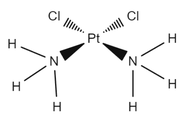
Synthetic pathways of platinum(IV) 2-phenylpyridine halogenic derivatives as potential anticancer agents

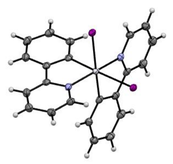
By Pierce Brooks

Introduction

Ever since the discovery of cisplatin's inhibition of sarcoma 180 cells in mice, cisplatin has been a staple anticancer drug.[1] However, literature has cited cisplatin resistance in sarcoma 180 cells in mice.[2] Furthermore, the usage of this drug is held back by its severe side effects.[3] Thus, further development of the field of platinum matallochemical anticancer research is needed. One promising avenue for this research is 2-phenylpyridine halogenic derivatives like Pt(IV)(ppy)2Cl2, which has demonstrated anticancer properties.[4] Therefore, I decided to try to synthesize halogenic variations of the form Pt(ppy)2X2 with the intention of testing and comparing the different derivatives' anticancer properties. The scope of this poster and my research up until now has been to develop a synthetic pathway to create variations with iodine.



Cisplatin



$Pt(ppy)_2X_2$

The Compounds

During my research, I dealt with multiple intermediates and multiple pathways. For conciseness, I have labeled these compounds according to overall order of synthesis (see "Synthesis" section). Characteristics reported to the right were attained by my experimentation.

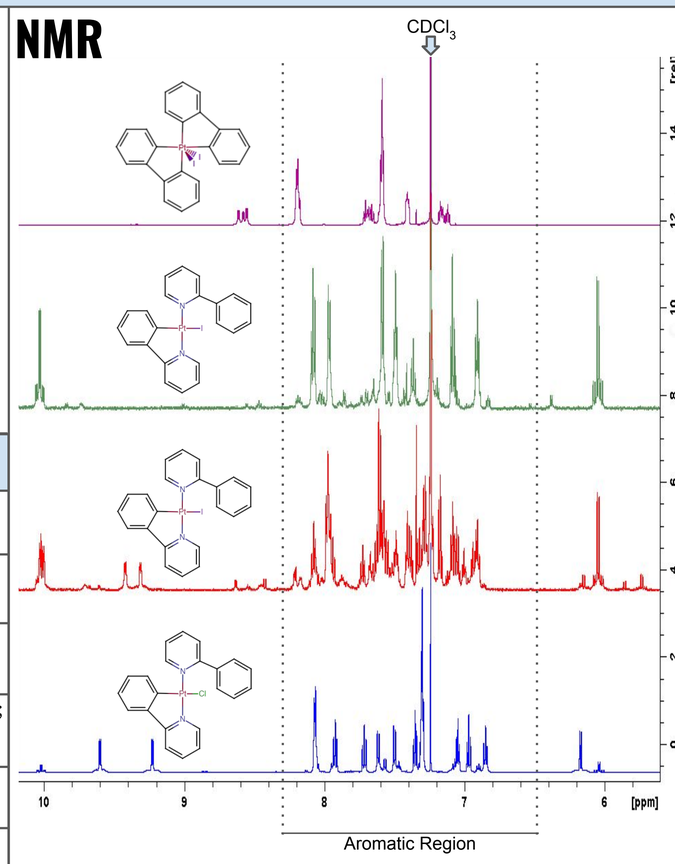
Of particular interest is Compound 4, the synthesis and properties of which has not yet reported in the scientific literature.

Future research is to include further halogenic variation of the compounds.

Compound	Identity	Characteristics
Compound 0	K2PtCl4	Red powder; sl. sol. H2O/tert-butanol; polymerizes quickly in H2O
Compound 1	Pt(ppy)(ppyH)Cl	Yellow powder; v. sol. DMF; sl. sol. THF, acetone; sol. CHCl3; insol. methanol
Compound 2	Pt(ppy)(ppyH)I	Dull yellow/tan brown powder; v. insol. H2O; insol. methanol; sl. sol. acetone
Compound 3	Pt(ppy)2I2	Tan; sol. THF; v. sl. sol. DMF, CHCl3, benzene; insol. propanol, methanol, pentane, H2O
Compound 4	Pt(ppy)2ICl	Unknown, not found in literature.
Compound 5	Pt(ppy)(ppyH)Br	Unknown

Table 1: labelling scheme and experimentally derived characteristics of experimental products and intermediates. Notice that Compounds 1-4 have different halogens. See "Synthesis" section for synthetic pathway.

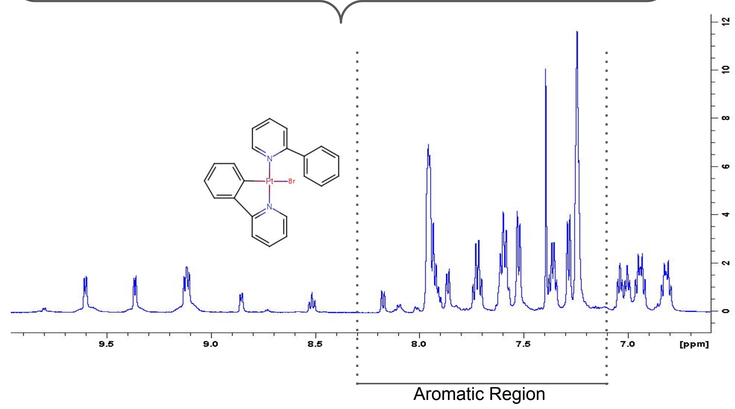
NMR



^{1}H NMR of compounds 1-3 in $CDCl_3$
Solvent peak = 7.24 ppm

Purple: Compound 3, path C
Green: Compound 2, Path D+E
Red: Compound 2, Path B
Blue: Compound 1, Path A

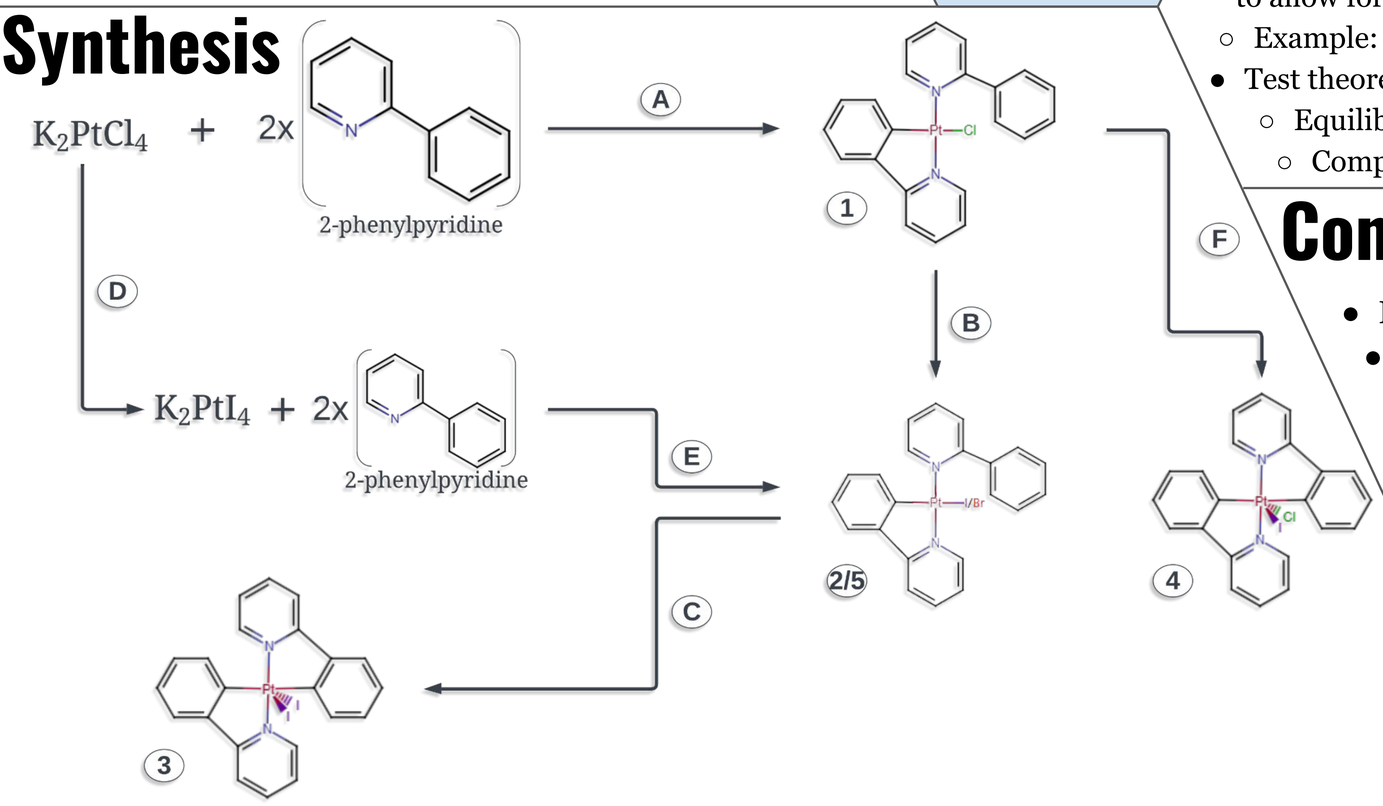
^{1}H NMR of Compound 5 in $CDCl_3$ + methanol-d4
Path B



Methods

Synthesis occurred according to multiple different theoretical pathways. Identities of products and reactants were determined the proton, ^{13}C, and ^{195}Pt NMR. Confirmation of a reaction's success was also done by noting variation between spectra of reactants and products.

Synthesis

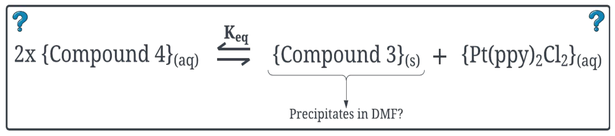


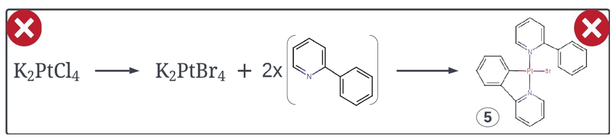
Path	Reagents	Product	Solution	Duration, Temp.	Wash	Yield
A	Compound 0, 2-phenylpyridine	Compound 1	1:1 H2O:*tert*-butanol	24 hr, 80°C	Vacuum filtration w/ methanol wash	76%
B	Compound 1, NaI/NaBr	Compound 2/5	Acetone/CHCl3+methanol	24 hr, 25°C	In vacuo evap., vacuum filtration w/ H2O wash	80%
C	Compound 2, I2	Compound 3	CHCl3	24 hr, 25°C	DMF washes, vacuum filtration w/ DMF wash	18%
D	Compound 0, NaI	K2PtI4	DI H2O	60 s, 25°C	No wash, proceed to path E	75%
E	K2PtI4, 2-phenylpyridine	Compound 2	1:1 H2O:*tert*-butanol	24 hr, 75°C	Vacuum filtration w/ methanol wash	75%
F	Compound 1, I2	Compound 4	CHCl3	20 min, 25°C	N/A	N/A

Future Research

Because this research is still ongoing and young, there is still more research in progress or to be done:

- Obtain and comprehensively analyze all compounds' ^{195}Pt and ^{13}C NMR spectra
- Conduct elemental analysis
- Conduct tests on cancer cultures
- Solvent modification in current synthesis pathways to allow for reactivity of different halogenic reagents
  - Example: Path B, Compound 5
- Test theoretical reactions
  - Equilibrium and precipitation selectivity
  - Compound 0 bromination





Conclusions

- Pathways A-E are effective means of producing Compounds 1, 2, 3, and 5
  - Pathway F is ineffective
    - Many NaX's do not effectively substitute NaI in pathway D, likely due to lowered free ion stability (as per Finkelstein reaction).
      - Solvent variation of successful paths (example: Compound 5, Path B) appears to be an effective means of ligating other halogens
        - The isolation process of Compound 2 is a substantial hazard to sanity
          - Pathway A is highly effective and consistent
            - Equilibrium may prove effective route to selective compound synthesis

Acknowledgements

Dr. Murphy for help with NMR, Dr. Howard for mentorship, Dr. Keller for help with WebMO, Shadrach Stitz for being a great lab partner, and Dr. Drew for guidance in research involvement.

References

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Research reported in this publication was supported by an Undergraduate Research and Scholarly Activity funding by the University of Alaska Fairbanks.