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Structural studies reveal the enantiospecific recognition of a DNA G-quadruplex by a ruthenium polypyridyl complex

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Abstract: Using X-ray crystallography, we show an enantiospecificity in DNA G-quadruplex binding, using the complexes Λ/Δ-$[Ru(TAP)_2(dppz\text{-}11\text{-}CN)]^{2+}$ (TAP=1,4,5,8-tetraazaphenanthrene) containing the dppz (dipyridophenazine) ligand, paralleling the specificity of the complexes with duplex DNA. The Λ complex crystallises with the normally parallel stranded d(TAGGGTTA) tetraplex to give the first such antiparallel strand assembly in which *syn*-guanosine is adjacent to the complex at the 5' end of the quadruplex core. SRCD measurements confirm that the same conformational switch occurs in solution. The Δ enantiomer, by contrast, is present in the structure but stacked at the ends of the assembly. In addition, we report the structure of Λ-$[Ru(phen)_2(11\text{-}CN\text{-}dppz)]^{2+}$ bound to d(TCGGCGCCGA), a duplex forming sequence, and use both structural models to aid in the elucidation of the motif-specific luminescence response of the isostructural phen analogue enantiomers.

Guanine quadruplexes are four-stranded nucleic acid structures, formed by G-rich DNA and RNA sequences. They have been shown to play an important role in gene expression,[1] regulation[2] and have been visualised in human cells.[3] Targeting the G-quadruplex, by small-molecule binders, is an area of significant interest as stabilisation of the structure is an effective method of inducing apoptosis in cancer cells.[4] Development has focussed on compounds able to discriminate between duplex and quadruplex-forming DNA to favour the four stranded structure,[5] with examples including metallo-porphyrins,[6] acridines,[7] naphthalene-based compounds[8] and Pt-terpyridines.[9] The development of quadruplex-binding compounds as luminescent probes offers an attractive way of visualising such structures *in-vivo*. Octahedral polypyridyl ruthenium complexes are not only able to bind to and stabilise DNA G-quadruplexes but also possess a range of useful photophysical properties. For example, complexes containing the 1,10-phenanthroline (phen) and dipyridophenazine (dppz) ligand can act as "light-switch" complexes, luminescing strongly when bound to DNA due to protection against excited state quenching via H-bonding with aqueous media.[10] Some examples have luminescence visible to the naked eye and are specific for G-quadruplexes.[11] Others can stabilise specific conformations of the human telomeric G-quadruplex sequence.[12] In contrast, ruthenium complexes containing the 1,4,5,8-tetraazaphenanthrene (TAP) ligand cause direct DNA damage, by guanine photooxidation, when exposed to visible radiation.[13] The absorption of light by the complex localises the damage to within several Å of the metal centre, as we have shown in both solution[14] and crystalline states,[15] and G-quadruplexes are particularly vulnerable to damage.[16]

Recently we explored the structural effect of substitution on the distal ring of $[Ru(TAP)_2(dppz)]^{2+}$.[17] We found that the addition of a nitrile substituent to give $[Ru(TAP)_2(11\text{-}CN\text{-}dppz)]^{2+}$ (**1**)(Figure 1a) caused (so far uniquely) the formation of a complete intercalation cavity when the lambda complex (Λ-**1**) bound to the d(TCGGCGCCGA) duplex,[18] showing that even this small modification of the dppz ligand strengthened the stacking interaction. Based on this finding we explored the binding of this compound **1** with a G-quadruplex forming sequence, reasoning that a G-quartet has a larger surface area available for π-stacking and therefore could accommodate the full footprint of the derivatised dppz group. This has led not only to the first crystal structure showing a mononuclear ruthenium polypyridyl complex bound to a DNA G-quadruplex but has also shed light on the structure-selective luminescence behaviour of the isostructural analogue, $[Ru(phen)_2(11\text{-}CN\text{-}dppz)]^{2+}$ (**2**). Most published structures of ligand binding to quadruplexes show extensive stacking (end-pasting) by a flexible planar ligand on the G-quartet surface, whereas the work reported here shows the additional feature of interaction with a ribose sugar. A summary of all metal containing ligands bound to G-quadruplexes that have been structurally characterised by X-ray or NMR is provided as Table S2. More generally, most of the compounds under development for specific targeting of key G-quadruplex containing genes are flat and often angled chromophores with short flexible substituents. [19]

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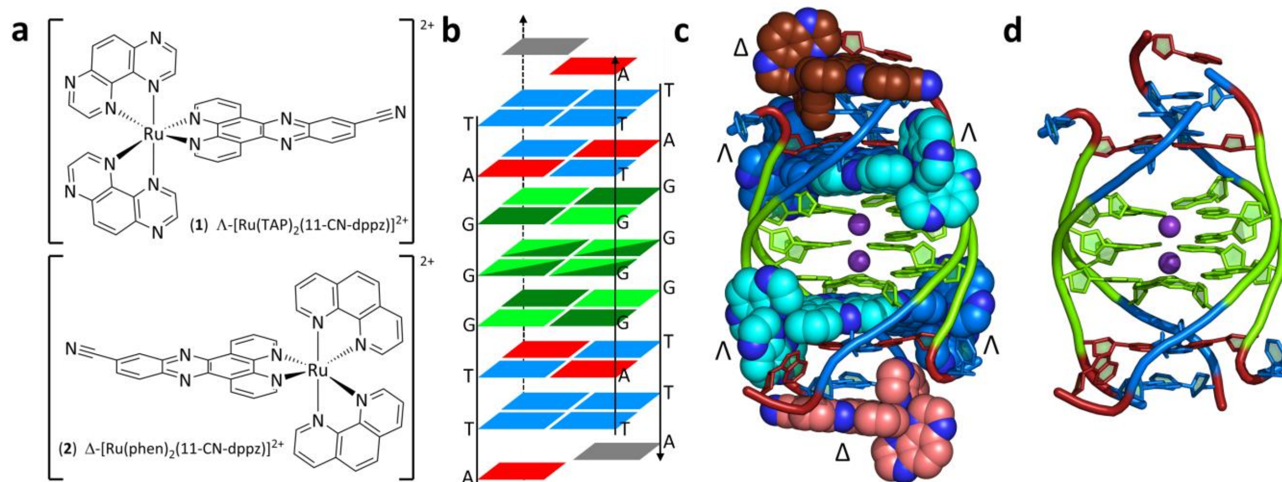

Figure 1 – (a) Skeletal formulae of the complexes, $[Ru(TAP)_2(11\text{-}CN\text{-}dppz)]^{2+}$ (**1**) and $[Ru(phen)_2(11\text{-}CN\text{-}dppz)]^{2+}$ (**2**). (b) Graphical representation of the crystallographic DNA assembly of d(TAGGGTTA) where adenine, guanine and thymine are coloured in red, green and blue respectively. Syn/Anti conformations of guanosine are highlighted using dark and light green, respectively. Grey marks a disordered base. (c) and (d) Crystallographic models (PDB:5LS8) showing Λ/Δ-**1** crystallised with the tetramolecular G-quadruplex d(TAGGGTTA) with and without the complex coordinates included, respectively. Λ-**1** complexes have been shown in teal or marine blue whereas Δ-**1** is shown in brown or salmon pink. Barium ions are shown in silver and potassium in purple. The oligonucleotide and the metal complex were annealed before crystallisation, and the resolution of the final dataset is 1.78 Å.

The parallel quadruplex forming sequence d(TAGGGTTA) has been widely studied but never previously crystallised.[20] Crystallization screening was performed using *rac*-**1** and this sequence, yielding crystals from which an X-ray structure was obtained (Figure 1b-d and S1-2). Crystallisation details and refinement results can be found in SI (Section S1.5 and Table S1). Structural analysis of binding between **1** and d(TAGGGTTA) reveals the direct interaction of Λ-**1** with the G-tetrad stack (Figure 2a-b), with the quadruplex unexpectedly adopting an antiparallel topology. The core of the quadruplex is stabilised by two potassium cations which coordinate to the O6 oxygen atoms in the three G-quartets. On either side of the central G-quartet stack, two Λ-**1** complexes are intercalated, giving an overall stoichiometry of one Λ-**1** per d(TAGGGTTA) strand, or four molecules bound to the tetraplex all bound with the same geometry. Inspection of the refined electron density shows that in the central quartet the guanine nucleosides are disordered, with all four bases split 50:50 between the *syn* and

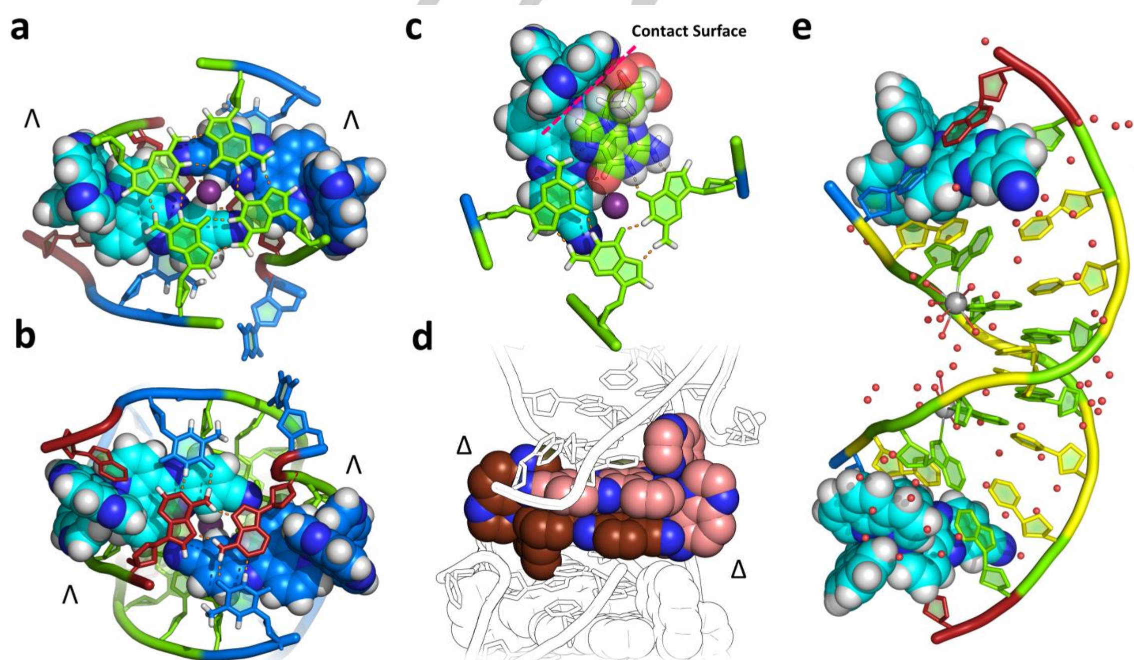

Figure 2 – (a-b) Crystallographic models showing the stacking environment of Λ-**1** to the adjacent B-DNA TA-TA side and the G-quadruplex tetrad respectively; (c) the overall guanine interaction of Λ-**1** highlighting the contact surface that we hypothesise determines intercalation angle and depth; (d) Δ-**1** stacking on the ends of the DNA assembly providing crystal packing between the biological units. (e) The complete duplex assembly of Λ-**2** crystallised with the duplex forming d(TCGGCGCCGA) PDB: 6HWG (see SI for further analysis).

anti-conformation (Figure S3), and that in the flanking quartets, *syn* and *anti* conformations alternate with neighbouring strands. The disorder means that all four strands exhibit the same ordering of conformations in a 5'-*syn*-*mix*-*anti*-3' manner, hence generating a π-stacking environment which is the same for each bound Λ-**1** complex. The 5'-*syn* guanosine residue interacts directly with one ancillary TAP ligand of Λ-**1**, with the face of the deoxyribose sugar contacting the face of the TAP ligand (Figure 2c). This *syn* arrangement results in a maximal stacking interaction between the surface of the 11-CN-dppz ligand and the purine bases. Each 11-CN-dppz ligand contacts three out of four of the guanine bases, stacking fully on two of them with the nitrile substituent forming a polar contact to the 2-NH_2 substituent of a third guanine. The combination of these interactions, with the nitrile group perfectly aligned to the G6 carbonyl lone pair, provides an optimal fit between complex and G-quartet surface where all four lambda complexes show the same set of interactions with the G-quartet. Δ-**1** is present in the structure where it stacks between the terminal T-T wobble pairs, bridging neighbouring biological units in the crystal packing, and showing no direct interaction with any G-quartet (Figure 2d).

This structure shows how mononuclear ruthenium polypyridyl complexes can bind to DNA G-quadruplexes, demonstrating the complexities of ligand intercalation and providing potential binder design leads for next generation DNA probes and damage agents. The same Λ-**1** isomer bound in a duplex cavity also showed the features of *syn* guanosine stabilisation, maximisation of the stacking interaction and polarity alignment with the guanine substituents,[18] suggesting that these are key features for ligand design. Such characteristics are also observed in the structure reported here, of the isostructural 'light-switch' complex Λ-[Ru(phen)$_2$(11-CN-dppz)]$^{2+}$ (**2**) bound to the same d(TCGGCGCCGA) duplex (Figure 2e and S4-6). This structure further reinforces observations to date that the spatial binding modes of phen derived complexes are comparable to those of the analogues containing TAP.[18] In all these cases, the stabilisation of *syn*-guanosine, but not *syn*-adenosine, is notable. Figure 3 presents how the binding cavity of the interaction of Λ-**2** to the duplex is isostructural to that previously reported for the TAP analogue and highlights the similarity between duplex and quadruplex intercalation angles; in both cases determined by the enantiospecific contact between ancillary ligand and the adjacent sugar.

Enantiospecificity in the photooxidation of d(G_5C_5) by [Ru(TAP)$_2$(dppz)]$^{2+}$ has been previously explored, and we found that the Λ enantiomer is more efficient than the Δ and also gives a higher quantum yield compared to the oxidation of d(GC)$_5$.[21] We interpreted this effect of sequence as due to the favourability of electron transfer through a stack of guanine bases and would expect the present assembly also to be a hotspot for photodamage. We suggest the observed enantiomeric disparities in photooxidation may be explained by a difference in proximity of the photoactive metal centre to the nucleotide. Favourable contact with the 5' sugar on the terminal guanosine allows the Λ complex to stack efficiently on the G-quartet surface in a way not possible if the chirality is reversed. The vulnerability of the 5'-guanosine of a G-quadruplex to chemical damage has been established in a detailed study by Burrows *et al*.[22]

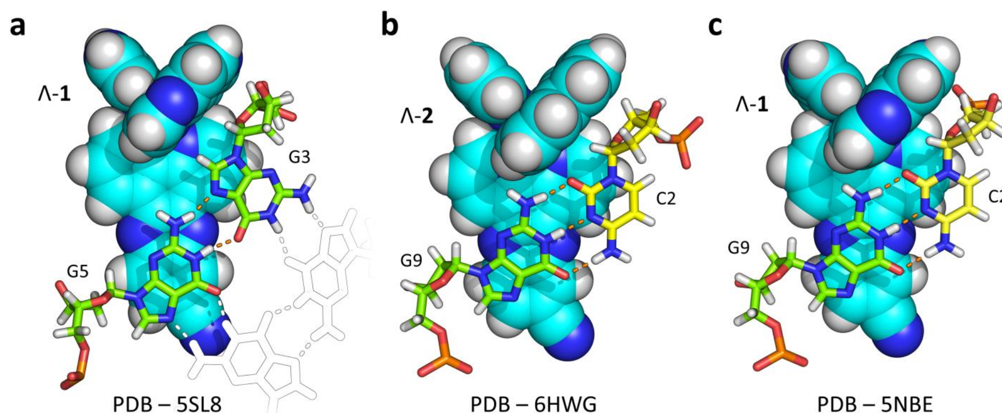

***Figure* 3–** X-ray crystallographic models highlighting the similarities in binding between Λ-**1**/**2** to (a) the guanine tetrad; (b) and (c) B-DNA forming d(TCGGCGCCGA). Each structure shows the feature that favourable stacking of the ancillary ligand to the 5'- sugar determines the binding geometry. In the case of (a) this stabilises the formation of *syn* guanosine; in all the cases the adjacent guanosine is *anti* and is aligned remarkably similarly in both tetrad and B-DNA interactions, presumably to increase favourable π orbital overlap. Comparison of (b) and (c) shows the striking similarity of the binding orientations of Λ-**1** and Λ-**2**.

Only two NMR structures of binuclear ruthenium complexes bound to G-quadruplexes have previously been reported,[23] with the Λ,Λ-enantiomer of the binuclear ruthenium complex threaded through a diagonal loop of an antiparallel quadruplex, but the Δ,Δ-enantiomer end-stacked to the lateral loop end of the same conformation. In the Λ,Λ- enantiomer model there are stacking interactions between an ancillary bpy ligand and a thymine residue in the loop, and it is estimated to bind about 40 times more strongly (Figure S10). For mononuclear complexes there are modelling studies [24] rather than NMR or crystal structure evidence. There are only four other published crystal structures showing metal complex binding to quadruplexes – and these are structurally unrelated planar species - two salphen complexes,[25] and two gold complexes[26,27] and with all these giving parallel-stranded assemblies in the crystal, in contrast to the antiparallel arrangement reported here. The most recently reported second gold complex structure shows a disordered end-pasted binding mode (Figure S11). [27]

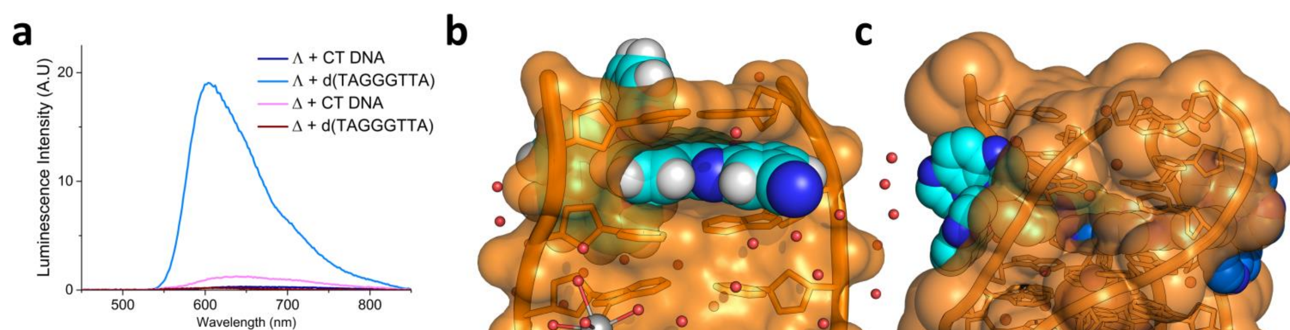

Figure 4 – (a) Emission spectra highlighting the luminescence intensity of Λ/Δ-**2** in the presence of CT DNA and G-quadruplex forming DNA d(TAGGGTTA), where λ_{ex}=440 nm. Spectra were run after annealing of the DNA samples in the presence of complex. (b), Calculated Van der Waals surfaces from the crystallographic models, highlighting how when bound to B-DNA a large proportion of the distal region of Λ-**2** is exposed in the major groove, allowing non-radiative relaxation pathways via H-bonding; and that when bound to a G-quadruplex (c) almost the entirety of the stacked ligand is encapsulated, giving protection from aqueous solvent.

We have previously used structural data to relate luminescence intensity of the 'light-switch' complex $[Ru(phen)_2(dppz)]^{2+}$ to the degree of encapsulation of the dppz ligand.[28] While we would predict that the phenazine nitrogens are at least partially blocked when bound to most duplex DNA base steps,[29] the crystal structure of Λ-**2** bound to d(TCGGCGCCGA) shows that the nitrile moiety protrudes into the major groove and is thus accessible to solvent. Λ-**2** could be expected to be luminescent with d(TAGGGTTA) if the entirety of the intercalating ligand were to be encapsulated within the tetra-stranded motif as observed in the reported structure. In contrast it would be non-emissive when bound to duplex DNA as a result of the exposed substituent.

To investigate this, the enantiomers of **2** were separated by preparative chiral HPLC and the luminescence selectivity of the separated optical isomers was assessed using fluorescence spectroscopy. Figure 4a highlights a disparity in the observed luminescence intensity between the binding modes of **2** to a G-quadruplex and to calf thymus DNA (CT DNA), where the lambda enantiomer (Λ-**2**) is essentially non-emissive in the presence of B-DNA but luminesces brightly when bound to d(TAGGGTTA). The delta enantiomer (Δ-**2**) in contrast, exhibits little luminescence when bound to CT DNA and is non-emissive in the presence of the G-quadruplex. Figures 4b and 4c show how this luminescence enhancement can be related to the extent of encapsulation of the chromophore, and parallels the implication that the delta either does not intercalate into the quadruplex or does so but not deeply.

SRCD melting experiments were performed to examine the conformation of the quadruplex in solution, both in the presence and absence of the complex (Figure S8). All DNA samples were annealed in the presence of complex, and measured within 24 hours. The structure of the native tetrameric d(TAGGGTTA) assembly was assumed to be a parallel form, based on NMR data for the d(TGGGGT) quadruplex assembly.[30] Subsequently this parallel stranded model has been widely used to interpret ligand binding with this sequence.[20,31]. SRCD spectra that we obtained confirmed this topology assignment and this parallel conformation was maintained in the presence of a 4:1 ratio of the delta enantiomer (Δ-**1**). With the Λ enantiomer (Λ-**1**) the quadruplex was found to adopt an antiparallel topology, consistent with the crystal structure reported here (Figure S9). For full details of the SRCD assignment see sections S1.6 and 2.8 in the supplementary information.

The structural evidence reported here is the first showing how a mononuclear ruthenium polypyridyl complex can bind to a DNA G-quadruplex, part of a larger programme of work which included studies towards a unimolecular G-quadruplex structure with these compounds. Unexpectedly, the Λ-enantiomer was shown to direct the formation of the quadruplex into an antiparallel assembly, an observation not mirrored by the Δ isomer; we postulate that this is a consequence of the increased stabilisation of *syn*-guanosine by the derivatised isomer. The rationalisation of the DNA structure-selective luminescence behaviour demonstrated here will not only allow for the systematic design of new complexes with increased luminescence response selectivity between duplex and higher-order DNA forms, but will allow us to extend this understanding to the design of new photooxidising agents to specifically damage the G-quadruplex, potentially with topological precision.

Experimental Section

For experimental please see supporting information.

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Keywords: G-quadruplex • Ruthenium polypyridyl • X-ray crystallography • Enantiospecificity • 'Light-switch'

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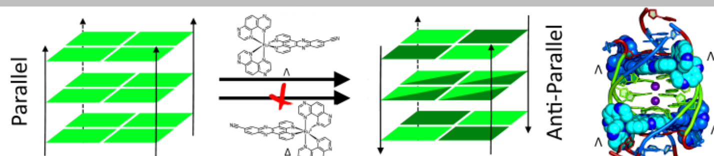

Enantiospecificity has been observed in the binding of a ruthenium polypyridyl complex, Λ/Δ-[Ru(TAP)$_2$(11-CN-dppz)]$^{2+}$, to the G-quadruplex forming sequence d(TAGGGTTA). Crystallographic studies yielded the first mononuclear ruthenium-DNA crystal structure and reveals how the quadruplex adopts an anti-parallel topology in the presence of the Λ isomer, but retains its parallel conformation with the Δ isomer.

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Page No. – Page No.

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