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Theoretical Study on the Site and Regularity of Chiral Ru(II) Polypyridyl Complexes Binding to Mismatched DNA-Base-Pair

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In order to perform theoretical studies on the interactions between Ru(II) complexes and DNA, a combined methodology of molecular mechanics (MM+), quantum chemistry (DFT) and molecular docking was applied to establish the valuable model and hereby to study the interaction of Ru(II) complexes with mismatched DNA containing sheared G×A base pairs. The groove selectivity, base pair recognition, binding energy at different base pair site and binding configuration were investigated, using well-known DNA intercalator $[Ru(phen)_2(dppz)]^{2+}$ as a molecular probe. On the basis of these testing researches, a series of chiral Ru(II) complexes Δ, Λ-$[Ru(bpy)_2L]^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hpip] {hpip = 2-(hydroxyphenyl)imidazo[4,5-f][1,10-phenanthroline]} were selected to carry out a significant study on their DNA-groove selectivity, DNA-binding energy and binding configuration at the specific base-pair site which has been specially recognized by $[Ru(phen)_2(dppz)]^{2+}$ molecular probe. The effects of chirality, different position of substitute group and intramolecular hydrogen bond of these studied complexes on the complex-DNA interaction were also discussed and the related regularities were well revealed. The obtained results help to understanding the control regulations and the action mechanism between the complex and DNA and further directing the design and synthesis of this kind of Ru(II) polypyridyl complex.

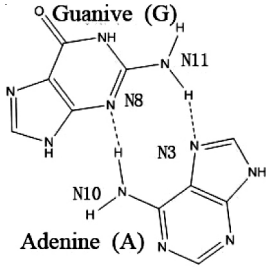
Key Words: Ru(II) polypyridyl complex, DNA, Molecular mechanism, DFT calculation, Docking analysis.

INTRODUCTION

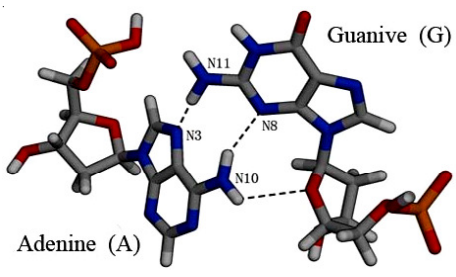
DNA sequences usually contain mismatched base pairs which have been suggested to form stable duplex and hairpin structures[1,2]. Among all types of mismatched base pairs, so-called sheared G × A base pair[3], as shown in (a) simplified 2D-structure of G × A base pair (b) 3D-structure of G × A base pair.

Fig. 1, is of particular interest due to its great potential in important biological functions such as DNA replication and centromere formation. Sheared G × A base pair can present a significant target site recognized and affected by small ligands and proteins[4]. Exploring the interaction between DNA binding agent and G × A base pair as well as the related regulations will provide a better understanding of identification and repair of nucleic acid sequences and will help to the diagnosis and treatment of cancers and inherited diseases.

Ru(II) polypyridyl complexes are considered as one of the most promising kinds of DNA binding agents[5-9] due to their valuable applications such as DNA structure probes, DNA molecular "light switches", DNA photocleavage reagents,



(a) Simplified 2D-structure of G × A base pair



(b) 3D-structure of G × A base pair

Fig. 1. Structure of mismatched G × A base pair

antitumor drugs and nonlinear optical materials. So far, a great deal of theoretical and experimental investigations on the interaction between Ru(II) polypyridyl complexes and DNA have been reported[10-14]. However, the studies based on a reasonable whole model for the intercalative modes, conformations as well as related regulations of these complexes intercalating the mismatched DNA base-pairs, retain scarcely found[15]. Moreover, when these Ru(II) complexes intercalate DNA base-pairs, their identification ability to DNA sequence, groove selectivity and enantiomer selectivity are still under intensive controversy. Most of crystal structures of Ru(II) complex-DNA composites have not been determined up to now, therefore, available experimental techniques can only give a limited description on Ru(II) complex-DNA interaction[16-18]. With a rapid development of computational technology, the integral interaction models between Ru(II) complexes and DNA base pairs can be effectively simulated and thus the interaction energies, binding modes, conformations as well as related regulations can be successfully revealed. However, the pure quantum chemistry calculations for the integral Ru(II) complex-DNA models are too computationally expensive to perform. At present, the theoretical study on the interactions between the complexes and DNA base-pairs can be only based on the respective calculations of complexes and DNA base-pairs using quantum chemistry method[19-21]. Therefore, it is significant work to establish some reasonable integral complex-DNA models and deeply investigate them by means of a combined methodology of molecular mechanics[22,23] and quantum chemistry.

In this paper, a combined methodology of molecular mechanism (MM+), quantum chemistry (DFT) and molecular docking was applied to study the interaction of Ru(II) complexes with mismatched DNA base-pairs. A mismatched DNA sequence d(CCGAATGAGG)$_2$ was selected to establish the DNA base-pair model intercalated by Ru(II) complexes[24-29]. The mismatched DNA sequence d(CCGAATGAGG)$_2$ contains four tandem sheared G × A base pairs in which the centromerecore sequence motif GAATG is embedded[4], as shown in Fig. 2. Meanwhile, the well-known typical DNA-intercalator $[Ru(phen)_2(dppz)]^{2+}$, (phen = 1,10-phenanthroline, dppz = dipyrido[3,2-a:2',3'-c]phenazine) **1**, as shown in Fig. 3, was selected as a molecular probe in order to obtain some basic binding information. On the basis of these testing, a series of recently reported chiral Ru(II) complexes Δ, Λ- $[Ru(bpy)_2(L)]^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hphp] (bpy = 2,2'-bipyridine, hpip = 2-(hydroxyphenyl) imidazo[4,5-f][1,10-phenanthroline], as shown in Fig. 4, were selected to perform a subject study. The purpose of this article mainly focuses on revealing the DNA-binding regulations of this series of chiral Ru(II) complexes *via* establishing an integral and available complex-DNA model. In this work, the DNA-groove selectivity, DNA-binding energy and binding configuration, as well as the effects of chirality, different position of substitute group and intramolecular hydrogen bond of these studied complexes on complex-DNA interaction were deeply discussed. We expect the obtained results help to understanding the action mechanism, revealing the control regulations and thus directing the functional molecular deign of this kind of complex.

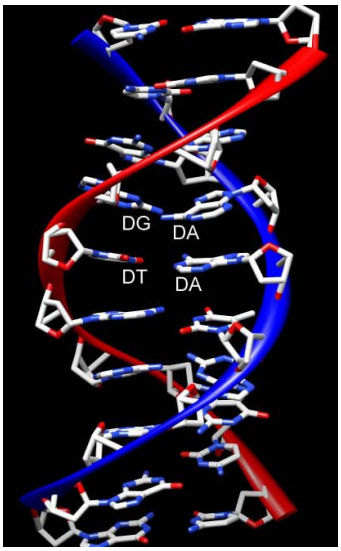


Fig. 2. Mismatched DNA sequence d(CCGAATGAGG)$_2$

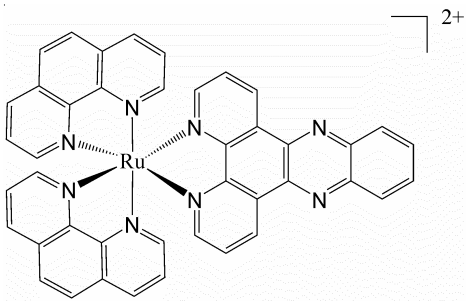


Fig. 3. Molecular structure of $[Ru(phen)_2(dppz)]^{2+}$ as a DNA-molecular probe

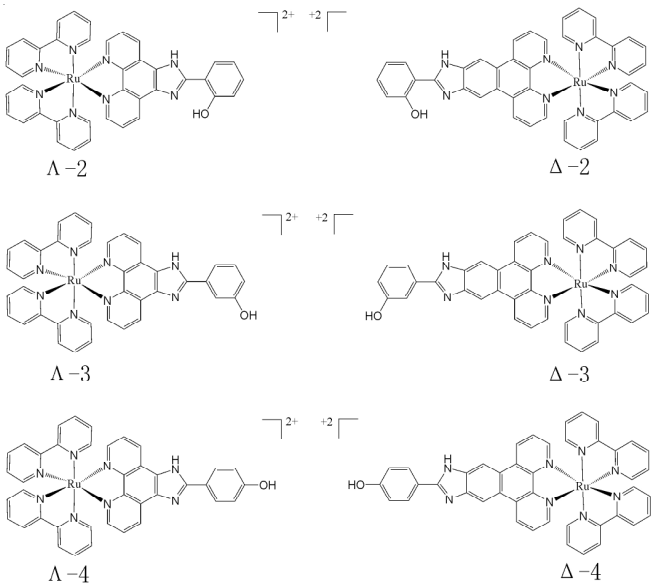


Fig. 4. Molecular structures of chiral Ru(II) complexes Δ, Λ- $[Ru(bpy)_2L]^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hpip]

COMPUTATIONAL METHOD

Preparation of $[Ru(phen)_2(dppz)]^{2+}$-DNA integral model: Mismatched DNA sequence d(CCGAATGAGG)$_2$, ID 1d8x, was downloaded from Protein Data Bank. Mismatched DNA sequence model was prepared in Chimera[30] in a way that only Chain A and Chain B were reserved and that all water

molecules and metal ions were removed. The structure of $[Ru(phen)_2(dppz)]^{2+}$ molecular probe was obtained from DFT calculation at B3LYP/Lanl2DZ level. $[Ru(phen)_2(dppz)]^{2+}$-DNA integral models were built in HyperChem Program as follows: (i) The main ligand dppz of $[Ru(phen)_2(dppz)]^{2+}$ molecular probe was manually intercalated between the base pairs so that dppz was inserted into the stacking spaces. The conjugate gradient minimization of these integral models in MM+ force field was performed until the RMS value was lower than 0.5 Kcal/mol. (ii) In order to seek the most stable interaction model, the ligand dppz was kept parallel to the base pairs and the insertion depth of $[Ru(phen)_2(dppz)]^{2+}$ was manually changed. The integral models at each depth were further minimized until RMS value was lower than 0.05 Kcal/mol. Total 14 intercalations of $[Ru(phen)_2(dppz)]^{2+}$ into 7 stacking spaces sites of sequence $d(CCGAATGAGG)_2$ from major and minor groove, respectively were simulated, C1G1/C2G2 and G9C9/G10C10 sites were not taken into consideration because of terminal effect. Finally, 14 most stable interaction models with the lowest energy values at each orientation were selected to perform the following DFT single point calculations.

DFT calculations of binding energies: To obtain accurate energies, every one of 14 intercalation models, which includes $[Ru(phen)_2(dppz)]^{2+}$ molecular probe, eight base pairs most adjacent to dppz and corresponding phosphate frameworks, were further extracted and then the DFT single point calculations were applied to obtain the exact binding energies ($\Delta E_{binding}$) between $[Ru(phen)_2(dppz)]^{2+}$ and DNA base-pairs via the following eqn. 1.

$$\Delta E_{binding} = E_{base} + E_{ligand} - E_{total} \quad (1)$$

in which E_{total} is total energy of intercalation model including the complex and eight adjacent base pairs, E_{base} is the energy of eight adjacent base pairs before intercalation, E_{ligand} is the energy of optimized $[Ru(phen)_2(dppz)]^{2+}$ and $\Delta E_{binding}$ expresses the binding energy of such a model. All DFT calculations were performed at B3LYP/Lanl2DZ level using Gaussian03 package[31].

Docking study: A docking study was also performed with DOCK 6.2 Program[32] to obtain the binding information of $[Ru(phen)_2(dppz)]^{2+}$ molecular probe. The parameters of Ru in DOCK 6.2 are radius of 1.89 and well_depth of 0.05. DNA receptor models were extracted from the most stable interaction models calculated by MM+. Gasteiger Hückel charges were added to DNA sequence by Sybyl 6.9[33]. Hydrogen positions were minimized using Powell method. The surface of DNA was calculated with DMS Program[34] and the binding site was identified using Sphgen module. $[Ru(phen)_2(dppz)]^{2+}$ molecular probe was automatically docked into the 7 sites of base pair stacking spaces from major and minor groove, respectively. The binding sites were enclosed in a grid box with extra margin of 20 Å added in six directions. The grid space and max orientation were set 0.3 Å and 100,000, respectively.

Calculations of Δ,Λ-$[Ru(bpy)_2L]^{2+}$-DNA integral model: The structures of Δ,Λ-$[Ru(bpy)_2L]^{2+}$ were obtained from DFT calculations at B3LYP/Lanl2DZ level. The interactions between mismatched DNA sequence and Δ,Λ-$[Ru(bpy)_2L]^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hphp] were investigated only focusing on the base-pair sites that the molecular probe $[Ru(phen)_2(dppz)]^{2+}$ can specially recognize. The total 12 intercalations of Δ,Λ- $[Ru(bpy)_2L]^{2+}$ into stacking space sites from major and minor groove were computed by the same method as the molecular probe $[Ru(phen)_2(dppz)]^{2+}$ intercalations.

RESULTS AND DISCUSSION

Base-pair sequence recognition by $[Ru(phen)_2(dppz)]^{2+}$ as molecular probe: Binding energy $\Delta E_{binding}$ at each base pair site is used to investigate the site which the molecular probe $[Ru(phen)_2(dppz)]^{2+}$ specially recognizes. The DFT calculation results of $[Ru(phen)_2(dppz)]^{2+}$-DNA models for the intercalations from major and minor groove are showed in Tables 1 and 2, respectively.

From Tables 1 and 2, we can see that at A5T5/T6A6 site, the binding energies ($\Delta E_{binding}$) of $[Ru(phen)_2(dppz)]^{2+}$-DNA models for both major and minor grooves are all negative and very great, suggesting that $[Ru(phen)_2(dppz)]^{2+}$ can not intercalate the mismatched DNA sequence from A5T5/T6A6 site. The binding energy $\Delta E_{binding}$ of $[Ru(phen)_2(dppz)]^{2+}$-DNA model at A4G4/A5T5 site intercalated by the complex from minor groove is the largest among all base-pair sites, suggesting that $[Ru(phen)_2(dppz)]^{2+}$ molecular probe can specially recognize A4G4/A5T5 site. The intercalation depth of dppz is

TABLE-1
DFT CALCULATION RESULTS AT EACH SITE OF INTERCALATION FROM MAJOR GROOVE

Site	C2G2/G3A3	G3A3/A4G4	A4G4/A5T5	A5T5/T6A6	T6A6/G7A7	G7A7/A8G8	A8G8/G9C9
E_{total} (a.u.)	-10655.58	-10639.61	-10623.27	-10623.35	-10623.52	-10639.52	-10655.60
E_{base} (a.u.)	-8507.43	-8491.02	-8474.92	-8553.59	-8474.95	-8491.40	-8507.43
E_{ligand} (a.u.)	-2147.48	-2147.48	-2147.48	-2147.48	-2147.48	-2147.48	-2147.49
$E_{binding}$ (a.u.)	0.67	1.11	0.87	-77.72	1.085	0.63	0.69
$\Delta E_{binding}$ (Kcal/mol)	424.29	700.19	547.74	-48774.52	681.26	397.64	436.52

TABLE-2
DFT CALCULATION RESULTS AT EACH SITE OF INTERCALATION FROM MINOR GROOVE

Site	C2G2/G3A3	G3A3/A4G4	A4G4/A5T5	A5T5/T6A6	T6A6/G7A7	G7A7/A8G8	A8G8/G9C9
E_{total} (a.u.)	-10655.58	-10639.67	-10623.57	-10623.53	-10623.18	-10639.66	-10655.67
E_{base} (a.u.)	-8507.43	-8491.02	-8474.92	-8553.60	-8474.96	-8491.41	-8507.43
E_{ligand} (a.u.)	-2147.48	-2147.49	-2147.48	-2147.48	-2147.48	-2147.48	-2147.48
$E_{binding}$ (a.u.)	0.67	1.17	1.17	-77.55	0.74	0.77	0.75
$\Delta E_{binding}$ (Kcal/mol)	420.20	732.60	734.43	-48662.02	465.13	481.26	473.61

ca. 8 Å and the distance between adjacent base-pair and dppz is *ca.* 3.4 Å, indicating that after intercalation of $[Ru(phen)_2(dppz)]^{2+}$, the phosphate framework of DNA is obviously stretched and the distance between base pair is also greatly increased from 3.4-6.8 Å.

Groove selectivity of the molecular probe $[Ru(phen)_2(dppz)]^{2+}$: The calculation results also show that the binding energy $\Delta E_{binding}$ (734.4 Kcal/mol) obtained from minor groove at A4G4/A5T5 site is obviously greater than that from major groove (547.7 Kcal/mol), indicating that at this site, minor groove intercalation is preferential to major groove intercalation. Docking scoring at A4G4/A5T5 site also confirms such result (Tables 3 and 4). Minor groove preference at A4G4/A5T5 for $[Ru(phen)_2(dppz)]^{2+}$ may relate to the steric effect. An arch curve on DNA phosphate framework appears on the minor groove direction at A4G4/A5T5 site, which can effectively accommodate the ancillary ligand phen, as shown in Fig. 5. On the major groove direction, however, there is not such an arch curve so that phen can not be effectively accommodated on phosphate framework.

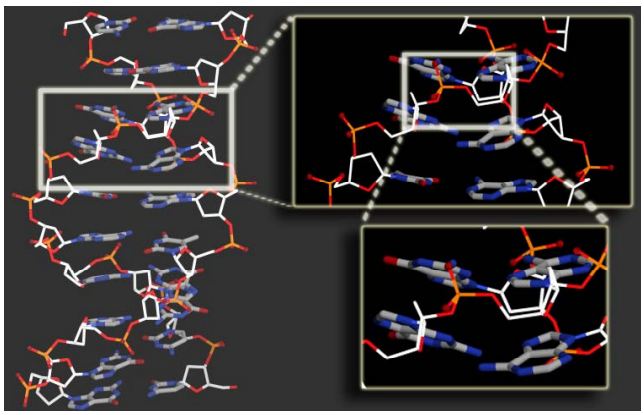


Fig. 5. Arch curve on DNA phosphate framework existing on the minor groove direction at A4G4/A5T5 site

Trend in binding affinities of Δ,Λ-$[Ru(bpy)_2L]^{2+}$ intercalating the mismatched DNA sequence: The DNA binding properties of Δ,Λ-$[Ru(bpy)_2L]^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hpip] have experimentally been reported and the binding affinities can be quantitatively expressed by binding constant (K_b). Some theoretical investigations based on the respective calculations of complexes and DNA base-pairs using the DFT method have also been carried out. Here, we present the calculated results based on the integral and available complex-DNA models.

As the above-mentioned, the test of the molecular probe $[Ru(phen)_2(dppz)]^{2+}$ has indicated that A4G4/A5T5 site is the most possible binding site. It is assumed that this site is also the most possible binding site for this series of Ru(II) polypyridyl complexes and then investigate the trend in the DNA-binding affinities of these complexes in intercalation mode. The calculated results on the binding energies ($\Delta E_{binding}$) along with the corresponding experimental K_b value are shown in Table-5.

From Table-5, we can clearly see that the calculated results are in good agreement with the experimental ones, in which the trend in the DNA-binding affinities of these complexes is as follows:

$$K_b([Ru(bpy)_2(o\text{-hpip})]^{2+}) > K_b([Ru(bpy)_2(m\text{-hpip})]^{2+}) > K_b([Ru(bpy)_2(p\text{-hpip})]^{2+})$$

Moreover, it is interesting to find that the obtained trends are all the same for both chiral Δ- and Λ-complexes and for both major and minor groove intercalations. It further confirms that the established models are reasonable and acceptable.

In addition, the DFT calculations visually show there is an intramolecular H-bond on ligand *o*-hpip, as shown in Fig. 6. This intramolecular H-bond extends the conjugate area and enhances π-π stacking action between *o*-hpip and adjacent base pairs and thus increases the binding affinity of $[Ru(bpy)_2(o\text{-hpip})]^{2+}$ to DNA. It is the reason why $[Ru(bpy)_2(o\text{-hpip})]^{2+}$ has much stronger DNA-binding affinity than the other isomers.

Groove selectivity of Δ,Λ-$[Ru(bpy)_2L]^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hpip]: From Table-5 showed that for every enantiomer, $\Delta E_{binding}$ from minor groove intercalation is greater than that from major groove intercalation. This trend can be further visualized in Fig. 7, suggesting that minor groove intercalation is preferential to major groove intercalation.

In order to confirm the trend in groove selections, docking study was also carried out. The calculational results are shown in Table-6. Form Table-6, we see that Δ,Λ-$[Ru(bpy)_2L]^{2+}$ can be automatically docked into A4G4/A5T5 site from minor groove because their docking scoring or docking energy expressed as E_{total} are all negative values. Meanwhile, we also see that Δ-$[Ru(bpy)_2(o\text{-hpip})]^{2+}$, Λ-$[Ru(bpy)_2(m\text{-hpip})]^{2+}$ and Λ-$[Ru(bpy)_2(p\text{-hpip})]^{2+}$ also can be docked into A4G4/A5T5 site from major groove however, the scoring values (E_{total}) from major groove are much higher than those from minor groove, respectively. In addition, Λ-$[Ru(bpy)_2(o\text{-hpip})]^{2+}$, Δ-$[Ru(bpy)_2(m\text{-hpip})]^{2+}$ and Λ-$[Ru(bpy)_2(p\text{-hpip})]^{2+}$ can not even be docked into A4G4/A5T5 site from major

TABLE-3
DOCKING SCORING AT EACH SITE INTERCALATED FROM MAJOR GROOVE

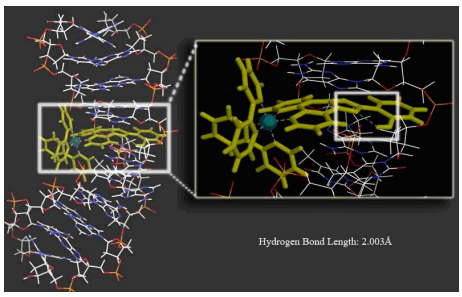
Site	C2G2/G3A3	G3A3/A4G4	A4G4/A5T5	A5T5/T6A6	T6A6/G7A7	G7A7/A8G8	A8G8/G9C9
E_{total} (Kcal/mol)	-68.41	-71.44	-73.58	-88.00	-74.75	-76.38	-69.02
E_{vdw} (Kcal/mol)	-48.74	-50.79	-49.25	-60.21	-51.96	-51.65	-49.36
E_{elect} (Kcal/mol)	-19.67	-20.65	-24.33	-27.79	-22.80	-24.73	-19.66

TABLE-4
DOCKING SCORING AT EACH SITE INTERCALATED FROM MINOR GROOVE

Site	C2G2/G3A3	G3A3/A4G4	A4G4/A5T5	A5T5/T6A6	T6A6/G7A7	G7A7/A8G8	A8G8/G9C9
E_{total} (Kcal/mol)	-66.07	-62.48	-80.19	-79.60	-52.73	-60.01	-68.18
E_{vdw} (Kcal/mol)	-49.95	-47.17	-59.96	-60.90	-38.00	-44.95	-53.22
E_{elect} (Kcal/mol)	-16.12	-15.30	-20.23	-18.71	-14.73	-15.06	-14.95

TABLE-5
THEORETICAL $\Delta E_{binding}$ AND EXPERIMENTAL K_b of Δ,Λ-$[Ru(bpy)_2L]^{2+}$

	K_b ($10^5 M^{-1}$)	$\Delta E_{binding}$ (major groove), (Kcal/mol)	$\Delta E_{binding}$ (minor groove), (Kcal/mol)
Δ- $[Ru(bpy)_2(o\text{-hpip})]^{2+}$	6.8	569.57	668.27
Δ- $[Ru(bpy)_2(m\text{-hpip})]^{2+}$	1.5	536.26	662.79
Δ- $[Ru(bpy)_2(p\text{-hpip})]^{2+}$	1.0	528.97	657.00
Λ- $[Ru(bpy)_2(o\text{-hpip})]^{2+}$	5.3	529.08	692.57
Λ- $[Ru(bpy)_2(m\text{-hpip})]^{2+}$	1.0	520.55	688.92
Λ- $[Ru(bpy)_2(p\text{-hpip})]^{2+}$	0.7	473.85	687.26



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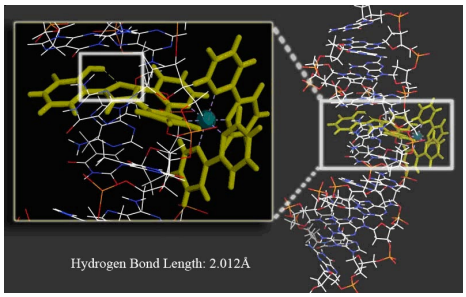

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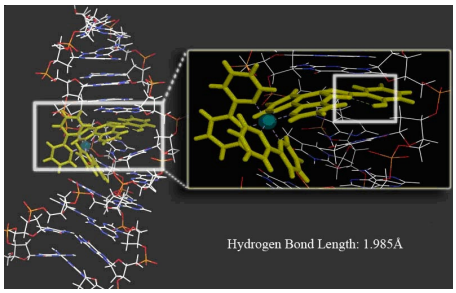

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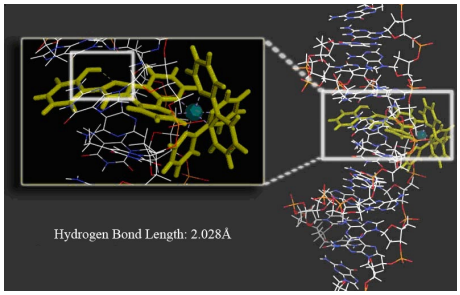
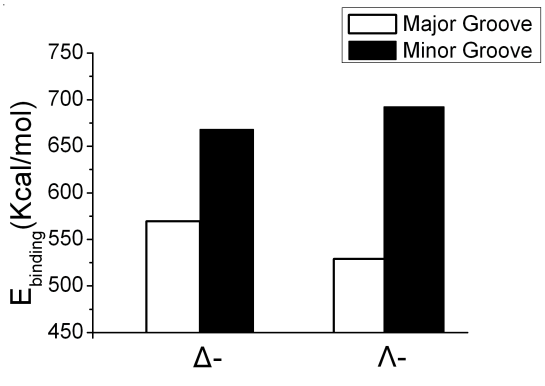


(d)

Fig. 6. Conformations of intercalation of $[Ru(bpy)_2(o\text{-hpip})]^{2+}$ to A4G4/A5T5 site. (a) Δ-[Ru(bpy)2(o-hpip)]$^{2+}$ intercalation from major groove. (b) Δ-$[Ru(bpy)_2(o\text{-hpip})]^{2+}$ intercalation from minor groove. (c) Δ-$[Ru(bpy)_2(o\text{-hpip})]^{2+}$ intercalation from major groove. (d) Δ-$[Ru(bpy)_2(o\text{-hpip})]^{2+}$ intercalation from minor groove



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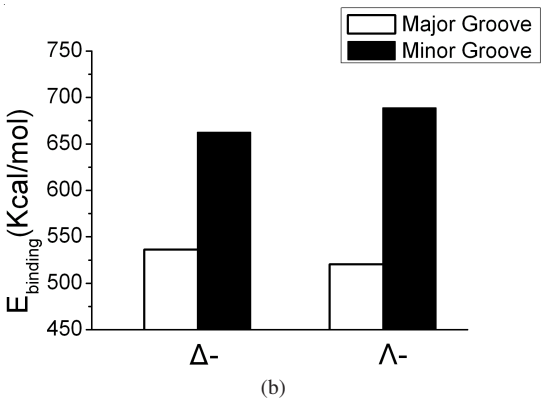

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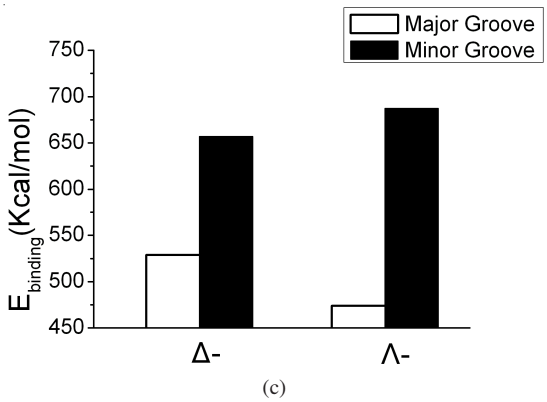


(c)

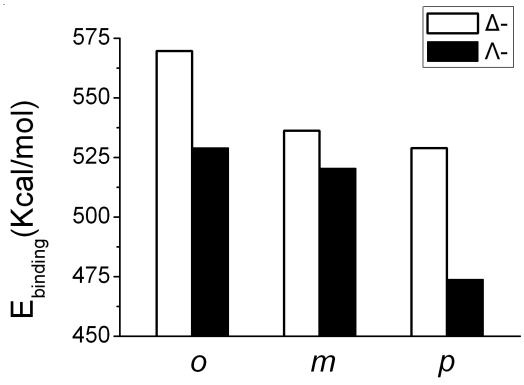
Fig. 7. Comparisons between minor and major groove intercalations. (a) $[Ru(bpy)_2(o\text{-hpip})]^{2+}$, (b) $[Ru(bpy)_2(m\text{-hpip})]^{2+}$, (c) $[Ru(bpy)_2(p\text{-hpip})]^{2+}$

TABLE-6
DOCKING SCORING OF Δ,Λ-$[Ru(bpy)_2L]^{2+}$ INTERCALATED AT A4G4/A5T5 SITE

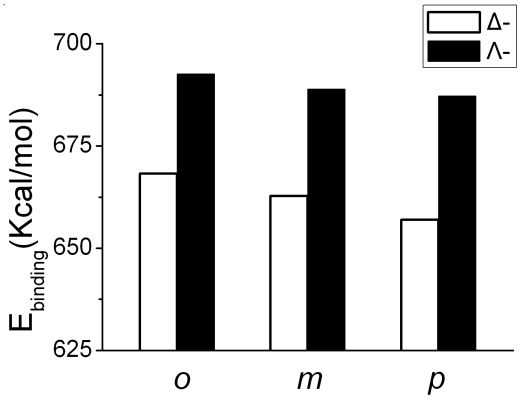
	E_{total} (Kcal/mol) (major groove)	E_{total} (Kcal/mol) (ninor groove)
Δ-$[Ru(bpy)_2(o\text{-hpip})]^{2+}$	-66.33	-68.93
Δ-$[Ru(bpy)_2(m\text{-hpip})]^{2+}$	–	-67.05
Δ-$[Ru(bpy)_2(p\text{-hpip})]^{2+}$	–	-70.05
Λ-$[Ru(bpy)_2(o\text{-hpip})]^{2+}$	–	-68.00
Λ-$[Ru(bpy)_2(m\text{-hpip})]^{2+}$	-64.13	-69.81
Λ-$[Ru(bpy)_2(p\text{-hpip})]^{2+}$	-68.08	-76.96

groove, because we can not obtain their scoring values (E_{total}) in intercalation. In short, the docking results show that the major groove intercalation is less stable than minor groove intercalation for every chiral Ru(II) complex $[Ru(bpy)_2L]$ (L = o-hpip, m-hpip, p-hpip) binding to DNA.

Enantiomer selectivity of Δ,Λ-[Ru(bpy)$_2$L]$^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hphp]: From Table-5, we can also see that for the intercalation of every isomer of [Ru(bpy)$_2$L]$^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hphp] at the same direction (major or minor groove), $\Delta E_{binding}$ values of Δ-complexes are greater than those of Λ-complexes at major groove, respectively, however, the trend is just in contrary at minor groove. These trends are further visualized in Fig. 8, suggesting that Δ-complex intercalation prefer major groove whereas Λ-complex intercalation prefer minor groove if the intercalation happens at the same direction.



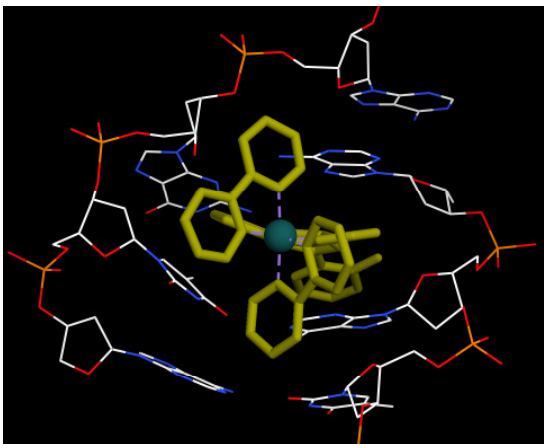
(a)



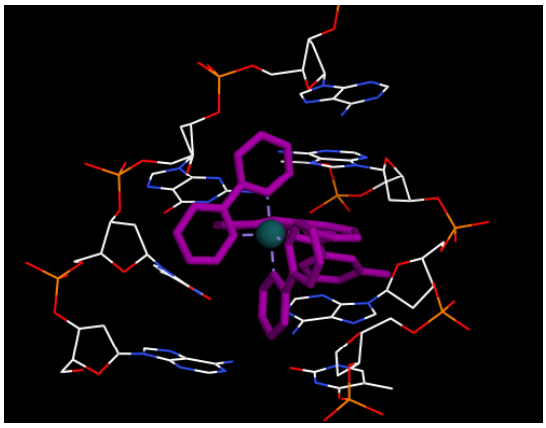
(b)

Fig. 8. Enantiomer selectivity of Δ,Λ-[Ru(bpy)$_2$L]$^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hpip]. (a) Major groove intercalation; (b) Minor groove intercalation

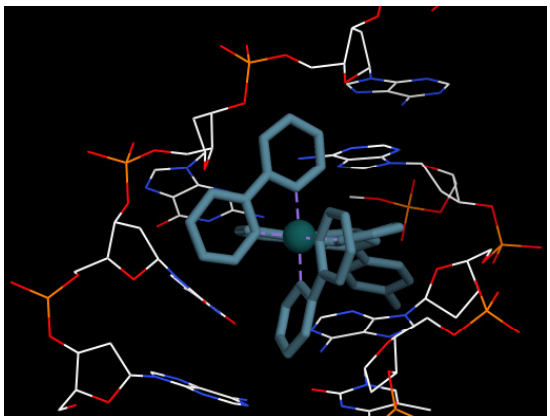
Such an enantiomer selectivity of Δ,Λ-[Ru(bpy)$_2$L]$^{2+}$ may owe if two ancillary ligands (bpy) is on speaking terms with the DNA phosphate framework in intercalative mode (expressing main ligand intercaltion). Δ enantiomers can preferentially intercalate DNA base-pairs from major groove because their two bpy ancillary ligands just match with the helix orientation of phosphate framework, whereas for the intercalation of Δ enantiomers from minor groove, the interspace between two DNA phosphate helixes is obviously small and thus the static hindrance obviously occurs. However, as depicted in 3.2, an arch curve on DNA phosphate framework appears on the minor groove direction at A4G4/A5T5 site, but there is not such an arch curve on the major groove direction. When Δ enantiomer of [Ru(bpy)$_2$L]$^{2+}$ intercalates the base-pairs A4G4/A5T5, this arch curve can effectively accommodates its ancillary ligands (bpy), shown in Fig. 9. It may be the reason that the enantiomers Δ,Λ-[Ru(bpy)$_2$L]$^{2+}$ have different selectivity for major and minor grooves.



(a)



(b)



(c)

Fig. 9. Minor groove binding configurations of Λ-[Ru(bpy)$_2$L]$^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hphp] at A4G4/A5T5 site. (a) Λ-[Ru(bpy)$_2$(*o*-hpip)]$^{2+}$; (b) Λ-[Ru(bpy)$_2$(*m*-hpip)]$^{2+}$; (c) Λ-[Ru(bpy)$_2$(*p*-hpip)]$^{2+}$

Conclusion

The interactions of Ru(II) polypyridyl complexes with mismatched DNA were investigated by using a combined methodology of molecular mechanics (MM+), quantum chemistry (DFT) and molecular docking. Some conclusions are drawn as follows:

(1) The probe-intercalation of $[Ru(phen)_2(dppz)]^{2+}$ into mismatched A4G4/A5T5 site is more preferential than other sites. Meanwhile, at A4G4/A5T5 base pair site, the intercalation of $[Ru(phen)_2(dppz)]^{2+}$ from minor groove is more preferential than that from major groove.

(2) At A4G4/A5T5 base pair site which is specially recognized by molecular probe $[Ru(phen)_2(dppz)]^{2+}$, the trend in binding energies of Δ,Λ-$[Ru(bpy)_2L]^{2+}$ is $\Delta E([Ru(bpy)_2(o\text{-hpip})]^{2+}) > \Delta E([Ru(bpy)_2(m\text{-hpip})]^{2+}) > \Delta E([Ru(bpy)_2(p\text{-hpip})]^{2+})$, which is in good agreement with experimental results. That Δ,Λ-$[Ru(bpy)_2(o\text{-hpip})]^{2+}$ have the highest binding energies in this series of complexes can owe to an intramolecular hydrogen bond on their main ligand *o*-hpip because it enlarges the conjugated area and reinforces the π-π interaction.

(3) For every one of six isomers Δ,Λ-$[Ru(bpy)_2L]^{2+}$, the binding energy from minor groove intercalation at A4G4/A5T5 site is greater than that from major groove intercalation and thus the intercalation of Δ,Λ-$[Ru(bpy)_2L]^{2+}$ from minor groove should be preferential to the intercalation from major groove.

(4) For minor groove intercalations, the binding energies of Λ-$[Ru(bpy)_2L]^{2+}$ are greater than those of Δ-$[Ru(bpy)_2L]^{2+}$, respectively; whereas for major groove intercalations. The binding energies of Δ-$[Ru(bpy)_2L]^{2+}$ are greater than those of Λ-$[Ru(bpy)_2L]^{2+}$, respectively. The former trend can be attributed to the DNA helix direction in line with the conformations of Δ enantiomers so that Δ enantiomers prefer major groove binding and the latter trend can be attributed to an arch bending on minor groove direction, which can effectively keep on speaking terms with the two bpy ancillary ligands of Λ-$[Ru(bpy)_2L]^{2+}$.

(5) For both $[Ru(phen)_2(dppz)]^{2+}$ molecular probe and Δ,Λ-$[Ru(bpy)_2L]^{2+}$ [L = *o*-hpip, *m*-hpip, *p*-hpip], molecular docking results are in satisfying agreement with the DFT calculations using the integral models built by the molecular mechanism method, suggesting that the established integral DNA-complex models are acceptable and docking study is also reliable to the conformation analysis.

It should be emphasized that the theoretical study on the interactions of Ru(II) polypyridyl complexes with mismatched DNA are very complicated. Here is only our limited work, which can be improved in a future work going with the advanced calculational methods.

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