

CHEM 280 Spring 2021
Reading Assignment 1
Assigned 02/24/2021, due 03/10/2021 (in class)

Introduction:

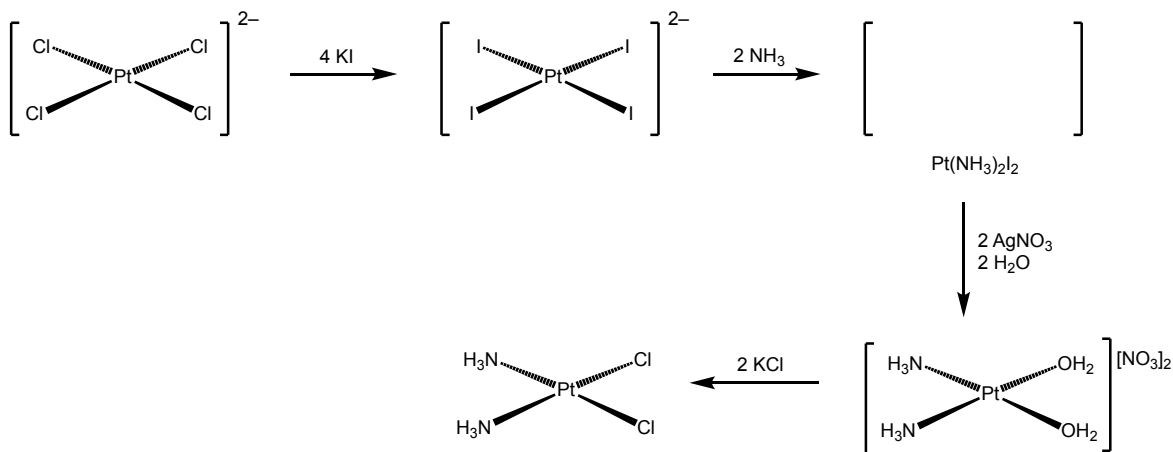
By reading the provided articles consisting of two review articles and one research article, you will gain an in-depth understanding of platinum-based cancer therapeutic agents. Various aspects of these compounds including structures, reactivity, mode of actions as anti-cancer drugs are comprehensively described.

Instructions:

- Answers must be written in an organized, concise, and legible manner or your assignment will be returned without being graded.
- Your complete assignment must be stapled. 4 points penalty will be imposed for an unstapled assignment.
- This assignment is worth 40 points.

Please read the review article entitled “*Discovery, Chemistry, Anticancer Action and Targeting of Cisplatin*” and answer the following questions in your own words:

- 1) Describe the structure of cisplatin. What are the common features for cisplatin-type drugs?
- 2) Cisplatin is most commonly prepared by a multi-step reaction from $[\text{PtCl}_4]^{2-}$ (*Indian J. Chem.* **1970**, *8*, 193). Please draw the structure of the intermediate formed in the Scheme 1 with the appropriate stereochemistry.



Scheme 1. Synthesis of cisplatin from $[\text{PtCl}_4]^{2-}$

- 3) Explain why cisplatin undergoes ligand substitution reactions with water molecules once it has entered a cancer cell. Propose a plausible mechanism for this ligand substitution reaction.
- 4) It is estimated that only 1% of cisplatin reaches the targeted cancer cells due to its side reactions with biomolecules containing thiol groups ($-\text{SR}_2$) in blood stream. What does this statement suggest about the affinity between cisplatin and a sulfur ion in the thiol groups? Please provide one reason to support your answer.
- 5) Cisplatin exclusively binds to 2 guanine groups in a DNA strand, which leads to the its deformation, and ultimately causes an apoptosis of the cancer cell. Draw a series of chemical equations for the formation of the guanine-based cisplatin, starting from cisplatin. Make sure to include every intermediate.

Please read the (ancient) research article entitled “*Crystal structure of double stranded DNA containing the major adduct of the anticancer drug cisplatin*”, and answer the following questions in your own words:

- 6) This article was the first to report the exact binding mode of cisplatin to the double-stranded DNA (and hence a publication in *Nature*). Please briefly summarize the breakthrough discovery that was reported from this article.
- 7) Describe the change or changes in the DNA structure once it has coordinated to cisplatin.
- 8) Based on the crystal structure of cisplatin-coordinated DNA, explain why only cisplatin exhibits considerable activity toward cancer cells, but not its *trans* isomer, transplatin.

Please read the review article entitled “*Anticancer platinum-based complexes with non-classical structures*”, and answer the following questions in your own words:

- 9) Even though cisplatin exhibits high reactivity toward cancer cells, there have been efforts to develop alternative anticancer drugs, which some of them are described in this article. What are the reasons to replace cisplatin?
- 10) One potential class of compounds contains sterically hindered ligands such as picolin. Even though these compounds exhibit reduced DNA binding capacity, they do offer one benefit over cisplatin: the decrease in side reactions with thiol-containing biomolecules. Please provide a reason for the two observations described in the previous sentence.
- 11) Platinum(IV) compounds have been proposed as a less toxic alternative to cisplatin due to their high stability and inertness. Please use the crystal field theory to explain the inertness behavior of platinum(IV) compounds.
- 12) Platinum(IV) compounds are commonly octahedral in shape, while platinum(II) compounds have a square planar geometry. Explain.
- 13) Explain how prodrug and inactive Pt(IV) compounds can transform to active Pt(II) species. What reagent is required for this transformation?

Lastly, please write a short summary on cisplatin as anticancer drug in one paragraph (<10 lines). Your summary must include some basic information of cisplatin (structure, components, etc.), mode of actions as anti-cancer drugs, binding mode to the DNA strand, its drawback, and potential alternative replacement (with short explanation).

—End of assignment—