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Citation: *Applied Physics Letters* **98**, 053702 (2011); doi: 10.1063/1.3551713

View online: <http://dx.doi.org/10.1063/1.3551713>

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Charge transport in fibrous/not fibrous α_3 -helical and (5Q,7Q) α_3 variant peptides

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(Received 30 November 2010; accepted 14 January 2011; published online 2 February 2011)

Although differing only by the Ala→Gln substitution at the fifth or seventh position of the α_3 -peptide amino acid sequence (Leu-Glu-Thr-Leu-Ala-Lys-Ala)₃, the 5Q α_3 variant forms fibrous assemblies more attenuated than those of the α_3 -peptide, while the 7Q α_3 variant does not form fibrils. A tight-binding transport modeling was performed to obtain their current-voltage patterns, with hopping energies of the dipeptides calculated within the density functional theory framework. Beyond the semiconductor character, we obtain that the current pattern can be used to distinguish them, suggesting that it can be useful for the development of devices as diagnostics tools for amyloidosislike diseases. © 2011 American Institute of Physics. [doi:10.1063/1.3551713]

The interest in charge transport in proteins and peptides dates back to 1941, when Szent-Györgyi reported that proteins can be semiconductors instead of insulators.^{1,2} The initial theoretical investigations on charge transport in polypeptides focused on the calculation of band structures through semiempirical and *ab initio* methods. Initially it was suggested that the conductivity of proteins was caused by electronic delocalization, but later the possibility of hopping conductivity was considered. Ye and Ladik³ developed, using *ab initio* methods, a theory of hopping conductivity in pig insulin, one of the smallest native protein hormones, obtaining formulas which allowed the calculation of primary hopping frequencies. Their results confirmed that the ac conductivity of a native protein could be caused by hopping of the charge carriers between different localized centers of orbitals. In general, electrical conduction in dry proteins is nowadays believed to be of semiconductor type.⁴ Two terminal charge transport and intrinsic fluorescence experiments in amyloid-like fibrils at the microscale and nanoscale were performed recently, demonstrating that the nanofibrils can sustain significant electrical conduction in the solid state at ambient conditions, having remarkable potential applications.⁵

The focus of this work is on the *de novo*-designed α_3 -peptide by gene engineering,⁶ as well as its variants 5Q α_3 and 7Q α_3 . Their charge transport properties are investigated with a tight-binding model Hamiltonian where *input* parameters (amino acid vertical ionization and dipeptide hopping energy) were obtained by performing *ab initio* calculations within the density functional theory (DFT). The purpose is to know if the biased α_3 -peptide and its 5Q α_3 and 7Q α_3 variants can be identified by charge transport measurements. α_3 is a 21-residue peptide with three repeats of the seven-residue (heptad) sequence Leu-Glu-Thr-Leu-Ala-Lys-Ala, which forms an α -helical bundle structure through hydrophobic interaction between Leu residues.⁷ The 5Q α_3

and 7Q α_3 peptides are obtained by Ala→Gln substitution at the *e* (fifth) and *g* (seventh) positions, respectively, of the α_3 -peptide amino acid sequence. The α_3 -peptide has the ability to form fibrous assemblies that are observed by transmission electron microscopy and atomic force microscopy.^{6,7} However, the α -helix of the α_3 -peptide was destabilized by the substitution of Ala residues at the *e* position in the heptad sequence with Gln residues, and much more prominently by the substitution at the *g* position. As a result, among the peptides examined, the 7Q α_3 peptide had the most unstable α -helix.⁷ On the other hand, the Ala→Gln substitution attenuates the formation of fibrils, which become very short in the 5Q α_3 case and are not observed in 7Q α_3 .⁷

The charge transport properties of the biased α_3 -peptide and its (5Q,7Q) α_3 variants are calculated using Dyson's equation together with a transfer-matrix treatment to solve a time independent Schrödinger equation, with the following electronic tight-binding model Hamiltonian:⁸

$$H = \sum_n \epsilon_n |\psi_n\rangle \langle \psi_n| + \sum_{n,m} V_{n,m} |\psi_n\rangle \langle \psi_m|, \quad (1)$$

which describes the carrier moving through the primary peptide structure sandwiched by two electrodes (donor DN and acceptor AC), with a single orbital per site and nearest-neighbor interactions. ϵ_n is the single carrier energy (isolated amino acid vertical ionization energy) at the orbital ψ_n . $V_{n,m}$ is the first-neighbor electronic overlaps (hopping amplitude, obtained from the overlap integrals of the isolated dipeptides). For simplicity, we are considering that the charge carriers are traveling from DN to AC platinum electrodes by hopping between the α_3 -, 5Q α_3 , and 7Q α_3 peptide discrete molecular orbitals.

With the tight-binding Hamiltonian given above, one can evaluate the I-V characteristics by applying the Landauer-Büttiker formulation^{9,10}

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$$I(V) = \frac{2e}{h} \int_{-\infty}^{+\infty} T_N(E) [f_{\text{DN}}(E) - f_{\text{AC}}(E)] dE, \quad (2)$$

where $f_{\text{DN(AC)}} = \{\exp[(E - \mu_{\text{DN(AC)}})/k_B T] + 1\}^{-1}$ is the Fermi-Dirac distribution, $\mu_{\text{DN(AC)}}$ is the electrochemical potential of the two leads fixed by the applied bias voltage V as $|\mu_{\text{DN}} - \mu_{\text{AC}}| = eV$, and $T_N(E)$ is the transmission coefficient, which is calculated through a transfer-matrix method used to solve the corresponding time independent Schrödinger equation related to the tight-binding Hamiltonian.¹¹ We have considered $k_B T = 0.02675$ eV (here k_B is the Boltzmann constant), which means a temperature $T = 310.32$ K, i.e., 37.17 °C, closer to the normal human body temperature (37 °C). The current onset is crucially dependent on the electrochemical potentials of the leads. For simplicity, before the bias voltage is applied, the electrochemical potential of the whole system is taken to be zero.

The vertical ionization energies and hopping terms for isolated amino acids and dipeptides, respectively, were obtained by first principles calculations considering only the primary amino acid sequence of the peptides. The isolated amino acid and dipeptide conformers of smaller energies were discovered through a minimization energy process within the DFT framework using the DMOL3 code.¹² The generalized gradient approximation Perdew–Burke–Ernzerhof exchange-correlation functional¹³ was adopted, and a double numerical plus polarization basis set was chosen to expand the Kohn–Sham wave functions. All electrons, valence and core, were taken into account. The geometry optimization convergence thresholds were 10^{-5} hartree for the total energy variation, 0.002 hartree/Å for the maximum force per atom, and 0.005 Å for the maximum atomic displacement. In the case of the amino acid conformers, those we found are in good agreement with the lowest energy amino acid conformers discovered by others authors.^{14,15} Since works on the conformers of dipeptides are scarce, it was not possible to compare the dipeptide conformers we found with any published result.

To obtain the vertical ionization energies of the amino acids, the total energy differences between the N -electron ground state and the excited states of the amino acids conformers of smaller energies were computed. The lowest single-electron excitations are the (first) amino acid vertical ionization potential $IE = E(N-1) - E(N)$, where the ionized amino acids with one missing electron are characterized by the total energies $E(N-1)$.¹⁴ The calculated amino acid vertical IE 's of the $\alpha 3$ -helical peptides and the (5Q,7Q) $\alpha 3$ variants obtained are as follows: alanine, 9.25 eV; glutamine, 8.52 eV; lysine, 8.00 eV; glutamic acid, 8.63 eV; threonine, 9.05 eV; and leucine, 8.85 eV. The hopping terms, on the other hand, are estimated through the following relation:¹⁶ $V_{n,m} = \frac{1}{2}(E_{n,m}^{\text{HOMO}} - E_{n,m}^{\text{HOMO}-1})$, where $E_{n,m}^{\text{HOMO}}$ and $E_{n,m}^{\text{HOMO}-1}$ are, respectively, the first and second highest occupied molecular orbital energies for the dipeptides formed by the n, m amino acid residues (Table I). The charge carriers are supposed to be traveling between the biased platinum electrodes by hopping through discrete molecular orbitals of the $\alpha 3$ -helical peptides and the (5Q,7Q) $\alpha 3$ variants. The energy of the platinum electrode is 5.36 eV, which is related to the work function of this metal.¹⁷

Although the $\alpha 3$ -helical peptides and its (5Q,7Q) $\alpha 3$ variants differ only by the Ala $\rightarrow$ Gln substitutions, their

TABLE I. The two highest occupied molecular orbitals of dipeptides n, m and hopping energies $V_{n,m}$ (in eV) of the $\alpha 3$ -helical peptide and its (5Q,7Q) $\alpha 3$ variants.

n, m	$E_{n,m}^{\text{HOMO}-1}$ (eV)	$E_{n,m}^{\text{HOMO}}$ (eV)	$V_{n,m}$ (eV)
Leu-Glu	-5.960	-5.503	0.229
Glu-Thr	-6.147	-5.906	0.121
Thr-Leu	-6.046	-5.638	0.204
Leu-Gln	-5.815	-5.414	0.201
Gln-Lys	-5.643	-5.179	0.232
Lys-Ala	-5.485	-5.120	0.183
Ala-Leu	-6.147	-5.830	0.159
Leu-Ala	-5.959	-5.254	0.353
Ala-Lys	-5.494	-5.052	0.221
Lys-Gln	-5.725	-5.324	0.201
Gln-Leu	-6.151	-5.418	0.367

IV_{bias} relationship should change considerably due the degree of fibril formation. This allows us to distinguish the $\alpha 3$ -, 5Q $\alpha 3$, and 7Q $\alpha 3$ peptides and consequently to point the existence (or not!) of fibrous assemblies. This means that charge transport can be used as a tool for characterizing their fibrous assemblies. Figure 1 shows the behavior of the current in the positive and negative biased peptides. For both the positive and negative polarities, there is a characteristic Ohmic region for $-1.0 \leq V_{\text{bias}} \leq +1.0$ eV, and nonlinear regions indicating transitions toward current saturation for $V_{\text{bias}} < -1.0$ eV and $V_{\text{bias}} > +1.0$ eV. The inset in Fig. 1 shows the transconductance $dI/dV \times V$ of the devices, which are highly nonlinear. On the basis of the dI/dV characteristics, the peptides $\alpha 3$ -, 5Q $\alpha 3$ -, and 7Q $\alpha 3$ have average energy gaps of 3.25, 3.32, and 3.53 eV, respectively. They have semiconductor characteristics, as in the case of dry proteins.^{4,18}

Each peptide has a characteristic current pattern, which was assumed to depend mainly on its primary structure. The result of the straightforward calculations is that the fibrous/not fibrous $\alpha 3$ -, 5Q $\alpha 3$ -, and 7Q $\alpha 3$ peptides can be distinguished by charge transport measurements. As a matter of fact, the $\alpha 3$ -peptide, which has the most fibrous assemblies, shows the smaller current saturation; the 5Q $\alpha 3$ variant, which forms fibrous assemblies more attenuated than those of the $\alpha 3$ peptide, has a current saturation higher than $\alpha 3$, but

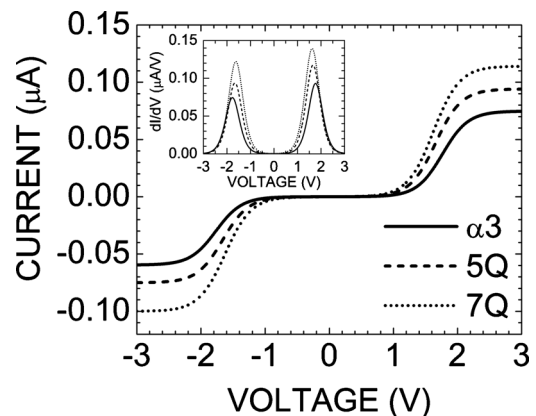


FIG. 1. The current through the biased $\alpha 3$ (dotted curve), 5Q $\alpha 3$ (dashed curve), and 7Q $\alpha 3$ (solid curve) peptides. The inset shows the transconductance $dI/dV \times V$ of the devices.

smaller than $7Q\alpha_3$; finally, the $7Q\alpha_3$ variant does not form fibrils and shows the highest current saturation. If the secondary structure of the peptides is considered, the number of charge transport channels should increase due to hydrogen bonding related to the secondary structure, further increasing saturation currents, but not specifically enough to change the order $I(\alpha_3) < I(5Q\alpha_3) < I(7Q\alpha_3)$. Further development on this line is hampered by the absence of crystallographic data allowing the characterization of the fibrous/not fibrous α_3 - and $(5Q,7Q)\alpha_3$ peptide secondary structures.

In summary, by taking full advantage of the vertical ionization (hopping) energies of the α_3 -helical and its $(5Q,7Q)\alpha_3$ variant peptides (dipeptides) calculated within the DFT framework, their charge transport properties were calculated within a tight-binding Hamiltonian model approach. They showed semiconductor character, in agreement with electrical conduction in dry proteins,⁴ with their current saturation behavior being very useful to discover the existence (or not) of fibrous assemblies. Experimental works focused their synthesis/characterization and the role of Ala residues for fibrous structure formation.^{6,7} Neither spectroscopic nor photoconductivity measurements were performed yet to estimate their structure (by nuclear magnetic resonance, for example) and transport/optical parameters like their energy gaps. Nevertheless, since the formation of fibrous assemblies is characteristic of Alzheimer, Parkinson, and Creutzfeldt–Jakob (prion) diseases, for example, our result allows us to suggest that charge transport in peptides can turn to be a useful tool for the development of biosensors to probe the onset of amyloidosislike diseases. The outstanding work of del Mercato *et al.*⁵ is already a clear step toward this remarkable biomedical application of the charge transport in proteins and polypeptides. It is the authors hope that the results presented here should stimulate experimental and engineering developments in this sense.

The authors would like to thank Professor D. L. Azevedo who kindly allowed us to use the DMOL3 software package. This work received financial support from the Brazilian Research Agencies CAPES (PROCAD and Rede NanoBioTec), CNPq [INCT-Nano(Bio)Simes], and FAPERN/CNPq (Pronex).

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