

# Theoretical Study on the Structure, Stability, and Electronic Properties of the Guanine–Zn–Cytosine Base Pair in M-DNA

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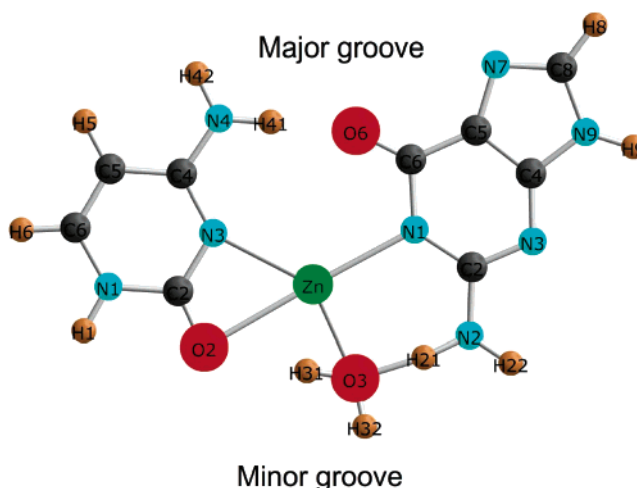
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M-DNA is a type of metalated DNA that forms at high pH and in the presence of Zn, Ni, and Co, with the metals placed in between each base pair, as in G–Zn–C. Experiments have found that M-DNA could be a promising candidate for a variety of nanotechnological applications, as it is speculated that the metal d-states enhance the conductivity, but controversy still clouds these findings. In this paper, we carry out a comprehensive ab initio study of eight G–Zn–C models in the gas phase to help discern the structure and electronic properties of Zn-DNA. Specifically, we study whether a model prefers to be planar and has electronic properties that correlate with Zn-DNA having a metallic-like conductivity. Out of all the studied models, there is only one which preserves its planarity upon full geometry optimization. Nevertheless, starting from this model, one can deduce a parallel Zn-DNA architecture only. This duplex would contain the imino proton, in contrast to what has been proposed experimentally. Among the nonplanar models, there is one that requires less than 8 kcal/mol to flatten (both in gas and solvent conditions), and we propose that it is a plausible model for building an antiparallel duplex. In this duplex, the imino proton would be replaced by Zn, in accordance with experimental models. Neither planar nor nonplanar models have electronic properties that correlate with Zn-DNA having a metallic-like conductivity due to Zn d-states. To understand whether density functional theory (DFT) can describe appropriately the electronic properties of M-DNAs, we have investigated the electronic properties of G–Co–C base pairs. We have found that when self-interaction corrections (SIC) are not included the HOMO state contains Co d-levels, whereas these levels are moved below the HOMO state when SIC are considered. This result indicates that caution should be exercised when studying the electronic properties of M-DNAs with functionals that do not account for strong electronic correlations.

## I. Introduction

In 1993, Lee and co-workers proposed that adding Zn to a solution of DNA at a high pH, ca. 8, produces a new structure of DNA.<sup>1</sup> This new structure is known as M-DNA, where M stands for metal. When M-DNA was studied with NMR, the imino proton of guanine (G) and thymine (T) did not appear.<sup>1</sup> (The imino proton is the hydrogen atom that is bound to the nitrogen atoms commonly denoted as N1 and N3 for G and T, respectively.) The deprotonation of G and T was interpreted as being due to either a replacement of the imino proton by Zn<sup>2+</sup> or the formation of a complex which allows for a rapid exchange of the imino proton with solvent. In 1999, Lee and co-workers favored the former interpretation and proposed a model structure for M-DNA.<sup>2</sup> In this model, the metal atom enters a base pair through the minor groove, replaces the imino proton of G and T, and places itself between each base pair in the duplex. Figure 1 shows the guanine–Zn–cytosine base pair in M-DNA as proposed in ref 2. Here, this model is referred to as the Lee



**Figure 1.** Model proposed by Lee et al. for the guanine–Zn–cytosine base pair in M-DNA.<sup>2</sup> This model is called the Lee model. Color code: oxygen, red; carbon, gray; zinc, green; hydrogen, maroon; nitrogen, blue.

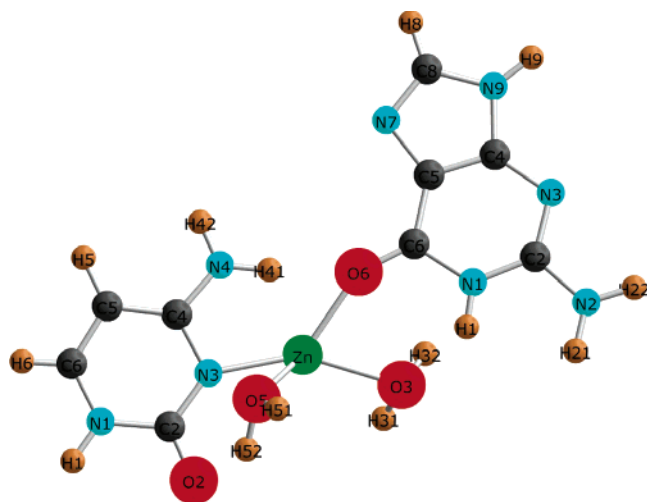
model. M-DNA also appears when Co and Ni are added to a solution of DNA at high pH.<sup>2</sup>

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**Figure 2.** Model proposed by Fusch and Lippert for the G–Zn–C base pair in a partially melted duplex.<sup>9</sup> This model is called the Lippert model.

Throughout the years, Lee and co-workers have shown that M-DNA is suitable for a variety of interesting nanotechnological applications,<sup>3–5</sup> but despite this potential, the existence, structure, and properties of M-DNA remain controversial.<sup>6–8</sup> To help clarify this controversy, knowing the structure of M-DNA is crucial. Unfortunately, there are no X-ray crystallography studies on M-DNA.

A literature search reveals a paper that might help the understanding of M-DNA's structure. In ref 9, Fusch and Lippert isolated a trinuclear Zn complex and studied it by X-ray crystallography; this complex contains cytosine–Zn–cytosine (ZnC<sub>2</sub>) “base pairs” that are connected to each other by OH<sup>–</sup> groups. They proposed that this complex could explain how, in a partially melted duplex, base pairs are kept in register with a partial loss of hydrogen bonds (H bonds). Specifically, the authors extrapolated the findings for ZnC<sub>2</sub> to Watson–Crick (WC) G–C and A–T base pairs proposing that the Zn ions could be placed between G–C and A–T base pairs. Figure 2 shows the guanine–Zn–cytosine base pair in a partially melted duplex; here, this model is referred to as the Lippert model.

A comparison between the Lee and Lippert models reveals numerous similarities. (i) As compared to a WC G–C base pair, both models lack the two H bonds on the minor groove, i.e., N3(C)–N1(G) and O2(C)–N2(G); only N4(C)–O6(G), located in the major groove, remains. (ii) The bases are rotated, which brings them farther apart allowing the Zn atom to enter the base pair by the minor groove. (iii) The Zn atom mediates the binding between G and C. (iv) The two missing H bonds are supposed to reappear upon reconversion from M-DNA (or a partially melted duplex) to a normal one. For example, in ref 9, it was argued that upon duplex renaturation the progressing base pair would extrude the Zn atom. Lee and co-workers do not offer an explanation as to how the Zn atom could be extruded, but they have observed that adding EDTA to a solution of M-DNA produces a rapid conversion to biological DNA (B-DNA). (All the similarities related above also occur when comparing the Lee and Lippert models for the A–Zn–T base pair.)

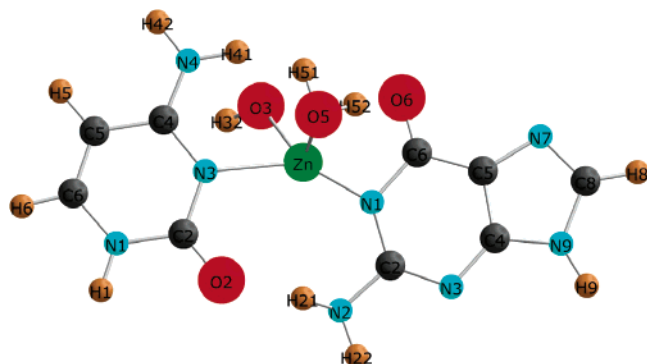
There are also differences between the Lee and Lippert models. (i) The Lee model has one extra H bond binding the oxygen of the water molecule to N2(G). (ii) In the Lee model, the Zn atom is squarelike coordinated by N3(C), O2(C), N1(G), and a water molecule, whereas in the Lippert model, the Zn atom is tetrahedrally like coordinated by two water molecules, N3(C) and O6(G). (iii) But the most important difference

is that the imino proton is present in the Lippert model and replaced by the metal atom in the Lee model. As a consequence, the Lippert and Lee models have different charges, 2+ and 1+, respectively. This difference is rather relevant because it means that if one were to build an M-DNA duplex from the Lippert model NMR measurements on this duplex would show the imino proton. This would disagree with the NMR data on M-DNA.<sup>1</sup> However, as mentioned above, in 1993 Lee and co-workers speculated that the imino proton could be absent due to the formation of a complex that allows rapid exchange of the imino proton with the solvent. We do not know whether the Lippert model is that complex, but in light of the similarities related above, it seems reasonable to keep this model in mind when thinking about the structure of M-DNA.

Theoretical studies can help to discern the structure of M-DNA. For example, one can study either metalated bases or metalated base pairs, such as the Lee and Lippert models, and then use this information to build a structure for M-DNA. Metalated bases have not been studied in the context of M-DNA yet, but this might be possible now thanks to a recent paper by Knobloch et al.<sup>10</sup> Knobloch et al. synthesized uridine and thymidine nucleosides in which a metal ion replaces the imino proton. They proposed several models for these nucleosides, and this information might be valuable in the context of M-DNA. But so far, theoretical efforts have been focused on investigating metalated base pairs.<sup>8,11</sup> This is also our focus, and as in previous studies, our goal is to find a reasonable metalated base pair that remains planar. This is a very restrictive geometrical criterion, but it is based on the idea that such a “planar” model is more suitable than a “nonplanar” one for building an M-DNA duplex: favorable stacking of consecutive base pairs is easier when the base pairs are planar.

In ref 8, Di Felice et al. used *ab initio* techniques to investigate the guanine–Zn–cytosine base pair model shown in Figure 1. Their results, although preliminary, indicated that this model is nonplanar and as so is unsuitable for building an M-DNA duplex. They also found that the electronic properties of this model did not correlate with M-DNA having a metallic conductivity. The questions then arose as to whether planarity could be recovered through stacking interactions and whether there exists other base pair models that are more appropriate for building a duplex. To our knowledge, there has not been a follow-up paper to answer these questions.

Recently, Alexandre et al.<sup>11</sup> used density functional theory (DFT) to investigate three different isolated G–Zn–C monomers which included the sugar and phosphate groups. Each model had a different coordination geometry for Zn: square-planar, octahedral, and tetrahedral (see Figure 1 of ref 11). Relaxation of the octahedral and square-planar models led to the same structure, in which Zn was tetrahedrally coordinated by one H<sub>2</sub>O molecule and one OH<sup>–</sup> group. Alexandre et al. then used a similar G–Zn–C model, but with two OH<sup>–</sup> groups coordinating Zn and the Zn atom placed in the major groove, to build an M-DNA duplex (see Figure 2 in ref 11; in the caption of this figure, the major and minor grooves are designated incorrectly). This duplex has a zigzag chain made of OH–Zn–OH that connects planes of G–Zn–C base pairs (the chain runs through the major groove of the duplex). This arrangement is similar to the one that occurs in the trinuclear Zn complex synthesized by Fusch and Lippert,<sup>9</sup> where an OH–Zn–OH chain connects planes of C–Zn–C base pairs. The M-DNA duplex proposed by Alexandre et al. lacks the imino proton. On the basis of the structural description and Figures 1 and 2 of ref 11, we have built the Alexandre model, which is shown



**Figure 3.** Alexandre model, which was created following the optimized model in ref 11.

in Figure 3. This model is very different from both the Lee and the Lippert model because it not only is neutral (due to the OH<sup>−</sup> group) but also contains a Zn atom placed in the major instead of the minor groove. The Alexandre model is also investigated in this paper.

In ref 11, DFT was also used to investigate the electronic properties of two periodic M-DNA duplexes, each containing Fe and Co instead of Zn. It was found that the top of the valence band of Co-(Fe)-DNA contains Co (Fe) d-states. From this, it was inferred that these duplexes might be useful as nanowires because the metal atoms might enhance the electronic conductivity. These systems are however likely to show strong electronic correlations, and if so, it is not clear whether DFT is able to describe them.

Clearly, there have been many efforts to understand the structure and electronic properties of M-DNA, but both issues, and others, still remain unclear. For example, one can ask why M-DNA only forms with Zn, Ni, and Co and not Mg and Ca. What is the process by which adding EDTA allows a reconversion from M-DNA to B-DNA? And, does the metal replace the imino proton? Furthermore, the recent work by Alexandre et al. raises a new question, this time regarding the suitability of DFT to study the electronic properties of certain types of M-DNAs.

In this paper, we carry out a comprehensive *ab initio* study of eight plausible models for the G-Zn-C base pair, five of which are being investigated for the first time. Our goal is to gather data to help elucidate the structure and electronic properties of M-DNA. We investigate the plausibility of models where the imino proton is replaced by the metal, is absent, or is present, to avoid ruling out any possible explanation for the absence of the imino proton in NMR experiments of M-DNA. We also probe whether any of the models studied have electronic properties that could help explain the metallic-like conductivity of M-DNA. The effect of strong electronic correlation on G-Co-C base pairs is investigated to gauge whether DFT can describe this particular system appropriately.

## II. Description of the Models

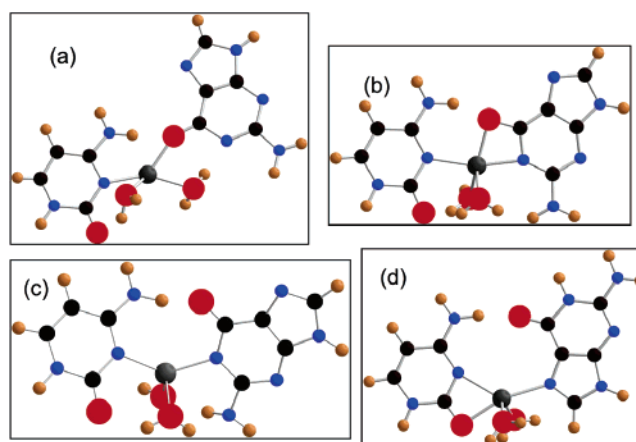
Table 1 compiles the models we have studied, and the models can be classified into three categories. In the first category, the imino proton (the H1 atom of the G base) is replaced by the metal. Models in the second category lack the imino proton, and models in the third have the imino proton. The Lee and Alexandre models belong to the first category, and the Lippert model belongs to the third.

The hybrid model, shown in Figure 4 a, is the only one that belongs to the second category. This model is like the Lippert model but without the imino proton. We view the hybrid model

**TABLE 1: Models Studied in This Work**

model	category	charge	initial (final) <sup>d</sup> geometry	figure for initial (final) geometry
Lee <sup>a</sup>	I	1+	planar (nonplanar)	1 (5)
Lippert <sup>b</sup>	III	2+	planar (planar)	2 (11)
Alexandre <sup>c</sup>	I	0	planar (nonplanar)	3 (9)
hybrid	II	1+	planar (nonplanar)	4a (10)
Lee penta	I	1+	planar (nonplanar)	4b (7)
Lee OH	I	0	planar (nonplanar)	4c (8)
Lippert syn	III	2+	planar (nonplanar)	4d (12)
planar Lee	I	1+	planar (planar) <sup>e</sup>	1 (6)

<sup>a</sup> Model proposed in ref 2. <sup>b</sup> Model proposed in ref 9. <sup>c</sup> This model was generated by following the structural description in ref 11. The rest of the models have not been considered until now. <sup>d</sup> Final geometry stands for the structure obtained after optimization. <sup>e</sup> Final geometry obtained by means of a restricted optimization that enforced planarity.



**Figure 4.** Other models studied in this work. (a) Hybrid model. (b) Lee penta model. (c) Lee OH model. (d) Lippert syn model. Color code: oxygen, red; carbon, black; zinc, gray; hydrogen, maroon; nitrogen, blue.

as the state the Lippert model would acquire after losing the imino proton and before replacing it by the metal atom or solvent. The charge of the hybrid model is 1+.

The Lee penta model, shown in Figure 4b, belongs to the first category. Originally, this model had three instead of two water molecules, as we wanted to study a model that accounts not only for the replacement of the imino proton by the metal atom but also for an octahedral coordination of the Zn atom. However, during our calculations, we noticed that one water molecule was lost and that the Zn atom acquired a coordination geometry with five instead of six neighbors. This led to the exploration of the stability of a coordination geometry with five neighbors: the Lee penta model, with a charge of 1+.

The Lee OH model, Figure 4c, belongs to the first category. This model is similar to the Alexandre model, except the metal atom enters the GC base pair by the minor instead of the major groove. Like the Alexandre model, the Lee OH model is neutral.

The Lippert syn model, shown in Figure 4d, belongs to the third category. This model is similar to the Lippert model, and the total charge of the complex is 2+; i.e., the imino proton is preserved. The guanine is connected to zinc through the N7 position, which enables a syn mutual orientation of the nucleobases. The reason for choosing the syn conformation will be explained later, when the results for the Lippert model are discussed.

Finally, the planar Lee model has the same initial structure and charge as the Lee model, and so it also belongs to the first category.



**TABLE 2: Information Regarding the Calculation of the Binding Energy,  $\Delta E$ , for Each System<sup>a</sup>**

number	model	$\Delta E$	character	charge	monomer1	monomer 2	monomer 3
1	Lee	−81.0	dimer	1+	C	G <sup>−</sup> -H <sub>2</sub> O-Zn <sup>2+</sup>	—
2	Lee penta	−52.6	dimer	1+	C	G <sup>−</sup> -2H <sub>2</sub> O-Zn <sup>2+</sup>	—
3	planar Lee	−76.5	dimer	1+	C	G <sup>−</sup> -H <sub>2</sub> O-Zn <sup>2+</sup>	—
4	Lee OH	−34.6	dimer	0	C	G <sup>−</sup> -H <sub>2</sub> O-OH-Zn <sup>2+</sup>	—
5	Alexandre	−174.1	dimer	0	C−	G <sup>−</sup> -2H <sub>2</sub> O-Zn <sup>2+</sup>	—
6	Lippert	−204.8	trimer	2+	C	G	2H <sub>2</sub> O-Zn <sup>2+</sup>
7	Lippert syn	−201.1	trimer	2+	C	G	2H <sub>2</sub> O-Zn <sup>2+</sup>
8	hybrid	−114.7	trimer	1+	C	G	H <sub>2</sub> O-OH <sup>−</sup> -Zn <sup>2+</sup>
8'	hybrid	−64.5	dimer	1+	C	G-H <sub>2</sub> O-OH-Zn <sup>2+</sup>	—

<sup>a</sup>Character refers to whether the system was considered a dimer or a trimer. Monomers 1, 2, and 3 refer to the monomer the dimers and trimers were divided into for calculating their binding energies according to eq 1.

All these models are planar; i.e., they contain the G and C bases in the same plane. In what follows, it will be seen that these models change significantly once they are relaxed; however, for simplicity, we will continue referring to them by the names given above. To avoid confusion, whenever necessary we will use the words original and relaxed to refer to an original model and its relaxed counterpart.

### III. Method

The Lee OH and Alexandre models were optimized with Gaussian;<sup>12</sup> the rest were optimized with the NWChem suite of programs.<sup>13</sup> The optimizations were carried out with density functional theory (DFT) with the hybrid functional B3LYP<sup>14</sup> for the exchange-correlation potential. The basis set used throughout this study is 6-31G\*\*.

The binding energies were calculated by dividing each model into smaller components, i.e., monomers. The number of monomers depends on whether the imino proton is replaced by Zn. If the imino proton is replaced by Zn, the system is considered as a dimer and its binding energy is computed by dividing it into two monomers. Otherwise, the system is a trimer and it is divided into three monomers. Table 2 contains the information regarding which system is a dimer and which is a trimer, as well as the set of corresponding monomers.

The binding energy for a dimer (trimer) system is given by:

$$\Delta E_{\text{dimer(trimer)}}^{\text{binding}} = E^{\text{dimer(trimer)}} - E^{\text{BSSE}} - \Delta E^{\text{Def}} \quad (1)$$

$E^{\text{dimer(trimer)}}$  stands for the energy of the relaxed system.  $E^{\text{BSSE}}$  is used to eliminate the basis set superposition error (BSSE) by the counterpoise procedure and is defined as follows:

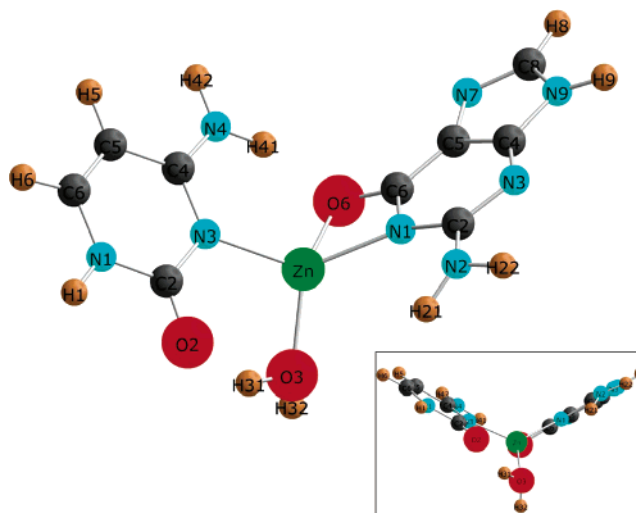
$$E^{\text{BSSE}} = \sum_{i=1}^N E_i^{\text{ghost}} \quad (2)$$

where  $N = 2$  (3) for a dimer (trimer) and  $E_i^{\text{ghost}}$  is the energy of the monomer  $i$  with its geometry taken from the optimized dimer (trimer) and with all the dimer (trimer) basis functions present.

Finally,  $\Delta E^{\text{Def}}$  in eq 1 is the deformation energy and is given by the expression

$$\Delta E^{\text{Def}} = \sum_{i=1}^N (E_i^{\text{opt}} - E_i) \quad (3)$$

where  $N = 2$  (3) for a dimer (trimer),  $E_i^{\text{opt}}$  is the energy of the relaxed monomer  $i$ , and  $E_i$  is the energy of the monomer  $i$  with its structure given by the structure it has in the optimized dimer (trimer). The Supporting Information contains the structure of the monomers and the corresponding energies. The binding energies were computed with Gaussian.<sup>12</sup>



**Figure 5.** Relaxed Lee model. The inset in this figure shows the model as it will be seen by looking from the bottom of the page. Figures 6–12 contain similar insets.

The electronic properties were studied with DFT and the following forms for the exchange-correlation potential: local density approximation (LDA),<sup>16</sup> generalized gradient approximation (GGA),<sup>17</sup> and the hybrid forms B3LYP<sup>14</sup> and PBE0.<sup>18</sup> Strong electronic correlation effects were accounted for by introducing the self-interaction correction (SIC)<sup>19</sup> to the PBE0 functional.

As it will be seen later, geometry relaxation leads to nonplanar models. As we wanted to understand how much energy it takes to recover planarity, we also investigated the planar Lee model. This model was obtained by performing a restricted optimization in which the bases were forced to remain coplanar by not allowing the atoms of the aromatic rings to move out of the plane; all parameters of the Zn atom and the H<sub>2</sub>O molecule were relaxed without geometrical restrictions. The optimization was performed with Gaussian<sup>12</sup> in both gas-phase and solvent conditions. The solvent is water, which was mimicked with the COSMO dielectric continuum model.<sup>15</sup>

### IV. Results

**A. Structural Properties.** In this section, we present the structural data of each geometry optimized model, emphasizing whether it is planar. We emphasize planarity because a planar model is more suitable than a nonplanar one for building a Zn-DNA duplex. The optimized structures for the models Lee, planar Lee, Lee penta, Lee OH, Alexandre, hybrid, Lippert, and Lippert syn are shown in Figures 5–12, respectively.

In what follows, X(Zn<sub>c</sub>), X = (O3; O5), denotes the X atom that is attached to the Zn cluster (this cluster contains one Zn atom, H<sub>2</sub>O, and/or OH<sup>−</sup>). For example, denoting O3(Zn<sub>c</sub>) as

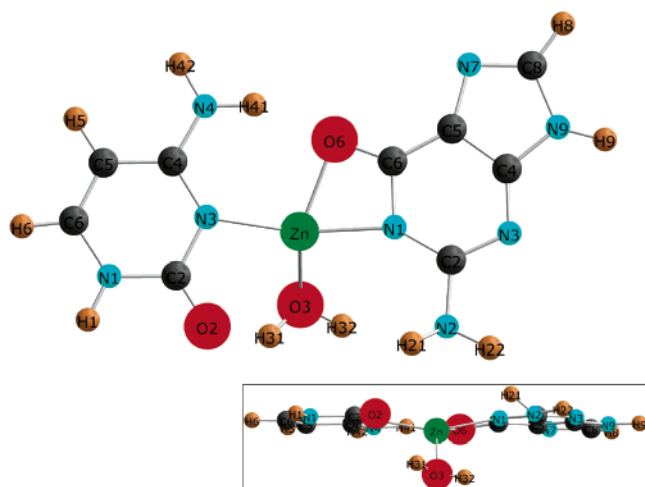


Figure 6. Relaxed planar Lee model.

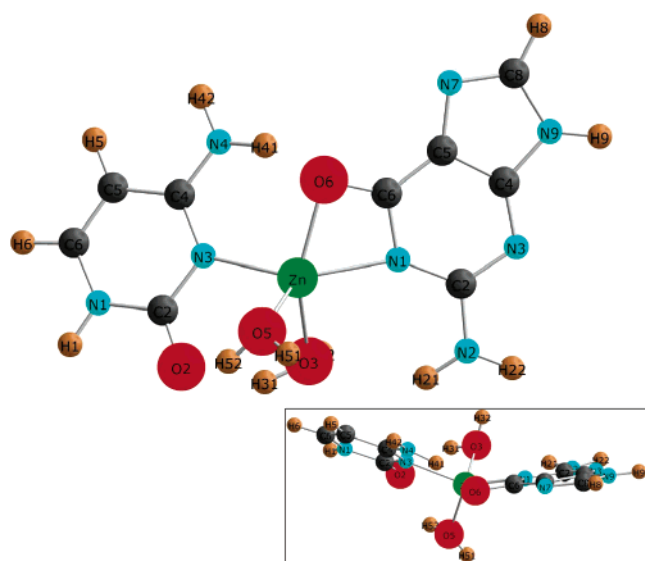


Figure 7. Relaxed Lee penta model.

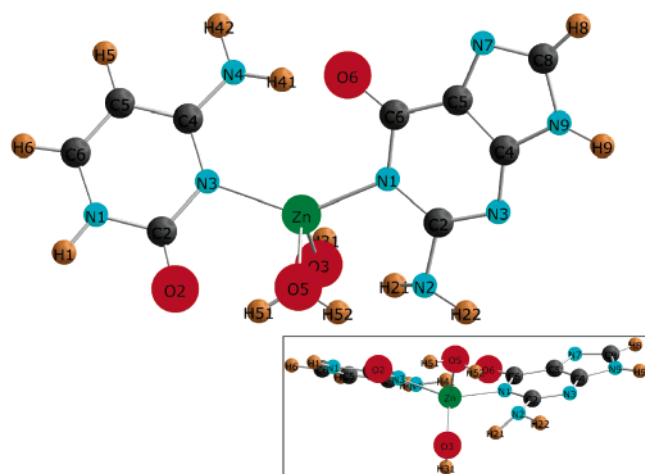


Figure 8. Relaxed Lee OH model.

the O3 atom that is attached to the Zn cluster in the Lee model is similar to denoting O6(G) as the O6 atom that is attached to G in a WC G–C base pair. (Structural information for each model can be found in the Supporting Information; here, we only describe the most relevant characteristics of each model.)

The models Lee, planar Lee, Lee penta, Lee OH, and Alexandre have the imino proton replaced by the metal atom,

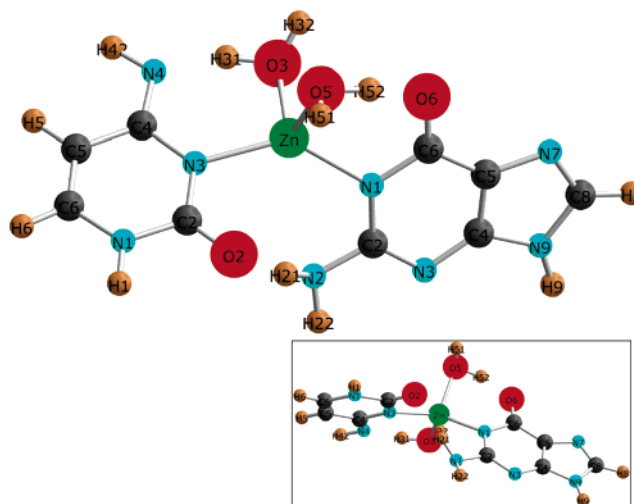


Figure 9. Relaxed Alexandre model.

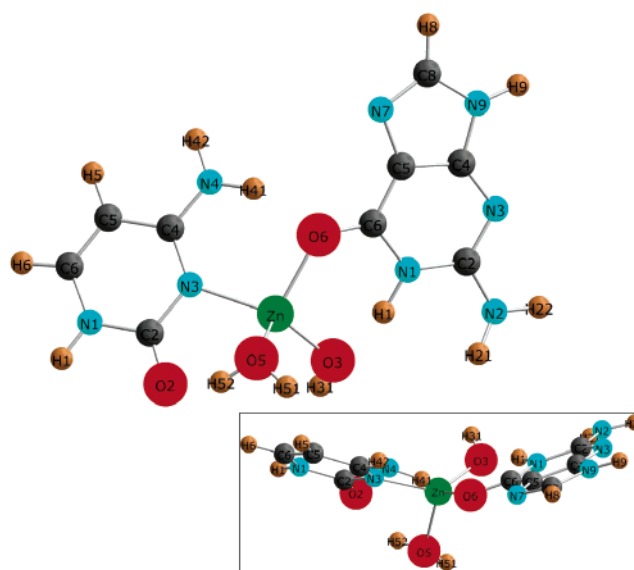


Figure 10. Relaxed hybrid model.

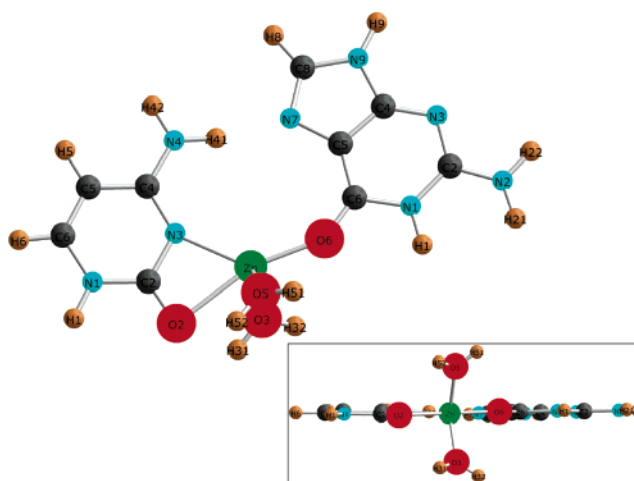


Figure 11. Relaxed Lippert model.

but only the first two can be compared to the original Lee model. When comparisons are made, the following differences can be found. The original Lee model is planar, and the Zn atom is square-like coordinated by N1(G), N3(C), O2(C), and O3(Zn<sub>C</sub>). In contrast, the relaxed Lee model is nonplanar (see the inset of Figure 5) and the Zn atom is coordinated by N1(G), N3(C),

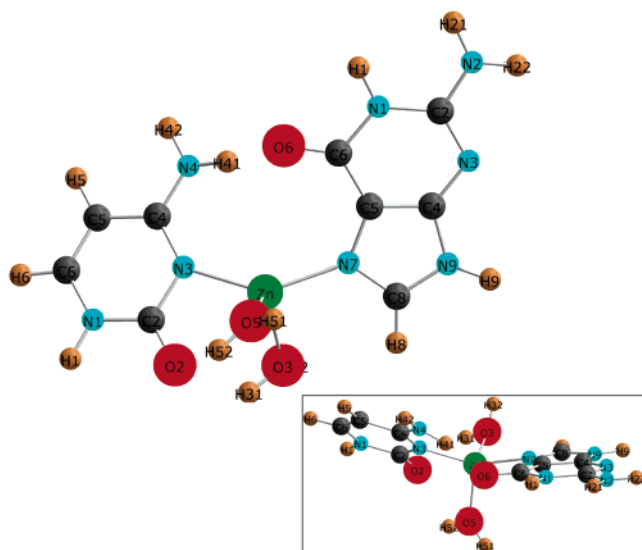


Figure 12. Relaxed Lippert syn model.

O6(G), and O<sub>3</sub> (Zn<sub>c</sub>) in a distorted tetrahedral arrangement; this coordination is similar to that in the planar Lee model, which of course is planar because it was relaxed in a restricted fashion that enforced planarity. Furthermore, in the original Lee model, O<sub>3</sub> (Zn<sub>c</sub>) is hydrogen-bonded to N2(G), whereas in the planar Lee and relaxed Lee models, O<sub>3</sub>(Zn<sub>c</sub>) is hydrogen bonded to O2(C). That the planar Lee and Lee models have a similar bonding mechanism, but a mechanism that is different from that in the original Lee model, indicates that the original Lee model cannot provide a true representation of the base pairing in Zn-DNA.

The Lee penta model was introduced in this study to check whether coordinating Zn with five neighbors leads to planarity. The inset of Figure 7 shows that planarity is not achievable in this fashion. As compared to the Lee model, the Lee penta model has one extra H bond, i.e., O5(Zn<sub>c</sub>)–O2(C).

Studying the Lee OH model and Alexandre model allows us to explore whether placing the metal in different grooves affects planarity. In the Lee OH model, the metal atom is placed in the minor groove, as proposed by Lee and co-workers<sup>2</sup> and Fusch and Lippert.<sup>9</sup> In contrast, in the Alexandre model, the metal atom is placed in the major groove. As seen in the insets of Figures 8 and 9, neither the Lee OH model nor the Alexandre model is planar.

It will be useful to compare the Alexandre model generated here to the model generated in ref 11, but comparisons are difficult. This is because the model in ref 11 was generated using a procedure that focused on the creation of a Zn-DNA duplex. This procedure can be described as follows: a planar G–Zn–C base pair, with a backbone included and with the metal in the major groove, was proposed as suitable for building a Zn-DNA duplex. This base pair was used to form three stacked base pairs in an A-form arrangement. This arrangement was then optimized, and the central base pair was extracted and used to build the duplex. We can try comparing the central base pair to our Alexandre model, but detailed structural information for the central base pair was not given in ref 11. However, the authors reported that the distance between consecutive base pairs steps in Zn-DNA is 2.89 Å, instead of 3.446 Å as observed in pure A-form DNA. This reduction is due to the central base pair being nonplanar, which agrees with our results regarding the nonplanarity of the Alexandre model.

In view of the results above, one can say that replacing the imino proton with the metal atoms leads to models that are

nonplanar, independently of whether the metal is placed in the minor or major groove. The question remains as to how much energy is needed to flatten any of these models. For this, one can compare the binding energies of the Lee and planar Lee models. This is done in the next section. Now, we wish to discuss if planarity could be achieved by not replacing the imino proton with the metal, i.e., by simply removing the imino proton.

In the original hybrid model (Figure 4a), the imino proton was removed, but as seen in Figure 10, the relaxation detached an H atom from an H<sub>2</sub>O molecule and attached it to N1(G). Then, after relaxation, the hybrid model recovered the imino proton. This, unfortunately, precludes us from considering in our study a model that has lost the imino proton. At the same time, this permits checking whether a Lippert model with an OH<sup>–</sup> group remains planar or becomes nonplanar. (This is because the relaxed hybrid model is similar to the original Lippert model, except that Zn is coordinated by one H<sub>2</sub>O and one OH<sup>–</sup> group, instead of by two H<sub>2</sub>O molecules.) As seen in the inset of Figure 10, the hybrid model, i.e., a Lippert model with an OH<sup>–</sup> group, is nonplanar.

The imino proton is still present in the relaxed Lippert model, Figure 11, which is a very unique model. The relaxed Lippert model not only has a different bonding mechanism, due to a considerable rotation of the bases during relaxation, but also is a planar model. However, this model is not suitable for building an antiparallel stranded Zn-DNA because the groups corresponding to the glycosidic bonds, i.e., N1H of C and N9H of G, are transoid. The relaxed Lippert model might be suitable for building a parallel stranded Zn-DNA, though. Such a duplex would contain the imino proton, which should appear in NMR experiments, unless the imino proton undergoes a rapid exchange with solvent. It should be noted that when the Lippert model is relaxed with Gaussian<sup>12</sup> it becomes quasiplanar (this structure is also included in the Supporting Information); this quasiplanar structure is practically isoenergetic with the NWChem relaxed Lippert model.

The result above prompted us to ask the following: is it possible to modify the relaxed Lippert model so it will lead to a planar model suitable for building an antiparallel duplex? For example, what would happen if the metal moves toward the “inside” of the base pair, eventually forming a link between N3(C) and N7(G)? In this case, G could rotate to form an H bond between O6(G) and N4(C), and the “glycosidic bonds” would again be in an orientation which is expected for normal antiparallel Zn-DNA, with G in a syn orientation relative to the sugar. Let us recall that in common antiparallel DNA structures the glycosidic bond conformation is anti. In fact, the syn conformation would give rise to a parallel DNA structure. Nevertheless, this would require close contact between the bulky sugar and nucleobase moieties, which, especially for guanosine, is energetically highly unfavorable. This way of thinking led us to investigate the Lippert syn model, which is similar to the Lippert model except with the G base in the syn orientation. As seen in Figure 12, the Lippert syn model is not planar.

In summary, if one assumes the ideal situation that only a planar model is suitable for building a duplex, the following conclusion is found: models suitable for building an antiparallel Zn-DNA are not possible when the imino proton is kept or when it is replaced by the metal, but a model suitable for building a parallel Zn-DNA is possible when the imino proton is kept. Indeed, by analyzing the H-bonding patterns of all eight studied models, we recognize that in fact the Lippert model is the only one which contains an interbase H bond involving an endocyclic heteroatom. This might be the clue why the optimized Lippert



model is planar whereas others are not. In the next section, we present the binding energies of these models and investigate how much energy it takes to flatten the Lee model.

**B. Binding Energies.** Binding energies can be compared to determine the relative stability of each model. Table 2 shows the binding energy, character (dimer or trimer), charge, and monomers of each model. A dimer model has two monomers, and a trimer has three. The binding energy of a dimer (trimer) is given by eq 1.

We will use the following convention to list those models for which binding energy can be compared. The models are referred to by the number given in the first column of Table 2, and those for which energies can be compared are grouped as follows: (1,2,3), (6,7), (4), (5), (8), and (1,2,3,8'). In the last set, 8' stands for the hybrid model with its binding energy calculated as if it were a dimer: doing this enables comparison of the binding energy of models with the imino proton (the hybrid model) to that of models where the imino proton is replaced by the metal atom (the Lee, planar Lee, and Lee penta model).

We start with the set (1,2,3). As seen in Table 2, the Lee model is the most stable one, followed by the planar Lee and Lee penta models. The difference in binding energy between the Lee and planar Lee models can be seen as the energy needed to flatten the Lee model. This energy is surprisingly small, just 4.5 kcal/mol. To see whether this energy changes significantly in the presence of polar solvent, we carried out single-point energy calculations with the COSMO dielectric continuum model.<sup>15</sup> These calculations show that the Lee model is 7.1 kcal/mol more stable than the planar Lee model. That this is not an excessively large difference suggests that the planar Lee model is suitable for building an antiparallel Zn-DNA duplex. This duplex would have the imino proton replaced by the metal atom, as proposed by Lee and co-workers. Therefore, and also in accordance with Lee and co-workers,<sup>1</sup> NMR measurements of this duplex would not show the imino proton.

The set (6,7) contains the Lippert and Lippert syn models, respectively. As seen in Table 2, the Lippert model is about 3.7 kcal/mol more stable than the Lippert syn model, which is surprising given that the former is planar. This result indicates that the Lippert model might contribute a greater intrinsic stability to periodic duplex architectures than its syn counterpart.

The binding energies of the Lee OH<sup>-</sup> and the Alexandre model (numbers 4 and 5, respectively) cannot be directly compared, and this is unfortunate because it precludes us from determining whether the metal prefers being in the minor or major groove. According to Lee and co-workers and Fush and Lippert,<sup>9</sup> the metal prefers being in the minor groove, but Alexandre et al.<sup>11</sup> proposed a Zn-DNA duplex with Zn in the major groove. It is in fact very interesting to speculate which groove side of the WC GC base pair is more appropriate to open for metal cross-linking. If the metal comes through the major groove, it will probably never get into a cross-linking position because it will be trapped by binding to N7 of G. This is because N7-metalated complexes of G are very stable, about 20–30% more stable than a WC GC base pair.<sup>21,22</sup> In contrast, when entering via the minor groove, the most exposed electron donor site is O2(C). Metal binding to O2(C) should weaken GC WC because it deteriorates the H bond between N2(G) and O2(C). This in turn should allow the metal atom to enter the base pair and occupy a cross-linking position. Thus, it is reasonable to expect that the Zn ion prefers penetrating the DNA double helix via the minor groove side.

Finally, we discuss the set (1,2,3,8'). This set is very

**TABLE 3: HOMO–LUMO Gaps (eV) for the Models Studied and the WC G–C Base Pair<sup>20</sup>**

model	LDA	GGA	B3LYP
Lee	1.785	1.794	3.244
planar Lee	1.935	1.933	3.380
Lee penta	1.666	1.683	3.151
Lee OH	1.805	1.803	3.224
Alexandre	2.493	2.540	4.028
Lippert	3.046	3.053	4.539
Lippert syn	2.940	2.959	4.445
hybrid	2.375	2.395	3.868
WC G–C	2.303	2.345	3.830

interesting because it allows us to determine which is energetically more favorable, to keep the imino proton or to replace it with the metal atom. As seen in Table 2, the answer is to replace it.

**C. Electronic Properties.** DNA can be assembled in 2D and 3D nanostructures,<sup>23</sup> which makes it a very attractive molecule for the field of nanotechnology. Unfortunately, it is not yet clear whether DNA conducts electricity, and this had led to seeking alternative molecules. M-DNA is thought to be an alternative. (In this section, we will use the terms Zn-DNA and Co-DNA to refer to M-DNAs where M = Zn and Co, respectively.)

Rakitin et al.<sup>3</sup> placed  $\lambda$ -DNA between gold electrodes and measured its electrical conductivity before and after converting it to Zn-DNA. It was shown that Zn-DNA conducts in a metallic-like fashion. This was explained by proposing (i) that Zn-DNA contains a band of Zn d-states and (ii) that this band is aligned with the Fermi level of the electrodes. Theoretical studies have questioned this explanation.

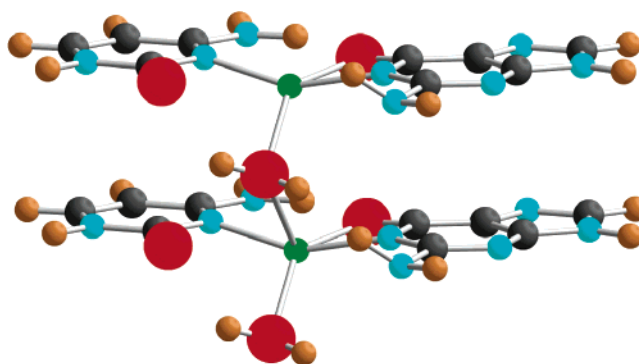
Di Felice et al.<sup>8</sup> used ab initio techniques to study the electronic properties of a G–Zn–C base pair model. They found that the electronic properties of G–Zn–C and WC GC differ in one significant aspect only: the HOMO–LUMO gap of the former is 50% smaller. They also found that the HOMO level of G–Zn–C did not show Zn d-states, and this in turn made it difficult to justify the existence of a Zn d-band that accounts for Zn-DNA metallic conductivity. A similar conclusion has recently been reached by Alexandre et al.<sup>11</sup> They studied the electronic properties of Zn-DNA and found that the Zn d-states are below the HOMO level. They also found that the HOMO–LUMO gap of this duplex is just 0.65 eV. This was explained as being due to the distortion that occurs between neighboring G bases on the same strand. The distortion brings the G bases closer than they are in natural DNA, and this increases their  $\pi$ – $\pi$  stacking interactions, which in turn reduces the HOMO–LUMO gap of the duplex. Alexandre et al. pointed out that Zn-DNA is a good candidate for molecular wire applications and that its conductivity is most likely governed by the “ $\pi$ -way”, as in natural DNA, but not by the metal.

We have calculated the nature of the HOMO level and the value of the HOMO–LUMO gap for each of the previously presented G–Zn–C models. We used three different exchange-correlation functionals, the local density approximation (LDA), the generalized gradient approximation (GGA), and the hybrid functional B3LYP. The HOMO level of neither of the models studied contains Zn d-states, irrespective of the approximation used. This result agrees with the findings by both Di Felice et al. and Alexandre et al., indicating that it is indeed unlikely that Zn-DNA has a Zn d-band situated at the Fermi level that could facilitate charge transport.

The calculated HOMO–LUMO gaps for the various models and methods are given in Table 3. For comparison purposes,

we also have included the HOMO–LUMO gap of the WC GC base pair.<sup>20</sup> In Table 3, one notices the considerably larger gaps obtained with B3LYP compared to both the LDA and GGA values; however, replacing the LDA approximation with the GGA approximation has only a minor effect on the values for the energy gaps. The GGA HOMO–LUMO gaps of the Lee, planar Lee, Lee penta, and Lee OH model are about 23, 17, 28, and 23% smaller than that of WC GC (the G–Zn–C model investigated by Di Felice et al.<sup>8</sup> which is similar to our relaxed Lee model, finds a HOMO–LUMO gap 50% smaller than that of WC GC). It is tempting to associate this reduction of the HOMO–LUMO gap with the replacement of the imino proton by the metal atom. Indeed, when the imino proton is conserved, the gaps are larger than that of WC GC: the gaps of the Lippert, Lippert syn, and hybrid models are about 23, 20, and 2% larger than that of WC GC (see Table 3). The Alexandre model is the exception to the rule, as the imino proton is replaced by the metal atom, and yet the HOMO–LUMO gap is 7.7% larger than that of WC GC. Interestingly, the Alexandre model is the only model where the metal atom enters through the major groove.

At this point, we wish to elaborate on the appropriateness of DFT for describing the electronic properties of metalated-DNAs with transition-metal atoms. As such, the DFT is an exact theory, and it is only the various approximations to the exchange and correlation functionals that lead to errors in the electronic structure calculations. The LDA approximation inherently assumes delocalized electrons and is very successful in describing the electronic structure of metals and alloys. The assumption of an infinitely extended homogeneous electron gas underpinning the LDA approximation is however not adequate for the description of spatially restricted molecules. The LDA approximation does not account for exchange and correlation beyond those of the homogeneous electron gas and introduces an unphysical interaction of the electron with itself. This self-interaction pushes the occupied levels higher, whereas it leaves the unoccupied levels untouched, which results in reduced HOMO–LUMO gaps<sup>25</sup> not in agreement with experiment. The GGA, which takes into account the density gradient, outperforms LDA in many respects but is plagued by this same self-interaction and generally does not lead to improved energy gaps with respect to LDA. This is also observed in our current calculations on G–Zn–C base pairs (see Table 3). A different approach from DFT, the Hartree–Fock (HF) method, does not take into account correlation, but a similar contribution in the Coulomb and exchange term leads to a cancellation of the self-interaction. Hybrid functionals, such as B3LYP and PBE0, make use of the adiabatic connection formula to add certain amounts of exact exchange. Both B3LYP and PBE0 can be seen as a mixture of DFT exchange and HF exchange. This mixture leads to a reduction of the self-interaction, which considerably increases the calculated energy gaps. An example of how the hybrid functional increases the energy gaps can be seen in column 4 of Table 3 for the case of B3LYP. A framework for the self-consistent calculation of self-interaction corrections (SIC) to the density functional theory (DFT) based on the original method due to Perdew and Zunger<sup>19</sup> can be implemented based on a number of variants. One approach uses the Kohn–Sham orbitals determined from the self-consistent calculations and performs a localization with the Foster–Boys algorithm. We have used this approach, which is implemented within the suite of NWChem programs,<sup>13</sup> and included self-interaction corrections to the PBE0 functional; we refer to this set of calculations as SIC-PBE0.



**Figure 13.** Two stacked G–Co–C base pairs. Each base pair has the same structure as the planar Lee model for G–Zn–C. The stacking distance is 3.4 Å, and the rotation angle is 0°. Color code: oxygen, red; carbon, gray; cobalt, green; hydrogen, maroon; nitrogen, blue.

**TABLE 4: Co d-State Contribution to the HOMO and LUMO Levels of an Isolated G–Co–C Base Pair and Two Stacked G–Co–C Base Pairs<sup>a</sup>**

	G–Co–C			
	LDA	B3LYP	PBE0	SIC-PBE0
HOMO	✓	X	X	X
LUMO	✓	✓	✓	✓
	Two Stacked G–Co–C			
	LDA	B3LYP	PBE0	SIC-PBE0
HOMO	✓	✓	✓	X
LUMO	✓	✓	✓	✓

<sup>a</sup>The symbol ✓ (X) means that the corresponding state has (has no) Co d-states. The energetics of each level and atomic contributions are given in the Supporting Information.

To investigate in more detail the effects of self-interaction on the nature of the HOMO and LUMO states, we studied the base pairs of Co-DNA using LDA, B3LYP, PBE0, and SIC-PBE0. (Base pairs of Co-DNA instead of Zn-DNA are considered because one expects correlation effects to be more prominent in Co-DNA than in Zn-DNA.) We have investigated two systems. First, we studied an isolated G–Co–C base pair with the same structure as the planar Lee model for G–Zn–C. This system has a charge of 1+, and we used spin-polarized calculations to study the electronic properties of the doublet state. Second, we studied two stacked G–Co–C base pairs at 3.4 Å and a rotation angle of 0 degrees; each individual G–Co–C base pair also has the same structure as the planar Lee model for G–Zn–C. This system is shown in Figure 13, and it contains a H<sub>2</sub>O–Co–H<sub>2</sub>O chain. The distance between a Co from one base pair and the O atom of the H<sub>2</sub>O molecule of the next base pair is 2.54 Å. The system has a charge of 2+, and spin-polarized calculations were used to study the electronic properties of the singlet state. Studying two stacked G–Co–C base pairs with a rotation angle of 0° allows us to investigate a situation where the correlation effects could be very relevant. However, our results should be considered as an upper limit because in Co-DNA the rotation angle between consecutive base pairs should be larger than 0°.

Table 4 shows the results concerning the nature of the HOMO and LUMO states. The symbol ✓ (X) means that the corresponding state has (has no) Co d-states. With respect to the isolated base pair, we notice that the LDA places Co d-states both in the HOMO and LUMO levels. If instead B3LYP or PBE0 is used, the d-states are still present in the LUMO level but have vanished from the HOMO level. This means that accounting for exact exchange, as B3LYP and PBE0 do,



removes the d-states from the HOMO level of an isolated G–Co–C base pair. The situation is rather different for the stacked G–Co–C base pairs. Here, both the LUMO and the HOMO levels contain Co d-states irrespective of whether LDA, B3LYP, or PBE0 is used. Then, in this case, the fact that hybrid functionals reduce the self-interaction error does not seem to affect the nature of the HOMO level. However, if the self-interaction is fully taken into account, as with SIC-PBE0, the d-states vanish from the HOMO level in both the isolated base pair and the stacked base pairs. In the stacked base pairs, depending on the relative scale of hybridization and d–d correlation energies, the Co d-states of the O–Co–O–Co chain will either form a molecular orbital or remain localized at their site. LDA, B3LYP, and PBE0 favor hybridization, and SIC-PBE0 results in a considerable energy gain assuming localized d-states. Given that the energetics of LDA, B3LYP, and PBE0 cannot be directly compared to that of SIC-PBE0, it is not possible to determine yet which approximation gives a better representation of the ground state of the stacked G–Co–C pair.

Alexandre et al.<sup>11</sup> studied the electronic properties of Co-DNA using DFT with a GGA functional.<sup>24</sup> They observed that the HOMO level of this duplex has large electronic contributions from Co d-states. This not only led to small HOMO–LUMO gaps but also indicated that the mechanism of conductivity in Co-DNA is governed by Co. Our results concerning G–Co–C base pairs question GGA's reliability for studying the electronic properties of Co-DNA. One might expect it to be reliable if the Co–O distance in the O–Co–O–Co chain is relatively small, such that the hybridization energy overcomes the trend toward localization. Otherwise, the Co d-electrons will prefer staying localized on each of their sites. In this scenario, the d-electrons will not be placed in the HOMO level because this would be just an artifact of the GGA approximation, and instead, the localized d-levels will be situated below the HOMO level. If so, the situation would be similar to that in strongly correlated compounds such as transition-metal oxides (TMOs; TM = Ni, Mn, Fe, Co).<sup>26</sup> GGA not only underestimates the energy gaps of TMOs but also wrongly predicts that their valence band maximum states (equivalent to the HOMO level of a molecule) consist of delocalized TM d-band states. Indeed, considerable experimental evidence points toward TMOs being Mott insulators with localized d-states situated well below the valence band maximum.

The question remains as to whether M-DNAs are strongly correlated molecules and whether the physics of TMOs is relevant in the context of M-DNAs. A possible approach to answer the first question would be to use the SIC-LDA<sup>27,28</sup> formalism on M-DNA. The basis of this formalism is a self-interaction free total energy, obtained by subtracting, from the LDA total energy functional, the spurious self-interaction of each occupied orbital. Both localized and itinerant d-states are expanded in the same basis set and thus treated on an equal footing. With respect to the Co ion in Co-DNA, for example, atomic configurations with different numbers of localized d-electrons can be assumed, ranging from the Co (d<sup>0</sup>) SIC-LSD scenario to the fully localized Co (d<sup>7</sup>) scenario. The self-consistent total energy minimization for each of these scenarios leads to as many local minima of the same functional. Hence, their total energies may be compared, and the configuration with the lowest energy (global energy minimum) defines the ground-state configuration.<sup>29</sup>

## V. Conclusions

In this paper, we have carried out a comprehensive *ab initio* study to help elucidate the structure and electronic properties

of Zn-DNA. For this, we have studied eight different models of G–Zn–C base pairs in the gas phase. The models were chosen to probe how planarity is effected by the presence or absence of the imino proton and the positioning of Zn in the major or minor groove. Our focus on planarity stems from the fact that a planar model is more suitable than a nonplanar one for building Zn-DNA. This is, of course, an idealization because not even in natural DNA are the base pairs perfectly planar. Still, the planarity suitability criterion allows us to establish comparisons using a well-defined reference. Out of all the studied models, there is only one which preserves its planarity upon full geometry optimization. Nevertheless, starting from this model, one can deduce a parallel Zn-DNA architecture only. This duplex should show the imino proton in NMR experiments, unless this proton undergoes a rapid exchange with solvent. To our knowledge, the existence of such a duplex has not been proven yet, and we hope that our research will encourage experiments in this direction. To estimate how much energy it takes to flatten a nonplanar model, we have investigated the difference in energy between a nonplanar model and its planar counterpart (obtained by means of a restricted optimization). For this task, we chose a model in which the imino proton is replaced by Zn that, in turn, sits in the minor groove of the GC base pair. We have found that this particular model requires only 4.5 and 7.1 kcal/mol to be flattened in gas and solvent conditions, respectively, and so suggest that the planar model is a good starting point for creating an antiparallel Zn-DNA duplex that would satisfy the following two criteria. First, this duplex should not show the imino proton in NMR measurements, which would agree with the experimental evidence for Zn-DNA. Second, this duplex would have the metal atom placed in the minor groove, a positioning that has been suggested by other authors as well.

Energetic comparisons across the base pair models were only possible among a few. For example, we originally wanted to compare the energy of a model with Zn in the minor groove to that of a model with Zn in the major groove. Unfortunately, relaxation led to structures that made this task impossible, and we could only speculate that the minor groove of the GC base pair is more welcoming to Zn than the major groove. In contrast, we were able to compare the energy of a model that lacks the imino proton to those of three models that have the imino proton replaced by Zn: we found that it is more energetically favorable to replace the imino proton with Zn, providing that it is 4-fold coordinated. We have also been able to compare the energies of two models that contain the imino proton and found that the model with the G base in the syn conformation is less stable than the model with the G base in the anti conformation. The former is also the model that we suggest could be used to build a parallel Zn-DNA.

Concerning the electronic properties, neither of the base pair models studied has electronic properties that can be used to explain the conductivity of Zn-DNA in terms of a d-band, as an experiment proposed.<sup>3</sup> The enhanced conductivity could be due to a significant decrease of the HOMO–LUMO gap of Zn-DNA as compared to that of DNA. Indeed, we did find that the HOMO–LUMO gap of the G–Zn–C base pairs is, at most, 28% smaller than that of a WC GC base pair, but more research will be needed to understand whether further reduction in the HOMO–LUMO gap takes place upon stacking base pairs. Finally, we have investigated the effect of strong electronic correlation in G–Co–C systems. This was motivated by the fact that we wished to probe whether such effects should be taken into account when studying the electronic properties of

Co-DNA or other duplexes containing transition-metal atoms susceptible of showing strong electronic correlation effects. We found that including or excluding self-interaction corrections (SIC) can lead to different results. In particular, in two stacked G–Co–C base pairs, LDA, B3LYP, and PBE0 place Co d-states in the HOMO whereas SIC-PBE0 removes them. More research is needed to determine what is more energetically favorable, to have the d-levels delocalized and hybridized with the HOMO state or to have them localized and placed below the HOMO state. At this moment, we are not able to answer that question, but our results indicate that if M-DNA's (M = Co; Ni) physics resembles that of transition metal oxides, it is wise to be cautious about the use of LDA, GGA, or hybrid functionals to study the electronic properties of M-DNAs.

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**Supporting Information Available:** Cartesian coordinates for the optimized structures and Tables 1–12. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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