The relevance of hydrogen bonding in the mechanism of action of platinum antitumor compounds

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Abstract

A brief review is presented dealing with the mechanism of action of platinum antitumor drugs with the general formula *cis*-$PtX_2(NHR_2)_2$, in which R can be almost any organic fragment, and X can be any leaving group, such as chloride, sulfate, or (chelating bis)carboxylate. Special emphasis is given on the role of hydrogen bonding in the several reactions taking place. It turns out that the N–H group in the amine is important in determining the overall activity of the Pt compound. It is also likely to be responsible for the preferred ionic/dipolar interaction with nucleic acids, over proteins. Studies with single-stranded and double-stranded oligonucleotides have shown that the N–H group also plays a role in discriminating between adenine and guanine. Finally the stabilization of the distorted DNA, after Pt binding, has been shown to originate from N–H···O–phosphate interactions.

History and introduction

Even though antitumor activity for inorganic compounds was reported more than 25 years ago [1], it was not until 1969 that the classical compound *cis*-$PtCl_2(NH_3)_2$ was found to be able to kill tumors in animals [2]. The first clinical trials on human tumors were reported to be successful in 1971 [3]. The first papers in this journal referring to this exciting research area were published in 1973–4 [4].

The antitumor compound *cis*-$PtCl_2(NH_3)_2$ (often abbreviated as cis-Pt, cisplatin, cisDDP, CDDP) is well known to react with cellular components, such as DNA and proteins [5]. However, details of the interaction on the molecular level remain scarce, despite many years of research in this area. After the discovery of DNA binding, almost two decades ago [6], most attention has been focussed on studies of binding between cis-Pt and nucleic acids [7]. It is now generally accepted that the antitumor properties of cis-Pt are based upon a selective interaction with DNA inside the cells.

Due to its successful curing results, cisplatin has become a very important antitumor drug; the major targets of cisplatin and derivatives are urogenital tumors, tumors of the head and neck, whereas more recently treatment of small cell lung cancer, bladder and squamous cell carcinoma has also been reported [8].

The now famous drug (since 1983 the biggest selling antitumor drug in the USA) has nevertheless some drawbacks when used in therapy; to be mentioned are [9]:

- poor solubility in saline
- severe toxicity effects
- development of resistance
- still a narrow range of tumors

A detailed description of its history would take too much space; however, some generally accepted important highlights are:

1964: growth of bacteria blocked in an electric field
1966: growth blocking is caused by dissolved Pt compounds from electrodes
1969: such Pt compounds appear active against tumors
1971: first clinical trials for *cis*-$PtCl_2(NH_3)_2$ successful
1974: first indications that DNA is the major target
1976: improvement of cis-Pt by use of combination therapy
1979: routine use of cis-Pt in curing of certain tumors
1981: clinical trials with analogs and tests with rescue agents
1983: cis-Pt can form a bis-N7 chelate at –GG– sequences in DNA and also in ss and ds oligonucleotides
1985: distortion of DNA after cis-Pt chelation appears to be small
1987: X-ray structures prove chelation at GG sites in ss DNA
1989: discovery of Damage Recognition Protein binding at Pt–GG

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1991: introduction of 'non-classical' Pt drugs and Pt drugs that can be administered orally

Structure activity relations

Already at an early stage it became clear that only the *cis* isomer, and not the *trans* isomer, of $PtCl_2(NH_3)_2$ showed antitumor activity; structures are given schematically in Fig. 1. Other compounds showing very good activity are depicted schematically in Fig. 2. From these compounds the so-called CBDCA derivatives (for the parent compound see Fig. 3) are used clinically on a still increasing scale [10]. A next generation of active compounds, including the Pt(IV) compounds that show promising activity upon oral administration, are drawn in Fig. 4.

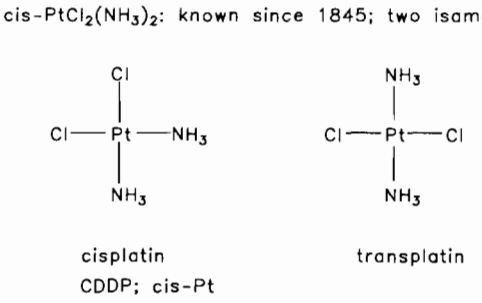

Fig. 1. Structures of the classical compounds cis-Pt and trans-Pt.

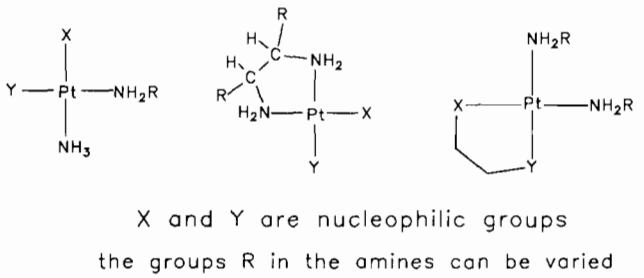

Fig. 2. Some classical derivatives of cis-Pt exhibiting antitumor activity.

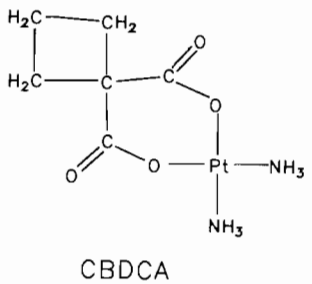

Fig. 3. Structure of the clinically used, second generation drug CBDCA.

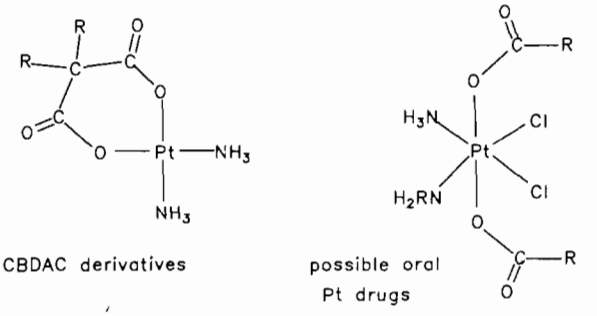

Fig. 4. Some newer derivatives of Pt(II) and oral Pt(IV) compounds.

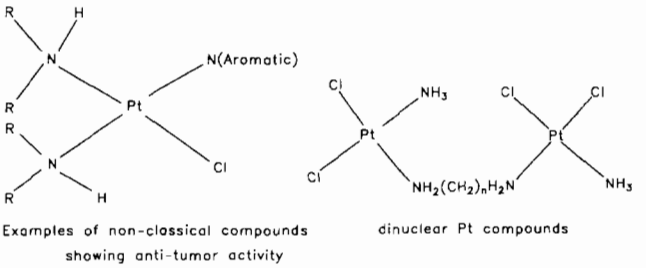

Fig. 5. Examples of unusual and non-classical Pt compounds with antitumor activity.

One could ask why platinum is so important; and why Pd is not; the kinetics is certainly an important parameter, as it is well known that comparable Pt compounds always react slower by a factor of 10^3 than the corresponding Pd compounds.

The kinetics of hydrolysis of cis-Pt has been investigated in great detail [11], and it has become evident that hydrolysis takes place before binding to DNA can occur. Another requirement for Pt compounds with amine ligands is the presence of an N–H group on the amine, both for Pt(II) and Pt(IV) compounds [12]. This H-bonding donor effect will be discussed in more detail below.

More recently, a variety of Pt and non-Pt (both classical and non-classical) compounds has been found [13]; these compounds will not be discussed further in this review. A few representative examples of other Pt compounds with antitumor activity are depicted in Fig. 5. Whether or not these compounds will reach the stage of clinical trials remains to be seen.

cis-Pt under in vivo conditions

Concerning the *in vivo* mechanism of action, many results are already known, and only a brief summary will be given here of the reaction pathway leading to the ultimate event: binding to the DNA in the cellular nucleus.

After injection or infusion in the blood, the cis-Pt drug is transported through the body, almost unchanged (clearly due to the relative high concentration of chloride

ions in blood), entering both normal and tumor cells. Either inside the cell, or during passage of the cell wall, relatively slow ($t_{1/2}$ of a few hours at 37 °C [11]) hydrolysis occurs, followed by binding to nucleic acids and probably many possible other targets. Although the major target in the cell appears to be DNA, many low-molecular weight competitors for cisplatin–DNA reactions in the cell are known. To be mentioned are: Simple ions and molecules like:

Cl^-, $(HPO_4)^{2-}$, OH^- and H_2O (concentration 55 M!)

Amino acids, peptides and polyphosphates:

His, Met, Cys; glutathione, metallothionein; ATP

Theoretically, metal compounds (including Pt) have several possible binding sites in the cell. In the cell several targets exist, such as the nucleobases of DNA, but others are also possible, such as the S-donor ligand glutathione. The sites at proteins are believed to be the most likely origin of the several toxic side effects of cis-Pt and its several derivatives [5, 10, 14]. It has been known for some time that significant amounts of administered cis-Pt are lost as a result of binding to proteins; some of these bonds can be 'rescued' by certain agents, like thiourea. Possibly, cis-Pt derivatives, with different kinetics in DNA (and protein) binding may result in better protocols [15].

To explore this type of protein-binding reaction a variety of Pt amine compounds (including the inactive *trans* isomer of cis-Pt and also the reference compound [PtCl(dien)]Cl) have been reacted with synthetic peptides and with proteins. Competition between proteins and nucleic acids has been studied with *in vitro* reactions for Pt compounds and nucleopeptides. It has been found that the degree of hydrolysis of cis-Pt determines the rate of binding to DNA (at guanine-N7) and to S-donor atoms (most rapidly at thioethers) in proteins and peptides [5].

Using advanced NMR techniques, in combination with spectroscopy and X-ray diffraction studies, the structures and conformations of the obtained Pt–DNA adducts and Pt–peptide adducts have been determined. The importance of hydrogen bonding in the kinetics of the approach and the stability of the formed adducts is shown to be of great importance for the understanding of the mechanism of action for cis-Pt and related compounds. The results of these studies are being used to make predictions for possible third-generation Pt compounds.

In the present paper the low-molecular approach will receive special attention. However, it should at least be mentioned that recently fascinating results have been obtained in the more biological part of this field, where the results of Lippard and co-workers [16] and van der Putte and co-workers [17] on proteins that bind at the Pt–DNA site have attracted considerable attention, and stimulated much research in molecular biology.

Much is already known about the mechanism of Pt antitumor compounds – not only from previous volumes of *Inorganica Chimica Acta* and numerous other papers; even textbooks nowadays present a brief description of the history and mechanism of Pt antitumor compounds [18].

After a few introductory paragraphs the major part of the paper will deal with the role of hydrogen-bonding interactions in this exciting topic. Subsequently, I will deal with the several aspects of hydrogen bonding in the compounds themselves, as well as in their reactions with cellular components, like DNA and proteins.

The importance of physical methods

In the study of the molecular aspects of platinum antitumor chemistry, physical methods have played a very important role. In all studies the role of NMR spectroscopy has been very important, and major conclusions have been drawn about structure, kinetics and stability using:

(1) commonly used nuclei: ^{1}H, ^{13}C, ^{15}N, ^{17}O, ^{31}P, ^{195}Pt

(2) determination of Pt binding sites at DNA (pH effects!)

(3) monitor the hydrolysis of Pt compounds and DNA binding

(4) study the kinetics of Pt binding to DNA and proteins

(5) competition reactions for Pt between DNA, proteins, rescue agents

(6) 3D structure determination of oligonucleotides (applying 2D, 3D techniques)

(7) comparison of DNA and oligonucleotide structures after Pt binding

Unfortunately, the space in the present paper will not allow a detailed discussion of these techniques. The reader is referred to some of the reviews which have appeared recently [19].

Competition between proteins and DNA

It is quite clear that in the cells, after the relatively slow hydrolysis, cis-Pt must have a preference for DNA over proteins (kinetics of approach); proteins have the following ligands available:

- the amine side groups, but these always occur in the hydronated state (and form $-NH_3^+$);
- the carboxylates, although negatively charged, have a small Pt binding affinity;

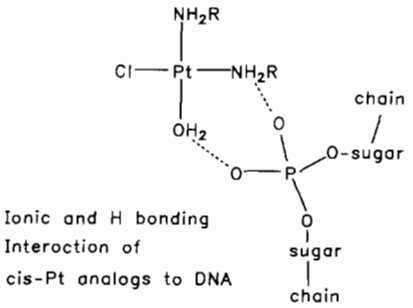

Fig. 6. Electrostatic DNA phosphate interaction with Pt hydrolyzed amine compounds.

- the imidazole groups of histidine side chains; these are likely candidates for binding;
- the S-donor atoms in proteins (and small peptides, such as glutathione) are strong competitors under certain conditions [20].

On the other hand DNA contains a negatively charged phosphate chain, and as a result an electrostatic interaction can take place with the positively charged Pt ions and the amine N–H groups (especially in the kinetics of the process). A schematic of this electrostatic interaction is depicted in Fig. 6. We believe that this interaction contributes strongly to DNA preference for cis-Pt. Studies are ongoing which deal with competition reactions (of Pt binding) between DNA (and its small ss fragments) and peptides (like glutathione) [21].

Preferred binding sites on DNA; the first binding step

As is well known, hydrogen bonding between bases from different strands is a major structure factor keeping DNA together in a ds (double stranded) helical form (so-called Watson–Crick base-pairing). It is quite likely that cis-Pt binding (like any other binding of a drug to DNA), irrespective of its binding site, will influence this type of base pairing, although binding at certain sites in the major groove would not necessarily lead to significant distortions of the ds helix.

Considering the possible binding sites on the DNA for a class-B metal ion like Pt, leads to the N atoms of the bases as the most likely binding sites. When hydronated sites (like N3 in thymine), aromatic sites without a σ lone pair (like the NH_2 side groups) and sterically hindered sites (like the N3 atoms in purines) are excluded, only four binding sites remain, i.e. the N7 atoms of guanine and adenine, the N1 atom of adenine and the N3 atom in cytidine. These sites are arrow-marked in Fig. 7 as possible binding sites. In fact, early studies have shown that these sites can indeed be platinated [22]. Coordination of platinum at an N-donor site in a base is usually easily derived from

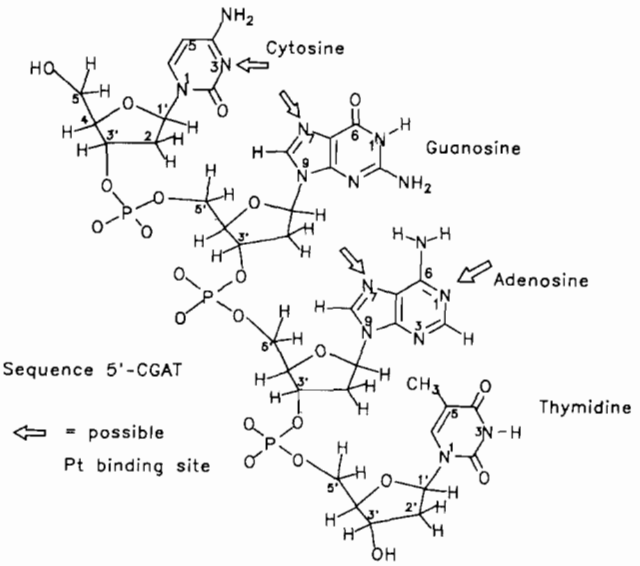

Fig. 7. A fragment of 4 nucleosides with the 4 bases of DNA and the used numbering of sugar and bases; possible Pt-binding sites are indicated with arrows.

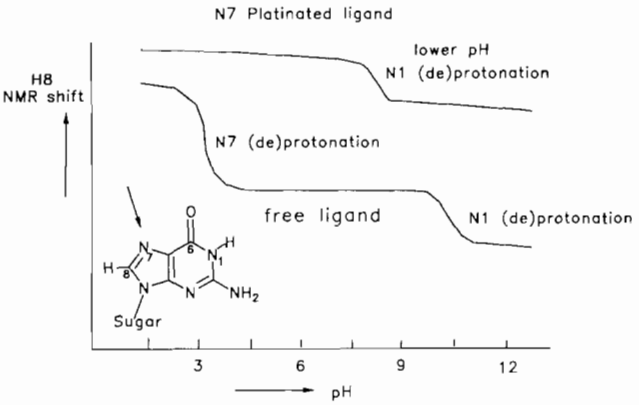

Fig. 8. NMR H8 shift in a titration of protons from guanosine as a function of Pt binding.

the NMR chemical shift of a nearby proton (about 0.5 ppm downfield), and at low magnetic field even $^3J(^{195}Pt–^1H)$ couplings can be observed as satellites [23]. When using larger fragments of DNA it is not always easy to assign the several protons, because of overlapping signals, so that higher frequencies have to be used for resolution of all peaks. However, in that case the ^{195}Pt satellites are broadened too much [23] and are not observed anymore. For analysis of such spectra, usually the pH-titration method is followed, as schematically depicted in Fig. 8. When a proton binds to N7 of a purine, a significant downfield chemical shift is observed. However, when this site is blocked by covalent Pt binding, no proton effect is seen anymore below pH = 4. In fact the loss of H^+ at N1, now occurs earlier (due to the 2+ charge added at N7 of the purine) (see Fig. 8).

After realizing that cis-Pt preferably binds at two neighboring purine bases, a variety of studies inves-

tigating the binding of platinum compounds with relatively small single-stranded and double-stranded oligonucleotides was undertaken by several laboratories. Under a variety of *in vitro* conditions a quite clear picture of the DNA distortion after chelation at GG by cis-Pt has resulted. Reviews about the degree of this distortion are available [19, 24], and will only briefly be summarized here.

The surprising preference of cis-Pt for guanine was also realized early, and NMR was again very helpful in structure determination; nevertheless the strong selectivity of guanines over adenines has for a long time been quite puzzling for chemists. This preference appears not only to be related to an intrinsic stronger basicity of the G-N7 atom (compared with A-N7 nd A-N1), but it is also strongly related to hydrogen bonding. As is clear from Fig. 9, not only the Pt binding at N7 is relevant, but also a secondary interaction with the nearby O6 atom (or repulsion with NH_2 in adenine) plays a key role, both in the kinetics of the approach, and in thermodynamic stabilization after the binding to the N7 atom. In fact it is known that Pt removal from a guanine-N7 site is very slow under normal conditions ($t_{1/2}$ upto 24 h), and only strong nucleophiles like CN^-, thiolates and thiourea can remove Pt relatively fast [25].

Even though the first binding step shows a strong preference for guanine-N7, as stated above it is not only G that forms the binding site for metals. Other possible targets for platinum in cells are the nitrogen atoms of the bases, such as adenine-N1 and adenine-N7, and also cytidine-N3 does bind Pt when sterically accessible in a second, slower (chelating) step.

As found from degradation studies of platinated DNA [26], there appears to be a strong preference of Pt for attack of a G in a GG sequence; a minor adduct appears to be the 5′AG–N7(1),N7(2) complex. It is not yet clear why there is such a strong preference for GG, since is quite well known that Pt binding occurs in two subsequent steps. Apparently, in the (electrostatic) approach of the (predominant) $[Pt(NH_3)_2Cl(H_2O)]$ species recognizes already two neighboring guanines, and even a sequence 5′AG. The hydrogen bonding donor properties of the amines (and the coordinated water molecule) of course could also play a role in 'recognition' of the O6 sites of the guanines in the major groove.

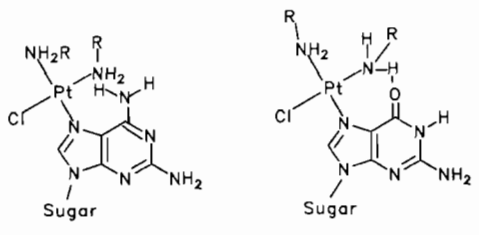

Fig. 9. cis-Pt binding at G vs. A; the preference for G can be explained by H bonding.

A very interesting question in this problem of selectivity is: which G in a GG sequence is attacked first (the one at the 3′ side or at the 5′ side?). Studies with $[Pt(dien)Cl]^+$ as a model for the monofunctional binding step and with asymmetric amines coordinated to Pt are ongoing in our laboratories, with the aim to find out what the steric effects are, and how they can be distinguished from the electrostatic and H-bonding effect in this process. With single-stranded d(GpG) monofunctional Pt compounds preferentially bind at the 5′ G. Preliminary results indicate that a 5′ phosphate group strongly favors the Pt binding at that site (ongoing research [27]). It is quite clear that the role of hydrogen-bond acceptor by guanine-O6 and the donor role of the amines are crucial. Earlier studies had shown that a free 5′ phosphate strongly favors the 5′ G platination [28].

A similar study with cis-Pt binding to oligonucleotides is being performed by Chottard [29], and has resulted in the determination of kinetic parameters for both the binding at the 5′ G and 3′ G.

The second binding step; changes in the structure of DNA after Pt binding

The specific secondary binding to DNA, i.e. after the first binding to DNA has occurred, takes place at an A or at a G. For this reaction to occur, a rotation about the Pt–N bond must take place. This rotation can only take place when the Pt has an amine ligand allowing this (a small steric barrier for rotation, since Pt compounds with tertiary amines – even though they bind to DNA [30] – are inactive as antitumor drugs). Perhaps the presence of an N–H on the amine is also required to minimize steric strain. It is well known that the chelate formation of cis-Pt is quite slow ($t_{1/2}$ = 2–3 h [31]), as determined using ^{195}Pt studies *in vitro*.

When we started to study this kind of chelation with ss (single-stranded) DNA using the smallest possible unit, i.e. GpG, it was by no means clear beforehand that cis-Pt could form a so-called macrochelate (a 17-membered ring is not easily formed in coordination chemistry!); however, NMR clearly and unambiguously proved the chelate formation and the structure. The high-quality, well-resolved NMR spectra of the adduct [*cis*-$Pt(NH_3)_3$(GpG-N7(1),N7(2)] even allowed us to perform an NMR conformation analysis, resulting in a detailed 3-D structure [19a]. This structure was confirmed a few years later by Lippard and co-workers [32], who performed an X-ray analysis on the adduct with pGpG (just one extra phosphate). In fact our

findings were completely confirmed, even though packing effects were expected to have at least a minor effect on the primary molecular structure.

In a next stage of our programme, we added an extra base to the sequence and were successful in determining both solid state and solution structures of [*cis*-$Pt(NH_3)_3$(CpGpG–N7(2),N7(3)]; not surprisingly the chelating parts were again almost identical [33]. However, the non-Pt binding parts (the cytidine residue) differ in orientation, not only between the solution and the solid [34], but in fact in the solid three different molecules occur, each with a different C orientation, but with the same basic unit [*cis*-$Pt(NH_3)_3$(---GpG–N7(2),N7(3)]. As an example a PLUTO drawing of one of the molecules from the unit cell is depicted in Fig. 10. The crystal structure consists of a complicated network of hydrogen bonds (G:C) and stacking interactions (G on G, C on C), which will not be described here [34].

Finally, we moved to ds DNA, for which enzymatic digestion [26] and NMR analysis has shown that similar GG adducts (and minor amounts of other adducts, like AG) are formed. The first experiments were done [35] with a double-stranded decanucleotide, i.e. 5′-d(TCTCGGTCTC)/3′-d(AGAGCCAGAG), with cis-Pt attached at the N7 atoms of the central GG unit. This study clearly showed that Watson–Crick base pairing remained possible, although fraying of the helix was found to occur easier and that the helix had distorted to some degree. This very important conclusion has been confirmed later by other laboratories using different sequences [24, 28]. The overall conclusions out of work from others and from our work can be summarized as follows.

(1) In the cis-Pt adducts at GG sequences, the two bases are coordinated via N7 in a 'head-to-head' orientation; the deoxyribose moiety of the 5′ guanine has adopted an almost pure N-type conformation, compared to the S-type conformation in free d(GpG). The other conformational characteristics of the sugar hardly change upon platination.

(2) Detailed analysis of proton and phosphorus NMR spectra and consideration of the CD spectra led to the conclusion that the double-helix is somewhat destabilized after the platination, as reflected by the decrease of the 'melting' temperature of the duplex by 10–20 °C at NMR concentrations (3 mM). Base-pair formation by hydrogen bonding appears still possible after the platination, as reflected by the appearance of all imino-proton resonances. For the central GG sequence, these signals are only observed at low temperature, although shifted to lower field and broadened. It appears that these particular base pairs are first fraying upon heating.

(3) Detailed analysis of chemical shift and coupling constant from the NMR spectra, followed by conformational analysis suggests a rather small, but significant distortion of the double helix of the larger oligonucleotides upon platination, which has been described as a 'kink' of about 40° in the helical axis at, or around, the GG lesion. In addition a helical twist of about 10° has been proposed [24e].

(4) Comparison of CD spectra and ^{31}P NMR spectra of platinated DNA from several sources with the platinated ds decanucleotide, strongly suggests similar distortions for both cases.

(5) The interactions with the 5′-phosphate group in the DNA seem to be important, i.e. it is involved in a hydrogen bond with an NH_3 (or other amine) ligand of platinum. This is quite likely to be the origin for the observation that active 'classic' platinum antitumor drugs require an acid N–H group. The phosphate–ammonia interaction could induce and/or stabilize DNA distortions, thereby interfering with the replication process. Details of this H bonding in the ds species have most recently been modelled by Chottard and co-workers [24e].

A possible structure, in agreement with NMR spectroscopy, for the above-mentioned double-stranded decanucleotide with a cis-Pt attached to the central –GG– is depicted in Fig. 11.

Recently we have found that even after the first binding step of cis-Pt the structural consequences for the distortion of the DNA are significant. After binding to DNA at a G site – as studied with $Pt(dien)^{2+}$ [36] – and in species like AGA [37], CGT [38] and even in ds TCTCGTCTC [39] the distortion is also significant as deduced from NMR analysis. The structure of the first binding product has also been studied in the solid state for the case of Pt(dien)(dApGpA) [37]. In this case a number of unprecedented and unusual H-bonding interactions between bases have been observed. They are redrawn in Fig. 12.

Hydrogen bonding is also known to play a key role in protein–DNA binding interactions. When cis-Pt has

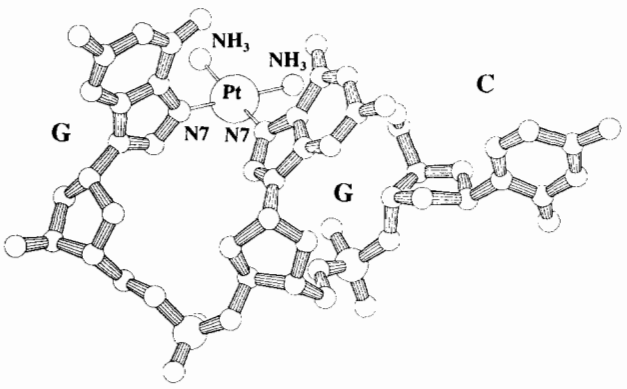

Fig. 10. Projection of the structure of a molecule in [*cis*-$Pt(NH_3)_3$(CpGpG–N7(2),N7(3)] as deduced from the crystal structure.

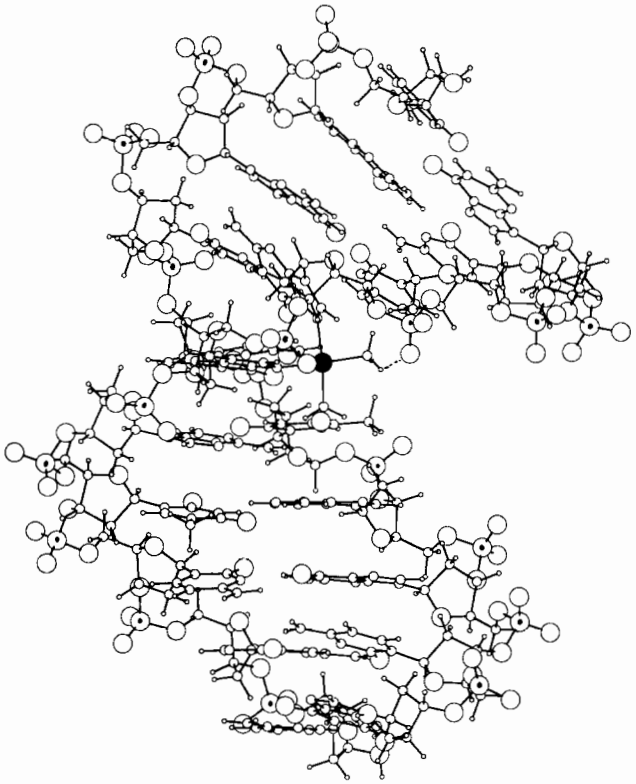

Fig. 11. Distortion of the double helix decamer (TCTCGGTCTC/GAGACCGAGA) after chelation of the central –GG– to *cis*-$Pt(NH_3)_2^{2+}$, as deduced from NMR spectroscopy. An NH_3–O–phosphate hydrogen bond is indicated. The black dot represents Pt; P and O atoms are depicted as large open circles.

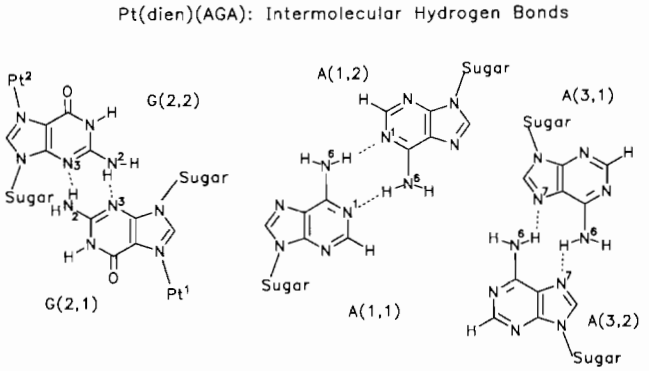

Fig. 12. Unusual hydrogen-bonded base pairs as found in the solid-state structure of Pt(dien)(d(AGA)-N7(3)). The bases, like G(2,1), are indicated by their sequence (in AGA) and their symmetry (1 or 2).

such an important effect on the structure of the DNA, it is to be expected that also for protein–DNA interactions the binding of Pt to DNA plays a role. Binding of proteins to platinated DNA is known to occur for the repair enzymes in prokaryotes [17] and for the recently discovered DRP protein found in eukaryotes [16]. Platinum binding at, and distortion of, the DNA can have a dramatic influence on biochemical processes.

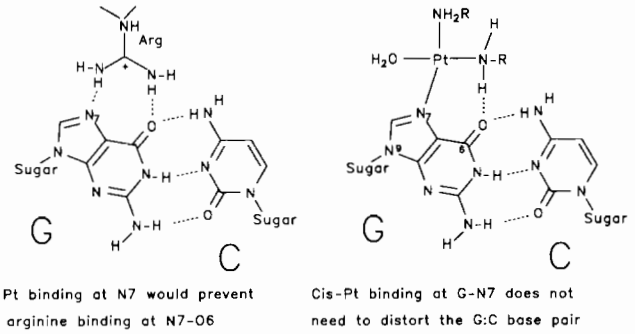

Fig. 13. Schematic representation of the binding of arginine and Pt at N7O6 of a GC base pair in the major groove of DNA.

Studies of zinc fingers bound to DNA have shown that binding occurs in the major groove at G-rich strands, using arginine–N7O6 contacts [40]. When Pt is coordinated at N7, this binding changes dramatically, although structures are not known in detail. In Fig. 13 it is shown that in fact cis-Pt binds at the same place as the arginine. This confirms that Pt binding at N7 does not necessarily lead to a big distortion of the DNA.

Concluding remarks and outlook to the future

In the present overview paper many interesting aspects could not be mentioned. The exciting studies on the first binding step to DNA, mimicked with Pt(dien) could only briefly be mentioned. The binding studies [21, 41] of Pt compounds to *S*-adenosyl-homocysteine (SAH) and *S*-guanosyl-homocysteine (SGH) with quite exciting conclusions about the preference of Pt for certain sites, the studies using trans-Pt in binding to DNA and the resulting small distortions in certain cases [42] and also the work on Pt binding to the rescue agents [43] had to be left unmentioned.

As common in science after a period of extensive research, we believe many important questions have been answered; however, at the same time we have raised several exciting new questions. Many of these other questions, some of which are beginning to be answered, are listed below in the next paragraphs.

From the results reviewed above, some conclusions and a few predictions seem to be justified. It is quite likely that criteria of relevance for future 'classical' Pt drugs will be:

(1) good water solubility and stability in 0.1 M NaCl

(2) in blood reactions with ligands containing S donor atoms should be suppressed

(3) in cells hydrolysis reactions should be optimized

(4) reaction kinetics with DNA should be optimal; resulting distortion should be limited

(5) undesired reactions in cells should be suppressed as well

These properties are to be controlled by:

- the amine ligand at platinum (chelating or not; H-bond donor; steric effects)
- the leaving groups at platinum (non-toxic; optimal kinetics)

For clinicians and pharmacologists some important research areas appear to be:

(a) testing of new Pt compounds (classical ones; oral Pt drugs; non-classical ones)

(b) improvement of administration protocols; combination therapy; prediction of curing success, using lab tests with DNA from blood cells

(c) applications of rescue agents (competition with side reactions)

Molecular geneticists and biochemists will find interesting challenges in the study of:

(d) isolation, purification and structure of repair enzymes

(e) study of binding of repair enzymes to platinated DNA

(f) binding of platinum compounds to proteins and enzymes

(g) how Pt can be removed from proteins and from DNA

The synthetic chemists, in particular, will find challenges in:

(h) classical Pt amine compounds with at least an N–H donor (asymmetry; steric effects; protein recognition); orally administered drugs

(j) design and synthesis of non-classical Pt compounds: almost unlimited variation possibilities

The more general bioinorganic chemists will find exciting study areas in:

(k) study of the classical compounds: details of distorted DNA structure (X-ray?)

(l) the understanding of the first step of DNA binding; preference for certain (?) –GG– sequences?

(m) understanding the molecular basis of toxicity

(n) study of kinetics to DNA and proteins; might lead to new drugs

(o) non-classical compounds: what is the cellular target? Is it (also) the DNA, or perhaps protein?

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