General Chemistry Flipped Classroom Module

In-class Activity

"Cisplatin and Anticancer Therapy: The Role of Chemical Equilibrium"

Cisplatin, cis-$[Pt(Cl)_2(NH_3)_2]$, is a widely used anticancer agent. It has seen clinical success in treating a variety of cancers, including testicular, ovarian, and a variety of head/neck tumors. Alderden, *et al*. have reviewed the history of the discovery and use of cisplatin as a chemotherapy, and the authors describe the mechanism by which cisplatin is able to inhibit the growth of tumor cells and/or impart tumor cell death. The authors also describe how chemical equilibrium plays a role in this mechanism.[1]

The schematic in Figure 1 depicts the general reaction that takes place in the tumor cell, and shows the active form of the drug that leads to tumor cell death.

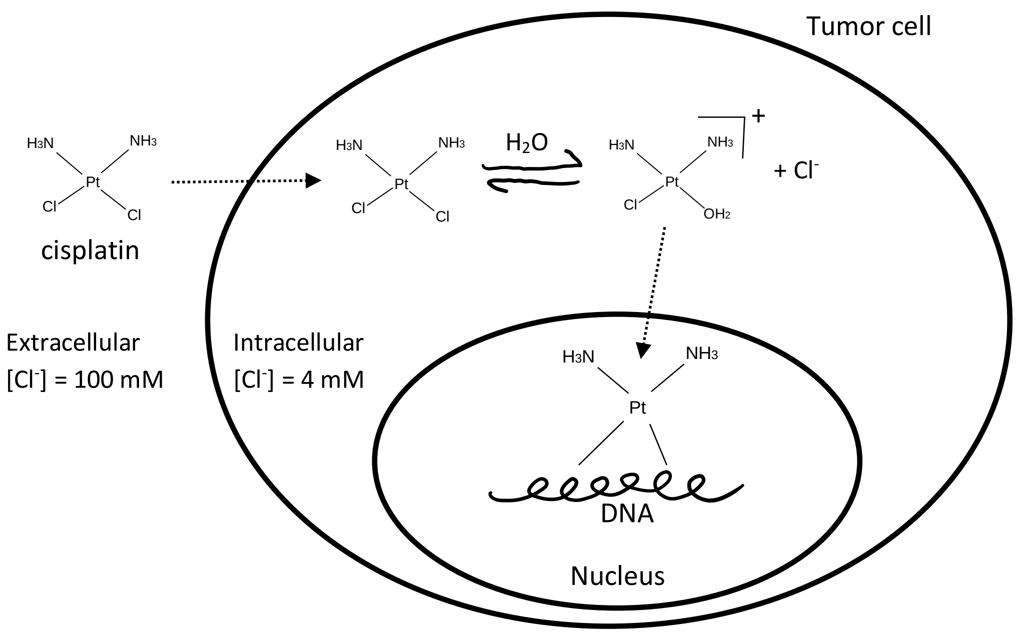

Figure 1: General mechanism for how cisplatin enters the tumor cell, undergoes an equilibrium reaction to form aquated cisplatin (structure in which one chloride ligand has been replaced by a water molecule), and then enters the cell nucleus. When aquated cisplatin binds to the DNA it distorts the DNA structure, which then causes DNA binding proteins to either initiate DNA repair or initiate cell apoptosis (cell death).[1]

[1]Rebecca A. Alderden, Matthew D. Hall, and Trevor W. Hambley, *Journal of Chemical Education*, 2006, 83 (5), 728-734 (https://pubs.acs.org/doi/abs/10.1021/ed083p728).

<u>In-class Activity Questions:</u>

1. Write out the equilibrium expression for the reaction in which cisplatin is aquated (the equilibrium reaction is shown in Figure 1).

2. The aquated form of cisplatin is actually the active form of the drug. This is due to the fact that cisplatin will not enter the nucleus and bind to DNA unless one of the chloride ligands has been substituted by a water ligand. We will work under the assumption that the estimated equilibrium constant for the reaction in which cisplatin forms the aquated cisplatin is 4.00. If cisplatin is administered to a patient and we assume 10.0 µM cisplatin is the initial concentration of the drug inside the tumor cell, determine the concentration of aquated cisplatin cis-$[Pt(Cl)(H_2O)(NH_3)_2]^+$ inside the tumor cell after equilibrium has been reached (use µM concentration units for all species in the reaction).

3. What concentration of cisplatin cis-$[Pt(Cl)_2(NH_3)_2]$ would remain in the tumor cell environment once equilibrium is reached?

4. If the equilibrium constant for the reaction of cisplatin with water to form aquated cisplatin is 4.0, this suggests the products of the reaction should be slightly favored. Your answer for question #2 is likely lower than you might expect given this equilibrium constant. How can you explain this observation (hint: consider the chloride concentration present inside the cell)?

5. If 2.00 µM aquated cisplatin cis-$[Pt(Cl)(H_2O)(NH_3)_2]^+$ is the minimum concentration required inside the tumor cell to initiate tumor cell death, what is the initial concentration of cisplatin required inside the cell to achieve this minimum therapeutic threshold?

6. Cisplatin is more likely to form the aquated complex cis-$[Pt(Cl)(H_2O)(NH_3)_2]^+$ inside the tumor cell than it is outside of the cell (in the extracellular fluid and/or blood stream). Use Figure 1 above to explain this phenomenon (Hint: be sure to include Le Chatelier's Principle in your explanation).

7. Cisplatin is administered to a culture of tumor cells and the concentrations of cisplatin, aquated cisplatin, and chloride ion inside the cells are determined to be:

cis-$[Pt(Cl)_2(NH_3)_2]$ = 4.00 µM

cis-$[Pt(Cl)(H_2O)(NH_3)_2]^+$ = 0.00100 µM

$[Cl^-]$ = 4.00 mM

The reaction in which the aquated form of cisplatin is produced would shift in which way? (Hint: assume the equilibrium constant is 4.00).