Ru Metal Complex Interaction with DNA of Tumor Cells

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Abstract

In this project, computational chemistry was used to dock variations of (*p*-Cymene)Ru(curcuminato)chloro(Ru-cur) in DNA strands to find the best affinity for potential anti-cancer drugs. The Ru-cur complex has been chosen as the metal anticancer complex because it is not very toxic, selective for cancer cells, and has ligand exchange kinetics similar to those of platinum. First the geometry of the Ru-cur complex was optimized via a quantum mechanical method. Once the geometry of the complex was optimized, docking programs were explored to find the best docking poses and binding energies for the complex in DNA strands. Promising positions of the complex was refined using molecular dynamics programs such as Charmm.

(p-Cymene)Ru(curcuminato)chloro(Ru-cur)

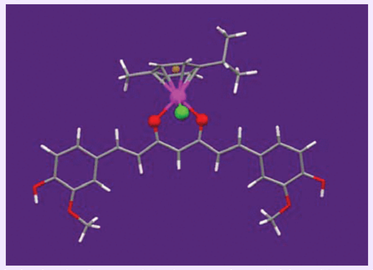

Figure 1. This is the (*p*-Cymene)Ru(curcuminato)chloro(Ru-cur) complex from the original literature article.

Background

Cancer has been a major public health problem worldwide for years as well as the second leading cause of death in the United States. Despite the increase in efficient anticancer drugs and prevention methods, an effective treatment has yet to be found for many types of cancer. Many medicinal drug candidates consist of organic compounds, but metal complexes provide various mechanisms which organic compounds do not. The three platinum bases drugs which are primarily used are cisplatin, carboplatin, and oxaliplatin. Unfortunately, cisplatin is a non-specific drug which causes systemic toxicity and serious long-term damage to normal cells.

Cisplatin Mechanism of Action.

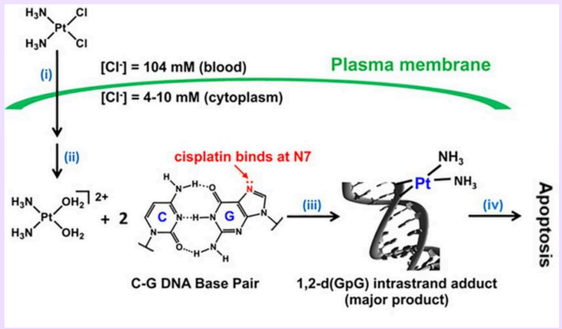

Figure 2. This diagram is representative of the cisplatin mechanism of action in tumor cells once it enters the plasma membrane.

Platinum v Ruthenium

Ruthenium has been found to be a very promising alternate to platinum. There are many advantages:

- Lower toxicity
- Broader range of oxidation states
- Slow rate of ligand exchange
- Different mode of action and reactivity
- Better water solubility in biological environment

Methods and Materials

Ru Complex.

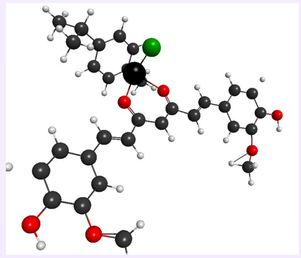

Figure 3. The above complex was built in Avogadro and further optimized for rough visualization of the complex.

Creation of Ru Complex.

- Ruthenium complex created in Avogadro
- Optimized through GAMESS
- Transferred to MSI
- Minimum energy structure generated

No Ru Complex.

- Additional complex was made without ruthenium for preliminary trials
- Built DNA structure for complex
- Analyzed structure with DNA through CHARMM-GUI Ligand Reader and Modeler
- Structure was further optimized with CHARMM
- DNA templates were created

Curcumin and p-Cymene Complex.

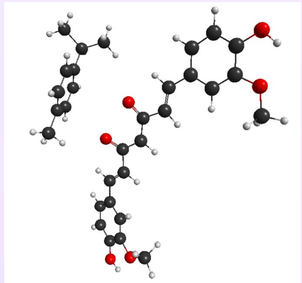

Figure 4. Ruthenium was taken out of the complex for preliminary trials because it was too large and bulky for the initial software programs being used.

Complex from DNA Test.

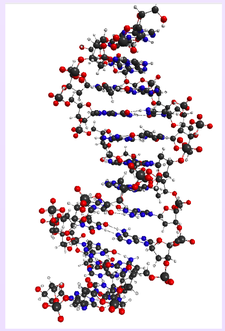

Figure 5. The above complex was generated to be used for further DNA tests.

DNA Test.

- Multiple trials were run due to abnormal results
- The final DNA template was generated
- The optimized structure was used further for system solvating

System Solvating.

- Solvation calculation was run to obtain the necessary files for further docking procedures
- A rough preliminary optimization was run
- The system was solvated to place counterions

DNA Complex Post Solvation

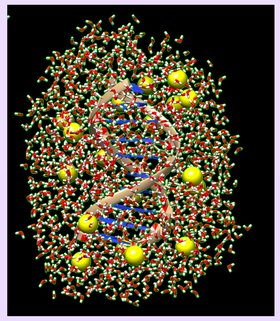

Figure 6. DNA complex after it was solvated.

Results

Docking.

- Generate electrostatic potential grid of the whole system
  - Docked in multiple configurations
- Ten different configurations were tested first, and energies were compiled
- Then 50 different configurations were tested, and the energy values were compiled again
- Docked ligand in macromolecule
- Sorted lowest energy configurations

Energy Configurations Pt 1.

Trial	Energy (kcal/mol)
1.	-103.75
4.	-103.20
6.	-102.31
7.	-88.97

Table 1. Data collected from the ten configurations generated the following energy values. The lowest three energy values and highest energy value were kept to compare to further energy values.

Energy Configurations Pt 2.

Trial	Energy (kcal/mol)
2.	-103.23
7.	-106.16
9.	443,564
18.	-105.55
29.	-104.92
33.	-103.70
36.	848.51
37.	-104.82

Table 2. Data collected from the 50 configurations generated the following energy values. The lowest six energy values and highest two energy values were kept to compare to previous energy values. The lowest of these (Trial 7) was used for further optimization.

Lowest Energy Configuration Docked.

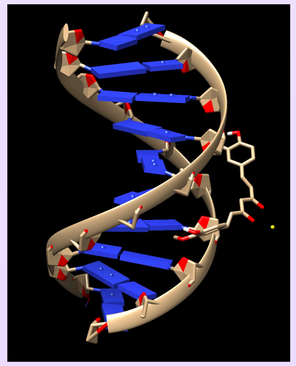

Figure 7. Visualization of configuration seven from part two of the docking simulation.

- Configuration seven was chosen to be docked as it was the lowest energy value obtained
- The complex was visualized through Chimera
- This configuration was used to align the complex in the minor groove of the DNA strand

Literature Curcumin Docked.

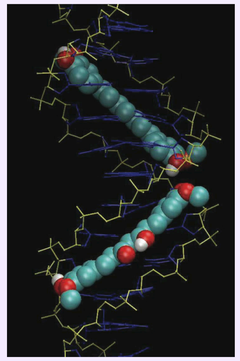

Figure 8. Visualization of two curcumin molecules docked in DNA strands.

- Data obtained was compared to literature to assess the relative spacial positions of the complex
- Literature compared two curcumin molecules docked in DNA strands
- Good agreement of the docked molecules were found in literature as well
  - Similar spacial positions were visualized from literature and experimental data

Conclusion

It has been concluded thus far that there was good agreement between the calculations in this work and in the literature for the structure of the curcumin molecule docked in DNA.

Future Procedures

- Further refinement of docked structure will be generated
- Molecular dynamics simulation can be further run because of this agreement with ruthenium and *p*-cymene added back into the structure
  - Predicts motions of atoms within system under given conditions
- Analyzes how well the complex binds with DNA
  - What types of interactions are present

Acknowledgements

Thank you to the Winona State Chemistry Department and University of Minnesota Twin Cities MSI for supplying instrumentation used in this research. A special thanks to Dr.Leverentz-Culp for her continual guidance on this project. Another thank you to Dr.West as well for providing literature and inspiration for this project.

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