Computational Modeling, Energy State Calculations, and Determination of the Barriers to Rotation of Atropisomeric β-Carbolines

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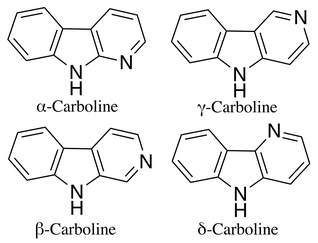
Project Abstract

Axially chiral molecules that have high barriers to rotation about a single bond are called atropisomers [1]. Methods to generate single-chirality atropisomers and other axial chiral molecules are still scarce in the field of organic chemistry. This project aims to fill this gap by utilizing computational chemistry to generate energy profiles and determine the barriers to rotation of a library of atropisomeric β-carboline compounds using the program Spartan. Computational data will be useful to guide experimental synthesis in the future. Various substituents on the atropisomeric β-carboline scaffold can impact the steric strain in the molecule, the electronic effects including induction and conjugation, and any intramolecular hydrogen bonding that could occur. All these factors can impede bond rotation [2]. With knowledge about these substituent's impact on the magnitude of the barrier to rotation, we will be able to determine which atropisomeric β-carbolines are the best suited to synthesize experimentally.

What are carbolines and why use β-carbolines in the project?

- Carbolines are cyclic molecules that contain three fused, aromatic rings and nitrogen atoms located at different positions in one of the six-membered rings
- Four different classes of carbolines are distinguished by the location of the nitrogen atom in one of the six-membered rings

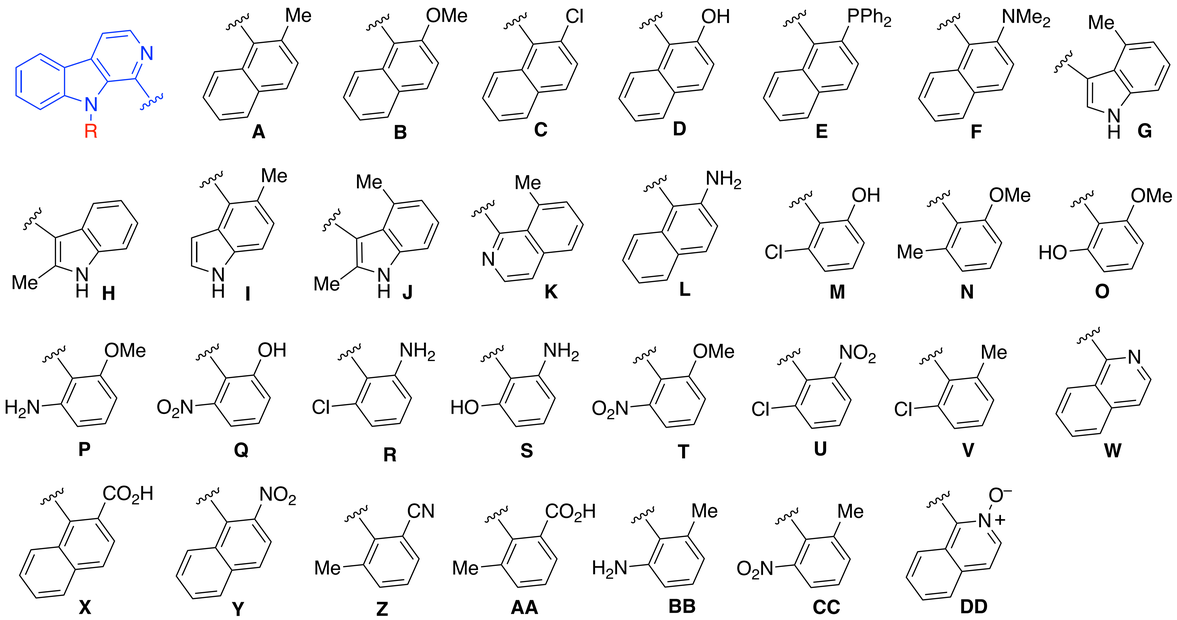


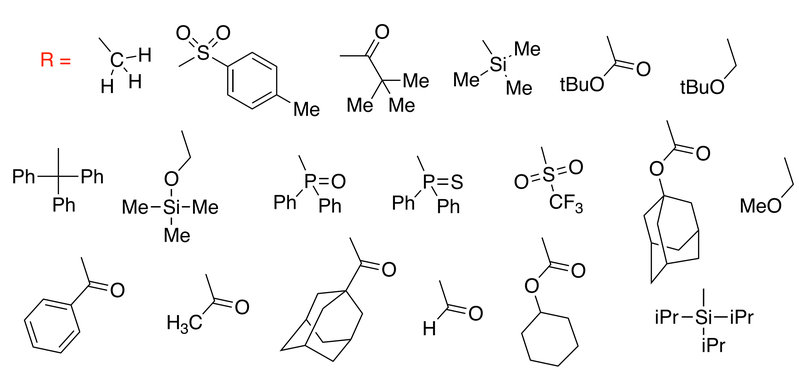
- β-carbolines are useful because they have been shown to be ligands, or molecules that bind to other molecules, for macromolecules such as protein receptors and even DNA

What was accomplished in the research?

- A library of differently-substituted atropisomeric β-carbolines was prepared
- Molecules were modeled using the computational chemistry software Spartan
- Equilibrium geometries and energy profiles were computed using multiple computational chemistry theories:
  - Møller–Plesset Perturbation (MP3)
  - Hartree-Fock (HF)
  - Density-functional theory (DFT)
- The atropisomeric β-carbolines with the largest energetic barriers to rotation were evaluated for their feasibility to synthesize in the lab

Computational Library of Differently-Functionalized Atropisomeric β-Carbolines



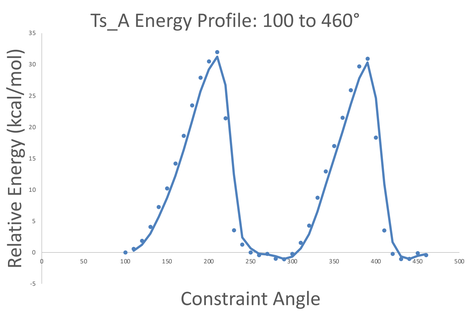


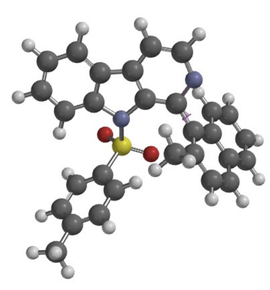
Features of the Library

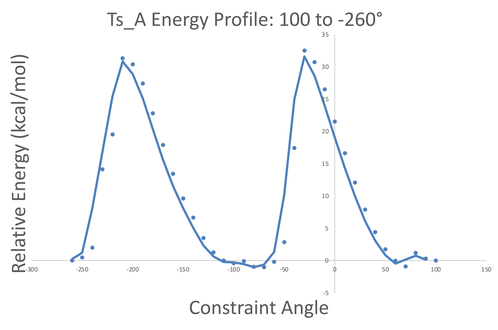
- All molecules contain the β-carboline scaffold
- 30 uniquely functionalized steric groups (A through DD)
- 19 nitrogen protecting groups
- Each molecule was computationally modeled using Spartan
- Two energy profiles (forward and reverse rotation) obtained for each molecule
- Barriers to rotation determined for each atropisomeric β-carboline

Sample Energy Profiles and Spartan Computational Geometry Model of Ts_A

- The atropisomeric β-carboline modeled below contains a Tosyl group on the nitrogen atom and steric group "A" from the library shown above
- Molecules will always follow the lowest-energy pathway to rotation
- Two barriers to rotation for forward and reverse rotation were obtained

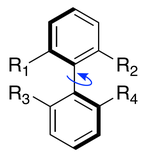






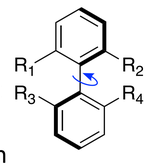
What are atropisomers?

- A class of isomeric compounds that have restricted rotation around a single bond
- Contain an axis of chirality
- Multiple enantiomeric forms of an atropisomer can be distinguished from one another



In the figures to the right:

- The single bond connecting the two rings in the molecule shown to the right cannot undergo unrestricted rotation
- Sterically bulky "R" groups restrict rotation

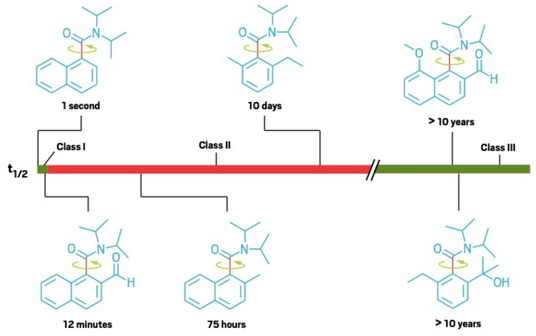


Atropisomers in Pharmaceuticals

- 15% of small molecules approved by the FDA are atropisomeric [3]
- Rapidly interconverting atropisomers are nearly ubiquitous in drug discovery [3]
- Contribute to the structure-function relationship:
  - One atropisomer may be more selective or effective towards a specific target than the other one

Atropisomer Stability

	Barrier to Rotation (kcal/mol)	Time required to Racemize ($t_{1/2}$)
Class I	< 20	Seconds to Minutes
Class II	20-30	Hours to Days
Class III	> 30	Years



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2. Bott, G.; Field, L. D.; Sternhell, S. Steric Effects. A Study of a Rationally Designed System. *Journal of the American Chemical Society* **1980**, *102*, 5618-5626.
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Acknowledgments

We gratefully acknowledge Providence College for financial support for this research. Special thanks to Colby Agostino, Riley Hughes, and Michael Shaw.