DALTON
PERSPECTIVE

Effects of metal-ion binding on nucleobase pairing: stabilization, prevention and mismatch formation †

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Depending on the site of metal binding to a nucleic acid constituent and the geometry of the metal entity, either a stabilization of a nucleobase ensemble, complementary or not ('metal-modified' base pair, triplet or quartet), or a prevention of nucleobase pairing may result.

Base Pairing in Nucleic Acids

Of the 28 possible base-pairing schemes between the four common nucleobases guanine (G), adenine (A), cytosine (C) and thymine (T) [or uracil (U)] involving at least two hydrogen bonds, nature uses relatively few only.[1] In double-stranded DNA, pairing between the complementary bases G and C as well as A and T is predominantly according to the Watson–Crick fashion (Fig. 1). This pairing scheme allows for antiparallel strand orientation (aps-DNA) in A, B and Z DNA. Disturbance of the regular duplex structure, *e.g.* in the presence of an intercalating agent,[2] may lead to a switch from Watson–Crick to Hoogsteen pattern, with the principal features of complementarity and aps-orientation maintained. Violation of the complementarity rule leads to mismatch formation, considered to be the major source of mutation. Mismatches have been studied with short synthetic DNA fragments, using primarily single-crystal X-ray crystallography and ^{1}H NMR spectroscopy.[3] Base mispairing under biological conditions may have its origin in a shift in tautomer structure, spontaneously[4] or caused by a chemical modification of a base (*e.g.* alkylation, hydroxylation or metallation),[5] in a switch of a purine nucleobase from *anti* to *syn*,[4] or in the presence of ionized or protonated bases.[6]

Knowledge that DNA may adopt a structure with two strands running parallel (ps-DNA) is quite new. First proposed by Pattabiraman[7] in 1986, this possibility was later confirmed by van de Sande *et al.*[8] The H-bonding patterns between complementary bases are of the reversed Watson–Crick (or Donohue) type. Very recently, the existence of a double-helical, parallel structure (ps-DNA) with Hoogsteen pairing at moderately acidic pH has been demonstrated.[9] Base pairing between stretches of identical bases (homo base pairing), *e.g.* between hemiprotonated cytosines [$CH^+ \equiv C$] or between protonated adenines [$AH^+ = AH^+$], has been long known to lead to parallel strands,[1] and this feature has been extended to ps-DNA containing homo base pairs of T, G and neutral A.[10]

Triple-helical DNA was discovered in 1957,[11] not long after the structure of double-stranded DNA had been established. While the existence of base triplets in tRNA's has been known for quite some time, DNA triplexes[12] and DNA base triplets[13] so far have been studied only in a few cases by X-ray diffraction and in others by NMR. Triple-stranded DNA exists in many variants as far as strand directions, H-bonding patterns and composition of the third strand are concerned.[14] Triplex formation may originate from addition of a single strand of an oligonucleotide to an existing DNA duplex or alternatively from intramolecular back-folding of a duplex.[15] A major interest in intermolecular DNA triplexes stems from the possibility of recognizing ds-DNA in a sequence-specific manner.[16]

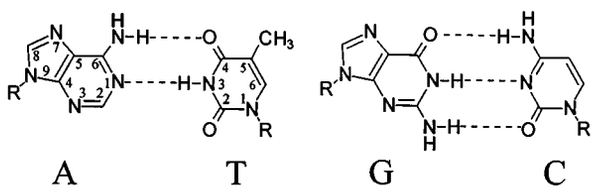

Fig. 1 Complementary Watson–Crick AT and GC base pairs and atom numbering scheme of nucleobases

Four-stranded DNA, composed of two H bonded DNA duplexes, has been implicated in DNA exchange processes.[17] Similarly, four-way DNA junctions ('Holliday junctions') are considered crucial intermediates during genetic recombination.[18] In addition, four-stranded DNA structures occur at the ends of chromosomes ('telomeres') and consist of cyclic guanine quartets. They are formed of G-rich 3′ single-strand overhangs of the chromosome ends with various strand directions possible.[19] While T's in these overhangs are generally found to form the loops, they may also form quartets. With four-stranded RNA, uracil quartets have been established.[20] A special kind of four-stranded oligonucleotide is that of hemiprotonated cytosine tracts ('i-motif') which form a fully intercalated structure of two parallel duplexes.[21] Many additional topologies of nucleic acids (knots, junctions *etc.*) are feasible which are outside the scope of this discussion, however.

The Role of Metal Ions: General Aspects

Our present understanding of basic principles of metal ion–nucleobase/nucleic acid interactions[22] is far from comprehensive. Despite a rapid increase in structural information derived from X-ray data[23] and NMR work,[24] or of thermodynamic data (stability constants) of model systems,[25] many essential features of the effects of metal ions on nucleic acids or their constituents are still incompletely understood. To give two examples: (*i*) metal ions are essential in stabilizing duplex, triplex and quadruplex structures for the sheer relief of repulsion between the negatively charged polynucleotide strands. In many cases (tRNA's; G quartets; Holliday junctions; purine,purine, pyrimidine triplexes) metal ion binding is highly specific.[26] Very low concentrations of cationic metal species invariably lead to a thermal stabilization of duplex structures. However, depending on the type of metal ion (main group or transition metal; charge; d-electron configuration; hard- or soft-ness), its binding preference (phosphate oxygens; heterocyclic part; site of heterocycle; mono- or multi-functional), and other ligands already bound to the metal ion, the net effect on the nucleic acid (duplex) at higher metallation levels may be anywhere between

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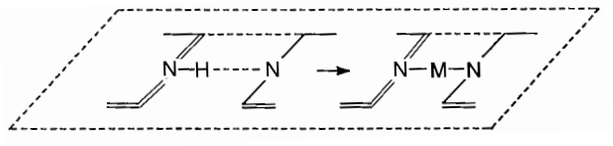


Scheme 1

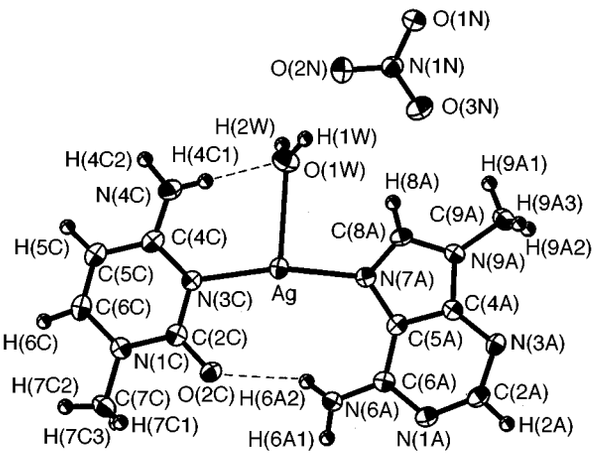


Fig. 2 Mixed 1-methylcytosine, 9-methyladenine complex of Ag^{I}. Two non-complementary nucleobases are cross-linked by a metal ion with a water molecule included in the H-bonding pattern. Relative orientations of the CH_3 groups, corresponding to sugar entities in nucleic acids, preclude this structure from being realized in regular aps-DNA (Reproduced from ref. 31 with permission)

strong thermal stabilization and pronounced destabilization due to complete disruption of an ordered structure. (*ii*) It is unclear as to what the contributions are of the various physical effects (polarization; charge transfer; dipole moment; back-bonding) of a metal entity bound to a certain site of a nucleobase, *e.g.* N^7 of a purine, on the base pairing and base stacking properties. In any case, it can be anticipated that metal binding disturbs the electronic complementarity with its pyrimidine base partner, even if the geometrical complementarity is unaltered. Theoretical work (gas phase) is beginning to shed light on these questions.[27]

Metal-modified Base Pairs

Formally, protons involved in H bonds between nucleobases may be replaced by metal entities of suitable geometry (Scheme 1). In this case 'metal-modified' base pairs are generated. The analogy relates both to homo base pairs (*e.g.* hemiprotonated cytosine, hemiprotonated guanine, or hemiprotonated 7-methylguanine and protonated adenine),[28] to Watson–Crick,[29] reversed Watson–Crick,[28] Hoogsteen[29] and reversed Hoogsteen pairs[30,31] of complementary bases as well as nucleobase mismatches. 'Suitable' geometry means that metal ions and/or entities display a linear co-ordination geometry [co-ordination numbers 2, 4 (*trans*-square planar) or 6 (*trans*-octahedral)], a trigonal-planar one,[31] and in certain cases even a tetrahedral one.[32] With Hoogsteen or reversed Hoogsteen-like arrangements of the two bases, H-bonding between the cross-linked bases is retained in part, but occasionally interbase H-bonding is replaced by bridging water molecules.[29,31] This feature is by itself of interest considering the fact that nucleobase hydration can contribute to nucleobase tautomerization[33] and base mispairing.[3] Examples of metal-modified base pairs of Ag^{+} and *trans*-$Pt^{II}(amine)_2$ are given in Fig. 2 and Fig. 3. These metallated base pairs may be considered structural models of DNA interstrand cross-linking adducts formed by various metal ions, including cross-links of *trans*-$[PtCl_2(NH_3)_2]$.[34] A recent theoretical study[35] on a metal analogue of the AT Watson–Crick pair has, for the first time, provided an understanding of the effect

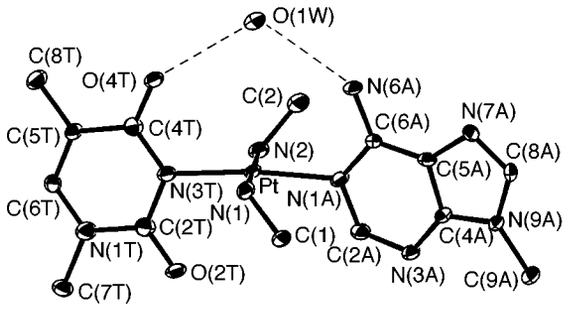


Fig. 3 Mixed 1-methylthymine, 9-methyladenine complex (cation only) of *trans*-$[Pt^{II}(NH_2Me)_2]$ with the two bases oriented in a Watson–Crick fashion with the proton at N^3 of T replaced by Pt^{II}. A water molecule, H bonded to exocyclic nucleobase groups, contributes to the near-planarity of the two bases (Reproduced from ref. 29 with permission)

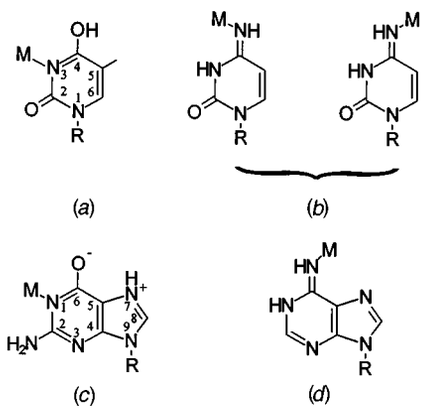
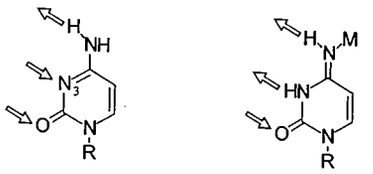


Fig. 4 Schematic representations of metal-stabilized rare nucleobase tautomers: (*a*) 4-hydroxo-2-oxo-tautomer of U and T; (*b*) two rotamers of iminooxo tautomer of C; (*c*) betaine tautomer of G; (*d*) imino tautomer of A with M *anti* relative to N^1

of the metal entity *trans*-$[Pt^{II}(NH_2Me)_2]$ on the electronic structure of the AT pair.

Metal-stabilized Rare Nucleobase Tautomers

Metal binding to a certain site of the heterocyclic nucleobase may cause a shift of a weakly acidic proton to another site, thereby generating a metal complex of a nucleobase tautomer structure normally present in a concentration too low to be detected experimentally, *e.g.* in a ratio of 10^{-4}–10^{-5} : 1 relative to the major tautomer. Applying kinetically inert metal species, frequently Pt^{II} and Pt^{IV}, we have prepared and isolated a series of complexes of these metal ions with rare nucleobase tautomers, and in several cases characterized them by X-ray crystallography. They include 4-hydroxo-2-oxo tautomers of 1-methyluracil[36] and 1-methylthymine,[37] the iminooxo tautomer of 1-methylcytosine,[38,39] the betaine tautomer of 9-ethylguanine,[40] and the imino tautomer of 9-methyladenine[41] (Fig. 4). It needs to be emphasized that the complexes isolated are not necessarily relevant to the question of mutagenicity of Pt^{II}, Pt^{IV} or Hg^{II} but rather that they represent *structural* models of *any metal ion* interacting with a nucleobase and changing its tautomer structure. Moreover, precise X-ray data of such complexes and knowledge of the effects of a co-ordinated metal ion on the geometry of a heterocyclic ring permit an estimation of geometrical parameters of the rare nucleobase tautomer.[38] This strategy therefore provides a means to compare experimental data with data obtained from theoretical calculations. With regard to H-bonding considerations, there are two important features to be recognized. First, as a consequence of the shift of the acidic proton, its pK_a value and consequently also the pK_b value of the N atom can be altered quite dramatically. For



Scheme 2

example, while a proton at N^3 of C has a pK_a of 4–5, it is between 6 and 9 when Pt^{IV} or Pt^{II} entities reside at the exocyclic N^4 atom.[38,39] Secondly, the relative orientation of the metal entity, when attached to an *exocyclic group* of the nucleobase, is crucial.[39,41] If *syn* with respect to the H-bonding sites, H-bonding with the complementary (or any other) base is prevented or at least hampered. Taken together, this implies that even if the metal is *anti*, base pairing with G may be impossible due to the fact that N^3 of C has been changed from an acceptor for protons to a H donor (Scheme 2). Only if this site becomes deprotonated, H-bonding with G is possible. However, pK_a arguments must not be overemphasized. There is ample evidence that charged species (*e.g.* protonated cytosine *etc.*) can exist at physiological pH irrespective of a $pK_a \ll 7$, and there is a proposal that the polymerase active sites are in fact well suited to stabilize ionic states, even better than water does.[42]

Blocking H-Bonding Sites

It is obvious that H bonding at a nucleobase is not possible at all if an *endocyclic* nitrogen that is normally involved in H-bonding is blocked by the metal, unless 'metal-modified' base pairing is considered (*cf.* above). For example, a metal attached to N^1 of a guanine nucleobase prevents H-bonding with the complementary base cytosine according to the Watson–Crick pattern. In that case H-bonding in a Hoogsteen or another fashion can be expected. Applying differently methylated guanine model nucleobases (N^1,N^9; N^7,N^9; O^6,N^9) and their respective metal complexes, we are studying also alternative H-bonding patterns between complementary and non-complementary bases. As a first result, we have now observed H-bonding between 1-methylcytosine and a guanine, substituted by alkyl groups at N^7 and N^9, and blocked by a Pt^{II} entity at N^1, in which N^3 and N^2 of guanine and N^4 and N^3 of cytosine are involved.[43] This finding is of interest because it implies that an association of guanine and cytosine *via* minor groove sites of G is possible, in principle. At the same time it represents yet another H-bonding pattern between (modified) G and C nucleobases, previously not observed.

Purine-N^7 Metallation and H Bonding

The N^7 sites of G and A, located in the major groove of double-stranded DNA, are preferred metal binding sites. Amongst others, the antitumor agent *cis*-$[PtCl_2(NH_3)_2]$ (cisplatin) binds to these positons.[44] The resulting distortion of DNA and possible biological consequences have been the main focus of previous work.[45] Considerably less is known about more subtle effects of these adducts or even of monofunctional binding of a metal electrophile on H-bonding properties or base stacking of these purine bases (*cf.* above). Present experimental findings on this topic may be summarized as follows: (*i*) N^7 platinated G still forms a Watson–Crick pair with C. This conclusion has been derived from ^1H NMR studies in $(CD_3)_2SO$ with model compounds,[46] from NMR work with oligonucleotides,[47] and from X-ray crystallography with DNA fragments[45,48] and a model compound,[49] respectively. In the latter compound, *trans*-$[Pt(NH_2Me)_2(G\text{-}N^7)(C\text{-}N^3)]X_2 \cdot C$, a platinated G forms a Watson–Crick pair with C and thus represents an example of a 'metal-modified' nucleobase triplet (Fig. 5). Association constants of platinated G and C have not been determined systematically. Preliminary data obtained for model systems in our

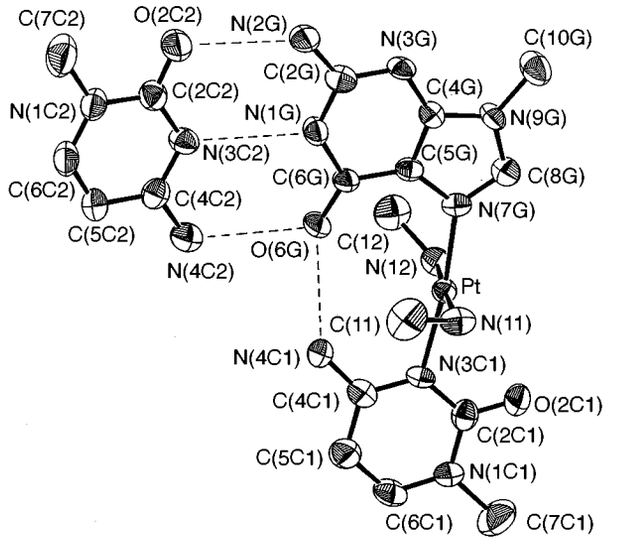


Fig. 5 Metal-modified nucleobase triplet consisting of a normal Watson–Crick pair between C and G, and a Hoogsteen arrangement between G and the second C, with the required proton replaced by a *trans*-$[Pt^{II}(NH_2Me)_2]$ entity. All three bases are essentially co-planar (Reproduced from ref. 49 with permission)

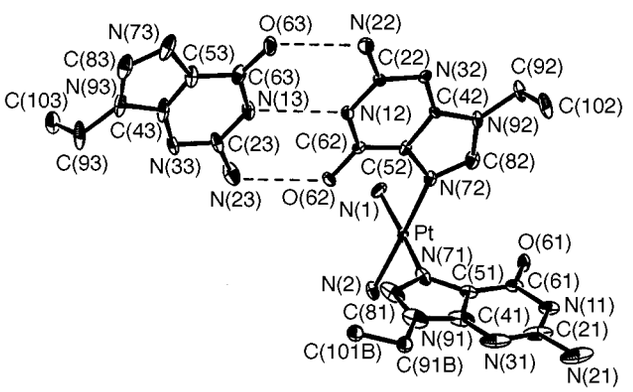


Fig. 6 Mispair between N^7 platinated, N^1 deprotonated guanine and neutral guanine as found in the model nucleobase complex *cis*-$[Pt(NH_3)_2(egua)_2] \cdot$Hegua (Hegua = 9-ethylguanine)[50b]

laboratory suggest that in dmso (dimethyl sulfoxide) and in the absence of any steric constraints arising from a distorted DNA structure (as a consequence of bifunctional binding of the metal entity) Pt^{II} at N^7 of G actually could stabilize the Watson–Crick GC pair.[50a] These data imply that the opposing effects of increased N^1H and N^2H_2 acidities and reduced O^6 basicity lead to a net increase in H-bonding affinity between N^7 platinated G and the complementary base C. It remains to be seen as to what extent this feature depends on the nature of the Pt entity (geometry; other ligands; charge) and whether or not it holds up for *any* metal ion. (*ii*) N^7 platinated, N^1 deprotonated G mispairs with neutral G. Platinum(II) binding to G-N^7 acidifies the proton at N^1 by 1.5–2 log units, thereby facilitating deprotonation of this site.[50b] Self-association of platinated and deprotonated G, as seen in the model compound *cis*-$[Pt(NH_3)_2(egua\text{-}N^7)_2]$ (egua = 9-ethylguanine anion), takes place *via* a pair of H bonds involving the N^1 position and the amino group at N^2.[50b] Neutral guanine, regardless if platinated at N^7 or not, interacts with N^7 platinated, N^1 deprotonated guanine *via* 3 H bonds (Fig. 6), as verified by ^1H NMR spectroscopy[46] and X-ray crystallography.[50b,51] These GG pairs represent the first unambiguous examples of mismatches between two bases that are eventually brought about by attachment of a metal ion to a nucleobase. (*iii*) The effect of N^7 platination on the H-bonding behaviour of A remains obscure. For reasons as yet unknown, the d(ApG) adduct of cisplatin in DNA is at least five times

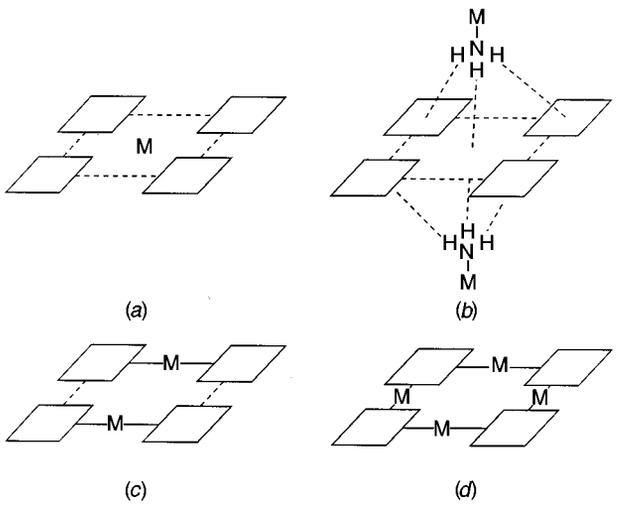


Fig. 7 Schematic representations of nucleobase quartets: (*a*) metal ion (M) in center of quartet with H bonds (– – –) between the bases; (*b*) M–NH_3 groups above and below the quartet with H-bonding between the four bases and NH_3; (*c*) association of metallated base pairs *via* H-bonding; (*d*) cyclic purine quartet with four metals cross-linking the purines

more mutagenic than the more frequent d(GpG) cross-link.[52a] A high mutation specificity exists for the 5′ base adenine, which leads predominantly to A ⟶ T transversions. In principle, such a mutational pathway involves an adenine,adenine mispair, with one of the two adenines present in the rare imino tautomeric form. Attempts[52b] to prove that N^7 platination of adenine has an effect on the tautomer equilibrium by application of the 'method of basicity measurements'[53] were inconclusive. Clearly, theoretical calculations could be of considerable help in resolving this as well as related questions.

Nucleobase Quartets and Metals

Nucleobase quartets in telomeres of DNA or four-stranded RNA require metal ions for stabilization. With G quartets, K^+ or Na^+ cations are located in the center of the quartet and/or half-way between two G_4 stacks,[19] thereby allowing for four (or eight) $M^+ \cdots O^6$ contacts. For the uracil quartet found in the RNA tetraplex $r(UGGGGU)_4$,[20] a metal ion appears to be likewise crucial for stabilization. Of the two U quartets observed in this structure, one is markedly non-planar. The two U quartets are layered at either side of a central tetrad of G quartets and display cyclic arrangements of H bonds between O^4 and N^3 positions.

Applying simple uracil (and thymine) model nucleobases, we have been able to obtain adducts with alkali salts such as $Na[AuCl_4]$[54] or *trans*-$K[Au(CN)_2Cl_2]$[55] or the neutral ammine complex *trans*-$[PtCl_4(NH_3)_2]$[56] which, in the solid state, display quartet structures of the pyrimidine nucleobases reminescent of U_4 (Fig. 7). In $[Na(Hmeura)_4][AuCl_4]$[54] (Hmeura = 1-methyluracil), a central Na^+ is bound to four O^4 sites of four uracil bases, which are co-planar and connected through four cyclic $N^3H \cdots O^4$ hydrogen bonds, very much as in the U_4 quartets of $r(UGGGGU)_4$. In *trans*-$[PtCl_4(NH_3)_2]$·2Hmeura the Na^+ ion is replaced by two NH_3 ligands of Pt^{IV}, located above and below a markedly non-planar quartet of Hmeura bases, which again are connected by four cyclic H bonds between N^3H and O^4 sites. These findings are in a way surprising considering the fact that quartet structures of U and T appear not to have been considered intrinsically stable.

A nucleobase quartet of very much different composition forms during self-association of the model compound *trans*-$[Pt(NH_3)_2(egua\text{-}N^7)(mcyt\text{-}N^3)]^+$ (mcyt = 1-methylcytosine).[57] This cation contains two complementary ends and therefore forms a two-fold metallated base quartet containing a mixture

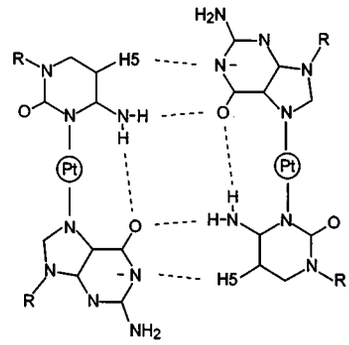


Fig. 8 Schematic view of nucleobase quartet consisting of a pair of self-complementary metal-modified base pairs of composition *trans*-$[Pt(NH_2Me)_2(egua)(mcyt)]^+$. Dimerization is evident from electrospray ionization mass spectrometry and ^1H NMR spectroscopy (concentration-dependent shifts of H^5 and N^4H of C) (Reproduced from ref. 57 with permission)

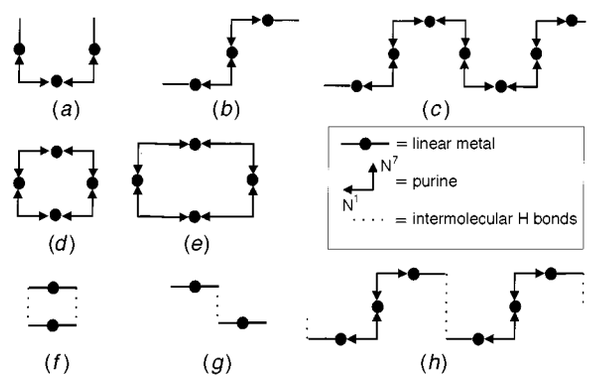


Fig. 9 Different topologies of purine complexes of *trans*-$Pt^{II}(amine)_2$ or a suitable other metal entity with covalent linkages leading to U-form, S-form, meander, square and rectangle (*a*)–(*e*) or H-bonding associates (*f*)–(*h*) (Reproduced from ref. 60 with permission)

of N–Pt–N and hydrogen bonds (Fig. 8). The H-bonding pattern is unprecedented in nucleic acid chemistry in that an aromatic proton of a nucleobase, H^5 of cytosine, is involved in H bonding with the deprotonated N^1 position of guanine. The only other, related example of such unusual base pairing is that found in r(UUCGCG), with H^5 and O sites of uracil interacting in a UU pair.[58] Side-by-side pairing of nucleobase pairs from two different duplexes to give a tetraplex, followed by re-pairing of strands of different duplexes, has been implicated with strand exchange processes.[17] Metal ions could be important in holding base pairs in register in the way seen in this model compound. Platinum(II) is, of course, unsuitable for such a dynamic process due to the inertness of the Pt–N bonds which prevents completion of the exchange, but it undoubtedly provides a good structural model of a feasible step in this hypothetical process.

Finally, purine nucleobase quartets of a yet different type are the goal of ongoing work in our laboratory. Having shown that the two M–N vectors in N^1,N^7 dimetallated purine nucleobases (A, G) are at right angles and co-planar,[59] we reasoned that the generation of 'molecular squares' with metal ions of linear co-ordination geometry representing the sides and the purines providing the 90° angles should be possible.

Toward Supramolecular Assemblies

By taking advantage of intercomplex H-bond formation between exocyclic groups of suitably cross-linked nucleobases, the orthogonality of M–N^1 and M–N^7 vectors in dimetallated purine nucleobases, as well as intermolecular H bonding between nucleobases (*e.g.* hemideprotonated G, see above), it is feasible to generate supramolecular assemblies of varying topologies (Fig. 9).[60] Intermolecular H bonding may involve

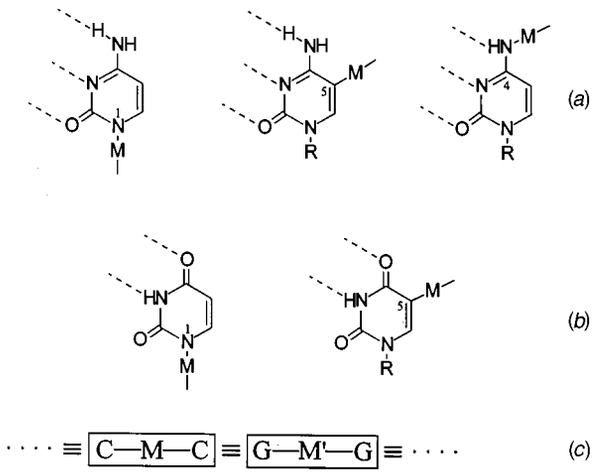


Fig. 10 Metallated cytosine (*a*) and uracil (*b*) nucleobases which, in principle, can be expected to maintain H bonding with metal complexes of their natural complementary partners. See, for example, between M–C and M′–G (*c*)

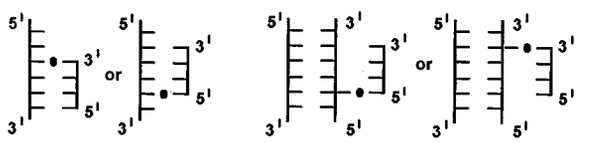


Fig. 11 Schematic representation of the potential usefulness of metallated oligonucleotides in the antisense or antigene approach. Recognition of the target sequence is through H bonding while the metal (●) accomplishes cross-linking (Reproduced from ref. 29 with permission)

identical nucleobases or complementary ones, but in either case the availability of H-bonding sites is required. With cytosine nucleobases this means, for example, that a metal entity has to be either at N^1 (unsubstituted cytosine) or C^5 or N^4 (*anti* with respect to N^3) to accomplish pairing with a N^7 metallated guanine. Similarly, a N^1 metallated uracil or thymine (unsubstituted base) or a C^5 metallated uracil could, in principle, still pair with a N^7 metallated adenine (Fig. 10). As pointed out above, the alteration in pK_a (pK_b) values of the H-bonding sites will affect the pH range in which association will take place and its strength, respectively. Depending on the type of metal ion (geometry; stoichiometry of complex) bound to the nucleobases interacting through H-bond formation, versatile patterns of supramolecular assemblies are possible. Having prepared many of the above mentioned building blocks,[61] we are now in a position experimentally to test this concept, which has successfully been applied to other systems already,[62,63] though the aims were different.

Outlook

The systematic synthesis and structural characterization of models of possible cross-linking adducts of the antitumor agent *cis*-$[PtCl_2(NH_3)_2]$ (cisplatin) [64] and its inactive geometrical *trans* isomer[65] with DNA had been the starting point of this work. As it turned out, many aspects relevant to metal-nucleic acid interactions in general are to be learned from this kind of work.[66] In this account primarily model compounds containing linear geometries have been dealt with. It has been pointed out that aspects of molecular recognition and supramolecular chemistry are beginning to emerge.

As to future directions of this work, we are currently focusing on the potential usefulness of metallated (specifically: platinated) oligonucleotides in the so-called antisense and antigene approaches. In these strategies either mRNA or ds-DNA are targeted by oligonucleotides with the aim of inhibiting translation of RNA (antisense) or transcription of DNA (antigene).[67] Recognition of the target sequence is through H bonding according to Watson and Crick (with mRNA) or triplex formation (with DNA). Among many obstacles that have to be overcome in order successfully to apply this technique in therapy, one is that of tight and long lasting binding of the oligonucleotide to the target. Kinetically inert metal ions could possibly be of help (Fig. 11), during 'metal-modification' of nucleobase pairs or triplets. As we have already demonstrated,[68] it is possible to direct monofunctionally *trans*-$[Pt^{II}(NH_3)_2]$-modified homopyrimidine oligonucleotides to the complementary purine-rich strand of a duplex DNA and to cross-link these strands *via* Pt.

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