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Published in: Journal of Physical Chemistry Letters

DOI: 10.1021/acs.jpclett.8b01908

Published: 16/08/2018

Document Version Publisher's PDF, also known as Version of record

Please cite the original version: Chen, X., Makkonen, E., Golze, D., & Lopez-Acevedo, O. (2018). Silver-Stabilized Guanine Duplex: Structural and Optical Properties. *Journal of Physical Chemistry Letters*, *9*(16), 4789-4794. https://doi.org/10.1021/acs.jpclett.8b01908

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# THE JOURNAL OF PHYSICAL CHEMISTRY Letters © Cite This: J. Phys. Chem. Lett. 2018, 9, 4789–4794



# Silver-Stabilized Guanine Duplex: Structural and Optical Properties

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**Supporting Information** 

ABSTRACT: Recent experimental duplexes of DNA stabilized by Ag cations, pairing homostrands of guanine-guanine, cytosine-cytosine, adenine-thymine, and thymine-thymine, display much higher stability than the Watson-Crick paired DNA duplexes; these broaden the range of applications for DNA nanotechnology. Here we focus on silver-stabilized guanine duplexes in water. Using hybrid quantum mechanics/molecular mechanics simulations, we propose an atomic structure for the Ag+mediated guanine duplex with two nucleobases per strand,  $G_2 - Ag_2^+ - G_2$ . We then compare experimental and time-dependent density functional



theory-simulated electronic circular dichroism (ECD) spectra to validate our results. Both experimental and simulated ECD share two negative peaks around 220 and 280 nm, with no positive signal in the measured wavelength range. We found that the left- or right-handed disposition of bases in the structure has a decisive effect on the signs of the ECD. We conclude that  $G_2$ -Ag<sub>2</sub><sup>+</sup>-G<sub>2</sub> is left-hand-oriented, and extrapolation of this orientation to longer strands gives rise to a left-hand-oriented parallel helix stabilized by interplanar H bonds.

### INTRODUCTION

The DNA double helix is the pivotal biological structure for encoding genetic information in life. Strongly bound metal cations can integrate DNA-based nanomaterials and potentiate them with enhanced thermal stability, new physical and chemical properties, and diverse functionalities. Thus hybrid metal-DNA materials now extend the DNA's longstanding versatility from biology to nanotechnology. For example, they are promising candidates for conducting nanowires,<sup>1</sup> nanophotonics,<sup>2</sup> molecular devices,<sup>3</sup> toxic metal detection,<sup>4</sup> biosensing, and biolabeling.<sup>5-7</sup> Among different metal cations, Ag<sup>+</sup> is particularly interesting, because it has low toxicity and it binds exclusively to the DNA bases rather than to the negatively charged sugar-phosphate backbones. A recent flurry of attention has focused on fluorescent DNA-stabilized silver clusters because of their chemical and biochemical sensing applications. $^{6-8}$  Different experiments and our own simulations indicate that Ag<sup>+</sup>-DNA interactions are the key to stabilizing the fluorescent clusters.<sup>9–14</sup>

Among the various DNA bases interacting with Ag<sup>+</sup>, the first reported is the bridging configuration  $C-Ag^+-C$  (C: cytosine) between DNA duplexes; it is also the most studied case, both theoretically and experimentally.<sup>14-18</sup> Duplexes linked through  $G-Ag^+-G$ ,  $C-Ag^+-G$ ,  $T-Ag^+-A$ , and  $T-Ag^+-T$  (G: guanine, A: adenine, and T: thymine) were also reported.<sup>1,14,16</sup> A systematic study of Ag<sup>+</sup>-mediated DNA geometry is a computational challenge. Even with 10 base DNA duplexes that combine C, G, A, and T nucleobases, there are more than 1 million different compositions. However, homobase Ag<sup>+</sup>- mediated DNA duplexes have been recently reported.<sup>14</sup> Because of its reduced complexity, it is an ideal model system to gain computational insight into Ag<sup>+</sup>-DNA interactions.

Previously, we simulated Ag<sup>+</sup>-bridged cytosine homo duplexes and found that they prefer the parallel conformation, in which interplanar H bonds play an important stabilizing role.<sup>19,20</sup> Here we focus on Ag<sup>+</sup>-bridged guanine duplexes. The Ag<sup>+</sup>-guanine combination is alluring for several reasons. First, experiments show that G<sub>N</sub> strands form fully Ag<sup>+</sup>-bridged duplexes<sup>14</sup> with increasing Ag concentration, whereas cytosine always presents a combination of single-strand Ag<sup>+</sup> complexes and Ag<sup>+</sup>-bridged duplexes. As with other Ag<sup>+</sup>-bridged duplexes, the duplex  $G_N - Ag_N^+ - G_N$  offers greater stability than the Watson–Crick paired  $C_N$ – $G_N$  duplex, which may broaden the range of applications for DNA nanotechnology (this was limited by the low thermal melting temperatures imposed by Watson-Crick pairing).<sup>14</sup> Second, guanine- (or cytosine-) rich DNA sequences are present in DNA sequences that stabilize fluorescent Ag clusters.<sup>21</sup> Understanding guanine-Ag<sup>+</sup> interactions will be the first step toward the rational design of such florescent clusters. Third, in biochemistry, the strong interactions of G bases with  $Pt^{2+}$  are thought to be the key to important chemotherapy drugs.<sup>22,23</sup> Understanding the guanine-Ag<sup>+</sup> interactions might help to develop novel drugs for cancer therapy.

Received: June 18, 2018 Accepted: August 6, 2018 Published: August 6, 2018

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Structural arrangements of metal-DNA hybrid materials (M-DNA) are particularly difficult to obtain experimentally via crystallization. Therefore, theoretical calculations using quantum chemistry methods are the most promising tools to propose geometries and interpret the experimental spectroscopy. In this context, electronic circular dichroism (ECD) is a proven, powerful tool for characterizing DNA's secondary (and higher) structure, and it significantly participates in all basic conformational findings on DNA,<sup>24</sup> including the Ag<sup>+</sup>-mediated cytosine duplexes.<sup>19</sup> By comparing computed with measured ECD spectra, the structure of M-DNA can be inferred. Here we extend this method to propose an atomic structure for Ag+-mediated guanine duplexes in water and determine the factors affecting the ECD of such systems. Considering both computational accuracy and efficiency, we chose the smallest unit of Ag<sup>+</sup>-bridged guanine duplexes, G<sub>2</sub>- $Ag_2^+-G_2$ , namely, the  $Ag^+$ -bridged guanine tetramer.

To explore the Ag<sup>+</sup>-guanine tetramer's possible structural arrangements, we built two initial structures using the 3DNA software.<sup>25</sup> One is a left-handed tetramer (Configuration L) and the other is a right-handed tetramer with the same handedness as the natural B-DNA (Configuration R). We want to stress that the only difference between the configurations is tetramer's handedness; the strands' components are the same. Prior computational studies of Ag<sup>+</sup>-guanine duplexes have been challenging due to the plethora of possible binding geometries for guanine. However, recently reported crystal structures that contain G-Ag<sup>+</sup>-G pairs and density functional theory (DFT) simulations both suggest that  $Ag^+$  binds to N7, N7' in the Hoogsteen region.<sup>1,14,10</sup> In addition, our previous DFT simulation strongly indicates that the silver-mediated guanine dimer is most stable in a trans configuration corresponding to the parallel strand orientation.<sup>14</sup> Thus in both initial structures of Configuration L and Configuration R, Ag<sup>+</sup> bonds to N7, N7', and the DNA has parallel strand orientation (see Figure 1). The configuration in which Ag<sup>+</sup>



**Figure 1.** Ground state of the guanine $-Ag^+$ -guanine complex with the two guanines in a trans configuration. The silver cation binds to the nitrogen atoms in the Hoogsteen region.

binds to N7 and O6' has also been simulated. Ag<sup>+</sup> moved to the bridge position between N7 and N7' during the geometry optimization in vacuum, which indicates that Ag<sup>+</sup> energetically prefers to bind to N instead of O. Once we include the solvent, the system's size is prohibitive for full quantum calculations, so we performed hybrid quantum mechanics/molecular mechanics (QM/MM) simulations. We calculated the silver and DNA atoms at the QM level within the Kohn–Sham DFT approximation, whereas the solvation was modeled with a 4 nm box of classical water molecules and the Amber force field.<sup>26</sup> van der Waals interactions between the QM and MM regions were approximated by classical force fields. Electrostatic interactions between the two subsystems were accounted for using an embedding approach, where the point charges located at the water molecules (MM region) can polarize the Ag<sup>+</sup>-mediated DNA (QM region). Details can be found in the Computational Details section. Before the QM/MM simulations, the systems were first equilibrated at 300 K with a classical NVT run of 2 ns. Then, the QM/MM simulations were performed within the NVT ensemble for 21 ps. By comparing the root-mean-square (RMS) distance of the heavy atoms to the initial structure positions (Figure 2A), we can conclude that the system reached an equilibrium regime after 16 ps. Therefore, we used only the last 5 ps of the trajectory for analysis.

During the last 5 ps of the simulation, the average Ag-Ag distance in Configuration L is 3.45 Å with a standard deviation of 0.27 Å (Figure 2B), whereas the average Ag–Ag distance in Configuration R is 3.61 Å with a standard deviation of 0.25 Å. They are both comparable to the Ag–Ag distance in the Ag<sup>+</sup>bridged cytosine tetramer, which oscillates around an average value of 3.5 Å with a standard deviation of 0.21 Å. The simulated solvated average Ag-Ag distance is therefore longer than the average Ag–Ag distance (3.15 Å) observed in comparable DNA crystal structures  $^{1,16}$  and would then correspond to a solvated free-energy minimum. Similar to the cytosine-Ag<sup>+</sup> tetramer, interplanar hydrogen bonds may form between guanine bases in  $G_2$ - $Ag_2^+$ - $G_2$  (O6-H8', O6'-H8). The residence times of the H bonds in Configuration L are 79.6 and 60.6% with a cutoff of 2.2 Å, whereas the residence times of H bonds in Configuration R are 74.0 and 18.4% with the same cutoff (Figure S1).

A typical solvated structure of Configuration L from the final 0.5 ps of the QM/MM run can be seen in Figure 3; see also Figure S2 for Configuration R. Because of a smaller Ag–Ag distance and more hydrogen bonds that introduce higher stability, we expect that Configuration L may be more stable, and it corresponds to the structure of  $Ag^+$ -bridged guanine duplexes in water. To test the proposed structural configuration, we calculated the ECD of Configurations L and R and compared them with experimental ECD in the following. Because ECD is highly sensitive to small structural changes, it offers a reliable method to validate our simulations.

The experimental ECD spectra for three  $Ag^+$ -mediated guanine species are shown in Figure 4A, which is reproduced here from a previous reference.<sup>27</sup> The spectra of  $G_N - Ag_N^+ - G_N$  for N = 2, 6, and 20 have two negative peaks around 220 and 280 nm, which are therefore size-independent. The spectrum of  $G_2 - Ag_2^+ - G_2$  differs in the intensity of the 220 nm peak, potentially caused by aggregation induced by  $Ag^+$  ions.<sup>27</sup> It is striking that no positive signal exists in all three measured ECD spectra. The size-independent negative peaks suggest that they share the same structural configuration.

The ECD spectra were calculated using the linear-response time-dependent density functional theory (TDDFT) with the LB94 exchange-correlation functional.<sup>28</sup> The Computational Details section provides detailed information on the computational setup. Figure 4B shows the calculated average ECD of 10 snapshots from the last 5 ps QM/MM simulation of Configuration L. To make sure that 10 snapshots are enough to converge the average ECD's main features, three uncorrelated sets of structures have been calculated for comparison. They are snapshots from the QM/MM trajectory, starting from 16.0, 16.2, and 16.3 ps, collected at time intervals of 0.5 ps (marked by black, blue, and red dots in Figure 2B,



Figure 2. (A) Root-mean-square distance to the initial positions of the heavy atoms in configuration L during the QM/MM simulation. (B) Ag–Ag distance in Configuration L during the final 5 ps of QM/MM simulation; the colorful dots indicate where samples are taken for ECD calculations in Figure 4b.



Figure 3. One typical solvated structure of Configuration L from the final 0.5 ps of the QM/MM run. The interplanar H bond is highlighted with a green line. Color code: Ag: silver, N: blue, C: black, O: red, P: olive, and H: white.

respectively). From Figure 4B, we can see that the three average ECD spectra are qualitatively the same. The ECD of some individual snapshots can been found in Figure S3. The calculated ECD of Configuration L and measured ECD of  $G_N-Ag_N^+-G_N$  agree well with each other. This suggests that the configuration L, in which  $Ag^+$  binds to the N atoms in the Hoogsteen region and the DNA strands form a parallel lefthand helix, should be a common configuration for the  $Ag^+$ -mediated guanine duplex. To test the ECD dependence on the choice of the exchange-correlation functional, we repeated the ECD calculation for set 1 with different type of DFT functionals, namely, B3LYP<sup>29</sup> and PBE<sup>30</sup> (see Figure 4C,D). All of the calculated average ECD spectra share two negative peaks, with the main difference being that the ECD calculated from B3LYP is shifted toward the lower wavelength direction.

We then also performed ECD simulations on Configuration R using the same average method and the same functional LB94 (Figure 5). The ECD of Configuration R has a positive

peak around 220 nm and a smaller positive peak around 270 nm. The ECD of Configuration R is almost mirrored in intensity with respect to the ECD of Configuration L. Importantly, we found that the overall handedness, namely, the left-handed or right-handed disposition of bases in the tetramer, has a decisive effect on the signs of the ECD. By comparing the calculated and measured ECD, we conclude that the Ag<sup>+</sup>-mediated guanine tetramer is left-hand-oriented and would give rise (by extrapolating this orientation to longer strands) to a left-hand-oriented helix.

Our simulations predict that both the cytosine<sup>19,20</sup> and guanine would form, independent of size, a parallel  $Ag^+$ mediated double helix stabilized by interplanar H bonds. It is, however, interesting to point out the differences between the  $Ag^+$ -mediated cytosine and guanine cases. The  $Ag^+$ -mediated cytosine duplex would form a right-handed helix, similar to the B-DNA's handedness, whereas  $Ag^+$ -mediated guanine would form a left-handed helix. For cytosine,  $Ag^+$  would bind to

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**Figure 4.** (A) Experimental electronic circular dichroism (ECD) of  $Ag^+$ -mediated  $G_2$ ,  $G_6$ , and  $G_{20}$  duplexes (G: guanine). Reprinted with permission from ref 27. Copyright 2016 IOP Publishing Ltd. and Deutsche Physikalische Gesellschaft. (B) LB94 calculated average ECD of three sets of structures, where the color of the curves corresponds to the dots with same color in Figure 2b. The calculated ECD of set 1 by using the (C) B3LYP and (D) PBE functionals.



Figure 5. Calculated average ECD of Configuration L and Configuration R using 10 structures.

cytosine N atoms in the Watson–Crick region, whereas for guanine,  $Ag^+$  would bind to N atoms in the Hoogsteen region.

In summary, combining QM/MM hybrid molecular dynamics and TDDFT methods, we propose a structural configuration for  $Ag^+$ -mediated guanine duplexes in water.  $Ag^+$  ions bind to the N atoms in the Hoogsteen region, and the DNA forms a parallel left-handed helix, in which interplanar hydrogen bonds help stabilize the whole structure. Its simulated ECD agrees satisfactorily with the reference experimental spectra. Both experimental and simulated spectra share two ECD negative peaks around 220 and 280 nm, with no positive signal in the measured wavelength range. Determining the structural conformation of the  $Ag^+$ -mediated guanine duplex, along with previous work on the  $Ag^+$ -mediated

cytosine duplex, opens the door to computational study of more complex Ag–DNA nanomaterials, such as fluorescent DNA-stabilized Ag clusters. It is an important step toward the rational design of such materials.

#### COMPUTATIONAL DETAILS

All QM/MM simulations were carried out with the CP2K program package.<sup>31</sup> The Ag<sup>+</sup>-bridged DNA structures were treated at the Kohn-Sham DFT level, whereas the solvent molecules were described by standard Amber force fields<sup>26</sup> at the MM level. The DFT calculations were performed within the Gaussian and plane-wave scheme.<sup>32,33</sup> The double- $\zeta$ valence plus polarization (DZVP) basis sets of the MOLOPT type<sup>34</sup> were used to describe the valence electrons. Normconserving Goedecker-Teter-Hutter (GTH) pseudopotentials<sup>35–37</sup> were used to approximate the atomic cores and their interaction with the valence electrons. The exchange and correlation potential was described by the Perdew-Burke-Ernzerhof (PBE) functional.<sup>30</sup> Grimme's D3 dispersive correction<sup>38</sup> was used to account for long-range van der Waals interactions. The electron density was expanded in an auxiliary set of plane waves with a cutoff energy of 300 Ry. The electrostatic interactions between the QM and MM subsystems were modeled by charge sets of the Amber force field employing the electrostatic coupling procedure implemented in the QM/MM module<sup>39,40</sup> in CP2K to correctly account for periodic boundary conditions. The QM and MM box have been set to the same size of 40.61 Å to avoid computationally expensive decoupling between QM images. Dispersion interactions between the guanine-Ag<sup>+</sup> tetramer and water

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molecules were reproduced by an empirical potential of the Lennard-Jones type using Amber parameters.

Molecular dynamics (MD) simulations were performed within the canonical (NVT) ensemble at 300 K using a time step of 0.5 fs. Before starting the QM/MM simulations, the solvent structures had been pre-equilibrated for 2 ns at the MM level, keeping the guanine $-Ag^+$  tetramer fixed in its DFToptimized structure and employing the Amber potential for the solvent. Then, the QM/MM simulation was performed for 21 ps using the last 5 ps of trajectory for analysis.

The ECD spectra were mainly calculated using the linearresponse time-dependent DFT implemented in the GPAW code.<sup>41,42</sup> GPAW is a DFT code based on the projectoraugmented wave (PAW) method. The wave functions are described with real-space uniform grids. The grid spacing was 0.2 Å in this work. The silver ions and all DNA atoms were included in the GPAW simulations. Per atom, the electronic configurations of valence electrons are  $H(1s^1)$  (2s<sup>2</sup>2p<sup>4</sup>),  $C(2s^{2}2p^{2})$ ,  $N(2s^{2}2p^{3})$ , and  $Ag(4p^{6}4d^{10}5s^{1})$ , with a scalar relativistic correction and a frozen core. The LB94 exchangecorrelation functional was used in the calculations. The two POO groups in the backbone were protonated to POOH to present water's screening effect. GPAW use the rotatory strength convoluted with gaussians as the output of ECD. To get the  $\Delta \varepsilon$ , we have multiplied the output data by the energy and the constant taken from ref 43.

The ECD of set 1 (10 structures) was also calculated by the software package Gaussian  $16^{44}$  using the functionals B3LYP and PBE. The Gaussian code is used with a LANL2DZ/ECP basis set for the silver atom and maug-cc-pvdz for the remaining atoms. The sugar-phosphate backbones were replaced by H atoms in the simulations. The replacement hydrogen atoms were then relaxed at the B3LYP/6-31G\*\* level while keeping the rest of the atoms frozen.

#### ASSOCIATED CONTENT

#### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jp-clett.8b01908.

Details of the hydrogen bonds in simulated structures, a typical solvated structure of Configuration R in water, and the calculated individual ECD of Configuration L. Figure S1: The O-H distances in Configuration L and Configuration R as a function of time. Figure S2: One typical solvated structure of Configuration R from the final 0.5 ps of the QM/MM run. Figure S3: The calculated ECD of five structures of Configuration L. (PDF)

Coordinates of one snapshot from the silver-stabilized guanine duplex dynamics (XYZ)

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# Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We thank Prof. Elizabeth Gwinn for discussion and comments on the manuscript. This work was supported by the Academy of Finland Projects 308647, 314298, 279240, and 312556. D.G. acknowledges financial support by the Swiss National Science Foundation (SNF) under project no. P2ZHP2 168444. We thank CSC, the Finnish IT Center for Science Espoo, for computational resources.

#### REFERENCES

(1) Kondo, J.; Tada, Y.; Dairaku, T.; Hattori, Y.; Saneyoshi, H.; Ono, A.; Tanaka, Y. A metallo-DNA nanowire with uninterrupted onedimensional silver array. *Nat. Chem.* **2017**, *9*, 956–960.

(2) Copp, S. M.; Schultz, D. E.; Swasey, S.; Gwinn, E. G. Atomically precise arrays of fluorescent silver clusters: a modular approach for metal cluster photonics on DNA nanostructures. *ACS Nano* **2015**, *9*, 2303–2310.

(3) Takezawa, Y.; Shionoya, M. Metal-mediated DNA base pairing: alternatives to hydrogen-bonded Watson-Crick base pairs. *Acc. Chem. Res.* **2012**, *45*, 2066–2076.

(4) Zhou, W.; Saran, R.; Liu, J. Metal Sensing by DNA. *Chem. Rev.* 2017, 117, 8272–8325.

(5) Guo, W.; Yuan, J.; Dong, Q.; Wang, E. Highly sequencedependent formation of fluorescent silver nanoclusters in hybridized DNA duplexes for single nucleotide mutation identification. *J. Am. Chem. Soc.* **2010**, *132*, 932–934.

(6) Yuan, Z.; Chen, Y.-C.; Li, H.-W.; Chang, H.-T. Fluorescent silver nanoclusters stabilized by DNA scaffolds. *Chem. Commun.* **2014**, *50*, 9800–9815.

(7) Gwinn, E.; Schultz, D.; Copp, S. M.; Swasey, S. DNA-protected silver clusters for nanophotonics. *Nanomaterials* **2015**, *5*, 180–207.

(8) Ramazanov, R. R.; Sych, T. S.; Reveguk, Z. V.; Maksimov, D. A.; Vdovichev, A. A.; Kononov, A. I. Ag-DNA emitter: metal nanorod or supramolecular complex? *J. Phys. Chem. Lett.* **2016**, *7*, 3560–3566.

(9) Copp, S. M.; Schultz, D.; Swasey, S.; Pavlovich, J.; Debord, M.; Chiu, A.; Olsson, K.; Gwinn, E. Magic numbers in DNA-stabilized fluorescent silver clusters lead to magic colors. *J. Phys. Chem. Lett.* **2014**, *5*, 959–963.

(10) Copp, S. M.; Schultz, D.; Swasey, S. M.; Faris, A.; Gwinn, E. G. Cluster plasmonics: dielectric and shape effects on DNA-stabilized silver clusters. *Nano Lett.* **2016**, *16*, 3594–3599.

(11) Swasey, S. M.; Karimova, N.; Aikens, C. M.; Schultz, D. E.; Simon, A. J.; Gwinn, E. G. Chiral electronic transitions in fluorescent silver clusters stabilized by DNA. *ACS Nano* **2014**, *8*, 6883–6892.

(12) Petty, J. T.; Sergev, O. O.; Ganguly, M.; Rankine, I. J.; Chevrier, D. M.; Zhang, P. A segregated, partially oxidized, and compact Ag<sub>10</sub> cluster within an encapsulating DNA host. *J. Am. Chem. Soc.* **2016**, 138, 3469–3477.

(13) Schultz, D.; Gardner, K.; Oemrawsingh, S. S. R.; Markešević, N.; Olsson, K.; Debord, M.; Bouwmeester, D.; Gwinn, E. Evidence for rod-shaped DNA-stabilized silver nanocluster emitters. *Adv. Mater.* **2013**, *25*, 2797–2803.

(14) Swasey, S. M.; Leal, L. E.; Lopez-Acevedo, O.; Pavlovich, J.; Gwinn, E. G. Silver (I) as DNA glue: Ag<sup>+</sup>-mediated guanine pairing revealed by removing Watson-Crick constraints. *Sci. Rep.* **2015**, *5*, 10163–10171.

(15) Ono, A.; Cao, S.; Togashi, H.; Tashiro, M.; Fujimoto, T.; Machinami, T.; Oda, S.; Miyake, Y.; Okamoto, I.; Tanaka, Y. Specific interactions between silver(I) ions and cytosine-cytosine pairs in DNA duplexes. *Chem. Commun.* **2008**, 4825–4827.

(16) Liu, H.; Shen, F.; Haruehanroengra, P.; Yao, Q.; Cheng, Y.; Chen, Y.; Yang, C.; Zhang, J.; Wu, B.; Luo, Q.; et al. A DNA structure containing Ag<sup>1</sup>-mediated G: G and C: C base pairs. *Angew. Chem., Int. Ed.* **201**7, *56*, 9430–9434.

(17) Berdakin, M.; Féraud, G.; Dedonder-Lardeux, C.; Jouvet, C.; Pino, G. A. Effect of  $Ag^+$  on the excited-state properties of a gas-phase (cytosine)<sub>2</sub> $Ag^+$  complex: electronic transition and estimated lifetime. *J. Phys. Chem. Lett.* **2014**, *5*, 2295–2301.

#### The Journal of Physical Chemistry Letters

(19) Espinosa Leal, L. A.; Karpenko, A.; Swasey, S.; Gwinn, E. G.; Rojas-Cervellera, V.; Rovira, C.; Lopez-Acevedo, O. The role of hydrogen bonds in the stabilization of silver-mediated cytosine tetramers. *J. Phys. Chem. Lett.* **2015**, *6*, 4061–4066.

(20) Chen, X.; Karpenko, A.; Lopez-Acevedo, O. Silver-mediated double helix: structural parameters for a robust DNA building block. *ACS Omega* **201**7, *2*, 7343–7348.

(21) Copp, S. M.; Bogdanov, P.; Debord, M.; Singh, A.; Gwinn, E. Base motif recognition and design of DNA templates for fluorescent silver clusters by Machine Learning. *Adv. Mater.* **2014**, *26*, 5839–5845.

(22) Fichtinger-Schepman, A. M. J.; Van der Veer, J. L.; Den Hartog, J. H. J.; Lohman, P. H. M.; Reedijk, J. Adducts of the antitumor drug cis-diamminedichloroplatinum(II) with DNA: formation, identification, and quantitation. *Biochemistry* **1985**, *24*, 707–713.

(23) Garbutcheon-Singh, K. B.; Grant, M. P.; Harper, B. W.; Krause-Heuer, A. M.; Manohar, M.; Orkey, N.; Aldrich-Wright, J. R. Transition metal based anticancer drugs. *Curr. Top. Med. Chem.* **2011**, *11*, 521–542.

(24) Kypr, J.; Kejnovská, I.; Renčiuk, D.; Vorlíčková, M. Circular dichroism and conformational polymorphism of DNA. *Nucleic Acids Res.* **2009**, *37*, 1713–1725.

(25) Lu, X.-J.; Olson, W. K. 3DNA: a software package for the analysis, rebuilding and visualization of three-dimensional nucleic acid structures. *Nucleic Acids Res.* **2003**, *31*, 5108–5121.

(26) Ponder, J. W.; Case, D. A. Force Fields for Protein Simulations. *Adv. Protein Chem.* **2003**, *66*, 27–85.

(27) Swasey, S.; Gwinn, E. Silver-mediated base pairings: towards dynamic DNA nanostructures with enhanced chemical and thermal stability. *New J. Phys.* **2016**, *18*, 045008–045025.

(28) van Leeuwen, R.; Baerends, E. J. Exchange-correlation potential with correct asymptotic behavior. *Phys. Rev. A: At., Mol., Opt. Phys.* **1994**, 49, 2421–2431.

(29) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. Ab initio calculation of vibrational absorption and circular dichroism spectra using Density Functional force fields. *J. Phys. Chem.* **1994**, *98*, 11623–11627.

(30) Perdew, J. P.; Burke, K.; Ernzerhof, M. Generalized gradient approximation made simple. *Phys. Rev. Lett.* **1996**, *77*, 3865–3868.

(31) Hutter, J.; Iannuzzi, M.; Schiffmann, F.; VandeVondele, J. cp2k: atomistic simulations of condensed matter systems. *WIREs Comput. Mol. Sci.* **2014**, *4*, 15–25.

(32) Lippert, G.; Hutter, J.; Parrinello, M. A hybrid Gaussian and plane wave density functional scheme. *Mol. Phys.* **1997**, *92*, 477–488.

(33) VandeVondele, J.; Krack, M.; Mohamed, F.; Parrinello, M.; Chassaing, T.; Hutter, J. QUICKSTEP: Fast and accurate density functional calculations using a mixed Gaussian and plane waves approach. *Comput. Phys. Commun.* **2005**, *167*, 103–128.

(34) VandeVondele, J.; Hutter, J. Gaussian basis sets for accurate calculations on molecular systems in gas and condensed phases. *J. Chem. Phys.* **2007**, *127*, 114105.

(35) Goedecker, S.; Teter, M.; Hutter, J. Separable dual-space Gaussian pseudopotentials. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1996**, *54*, 1703–1710.

(36) Hartwigsen, C.; Goedecker, S.; Hutter, J. Relativistic separable dual-space Gaussian pseudopotentials from H to Rn. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1998**, *58*, 3641–3662.

(37) Krack, M. Pseudopotentials for H to Kr optimized for gradientcorrected exchange-correlation functionals. *Theor. Chem. Acc.* 2005, *114*, 145–152.

(38) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A consistent and accurate *ab initio* parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* **2010**, 132, 154104.

(39) Laino, T.; Mohamed, F.; Laio, A.; Parrinello, M. An efficient real space multigrid QM/MM electrostatic coupling. *J. Chem. Theory Comput.* **2005**, *1*, 1176–1184.

(40) Laino, T.; Mohamed, F.; Laio, A.; Parrinello, M. An efficient linear-scaling electrostatic coupling for treating periodic boundary conditions in QM/MM simulations. *J. Chem. Theory Comput.* **2006**, *2*, 1370–1378.

(41) Enkovaara, J.; Rostgaard, C.; Mortensen, J. J.; Chen, J.; Dulak, M.; Ferrighi, L.; Gavnholt, J.; Glinsvad, C.; Haikola, V.; Hansen, H. A.; et al. Electronic structure calculations with GPAW: a real-space implementation of the projector augmented-wave method. *J. Phys.: Condens. Matter* **2010**, *22*, 253202–253225.

(42) Walter, M.; Häkkinen, H.; Lehtovaara, L.; Puska, M.; Enkovaara, J.; Rostgaard, C.; Mortensen, J. J. Time-dependent density-functional theory in the projector augmented-wave method. *J. Chem. Phys.* **2008**, *128*, 244101–244110.

(43) Lopez-Acevedo, O.; Tsunoyama, H.; Tsukuda, T.; Häkkinen, H.; Aikens, C. M. J. Am. Chem. Soc. 2010, 132, 8210-8218.

(44) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A. J.; Vreven, T.; Kudin, K. N.; Burant, J. C.; et al. *Gaussian 03*; Gaussian, Inc.: Wallingford, CT, 2004.