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COMMUNICATION

Molecular "light switch" for G-quadruplex DNA: cycling the switch on and off†

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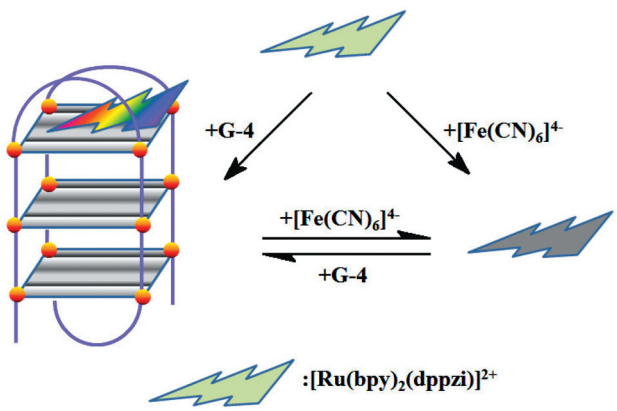
We report a new G-quadruplex DNA "light switch", where the light switch can be cycled on and off through the successive introduction of G-quadruplex DNA and $[Fe(CN)_6]^{4-}$ ions.

Since the structure of the DNA double helix was proposed by Watson and Crick in 1953, new structures of nucleic acids have continued to emerge at an ever-increasing rate.[1] Among the different noncanonical DNA motifs, quadruplex DNA structures are probably the most extensively studied. Such structures are made up of G-quartet subunits, where four coplanar guanines (G) are linked together by Hoogsteen hydrogen bonds.[2] It has been suggested that these secondary DNA structures could be involved in the regulation of several key biological processes.[3] For example, the G-quadruplex has been suggested to act as a negative regulator of telomere elongation by telomerase *in vivo* and is currently considered as a potential target for cancer therapy.[4] In addition, many promoter elements within the human genome contain G-rich sequences that are thought to be involved in controlling gene expression.[3,5] These potential roles of G-quadruplex DNA structures have stimulated the search for specific molecules that may serve either as biological probes for these structures or perhaps as therapeutic agents.

The interaction of nucleic acids with small molecules has been a primary area of interest and research for over half a century.[6] Among these small molecules, polypyridyl complexes incorporating planar aromatic ligands have attracted much attention.[7] The pioneering work of Murphy and Barton[8] has provided detailed information about the recognition and reactions of double helical DNA by transition metal complexes. They first reported the luminescence of $[Ru(L)_2(dppz)]^{2+}$ ((L) = bpy (2,2′-bipyridine) or phen = (1,10-phenanthroline) and dppz = (dipyrido[3,2-*a*:2′,3′-*c*] phenazine)) to be almost non-emissive in water but "switched on" in the presence of duplex DNA. Since then, many efforts have focused on the design and development of molecular "light switch" complexes. Dunbar and Turro have achieved chemical cycling of the molecular "light switch" on and off processes by successive additions of Co^{2+} ions and EDTA, respectively.[9] Recently, Li reported a metallointercalator-based luminescent DNA film and the light-switch behaviour of the cast film through chemical modulation of the solid–liquid interface.[10] The principle of the emission can be "turned off" by coordination of various foreign metal ions to a vacant multidentate ligand. These DNA "light switch" complexes may prove to be useful in applications such as molecular-scale logic gates, DNA sensing, the detection of mismatches and the signaling of DNA–protein binding.[11] However, as the unique properties of metal complexes have been successfully used to probe duplex DNA, it is important to note that these complexes are only in the beginning stages of development and are not as evolved as metal complexes that bind G-quadruplex DNA. Recently, our laboratory found that $[Ru(phen)_2(dppz)]^{2+}$ can serve as a prominent molecular "light switch" for both G-quadruplexes and i-motif DNA, which prefers binding to G-quadruplexes over the i-motif.[12] Herein, we describe the first example of a new G-quadruplex DNA "light switch" complex, which can be repeatedly cycled on and off through the addition of external agents. Scheme 1 illustrates how the switch can be cycled through the successive introduction of $[Fe(CN)_6]^{4-}$ ions and G-quadruplex DNA. The synthetic routes for the preparation of the $[Ru(bpy)_2(dppzi)]^{2+}$ complex are shown in Scheme 2 ((dppzi) = dipyrido[3,2-*a*:2′,3′-*c*]phenazine-10,11-imidazole). Human telomeric fragments of 5′-AGGGTTAGGGTTAGGGTTAGGG-3′



Scheme 1 Schematic illustration of the light switching behaviour of the ruthenium complex in the presence of G-quadruplex DNA (G-4).

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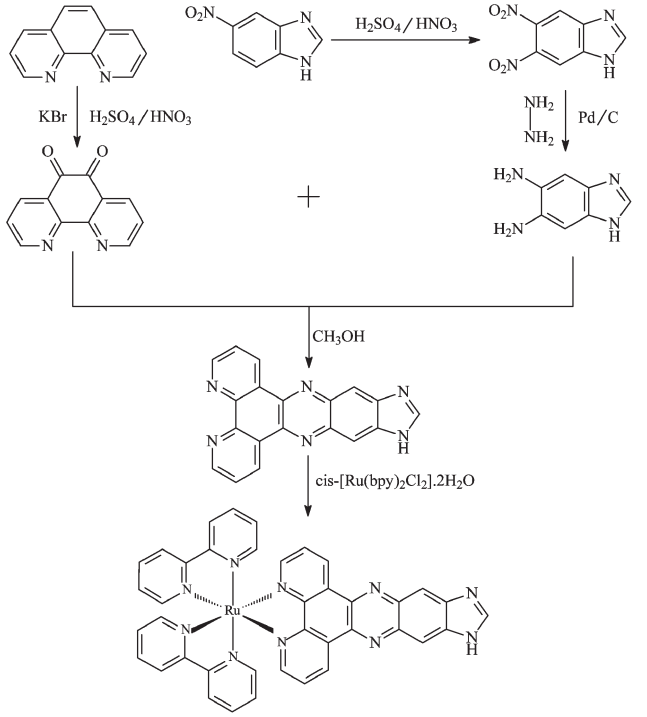
†Electronic supplementary information (ESI) available: synthetic procedures for $[Ru(bpy)_2(dppzi)]^{2+}$ and details of the experimental materials and methods. See DOI: 10.1039/c2dt30076a



Scheme 2 The synthetic routes for the preparation of the [Ru(bpy)$_2$(dppzi)]$^{2+}$ complex.

(denoted 22AG) were chosen for this investigation, of which the crystal and solution structures are known. The structure and the stability of the G-quadruplex depend on the monocations; the NMR structure of 22AG in the presence of Na^+ is known to be an antiparallel basket quadruplex; however, the same sequence favors a mixed parallel/antiparallel structure in the presence of a K^+ solution.[13]

The electronic spectra of [Ru(bpy)$_2$(dppzi)]$^{2+}$ have been characterized by an intense ligand-centered (LC) transition in the UV region and a metal-to-ligand charge transfer (MLCT) in the visible region, which are typical of polypyridylruthenium(II) complexes.[14] The ultraviolet bands around 287 nm for [Ru(bpy)$_2$(dppzi)]$^{2+}$ can be attributed to the (bpy) $\pi \rightarrow \pi^*$ transition; the band at 430 nm for [Ru(bpy)$_2$(dppzi)]$^{2+}$ can be attributed to the overlap of Ru(dπ) $\rightarrow$ bpy (π^*) and Ru(dπ) $\rightarrow$ dppzi (π^*). Apart from these, the absorption band around 386 nm can be assigned to the intraligand (IL) transition of dppzi.

The interaction with G-quadruplex DNA in either a K^+ or Na^+ buffer was evident from the absorption titration spectra. The changes in the spectral profiles during titration are shown in Fig. 1. The hypochromism and red shift in the intraligand absorption band (~386 nm) of the dppzi ligand, as well as the MLCT band, are a little more pronounced for the mixed parallel/antiparallel G-quadruplex (K^+ buffer) compared to the form bound to the antiparallel basket G-quadruplex DNA (Na^+ buffer). For example, the addition of 22AG to a solution of [Ru(bpy)$_2$(dppzi)]$^{2+}$ in K^+ buffer led to a 3 nm red shift and 40.2% hypochromism of the band at 386 nm (Fig. 1a) and addition of antiparallel basket G-quadruplex DNA in Na^+ buffer led to the same red shift and 35.0% hypochromism of the band at 386 nm (Fig. 1b). The isosbestic points are located at 322 and 477 nm.

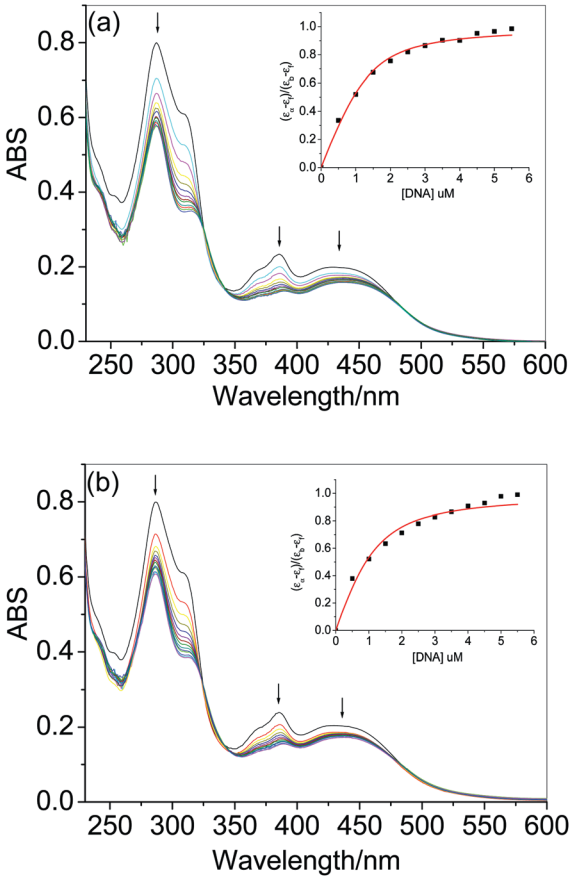


Fig. 1 Absorption spectra of [Ru(bpy)$_2$(dppzi)]$^{2+}$ in the presence of 22AG in (a) K^+ and (b) Na^+ buffer (100 mM KCl/NaCl, 10 mM Tris, pH 7.0) ([Ru] = 10 μM, [DNA] = 0–100 μM). Insets: plots of $(\varepsilon_a - \varepsilon_f)/(\varepsilon_b - \varepsilon_f)$ *vs.* [DNA] for the titration of the Ru(II) complexes.

Hypochromism and red shifting indicates the strong interactions between the DNA bases and the complex. The intrinsic binding constants, K_b, of [Ru(bpy)$_2$(dppzi)]$^{2+}$ and the antiparallel basket quadruplex and mixed parallel/antiparallel quadruplex were determined to be 9.5×10^5 M^{-1} (s = 1.3) and 5.1×10^5 M^{-1} (s = 1.0), respectively. That is to say, [Ru(bpy)$_2$(dppzi)]$^{2+}$ preferentially binds to the mixed parallel/antiparallel quadruplex over the antiparallel basket quadruplex. The exact data are shown in Table S1 (ESI†).

To gain insight into the interaction between [Ru(bpy)$_2$(dppzi)]$^{2+}$ and the G-quadruplex, we examined the ability of [Ru(bpy)$_2$(dppzi)]$^{2+}$ to stabilize G-quadruplex DNA by thermal denaturation profiles. In accordance with previous studies,[15] 295 nm was chosen to study the influence of the complex on the stability of the G-quadruplex. As expected, the melting profiles of 22AG in the absence of K^+ and Na^+ showed almost no transition (data not shown), suggesting that it did not form a stable G-quadruplex structure. As for the dissociation of the G-quadruplex, the T_m of the monovalent K^+ ion induced intramolecular G-quartet structure of the 22AG sequence was more stable than its Na^+ counterpart. Concentration-dependent melting curves for each G-quadruplex DNA upon binding to [Ru(bpy)$_2$(dppzi)]$^{2+}$ are shown in Fig. 2. Upon the addition of the complex, *i.e.*, changing the [Ru]/[DNA] ratio of 1 : 1 to 3 : 1

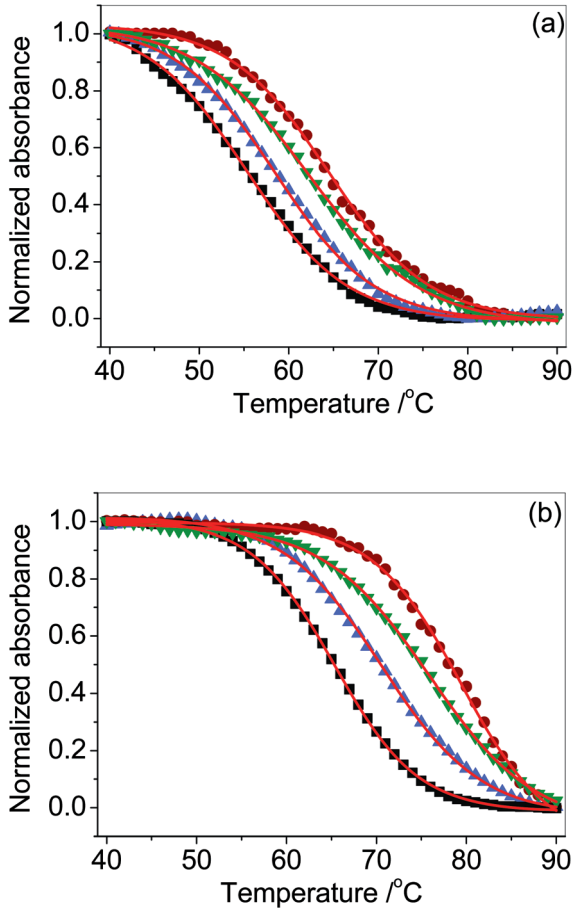


Fig. 2 Normalized UV melting curves for 5 μM of the antiparallel G-quadruplex (a) and the mixed-hybrid G-quadruplex (b) in the absence and the presence of $[Ru(bpy)_2(dppzi)]^{2+}$ at different [Ru]/[DNA] ratios (DNA alone (■), 1 : 1 (▲), 3 : 1(▼), 5 : 1 (●)). The stability of the G-quadruplex DNA was assessed by UV absorbance at 295 nm.

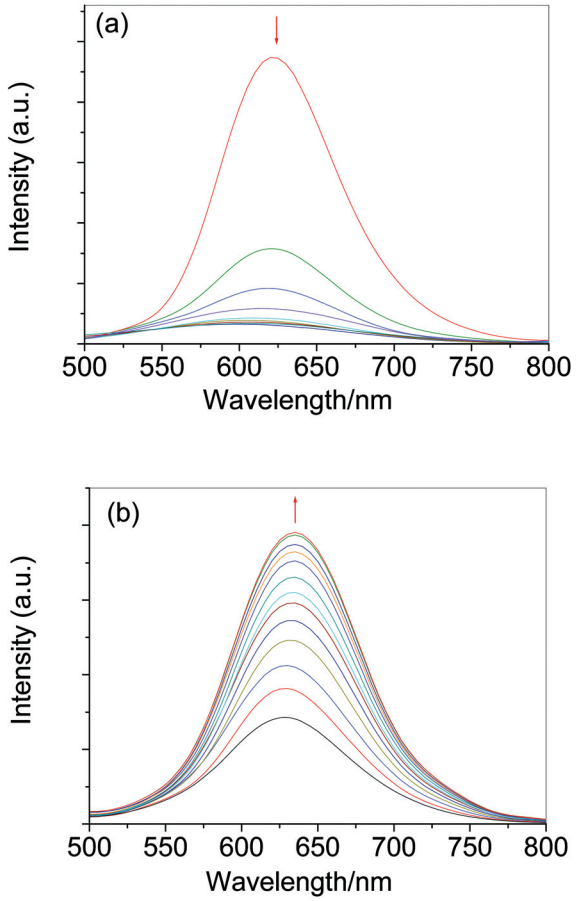


Fig. 3 Emission spectra of $[Ru(bpy)_2(dppzi)]^{2+}$ in the presence of increasing amounts of (a) $[Fe(CN)_6]^{4-}$ or (b) G-quadruplex DNA; [Ru] = 5 μM, [DNA] = 0–50 μM in 100 mM K^+ buffer. The arrows show the emission intensity changes upon increasing $[Fe(CN)_6]^{4-}$ ion or G-quadruplex DNA concentrations.

and 5 : 1, the T_m of the G-quadruplex DNA increased dramatically, which is comparable to that observed for classic G-quadruplex binders.[16] At a ratio of 5 : 1 ($[Ru(bpy)_2(dppzi)]^{2+}$ to 22AG), the transition temperature of the G-quadruplex increased from 55.3 to 64.3 °C in Na^+ buffer and increased from 65.3 to 79.4 °C in K^+ buffer, in which an increase in the melting temperature of the quadruplex indicated an effective stabilizing effect.[16]

In the absence of G-quadruplex DNA, $[Ru(bpy)_2(dppzi)]^{2+}$ can emit luminescence at the excited wavelength of 440 nm in a buffer solution at ambient temperature and its maximum appears at 625 nm. Upon addition of $[Fe(CN)_6]^{4-}$ ions, the luminescence of $[Ru(bpy)_2(dppzi)]^{2+}$ can be fully quenched in the absence of the G-quadruplex (Fig. 3a). The quenching is due to a reductive electron transfer.[17] The results of the emission titrations for $[Ru(bpy)_2(dppzi)]^{2+}$ with G-quadruplex DNA are illustrated in Fig. 3b. Upon addition of G-quadruplex DNA in 100 mM K^+ buffer, the emission intensities of the $[Ru(bpy)_2(dppzi)]^{2+}$ complex increase to around 2.46 times larger than the original. This implies that $[Ru(bpy)_2(dppzi)]^{2+}$ can interact with G-quadruplex DNA and be protected by DNA efficiently. Upon addition of $[Fe(CN)_6]^{4-}$ ions into the 100 mM K^+ buffer system containing $[Ru(bpy)_2(dppzi)]^{2+}$ with G-quadruplex DNA, the emission intensity of the complex is quenched again. Interestingly, by adding an excess of G-quadruplex DNA to the buffer system containing G-quadruplex DNA-bound $[Ru(bpy)_2(dppzi)]^{2+}$ with $[Fe(CN)_6]^{4-}$ ions, the emission intensity can be recovered again. A similar phenomenon was observed in the Na^+ buffered solution as well. Therefore, it is interesting to investigate whether the photoluminescence of DNA-bound $[Ru(bpy)_2(dppzi)]^{2+}$ could be tuned by the successive introduction of $[Fe(CN)_6]^{4-}$ ions and G-quadruplex DNA. In an appropriate buffer (100 mM K^+ or Na^+) and at a ratio of 1 : 1 (ruthenium to nucleotide), the emission was monitored at the emission maxima of the complex at various concentrations of $[Fe(CN)_6]^{4-}$ and G-quadruplex DNA at 20 °C. Fig. 4 shows the changes in the relative emission intensity of $[Ru(bpy)_2(dppzi)]^{2+}$ bound to G-quadruplex DNA as $[Fe(CN)_6]^{4-}$ ions and G-quadruplex DNA are added successively, thus flipping the DNA "light switch" on and off over a series of cycles. In this system the emission quenching and recovery is observed immediately following the addition of either $[Fe(CN)_6]^{4-}$ ions or G-quadruplex DNA, respectively.

To perform a detailed thermodynamic study of G-quadruplex DNA molecules and $[Ru(bpy)_2(dppzi)]^{2+}$, fluorimetric titrations were performed at 15, 30, 37 and 45 °C.[18] The binding constants (K_b) for the complex formed between $[Ru(bpy)_2(dppzi)]^{2+}$ and

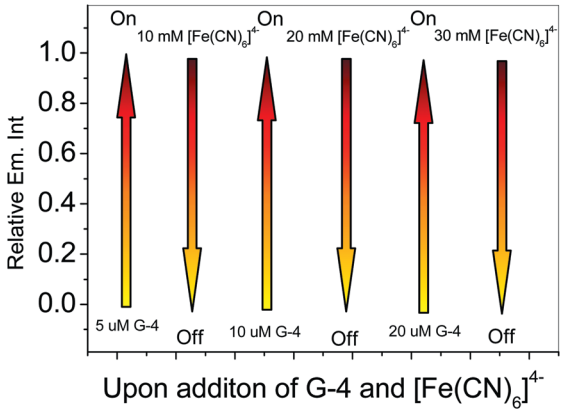


Fig. 4 The relative emission intensity of $[Ru(bpy)_2(dppzi)]^{2+}$ upon successive additions of G-quadruplex DNA (G-4) and $[Fe(CN)_6]^{4-}$ in 100 mM K^+ buffer.

G-quadruplex DNA were determined from a complete titration at the particular temperature. The values of the binding constant were found to be comparable to the values obtained from the absorption titration. The thermodynamic parameters, ΔG^0, ΔS^0 and ΔH^0, were calculated from the van't Hoff equation and are reported in Table S2 (ESI†). It can be seen that the binding of $[Ru(bpy)_2(dppzi)]^{2+}$ to G-quadruplex DNA is characterized by negative enthalpy and negative entropy changes. The negative ΔG^0 values suggest that the energy of the complex–DNA adduct is lower than the sum of the energies of the free complex and DNA. The negative ΔH^0 values suggest that the binding of the complex to DNA is exothermic and driven by enthalpy. The negative entropy values indicate that the degree of freedom of the Ru(II) complex is decreased after binding and that the DNA conformational freedom is also reduced upon complex–DNA binding.

Small molecules can potentially bind to a G-quadruplex DNA by externally stacking on the G-quartets, intercalating between the quartets or non-specifically binding to some random location on the DNA strand.[19] Molecules bound to the surface of the helix or quartets will be accessible to the quencher, while those intercalating inside the helix or quartets will be protected from the quencher.[20] Ferrocyanide ions proved to be excellent quenchers for the complex in the presence of DNA. The $[Fe(CN)_6]^{4-}$ ion will be prevented from entering the helix due to an electrostatic barrier as a result of the phosphate group and, consequently, very little quenching will be observed in the case of true intercalators. As illustrated in Fig. 4, the luminescence of DNA-bound $[Ru(bpy)_2(dppzi)]^{2+}$ could be tuned by the successive introduction of $[Fe(CN)_6]^{4-}$ ions and G-quadruplex DNA. These results therefore suggest that the binding modes of $[Ru(bpy)_2(dppzi)]^{2+}$ may not be intercalative. Given the large and flat aromatic moiety of the dppzi ligand and the structures of the G-quadruplex, we propose that $[Ru(bpy)_2(dppzi)]^{2+}$ stacks on the ends of the G-quadruplexes like a similar complex, $[Pt^{II}(dppz\text{-}COOH)(N\Lambda C)]CF_3SO_3$, does.[21] This binding mode is not very strong and both G-quadruplex DNA and $[Fe(CN)_6]^{4-}$ can access the $[Ru(bpy)_2(dppzi)]^{2+}$ complex easily. The environment of $[Ru(bpy)_2(dppzi)]^{2+}$ will change depending on the amount of G-quadruplex DNA and $[Fe(CN)_6]^{4-}$ and the luminescence of the $[Ru(bpy)_2(dppzi)]^{2+}$ complex can thus be tuned.

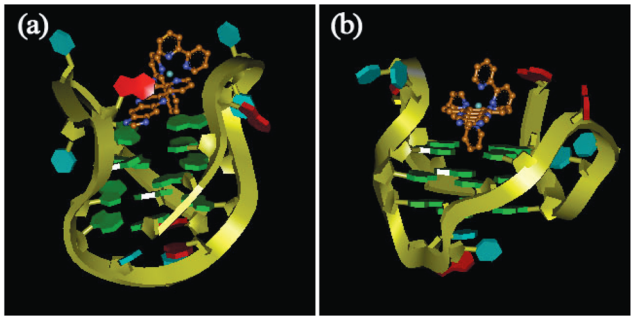


Fig. 5 The minimized model of the complex between $[Ru(bpy)_2(dppzi)]^{2+}$ and the 22AG antiparallel G-quadruplex (a) and the mixed-hybrid G-quadruplex (b). G is shown in green, A is shown in red, T is shown in cyan and $[Ru(bpy)_2(dppzi)]^{2+}$ is shown in brown and blue.

To compare the DNA binding of $[Ru(bpy)_2(dppzi)]^{2+}$ for G-quadruplex DNA and duplex DNA, emission titrations for $[Ru(bpy)_2(dppzi)]^{2+}$ with calf thymus DNA (CT-DNA) were performed and are presented in Fig. S1 (ESI†). Upon addition of CT-DNA in 100 mM K^+ buffer, the emission intensities of the $[Ru(bpy)_2(dppzi)]^{2+}$ complex increase to around 2.03 times that of the original. This implies that $[Ru(bpy)_2(dppzi)]^{2+}$ can interact with CT-DNA and also be protected by DNA efficiently. Though $[Ru(bpy)_2(dppzi)]^{2+}$ showed a prominent G-quadruplex binding affinity, a modest selectivity for the quadruplex over the duplex was observed. It still suffered from the classic drawback of lack of specificity for the quadruplex. On the other hand, a dramatic preference for the quadruplex over the i-motif was observed. Upon addition of i-motif DNA in the same buffer, the fluorescence of the complex hardly increased at all (Fig. S2) (ESI†), which is similar to star molecular $[Ru(phen)_2(dppz)]^{2+}$.[12]

Molecular docking studies were carried out to determine the binding mode between $[Ru(bpy)_2(dppzi)]^{2+}$ and the G-quadruplex, which corroborates the experimental results.[22] The antiparallel basket NMR G-quadruplex structure (PDB 143D) and a 26-mer mixed hybrid-type NMR G-quadruplex structure (PDB 2HY9) were used as templates for the docking studies. To compare both conformations, we removed two adenines from each end of the mixed hybrid-type structure.[23] As shown in Fig. 5, the docking study confirms that each intramolecular G-quadruplex molecule binds to one $[Ru(bpy)_2(dppzi)]^{2+}$ molecule. It has previously been shown that G-quadruplex binders can stack on the surface of both terminal G-quartet planes.[3,4,22,23] $[Ru(bpy)_2(dppzi)]^{2+}$ contains a square π-aromatic surface and the dppzi ligand prefers to stack in the center of the terminal G-quartet end. For the antiparallel basket G-quadruplex structure, both diagonal loop and parallel loop binding positions were considered. When $[Ru(bpy)_2(dppzi)]^{2+}$ binds in the diagonal loop position, π–π stacking becomes less stable than in the parallel loop binding position, as shown by energy calculations. So $[Ru(bpy)_2(dppzi)]^{2+}$ prefers to stack on the center between the parallel loop and the terminal G-quartet (Fig. 5a). The predicted favorable binding site between $[Ru(bpy)_2(dppzi)]^{2+}$ and the mixed-hybrid G-quadruplex DNA was found to be stacking on the external G-quartets at the 5′ end of the oligonucleotide (Fig. 5b). The modeling study revealed that the complex binds to the mixed-hybrid G-quadruplex and antiparallel basket G-quadruplex with a calculated binding energy of *ca.* −13.4 and

−10.0 kcal mol^{-1}, respectively, which is comparable with the energies obtained from the fluorimetric titration Table S2 (ESI†). It was also noteworthy that $[Ru(bpy)_2(dppzi)]^{2+}$ possessed a much more favorable binding interaction (lower binding free energy) with the hybrid-type G-quadruplex than the antiparallel basket G-quadruplex. Such reliable end-stacking of compounds onto the G-quartet are in agreement with previously reported aromatic quadruplex ligands.[3,4] Thus, the molecular modeling studies explained why the photoluminescence of $[Ru(bpy)_2(dppzi)]^{2+}$ can be tuned by the successive introduction of $[Fe(CN)_6]^{4-}$ ions and G-quadruplex DNA and confirmed the excellent complementarity in the binding modes.

In summary, cycling of the G-quadruplex DNA "light switch" off and on has been accomplished for $[Ru(bpy)_2(dppzi)]^{2+}$ through the successive introduction of $[Fe(CN)_6]^{4-}$ ions and G-quadruplex DNA, respectively. To the best of our knowledge, this work presents the first example of a reversible G-quadruplex DNA light switch. Furthermore, the mechanism of cycling of the G-quadruplex DNA "light switch" in this work is different from the mechanism reported in other "light switches".[9,10] The switch can be cycled through the competition of $[Fe(CN)_6]^{4-}$ ions and G-quadruplex DNA. The discovery of the binding features of $[Ru(bpy)_2(dppzi)]^{2+}$ with G-quadruplex DNA may show promise for probing G-quadruplex DNA and provide a more comprehensive understanding of the molecular recognition of G-quadruplex DNA.

Acknowledgements

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