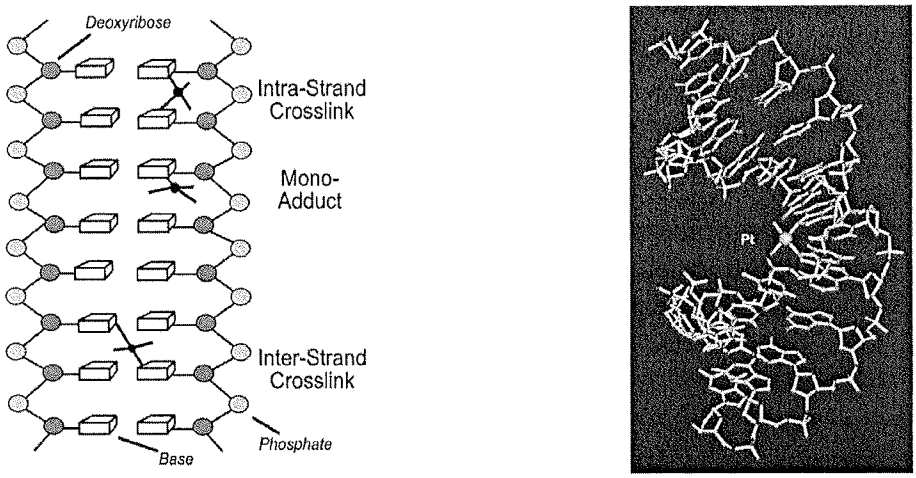
Overcoming Resistance to the Antitumor Action of Cisplatin: New Compounds and Modes of Delivery

Jane L. Stanley Inorganic Literature Seminar October 18, 2004

The compound cis-diamminedichloroplatinum(II), otherwise known as cisplatin, has been used as an anticancer agent against a myriad of cancer-types since the 1970's.[1] The mechanism of action of cisplatin has not been completely elucidated, but it is known that after injection, cisplatin enters the tumor cells and undergoes substitution of the chloride ligands by water thereby activating it and allowing it to bind to DNA.[2] Studies have shown that cisplatin binds preferentially to two guanine bases on the same DNA strand (or to one guanine and one adenine), forming what are called 1,2-intrastrand crosslinks as the main product(s) as well as other minor products, such as 1,3-interstrand crosslinks (bound to one guanine on each strand) and mono-adducts (Figure 1a).[2] Binding to DNA in this manner induces a kink in the double helix of approximately 40-80° and results in a localized unwinding of approximately 23° (Figure 1b).[2] Such deformation of the DNA double helix can attract the attention of damage-recognition repair proteins that work to remove the kink and nullify the antitumor action. In cancer cells repair is blocked whereas in healthy cells or cells resistant to cisplatin, DNA repair occurs rapidly and results in the development of cisplatin-resistant tumor cell lines.[3a,3b] Aiding in resistance are reduced cellular uptake and the deactivation of cisplatin as it moves to the target site via interactions between its labile chloride ligand(s) and the various proteins it may encounter. The deactivation also results in the toxic side effects observed with use of cisplatin.[1,2,4a]



(a) (b)

Figure 1: (a) Schematic of possible cisplatin-DNA adducts[2] and (b) a model of a cisplatin-DNA adduct demonstrating kinking of the double helix. [5] (structure reference: PDBid, 1AIO)

Overcoming resistance to cisplatin as well as to its toxic side-effects has required the development of novel compounds. The most promising new research avenues involve platinum compounds that are multinuclear (di-, tri-, and even tetra-) with varying degrees of functionality (mono-, di-, tri- and tetra-).[4b,6] Recent emphasis has been placed on Farrell's compound, BBR3464 (Figure 2) which is currently in Phase II human trials. This compound is capable of forming novel 1,4- and 1,6-interstrand crosslinks with DNA.[6] Also of interest is Reedijk's azole-bridged dinuclear Pt(II) complex ([{cis-$Pt(NH_3)_2\}_2$(μ-OH)(μ-1,2,3-ta-N1,N2)]$(NO_3)_2$ where 1,2,3-ta = 1,2,3-triazolate), which is capable of a novel isomerization process allowing for the formation of a number of possible crosslinks.[7] Both of these compounds are resistant to cellular repair mechanisms by virtue of the new types of crosslinks they form, allowing antitumor activity that is comparable if not better than that of cisplatin.

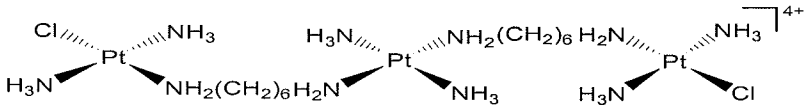
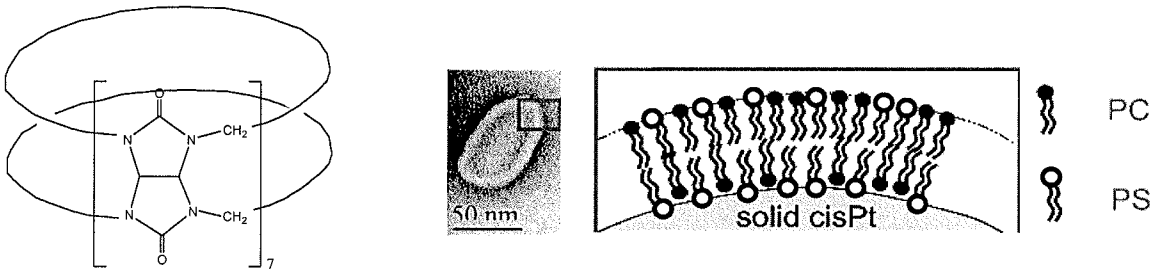


Figure 2: Structure of BBR3464.

The development of new compounds has made headway in overcoming some modes of cisplatin resistance, but overcoming natural resistance (associated with reduced cellular uptake) may require novel delivery modes of both new and old compounds. Wheate et al. are utilizing a well known organic host molecule, cucurbit[7]uril[8a] (Figure 3a), in an attempt to minimize deactivation of a newer dpzm-bridged di-platinum compound, trans-[{$Pt(NH_3)_2Cl$}μ-dpzm]$^{2+}$ (where dpzm = 4,4'-dipyrazolylmethane). This delivery method could prove useful in reducing the toxic side effects of some Pt-drugs by protecting them from deactivation.[8b] On the other hand, de Kruijff et al. are currently developing nanocapsules wherein a solid core of cisplatin is surrounded by a rigid phospholipid bilayer composed of phosphatidylserine (PS) and phosphatidylcholine (PC) (Figure 3b). These nanocapsules are easily taken up into the cell via phagocytosis, and broken-down releasing a super concentrated dosage of cisplatin inside the cell. These nanocapsules have shown themselves to be 1000 times more cytotoxic against cisplatin-resistant cell lines than cisplatin itself.[9]



(a) (b)

Figure 3: (a) Representation of cucurbit[7]uril host molecular structure[8b] and (b) a negative stain electron microscopy (EM) image and a depiction of the nanocapsules structure.[9]

Cisplatin remains one of the most important examples of biologically active transition metal complexes. The problems that are associated with it, however, are too important to be overlooked and in response new compounds with novel mechanisms of action have been developed. New modes of delivery may allow cisplatin to stay in mainstream use while also addressing some of the toxicity associated with all platinum-containing antitumor agents.

References

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