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Molecular modeling on the recognition of DNA sequence and conformational repair of sheared DNA by novel chiral metal complex *D*, *L*-[Co(phen)$_2$hpip]$^{3+}$

WU Yanbo, ZHANG Cuiping & YANG Pin

Institute of Molecular Science, Key Laboratory of Chemical Biology of Molecular Engineering of Ministry of Education, Shanxi University, Taiyuan 030006, China
Correspondence should be addressed to Yang Pin (email: yangpin@sxu.edu.cn)

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Abstract A study on the recognition of DNA sequence and conformational repair of sheared DNA by Novel Chiral Metal complex *D*,*L*-[Co(phen)$_2$hpip]$^{3+}$ (phen=1,10 phenanthroline, hpip=2-[2-hydroxyphenyl] imidazole [4,5-f][1,10] phenanthroline) is carried out with molecular simulations. The results reveal that two isomers of the complex could both recognize the normal DNA in the minor groove orientation, while recognize the sheared DNA in the major groove orientation and both isomers could convert the conformation of mismatched bases from sheared form to parallel form. Further analysis shows that the steric details of complex's intercalation to base stack determine the results of recognition, which is induced by the steric collision among ancillary ligand phen, bases and DNA backbone, and by the steric crowding occurring in the process of structural expansion of bases and DNA backbone. Detailed analysis reveals that the conformational repair of mismatched bases relates not only to the steric interactions, but also to the π-π stack among normal bases, mismatched bases and hpip ligand.

Keywords: mismatched DNA, metal complex, molecular modeling, docking.

Recent studies revealed that DNA, once considered as a very stable macromolecular, is rather unstable. Familiar factors, like heavy metal, microbe, high frequency electromagnetic radiation and so on, could easily damage the structure of DNA in different ways, such as the break of side chain, the absence of bases, the structural modification and aberration. Sometimes, the functional abnormity of enzyme could damage the DNA, too. In most cases, the repair system in the cell could repair the damage immediately. Even when the repair was unsuccessful, the immune system of life would kill the cell containing the damaged DNA to protect the whole body. However, in case that the immune system is inefficient, the cell containing the damaged DNA will become the endogenesis, which could lead to different kinds of molecular diseases, such as cancer[1−4].

Base mismatch is a kind of structural modification and aberration and in most cases is considered a kind of dangerous DNA damage. In mismatch family, the sheared double G:A mismatch damages the DNA structure and function more seriously. Bases G and A in sheared region are parallel to the bases G and A on the other side chain, which stabilizes the badly dis-

torted structure by conjugate stack. It is difficult for repair system in the cell to repair sheared mismatch directly.

In the studies of DNA recognition, metal complexes of general form $[M(phen)_2L]^{n+}$ (M is transition metal ions, ancillary ligand phen could be replaced by bidentate ligand like bpy (2,2′-bipyridyl), phi (9,10-phenanthrenequinone diimine) and so on, and bidentate ligand L has a planar aromatic heterocyclic functionality that can enter and stack between the base pairs of double helical DNA) have contributed to our understanding of fundamental nucleic acid recognition[5−13]. In the former work[1)], we found accidentally that L-isomer of $[Co(phen)_2dpq]^{3+}$ could repair the sheared mismatch at the conformational level. Therefore, we could predict a new function of this kind of complexes.

To acquire further knowledge of DNA recognition and repair by this kind of complexes, we investigated the interactions between normal, sheared DNA and metal complex $[Co(phen)_2hpip]^{3+}$. Because hpip ligand has two conformational isomers, each enantiomer of mixed-ligand complex $[Co(phen)_2hpip]^{3+}$ has two different structures (Fig. 1). The optimal energies of form I and form II are −633.19 and −613.87 kJ/mol respectively. Their differences in energy could be offered by system at room temperature. When the ligand hpip is inserted into the DNA base stack whether in form I or in form II, the steric hindrance and conjugated stack will stabilize the structure so that it could not convert to the other form. Therefore, we must consider the differences of recognition and repair brought by structural differences between the two forms when DNA binding interactions were investigated.

In the former work, we had simulated the recognition interaction between complexes of form I and DNA in vacuum[14,15]. In this work, the interactions between normal, sheared DNA and complex of form II were investigated. Considering the stabilization effect of water on DNA, all simulations of the system containing DNA were carried out in aqueous solution.

1 Calculating method

All simulations were performed in SGI workstation with Insight II software package. The main calculating program was DISCOVER 98. Default settings for that program were used unless specified otherwise. The system studied contained DNA and a Co atom with octahedral coordination structure, which could be dealt with efficiently by ESFF force field and could offer more output information for analysis, so this force field was used with its default parameters.

Electroneutrality of each docked structure was achieved with the addition of 17 Na^+ counterions in the model of complex-normal DNA association and 15 Na^+ counterions for complex-sheared DNA association by standard procedures to balance the phosphate anions on the DNA side chain and the positively charged metal complex. At the beginning of optimization and energy minimization, the Steepest Descent method was used until the RMS derivation was less than 21 kJ/mol. Then it was switched to Conjugate Gradient method automatically by the DISCOVER 98 program. When the RMS derivation was less than 2.1 kJ/mol,

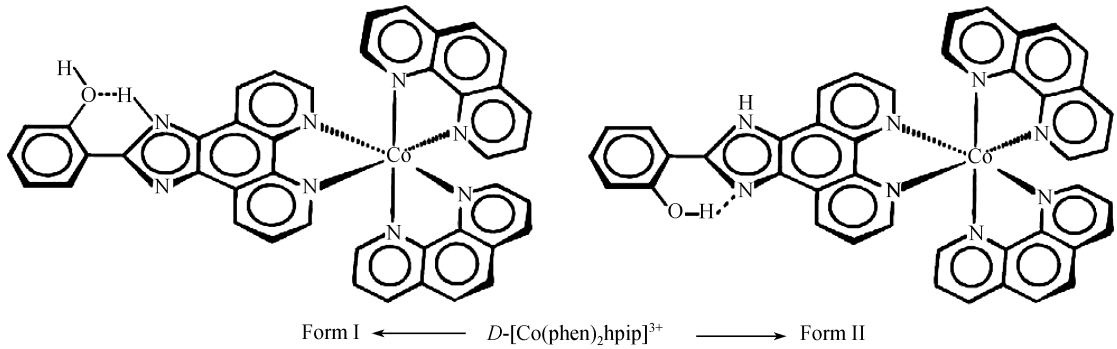

Fig. 1. Two forms of the complex. Form II was studied in this work.

1) J. Mol. Struc. (Theochem.) (in review).

optimization and energy minimization was stopped.

As a starting point, the metal complex was constructed in the BUILDER module and optimized in ESFF force field. The X-ray structure of sheared DNA 5′-(CC**GA**AT**GA**GG)$_2$-3′ (Fig. 2) was downloaded from the National Center for Biotechnology Information[16]. Firstly, the metal ions and all H_2O molecules of the model were eliminated and all bonds types and atom types were reset. Secondly, the DNA structure was optimized under Amber force field. The normal sequence 5′-d(CCGTCGACGG)$_2$-3′ was constructed in BIOPOLYMER module and then underwent geometry and energy minimization optimization. Each isomer was docked manually into the DNA base stack between double base pairs except the CC/GG region of both sheared DNA and normal DNA at the termini, and intercalations simulated in the major groove and minor groove respectively. As a beginning, the hpip plane was placed nearly parallel to the base pairs plane (perpendicular to DNA helix axis) and just out of the DNA helix. This point was regarded as the first checkpoint and its intercalation depth was defined as 0. Then, Co (III) complex was docked into base stack until the hpip ligand was intercalated into the base stack entirely. We selected the checkpoint for every 0.2 nm, and the intercalation depths were thus defined as 0.2, 0.4 nm, etc. Then based on the potential energy distribution, we could acquire the optimal interaction model for each isomer and DNA. Though the hpip ligand is asymmetric, considering the DNA sequence is symmetric, we did not calculate all the sites repeatedly. Simulations of all systems containing DNA were carried out in aqueous solution, while other systems in vacuum.

2 Results

Calculating results are listed in the tables in the Supporting Information. A look at the tables revealed that the complex could be intercalated into the base stack at all sites of both normal or sheared DNA. The only distinction among those models was stability of the complex-DNA association. For normal DNA recognition, both isomers selected the minor groove as their interaction orientation. The *L*-isomer recognized the C_4G_5 region, while the *D*-isomer recognized the T_3C_4 region. However, both isomers recognized the T_5G_6 region of the sheared DNA in the major groove orientation. Based on the distinctness of potential energy, we know that *D*-isomer is preferential in normal DNA recognition and a little preferential in sheared DNA recognition. When the optimal models were investigated, we found that both isomers could repair the sheared DNA at the conformational level: *L*-isomer's interaction converted G_6:A_3 bases pairs from sheared form to parallel form, while the *D*-isomer's interaction converted two mismatched base pairs to parallel form (Fig. 3).

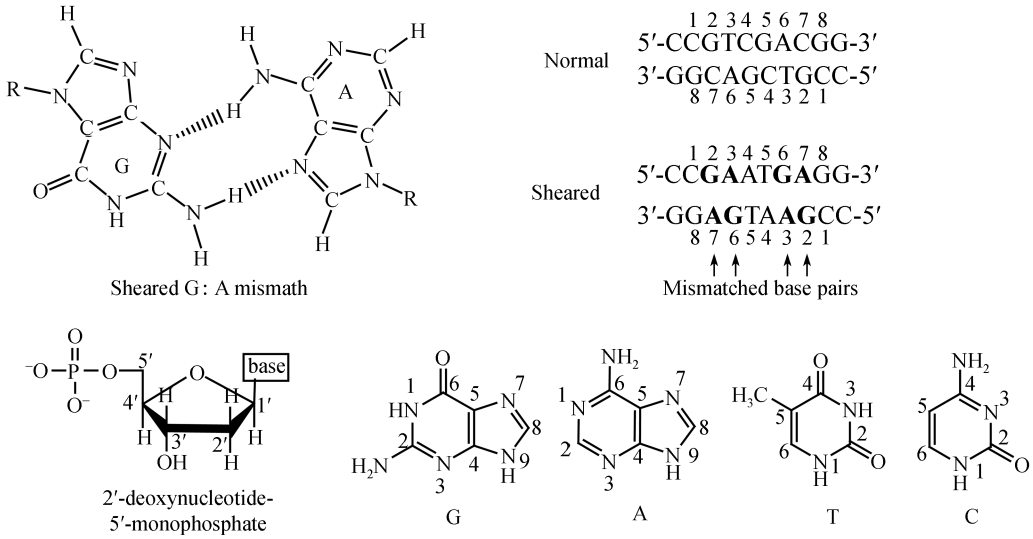

Fig. 2. Sheared G: A mismatch and the DNA sequence studied in this work.

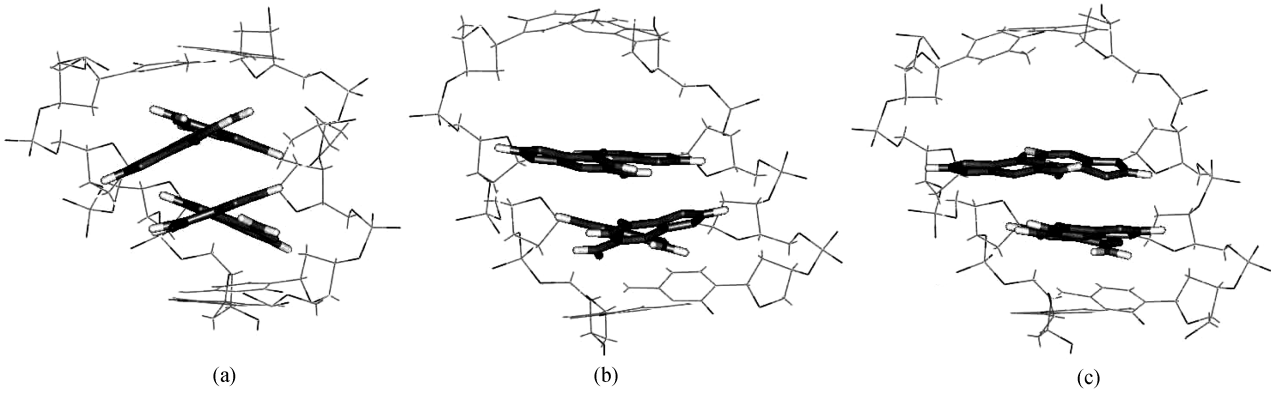

Fig. 3. (a) Sheared mismatch; (b) and (c) conformation of mismatched base pairs after repair for *L*-isomer and *D*-isomer.

3 Discussion

3.1 DNA recognition events

Based on the above analysis, we knew that the DNA recognition events showed groove-selectivity. The complex recognized the normal DNA in the minor groove orientation, which showed enantio-selectivity, while the complex recognized the sheared DNA in the major groove orientation, which showed site-specificity.

(i) Selectivity and specificity. Detailed structural analysis shows that selectivity and specificity are determined by the steric interactions. For normal DNA recognition, the steric collision between nucleobases and ancillary ligand phen determines the selectivity and specificity. Firstly, the stretch orientation determines the groove-selectivity. As shown in Fig. 4, the bases in normal DNA stretch from the minor groove to the major groove. When the intercalation starts from the major groove (Fig. 4(a)), nucleobases have to move toward the close-constructed minor groove region due to steric hindrance that makes the base pairs crowding (arrow 1). At the same time, to accommodate the complex, the intercalation will be accompanied by structural distension (arrow 1′) of the side chain, which is limited by a counterforce of whole Oligodeoxyribonucleotide (ODN) (arrow 1″). When the intercalation starts from the minor groove, as shown in Fig. 4(b), the nucleobases will move to the open-constructed major groove region (arrow 2), and there have few structural limitations to distension (arrow 2′) of ODN side chain. So the intercalation from the major groove will encounter more steric collisions than that from the minor groove. We conclude that it is the structural characteristics of DNA that lead to the facile binding interactions in the minor groove.

Secondly, the enantio-selectivity is determined by the differences of steric collisions brought by different kinds of bases. With four Watson-Crick bases, purine bases A and G are larger than pyrimidine bases C and T, so purine base will bring more steric collisions than pyrimidine base when the metal complex is intercalated into ODN base stack. Take the situation in the C_4G_5/G_5C_4 and T_3C_4/A_6G_5 regions as an example. When the complex is intercalated into the T_3C_4/A_6G_5 region, both isomers have one ancillary ligand phen colliding with purine base and the other colliding with pyrimidine base. Under this condition, the *D*-isomer fits the right hand conformation. Therefore, *D*-isomer's binding is preferential in the T_3C_4/A_6G_5 region. When the complex collides with nucleobases in the C_4G_5/G_5C_4 region, the ancillary ligand phen of *L*-isomer faces pyrimidine base C, while the phen of *D*-isomer faces purine base G. Obviously, *L*-isomer's binding is preferential. Though interacting with right hand double helical DNA, *L*-isomer has almost the same probability to be intercalated into DNA with that of *D*-isomer due to the minor steric collisions. Contrary to the recognition by $[Co(phen)_2dpq]^{3+}$, *D*-isomer has priority (only a little) to bind with normal DNA. Because hpip is much larger than dpq in size, we know that the ancillary ligand phen of complex containing longer intercalator has less effect on the enantioselectivity than that of the complex containing shorter intercalator.

The arrangement of bases in sheared DNA is much different from that in normal DNA, which means that

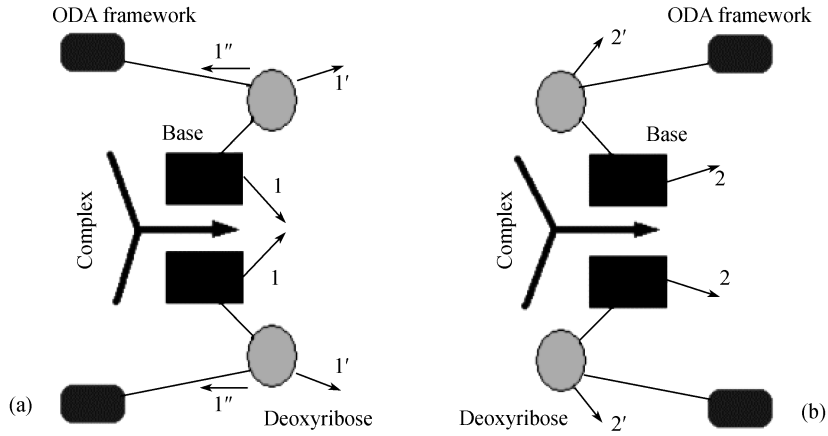

Fig. 4. The sketch map of steric hindrance. (a) Intercalation from the major groove, (b) intercalation from the minor groove.

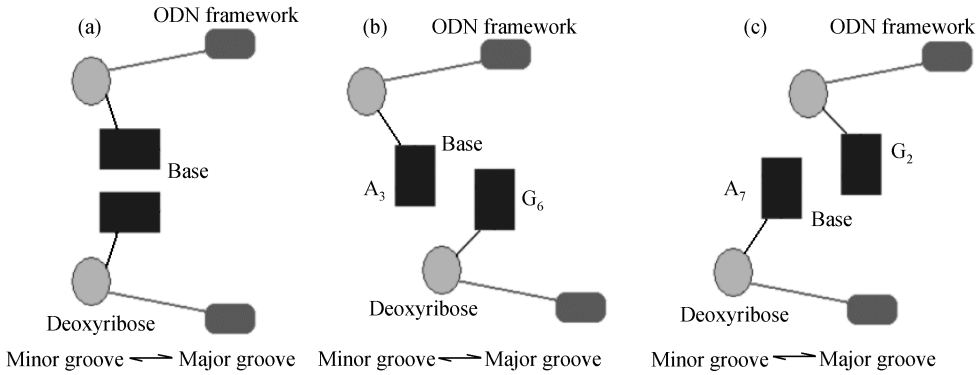

Fig. 5. (a) The arrangement of normal bases. (b) and (c), the arrangement of mismatched bases for G_6:A_3 and A_7:G_2 bases pairs.

the recognition events in sheared DNA are a little different. Firstly, the normal bases in sheared DNA stretch slightly from the minor groove to the major groove (Fig. 5(a)). Secondly, the mismatched bases all stretch from the minor groove to the major groove, but the intercalation at mismatched site will encounter great steric collision, which is brought by arrangement of mismatched bases (Fig. 5(b) and (c)). So the complex cannot recognize the sheared site directly. Significantly, the groove-selectivity and site-specificity still can be confirmed. Contrary to the normal DNA recognition, both isomers of the complex recognize the sheared DNA in the major groove orientation, which is determined by the following two steric factors: (1) For normal DNA recognition, there are obvious differences of steric hindrance between the intercalation from the major and minor groove. However, those differences do not exist in the sheared DNA recognition due to special arrangement of mismatched bases; (2) The structural distortion of DNA induced by mismatch bases forms a hydrophobe cavity in the middle of sheared DNA major groove orientation, which is just suitable for entry of the complex (Fig. 6). Therefore, both isomers recognize the sheared DNA in the major groove orientation. Moreover, both isomers recognize the T_5G_6/A_4A_3 region, which shows obvious site-specificity.

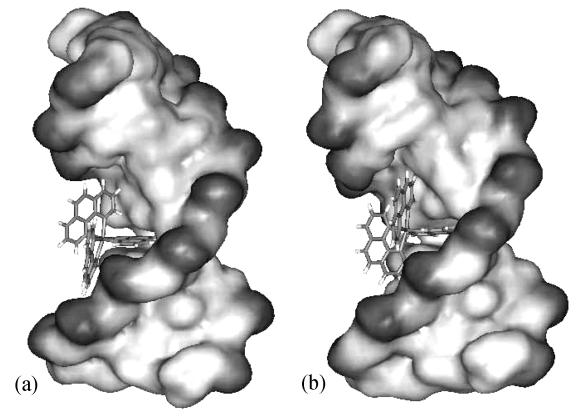

Fig. 6. The complex ((a) *L*-isomer and (b) *D*-isomer) entered the hydrophobe cavity from major groove orientation.

(ii) Electrostatic interaction. Based on former calculation experiences of our work group[14,15,17,18], the electrostatics interactions are the important factors influencing the final results. In this work, the sub-items of total energy of optimal depths in the minor groove for the normal DNA recognition and those in the major groove for sheared DNA recognition are viewed. The results are shown in Tables 1 and 2. In this table, Total means total energy; VDW means van de Waals energy; Elect means electrostatic energy; Non-bond means non-bond energy (the sum of the VDW and electrostatic energy), which describes the steric interactions; Internal means internal energy, which describes the bond properties. For normal DNA recognition, as the tables show, the steric (non-bond) items are more influential than the internal items, which is consistent with our discussion described above. With non-bond interaction, the electrostatic energies are larger than the VDW energy for 10^2-10^3 times, which means that the magnitude of electrostatic energy determines the magnitude of potential energy. In general, only when the electrostatic energies of several modeling are much similar will the bond interactions determine the recognition.

3.2 Comparison between the simulations in vacuum and in aqueous solution

In the former work, we had simulated the interactions between DNA and the complex of form I in vacuum. In this work, the interaction was simulated in aqueous solution. It is essential to compare the results in aqueous solution with those in vacuum. As shown in Table 3, the simulating circumstance influences results greatly. We think that the existence of water makes it possible to model the influence of π-π stack and the hydrophobe circumstance of DNA internal structure. Take the comparison between the former work and this work as an example. Both isomers could recognize the sheared DNA but could not recognize the normal DNA when simulations are performed in vacuum. While the complex could recognize both normal and sheared DNA when simulations are performed in aqueous solution. The structure of sheared DNA is distorted badly, which makes the π-π stack of whole DNA unsound, so sheared DNA recognition is less influenced by the aqueous solution. But the normal DNA recognition is affected greatly by the aqueous solution because of the intact π-π stack. In addition, the experimental studies of our group showed that the complex could be inserted into calf thymus DNA[19], which indicates that the simulation in aqueous is closer to the experimental situations than that in vacuum. Moreover, results from this work revealed that the complex was intercalated into T_5G_6/A_4A_3 region of sheared DNA and could repair the sheared mismatch at the conformational level, while the results

Table 1 Detailed energy distribution for interactions of the complex in normal DNA minor groove orientation (kJ • mol^{-1})

Items	*L*-isomer in				*D*-isomer in			
	C_1G_2	T_3C_4	C_4G_5	A_6C_7	C_1G_2	T_3C_4	C_4G_5	A_6C_7
Total	11131.26	10821.30	**10775.10**	10980.06	10996.02	**10694.46**	10766.70	10913.28
Internal	2685.48	2774.10	2706.06	2665.32	2701.86	2689.26	2674.14	2717.82
Nonbond	8445.78	8047.20	8069.04	8314.74	8294.16	8005.20	8092.56	8195.46
VDW	36.96	32.34	51.66	−14.70	57.96	25.20	36.96	−13.02
Elect	8408.82	8014.86	8017.38	8329.44	8236.20	7980.00	8055.60	8208.48

Table 2 Detailed energy distribution for interactions of the complex in sheared DNA major groove orientation (kJ • mol^{-1})

Items	*L*-isomer in				*D*-isomer in			
	C_1G_2	A_4T_5	T_5G_6	G_6A_7	A_4T_5	T_5G_6	G_6A_7	A_7G_8
Total	11563.86	11626.86	**11271.96**	11434.50	11497.08	**11267.76**	11698.26	11659.62
Internal	2803.92	2932.02	2682.12	2765.70	2721.60	2814.00	2753.94	2647.26
Nonbond	8759.94	11353.44	8589.84	8668.80	8775.48	8453.76	8944.32	9012.36
VDW	−44.10	31.08	−52.50	1.68	−51.66	−0.84	−6.72	−39.06
Elect	8804.04	8676.36	8642.34	8667.12	8827.14	8454.60	8951.04	9051.42

Table 3 The comparison of simulations in different circumstances

Compared items	Former work	This work
Circumstance	vacuum	aqueous solution
Recognize the sheared DNA?	yes (recognize A_4T_5/T_5A_4 region)	yes (recognize T_5G_6/A_4A_3 region)
Recognize the normal DNA?	no	yes
Repair the sheared DNA?	no	yes

from the simulations in vacuum indicated that the complex was inserted into A_4T_5/T_5A_4 region. Significantly, the mismatch was not repaired. This distinction is also caused by the different influential ability of π-π stack in vacuum and aqueous solution. For simulations in aqueous solution, when the complex is intercalated into T_5G_6/A_4A_3 region, the interactions between them break the sheared stack of mismatched bases and form a relatively intact π-π stack containing normal bases, sheared bases and ligand hpip, which is very stable in the aqueous solution. Even if the intercalated steric collision in T_5G_6/A_4A_3 region is a little larger than that in A_4T_5/T_5A_4 region, the complex selects the former to interact with DNA.

3.3 Conformational repair of sheared DNA

In the former work, we found that *L*-isomer of $[Co(phen)_2dpq]^{3+}$ could repair the sheared mismatch at the conformational level. In this work, we found that both isomer could repair the sheared mismatch, of which the *L*-isomer repaired only one bases pair (G_6:A_3), while *D*-isomer repaired double sheared mismatch wholly (G_6:A_3 and A_7:G_2 were both repaired). The repair mechanism is discussed as follows.

(i) Energy analysis. As shown in Table 2, the potential energies of the system for both isomer-DNA associations are very similar and are both determined mainly by Elect energy. However, their detailed sub-items of energy contribute differently to the total energy. Firstly, for *L*-isomer-DNA association in T_5G_6 region, its Elect energy is similar with that at neighboring sites, while the Internal energy is lower than at those sites considerably, which indicates that hpip ligand stacks tightly with the DNA bases. So the potential energy is decreased at the chemical bond level. Secondly, for *D*-isomer-DNA association in T_5G_6 region, its Internal energy is higher than that at neighboring sites, while the Elect energy was much lower than that at those sites, which indicates a minor steric collision between the complex and DNA and among the subunits of DNA. Under this condition, the π-π stack is relatively untight. However, the relatively intact stack and the better steric matching of whole system decrease the total energy to the lowest level.

(ii) Structural analysis. To validate the results from energy analysis, two optimal models of isomer-DNA associations were picked up. As shown in Fig. 7(a), when *L*-isomer interacted in T_5G_6 region in sheared DNA major groove orientation, to accommodate the hpip ligand, the average distance between base pairs G_6:A_3 and T_5:A_4 was expanded to about 0.635 nm and hpip ligand was located just in the middle of base pairs layers. Corresponding distance between base pairs and hpip ligand is about 0.3175 nm, which is much shorter than the distance of 0.34 nm between standard base pairs, indicating a closer π-π stack. Because the other mismatched base pairs are not converted to parallel form, the steric collision was increased greatly. Consistent with the results of energy analysis, its non-bond energy is not at the lower level. As shown in Fig. 7(b), to accommodate the hpip of *D*-isomer, the average distance between base pairs G_6:A_3 and T_5:A_4 is expanded to about 0.672 nm, which is a little bit shorter than the doubled standard distance of 0.68 nm but much longer than 0.635 nm. Considering the block effect of other base pairs on the distention, 0.672 nm is in the normal range. However, when compared with *L*-isomer's interaction, the increase of this distance decreases the distance between mismatched base pairs, therefore repulsive effects would break the sheared stack of A_7:G_2 base pairs, and convert its conformation from sheared form to parallel form, which decreases the steric collision between DNA bases greatly, indicating a close correspondence with the results of energy analysis.

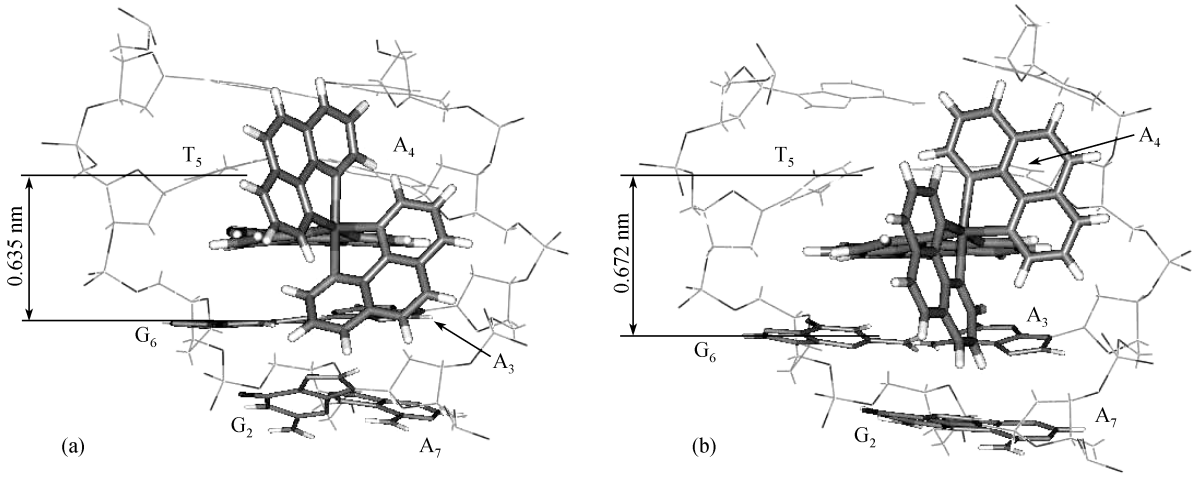

Fig. 7. The structure of *L*-isomer-DNA association (a) and that of *D*-isomer-DNA association (b).

4 Conclusion

From aforesaid simulations and analyses, we could prognosticate the following events. Firstly, mixed-ligand complex $[Co(phen)_2hpip]^{3+}$ could recognize both normal and sheared DNA and the recognition processes showed obvious groove selectivity, site specificity and enantio selectivity. For normal DNA, both isomers recognize it from the minor groove orientation and the *L*-isomer and *D*-isomer recognize the CG/GC and TC/AG region respectively and this process shows enantio selectivity: the *D*-isomer is preferential. Both isomers recognize the sheared DNA from the major groove orientation and they all recognize the T_5G_6/A_4A_3 region, which shows site specificity. Secondly, the complex could repair the sheared mismatch at the conformational level, of which the *L*-isomer could repair the mismatched base pairs at the recognition site (G_6:A_3 base pairs), while the *D*-isomer could repair both base pairs (G_6:A_3 and A_7:G_2 base pairs). Thirdly, further analysis reveals that the recognition events are determined by steric interactions, while the repair events are determined not only by steric interactions, but also by a relatively intact π-π stack among normal bases, sheared bases and ligand hpip. In addition, by comparing the simulations in aqueous solution with those in vacuum, the former is found more similar to the real system.

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