Structural Determination and Evaluation of Theoretical Models and Basis Sets of Cisplatin-Amino Acid Analogues by IRMPD Action Spectroscopy

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Cisplatin

- Anti-cancer drug
- Chemical probe for structural RNA
- Resistance, neurotoxicity ...

Cisplatin
[cis-diamminedichloroplatinum(II)]

- Carrier ligands determine the adduct profile
- Purine N7 position; G > A
- Amino acids are great ligands

Lippert, B. *Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug*; Verlag Helvetica Chimica Acta; Wiley-VCH: Zürich
Cisplatin Amino-acid Derivatives

- Shows preference to A over G
- Proven at the nucleoside and structural RNA level
- When binding to adenosine, two different isomers have been observed
- Simplicity and less flexibility
- Low computational cost

Chow Group and Rodgers Group, unpublished data
Instrumentation

(Infrared Multiple Photon Dissociation)
IRMPD Action Spectroscopy

Sample:
~1-7 mM Glyplatin
dissolved in
MeOH:H₂O (50:50)
no acid

IRMPD yield = (∑I_f)/(I_p + ∑I_f)

IRMPD Mechanism

- Rapid intramolecular vibrational relaxation.

- Initially absorbed photon energy is distributed through the ion and is ready for the next photon absorption.

- The ion continues to absorb photons and redistribute that energy until the dissociation threshold is reached.

- IRMPD requires the absorption of tens to hundreds of photons.

Hybrid Basis Sets

- **Density Functional Theory Methods**
  - B3LYP, CAM-B3LYP, LC-ωPBE, PBE0, B3PW91, mPW1PW91, M06
- **Treatment of Platinum (Pt)**
  - Effective Core Potential
  - All-Electron Basis Sets
- **Basis Sets for non-Metal Atoms**
  - Pople, def2, Dunning

EMSL Basis Set Exchange https://bse.pnl.gov/bse/portal
# Basis Set for non-Metal Atoms

<table>
<thead>
<tr>
<th>Double Zeta</th>
<th>Pople</th>
<th>def2 (Ahlrichs)</th>
<th>Dunning</th>
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</thead>
<tbody>
<tr>
<td>6-31G</td>
<td>def2-SVP</td>
<td>cc-pVDZ</td>
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<tr>
<td>6-31G(d)</td>
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<td>aug-cc-pVDZ</td>
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<tr>
<td>6-31+G(d)</td>
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<tr>
<td>6-31+G(d,p)</td>
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<tr>
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<th>def2-TZVP</th>
<th>cc-pVTZ</th>
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<td>6-311+G(d,p)</td>
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<tr>
<td>6-311++G(d,p)</td>
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<td>6-311+(2d,2p)</td>
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<td>6-311+(3df,3dp)</td>
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<th>Quadruple Zeta</th>
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Gaussian 09
IRMPD Experiment for Glyplatin

B3LYP/def2-TZVPPD

Pt: def2 ECP (Effective Core Potential)

Scaling Factor: 0.98/0.95

[Pt(Gly-H)Cl\textsubscript{2}]\textsuperscript{-} NO binding

[Pt(Gly-H)Cl\textsubscript{2}]\textsuperscript{-} OO binding

[Pt(Gly-H)Cl\textsubscript{2}]\textsuperscript{-} O binding

Frequency (cm\textsuperscript{-1})

Relative Intensity

Intensity
Basis Sets Evaluation for Glyplatin

B3LYP/LANL2DZ/varing Pt:LANL2DZ ECP

[Pt(Gly-H)Cl2]−

6-31G, 6-31G(d), 6-31+G(d), 6-31+G(d,p), 6-311+G(d,p), 6-311+G(2d,2p), 6-311+G(3df,3pd).

Experimental
Conclusions

• Best result with the lowest cost: B3LYP/mDZP/def2-TZVP
• Selected based on structural information, not necessarily good for energetic description
Sidechain Effects

![Graph showing the frequency vs. relative intensity for different complexes: [Pt(Gly-H)Cl2]−, [Pt(Orn)Cl]⁺, and [Pt(Lys)Cl]⁺. Each complex is represented by a line graph with peaks at specific frequencies.]

- [Pt(Gly-H)Cl2]−
- [Pt(Orn)Cl]⁺
- [Pt(Lys)Cl]⁺

The graphs display the frequency (cm⁻¹) on the x-axis and relative intensity on the y-axis.
Acknowledgements

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