Assembly of Nucleobases into Rings and Cages via Metal Ions

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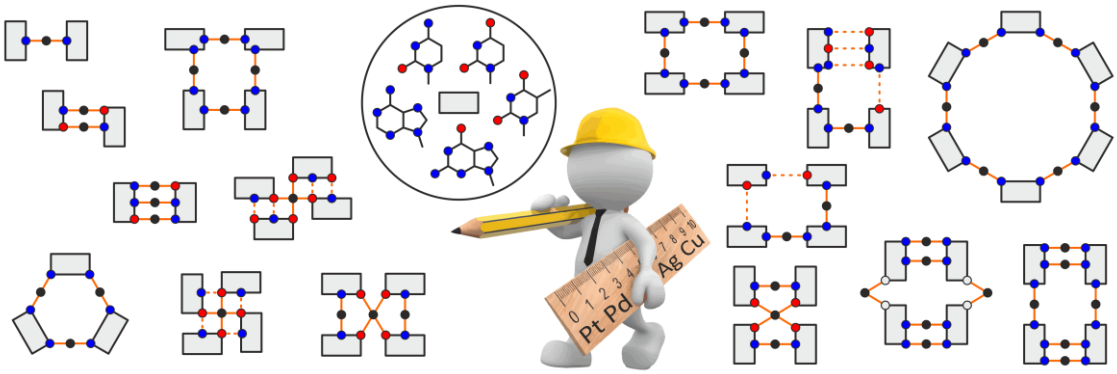

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Abstract

Metal ions are natural counterparts of nucleic acids and crucial in stabilizing many specific structures. While the relevant bulk main group metal ions (Na^+, K^+, Mg^{2+}) are predominantly important in keeping base pairs in register and/or allowing the formation of particular specific RNA structures, transition metal ions, and specifically the soft ones, display a pronounced affinity for donor atoms of the heterocyclic nucleobases as part of nucleic acids. Their nature in fact provides a large number of different binding patterns, including specific cross-links and/or the formation of cyclic entities and/or cages. This review article summarizes constructs obtained this way, without over-emphasizing their biological relevance. Nevertheless, it can be claimed that in a number of cases model findings have preceded their discoveries in biorelevant events.

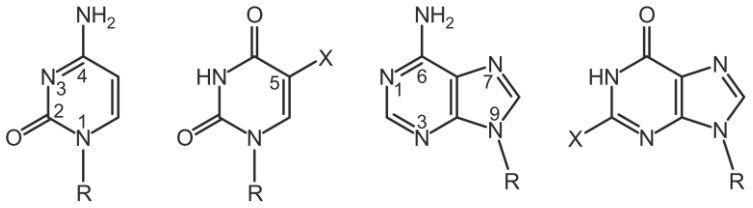
1. Introduction

Single-stranded oligonucleotides can associate into numerous supramolecular entities such as the common duplexes or the more rarely occurring triplexes or quadruplexes. Even higher-order structures are possible [1, 2]. In highly condensed states, a plethora of interactions between individual strands seems possible. Weak forces such as hydrogen bonding, stacking, and hydrophobic interactions are dominating, but numerous other features like nucleobase protonation (e.g. “i-motif”, or GC^+ Hoogsteen pair, with G = guanine and C^+ = protonated cytosine), inclusion of water molecules, and metal ion binding for charge neutralization are contributing as well. Metal ions (M) are, apart from

protonated amines, the natural counter ions of nucleic acids [3], and in particular the stabilization of unique tertiary nucleic acid structures requires the involvement of metal ions [4, 5]. Formally there is frequently a close analogy between metal binding and proton binding as observed in inter-base hydrogen bonding. For example, the *trans*-$(NH_3)_2Pt^{II}$ DNA interstrand cross-link between G-*N7* and C-*N3* [6] is nothing but a metalated analogue of the Hoogsteen pair between G and a protonated C, a scenario termed by us as "metal-modified base pair" [7].

2. Scope and Aims

This review deals predominantly with discrete metal-nucleobase complexes which are cyclic (2D, 3D), with metal ions cross-linking the bases. We also briefly refer to cases where metal ions orient nucleobases in space such that they interact through hydrogen bond formation or partial stacking. In the majority of cases model nucleobases such as N1-alkylated pyrimidine (pym) nucleobases or N9-alkylated purine (pur) bases will be considered (Scheme 1). Thus, primarily metal-bridging modes involving endo- and exocyclic donor atoms of the heterocyclic parts of nucleobases are dealt with, a restriction certainly reasonable for the binding of soft metal ions. With nucleosides and nucleotides, additional involvement of sugar-O and phosphate-O sites is possible. Parent nucleobases (with substitutable protons an N1 (pym) or N9 (pur) sites) will be not discussed, even though these provide a rich supramolecular chemistry [8,9]. It needs to be pointed out that formation of cyclic metal metal-bridging model nucleobase complexes can either occur spontaneously or in a stepwise manner. The latter is in particular the case when slowly reacting metal ions are involved, *e.g.* Pt^{II} species, or if different metal ions are attached to nucleobases. Related to slow kinetics, the problem of possible linkage isomerism can become a major obstacle with regard to high yield products.



Scheme 1 *Representations and atom numbering schemes of DNA and RNA nucleobases (A = adenine, C = cytosine, G = guanine, Hx = hypoxanthine, T = thymine, U = uracil) with R = alkyl group (model base) or sugar (nucleoside) or sugar phosphate (nucleotide).*

The aims of supramolecular chemistry between metal ions and nucleobases can be defined as follows: the synthesis of structural models of natural, biologically relevant supramolecular entities and the understanding of principles of their formation, the synthesis of artificial analogues of such constructs and their interactions with their natural counterparts, and finally the generation of novel supramolecular entities which have no analogy in biology. Selected aspects of this chemistry have been treated also in earlier reviews [8–14].

3. Cyclic Metal Nucleobase Complexes

3.1. Chelates

The simplest examples of cyclic species consisting of a single metal ion and a nucleobase are the so called “macrochelates”, hence nucleotide complexes in which the metal is coordinated simultaneously to a donor atom of the heterocyclic part of the nucleotide and to a phosphate oxygen atom [15]. Of course, any dinucleotide or larger oligonucleotide cross-linked by a single metal ion via two heterocyclic donor atoms represents a macrochelate as well [16], but these shall not be considered here. Rather we concentrate on nucleobase complexes carrying more than a single metal atom and/or more than a single nucleobase in the ring structure. We shall define the ratio *r* between the metal M and the nucleobase (nb) as *r* = M : nb.

3.2. Dinuclear Complexes

An alternative to intramolecular chelation of a metal ion by a nucleotide, which provides the mentioned macrochelate, is intermolecular metal binding, leading to a dinuclear complex. [Pt(en)(5'-CMP)]$_2$ (with 5'-CMP = 5'-cytidine monophosphate) [17] is a typical example. In it, both Pt^{II} ions bind to N3 of the cytosine and an oxygen atom of the phosphate group each, thereby producing a head-tail dinuclear species. There is even the possibility of having exclusive metal binding to two bridging phosphate groups, with the nucleobases not involved in metal binding at all, such as in [Cu(L)(H_2O)(5'-UMP)]$_2$ [17] (with L = *o*-phenanthroline and 5'-UMP = 5'-uridine monophosphate), but of course, this pattern is phosphate —rather than nucleobase— specific. Related to this pattern are dinuclear nucleobase complexes with other bridging ligands such as hydroxide [18] or halide [19], and terminal nucleobases, which we likewise will not discuss further. The more typical 2:2-complexes are those, in which both metal ions cross-link donor sites of the heterocyclic rings. Examples include today virtually all common nucleobases.

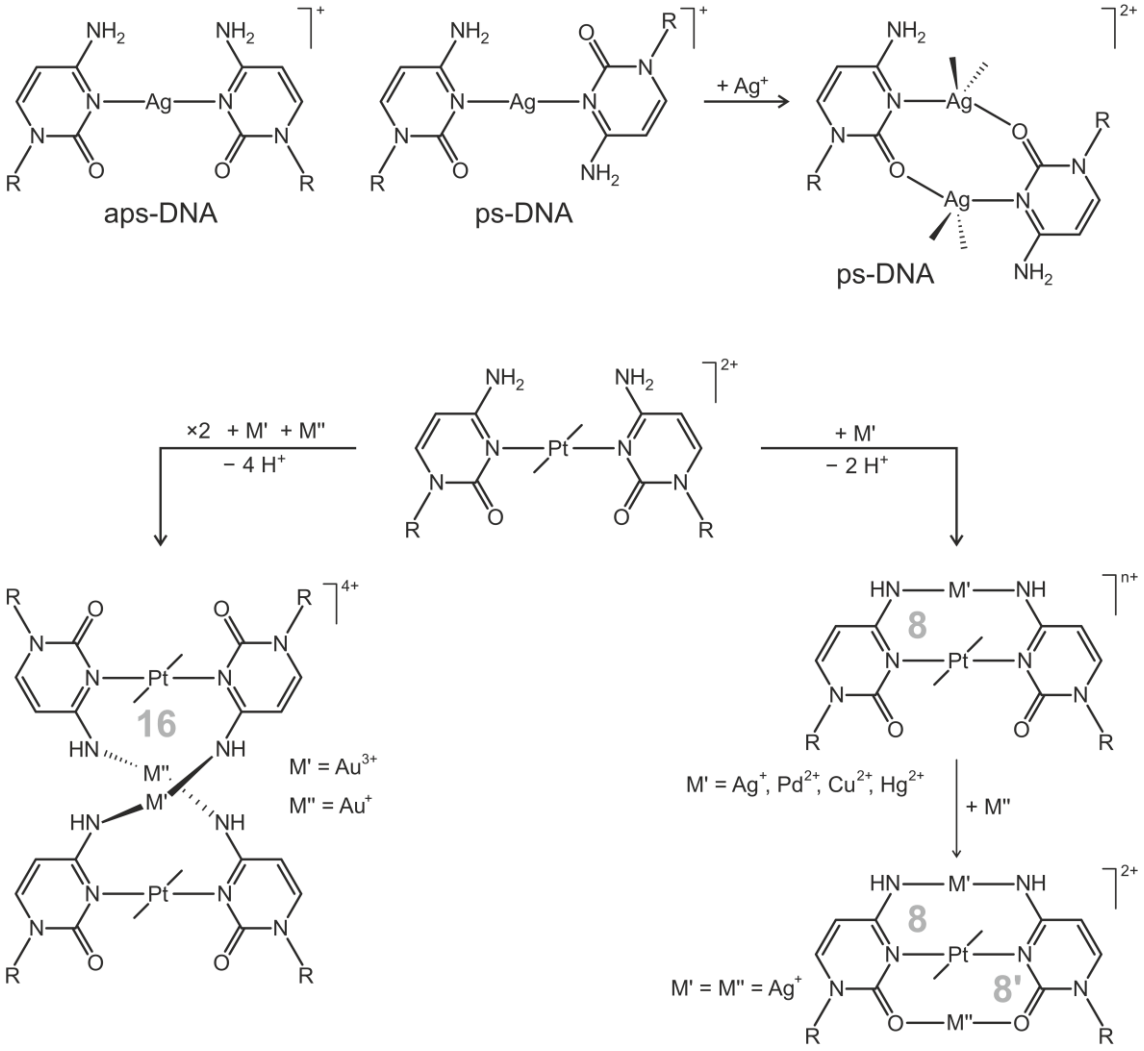
3.2.1. Cytosine

[Ag(1MeC-*N3,O2*)]$_2$(NO_3)$_2$ (with 1MeC = 1-methylcytosine) [20] was the first X-ray structurally characterized cytosine complex of this type. The centrosymmetric dinuclear cation displays alternating Ag^+ cross-links via N3 and O2, thereby generating an 8-membered, folded metallacyclic ring. The Ag^+ ions have distorted tetrahedral coordination geometries, forming bonds to O2 sites of the rings below and above, respectively. Coordinated nitrate anions complete the coordination spheres of the Ag^+ ions. A similar arrangement, as far as the 8-membered metallacyclic ring is concerned, is also observed in [$ZnCl_2$(1MeC-*N3,O2*)]$_2$ [21], and a variant of the former is also present in [Tl(1MeC-*N3,O2*)]NO_3 [22].

Regarding the model character of the Ag^+ complex to DNA or RNA cross-links, it is likely that a centrosymmetric arrangement of two 1-methylcytosines (with the N1-CH_3 groups, corresponding to the glycosidic groups of the nucleoside, mutually trans) is possible in a parallel-stranded (ps) duplex only, as found in hemiprotonated polyC (with polyC = polycytidylic acid) for example, yet not in an antiparallel (aps) double helix. CC mispairs in aps B-DNA can nevertheless be recognized by Ag^+ ions [23], but the stoichiometry is different, namely 1:2. In other words, a single Ag^+ ion cross-links the N3 sites of two cytosine bases. In principle, the two O2 sites would still be available for binding of a second Ag^+, but the association constant is probably low.

A distinctly different situation is realized, if the bridging metal ion is of higher positive charge and capable of substantially acidifying the exocyclic amino group to the extent, that a second metal ion can

successfully compete with a proton of $N4H_2$ (Scheme 2). This is the case, for example, with a_2Pt^{II} being the metal to link two N3 positions of two cytosine bases. We have prepared and structurally characterized a series of mixed metal complexes derived from *trans*-$[Pta_2(1MeC\text{-}N3)]^{2+}$ (with a = NH_3 or amine), having a second metal ion (Ag^+, Cu^{2+}, Pd^{2+}, Hg^{2+}) between the two $N4H^-$ sites [24] and occasionally a third one between O2 sites [25], or even at C5. An inversion of metals, hence Pt between the $N4H^-$ sites and the heterometal ion between the N3 positions, is likewise possible [26]. In all cases, flat 8-membered metallacyclic rings are formed, or even larger ones.

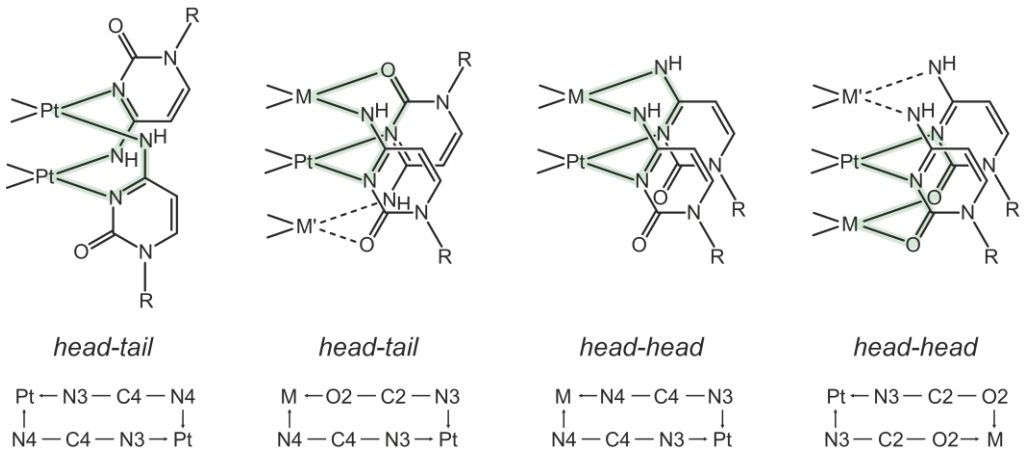


Scheme 2 *Feasible Ag-C adducts in duplex DNA (top) and heteronuclear derivatives following deprotonation of the exocyclic amino groups of C caused by initial metal binding to two C-N3 sites (lower part).*

The above-mentioned heteronuclear complexes provide, in addition to their potential relevance for metal-nucleic acid interactions, a wealth of features interesting for fundamental Inorganic Chemistry aspects, *e.g.* dative metal-metal interactions, among others [27].

Changing the initially bonded *trans*-a_2Pt^{II} entity to its cis isomer does not greatly alter the picture of nucleobase deprotonation and subsequent metal binding to the anionic $1MeC_{-H}$ ligand, except for

the shapes of the 8-membered metallacyclic rings: of staircase fashion in the Ag and Zn complexes, and essentially flat in the di- and trinuclear complexes derived from *trans*-a_2Pt^{II}, they are folded across the central Pt–M vectors in the complexes containing *cis*-a_2Pt^{II}. The sequence of atoms in these folded rings depends upon the way by which the di- or trinuclear products are prepared (Scheme 3). The 1:2-complex *cis*-$[Pta_2(1MeC\text{-}N3)_2]^{2+}$, when reacted with *cis*-a_2Pd^{II}, produces either a dinuclear PtPd [28] or a trinuclear PtPdPt complex [29], depending on the arrangement of the two $1MeC_{-H}$ ligands, head-head or head-tail. In the first, rare case, the second metal is bonded to two $N4H^-$ sites, whereas the two Pd ions in the second case are bonded through pairs of $N4H^-$ and O2 sites.



Scheme 3 *Four variations of folded 8-membered rings observed in di- (or tri-) nuclear complexes derived from head-tail and head-head oriented deprotonated C ligands attached to cis-a_2Pt^{II} entities.*

The mono(nucleobase) complexes *cis*-$[Pta_2(1MeC\text{-}N3)(OH)]^+$ and likewise the corresponding *cis*-$(PMe_3)_2Pt^{II}$ analogue readily dimerize to head-tail dinuclear complexes [30,31]. These dimers are inherently chiral [32]. One way to their formation has been detected, which involves a rather unconventional tricyclic system comprised of a single bridging $1MeC_{-H}$ ligand and four metal ions, namely Pt^{II}, Pd^{II}, and 2 Ag^+ [33].

Finally, from the tetrakis(1-methylcytosine) complex $[Pt(1MeC\text{-}N3)_4]^{2+}$ heteronuclear derivatives with metal ions either symmetrically coordinated by two $N4H^-$ and two O2 sites, or unsymmetrically by four $N4H^-$ and four O2 positions can be obtained, depending on the mutual orientations of the four nucleobases [34]. Again, the closeness of the metals in such compounds gives rise to metal-metal interactions or bond formation [35].

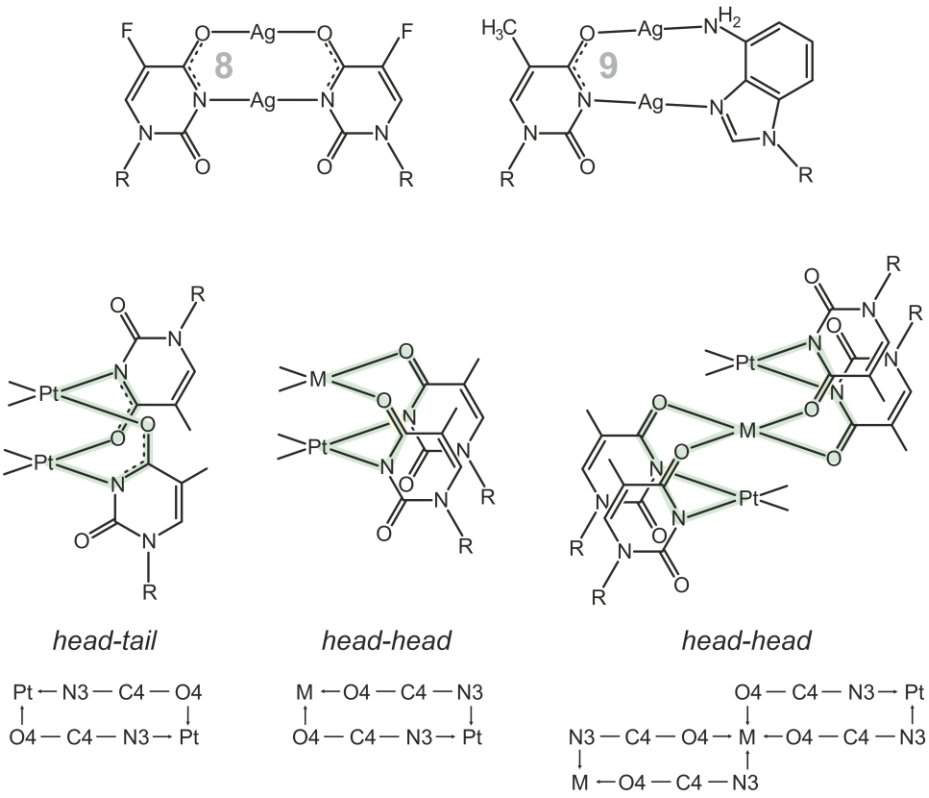
In summarizing the structural properties of the complexes reported thus far, which contain $1MeC_{-H}$ ligands with a metal coordinated to $N4H^-$, the folding patterns within the 8-membered rings are overwhelmingly such that the metals at N3 and $N4H^-$ are *syn* to each other, with N4 being essentially sp^2 hybridized. An exception, with the two metals being *anti* but maintaining a sp^2 hybridization state of N4, is seen in trinuclear metallacycles of $1MeC_{-H}$ (see 3.3.1). The other exception is the mentioned Pt,Pd,Ag_2 complex, in which N4 is sp^3 hybridized [33].

3.2.2. Uracil and Thymine

Many of the features discussed with cytosine-containing metallacycles apply to complexes derived from the other pym nucleobases, the RNA base uracil (U) and the DNA base thymine (T). Superficially, a qualitative difference exists due to the fact that the N3 positions of U and T are carrying protons, which need to be removed prior to metal coordination or shifted to produce a rare hydroxo,oxo tautomer. However, metal binding to N3 may be preceded by initial metal coordination to any of the exocyclic O atoms and, following N3H acidification, subsequent metal migration to N3 [36]. Alternatively, metal species carrying an OH^- ligand may do the job. In any case, numerous metals (*e.g.* Pd^{II}, Pt^{II}, Hg^{II}) can bind to N3 in moderately acidic solution, hence well below a pH corresponding to the pK_a of N3H, which is between 9 and 10. Multiple metal binding to U and T appears to be the rule rather than the exception, as first observed for Ag^+ coordination to polyU [37] and model nucleobases of T and U [38], and likewise numerously for Pt^{II} complexes [39]. More recently, 2:2 complex formation of Ag^+ has been reported also for pairs of 5-fluorouracil (5FU), 2-thiouracil (2TU), 4-thiouracil (4TU) [40] as well as for a mispair of thymine with 1,3-dideazaadenine (1,3DDA) incorporated into regular DNA double helices [41]. In all cases this behavior is a consequence of delocalization of negative charge of the pym nucleobase anion within the heterocyclic ring, which includes the exocyclic oxygen atoms and specifically O4. Even coordination of a third metal ion, K^+ or Na^+ can be realized in Ag_2 or mixed Pt,Ag complexes [42].

Hg^{II} coordination to two thymine bases in a DNA TT mispair seems to be an exception in this respect, as it appears to cross-link the two deprotonated N3 positions only, hence leads to a 1:2 complex (*r* = 0.5) [43]. However, we believe that Hg^{II} does not behave inherently different from the other transition metal ions, but rather that a markedly lower second association constant (leading to the 2:2 product), charge repulsion between two Hg ions at close distance, and/or ionic strength effects prevent such a pattern to be readily observed with nucleic acids. Model studies by Beauchamp and coworkers in fact have numerously demonstrated that binding of more than a single Hg^{II} to an isolated nucleobase is possible, provided the base has become an anion [44].

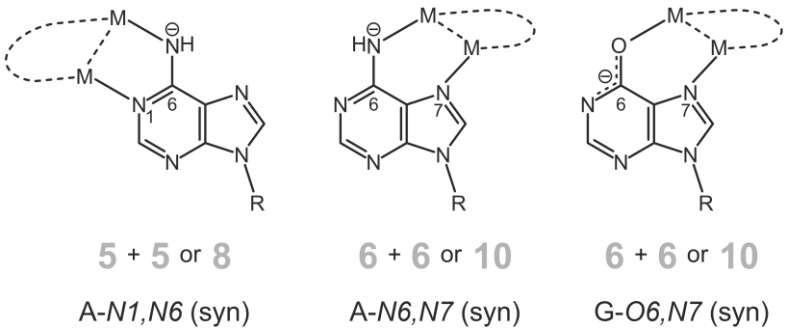
Metal cross-linking via N3 and one of the two (or both) exocyclic oxygen atoms in di-and trinuclear species again leads to 8-membered rings, with these being essentially flat, or folded via the central M–M' vector, depending on the coordination geometry (trans or cis) about the central M (Scheme 4). As with $1MeC_{-H}$ complexes, M and M' are *syn* in the majority of cases, and there is the possibility for M–M' interactions or bonding if M = Pt [39]. There are numerous structural variants of multinuclear U and T complexes feasible, which include, among others, formation of “spiro” type compounds, mixed 1MeU,1MeC complexes, or association via multiple H_2O/OH bridges into star-shaped supramolecular aggregates [45].



Scheme 4 *Schematic representations of cross-links of base pairs ([5-FU]$_2$; T/1,3-DDA) with linear metal ions (Ag^+), and binding of metals in 1-MeU/1-MeT complexes of cis-a_2Pt^{II}. In all cases the pym ligands are anionic (deprotonated at N3).*

3.2.3. Purine Nucleobases

Cyclic dinuclear purine complexes involve either combinations of N1 and N6 metal binding sites (adenine), or combinations of N7 and X6 with guanine/hypoxanthine (X = O) or adenine (X = NH^-) [46]. The first one is comparable to that of deprotonated C. All options can be realized in head-tail or head-head fashion, and charges of the nucleobases (anionic; neutral in normal or rare tautomeric form) are a function of pH. Depending on the existence or absence of bonds between the two metals, either two fused 5-ring chelates or a folded 8-membered ring are present in the first case, whereas two fused 6-ring chelates or a continuous 10-membered ring are present in the second case (Scheme 5). Typical examples include a diplatinum(II) complex of 9EtA (N1,N6; head-tail; no M–M bond; 8-ring) [47], a dirhenium(II) complex of 9EtA (N1,N6; head-head; fused 5-rings) [48], or a Cu(II) complex of inosine monophosphate, IMP (N7,O6; head-tail; no M-M bond; 10-ring) [49]. This latter compound displays a variation of the N7,O6 binding mode in that in addition Cu ions bind to the N1 sites of the deprotonated hypoxanthine ligands. Similar variations occur also in N1,N6 bridged 9MeA [50] or in N1,N6 bridged 8-aza-9-methyladenine complexes [51] with metal entities bonded in monofunctional ways to N7 positions of the two purine ligands. Interestingly, the tetracarboxylate complex of dirhodium(II) reacts with d(GpG) and d(pGpG) dinucleotides with substitution of two carboxylate bridges and formation of two head-head N7,O6 chelates of the two guanine bases [52].



Scheme 5 *X-ray structurally established metal coordination patterns in cyclic dinuclear complexes of A and G, without and with M–M bonds. The sequence of atoms within the rings depends upon relative orientations (head-tail or head-head) of the second purine base. For variations and protonation states of the bases, see text.*

In all mentioned complexes, the metals bridged by the purine bases are mutually *syn*, hence the two metals are roughly within the nucleobase plane by which they are joined, and facing each other. It is obvious that a strict *anti* orientation of the two metals, which is possible in acyclic dinuclear complexes, precludes a dinuclear closed ring structure.

3.2.4. Artificial nucleobase surrogates

A major development in recent years has been the synthesis of nucleobase surrogates that can be cross-linked by metal entities of suitable geometries [53]. Pyrrolocytosine and imidazolocytosine are representative examples [54]. The search for an optimization of their metal binding properties, for luminescence studies (e.g. quenching by Ag^+ ions), and surface patterning [55] have been driving forces behind these efforts.

3.3. Triangular Complexes

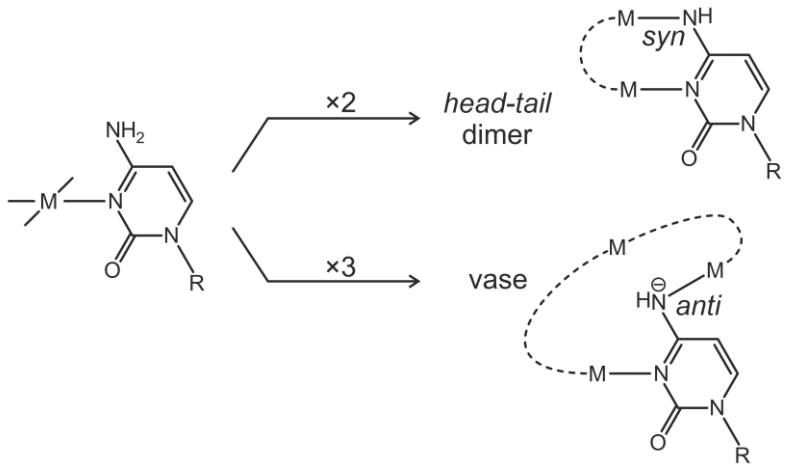
It is a frequently observed phenomenon in supramolecular chemistry with metals and organic ligands that spontaneously formed constructs come in different sizes ("supramolecular isomerism"), while the coordination sites are identical. Numerous variables such as solvent, temperature, counter ions, templating molecules, thermodynamics, entropy, as well as other factors can have an influence. Cyclic metal nucleobase complexes are no exception to this.

Apart from size, and restricting the bridging mode to a single one for all three nucleobases, there is nevertheless a considerable degree of complexity in such systems, which arises from the low symmetry of the nucleobases (C_s), the possibility of linkage isomerism, *and* the ability of the heterocyclic rings to adopt different rotamer states [8]. All possible stereoisomers are chiral.

3.3.1. Cytosine

As mentioned above, *cis*-$(PMe_3)_2Pt^{II}$ forms a dinuclear head-tail complex with 1MeC [31], but likewise a C_3 symmetrical cyclic trimer [56]. With the closely related *cis*-$(PMe_2Ph)_2Pt^{II}$ the initially formed head-tail dimer converts quantitatively into an analogous cyclic trimer when heated in DMSO, yet to an unsymmetrical cyclic trimer (second linkage isomer) in $CDCl_3$, as established by NMR spectroscopy [57].

Self-condensation reactions of [Pd(tmeda)(C-*N3*)(OH)]$^{+}$ with C = 1MeC [58] or cytidine [59] likewise lead to the symmetrical cyclic trimer. In it, a 12-membered ring [-M-N3-C4-N4-]$_3$, formally to be considered also a [12]metallaazacrown-3, functions as a belt in a double-cone structure, with three cytosine rings on one side, and three (tmeda)Pd^{II} entities on the other. As compared to the head-tail dimers of 1MeC$_{-H}$, the major structural difference in the C_3 symmetrical cycle refers, apart from ring size, to the different spatial orientations of the metals: They are *anti* in the trimer as opposed to *syn* in the dimer (Scheme 6 and Figure 1). It is likely that it is the steric bulk of the tmeda ligand in the Pd trimers which prevents head-tail dimer formation and drives the equilibrium toward the larger cycle.



Scheme 6 *Different relative orientations of metal ions in cyclic di- and trinuclear cytosine complexes. The C ligands are deprotonated at N4.*

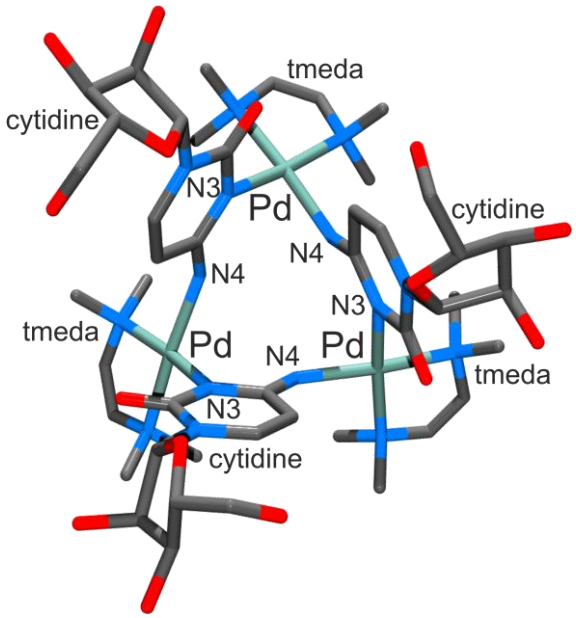
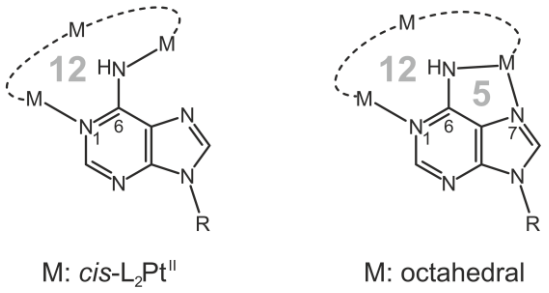


Figure 1 *View of the vase-shaped [(tmeda)Pd(C^{-})]$_3$ trimer (C^{-} = cytidine anion) [59].*

3.3.2. Adenine

C_3 symmetrical, cone-shaped metal complexes of adenine ligands (9MeA, 9EtA, AMP) have been known since 1992 [60] and have been reported, with different octahedral (Rh^{III} [60,61], Ru^{II} [62], Pt^{IV} [63], Ir^{III} [61]) or *cis*-square planar Pt^{II} metal entities [64]. As with the cyclic cytosine trimers, the bridged metals are *anti* with respect to each other, and the intermetallic distances within the 12-membered ring [-M-N1-C6-N6-]$_3$ are similar to those in the cytosine vase (5.2 – 5.5 Å), but the three π-faces in the adenine vases expectedly are larger. The difference between the cycles containing octahedral metal ions as opposed to a square-planar Pt^{II} is that in the former also N7 of the purine ring is involved in metal binding, hence that the octahedral metal ion is part of a 5-membered chelate ring as well (Scheme 7). Although possible based on structural considerations, isomers with N6,N7 bridge formation or cyclic trimers of lower symmetry (*e.g.* linkage isomers with N1,N6 bridging modes) have not been observed as yet.

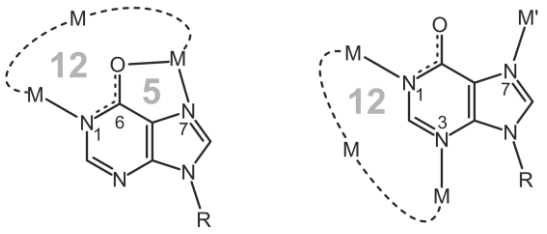


Scheme 7 *Different metal coordination patterns in cyclic adenine trimers, depending on the stereochemistry of the metal ions. The A ligands are deprotonated at N6.*

A major feature of the adenine vases is their receptor properties both for anions as well as a series of amino acids and carboxylic acids [65]. Since all C_3 symmetrical purine trimers are chiral, they form diastereomers when carrying chiral sugar moieties at their N9 positions, as is the case with adenosine, for example. K. Yamanari and coworkers have been able to isolate individual diastereomers of Cp^*M^{III} complexes (M = Rh, Ir) of adenosine nucleobases, and to assign their structures [61].

3.3.3. Hypoxanthine

Two qualitatively different metallacyclic trimers have been described which contain 9-alkylhypoxanthine (9RHx) anions: a Cp^*Rh^{III} analogue of the 9-methyladeninate complex referred to above [66] displaying O6,N7 chelation and additional bridging via N1 and N7, as well as a mixed Pt,Pd complex, in which a coordinatively saturated $(NH_3)_3Pt^{II}$ unit blocks N7, while three $(en)Pd^{II}$ entities cross-link N1 and N3 sites of 9RHx [67] (Scheme 8, Figure 2). A 12-membered ring as well, [-Pd-N1-C2-N3-]$_3$ is larger in the Pt_3Pd_3 vase than in the Rh_3 vase, with Pd–Pd distances of 5.7 – 5.8 Å. The inner cavity of the Pt_3Pd_3 vase fits perfectly for a perchlorate anion, which is stabilized inside by electrostatics, by anion- π interactions between the oxygen atom of the perchlorate and the three pyrimidine rings of the nucleobases, and by hydrogen bonding between the NH_3 groups and the three oxygen atoms of the perchlorate anion.



Scheme 8 *Two types of cyclic trimers containing N1-deprotonated 9RHx.*

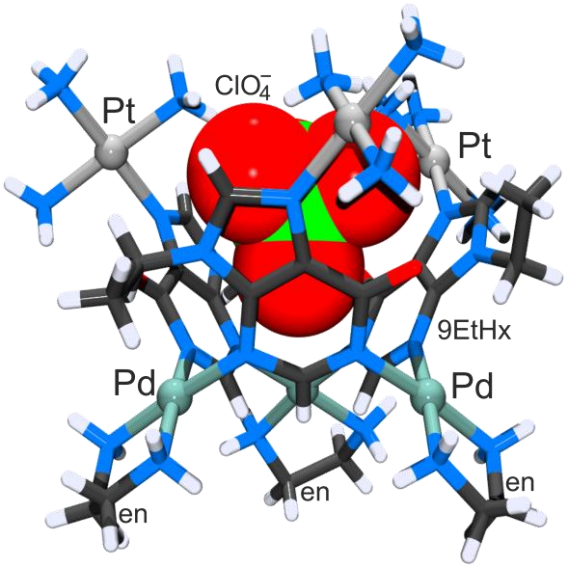
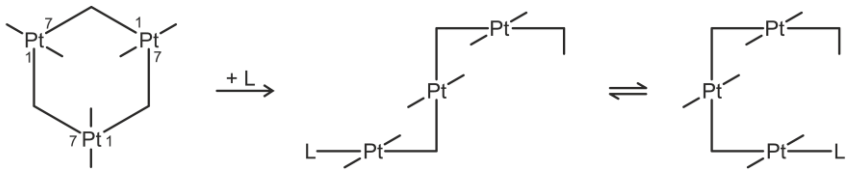


Figure 2 *View of the Pt$_3$Pd$_3$ vase [67].*

3.3.4. 9-Methylpurine

9-Methylpurine (9Mepur) is the parent compound of all purine model nucleobases, although it lacks the exocyclic groups of the biologically relevant purine bases. We nevertheless mention here a cyclic trimer structure containing this ligand, because it is unique, as it is flat. It forms as a byproduct during the synthesis of a flat molecular square (see 3.4.2) upon reacting 9-methylpurine with *trans*-(NH$_3$)$_2$Pt^{II} [68]. The trimer is highly strained and in the presence of nucleophiles readily opens up to give U or/and Z shaped cations with preferred 90° angles between Pt–N1 and Pt–N7 vectors (Scheme 9).



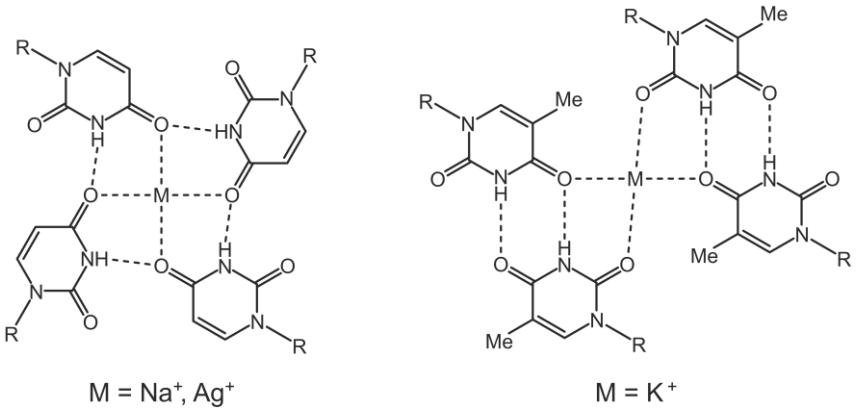
Scheme 9 *Ring opening of highly strained flat 9-methylpurine trimer in presence of a nucleophile L to relaxed states with 90° angles between Pt–N1 and Pt–N9 vectors.*

4. Molecular Squares and Boxes

4.1. Metals in the Center

The guanine quartet (G_4) found in quadruplex nucleic acids has become a major focus of structural biochemistry and biomedical research in recent years [4,69]. Of relevance to ageing, gene regulation, development of cancer and other diseases, as well as ways to interfere with these processes on rational, chemistry-guided strategies, has made the field of tetrastranded nucleic acids a highly active area. At the same time, G_4 provides a supramolecule *par excellence*, as it combines interbase hydrogen bonding with metal coordination (Na^+, K^+) and, in G_4 tetrads, also π-stacking. Reports on nucleobase quartets with any of the other bases (A_4, C_4, T_4, U_4) or mixtures of bases (e.g. $[GC]_2$, $[TA]_2$, $[AG]_2$, [GCAT]) and with different cation fillings (e.g. also with NH_4^+, Ba^{2+}, Sr^{2+}, Pb^{2+}, Tl^+,…) is ever increasing. There is even the question if anions might be able to stabilize particular C_4 or A_4 structures [70]. From structural studies it has become clear that, with the possible exception of G_4, many of the other quartets are dynamic and come in variants, and that consequently any X-ray structure of a nucleobase quartet may be considered a snapshot of a specific bonding situation only.

It is a paradoxical situation that there is presently no X-ray crystal structure of G_4 with simple model nucleobases available. Rather these G models seem to form preferentially polymeric 2D tape structures with intermolecular hydrogen bonds between the bases. In contrast, the model pym nucleobases 1-methyluracil, 1-hexyluracil, or 1-ethylthymine form quartet structures in the presence of suitable metal salts. Thus, a 1-methyluracil quartet with a central Na^+ and a planar anion, $[AuCl_4]^-$, has been reported in 1990 [71], a perfect model of U_4 observed in a RNA tetraplex more than a decade later [72]. Also a saddle-shaped variant of this quartet, stabilized by a central $(NH_3)Pt^{IV}$ unit [73], and more recently, a 1-hexyluracil quartet with a central Ag^+ ion have been described [74]. 1-Ethylthymine (1EtT), on the other hand, does not behave strictly analogous to 1-methyluracil, neither with Na^+ nor with the larger K^+ [75]. Instead, different nucleobase association motifs are seen which, among others, correspond to a segregation of a putative quartet into two doublets connected by K^+ (Scheme 10). In the presence of a central tetrahedral metal ion, e.g. Co^{2+}, any nucleobase quartet cannot adopt a planar structure, as shown by De Munno et al in the case of $[Co(1MeC\text{-}N3)_4]^{2+}$ [76]. On the other hand, metal hexaqua cations (M = Co^{2+}, Mn^{2+} [76], or Mg^{2+} [77]) can spatially organize four or six 1MeC model nucleobases around the metal center in a combination of direct coordination (through O2) and H bond formation involving the aqua ligands [77], or exclusive H bonding [76,77]. As proposed by the authors, in solution both structures may co-exist.

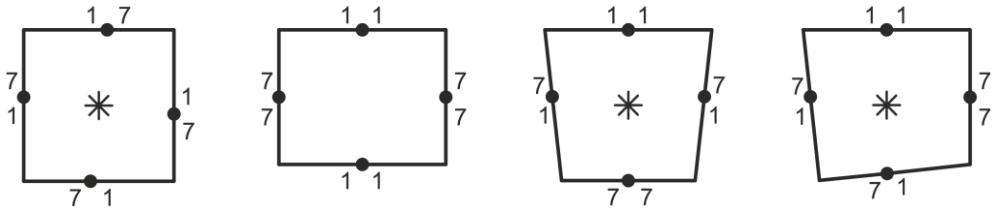


Scheme 10 *Uracil quartet (left) and two TT pairs joined via K^+ (right). Additional TT pairing patterns in dependence of anions present are realized, but not shown.*

4.1.1. Metals at the Periphery

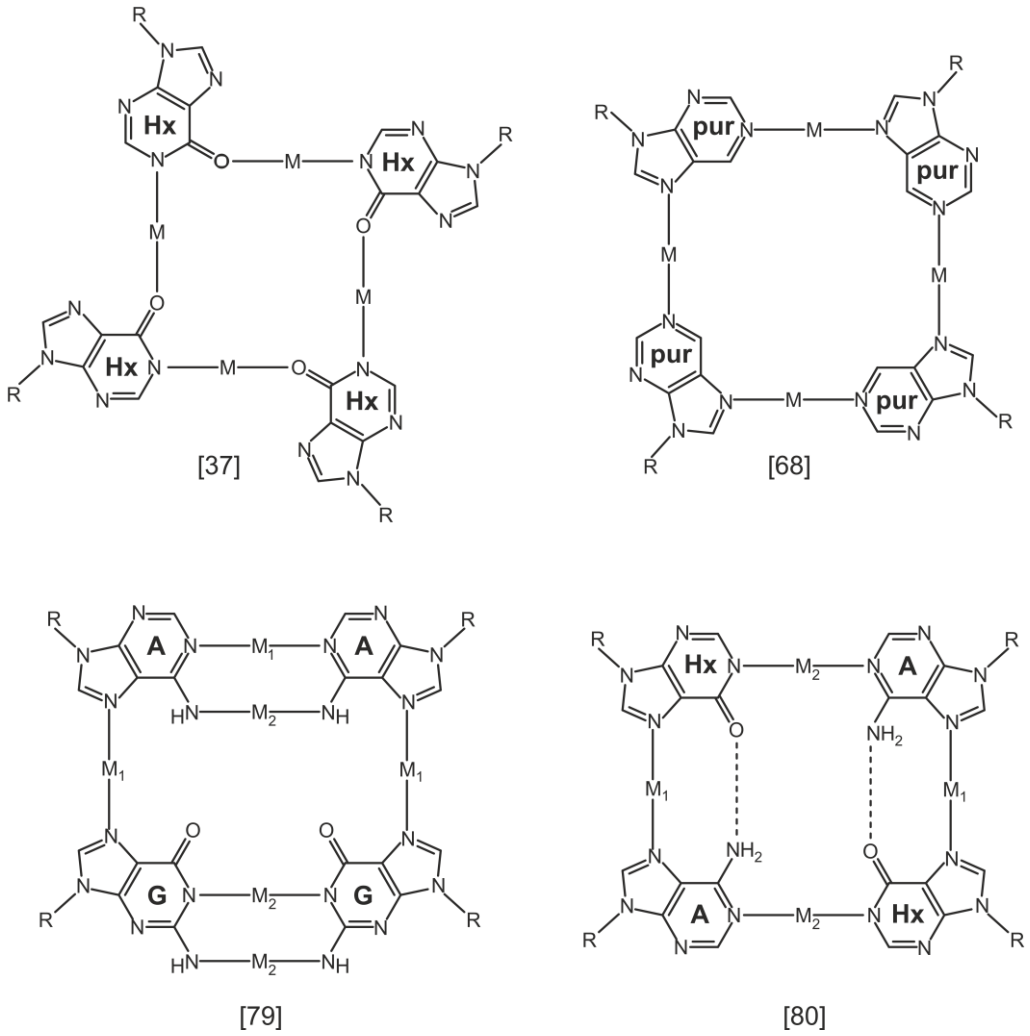
In 1980, on the basis of X-ray powder diffraction data, Y. A. Shin and G. L. Eichhorn proposed a model of how polyinosinic acid (polyI) reacts with Ag^+ [37]. According to their analysis, the hypoxanthine (Hx) bases become deprotonated at pH 8 at N1, and four polyI strands are then cross-linked in linear fashions by Ag^+ ions via N1 and O6 positions in *anti* orientations to give a metalated tetraplex with stacked $[AgHx]_4$ quartets. However, based on model building, it would appear that other combinations such as N1,N7 or N7,N6(*anti*) would be equally or even more suitable to allow for an unstrained tetrastranded structure, and that the proposed N1,O6(*anti*) pattern would be more suitable for an association of more than four strands.

Taking into consideration that N7 and N1 sites are the preferred metal binding sites in purines, and that M–N1 and M–N7 vectors in purines form angles of close to 90°, we later set out to synthesize "flat" quartets applying linear *trans*-a_2Pt^{II}, sometimes in combination with linear Ag^+ or linear Hg^{2+} ions. In the simplest case —four identical purines, four identical linear metal entities— four linkage isomers differing in their connectivity patterns, are feasible (Scheme 11): an ideal square, a rectangle, and two irregular squares. While the former two are planar, the latter two are markedly non-planar. With the exception of the rectangle, the three other linkage isomers are chiral. Combinations of different purines, *e.g.* of A and G, lead to many more isomers but can provide the opportunity of favorable hydrogen interactions between exocyclic O6 (G, H) and $N6H_2$ sites (A) inside the cycle. For two adenine bases cross-linked through their N7 atoms, the additional possibility exists that loss of a single proton from one of the two $N6H_2$ groups allows for an extra stabilization by a $N6H^-\cdots HN6H$ hydrogen bond [78].



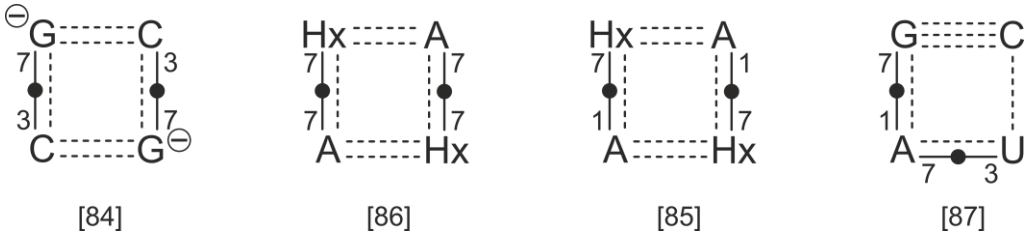
Scheme 11 *Schematic representations of the four possible isomers of cyclic metal-purine tetramers (single type of purine and metal) with exclusive metal coordination through N1 and N7. Chiral entities are marked.*

Scheme 12 provides schematic views of the Shin/Eichhorn model [37] and of selected metalated molecular squares from the Lippert group [68,79–82]. Of similar dimensions as the natural purine squares, these artificial metalated purine squares combine properties which are both similar and contrasting to the natural ones. A major difference are anion binding properties of the metalated squares, which are a consequence of their different overall charges and the presence of co-ligands capable of acting as hydrogen bond donors if *trans*-a_2Pt^{II} is the metal entity [30a,68]. Surprisingly, however, these cationic squares occasionally also have the ability to bind alkali metal ions, very much like G_4 (see also below). After all, a *trans*-a_2Pt^{II} rectangle comprised of four 9MeG model bases has its four O6 atoms located at the corners of an almost ideal square of 4.1×4.1 Å [81].



Scheme 12 *Schematic views of postulated Hx-Ag⁺ quartet [37] and of X-ray structurally characterized purine square [68] and rectangles [79,80].*

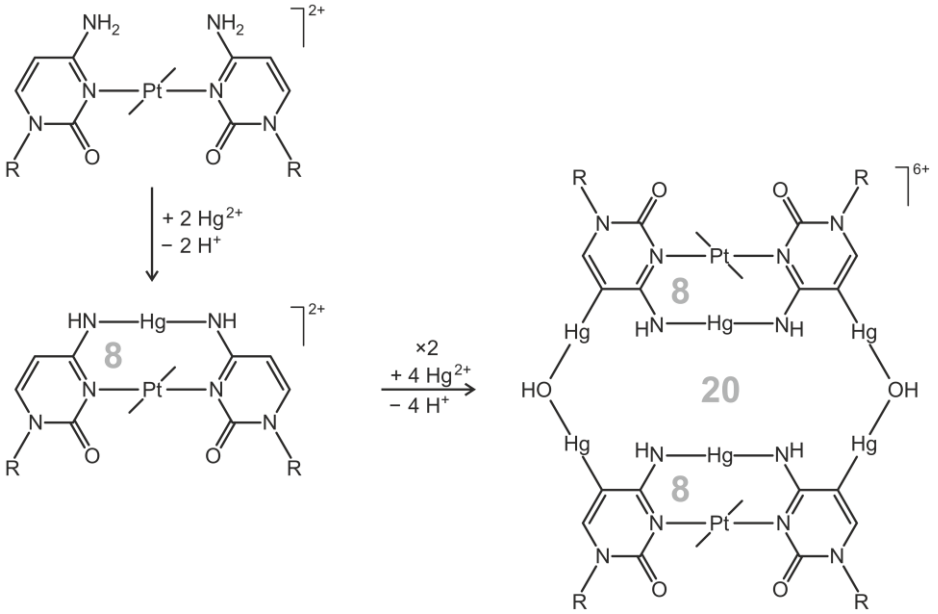
In addition to forming closed tetranuclear cycles with eight coordinative M–N(pur) bonds, there exists also the possibility that open $M_3(nb)_4$ fragments form [82], or quartets that are joined through hydrogen bonds, thereby producing closed structures [83–87]. Selected examples are given in Scheme 13. Complementarity between individual components, *e.g.* between metalated base pairs, e.g. (A)–M–(Hx), or between a metalated nucleobase, *e.g.* G, and its natural counterpart C is key, and consequently not just a solid state effect, but also detectable in solution. Surprisingly, occasionally also unconventional base pairing patterns, involving aromatic H atoms, are observed [83,84,87], which have become subject to computational studies [88].



Scheme 13 *Schematic representations of metalated nucleobase squares which combine metal coordination with hydrogen bonding between complementary faces and/or exocyclic groups.*

Thus far, we have concentrated on systems of metalated purine squares in which largely or exclusively N1 and N7 positions are used as metal binding sites. As demonstrated in an impressive way by S. Verma and his group, modifications of the 9-substituents of adenine model nucleobases allows for a plethora of additional metal coordination patterns [89]. Because in many cases the complexes isolated proved polymeric, they will not be further discussed here. It suffices to say that that other sites than N1 and N7 also become involved in metal binding.

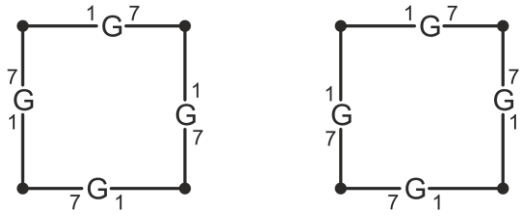
There is presently no small-molecule, biorelevant model of a metal-containing flat cytosine quartet available. However, an artificial, highly metalated Pt_2Hg_6 species has been obtained by reacting *trans*-$[a_2Pt(1MeC\text{-}N3)_2]^{2+}$ with an excess of Hg^{2+} [90]. In this complex, Hg^{II} cross-links two N4H$^-$ positions of head-head oriented C ligands, and in addition, there are two Hg–OH–Hg bridges between the four 5-positions of the 1-methylcytosinato dianions (Scheme 14). The cation, which displays two 8-membered rings of the type discussed above and a central 20-membered ring, is essentially flat.



Scheme 14 *Flat, heavily metalated cytosine quartet [90].*

Coordination of two N-heterocyclic rings to a metal ion of cis-square planar or cis-octahedral geometry inevitably prevents a coplanar orientation of these, but rather forces them to adopt large dihedral angles, up to the point that the two planes may be perpendicular to each other. If arranged in a cyclic, closed fashion, this provides then the impression of a 3D prism. In the case of four metal ions, ideally an "open box" structure is formed. With the unsymmetrical purines, a large number of stereoisomers exist if again only N1 and N7 are considered metal binding sites. This is a consequence of linkage isomerism *and* the possibility to adopt different rotamer states, in principle [8]. Applying the calix[4]arene nomenclature, these rotamers may be considered to have cone, partial cone, 1,2-alternate or 1,3-alternate conformations. Due to differences in energy, only a limited number of these stereoisomers is expected to be formed, however. Regarding the existence of a C_4 symmetrical metalated G_4 box, obtained by reacting $(en)Pd^{II}$ with 5'-guanosine monophosphate (5'-GMP) or the analogous 5'-IMP in water for several days, it was first postulated by I. Harada et al. in 1989 [91]. W. S. Sheldrick and coworkers later confirmed formation of a cyclic tetramer by use of mass spectrometry, but assigned it a lower symmetry as a consequence of pairwise coordination of Pd to two N7 sites in

two opposite corners, and two N1 sites in the others [92] (Scheme 15). This finding was essentially confirmed by J. A. Walmsley [93], who also noticed a ring expansion to a cyclic hexamer in the presence of hydrophobic guest molecules.



Scheme 15 *Cyclic 5'-GMP quartets of (en)Pd^{II} as proposed by Harada (left) and by Sheldrick (right).*

N1,N7 bridging of Cu^{II} ions in the four corners of a box by 9MeA is realized in a compound reported by S. Pérez-Yánez and O. Castillo et al. [94]. Although a polymer, we mention it here, as the polymeric nature is propagated by isophthalato ligands rather than the adenine nucleobases. The four purines are disposed in an alternating fashion up and down (1,3-alternate), but within each side there is a 50:50 disorder due to an inversion of N1 and N7 coordination sites.

By applying N9-amine-tethered purine nucleobases, A. Houlton and coworkers have prepared a series of metal complexes with interesting features [11]. Among these, tetrameric guanine species have been crystallized which, depending on the metal and its co-ligands applied, had the shapes of a "box" (Pd_4 species) or of a flat rectangle (Cd_4 species). The structural difference originates from the fact that in the Cu complex the metal ion displays N3 coordination in addition to involvement of N7 and the chelate formed by the amine tether, unlike in the Cd compound [95]. As pointed out by these authors "these two base quartets may be considered as open and closed counterparts", suggesting that small, external ligands binding to a metal or being removed, might shift one form of a purine quartet to another one.

Yet another shape of a hypoxanthine quartet with metal ions cross-linking N1 and N7 positions is generated, if linear metal entities (*trans*-a$_2$Pt^{II}) *and* cis-square planar ones ((en)Pd^{II}) are used in combination. Upon reaction of *trans*-[Pta$_2$(9MeHxH-*N*7)$_2$]$^{2+}$ with (en)Pd^{II}, a tetranuclear Pt_2Pd_2 complex is obtained, which displays the shape of an "open book" [96]. Despite the required deprotonation of all four 9-methylhypoxanthine ligands, no alkaline pH is required to accomplish this reaction. Interestingly, the +4 cation of composition [{Pt(NH$_3$)$_2$}$_2${Pd(en)}$_2$(9MeHx-*N7,N1*)$_4$]$^{4+}$ picks up alkali metal ions (Na^+, K^+) during crystallization from water, to give a corresponding alkali adduct (Figure 3). Binding of the alkali metal ion takes place via the four exocyclic O6 oxygen atoms of the four 9-methylhypoxanthinate ligands, which again appears to be a consequence of nucleobase deprotonation and is reminiscent of the behavior of natural G quartets to bind cations. O–O distances within the squares formed by the four O6 atoms are very similar, averaging 3.100(5) Å.

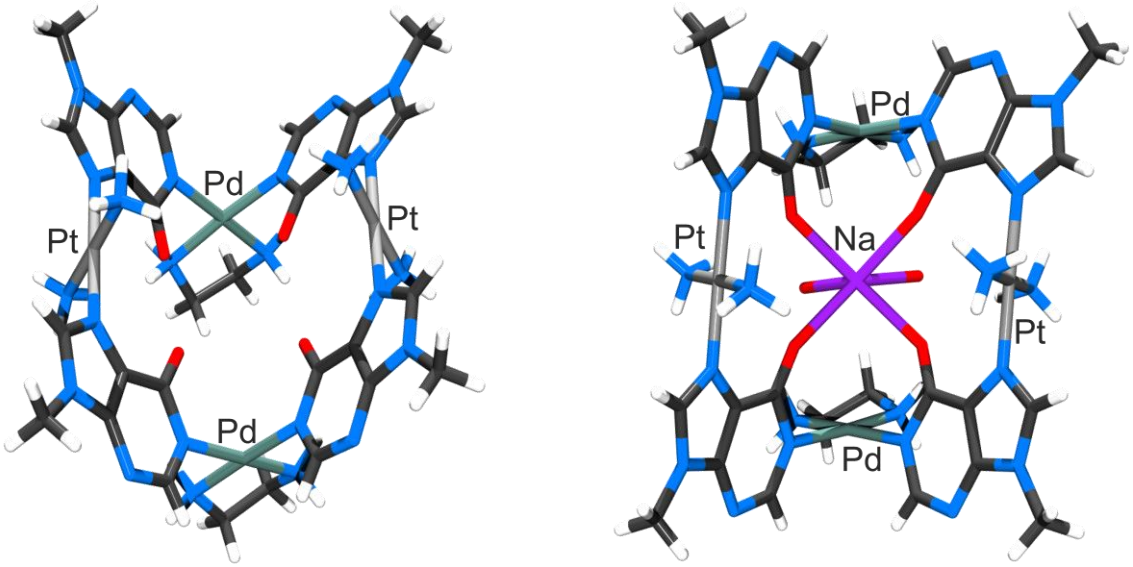
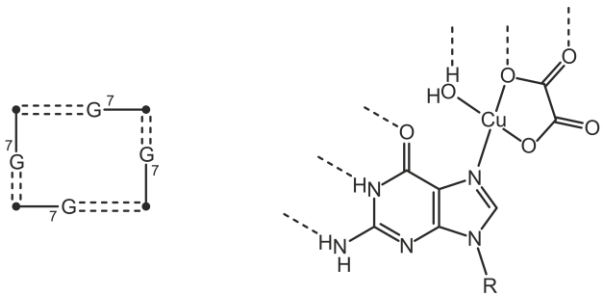


Figure 3 *Schematic view of "open book" structure with four anionic 9MeHx ligands (left) and view of cation with Na^+ bonded to the four O6 atoms of the Hx ligands.*

A straightforward way of assembling purine metal complexes in a defined alternating $[N1,N7]_n$ way is, at least for kinetically robust complexes, if monomeric M(*N1*-pur) or M(*N7*-pur) complexes are applied as precursors (*c.f.* for cytosine complexes). With 9-alkylguanine and 9-alkyladenine compounds this strategy has thus far not been successful. A conceptually similar approach has been applied with a neutral Cu^{II} complex, $Cu(ox)(H_2O)_2$(9MeGH-*N7*) (with ox = oxalate) [97], albeit with a somewhat different result: Rather than using Cu–(*N1*-9MeG) bonds to generate a cyclic array, hydrogen bonds involving the Watson-Crick face of the neutral guanine as well as hydrogen bonds of the oxalate and the coordinated water molecule are utilized for the generation of a rectangular construct (Scheme 16).



Scheme 16 *Generation of a metalated G rectangle employing coordinative bond formation to N7 and hydrogen boding between the G ligands and co-ligands at the metal [97].*

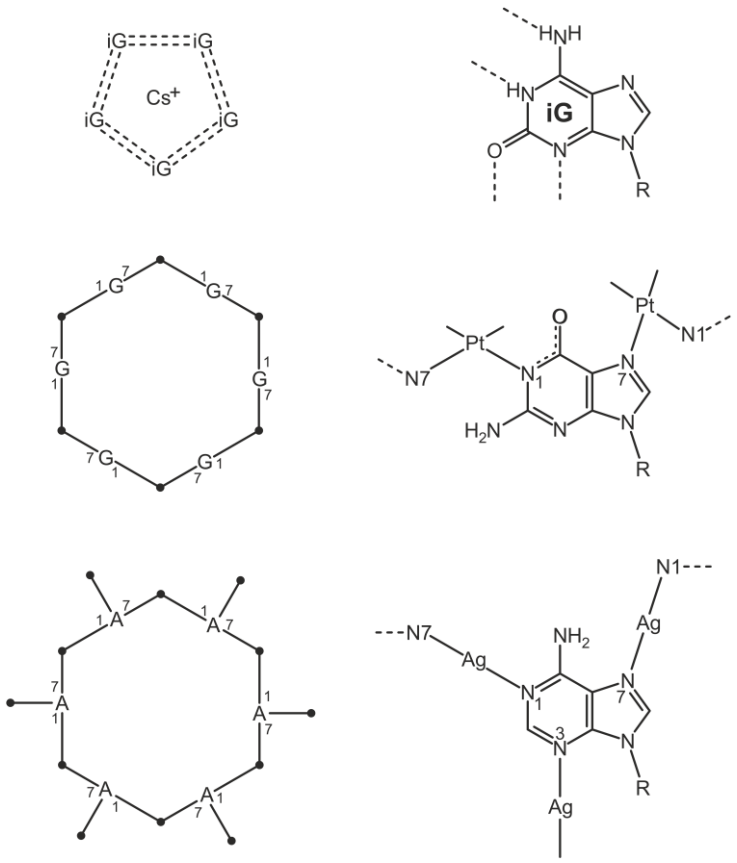
4.1.2. Boxes Derived from M(nb)4 Species

In several cases heteronuclear derivatives of tetrakis(nucleobase) complexes of Pt^{II}/Pd^{II} with nb = 1MeU [98], 1MeC [34], and 9MeHxH [99] have been prepared and characterized. With M being bonded through N3 (1MeU, 1MeC) and N7 (9MeHxH), respectively, the heterometals are coordinated through exocyclic nucleobase donor atoms (O4 of 1MeU, N4 and O2 of 1MeC, O6 of 9MeHxH), thereby producing box-like structures. Frequently, these compounds display short intermetallic distances.

4.2. Larger Cycles and Cages

4.2.1. Isoguanine Pentamer

Although a non-standard nucleobase, N9-substituted isoguanine (iG) displays a unique association pattern in the presence of alkali metal ions. With K^+ it forms an octamer, which consist of two bowl-shaped tetramers with a K^+ ion interconnecting the eight O6 atoms [100], whereas in the presence of the larger Cs^+ ion, iG aggregates into a flat pentamer [101] which, if incorporated into an oligonucleotide, can be used to construct a DNA pentaplex [102]. Interbase hydrogen bonding is through the Watson-Crick face and the sugar edge of the isoguanine (Scheme 17).



Scheme 17 *Illustrations of iG pentamer (top) [101,102], platinated G hexamer (middle) [103], and section of a polymeric Ag^+ complex of an A ligand carrying a coordinating carboxylate function at the N9 position [105].*

4.2.2. Metalated Hexamers

Nucleobase hexads occurring in multistranded DNA or RNA frequently are composed of a central G_4 unit with additional bases hydrogen-bonded to the outside [1]. There are, however, very few cases where transition metal ions cross-link six nucleobases. The first example, reported by B. Longato and coworkers in 1995 [103], is a cyclic hexamer of S_3 symmetry, in which six *cis*-$(PMe_3)Pt^{II}$ centers are bridged by six 9-methylguaninato bases in strictly alternating N1,N7 fashion, with O6 atoms of the 9MeG ligands pointing up, down, up, down, up, down. As can be expected, the purines form large angles (ca. 50°) with the best mean plane through the six Pt atoms (Scheme 17).

An interesting alternative structure of a hexanuclear 6-purinethione riboside metal complex is realized with $[M(Cp^*)(H_2O)_3]^{2+}$ (M = Rh^{III}, Ir^{III}) [104]: In the Rh complex, for which an X-ray crystal structure is available, the six purines form the sides of a cube, and the cation is of S_6 symmetry. Each purine base chelates one metal through N7 and S6, while bridging at the same time to N1.

A polymeric structure of a Ag^+ compound with 9-(carboxypropyl)adenine nucleobases has been described by S. Verma et al., in which likewise distinct hexameric ring motifs are seen [105]. The adenine rings in the cycle consist of strictly alternating N1,N7 bridging ligands, with additional Ag^+ ions protruding from the N3 positions of each adenine, while the $N6H_2$ groups are pointing toward the center of the puckered hexagon (Scheme 17).

4.2.3. Metalated Octamers

Two cases of octanuclear metal nucleobase complexes, both having "wheel" structures and composed of eight Cu^{2+} ions and eight pym nucleosides, need to be mentioned: a uridine complex [106] and a cytidine complex [107]. These compounds not only involve Cu^{II} binding to the heterocyclic nucleobases (N3,O2 chelation in case of cytidine, N3 binding to uridine), but also to deprotonated sugar moieties (singly deprotonated with cytidine; twofold deprotonated in case of uridine). Thus, cytidine has a charge of –1, whereas uridine has one of –3, as N3 is deprotonated as well. As a result, and ignoring anions coordinated to the Cu centers, the cytidine wheel is formally a +8 cation, whereas the uridine wheel is formally a –8 anion. In both ions the metals occupy corners of a distorted square antiprism, with closest Cu–Cu distances being in the order of 3 Å. There is yet another feature common to both structures, namely the presence of a hexaquametal cation in the center, $[Na(H_2O)_6]^+$ in the uridine complex, and $[Cu(H_2O)_6]^{2+}$ in the cytidine complex.

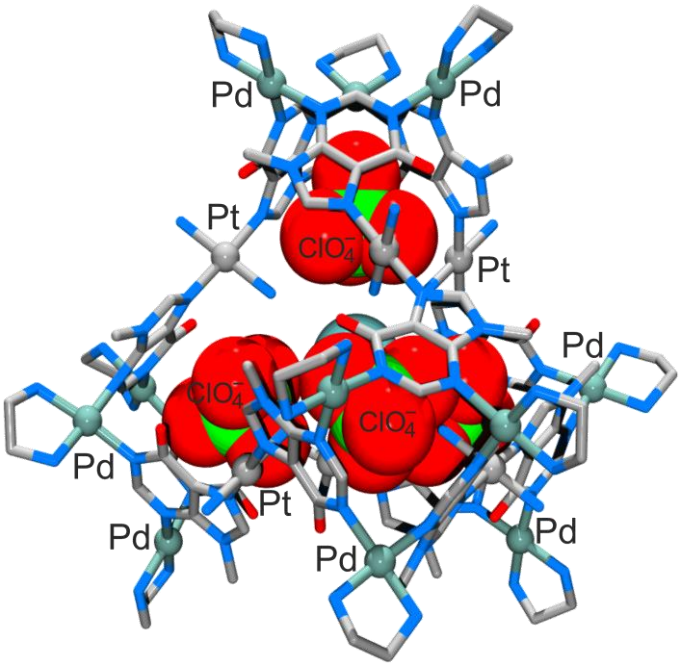
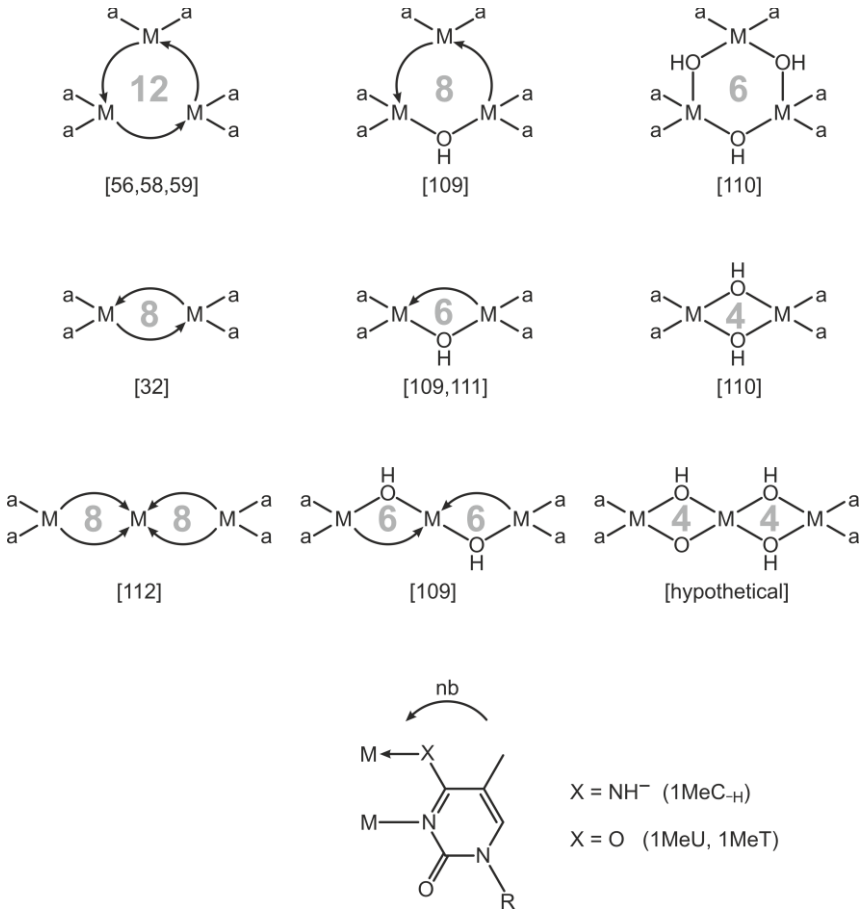


Figure 4 *Schematic view of the Pt_6Pd_{12} truncated tetrahedron [96], including four perchlorate anions and a water molecule as guests.*

In addition, a folded hypoxanthine rectangle was mentioned (see 3.4.2), which has the shape of an "open book" and which was obtained by reacting *trans*-$[Pt(NH_3)_2(9MeHxH\text{-}N7)_2]^{2+}$ with $(en)Pd^{II}$. A seemingly minor change in pH, from ca. 7 to ca. 4 has a profound effect on the outcome of the reaction: instead of producing the tetranuclear Pt_2Pd_2 complex, a Pt_6Pd_{12} complex is formed at lower pH, which has the shape of a truncated tetrahedron [96]. It is composed of four molecular vases of the type described, hence with N1,N3 bridged $(en)Pd^{II}$ ions, which in turn are cross-linked by *trans*-$(NH_3)_2Pt^{II}$ via N7 sites rather than carrying $(NH_3)_3Pt^{II}$ units at this position. The four vases are directed toward the corners of a tetrahedron (Figure 4). The inner cavity is occupied by four perchlorate anions and a water molecule. As in the case of the Pt_3Pd_3 vases, electrostatics, anion- π interactions, and hydrogen bonding keep the guests within the tetrahedron.

4.3. Mixed Bridging Entities

In a number of cases cyclic compounds of Pt^{II}/Pd^{II} containing simultaneously bridging $1MeC_{-H}$ and bridging hydroxide ligands have been isolated [33,108,109]. Formally, these mixed μ-nb, μ-OH species may be derived from cyclic compounds containing exclusively μ-OH [110] or exclusively μ-nb bridges (Scheme 18). Their realization is associated with ring size expansion or ring size reduction. Analogous structures may be derived from the other common nucleobases as well [109], but only for 1MeU and 1MeT a limited number of analogues is available [111,112].



Scheme 18 *Mixed μ-nb, μ-OH species (center) derived from μ-nb compounds (left) or μ-OH compounds (right). M = Pd^{II} or Pt^{II}, a = NH_3, a_2 = diamine.*

In a variation of this theme, pentanuclear compounds containing both μ-OH and μ-NH_2 bridges in addition to μ-1MeC$_{-H}$ ligands have also been prepared and structurally as well as spectroscopically characterized [108,109]. Ring closure in these Pt_2Pd_2Ag and Pt_4Ag species is achieved by Ag^+ in a combination of weak N4 binding to one of the 1MeC$_{-H}$ bridges as well as dative bonds between the four d^8 metal ions and a central Ag^+ ion. By further utilizing also available O2 sites of the bridging 1MeC$_{-H}$ nucleobases in the presence of excess Ag* ions, these pentanuclear units can be expanded to either discrete dodecanuclear $Pt_4Pd_4Ag_4$ species [108], or to a coordination polymer of composition Pt_4Ag_2 [109].

4.4. Miscellaneous

Principles leading to the formation of cyclic metal complexes with isolated nucleobases, as described in this review, can also be transferred to covalently linked nucleobases. For example, 5,5'-diuracilyl, generated from monomeric uracil via an oxidative dimerization accomplished by $[AuCl_4]^-$, binds Na^+ ions through its exocyclic oxygen atoms, forming simultaneously 7- and 12-membered rings [113], and bis(1-methyluracil-5-yl)methane, when coordinated to *cis*-a_2Pt^{II} or (en)Pd^{II} via N3 sites, arranges into cyclic metallacalix[*n*]arene structures of different size, nuclearity, and shape [114].

5. Summary and Outlook

Having highlighted a large number of cyclic metal nucleobase complexes, some comments regarding their relationship to Supramolecular Chemistry are appropriate. It would certainly be undue to claim that nucleobases are “ideal” constituents to generate supramolecular constructs in a spontaneous fashion. Although providing numerous metal binding sites, the low symmetry of nucleobases (C_s) and the electronically different donor sites make them, in general, poor building blocks for high-yield self-assembly processes. Exceptions are the natural nucleobase quartets which combine cyclic hydrogen bond formation with metal binding in their center. The situation thus contrasts that of highly symmetrical ligands which can form large symmetrical entities [115]. The inherent differences in the strengths of metal-donor bonds in a low-symmetry ligand necessarily reduces chances of self-healing processes during aggregation, in particular if kinetically robust metal-ligand bonds are formed. Similar to the situation in classical organic synthesis, a stepwise build-up of larger aggregates appears to be a way out of this dilemma. As has been shown in numerous cases, starting from 1:1 or 1:2 complexes having the kinetically or thermodynamically preferred metal-nucleobase bonds, subsequent utilization of other donor sites eventually can lead to larger supramolecular units, the structures of which markedly depend upon the spatial orientation of the metals (*syn* or *anti*) and on rotational isomerism of the nucleobases, however. Regarding the future and possible applications of this chemistry with nucleobases, apart from uses as telomerase inhibitors [116], as receptor molecules [65], components of Metal Organic Frameworks [94], and for surface patterning [89], an extension to polynucleotides and DNA is highly promising [117], as it leads into a field of novel functional nanomaterials.

6. Acknowledgements

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