Coordination Chemistry Reviews 465 (2022) 214566

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

# Beyond sole models for the first steps of Pt-DNA interactions: Fundamental properties of mono(nucleobase) adducts of $Pt^{II}$ coordination compounds

Bernhard Lippert [a,*], Pablo J. Sanz Miguel [b,*]

[a] Fakultät Chemie und Chemische Biologie, TU Dortmund, 44221 Dortmund, Germany
[b] Departamento de Química Inorgánica, Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain

ARTICLE INFO

*Article history:*
Received 4 February 2022
Accepted 6 April 2022
Available online 29 April 2022

*Keywords:*
Pt-nucleobase chemistry
Cyclic derivatives
Head–tail dimers
Chirality

ABSTRACT

A major feature of mono(nucleobase) complexes of $Pt^{II}$ containing one or more aqua ligands is their ability to engage in intermolecular condensation reactions leading to multinuclear species with bridging nucleobases, bridging hydroxido or amido ligands. Their chemistry appears to be more versatile with isolated model nucleobases than is the case when relevant $Pt^{II}$ species interact with nucleic acids. Special emphasis of this review article is on compounds obtained with pyrimidine model nucleobases (1-methylcytosine, 1-metylthymine, 1-methyluracil) and their cyclic condensation products. Aspects of chirality of mononuclear as well as head–tail dinuclear species will be discussed.



**Contents**



* Corresponding authors.
*E-mail addresses:* bernhard.lippert@tu-dortmund.de (B. Lippert), pablo.sanz@unizar.es (P.J. Sanz Miguel).

https://doi.org/10.1016/j.ccr.2022.214566
0010-8545/

## 1. Introduction

Cationic Pt$^{II}$ complexes display a natural attraction for polyanionic macromolecules such as DNA and RNA. The mode of action of the unique anticancer agent Cisplatin, *cis*-[Pt(NH$_3$)$_2$Cl$_2$] and its hydrolysis products, appears to be ultimately connected with this scenario [1–4]. Other Pt-am(m)ine compounds such as *trans*-[Pt(NH$_3$)$_2$Cl$_2$], [Pt(NH$_3$)$_3$Cl]$^+$, or [Pt(dien)Cl]$^+$ etc. (dien = diethylenetriamine) share similar reactivity patterns, yet are less potent in terms of anticancer activity, or are even inactive. On the other hand, there are numerous "non-classical" Pt compounds known to date, which exhibit remarkable antitumor activity, but do not follow the "structural rules" of the clinically successful Pt drugs like Cisplatin, Carboplatin, Oxaliplatin, Nedaplatin, etc. [5–7]. Among these, Pt compounds with a single leaving group, e.g. chlorido, hence compounds which seem to be capable of binding to DNA in a monofunctional way only, have received considerable attention. Representative examples are compounds of general composition *cis*-[Pt(NH$_3$)$_2$LCl]$^+$ with L = cytosine [8,9], pyridine [10], or phenanthridine [11]. Similarly, substitution of one of the NH$_3$ ligands of Transplatin by a planar N-heterocycle endows such compounds with antitumor activity (see also 2.4) [12].

We and others have, over the years, synthesized and structurally characterized a large number of complexes of type *cis*- and *trans*-[Pt(NH$_3$)$_2$(nb)Cl] (with nb = anionic, neutral, or even cationic model nucleobases; charges omitted) with the aim to model possible primary DNA adducts of Cisplatin and Transplatin, and to convert them eventually into models for bis(nucleobase) adducts. Any testing for possible antitumor activity of these mono(nucleobase) compounds has not been in our focus. During the course of our work we not only were able to obtain models of established DNA nucleobase cross-links, e.g. intrastrand cross-links of Cisplatin between adjacent guanine bases [13] and between adenine and guanine [14,15], or the major interstrand cross-link of Transplatin with guanine and cytosine [16], and to study them in detail, but discovered a multitude of unexpected reactivity patterns of the mono(nucleobase) precursors. This review is an attempt to summarize these findings and to point out salient features regarding their chemistry, which goes well beyond their sole usefulness as starting materials for model compounds of Pt-DNA cross-links. As we will demonstrate, self-condensation reactions are a unique and frequently executed propensity of these compounds. Whether or not this observation is of any relevance for biological systems, remains to be seen.

At present it seems that the chemistry of structural models, originally considered by us to "simplify" things, in many ways is more complex than the chemistry occurring at least with double-stranded DNA and its steric restrictions regarding metal binding sites. This caution applies even more so to parent nucleobases as the additional available binding sites (N1 in pyrimidine (pym) bases; N9 in purine (pu) bases) open even more metal binding options. We have previously elaborated on different aspects of this topic with a focus on unsubstituted pyrimidine nucleobases [17–19]. Similarly, if nucleobase-ligand conjugates are employed, and/or metals other than the d$^8$ metal ions discussed here preferentially, are included, fascinating constructs are emerging, leading into the realms of supramolecular chemistry, crystal engineering, and materials research [20–32]. We explicitly do not wish to embark here on nucleic acid-based nanotechnology, a field that develops at an astonishing rate [33].

In the following the focus will be largely on model nucleobases, in which the glycosidic entities of nucleosides are replaced by alkyl groups. This simplification avoids the generation of diastereomers in cases of chiral metal complexes. As far as charge is concerned, the analogy between model nucleobases and nucleosides is almost perfect. Potential secondary interactions of the metal ion with oxygen donor sites of the sugar entities are not considered, because they are relatively rare with Pd$^{II}$ and Pt$^{II}$ [34]. Fig. 1 depicts the most common DNA and RNA nucleobases. The respective model nucleobases discussed hereafter are mainly 1-methylcytosine (1MeC), 1-methyluracil (1MeUH), 1-methylthymine (1MeTH), 9-methyl- or 9-ethyladenine (9RA), 9-methyl- or 9-ethylguanine (9RGH), and 9-methylhypoxanthine (9MeHxH). The letter "H" indicates a proton sitting at an endocyclic N atom of the nucleobase. While the mentioned nucleobases in general are neutral in the physiologically relevant pH range, metalation of the heterocyclic part and a favorable microenvironment can strongly change the protonation state, hence affect the p$K_a$. We have extensively studied such p$K_a$ shifts and have elaborated on their potential biological relevance [35–41]. In their metal complexes, nucleobases frequently occur in their deprotonated forms. In the following we differentiate whether the base has lost a proton from an endocyclic NH group (e.g. anion of 1-methyluracil = 1MeU; p$K_a$ values below 10 for free base) or from an exocyclic NH$_2$ group (e.g. 1MeC$_{-H}$; p$K_a$ values above 16 for free base). Throughout this text, we frequently delete the charge of the metal complex, when the protonation state of the nucleobase (neutral or deprotonated) is not specified.

Metal coordination to N3 of U and T requires deprotonation of this site (1MeU, 1MeT), as does metal binding to N1 of G and Hx (9RG, 9RHx), but binding to N7 can occur at neutral 9RGH and 9RHxH, with subsequent deprotonation of N1, however (9RG, 9RHx). Metal binding to neutral 1MeC can take place at N3, but twofold metal coordination to N3 and N4 requires deprotonation of the exocyclic amino group (1MeC$_{-H}$). Exclusive metal binding via deprotonated N4 can either lead to the coordinated anion (1MeC$_{-H}$) or, following protonation of the N3 site, to the metalated neutral rare iminooxo tautomer form (1MeC*). Similarly, the N3 metalated 1MeU/1MeT anion can become protonated at O4, thereby generating a "metal-stabilized rare nucleobase tautomer" (e.g. 1MeUH*), and likewise can N1 metalated 9RG be converted

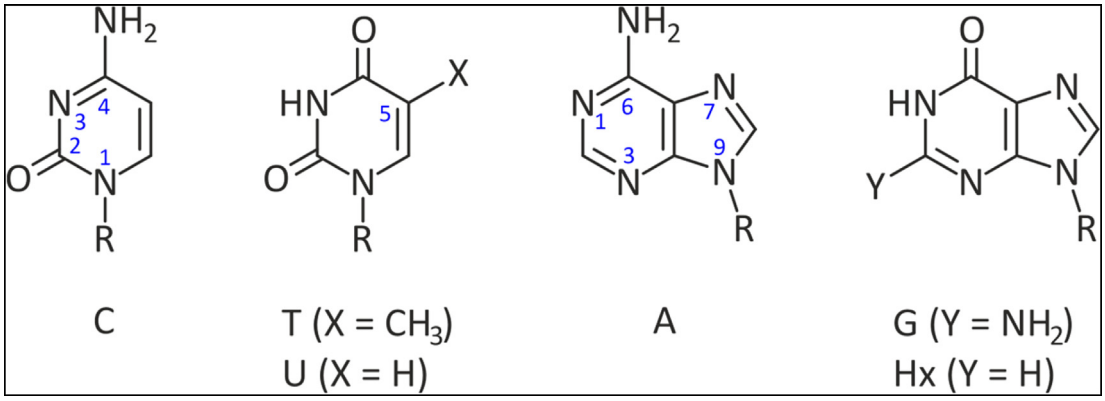


**Fig. 1.** Major DNA and RNA nucleobases (C = cytosine, T = thymine, U = uracil, A = adenine, G = guanine, Hx = hypoxanthine) with R being alkyl groups (model nucleobase), sugar (nucleoside), or sugar phosphate (nucleotide).

to a rare tautomer via protonation of N7. As to the situation with adenine: While metal binding to neutral 9RA can occur either through N1 or N7, or to both sites simultaneously, metal coordination involving the exocyclic amino group N6, alone or in conjunction with N1 and/or N7, requires deprotonation of the amino group ($9RA_{-H}$). Again, metal binding patterns involving N6 can lead to a rare imino tautomer structure ($9RA^{*}$) through protonation of the anionic nucleobase [42]. Finally, N7 or N1 metalated 9RA can undergo protonation at low pH to become an adeninium ligand ($9RAH^{+}$), and N7 metalated 9RGH can accept a proton at N3 to become a guaninium entity ($9RGH_2^{+}$) at low pH (see also chapter 6). In rare cases also organometallic compounds are observed, with $Pt^{II}$ being bonded to a carbon atom, e.g. C5 of 1MeU [43]. We shall not discuss this possibility here further.

## 2. Mono(nucleobase) complexes of type *cis*-[Pt(L,L')(nb)X]

### 2.1. Examples

The by far largest number of compounds of this type with model nucleobases and variable X ligands are available for X = halido, notably $Cl^{-}$, with occasional substitution by iodide, hydroxide, nitrate, or water. 1MeC compounds (with N3 coordination) are leading in numbers. The CSD lists a majority number of examples for L = L' = $NH_3$ for obvious reasons (relevance to Cisplatin chemistry), fewer examples for chelating diamines and diimines, for tris(alkyl)phosphine and related ligands, as well as rare cases of non-symmetrical co-ligands (such as a L,L' = cyclometalated C, N-chelating one) [44,45]. In the following, only few selected examples shall be discussed in more detail. Their syntheses are usually achieved by direct reaction of *cis*-[Pt(L,L')$X_2$] (X = Cl or I) with the respective nucleobase in water or DMF, and prior or subsequent exchange of an X ligand, if appropriate. Oxidative addition of a $Pt^{0}$ species to 1MeTH has also been reported as another possible route [46,47]. Yields of the 1:1-complexes are frequently moderate or low due to concomitant formation of the corresponding bis(nucleobase) complex, and the possibility of subsequent secondary reactions of either species with the remaining available Pt starting compound [48]. Occasionally, detour reactions to obtain the desired mono(nucleobase) species can be advantageous [49]. Binding sites of the model nucleobase to $Pt^{II}$ usually follow expectations [50], as outlined above. While this text concentrates largely on $Pt^{II}$ complexes, we also refer to analogous $Pd^{II}$ compounds, as these appear to be rather similar as far as structural aspects are concerned. The main difference refers to kinetics, which are considerable faster for $Pd^{II}$ species.

### 2.2. Aqua species

The ultimately reactive species of *cis*-[Pt(L,L')(nb)X] compounds for self-condensation reactions or reactions leading to bis(nucleobase) products are the respective aqua complexes, hence X = $H_2O$. Depending on the Pt binding site, these species have at least two sets of relevant acid-base equilibria, involving the aqua ligand *and* the nucleobase. Determined by $^{1}H$ NMR spectroscopy, $pK_a$ values for aqua ligands in the various model nucleobase complexes of *cis*-$(NH_3)_2Pt^{II}$ range from ca. 4.8 – 7.0, depending on complex charge (+2 or +1) and a balance of electron donor properties of the co-ligands (σ- and π-bonding) and the metal (π-backbonding). In addition, the microenvironment (intramolecular H bonding) seems to play a role [40,51]. Relevant $pK_a$ values agree, for 1MeC (5.8) and 1MeU (7.0) model compounds, excellently with data for the corresponding nucleoside complexes as determined by Barnham applying $^{15}N$ and $^{195}Pt$ spectroscopy [52]. For guanine (6.2) and adenine model nucleobase compounds (4.8, N7-linkage isomer), deviations with nucleoside complexes are larger (0.3 – 0.7 log units), as a consequence of the overlap of the two individual acid-base equilibria and differences in the treatment of the pH-dependent shift data (simplified graphical evaluation or computational least-squares method). As briefly mentioned above, aqua groups with $pK_a$ values close to 7 are potentially suitable to become involved in acid-base catalysis, as are, of course, also strongly shifted $pK_a$ values of the nucleobases. Moreover, it needs to be pointed out that Pt–OH and Pd–OH groups present at weakly acidic pH are capable of deprotonating nucleobases (and coordinating to them) at pH values substantially below their $pK_a$ values. Typical examples are the formation of 1MeU-*N3*, 1MeT-*N3*, or $1MeC_{-H}$-*N3,N4* complexes even in slightly acidic solutions.

Regarding $pK_a$ values of the coordinated model nucleobases, they are spread over a much larger range in the case of the *mononuclear* complexes. With the exception of N1 deprotonation of N7-platinated guanines (7.8 – 8.4) [53], these values are too far off from 7 to be of any likely biorelevance. Thus, protonation of bound nucleobases occurs for 1MeU-*N3* with $pK_a \simeq 0.9$ and 1.2 for 9RA-*N7*, while deprotonation of 1MeC-*N3* takes place with $pK_a \geq 13$. Values for deprotonation of the exocyclic amino group of adenine nucleobases in *mononuclear* complexes are still approximates [54], but similar to those of cytosine bases, ≥ 13 for 9RA-*N7* and ≥ 11 for 9RA-*N1*. Favorable intramolecular interactions can lead to dramatic acidifications, however, which then shift the $pK_a$ value well into the physiologically relevant pH range (see 3.3). This is also true for mononuclear compounds with metals in higher oxidation states than +2 [41], not to be discussed here.

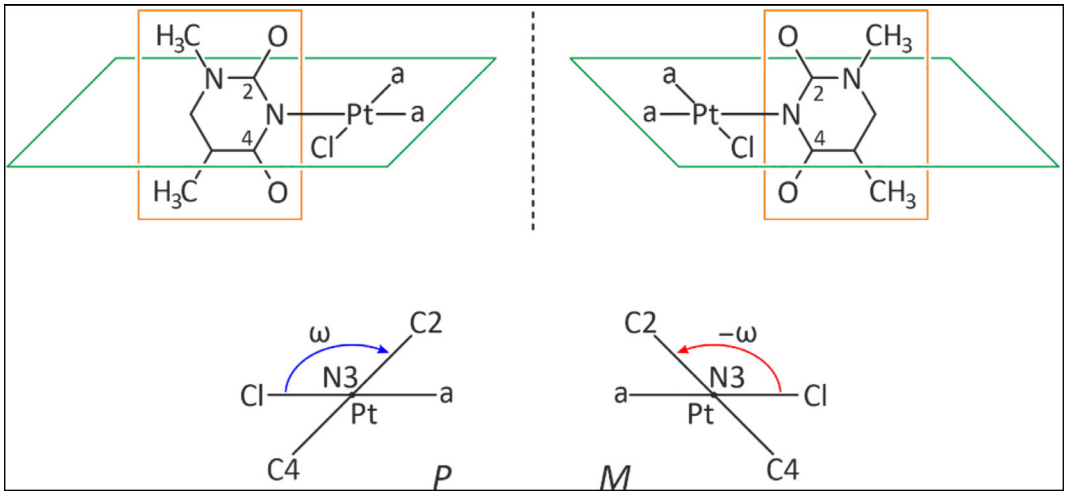


**Fig. 2.** Schematic views of the two enantiomers of *cis*-[Pt($NH_3$)$_2$(1MeT-*N3*)Cl] (top), and determination of their chirality terms with views along the a–Pt–N3 vectors (a = $NH_3$) (bottom): The "far bond" N3–C2 rotates clockwise with respect to the "near bond" Cl–Pt (*P* enantiomer) or counter-clockwise in the other enantiomer (*M* enantiomer). As in most other figures, bond orders within the heterocyclic rings are not indicated.

### 2.3. Chirality of cis-[Pt(L,L')(nb)X]

All mentioned 1:1-nucleobase complexes of composition *cis*-[Pt(L,L')(nb)X] display *planar chirality* as a consequence of monodentate binding of the respective nucleobase ($C_s$ local symmetry) and its exocyclic substituents adjacent to the metal coordination site (endocyclic N atom) which prevent a coplanar orientation of the nucleobase with the metal coordination plane [55], and hence rapid rotation about the Pt–N(nb) bonds and consequently racemization, at least for pym-*N3* and pu-*N1* compounds [56,57]. For [Pt(en)(cytidine-*N3*)($D_2O$)]$^{2+}$ the occurrence of diastereomers in $D_2O$ solution is a clear indication for hindered rotation of the nucleobase [57]. In solid state the compounds occur as pairs of enantiomers (racemates), as required by the centrosymmetric space groups of the crystalline materials. Fig. 2 gives, as a representative example, schematic views of the two enantiomers of *cis*-[Pt($NH_3$)$_2$(1MeT-*N3*)Cl] [58].

The individual enantiomers are characterized by their torsion angle ω, which describes the orientation of the Pt–Cl and N3–C2 bonds relative to the central Pt–N3 bond (or the angle between the Cl–Pt–N3 and the Pt–N3–C2 planes). The choice of Cl and C2 follows the CIP priority rules of substituents of the two planes. The respective chirality terms are determined as follows: When viewed along the Pt–N3 bond, the far bond (N3–C2) is either clockwise rotated with respect to the near bond (Cl–Pt) or counter-clockwise. In the first case ω is positive (right-handed helix) and the chirality term is *P*, whereas in the second case ω is negative (left-handed helix), and the chirality term is *M*.

Regarding the example *cis*-[Pt($NH_3$)$_2$(1MeT-*N3*)Cl] torsional angles are +104.9° and –104.9°, respectively, with the 1MeT plane forming an angle of 76.5° with the Pt coordination plane.

### 2.4. Uses of cis-[Pt(L,L')(nb)X]

Given the number of possible DNA adducts (monofunctional binding or cross-linking) of Cisplatin (L = L' = $NH_3$) [59,60], the mono-adduct models reported above provided ideal compounds for studying their basic properties (e.g. acid-base chemistry, see above; base pairing properties; biological activity) and at the same time useful starting materials for models of mixed-nucleobase adducts.

As to biological effects of *cis*-[Pt(L,L')(nb)X] compounds: In a pioneering study, Hollis and coworkers had synthesized and tested a large number of compounds of composition *cis*-[Pt($NH_3$)$_2$(N-donor)Cl]$^+$ with N-donor representing various amines as well as N-heterocyclic ligands including differently substituted pyridines, cytosine, 1MeC, cytidine, and guanosine [8]. The surprising antitumor activity of most of these compounds, which contradicted earlier views of the mode of action of antitumor Pt drugs, was later confirmed for related compounds on a large number of tumor lines [61]. It is well established today that these monofunctional Pt agents represent a new class of antitumor agents which, after release of the labile chlorido ligand, bind to DNA via guanosine-*N7* sites, thereby producing a blocking site for DNA replicating polymerases. This research, carried out initially with the cytosine compound [9], and subsequently in detail with the pyridine compound ("pyriplatin") by the Lippard group [10,62] has later been extended to the phenanthridine analogue ("phenantriplatin"), which indeed appears to be another promising drug candidate [11]. The inactivity of [Pt($NH_3$)$_3$($H_2O$)]$^{2+}$, assumed to also bind to guanosine-*N7* in the major groove of DNA, may therefore only be a matter of size, namely the $NH_3$ ligand being sterically too small to efficiently block essential biomolecules to interact with DNA, hence to interfere with transcription [63]. Whether or not related mononuclear Pt- and Pd-1MeT or -thymidine complexes with antiproliferative activity [46] are fully analogous in their modes of action to the above-mentioned compounds, remains to be seen.

At least two other topics, the antiviral activity of mononuclear complexes of $Pt^{II}$ containing guanine-type ligands (acyclovir; penciclovir) [64], and the effects of several monofunctional $Pt^{II}$ compounds on bacterial growth in general [65] —reminiscence of the discovery of the antitumor agent Cisplatin by Barnett Rosenberg— should be mentioned here with regard to biological effects.

Regarding models of feasible Cisplatin cross-links with sites in double-stranded DNA and single-stranded DNA or RNA, *cis*-[Pt(L,L')(nb)X] compounds are ideal precursors for mixed-nucleobase species. Examples include such between 9EtGH and 1MeC [66], 9MeA and 1MeC [67], 1MeU and 1MeC [68], 9MeAH and 1MeT [69], as well as 9MeA and 9EtGH [14,15]. Except for the latter, which is a model for the second most abundant Cisplatin cross-link in duplex DNA, the biological significance of the other cross-links is presently unclear. For model compounds involving N1 of 9RG see also chapter 7. All these compounds are inherently chiral, occurring in the solid state as pairs of enantiomers [55]. With the AG model cross-link, minor structural differences in dependence of the counter anion are seen [14,15].

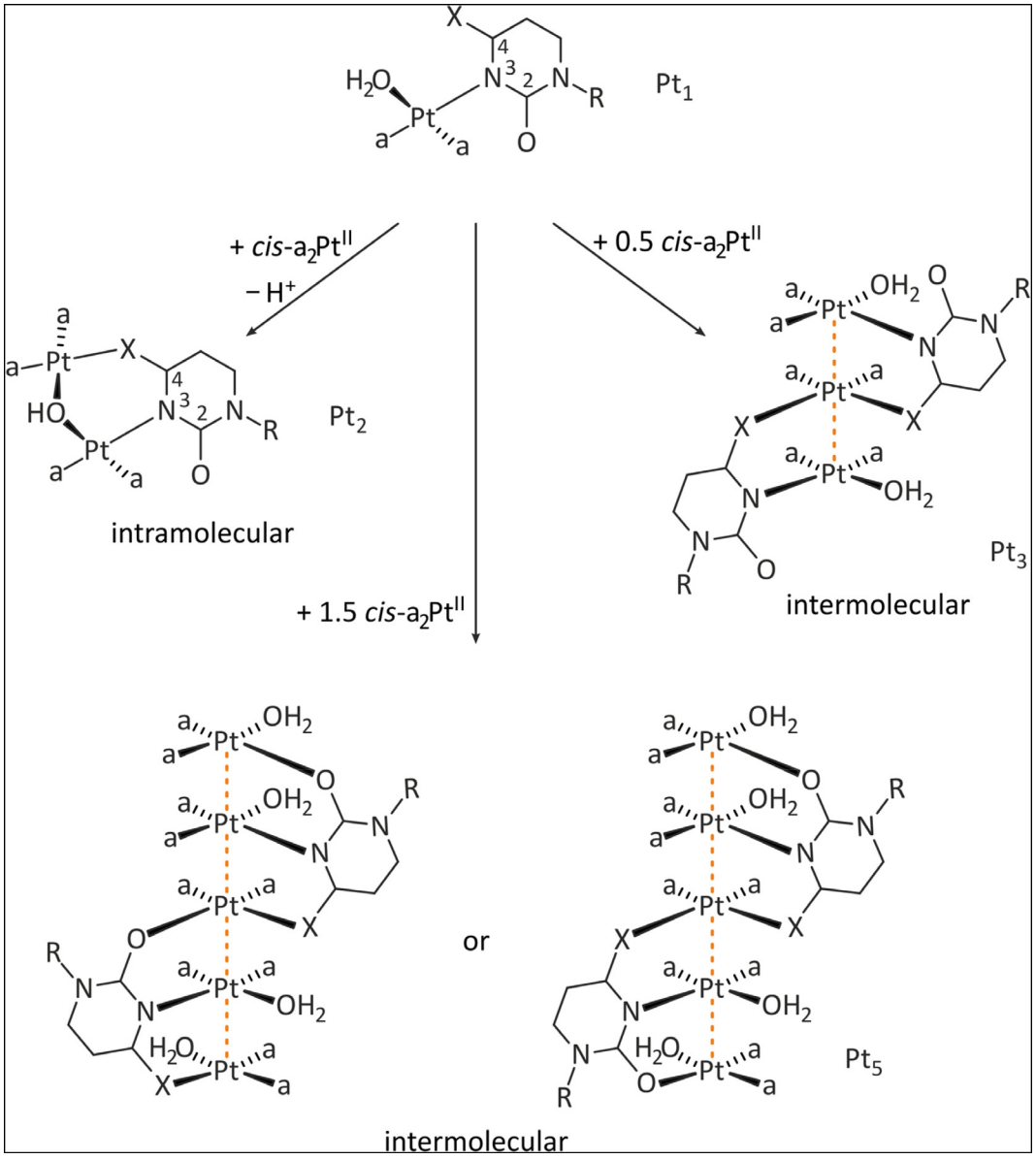


**Fig. 3.** Intra- and intermolecular condensation reactions between *cis*-$[Pt(a)_2(pym\text{-}N3)(H_2O)]^{n+}$ and *cis*-$[Pt(a)_2(H_2O)_2]^{2+}$ involving X4 positions only (top), or simultaneously also O2 (bottom). In the condensation products X4 refers to either O (1MeU, 1MeT) or NH ($1MeC_{-H}$). Charges have been omitted, as have been double bonds in the heterocyclic nucleobases, like in later schemes.

### *2.5. Metal binding properties of mono(nucleobase) complexes*

We have extensively published on the metal binding properties of bis(pym-nucleobase) complexes of *cis*- and *trans*-$a_2Pt^{II}$ and described numerous homo- and heteronuclear examples [69,70]. In brief, coordination of the second metal usually requires *two* suitably positioned exocyclic donor atoms of two ligands, in most cases X4 (X = O for 1MeU and 1MeT; X = NH for $1MeC_{-H}$). The situation with mono(pym-nucleobase) compounds is different in that there is no second X4 site available. However, a small ligand at Pt present, such as $OH^-$ [47,71,72] or a halido [73] can serve this purpose to generate 6-membered chelate rings following an *intramolecular* condensation, as sketched for the reaction of the mononuclear Pt complex with additional *cis*-$(NH_3)_2Pt^{II}$ in Fig. 3 (top left). For related aspects see also 2.6.9. As a hypothetical alternative (top right and bottom), *intermolecular* condensation involving exocyclic donor groups from adjacent mono(pym-nucleobase) complexes are feasible. It could lead to arrangements of different stoichiometries and compositions. In the simplest case, with exclusive use of N3 and X4 sites, a product of type $[Pt_3(pym\text{-}nb)_2(H_2O)_2]$ could be envisaged. If in addition also involvement of O2 is considered, a composition of $[Pt_5(pym\text{-}nb)_2(H_2O)_4]$ is possible, and so on. Such multinuclear species appear to be reasonable if reactions of excess *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with pym-nucleobases are considered. In principle, the stacked versions would allow for short Pt···Pt contacts, including the possibility of partial metal oxidation. Furthermore, the terminal aqua ligands have the capacity to engage in additional association patterns via hydroxido bridges. We shall not further consider such a possibility here, however. It can be expected, that concentration and pH determine whether condensation reactions of this kind occur in an intra- or intermolecular way.

Interestingly, analogues of the proposed structures for $Pt_3$ and $Pt_5$ species might also be possible for products formed between $[Pt(NH_3)_3(pym\text{-}nb\text{-}N3)]^{n+}$ and *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$.

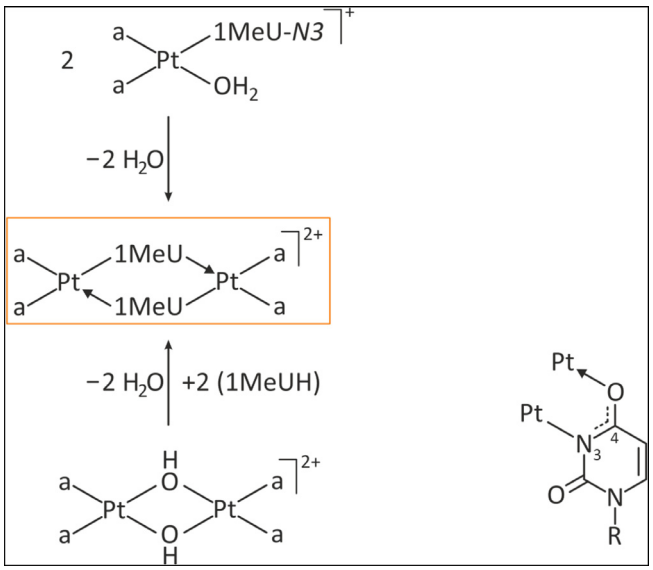


**Fig. 4.** Commonly applied synthetic ways to generate head–tail dinuclear complexes of *cis*-$Pt^{II}(a)_2$, schematically outlined for 1-methyluracil.

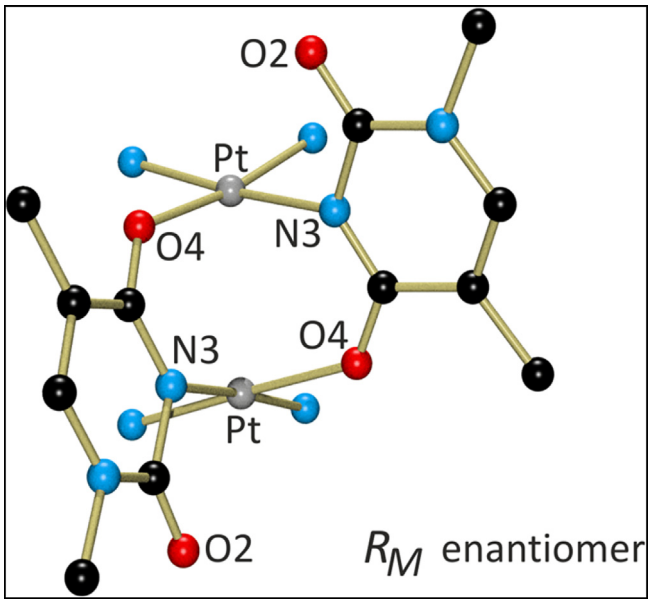


**Fig. 5.** View of cation *cis*-$[(NH_3)_2Pt(\mu\text{-}1MeT\text{-}N3,O4)]_2^{2+}$ ($R_M$ enantiomer) [85].

## 2.6. Cyclic derivatives of cis-[Pt(L,L')(nb)X]

### 2.6.1. Requirements for their formation

In order to produce cyclic constructs starting from *cis*-[Pt(L,L')(nb)X] two requirements must be fulfilled: (i) The nucleobase needs to have a second suitable donor site of sufficient basicity available, e.g. an exocyclic O atom (in case of 1MeU, 1MeT, or 9RGH), a second endocyclic N atom (9RA, 9RGH, or 9RG anion), or a sufficiently acidic amino group, as metal binding requires deprotonation of the $NH_2$ group (in case of 1MeC, 9RA) [74,75]. Pt coordination to an endocyclic ring N atom, which is accompanied by displacement of a proton (T-*N3*, U-*N3*, G-*N1*) fulfills this criterion, as electron density is shifted to the adjacent carbonyl oxygen atoms [76]. Pt coordination to a free endocyclic N atom (N3 of C, N1 of A, N7 of A, N3 of G) acidifies the protons of the adjacent amino groups markedly (see above), albeit not nearly to the same extent as does methylation or protonation of the adjacent endocyclic N atom, which in the case of cytosine bases is ca. $10^6$ [77]. (ii) *cis*-[Pt(L,L')(nb)X] needs to have a good leaving group X, which, if reactions are carried out in water, is a $H_2O$ ligand. X = $OH^-$ is a poor leaving group, but it can achieve deprotonation of a N–H nucleobase function (see above) and consequently likewise favor μ-nb formation. On the other hand, hydroxido ligands can be potent competitors for the formation of cyclic nucleobase complexes, in that $Pt^{II}$ has a pronounced tendency to also form μ-OH species [78]. Clearly, the distribution of hydroxido- and nucleobase-bridged species is also pH-dependent and a combination of both bridging modes is also feasible. In rare cases even μ-$NH_2$ formation (through intermolecular condensation between $NH_3$ and $OH^-$ ligands) has been observed [72].

Ignoring these competitive reactions for the moment and concentrating solely on metalacyclic nucleobase species, these may involve the following combinations: T or U: *N3,O4* and *N3,O2*, C: *N3,O2* and *N3,N4*, A: *N1,N6* as well as *N7,N6,* and *N1,N7*, G: *N1,O6* as well as *N7,O6,* and *N1,N7*. The involvement of G-*N2* in combination with G-*N1*, although occasionally seen with $Hg^{II}$ [79], has not yet been verified with *cis*-[Pt(L,L')(nb)X]. Likewise, there is no established case of a cyclic species involving G-*N3* and G-*N2*.

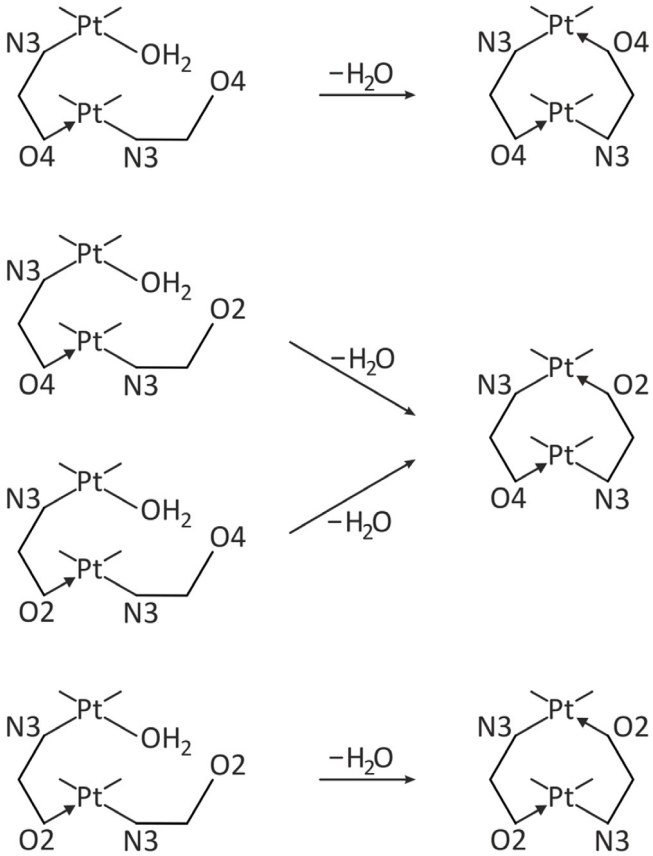


**Fig. 6.** Possible dinuclear linkage isomers derived from *cis*-$[Pt(a)_2(pym\text{-}N3)(H_2O)]^+$ (with pym = 1MeU or 1MeT). The head–tail dimer with twofold N3,O4 bridging is the thermodynamically most stable product. The two other head–tail isomers may represent kinetic products.

### 2.6.2. Head-tail dimers with Pt centers facing each other

The smallest cycles formed by condensation of two *cis*-$[Pt(L,L')(nb)(H_2O)]^{n+}$ are folded 8-membered rings (all pym nucleobases and *N1,X6* combinations for pu nucleobases) as well as folded 10-membered rings (*N7,X6* combinations for pu nucleobases), with *X6* being either O (G) or $NH^-$ (A). Synthesis of these dinuclear com-

plexes is achieved either by rational dimerization of *cis*-[Pt(L,L')(nb)($H_2O$)]$^+$ (if nb is a deprotonated nucleobase, e.g. 1MeT, 1MeU, 9RG) or *cis*-[Pt(L,L')(nb)(OH)]$^+$ (if nb is a neutral nucleobase, e.g. 1MeC, 9RA, 9RGH), or by numerous other ways. One of these involves a mixed metal, mixed μ-hydroxido/μ-1-methylcytosinato intermediate, in which the $Pd^{II}$ exercises a catalytic function to eventually give the $Pt^{II}$-head–tail dimer [71].

A commonly applied method to obtain head–tail dimers is also to react hydroxido-bridged dinuclear *cis*-[(L,L')Pt(μ-$OH)_2$Pt(L,L')]$^{n+}$ (with L,L' being $NH_3$ or another monodentate ligand such as phosphine, a chelating, symmetrical or unsymmetrical N,N' ligand, a diphosphine, or an anionic cyclometalating C,N ligand) with neutral nucleobases (1MeTH, 1MeUH, 1MeC, 9EtA) [80–83] (Fig. 4). For analogous $Pd^{II}$ complexes, identical procedures work.

The first structurally characterized example of this type of head–tail dimers was that of 1MeT [84], followed by analogous structures with 1MeU [85], a second modification of the 1MeT dimer [86], and several examples of $1MeC_{-H}$ [87–89]. Fig. 5 depicts a representative structure (1MeT). The dinuclear cation is chiral (see 2.6.3), but only one of the two enantiomers (*M*) present in the unit cell is shown.

As can be seen, the cation *cis*-[$(NH_3)_2$Pt(μ-1MeT-*N3,O4*)]$_2^{2+}$ displays two tilted (36°) and at the same time slightly rotated (14°) Pt coordination planes, which face each other. The intramolecular Pt–Pt distance is 2.974(1) Å. Each Pt atom is bonded to a N3 site as well as an O4 of 1MeT, and carries two $NH_3$ ligands. Because of the pseudo-twofold axis bisecting the 1MeT plane through N3 and C6, there could be an ambiguity regarding the coordinating oxygen atoms (O4 or O2), but the thermal parameters of N1 and C5 rule out that O2 is bonded. Moreover, all crystallographically studied Pt dimers with 1MeU bridges reveal O4 as the second binding site. Nevertheless, O2 should not be fully excluded as a Pt binding site in 1MeT (and 1MeU) compounds, as it could be present in kinetic products, which during the crystallization process, convert

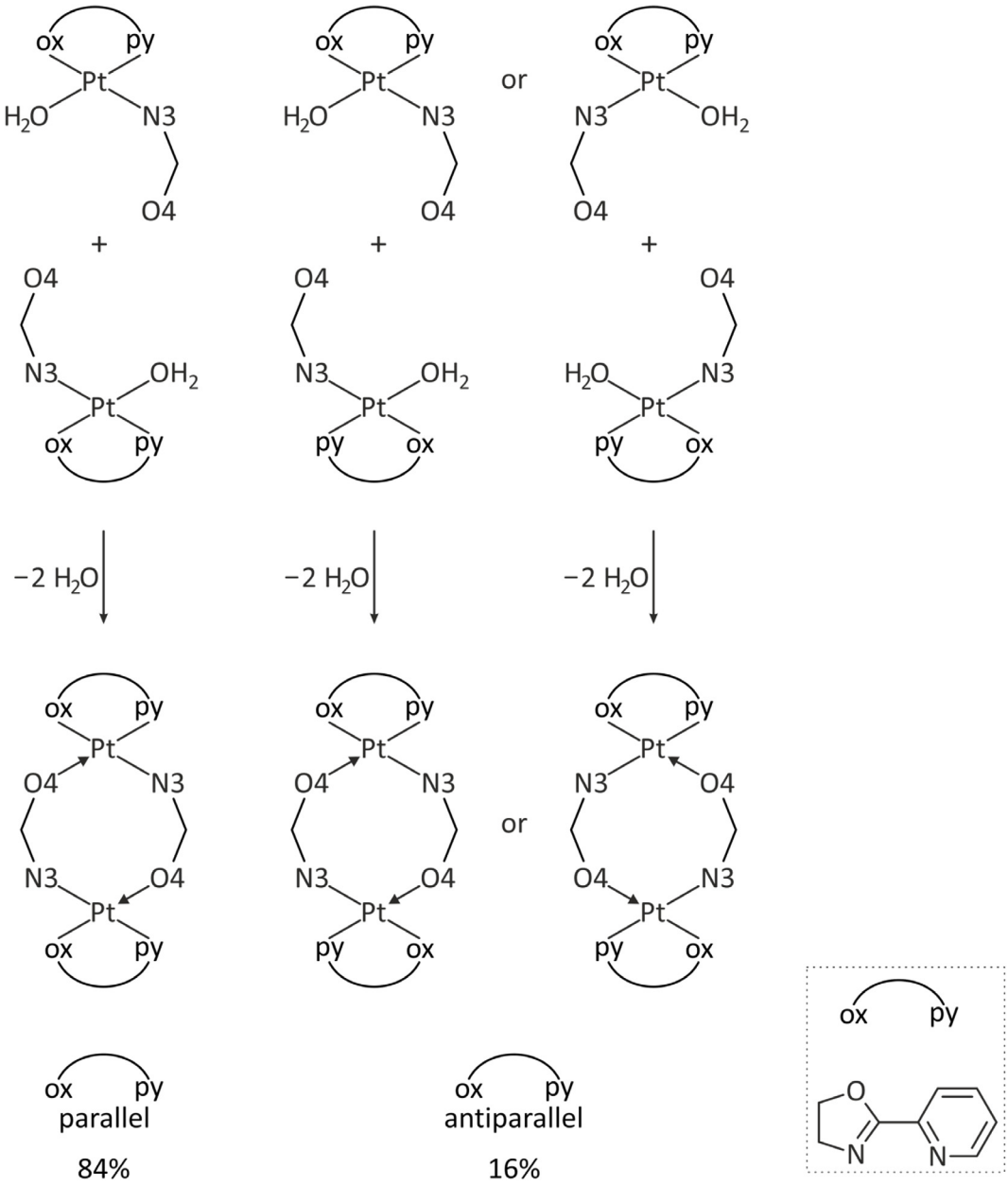


**Fig. 7.** Attempt to rationalize the crystallographic analysis of the head–tail dimers derived from [Pt(po)(1MeU-*N3*)($H_2O$)]$^+$ (with po = 2-(pyridine-2-yl)-2-oxazoline) with parallel and antiparallel po co-ligands.

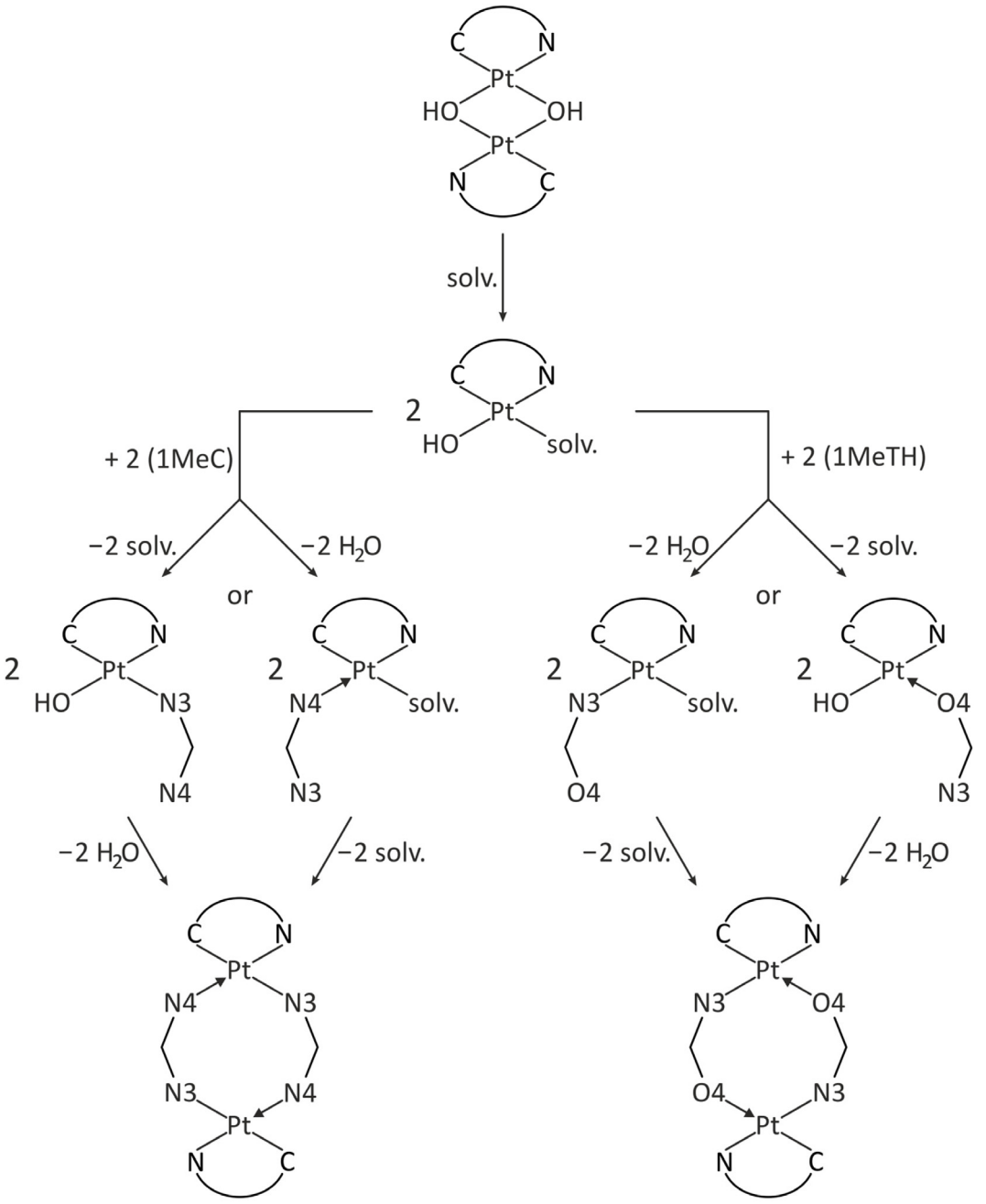


**Fig. 8.** Possible routes to head–tail dimers derived from the μ-OH dimer of $Pt^{II}$(dmba) (with dmba = 2((dimethylamino)methyl)phenyl) and 1MeC and 1MeTH, respectively, explaining the differences of the pym-N3 positions with respect to the unsymmetrical co-ligands.

to the thermodynamically stable one seen in the solid state structures (see also section 2.6.8). Regarding the formation of the head–tail dimers, intermediate open structures with a still available aqua ligand at one of the two Pt atoms, seem possible. Taken together, it is obvious that prior to precipitation of the most stable product, a series of intermediates or thermodynamically less stable products may exist in solution (Fig. 6). They might explain, at least in part, the complexity of $^1$H NMR spectra of freshly prepared *cis*-[Pt$(NH_3)_2$(1MeU)$(D_2O)$]$^+$ solutions [48,49].

The use of unsymmetrical rather than symmetrical co-ligands ($(NH_3)_2$, en, 2,2′-bpy, etc.) at the metal entity (M = Pt or Pd) provides a number of interesting aspects with regard to the formation of dinuclear head–tail nucleobase compounds. For example, the group of Krebs has used unsymmetrical chelating N,N' co-ligands such as mipk (1-methylimidazol-2-yl pyridin-2-yl ketone) [90], po (2-(pyridine-2-yl)-2-oxazoline [91], and cmpp (3-chloro-6-(3-methylpyrazol-1-yl)pyridazine) [92] to prepare the corresponding dinuclear 1MeT-*N3,O4* and 1MeU-*N3,O4* complexes of $Pt^{II}$ and $Pd^{II}$. In all cases the synthesis involved reaction of monomeric Pt/Pd species with the pym nucleobase in a 1:1-ratio. Findings in the 1MeT system with (po)$Pt^{II}$ and (po)$Pd^{II}$ are in a way surprising in that in the Pt compound the coordinating N3 positions are trans to the oxazoline-N, whereas in the Pd compound the N3 sites of 1MeT are trans to the pyridine-N. As the unsymmetrical co-ligands are arranged in an antiparallel fashion in both compounds, a plausible explanation for the observed difference in the crystallized products could be that the head–tail dimers originate from dimerization of two *different* monomeric linkage isomers, hence

from one with the po ligand bonded through the oxazoline-N in [Pt(po)(1MeT-*N3*)($H_2O$)]$^+$, yet from one bonded through the pyridine-N in [Pd(po)(1MeT-*N3*)($H_2O$)]$^+$. Whether or not the respective other linkage isomers exist in solution and whether in fact also "mixed" species may form, needs to be further studied. Findings with the closely related 1MeU compound head–tail-[$Pt_2$(po)$_2$(1MeU-*N3,O4*)$_2$]$^{2+}$ indeed suggest the latter possibility in that a disorder of the po ligand at *one of the two* Pt atoms is observed in this complex: While the crystallographic refinement suggests that 84% of the po ligands are arranged in a parallel fashion, with oxazoline and pyridine rings at the two metal centers facing each other, only 16% of the po ligands are arranged in an antiparallel way. A possible explanation could be that in the majority of dimerization processes two *different* linkage isomers of [Pt(po)(1MeU-*N3*)($H_2O$)]$^+$ combine to the head–tail dimer, while the association of *identical* linkage isomers (with 1MeU either trans to pyridine-N *or* trans to oxazoline-N) represents a minor pathway (Fig. 7). Of course, this picture applies only to the crystal picked for the crystallographic study.

In yet another study from the Krebs group, a 1:1-mixture of mononuclear Pt species containing two symmetrical, yet *different* N,N ligands (dpa = 2,2′-dipyridylamine and dpma = (2,2′-dipyridyl)-methylamine) had been reacted with 1MeU [93]. The crystal of the isolated head–tail dimer studied contains both co-ligands present in a 1:1-ratio, thereby proving (again) that "self-sorting", as frequently observed in supramolecular chemistry [94,95], appears not to be a general rule in processes leading to head–tail dimers of the pym nucleobases.

An additional variation of this theme, the preparation of mixed pym-nucleobases (e.g. 1MeU and 1MeC) in head–tail dimer structures may further shed light on such processes, but has not yet been conducted.

The group of Ruiz has likewise applied a chelating unsymmetrical co-ligand, dmba (dmba = 2((dimethylamino)methyl)phenyl) and $Pd^{II}$ to prepare head–tail dimers of 1MeT and 1MeC [83]. Starting from the dinuclear, hydroxido-bridged [(dmba)Pd(μ-OH)$_2$Pd(dmba)] and reacting it with 2 equiv of the pym-nucleobase, head–tail dimers are obtained. In both cases the N,C-coligands are oriented in an antiparallel fashion. However, the bridging pym-nucleobases are arranged in different ways, namely such that in the 1MeT case the N3 atoms are trans to N of dmba, whereas in the 1MeC dimer the N3 atoms are trans to C of dmba. This is at first glance surprising since in mononuclear [Pd(dmba)(1MeU-*N3*)($PPh_3$)] the N3 donor atom is trans to C [83] as is, incidentally, also the case with N3 of 1MeC in [Pt(dmba)(1MeC-*N3*)(DMSO)]$^+$ [44]. The experimental findings with the two head–tail dimers can possibly be rationalized by a scenario as outlined in Fig. 8.

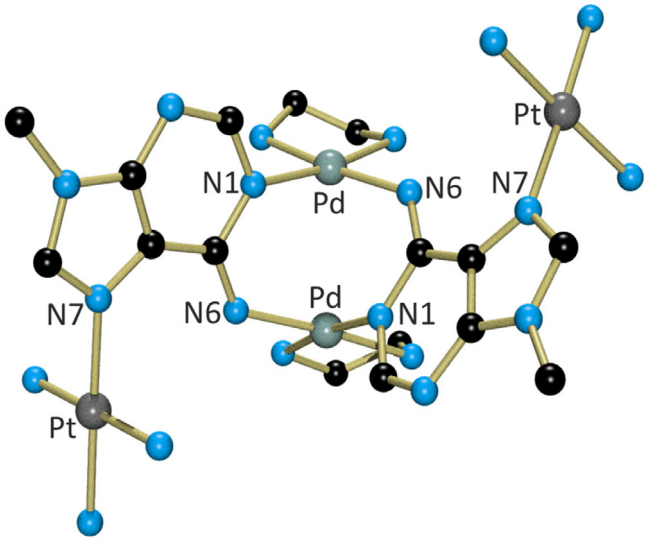


**Fig. 9.** View of cation *head,tail*-[{(en)Pd}$_2${(*N1,N6*-9MeA-*N7*)Pt($NH_3$)$_3$}$_2$]$^{6+}$ [102].

According to it, the hydroxido-bridged starting compound could be in equilibrium with a monomeric solvent species (solvent = dichloromethane; trans to C), which then binds a neutral 1MeC through its N3 position with replacement of the solvent before undergoing deprotonation at the amino group in position 4 by the hydroxido ligand and subsequent dimerization. Alternatively, the initial reaction occurring between Pt–OH and N(4)$H_2$ could lead to a 1-methylcytosinato species which subsequently replaces the solvent with formation of the Pt–N3 bond. It should be mentioned here that the Longato group has shown that such species ($Pt^{II}$ bonded monofunctionally to the deprotonated N4 position) indeed can be isolated [96]. As to the head–tail 1MeT dimer, it likewise could be formed in two ways, depending whether N3 binding and nucleobase deprotonation takes place in the first or second step, or whether neutral 1MeTH binds via its O4 position: The neutral 1MeTH could either become first bonded as an anion through N3, by condensation with the hydroxido ligand, or alternatively by initial binding as a neutral molecule through its exocyclic O4. In either case the resulting head–tail dimer would have the N3 positions of 1MeT trans to N of the unsymmetrical dmba co-ligands.

Analogous crystallographically confirmed structures with head–tail N1,O6 bridged dinuclear $Pt^{II}$ or $Pd^{II}$ guanine complexes (involving the pyrimidine part of the purine ligand) are presently not available. Likewise, structures with a head–tail N7,O6 bridging modes are obsolete for these $d^8$ metal ions, although well established for other metal ions, occasionally with additional metal binding through the deprotonated N1 site [97–100], or when bridging is in head-head fashion [100]. A comprehensive review on relevant guanine and adenine complexes of Rh, Re, and Ru and their interactions with DNA has been published by Chifotides and Dunbar [101].

Dinuclear $Pt^{II}$ and $Pd^{II}$ complexes of adenine model nucleobases with head–tail arrangements through N1,N6 are likewise rare. In fact, Longato and coworkers have reported the first and so far only head–tail dinuclear 9EtA$_{-H}$ complex of $Pt^{II}$ with N1,N6 bridging of the nucleobases [81]. Like in the head–tail dinuclear 1MeC$_{-H}$ complexes (see above), the exocyclic amino group of 9EtA has undergone deprotonation, and the resulting metalacyclic ring is 8-membered. In a variation of this theme, head–tail bridging via N6 and N1 by two (en)$Pd^{II}$ entities has been observed in a heteronuclear $Pt_2Pd_2$ complex, in which the two 9MeA nucleobases carry in addition $Pt^{II}(NH_3)_3$ units at their N7 positions (see also chapter 7) [102]. In aqueous solution, this compound exists in an equilibrium with the corresponding head-head dimer. Both isomers display distinct anion ($ClO_4^-$) binding properties in the solid state and differ in their intramolecular Pd–Pd distances (Fig. 9).

An analogous structure of a $Rh^{I}$(cod), with monofunctional binding to N7 and head–tail dimerization via N1 and N6 has been reported by Sheldrick with the related 8-aza-9-methyladenine [103].

As to adenine N7,N6 bridging by *cis*-Pt($a_2$) entities, unlike for other transition metals [101], no crystallographically established cases exist.

### 2.6.3. Chirality of head–tail Pt and Pd dimers

All head–tail dinuclear nucleobase complexes discussed above and containing two identical co-ligands at the metals (e.g. $NH_3$), a symmetrical chelating co-ligand (e.g. en, 2,2′-bpy), or an unsymmetrical chelating co-ligand in antiparallel fashion at the two metal centers (see previous paragraph), are chiral. The two mirror images are non-superimposable and consequently represent enantiomers. Formally, these head–tail dimers are the condensation

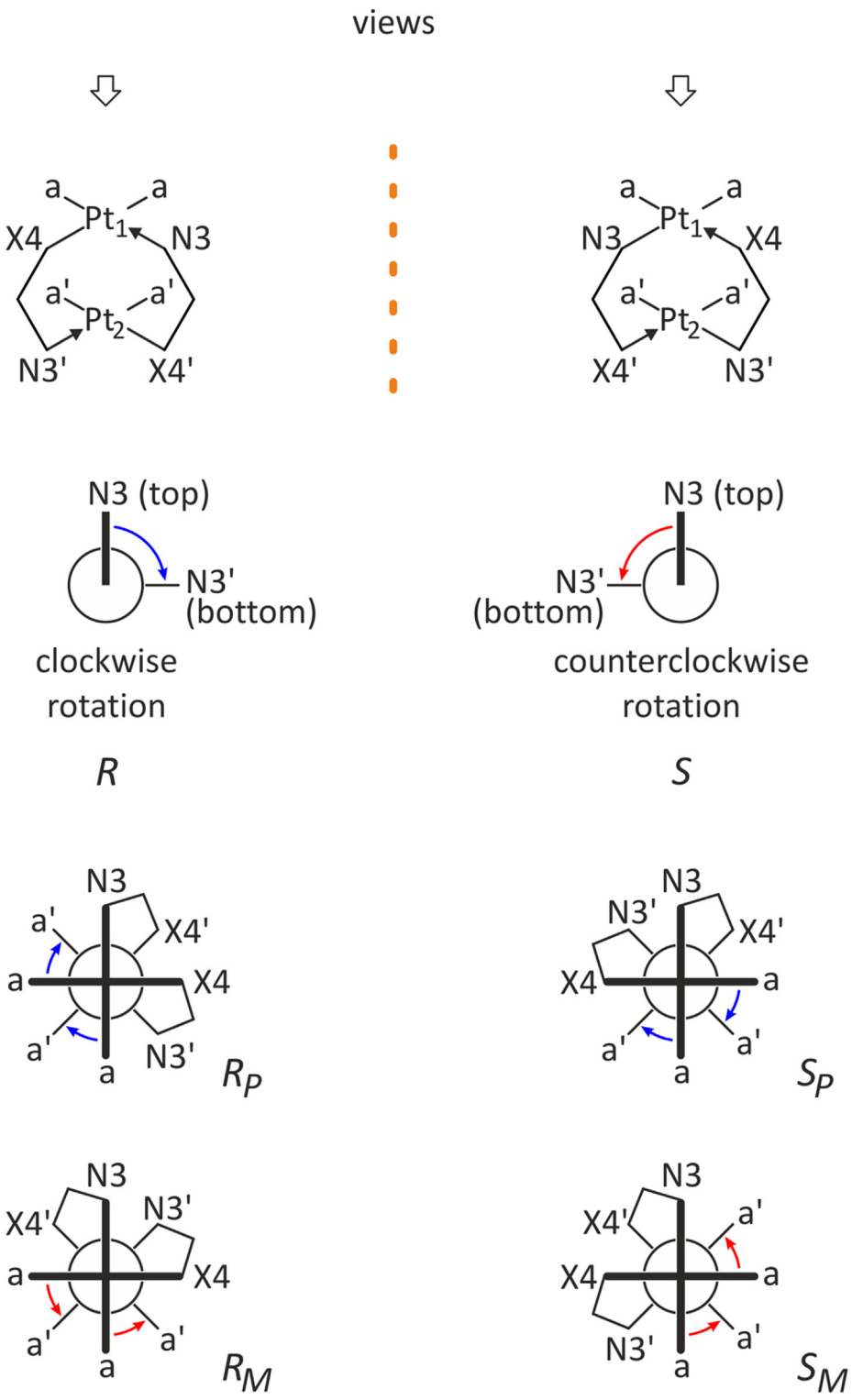


**Fig. 10.** (top): Idealized representation of the two enantiomers of head–tail dimers of *cis*-{[Pt(a)$_2$(pym-*N3,X4*)]$_2$}$^{2+}$ assuming eclipsed orientations of the Pt planes. (bottom): Refined representation, taking into account that both pym and (a) ligands are twisted. Views are in all cases from top (bold lines) to bottom (thin lines). Altogether four head–tail dimers of different stereochemistry are possible.

products of two *identical* enantiomers of chiral *cis*-[Pt(L,L')(nb)(H$_2$O)] species. Condensation of two *different* mononuclear enantiomers leads to products of a different structure (see 2.6.4).

To a first approximation, individual head–tail enantiomers can be differentiated according to the recommended *R* and *S* chirality terms (Fig. 10, top) [104,105]. However, as the two metal planes, based on X-ray data, never adopt a perfectly eclipsed configuration but rather are twisted, this situation leads to torsional angles along the Pt–Pt vectors. These are defined in *P* and *M* terms which, together with *R* and *S*, describe the stereochemistry of four feasible head–tail dinuclear complexes in total (Fig. 10, bottom). Differentiation of the enantiomers based on their torsion angles ω is

achieved as follows: When the dimer is viewed from the top, along the metal–metal vector, the Pt–a bonds nearest to the observer (Pt1), and the Pt–a bonds below (Pt2) are rotated against each other. If the lower Pt-a bonds are rotated clockwise with respect to the upper ones, the chirality term is *P*, if the lower Pt–a bonds are rotated counter-clockwise, the chirality term is *M*. In a similar fashion, head–tail dinuclear pu-dimers, with N1 and X6 metal coordination, can be differentiated. Usually torsion angles ω for the two sets are not exactly the same and therefore are averaged. They contribute to the metal–metal distance in the dimer, together with other variables such as bite distance of the bridging nucleobase, tilt angle of the metal planes, steric demand of the co-ligands, crystal packing pattern, etc. [106,107].

An alternative description of *R* and *S* enantiomers might be that of Δ and Λ enantiomers, based on the skew-line convention, as frequently used to differentiate head–tail isomers of mononuclear complexes of type *cis*-[Pt(a)$_2$(nb)$_2$], hence compounds containing two identical nucleobases in a monodentate fashion [108–110]. If applied to the here discussed head–tail dimers, skew lines would refer to Pt–Pt vectors and to N3–N3 vectors, and Δ would correspond to *R* and Λ to *S*.

In Fig. 11 different views of the dinuclear cation of head–tail-*cis*-[(NH$_3$)$_2$Pt(1MeC$_{-H}$)$_2$Pt(NH$_3$)$_2$]Cl(NO$_3$)·2H$_2$O are shown. Both enantiomers are depicted. The averaged torsion angle ω is –22° [88].

Attempts to separate enantiomers of a typical example, shown to be stable in *i*-propanol for an extended period of time, head–tail-*cis*-[(NH$_3$)$_2$Pt(1MeC$_{-H}$-*N3,N4*)$_2$Pt(NH$_3$)$_2$][BPh$_4$]$_2$, on a HPLC column containing a chiral, cyclodextrin-based material, proved unsuccessful. It is noted that with another chiral head–tail dimer, di(μ-2-aminoethyl 2-pyridyl sulphido)-bis[chloridoplatinum(II)]chloride trihydrate, the two enantiomers could be resolved by use of a chiral anion [111].

*2.6.4. Alternatives for head–tail dimers?*

There are two crystal structures of dinuclear, *centrosymmetric* 1MeC complexes available, containing Ag$^+$ [112] and Zn$^{2+}$ [113], in which the two nucleobases, bridging the two metals via O2 and N3, are arranged head–tail. In both cases the metal ions adopt tetrahedral coordination geometries (Fig. 12). From model building there seem to be no restrictions regarding a *cis*-square-planar metal entity (e.g. *cis*-a$_2$Pt$^{II}$) to adopt an analogous structure involving an endocyclic N atom and an adjacent exocyclic donor atom. Yet what is required to come up with such an alternative head–tail structure is the condensation of two *different* enantiomers of mononuclear chiral *cis*-[Pt(L,L')(nb)(H$_2$O)] species. However, this has not been observed thus far.

Major differences with respect to the chiral head–tail dimers discussed above are as follows: First, the two nucleobases are arranged in an antiparallel staircase fashion. Second, the metal centers and likewise the co-ligands are not facing each other, as in the case of the chiral head–tail dimers, but rather pointing away from each other. Third, the metal–metal separation, below or around 3 Å with the chiral head–tail dimers of Pt$^{II}$ and Pd$^{II}$, would be considerably longer in such structures, estimated longer than the 3.9 Å found with the Zn complex. It is obvious that, for example with the Zn compound, the chlorido co-ligands would be in their way when the metals were to face each other and were to have a tetrahedral coordination geometry. Similar arguments apply to tetrahedrally coordinated Ag$^+$ ions with their bridging nitrate anions. These arguments apply, in principle, also to N1,X6-bridged purine dimers and possibly even to N7,X6-bridged ones. A possible rationale for the absence of such an arrangement in case of Pt$^{II}$ and Pd$^{II}$ might be that these square-planar d$^8$ metal ions favor weak metallophilic interactions as a consequence of a "configuration interaction", as numerously seen in dinuclear complexes and 1D-networks of these metal ions [114–117]. It is noted that in

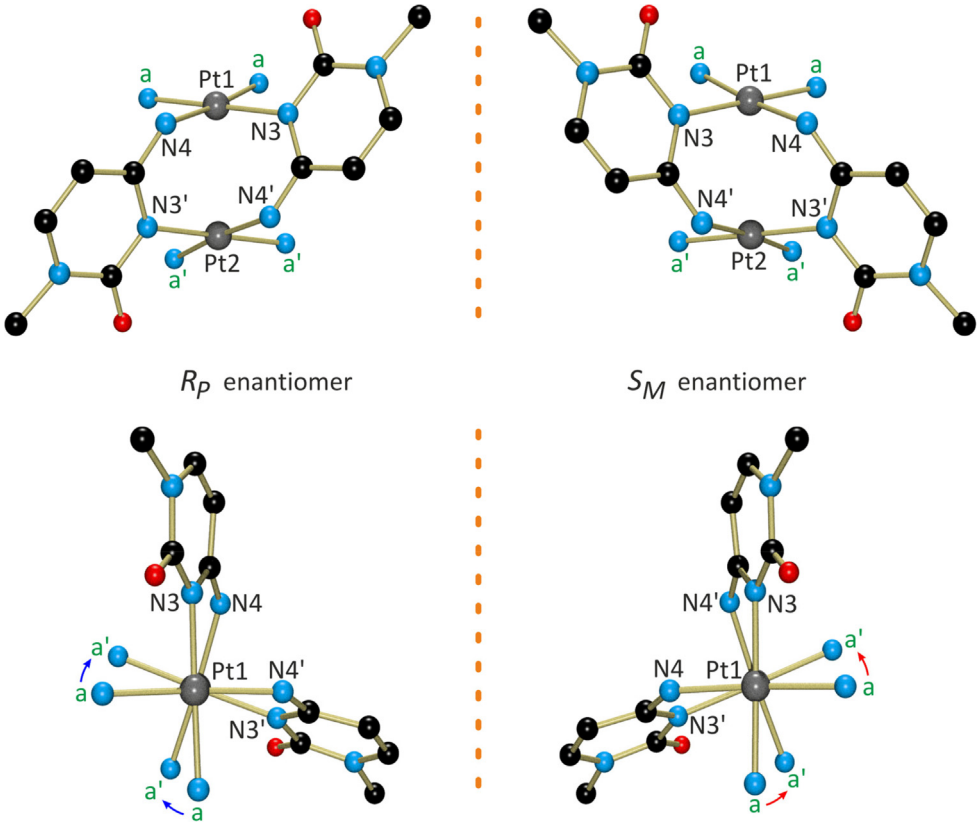


**Fig. 11.** Top and side perspectives of both enantiomers present in the unit cell of cation head–tail-*cis*-[(NH$_3$)$_2$Pt(1MeC$_{-H}$-*N3,N4*)$_2$Pt(NH$_3$)$_2$]$^{2+}$ [88].

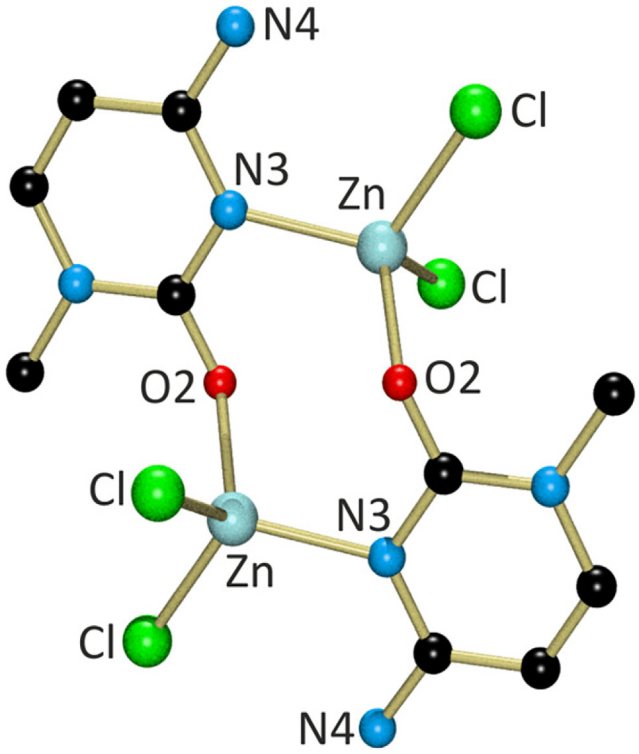


**Fig. 12.** View of the centrosymmetric dimer $[Zn(1MeC\text{-}N3,O2)Cl_2]_2$ [113].

special dinuclear $Pt^{II}$ complexes switching reactions ("pivot-hinge motion") between the metal centers can be achieved by a simple pH stimulus, leading to largely different intramolecular Pt–Pt distances (3.19 Å vs. 5.56 Å) [118]. If relevant to head–tail nucleobase dimers, such a process would require the opening of one of the Pt–O bonds.

Findings with a dinuclear $Pt^{II}$ complex with two 2-aminopyridine bridges and a Pt–Pt distance of 4.077(1) Å [119], in which the two head–tail arranged ligands are almost parallel and the Pt coordination planes bonded to the exocyclic amino group almost perpendicular to the 2-aminopyridine rings, seem unlikely to apply to 1MeC for the following reason: The exocyclic amino group of $1MeC_{-H}$ is essentially $sp^2$-hybridized (double-bond character of C4–N4), thus ruling out any substantial metal binding perpendicular to the pym plane.

*2.6.5. Reactivity and uses of Pt and Pd head–tail dimers*

The arrangement of the metals in the head–tail dinuclear $Pt^{II}$ complexes described in 2.6.2 permits relatively easy oxidation to dinuclear $Pt^{III}$ species. These diamagnetic complexes are likewise chiral, the metal centers are connected by short Pt–Pt single bonds, and the metal ions have extended their coordination number to six. Numerous examples are known for 1MeU [120,121] and 1MeC [87–89,122,123], with a variety of axial ligands, including other nucleobases. Most likely oxidation proceeds through a paramagnetic $Pt^{II},Pt^{III}$ intermediate, but such a compound thus far has not been isolated. Unlike the dinuclear 1MeU compound with head-head arrangement of the pym nucleobases, which can be oxidized to a mixed-valence tetranuclear dimer-of-dimer structure with an average oxidation state of Pt(2.25) [124,125], these head–tail dimers cannot be expected to form analogous structures. The location of the exocyclic O2 groups in the head–tail pym nucleobase complexes, although capable of interconnecting adjacent head–tail dimer cations via intermolecular hydrogen bonds with $NH_3$ ligands [86], prevents any close intermolecular Pt contacts required for partial oxidation of an extended Pt chain. At most an axial bridging ligand between two head–tail dimer units (e.g. $Cl^-$), similar to the situation seen with a head-head dimer [126], could accomplish a larger mixed-valence system. Only if sterically undemanding bridging ligands are applied, e.g. acetamidate, a head–tail arrangement of these permits aggregation of dimer entities and partial oxidation to a hexanuclear trimer-of-dimer structure with an average Pt(2.33) oxidation state [127]. Not unexpectedly, a head-head arrangement of acetamidate ligands permits even longer discrete chains [128,129].

While the presence of the exocyclic O2 sites in head–tail dinuclear $Pt^{II}$ complexes of 1MeU, 1MeT, and 1MeC prevents formation of mixed-valence state compounds, their presence allows for formation of heteronuclear compounds. Thus, in the presence of $Ag^+$ ions, *cis*-$[(NH_3)_2Pt(\mu\text{-}1MeU\text{-}N3,O4)]_2^{2+}$ forms discrete tetranuclear $Pt_2Ag_2$ species, with the two $Ag^+$ coordinated to the two O2 positions of the 1MeU ligands [130]. Neighboring cations are separated by nitrate anions. A second species of $Pt_1Ag_1$ stoichiometry was likewise isolated, yet not crystallographically characterized. A structure of $Pt_2Ag_1$ stoichiometry has been obtained upon co-crystallization of the head–tail dimer *cis*-$[(NH_3)_2Pt(\mu\text{-}1MeC_{-H}\text{-}N3,N4)]_2^{2+}$ with $Ag^+$ [71]. This compound likewise displays $Ag^+$ coordination to the available O2 sites, yet in a bridging fashion, leading to a coordination polymer. As a consequence of the chirality of the head–tail dimer, the polymer represents a racemic mixture of right-handed *P* and left-handed *M* helices (Fig. 13).

These findings tentatively suggest that the $Ag^+$ ions might also be substituted by other hetero metal ions, including by *cis*-$Pt^{II}(NH_3)_2$ units, thereby generating oligomeric species, with the possibility to undergo partial oxidation. In fact, "platinum blues" are also formed from head-tail dinuclear complexes of 1MeU, the composition and ways of formation of which remains unclear, however [49].

A number of these head–tail dinuclear Pt and Pd complexes with pym nucleobases have been tested for antitumor activity [47,83] and their interactions with plasmid DNA studied by electrophoresis, spectroscopic techniques as well as AFM (Atomic Force Microscopy), respectively [44,83]. In general, in vitro activity against the selected tumor cell lines is good, sometimes even surpassing that of Cisplatin. According to AFM, the morphology of plasmid DNA (pBR322) is changed in a way similar to that of Cisplatin and also the mono-nucleobase complexes (see 2.4), possibly implying that the interaction with DNA occurs following the dissociation of the head–tail dimers into their monomeric precursors. Such processes have been observed for *cis*-$[(NH_3)_2Pt(\mu\text{-}1MeT\text{-}N3,O4)]_2^{2+}$ in the presence of NaCl, for example [86]. Any enantiospecific non-covalent interactions between positively charged head–tail dimers and DNA would be interesting, but neither has a separation into their enantiomers been achieved (see 2.6.3), nor has such a study been performed to date. Only with chiral octahedral metal complexes and ligands other than nucleobases has such work been carried out [131].

As a final point of challenging future work, the possibility of dinuclear $Pt^{II}$ nucleobase complexes to be studied for their luminescent properties and possible applications in opto-electronic devices should be mentioned [132]. To the best of our knowledge, no such work has been carried out in a systematic way thus far.

*2.6.6. Larger metalacycles*

Metalacyclic compounds frequently come in different ring sizes as influenced by entropic and enthalpic properties of the system, with factors such as nature of the metal, ring strain, concentration, solvent, temperature, guest molecules and counter ions playing major roles. For example, in triangle-square equilibria of $Pd^{II}$ complexes with N,N-ligands, the triangle tends to be entropically

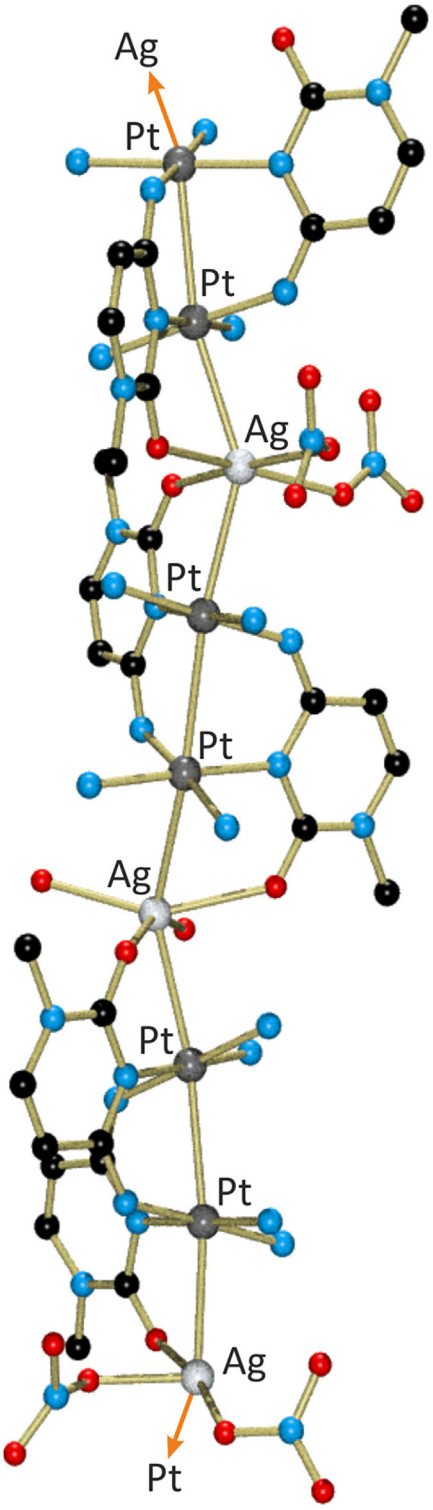


**Fig. 13.** Section of the helical *cis*-[{Pt(NH$_3$)$_2$(1MeC$_{-H}$-*N3,N4*)}$_2$Ag](NO$_3$)$_3$·H$_2$O polymer [71]. The left-handed (*M*) enantiomer is shown. Average Pt···Pt and Ag···Pt distances are 2.93 Å, and 2.89 Å, respectively.

favored as it is formed from fewer components, whereas high concentration favors formation of squares and, if less strained, brings an enthalpic advantage [133–141]. These "rules" undoubtedly also apply to cyclic metal nucleobase complexes, but the topic has not been studied in a systematic way in these systems. In fact, the majority of cyclic nucleobase complexes of Pt$^{II}$ and Pd$^{II}$ with three or more metal ions represent isolated examples. A rare case of a system with *identical metals* and *identical co-ligands* is *cis*-[Pt(PMe$_3$)$_2$(1MeC$_{-H}$-*N3,N4*)]$_n^{n+}$ (with n = 2 and 3) reported by the Longato group [80,142]: The head–tail dimer (n = 2) with its 8-membered ring is clearly strained as reflected by the significant deviations of the Pt ions from the coordination planes (0.195 Å, av.) and the large angle (46.2°) between the two Pt planes. Heating to 80 °C converts the dimer into the larger 12-membered ring of the cyclic trimer which is thermodynamically more stable and is not decomposed even at 100 °C. In it, the Pt ions are virtually within the PtN$_2$P$_2$ coordination planes. A major difference between the two structures refers to the relative orientation of the metal centers and the intramolecular Pt–Pt separations. Similar to the situation mentioned in 2.6.4 for a hypothetical alternative head–tail dimer structure, the Pt's at the N4 positions of 1MeC$_{-H}$ are substantially out of plane formed by 1MeC and the N3 bonded Pt, therefore pointing away from each other (almost *anti*), unlike in the established head–tail dimer structure. Consequently, the Pt–Pt distances in the trimer are considerably longer (5.3 Å, av.) than in the head–tail dimer (3.199(2) Å).

Likewise, a symmetrical cyclic trimer has been reported with PMe$_2$Ph co-ligands instead of PMe$_3$ and 1MeC. It is formed from the head–tail dimer upon heating at 80 °C in DMSO. Interestingly, a trinuclear linkage isomer with *unsymmetrical* bridging of 1MeC is obtained as major product when *cis*-[(PMe$_2$Ph)$_2$Pt(μ-OH)$_2$Pt(PMe$_2$Ph)$_2$]$^{2+}$ is reacted with 1MeC in a different solvent, CH$_2$Cl$_2$ [96]. Clearly, this second trimer is not formed via a trimerization of the mono-nucleobase species *cis*-[(PMe$_2$Ph)$_2$Pt(1MeC-*N3*)(solvent)]$^{2+}$, as it contains a *cis*-[(PMe$_2$Ph)$_2$Pt(1MeC-*N3*)$_2$] fragment. However, in CDCl$_3$ this unsymmetrical trimer eventually isomerizes to the symmetrical one. This careful study, summarized in Fig. 14, reveals the importance of reaction conditions (solvents, temperature) on the size and structure of the cyclic products.

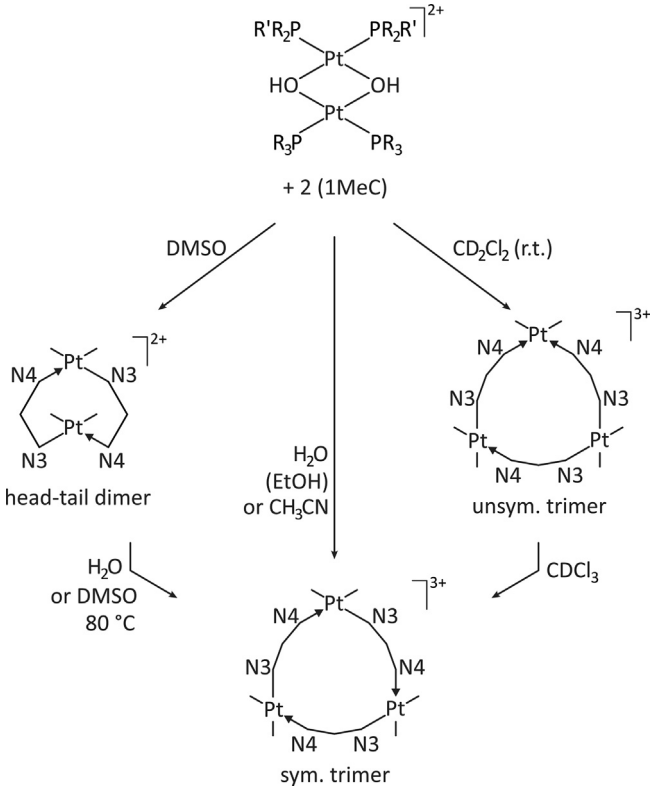


**Fig. 14.** Relationship of cyclic dimer and trimers in dependence of solvent (PR$_2$R' = PMe$_2$Ph) [96].

Steric interference between co-ligands probably is the reason why 1MeC [143] and likewise cytidine [144] form cyclic trimers when reacted with $[(tmeda)Pd(\mu\text{-}OH)_2Pd(tmeda)]^{2+}$ (tmeda = *N,N,N',N'*-tetramethylethylenediamine), yet no head–tail dimers. As in the other symmetrical cyclic trimers mentioned above, relative orientations of two adjacent metal ions at each nucleobase are *anti*, and the compounds can formally be considered [12] metalaazacrowns-3 ([12]mac-3) [143] (Fig. 15). The pronounced double cone structure of $[\{(tmeda)Pd(C_{-H})\}_3]^{3+}$ (with $C_{-H}$ = 1MeC or cytidine anion, deprotonated at N4) favors anion binding ($ClO_4^-$, $F^-$).

With N9-alkyladenines and metal binding through N1 and the deprotonated N6 positions, the situation is similar to that with N1-substituted cytosine nucleobases. Again, with *cis*-$(PMe_3)_2Pt^{II}$ and 9EtA a severely strained head–tail dimer (Pt deviation from $P_2N_2$ plane; large angle between Pt planes) is isolated, which appears to remain stable in DMSO $d_6$ at 60 °C for at least several hours [81]. On the other hand, with 9MeA and the sterically more demanding *cis*-$(PMePh_2)_2Pt^{II}$ the cyclic trimer is formed in high yield in a series of organic solvents ($CH_3CN$, $CH_2Cl_2$, DMF) [145]. However, when dissolved in DMSO $d_6$, this complex undergoes fragmentation reactions to different products, including one in which Pt chelates the deprotonated exocyclic amino group via N6 and N7.

All cyclic, trinuclear complexes of 1MeC/cytidine or N9-substituted adenine nucleobases of $Pt^{II}$ and $Pd^{II}$ discussed here display N3,N4 and N1,N6 bridging, respectively, and adopt approximate $C_3$ symmetry in their solid state structures. Formally these complexes can also be considered metalacalix[3]arenes [17] in their cone conformation. In no instance has a partial cone conformation (two nucleobases up, one down) been observed, even though with other bridging heterocyclic ligands this possibility is well established [146,147].

Just for the sake of completeness: There are a number of trinuclear cyclic complexes with 9-substituted adenine nucleobases known to date, which contain other metal entities such as $Cp^*Rh^{III}$, ($\eta^6$-*p*-cymene)$Ru^{II}$, or *fac*-$Me_3Pt^{IV}$ [148–151]. Again, these cycles adopt approximately $C_3$ symmetry, have the metal ions at N1 and N6 in *anti* orientations, but in addition and in contrast to the discussed $d^8$ metal complexes, these metal ions are bonded also to N7, hence form a N7,N6 chelate rather than binding to N6 in a monodentate fashion only. With 9EtHx an analogous cyclic trimer (N6 replaced by O6) has been reported [152].

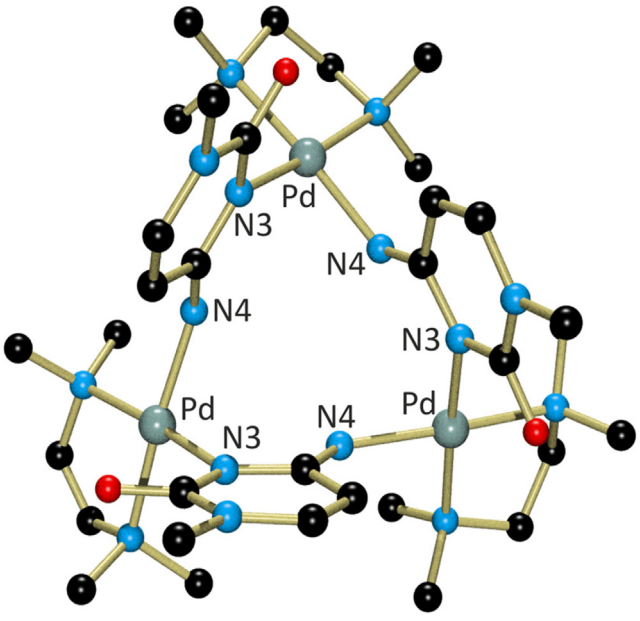


**Fig. 15.** View of the $C_3$ symmetric cation $[\{(tmeda)Pd(1MeC_{-H}\text{-}N3,N4)\}_3^{3+}$ [143].

Concerning the structures of model nucleobase complexes derived from *cis*-(L,L')$M^{II}$ with cyclic structures and ring sizes of four or higher, examples become very rare. While crystal structures of tetra-, hexa- and octanuclear complexes containing unsubstituted parent nucleobases are available [153–157], a problem arises if structural data are not available. For example, although it is well established, among others by mass spectrometry, that $(en)Pd^{II}$ forms tetranuclear cycles with N7,N1 bridging when reacted with 9-blocked guanine ligands (guanosine, various guanosine monophosphates) the connectivity sequences are unclear [158–161]. In other words, for a cyclic $Pd_4G_4$ it is difficult to find out, whether such a complex is formed by cyclization of four mononuclear $[Pd(en)(Guo\text{-}N7)]^{2+}$ units, which would give rise to a repeating N7,N1 connectivity pattern, or if two $[Pd(en)(Guo\text{-}N7)_2]^{2+}$ species are connected in a condensation reaction with two $[Pd(en)(OH)_2]$ molecules, thereby leading to alternating N7, N7 and N1,N1 linkage patterns. Similar arguments apply to cyclic hexamers [161]. The only X-ray crystal structure of a cyclic hexanuclear 9MeG complex with *cis*-$(PMe_3)_2Pt^{II}$ has been reported by the Longato group, already in 1995 [162]. The connectivity pattern is uniform, through N7 and the deprotonated N1 position. Therefore, it can be considered a metalacycle formed from condensation of six monomeric *cis*-$[(PMe_3)_2Pt(9MeGH\text{-}N7)(H_2O)]^{2+}$ with occurs with loss of $H_3O^+$. The six 9-methylguaninato ligands are arranged in an alternate way, above and below the mean $Pt_6$ plane, thereby minimizing steric interference between the pairs of phosphine ligands at each Pt. NMR spectra suggest that the cyclic hexamer, although isolated in high yield, does not represent the only oligomer formed under the experimental conditions.

### 2.6.7. Oligomerization vs. cyclization

The cyclic nucleobase compounds discussed thus far are well-defined, discrete species. An obvious crucial question remains: What happens, when cyclization of di- or trinuclear entities or even larger ones does not occur, or when cyclic species open, either by cleavage of a Pt–X4 bond (in pym complexes) or possibly even a Pt–N3 bond ($1MeC_{-H}$)? Mass spectra carried out to answer the question regarding the composition of species larger than dimers or trimers are inconclusive considering the multitude of feasible structures [49,163]. Even if assuming that the nucleobase donor atoms remain as seen in the cyclic species within a linear oligomer, namely preferentially through N3 and X4 for the pym bases, the number of feasible open chain structures is large. Only if a *syn* arrangement of N3 and X4, and consequently a facing of the Pt coordination planes as seen in the head–tail dimers, were to be retained, a helical structure with short Pt···Pt contacts would be possible (Fig. 16).

If the arrangement of N3 and X4 is *anti*, as seen in the cyclic $1MeC_{-H}$ trimer (see 2.6.6), or a mixture of *syn* and *anti*, the possible product structures are even more versatile, but continuous Pt···Pt interactions seem to be less likely.

### 2.6.8. Special case: Bis(1-methyluracil-5-yl) methane system

In the course of a project aimed at studying hybrid systems between classical and metalacalix[n]arenes with the arene being a 1-methyluracil entity, we have prepared the ditopic ligand bis (1-methyluracil-5-yl)methane and studied its coordinating properties toward *cis*-$(PPh_3)_2Pt^{II}$, (2,2′-bpy)$Pt^{II}$, (bipzp)$Pd^{II}$ (bipzp = bis(p yrazol-1-yl)propane), and *cis*-$(NH_3)_2Pt^{II}$ [164,165]. Among others, a series of cyclic tetranuclear compounds and a hexanuclear complex were isolated and investigated by X-ray crystallography. In the majority of cases, two and three pairs of $Pt^{II}$ and $Pd^{II}$ ions at close distances (in the order of 2.8 – 2.9 Å) are arranged in head–

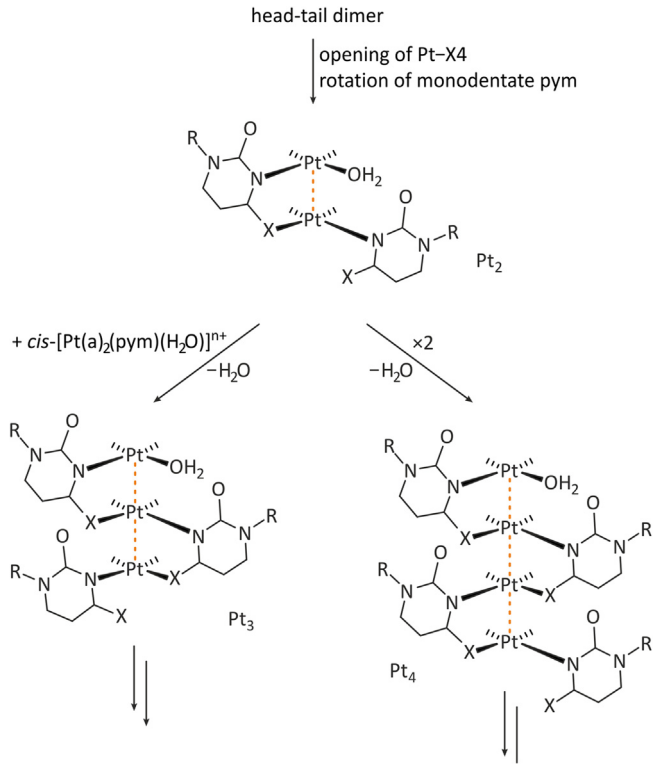


**Fig. 16.** Oligomers derived from ring-opened head–tail dimer upon subsequent reaction with a monomer or dimerization. If N3 and X4 remain essentially *syn* to each other, Pt atoms are facing each other in the $Pt_3$ and $Pt_4$ species.

tail fashions via the deprotonated N3 positions and the adjacent exocyclic O4. Although this ligand with its two 1MeUH ends is not relevant for intact RNA, we mention it here because in one instance, with $\{[cis\text{-}Pt(NH_3)_2]_2L\}_2^{4+}$ (L = dianion of bis(1-methylura cil-5-yl)methane), an interesting linkage isomerization process is observed [165]: In one of the two crystallized forms of this complex, the two pairs of *cis*-$(NH_3)_2Pt^{II}$ units uniformly adopt the common head–tail arrangements via N3,O4 sites. However, a slight modification of the synthetic procedure also generates a closely similar second form, in which head–tail bridging via N3,O4 is realized in only one of the two ends of the cation. On the other end, a combination of two different bridging modes is realized, namely via N3,O4 *and* N3,O2. In fact, this appears to be the first case of Pt binding to N3 and O2 in a dinuclear 1MeU motif. As the crystal structure reveals, conversion of N3,O4 bridging to N3,O2 bridging does not involve a simple rotation of one of the uracil moieties about the Pt–N3 bond, but rather a slippage of one of the uracil rings as a whole (Fig. 17). As a consequence, the coordination patterns of the two Pt centers has changed from $N_2N'O$ at both metals to $N_2O_2$ and $N_2N'_2$. In other words, an unsymmetrical head-head arrangement is produced. Thus, the situation is different from that of the "classical" head-head dimers of *cis*-$(NH_3)_2Pt^{II}$ with 1MeU and also 1MeT, which show pairwise N3,O4 bridging, and which are achiral [69]. Although speculative at this stage, mutual isomerization processes between head–tail and head-head dinuclear Pt complexes of 1MeU or 1MeT could also feasibly occur through such a "slippage" process and a concomitant rotation of one of the nucleobase anions about the Pt–N3 bond.

### 2.6.9. μ-OH and μ-$NH_2$ bridging combined with nucleobase bridging

Throughout this text we have mentioned at several occasions the possible competition between μ-$OH^-$ and μ-nucleobase binding patterns on one hand, and the possible combined occurrence of both. Before progressing to mono(nucleobase) complexes of other $Pt^{II}$ and $Pd^{II}$ species of different geometries, a brief summary can be made (Fig. 18): (i) Exclusive hydroxido bridging. First

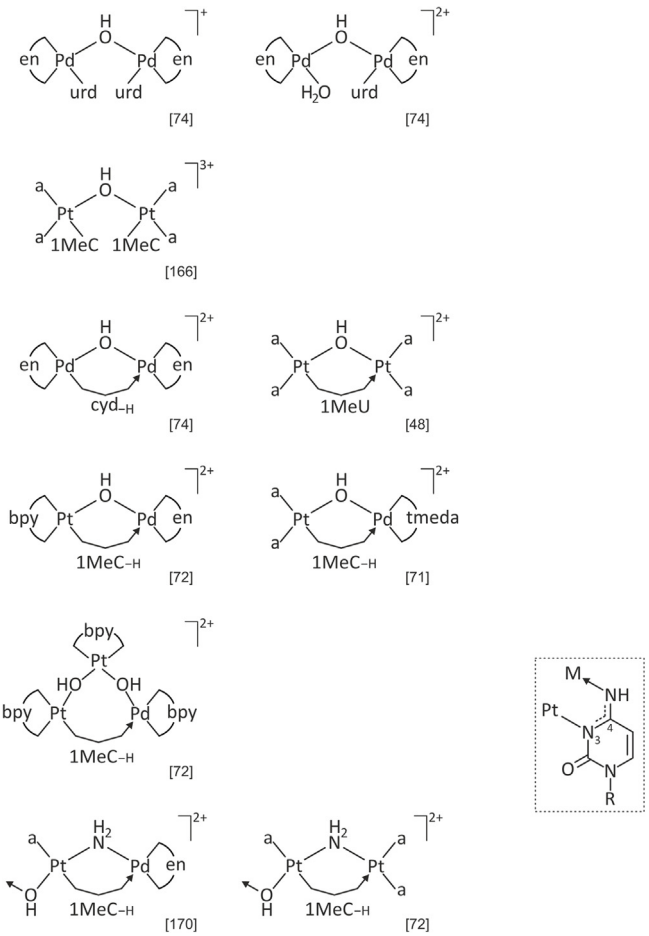


**Fig. 18.** μ-OH and μ-$NH_2$ species identified spectroscopically (top 5 examples) and characterized by X-ray crystallography (lower 5 examples).

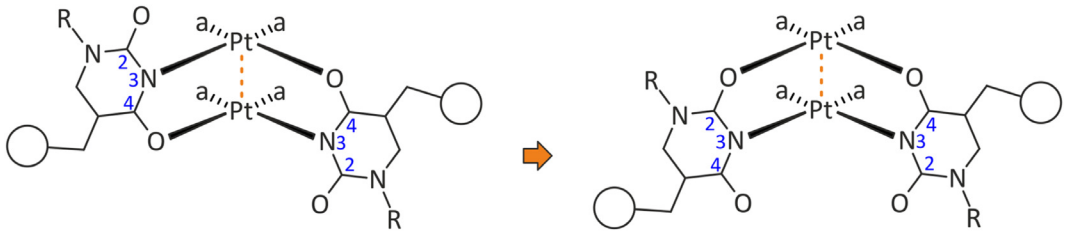

**Fig. 17.** Conceptual uracil slippage from N3,O4 to O2,N3 in $Pt_2$ dimers [165].

reported in 1983 in the *cis*-$Pt^{II}(NH_3)_2$/1MeC [166] and the $Pd^{II}$(en)/urd (urd = uridine) systems [74], X-ray crystal structures of such compounds are presently not available, but there is definite proof that single hydroxido bridges $Pt^{II}$ exist [74,167]. (ii) More common are examples with simultaneous μ-OH and μ-nb bridging. Formed either by reaction of *cis*-$[Pt(a)_2$(pym-nb-*N3*$)(H_2O)]^{n+}$ with a diaqua species *cis*-$[M(a)_2(H_2O)]^{2+}$crystal structures of neutral compounds (M = Pd or Pt) [48] or by reacting *cis*-$[(a)_2M(OH)_2M(a)_2]^{2+}$ with pym-nb in a 1:1-ratio, such compounds form unstrained six-membered rings, as also observed in mixed Pd- hydroxido/acetamidate [168] or mixed Pt- hydroxido/acetate compounds [169], for example. Even folded eight-membered rings can form when *cis*-$[Pt(a)_2$(1MeC-*N3*$)(OH_2)]^{2+}$ is reacted with an excess of *cis*-$[Pd(a)_2(H_2O)_2]^{2+}$ [72]. (iii) Simultaneous μ-$NH_2$ and μ-nb bridging. This pattern has been observed by us twice, both in mixed Pt, Pd and in $Pt_2$ segments containing μ-1MeC$_{-H}$ [72,170]. Obviously, an ammine ligand of $Pt^{II}$ bonded to N3 of the 1MeC nucleobase has been converted into a bridging amido ligand. Again, these complexes are the result of reactions between mono-1MeC complexes of *cis*-$Pt^{II}(a)_2$ (a = $NH_3$ or $a_2$ = 2,2′-bpy) and diaqua species of *cis*-$Pd^{II}(a)_2$ or *cis*-$Pt^{II}(a)_2$.

In most of the structurally characterized examples (ii) and (iii), additional $Ag^+$ ions are found to co-crystallize, being bonded via O2 of the nucleobase and/or Pt/Pd···Ag metal bonds [71,72,170].

## 3. Mono(nucleobase) complexes of type *trans*-[Pt(a)$_2$(nb)X] (a = $NH_3$ or $MeNH_2$)

### 3.1. Background

A major question related to the phenomenon of antitumor activity of Cisplatin has been, and still is, the question as to why its *trans*-isomer (Transplatin) is inactive, given that it also reacts extensively with DNA [171]. There are, however, also several major differences in reactivity patterns of the two isomers toward DNA, which refer, for example, to the long life time of the primary mono adduct of Transplatin (with guanine-*N7*, half-life ca. 12 h), its preference for interstrand cross-links with guanine and cytosine [172], its tendency to undergo ligand isomerization processes [173,174], and to form DNA-protein cross-links. As already briefly mentioned in the Introduction, *trans*-geometries about the $Pt^{II}$ not necessarily prevent biological activity, contrary to the structure–activity "rules of thumb" established during the early days of Cisplatin. In fact, numerous exceptions of antitumor active $Pt^{II}$ compounds displaying *trans*-geometries are known today [5,6,12].

### 3.2. Examples and properties

The list of X-ray structurally characterized mono(nucleobase) complexes of *trans*-$a_2Pt^{II}$ is relatively limited, restricted to 1MeC and X = $Cl^-$ as well as X = glycine [175], 9MeGH [176], 1,3-dimethyluracil-5-yl [177], 9MeA [178,179], and guanosine [180]. The metal coordination sites are as expected, namely N3 with 1MeC, N7 with 9MeGH, 9MeA, and guanosine, as well as C5 with 1,3DimeU. There are no unexpected structural features, and the nucleobases are roughly perpendicular to the Pt coordination plane. The compounds are achiral. Formation of these 1:1-complexes from *trans*-$[Pt(a)_2Cl_2]$ requires the presence of extra chloride (e.g. from NaCl) in order to prevent formation of the respective bis(nucleobase) compound. As to the behavior of the mono(nucleobase) complexes in water, two observations are worth mentioning: First, *trans*-$[Pt(a)_2$(nb)Cl]Cl (with nb = 1MeC [181] and 9EtGH [182]) undergo a partial redistribution when dissolved in water, according to

2 *trans*-$[Pt(a)_2$(nb)Cl]Cl → *trans*-$[Pt(a)_2(nb)_2]Cl_2$ + *trans*-$[Pt(a)_2Cl_2]$.

A similar ligand rearrangement has also been observed with *trans*-$[Pt(NH_3)_2(H_2O)Cl]^+$ [183]. As we have outlined [184], this reaction may be relevant to the self-removal of a monofunctional Transplatin adduct from DNA.

Second, *trans*-$[Pt(a)_2(nb)Cl]^+$ (with nb = 9EtGH [182] and 9MeA [178]) following hydrolysis of the chlorido ligand, undergoes rapid self-condensation, leading to N7,N1-bridged species (as well as possibly other products in case of 9MeA). While in the case of guanine this process involves deprotonation of the N1 position according to

2 *trans*-$[Pt(a)_2$(9EtGH-*N7*$)(H_2O)]^{2+}$ → *trans*-$[(a)_2$(9EtGH-*N7*$)Pt$(9EtG-*N7,N1*$)Pt(a)_2(H_2O)]^{3+}$ + $H_3O^+$.

No proton loss is necessary in the case of N7,N1 bridged adenine species:

2 *trans*-$[Pt(a)_2$(9MeA-*N7*$)(H_2O)]^{2+}$ → *trans*-$[(a)_2$(9MeA-*N7*$)Pt$(9MeA-*N7,N1*$)Pt(a)_2(H_2O)]^{4+}$ + $H_2O$.

Moreover, these condensation reactions do not stop at the dimer level but rather progress further, depending on concentration. The extreme complexity of the self-condensation behavior of *trans*-$[Pt(NH_3)_2$(9MeA-*N7*$)(H_2O)]^{2+}$ has been studied by us in some detail [178]. With the 9MeA linkage isomer *trans*-$[Pt(NH_3)_2$(9MeA-*N1*$)(H_2O)]^{2+}$ (no X-ray structure available), analogous condensation reactions are feasible as well, leading to similar or identical open or cyclic oligomers.

### 3.3. $pK_a$ values of aqua species

Acidities of aqua and nb ligands in mononuclear *trans*-$[Pt(a)_2(nb)(H_2O)]^{n+}$ complexes are non-spectacular, and with nb = 1MeC-*N3*, 9EtGH-*N7*, and 9MeA-*N7* $pK_a$ values of the aqua ligands are 5.2, 5.3, and 4.6, respectively [40,178]. In other words, there is a trend towards higher acidities of aqua ligands of the *trans*-isomers as compared to the respective *cis*-isomers (*cf.* 2.2), a feature seen also with the two isomers of $[Pt(NH_3)_2(OH_2)_2]^{2+}$ [185]. Acidities of the model nucleobases are 8.9 (deprotonation of 9EtGH) and 1.2 (deprotonation of $9MeAH^+$). For nb = guanosine-*N7*, cytidine-*N3*, and uridine-*N3* $pK_a$ values of the aqua ligands are 5.0, 5.7, and 6.1, respectively [52]. Again, treatment of the pH-dependent $^{15}N$ NMR data considering two overlapping deprotonation processes [186] gives a lower $pK_a$ for guanosine (7.70) than for 9EtGH (*cf.* also 2.2). Regarding the effects of a favorable microenvironment on the acidity of exocyclic amino groups, see the next paragraph.

### 3.4. Uses of trans-[Pt(a)$_2$(nb)X]

As pointed out above, one of our initial goals had been the synthesis of potential model cross-links of Transplatin with nucleobases possibly relevant for double-stranded DNA. Mono(nb) complexes are appropriate precursors for such compounds. We have reported extensively on such mixed-nucleobase complexes (for reviews, see [19,38,184]) including on "metal-modified" Watson-Crick and Hoogsteen pairs between complementary bases as well as cross-links between non-complementary ones. Among others, also the most frequent interstrand DNA cross-link of Transplatin between guanine-*N7* and cytosine-*N3* has been described, and we have proposed a feasible way of its formation [16].

This work has eventually also led to a considerable number of open, "metal-modified nucleobase-triplets and quartets" as well as cyclic supramolecular multi-nucleobase constructs, likewise discussed in detail elsewhere [38]. For more recent examples see, e.g. [178,187–189]. The (approximate) perpendicularity of Pt–N vectors in N1,N7-diplatinated purine ligands connected by *trans*-$(NH_3)_2Pt^{II}$ units (or other metal ions of linear coordination chemistry) is key to this feature (see also 3.5).

At least with single-stranded oligonucleotides also bis(nucleobase) complexes of Transplatin containing two identical nucleobases are possible [173]. The preparation of relevant Pt model compounds is straightforward. In the solid state they usually contain the two bases in a head–tail arrangement, but in solution an equilibrium of head–tail and head-head rotamers is realized, with an influence of the solvent on relative amounts. In the presence of transition metal ions such as $Pd^{2+}$, $Hg^{2+}$, $Cu^{2+}$, or $Ag^{+}$ individual rotamers can be stabilized as heteronuclear species with the added transition metal ions bridging exocyclic nucleobase groups. In the majority of cases it is the head-head rotamers that are stabilized this way. In the case of *trans*-$[(MeNH_2)_2Pt(1MeC\text{-}N3)_2]^{2+}$ rotational features of the nucleobases following the removal of $Hg^{2+}$ from the heteronuclear Pt,Hg derivative could be established [56,190]. Both X-ray crystallography and computational work reveal a substantial lengthening of the Pt–N3 bond as the rotating nucleobase reaches coplanarity with the Pt coordination plane.

There are, at least, two additional aspects, that deserve mentioning in the context of this review: First, and related to 3.3, this work has demonstrated that enormous acidifications of exocyclic amino groups of (metal-carrying) nucleobases is achieved by favorable H bonding interactions with exocyclic functions of adjacent (and metal-cross-linked) nucleobases which stabilize the deprotonated site [37,191]. Measured nucleobase acidifications equal or exceed those of N-methylation or N-protonation substantially and can reach up to 9 log units in the case of adenine nucleobases. Possibly, a "resonance-assisted H bond" situation might account this observation [192]. The phenomenon of "shifting $pK_a$ values" of metalated nucleobases into the physiological pH range, as caused by the effects of the metal/s itself/themselves, by alterations of the tautomeric structure of the nucleobase, and by the microenvironment, opens novel aspects on general acid-base catalysis involving nucleobases [41]. Although studied primarily with metal complexes containing *trans*-$a_2Pt^{II}$ entities, these findings may very well apply to other metal ions as well.

Second, our model compounds suggested to us that monofunctionally-modified *trans*-$(NH_3)_2Pt^{II}$ oligonucleotides might be used in antisense or antigene approaches (reviewed in [38]). While the concepts seemed to be reasonable, based on structural work derived from our model chemistry, the slow kinetics of the Pt-cross-linking reactions thus far proved unfavorable for any practical purpose.

### 3.5. Cyclic and open derivatives

As already mentioned in the previous paragraph, the approximate right angle between purine-N1 and purine-N7 metal vectors makes this metal binding pattern particularly suitable for the construction of cyclic and open structures. In most cases these compounds have been prepared in a stepwise manner, frequently starting from bis(pu-nucleobase) precursors. Only in one instance has spontaneous cyclization of a mononuclear species, *trans*-$[Pt(NH_3)_2(9Mepu\text{-}N7)(H_2O)]^{2+}$ (9Mepu = 9-methylpurine) been accomplished [193]. Cyclization leads to the expected molecular square and in parallel to a molecular triangle. The latter compound is highly strained as a consequence of the compressed angle between N1–Pt and N7–Pt vectors (ca. 70°, av.). In the presence of other ligands, it readily converts to an open trinuclear species. The two cyclic compounds show, due to the positive charges of the cations (+8 and +6, respectively) and the H-bonding properties of the $NH_3$ co-ligands, a high affinity for anions, both in their solid-state structures, and in solution, when mixed with other anions. In particular, the surprisingly high association constant of sulfate with the molecular square *in water* ($(7.2 \pm 1.2) \times 10^4\ M^{-1}$) is noteworthy. An interesting detail of the X-ray crystal structure of the triangular complex *trans*-$\{[Pt(NH_3)_2(9Mepu\text{-}N1,N7)]_3\}[PF_6]_6\cdot 6H_2O$ is the following: The molecular triangles, interconnected by $PF_6^-$ anions, are arranged in a right-handed helix, with twelve triangles completing a full turn, in the crystal studied. It is likely that the compound in fact crystallizes as a conglomerate, containing also crystals with the opposite left-helical arrangement of triangular cations.

Analogous constructs derived from *trans*-$[Pt(NH_3)_2(9RGH\text{-}N7)(OH)]^{+}$, hence species with N7–Pt–N1 linkages, could not be obtained. Similarly, our attempts to produce cyclic μ-9MeA complexes by starting out from *trans*-$[Pt(NH_3)_2(9MeA\text{-}N7)(H_2O)]^{2+}$ proved unsuccessful in that, according to $^1H$ NMR spectroscopy, the number of self-condensation products was very high and did not allow even an identification of species, notwithstanding the crystallization of individual ones [178]. Segments of polymeric $[Ag(9MeA\text{-}N7,N1)]NO_3\cdot H_2O$, which displays N1,N7-bridging [194], open or cyclized, could be appropriate analogues for complexes of Transplatin with 9MeA.

For nb being a pym nucleobase bonded to Pt via N3 or a pu nucleobase bonded to Pt via N1, a head–tail dimerization involving X4 and X6 sites, respectively, seems to be sterically unfavorable due to a clash between the parallel oriented $NH_3$ co-ligands. However, larger cycles (with n = 4, 5, or 6) and the metal entities at N3, X4 and N1,X6 in mutual *anti* orientations seem to be possible, as there is no steric interference between adjacent co-ligands.

A further complication, feasible for all species of composition *trans*-$[Pt(NH_3)_2(nb)(H_2O)]^{n+}$ relates to the ability to also form μ-OH species or chains with alternating μ-OH and μ-nb bridges.

## 4. Mono(nucleobase) complexes of type *trans*-$[Pt(NH_3)(nb)X_2]$

### 4.1. Examples, formation and potential relevance

The concept of *trans*-effect has been and still is extremely helpful in Pt coordination chemistry. While largely applied to preparative work with the aim to direct reactions with strong external nucleophiles, it holds up even in cases when the nucleophile is weaker, yet available in excess. The displacement of an $NH_3$ ligand trans to $Cl^-$, as first observed in a mass-spectrometric study of *cis*-$[Pt(NH_3)_2(1MeC\text{-}N3)Cl]^{+}$ and the corresponding 9MeA complex, published already in 1974 [195], has proven to also apply to the situation in aqueous solution [196]. By replacing a chlorido ligand X by a halido ligand of higher *trans*-effect, e.g. by iodide, we have later demonstrated that it is possible to convert *cis*-$[Pt(NH_3)_2(nb)X]$ compounds in reasonable yields readily into *trans*-$[Pt(NH_3)(nb)X_2]$ [163]. Examples with nb being purine bases have likewise been obtained this way [197], as have been two species containing the pyrimidine base 1MeU [49,73].

$$cis\text{-}[Pt(NH_3)_2(nb)X]^{+} + X^{-} \rightarrow trans\text{-}[Pt(NH_3)(nb)X_2] + NH_3.$$

Acidic conditions facilitate this reaction as $NH_3$ is converted to $NH_4^+$ and prevented from back-reaction. With nb being a deprotonated nucleobase, such as 1MeU, for example, the product is no longer neutral but anionic. The X ligands in *trans*-$[Pt(NH_3)(nb)X_2]$ can subsequently be substituted by one or two identical or different nucleobases, giving bis- [198] or even tris(nucleobase) complexes [199]. As we have mentioned before, this reactivity pattern, and specifically that leading to adducts containing three nucleobases, is unique for Cisplatin and not expected for Transplatin [199]. Several examples of such compounds have been synthesized with model nucleobases and structurally characterized [73,200], including one containing three different nucleobases, SP-4-4-$[Pt(1MeC\text{-}N3)(9EtG\text{-}N7)(9MeA\text{-}N7)(NH_3)](NO_3)\cdot 2H_2O$ [198].

The products of the replacement of an ammonia ligand in *trans*-$[Pt(NH_3)_2Cl_2]$ by planar N-heterocycles such as L = pyridine, picoline, quinoline, or thiazole, hence compounds of composition *trans*-$[Pt(NH_3)(L)Cl_2]$, represent important members of the class of so-called "nonclassical" Pt antitumor compounds [6,12,201].

### *4.2. Di- or/and multinuclear derivatives of trans-[Pt(NH$_3$)(nb)(H$_2$O)$_2$]$^{n+}$*

The abstraction of the two halido ligands X from *trans*-$[Pt(NH_3)(1MeC\text{-}N3)X_2]$ by means of $AgNO_3$ initially leads to the corresponding, likewise achiral, diaqua species *trans*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$. It rapidly converts, with loss of protons, to the chiral dinuclear head–tail complex $[(NH_3)(H_2O)Pt(1MeC_{-H}\text{-}N3,N4)_2Pt(H_2O)(NH_3)]^{2+}$ and a purple, unidentified, mixed-valence Pt compound (Fig. 19) [202]. The composition of the diamagnetic head–tail dimer has been deduced from $^1$H NMR spectroscopy data (characteristic upfield shifts of H6 and H5 resonances as compared to those of N3 platinated 1MeC), as subsequently confirmed by X-ray crystal structures of two diplatinum(III) derivatives: If the condensation reaction of *trans*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$ takes place in the presence of the amino acid glycine, a head–tail dinu-

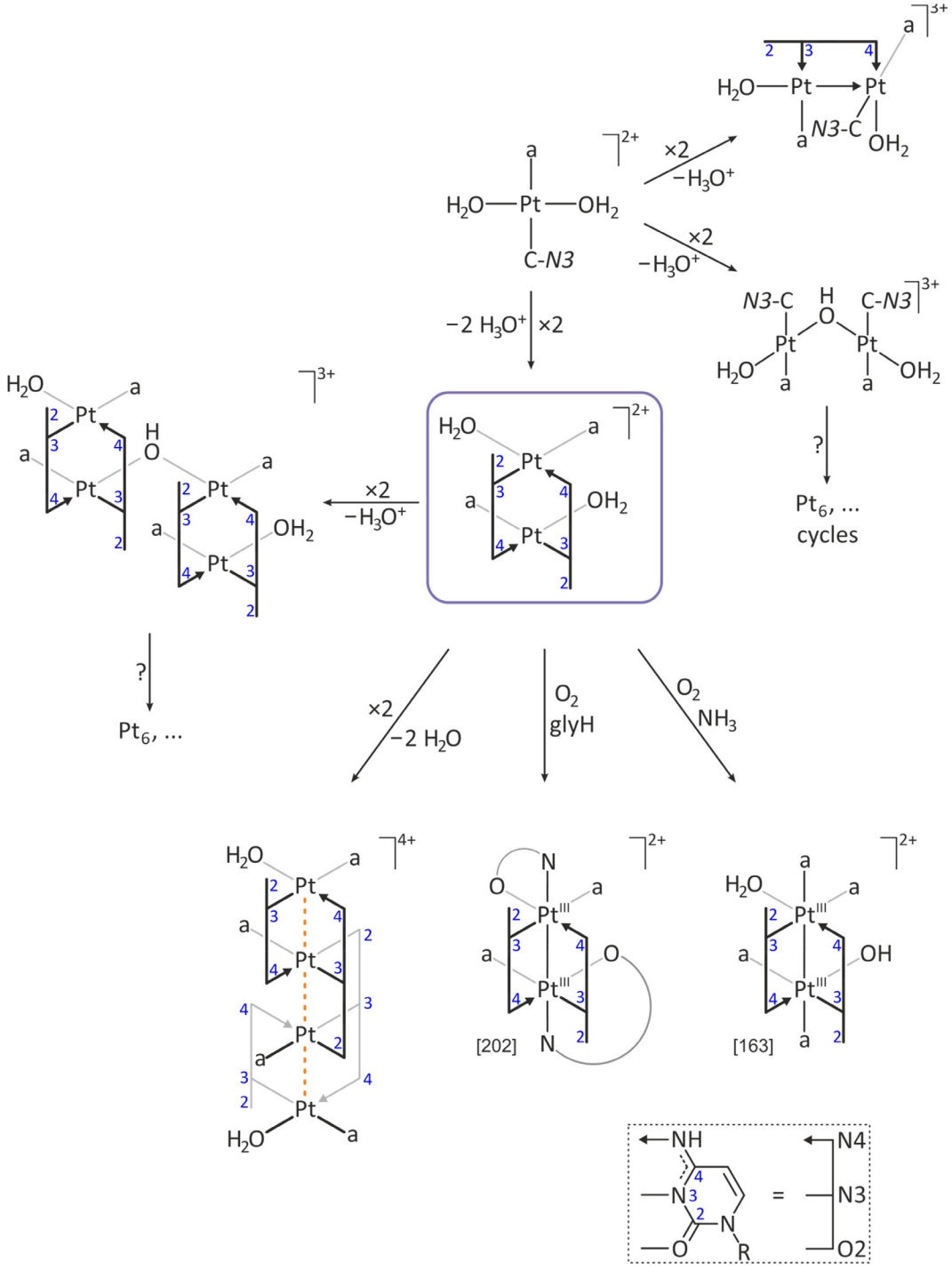


**Fig. 19.** Feasible condensation products of mononuclear *trans*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$ and X-ray structurally characterized diplatinum(III) derivatives. The proposed tetranuclear is composed of two identical enantiomers of the head–tail dimer. NO chelates refer to amino acid anions.

clear compound forms, in which the two Pt centers have undergone a "spontaneous" oxidation to Pt(III), and glycine anions chelate the metals via axial ($NH_2$) and equatorial (O) positions. The compound formed, $[Pt_2(NH_3)_2(1MeC_{-H}\text{-}N3,N4)_2(gly\text{-}N,O)_2](NO_3)_2\cdot 3H_2O$, is chiral. If carried out in the presence of L-alanine, the condensation reaction leads to a pair of diastereomers of diplatinum (III) species, as evident from the characteristic doubling of the $^1H$ NMR resonances [202]. Likewise a "spontaneous" oxidation (by air) of the dinuclear head–tail-$[(NH_3)(H_2O)Pt(1MeC_{-H}\text{-}N3,N4)_2Pt(H_2O)(NH_3)]^{2+}$ to the diplatinum(III) complex $[(NH_3)_2(OH)Pt(1MeC_{-H}\text{-}N3,N4)_2Pt(OH)(NH_3)_2]^{2+}$ rather than formation of the anticipated diplatinum(II) compound head–tail-*cis*-$[(NH_3)_2Pt(1MeC_{-H}\text{-}N3,N4)_2Pt(NH_3)_2]^{2+}$ occurs, when $NH_3$ is added [163]. These findings point to an exceptionally easy oxidation of the Pt (II) centers in the mentioned head–tail dimer with a mixed ammine, aqua sphere at each Pt. It contrasts the situation with head–tail-*cis*-$[(NH_3)_2Pt(1MeC_{-H}\text{-}N3,N4)_2Pt(NH_3)_2]^{2+}$, the conversion of which to diplatinum(III) derivatives requires oxidizing agents (conc. $HNO_3$; conc. $HClO_4$; $K_2S_2O_8$) [123].

In principle, several more condensation patterns other than the one realized with *trans*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$ to give the head–tail dimer, are feasible, some of which are also schematically outlined in Fig. 19: Condensation reactions may involve μ-OH formation of mononuclear or head–tail dinuclear species or combinations thereof, or stacked units involving in addition also O2 sites of the $1MeC_{-H}$, following intermolecular condensation between the aqua group(s) of the head–tail dimer and O2 of the pym ligands. After all, threefold metal coordination via N3, N4, and O2 is not uncommon with $1MeC_{-H}$ [203,204]. It would allow the formation of chains with short Pt–Pt contacts and the possibility of partial oxidation. The dimer-of-dimer species sketched in Fig. 19 is derived from two *identical* enantiomers of the head–tail dimer. If *different* enantiomers are combined (not shown), the resulting tetranuclear species would be centrosymmetric, yet there is no continuous Pt-chain, but rather steps of separated $Pt_2$ units. Moreover, the O2–Pt bond would be roughly perpendicular to the nucleobase plane (see also 2.6.4). Even unusual species displaying Pt→Pt donor bonds (with Pt planes being perpendicular to each other, hence "T over square") are feasible [205]. As indicated, most of these condensation reactions are pH-dependent.

Our attempts, to also crystallize condensation products derived from the analogous *trans*-$[Pt(NH_3)(1MeU\text{-}N3)(H_2O)_2]^+$ proved unsuccessful. Rather, formation of deeply colored, yet unidentified species has been observed [49], which likely relate to the class of partially oxidized "platinum pyrimidine blues" [206]. It is evident that as in the case of the 1MeC condensation products, coordination involving the three sites N3, O4, and O2 of 1MeU would lead to Pt chains ($n \geq 3$) and short intermetallic distances.

## 5. Mono(nucleobase) complexes of type *cis*-$[Pt(NH_3)(nb)X_2]$

### 5.1. Synthesis and properties

Complexes of this composition are prepared by treating $[Pt(NH_3)Cl_3]^-$ with a neutral nucleobase, taking advantage of the concept of the classical trans effect:

$$[Pt(NH_3)Cl_3]^- + nb \rightarrow cis\text{-}[Pt(NH_3)(nb)Cl_2] + Cl^-.$$

Alternatively, careful treatment of $[Pt(nbH)Cl_3]$ (with nbH = protonated adenine ligand) with $NH_3$ yields the identical product (see also chapter 6) [207]. Recrystallization from dilute HCl solution gives crystals of *cis*-$[Pt(NH_3)(nbH)Cl_2]Cl$ and *cis*-$[Pt(NH_3)(nb)Cl_2]$, respectively.

Examples with nbH = 1,9DiMeAH [207], and nb = 1MeC and 1Et5MeC [163] have been structurally characterized. Like other mixed ammine, N-heterocyclic ligand complexes having cis geometries (e.g. Picoplatin, AMD 473: *cis*-$[Pt(NH_3)(2\text{-picoline})Cl_2]$), compounds of this composition can be expected to display antitumor activity [208]. Indeed, *cis*-$[Pt(NH_3)(1MeC\text{-}N3)Cl_2]$ shows antiproliferative activity against a series of human cancer cell lines [163]. Compounds of this composition are chiral, and enantiomers can be differentiated applying *P* and *M* terms (see 2.3). Individual enantiomers have not been resolved, however, and consequently it is unclear if the observed biological effects are to be attributed to one of the two enantiomers.

Reactions of *cis*-$[Pt(NH_3)(1MeC\text{-}N3)Cl_2]$ with 9EtGH were followed by $^1H$ NMR spectroscopy in order to find out about differences in formation of primary adducts of this compound as compared to Cisplatin itself. Clearly, *cis*-$[Pt(NH_3)(1MeC\text{-}N3)Cl_2]$ forms two different adducts with the guanine base, the latter either trans to 1MeC (SP-4-4) or cis to 1MeC (SP-4-2), before giving the bis(guanine) end product *cis*-$[Pt(NH_3)(1MeC\text{-}N3)(9EtGH\text{-}N7)_2]^{2+}$ [163]. If relevant to an interaction with double-stranded DNA and coordination to guanine bases via N7, speculations concerning the effects of the ligands located in the major groove of DNA in both the mono- and the bis(guanine) adduct can be evoked, similar to the situation with *cis*-$[Pt(NH_3)(2\text{-picoline})Cl_2]$ [208].

There is presently no evidence that compounds of composition *cis*-$[Pt(NH_3)(nb)Cl_2]$ undergo isomerization to their respective *trans*-isomers in solution, a reaction seen occasionally with complexes of type *cis*-$[Pt(L)_2Cl_2]$ (with L being a variety of ligands, e.g. $PR_3$ or $SMe_2$), or even in solid state upon heating [209].

### 5.2. Condensation reactions of the diaqua species

Chloride abstraction from *cis*-$[Pt(NH_3)(1MeC\text{-}N3)Cl_2]$ in water produces the diaqua species *cis*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$, which is highly acidic (pH 1 – 2). Although individual $pK_a$ values were not determined, the two $H_2O$ ligands are expected to display slightly different acidities, and the compound thus has four different $pK_a$ values for its two aqua groups. Within 24 h a solution of c = 0.02 $molL^{-1}$ forms, in a clean reaction, a dinuclear species in ca 20 % yield which, based on the $^1H$ NMR chemical shifts and comparison with shifts of the head–tail dinuclear species discussed above, is assigned to head–tail-$[(NH_3)(H_2O)Pt(1MeC_{-H}\text{-}N3,N4)_2Pt(H_2O)(NH_3)]^{2+}$ [163]. The compound is, however, an isomer of the compound of identical composition discussed in 4.2, in that $NH_3$ and $H_2O$ ligands at the two Pt atoms are inverted in their positions, hence $H_2O$ is trans to N3 of $1MeC_{-H}$ and $NH_3$ is trans to N4 of $1MeC_{-H}$ (Fig. 20). As in the situation described for *trans*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$ in 4.2, numerous ways of association of mononuclear *cis*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$ or its head–tail condensation product are feasible.

These include A-frame structures (with $OH^-$ or $NH_2^-$ bridge-head functionalities), dinuclear species with a Pt→Pt dative bond, numerous ways of hydroxido bridging (see below), as well as stacked dimer-of-dimer species (or larger aggregates) involving N3,N4,O2. Depending on whether *identical* or *different* enantiomers of the head–tail dimers interact via O2 sites, numerous isomers are possible. Unlike in the situation discussed in 4.2, in both isomers Pt chains are possible. The tetranuclear complex derived from two *different* head–tail dimers is centrosymmetric.

Once the pH of an aqueous solution of *cis*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$ is raised to ca. 5, the condensation patterns become much more complicated, as judged from the numerous new 1MeC resonances emerging in the $^1H$ NMR spectra [163]. They are characteristic of several (at least three) additional $\mu\text{-}1MeC_{-H}$ species, the nature of which is presently unclear. However, the majority of newly formed compounds at higher pH are likely to arise from μ-OH species derived from mononuclear compounds, as their 1MeC NMR resonances are close to those of the monomeric

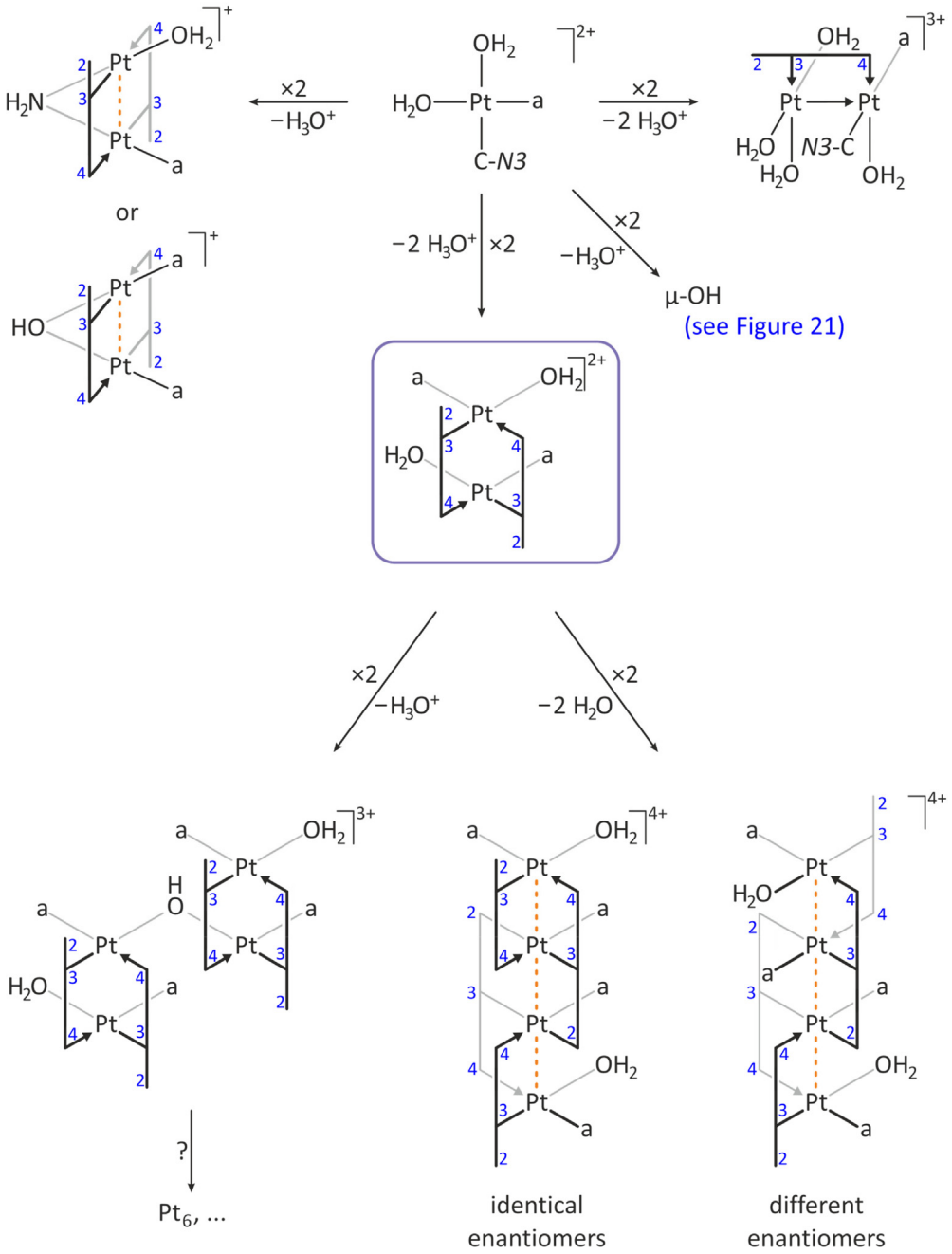


**Fig. 20.** Proposal for possible condensation patterns of mononuclear *cis*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$ and its head–tail dimer.

starting material *cis*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$, hence are indicative of terminal 1MeC-*N3* ligands. The number of putative condensation products with hydroxido bridges and terminal 1MeC-*N3* ligands is extremely high due to the following reasons: Depending on which of the two aqua ligands in *cis*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$ condense (identical ones, or different ones, or combinations), to what extent the monomers condense (dimer, trimer,...), whether they form open or cyclic oligomers, and what the rotational states of the terminal 1MeC ligands are, the number of possibilities and possible isomers is huge. In Fig. 21 examples are given, which are restricted to the dimer level. In contrast to the diaqua species of Cisplatin, open and cyclic dimers can occur in different isomer forms, and as with *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and $[Pt(en)(H_2O)_2]^{2+}$, oligomerization can, in principle, proceed beyond the dimer level, hence to trimers [210,211] and tetramers [212] (not shown). ESI mass spectra (ESI = Electro Spray Ionization) of freshly prepared as well as aged solutions of *cis*-$[Pt(NH_3)(1MeC\text{-}N3)(H_2O)_2]^{2+}$ indeed confirm the presence of di-, tri-, and tetranuclear species in the gas phase [163].

## 6. Mono(nucleobase) complexes of type $[Pt(nb)X_3]^-$

### 6.1. Examples

The reaction of $[PtCl_4]^{2-}$ with nucleobases is, most likely, not relevant to any biologically relevant process, especially if reactions are carried out at low pH, which can lead to protonation of nucleobases in the case of purines. X-ray crystal structures of neutral compounds of composition $[Pt(nbH)Cl_3]$ are available, among

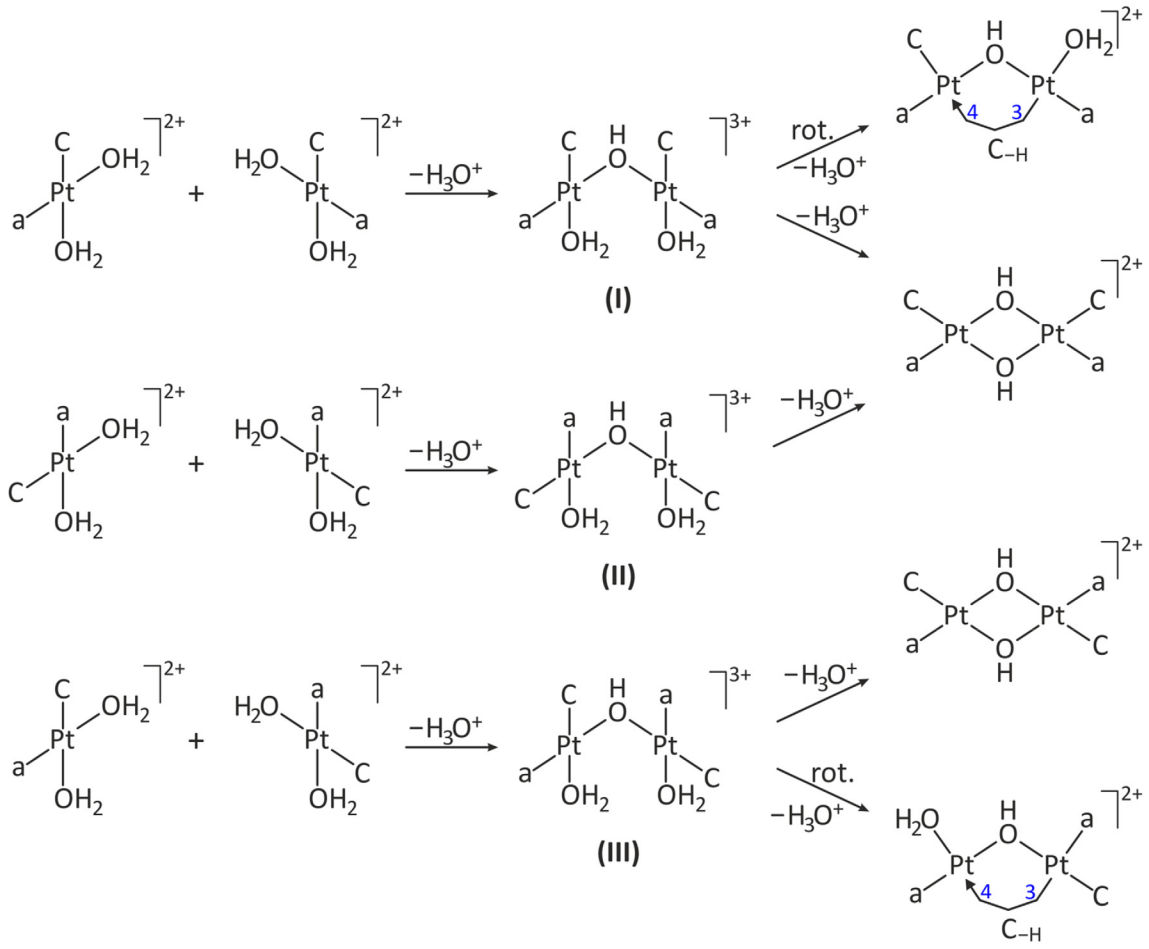


**Fig. 21.** Feasible dinuclear condensation products derived from *cis*-[Pt($NH_3$)(1MeC-*N3*)($H_2O$)$_2$]$^{2+}$: Three different open μ-OH dimers (I, II, III), two bis(μ-OH) dimers, and two different mixed μ-OH, μ-1MeC$_{-H}$ dimers. Rotation about Pt–OH bonds in the open dimers II and III and subsequent condensation between $OH_2$ and $NH_3$ ligands could also lead to mixed μ-OH, μ-$NH_2$ bridging (not included). a = $NH_3$; C = 1MeC-*N3*.

others, for nbH = 9MeAH$^+$ [213], 9RGH$_2^+$ [214], and 6,9DiMeAH$^+$ [207]. With nb = neutral, unsubstituted cytosine the charge of the complex ion is negative [215]. The successive or complete displacement of the chlorido ligands by $NH_3$, diamines, and nucleobases allows for the synthesis of a large number of derivatives. Hence, the trichlorido complexes are very suitable starting materials.

### 6.2. Selected derivatives

The full synthetic potential of these mono(nucleobase) starting materials has not been evaluated yet, specifically not the synthesis of bis-, tris-, and tetrakis-nucleobase complexes derived from [Pt(nb)$X_3$]$^-$ or of bis- and tris-nucleobase compounds derived from *cis*-[Pt($NH_3$)(nb)$Cl_2$]. Published work essentially refers to reactions with $NH_3$ only, leading either to compounds of composition *cis*-[Pt($NH_3$)(nb)$Cl_2$] or *cis*-[Pt($NH_3$)(nbH)$Cl_2$]Cl (see also 5.1), as expected. With an excess of $NH_3$, reactions proceeds to [Pt($NH_3$)$_3$(nb)]$^{2+}$ [207,215,216].

## 7. Mono(nucleobase) complexes of type [Pt(nb)a$_3$]$^{2+}$

Next to Cisplatin and Transplatin, interactions of monofunctional [Pt(dien)($H_2O$)]$^{2+}$ (dien = diethylenediamine), hence the analogue of [Pt($NH_3$)$_3$($H_2O$)]$^{2+}$, or of [Pt(trpy)($H_2O$)]$^{2+}$, and DNA and its isolated nucleobase components, respectively, have been fundamental in our present understanding of the sites and effects of Pt-DNA binding [217]. From a synthesis-point-of-view, the preparation of such model compounds is not overly challenging in that their isolation is straightforward when combining the Pt entity with the appropriate nucleobase. Occasionally observations were made with model nucleobase complexes of these Pt compounds which may bear a biological relevance, such as the enhancement of the Watson-Crick pair between guanine and cytosine following N7 Pt binding to G [218] or the conversion of Pt-coordinated 1MeC into a 1MeU ligand, hence nucleobase deamination [219]. This process, observed and studied in more detail previously by us with several more Pt$^{II}$ species and including also 1,5DimeC [220], may add to scenarios discussed in the context of mutagenesis following cytosine deamination [221]. Similar deamination reactions leading to 9-methylhypoxanthine have also been reported for 9MeA bound to Pt$^{II}$ via N7 [222] or via N1 [223]. Interestingly, in both systems (C and A), metal migration processes to the (deprotonated) amino groups take place in parallel ways.

In the large majority of cases, these [Pt(nb)a$_3$]$^{2+}$ complexes mainly provide information on basic inorganic chemistry properties of coordinated nucleobases (e.g. p$K_a$; affinity and binding sequence of additional metal entities; stacking and H bonding properties) and enable the construction of larger metal–nucleobase entities, including supramolecular ones (see below).

Fig. 22 gives an overview on the synthetic potential to systematically synthesize di-, tri-, and tetranuclear metal complexes derived from mononuclear [M(a)$_3$(9RA-*N7*)]$^{2+}$ (M = Pt$^{II}$ of Pd$^{II}$) as

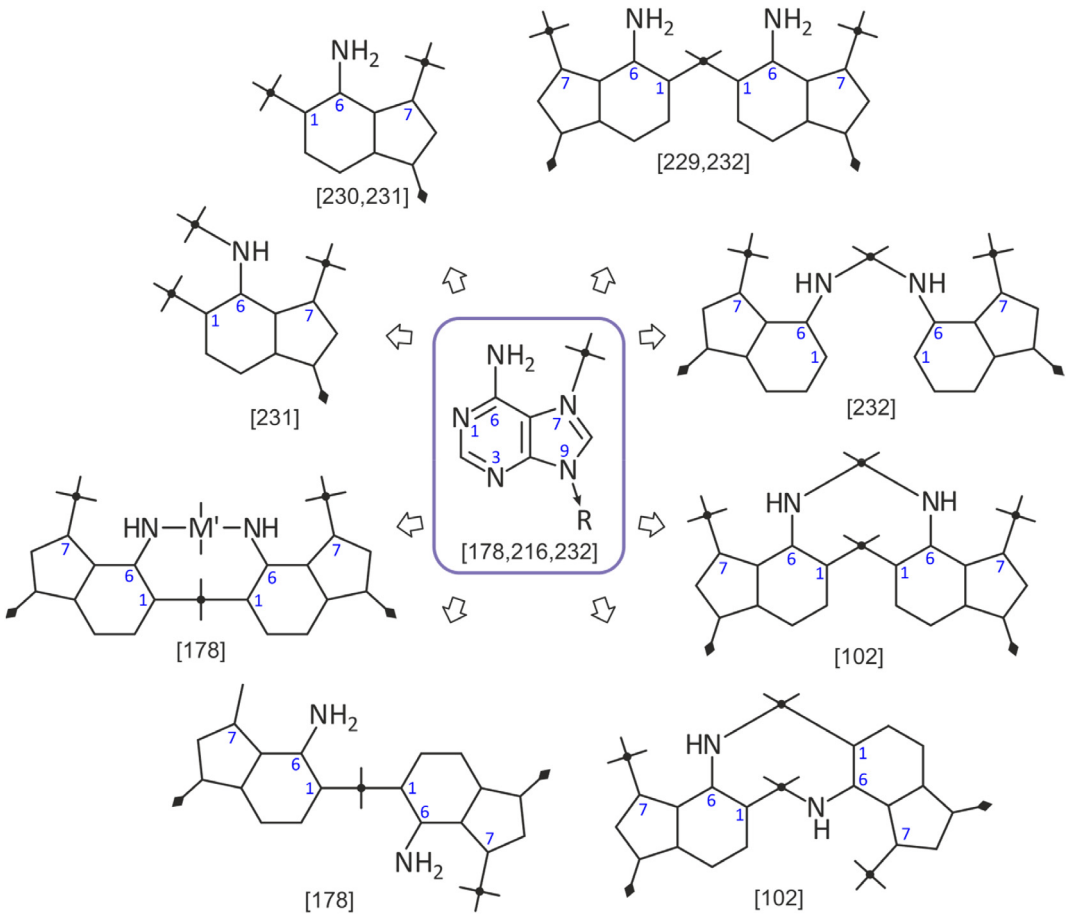


**Fig. 22.** X-ray structurally characterized multinuclear complexes derived from $[M(a)_3(9RA\text{-}N7)]^{2+}$ (with M = $Pt^{II}$ or $Pd^{II}$; $(a)_3$ = $(NH_3)_3$ or dien or trpy). Metal entities connecting two pu bases are either *cis*- or *trans*-$(a)_2M^{II}$ (with $(a)_2$ = $(NH_3)_2$ or en) or M' = $Cu^{II}$ or $Hg^{II}$.

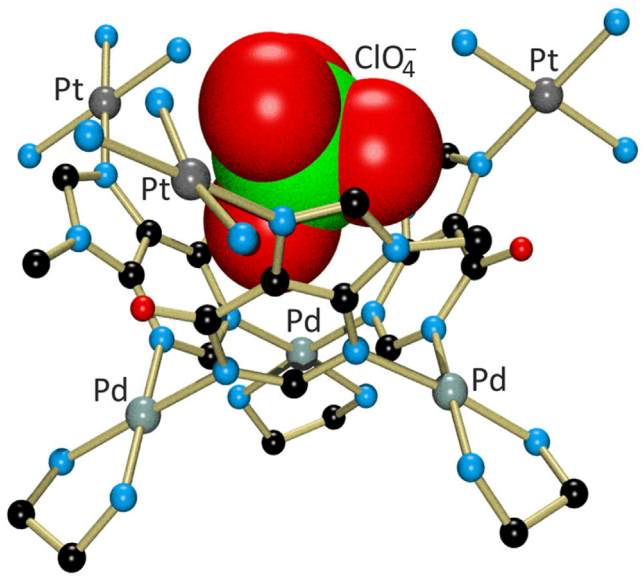


**Fig. 23.** View of the $C_3$-symmetric $Pt_3Pd_3$ host–guest system with perchlorate [238].

a typical example. We have chosen this example, since early work on binding of $[Pt(dien)Cl]^+$ and $[Pt(NH_3)_3Cl]^+$ to adenosine has demonstrated that the N7-bonded species represented the major product of such reactions, but that additional species are formed (e.g. N1 linkage isomer; N1,N7-diplatinated species; others), not all of which were fully identified then [224–227]. Clearly, the various model compounds listed provide evidence for the ability of this purine base to utilize its numerous donor sites sequentially or in dependence on pH for metal binding. If access to the preferred endocyclic N7 and N1 sites as well as the exocyclic amino group is prevented, e.g. by methylation of the latter, $(dien)M^{II}$ (with M = Pt, Pd) is directed toward the N3 position [228]. Structural details regarding the compounds listed in Fig. 22 have been published [229–232].

Although less explored, N7-blocked $(a)_3Pt^{II}$ complexes of 6-oxopurines (9RGH, 9RHxH) likewise are ideal starting materials for the synthesis of multinuclear derivatives as well as models for Cisplatin cross-links involving nucleobase donor sites normally residing in the interior of duplex DNA or duplex RNA (uracil-N3, cytosine-N3, guanine-N1). Such compounds were synthesized by initially blocking the N7 position of 9RGH with $(dien)Pt^{II}$, followed by Pt cross-linking its N1 site with a second nucleobase, and subsequent removal of $(dien)Pt^{II}$ with the strong nucleophile cyanide [233]. Other examples include dinuclear (N7,N1) [234,235] and trinuclear (N7,N1,N3) $Pt^{II}$ complexes [236], heteronuclear ones involving O6 as another metal binding site [233,237] and a cyclic $C_3$-symmetric species derived from $[Pt(NH_3)_3(9EtHxH\text{-}N7)]^{2+}$ and $(en)Pd^{II}$ [238]. This latter product combines lessons learnt from simple model compounds —acidification of N1H by Pt coordination to N7, subsequent coordination of $Pd^{II}$ to N1 and then to N3— to eventually lead to a $Pt_3/Pd_3$ product. Interestingly, although using N1 and N3 sites of the pym part of the pu nucleobase for Pd bridging, this reaction does not produce a tetranuclear cycle, as numer-

ously observed by us with the parent pym nucleobases uracil and cytosine [154], nor a cyclic hexamer [155] or an octamer [154], but rather a cyclic trimer. The 12-membered ring formed by the combination of three 90° angles at the Pd centers and the 120° angles at the three bridging pym parts is unstrained only when the nucleobases are substantially inclined with respect to the $Pd_3$ plane (60°). Quite obviously, the exocyclic C2-substituents —protons in case of 9EtHx— allow for this arrangement, whereas space-requiring exocyclic oxygen atoms as present in all pym nucleobases lead to larger sing sizes. For the same reason (exocyclic amino group in 2-position) a cyclic $C_3$-symmetric 9RG analogue is unlikely to exist. Not even partial-cone arrangements of three nucleobases in cyclic arrangements are expected to resolve this steric problem. The cone structure of this $C_3$-symmetric compound (Fig. 23), and its positive charge is ideally suited to act as a receptor for tetrahedral anions, as experimentally confirmed [238].

## 8. Summary

In this review, 1:1-complexes derived from *cis*- and *trans*-[Pt(a)$_2$X$_2$], [Pt(a)X$_3$]$^-$, [PtX$_4$]$^{2-}$, as well as [Pt(a)$_3$X]$^+$ (with X = Cl$^-$, a = NH$_3$ or (a)$_2$ = chelating diamine or a$_3$ = chelating triamine) and model nucleobases (nb) are being discussed. They represent real or at least feasible models of interactions of the mentioned Pt$^{II}$ entities with nucleic acids. Apart from their relevance with regard to the mode of action of certain antitumor active Pt$^{II}$ drugs, these mono(nucleobase) complexes display a rich and multifaceted chemistry of their own. The latter refers to general and preparative coordination chemistry rather than any medicinal or biochemical applications. Multiple self-condensation reactions of mixed nucleobase/aqua complexes leading to discrete cyclic species as well as —still poorly understood— oligomers with μ-nb, μ-OH, and μ-NH$_2$ bridging modes are a hallmark of this chemistry. Chiral head–tail dinuclear nucleobase species represent the smallest condensation products of *cis*-[Pt(a)$_2$(nb)(H$_2$O)]$^{n+}$ and of *trans*-[Pt(NH$_3$)$_2$(nb)(H$_2$O)]$^{n+}$ and are treated in detail.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: P. J. Sanz Miguel reports financial support was provided by University of Zaragoza. B. Lippert reports financial support was provided by TU Dortmund University.

## Acknowledgements

We acknowledge support from TU Dortmund and the University of Zaragoza. Thanks to the following colleagues for helpful comments: Prof. Bernt Krebs, Münster, Dr. Diego Montagner, Dublin, Prof. Steve J. Lippard, Cambridge, and Prof. Timothy C. Johnstone, Santa Cruz. We also thank Prof. Hans-Günther Schmalz, Köln, for HPLC measurements. We dedicate this paper to two colleagues and friends, Professors Jorma Arpalahti, University of Turku, Turku (Finland), and Michal Sabat, University of Virginia, Charlottesville (USA) for numerous discussions on this topic over many years.

## References

[1] S. Dhar, S.J. Lippard, in: E. Alessio (Ed.), Bioinorganic Medicinal Chemistry, Wiley-VCH, Weinheim, 2011, pp. 79-95 and refs. cited.
[2] J. Reedijk, Inorg. Chim. Acta 452 (2016) 268–272.
[3] L.G. Marzilli, T.J. Kistenmacher, G.L. Eichhorn, in: Nucleic Acid-Metal Ion Interactions, Wiley-Interscience, New York, 1980, pp. 179–256.
[4] B. Lippert (Ed.), Cisplatin – Chemistry and Biochemistry of a Leading Anticancer Drug, and Wiley-VCH, Weinheim, 1999.
[5] G. Natile, M. Coluccia, Coord. Chem. Rev. 216–217 (2001) 383–410.
[6] S.M. Aris, N.P. Farrell, Eur. J. Inorg. Chem. (2009) 1293–1302.
[7] T.C. Johnstone, J.J. Wilson, S.J. Lippard, Inorg. Chem. 52 (2013) 12234–12249.
[8] S.J. Hollis, A.R. Amundsen, E.W. Stern, J. Med. Chem. 32 (1989) 128–136.
[9] S.F. Bellon, S.J. Lippard, Biophys. Chem. 35 (1990) 179–188.
[10] D. Wang, G. Zhu, X. Huang, S.J. Lippard, PNAS 107 (2010) 9584–9589.
[11] T.C. Johnstone, S.J. Lippard, J. Am. Chem. Soc. 136 (2014) 2126–2134.
[12] U. Bierbach, Y. Qu, T.W. Hambley, J. Peroutka, H.L. Nguyen, M. Doedee, N. Farrell, Inorg. Chem. 38 (1999) 3535–3542.
[13] H. Schöllhorn, G. Raudaschl-Sieber, G. Müller, U. Thewalt, B. Lippert, J. Am. Chem. Soc. 107 (1985) 5932–15927.
[14] G. Schröder, J. Kozelka, M. Sabat, M.-H. Fouchet, R. Beyerle-Pfnür, B. Lippert, Inorg. Chem. 35 (1996) 1647–1652.
[15] G. Schröder, M. Sabat, I. Baxter, J. Kozelka, B. Lippert, Inorg. Chem. 36 (1997) 490–493.
[16] A. Erxleben, S. Metzger, J.F. Britten, C.J.L. Lock, A. Albinati, B. Lippert, Inorg. Chim. Acta 339 (2002) 461–469.
[17] B. Lippert, P.J. Sanz Miguel, Chem. Soc. Rev. 40 (2011) 4475–4487.
[18] B. Lippert, P.J. Sanz Miguel, Acc. Chem. Res. 49 (2016) 1537–1545.
[19] B. Lippert, P.J. Sanz Miguel, Adv. Inorg. Chem. 71 (2018) 277–326.
[20] A.D. Burrows, C.-W. Chan, M.M. Chowdhry, J.E. McGrady, D.M. Mingos, Chem. Soc. Rev. (1995) 329–339.
[21] A. Houlton, Adv. Inorg. Chem. 53 (2002) 87–158.
[22] D. Badura, H. Vahrenkamp, Inorg. Chem. 41 (2002) 6020–6027.
[23] S. Sivakova, S.J. Rowan, Chem. Soc. Rev. 34 (2005) 9–21.
[24] S. Verma, A.K. Mishra, J. Kumar, Acc. Chem. Res. 43 (2010) 79–91.
[25] G. Beobide, O. Castillo, J. Cepeda, A. Luque, S. Pérez-Yáñez, P. Román, J. Thomas-Gipson, Coord. Chem. Rev. 257 (2013) 2716–2736.
[26] P. Amo-Ochoa, F. Zamora, Coord. Chem. Rev. 276 (2014) 34–58.
[27] N. Maldonado, V.C. Vegas, O. Halevi, J.I. Martínez, P.S. Lee, S. Magdassi, M.T. Wharmby, A.E. Olatero-Prats, C. Moreno, F. Zamora, P. Amo-Ochoa, Adv. Funct. Mater. (2019) 1808424.
[28] D. Armentano, N. Marino, T.F. Mastropietro, J. Martínez-Lillo, J. Cano, M. Julve, F. Lloret, G. De Munno, Inorg. Chem. 47 (2008) 10229–10231.
[29] C. Kahlfuss, E. Starck, E. Tufenkjian, N. Kyritsakas, A. Jouaiti, S.A. Baudron, M. W. Hosseini, V. Bulach, CrystEngComm 23 (2021) 944–954.
[30] S. Naskar, R. Guha, J. Müller, Angew. Chem. Int. Ed. 59 (2020) 1397–1406.
[31] A. Terrón, B. Moreno-Vachiano, A. Bauzá, A. García-Raso, J.J. Fiol, M. Barceló-Oliver, E. Molins, A. Frontera, Chem. Eur. J. 23 (2017) 2103–2108.
[32] F. Linares, E. García-Fernández, F.J. López-Garzón, M. Domingo-García, A. Orte, A. Rodríguez-Diéguez, M.A. Galindo, Chem. Sci. 10 (2019) 1126–1137.
[33] E. Stulz, G.H. Clever (Eds.), DNA in Supramolecular Chemistry and Nanotechnology, Wiley, Chichester, 2015.
[34] T. Allscher, P. Klüfers, Chem. Eur. J. 18 (2012) 10571–10584.
[35] G. Schröder, B. Lippert, M. Sabat, C.J.L. Lock, R. Faggiani, B. Song, B. Lippert, H. Sigel, J. Chem. Soc. Dalton Trans. (1995) 3767–3775.
[36] M. Roitzsch, B. Lippert, J. Am. Chem. Soc. 126 (2004) 2421–2424.
[37] M. Garijo Añorbe, M.S. Lüth, M. Roitzsch, M. Morell Cerdà, P. Lax, G. Kampf, H. Sigel, B. Lippert, Chem. Eur. J. 10 (2004) 1046–1057.
[38] B. Lippert, Prog. Inorg. Chem. 54 (2005) 385–447.
[39] M. Roitzsch, M. Garijo Añorbe, P.J. Sanz Miguel, B. Müller, B. Lippert, J. Biol. Inorg. Chem. 10 (2015) 800–812.
[40] P.M. Lax, M. Garijo Añorbe, B. Müller, E.Y. Bivián-Castro, B. Lippert, Inorg. Chem. 46 (2007) 4036–4043.
[41] B. Lippert, Chem. Biodivers. 5 (2008) 1455–1474.
[42] B. Lippert, D. Gupta, Dalton Trans. (2009) 4619–4634.
[43] L. Holland, W.-Z. Shen, W. Micklitz, B. Lippert, Inorg. Chem. 46 (2007) 11356–11365.
[44] J. Ruiz, N. Cutillas, C. Vicente, M.D. Villa, G. López, J. Lorenzo, F.X. Avilés, V. Moreno, Inorg. Chem. 44 (2005) 7365–7376.
[45] There are 25 complexes of type *cis*-[Pt(L,L')(nb)X], extracted from the CSD (version 2022). No analogous Pd-complexes were found.
[46] L. de Napoli, R. Iacovino, A. Messere, D. Montesarchio, G. Piccialli, A. Romanelli, F. Ruffo, M. Saviano, Dalton Trans. (1999) 1945–1949.
[47] A. Messere, E. Fabbri, M. Borgatti, R. Gambari, B. Di Blasio, C. Pedone, A. Romanelli, J. Inorg. Biochem. 101 (2007) 254–260.
[48] S. Pullen, W.G. Hiller, B. Lippert, Inorg. Chim. Acta 494 (2019) 168–180.
[49] S. Pullen, A. Hegmans, W.G. Hiller, A. Platzek, E. Freisinger, B. Lippert, Chem. 10 (2021) 28–45.
[50] B. Lippert, Coord. Chem. Rev. 200–202 (2000) 487–516.
[51] E.Y. Bivián Castro, M. Roitzsch, D. Gupta, B. Lippert, Inorg. Chim. Acta 358 (2005) 2395–2402.
[52] K.J. Barnham, Ph.D. Thesis University of Queensland (1992).
[53] R. Griesser, G. Kampf, L.E. Kapinos, S. Komeda, B. Lippert, J. Reedijk, H. Sigel, Inorg. Chem. 42 (2003) 32–41.
[54] J.H.J. den Hartog, H. den Elst, J. Reedijk, J. Inorg. Biochem. 21 (1984) 83–92.
[55] M.C. Biagini, M. Ferrari, M. Lanfranchi, L. Marchiò, M.A. Pellinghelli, J. Chem. Soc., Dalton Trans. (1999) 1575–1580.
[56] J.E. Šponer, F. Glahé, J. Leszcynski, B. Lippert, J. Šponer, J. Phys. Chem. B 105 (2001) 12171–12179.
[57] M.D. Reily, L.G. Marzilli, J. Am. Chem. Soc. 108 (1986) 6785–6793.
[58] H. Schöllhorn, U. Thewalt, B. Lippert, Inorg. Chim. Acta 106 (1985) 177–180.
[59] A.M.J. Fichtinger-Schepman, J.L. van der Veer, J.H.J. den Hartog, P.H.M. Lohman, J. Reedijk, Biochemistry 24 (1985) 707–713.
[60] A. Eastman, Biochemistry 25 (1986) 3912–3915.

[61] N. Margiotta, G. Natile, F. Capitelli, F.P. Fanizzi, A. Boccarelli, P. De Rinaldis, D. Giordano, M. Coluccia, J. Inorg. Biochem. 100 (2006) 1849–1857.
[62] K.S. Lovejoy, R.C. Todd, S. Zhang, M.S. McCormick, J.A. D'Aquino, J.T. Reardon, A. Sancar, K.M. Giacomini, S.J. Lippard, PNAS 105 (2008) 8902–8907.
[63] R.C. Todd, S.J. Lippard, Metallomics 1 (2009) 280–291.
[64] N. Margiotta, A. Bergamo, G. Sava, G. Padovano, E. de Clercq, G. Natile, J. Inorg. Biochem. 98 (2004) 1385–1390.
[65] T.C. Johnstone, S.M. Alexander, W. Lin, S.J. Lippard, J. Am. Chem. Soc. 136 (2014) 116–118.
[66] R. Faggiani, B. Lippert, C.J.L. Lock, R.A. Speranzini, Inorg. Chem. 21 (1982) 3216–3225.
[67] R. Beyerle-Pfnür, B. Brown, R. Faggiani, B. Lippert, C.J.L. Lock, Inorg. Chem. 24 (1985) 4001–4009.
[68] B. Lippert, U. Thewalt, H. Schöllhorn, D.M.L. Goodgame, R.W. Rollins, Inorg. Chem. 23 (1984) 2807–2813.
[69] B. Lippert, Prog. Inorg. Chem. 37 (1989) 1–97.
[70] E. Zangrando, F. Pichierri, L. Randaccio, B. Lippert, Coord. Chem. Rev. 156 (1996) 275–332.
[71] L. Yin, P.J. Sanz Miguel, W.-Z. Shen, B. Lippert, Chem. Eur. J. 15 (2009) 10723–10726.
[72] L. Yin-Bandur, P.J. Sanz Miguel, L. Rodríguez-Santiago, M. Sodupe, M. Berghaus, B. Lippert, Chem. Eur. J. 22 (2016) 13653–13668.
[73] E. Freisinger, A. Schneider, M. Drumm, A. Hegmans, S. Meier, B. Lippert, J. Chem. Soc., Dalton Trans. (2000) 3281–3287.
[74] U.K. Häring, R.B. Martin, Inorg. Chim. Acta 78 (1983) 259–267.
[75] C. Fonseca Guerra, P.J. Sanz Miguel, A. Cebollada, F.M. Bickelhaupt, B. Lippert, Chem. Eur. J. 20 (2014) 9494–9499.
[76] B. Lippert, Inorg. Chim. Acta 55 (1981) 5–14.
[77] B. McConnell, Biochemistry 17 (1978) 3168–3176.
[78] B. Lippert, P.J. Sanz Miguel, Coord. Chem. Rev. 327–328 (2016) 333–348.
[79] M.S. Lüth, E. Freisinger, F. Glahé, B. Lippert, Inorg. Chem. 37 (1998) 5044–5045.
[80] G. Trovó, G. Bandoli, U. Casellato, B. Corain, M. Nicolini, B. Longato, Inorg. Chem. 29 (1990) 4616–4621.
[81] G. Trovó, G. Bandoli, M. Nicolini, B. Longato, Inorg. Chim. Acta 211 (1993) 95–99.
[82] M. Grehl, B. Krebs, Inorg. Chem. 33 (1994) 3877–3885.
[83] J. Ruiz, J. Lorenzo, L. Sanglas, N. Cutillas, C. Vicente, M.D. Villa, F.X. Avilés, G. López, V. Moreno, J. Pérez, D. Bautista, Inorg. Chem. 45 (2006) 6347–6360.
[84] C.J.L. Lock, H.J. Peresie, B. Rosenberg, G. Turner, J. Am. Chem. Soc. 100 (1978) 3371–3374.
[85] R. Faggiani, C.J.L. Lock, R.J. Pollock, B. Rosenberg, G. Turner, Inorg. Chem. 20 (1981) 804–807.
[86] D. Neugebauer, B. Lippert, Inorg. Chim. Acta 67 (1982) 151–158.
[87] R. Faggiani, B. Lippert, C.J.L. Lock, R.A. Speranzini, J. Am. Chem. Soc. 103 (1981) 1111–1120.
[88] P.J. Sanz Miguel, M. Roitzsch, L. Yin, P.M. Lax, L. Holland, O. Krizanovic, M. Lutterbeck, M. Schürmann, E.C. Fusch, B. Lippert, Dalton Trans. (2009) 10774–10786.
[89] V.M. Djinovic, M. Galanski, V.B. Arion, B.K. Keppler, Dalton Trans. 39 (2010) 3633–3643.
[90] H. Engelking, B. Krebs, J. Chem. Soc., Dalton Trans. (1996) 2409–2416.
[91] N. Paschke, A. Röndigs, H. Poppenborg, J.E.A. Wolff, B. Krebs, Inorg. Chim. Acta 264 (1997) 239–248.
[92] M.J. Rauterkus, I. Puscasu, B. Krebs, Inorg. Chim. Acta 339 (2002) 438–444.
[93] M.J. Rauterkus, S. Fakih, C. Mock, I. Puscasu, B. Krebs, Inorg. Chim. Acta 350 (2003) 355–365.
[94] A. Wu, L. Isaacs, J. Am. Chem. Soc. 125 (2003) 4831–4835.
[95] S. Ghosh, D.R. Turner, S.R. Batten, P.S. Mukherjee, Dalton Trans. (2007) 1869–1871.
[96] B. Longato, D. Montagner, E. Zangrando, Inorg. Chem. 45 (2006) 8179–8187.
[97] R.W. Gellert, B.E. Fischer, R. Bau, J. Am. Chem. Soc. 102 (1980) 7812–7815.
[98] M. Kao, A.K. Sah, T. Tanase, M. Mikuriya, Eur. J. Inorg. Chem. (2006) 2504–2513.
[99] K.R. Dunbar, J.H. Matonic, V.P. Saharan, C.A. Crawford, G. Christou, J. Am. Chem. Soc. 116 (1994) 2201–2202.
[100] C.A. Crawford, E.F. Day, V.P. Saharan, K. Folting, J.C. Huffman, K.R. Dunbar, G. Christou, Chem. Commun. (1996) 1113–1114.
[101] H.T. Chifotides, K.R. Dunbar, Acc. Chem. Res. 38 (2005) 146–156.
[102] S. Ibáñez, F.M. Albertí, P.J. Sanz Miguel, B. Lippert, Inorg. Chem. 50 (2011) 10439–10447.
[103] W.S. Sheldrick, B. Günther, J. Organomet. Chem. 375 (1989) 233–243.
[104] G.P. Moss, Pure Appl. Chem. 68 (1996) 2193–2222.
[105] I.O. Koshevoy, P. Lahuerta, M. Sanaú, M.A. Ubeda, A. Doménech, Dalton Trans. (2006) 5536–5541.
[106] L.S. Hollis, S.J. Lippard, J. Am. Chem. Soc. 105 (1983) 3494–3503.
[107] H. Schöllhorn, U. Thewalt, B. Lippert, Inorg. Chim. Acta 93 (1984) 19–26.
[108] R.E. Cramer, P.L. Dahlstrom, Inorg. Chem. 24 (1985) 3420–3424.
[109] S.O. Ano, Z. Kuklenyik, L.G. Marzilli, in: Cisplatin – Chemistry and Biochemistry of a Leading Anticancer Drug, VHCA, Zürich, and Wiley-VCH, Weinheim, 1999, pp. 247–291.
[110] J.S. Saad, M. Benedetti, G. Natile, L.G. Marzilli, Inorg. Chem. 49 (2010) 5573–5583.
[111] K. Umakoshi, I. Kinoshita, Y. Fukui-Yasuba, K. Matsumoto, S. Ooi, J. Chem. Soc., Dalton Trans. (1989) 815–819.
[112] T.J. Kistenmacher, M. Rossi, L.G. Marzilli, Inorg. Chem. 18 (1979) 240–244.
[113] P. Amo-Ochoa, O. Castillo, P.J. Sanz Miguel, F. Zamora, J. Inorg. Biochem. 102 (2008) 203–208.
[114] K. Krogmann, Angew. Chem. Int. Ed. Engl. 8 (1969) 35–42.
[115] W.R. Connick, R.E. Marsh, W.P. Schaefer, H.B. Gray, Inorg. Chem. 36 (1997) 913–922.
[116] A. Poater, S. Moradell, E. Pinilla, J. Poater, M Solá, M.A. Martínez, A. Llobet, Dalton Trans. (2006) 1188–1196.
[117] J.J. Novoa, G. Aullón, P. Alemany, S. Alvarez, J. Am. Chem. Soc. 117 (1995) 7169–7171.
[118] C.-K. Koo, B. Lam, S.-K. Leung, M.-H.-W. Lam, W.-Y. Wong, J. Am. Chem. Soc. 128 (2006) 16434–16435.
[119] J.M. Casas, B.E. Diosdado, J. Forniés, A. Martín, A.J. Rueda, A.G. Orpen, Inorg. Chem. 47 (2008) 8767–8775.
[120] B. Lippert, H. Schöllhorn, U. Thewalt, Z. Naturforsch. 38b (1983) 1441–1445.
[121] H. Schöllhorn, P. Eisenmann, U. Thewalt, B. Lippert, Inorg. Chem. 25 (1986) 3384–3391.
[122] G. Kampf, M. Willermann, E. Zangrando, L. Randaccio, B. Lippert, Chem. Commun. (2001) 747–748.
[123] G. Kampf, M. Willermann, E. Freisinger, B. Lippert, Inorg. Chim. Acta 330 (2002) 179–188.
[124] P.K. Mascharak, I.D. Williams, S.J. Lippard, J. Am. Chem. Soc. 106 (1984) 6428–6430.
[125] B. Lippert, H. Schöllhorn, U. Thewalt, Inorg. Chem. 26 (1987) 1736–1741.
[126] O. Renn, A. Albinati, B. Lippert, Angew. Chem. Int. Ed. Engl. 29 (1990) 84–85.
[127] M. Yoshida, N. Yashiro, H. Shitama, A. Kobayashi, M. Kato, Chem. Eur. J. 22 (2016) 491–495.
[128] K. Sakai, K. Matsumoto, J. Am. Chem. Soc. 111 (1989) 3074–3075.
[129] K. Matsumoto, K. Sakai, K. Nishio, Y. Tokisue, R. Ito, T. Nishide, Y. Shichi, J. Am. Chem. Soc. 114 (1992) 8110–8118.
[130] U. Thewalt, D. Neugebauer, B. Lippert, Inorg. Chem. 23 (1984) 1713–1718.
[131] J.K. Barton, Science 233 (1986) 727–734.
[132] V.-W.-W. Yam, V.-K.-M. Au, S.-Y.-L. Leung, Chem. Rev. 115 (2015) 7589–7728.
[133] M. Fujita, M. Tominaga, A. Hori, B. Therrien, Acc. Chem. Res. 38 (2005) 371–380.
[134] J.M. Ludlow III, M. Tominaga, Y. Chujo, A. Schultz, X. Lu, T. Xie, K. Guo, C.N. Moorefield, C. Wesdemiotis, G.R. Newkome, Dalton Trans 43 (2014) 9604–9611.
[135] M.A. Galindo, S. Galli, J.A.R. Navarro, M. Angustias Romero, Dalton Trans. (2004) 2780–2785.
[136] M. Rancan, A. Dolmella, R. Seraglia, S. Orlandi, S. Quici, L. Armelao, Chem. Commun. 48 (2012) 3115–3117.
[137] T.R. Cook, V. Vajpayee, M.H. Lee, P.J. Stang, K.-W. Chi, Acc. Chem. Res. 46 (2013) 2464–2474.
[138] J.R. Hooley, Inorg. Chem. 57 (2008) 3497–3499, and refs. cited.
[139] E. Zangrando, M. Casanova, E. Alessio, Chem. Rev. 108 (2008) 4979–5013.
[140] A. Mishra, R. Gupta, Dalton Trans. 43 (2014) 7668–7682.
[141] S. Alvarez, E. Ruiz, in: Supramolecular Chemistry: From Molecules to Nanomaterials, John Wiley & Sons, Chichester, UK, 2012, pp. 1993–2044.
[142] L. Schenetti, G. Bandoli, A. Dolmella, G. Trovó, B. Logato, Inorg. Chem. 33 (1994) 3169–3176.
[143] W.-Z. Shen, D. Gupta, B. Lippert, Inorg. Chem. 44 (2005) 8249–8258.
[144] W.-Z. Shen, B. Lippert, J. Inorg. Biochem. 102 (2008) 1134–1140.
[145] B. Longato, L. Pasquato, A. Mucci, L. Schenetti, E. Zangrando, Inorg. Chem. 42 (2003) 7861–7871.
[146] S.-W. Lai, M.-C.-W. Chan, S.-W. Peng, C.-M. Che, Angew. Chem. Int. Ed. 38 (1999) 669–671.
[147] P. Chaudhuri, I. Karpenstein, M. Winter, C. Butzlaff, E. Bill, A.X. Trautwein, U. Flörke, H.-J. Haupt, J. Chem. Soc., Chem. Commun. (1992) 321–322.
[148] R.H. Fish, Coord. Chem. Rev. 185–186 (1999) 569–584.
[149] S. Korn, W.S. Sheldrick, Inorg. Chim. Acta 254 (1997) 85–91.
[150] P. Annen, S. Schildberg, W.S. Sheldrick, Inorg. Chim. Acta 307 (2000) 115–124.
[151] X. Zhu, E. Rusanov, R. Kluge, H. Schmidt, D. Steinborn, Inorg. Chem. 41 (2002) 2667–2671.
[152] H. Chen, M.M. Olmstead, D.P. Smith, M.F. Maestra, R.H. Fish, Angew. Chem., Int, Ed. Engl. 34 (1995) 1514–1517.
[153] H. Rauter, E.C. Hillgeris, A. Erxleben, B. Lippert, J. Am. Chem. Soc. 116 (1994) 616–624.
[154] E. Gil-Bardaji, E. Freisinger, B. Costisella, C.A. Schalley, W. Brüning, M. Sabat, B. Lippert, Chem. Eur. J. 13 (2007) 6019–6039.
[155] A. Khutia, P.J. Sanz Miguel, B. Lippert, Chem. Eur. J. 17 (2011) 4195–4204.
[156] A. Khutia, P.J. Sanz Miguel, B. Lippert, Chem. Eur. J. 17 (2011) 4205–4216.
[157] A. Khutia, P.J. Sanz Miguel, Inorg. Chem. 49 (2010) 7635–7637.
[158] K. Uchida, A. Toyama, Y. Tamura, M. Sugimura, F. Mitsumori, Y. Furukawa, H. Takeuchi, I. Harada, Inorg. Chem. 28 (1989) 2067–2073.
[159] W. Wirth, J. Blotevogel-Baltronat, U. Kleinkes, W.S. Sheldrick, Inorg. Chim. Acta 339 (2002) 14–26.
[160] S. Zhu, A. Matilla, J.M. Tercero, V. Vijayaragavan, J.A. Walmsley, Inorg. Chim. Acta 357 (2004) 411–420.
[161] J.A. Walmsley, S. Zhu, A. Matilla, T.G. Donowick, J.E. Cramp, J.M. Tercero, T. Dalrymple, Inorg. Chem. 46 (2007) 9945–9953.
[162] B. Longato, G. Bandoli, G. Trovó, E. Marasciulo, G. Valle, Inorg. Chem. 34 (1995) 1745–1750.
[163] S. Siebel, C. Dammann, P.J. Sanz Miguel, T. Drewello, G. Kampf, N. Teubner, P.J. Bednarski, E. Freisinger, B. Lippert, Chem. Eur. J. 21 (2015) 17827–17843.
[164] N. Das, P.J. Sanz Miguel, A. Khutia, M. Lazar, B. Lippert, Dalton Trans. (2009) 9120–9122.

[165] A. Khutia, W.-Z. Shen, N. Das, P.J. Sanz Miguel, B. Lippert, Inorg. Chim. Acta 417 (2014) 274–286.
[166] B. Lippert, D. Neugebauer, G. Raudaschl, Inorg. Chim. Acta 78 (1983) 161–170.
[167] L.E. Erickson, H.L. Erickson, T.Y. Meyer, Inorg. Chem. 26 (1987) 997–999.
[168] R.A. Adrian, S. Zhu, D.R. Powell, G.A. Broker, E.R.T. Tiekink, J.A. Walmsley, Dalton Trans. (2007) 4399–4404.
[169] K. Sakai, M. Takeshita, Y. Tanaka, T. Ue, M. Yanagisawa, M. Kosaka, T. Tsubomura, M. Ato, T. Nakano, J. Am. Chem. Soc. 120 (1998) 11353–11363.
[170] G. Kampf, P.J. Sanz Miguel, M. Morell Cerdà, M. Willermann, A. Schneider, B. Lippert, Chem. Eur. J. 14 (2008) 6882–6891.
[171] A. Eastman, M.M. Jennerwein, D.L. Nagel, Chem.-Biol. Interact. 67 (1988) 71–80.
[172] V. Brabec, M. Leng, PNAS 90 (1991) 5345–5349.
[173] R. Dalbiès, D. Payet, M. Leng, PNAS 91 (1994) 8147–8151.
[174] B. Andersen, E. Bernal-Méndez, M. Leng, E. Sletten, Eur. J. Inorg. Chem. (2000) 1201–1210.
[175] F.J. Pesch, H. Preut, B. Lippert, Inorg. Chim. Acta 169 (1990) 195–200.
[176] G. Raudaschl, B. Lippert, Inorg. Chim. Acta 80 (1983) L49.
[177] M. Höpp, A. Erxleben, I. Rombeck, B. Lippert, Inorg. Chem. 35 (1996) 397–403.
[178] S. Ibáñez, B. Mihály, P.J. Sanz Miguel, D. Steinborn, I. Pretzer, W. Hiller, B. Lippert, Chem. Eur. J. 21 (2015) 5794–5806.
[179] J. Arpalahti, E. Niskanen, R. Sillanpää, Chem. Eur. J. 5 (1999) 2306–2311.
[180] G.M. Arvanitis, D. Gibson, T.J. Emge, H.M. Berman, Acta Cryst. C50 (1994) 1217–1220.
[181] O. Krizanovic, F.J. Pesch, B. Lippert, Inorg. Chim. Acta 165 (1989) 145–146.
[182] F.J. Pesch, M. Wienken, H. Preut, A. Tenten, B. Lippert, Inorg. Chim. Acta 197 (1992) 2434–2439.
[183] T. Appleton, Inorg. Chem. 31 (1992) 3077–3082.
[184] B. Lippert, Met. Ions Biol. Syst. 33 (1996) 105–141.
[185] R.B. Martin, in: Cisplatin – Chemistry and Biochemistry of a Leading Anticancer Drug, VHCA, Zürich, and Wiley-VCH, Weinheim, 1999, pp. 183–205.
[186] T. Appleton, Inorg. Chem. 28 (1989) 1989–1993.
[187] M. Roitzsch, B. Lippert, Chem. Commun. (2005) 5991–5993.
[188] B. Müller, W.-Z. Shen, P.J. Sanz Miguel, F.M. Albertí, T. van der Wijst, M. Noguera, L. Rodríguez-Santiago, M. Sodupe, B. Lippert, Chem. Eur. J. 17 (2011) 9970–9983.
[189] F.M. Albertí, L. Rodríguez-Santiago, M. Sodupe, A. Mirats, H. Kaitsiotou, P.J. Sanz Miguel, B. Lippert, Chem. Eur. J. 20 (2014) 3393–3407.
[190] D. Holthenrich, I. Sóvágó, G. Fusch, A. Erxleben, E.C. Fusch, I. Rombeck, B. Lippert, Z. Naturforsch., 1995, 50b, 1767-1775 and 1996, 51b, 1368.
[191] M.S. Lüth, E. Freisinger, G. Kampf, M. Garijo Añorbe, R. Griesser, B.P. Operschall, H. Sigel, B. Lippert, J. Inorg. Biochem. 148 (2015) 93–104.
[192] P. Gilli, L. Pretto, V. Bertolasi, G. Gilli, Acc. Chem. Res. 42 (2009) 33–44.
[193] M. Roitzsch, B. Lippert, Angew. Chem. Int. Ed. 45 (2006) 147–150.
[194] C. Gagnon, A.L. Beauchamp, Acta Cryst. B33 (1977) 1448–1454.
[195] I.A.G. Roos, A.J. Thomson, J. Eagles, Chem.-Biol. Interact. 8 (1974) 421–427.
[196] B. Lippert, C.J.L. Lock, R.A. Speranzini, Inorg. Chem. 20 (1981) 808–8013.
[197] A. Hegmans, M. Sabat, I. Baxter, E. Freisinger, B. Lippert, Inorg. Chem. 37 (1998) 4921–4928.
[198] A. Wienkötter, M. Sabat, G. Trötscher-Kaus, B. Lippert, Inorg. Chim. Acta 255 (1997) 361–366.
[199] B. Lippert, Inorg. Chim. Acta 56 (1981) L23–L24.
[200] R. Faggiani, C.J.L. Lock, B. Lippert, Inorg. Chim. Acta 106 (1985) 75–79.
[201] G. McGowan, S. Parsons, P.J. Sadler, Inorg. Chem. 44 (2005) 7459–7467.
[202] A. Wienkötter, M. Sabat, G. Fusch, B. Lippert, Inorg. Chem. 34 (1995) 1022–1029.
[203] D. Holthenrich, E. Zangrando, E. Chiarparin, B. Lippert, L. Randaccio, J. Chem. Soc., Dalton Trans. (1997) 4407–4410.
[204] L. Yin, P.J. Sanz Miguel, W. Hiller, B. Lippert, Inorg. Chem. 51 (2012) 6784–6793.
[205] C. Mealli, F. Pichierri, L. Randaccio, E. Zangrando, M. Krumm, D. Holthenrich, B. Lippert, Inorg. Chem. 34 (1995) 3418–3424.
[206] J.P. Davidson, P.J. Faber, R.G. Fischer Jr., S. Mansy, H.J. Peresie, B. Rosenberg, L. Van Camp, Cancer Chemother. Rep. 59 (1975) 287–300.
[207] B. Lippert, U. Schöllhorn, U. Thewalt, Inorg. Chim. Acta 198–200 (1992) 723–732.
[208] Z. Guo, P.J. Sadler, Angew. Chem. Int. Ed. 38 (1999) 1512–1531, and refs. cited.
[209] G.K. Anderson, R.J. Cross, Chem. Soc. Rev. 9 (1980) 185–215, and refs. cited.
[210] R. Faggiani, B. Lippert, C.J.L. Lock, B. Rosenberg, Inorg. Chem. 16 (1977) 1192–1196.
[211] R. Faggiani, B. Lippert, C.J.L. Lock, B. Rosenberg, Inorg. Chem. 17 (1978) 1941–1945.
[212] F.D. Rochon, A. Morneau, R. Melanson, Inorg. Chem. 27 (1988) 10–13.
[213] A. Terzis, Inorg. Chem. 15 (1976) 793–796.
[214] A. Terzis, D. Mentzafos, Inorg. Chem. 22 (1983) 1140–1143.
[215] S. Jaworski, H. Schöllhorn, P. Eisenmann, U. Thewalt, B. Lippert, Inorg. Chim. Acta 153 (1988) 31–38.
[216] R. Beyerle-Pfnür, S. Jaworski, B. Lippert, H. Schöllhorn, U. Thewalt, Inorg. Chim. Acta 107 (1985) 217–222.
[217] V. Brabec, J. Reedijk, M. Leng, Biochemistry 31 (1992) 12387–12402.
[218] R.K.O. Sigel, B. Lippert, Chem. Commun. (1999) 2167–2168.
[219] P.J. Sanz Miguel, P. Lax, B. Lippert, J. Inorg. Biochem. 100 (2006) 980–991.
[220] J.E. Šponer, P.J. Sanz Miguel, L. Rodriguez-Santiago, A. Erxleben, M. Krumm, M. Sodupe, J. Šponer, B. Lippert, Angew. Chem. Int. Ed. 43 (2004) 5396–5399.
[221] C.A. Lewis Jr., J. Crayle, S. Zhou, R. Swanstrom, R. Wolfenden, PNAS (2016) 8194–8199.
[222] J. Arpalahti, K.D. Klika, Eur. J. Inorg. Chem. (2003) 4195–4201.
[223] K.D. Klika, J. Arpalahti, Chem. Commun. (2004) 666–667.
[224] S. Mansy, B. Rosenberg, A.J. Thomson, J. Am. Chem. Soc. 95 (1973) 1633–1640.
[225] P.-C. Kong, T. Theophanides, Inorg. Chem. 13 (1974) 1981–1985.
[226] M.C. Lim, R.B. Martin, J. Inorg. Nucl. Chem. 38 (1976) 1915–1918.
[227] K. Inagaki, Y. Kidani, Inorg. Chim. Acta 80 (1983) 171–176.
[228] C. Meiser, B. Song, E. Freisinger, M. Peilert, H. Sigel, B. Lippert, Chem. Eur. J. 3 (1997) 388–398.
[229] S. Jaworski, S. Menzer, B. Lippert, M. Sabat, Inorg. Chim. Acta 205 (1983) 31–34.
[230] F.M. Albertí, T. Mihály, B. Lippert, P.J. Sanz Miguel, CrystEngComm 14 (2012) 6178–6181.
[231] T. Mihály, M. Garijo Añorbe, F.M. Albertí, P.J. Sanz Miguel, B. Lippert, Inorg. Chem. 51 (2012) 10437–10446.
[232] M. Garijo Añorbe, T. Welzel, B. Lippert, Inorg. Chem. 46 (2007) 8222–8227.
[233] G. Frommer, I. Mutikainen, F.J. Pesch, E.C. Hillgeris, H. Preut, B. Lippert, Inorg. Chem. 31 (1992) 2429–2434.
[234] J.L. Van der Veer, H. van den Elst, J. Reedijk, Inorg. Chem. 26 (1987) 1536–1540.
[235] G. Frommer, H. Schöllhorn, U. Thewalt, B. Lippert, Inorg. Chem. 29 (1990) 1417–1422.
[236] G. Raudaschl-Sieber, H. Schöllhorn, U. Thewalt, B. Lippert, J. Am. Chem. Soc. 107 (1985) 3591–3595.
[237] B. Knobloch, R.K.O. Sigel, B. Lippert, H. Sigel, Angew. Chem. Int. Ed. 43 (2004) 3793–3795.
[238] S. Ibáñez, F.M. Albertí, P.J. Sanz Miguel, B. Lippert, Chem. Eur. J. 17 (2011) 8283–9287.