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Doping hepta-alanine with tryptophan: A theoretical study of its effect on the electrical conductance of peptide-based single-molecule junctions

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ABSTRACT

Motivated by a recent experiment [C. Guo *et al.*, Proc. Natl. Acad. Sci. U. S. A. **113**, 10785 (2016)], we carry out a theoretical study of electron transport through peptide-based single-molecule junctions. We analyze the pristine hepta-alanine and its functionalizations with a single tryptophan unit, which is placed in three different locations along the backbone. Contrary to expectations from the experiment on self-assembled monolayers, we find that insertion of tryptophan does not raise the electrical conductance and that the resulting peptides instead remain insulating in the framework of a coherent transport picture. The poor performance of these molecules as conductors can be ascribed to the strongly off-resonant transport and low electrode-molecule coupling of the frontier orbitals. Although the introduction of tryptophan increases the energy of the highest occupied molecular orbital (HOMO) of the peptides in the gas phase, the new HOMO states are localized on the tryptophan unit and therefore essentially do not contribute to coherent charge transport.

I. INTRODUCTION

The study of electron transport through biomolecules in solid-state junctions aims at shedding new light on charge transfer in these systems, which is a fundamental process underlying many biological functions such as respiration, photosynthesis, enzymatic processes, and cellular signal transduction.[1] This field of "biomolecular electronics" presently receives much attention,[2–15] and the hope is to build novel bio-inspired electronic devices that exploit the versatile chemical properties of biomolecules. For instance, electron transport via peptide matrices in proteins has been found to be surprisingly fast and efficient,[16] which may allow us to create electronic devices incorporating proteins, where conductance properties can be tailored by chemical modification.[16,17] On a more fundamental level, the exact mechanism of electron transport in protein-based molecular junctions is still under debate.[2,3,18] For this reason, the study of the conduction properties of individual peptides and polypeptides, which are their building blocks, is essential and sparking interest recently.[1,19–31] It is well known that peptides can act as bridges for long-range electron transfer and that this process depends on details of the amino acid sequence as well as on their secondary structure.[32,33] The situation is not so clear in the case of electron transport through peptide-based molecular junctions, where it has been reported that homopeptide monolayers can be more conductive than, for instance, alkane chains.[29] However, it has also been shown that peptide bonds actually reduce the

conductance of single-molecule junctions below those of saturated carbon chains.[31]

This work is motivated by the experimental results of Ref. 34. In that paper, the authors reported that doping a 7-alanine (7A) homopeptide with a tryptophan unit can significantly enhance the conductance of junctions formed by contacting self-assembled monolayers (SAMs) to gold electrodes. Concluding from the observation of rather temperature-independent transport, the results were interpreted in terms of coherent tunneling.[34] Tryptophan doping was chosen because an earlier study of the same group had shown more efficient electron transfer through heptatryptophan than through 7A,[29] and this had in turn been ascribed to the difference in the ionization potential of the two peptides. Interestingly, the increase in conductance induced by insertion of tryptophan in 7A was found to depend on its position along the backbone.[34] The intriguing experimental results thus suggest that one can tailor the sequence of peptides to alter the electrical conductance via a modification of the energy barrier height and the electrode-peptide coupling.

The results of Ref. 34 were rationalized with the help of density functional theory (DFT) calculations of the electronic structure of the peptide molecules in the gas phase. Conductance enhancement was attributed to the fact that tryptophan raises the highest occupied molecular orbital (HOMO) level, which is expected to dominate the transport, by 1–2 eV.[34] However, a theoretical analysis of the electron transport in these junctions has not yet been reported, and we want to fill this gap with this manuscript.

Revealing the transport mechanism through biomolecules is a complicated task, and it therefore appears sensible to take a stepwise approach. Therefore, we use here Landauer scattering theory for a description of coherent transport only, the mechanism that has been argued to be present in the experiments.[34] At variance with the experiments on SAMs,[34] however, we focus on single-molecule junctions to better assess the conduction properties of the individual molecules. We study the same peptide-based compounds as Ref. 34 in contact to gold electrodes and obtain a parameter-free transport description by combining nonequilibrium Green's function (NEGF) techniques with DFT. Our calculations show that the molecules are actually poor conductors for the studied junction geometries of fully stretched-out peptides and if phase-coherent elastic transport is assumed. In this setting, tryptophan doping is found to essentially not influence the conductance, which we attribute to the localized character of energetically high-lying electronic states on the tryptophan unit.

Let us stress that our study does not aim at reproducing the experiments reported in Ref. 34. In SAMs, a number of collective effects may influence the charge transport mechanism, which are difficult to model correctly, as we will discuss further below. Nonetheless, we hope that this work contributes to ultimately resolving the charge transport mechanisms in biomolecules by ruling out the fully coherent mechanism.

II. THEORETICAL METHODS

We describe the electronic transport through peptide-based single-molecule junctions as phase-coherent and elastic in terms of the Landauer scattering theory.[35] The conductance at sufficiently low temperatures

$$G = G_0 \tau(E_F) \quad (1)$$

is determined by the transmission function, evaluated at the Fermi energy E_F, multiplied by the conductance quantum $G_0 = 2e^2/h$. The energy-dependent, elastic transmission $\tau(E)$ is computed without any free parameters by combining DFT with NEGF techniques. The theoretical approach is discussed further in Ref. 36.

In detail, our calculations of the linear conductance of the molecular junctions involve the following steps. First, the geometries of the four different peptides under study are optimized in the gas phase (see Fig. 1). Second, the molecules are placed between two Au_{20} clusters to form the junctions. In this step, we relax both the molecule and the four gold atoms on each side that are closest to the molecule, while the positions of the rest of the gold atoms in the metal clusters are frozen. Subsequently, the size of each gold cluster is extended to 53 atoms in order to converge the charge transfer and the level alignment between the molecule and the metal within DFT. At this stage, the electronic structure of the extended junction geometry is obtained by running a single-point DFT calculation. Finally, $\tau(E)$ and, from Eq. (1), G are computed with the help of Green's functions and by modeling the gold electrodes as surfaces of semi-infinite perfect crystals, whose electronic structure is treated consistently at the same level of DFT as the extended junction part.[36]

Beyond the elastic treatment of transport, we also study inelastic corrections due to vibrations. Inelastic electron tunneling (IET) spectra are determined as presented in Ref. 37 by computing electron-vibration couplings through density functional perturbation theory and using a lowest order expansion for the current in terms of the electron-vibration couplings together with a wide-band approximation. In the calculations discussed below, we assume the

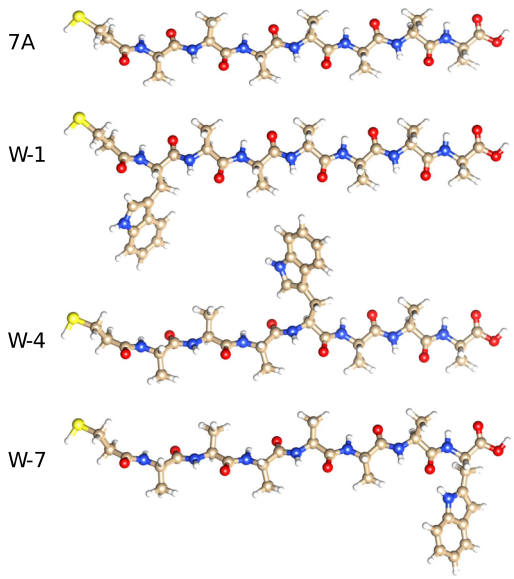

FIG. 1. Structure of the four peptide molecules analyzed: hepta-alanine (7A) and three heptapeptides composed of six alanines and a single tryptophan located at the N-terminus (W-1), in the middle of the peptide (W-4), and at the C-terminus (W-7).

modulation voltage to vanish and employ a small phenomenological vibrational broadening of $\eta = 0.01$ meV.

All our DFT calculations are performed with the quantum chemistry code TURBOMOLE,[38] employing the def-SV(P) Gaussian basis set[39] and the Perdew–Burke–Ernzerhof (PBE) exchange-correlation functional.[40] Total energies are converged to a precision of better than 10^{-8} a.u., and geometry optimizations are carried out until the change of the maximum norm of the Cartesian gradient is below 10^{-5} a.u. Transport programs for computing the elastic transmission and IET spectra are custom-built and interfaced with TURBOMOLE.[36,37]

III. RESULTS AND DISCUSSION

Inspired by Ref. 34, we study here the electronic transport through single-molecule junctions based on the four different peptides shown in Fig. 1: hepta-alanine (7A) and three heptapeptides composed of six alanines and a single tryptophan located at the N-terminus (W-1), in the middle of the peptide (W-4), and at the C-terminus (W-7). Let us recall that peptides usually have an "N-terminal" and a "C-terminal" residue at their end, corresponding to an amine (NH_2) and a carboxyl (COOH) group, respectively. In our case, and following Ref. 34, a mercaptopropionic acid (MPA) is bound to the N-terminus.

To begin with, we analyzed the density of states (DOS) for all four molecules, as displayed in Fig. 2. In agreement with the theoretical calculations presented in Ref. 34, we find that replacing one alanine with one tryptophan leads to an important change of the electronic structure: the HOMO levels in W-1, W-4, and W-7 are energetically higher than in 7A, and they are localized on the tryptophan unit. In the tryptophan-doped molecules, the HOMO-1 resembles the HOMO of 7A. It is located on the MPA (see Fig. 2) with an approximately constant energy of −5.0 eV. The HOMO energy, on the other hand, depends on the position of the tryptophan in the peptide chain: starting with −4.6 eV in W-1, −4.8 eV in W-4, it shifts up to −3.8 eV for W-7. This means that the functionalization of 7A with tryptophan can increase the HOMO of the gas-phase molecule by up to 1 eV. Naively, this suggests that the inclusion of the tryptophan unit should lead to a corresponding increase of the electrical conductance, as discussed in Ref. 34. However, as shown below, this is actually not the case, if we assume a fully coherent transport picture.

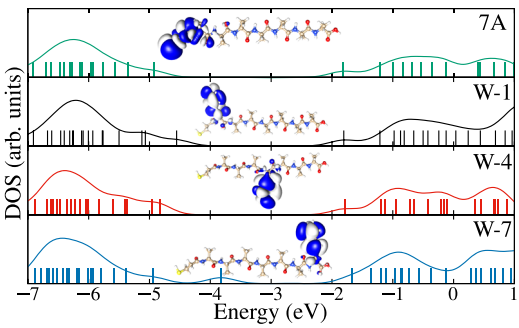

FIG. 2. Density of states (DOS) for all four studied peptide molecules in the gas phase. Insets visualize the corresponding HOMO wavefunctions.

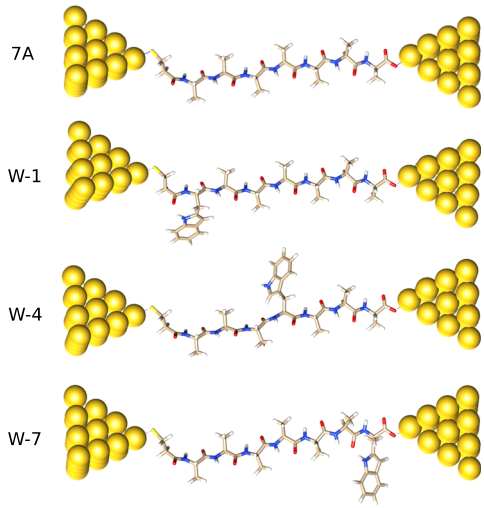

FIG. 3. Junction geometries studied for 7A, W-1, W-4, and W-7. The peptides are connected to gold tip atoms through a sulfur atom at the left end and through an oxygen atom at the right end. For each molecule, hydrogen atoms at the thiol and carboxyl termini have been removed as compared to the gas phase geometries in Fig. 1, yielding a thiolate at the left side and a carboxylate at the right side.

In order to analyze the electronic transport properties, we build Au-peptide-Au junctions with comparable molecular configurations and binding to the gold electrodes: peptides are assumed to be fully elongated, and they are connected to a gold tip atom of the pyramid-shaped electrodes through the sulfur atom of the MPA at the N-terminus and through the oxygen atom at the C-terminus. Similar to the removal of the hydrogen atom at the thiol group, the literature suggests the removal of the hydrogen atom of the carboxyl group upon binding to gold.[41–46] Following the literature, the resulting junction geometries are shown in Fig. 3 for all four molecules, exhibiting a thiolate group at the N-terminus and a carboxylate group at the C-terminus.

The zero-bias transmission as a function of energy is displayed in Fig. 4. Let us stress that in this work, we are assuming that the transport is dominated by coherent processes. The conductance is then directly proportional to the elastic transmission, as expressed in Eq. (1). Conductance values determined from the transmission

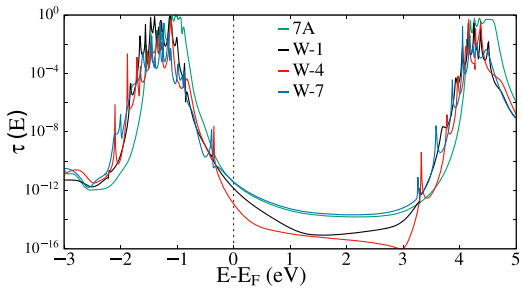

FIG. 4. Transmission as a function of energy for the single-molecule junctions of Fig. 3.

function at the Fermi energy are listed in Table I. The transmission curves shown in Fig. 4 suggest that the current is hole-dominated in all cases, i.e., flows through the HOMO of the molecules. Moreover, we notice that the conductance values are consistently very low with all $G < 4 \times 10^{-12} G_0$.

Among the tryptophan-doped molecules, the lowest conductance is obtained for W-4. This is not surprising, since in this heteropeptide, the tryptophan unit is placed in the middle, and it is thus more decoupled from the leads than in the other two cases. For W-1, W-4, and W-7, narrow peaks close to the Fermi level at around $E_F - 0.4$ eV are observed that are absent for 7A. Our analysis reveals that they originate from electronic states localized at the tryptophan unit, i.e., the HOMO states of the gas phase molecules (see Fig. 2). Contrary to the naive expectation, our results show that tryptophan doping does not significantly increase the conductance. The reason is that the energetically high-lying electronic states of this moiety lead to very narrow transmission resonances with a low peak value due to the weak coupling to the electrodes. In other words, the localized states on the tryptophan do not participate in charge transport.

To gain further insight, we analyze the eigenchannel decomposition of the transmission and the corresponding wavefunctions at the Fermi energy. Let us recall that within the Landauer approach, the total transmission can be expressed as a sum of independent contributions $\tau(E) = \sum_n \tau_n(E)$. The transmission coefficients $\tau_n(E)$ are eigenvalues of the transmission probability matrix, and the corresponding eigenfunctions are known as eigenchannels. Depending on the boundary conditions for the incident scattering states, left- and right-incoming eigenchannels are distinguished.[47,48] For all of the peptide-based single-molecule junctions, we find that the transmission at the Fermi energy is determined by a single channel $n = 1$. As shown in Fig. 5, the amplitude of the eigenchannels decays exponentially along the propagation direction inside the molecule, as expected in an off-resonant situation. For the left-incoming eigenchannels, the spatial distribution of the wavefunction is quite similar for all molecules, exhibiting a high weight on the N-terminus. For the right-incoming eigenchannels, the same is true for 7A, W-1, and W-4: the main weight is located on the C-terminus and on the atoms close to it. For W-7 instead, the eigenchannel wavefunction also involves the tryptophan moiety. This effect explains the slightly higher conductance of W-7 with respect to the other tryptophan-doped systems through an increased electrode-molecule coupling at the C-terminus.

In Ref. 34, IET spectra measured at a temperature of 10 K were also reported for the peptide-based molecular junctions. In IET spectra, peaks observed in the second derivative of the current at specific bias signal the interaction of electrons with vibrational modes. The inelastic signal should thus be characteristic for the path of carriers through the junction. In Ref. 34, the position of the peaks suggested that the inelastic process was preferentially due to all parts of the molecule that take part in the charge transport rather than to the molecule-electrode interface.

TABLE I. Conductance values for the peptide-based single-molecule junctions of Fig. 1.

Peptide	G (G_0)
7A	3.49×10^{-12}
W-1	1.35×10^{-12}
W-4	1.17×10^{-13}
W-7	3.87×10^{-12}

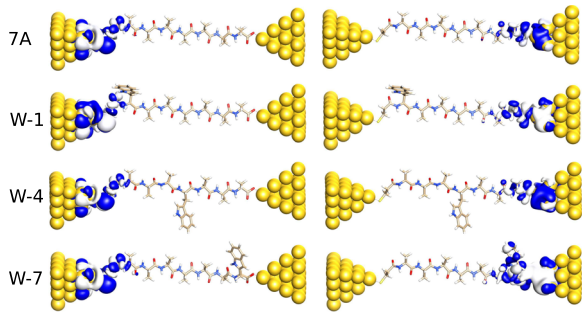

FIG. 5. Wavefunction of the dominant left-incoming (left side) or right-incoming (right side) transmission eigenchannel for all four studied junctions of Fig. 3. While isosurface values are chosen to be identical for left- and right-incoming eigenchannels, respectively, to facilitate the comparison between the different molecules, the isosurface value of the right-incoming eigenchannels is three orders of magnitudes smaller than for the left-incoming ones for visualization reasons. This is a result of the asymmetric peptides, leading to a much easier tunneling into the thiolate-terminated end than into the carboxylate end.

In Fig. 6, we show IET spectra computed for the junctions of Fig. 3, assuming a temperature of $T = 10$ K as in the experiments of Ref. 34. Analyzing the inelastic contribution of each vibrational mode to the spectra, we find that the peaks marked with arrows between 185 and 211 mV originate from vibrations, which involve the tryptophan unit to a large extent. While there are these signatures, which indicate the presence of tryptophan, we find at the same time that these signals are not particularly strong. Indeed, since the elastic transmission inside the electronic gap exhibits only very faint and narrow features stemming from tryptophan, we expect similarly weak inelastic signals. Furthermore, it is important to note that the tryptophan-related peaks highly overlap with

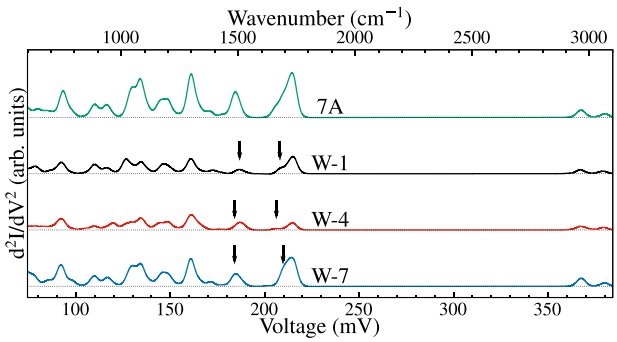

FIG. 6. IET spectra, i.e., second derivative of current I with respect to voltage V, for the carboxylate junctions of Fig. 3. The upper horizontal axis shows the conversion of the voltage scale to wavenumbers.

contributions of other vibrational modes, e.g., C—N stretching at around 186–190 mV or C=O stretching at 208–213 mV in the case of the W-7 molecule (and similarly for the other peptides). The lack of specificity of the tryptophan-derived inelastic signals is also illustrated by the fact that the corresponding peaks appear to a similar extent in the IET spectra of the 7A molecule. For this reason, a clear-cut identification of the tryptophan-doped peptides through IET spectra in the studied junction geometries appears to be difficult.

A direct comparison of our theoretical results with the experimental ones reported in Ref. 34 is complicated by the fact that we study single-molecule junctions, while the experiment analyzes SAMs. In SAMs, ensemble effects can be important. Thus, dipolar interactions may change metal workfunctions, band alignments, and electronic gaps,[49] and intermolecular transport should be taken into account in addition to intramolecular pathways.[50] Molecular geometries may also be different. We concentrate here on fully stretched-out peptides with a length of around 29 Å between terminal sulfur and oxygen atoms, where the molecules connect to gold tips via the terminal groups. We do so in order to compare single-molecule conduction properties in as similar conditions as possible. However, other geometries are conceivable. For instance, a previous study on homopeptides suggested that bonding could be established via physisorption of a tryptophan unit onto gold,[30] and other binding configurations for the thiolate or carboxylate groups have been explored.[51–54] In the experiments, variable SAM heights between 20 and 26 Å have been observed. This means that molecules may be slightly tilted or crumpled in the ensemble junctions. Despite these complications, we may still attempt to get a hint about the relevant transport mechanism from our calculations. Reference 34 reported the following trend for conductance of the four peptide junctions: $G_{\text{W-7}} > G_{\text{W-1}} \approx G_{\text{W-4}} \gg G_{\text{7A}}$. The observation was explained in a phase-coherent tunneling picture by a decrease of the effective transport barrier through tryptophan doping. Instead, we find that all the peptides show an insulating behavior and basically no change of conductance with tryptophan doping. Taking the typical overestimation of conductance values in the standard DFT-NEGF formalism into account,[55] the conductance values listed in Table I may even be seen as an upper bound. Given the extremely low conductance in the coherent transport picture, it is likely that other incoherent transport mechanisms such as hopping are more relevant. In this context, it is very important to develop new transport models that can describe both coherent and incoherent processes simultaneously in realistic systems so that no decision on the charge transport mechanism is made by the theoretical method chosen.[56] The experiments of Ref. 34 were conducted between 10 and 300 K, and the temperature-independent current at a fixed voltage was interpreted as a sign of off-resonant coherent transport. In this context, it is important to point out that temperature-independent transport does not necessarily imply that transport is coherent tunneling. Instead, it may also be hopping with a low or no barrier, for instance, in the inverted regime.[57] Experimental uncertainties could also play a role.[34] The number of molecules in the molecular junctions is not precisely known. Estimates range between 100 and 10 000. SAMs may show imperfections due to surface corrugation, and the electrophoretic trapping of SAM-encapsulated gold nanowires may actually lead to the formation of double-SAM instead of desired single-SAM junctions.[34] Refined theoretical and experimental studies are thus needed to ultimately clarify the conduction mechanism in peptide-based junctions.

IV. CONCLUSIONS

We have performed a theoretical study of the electron-transport properties of single-molecule junctions based on four different molecules: 7A in its original state and doped by a tryptophan unit placed in three different positions along the backbone, yielding W-1, W-4, and W-7. Assuming fully coherent transport, our first principles description yields a very low conductance for all four junctions considered ($G < 4 \times 10^{-12} G_0$). Insertion of tryptophan does basically not affect G, despite the higher position of the HOMO in the gas phase for the doped systems W-1, W-4, and W-7 as compared to the pristine 7A. We attribute the poor performance of these molecules as conductors to the strongly off-resonant transport and the low molecule-electrode coupling of the orbitals responsible for the electrical transmission.

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