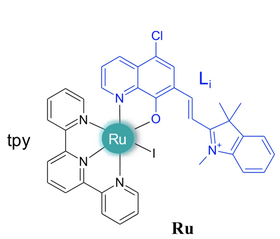
On the Nose: Exploring the Noncovalent Driving Forces of DNA Intercalation for Ru-Based Chemotherapeutic Agents

Nico Buksic and Dominic A. Sirianni

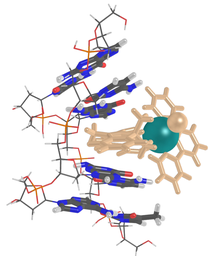
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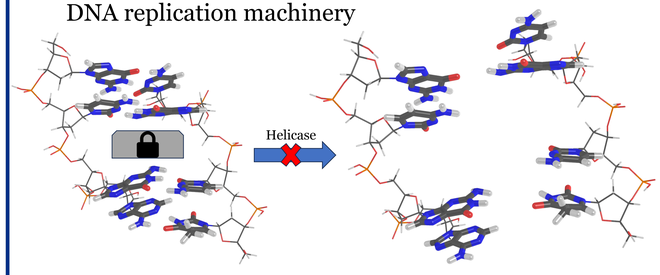
Project Background



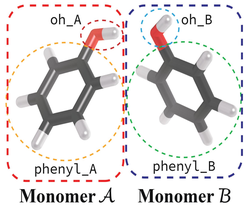
Ru



- Ru(III) is inert under normal physiological conditions
- Ru(III) is reduced to Ru(II) in acidic environments, such as cancer cells and will actively bind to DNA
- Strong axial Ru(II)–N binding w/ adjacent nucleotides
- Bound Ru(II) intercalator with associated scaffolding may act as targeted chemotherapy by interfering with DNA replication machinery



Computational Methods



Monomer $\mathcal{A}$ Monomer $\mathcal{B}$

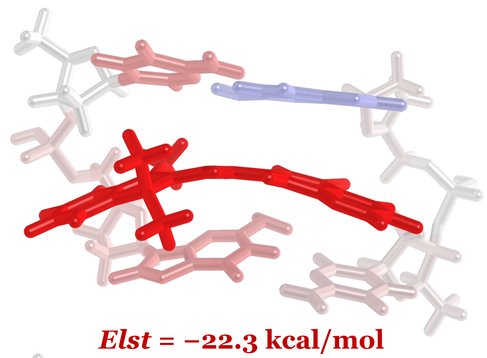
$$\mathrm{IE}^{\mathrm{F-/ISAPT0}}_{\mathcal{A}\cdot\mathcal{B}} = E^{(10)}_{\mathrm{elst}} + E^{(10)}_{\mathrm{exch}} + E^{(20)}_{\mathrm{ind,resp}} + E^{(20)}_{\mathrm{exch-ind,resp}} + E^{(20)}_{\mathrm{disp}} + E^{(20)}_{\mathrm{exch-disp}} + \delta^{(2)}_{\mathrm{HF}}$$

$$\mathrm{IE}^{\mathrm{F-/ISAPT0}}_{f_i^{\mathcal{A}}\cdot\mathcal{B}} = E^{(10)}_{\mathrm{elst}} + E^{(10)}_{\mathrm{exch}} + E^{(20)}_{\mathrm{ind,resp}} + E^{(20)}_{\mathrm{exch-ind,resp}} + E^{(20)}_{\mathrm{disp}} + E^{(20)}_{\mathrm{exch-disp}}$$

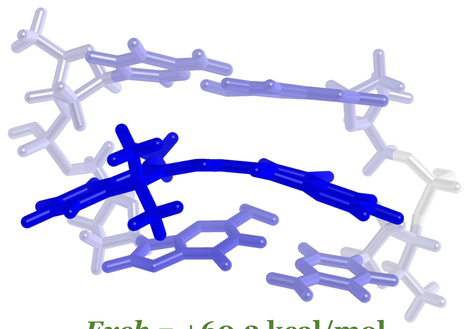
$$\mathrm{IE}^{\mathrm{F-/ISAPT0}}_{f_i^{\mathcal{A}}\cdot f_j^{\mathcal{B}}} = E^{(10)}_{\mathrm{elst}} + E^{(10)}_{\mathrm{exch}} + E^{(20)}_{\mathrm{ind,resp}} + E^{(20)}_{\mathrm{exch-ind,resp}} + E^{(20)}_{\mathrm{disp}} + E^{(20)}_{\mathrm{exch-disp}}$$

- F/I-SAPT[1,2] used to compute noncovalent interaction energies and components between monomers and their associated functional groups
- QM-refined Ru-I system[3] was partitioned into closest DNA tetramer with (mono B) and ligand L(mono A)

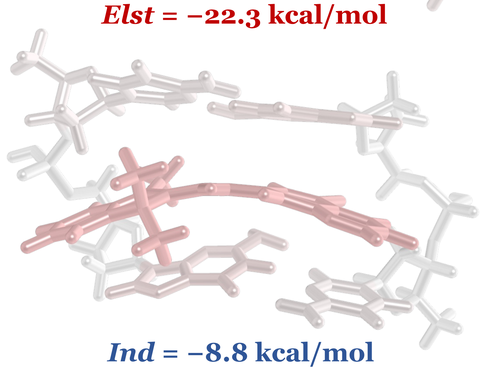
Ru-I F/I-SAPT Results (kmol/mol)



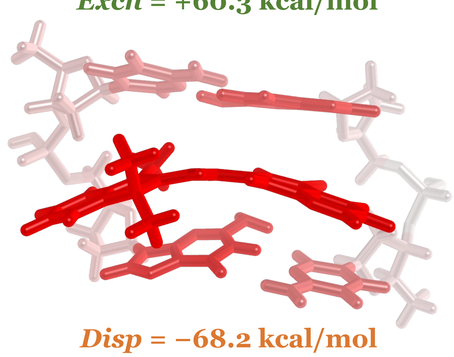
***Elst* = −22.3 kcal/mol**



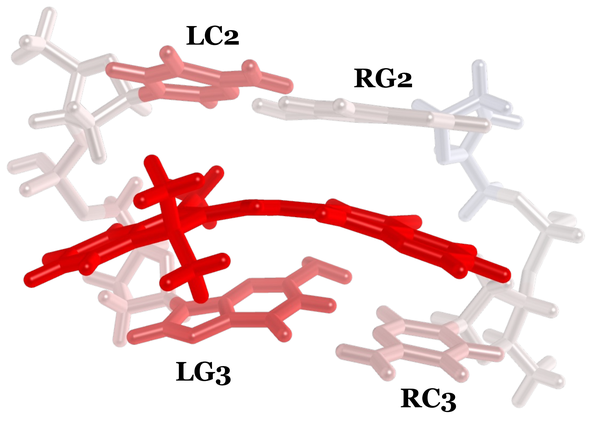
***Exch* = +60.3 kcal/mol**



***Ind* = −8.8 kcal/mol**



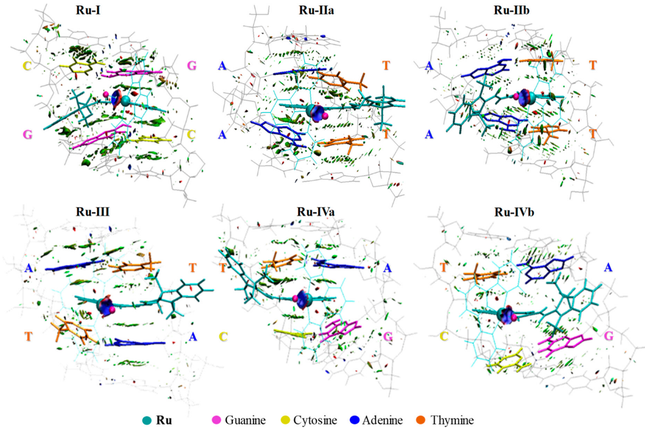
***Disp* = −68.2 kcal/mol**



Total IE = −39.0 kcal/mol



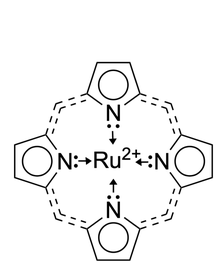
Comparison w/ Mazzone & co.[3]

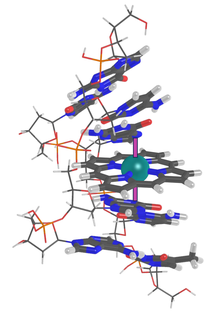


Preliminary Conclusions

- Repulsive electrostatic contact between Ligand—G2 missed by Mazzone & Co. may arise from unfavorable dipole alignment
- Overall favorable binding energy driven primarily by electrostatics and dispersion

Future Work





- Planar porphyrin-based scaffold may better intercalate & encourage axial Ru(II) binding
- Investigate F-/ISAPT dependence on remaining binding poses (Ru-IIa, Ru-IIb, Ru-III, Ru-IVa, Ru-IVb), use information to guide design of "nose" for porphyrin scaffold
- Synthesize novel intercalators and analyze binding

Acknowledgements: The authors wish to acknowledge funding support from Daemen University via a Think-Tank grant (#1-059050-51520) and computational support provided by the Palmetto Supercomputing Center made available through the MERCURY consortium and the National Science Foundation (Grants CHE-1626238, CHE-1662030, and CHE-2018427). D.A.S. also gratefully acknowledges financial support from the U.S. National Science Foundation (Grant No. OAC-2321044).

References:

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2. R. M. Parrish *et al. J. Chem. Phys.* **143**, 051103 (2015)
3. F. Ponte *et al. Inorg. Chem.* **62**, 8948 (2023)

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