Comparing Pt^{II}- and Pd^{II}-nucleobase coordination chemistry: Why Pd^{II} not always is a good substitute for Pt^{II}

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Abstract

As is well established, numerous similarities exist as far as reactivity patterns and structural features of the d^8 metal ions M = Pd^{2+} and Pt^{2+} are concerned. Here reactions of metal complexes of type *cis*-$[M(a)_2X_2]$ (a = NH_3 or $(a)_2$ = diamine or diimine; X = monodentate or X_2 = bidentate leaving groups) with nucleobases, the constituents of nucleic acids, are discussed and differences regarding intrinsic stability of the starting compounds, kinetics of formation of products, thermodynamics of products, as well as donor site selectivity are pointed out. It is concluded that Pd^{II} complexes representing strict or close analogues of established antitumor Pt^{II} drugs of the Cisplatin-type, if active under *in-vivo* conditions at all, are unlikely to have a similar mode of action as their Pt^{II} congeners. Relationships to supramolecular constructs containing *cis*-$[M(a)_2]^{2+}$ entities are likewise discussed.

1. Introduction

It is widely accepted among inorganic chemists that the d^8 metal ion Pd^{2+} and its congener Pt^{2+} display similar reaction patterns, in particular if the ligands are identical or closely similar. After all, the two metal ions have practically identical size, usually adopt square-planar coordination geometries, are considered essentially of "soft" nature, but nevertheless have a pronounced affinity for N-donor ligands [1]. Differences in redox chemical behavior of the two metal ions exist, but are probably irrelevant for their biological chemistry. A, or possibly even *the* major difference refers to reactivity: Pd^{II} is estimated to undergo ligand substitution reactions 10^4–10^5 times more rapidly than Pt^{II} [2], a

consequence of the lower electron density of Pd^{2+} (44 vs. 76 electrons) and the reduced repulsion in the 5-coordinate transition state. Among simple coordination complexes with a large variety of ligands, e.g. ammonia or amines, halides, or phosphanes, there are indeed numerous isostructural representatives known. It consequently cannot be a surprise that soon after the discovery of the antitumor activity of *cis*-$Pt(NH_3)_2Cl_2$ (Cisplatin) and several related Pt^{II} compounds, the search for active Pd^{II} analogues took off. Although isostructural Pd analogues of clinically applied Pt drugs have been synthesized [3] and tested [4], and despite numerous reports on cytotoxic effects of Pd^{II} complexes in general [5], there is presently no Pd-containing drug clinically approved, in contrast to half a dozen of Pt^{II} compounds as well as several more in clinical trials.

This commentary tries to provide a rationale for this situation by comparing fundamental properties of these two metal ions and their compounds, respectively, and in particular by comparing their reactivity against nucleic acid constituents. One certainly cannot exclude the possibility that someday a Pd^{II} compound may be routinely used in the treatment of cancer. However, it appears unlikely that such a compound will act in a way strictly identical with that of its Pt^{II} analogue, as had been assumed in the early days. At present there is strong evidence that the mode of action of antitumor Pt^{II} complexes of the Cisplatin type ultimately involves specific adduct formation with DNA nucleobases [6]. For non-classical antitumor Pt drugs, different scenarios are feasible [7,8].

Here we shall concentrate on Cisplatin and Cisplatin-like compounds and their Pd analogues in particular with regard to their reactions with nucleic acid constituents and their models, respectively. If appropriate, we will also consider their trans-isomers.

2. Discussion

2.1. Similarities and differences between PtII and PdII analogues

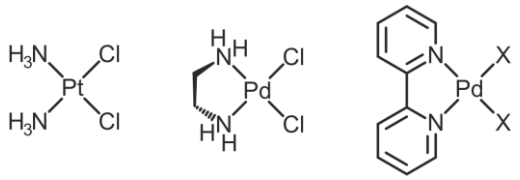
The generally used methods to synthesize *cis*-$Pt(NH_3)_2Cl_2$ or $Pt(en)Cl_2$ is by treatment of $[PtX_4]^{2-}$ (X = Cl or I) with NH_3 and en, respectively, and, in case of X = I, subsequent replacement of iodide by chloride [9]. *Trans*-$Pt(NH_3)_2Cl_2$ is prepared by heating an aqueous solution of $[Pt(NH_3)_4]Cl_2$ with HCl [10]. *Cis*-$Pd(NH_3)_2Cl_2$, on the other hand, is obtained by allowing a $HClO_4$-acidic solution of $[Pd(NH_3)_4](ClO_4)_2$ to stand at room temperature, and subsequent addition of a concentrated solution of NaCl [11]. Warming has to be avoided in the latter case, as it causes rapid isomerization. *Trans*-$Pd(NH_3)_2Cl_2$ is precipitated from a cold aqueous solution of $[Pd(NH_3)_4]Cl_2$ treated with portions of 6N HCl [12].

A careful ^{15}N NMR study employing ^{15}N enriched ammonia ligands, conducted by T. G. Appleton et al. [13], demonstrated that the Pd-ammonia system in fact is quite complex, in that not only reverse isomerization reactions, hence from trans- to cis-isomer, but additionally time-dependent disproportionation reactions to mono- and triammine species take place in solution. Even free NH_4^+ is being formed.

As far as structural aspects of cis- and trans-isomers of the diamminedichlorido species of the two metals are concerned, they expectedly do not reveal any significant differences in metal-ligand bond lengths and angles in their square-planar coordination spheres [14–16].

Given the lability of the ammonia ligands of *cis*-$Pd(NH_3)_2Cl_2$ in solution, it becomes immediately evident that any strict comparison with the antitumor agent Cisplatin regarding reactions with biomolecules is obsolete. Moreover, a facile trans-cis isomerization of $Pd(NH_3)_2$ entities in a model nucleobase complex has been reported [17]. The reversibility of Pd-ligand bond formation has been recognized early on, and consequently Pd^{II}(diamine or diimine)-type complexes rather than *cis*-

$Pd(NH_3)_2X_2$ compounds (X = monodentate or X_2 = bidentate leaving groups) have become the compounds of choice, assuming that a chelating diamine/diimine ligand would provide sufficient kinetic stability to the compound to make a comparison with Cisplatin more meaningful (Scheme 1). Even this assumption must, however, be challenged in view of more recent findings in model nucleobase complexes, which revealed occasional loss of chelated ethylenediamine (en) ligands from Pd^{II}, possibly as a consequence of a ligand disproportionation reaction of the kind 2 Pd(en)XY ⇋ $[Pd(en)_2]^{2+}$ + $[Pd(XY)_2]^{2-}$, or even a complete dissociation of a Pd^{II}(en) entity from an initial adduct (for details see 2.7.). It certainly is less of a surprise that the thioether function of methionine can lead to a release of ethylenediamine from a Pd^{II}(en) moiety [18].



Scheme 1. Cisplatin (left), $Pd(en)Cl_2$ (middle), and Pd(2,2'-bpy)X_2 (right).

In contrast, Pt^{II}-ligand bonds are considerably more robust from a *kinetic* point of view. Nevertheless it must *not* be assumed that ligands of *cis*- or *trans*-$Pt(a)_2X_2$ (a = NH_3 or other amine; X = Cl or other ligand) are *always* inert to substitution. While it is not surprising that ligands with a strong trans-labilizing effect (e.g. cyanide, thiourea [e.g. in the Kurnakov test for differentiation of cis and trans isomer], sulfur containing amino acids and proteins [19–23], etc.) are capable of displacing ammonia/amine ligands, it is more surprising that occasionally, and under mild conditions, even chloride can substitute an ammonia ligand from a *cis*-$Pt^{II}(NH_3)_2$ entity [24]. Finally, the conversion of Pt–NH_3 groups into Pt(μ-NH_2)M (M = Pd or Pt) [25] seems to question the long-standing dogma concerning the innocence of the NH_3 ligands in Cisplatin. While cases of cis-trans or reverse isomerization reactions seem not to be realized in reactions of Pt^{II} compounds with nucleobases, it needs to be mentioned that there are a number of instances where a nucleobase initially bonded via a N donor to either a *cis*- or a *trans*-$Pt(NH_3)_2$ unit in a nucleic acid strand is displaced by another nucleobase, hence that the $Pt^{II}(NH_3)_2$ units undergo migration or linkage isomerization, sometimes "violating" expectations regarding relative Pt–N(nucleobase) donor strengths. For example, when a Pt–(G-*N7*) bond in DNA is changed into a Pt–(C-*N3*) bond (see 2.2.), this is unexpected with regard to complex stability (see 2.3.), yet tells that forces executed by the DNA macromolecule can overcome simple metal-donor atom bond strength arguments.

$Pt(en)Cl_2$ reacts closely similar to Cisplatin with nucleobases, avoiding loss of the coordinated chelate ligand, however. Reactions, in which the ethylenediamine ligand is bonded in a monodentate fashion are presently unknown for complexes with nucleobases. With $[Pt(dien)Cl]^+$ (dien = diethylentriamine) ring-opening of the chelating dien ligand has been observed in the presence of L-methionine, albeit not with a nucleobase [26].

There are close similarities between the complexes *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$, $[Pt(en)(OH_2)_2]^{2+}$, and $[Pd(en)(OH_2)_2]^{2+}$, in terms of pK_a values of the aqua ligands (pK_{a1} ≈ 5.7; pK_{a2} ≈ 7.5) and their propensity to form hydroxido-bridged condensation products, either open or cyclic μ-OH complexes. Their existence has been proven both in solution [18,27–29] and in the solid state [30,31]. If not taken into consideration, solution studies lead to thermodynamic equilibrium constants of Pt^{II} complexes with biomolecules as ligands which are much too low, simply because hydroxido ligands, unlike aqua

ligands, are poor leaving groups [32]. Moreover, rates of complexation of other ligands, e.g. of nucleobases, are strongly retarded, at least by Pt–OH groups [33], but at the same time these groups can function as bases in the deprotonation of ligands, e.g. of weakly acidic N-H functionalities in nucleobases, thereby generating labile aqua ligands [30]. We explicitly mention this fact here because OH^- bridge formation is occasionally retained in di- and multinuclear adducts with nucleobases (see also 2.7.) [18,25,34–36].

2.2. Types of DNA adducts

Early studies, in particular by A. M. J. Fichtinger-Schepman, J. Reedijk [37], and A. Eastman [38], have provided a rather detailed picture of the major DNA adducts of the antitumor agents Cisplatin and $Pt(en)Cl_2$, respectively. These are initially d(G) mono-adducts, subsequently followed by formation of bis-adducts, namely the intrastrand d(GpG), d(ApG), and d(GpNpG) lesions as well as interstrand d(G)-d(G) and d(G)-protein cross-links (G = guanine, A = adenine, N = any nucleobase). These established adducts account for approximately 90% of the bound Pt, with N7 of G and A being the binding sites. The remaining minor adducts are as yet unknown, but can be expected to present other combinations (nucleobase; binding site) than the mentioned major adducts.

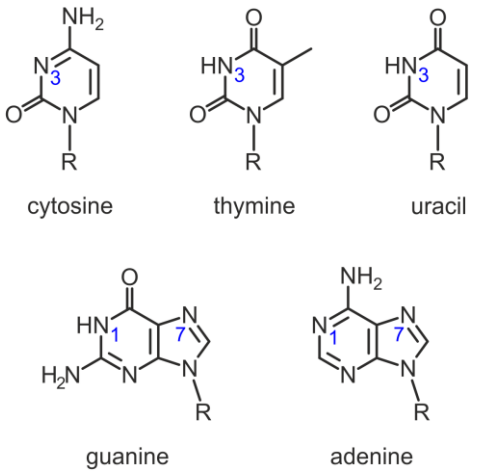
With the inactive *trans*-$Pt(NH_3)_2Cl_2$ the DNA adduct spectrum is different [39]. Adduct formation is markedly affected by the appearance of DNA (single- *or* double-stranded) and linkage isomerization reactions, e.g. of an intrastrand d(GpNpG) adduct to either an intrastrand d(C)-d(G) 1,4 adduct (with C = cytosine) [40], an interstrand d(G)-d(C) [41], or an interstrand d(G)-d(A-*N1*) adduct [42], are not uncommon, as has been observed by 2D-NMR spectroscopy, among others.

There exist numerous DNA binding studies of Pd^{II} compounds [4], yet in most cases they concentrate on gross changes of DNA properties such as circular dichroism, UV absorption spectra, electrophoretic mobility, or shape [43,44]. Quantitative data on adduct distributions are presently not available, unlike in the case of Cisplatin or $Pt(en)Cl_2$ (see above). Intercalative DNA binding modes of Pd complexes with π-acidic chelate ligands (e.g. 2,2'-bpy, *o*-phen, cyclometalated ligands) appear to be frequent, but in compounds containing at the same time more weakly bonded ligands (e.g. chloride), coordinative binding to nucleobase-*N* sites should be possible in principle, even though this mode has been established primarily in model chemistry, yet not clearly for DNA.

2.3. Stability of Pd nucleobase complexes (1:1-stoichiometry)

Work carried out in particular by the groups of R. B. Martin and I. Sóvágó has provided a rather comprehensive picture on the thermodynamic stabilities of 1:1-Pd-nucleobase complexes. In the majority of cases stability constants were determined for compounds containing a chelating tridentate co-ligand such as dien [45,46], pmdien (pmdien = 1,1,4,7,7-pentamethyldiethylenetriamine) [47], trpy (trpy = 2,2':6'',2''-terpyridine) [48], 2,6-disubstituted pyridines [49], dipeptides [50,51], or a mixed PtPd compound containing a Pt–Pd dative bond [52]. Despite differences in detail in dependence of the nature of these co-ligands (sterics, electronics) as well as the nucleobases (model nucleobase, nucleoside, nucleotide), the overall picture is similar in that the stability order is T-*N3* > U-*N3* > G-*N1* > G-*N7* > C-*N3* > A-*N1* > A-*N7*, with T-*N3* = thymine anion metalated at N3, U-*N3* = uracil anion metalated at N3, G-*N1* = guanine anion metalated at N1, G-*N7* = neutral guanine metalated at N7, C-*N3* = neutral cytosine metalated at N3, A-*N1* = neutral adenine metalated at N1, and A-*N7* = neutral adenine metalated at N7 (Scheme 2). For $[Pd(dien)(OH_2)]^{2+}$ log*K* values range from *ca*. 9.0–8.5 for thymine and uracil nucleobases to *ca*. 4 for adenine-*N7* [53]. If $[Pd(dien)Cl]^+$ is applied, or in the presence of chloride

in general, log*K* values are lower due to competition between chloride and the respective nucleobase [46]. If compared with stability constants of first row transition metal ions, e.g. Cu^{2+} [54] it is immediately evident that any Pd^{II} species binds much more strongly to nucleobases.



Scheme 2. Representation of common nucleobases and their most important donor atoms.

With regard to the relevance of these values for biological systems, it needs to be taken into account that at physiological pH (ca. 7.4) there is competition between metal binding to a nucleobase and protonation of the nucleobase. This is done by converting *stability constants* K^{M}_{ML} into *stability values* X^{M}_{ML} (or *conditional stability constants*) which are valid for a particular pH, e.g. the physiological pH =7.4, and which consider pK_a values of the ligands as well [55]. Thus, at physiological pH the order of preference of Pd^{II}(dien) for the common nucleobases is somewhat different, giving G-*N7* > U-*N3,* T-*N3*, G-*N1* > C-*N3* > A-*N1* > A-*N7* [53]. Moreover, the spreading of *stability values* is slightly smaller as compared to the mentioned *stability constants* (see above), less than 4 log units for the common nucleosides. In other words, at physiological pH G-*N7* is the preferred binding site of Pd^{II}(dien), and there is a "cross-over" in preference of nucleobase coordination site at the guanine base from G-*N1* (see above) to G-*N7* [53]. It needs to be stressed that the mentioned sequence strictly applies to systems containing the *isolated* nucleobases (alone or in a mixture) and a monofunctional Pd^{II} species, and possibly also to single-stranded DNA, yet *not* necessarily to double-stranded DNA due to its structure-related limitations of donor site availabilities and probably also due to sequence-dependent electronic effects [56].

It is quite obvious that the basicity of a nucleobase N atom, hence its affinity for the proton, does *not* reflect the preference of Pd^{II} for this site. Otherwise C-*N3* and A-*N1* (pK_a values in the order of 4) should outrun G-*N7*, which has a pK_a of ca. 2 only. However, it is long known that exocyclic amino groups (N4 in case of C, N6 in case of A), for steric reasons, retard metal binding to neighboring N donor atoms [45,57].

There are additional factors which complicate the analysis of solution equilibria, namely the possibility to also form 2:1- or even 3:1-complexes (metal : nucleobase), namely if additional metal binding occurs at exocyclic amino groups (with displacement of protons) or multiple coordination (N1,N3,N7) to purine sites, or exocyclic O groups in U and T. For example, deprotonation of $N4H_2$ of cytosine and Pd coordination to this site starts even at acidic pH, hence more than 10 pH units below the pK_a of this group in the free nucleobase. Intramolecular Pd migration to another site is a further

possibility, such as reported for cytidine upon addition of OH^-, from N3 to N4 [58]. Moreover, formation of multinuclear complexes containing hydroxido bridges in addition to nucleobases is possible (see 2.7.). In model compounds numerous examples for such binding patterns exist. Although formed in particular with an excess of metal over nucleobase present, at least the possibility of 2:1-complex formation must not be excluded even in nucleic acid structures.

For simple systems, e.g. systems allowing for 1:1 complex formation of Pd^{II} with a nucleobase or a competing second ligand, it is possible to calculate speciation plots at given absolute and relative concentrations of the metal and the nucleobases, because thermodynamic equilibrium is reached very quickly.

It is obvious that for metal entities with the ability to bind two nucleobases things become considerably more complicated (1:1 and 1:2 complexes; possibility for mixed nucleobase complexes; linkage isomers; multinuclear complexes with bridging nucleobases; μ-OH^- bridging), and this applies even more so to nucleic acids, where potential donor sites in DNA or RNA may be sterically inaccessible.

2.4. Stability of PtII nucleobase complexes

Unfortunately, analogous experiments regarding the determination of stability constants of Pt^{II} nucleobase complexes cannot easily be carried out because of the slowness by which thermodynamic equilibrium is reached. While with Pd^{II} equilibrium is reached in the order of seconds or less, in the case of Pt^{II} it takes hours or even days. Thus, this feature is a major difference between Pd^{II} and Pt^{II} species. However, it has been estimated that Pt^{II} species are more stable than their Pd^{II} analogues at least by a factor of 10 [27], as later confirmed for Pt complexes of thymidine and uridine [59,60]. This feature is possibly a consequence of the higher significance of π-bonding effects in the case of Pt^{II} as compared to Pd^{II} [61].

Returning to the DNA adducts of *cis*- and *trans*-$Pt^{II}(NH_3)_2$ (see 2.2.), it is evident that (at physiological pH) not only binding to the thermodynamically favored G-*N7* sites takes place, but that in addition thermodynamically inferior sites such as C-*N3*, A-*N1*, or A-*N7* can be involved in Pt coordination. In other words, the availability of suitable donor atoms, combined with the inertness of the Pt–nucleobase bond formed determines the adduct spectrum, rather than thermodynamical considerations based on complexes of isolated nucleobases. Thus, formation of the second most abundant Cisplatin intrastrand cross-link to d(ApG) involving the N7 sites of the two nucleobases is to be rationalized on steric arguments (initial coordination of Pt^{II} to 3'-G-*N7*; closeness of A-*N7* at 5'-side for chelate closure [62]) rather than on the basis of the donor strength of the adenine. In fact, A-*N7* is the poorest N-donor atom of the common nucleobases (see 2.3.)! This tendency of Pt^{II} not to select its binding sites exclusively on thermodynamic grounds, appears to be further facilitated by the influence of the DNA macromolecule as a whole, which exerts forces on the Pt-nucleobase bonds. The numerous Pt^{II} linkage isomerization processes of *trans*-$Pt^{II}(NH_3)_2$ seen in model studies, which lead to rupture of an initially formed bond to a G-*N7* site, provide ample evidence for this view, as does the structural distortion of the Pt coordination sphere in the intrastrand *cis*-$Pt^{II}(NH_3)_2G_2$ adduct of a DNA dodecamer [63].

The question remains why, despite their obvious stability (see 2.3.), Pt-thymine adducts in DNA are not among the major ones of Cisplatin, or occurring only under special conditions (e.g. AT-rich sequences [64]) and in model systems [65]. Clearly, in duplex-DNA involvement of T-*N3H* in base pairing with A-*N1* restricts the availability of this site. However, the main reason seems to be the slow kinetics of thymine deprotonation and Pt–N bond formation. Even in model compounds with isolated

T (or U) bases, where complementary base pairing is absent, this reaction (at pH 7–8) is slow and requires heating to become reasonably fast. Only a P donor atom trans to a chlorido ligand accelerates coordination of Pt^{II} to T-*N3* substantially [66]. This is in contrast to the situation with similar Pd^{II} species, where rapid complexation sets on at room temperature even at pH 2, with virtual complete reaction in the range pH 6–10 [67]. Pt^{II}–thyminate bonds, and likewise the analogous Pt^{II}–uracilate bonds are remarkably resistant toward the strong nucleophile CN^-, probably due to steric shielding of the metal center by the two adjacent exocyclic oxygen atoms *O2* and *O4* [68]. This observation has led us to propose that thymine adducts are possibly among the as yet unidentified minor DNA adducts of Cisplatin, given the fact that excess CN^- appears to be unable to fully remove Pt from platinated DNA.

There is yet another remarkable structural difference between coordination of thymine to Pt^{II} and Pd^{II} to be mentioned, which refers to involvement of N3 and O4 of thyminate in metal coordination. While there is a plethora of examples of Pt^{II} and Pd^{II} binding to these two sides in a *bridging* fashion, for Pd^{II} there are also two rare cases of X-ray structurally characterized examples with 1-methylthyminate acting as a *chelating* ligand [69].

2.5. Bis(nucleobase) complexes

For Pd^{II}(en), which can form 1:1 and 1:2 nucleobase complexes, available stability constants are considerably fewer than for monofunctional Pd^{II} species. Thus, the stability constants $\log\beta_2$ for $[Pd(en)(L)_2]$ complexes with L = uracil or thymine derivative are in the order of 14.8 , while that for L = 1-methylcytosine is 11.4 only [18]. $\log\beta_1$ values for the 1:1-species are around 9 and 6 for U and C nucleobases, respectively, and thus similar to values for the corresponding Pd^{II}(dien) complexes (*cf.* 2.3.). It can be assumed that stability constants for related bifunctional metal species such as Pd^{II}(bpy) (bpy = 2,2'-bipyridine) or Pd^{II}(picam) (picam = 2-picolylamine), Pd^{II}(tmeda) (tmeda = *N,N,N',N'*-tetramethylethylenediamine) display similar values, subject to slight variations in dependence of electronic and steric properties of these co-ligands. In an excellent piece of work, U. K. Häring and R. B. Martin have studied the solution speciation of Pd^{II}(en) with uridine and cytidine, respectively, and have identified a considerable number of mono- and dinuclear species present in dilute aqueous solutions and determined their distribution over a wide pH range [34]. Dinuclear species include both μ-OH^- (uridine, cytidine) and anionic μ-nucleobase complexes (cytidine). It is somewhat surprising that in the uridine system no dinuclear species with uridinato bridges (*head-head* or *head-tail*) were identified in solution, even though such compounds have been numerously isolated with 1-methyluracil and 1-methylthymine model nucleobase [65,70]. As to mixed cytidine,uridine complexes of Pd^{II}(en), also studied by these authors, see discussion below (see 2.6.).

2.6. Structures of model nucleobase adducts

There exists a large number of X-ray crystal structures and/or sophisticated NMR structures on cross-links of *cis*- and *trans*-$Pt^{II}(NH_3)_2$ or analogous Pt entities with model nucleobases, nucleosides, nucleotides, and oligonucleotides, including duplex DNA [65,71–74]. These include, among others, identical as well as different nucleobases, represent models of the known major adducts (e.g. *cis*-Pta_2GG, *cis*-Pta_2AG, *trans*-Pta_2GG, *trans*-Pta_2GC), and all kinds of feasible minor adducts (e.g. *cis*-Pta_2GC, *cis*-Pta_2AC, *trans*-Pta_2AC), *trans*-Pta_2AG [42]. Given this multitude of available data, the scarcity of relevant structural studies on analogous 1:2-Pd^{II} complexes is very surprising indeed. The Cambridge Crystallographic Data Centre (as of February 21, 2017) lists a mere four relevant structures, namely *trans*-$[Pd(NH_3)_2(1MeC\text{-}N3)_2]^{2+}$ (1MeC = 1-methylcytosine) [17], as well as three examples of *cis*-

[Pd(en)L_2] compounds (with L = guanosine-5'-monophosphate [3], inosine-5-monophosphate [75], unsubstituted cytosine [76]). There is no single case of an X-ray crystal structure of either a Pd^{II}(en) or a *trans*-$Pd^{II}(NH_3)_2$ complex available which contains two different common nucleobases. The only exception is a complex containing two differently substituted purine ligands in mutual trans-position, 8-(methylthio)theophyllinate (*N7* coordination) and theophyllinate (*C8* binding), the formation of which involves a combination of symmetrization of the original 1:1-complex and partial loss of the methylthio substituent [77]. Surprisingly, attempts to obtain a mixed 8-(methylthio)theophyllinate/adenine complex failed, leading again to the product with 8-(methylthio)theophyllinate and theophyllinate ligands.

It is to be assumed that the lack of isolated and structurally characterized mixed-nucleobase complexes of Pd^{II} is primarily due to the difficulty of preparing them in a stepwise manner, as is the usual procedure with the kinetically (more) robust Pt analogues. Virtually all mixed model nucleobase complexes of Pt^{II}, very much like cross-links with DNA studied by NMR techniques, were obtained in a sequential manner, with fixation of one nucleobase in a precursor complex, *cis*- or *trans*-$Pt(NH_3)_2L_1X$ (L_1 = first nucleobase or DNA single strand; X = Cl^- or OH_2), followed by reaction with the second (different) nucleobase L_2 or the complementary DNA strand. It is possible that the presence of chloride, hence X = Cl^- in the analogous Pd^{II} precursor compound, needs to be avoided in order not to labilize the ligand in trans position. Even with *cis*- and *trans*-[$Pt(NH_3)_2$(1MeC-*N3*)Cl]$^+$ has partial release of NH_3 and 1MeC ligands, respectively, been observed [24,78,79]. This may suggest that similar reactions are facilitated in the case of Pd^{II}, given the kinetic lability of its bonds to ligands. In analogy to our observation with *trans*-[$Pt(NH_3)_2$(1MeC-*N3*)Cl]$^+$ [79], an even more facile symmetrization according to *trans*-[$Pd(NH_3)_2$(1MeC-*N3*)Cl]$^+$ ⇋ 0.5 *trans*-[$Pd(NH_3)_2$(1MeC-*N3*)$_2$]$^{2+}$ + 0.5 *trans*-[$Pd(NH_3)_2Cl_2$] could be envisaged.

As briefly mentioned above, formation of the quaternary complex [Pd(en)(cytidine-*N3*)(uridinate-*N3*)]$^+$ has been observed in water [34]. Its formation in a 1:1:1-mixture of the diaqua complex [Pd(en)$(D_2O)_2$]$^{2+}$, cytidine, and uridine (50 m*M* each) is remarkable in that its degree of formation exceeds the statistically expected one in comparison to the bis(cytidine) and bis(uridine) species, with the latter expected to have the highest logβ_2 value. The authors have attributed this feature to a "resistance of Pd to bind a second ionic uridine ligand" [34]. Unfortunately more comprehensive solution or computational studies regarding the existence of mixed nucleobase complexes of Pd^{II} are presently missing, and the understanding of the interplay of donor basicity and steric effects introduced by both the nucleobase groups adjacent to the donor site and the co-ligands at the metal is anything but straightforward.

It is interesting to note that in a related system with N-heterocyclic ligands, namely a 1:1:1- mixture of 2,6-dimethylpyridine (2,6-Dimepy), unsubstituted pyridine (py), and Pd^{II}(en)$(NO_3)_2$ in water, a highly (>80 %) preferential formation of the mixed complex, hence [Pd(en)(2,6-Dimepy)(py)]$^{2+}$, is observed [80]. Due to unfavorable steric interactions between the exocyclic methyl groups, formation of the homoleptic [Pd(en)(2,6-Dimepy)$_2$]$^{2+}$ is avoided, but the higher basicity of 2,6-Dimepy (pK_a = 6.75) as compared to py (pK_a = 5.2) favors binding of at least one 2,6-Dimepy ligand. Similar arguments can be applied also to mixtures of 4,4'-bpy and 2,2',6,6'-tetramethyl-4,4'-bpy ligands and their association to molecular squares in the presence of Pd^{II}(en) [80]. By utilizing linear ligands with two different "pyridine ends" of different basicities and different steric constraints, this strategy has also been used to prepare molecular squares of *cis*-$Pt^{II}(PMe_3)_2$ in an absolute self-organization process [81]. A neat transfer of these findings to the nucleobase coordination chemistry of Pd^{II}(en) is not possible, however, as the nature of exocyclic nucleobase groups (NH_2; keto-O) is quite different from methyl groups with

regard to the possibility of internucleobase hydrogen bonding or hydrogen bond formation between the ethylenediamine co-ligand and nucleobase-carbonyl groups.

2.7. Mixed Pt,Pd nucleobase complexes

We have, for different reasons, numerously utilized stepwise binding of both Pt^{II} *and* Pd^{II} entities to nucleobases, varying at the same time also the am(m)ine ligands at the metals (NH_3, en, tmeda, 2,2'-bpy, dien, trpy) [25,82–88]. In no case was displacement of the originally bonded Pt^{II} by Pd^{II} observed, not even when Pt^{II} was bonded to a thermodynamically less favored site. Rather, Pt–N(nucleobase) bonds are "ignored" by Pd^{II}, and Pd^{II} coordinates to other donor sites available. For example, when Pt-(adenine-*N7*) complexes are reacted with Pd^{II} electrophiles, the latter bind primarily to N1 (and eventually also to the deprotonated N6 site) [83,86]. Reactions in which Pd^{II} bonded to a nucleobase is replaced by Pt^{II} seem to be possible, given the higher thermodynamic stability of the Pt^{II} nucleobase bond. However such reactions appear not to have been carried out to date.

Without going into more detail here, and ignoring subtle differences as a consequence of changing the metal and the co-ligand, we wish to point out that the X-ray crystal structures of some of these mixed-metal complexes can be considered good models of complexes of Pd^{II}(en) with pyrimidine nucleobases as reported by Häring and Martin [34]. For example, an analogue of the elusive dinuclear complex [(en)Pd(μ-OH)(μ-cytidinate-*N3,N4*)Pd(en)]$^{2+}$ has recently been crystallized by us, the difference being that the N3-bonded metal entity is not Pd^{II}(en) but rather Pt(2,2'-bpy) [25]. In the solid state the proposed coplanar arrangement of the cytosine ring, the OH^- bridge, and the two metals is not quite realized, but DFT calculations are suggestive of a planar structure in the presence of water molecules, as originally proposed by Häring and Martin as explanation for the achirality of [(en)Pd(μ-OH)(μ-cytidinate-*N3,N4*)Pd(en)]$^{2+}$. Our preparative work has, moreover, revealed that additional products can be formed when reacting [Pt(2,2'-bpy)(1MeC-*N3*)(H_2O)]$^{2+}$ with Pd^{II}(2,2'-bpy), such as a complex of Pt_2Pd stoichiometry containing two hydroxido bridges, in which Pd^{II}(en) has lost its ethylenediamine ligand, or a $PtPd_2$ complex, in which a dinuclear [(2,2'-bpy)Pd(μ-OH)Pd(2,2'-bpy)]$^{3+}$ unit is inserted between the Pt–OH group and N4 of the anionic 1MeC ligand, instead of a single Pd unit as in [(en)Pd(μ-OH)(μ-cytidinate-*N3,N4*)Pd(en)]$^{2+}$ [25]. Admittedly, π-stacking interactions between the 2,2'-bpy co-ligands support realization of this metallomacrocycle. Also, a mixed Pt,Pd analogue of the *head-head* dinuclear complex [(en)Pd(cytidinate-*N3,N4*)$_2$Pd(en)]$^{2+}$ assigned by Häring and Martin has eventually been crystallized in form of [(2,2'-bpy)Pt(1MeC$_{-H}$-*N3,N4*)$_2$Pd(en)]$^{2+}$ (1MeC$_{-H}$ = anion of 1MeC) [85]. X-ray crystal structures of all other complexes seen in the solution work with Pd^{II}(en) (1:1, 1:2, and *head-tail* 2:2 complexes) have previously been reported in form of their *cis*-$Pt^{II}a_2$ analogues. Certainly the most unexpected feature involving a Pd^{II}(tmeda) entity and a nucleobase has been observed by us in the reaction of a discrete tetranuclear $PtPdAg_2$ complex containing a bridging 1MeC$_{-H}$ anion, which converted into a Pt_2Ag helical coordination polymer with complete release of Pd^{II}(tmeda) [36]. In essence, in this sequence of steps Pd^{II} functions as a catalyst for the formation of the head-tail dimer *cis*-[{Pt(NH_3)$_2$(1MeC$_{-H}$-*N3,N4*)}$_2$]$^{2+}$ from monomeric *cis*-[Pt(NH_3)$_2$(1MeC-*N3*)(OH_2)]$^{2+}$, with the dinuclear units further joined by Ag^+ ions.

In an interesting study, the reaction behavior of dinuclear mixed Pt,Pd complexes of composition [(L)PdCl(μ-pyrazine)PtCl(L)]$^{2+}$ (with L = en or 2,2'-bpy) toward selected nucleophiles (among others 5'-GMP) and DNA has been reported [89]. It was found that with 5'-GMP reaction occurs in two steps, with the chlorido ligand at Pd^{II} substituted first, as expected, followed by chloride displacement at the Pt^{II} center. The second-order rate constants for the two processes differ by a factor of approximately 10^4 in the Pt,Pd compound with L = en. The interaction of Pt,Pd with calf-thymus DNA is less clear, but

appears to be also associated with displacement of ethidium bromide, thus suggesting intercalation as one (initial?) mode of DNA binding.

2.8. Cyclic supramolecular complexes derived from PdII(en) and cis-PtII(a)2

Although most likely not of any relevance to biological systems, the widespread use of Pd^{II}(en) for the generation of supramolecular constructs in self-assembly processes with a variety of ligands, but frequently with N-heterocycles, needs to be mentioned here [90]. Apart from the 90°-angle provided by the metal entity, it is the fast kinetics and the reversibility of the newly formed Pd-ligand bonds, which facilitates "self-healing" processes in incorrectly assembled products, which make this metal entity so useful in generating supramolecular entities. In a superficial way, such processes may be considered analogous to metal migration steps of initially formed *kinetic* products of Pd^{II} species with biomolecules and their rapid conversion to the *thermodynamic* products.

Analogous *cis*-$Pt^{II}(a)_2$ (a = NH_3 or a_2 = diamine) entities usually display similar abilities to form cyclic constructs, albeit examples are less frequent [91,92], unless *cis*-$Pt^{II}(PR_3)_2$ type metal entities are utilized which, as a consequence of the trans-effect of the phosphorous donor atoms, behave more "Pd^{II}(en)-like" [93]. Cross-catenation experiments carried out with Pt^{II} and Pd^{II} containing rings with pyridine (py) donor groups confirm that it is a kinetically labile Pd^{II}-py bond that opens up and allows threading into the more inert Pt^{II} containing ring [94]. Again, Pt-py bonds can likewise be cleaved, but it requires more stringent conditions such as heating to 100 °C in a highly polar aqueous medium (1-5 M $NaNO_3$) [95] or UV irradiation [96].

As to cyclic nucleobase complexes of Pd^{II}(en) (or Pd complexes with other diamine or diimine chelating ligands) and analogous *cis*-$Pt^{II}X_2$ (X = N or P donor) units, there appears to be a high degree of structural similarity for the two metals when it comes to dinuclear (*head-tail* or *head-head*) T-, U-, and C-pyrimidine nucleobase complexes [17,65,97-99], trinuclear cytosinate complexes [100-102], or larger aggregates [103]. Chelate-tethered modifications of purine nucleobase [104] or the combined use of Pt^{II} and Pd^{II} lead to further variations in 2- and 3-D shape [76,82,87,88,105]. As numerously demonstrated by us, it is of advantage to initially bind Pt^{II} to a nucleobase before reacting this kinetically robust adduct with Pd^{II}.

2.9. Competition reactions

With regard to any relevant interactions of Pd^{II}(en) or $Pt^{II}(NH_3)_2$ with biomolecules, not only those with nucleic acids but (at least) also with proteins and amino acids must be taken into account, in that such products could have profound consequences with regard to toxicity, detoxification, development of drug resistance, or even as drug reservoirs. In particular sulfur containing amino acids (methionine, cysteine), peptides (glutathione) and proteins (e.g. metallothionine) have to be considered [21,106,107]. Interestingly, and certainly in contrast to intuitive expectations based on the HSAB concept (*H*ard and *S*oft *A*cids and *B*ases), the initially formed bonds between Pt^{II} and the thioether group of methionine can, in slow reactions, been displaced by N7 of guanine bases, and even by N atoms of the imidazole group of histidine containing peptides [108]. A, T, and C nucleobases appear not to accomplish similar reactions with Pt^{II}, at least not in any reasonably "short" reaction time (in order of days), and Pt-thiolate bonds are not substituted by G-*N7*. As demonstrated by Sóvágó and co-workers [67], a thioether bond to Pd^{II}(dien) is spontaneously substituted by N3 of uridine at physiological pH. With other tridentate chelating ligands (methionine containing dipeptide; trpy) at the Pd^{II}, the S-bound species is virtually negligible at pH 7, hence binding to uridine is by far dominant.

The authors also carried out a detailed kinetic study employing Pd^{II}(dien), N-acetylmethionine (AcMet), and cytidine in a 1:2:2-ratio. It revealed very fast (ca. 100 ms) formation of the AcMet complex, and slower (ca. 500 ms) conversion to the cytidine complex. In absolute terms reactions of Pd^{II} species with methionine-containing ligands are expectedly much faster than those of Pt^{II}, but in addition not only guanine, but also uracil (and supposedly thymine) as well as cytosine nucleobases are able to convert Pd-thioether bonds into Pd-N(nucleobase) bonds.

3. Summary

Once considered "ideal" analogues of antitumor Cisplatin-like compounds, Pd^{II} complexes of composition *cis*-$[Pd(a)_2X_2]$ have not stood the test of time. The major disadvantage of these Pd^{II} species appears to derive from unfavorable, namely too fast ligand-exchange processes, as recognized early on [21,33,53,71,109,110]. The somewhat lower thermodynamic stability of Pd^{II}-nucleobase complexes as compared to their Pt^{II} congeners most likely is less crucial. Thus, while Pd^{II} reactions are thermodynamically controlled, hence in quest for the "best" choice, reactions of Pt^{II} are kinetically controlled, relatively slow, and dominated by "availability" of a particular donor in a competitive donor atoms situation such as DNA. It may be sheer coincidence that the most abundant Cisplatin-DNA adduct, the intrastrand GG cross-link in fact is also the thermodynamically most stable adduct at physiological pH, but even for the second most abundant cross-link, the intrastrand AG lesion, favorable thermodynamics cannot be responsible for its formation. Numerous other combinations involving, among others, G-*N1* or T-*N3* sites, most likely should produce thermodynamically more stable adducts. Here we have discussed a number of reactivity patterns of Pd^{II}-nucleobase complexes which in part markedly differ from the behavior of analogous Pt^{II} species. These observations seem to indicate that any analogy between structurally similar complexes of the two metal ions in terms of DNA binding and its consequences for antitumor activity is unlikely to be real.

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