Conductance Switching in Single-Peptide Molecules through Interferer Binding

Li-Wen Huang, † Yen-Hsun Su, †* and Chao-Cheng Kaun †, †*, ‡, 8

† Research Center for Applied Sciences, Academia Sinica, Taipei 11529, Taiwan, Republic of China
‡ Department of Material Science and Engineering, National Cheng Kung University, Tainan 70101, Taiwan, Republic of China
§ Department of Physics, National Tsing-Hua University, Hsinchu 30013, Taiwan, Republic of China

ABSTRACT: Detection of bioprocess-interfering metal ions and molecules is important for healthcare, and peptide single-molecule junctions have shown their potential toward sensing these targets efficiently. Using first-principles calculations, we investigate the conductance of Cys-Gly-Cys and cysteamine-Gly-Gly-Cys peptide junctions, and the effect of its change upon copper-ion (Cu2+) or bisphenol A (BPA) binding. The calculated conductance of the peptides and the Cu2+-peptide complexes agrees well with the experimental data and that of the BPA-bond peptides is further predicted. Our analyses show that the conductance switching mainly comes from the structure deformation of the peptide caused by Cu2+ binding or from the new conduction channel added by BPA binding. Our results suggest that the cysteamine-Gly-Gly-Cys junction can recognize Cu2+ and BPA better than the Cys-Gly-Cys one does.

INTRODUCTION

Sensors built of ensemble1–7 and individual8–10 peptides have shown their potential toward viable, mobile, and fast-response detection of polarized lights,1 metal ions,2 molecules,3 and solution pH values,9,10 partially because peptides present an astronomical number of ligands for binding specific metal ions3 or molecules,7 and such binding can trigger electric signals in devices efficiently. Peptides thus offer important recognition for healthcare, for example, sensing copper ions or bisphenol A [BPA and (CH3)2C(C6H4OH)2] molecules, as in a high concentration, the copper ions may involve symptoms11 or diseases,12 and the BPA molecules can affect reproductive systems.13 However, these key potentials can be fully explored only with a clear understanding of the driving physics.

Measured single-peptide conductance8 has been simulated14 via a tight-binding model, claiming that hollow binding sites consist of the contacts. However, under the stretching process in measurements,9 the top binding sites forming the contacts are recently suggested.15–17 Using a similar approach, the effects of the changes in conductance upon Cu- and Ni-ion binding on the cysteamine-Gly-Gly-Cys peptide have been calculated,18 but the jump values (ratios of transmission coefficients at their Fermi energy, −5.2 eV) are orders of magnitude smaller than the measured data.8 Therefore, although the single-molecule conductance of alkanedithiolate and benzenedithiolate, for instance, can be modeled quantitatively from first principles,15,16 such modeling of a single-molecule peptide, particularly in its switching upon metal-ion binding, is still a challenge. On the other hand, first-principles studies on cyclic and linear peptides in the β-strand,19,20 and helical20 conformations, and on quinolinedithiol21 and bis(2-pyridylmethyl)amine-based22 single-molecule junctions for ion detection were reported. Nevertheless, first-principles modeling of single-peptide junctions for Cu-ion and BPA identification is still absent.

In this work, the conduction properties of the Cys-Gly-Cys peptide, the cysteamine-Gly-Gly-Cys peptide, and their Cu or BPA complexes are studied from first principles. These peptides possess two thiol termini in contact with Au electrodes, have shown large conductance changes upon metal binding in measurements,8 and can form Cu or even BPA complexes. We investigate how to use these peptides to differentiate the presence of Cu or BPA via conductance modulation and further unravel its mechanism. Our results agree well with experimental data8 and provide an insight for efficient detection of Cu ions and BPA molecules with the use of single-molecule peptide junctions.

RESULTS AND DISCUSSION

We calculate the conduction properties of single-peptide junctions first. The optimized geometries of Cys-Gly-Cys and cysteamine-Gly-Gly-Cys peptide junctions are shown in Figure 1a,c, and their lengths from S to S atoms (S−S) are 11.95 and 15.75 Å, respectively. The calculated conductance values of Cys-Gly-Cys and cysteamine-Gly-Gly-Cys junctions are 7.40 × 10−6 and 5.36 × 10−7 G0, in good agreement with the experimental data of 5.3 × 10−6 and 5.0 × 10−7 G0, respectively8 (see Table 1). The conductance of the Cys-Gly-Cys peptide is about one order of magnitude larger than
that of the cysteamine-Gly-Gly-Cys one, as their local density of states (LDOS) at $E_F$, shown in Figure 1d,h, indicate that the former has a shorter effective tunneling distance than the latter. To further investigate the conduction characteristics, transmission spectra are calculated and plotted in Figure 1b,f, showing different shapes around $-1.00$, $-0.40$, and $-0.15$ eV.

The projected density of states (PDOS) on the peptide and the lead are shown in Figure 1c,g. As expected, the leads have a similar PDOS for both peptides. However, the PDOS peak around $-0.72$ eV of the Cys-Gly-Cys peptide is sharper than that around $-0.63$ eV of the cysteamine-Gly-Gly-Cys one. Comparing the shapes of the transmission spectra with those of the peptide PDOS indicates that they are correlated. In general, excluding the localized and symmetry-mismatched states, the transmission function of a molecule is proportional to its PDOS.

After the geometries of the Cu$_2^+$—peptide complexes with gold adatoms are optimized in between the leads, transport calculations are performed, and results are shown in Figure 2a,e. Upon copper-ion binding, the S–S distances of the Cys-Gly-Cys and cysteamine-Gly-Gly-Cys peptides are shortened by 12.6 and 13.3%, and their conductance values increase 8.3 and 81.3 times to $6.14 \times 10^{-5}$ and $4.36 \times 10^{-5}$ $G_0$, as consistent with the measured data of $2.3 \times 10^{-5}$ and $1.6 \times 10^{-4}$ $G_0$, respectively (Table 1). Therefore, the binding of copper ion to the peptides can be recognized from electric signals occurring in these junctions. The conductance values of these two complexes are similar, as well as their effective tunneling distances, presented by LDOS at $E_F$ in Figure 2d,h. However, the shapes of transmission spectra in Figure 2b,f are different, corresponding to different PDOS of the Cu$_2^+$—peptide complexes in Figure 2c,g. These PDOS curves of the complexes align with those of the peptides, as the Cu$^{2+}$ ion is screened after two electrons are donated to the peptide. The PDOS of complexes is thus mostly contributed by the PDOS of the peptides rather than that of Cu$^{2+}$. In addition, when the copper ion is removed from the complexes (other geometries fixed), the conductance of Cu$^{2+}$-removed junctions are $7.48 \times 10^{-5}$ and $1.94 \times 10^{-5}$ $G_0$, respectively, which is still close to that of the Cu$^{2+}$—peptide ones. Therefore, the conductance switching upon Cu$^{2+}$ binding comes from the structure changing.

Rather than involving the covalent bond in the Cu$^{2+}$—peptide complexes, the BPA molecule attaches to peptides via hydrogen bonds. Two hydroxyl groups of BPA, separated by 9.62 Å, bind to nitrogen and oxygen atoms of the Cys-Gly-Cys peptide and to two oxygen atoms of the cysteamine-Gly-Gly-Cys peptide, shown in Figure 3a,e, respectively. They form parallel circuits and lead to quantum interference. Upon BPA binding, the conductance of the Cys-Gly-Cys + BPA junction decreases a little to $5.02 \times 10^{-6}$ $G_0$, but that of the cysteamine-Gly-Gly-Cys + BPA one increases to $1.38 \times 10^{-5} G_0$ (Table 1). The BPA binding provides a new conduction channel, mostly through the hydrogen bonds and hydrox-

**Table 1. Conductance of Peptides and Their Complexes**

| peptide                  | conductance $[G_0]$   | peptide + Cu$^{2+}$ | peptide + BPA |
|--------------------------|-----------------------|----------------------|---------------|
| Cys-Gly-Cys              | $7.40 \times 10^{-6}$ | $6.14 \times 10^{-5}$ | $5.02 \times 10^{-6}$ |
| cysteamine-Gly-Gly-Cys   | $5.36 \times 10^{-7}$ | $4.36 \times 10^{-5}$ | $1.38 \times 10^{-5}$ |

*The measured data* are shown in parentheses.
yphenyl rings of the BPA molecule, as LDOS at $E_F$ indicates, shown in Figure 3d,h. This channel governs the junction conductance, causing a similar conductance of the two BPA-bond peptides. Figure 3b,f shows the transmission spectra of
Cys-Gly-Cys + BPA and cysteamine-Gly-Gly-Cys + BPA junctions, respectively, which are dominated by the PDOS of the complexes, plotted in Figure 3c,g. Although the PDOS of the complexes is similar with that of the peptides, two peaks around $-0.02$ and $-0.36$ eV align with those of BPA. The former peak dominates the LDOS at $E_F$ and thus the junction conductance. When BPA molecules are removed from these geometries, the conductance of the BPA-removed Cys-Gly-Cys (cysteamine-Gly-Gly-Cys) junction, $2.51 \times 10^{-6}$ ($8.0 \times 10^{-6}$) $G_0$, is a little smaller (higher) than the peptide one, $7.40 \times 10^{-6}$ ($5.36 \times 10^{-6}$) $G_0$, because of the slight deformation of the peptide caused by BPA binding. Overall, the cysteamine-Gly-Gly-Cys junction can detect both Cu$^{2+}$ and BPA well, whereas the Cys-Gly-Cys junction can only distinguish Cu$^{2+}$.

**CONCLUSIONS**

In summary, we investigate the electron transmission spectra of Cys-Gly-Cys and cysteamine-Gly-Gly-Cys peptide junctions, and their change upon Cu$^{2+}$ or BPA binding from first principles. We first compare the calculated results for detecting the Cu ion with the previous experimental work, bridging the long-standing gaps between theory and experiment. Next, we employ the same approach to make predictions about detecting the BPA molecule. For both the cases, Cu and BPA, there is a more significant change in the conductance of the junction with the cysteamine-Gly-Gly-Cys peptide than with the Cys-Gly-Cys peptide. We computationally show that the former peptide can act as sensors for both the copper ion and the BPA molecule via conductance modulation. Our results would promote further research in the field of sensing with molecular electronics.

**COMPUTATIONAL METHODS**

As the gold tip of a scanning probe microscope is retracted from the molecule, the gold nanowires along with the atomic contact form at the ends of the molecule, building the single-molecule junction. Therefore, the peptide junction consisted of three parts: the left electrode, the right electrode, and the scattering region (Figure 1a). Gold electrodes with unit cells repeating along the [001] direction were used. The scattering region included layers of electrode as buffer regions bonded through gold adatoms to a single peptide in between. The molecule, its complex, and two gold adatoms were fully relaxed by a SIESTA package, based on density functional theory (DFT), whereas the other gold atoms were kept fixed at the experimental lattice constant of 4.08 Å. The quantum transport properties were calculated by a Nanodcal pack-

**AUTHOR INFORMATION**

**Corresponding Authors**

*E-mail: yhsu@mail.ncku.edu.tw (Y.-H.S.).
*E-mail: kauncc@gate.sinica.edu.tw (C.-C.K.)

**ORCID**

Chao-Cheng Kaun: 0000-0002-5400-4758

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

This work was partially supported by the Ministry of Science and Technology, Taiwan, through no. 104-2112-M-001-008-MY3, no. 107-2112-M-001-036-MY3 and the National Center for Theoretical Sciences, Taiwan.

**REFERENCES**

1. Eckstein-Levi, M.; Capua, E.; Refaelly-Abramson, S.; et al. Cold denaturation induces inversion of dipole and spin transfer in chiral peptide monolayers. *Nat. Commun.* 2016, 7, 10744.
2. Viguier, B.; Zör, K.; Kasotakis, E.; Mitraki, A.; Clausen, C. H.; Svendsen, W. E.; Castillo-León, J. Development of an electrochemical metal-ion biosensor using self-assembled peptide nanofibrils. *ACS Appl. Mater. Interfaces* 2011, 3, 1594–1600.
3. de la Rica, R.; Matsu, H. Applications of peptide and protein-based materials in bionanotechnology. *Chem. Soc. Rev.* 2010, 39, 3499–3509.
4. de la Rica, R.; Mendoza, E.; Matsu, H. Bioinspired target-specific crystallization on peptide nanotubes for ultrasensitive Pb ion detection. *Small* 2010, 6, 1753–1756.
5. MacPhee, C. E.; Woolfson, D. N. Engineered and designed peptide-based fibrous biomaterials. *Curr. Opin. Solid State Mater. Sci.* 2004, 8, 141–149.
6. Aguilar, A. D.; Forzani, E. S.; Li, X.; Tao, N.; Nagahara, L. A.; Amlani, I.; Tsui, R. Chemical sensors using peptide-functionalized conducting polymer nanojunction arrays. *Appl. Phys. Lett.* 2005, 87, 193108.
7. Yang, J.; Kim, S.-E.; Cho, M.; Yoo, I.-K.; Choe, W.-S.; Lee, Y. Highly sensitive and selective determination of bisphenol-A using peptide-modified gold electrode. *Biosens. Bioelectron.* 2014, 61, 38–44.
8. Xiao, X.; Xu, B.; Tao, N. Changes in the conductance of single peptide molecules upon metal-ion binding. *Angew. Chem., Int. Ed.* 2004, 43, 6148–6152.
9. Xiao, X.; Xu, B.; Tao, N. Conductance titration of single-peptide molecules. *J. Am. Chem. Soc.* 2004, 126, 5370–5371.
10. Scullion, L.; Doneux, T.; Bouffier, L.; Fernig, D. G.; Higgins, S. J.; Bethell, D.; Nichols, R. J. Large conductance changes in peptide single molecule junctions controlled by pH. *J. Phys. Chem. C* 2011, 115, 8361–8368.
11. Chow, E.; Gooding, J. J. Peptide modified electrodes as electrochemical metal ion sensors. *Electroanalysis* 2006, 18, 1437–1448.
12. Yugay, D.; Goronzy, D. P.; Kawakami, L. M.; et al. Copper Ion Binding Site in b-Amyloid Peptide. *Nano Lett.* 2016, 16, 6282–6289.
13. Hunt, P. A.; Lawson, C.; Gieske, M.; Murdoch, B.; Smith, H.; Marre, A.; Hassold, T.; VandeVoort, C. A. Bisphenol A alters early oogenesis and follicle formation in the fetal ovary of the rhesus monkey. *PNAS* 2012, 109, 17525–17530.
14. Cardamone, D. M.; Kirczenow, G. Single-molecule device prototypes for protein-based nanoelectronics: Negative differential resistance and current rectification in oligopeptides. *Phys. Rev. B: Condens. Matter Mater. Phys.* 2008, 77, 165403.
15. Sen, A.; Lin, C.-J.; Kaun, C.-C. Single-Molecule Conductance through Chiral Gold Nanotubes. *J. Phys. Chem. C* 2013, 117, 13676–13680.
16. Sen, A.; Kaun, C.-C. Effect of electrode orientations on charge transport in alkanedithiol single-molecule junctions. *ACS Nano* 2010, 4, 6404–6408.
17. He, J.; Sankey, O.; Lee, M.; Tao, N.; Li, X.; Lindsay, S. Measuring Single Molecule Conductance with Break Junctions. *Faraday Discuss.* 2006, 131, 145–154.
18. Perrine, T. M.; Dunietz, B. D. Carbonyl mediated conductance through metal bound peptides: a computational study. *Nanotechnology* 2007, 18, 424003.
(19) Horsley, J. R.; Yu, J.; Abell, A. D. The Correlation of Electrochemical Measurements and Molecular Junction Conductance Simulations in β-Strand Peptides. *Chem.—Eur. J.* 2015, 21, 5926–5933.

(20) Yu, J.; Horsley, J. R.; Abell, A. D. Exploiting the interplay of quantum interference and backbone rigidity on electronic transport in peptides: a step towards bio-inspired quantum interferometers. *Mol. Syst. Des. Eng.* 2017, 2, 67–77.

(21) Chen, C. J.; Smeu, M.; Ratner, M. A. Modeling ion sensing in molecular electronics. *J. Chem. Phys.* 2014, 140, 054709.

(22) Das, B. Modeling selective single molecule sensors for transition metal ions. *J. Phys. Chem. C* 2009, 113, 16203–16209.

(23) Dou, K. P.; Kaun, C.-C. Conductance superposition rule in carbon nanowire junctions with parallel paths. *J. Phys. Chem. C* 2016, 120, 18939–18944.

(24) Soler, J. M.; Artacho, E.; Gale, J. D.; García, A.; Junquera, J.; Ordejón, P.; Sánchez-Portal, D. The SIESTA method for ab initio and electronic-structure materials simulation. *J. Phys.: Condens. Matter* 2002, 14, 2745–2779.

(25) Taylor, J.; Guo, H.; Wang, J. Ab initio modeling of quantum transport properties of molecular electronic devices. *Phys. Rev. B: Condens. Matter Mater. Phys.* 2001, 63, 245407.

(26) Waldron, D.; Liu, L.; Guo, H. Ab initio simulation of magnetic tunnel junctions. *Nanotechnology* 2007, 18, 424026.