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Interaction of Metal Complexes with G-Quadruplex DNA

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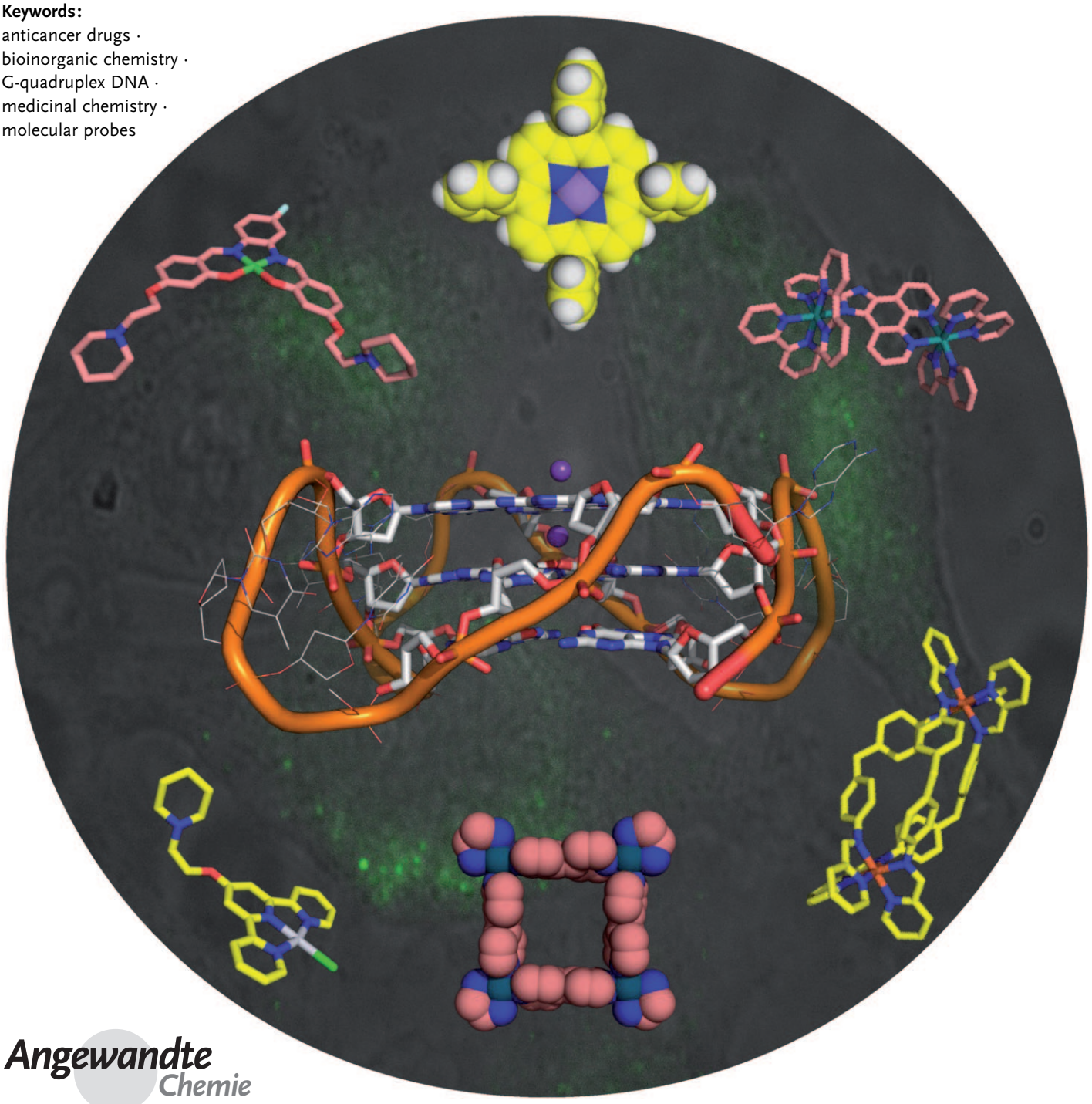

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Guanine-rich sequences of DNA can assemble into tetrastranded structures known as G-quadruplexes. It has been suggested that these secondary DNA structures could be involved in the regulation of several key biological processes. In the human genome, guanine-rich sequences with the potential to form G-quadruplexes exist in the telomere as well as in promoter regions of certain oncogenes. The identification of these sequences as novel targets for the development of anticancer drugs has sparked great interest in the design of molecules that can interact with quadruplex DNA. While most reported quadruplex DNA binders are based on purely organic templates, numerous metal complexes have more recently been shown to interact effectively with this DNA secondary structure. This Review provides an overview of the important roles that metal complexes can play as quadruplex DNA binding molecules, highlighting the unique properties metals can confer to these molecules.

From the Contents

1. Introduction

The ability of guanine residues to self-assemble into planar molecular squares was first reported over 40 years ago.[1] In these aggregates, now referred to as G-quartets or G-tetrads, four guanine residues mutually interact through hydrogen bonds between the Watson–Crick edge of each guanine base and the Hoogsteen edge of its neighbor (Figure 1a). The formation of G-tetrads in G-rich nucleic acid sequences gives rise to tetrastranded helices known as quadruplexes (Figure 1b and c). DNA quadruplexes are further stabilized by the presence of alkali-metal cations (such as Na^+ and K^+), which engage in electrostatic interactions with the guanine carbonyl groups. Quadruplexes can form intramolecularly from a single nucleic acid sequence or intermolecularly by bringing together two or more strands. The resulting structures can display a wide range of topologies depending on the relative orientation of the strands as well as the type of loops that link the G-rich units. The structures and topologies of quadruplex nucleic acids have been widely reviewed.[2]

The identification of G-rich repetitive sequences in the single-stranded DNA overhang known as telomere at the end of chromosomes as well as an enzyme responsible for its maintenance (telomerase) by Blackburn and co-workers[3] sparked great interest in studying the structural arrangements of quadruplex DNA. It was initially hypothesized that these higher order structures could play important roles in chromosomal maintenance. In addition to their presence in telomeric regions, recent bioinformatic studies have shown that G-rich DNA sequences with the potential to form quadruplexes are ubiquitous (ca. 370000 sequences) in the human genome.[4] Interestingly, a large number of them are present in the promoter regions of genes, thus suggesting that quadruplex assembly may be involved in regulating gene expression.

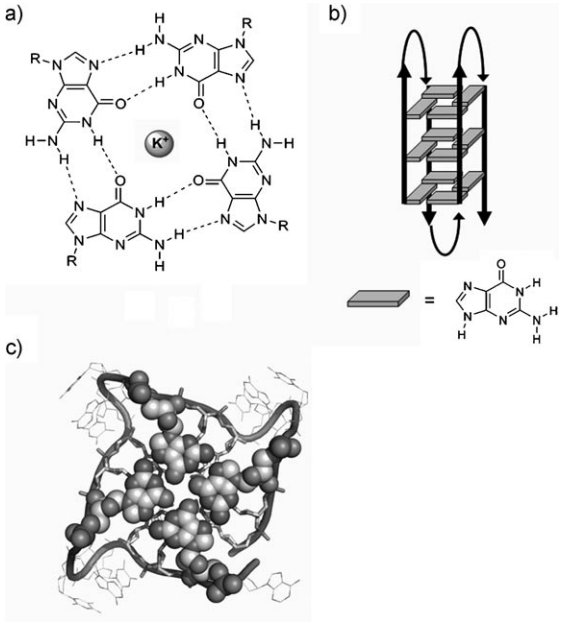

Figure 1. a) A G-quartet highlighting the hydrogen-bonding interactions between the Watson–Crick and Hoogsteen faces of the guanine bases, with an alkali-metal ion located at the center of the quartet. b) Schematic representation of an intramolecular quadruplex DNA structure. c) Top view of the X-ray crystal structure of a human telomeric quadruplex DNA generated with PyMol by using crystallographic data deposited in the PDB (PDB code: 1KF1).

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The biological functions now associated with quadruplex DNA make these structures appealing targets for drug development.[5] It has been shown that telomerase (which is over-expressed in approximately 85% of cancer cells and plays an important role in their immortalization[6]) is inhibited if single-stranded telomeric DNA is folded into a quadruplex.[7] In addition, the promoter regions of certain oncogenes (for example *c-myc* and *c-kit*) are among those containing G-rich sequences.[8] There is now mounting evidence that shows that quadruplex formation in these regions can regulate the transcription of the corresponding oncogene. Hence, there is great current interest in developing molecules that stabilize quadruplexes in either the telomeric region or in the promoter regions of oncogenes. Such molecules could provide a basis for the development of novel anticancer drugs. Indeed, the research groups of Balasubramanian,[9] Hurley,[10] Mergny,[11] Neidle,[12] and others[13] have reported molecules that interact strongly with quadruplex DNA and are able to inhibit telomerase and/or regulate the transcription of certain oncogenes.

Interactions between quadruplexes and their binders can be studied by using a range of experimental techniques. X-ray crystallography and NMR spectroscopy have been instrumental in providing structural information about quadruplex DNA in association with small molecules. Since quadruplexes are helical, circular dichroism (CD) spectroscopy has also provided useful insight into the structure of these species. The following spectroscopic and analytic techniques have been used to determine the strength of interaction between a given molecule and a quadruplex: fluorescence resonance energy transfer (FRET), UV/Vis spectroscopic melting assays, surface plasmon resonance (SPR), fluorescent indicator displacement (FID) assays, mass spectrometry, and dialysis.

Successful quadruplex DNA binders should not only interact strongly with their target but also exhibit high selectivity for quadruplex versus duplex DNA. Most binders reported to date are based on planar organic heteroaromatic systems, and are able to interact through π stacking with the G-quartets at the ends of a quadruplex.[13,14] However, it has become evident that other structural features of quadruplexes must also be taken into account when designing binders (see Figure 2). For example, quadruplexes contain distinct loops and grooves (the nature of which is sequence- and topology-dependent) and, therefore, interaction of the binder with the phosphate backbone and DNA bases outside of the G-tetrads needs to be considered. In addition, quadruplexes feature a central carbonyl-lined channel that can host alkali-metal ions, which can also be exploited.

Apart from the purely organic heteroaromatic compounds reported as DNA quadruplex binders, it has recently been shown that metal complexes can also interact strongly and selectively with quadruplex DNA, with the number of reported examples increasing rapidly over the past couple of years. In this Review we aim to provide an overview of the important roles that metal complexes can play as quadruplex DNA binders. The Review has been structured in sections that reflect the role of the metal in the specific type of compound (namely, whether it plays only a structural role, a

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Kogularamanan Suntharalingam was born in Manipay, Sri Lanka, in 1986. He obtained his MSci in Chemistry from Imperial College London in 2008, where he is currently pursuing PhD research under the supervision of Dr. Ramon Vilar. His research focuses on the study of interactions between metal complexes and G-quadruplex DNA.

Nurul Huda Abd Karim was born in Johor, Malaysia, in 1984. She received her BSc in Chemistry from the National University of Malaysia in 2006, where she carried out research under the supervision of Prof. Dr. Musa Ahmad on chemical sensors. In 2008, she joined Dr Ramon Vilar's group at Imperial College London for PhD research. Her current research interest is on the development of metal complexes with the ability to bind and stabilize G-quadruplex DNA.

Ramon Vilar obtained his MSci in Chemistry from the Universidad Nacional Autonoma de Mexico (1992) and a PhD from Imperial College London (1996) under the supervision of Prof. D. M. P. Mingos. He remained at Imperial College as a Lecturer, and was promoted to Senior Lecturer in 2003. In 2004 he took a Group Leader position at the Institute of Chemical Research of Catalonia (ICIQ, Spain), and returned to Imperial College in 2006, where he is now Reader in Inorganic Chemistry. His research group focuses on three main areas: the interaction of metal complexes with DNA and proteins, molecular recognition and self-assembly, and molecular imaging.

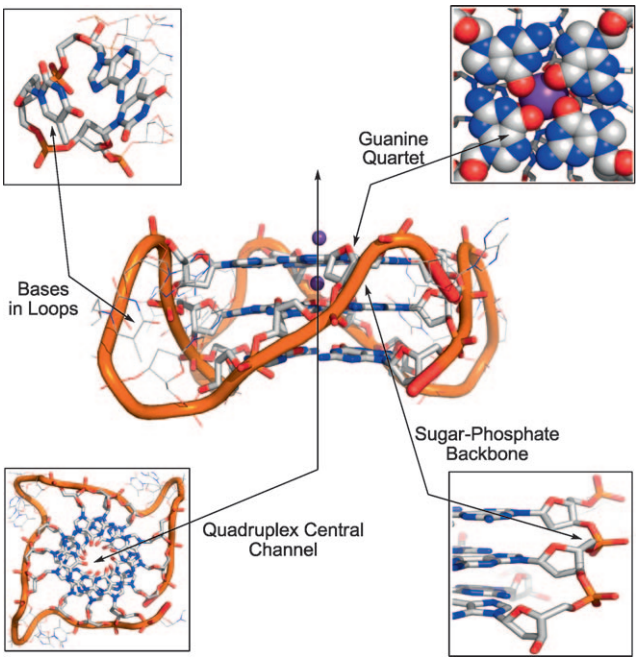

Figure 2. Structural features of quadruplex DNA that can be targeted for binding. The figure was generated with PyMol by using crystallographic data deposited in the PDB (PDB code: 1KF1).

functional role or interacts directly with the nucleic acid). It should be pointed out that the function of noncoordinated metal cations (such as Na^+ and K^+) in folding quadruplex DNA structures will not be discussed, since this has been reviewed recently.[15]

2. Why Metal Complexes?

Metal complexes have a very broad range of structural and electronic properties that can be successfully exploited when designing quadruplex DNA binders. Moreover, their often interesting optical, magnetic, or catalytic properties could, in principle, be exploited for the development of quadruplex probes and cleaving agents.

A metal center can be envisaged as a structural locus that organizes ligands in specific geometries and relative orientations for optimal quadruplex binding. The relative ease of synthesis of metal complexes can allow the generation of small libraries of related compounds. Variation can be introduced by modifying the ligands (but retaining the geometry around the metal center) or by changing the metal center (which can then furnish compounds of different geometries). This renders metal complexes advantageous over their organic counterparts, where analogous geometrical changes are often more difficult (and in some cases impossible) to introduce. Studying the interaction between the target DNA and these libraries of metal complexes can in turn allow one to establish structure–activity relationships.

In addition to their structural features, the electron-withdrawing properties of metal centers can reduce the electron density on coordinated aromatic ligands. This affords electron-poor systems, which are expected to display stronger π interactions with G-quartets. Also, the electropositive metal can, in principle, be positioned at the center of a G-quartet, thereby increasing the electrostatic stabilization by substituting the cationic charge of the alkali metal cation that would normally occupy this site.

The current strategy when designing quadruplex DNA binders is to use planar molecules, which possess the ability to interact through π stacking with G-quartets. While this is true for most organic molecules tested so far, some metal complexes have the ability to interact with nucleic acids (including quadruplex DNA) through alternative and/or additional modes, such as direct coordination to bases or the phosphate backbone.

3. Compounds Interacting with DNA Quadruplexes through π Stacking

3.1. Complexes with Macrocyclic Ligands

Metalloporphyrins were the earliest examples of metal complexes to be evaluated for their ability to interact with quadruplex DNA, most notably the telomeric G-rich sequence (H-telo).[16] The mode of binding for porphyrin-based as well as other porphyrin-like metal complexes was proposed to be π stacking of the metalloporphyrin system on top of the G-tetrads at the termini of the quadruplex (end stacking).[16b] This mode is analogous to the binding of free porphyrin bases,[17] and was supported by computational modeling and experimental data.[16b] While quadruplex adducts with unsubstituted hemin porphyrins are known,[18] synthetic metalloporphyrins with cationic meso substituents have proved more beneficial, as they lead to electrostatic interactions with the negative DNA backbone in the loops or grooves of the quadruplex. The metal ion was proposed to engage in additional electrostatic interactions that further enhance binding affinity.

The choice of the meso substituents on the porphyrin and the metal ion were the two major parameters that were determined to be critical for interaction. Metalloporphyrins with meso-methylpyridinium or methylquinolinium substitution (Figure 3a, entries 1 and 2) are quite effective in stabilizing the H-telo quadruplex and inhibiting telomerase in vitro,[16] thus supporting the notion that cationic substitution is essential for strong binding. The geometry of the complex, dictated by the metal center, has severe consequences for the end-stacking binding mode. The complexes of numerous metals—including main-group metals, transition metals, and lanthanides[16b]—with the prototypical $TMPyP_4$ (meso-methylpyridinium-substituted) porphyrin ligand have been investigated. Planar or square-pyramidal complexes (for example, of Cu^{II} and Zn^{II}, respectively[19]) bound strongly to preorganized quadruplexes. This would be anticipated based on the availability of a planar face in the molecule being accessible for π stacking. The complex/quadruplex binding stoichiometry was found to be 2:1 (and with certain DNA sequences 1:1).

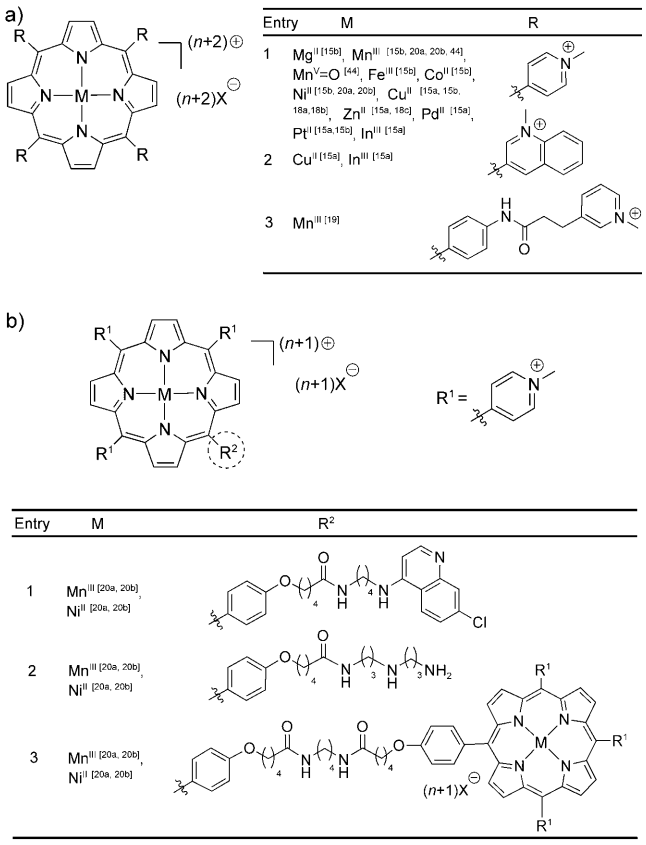

Figure 3. a) Symmetric cationic metalloporphyrins reported to bind quadruplex DNA through π stacking. b) Unsymmetric cationic metalloporphyrins, with one meso substituent different from the rest, designed to reinforce quadruplex binding by giving rise to additional interactions. *n* is the oxidation state of the metal.

In contrast, metals bearing two axial ligands would be considered poor binders for a rigid quadruplex structure. Nonetheless, some of them surprisingly appear to bind strongly to H-telo, thus implying that either this quadruplex remains highly dynamic and offers alternative modes of interaction or that the axial ligands become labile upon contact with the quadruplex and get replaced by, for example, DNA bases. One such example is a Mn^{II}-containing telomerase inhibitor (Figure 3a, entry 3) with extended (through an aryl amide linker) methylpyridinium cationic arms at all the meso positions. This complex discriminates between H-telo and duplex DNA by four orders of magnitude and has a binding constant of about $10^8\,M^{-1}$.[20] This complex benefits from electrostatic interactions between the side arms and the phosphate backbone, which are extended at longer distances and with a higher degree of freedom compared to earlier complexes. Other second generation metalloporphyrins share the extended side arm principle, which allows combining π stacking with other noncovalent interactions to reinforce binding. In one case, a meso substituent on a $TMPyP_4$-based complex was switched for a phenol-based linker, which connected to either an amine head group, to an aromatic moiety with the ability to intercalate between G-tetrads, or to a second metalloporphyrin to form a symmetric dimer (Figure 3b).[21]

Metallophthalocyanines provide a more extended aromatic system with nitrogen atoms in the meso positions in the ligand, which is very suitable in terms of spatial and electronic requirements to end-stack on a G-tetrad. Indeed, Zn^{II} and especially Ni^{II} complexes with phthalocyanines (Figure 4a and b) exhibited improved binding affinities for the H-telo quadruplex (in the μM range and below) relative to porphyrin-

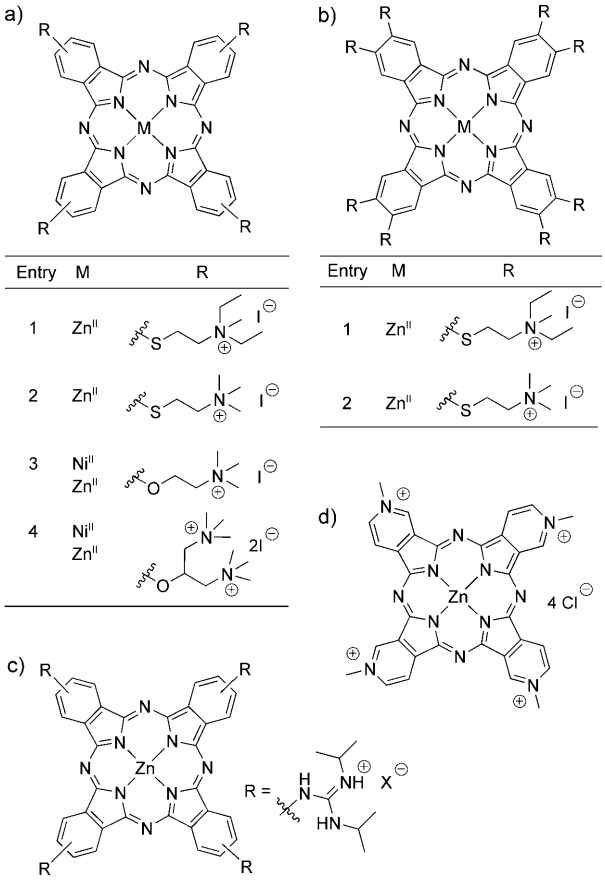

Figure 4. a,b) Metallophthalocyanines with four or eight cationic side arms, respectively, used to target quadruplex DNA.[22] c) A zinc(II) isopropylguanidinium-phthalocyanine complex with very high affinity and selectivity for the *c-myk*, H-telo,[23] and *KRAS*[24] G-quadruplexes. d) A zinc(II) tetra(*N*-methylpyrido)porphyrazine complex that binds to quadruplex DNA.[25]

based complexes.[22] The macrocyclic ligands were functionalized with oxygen or sulfur substituents to allow for attachment of (4 or 8) hydrophilic arms bearing quaternary ammonium centers. Increasing the number of cationic charges enhanced both the affinity for the quadruplex and inhibition of the telomerase. Members of this series were observed to have the ability to induce quadruplex formation or to convert one conformation into another.

The luminescent zinc complex of an isopropylguanidinium-modified phthalocyanine (Figure 4c) has been tested in vitro against several G-rich DNA sequences including the one from the *c-myc* oncogene promoter (dissociation constant

$K_d \leq 2$ nM by fluorescence), H-telo ($K_d = 6 \pm 4$ nM), and a sequence from the *KRAS* oncogene promoter.[23,24] This complex was shown to be highly selective for the above G-quadruplexes over other sequences, such as the C-rich sequences *c-myc-C* and H-telo-C, as well as over tRNA and CT-DNA. The isopropylguanidino substituents have proved critical for water solubility and uptake by cells, which occurs more readily than for previous cationic metallophthalocyanines. The addition of this compound (in noncytotoxic doses) to cells known to overexpress either *c-myc* or *KRAS* resulted in significant decrease in the expression of the corresponding oncogene.

A zinc(II) tetra(*N*-methylpyrido)porphyrazine (Figure 4d) has also been reported to be a strong and selective stabilizer of H-telo. The complex induces assembly of an antiparallel conformation in a process likened to the action of molecular chaperones.[25] Tetrapyridoporphyrazine systems are aza analogues of phthalocyanines, in which four pyridine moieties substitute the four benzene rings in the macrocycle periphery.

The trianionic corrole ligands are effective in unusually stabilizing high oxidation states of transition metals and offer additional geometric and electronic possibilities. For example, corrole complexes of Mn^{III} and Cu^{III} have been correlated to a saddle rather than a planar geometry.[26] Recent examples were used to target H-telo and the G-rich DNA sequence from the *c-myc* gene promoter region (Figure 5).[27] The reported ligands comprised either meso-pyridinium substituents or meso-benzene rings connected to cationic pyridinium or quaternary ammonium moieties through two different types of linker. The pyridinium-based Mn^{III} corrole complex was the strongest quadruplex stabilizer, and was the most selective in discriminating between quadruplex and duplex DNA, while both the Mn^{III} and Cu^{III} pyridinium corrole complexes induced a structural transition to H-telo from the antiparallel form to a hybrid. Interestingly, the Cu^{III} complexes of corrole ligands with a phenol linker favored the antiparallel conformation.

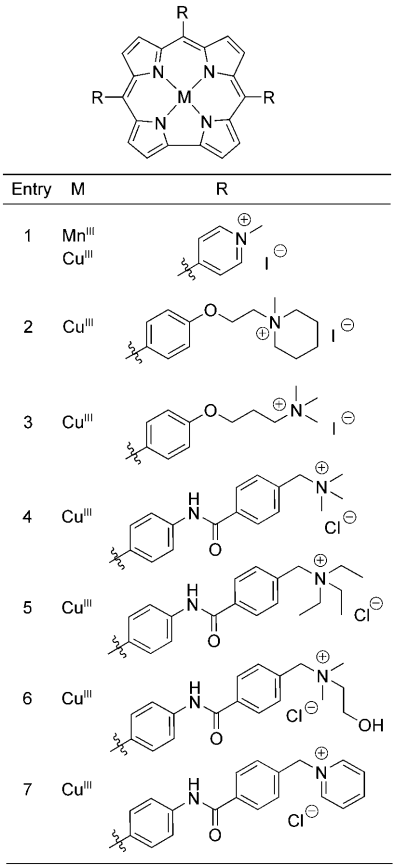

Figure 5. Corrole complexes with cationic side arms used to bind quadruplex DNA.[27]

3.2. Planar Complexes with Nonmacrocyclic Polydentate Ligands

Metal complexes of nonmacrocyclic, extended π-delocalized, polydentate chelates have also received considerable attention as potential quadruplex stabilizers in recent years. Unlike complexes with macrocyclic ligands (see Section 3.1), the metal ion in this case often induces a planar ligand conformation not intrinsic to the free ligand, thus playing a critical structural role. In fact, in most cases the free ligands are poor quadruplex binders without the ability to interact effectively through π stacking with the G-quartets. This type of metal complex also benefits from amine-based side arms (protonated under physiological conditions), which allow favorable electrostatic interactions with the loops and grooves of the phosphate backbone of quadruplex DNA.

Work conducted in our research group (in collaboration with Neidle) has shown functionalized nickel(II) salphen complexes (Figure 6) and a salen analogue with cyclic amine side chains to be excellent quadruplex binders.[28] They display

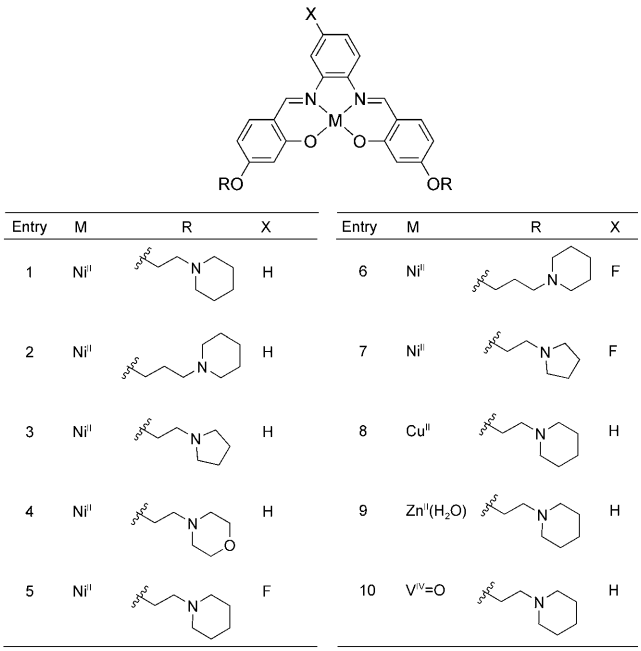

Figure 6. Metal salphen complexes with cyclic amine side arms.[28,29]

some of the highest degrees of stabilization recorded by the FRET assay (at best $\Delta T_m = 33\,^{\circ}C$ at 1 μM) and considerable selectivity (50-fold) for H-telo versus duplex DNA. Furthermore, some of these complexes are potent in inhibiting human telomerase ($^{tel}EC_{50}$ values in the low μM range by the TRAP-LIG assay) in vitro. A representative member of this series stabilized the parallel conformation of H-telo, as evidenced by CD spectroscopy. A comparative study of the nickel(II), copper(II), zinc(II), and vanadyl complexes (Figure 6) with the same salphen ligand illustrated the significance of the complex geometry for improved binding to H-telo.[29] Square-planar complexes typically appeared superior to square-pyramidal ones. More recently, a very similar series of Pt^{II} complexes of salphen and salen were prepared by Che et al.[30] and evaluated in terms of their ability to regulate the activity of the c-*myc* gene promoter in a cell-free system as well as suppress c-*myc* transcription in cancer cells.

Teulade-Fichou and co-workers recognized the potential of metal terpyridine complexes as efficient quadruplex binders.[31] The affinity and selectivity for telomeric quadruplex DNA in this case was also shown to be dependent on the geometry of the complex. Studies on Cu^{II}, Pt^{II}, Zn^{II}, and Ru^{III} complexes of terpyridine (Figure 7a) demonstrated the need

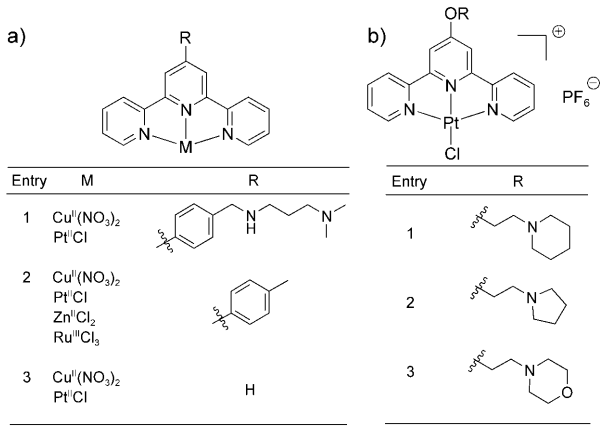

Figure 7. a) Terpyridine complexes used to investigate the relationship between the geometry around the metal center and quadruplex DNA binding affinity.[31] b) Functionalized platinum(II) terpyridine complexes were found to bind strongly to quadruplex DNA.[32]

for quadruplex stabilizers to have at least one accessible planar surface to engage in effective π-stacking interactions with the terminal G-tetrad, thus Cu^{II} and Pt^{II} were further studied. Our studies on platinum(II) terpyridine complexes (Figure 7b) showed that the addition of side chains with cyclic amine head groups on the ligand can result in a moderate binding enhancement.[32]

Square-planar platinum(II) phenanthroline complexes are also reasonably successful in targeting telomeric quadruplex DNA. Phenanthroline modified with a pendant cyclic amine or pyridine side arm through a single amide link affords complexes that exhibit high affinity for H-telo and moderate inhibition of telomerase (Figure 8a).[33] The metal is necessary for interaction with the target. Furthermore, the platinum(II) phenanthroline-ethylenediamine complex (Figure 8b) and

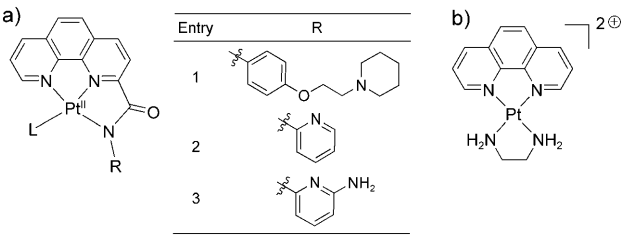

Figure 8. a) Unsymmetric platinum(II) amidophenanthroline complexes.[33] L = Cl or sp^2-hybridized N donor of a pyridyl substituent of a second molecule (dimer formation). b) The phenanthroline-ethylenediamine platinum(II) complex.[34]

several methylated analogues have been reported to bind quadruplexes. The metal complex/DNA adducts can conveniently be detected by electrospray ionization mass spectrometry.[34] The in situ formation of nickel(II) phenanthroline complexes that bind H-telo has also been described.[35]

Several studies on structurally analogous platinum(II) complexes (Figure 9) with interesting optical properties (see

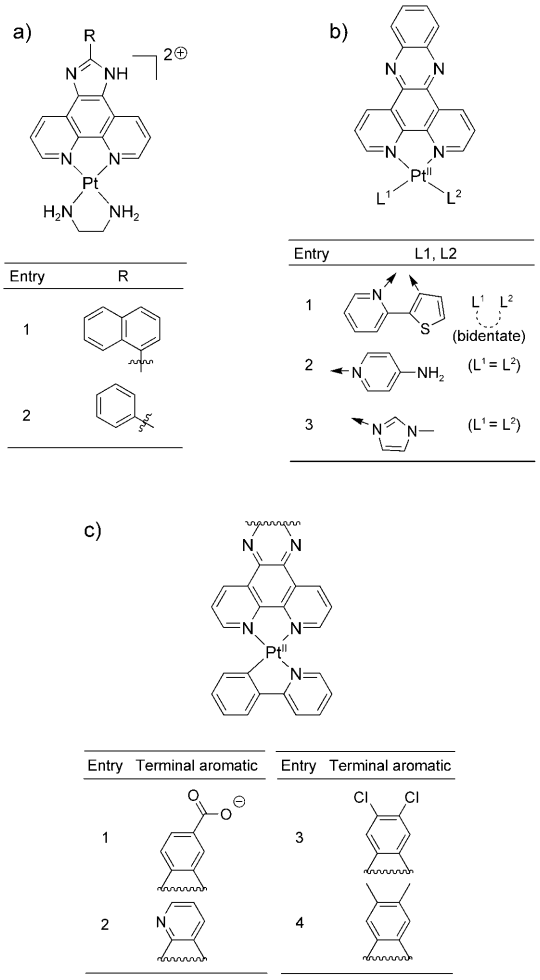

Figure 9. Luminescent platinum(II) complexes of a) phenanthroimidazol,[36] b) dipyridophenazine[37] (arrows indicate coordinating atoms), and c) C-coordinated phenylpyridine.[37] All compounds bind strongly to quadruplex DNA.

Section 6) have been described, including ones with phenanthroimidazol,[36] dipyridophenazine,[37] and C-coordinated phenylpyridine[37] ligands. These square-planar complexes exhibit considerably stronger interactions with quadruplex DNA compared to the phenanthroline complexes, thus highlighting the need for ligands to possess an extended π surface. Photophysical measurements in some of these cases suggest that binding occurs through the expected external end-stacking mode, with affinities on the order of $10^6\,\text{M}^{-1}$. The ability of these complexes to inhibit telomerase in vitro has been demonstrated.

We have tested a series of palladium(II) pyridinebis(carboxyamide) complexes (Figure 10) against H-telo and found that they stabilize the quadruplex moderately, but only when the side arms contained a tertiary amine (entry 3).[33b]

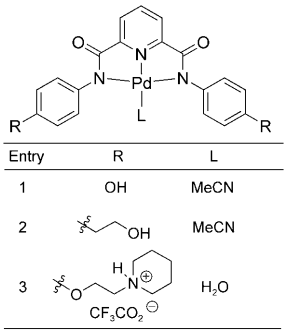

Figure 10. Palladium(II) pyridinebis(carboxyamide) complexes.[33b]

Although in all of the above cases the presence of the metal in the complexes was advantageous for binding to the quadruplex DNA target, it has been suggested that a metal ion under certain circumstances can have an adverse effect for ligand binding to quadruplex. The introduction of Cu^{II} into the strongly binding bisquinolinium ligand 360A, while the ligand is associated with quadruplex DNA, was proposed (based on CD spectroscopical data) to induce a conformational change to the ligand that dramatically weakens the binding (Figure 11).[38] This triggers unfolding of the quadruplex to the corresponding single-stranded form.

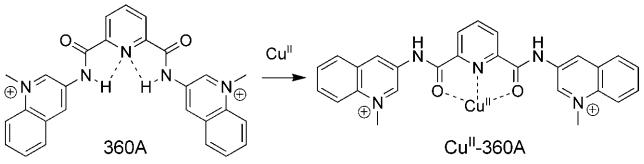

Figure 11. Introduction of copper(II) to free-ligand 360A while it is bound to a quadruplex induces a conformational change of the ligand that hampers quadruplex binding.[38]

3.3. Nonplanar Metal Assemblies with Flat Surfaces

3.3.1. Supramolecular Squares

Rationally designed supramolecular architectures afford endless possibilities for interactions with large biomolecular surfaces. A Pt^{II}-based square (Figure 12a), prepared in a single-step self-assembly process from 4,4′-bipyridyl and $[Pt(en)(NO_3)_2]$, has been used to target telomeric quadruplex DNA.[39] Its shape and size allow it to be effectively accommodated on top of the terminal G-quartet. Modeling studies suggest an energy-minimized bound conformation with the square parallel to the G-quartet, where the four metal ions at the corners give rise to close-range electrostatic interactions and the diamine ligands allow for hydrogen bonding with the DNA sugar-phosphate backbone (Figure 12b). This complex was found to be a very strong stabilizer of the H-telo quadruplex in the FRET assay, and a quite potent inhibitor of telomerase ($IC_{50} \approx 0.2\,\mu\text{M}$).

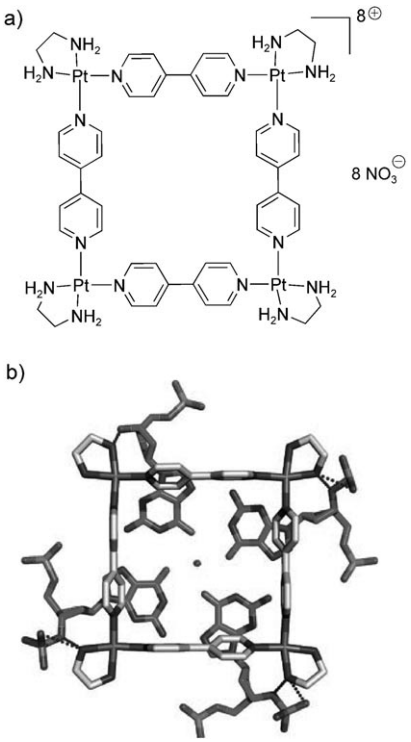

Figure 12. a) Structure of a supramolecular square that binds H-telo. b) Model of the complex formed between the square and a 22-mer DNA G-quadruplex (Figure reproduced from Ref. [39] with permission from The American Chemical Society).

3.3.2. Supramolecular Chiral Cylinders

A series of chiral bimetallic triple helicates/cylinders based on a diimine ditopic ligand (see Figure 13a) were reported several years ago by Hannon and co-workers. These complexes were shown to bind to different DNA topologies (for example, three-way junctions[40] and the major groove of duplex DNA[41]). More recently Qu and co-workers have reported that the same supramolecular complexes (with Ni^{II} or Fe^{II}) interact with H-telo quadruplex DNA.[42] This study showed that only one of the two enantiopure isomers (Figure 13b) has the ability to interact specifically with H-telo and to convert its antiparallel form into a hybrid form in the process. Discrimination was observed between quadru-

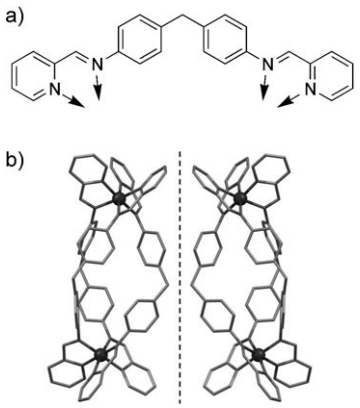

Figure 13. a) The ditopic ligand used to form the supramolecular chiral cylinder. b) The two chiral antipodes of the $[Ni_2L_3]^{4+}$ chiral cylinder. (The structure was generated using PyMol from the structural data deposited in the Cambridge Crystallographic Database; CCDC-622770.) Only the *P* enantiomer stabilizes H-telo.[42]

plex and duplex DNA as well as between different types of quadruplexes. An S1 nuclease cleavage assay indicates that binding of the *P* enantiomer protects the H-telo quadruplex from cleavage at the two ends, which suggests some type of end binding. In conjunction with the determined 1:1 stoichiometry, this finding has led to the hypothesis that the cylinder stacks through its extensive hydrophobic exterior to the top face of the quadruplex, while the metal centers engage in ionic interactions with loops and grooves. This example paves the way towards chiral anticancer drug candidates that combine small-molecule features with zinc-finger-like DNA-binding motifs.

3.3.3. Supramolecular Cubes

In the design of quadruplex binders it is highly desirable to eliminate the possibility of the intercalation of flat molecules so as to increase the selectivity for quadruplex versus duplex DNA. This principle was applied in the development of a series of supramolecular structures that bring together two tetrapyridinoporphyrins (with or without Zn^{II} in their center), bridged by 2,5-dihydroxy-1,4-benzoquinonato ligands, in an overall cubic arrangement (Figure 14).[43] Donor atoms from both the pyridine meso substituents and the bridging ligands are coordinated to ruthenium(II) atoms at the corners of the cube, with the tetrahedral coordination being completed by an arene ligand. The octacationic cubes bind strongly to both H-telo and *c-myc*. While π stacking is believed to be a critical component in the interaction with the quadruplexes, the moderate selectivity for quadruplex versus duplex DNA suggests that the high cationic charge probably gives rise to additional nonspecific electrostatic interactions with the DNA.

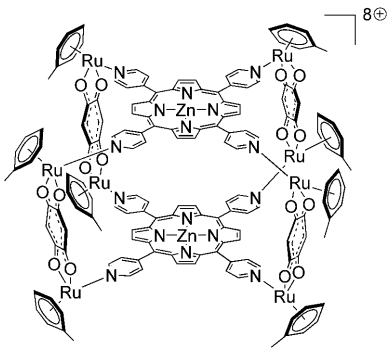

Figure 14. An octacationic supramolecular ruthenium coordination cube used as a G-quadruplex binder.

3.4. Octahedral Metal Complexes with Planar Ligands that are Involved in Groove/Loop Binding

Several Ru^{II} complexes in which the metal is found in a sterically "protected" octahedral environment, surrounded by bidentate aromatic nitrogen ligands have been studied in recent years in terms of their interaction with G-quadruplexes. In these cases, and as indicated by experimental findings, it is unlikely for the metal itself to be embedded in a π stacking unit or even in direct proximity to the G-tetrads.[44] However, the planar ligand surfaces do have the potential to (partially) stack on or intercalate between G-tetrads, and the charged molecules as a whole have been proposed to engage in interactions with the grooves and loops in the negatively charged sugar-phosphate backbone of the DNA.

One such complex (Figure 15a) has a pyridine ligand attached to a porphyrin[45] to increase the lipophilicity and bioavailability. This complex was reported to bind with high affinity to the H-telo quadruplex, thereby resulting in disruption of its parallel conformation.

A series of luminescent bimetallic Ru^{II} complexes with the ditopic ligands tetrapyridophenazine and tetraazatetrapyridopentacene (Figure 15b) were reported to bind quadruplex DNA in a process that was accompanied by significant emission enhancements.[44a] These complexes typically destabilize or moderately stabilize the quadruplex structure they interact with. "End-pasting" or threading through the lateral loops of the quadruplex were suggested as possible modes of interaction, while partial intercalation remained a possibility, especially when the highly dynamic nature of the quadruplex was considered. Studies on monometallic variants of these Ru^{II} complexes featuring a truncated central ligand (Figure 15c) and the corresponding nickel(II) derivatives have also been described;[34,37] all showed rather weak interactions and ligand-independent affinities towards DNA quadruplexes.

Another luminescent bimetallic complex (Figure 15d) induces quadruplex formation and stabilization of an antiparallel conformation in the H-Telo sequence in the absence of alkali-metal cations.[44b] The selectivity for the quadruplex is one order of magnitude higher than for the duplex DNA, based on emission enhancement.

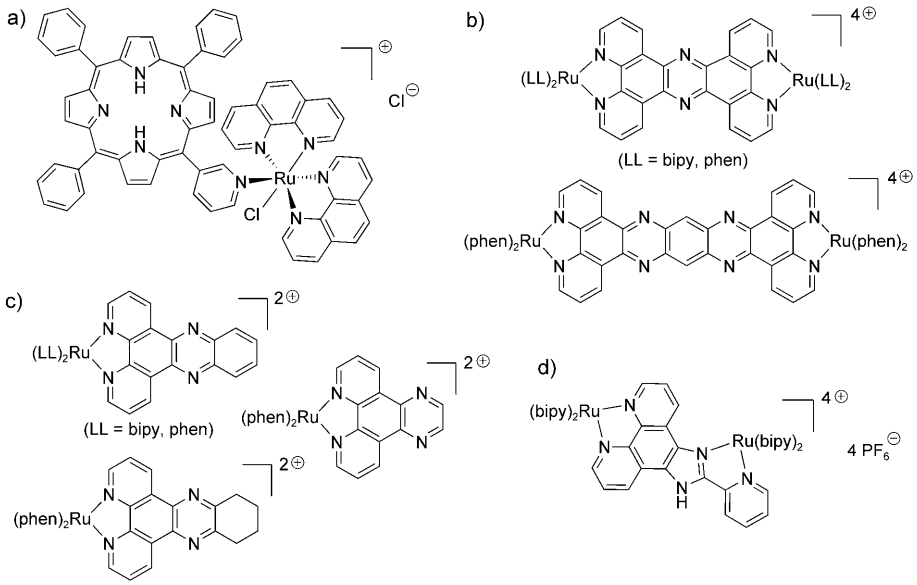

Figure 15. Examples of octahedral ruthenium(II) complexes that interact with DNA quadruplexes through a combination of ligand π stacking and groove/loop electrostatic interactions. a) $[RuCl(phen)_2(MPyTPP)]^+$.[45] b) Luminescent bimetallic complexes with aromatic diimine ligands[44a] and c) their monometallic counterparts.[34,37] d) The luminescent bimetallic $[Ru_2(obip)(bipy)_4]^{4+}$.[44b] bipy = 2,2′-bipyridyl, phen = 1,10-phenanthroline.

Some Pt^{II} complexes show a kinetic preference for platinating A-N7 over G-N7. Quantitative HPLC analysis of the progress of the reaction between H-telo and Pt-ACRAMTU (Figure 16b) shows that the preferred order of platination is A-N7 > G-N7 > A-N1 > A-N3.[48] Moreover, the levels of the A-N7 quadruplex adducts exceeded the corresponding ones for duplex and single-stranded DNA.

Studies conducted on a series of platinum(II) polypyridyl complexes (Figure 17a and b) suggest that they interact with an H-telo-like quadruplex structure through site-selective platination of certain adenine bases (present in either the latter or diagonal loops).[49] It is noteworthy that no platination occurs with the more-hindered 2,6-bis(quinolino)-pyridine complex (Figure 17c), which has the most extended π system in the series.

4. Direct Coordination of the Metal to Quadruplex DNA

In the examples presented above, the corresponding metal centers do not interact "directly" (through coordination) with DNA donor groups such as bases or phosphate groups. However, there have been reports that show that direct coordination of certain metal complexes to quadruplex DNA is possible.[46] For example, it has been shown that some Pt^{II} complexes coordinate to DNA nucleobases, especially to N7 sites of guanine residues.[47] The pattern of platination (single site or cross-linking) is dependent on the secondary structure of the quadruplex, accessibilities of the bases, and individual characteristics of the complexes.[47b,c] For example, cross-linking of two guanine bases was observed in the platination of an external G-tetrad of quadruplex DNA by dinuclear Pt^{II} complexes $[\{trans\text{-}PtCl(NH_3)_2\}_2H_2N(CH_2)_nNH_2]Cl_2$ (Figure 16a).[47b] Furthermore, *cis*- and *trans*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ complexes were used to cross-link sets of two guanine bases or adenine and guanine in preorganized telomeric quadruplexes from several species.[47c]

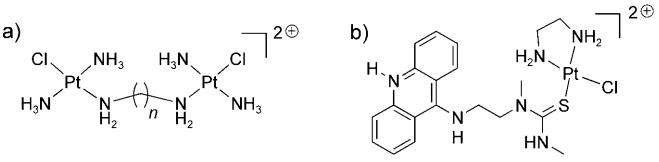

Figure 16. a) $[\{trans\text{-}PtCl(NH_3)_2\}_2H_2N(CH_2)_nNH_2]Cl_2$ ($n = 2$ or 6), an agent that cross-links guanine bases in quadruplex DNA;[47b] b) Pt-ACRAMTU, an agent that monoplatinates the A7 residue of H-telo.[48]

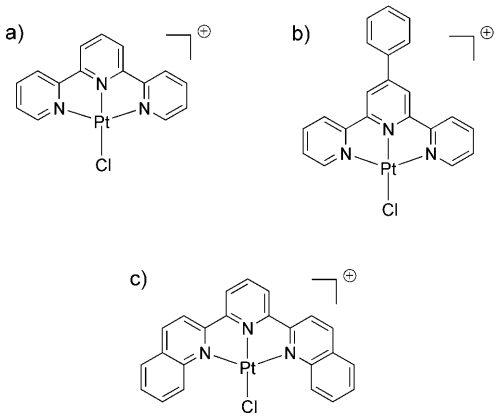

Figure 17. a,b) Platinum(II) terpyridine complexes effecting site-selective platination of DNA quadruplex:[49] a) $[PtCl(tpy)]^+$ attacks A7, b) $[PtCl(ttpy)]^+$ attacks A13. c) $[PtCl(dtpy)]^+$ is too hindered to allow platination to occur.

Similar to some other examples discussed in this section, the combination of noncovalent with covalent binding modes has been exploited in a compound consisting of a quinacridine aromatic moiety linked to a Pt^{II} complex through a hydrophilic linker (Figure 18a).[50] In this case the long linker spans the length of the G-tetrad stack and positions the metal in a way that allows platination to occur (at two alternative sites, G2 or G22; Figure 18b) on the opposite face of the quadruplex from the one interacting with the quinacridine plane. This construct stabilizes the antiparallel form of the 22-mer DNA quadruplex used.

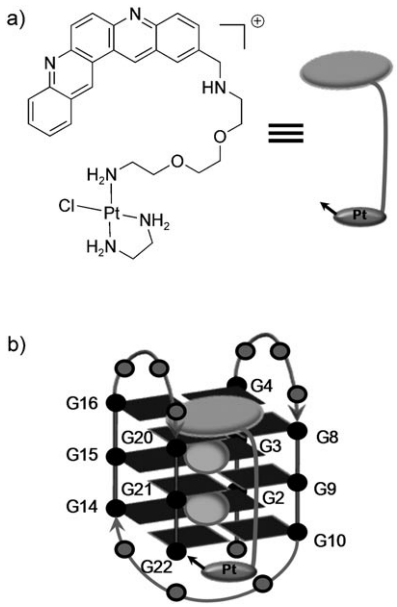

Figure 18. a) The complex Pt-MPQ π stacks on one face of a DNA quadruplex and platinates a tetrad guanine on the opposite face. b) Proposed mode of the interaction between Pt-MPQ and a 22-mer quadruplex DNA that leads to platination of G22.[50]

Although platination on preformed quadruplex DNA is well documented, reports of platination disrupting the stability of the quadruplexes are a recent development. CD spectroscopic studies showed that unfolding of telomeric quadruplexes Tel-1 and Tel-2 occurred upon exposure to *cis*- and *trans*-platin.[51] In contrast, the *c-myc* and PDGF-A DNA quadruplexes were not affected. The behavior of the telomeric sequences was explained in terms of the better accessibility of the N7 position of guanine bases within a G-tetrad compared to ones outside the stack, which makes them the preferred modification site for the platinating agent. Platination triggers disruption of that G-tetrad and destabilization of the overall structure(Figure 19). In the cases of *c-myc* and PDGF-A, it was suggested that several other guanine bases, located in loops outside of G-tetrads, are more exposed and thus serve as the primary platination sites, without compromising quadruplex stability. Destabilization of H-telo quadruplex by *cis*- and *trans*-platin was also observed in another study[52] (based on CD, UV-spectroscopically monitored thermal denaturation, and gel electrophoresis), which went on to show that the resulting platinated DNA adducts, despite not being able to form a quadruplex, were not recognized by telomerase, thus preventing elongation of the DNA sequence.

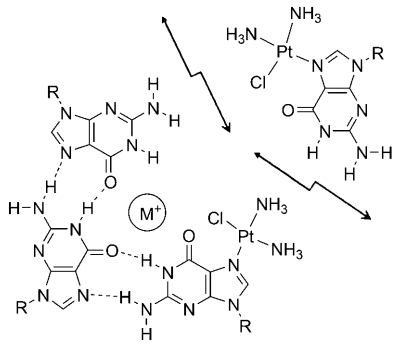

Figure 19. Proposed mechanism for the destabilization of a telomeric quadruplex G-tetrad by *cis*-platin.[51]

5. Cleavage of Quadruplex DNA by Metal Complexes

Several metal complexes with moieties that render them able to interact with quadruplexes may be designed to induce cleavage of the target DNA structure. An early example was an in situ formed oxomanganeseporphyrin based on the cationic $TMPyP_4$ ligand.[53] This complex was found to interact with the terminal G-tetrad of H-telo and effect guanine oxidation in that tetrad, as well as 1′-carbon atom hydroxylation of neighboring loop deoxyribose residues. The latter, followed by a series of eliminations, leads to cleavage of the DNA backbone, effectively allowing this complex to act as an artificial nuclease. The location of the cleavage sites was dependent on the type of secondary structure used.

Another example is a perylene-EDTA-iron(II) conjugate (Figure 20). This contains a known G-quadruplex perylene

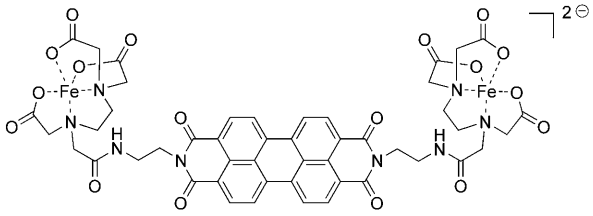

Figure 20. The perylene-EDTA-iron(II) complex π stacks to a DNA quadruplex through its polyaromatic core and cleaves the DNA through a hydroxyl radical mechanism.[54,55]

binder as a core, which is attached through flexible linkers to one iron(II)-EDTA complex on either side in such a way that enables their interaction with opposing grooves when the core end-stacks on a quadruplex.[54,55] Exposure of a quadruplex-duplex DNA construct to this agent in the presence of the reducing agent dithiothreitol caused selective cleavage of quadruplex DNA; this cleavage is believed to be mediated by hydroxyl radicals.

Cleavage of quadruplex DNA may also result from electron-transfer mechanisms, for example mediated by $[Ru(bipy)_3]^{2+}/[Fe(CN)_6]^{3-}$ [56] or from long-range charge transport using the planar photooxidant $[Rh(phi)_2(bipy)]^{3+}$ (phi = phenanthrenequinone diimine).[57] Although charge transfer appears to be associated with the G-tetrads, the mode of interaction between the quadruplex and metal agent was not investigated. These complexes can potentially interact in analogous ways to those discussed for complexes of similar geometries in previous sections.

More recently, Komiyama and co-workers have shown sequence-specific H-telo cleavage effected by the formation of an intermolecular quadruplex that recruits a cerium(IV) bimetallic complex.[58] An ethylenediaminetetramethylenephosphonic acid (EDTP) chelate, covalently incorporated right above a G-rich DNA sequence that contributes three stands to the quadruplex, was used to strongly bind to the lanthanide ions. Assembly of a full quadruplex between this engineered DNA molecule and H-telo resulted in the Ce^{IV} complex being positioned against a specific phosphodiester target site of the H-telo backbone, thereby catalyzing its hydrolytic cleavage (Figure 21).

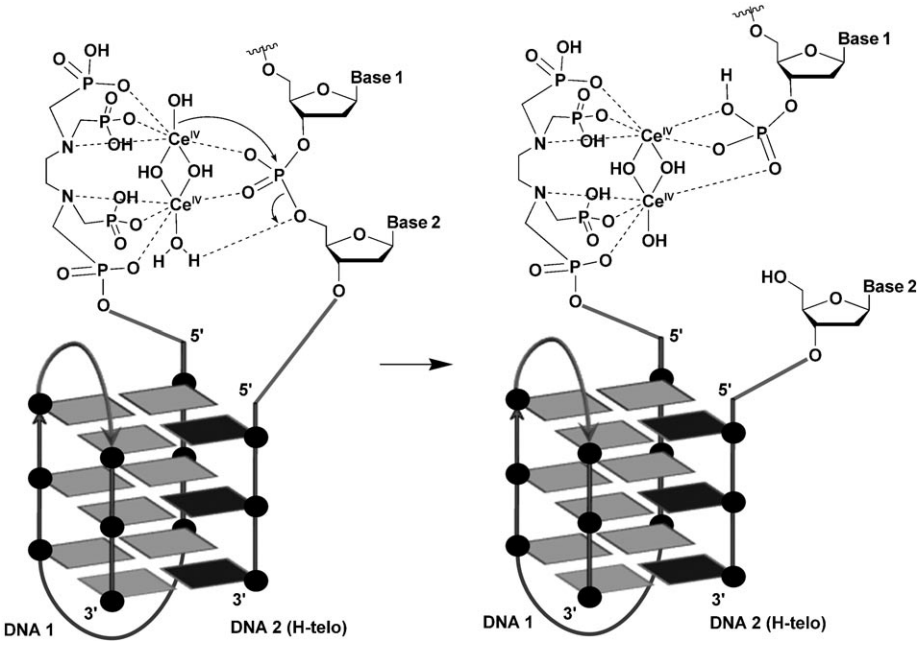

Figure 21. Proposed mechanism of H-telo cleavage by a DNA-EDTP-cerium(IV) complex in a [3+1] intermolecular quadruplex.[58] (The guanine bases contributed by H-telo are darker for clarity.)

6. Metal Complexes as Optical Probes for Quadruplex DNA

An area of tremendous interest is that of molecules that change their optical properties upon interaction with quadruplex DNA. This could yield valuable probes for the study of quadruplexes and their biological functions. To date, some metal complexes have been assayed for this purpose. A prominent case is Pt^{II} complexes with aromatic diimine ligands (Figure 9b and c), which have been reported as luminescent probes of quadruplexes.[37] Besides showing impressive binding affinities (see Section 3.2), some compounds such as the zwitterionic member of this series (Figure 9c, entry 1) display significant photoluminescence enhancements of about 300-fold upon binding to a DNA quadruplex, which is an order of magnitude higher than for duplex binding. The zwitterionic complex was also used as a fluorescent dye to stain quadruplex DNA on an electrophoretic gel.

A luminescent water-soluble alkynylplatinum(II) terpyridyl complex (Figure 22a) has proved useful for detecting the intermolecular formation of DNA quadruplex from unfolded DNA.[59] The positively charged planar complex is initially allowed to associate with the (anionic) single-stranded G-rich DNA through electrostatic interactions. The addition of K^+ ions and assembly of the G-quadruplex results in molecules of the complex (as is typical for some d^8 systems) being brought in proximity and their self-aggregation through Pt–Pt and π-stacking interactions (Figure 22b). This aggregation gives rise to a MMLCT band, which is readily observed by UV/Vis and emission spectroscopy. The formation of G-quadruplex was confirmed by CD spectroscopy, which indicated a pattern characteristic of a parallel quadruplex conformation.

Ruthenium(II) complexes are also potential optical probes for quadruplex DNA. In one case which featured two octahedral $[Ru(bipy)_3]^{2+}$ units interconnected through an azo bridge (Figure 23), an immediate color change was observed when the complex was mixed with telomeric quadruplex DNA.[60] The dramatic purple-to-blue shift was attributed to the change in the environment of the azo moiety as the complex engages in interactions with the quadruplex.

A distinctive metal-to-ligand charge-transfer (MLCT) emission or "light-switch effect" can be observed when bimetallic Ru^{II} complexes of tetrapyridophenazine and tetraazatetrapyridopentacene bind (as discussed in Section 3.4) to quadruplex DNA.[44a] This situation involves a significant enhancement of the luminescent signal of about 150-fold, which is 2.5 times more than for interaction with duplex DNA, accompanied by a "blue-shift". Members of this family (Figure 15b) have recently been used for in vivo direct imaging of nuclear DNA, including quadruplex, in eukaryotic and prokaryotic cells.[61] The dinuclear $[Ru_2(obip)(bipy)_4]^{4+}$ complex (Figure 15d) also demonstrates a moderate enhancement of the luminescence signal upon interaction with a quadruplex.[44b]

Finally, the recently reported zinc complex of the isopropylguanidinium-modified phthalocyanine (see Section 3.1 and Figure 4c) may be used as an optical probe in a cellular context to afford cellular localization that is markedly different from that of duplex DNA probes.[23,24] Its convenient "turn on" photoluminescent properties (200-fold increase in photoluminescence when saturated with nucleic acid) and its ability to knock down gene expression provide two orthogonal read outs, which are likely to allow future correlations between G-quadruplex structure and function in vivo.

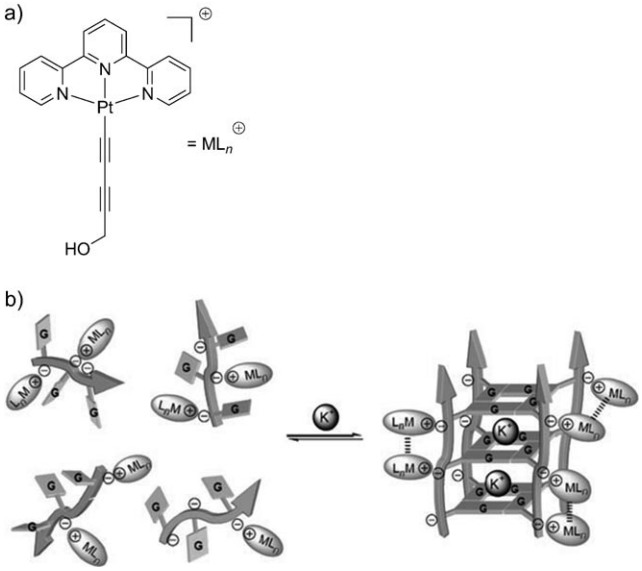

Figure 22. a) A luminescent alkynylplatinum(II) terpyridyl complex. b) K^+-induced intermolecular G-quadruplex assembly, which results in complex aggregation through Pt–Pt and π-stacking interactions and leads to a MMLCT transition. This transition can serve as an optical read-out that indicates quadruplex formation. (Figure reproduced with minor modification from Ref. [59] with permission from The Royal Society of Chemistry.)

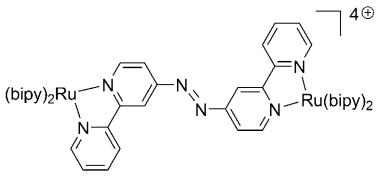

Figure 23. The $[\{Ru(bipy)_2\}_2(4\text{-azo})]^{4+}$ complex can act as an optical probe of DNA quadruplex.[60]

7. Summary and Outlook

The past ten years have seen a steady growth of molecules that are reported to interact with quadruplex DNA. In contrast to the large number of organic molecules reported to bind to this secondary structure of DNA, metal complexes have only recently started to be systematically investigated. These studies have shown the great potential metal complexes have in binding to (and stabilizing) quadruplexes, and in doing so, inhibiting telomerase or regulating gene expression of certain oncogenes. Considering the large number of sequences that are guanine-rich and can potentially form quadruplexes in the human genome, there is great interest in finding new molecules able to interact selectively with specific quadruplexes. As has been shown in this Review, metal complexes have provided new and important families of compounds for achieving this aim. In addition, because of their remarkable photophysical properties, several complexes have shown prominence as optical probes for quadruplex DNA. It is therefore not surprising that metal complexes have emerged as an increasingly important type of compound in the search for novel quadruplex DNA binders and probes.

As for the future direction of this area, the use of metal complexes as in vivo probes for quadruplex DNA structures is likely to be a particularly active one. In addition, since in vivo applications of metal-containing quadruplex DNA binders are still very scarce, it is expected that future research will focus on exploring the medicinal applications of these complexes.

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