



Theoretical studies on the related properties of Co(III) polypyridyl complexes interacting with DNA

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ABSTRACT

Theoretical studies on the related properties of Co(III) polypyridyl complexes $[\text{Co}(\text{phen})_2\text{L}]^{3+}$ (L: dppz = dipyrrodo[3,2-*a*:2',3'-*c*]phenazine; phen = 1,10-phenanthroline; dione = 1,10-phenanthroline-5,6-diketone) **1–3** interacting with DNA, including the DNA-binding, DNA-photocleavage and spectral properties, have been carried out. First, the full geometry-optimizations of these three complexes in their ground states were carried out in aqueous solution. The optimized structures of these three complexes were docked into DNA-base-pairs using the Dock6.0 program. Secondly, the binding modes of complexes **1–3** were revealed in detail and the trend in DNA-binding affinities was reasonably explained. Thirdly, the electronic absorption and emission spectra of docking model of the optimal complex **1** were calculated and simulated. The experimental intense absorption and emission bands of Co(III) complex **1** in the presence of DNA were explained in detail, in particular, the reason why the emission spectra of complex **1** in the presence of DNA are greatly stronger than those in the absence of DNA was theoretically elucidated. Finally, the DNA-photocleavage essential of complexes was explored and the DNA photocleavage efficiencies (φ), i.e., $\varphi(\mathbf{1}) > \varphi(\mathbf{2}) > \varphi(\mathbf{3})$, was also reasonably explained.

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1. Introduction

For decades, much attention has been focused on Ru(II) and Co(III) polypyridyl complexes owing to their potential utility as DNA-structure probes, DNA-molecular “light switches”, DNA-photocleavage reagents, anti-cancer drugs for tumors [1,2]. The well-known $[\text{Ru}(\text{phen})_2(\text{dppz})]^{2+}$ and $[\text{Ru}(\text{bpy})_2(\text{dppz})]^{2+}$ complexes are the most extensively investigated complexes because they were found to be excellent DNA-molecular “light switches”, which can exhibit a negligible background emission in water, but exhibit an intense luminescence in the presence of double-stranded DNA [3,4], moreover, they possess particular DNA-photocleavage properties. In order to obtain better “light switches” and DNA-photocleavage complexes, many Ru(II) and Co(III) polypyridyl complexes have been synthesized and their DNA-molecular “light switches” and DNA-photocleavage properties were explored experimentally [5–7]. Meanwhile, many theoretical studies on Ru(II) and Co(III) complexes have been reported by using quantum-chemical method or/and molecular mechanics method. [8–13] For the quantum-chemical method, its calculational precisions on the energy and geometry optimization are considerably high and many microscopic

properties relating to molecular orbitals can be also obtained from its calculations. However, so far the quantum-chemical computations on the interaction properties between DNA and the complex as a whole model are still very difficult because the computational system is too great to the general computer capabilities. For the molecular mechanics method, although it can be used to study some DNA-interaction properties of complexes, its calculational precision on the energy is worse so that its calculational result is not very convincing, in particular, many microscopic properties relating to molecular orbitals cannot be obtained from its calculations. Recently, some QM/MM (Quantum chemistry/Molecular mechanics) method, in which the outer-layer optimization of the whole model was performed by using molecular mechanics computations whereas the inner-layer optimization was performed by using quantum-chemical method, was also used to study on some DNA-interaction properties of Ru(II) polypyridyl complexes. [14] Although many significant results were obtained, the selected models in this reference were limited to only include two base pairs and thus the effects of the biological environment may be underestimated. In order to explore the reliability that QM/MM method is used to optimize the whole DNA-complex model including more DNA-base-pairs, many tests were also done by our research group. Our tests find that the optimized shapes of the DNA-base-pairs were greatly changed and thus the calculated related DNA-intercalator properties cannot be in a satisfying agreement with experiment results. Therefore, at present, more suitable models for such a greater DNA-complex system need still to be established and more

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suitable combination methods of quantum chemistry and molecular mechanics need also to be explored.

In this paper, we select the experimentally well-reported $[\text{Co}(\text{phen})_2(\text{dppz})]^{3+}$, $[\text{Co}(\text{phen})_3]^{3+}$ and $[\text{Co}(\text{phen})_2(\text{dione})]^{3+}$ [15,16] in DNA environment to perform theoretical study. As a novel point of this work, we have established a sheared whole DNA-complex model to perform the study on DNA-interaction properties of Co(III) polypyridyl complexes, by using a combination method of the quantum-chemistry and the molecular mechanics. The main purpose of this work is theoretically to reveal the related properties of Co(III) polypyridyl complexes $[\text{Co}(\text{phen})_2\text{L}]^{3+}$ (L = dppz, phen, dione) **1–3** interacting with DNA, including the DNA-binding, DNA-photocleavage and spectral properties. We find that such a computational method and the established model can obtain some DNA-interaction properties of Co(III) polypyridyl complexes and the theoretical results can be used to reasonably explain the related experimental phenomena on this kind of Co(III) complex interacting with DNA.

2. Computational methods

2.1. Studied compounds and molecular docking

The studied complexes are shown in Fig. 1. Since our recent reports have shown that the structures and related properties of Co(III) polypyridyl-type complexes with high positive charges are greatly influenced by the solvent effect [17,18], full geometry-optimizations of these three complexes in ground state were carried out in aqueous solution using the restricted B3LYP method and LanL2DZ basis set. For the obtained structures, the frequency calculations were also performed in order to verify the optimized structure to be an energy minimum. The optimized-in-aqueous-solution structure of these complexes were further docked into DNA (downloaded from Protein Data Bank, PDB ID: 454d) in vacuo using the Dock6.0 program [19–22]. The box size, grid space, energy cutoff distance, and maximum orientation were set as 20 Å, 0.3 Å, 9999 Å, and 200,000 Å, respectively. The other parameters used in docking were default and the docking results are shown in Fig. 2.

2.2. The calculation of absorption spectra of docking model

Since the obtained docking model is a quite great supramolecular system, the computation of absorption spectra of the docking model is beyond our computer capabilities, the docking model was sheared and only one base-pair (CG) was retained on both sides of the intercalative ligand of complex, respectively (see Fig. 3). Moreover, the edges of the cuts were saturated with the hydrogen atoms while keeping the bond length of $\text{O}_2\text{--H}_1$ 0.096 nm, the bond angle of $\text{H}_1\text{--O}_2\text{--C}_3$ 109.5° and the dihedral angle of $\text{H}_1\text{--O}_2\text{--C}_3\text{--C}_4$ 180.0°, so as to the saturated bond lengths are made close to those of DNA crystal structures. Based on the sheared model, the electronic absorption spectra in aqueous solution were calculated with the time-dissolved density functional theory (TDDFT) at the level of B3LYP/3-21G*. 800 singlet-excited-state energies of the model were calculated to reproduce electronic absorption spectra and 60 high occupied orbitals and 60 low

unoccupied orbitals were included in configuration interaction in order to save the calculational time.

2.3. The calculation of emission spectra of docking model

Based on the above sheared model, full geometry optimization of the lowest triplet state (T_1) (with triplet multiplicity) of complex **1** intercalating DNA-base-pairs was carried out using spin-unrestricted B3LYP method, the LanL2DZ basis set for Co atoms, the D95V basis set for C, N, H and O atoms and the LanL2DZ basis set including *d* polarization function for P atom. Since the molecular weight of the DNA-docking model is very great, the atoms of DNA were frozen during the T_1 geometry optimization. Based on the obtained T_1 geometry, 500 triplet excitation energies were calculated with the TDDFT method at B3LYP/3-21G* level to reproduce the emission spectra, and 20 high occupied orbitals and 20 low unoccupied orbitals were included in configuration interaction in order to save the calculational time. In addition, to compare the emission spectra of complex **1** in the absence of DNA with that in the presence of DNA, the emission spectra of complex **1** in the absence of DNA was also computed. As above-mentioned, Co(III) polypyridyl complexes are greatly influenced by the solvent effect, the full geometry optimization of the lowest triplet state (T_1) (with triplet multiplicity) of complex **1** was carried out in aqueous solution at UB3LYP/LanL2DZ level. Based on the computed T_1 geometry of complex **1**, 40 triplet excitation energies were calculated in aqueous solution with the TDDFT method at B3LYP/3-21G* level to reproduce emission spectra.

All the calculations were performed by means of the Gaussian03 program-package (revision D.01) [23]. Meanwhile, the conductor polarizable continuum model (CPCM) [24,25] was applied to the solvent effect in aqueous solution.

3. Results and discussion

3.1. DNA-binding mode of the complexes

The optimized-in-aqueous-solution structure of complexes **1–3** were docked into DNA, and the corresponding average values of energy scores of these complexes **1–3** are $-67.29 \text{ kcal}\cdot\text{mol}^{-1}$, $-64.55 \text{ kcal}\cdot\text{mol}^{-1}$ and $-61.88 \text{ kcal}\cdot\text{mol}^{-1}$, respectively. Such a result shows that the average energy score of complex **1** is lower than those of complexes **2** and **3**, suggesting that the DNA-interaction of complex **1** is stronger than those of complexes **2** and **3**. Such a result is in a satisfying agreement with the trend in DNA-binding affinities measured in experiment [$K_b(\mathbf{3}) < K_b(\mathbf{2}) < K_b(\mathbf{1})$] [15,16].

From Fig. 2, we can see that the intercalative ligand (dppz) of complex **1** is intercalated DNA-base-pairs from major groove, whereas complexes **2** and **3** bind to DNA through groove binding interactions within the minor groove. Although the experimental results show complex **1** bind to DNA in an intercalative mode [15,16], the interaction details of complex **1** with DNA, e.g., via the minor groove or major groove in the intercalative mode, has not been reported. Recently, the various intercalative modes of the analog $[\text{Ru}(\text{phen})_2(\text{dppz})]^{2+}$ have

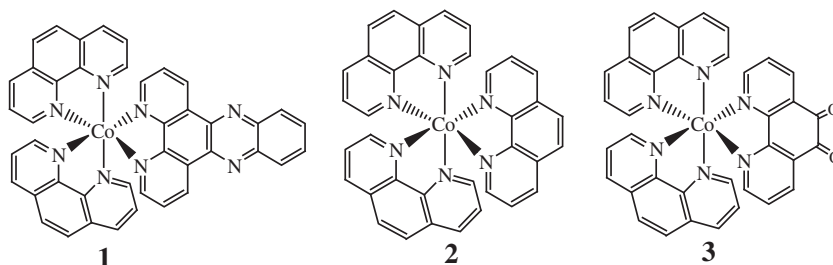


Fig. 1. Structural diagrams of the complexes **1–3**.

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