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Impact of Cisplatin on the recent development of Pt coordination chemistry: a case study

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Abstract

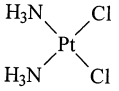
An overview is presented on recent developments in selected areas of Pt coordination chemistry which were a direct consequence of the discovery of the antitumor activity of *cis*-$Pt(NH_3)_2Cl_2$ (Cisplatin). These include complexes of Pt^{II} with oxygen donor atoms, mixed-valence state Pt compounds as well as diplatinum(III) complexes, and compounds containing nucleobases as well as a limited number of other heterocyclic ligands. Both the potential biological relevance of these compounds and the role *cis*- and *trans*-$(am)_2M^{II}$ ($am = NH_3$ or amine; M = Pt, Pd) entities are playing in the construction of regularly shaped molecules ('molecular architecture') are briefly outlined.

Keywords: Cisplatin; Transplatin; Nucleobases; Coordination chemistry

1. Introduction

Although in use as a metal since at least the 7th century B.C., the chemistry of platinum and the systematic study of its metallurgical and physico–chemical properties did not start until 250 years ago, following the rediscovery of platina (spanish: little silver) in Columbia by the Spanish, and its subsequent announcement in Europe. Platina was by no means a single metal as we know today, but rather an ore that contained approximately ten other metallic elements, among others all the other platinum group metals and Fe, Mn and traces of Cu. It immediately caught the attention of chemists at that time with studies carried out mainly in Spain and England. Among others, Proust was working on the purification of platinum while in Segovia and Madrid [1]. The 19th century brought the discovery of the first organometallic compound of any metal, $K[PtCl_3(C_2H_4)]\cdot H_2O$ by Zeise (1830), and numerous reports on inorganic platinum ammine complexes by scientists such as Peyrone, Reiset, Cossa, Cleve, and Magnus. It was the 'Theory of Coordination' of Werner which, by the end of last century, provided an explanation for the constitution of many of these complexes. During the 20th century the development of metal catalysts for industrial production processes, many of which contain Pt or platinum group metals [2], was a major goal. Termed once a 'master of transmutation', platinum has been estimated to be used in the manufacture of one out of five of today's products [3].

Rosenberg's serendipitous discovery of the ability of a metal coordination compound, *cis*-$Pt(NH_3)_2Cl_2$ (**1**), to block DNA replication and cell division [4] and subsequent findings that the very same agent, then termed Cisplatin, and many structural analogues are potent antitumor agents [5], has influenced tremendously the development of inorganic metal coordination chemistry over the last 30 years.



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For the first time the usefulness of drugs containing a heavy metal in cancer chemotherapy had been demonstrated. Today Cisplatin is considered one of the most successful antitumor agents [6]. It is generally agreed upon that the discovery of Cisplatin and attempts to understand its mode of action had a substantial impact on the research of interactions between metal ions and living matter in general, and on the whole field of Bioinorganic Chemistry [7]. The success of the conference series 'International Symposia on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy', launched in 1970 in East Lansing, USA, and the regular coverage of these aspects during the 'International Conferences on the Chemistry of the Platinum Group Metals', started in 1981 in Bristol, UK, as well as publication of excellent monographs [8] and review series [9] dealing with metal–biomolecule interactions, reflect this development.

This review tries to highlight some of the developments in the area of platinum coordination chemistry since the discovery of Cisplatin, and in particular in that of Pt-nucleobase chemistry. The examples chosen are close to the author's research interests and for this reason are not to be considered comprehensive. For in-depth coverage of Pt chemistry, other sources are to be consulted [10–12].

2. Platinum coordination chemistry: some old questions and new aspects

2.1. Pt^{II} compounds containing oxygen donor ligands

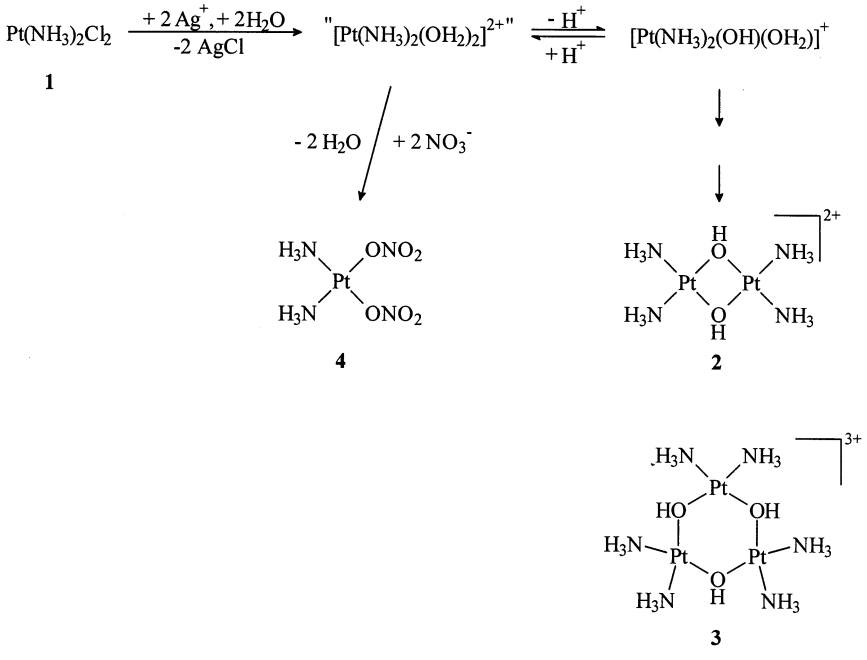
There has been a long-standing prejudice, possibly as a consequence of an over interpretation of the concept of hard and soft acids and bases (HSAB) [13], that the soft Pt^{II} ion might not be able to produce stable complexes with hard oxygen donor atoms, due to the inherent weakness of Pt^{II}–O bonds. This appeared to be true in particular for Pt^{II} hydroxo species, even though in the late 1960s it was generally agreed upon that stable bis-μ-hydroxo complexes of Pt^{II} exist and can be isolated [14]. Today the existence of such species as well as that of mononuclear ones with terminal OH groups is undisputed and their involvement in catalytic reactions is well established [15–17]. In contrast, compounds with two chelating or bridging oxygen donors as seen in acetylacetonato [18], carboxylato [19–21] or dicarboxylato ligands [22,23] have not been questioned [10]. In fact, the second most widely used antitumor drug today is $Pt(NH_3)_2$(cbdca), Carboplatin (cbdca = cyclobutane-

1,1-dicarboxylate), and its activity is ascribed to its robustness toward ligand displacement reactions and the slow opening of the dicarboxylato chelate [24]. t–O bond dissociation energies of *cis*-diam(m)ineplatinum(II) dicarboxylates are in the order of 380 kJ mol^{-1} and consequently comparable to the energy of C–C bonds [25]. Pt–O bonds in 2,4-dionato complexes are expectedly weaker (ca. 183 kJ mol^{-1}) [25].

The interest in hydroxo complexes of Pt^{II} was markedly influenced by the understanding that activation of the antitumor drug Cisplatin and the analogous $Pt(en)Cl_2$ compound (en = ethylenediamine) inside a cell occurs via a stepwise hydrolysis of the chloro ligands. The thermodynamics and kinetics of these processes and the speciation of the mononuclear solvolysis products are known today [26]. Their reactivities toward biomolecules, e.g. DNA, are different [27], and there is strong indication that the various species and/or possible condensation products may display different degrees of toxicity. For example, it has long been known that aqueous solutions of Cisplatin become more toxic on aging.

When the chloro ligands of Cisplatin are removed upon treatment with $AgNO_3$ in water, a complicated mixture of hydrolysis products forms, depending on pH and concentration (Scheme 1).

A number of different μ-OH-condensation products of Cisplatin have been crystallized and X-ray structurally characterized, e.g. di- (**2**) [28–30] and trinuclear (**3**) [31,32] compounds. Depending on the anion present, these species can display

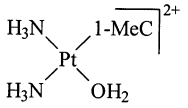


Scheme 1.

interesting variations in their solid state structures. A mononuclear complex, *cis*-$Pt(NH_3)_2(ONO_2)_2$ (**4**) has likewise been crystallized [33]. Considering the high neurotoxicity of **2** and **3** in mice [34], there is reason to believe that these species may be responsible for the adverse effects of aged solutions of Cisplatin. ^{195}Pt-NMR spectroscopy of aqueous solutions containing these species clearly revealed the inertness of these species in solution [35–37]. Also in the course of this work species with a single OH bridge have been detected [38,39], and more recently an interesting tetranuclear derivative of *cis*-$(NH_3)_2Pt^{II}$ with two μ_4-carbonato bridges has been structurally characterized [40]. With the Cisplatin analogues *cis*-Pt(dach)Cl_2 (dach = 1,2-diaminocyclohexane) [41] and $Pt(en)Cl_2$ similar hydrolysis products have been isolated, including a cyclic tetranuclear species $[\{Pt(en)OH\}_4](NO_3)_4$ [42].

Numerous other examples of bis-μ-OH-complexes of Pt^{II} have been reported since, such as with (diphenylphosphino)-ferrocene entities instead of am(m)ine groups [43], with a bent [44] instead of a planar dihydroxy bridge, or with a single OH bridge only [45,46]. It has also been shown that μ-dihydroxo bridges can be converted into (bent) oxo bridges [47,48] and a curious mixed-valence Pt(I,II) complex containing four Pt metal ions and two μ_3-oxo groups appears to have formed upon deprotonation of a bis-μ_2-OH precursor [49].

The existence of Pt^{II} compounds containing terminal aqua and hydroxo groups in the solid state is still rarely seen. Three X-ray structurally characterized examples, *cis*-$[Pt(NH_3)_2(1\text{-MeC})(OH_2)](NO_3)_2\cdot H_2O$ (**5**), *cis*-$[Pt(NH_3)_2(1\text{-MeC})(OH)]NO_3\cdot 2H_2O$ (**6**) (1-MeC = 1-methylcytosine [50]) and *trans*-$Pt(NH_3)_2Cl(OH)\cdot H_2O$ (**7**) [51] represent exceptions. Pt–O bond lengths are 2.052(8) (**5**), 2.027(9) (**6**) and 1.989(7) Å (**7**), but these values do not really provide a measure for the strength of the Pt–O bond. The Pt–O bonds in *cis*-$Pt(NH_3)_2(ONO_2)_2$ (**4**) are only 1.99(1) Å [33], yet the nitrate ligands undergo rapid solvolysis in water.



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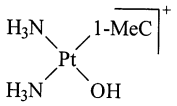

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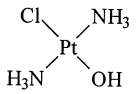

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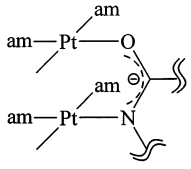
Finally, numerous examples of dinuclear complexes **8** of *cis*-am_2Pt^{II} (am = NH_3 or amine; $(am)_2$ = diamine) containing amide ligands (open or cyclic) have been prepared, which display Pt–O bonds. They will be discussed in more detail in Sections 2.2, 2.3 and 2.4. At this point it needs to be emphasized that this binding pattern does not depend upon formation of a Pt–Pt bonding interaction.



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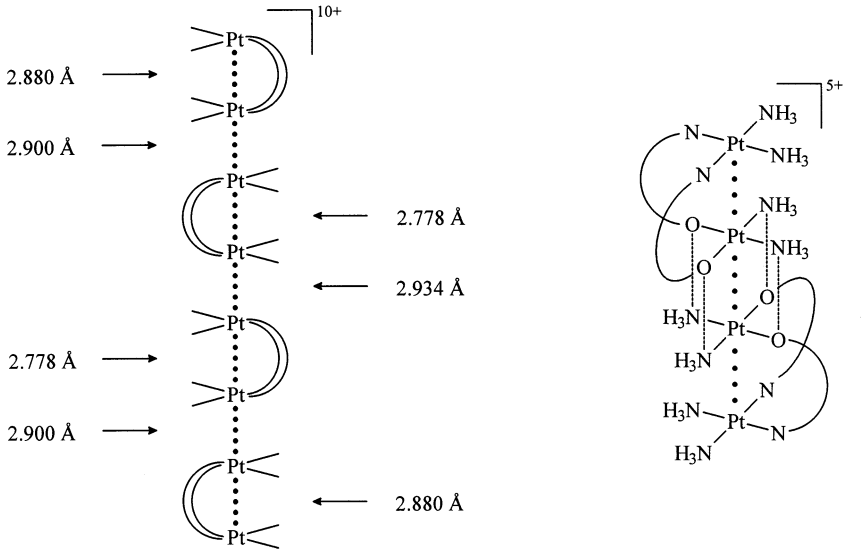
2.2. Mixed-valence Pt compounds

2.2.1. Platinum blues

Curiously colored Pt species have been known since the middle of the last century. For example, Wolfram had prepared a 'red salt' of composition $[Pt^{IV}(EtNH_2)_4Cl_2][Pt^{II}(EtNH_2)_4]Cl_4{\cdot}4H_2O$, the first example of a large series of linear chain complexes with bridging halide anions and alternating Pt^{IV} and Pt^{II} entities [52], and Söderbaum, in 1888, reported strongly colored Pt oxalate complexes, later identified as mixed-valence state Pt compounds of type $K_{1.6}[Pt(C_2O_4)_2]{\cdot}nH_2O$ [53]. These compounds consist of infinite and partially oxidized chains of $[Pt(C_2O_4)_2]^{2-}$ anions with short Pt–Pt separations of around 2.8 Å. They are structurally related to the partially oxidized tetracyanoplatinates, which had been reported as early as 1842 by Knop, even though the structures of these compounds have not been elucidated until some 30 years ago [54,55].

'Platinblau', first described by Hofmann and Bugge in 1908 and formulated as $Pt(CH_3CONH)_2{\cdot}H_2O$ [56], was obtained upon treatment of $PtCl_2(CH_3CN)_2$ with Ag^I salts. Its structure still remains a mystery, despite numerous attempts to unravel its secret [57]. While the conversion of the nitrile into an amide ligand at the Pt was clear from the beginning, and dinuclear Pt(III) complexes with acetamidato bridges had been characterized [58], it was only more recently that examples of blue mixed-valence Pt complexes, consisting of two or four dinuclear entities with bridging cyclic amidates, could be crystallized. However, all these compounds have in common *cis*-$(NH_3)_2Pt$ entities, unlike the original Platinblau. The largest chain compound known to date consists of four stacked dinuclear *cis*-$(NH_3)_2Pt$ entities with two head–head arranged acetamidato ligands each, and composition of $[Pt_8(NH_3)_{16}(CH_3CONH)_8](NO_3)_{10}{\cdot}4H_2O$ (**9**) [59]. In it the average oxidation state of Pt is 2.25, but the uneven Pt–Pt separations could tentatively be interpreted in terms of a mixture of a Pt(2.5) tetramer to which two Pt(2.0) dimers are added.

Elucidation of the solid state structure of **9** represented a climax of many efforts which were spurred by Rosenberg's report on 'platinum pyrimidine blues' in 1975 [60] and the promising antitumor activity of these blues ([60]c). During Raman spectroscopic work on the reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ (and its derivatives) with polyuridylic acid (poly U), Rosenberg's coworker Mansy discovered the unexpected formation of a blue color. As subsequently shown, reactions of the diaqua species of Cisplatin with a variety of pyrimidine-2,4-diones (uracil, thymine) as well as other cyclic amides gave blue, green and purple products as well. In line with high activity against a number of tumors, these 'blues' also represented excellent stains for nucleic acids in cells [61]. It is as yet unclear if mixed-valency is required for activity, but findings with head–head diplatinum(II) species seem to rule against such a possibility [62]. A major breakthrough in the understanding of the nature of these 'blues' was the X-ray structure determination of a tetranuclear 'α-pyridone-blue' **10** in Lippard's group

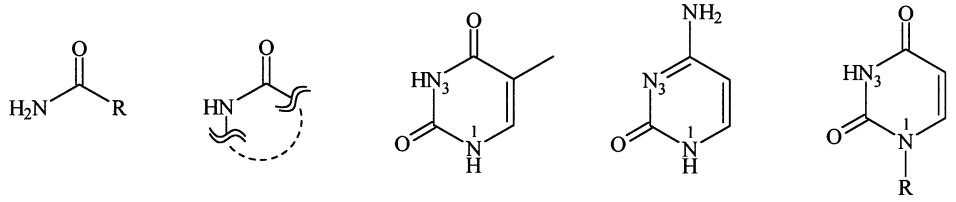


9 **10**

[63], with subsequent physico–chemical studies (EPR, XPS, magnetic measurements) as well as MO calculations providing a profound understanding of tetranuclear Pt(2.25) species [64].

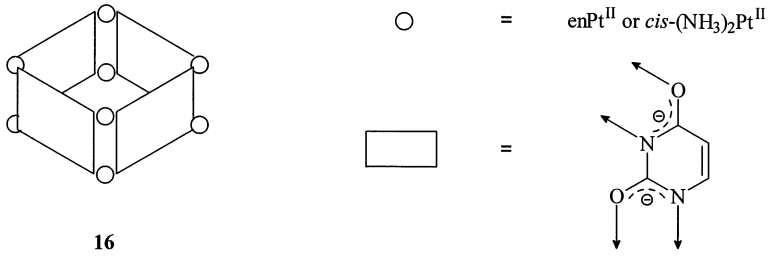
2.2.2. Alternative structures

Although a '1-methyluracil blue' with a solid-state structure analogous to that of the 'α-pyridone blue' has been reported [65], the case of 'platinum pyrimidine blues' is not to be considered closed. There is every reason to believe that the composition of Rosenberg's 'platinum pyrimidine blues' is more complex than suggested by the dimer-of-dimer or the octanuclear structures. For example, an early mass spectroscopic study had indicated the existence of clusters of a 'Pt-thymine blue' with masses of at least up to 3000 [66]. It is felt that the difference between simple amides (open or cyclic) and uracil or cytosine-derived blues stems from the larger number of exocyclic groups and their propensity to act as metal binding sites (see Section 2.4). While simple amides **11, 12** (in their deprotonated forms) provide two Pt binding sites via N and O, there are four available in uracil (**13**) and cytosine (**14**) nucleobases, and even if the N1 position is blocked, such as in 1-methyluracil (**15**), there are still three potential binding sites for Pt, namely N3, O4, O2.



11 12 13 14 15

Applying unsubstituted uracil and $enPt^{II}$ (instead of *cis*-$(NH_3)_2Pt^{II}$), we have structurally confirmed, using X-ray techniques, the existence of a cyclic, octanuclear Pt_8 species **16** with all four sites (N1, O2, N3, O4) occupied by Pt [67].



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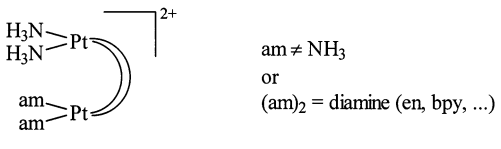
With cyclic amides a head–head orientation within the dinuclear entity is essential to permit dimer-of-dimer formation. This arrangement is necessary for steric reasons (bulk of cyclic amides) and to permit intercationic H bonding, which reinforces Pt–Pt bonding (c.f. **10**). Only, with open amides is this requirement not stringent. The extra functionalities of uracil and cytosine nucleobases provide more variability and more possibilities for H bonding interactions than amides. In addition, these extra functional groups may be utilized to interconnect building blocks, e.g. via other metal ions or, in acidic medium, protons. Others [68] and ourselves [69,70] have previously demonstrated that alkali metal ions can act as a 'glue' between metalated nucleobases, and if Ag^+ binds to a diplatinum(II) entity, redox reactions leading to mixed-valence Pt blues can take place [71,72], as follows:

$$[\{Pt_2^{2.0}L_2\}_2Ag]^{5+} \rightarrow [Pt_4^{2.25}L_4]^{5+} + Ag^{\circ}$$

If, within a dinuclear bridged Pt complex **17**, the two Pt entities are carrying different am(m)ine ligands, redox potentials leading to mixed-valence species are affected and the position of the am(m)ine ligand(s)—*trans* to N or *trans* to O of bridging nucleobases—influences the redox behavior [73–75].



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Finally, if loss of am(m)ine ligands from a mono- or dinuclear precursor of a 'platinum blue' is allowed—an assumption supported by experimental findings—the number of alternative structures of 'blues' further increases. As we have shown recently,

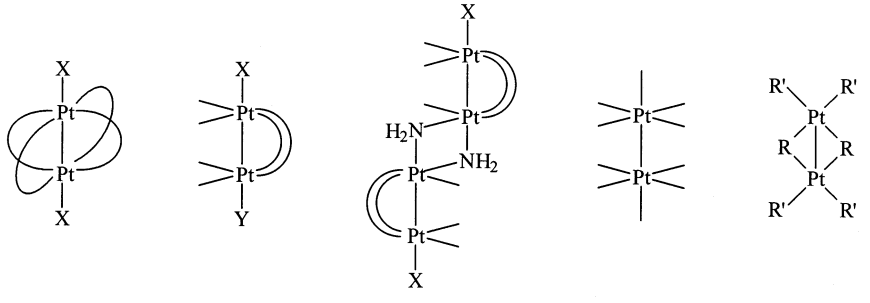
mono(ammine) complexes of 1-methylcytosine (1-MeC), originally prepared from *cis*-[Pt(NH_3)$_2$(1-MeC)Cl]Cl, display a pronounced tendency for oligomerization and spontaneous oxidation [76].

2.3. Diplatinum(III) compounds

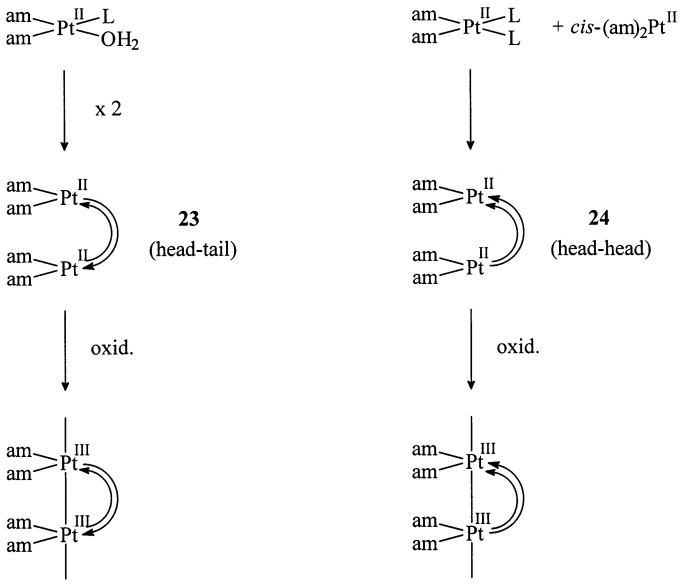
Monomeric Pt species in a +III oxidation state have been implicated, among others, as short-lived intermediates during substitution reactions of Pt^{IV} complexes and products of pulse-radiolysis in solution or γ-irridation in solid samples [77]. Until recently there had been a general consensus that with a possible single exception, all previously isolated Pt^{III} complexes actually were mixed valence Pt^{II}, Pt^{IV} compounds ([12]b). Today there is at least one well established case of an isolated mononuclear Pt^{III} compound, (N Bu_4) [Pt(C_6Cl_5)$_4$] [78]. Using appropriate ligands, Pt^{III} compounds can be generated in solution by electrochemical methods [79].

Diamagnetic diplatinum(III) complexes with a single Pt–Pt bond are much more common. The first X-ray structurally characterized example of this type of compounds was $K_2[Pt_2(SO_4)_4(OH_2)_2]$, reported in 1976 [80]. A number of structurally related compounds **18** with different axial (e.g. $(CH_3)_2SO$ or Cl) or bridging ligands (e.g. HPO_4^{2-}, PO_4^{3-}, $H_2P_2O_5^{2-}$, $CH_3CO_2^-$) and D_{4h} symmetry have been reported since then [81–83]. The complex with four μ_2-acetato bridges, $[Pt_2(CH_3CO_2)_4(H_2O)_2](ClO_4)_2$ displays the shortest Pt–Pt bond length yet reported, 2.3905(14) Å [83]. With four *N*,*N*′-formamidinate ligands, the series of Pt_2^{4+}, Pt_2^{5+}, and Pt_2^{6+} complexes has been reported, with the compounds having formal Pt–Pt σ bond orders of 0, 0.5, and 1, respectively [84]. The expected shortening of the metal–metal separation with increasing bond order is observed. Examples with S-containing bridges are likewise known [85].

A second class of dinuclear Pt^{III} complexes **19** only contains two bridging ligands (in the *cis*-position) as well as two other ligands, likewise in the *cis*-arrangement, and one or two axial ligands. In these compounds the two Pt coordination planes are slightly tilted and Pt–Pt distances are longer, generally 2.5–2.6 Å. Of all types of diplatinum(III) compounds, examples of this kind are most numerous, and with few exceptions, they contain two *cis*-$(NH_3)_2$Pt entities and two amide bridges in either a head–head or a head–tail arrangement. A variation of the dinuclear structure **19** is that seen in a tetranuclear bis-μ-NH_2 complex **20** containing four bridging α-pyrrolidonate ligands in head–head arrangement [86].



18 **19** **20** **21** **22**



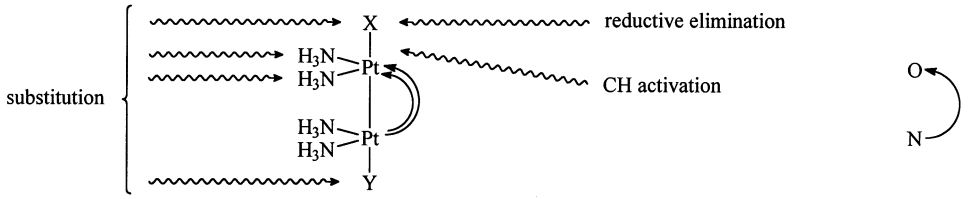
Scheme 2.

A third group of diplatinum(III) compounds is that of complexes with unsupported metal–metal bonds (**21**). There are presently very few examples of this type known [87,88].

Finally, an unusual type of diplatinum(III) complex **22** with the Pt–Pt bond in the metal coordination planes and μ-$C_6F_5^-$, μ-$C_6F_5Cl^{2-}$, μ-$C_6F_4O^{2-}$ as well as μ-$C_6F_4(OR)_2^{2-}$ ligands and terminal $C_6F_5^-$ groups has been described [89].

The study of diplatinum(III) complexes containing *cis*-$(NH_3)_2Pt$ entities originated from interest in the chemistry of the 'platinum blues' (c.f. Section 2.2). The first X-ray structural report of such a compound, with two 1-methylcytosinato nucleobases in a head–tail orientation, originally misinterpreted as a $[Pt^{2.5}]_2$ compound, appeared in early 1981 [90] and was followed by a series of reports on complexes containing α-pyridonate [91], 1-methyluracilate [92] and α-pyrrollidonate [86,93] as bridging ligands. Analogous tetramethyldiplatinum(III) compounds with μ-trifluoroacetato [94] and differently substituted α-pyridonate bridges [95] are likewise known. The synthesis of these compounds frequently involved the oxidation of the corresponding diplatinum(II) precursor in its fixed structure, head–tail (**23**) or head–head (**24**) (Scheme 2), but isomerization reactions of the $[Pt^{2.0}]_2$ species have occasionally been seen [96]. The fact that the head–tail dinuclear species are chiral and therefore enantiomers are formed during their synthesis, appears not to have been widely considered, even though it may be of relevance if, for example, reactions with DNA are considered. Apart from structural aspects such as Pt–Pt bond length, features responsible for the fine-tuning of the Pt–Pt distance, the *trans*-influence of this bond and the question of 5- or 6-coordination of the Pt centers as well as redox potentials, and reactivity of the diplatinum(III) species has received considerable attention. As

a rule, it can be postulated that the head–head isomers are more reactive than the head–tail forms, and that the loosely bonded axial ligands are easily exchanged. Reduction to the diplatinum(II) precursor is frequently seen as the pH is raised from strongly acidic to neutral medium, with either reductive elimination of an axial ligand ([91]e, [92]f,g) or water oxidation feasible ([93]b). Moreover, we have found ([92]c,g) that in the head–head $[Pt^{III}]_2$ species substitution reactions of both NH_3 ligands *trans* to the two oxygen donors of the bridging uracilate ligands by Cl^- in HCl acidic medium occur rapidly. Considering the relative inertness of $Pt–NH_3$ bonds (for exceptions see below), this is surprising. Finally, the special reactivity of one of the two Pt^{III} ions in head–head isomers **25** is also evident from various observations on CH activation and formation of $Pt^{III}–C$ bonds (c.f. Section 2.5).



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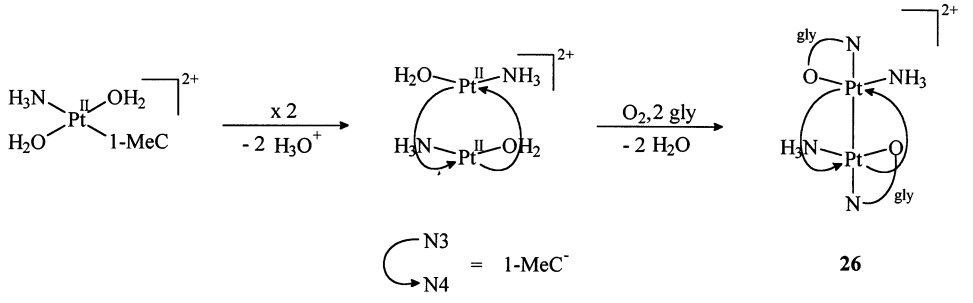
Until recently, all known diplatinum(III) complexes containing $(am)_2Pt$ entities were derived from *cis*-isomers. There is one exception to this rule, a diplatinum(III) complex obtained from *trans*-$[Pt(NH_3)(1\text{-MeC-}N3)(H_2O)_2]^{2+}$ [76]. The speciality of this compound, $[Pt_2(NH_3)_2(1\text{-MeC}^-\text{-}N3,N4)_2(\text{gly-N,O})_2](NO_3)_2{\cdot}3H_2O$ (**26**) (gly = glycinate anion), is its formation from a diplatinum(II) precursor in the absence of any other oxidizing agent but air (Scheme 3). If the chiral amino acid L-alanine is applied instead of glycine, formation of diastereomers of the analogous complex is evident from ^{1}H-NMR spectroscopy. Thus it appears that the presence of suitable chelating ligands (gly, ala) considerably reduces the oxidation potential required to go from $[Pt^{II}]_2$ to $[Pt^{III}]_2$.



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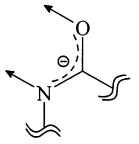
Scheme 3.

2.4. Heteronuclear complexes

The ready formation of di- and oligomeric Pt complexes with open or cyclic amides

(**27**) or the amidine functionality (**28**) of deprotonated cytosine (c.f. Sections 2.2 and 2.3) is a consequence of the good donor properties of the adjacent atoms N,O and N,N.



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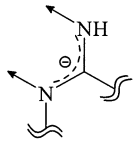
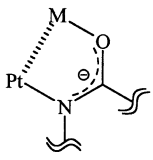


28

In a similar way, different metal ions can be successively bound to these ligands, thereby producing heteronuclear complexes in a planned fashion [97]. This procedure requires at least the first metal entity bound to be kinetically inert, e.g. being a Pt^{II} ion. Depending on the other ligands already bound to Pt^{II} (*cis*- or *trans*-geometry; steric bulk) different types of heteronuclear compounds can be prepared with the metal entities facing each other or being far apart (**29**–**35**). Types of binding patterns that can be obtained are as follows:



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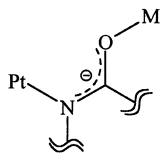

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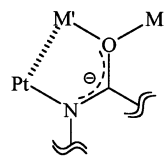

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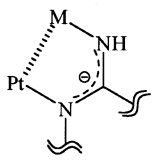

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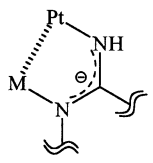

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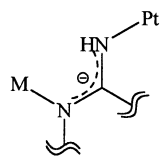

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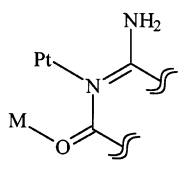
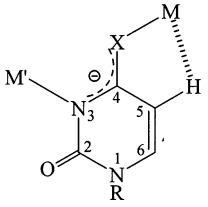


35

By far the largest number of examples obtained and structurally characterized are of type **29**, usually with 1-methyluracilate and 1-methylthyminate ligands [98], but also with acetamidate [99] followed by type **32** for 1-methylcytosinate [90,100]. Except for **30** [101], all other patterns (**31** [102], **33** [103], **34** [103]) are likewise confirmed by X-ray crystallography. Cytosine can also act in a neutral bridging mode via N3 and O2 (**35**) [104].

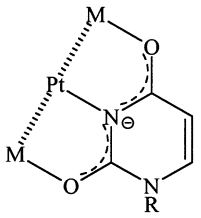
Compounds **30**, **31** and **34** are of particular interest with regard to activation of the C5 position of pyrimidine nucleobases. The effect of $M = Pt^{II}$ on the proton H5 is clearly seen in the ^{1}H-NMR spectrum of **36**, since it causes a dramatic downfield shift of this resonance [101,103].



X = NH or O

36

Heteronuclear complexes containing more than two metal ions bound to a pyrimidine nucleobase have likewise been obtained. They include an example of 1-methyluracilate with three different metal ions (**31**, $M' = Ag^+$, $M = Na^+$ [105], as well as examples of types **37** [71,72,106], **38** [107], and **39** [102]).



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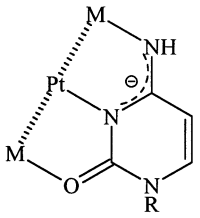

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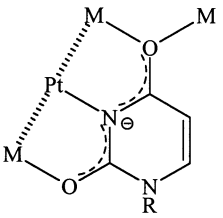


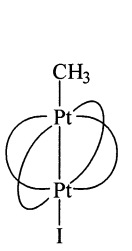
39

Structural details of many of these mixed-metal complexes of pyrimidine nucleobases have recently been reviewed and the treatment of Pt^{II}–heterometal interactions have been described [108–110]. Metal–metal bond formation strongly depends on (i) the geometry of the $(am)_2Pt^{II}$ entity (*cis* or *trans*), (ii) the electronic configuration of the heterometal ion(s), and (iii) the size of the heterometal ion. As a rule, intermetallic distances between Pt^{II} and a heterometal ion having incompletely filled d orbitals (e.g. Pd^{II}, Cu^{II}) are significantly shorter for the *trans*-$(am)_2Pt^{II}$ system due to the fact that this geometry permits the filled d_{z^2} orbital of Pt^{II} to act as a donor for the unfilled (d^8) or half filled (d^9) $d_{x^2-y^2}$ orbital of the heterometal. Pt–M bonds in type **32** compounds with *trans*-$(am)_2Pt^{II}$ have been found to be as short as 2.49 (Pt–Pd) and 2.50 (Pt–Cu) Å [100,109]. In contrast, with a *cis*-$(am)_2Pt^{II}$ geometry, the filled d_{z^2} orbital of Pt^{II} is facing another filled d orbital (at least in the cases most widely studied, with d^8–d^{10} heterometal ions) and unless electrons are removed by oxidation, no (or only very little) bonding between the metal centers will take place. Heteronuclear $Pt^{II}M$ complexes, like diplatinum(II) complexes of the *cis*-$(am)_2Pt^{II}$ type can ease this unfavorable situation by a relatively pronounced tilting of the metal coordination planes ([100]b, [109]). An extreme case of tilting has been observed with the main group metal ion Tl^I: in *cis*-$[(NH_3)_2Pt(1\text{-}MeT)_2Tl(1\text{-}MeT)_2Pt(NH_3)_2]NO_3 \cdot 7H_2O$, the stereoactive lone electron pair at Tl causes such a pronounced tilting that two 1-methylthyminate ligands from the two Pt entities become stacked and the trinuclear cation bent (Pt–Tl–Pt, 136.7(1)°) ([98]g).

These heteronuclear complexes have provided many possibilities for detailed spectroscopic studies [111,112] as well as application of other physico–chemical methods, e.g. cyclovoltammetry [113] or magnetic measurements [114].

2.5. C–H activation

The activation and functionalization of C–H bonds of hydrocarbons or organic compounds has, in general, largely been a domain of organometallic chemistry [115]. Considering the current interest in C–H bond activation by Pt compounds [116], a few examples of Pt coordination complexes capable of binding to C atoms with substitution of a proton are to be mentioned. Formation of Pt–C bonds under relatively mild conditions and with the help of diplatinum(III) complexes only rarely has been observed, e.g. with a tetrakis-μ-diphosphite bridged species (**40**) [117], with a bis-μ-1-methyluracilate bridged complex (**41**) [118], and with a bis-μ-pivalamidate complex (**42**) [119].



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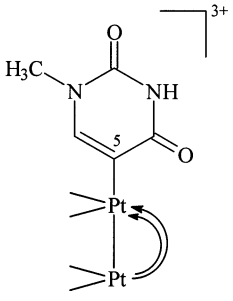

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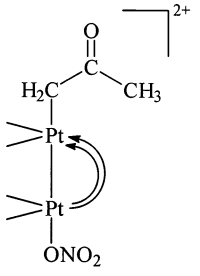
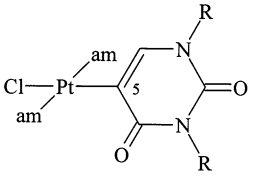


42

Both in **41** and **42** the diplatinum(III) core is built of two *cis*-$Pt(NH_3)_2$ entities and two bridging amidate ligands in head–head orientation. On the basis of the reversible redox behavior of such compounds (diplatinum(II), 'Pt blues', diplatinum(III)) they are presently investigated with regard to their usefulness as oxidation catalysts for organic substrates [120].

X-ray structural evidence of C–H activation by Pt^{II} species has recently been presented for uracil nucleobases (**43**) (binding via C5) [121] as well as acetone (**44**) [122].



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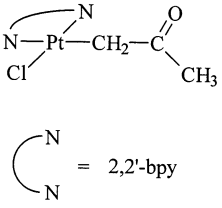

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2.6. Reactivity of Pt–N bonds

Chapter 2 started out with the description of Pt^{II} complexes containing Pt–O bonds which some 25 years ago were quite rare. In contrast, Pt–N bonds have generally been considered 'stable' and, once formed, inert. This assumption, while generally true, has been challenged in recent years, in that both the replacement of

Table 1
Metal binding patterns established by X-ray crystallography for N9-substituted guanine nucleobases

Pattern	Charge of guanine	Ref.
N7	0 or −1	[131]
N1	−1	[132]
N7, N1	−1	[133]
N7, O6 (bridging)	0 or −1	[134]
N7, N1, N3	−1	[135]
N7, N1, N2	−2	[136]

NH_3 groups from a *cis*-$(NH_3)_2Pt^{II}$ entity under relatively mild conditions, and the cleavage of Pt–N(nucleobase) bonds and unexpected metal migration processes of Pt^{II} and Pt^{IV} entities have been observed. Since all reported examples involve Pt-nucleobase compounds, this aspect will be discussed in more detail in chapter 3, specifically in Sections 3.8, 3.9 and 3.10. Another case of facile NH_3 substitution in a diplatinum(III) complex has already been mentioned (Section 2.3).

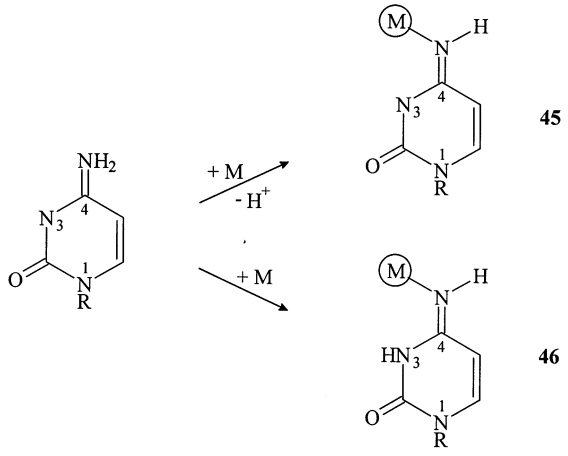
3. Coordination chemistry with nucleobases

Platinum binding to biomolecules has been a central theme for coordination chemistry since the discovery of the antitumor activity of Pt compounds. This is reflected by a large number of excellent review articles on reactions of simple Pt coordination compounds with amino acids [123] and nucleobases or nucleic acids [124]. In particular, early findings of a preferential inhibition of DNA replication [125] have led to a focus on Pt–DNA binding. Originally believed to be due to a simple steric distortion of the DNA template leading to an impairment of DNA polymerase, the present picture of the consequence of replication blockage is much more sophisticated [126].

3.1. Metal binding patterns

The systematic study of Pt nucleobase complex formation has yielded a wealth of structural and mechanistic information, unavailable at the onset of Pt–DNA chemistry in the early 1970s. Very few metal binding sites to the heterocyclic part of nucleobases had been firmly established then [127] and the field was open for speculation. Results of X-ray crystal structure analysis [128] and NMR [129] has helped greatly to change this situation. To give just one example, the exocyclic amino groups of cytosine and adenine had been generally considered metal binding sites, with the metal binding through the 'electron lone pair' of the amino group. However, with this 'pair' largely delocalized into the ring and therefore unavailable for metal binding, it was eventually shown that metal binding to these sites is possible only after deprotonation of this site (**45**) or following a tautomeric shift of the base (**46**), viz. migration of the proton to an endocyclic site (c.f. see also Section 3.6) [103,130].

Pt chemistry proved fortunate in this respect since Pt^{II}, and even more so Pt^{IV} species are frequently inert and permit these compounds to be crystallized and X-ray structurally characterized.



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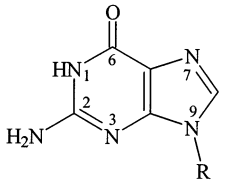
46

This is not the place to review all metal binding patterns of the four common nucleobases, but as an example the now established (X-ray crystal structure analysis) metal binding sites of guanine (**47**) (N9 position blocked, as in nucleic acids) are given in Table 1. With a single exception—N7,O6 bridging—in all other cases Pt^{II} is involved, although occasionally in conjunction with a heterometal ion. With hypoxanthine derivatives, additional metal binding modes are known, e.g. N1,O6 [97] or N1,N7,O6 [137].



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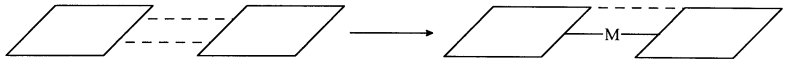
3.2. Models of DNA cross-links of Cisplatin

The major DNA lesions formed by *cis*-$Pt(NH_3)_2Cl_2$ are guanine,guanine as well as guanine,adenine intrastrand cross-links [138]. They are generally believed to account for the steric distortion of DNA. Structurally characterized compounds



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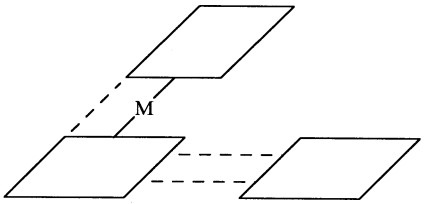
Scheme 4.



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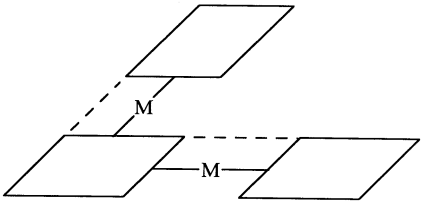


50

Scheme 5.

which adequately model the relative orientation of the two cross-linked bases (head–head) are relatively scarce. The first 'real' model compound of the guanine,guanine adduct was reported by us in 1984 [139], followed by three others shortly thereafter [131]. Salient features such as the large dihedral angles between the two bases (68–78°) were confirmed for the dinucleotide complex *cis*-$[Pt(NH_3)_2\{d(pGpG)\}]$ reported in 1985 [140] as well as for a complex with the trinucleotide d(CpGpG) [141]. An interesting aspect, not really fully realized in its possible consequences then, was the rather high flexibility of Pt^{II} relative to the nucleobase plane: it was found that the metal ion could be coplanar with the heterocyclic ring or deviate by as much as 0.36 Å from it. In the very best model of a DNA adduct of Cisplatin presently available, a platinated DNA dodecamer structure [142], this deviation reaches extreme values of 0.8 and 1.3 Å, strongly suggesting that the DNA structure imposes this unusually strained geometry on the Pt ion rather than *cis*-$Pt(NH_3)_2$ distorting DNA. The resulting weakening of the Pt–N7–nucleobase bonds may be crucial as far as reactions with cellular or external nucleophiles are concerned.

Structural models of the second most abundant DNA adduct, that between adenine–N7 and guanine–N7 in a 5′–dAG sequence of a DNA strand have only recently been reported by us [143].

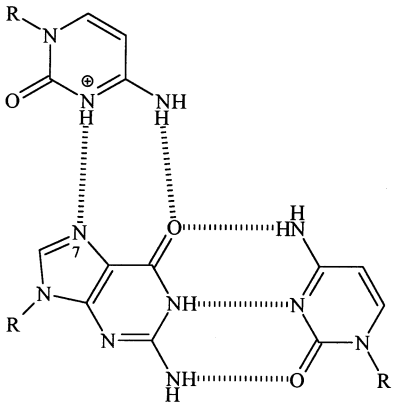
3.3. Metal-modified base pairs

The cross-linking adducts of the inactive or, to be more precise: less active, *trans*-$Pt(NH_3)_2Cl_2$ have been studied less intensively [144]. Potential cross-linking models with DNA bases have been characterized essentially on the model nucleobase level only [145]. These complexes differ from those of the *cis*-isomer profoundly in that the two bases, with very few exceptions, are close to coplanar, frequently assisted by interbase H bond formation. Formally, this situation may be considered then a 'metal modification' of a base pair [146] (Scheme 4). The two bases cross-linked (**48**) may be identical (homo base pairs) [147], complementary (with Watson–Crick [146], reversed Watson–Crick, Hoogsteen [146], reversed Hoogsteen pairing schemes), or non-complementary [148], and the interaction sites

may be of the conventional type (e.g. as seen in normal base pairs) or novel (e.g. via sites normally not involved in base pairing such as C5 of a pyrimidine base ([121], [149]a)). We have frequently applied *trans*-$(am)_2Pt^{II}$ ($am = NH_3$ or CH_3NH_2) as the appropriate metal entity, but other metal species with a linear or near-linear coordination geometry, e.g. Hg^{2+} [149], Ag^{+} [150], a *trans*-octahedral one such as *trans,trans*-$(NH_3)_2(OH)_2Pt^{IV}$ [151], and even a tetrahedral one (Zn^{2+}) [152] may apply to this notion as well.

3.4. Platinated base triplets

The concept of 'metal-modification' of a base pair can be extended to three bases (Scheme 5). As an example of type **49** we have prepared and X-ray structurally characterized *trans*-[{$Pt(CH_3NH_2)_2$(1-MeC-*N3*)(9-EtGH-*N7*)}·1-MeC]$^{2+}$ [153] and several examples of type **50** with a bridging 9-methyladenine entity [154]. Compound **49** can be considered a segment of a metalated DNA triplex, consisting of a Watson–Crick pair between guanine and cytosine and a third base, cytosine, attached through a metal linker via the major groove. Within the metalated form of CH^{+}GC triplet **51** of triple-stranded DNA (third strand parallel to second strand), the H bond between the protonated cytosine-N3 position and guanine-N7 is substituted by a linear *trans*-$(am)_2Pt^{II}$ entity (**52**).



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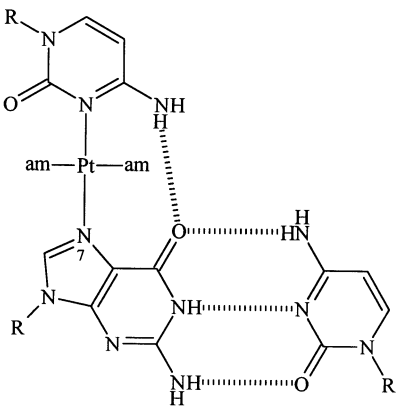
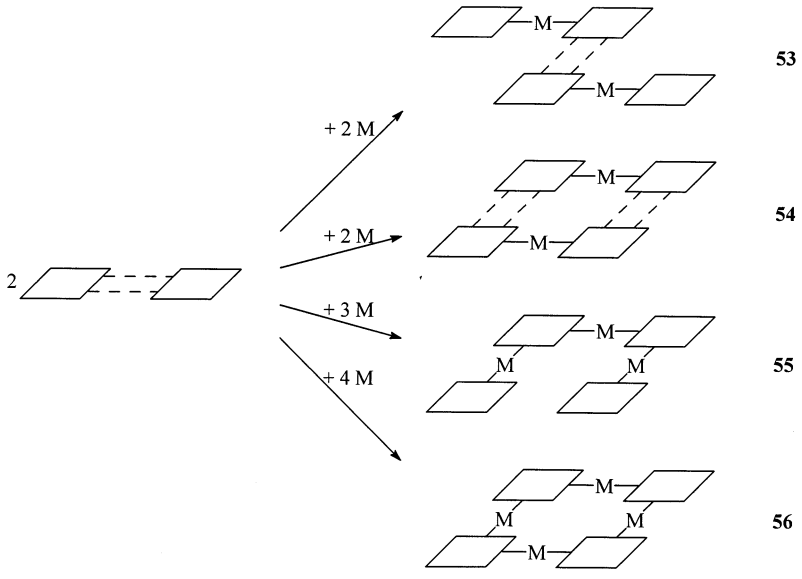


52

The composition of **52** has led us to pursue further work aimed at the potential application of *trans*-$(am)_2Pt^{II}$-modified oligonucleotides in the so-called 'antisense and antigene strategy' [155]. According to this concept, genes in DNA (antigene approach) crucial for the development of life-threatening diseases or the corresponding RNA transcripts (antisense approach) may be blocked by complementary oligonucleotide strands which strongly bind to the targets, thereby preventing translation to proteins. Experiments have already demonstrated that platinated oligonucleotides (19-mers) can recognize a target sequence and bind to it in a large DNA molecule containing some 2500 base pairs [156]. Work on the synthesis of *trans*-$(am)_2Pt^{II}$ modified oligonucleotides is in progress [157,158].



Scheme 6.

3.5. Nucleobase quartets and Pt

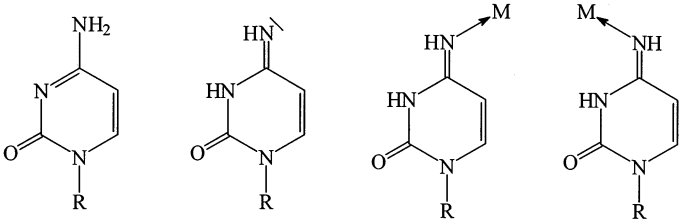
Open and closed nucleobase quartets of different topologies **53**–**56** (Scheme 6) represent a challenge for preparative chemistry. At the same time they are of substantial interest with regard to the emerging phenomenon of nucleobase quartet structures, the role that metal ions play in their stabilization [159,160], and supramolecular chemistry (c.f. Section 4). Realization of **53**–**56** depends on several features such as internucleobase H bond formation, e.g. between a neutral and an anionic platinated guanine (**53**) [161], self-complementarity and molecular recognition (**54**) [162], as well as 90° angles provided by diplatinated (N1,N7) purine nucleobases (**55**–**56**) [136,154,163]. Especially **54**, realized in *trans*-$[Pt(NH_3)_2(9\text{-EtG})(1\text{-MeC})]^+$ (9-EtG = 9-ethylguaninate, 1-MeC = 1-methylcytosine), is noteworthy in that it displays two unconventional and in nucleic acid chemistry hitherto not seen H bonds between the aromatic C5 proton of cytosine and the deprotonated N1 position of guanine [162].

3.6. Nucleobase platination and tautomerism

The proper tautomer structures of the four common DNA bases is essential for correct replication. If present in a rare tautomeric form, a nucleobase can cause mispairing and, if not repaired, lead to mutagenesis. Given the known mutagenic

potential of metal species in particular those of soft heavy metal ions, a feasible route to base mispairing could involve an increase in concentration of the rare tautomer (there are, of course, a number of other feasible ways, c.f., for example, Ref. [164]).

As we have demonstrated in a number of cases (4-hydroxo-2-oxo tautomer of U and T [165]; iminooxo tautomer of C [103,166]; betaine tautomer of G [132]; imino tautomer of A [167] with U = uracil, T = thymine, C = cytosine, G = guanine, A = adenine) metal ion coordination can stabilize rare tautomers (example cytosine, **57**).



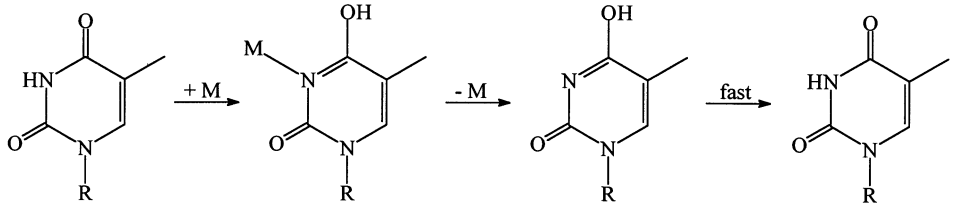
57 **57a**

major tautomer rare tautomer two rotamers of metal-stabilized rare tautomer

Provided the metal entity in the rare tautomer complex is oriented such that H bonding with other bases is not hampered for sterical reasons and hence the metal entity is *anti* with respect to the normal H bonding sites (**57**), the H bonding pattern is expected to be different from that of the major tautomer. If the *syn* rotamer (**57a**) is present, H bonding is expected to be severely hampered in any case and certainly not of the normal type.

A rare nucleobase tautomer **58** may also be formed temporarily only (Scheme 7) [165] and if sufficiently long-lived, it could feasibly mispair with the wrong base, e.g. with guanine instead of adenine.

Finally we note that, provided the X-ray crystal structure analysis of the metal complex of the rare tautomer is of sufficient accuracy, the effect of the metal ion may be 'subtracted' to give a good estimation of the geometry of the rare tautomer itself in a condensed phase [163]. The only other ways to get to this information,



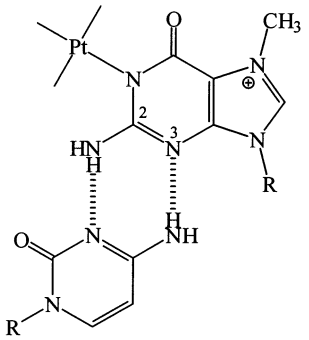
58

Scheme 7.

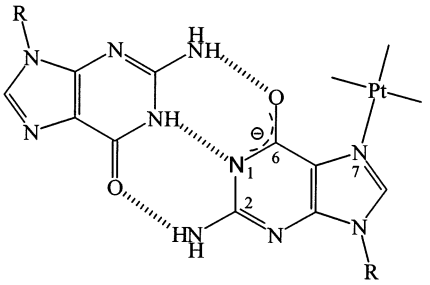
albeit usually for the gas phase or in an argon matrix at low temperature (via vibrational spectra) are ab initio calculations [168].

3.7. Unusual base pairing schemes

Blocking of a H bonding site by a metal entity may prevent base pairing completely or lead to an unusual pairing scheme or alternatively, it may also produce a novel one. For example, blocking of N1 and N7 sites in guanine residues can force the complementary base cytosine to pair with N2 and N3 of guanine, with O2 of cytosine being additionally involved in intermolecular H bonding with an amine ligand of the Pt at N1 (**59**) [169].



59



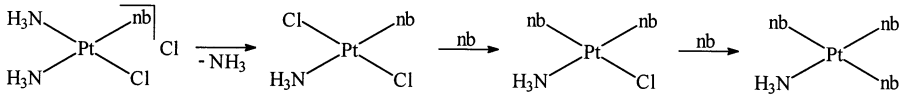
60

Apart from a purely sterical component that effects H bonding, there is also a pronounced electronic one. Best understood is the acidifying effect of a metal ion, frequently Pt^{II}, at N7 of guanine [170], on the proton at the N1 position. Deprotonation of this site occurs with a pK_a of ca. 8 [171] and as a consequence, either hemideprotonated, N7 platinated guanine [161,172] or the fully deprotonated, platinated guanine and a neutral guanine [173] mispair with each other.

The most dramatic electronic effects on a nucleobase site involved in H bonding is that exercised by a metal (Pt^{II}) bound to N3 of an adenine nucleobase. As a consequence, the basicity of N1 drops by 4 log units, strongly suggesting that this metal binding pattern severely impairs normal Watson–Crick pairing [174].

3.8. Tris(nucleobase) complexes derived from cis-$(NH_3)_2Pt^{II}$

As we have shown previously [175] the NH_3 ligands of *cis*-$Pt(NH_3)_2Cl_2$ are susceptable to displacement under certain conditions, e.g. in the nucleobase complex **61** to give **62**, allowing subsequent reaction with two additional nucleobases (**63**) leading eventually to tris(nucleobase) complexes **64** [176].



61 **62** **63** **64**

nb = nucleobase

This reaction represents a challenge to the generally accepted view that the two NH_3 groups are kinetically labile and that only the Cl ligands are exchangeable. This behaviour is unique for the *cis*-isomer and is not expected to take place with *trans*-$Pt(NH_3)_2Cl_2$. With this is mind, we have recently prepared and studied a series of complexes and precursors of tris(nucleobase) complexes, including examples of square-planar Pt^{II} complexes containing up to four different ligands, e.g. [PtI(1-MeC)(9-EtGH)(NH_3)]ClO_4 [177] or [Pt(1-MeC)(9-EtG)(9-MeA)(NH_3)]NO_3 ([176]c). This latter compound is the first example of a tris(nucleobase) complex containing three different nucleobases. These compounds can exist as three isomers, depending on the relative positioning of the individual ligands, and have configuration numbers (SP-4-2, SP-4-3, SP-4-4) which are given by the sequence of ligand priorities. In addition, there is the possibility that individual isomers exist in solution (and possibly also in the solid state) as different rotamers. This is a consequence of the presence of exocyclic groups adjacent to the Pt binding site, which can interact in various ways. Today there are very few examples of Pt^{II} complexes known containing four different ligands, despite the fact that the preparation of the three isomers of Pt(pyr)(NH_3)BrCl had been a convincing demonstration of the usefulness of the concept of the *trans*-effect [178].

3.9. Pt^{IV} chemistry

H_2O_2 oxidation of Pt^{II} species is a long known method for the preparation of the corresponding *trans*-dihydroxo derivatives of Pt^{IV} [179]. Although it has been applied to antitumor active Pt^{II} compounds early on [180], X-ray structural work on such compounds did not start until 1982 [181–186]. The importance of complete structural verification prior to testing and biochemical DNA work was most convincingly demonstrated by findings [187] which showed that lattice hydrogen peroxide present in *cis*,*cis*,*trans*-$PtCl_2(NH_3)_2(OH)_2 \cdot H_2O_2$ was responsible for DNA cleavage. This result seriously questioned earlier work on a potential second-generation Cisplatin analogue, *cis*,*cis*,*trans*-$Pt[(CH_3)_2CHNH_2]_2Cl_2(OH)_2$ (CHIP), for which DNA breakage had been reported [188]. Moreover, the surprisingly facile isomerization reaction of *trans*,*trans*,*trans*-$PtCl_2(NH_3)_2(OH)_2$ to *cis*,*trans*,*cis*-$PtCl_2(NH_3)_2(OH)_2$ upon recrystallization from water calls for careful characterization [182].

The recent discovery that carboxylation of axial hydroxo groups in Pt^{IV} compounds can lead to orally active anticancer drugs [189], that are absorbed unchanged be the gastrointestinal tract, has led to a renewed interest in Pt^{IV} antitumor drugs [190].

As to the way of how Pt^{IV} species interact with biomolecules, there is still a vivid controversy going on whether prior reduction to Pt^{II} by cellular components such as thiols of ascorbic acid is required to permit binding to biomolecules like DNA

or whether direct reaction can take place. While the first possibility—Pt^{IV} being a 'prodrug'—is generally favored [191], and reasonable on coordination chemistry grounds (faster ligand substitution reactions with Pt^{II} as compared to Pt^{IV}), there are nevertheless reports on direct reactions with DNA [192]. With light and catalytic amounts of Pt^{II} species having an effect on substitution kinetics, this question may not be easily settled. It is also highly likely that the overall geometry of a Pt^{IV} complex and the nature of the 'axial' ligands have a pronounced influence on the kinetics and thermodynamics of reduction. Although not nearly as often studied as with Pt^{II} compounds and generally not with antitumor Pt^{IV} compounds, direct reactions of Pt^{IV} species with biomolecules leading to Pt^{IV} complexes are documented in a number of cases. For example, amino acid complexes [123,124,193], as well as a limited number of nucleobase complexes [194], have been prepared starting from Pt^{IV}. Reaction of *mer*-[Pt(dien)Cl_3]Cl (dien = diethylenetriamine) with purine nucleobases leads to both Pt^{IV} and Pt^{II} species ([194]b) but the question of the oxidation product formed (oxidized nucleobase? O_2?) is not fully solved yet. Many more examples of Pt^{IV} compounds containing bioligands (amino acids [123,124,195], nucleobases [196]) have been prepared through oxidation of the respective Pt^{II} precursors. While this way of preparation is not biologically relevant, the compounds obtained nevertheless are of interest with respect to their reactivity patterns, e.g. ligand oxidation and metal reduction [197] or metal migration [103,130,198] (c.f. also Section 3.10).

3.10. Metal migration and rearrangement reactions

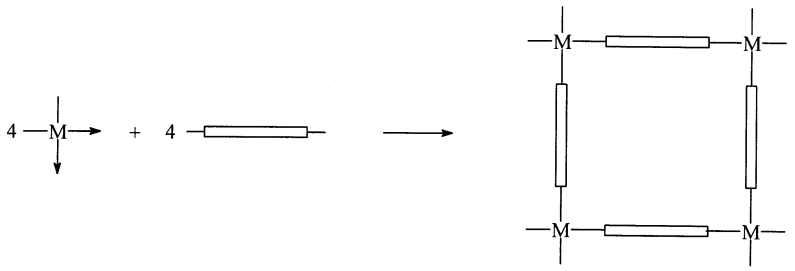
The general inertness of Pt–N bonds toward nucleophilic attack under mild conditions and in the absence of strongly *trans*-labilizing ligands, has been a credo in Pt-nucleic acid chemistry. For this reason, migration processes of Pt-am(m)ine species either within a base or between different nucleobases in single- or double-stranded oligonucleotides have not received much attention until recently. There had been only a few scattered reports on such reactions from model studies prior to 1990: for example, (dien)Pt^{II} had been found to switch from the kinetically preferred N7 site of 9-ethylguanine to N1 [199], and we had studied the migration of a *trans*,*trans*-$(NH_3)_2(OH)_2Pt^{IV}$ entity from the N3 position of 1-methylcytosine to N4, with starting compound, two intermediates and the end product isolated and X-ray structurally characterized [198]. In 1990, a cross-link of *cis*-$(NH_3)_2Pt^{II}$ with the ribodinucleotide r(GpA), assigned to a chelate involving N7 of guanine and N1 of adenine, had been reported to rearrange to other products with cleavage of the Pt–N1(adenine) bond [200], and in the same year a rather spectacular rearrangement of a 1,3-intrastrand adduct of *trans*-$(NH_3)_2Pt^{II}$ between two guanine-N7 positions into a 1,4-intrastrand cross-link, with a single guanine-N7 and a cytosine-N3 as binding sites, was observed [201]. This finding immediately led to a questioning of a long-standing dogma, namely that once bound to N7 of guanine, a Pt-am(m)ine entity would stick to it. Subsequent reports confirmed this unexpected instability [202] and extended the examples on linkage isomerizations to 1.3(intra) → 1.1(inter) for *trans*-$(NH_3)_2Pt^{II}$ [203] and 1.2(intra) → 1.4(inter) for *cis*-$(NH_3)_2Pt^{II}$

[204]. It has been proposed [205] that Pt rearrangement reactions in DNA might be catalyzed by suitably positioned oxygen atoms of the phosphodiester groups.

Lately migration processes of Pt^{II} from thioether-S atoms to N7 of guanine have been reported [206].

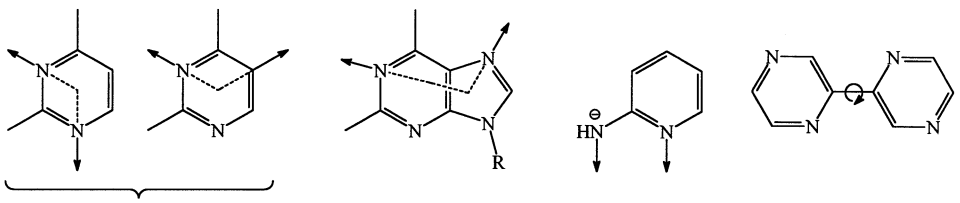
4. Special cases: molecular architecture with *cis*- and *trans*-$(am)_2Pt^{II}$

The 90° angle of *cis*-ML_2 entities ($M = Pd^{II}$ or Pt^{II}, L = am(m)ine or L_2 = diamine, diphosphine) and the 180° angle between donor atoms of suitable organic ligands such as 4,4′-bipyrimidine (*N*,*N*) or benzonitrile (*C*,*N*) provide the basis for the synthesis of 'molecular squares' [207,208] or 'open molecular boxes' **65**, to be more precise.



65

With $M = Pd^{II}$, these species are usually formed in a spontaneous self-assembly process. As we have demonstrated in a number of cases, analogous and different structures form upon combining a variety of different heterocyclic ligands such as pyrimidine nucleobases (**66**), purine nucleobases (**67**), 2-aminopyridine (**68**), or 2,2′-bipyrazine (**69**) with *cis*-ML_2, *trans*-ML_2, or heterometal ions displaying a linear coordination geometry. Apart from being aesthetically pleasing molecules, the interest in these species relates to their potential usefulness as receptors and sensors

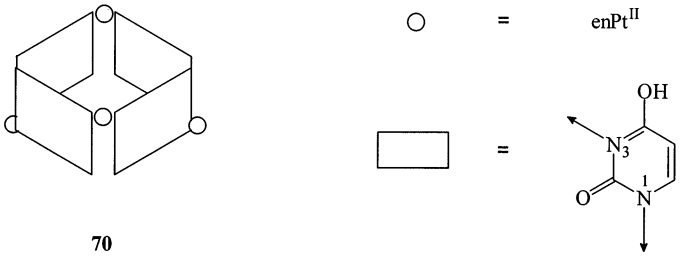


66 **67** **68** **69**

.4.1. Open boxes, squares and hexagons

Despite the 120° angle between N1 and N3 sites of uracil (**66**), four uracil anions

and four $enPt^{II}$ entities spontaneously self-assemble to a cyclic cation of composition $[(enPt)_4(C_5H_4N_2O_2)_4]^{4+}$ (**70**) [67,209].

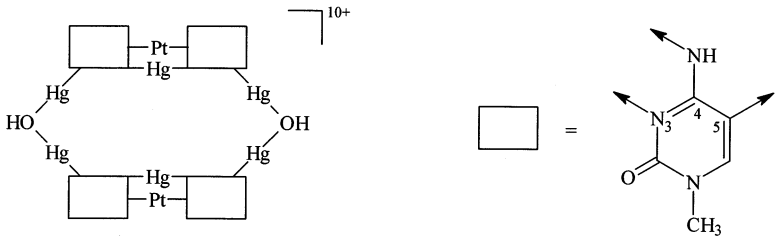


70

Cation **70** is an analogue of a calix[4]arene, both with regard to its solution dynamics (1,3-alternate $\rightleftharpoons$ cone equilibria), its properties to accept additional metal ions ('rim modification') [67], and its use as a receptor when present in its cone conformation [210].

Molecular squares in the strict sense can be prepared when the 90° angle provided by M–N1 and M–N7 vectors of purine nucleobases (**67**), combined with metal entities having a *trans*-geometry, e.g. *trans*-$(am)_2Pt^{II}$ or Hg^{II} are applied (c.f. Section 3.5).

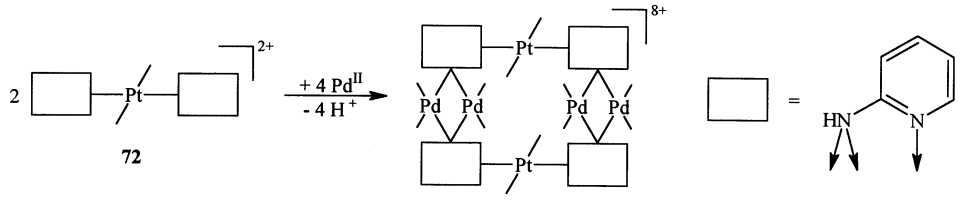
Likewise flat, yet of a hexagon shape is the molecular cation **71** derived from *trans*-$[Pt(CH_3NH_2)_2(1\text{-MeC})_2]^{2+}$ (1-MeC = 1-methylcytosine). With its head–head oriented nucleobases, the cation initially binds a Hg^{II} with deprotonation of the two exocyclic amino groups of the cytosine bases, followed by subsequent mercuration of the C5 positions of the two bases and dimerization via OH bridges [67].



71

4.2. Combining cis- and trans-$(am)_2M^{II}$

Two 2-aminopyridine molecules form with *trans*-$(CH_3NH_2)_2Pt^{II}$ the expected cationic bis(ligand) complex **72** which upon reaction with Pd^{II}, spontaneously dimerizes to the cyclic complex **73**, with each deprotonated amino group of aminopyridine (**68**) acting as a bridge between the Pd^{II} centers [67]. All four Pd^{II} ions adopt *cis*-geometries since only this allows construction of a cyclic entity. The resulting rectangle has an inner cavity of ca. 7 × 6.3 Å and may be used as an anion receptor.



72

73

4.3. Molecular triangles

2,2′-Bipyrazine (bpz) **69** is a versatile ligand in that it can act as a chelating ligand via the N1,N1′ positions or as a linear ligand via N4 and N4′, depending on the orientation of the two halves of the molecule with respect to the central C–C bond. Simultaneous use of N1 and N4 binding sites is also possible. Examples for these cases have been reported [211]. Of particular significance is a molecular triangle of C_2 symmetry consisting of three enPt^{II} entities and three bpz, bridging via the N4,N4′ sites. Rotation of the pyrazine rings about the C2–C2′ bond is easily achieved by metal chelation of the still available N1,N1′ positions to give a triangle of C_3 symmetry which displays a calix[3]arene-like cup structure and a pronounced anion affinity [212].

5. Summary

The discovery of Cisplatin being an antitumor agent has led to an unexpected revival of a mature discipline within inorganic chemistry—coordination chemistry—and at the same time has been instrumental in promoting a new burgeoning field—bioinorganic chemistry. With respect to topics of metal–metal interactions, the medicinial use of antitumor drugs, or metal–nucleic acid chemistry in general, Cisplatin has made an impact on all of these. The present interest in the usefulness of non-platinum metal compounds in medical applications or as probes in biology, the question of DNA being an electronic wire or an insulator, and the development of force fields for Pt–DNA adducts, to give just these additional examples, has been initiated by discovery of Cisplatin. This situation appears to have only few parallels in the more recent history of the chemical sciences.

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