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Review

Metal complexes as structure-selective binding agents for nucleic acids

F. Richard Keene[a,*], Jayden A. Smith[a], J. Grant Collins[b,**]

[a] School of Pharmacy & Molecular Sciences, James Cook University, Townsville, Queensland 4811, Australia
[b] School of Physical, Environmental and Mathematical Sciences, University College, University of New South Wales, Australian Defence Force Academy, Canberra, A.C.T. 2600, Australia

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ABSTRACT

Concomitant with our increasing knowledge of the structure and biological role of nucleic acids is the interest in the development of small molecules that can regulate DNA and RNA function. While considerable effort has been devoted to synthesising compounds that can target specific DNA and RNA sequences, there is growing interest in developing agents that can recognise nucleic acid structural features. In particular, it has now been established that a variety of non-duplex structures – such as bulges, hairpins and junctions – play an important role in the regulation of DNA transcription and RNA translation. Metal complexes have great diversity in size and structure, as well as useful photophysical and electrochemical properties in many cases, and consequently they have become an important class of structure-selective binding agents for nucleic acids. The present review addresses the range and biological significance of non-duplex structures that are found in DNA and RNA, as well as the specific types of metal complexes that recognise these structural features. Particular attention is given to dinuclear ruthenium complexes that have been shown to bind duplex DNA and RNA weakly, but associate strongly with non-duplex structures.

* Corresponding author. Tel.: +61 7 4781 4433; fax: +61 7 4781 6078.
** Corresponding author. Tel.: +61 2 6268 8077; fax: +61 2 6268 8002.
E-mail addresses: richard.keene@jcu.edu.au (F.R. Keene), g-collins@adfa.edu.au (J.G. Collins).

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1. Introduction

It is now 50 years since the central dogma of molecular biology was first proposed [1]. The human genome has been sequenced and the mechanism by which the information encoded in the base sequence of DNA is transcribed and translated into the synthesis of proteins has been established. As a consequence, there is enormous interest in developing small molecules that can selectively interact with DNA and RNA. Potentially, these molecules could be used as diagnostic probes of nucleic acid structure and function, as well as therapeutic agents for a variety of diseases. Developing molecules that can control gene expression is one of the dominant research areas within chemistry, biochemistry and molecular biology.

Traditionally, the design and development of small molecules that can selectively bind to nucleic acids centred upon organic chemistry; however, through the pioneering work of Dwyer [2], Lippard [3], Nordén [4], Barton [5] and others, there is now considerable interest in utilising transition metal complexes as nucleic acid binding agents. Metal complexes can interact with nucleic acids through a variety of modes, are amenable to modular assembly and have favourable spectroscopic, photophysical and electrochemical properties that allow a detailed examination of their binding and the potential to regulate DNA/RNA function [2–5].

Conceivably, metal complexes could regulate nucleic acid function by targeting specific sequences such as particular genes or their RNA products, or control points for gene transcription or translation. Alternatively, metal complexes can be developed that target non-duplex DNA and RNA structures that act as important regulation points in gene expression. While the duplex structure is the dominant form for DNA and an important form for RNA, there has been considerable recent interest in non-duplex structures as targets for drug development. This review focuses on recent developments in this growing field of bioinorganic chemistry, and in particular, on non-covalent recognition of nucleic acids. Although several reviews on non-duplex nucleic acids have been previously published {e.g. Belmont et al. (2001), Wadkins (2000) and Hurley (2001)} [6–8], none have been directed towards the range of structures that have been targeted by metal complexes. As a consequence, we also present a relatively detailed description of the structure and biological importance of a range of non-duplex nucleic acid secondary structures as a general introduction to the topic for inorganic chemists.

2. Nucleic acid structure

2.1. Primary structure

The naturally occurring nucleic acids, DNA and RNA, are biopolymers comprised of nucleotides – nitrogenous heterocyclic bases bound to a negatively charged furanose phosphate backbone (β-D-2′-deoxyribose in DNA, β-D-ribose in RNA). DNA is generally assembled from four such bases – adenine (A), guanine (G), cytosine (C) and thymine (T) – which are planar aromatic derivatives of purine (A and G) and pyrimidine (C and T). RNA is composed primarily of the same four bases, albeit with uracil (U) in place of the more stable thymine. Adjacent nucleotides in the polymeric chain are ligated together through a phosphodiester bond in which a phosphate group links the 5′-end of one sugar to the 3′-end of the next. Accordingly, the polymerisation of nucleotides gives rise to long, single-stranded polyanionic chains with a well-defined directionality (traditionally described in the 5′- to 3′-direction) which essentially constitutes the primary structure of the nucleic acid.

Nucleic acids often adopt a double-stranded arrangement as their secondary structure – DNA is almost exclusively double-stranded in its native state while duplex regions occur intermittently throughout the complex array of structures adopted by RNA.

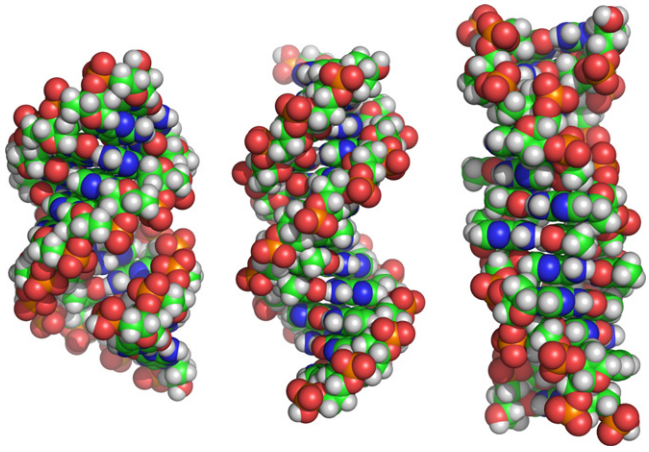

Fig. 1. Space-filling models of the three major conformations of DNA: (left-to-right) A-, B-, and Z-DNA.

The two strands of the duplex are held together by hydrogen bonding between bases on opposite strands: the most common "base-pairing" scheme (often called "Watson–Crick base pairing") involves G·C and A·T purine–pyrimidine inter-strand pairs. A variety of other, non-canonical base-pairings (Hoogsteen, wobble, etc.) have been found to arise regularly in RNA, however in DNA they are typically regarded as mutations ("base mismatches") and often corrected by genetic repair mechanisms. The overall stability of the double-helical arrangement is further supported by π–π interactions between the stacked hydrophobic aromatic rings of adjacent bases on the polynucleotide chains [9].

2.2. Conformations

Duplex nucleic acids are highly polymorphic – they are able to adopt a variety of different conformations (see Fig. 1) – as a consequence of the many points of articulation within the nucleic acid structure [10,11]. Ultimately, these parameters (Table 1) are themselves influenced by environmental factors (hydration and ionic strength) and the primary structure (base sequence) of the polynucleotide [12].

The conformational form of DNA most commonly encountered under physiological conditions (relatively high hydration, low ionic strength) is known as B-DNA, the structure of which was first described in the seminal paper by Watson and Crick in 1953 [13]. B-DNA is a right-handed helix with a diameter of approximately 20 Å, 10.5 base pairs (bp) per turn and a 3.4 Å step between base pairs that are nearly perpendicular to the helical axis. The separation of sugar-phosphate backbone chains due to base-pairing and stacking and the mutual repulsion of phosphate groups gives rise to a pair of grooves that run the length of the duplex, facilitating access to the

Table 1
Selected parameters of biologically relevant nucleic acid conformations[a].

Attribute	A-DNA	A-RNA	B-DNA	Z-DNA
Helical sense	Right-handed	Right-handed	Right-handed	Left-handed
Repeating unit	1 bp	1 bp	1 bp	2 bp
Residues per turn	11	11	10.5	11.6
Axial rise per residue	2.55 Å	2.8 Å	3.4 Å	3.7 Å
Inclination of bp to axis	22.6°	15.5°	2.8°	0.1°
Rotation per residue	32.7°	32.7°	36.0°	−60° (per 2 bp)
Glycosyl angle	*anti*	*anti*	*anti*	C: *anti* G: *syn*
Sugar pucker	C3′ *endo*	C3′ *endo*	C2′ *endo*	C: C2′ *endo* G: C3′ *endo*

[a] Parameters adapted from Belmont et al. [6] and Neidle [10].

Table 2
Groove dimensions (Å) of the three main DNA conformations[a,b].

Conformation	Major groove		Minor groove	
	Width	Depth	Width	Depth
A	2.2	13.0	11.1	2.6
B	11.6	8.5	6.0	8.2
Z	8.8	3.7	2.0	13.8

[a] Information adapted from Neidle [10].

[b] Groove width is typically defined as the perpendicular distance between phosphate groups on opposite strands, subtracting the 5.8 Å van der Waals diameter of a phosphate group; groove depth involves differences in cylindrical polar radii between phosphorous and N2 guanine (minor groove) or N6 adenine (major groove) atoms.

bases therein. In canonical B-DNA there exists a wide (11.6 Å) *major groove* and a narrow (6.0 Å) *minor groove*, with both grooves being of a similar depth (*ca.* 8 Å); however, these dimensions are very sensitive to the base sequence of the duplex region of interest. For example, AT-rich sequences are known to adopt a narrower and more flexible minor groove than GC-rich regions. The groove dimensions of the three major DNA conformations are compared in Table 2.

In environments of relatively low hydration (or a high concentration of cations), DNA assumes an A-form that is a wider, more compact structure (11 bp per helical turn) in which the bases are displaced off-centre of the helix resulting in an essentially hollow core [14]. The major groove of A-DNA is very deep, but restrictively narrow; conversely, the minor groove is wide and shallow. A definitive *in vivo* role of A-DNA has yet to be established, however a number of DNA-binding proteins are known to induce a B → A-DNA conformational change [15–17]. Duplex RNA and DNA–RNA hybrids commonly adopt an A-type conformation [18,19] – a result of the 2′-hydroxyl group of ribose forcing the RNA sugar into a C3′ *endo* conformation rather than the C2′ *endo* arrangement characteristic of B-DNA.

A second somewhat more drastic variation from the canonical B-DNA conformation is that of Z-DNA, which is a *left-handed* double helix [20]. Z-DNA, named for its zig-zagging backbone, occurs in solutions of high ionic strength (2.5 M NaCl or greater) [21], or in runs of appropriately modified bases [22]. Z-DNA is not a simple mirror image of B-DNA; in order to maintain Watson–Crick pairing the B → Z transition requires that bases be inverted [23]: it has a flattened (wide and relatively shallow) major groove, a deep and narrow minor groove, and an overall structure that is elongated and narrow relative to B-DNA. Ha et al. have recently obtained a crystal structure of a B → Z-DNA junction [24], nicely illustrating the dichotomy between the two conformations.

While Z-DNA has been conclusively demonstrated to occur *in vivo* [25–27], its specific function is still the matter of much speculation [28–30]. Nevertheless, there appears to be a telling correlation between regions of transcriptional activity and putatative Z-DNA forming sequences. Z-RNA has also been observed [31–33] and while anti-Z-RNA antibodies have been isolated [34], any *in vivo* role for this polynucleotide remains unknown.

While the A, B, and Z forms are perhaps the most biologically relevant duplex nucleic acid conformations, a significant portion of the alphabet has been appropriated in the designation of a myriad of double-helical nucleic acid polymorphs. However, many of these structures are sub-varieties of the three main conformations described above or, alternatively, exist solely as test-tube curiosities with (as yet) no known *in vivo* significance.

2.3. Non-duplex structures

2.3.1. Bulges

Amongst the most rudimentary deviations from the canonical duplex of nucleic acids are the stretches of unpaired nucleotides referred to as *bulges*, where one strand of the hydrogen-bonded duplex possesses one or more nucleotides which have no counterpart on the opposing strand (see Fig. 2). Bulges, typically less stable than the analogous sequence composed of standard Watson–Crick base pairs [35], can vary in size from a single unpaired nucleotide up to a run of several residues that are capable of forming a flexible loop-like extrusion from the double helix.

Unconstrained by the standard hydrogen-bonding schemes of base-pairing, bulged nucleotides possess considerable conformational freedom, yet generally they will assume either an intrahelical ("stacked-in") or an extrahelical ("looped-out") arrangement. While the looping-out of unpaired bases results in relatively little distortion of a typical double-helical conformation, the incorporation of bulged bases between the π-stacked base pairs of the duplex can induce kinking in the nucleic acid, the extent of which is dependent upon the identity of the bulged bases and the size of the bulge [38–43].

Biological occurrences of bulges are found in both DNA and RNA, but characterisation and understanding of such structures are much more extensive in the latter. Bulges in RNA tend to be of particular and well-defined architectural and functional significance, whereas in DNA they tend to be more transient in nature and are typically associated with mutagenic events. The disadvantageous formation of DNA bulges – due to replication errors, the recombination of imperfectly homologous sequences, or the repair of radiation- or carcinogen-induced DNA damage – can give rise to frameshift mutations in which one or more nucleotides are inserted into or deleted from a DNA strand [44–46]. Such mutations alter the reading frame of a gene, resulting in an altered translation product. While frameshift mutations can be beneficial to an organism – conferring resistance to HIV [47], for instance – the translated protein is often incomplete and/or non-functional; accordingly, such mutations are often implicated in a variety of common diseases, including hypercholesterolemia [48] and cancer [49,50]. Indeed, the tumour suppressor protein p53 is known to have a high affinity for bulges [51], as does the MutS DNA mismatch repair protein [52].

While DNA bulges are most often considered an unwanted aberration of the duplex DNA structure, there is some evidence of their involvement in regulatory processes by serving as recognition points for DNA-binding proteins [53–55]. It is conceivable that

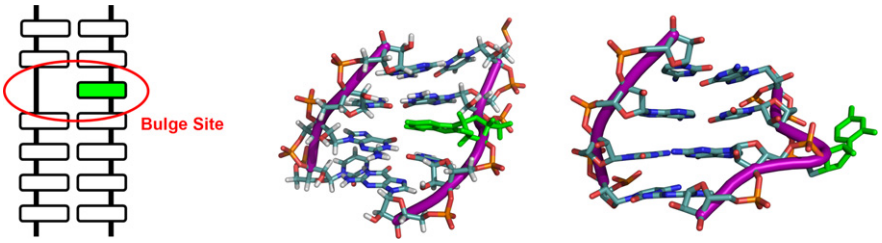

Fig. 2. Three representations of a single-base bulge site with the unpaired base depicted in black (green in the Web version). Left-to-right: schematic of a single-base bulge; render of PDB NMR structure **1rht** [36], a bacterial coat protein RNA binding site, featuring an *intrahelical* unpaired adenine; and a render of PDB crystal structure **1dqh** [37], a section of 5S rRNA, featuring an *extrahelical* unpaired cytosine. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

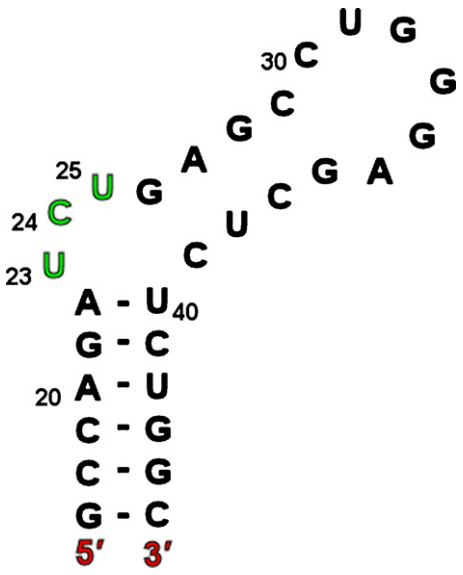

Fig. 3. The sequence of the Tat binding site of HIV-1 TAR RNA illustrating the stem loop/bulge secondary structure of the nucleic acid. The unpaired bulge nucleotides are numbered 23–25 (depicted in green in the Web version). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

the transient occurrence of unpaired nucleotides in DNA may serve as a common source of flexibility and subsequent protein-binding specificity.

In contrast to DNA, bulges are commonplace in RNA secondary structures as potential protein recognition sites [56,57]. Unpaired nucleotides may fulfil this role by either acting as direct contact points with RNA-binding proteins, or in an indirect manner by facilitating distortion of the RNA backbone. As the standard A-form of duplex RNA possesses a deep but narrow major groove, the information contained therein is largely unavailable to RNA-binding proteins [58]. Thus, distortions to the RNA backbone induced by bulge sites may potentially widen the information-rich major groove, allowing direct read-out of base sequence by a protein. Generally speaking, RNA-binding proteins have a tendency to target imperfections in the double helix [59], whereas in DNA the major groove is readily accessible and DNA-binding proteins are often *sequence* (primary structure)-specific.

Perhaps the best characterised of all the biologically relevant RNA bulges is that belonging to the *trans*-activation response (TAR) element of human immunodeficiency virus-1 (HIV-1) messenger RNAs (mRNAs). The TAR element is a 59-nucleotide stretch of RNA in a stem-loop structure near the 5′ end of HIV-1 transcripts (see Fig. 3) [60–63]. TAR serves as the binding site of the Tat protein, with the TAR-Tat complex greatly enhancing viral transcription [64–66]. Tat specifically targets the site of a three-base bulge (either UCU or UUU) on the stem of the TAR element, most likely due to the increased flexibility and more open major groove in this region [43,58,63,67–72]: in fact, numerous studies of TAR derivatives and mutants featuring systematic changes to the TAR sequence have demonstrated that the three-base bulge is necessary for optimal function of the TAR-Tat complex [60,69,73,74].

While the TAR bulge has received the most attention, it is certainly not the only documented RNA bulge of biological significance. A number of bacteriophage coat proteins have been found to target hairpin loop structures (see below) featuring a single bulge in the stem [75–78]. While there is some leniency in the identity of the bulged nucleotide – it need only be a pyrimidine – the bulge itself plays an essential role in the regulation of the viral replicase. In the free RNAs the unpaired nucleotides are believed to stack within the helix [36] (thus influencing helical structure and facilitating protein binding), whereas in at least one example the protein-bound bulge is found to loop out of the helix and bind in a hydrophobic pocket on the surface of the coat protein [78].

Bulges are also a common feature of ribosomal RNA. 5S rRNA possesses a ribosomal protein-binding site containing a single-base bulge that is highly evolutionary conserved, with the identity of the unpaired nucleotide varying between major phylogenetic divisions (A for aerobic bacteria, dinoflagellates and yeast; C for animals; U for plants, cyanobacteria, halophilic bacteria and anaerobic bacteria) [79].

Stabilisation of tertiary RNA structures is another important role of bulged bases as the function of several classes of RNA are very much dependent on their three-dimensional topology. One good example of this is the structure of the splice site of archaeal pre-tRNA (transfer RNA) endonuclease – a bulge-helix-bulge configuration, with the pre-tRNA being cleaved at two 3-nucleotide bulges that invoke a Z-like 3D structure in the molecule [80].

2.3.2. Internal loops

Internal loops differ from bulges in that the Watson–Crick base-pairing of a duplex polynucleotide is interrupted on *both* strands [57,81]. Such loops can be described as being symmetric (in which the same number of non-complementary bases occur on each strand), or asymmetric (differing numbers of non-complementary bases on each strand). Although relatively uncommon in DNA, RNA internal loops are stabilised by a myriad of different non-canonical base pairings between the two strands [82] and, as with bulges, they introduce a site of local flexibility [83].

There are numerous cases of internal loops serving as recognition sites for RNA-binding proteins, the best example of which is perhaps the HIV Rev-responsive element (RRE) RNA. The HIV-regulatory protein Rev binds with high affinity to the RRE viral transcript, with specific recognition of an internal loop [84,85]. In other well-characterised systems, the flexibility and proximity of such loops have led to speculation that they may allow RNA to bend and permit direct protein–protein interactions at adjacent binding sites [86,87].

2.3.3. Hairpin loops

Hairpin loops are deviations from the canonical duplex DNA or RNA structure that arise when a polynucleotide chain possessing self-complementarity loops back on itself to form a duplex stem terminating in a loop of unpaired bases (see Fig. 4). This “stem-loop” structure, as it is often called, is stabilised by base pairing (both canonical and non-canonical) within the stem. In DNA the stem typically assumes a B-type conformation, whereas in RNA it is typically of the A-form.

The stability of hairpin structures is governed primarily by the length and sequence of the loop rather than the sequence of the stem [89,90]. Loop length has been attributed a greater significance than loop sequence, with *in vitro* experiments suggesting an optimal loop length of 4–5 nucleotides in DNA and 6–7 nucleotides in RNA [89–92]. *In vivo*, tetraloops appear to be the most common, particularly in (ribosomal) RNA [93].

As with bulges, loops are typically considered “imperfections” to duplex DNA but are essential to the higher structure and functionality of RNA. In DNA they are commonly associated with the biophysical mechanism believed to be causative in a number of neurodegenerative diseases. Disorders such as Huntington’s disease [94–96], myotonic dystrophy [97,98], and fragile X syndrome [99,100] are all attributed to instabilities in trinucleotide repeat regions of particular genes [101,102]. Repetitive DNA sequences such as these are both abundant in the genome and highly polymorphic – expansions of such regions via many-fold duplication of the trinucleotide repeat are common during replication, repair and recombination events [103–105].

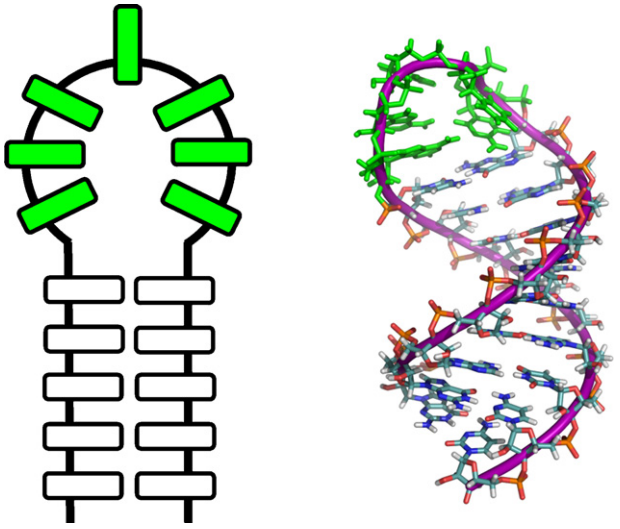

Fig. 4. Schematic representation of a hairpin loop and the NMR structure of a conserved rRNA 5-base loop (PDB identifier **15ki**) [88]. Unpaired bases are depicted in black (green in the Web version). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

One of the more accepted mechanisms explaining expansion phenomena is that of *polymerase slippage* in which DNA polymerase slips backwards along the template DNA strand during replication, resulting in the duplication of an integral number of trinucleotide repeats [106–113]. While long-range slippage events are energetically unfavourable due to the breaking of multiple hydrogen bonds, the energy difference between duplex and slipped DNA structures can be ameliorated by the formation of mediating, transient hairpin loops [96,103,114–116]. A variety of non-duplex structures have been postulated as having a role in the expansion of repeat sequences, however many experiments have demonstrated the propensity of trinucleotide repeat sequences to form stem-loop structures *in vitro* and *in vivo*, with the stability of these structures being dependent upon both their length and sequence [96,117–121]. Furthermore, the trinucleotide sequences most commonly associated with expansion-related disorders – CNG repeats (where N is any nucleotide) – have been shown to be more elusive to DNA repair mechanisms than sequences less proficient at giving rise to expansion [122].

While the *disadvantageous* nature of DNA hairpin loops has received the most attention, there nevertheless exists a number of instances in which DNA hairpins have been attributed regulatory roles in genome expression through either hairpin-induced conformational changes to the DNA or direct protein contact [89,123]. In one particularly interesting example of hairpin-mediated gene regulation, the proenkephalin gene – involved in pain regulation – possesses a sequence that has been found to switch between two different conformations, thus providing two distinct factor binding sites [124]. The palindromic nature of the sequence facilitates switching between a linear duplex and a cruciform structure (two hairpins opposite each other on antiparallel DNA strands, giving rise to a four-way junction), each of which provides a unique binding site essential for correct transcription of the gene.

Cruciforms are believed to commonly form from supercoiled DNA: the extrusion of the cruciform structure lowers the superhelical free energy of the system [123,125–127]. While supercoiling is itself linked to gene regulation [128–130], hairpin and cruciform structures extruded from supercoiled DNA are believed to often serve as protein recognition sites [131–133].

RNA hairpin loops are ubiquitous; 16S rRNA, for example, has some 70% of its length folded into 31 stem-loop structures [89]. Like bulges, hairpin loops are integral to the structure and function of the various types of RNA, providing stabilising tertiary contacts and nucleation sites for RNA folding, as well as distinct protein recognition sites.

Perhaps the most prominent occurrence of RNA hairpin loops takes place in the characteristic cloverleaf structure of tRNAs. The archetypical tRNA structure comprises three stem-loop structures, as well as an acceptor stem and a variable bulge/loop, each of which plays a significant role in the tertiary structure and function of the biomolecule [134–136]. The TAR and RRE HIV mRNAs mentioned earlier also feature stable hairpin loop structures that are involved in binding-site recognition by the Tat and Rev proteins, respectively. Mutational studies conducted with HIV-1 TAR have demonstrated that the sequence of bases in the loop is relatively unimportant in comparison to certain stem and bulge sequences; however the overall hairpin structure is still necessary for efficient protein binding [60,137,138]. Stem-loops structures also appear to be quite common in the untranslated regions (i.e. the ends) of mRNAs where they are believed to be crucial to modulating the longevity of transcripts [139–145].

2.3.4. Multiplexes

Certain nucleic acid sequences are able, if not prone, to form complexes of more than two strands, blurring the line between secondary and tertiary structure. Triple helices are typically comprised of a purine·pyrimidine Watson–Crick base-paired duplex with a third strand binding via a Hoogsteen bonding scheme in the major groove [146]. T•A*T triplexes are those most commonly described, however a number of triple-helical configurations have been theorised and observed. While early crystal and NMR structures implied a somewhat A-like helical form for such a structure [147,148], more recent investigations are suggestive of a B-type conformation [149,150]. Intramolecular triplexes, wherein a single strand folds back on itself, are particularly stable. A likely *in vivo* occurrence of triple helical structures is in the DNA structures known as H-DNA, an arrangement featuring a stretch of double-helical DNA in which the extremities of one strand loops back around to associate in the major groove of the duplex to form a triple helix. The formation of such structures has been associated with negative supercoiling or low pH of the appropriate repeat sequences [151–153]. While relatively little is known about the biological implications of naturally occurring triple helices, synthetic triplex-forming strands show promising application as diagnostic and therapeutic agents possessing sequence selectivity for relatively large polynucleotide strands [154–159]. Upon binding, the third strand may be utilised as a means of modulating gene expression or, properly functionalised, a sequence-specific cleavage agent.

The other commonly studied, biologically significant multi-stranded nucleic acid configuration is the quadruplex. Such structures are usually associated with guanine-rich sequences which have been found to aggregate together when properly stabilised by cations. In doing so, a structure forms in which groups of four guanines are able to hydrogen bond to one another in an arrangement known as a G-tetrad. The end result is a four-stranded structure that can be configured in a number of different ways: an intermolecular arrangement with four separate polynucleotide chains bonding together, a single strand folded back on itself several times, or the intermediate case in which two individual strands are folded into adjacent hairpin structures which subsequently bond with each other [160,161]. Many different quadruplex structures have been characterised via crystallographic and NMR techniques, with factors such as strand length and sequence, as well as the size of the stabilising counterions, dictating the ultimate configuration [162–166]. While typically composed primarily of guanine residues, other bases can be incorporated into the structure.

Most interest in the *in vivo* role of quadruplex DNA relates to its formation in telomeres, the guanine-rich repeat sequences

(TTAGGG in humans), several thousand bases long, that occur on the 3′-end of eukaryotic chromosomes where they essentially serve as a disposable buffer [167–169]. One strand of the telomere has an unpaired overhang several hundred bases long which has the potential to fold back into quadruplex configurations. During replication, DNA polymerase is unable to read to the very end of the chromosome; without a buffer, each successive cell division would result in the loss of information from the end of the chromosome. Instead, the telomeric DNA in somatic cells shrinks with every replication, ultimately leading to apoptosis when the telomere reaches a minimum length. As such, telomeres are likened to a "biological clock", limiting the number of times cells can proliferate, and they have consequently been linked to aging. This process is counteracted by a reverse-transcriptase enzyme known as telomerase that elongates the 3′-end of telomeric DNA [170]. Ordinarily, somatic cells are free of telomerase activity, however the majority of tumour cells do exhibit such activity which bolsters the replicative longevity of these cell lines, effectively imparting upon them "immortality". Quadruplex DNA, however, has been proven to impede telomerase activity [171], making the design of quadruplex-inducing/stabilising ligands a growing field of investigation in the fight against cancer [172–174]. Furthermore, with guanine being especially susceptible to UV light-induced damage [175], the G-rich telomeres may potentially serve as sacrificial photo-oxidation targets, protecting other regions within the chromosome. Putative quadruplex-forming sequences are prevalent throughout the human genome [176,177], many of which are associated with the promoter regions of an ever-increasing list of genes, including a number of proto-oncogenes, suggesting a regulatory role for such structures and a potential target for selective anti-cancer agents [178–182].

2.3.5. Junctions

Branched nucleic acid species, or junctions, are a common feature in the more convoluted landscape of higher-order RNA structures [57,183]. They arise as an inevitable consequence of the multiple arms ever present in tRNAs and rRNAs, and play an important role in the global folding of RNA structures as well as protein recognition and enzymatic processes. However, like so many of the more complex structural elements of nucleic acids, junctions typically occur as transient features in DNA [184]. The formation of cruciforms, as described earlier, gives rise to four-way junctions where the stem-loop structures extrude from the main duplex [185]. The process of homologous recombination, the exchanging of genetic material between chromosomes, also requires an intermediate four-way construct known as a Holliday Junction. When the DNA from two duplexes crosses over, the four strands arrange themselves into four anti-parallel base-paired arms, adopting a stacked X-like structure [186–188]. Migration of the branches and subsequent enzymatic resolution (cleavage) of the strands ultimately yields two recombinant helices [189,190]. Somewhat more complex junctions have been found in crystal structures of "DNA enzymes," which as the name suggests are DNA sequences that exhibit enzymatic capabilities [191].

2.3.6. Tertiary structures

With respect to nucleic acids, "tertiary structure" is typically reserved for reference to the overall three-dimensional configurations of RNAs. DNA structure at this level has received little in-depth attention. Tertiary structures are generally described in terms of interactions between secondary structural elements. Such motifs include kissing hairpins, wherein the unpaired bases of one hairpin loop pair up with those of another; pseudoknots, consisting of two stem-loop structures in which the loop of the first forms part of the stem of the second; and myriad loop–loop, bulge–loop, and bulge–bulge interactions (see Fig. 5 for an example) [81,134,183,192]. These intramolecular interactions ultimately define the global folding and structure of an RNA, and by extension, contribute to the functionality of the molecule. While the tertiary architecture of some RNAs (tRNA [134] and the hammerhead ribozyme [193,194], for instance) are fairly well established, a firm understanding of structure and its recognition at this level remains elusive.

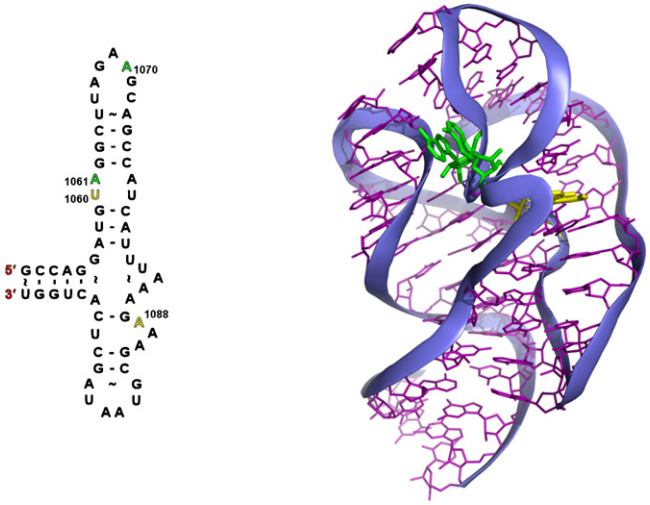

Fig. 5. Sequence and crystal structure (PDB identifier **1qa6**) [195] of a section of bulge-stabilised 23S rRNA. In the schematic representation of the rRNA (left) Watson–Crick base-pairs are indicated by a '—' while non-Watson–Crick base-pairs are indicated by a '~'. Several bulges/internal loops, hairpin loops, and a three-way junction are evident. In the crystal structure (right) the long-range stacking interaction between the A1061 and A1070 unpaired nucleotides (green) can be seen, as can the long-range *trans*-Hoogsteen base-pair between the bulged U1060 and A1088 nucleotides (yellow). Solvent molecules, counterions, and the bound L11 protein have been removed from the crystal structure for clarity.

3. Modes of nucleic acid binding

Given the biological importance of non-duplex nucleic acid structures, there is now considerable interest in developing small molecules that recognise these structural features. Compounds that can selectively recognise a non-duplex structure involved in the control of gene expression have considerable potential as chemotherapeutic agents for a variety of diseases. Metal complexes can interact with non-duplex structures through the same mechanisms as duplex DNA and RNA, i.e. covalent binding, intercalation and groove binding.

3.1. Covalent binding

Although the covalent binding of metal complexes with nucleic acids is generally kinetically controlled, the rate and site of metallation can be significantly modulated by the initial reversible non-covalent binding (pre-association) of the metal complex with the nucleic acid. As DNA and RNA are polyanions, the pre-association is particularly significant if the metal complex, or the reactive form of the metal complex, is cationic. The well-known and effective anti-cancer agent cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, is cytotoxic because of its ability to covalently bind DNA. Although cisplatin is neutral, it has been clearly established that it aquates inside the cell to its reactive cationic form, *cis*-$[PtCl(NH_3)_2(H_2O)]^+$. Sykfont et al. have demonstrated that the rate of reaction for *cis*-$[PtCl(NH_3)(c\text{-}C_6H_{11}NH_2)(H_2O)]^+$ ($c\text{-}C_6H_{11}NH_2$ = cyclohexylamine) with the single guanine in $d(T_nGT_{16-n})$ is at a maximum when the guanine is positioned in the middle of the oligonucleotide, but decreased as the guanine was positioned towards either the 5′- or

3′-termini [196]. This result demonstrated that the local concentration of pre-associated cationic complex influences the rate of covalent binding for the metal complex. Further studies have subsequently examined the effect of DNA and RNA secondary structure on the rate and site of platination by cisplatin and its analogues [197–200]. For example, Garnier and Bombard found that the reaction of *cis*-$[PtCl(NH_3)_2(H_2O)]^+$ with a DNA quadruplex was favoured over that of a duplex containing a GG binding site [200], while Papsai et al. reported that cisplatin reacted preferentially at a wobble base-pair region of a tRNA [199]. These studies provide hope that covalent binding metal complexes can be designed that will preferentially react with specific structural sites on both DNA and RNA, and thereby become more powerful therapeutic agents.

Although photo-induced covalent linking of polyazaaromatic ruthenium(II) complexes to guanine residues is not specific for DNA sites or sequences, Kirsch-De Mesmaeker and co-workers have outlined how this type of covalent binding could be used to target specific genes [201]. They proposed that if a synthetic oligonucleotide – derivatised with a photo-oxidising and photoreactive ruthenium(II) complex – is hybridised to a target gene through complementary base-pairing, irradiation would result in a covalent bond with a guanine residue in the gene sequence.

The multinuclear platinum complexes developed by Farrell and co-workers that contain two or three platinum coordination centres linked by aliphatic amine chains have shown excellent potential as anti-cancer agents [202]. These highly charged (+2 to +4) platinum complexes covalently bind two guanine residues similarly to cisplatin, but instead of forming the short-range 1,2-intrastrand adducts observed for cisplatin, they form long-range intra- and interstrand cross-links. Hegmans et al. demonstrated that the pre-association of the trinuclear complex BBR3464 in the DNA minor groove affected the kinetics and the structure of the final covalent adduct formed with N7 of the two guanines of the self-complementary duplex 5′-$d(ATATGTACATAT)_2$, located in the major groove [203]. While this study demonstrates the potential of the pre-association of the metal complex to influence the site of covalent binding on DNA, to our knowledge no studies on the binding of multinuclear platinum complexes to non-duplex DNA structures have been reported. It is tempting to speculate that by manipulation of the various components – e.g. replacement of ammine groups with bulky amine groups – these powerful anti-cancer agents could become selective for various non-duplex DNA structures, and hence be tailored for specific cancers.

3.2. Intercalation

Since the initial reports by Lippard and co-workers on the interaction with DNA of inert platinum complexes containing aromatic ligands that are coplanar with the metal coordination sites, there has been enormous interest in metallointercalators [204]. Metallointercalators bind DNA through the insertion of a planar polycyclic aromatic ligand into the π-stack between two base pairs [205]. Simple square-planar complexes such as $[Pt(en)(phen)]^{2+}$ (en = ethylenediamine; phen = 1,10-phenanthroline) show some specificity towards G·C base-pairs, but little reported preference for any non-standard DNA duplex structures. However, ruthenium(II) and rhodium(III) complexes containing similar ligands, but with octahedral geometry, do show significant structure selectivity in their DNA-binding [206–208].

At the most basic level, it was originally proposed that the Δ-enantiomer of $[Ru(DIP)_3]^{2+}$ (DIP = 4,7-diphenyl-1,10-phenanthroline) selectively binds right-handed B-DNA, while the Λ enantiomer only binds left-handed Z-DNA [205,209]. More recently, a study by Kim et al. demonstrated that the ruthenium(II) complex did not show any significant enantioselectivity in its interaction with DNA, nor did it bind by intercalation [210]. However, it has been generally shown that the Δ enantiomer binds B-DNA more strongly than the corresponding Λ enantiomer for intercalating ruthenium and rhodium complexes. This selectivity is due to the unfavourable steric interactions between the ancillary (non-intercalating) ligands of the Λ isomer with the sugar-phosphate backbone of DNA, whereas the Δ enantiomer fits easily within the right-handed helical groove [205].

At the next level of structure recognition, it has been demonstrated that inert ruthenium(II) complexes can intercalate from either the major or minor groove dependant upon the structure of the ligand that actually intercalates into the stacked bases of DNA. Proudfoot et al. studied the DNA binding of a series of ruthenium(II) complexes based upon $[Ru(R,R\text{-picchxn}Me_2)(\text{bidentate})]^{2+}$, where picchxn = *N*,*N*′-dimethyl-*N*,*N*′-di(2-picolyl)-1,2-diaminocyclohexane and the bidentate ligands = phen, dpq (dipyrido-[3,2-*f*:2′,3′-*h*]quinoxaline) and phi (9,10-phenanthrenequinone diimine) [211]. The results demonstrated that the dpq ligand, whose long axis is perpendicular to the long axis of the base-pairs, favoured intercalation from the minor groove, whereas, the phi ligand (whose long axis is parallel to the long axis of the base-pairs) intercalates from the major groove. Although the unusual ancillary ligand picchxn was used in these studies, the results were in agreement with those previously reported for the dpq and phi ligands where more "standard" ancillary ligands (such as phen) were used [205,212].

Metallo-porphyrins are another class of metal complexes that has been utilised as DNA binding agents. Tetradentate nickel(II) and copper(II) porphyrin complexes typically bind GC regions of DNA by intercalation, but associate in the grooves in AT regions [213,214]. However, Bejune et al. have demonstrated that zinc(II) complexes of relatively non-bulky porphyrins bind strictly by intercalation [215]. In another study Bejune and McMillin used hairpin sequences to study the DNA binding of a zinc(II) porphyrin complex, and interestingly found that the composition of the 4-base loop strongly affected the metal complex binding in the duplex region [216].

Dinuclear metal complexes that can simultaneously insert one ligand from each metal centre into the stacked bases of DNA (bis-intercalation) have been synthesised in an attempt to develop compounds with high DNA binding affinity and slow dissociation rates [217–220]. The DNA binding ability of these bis-intercalating complexes is controlled by the nature of the intercalating and linking ligands. For example, the dinuclear ruthenium complex $[\{Ru(phen)_2\}_2\{\mu\text{-C4(cpdppz)}_2\}]^{4+}$ {where C4(cpdppz)$_2$ = *N*,*N*′-bis(12-cyano-12,13-dihydro-11H-8-cyclopenta[*b*]dipyrido[3,2-*h*:2′,3′-*j*]phenazine-12-carbonyl)-1,4-diaminobutane} binds DNA very strongly, with a binding constant $>10^8\ M^{-1}$ [218]. More interestingly, the enantiomers were found to have markedly different rates of dissociation from DNA, with the authors concluding that the bis-intercalative binding mode introduces topological constraints on the rates of association and dissociation. It is highly likely that by linking mono-intercalating complexes that exhibit sequence or structure selectivity, new bis-intercalating complexes will be obtained that are selective for larger segments of DNA.

3.2.1. Selectivity of intercalating complexes for non-duplex structures

Examples of metallointercalators exhibiting significant preference for non-standard DNA or RNA duplex sequences have also been reported. For example, Lim and Barton reported that the complex $[Rh(phen)_2(phi)]^{3+}$ acts as a shape-selective probe for triple helices, particularly with RNA [221]. The rhodium complex was found to target and cleave RNA triplexes, but showed no cleavage with A-form RNA duplex structures. Furthermore, different cleavage patterns were noted for pyr•pur*pyr and pur•pur*pyr triplexes. Choi et al. demonstrated that ruthenium complexes, such as $[Ru(phen)_2(dppz)]^{2+}$ (dppz = dipyrido[3,2-*a*:2′,3′-*c*]phenazine)

bound DNA duplex or poly(dT*dA•dT) triplex structures in a similar intercalative fashion [222]. The results also showed that the degree of the stabilisation of the third-strand was dependent upon the nature of the intercalating ligand, with dppz > bdppz > phen (bdppz = benzodipyrido[3,2-*a*:2′,3′-*c*]phenazine).

Over the last few years, the Barton laboratory has introduced another type of intercalating agent – the metalloinsertor. Metalloinsertors contain planar polycyclic aromatic ligands that can be inserted into the π-stack; however, unlike metallointercalators which unwind the nucleic acid, the metalloinsertors displace the bases of a base-pair out of the π-stack [205]. Metalloinsertors, such as Δ-[Rh(bpy)$_2$(chrysi)]$^{3+}$ (chrysi = chrysene-5,6-quinone diimine) show a strong preference for DNA mismatch sequences and abasic and single bulge sites [205,223–225].

3.3. Groove binding

Although there has been considerable recent interest in utilising groove binding transition metal complexes as sequence- and structure-selective binding agents for nucleic acids, the Sigman group demonstrated almost 30 years ago that [Cu(phen)$_2$]$^+$ reversibly bound in the minor groove and could cleave the DNA [226]. Since the early work with the copper complex, it has been established that most mononuclear inert metal complexes associate in the DNA minor groove and show a preference for AT-rich sequences. For example, Liang et al. reported that square planar peptide complexes of Ni(II) associated in the minor groove at A/T rich sites [227], as did Franklin et al. for [Pt(en)$_2$]$^{2+}$ [228]. It has also been shown that non-intercalating octahedral complexes, such as [Ru(bpy)$_3$]$^{2+}$ (bpy = 2,2′-bipyridine) also bind in the minor groove at A/T rich sites. It has been proposed that the binding preference is due to the more favourable van der Waals and electrostatic interactions, coupled with potential hydrogen-bonding groups, obtained in the narrow minor groove at A/T rich regions.

Although most mononuclear inert transition metal complexes bind in the DNA minor groove, cobalt(III) am(m)ine complexes, e.g. [Co(NH$_3$)$_6$]$^{3+}$ and [Co(en)$_3$]$^{3+}$, have been shown to bind at GG sequences in the major groove, and can induce a conformational transition towards A-type DNA [229–231]. The major groove binding of the cobalt(III) complexes was proposed to be due to the greater negative electrostatic potential found at GG and GGG sequences, coupled with specific hydrogen bonds to either or both N7 and O6 groups of guanine. Metal complex binding can also induce a B to Z-type DNA conformational change in poly d(GC) nucleic acid [232,233]. For example, Rodger and co-workers have examined the conformational change induced by [Co(NH$_3$)$_6$]$^{3+}$ and [Co(en)$_3$]$^{3+}$ [232], while Spingler and Antoni found that a polypyrazoyl dinuclear nickel complex could also efficiently induce a B to Z-type DNA transition [233]. However, while the cobalt complexes reversibly associate in the major groove, it was proposed that the conformation change for the nickel complex was due to co-ordination to the N7 of guanine.

3.4. Non-duplex DNA

Bulky dinuclear inert ruthenium(II) complexes are ideal probes for non-duplex DNA. NMR experiments showed that the stereoisomers of [{Ru(Me$_2$bpy)$_2$}$_2$(μ-bpm)]$^{4+}$ {bpm = 2,2′-bipyrimidine; Me$_2$bpy = 4,4′-dimethyl-2,2′-bipyridine} – the structure of the *meso* form is represented in Fig. 6 – bound duplex DNA weakly ($K \approx 10^3$ M^{-1}) in the minor groove, despite the relative dimensions of the metal complex and the DNA groove [234]. The ruthenium complex is approximately 16 Å long and 8.0 Å wide, while for canonical form B-type DNA the width of the major and minor grooves are 11.6 Å and 6.0 Å, respectively. Of note, the stereoisomers of [{Ru(Me$_2$bpy)$_2$}$_2$(μ-bpm)]$^{4+}$ bound d(CAATCCGGATTG)$_2$ at the central CCGG sequence and at the CA/GT terminal residues, rather than at the expected A/T rich regions [234]. It was postulated that the relatively bulky ruthenium complex could not be easily accommodated at the particularly narrow minor groove found at A/T rich sites, but binds at the central CCGG site where the minor groove is more open. This finding, coupled with the reported preference of [{Ru(phen)$_2$}$_2$(μ-HAT)]$^{4+}$ {HAT = 1,4,5,8,9,12-hexaazatriphenylene} for partially denatured DNA [235], suggested that bulky dinuclear ruthenium complexes would selectively bind DNA secondary structures that contain a more open or flexible groove than duplex DNA [236].

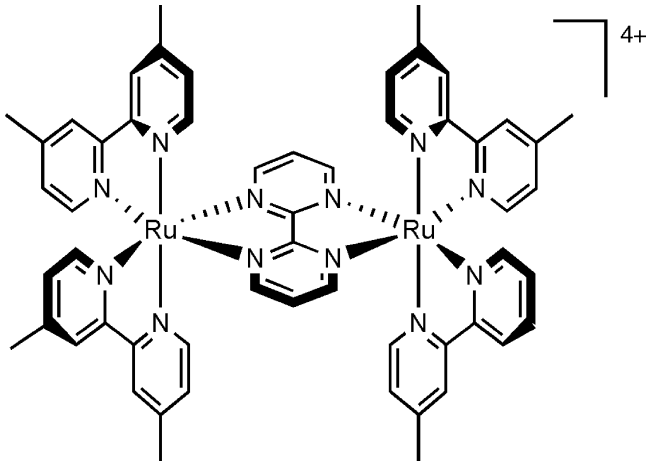

Fig. 6. The structure of *meso*(ΛΔ)-[{Ru(Me$_2$bpy)$_2$}$_2$(μ-bpm)]$^{4+}$ {bpm = 2,2′-bipyrimidine; Me$_2$bpy = 4,4′-dimethyl-2,2′-bipyridine}.

Dinuclear complexes offer considerable advantages compared with corresponding mononuclear complexes as probes for structural recognition of DNA. Mononuclear metal complexes are limited by their relatively small size, at best spanning only 4–6 base-pairs; typically they only have a footprint of two bases [237]. To approach the selectivity of nucleic acid-binding proteins, larger species such as di-, tri- and oligonuclear metal complexes are required. Dinuclear complexes have a greater stereochemical diversity than their mononuclear analogues, as the presence of two metal centres amplifies any possible chiral discrimination effects allowing them to more effectively probe the shape- and structure-recognition characteristics of nucleic acids than their mononuclear counterparts. Finally, dinuclear complexes generally possess a larger cationic charge and a greater number of hydrophobic ligands than their corresponding mononuclear complex, and hence should bind DNA with greater affinity. This last point was clearly demonstrated by Kelly and co-workers who compared the binding behaviour of the dinuclear complex [(bpy)$_2$Ru{μ-bb*n*}Ru(bpy)$_2$]$^{4+}$ (bb*n*: *n* = 5 {1,5-bis[4(4′-methyl-2,2′-bipyridyl)]pentane}; *n* = 7 {1,7-bis[4(4′-methyl-2,2′-bipyridyl)]heptane}) with its mononuclear analogues [Ru(bpy)$_3$]$^{2+}$ and [Ru(bpy)$_2$(Me$_2$bpy)]$^{2+}$ [238]. The results indicated that the dinuclear species bound with a much higher affinity and was more efficient at photosensitising DNA strand breaks than the mononuclear analogues.

3.4.1. Single-base DNA bulges

As bulky ruthenium complexes only bound DNA where the minor groove was relatively wide, it was proposed that they would preferentially bind DNA secondary structures that contain a more open or flexible groove than duplex DNA [236]. One such open DNA structure is a sequence that contains a so-called "bulge" – the inclusion of one or more bases on one strand that have no base(s) on the complementary strand with which to form a base-pair.

NMR experiments demonstrated that ΔΔ-[{Ru(Me$_2$bpy)$_2$}$_2$(μ-bpm)]$^{4+}$ bound the tridecanucleotide d(CCG**A**GAATTCCGG)$_2$ (where

the A in bold represents the adenine bulge) significantly more strongly than the corresponding control, non-bulged, oligonucleotide [236]. Simple binding models, consistent with the NOE data, showed that the adenine bulge site was intra-helical and base-stacked with the adjacent guanine residues. NOESY experiments indicated that the ruthenium complex bound specifically at the bulge site in the self-complementary tridecanucleotide, and that the DNA minor groove had significantly widened at the bulge site to accommodate the ruthenium complex. As the minor groove at the bulge site in the free tridecanucleotide was not significantly wider than canonical DNA, it was concluded that the bulge site introduces an increased flexibility into the local DNA structure that allows the specific metal complex binding [236].

The utility of these dinuclear ruthenium complexes as probes for bulge structures within DNA was confirmed by further experiments demonstrating total enantioselectivity in the binding of $[\{Ru(Me_2bpy)_2\}_2(\mu\text{-bpm})]^{4+}$ to the single bulge site [239]. Two-dimensional NMR spectra showed that the ΔΔ enantiomer bound strongly ($K > 10^5\ M^{-1}$) at the bulge site, whereas the ΛΛ enantiomer bound weakly to the central AT-rich region and the frayed ends of d(CCG**A**GAATTCCGG)$_2$. As might be expected, the *meso* isomer bound with intermediate selectivity and affinity. The ability of the non-symmetric dinuclear species $[\{Ru(Me_2bpy)_2\}(\mu\text{-bpm})\{Ru(bpy)_2\}]^{4+}$ to bind to the bulge sequence was also investigated [236]. The results demonstrated that the complex selectively bound at the bulge site with the $Ru(Me_2bpy)_2$ moiety projecting more deeply into the bulge site than the non-methylated end of the complex (see Fig. 7). This suggested that the hydrophobic interactions involved in secreting the Me_2bpy ligand away from the bulk aqueous solution are a significant factor in the thermodynamically favourable binding.

3.4.1.1. Effect of terminal ligands. Alterations in the identity of the terminal, non-bridging, ligands have also been investigated with respect to their effect on the affinity and selectivity on DNA bulge binding interactions [240]. Ruthenium complexes containing phen or Me_2phen {Me_2phen = 4,7-dimethyl-1,10-phenanthroline} terminal ligands were found to bind the single base bulge containing tridecanucleotide d(CCG**A**GAATTCCGG)$_2$ with the highest affinity. Interestingly, with the phen-based complexes, the *meso* isomer exhibited the strongest binding. It was postulated that the binding by the *meso* isomer requires less structural perturbation of the minor groove, compared to either of the ΔΔ or ΛΛ forms. This was in contrast to the binding by the corresponding bpy or Me_2bpy containing complexes with the same bridging ligand, where the ΔΔ isomer bound with greater affinity than the *meso* or ΛΛ isomers (as discussed above).

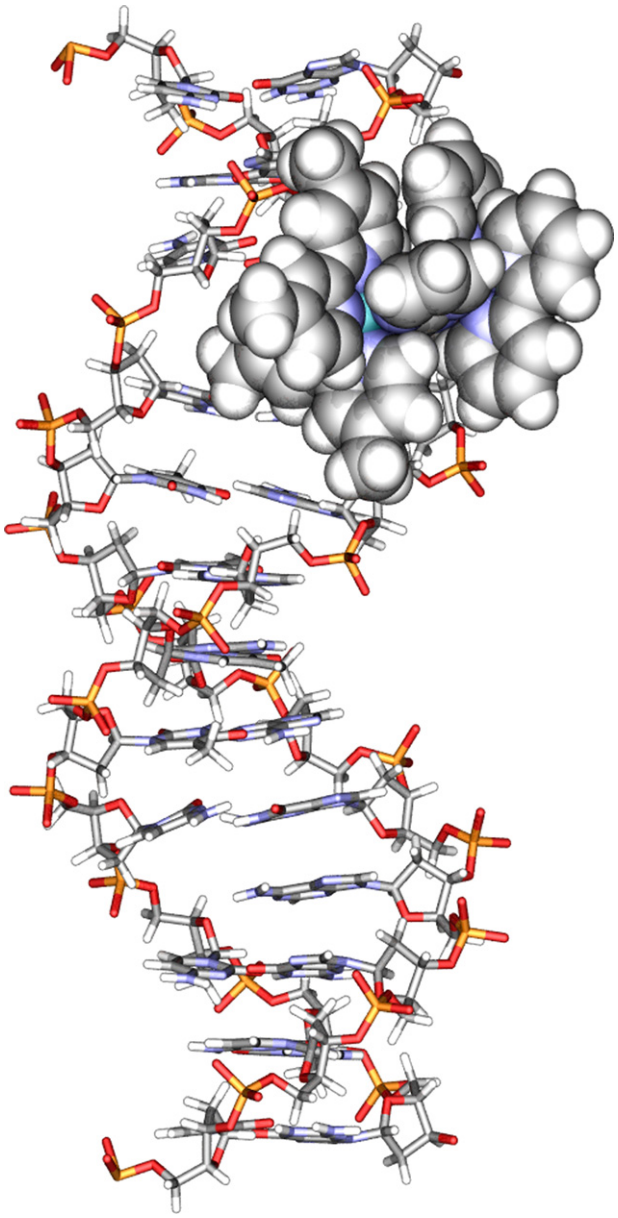

Fig. 7. Molecular model of ΔΔ-$[\{Ru(bpy)_2\}(\mu\text{-bpm})\{Ru(Me_2bpy)_2\}]^{4+}$ bound to d(CCG**A**GAATTCCGG)$_2$ at the single-base bulge site (**A**$_4$) [236]. The minor groove has widened at the binding site to accommodate the metal complex.

3.4.1.2. Effect of bridging ligand. While dinuclear ruthenium complexes that are bridged by rigid linking ligands, such as bpm, exhibit relatively strong binding to bulge structures, it is only possible for one metal centre to bind deeply within the minor groove. The rigid ruthenium complex cannot follow the curvature of the DNA groove, and hence the second metal centre must project out of the groove. It was proposed by Morgan et al. that dinuclear ruthenium complexes linked by a flexible chain would allow both metal centres to bind optimally in the minor groove [241].

Morgan et al. used a fluorescent dye-displacement assay to examine the binding of a series of metal complexes with bridging ligands that differed only in the length of their flexible methylene links (n = 2, 5, 7 and 10) to the bulge tridecanucleotide d(CCG**A**GAATTCCGG)$_2$ [241]. The bb7 bridged species, specifically the ΔΔ isomer, showed the strongest binding to the bulge containing tridecanucleotide. Furthermore, the affinity of the flexibly-linked complex ΔΔ-$[\{Ru(phen)_2\}_2(\mu\text{-bb7})]^{4+}$ for d(CCG**A**GAATTCCGG)$_2$ was found to be higher compared to complexes with rigid linking ligands. NMR investigations showed that one metal centre bound strongly at the bulge site while the other associated favourably but more loosely with the AT-rich region at the centre of the duplex. Molecular modelling indicated that the flexible linking ligand allowed the complex to follow the curvature of the DNA minor groove, as shown in Fig. 8.

The fact that the ΔΔ-$[\{Ru(phen)_2\}_2(\mu\text{-bb7})]^{4+}$ complex still selectively targeted the adenine bulge site suggests that mononuclear complexes would also do so. However, little selectivity has been observed for mononuclear complexes, probably because of a lack of general binding affinity. Consequently, flexibly-linked dinuclear complexes, like rigid complexes, will still exhibit selectivity for DNA bulge sites but they should be able to bind with higher affinity with one metal centre providing general binding affinity while the other ruthenium centre provides the site selectivity. It was speculated that flexibly-linked complexes could be of even greater value if both ruthenium centres exhibited site selectivity [241]. It is probable that complexes like ΔΔ-$[\{Ru(phen)_2\}_2(\mu\text{-bb7})]^{4+}$ could

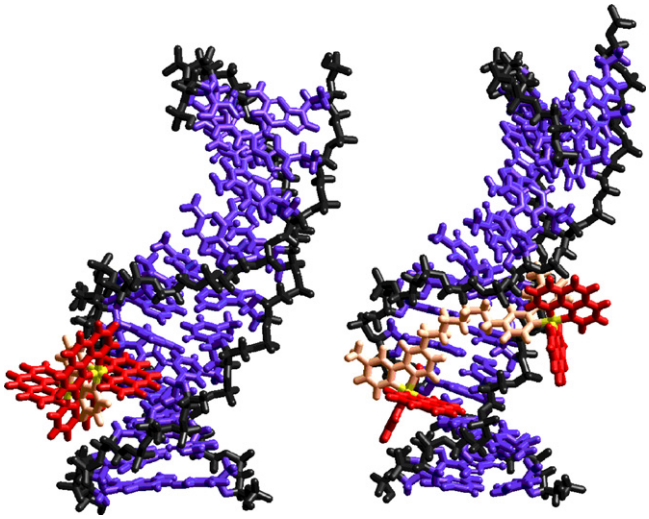

Fig. 8. Comparison of the binding of ΔΔ-[{Ru(phen)$_2$}$_2$(μ-bpm)]$^{4+}$ (left) and ΔΔ-[{Ru(phen)$_2$}$_2$(μ-bb7)]$^{4+}$ (right) to the adenine-bulged tridecanucleotide duplex [241]. The ability of the flexibly-linked complex ΔΔ-[{Ru(phen)$_2$}$_2$(μ-bb7)]$^{4+}$ to follow the curvature of the minor groove can be seen.

simultaneously bind two bulge sites that were separated by one or more paired bases with high affinity and selectivity. Such a model suggests that one could conceivably "fine-tune" the binding properties of flexibly-bridged species by selecting linker lengths that reflect the separation between two favourable bulge-binding sites in DNA. This could lead to a very high degree of selectivity for biologically important adjacent bulge sites.

3.4.2. Three-base DNA bulges

The binding of a range of dinuclear ruthenium complexes with a number of larger bulge sites was also investigated, with dppm-bridged complexes {dppm = 4,6-bis(2-pyridyl)pyrimidine} appearing to bind particularly well to 2- and 3-base bulge sites incorporated into duplex DNA [242]. Specifically, ΔΔ-[{Ru(phen)$_2$}$_2$(μ-dppm)]$^{4+}$ demonstrated a high affinity for the triple adenine bulge in the oligonucleotide d(GCATCG**AAA**GCTACG)•d(CGTAGCCGATGC). Selective broadening of bulge site minor-groove proton resonances and the confinement of all notable NOEs to this section of the oligonucleotide confirmed the bulge site as the preferred binding location. NMR titrations allowed the determination of a binding constant (4×10^5 M^{-1}) while molecular modelling showed the smaller helical twist of the oligonucleotide at the AAA bulge complemented the obtuse angle of the dppm bridge as it follows the minor groove (Fig. 9).

3.4.3. RNA bulges

Although the groove dimensions for RNA are not similar to that of B-type DNA, it has been shown that dinuclear ruthenium complexes also show selectivity for RNA bulge sites, compared to duplex RNA. RNA has a deep and very narrow major groove and a wide shallow minor groove, while DNA contains a wide major groove and a relatively narrow minor groove [10]. Spillane et al. studied the RNA binding of ΔΔ- and ΛΛ-[{Ru(Me$_2$bpy)$_2$}$_2$(μ-bpm)]$^{4+}$ with the RNA duplex r(CCGGAAUUCCGG)$_2$ and the corresponding bulge-containing r(CCG**A**GAAUUCCGG)$_2$ oligonucleotide [243]. In a similar fashion to what was observed with DNA, both enantiomers of the metal complex bound the bulge-free control sequence weakly ($K = 1 \times 10^3$ M^{-1}), but relatively strongly to the bulge-containing sequence. In NMR experiments, selective changes in chemical shift and the observation of intermolecular NOEs, indicated that the ruthenium complex selectively bound at the bulge site (Fig. 10). One noteworthy difference in the binding of [{Ru(Me$_2$bpy)$_2$}$_2$(μ-bpm)]$^{4+}$ with the RNA bulge-containing oligonucleotide, compared to the analogous DNA structure, was that no enantiomeric preference was exhibited with the RNA sequence [243]. Thus, while the selectivity of the metal complex for bulge sites is maintained with RNA, the observed enantioselectivity is negated when binding to an A-form RNA.

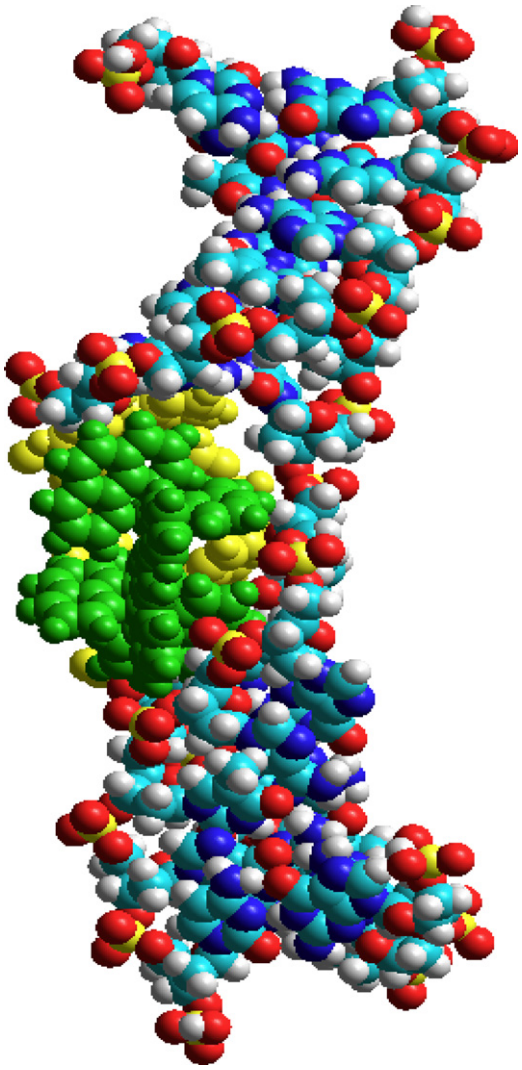

Fig. 9. An energy-minimised model of ΔΔ-[{Ru(phen)$_2$}$_2$(μ-dppm)]$^{4+}$ (black) bound at the bulge site of the A3-bulge oligonucleotide (the three adenine bulge bases are in yellow, while the dinuclear ruthenium complex is coloured green in the Web version) [242]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

More recently, Buck et al. demonstrated that ΔΔ-[{Ru(Me$_2$bpy)$_2$}$_2$(μ-bpm)]$^{4+}$ could also selectively bind a three-base RNA bulge site [244]. The ruthenium complex was found to bind the three-base bulge site of a modified TAR sequence of the HIV-1 virus. The TAR sequence, which contains two helical stem regions separated by a three-base bulge structure and capped by a six-base loop, is an important control point involved in the replication of the virus. In an earlier study [245], Neenhold and Rana utilised a rhodium complex [Rh(phen)$_2$(phi)]$^{3+}$ to examine the Tat protein binding at the RNA TAR site: the complex was previously developed by the Barton group [246] and does not bind duplex RNA but promotes cleavage when the RNA major groove is more open. The binding of the Tat protein at the TAR RNA site is an essential interaction for viral multiplication. The results showed that a bulge of two or more bases was required to sufficiently

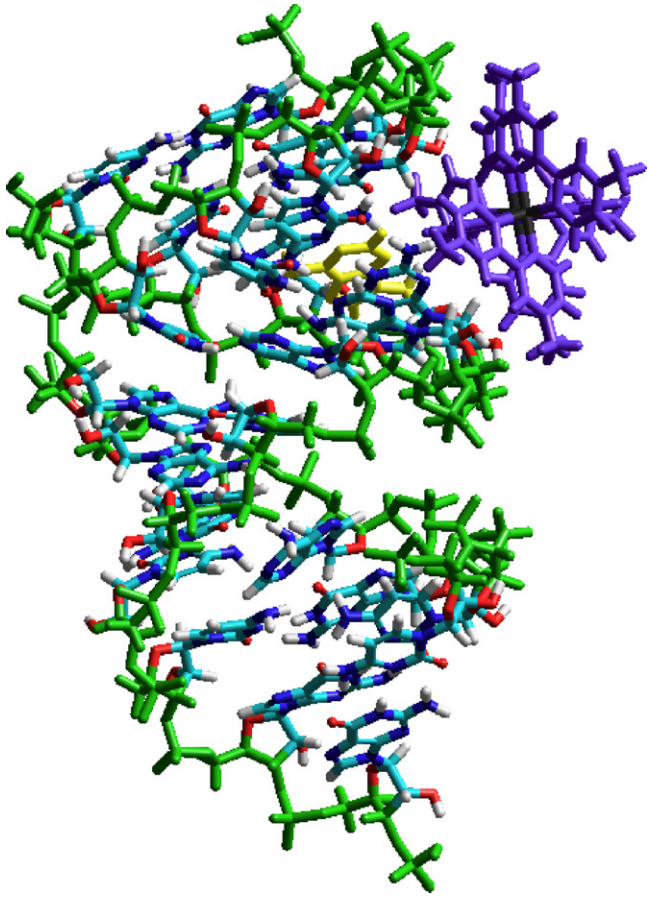

Fig. 10. The RNA tridecanucleotide duplex r(CCG**A**GAAUUCCGG)$_2$ with ΔΔ-[{Ru(Me$_2$bpy)$_2$}$_2$(μ-bpm)]$^{4+}$ bound, rendered using tubes and viewed looking down the minor groove at the binding site. The atoms of the RNA backbones are shown in green, the unpaired adenine base is yellow and the metal complex is purple [243].

widen the major groove to allow Tat binding and cleavage by the rhodium intercalator.

Tor and coworkers have shown that mononuclear complexes containing eilatin {eilatin = pyrido[2,3,4-*kl*]acridine; a bi-facial metal-chelating marine alkaloid} bind single-stranded RNA [247]. Furthermore, both Δ- and Λ-[Ru(bpy)$_2$(eilatin)]$^{2+}$ bind the HIV-1 virus RNA Rev responsive element (RRE) with high affinity and can displace the bound Rev protein. Since the RRE site contains bulge regions, it was postulated that the ruthenium complex binds at the internal bulge site of the RRE, which serves as the Rev binding site.

3.4.4. DNA hairpins

In a recent study, the DNA hairpin binding abilities of two series of dinuclear polypyridyl ruthenium(II) complexes were examined by fluorescent intercalator displacement assays and NMR spectroscopy [248]. From analysis of the binding affinity of the various ruthenium complexes, it was noted that a dinuclear complex with a HAT bridging ligand and phen or Me$_2$phen as terminal ligands, rather than bpy and Me$_2$bpy terminal ligands, gave the strongest binding with the hairpin structures. Furthermore, the *meso* diastereoisomer exhibited the greatest affinity for the hairpin structure, particularly in those complexes possessing phenanthroline ligands, compared to the corresponding ΔΔ and ΛΛ isomers. As previously noted, it was again proposed that the terminal ligands of a *meso* isomer are able to follow the contours of the minor groove, whereas the ΔΔ- and ΛΛ-enantiomeric forms of the complex encounter steric clashes at either end of the complex. The *meso*-[{Ru(phen)$_2$}$_2$(μ-HAT)]$^{4+}$ and *meso*-[{Ru(Me$_2$phen)$_2$}$_2$(μ-HAT)]$^{4+}$ complexes were shown to bind an icosanucleotide containing a 7-base-pair stem section and a 6-base loop region with greater affinity than a corresponding 4-base loop octadecanucleotide and three control duplex sequences.

The stronger binding by the complexes containing phen or Me$_2$phen terminal ligands suggested that metal complex binding is stabilised by van der Waals contacts with the walls of the minor groove, more favourable hydrophobic interactions, a semi-intercalative association with DNA bases – or a combination of all three. The stronger binding to the icosanucleotide hairpin structure by the Me$_2$phen-based complex, compared to the phen-based complex, is consistent with this proposal. Secretion of the hydrophobic methyl groups in the minor groove, and the subsequent displacement of solvent, was proposed as the driving force behind this greater binding ability of the methylated species [248]. While the *meso*-[{Ru(phen)$_2$}$_2$(μ-HAT)]$^{4+}$ complex exhibited lower affinity with the 6-base hairpin sequence than the corresponding Me$_2$phen-based complex, it did show greater selectivity in its binding compared to the control duplex structures (Fig. 11) [248].

Molecular models were constructed – informed by the NMR data – which showed that each ruthenium complex bound the icosanucleotide in the minor groove, with the HAT ligand positioned at the stem-loop interface with one set of terminal phenanthroline ligands projecting into the groove of the stem, and the other projecting into the loop region.

In a similar approach, Spillane et al. used a mononuclear ruthenium complex that contained a "long" and hydrophobic 4,4′-bis (benzothiazol-2-yl)-2,2′-bipyridine (bbtb) ligand as a hairpin-

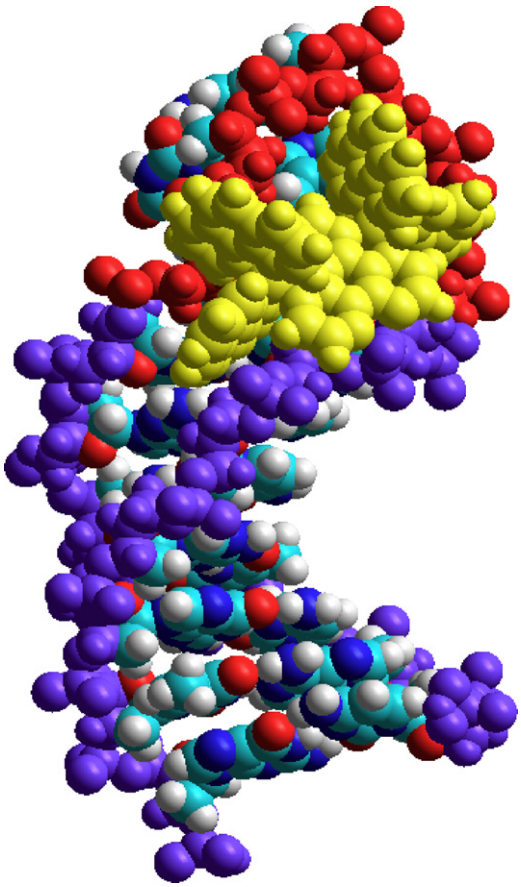

Fig. 11. Energy-minimised model of *meso*-[{Ru(phen)$_2$}$_2$(μ-HAT)]$^{4+}$ (black; yellow in the Web version) bound at the stem-loop interface of the hairpin icosanucleotide (the phosphate backbone of the duplex region of the complex is highlighted in purple, the loop region in red in the Web version) [248]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

binding agent [249]. Somewhat surprisingly, the Λ enantiomer bound the hairpin structure with a greater affinity than the Δ form. The metal centre of the Λ enantiomer was positioned at the stem-loop interface with the bbtb ligand projecting into the loop region. The duplex stem of the icosanucleotide remained intact upon binding of either of the Δ and Λ enantiomers. The Λ enantiomer bound better than the Δ form within the loop region of the icosanucleotide. In the Λ binding model, one of the benzothiazole arms appears to be deeply bound within the loop region, while the second arm lies adjacent to the sugar-phosphate backbone with one bpy ligand orientated along the groove; the other bpy ligand projects away from the icosanucleotide. For the bpy ligands of the Δ enantiomer, one lay perpendicular to the groove while the other orientated itself almost parallel to the groove.

3.4.5. Three-way junctions

Hannon and co-workers have developed a tetra-cationic dinuclear iron(II) supramolecular helicate that induces the formation of a three-way DNA junction [250,251]. The basis for the design of the helicate formed from three bis(pyridylimine) ligands and $FeCl_2$ was to synthesise structures that are similar in size to DNA binding domains of DNA-binding proteins – e.g. an α-helical recognition unit. The triple-stranded helicate, which is approximately 20 Å in length and 10 Å in diameter, is the correct size to bind in the DNA major groove (similarly to proteins) but too large to bind in the minor groove [252]. The helicate complex binds in the centre of the three-way junction formed by three duplex strands (a 1:3 helicate/ssDNA stoichiometry), where it is stabilised in a hydrophobic 3-fold symmetric environment. These studies represent the first example of regular palindromic duplex forming a three-way junction, with the recognition based on the size and shape of the molecular surface of the helicate matching that of the DNA binding site. Importantly, the ability of the helicate cation to induce the three-way junction was demonstrated in both the solid state and in solution.

Hannon and co-workers have synthesised and obtained enantiomerically pure ruthenium(II) helicates in addition to the iron(II) structures [253,254]. The dinuclear ruthenium triple-stranded helicates also bind in the DNA major groove inducing dramatic intramolecular coiling in natural DNA. Interestingly, these non-covalent binding ruthenium helicates have shown significant cyotoxicity against several cancer cell lines [253]. Dinuclear ruthenium(II) complexes containing only a single bis(pyridylimine) ligand and two bipyridyl units have been recently synthesised and shown to be significantly less cytotoxic than the corresponding helicate complexes [255]. These results not only may provide the design for a new class of anticancer agents, they also demonstrate the potential for bulky inert transition metal complexes to be extremely useful agents in molecular biology in general.

3.4.6. Quadruplexes

The guanine-rich quadruplex structures found at the 3′-termini of telomeric DNA have been proposed as potential new target sites for anti-cancer drugs [256–260], as approximately 90% of human cancer cells have elevated telomerase activity [261].

Several groups have utilised transition metal complexes to develop quadruplex-binding agents. Indeed, metal complexes are ideal as they full fill the basic requirements of a good quadruplex binding compound [258]: a π-delocalised system that can stack on the face of the quadruplex; a positive charge that can lie in the centre of the guanine-quartet; and positively charged terminal groups that can simultaneously bind in the grooves and loops of the quadruplex. Reed et al. showed that nickel(II)-salphen {salphen = *N*,*N*′-bis(salicylidene)-3,4-diaminobenzoic acid} complexes selectively bind and stabilise G-quadruplex DNA [258]. Thomas and co-workers have demonstrated that dinuclear ruthenium complexes, capable of binding DNA through intercalation or groove binding [259,260], also show significant affinity for G-quadruplex structures. Of particular note was the study where dinuclear ruthenium complexes containing azo-based linking ligands exhibited different and distinctive colour changes upon binding to quadruplex structures, compared with binding to a variety of duplex DNA structures [259].

Very recently, it has also been demonstrated that platinum(II) complexes can bind quadruplex structures with high affinity. Kieltyka et al. showed that relatively simple platinum phenanthroimidazole complexes that bind duplex DNA by intercalation can also bind quadruplex structures, and in some cases with significantly greater affinity [262]. Perhaps more interestingly, the same group (Sleiman and co-workers) designed and synthesised by "supramolecular self-assembly" a square-shaped platinum complex, $[Pt(en)(4,4'\text{-dipyridyl})]_4(NO_3)_8$, that binds quadruplexes with high affinity and inhibits telomerase activity [263].

Although studies such as those described above have examined the interaction of transition metal complexes with quadruplex structures, there is still a need to delineate greater details of the intermolecular interaction. Recently, Talib et al. have utilised electrospray ionisation mass spectrometry (ESI-MS) as a screening tool to examine the interaction of nickel, ruthenium and platinum complexes to duplex and quadruplex DNA [264]. The results demonstrated that ESI-MS is an excellent technique to compare binding affinity and binding mode (covalent or reversible) of the metal complexes with quadruplexes.

4. Conclusions

It is clear that transition metal complexes offer great potential as structure-selective binding agents for nucleic acids. Furthermore, as specific structures which play an important regulatory role in replication, transcription and translation are identified, it is probable that metal complexes can be designed that exhibit very high selectivity for these sites. Incorporation of hydrogen-bond donors and acceptors and/or van der Waals interaction recognition groups into metal complexes may allow the extremely high selectivity required for the metal complex to selectively bind a single nucleic acid site within a cell. Given the relatively rigid framework of a metal complex compared to organic molecules, it is likely that second generation metal complexes can be synthesised that have the additional recognition groups in the precise three-dimensional position required for complementary interactions with the putative nucleic acid binding site.

Although some non-duplex DNA structures do play an important role in gene regulation, RNA may prove to be a more attractive target for metal complexes – and particularly multinuclear complexes – in terms of obtaining greater binding site selectivity. RNA is more structurally rich than DNA – RNA contains a larger proportion of non-duplex type structures, forming complex three-dimensional structures comprising of loops, bulges, pseudo knots and turns [265]. In addition, viral and bacterial RNA often have "unusual" sequences and folds that could be specifically targeted. It has been postulated that a variety of diseases – e.g. cystic fibrosis, HIV-AIDS and certain cancers – could be successfully treated through the modulation of RNA function [84,265,266].

While metal complexes have considerable potential as structure-selective binding agents, and use as diagnostic agents could be expected, their use as therapeutic drugs also depends upon their ability to be transported into human cells and elicit some biological response. It is now well known that mononuclear and dinuclear platinum complexes are adequately transported into cells; however, there have been relatively few studies on the cellular transport and bio-activity of inert ruthenium and rhodium complexes. Puckett and Barton demonstrated that a series of

DNA-intercalating ruthenium complexes are transported across the cell membrane, with those having the greatest lipophilicity exhibiting the highest uptake [267]. Furthermore, a number of examples of inert ruthenium complexes having moderate cytotoxic properties have already been reported.

Non-duplex DNA and RNA structures have been shown to be important in the regulation of gene expression, and are now recognised as potential targets for therapeutic agents for a range of diseases. It is likely that inert transition metal complexes will play an important role in developing new agents for these structural features. This outcome will be aided by the vast amount of classical inorganic chemistry research that has evolved over the past few decades that will allow the development of metal complexes with a high selectivity and affinity for particular non-duplex structures.

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