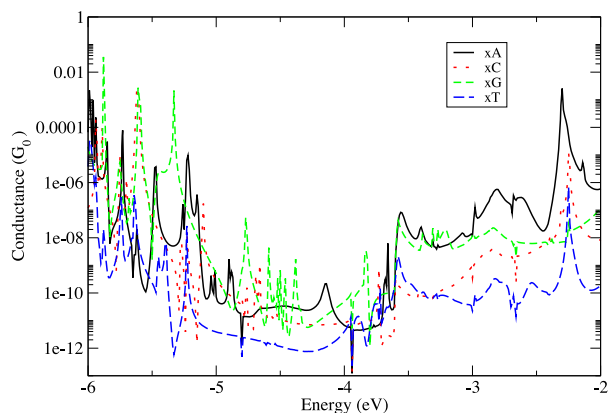


Figure 3. Quantum conductance of the x-bases. The bases are unrelaxed.

fixed. The optimization was carried out with Hartree–Fock and the minimal basis set STO-3G. The Hamiltonian matrices were computed using density functional theory, within the local density approximation (LDA) [12], in conjunction with the 3-21G basis set. Meunier and Sumpter have shown that the 3-21G basis set provides a reasonable compromise between accuracy and efficiency for conductivity calculations in CNT-based systems [13]. Figure 2 shows an optimized structure of the CNT/xA/CNT system when the distance between the CNT tips is 17.402 Å.

3. Results

The quantum conductance of the unrelaxed xA, xC, xG and xT, when placed between two CNTs whose tips are 17.402 Å apart, are shown in figure 3. Clearly, all the bases conduct poorly, but if one were to order their conductance from largest to smallest, the order would be $xA > xG \approx xT > xC$. Despite this, the small values of the conductance suggest that the bases are indistinguishable.

This finding prompted us to ask whether one could increase the conductance by reducing the distance between the electrodes. We investigated changes in xA's conductance as a function of the distance between the tip of the electrodes. We chose this base because it has the smallest HOMO–LUMO gap of all the x-bases (see table 1), so the changes should be more pronounced for xA than for the others. The results are shown in figure 4. It is seen that the conductance increases as the distance between the CNT electrodes decreases: however, despite having increased up to four orders of magnitude, the conductance is still relatively small.

To understand these results, we have also computed the density of states (DOS) for each of the distances and the results are shown in figure 5. One can see that at the Fermi level (-4.2 eV) there are no significant changes, whereas the states at about -3.2 eV are shifted in energy and broaden. This is a clear indication that these molecular states couple rather strongly with the electrodes.

4. Conclusions

Previous theoretical studies have found that, in attempting to sequence a ssDNA when threaded between two Au nanoelec-

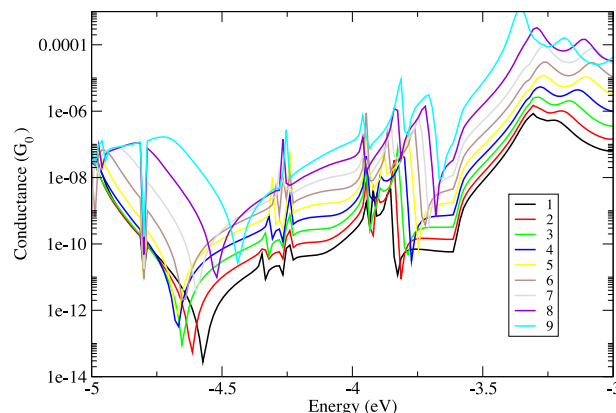


Figure 4. Quantum conductance of relaxed xA versus CNT-tip distance. The numbers 2, 3, etc., correspond to n as explained in the text. The Fermi level is placed at -4.2 eV.

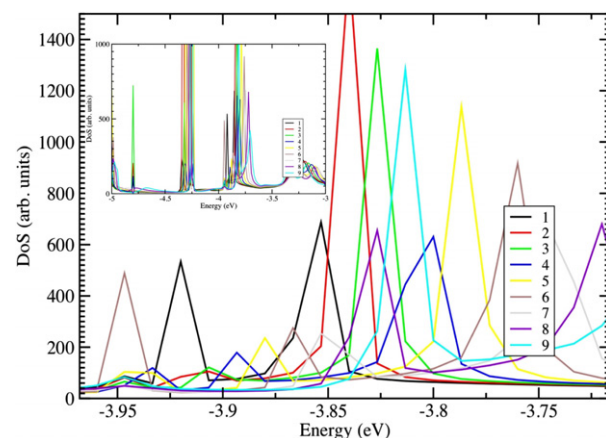


Figure 5. DOS for relaxed xA versus the distance between the electrodes at the energy range where the largest changes occur. The inset show the total DOS. The Fermi level is placed at -4.2 eV.

trodes by measuring transverse conductivity, the geometrical uncertainty makes the bases indistinguishable [2a, 2b]. The main problem is that the conductivity mechanism is driven by tunneling and not by resonance, for the Fermi level of the Au electrodes is very far from the HOMO and LUMO states of the DNA bases. To overcome this problem, we have sought to achieve resonance by using (5, 5) CNT electrodes and artificial DNA bases whose HOMO–LUMO gaps are smaller than those of their natural counterparts. The artificial bases chosen are known as x-bases. They can be seen as a fusion between a benzene molecule and a natural DNA base. These bases pair up with the natural ones in a Watson–Crick-like manner, and have been previously used to synthesize an artificial DNA known as xDNA. We sought to theoretically sequence an ssDNA by measuring the transverse conductance of a complementary ssxDNA that is threaded in between two CNT-electrodes. The results showed that for this set-up, the x-bases are rather difficult to distinguish in terms of their conductance signatures, while decreasing the distance between the electrodes can increase the conductance by as much as four orders of magnitude. The largest increase in conductance occurs when the base is closer to the tips of the electrodes, which

supports the idea that, for a proper conductivity signal, one should have covalent bonding between the molecule and the electrode [14]. Our results do not discard that the x-bases could be used to sequence DNA, but they do imply that sequencing is hardly achievable without bonding to the electrodes for, as shown here, not even reducing the HOMO–LUMO gap is enough if covalent binding does not exist.

Acknowledgments

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