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Heavy Metals as Useful Drugs

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Abstract. A brief overview of the key role for heavy-metal compounds in medicine is given, with a special focus on platinum compounds used in treatment of cancer. Molecular aspects of the mechanism of action are presented in more detail.

1. Introduction

The general public, and even many chemists, upon confrontation with the term 'heavy metals', will primarily have associations with toxicity and dangerous materials. Relatively few people will realize that quite a few compounds of heavy metals are extremely useful and required for life, and several of them are often applied as drugs to cure diseases. Most well-known examples deal with silver (to protect the skin after burning wounds), radioactive technetium compounds (as diagnostics for diseases), copper (arthritis treatment), bismuth (treatment of diarrhoea; curing of stomach ulcers), gold (treatment of arthritis) and platinum (efficient tumor curing). In the earlier days, also mercury, arsenic and antimony were used. In fact, all metals are poisons, depending on the dose; however, certain very toxic metals are nevertheless crucial for life, either as a trace element or as a drug. Some examples of the structures of such drugs are given in *Fig. 1*.

An important question dealing with the application and understanding of the mechanism of such drugs is: 'How dangerous are heavy metals and their compounds (*i.e.* curing over side effects)?'

For the chemist, the chemical form of heavy-metal compounds is crucial, and will determine whether or not such a compound can be used.

In a short note, it is impossible to deal with all these topics. By way of illustration, some highlights will be summarized with special attention to the development of new Pt antitumor drugs, based on earlier mechanistic investigations of the prototype cisplatin.

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2. Cisplatin

Very simple Pt compounds, like *cis*-$PtCl_2(NH_3)_2$ (abbreviated as CDDP, *cis*-Pt, cisplatin), have been known for over 150 years. However, the biological activity of the parent compound has been reported only in the mid-sixties as the result of a serendipitous discovery by *Rosenberg* [1]. More recently, several studies have been reported dealing with the antitumor properties of a gradually increasing number of Pt compounds of the classical type, but increasingly of completely new types. In *Fig. 2*, three of these newer types of compounds, with surprising activity, have been depicted.

The major chemistry facts that have led to a significant improvement of our insight into the mechanism of action in this case restricted to cisplatin, will now be briefly discussed.

The key elements in the mechanism of action appear to be:

1) a controlled hydrolysis of cisplatin, transport through membranes and in the cells, eventuelly followed by binding to DNA;

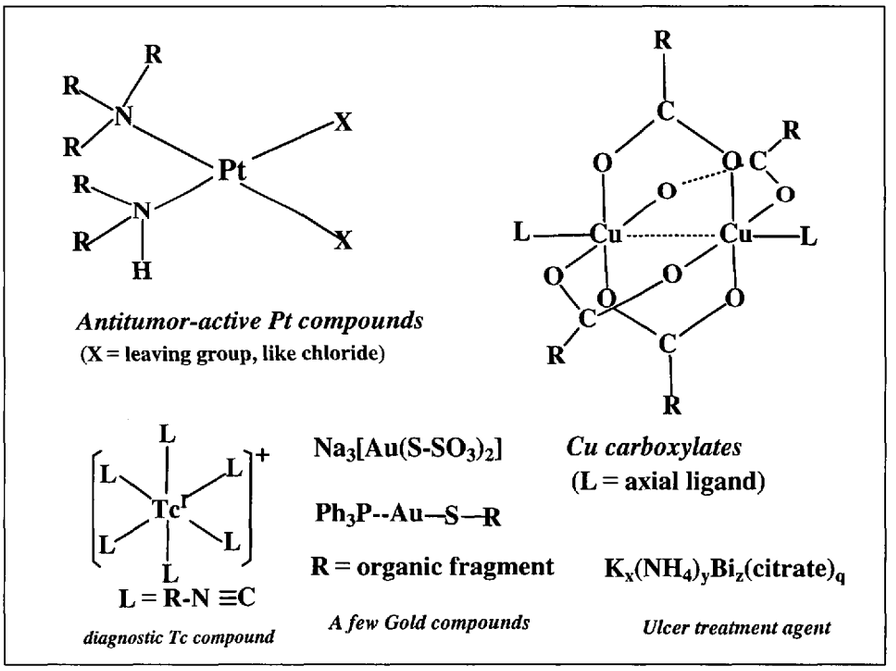


Fig. 1. *Examples of metals used in medicine*

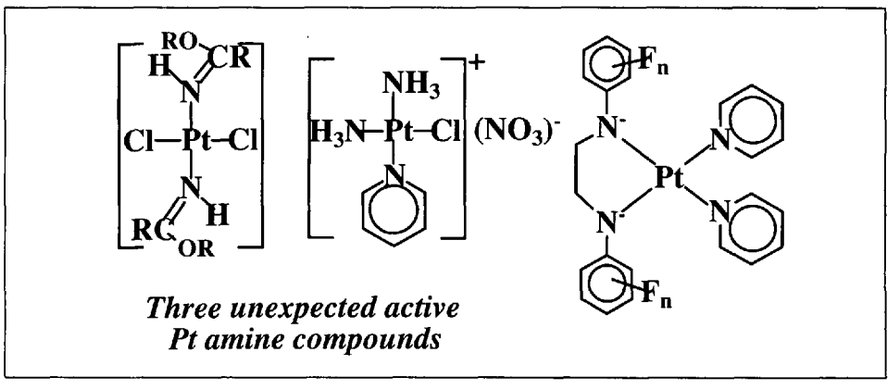


Fig. 2. *Some unusual, active Pt-amine compounds*

2) a selective binding at two neighbouring guanine bases; and especially
3) a highly specific distortion of DNA, changing its interactions with proteins.

Whether the new compounds, like the ones depicted in *Fig. 2*, will bind in the same way, remains to be seen. It soon became evident that cisplatin-DNA interactions are crucial for the carcinostatic effects [2], and most research during the last 15 years has been concentrating on this effect. The main conclusions of this type of research will be summarized below.

In the first step, formation of an hydrolytic equilibrium occurs, but the kinetics will be most important for the understanding of the reactions under *in vivo* conditions. This hydrolytic equilibrium has been reviewed before [3], and it is evident that for cisplatin the major species ready for *in vivo* reactions is [*cis*-$PtCl(H_2O)(NH_3)_2]^+$.

Over the years, many studies have been devoted to Pt-DNA binding and several reviews are available (see [4–7] for comprehensive discussions). It is proven unambiguously that the N(7) positions of A and G have a strong preference for metal binding, including Pt, but the N(7) of is usually highly favoured, presumebly for kinetic reasons and stabilization of the H-bond interaction with the O(6)-atom of the guanine [1].

Historically, first attention was given to the bindingof the simple nucleic-acid bases to cisplatin, followed by the nucleosides and the nucleotides. The first studies with dinucleotides were reported in the early 1980s, and we could prove that a chelate to two neighbouring guanosines in a 17-membered chelate ring does occur [8], and crystal structures for the dinucleotide and trinucleotide adducts confirmed this [9][10].

Den Hartog et al. were the first to show that chelation of cisplatin (after loss of two chlorides) is possible at neighbouring guanosines in double-stranded DNA [11]. The pioneering work of *Fichtinger et al.* [12] had shown unambiguously that also on DNA under *in vivo* conditions the *cis*-Pt unit chelates at N(7) of neighbouring G sites (60–70% of all Pt); this has subsequently been confirmed for many sources of DNA [13].

Relevant questions that have been answered by carrying out such studies are:

- How fast are the reactions of the Pt compounds with the DNA? Usually the half-life is a few hours.
- Does the DNA structure alter significantly after monofunctional binding of Pt species? Yes, the distortion can be quite significant [14][15].
- How is the DNA structure altered after chelation of *cis*-Pt compounds? A large kink and unwinding occurs, as proven by NMR and X-ray diffraction [11][16].
- What are the biological consequences of the altered DNA structure? It appears that certain proteins bind at the platinated DNA, subsequently interfering with gene expression and/or repair [17]
- Do the Pt(IV) compounds react directly with the DNA, or are they reduced before or during binding? This is not yet sure and seems to depend on the conditions.
- Do the recently reported Pt compounds (such as the new dinuclear ones) bind to the DNA in a way related to *cis*-Pt amines? Again, too little is known as yet, but quite different bindings have been found, such as a hairpin structure [18].

Finally, in the last two years, increasing evidence has been presented that Pt-protein interactions, and in particular Pt-thioether interactions, do play key roles in the mechanism of action, and especially in transport and toxic side effects [19][20]. In fact, it has been shown, *e.g.* in S-guanosyl-homocysteine, SGH (see *Fig. 3*), that Pt species can initially bind at thioethers and then migrate to guanine-N(7) sites.

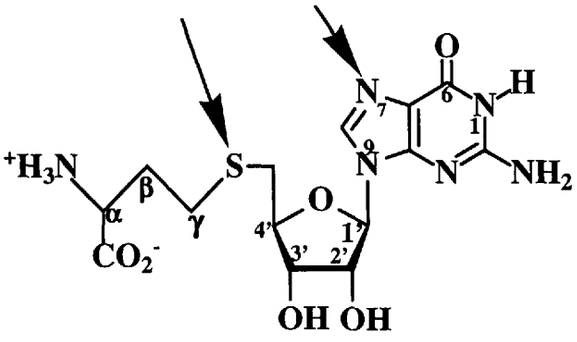
This result has raised interests to study other important questions, which are being addressed at the moment in a few laboratories. To be mentioned are:

- What is the chemical role of the other Pt-binding ligands that occur in the blood, in the cell membranes and inside the cells?
- What is the chemical role of so-called rescue agents (often S-donor ligands) in the mechanism of (in)activating platinum drugs?
- Do the ligands that occur inside the cell compete for the DNA, or are they perhaps intermediates in the reaction?

Questions of this type are currently addressed in our and other laboratories.

3. Concluding Remarks

It goes without doubt that the last decade has shown enormous progress in the understanding of the mechanism of action of cisplatin and other Pt compounds that exhibit anticancer activity. It is likely that improved antitumor drugs will become available based on the detailed knowledge of the Pt-DNA adducts and on the kinetics of their binding to cellular components, like proteins and DNA. A detailed knowledge of the structure of the Pt compounds and the adducts, and of the reactions of the several new Pt compounds on their route from injection, or even oral administration, to the DNA of the tumor cell will be of increasing importance.



SGH: S-guanosyl-homocysteine

Fig. 3. *Structure and Pt-binding sites in SGH*

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Selective Photocyclization of Amino Acids in Dipeptides

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Abstract. Amino acids in dipeptides which are substituted at the N-atom by a benzoylalkyl group can be selectively photocyclized *via* a triplet biradical. With valine as amino acid the cyclization leads mainly to one product out of eight possible isomers.

During the last years it became clear that the same rules of stereoselectivity govern the reactions of radicals as well as of non-radicals [1]. In diffusion-controlled radical-radical reactions the stereoselectivity nearly disappears, but if the two radical centers establish a triplet state, its lifetime might be long enough for a selection between different reaction pathways.

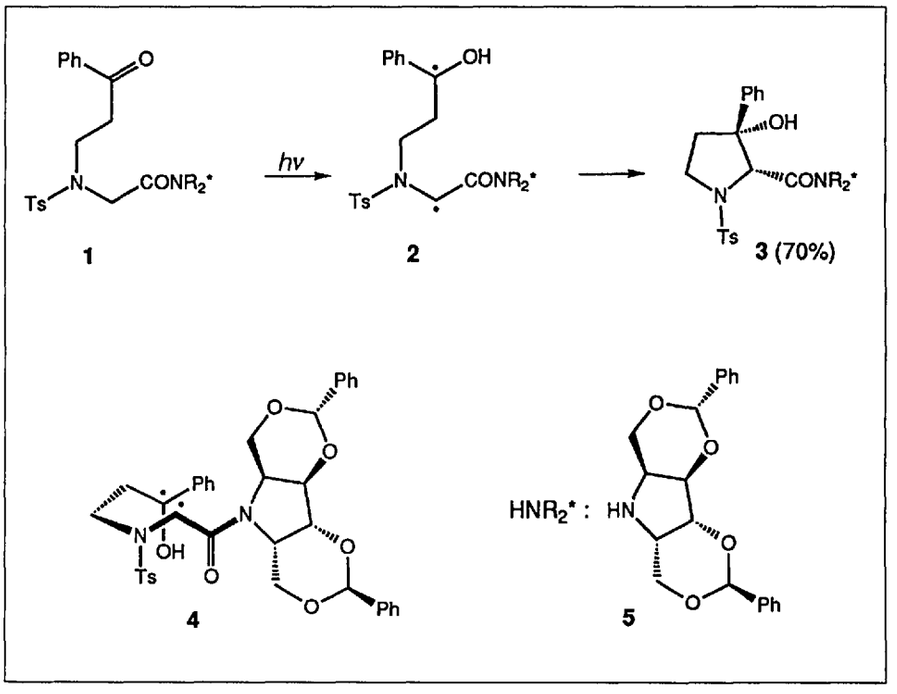
Recently, we have shown that the interconversion between glycine and proline derivatives (**1** → **3**) *via* the triplet biradical **2**, is completely stereoselective when the chiral auxiliary **5** is used [2]. We have explained this by the transition-state structure **4** (*Scheme 1*).

In order to learn whether stereochemical induction occurs also in the absence of auxiliary control, we synthesized dipeptides **10** by *Michael* addition (**6** + **7** → **8**) and subsequent amide formation (**8** + **9** → **10**) (*Scheme 2*).

Photolysis of dipeptides **10** occurred with high regioselectivity and simple diastereoselectivity as well as significant asymmetric induction [3]. From the eight possible isomers, the δ-lactams **11a** and **11b** are formed as major products (*Scheme 3*). The regioisomeric γ-lactams are not observed and *trans*-substituted δ-lactams are formed only in trace amounts (aprotic solvents).

It has turned out that this photocyclization is glycine-selective [4]. But if the length of the ether is reduced in one CH_2

Scheme 1



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