Quantum Mechanical Simulation of Fluorine-Containing Biomolecules

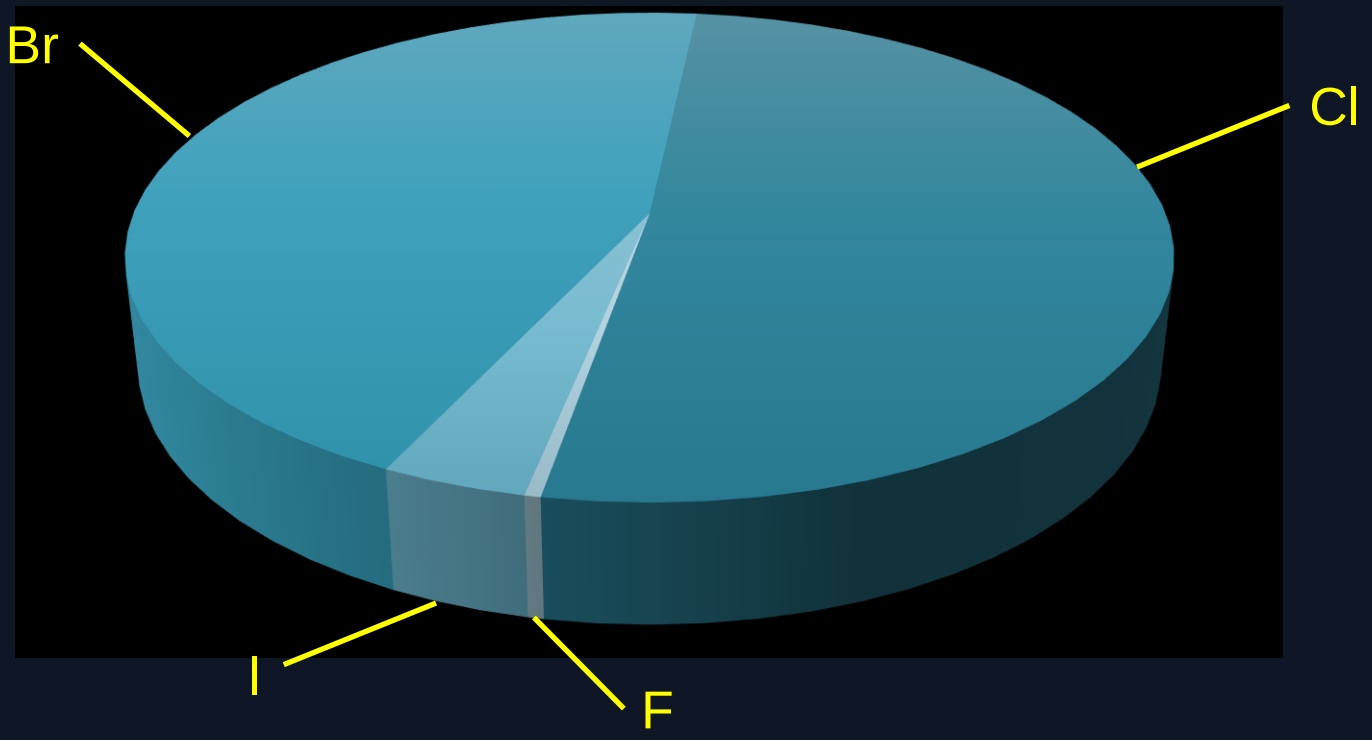
Student: Matthew Paolella, University of Rhode Island
mpaolell@uri.edu, 267-615-6502
Researcher: Dr. Fang Wang, University of Rhode Island
fangwang@uri.edu, 401-874-4243

04/19/2024

CAREERS CYBERTEAM

Fluorine plays almost no role in biosphere

There are about 4700 naturally occurring organohalogen compounds



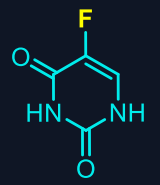
Chlorine-containing: 2400
Bromine-containing: 2100
Iodine-containing: 180
Fluorine-containing: 20

CAREERS CYBERTEAM

G. W. Gribble, *J. Chem. Educ.* **2004**, *81*, 1441; G. W. Gribble, *Naturally Occurring Organohalogen Compounds-A Comprehensive Update* **2010**, 1; M. C. Walker, M. C. Y. Chang, *Chem. Soc. Rev.* **2014**, *43*, 6527; L. Wang, X. Zhou, M. Fredimoses, S. Liao, Y. Liu, *RSC Advances* **2014**, *4*, 57350. K. K. J. Chan, D. O'Hagan, *in Methods Enzymol.*, 516, Academic Press, **2012**, 219.

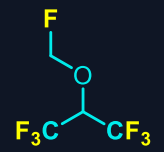
Fluorine is commonly used in bioactive molecules

To date, 20% of drugs and 30% of agrochemicals contain fluorine.

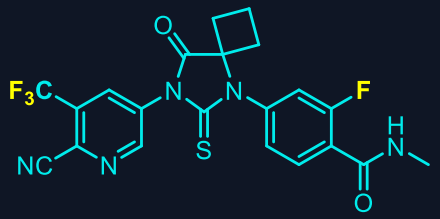


Fluorouracil
(5-FU, antitumor)

Isoflurane
(anesthetic)

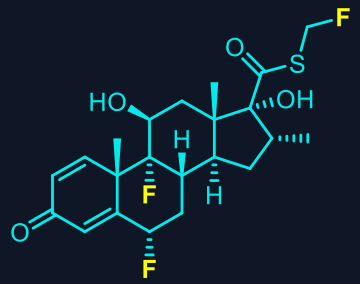


Sevoflurane
(anesthetic)

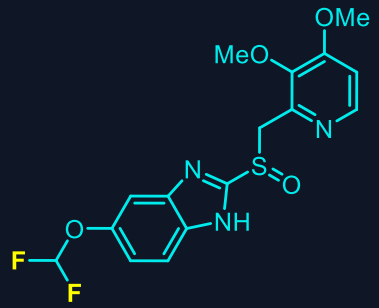


Erleada
(nonsteroidal antiandrogen)

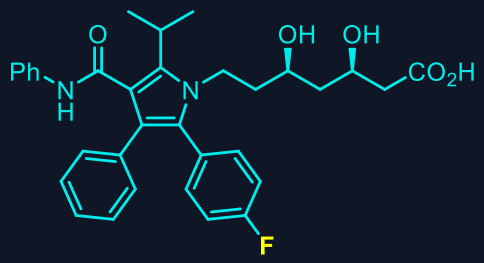
Efavirenz
(HIV-RT inhibitor)



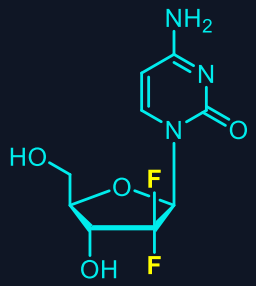
Fluticasone
(anti-inflammatory)



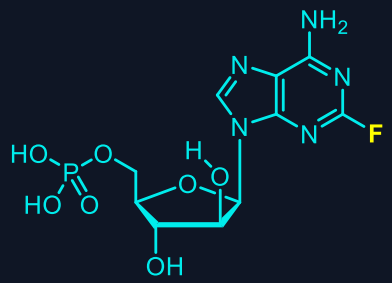
Pantoprazole
(treating stomach ulcers)



Lipitor
(treating high cholesterol)



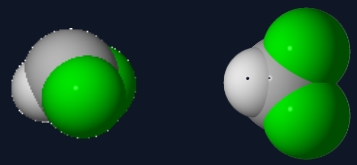
Gemcitabine
(chemotherapy drug)

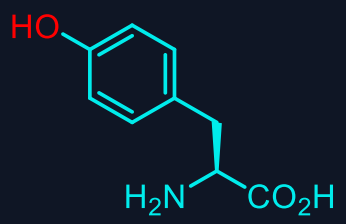


Fludarabine
(chemotherapy drug)

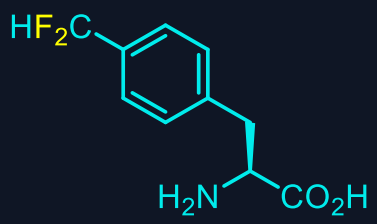
C. Ni, J. Hu, *Synlett* **2011,** 770-782, G. K. S. Prakash, **F. Wang**, *Chimica Oggi,* **2012**, *30*, No. 5.

Fluorine-containing moieties can be used to mimic other functional groups

substituent	electronegativity	*space filling model*
–CF_2H (difluoromethyl)	3.00	
–OH (hydroxyl)	3.51	



Tyrosine
(naturally occurring amino acid)



Fluorinated tyrosine mimic
(fluorine-containing amino acid)

CAREERS CYBERTEAM

Quantum Mechanical Simulation of Fluorine-Containing Biomolecules

- Goals
  - Compute the physicochemical properties of fluorine-substituted molecules using Density Functional Theory (DFT) to determine hydrogen bonding capabilities
  - Compare these theoretical calculations to experimental results obtained in the lab
  - Establish relationships between data sets as a basis for predicting the properties and interactions of these molecules

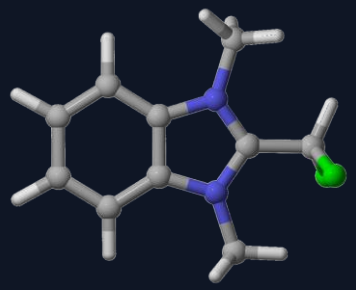
CAREERS CYBERTEAM

Quantum Mechanical Simulation of Fluorine-Containing Biomolecules

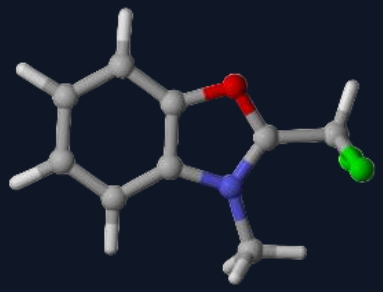
- Timeframe
  - Start date: October 1st, 2023
  - End date: April 1st, 2024

CAREERS CYBERTEAM

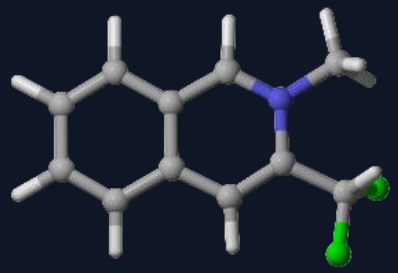
Fluorine Containing Molecules Investigated Through Theoretical Calculations



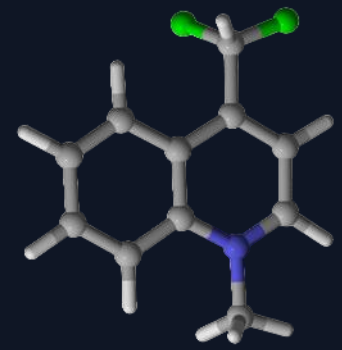
Fluorine substituted benzimidazole molecule



Fluorine substituted benzoxazole molecule



Fluorine substituted isoquinoline molecule



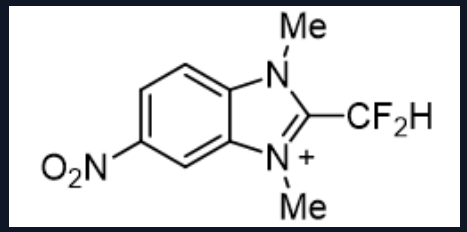
Fluorine substituted quinoline molecule

CAREERS CYBERTEAM

Optimized at the (IEFPCM-DMSO) M06-2X/6-31+G(d,p) level

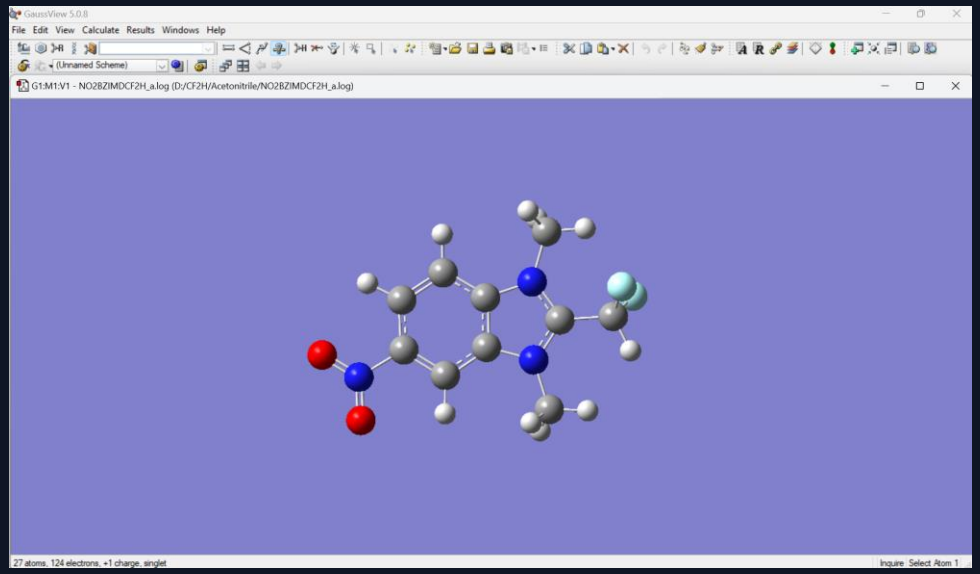
Gaussian Calculations Performed Using HPC

Simple Structure



Fluorine substituted nitro benzimidazole molecule

Gauss View Structure



Fluorine substituted nitro benzimidazole molecule

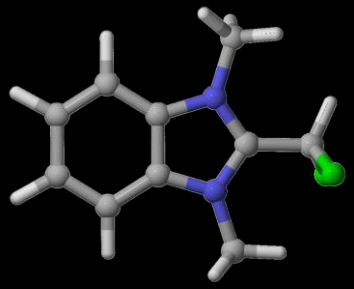
CAREERS CYBERTEAM

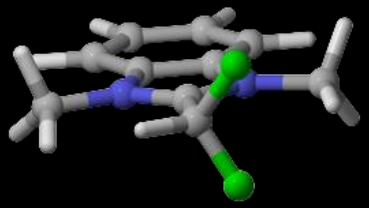
Gaussian Calculations Performed Using HPC

- Optimization → Geometric optimization
- Frequency → Vibrational frequencies
- Energy → Single point energy
- NMR → Shielding of nuclei
- Scan → Potential energy surface scan

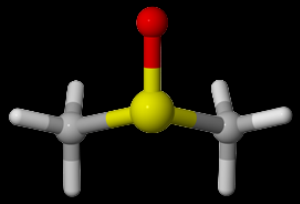
CAREERS CYBERTEAM

Theoretical Hydrogen Bonding Energy Determined by Data Obtained from Gaussian Optimizations

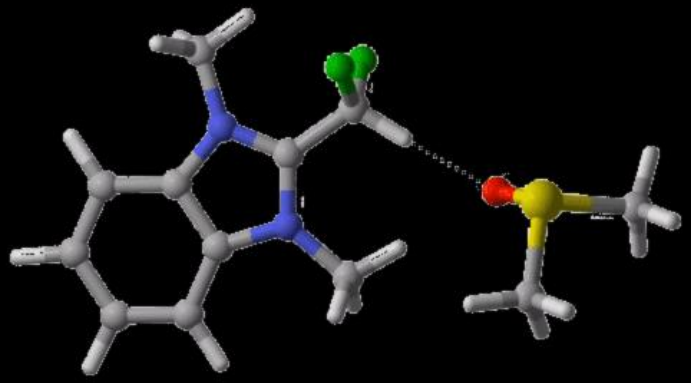




Fluorine substituted benzimidazole molecule



Dimethyl sulfoxide (DMSO)



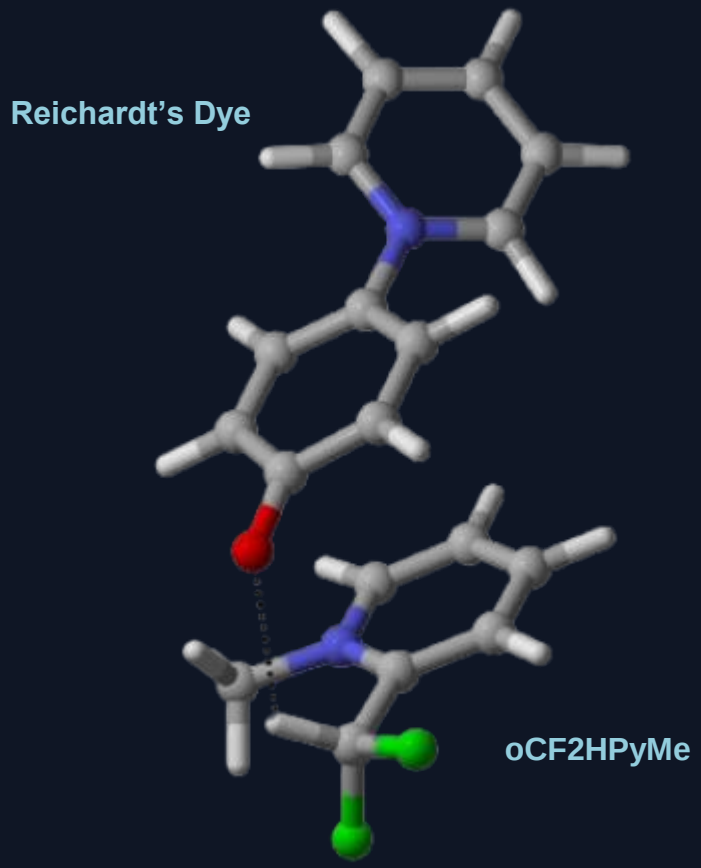
ΔE= -6.8 kcal/mol
ΔG= 2.3 kcal/mol
NBO H Charge= 0.28
K_a= 48.6 M^{-1}

Hydrogen bonding complex between fluorine substituted benzimidazole and DMSO

CAREERS CYBERTEAM

Optimized at the (IEFPCM-DMSO) M06-2X/6-31+G(d,p) level

Experimental Procedures to Generate Data for Comparison

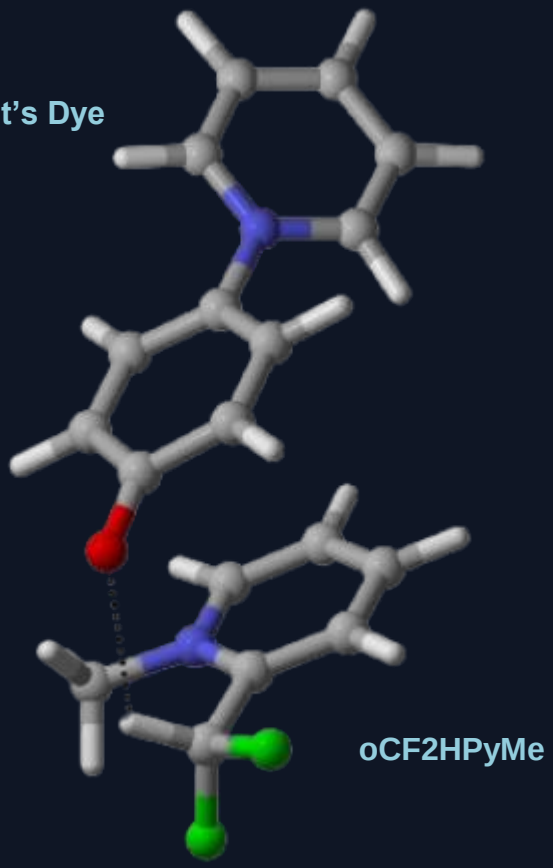


- UV-Vis Titration
  - Measuring change in absorption of a solution as concentration changes
  - A hydrogen bond changes the absorption of Reichardt's Dye
  - The concentration and absorption change can be used to calculate an association constant

CAREERS CYBERTEAM

Optimized at the (IEFPCM-Acetonitrile) M06-2X/6-31+G(d,p) level

Experimental Procedures to Generate Data for Comparison



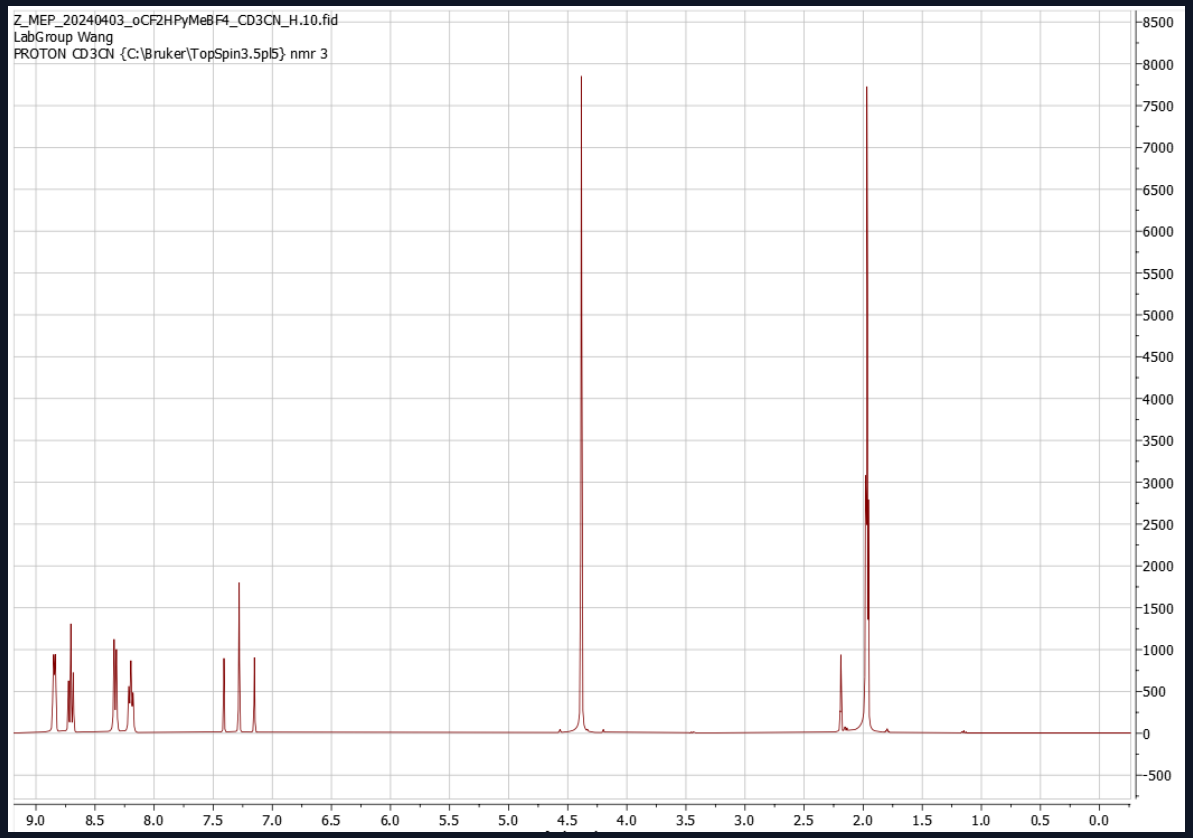
Theoretical: $K_a = 113.1\ M^{-1}$

Experimental: $K_a = 152.74\ M^{-1}$

CAREERS CYBERTEAM

Optimized at the (IEFPCM-Acetonitrile) M06-2X/6-31+G(d,p) level

Nuclear Magnetic Resonance (NMR) Experiments

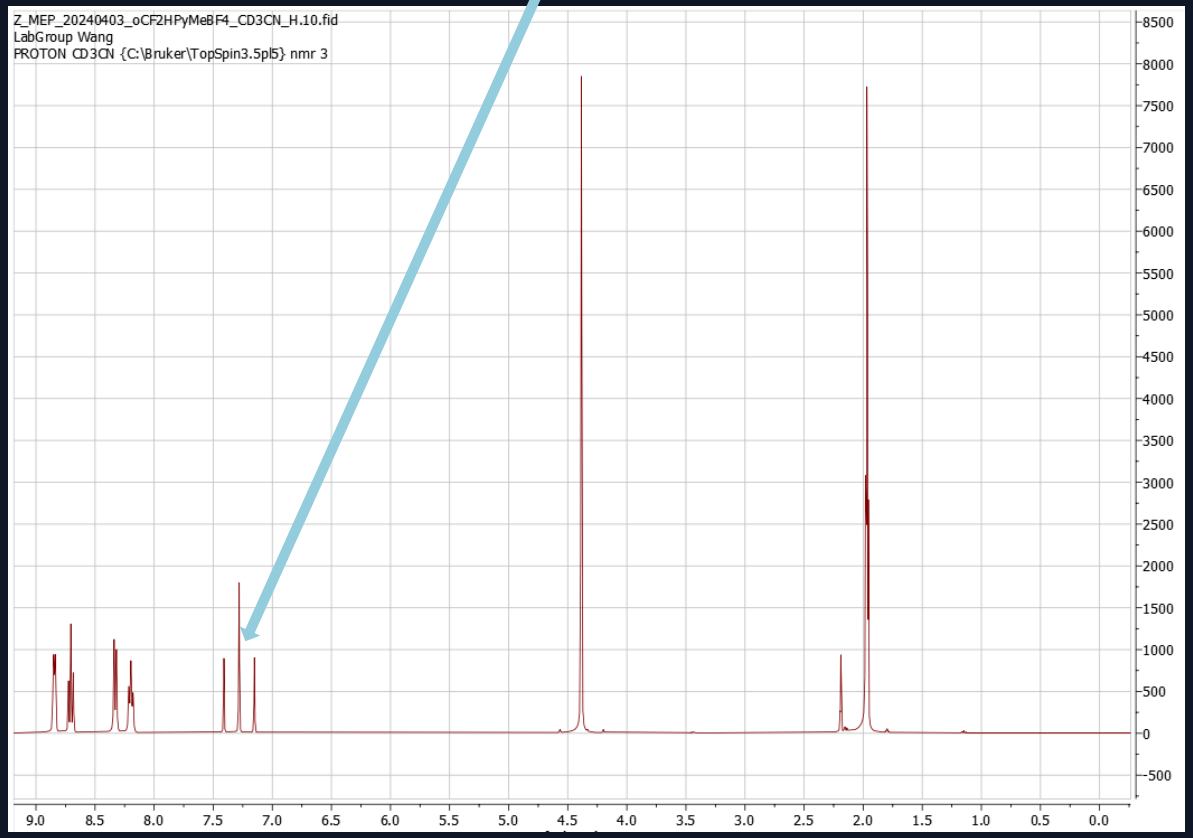


- An “MRI For Molecules”
  - Each peak corresponds to an atom within the molecule

CAREERS CYBERTEAM

NMR Spectrum of Fluorine Substituted Methyl Pyridine

```
  10   H     Isotropic =     24.3707   Anisotropy =      4.2253
XX=     22.5991   YX=     -1.4226   ZX=     -0.5973
XY=     -1.6454   YY=     26.1591   ZY=     -1.1677
XZ=     -3.1934   YZ=     -2.1563   ZZ=     24.3537
```

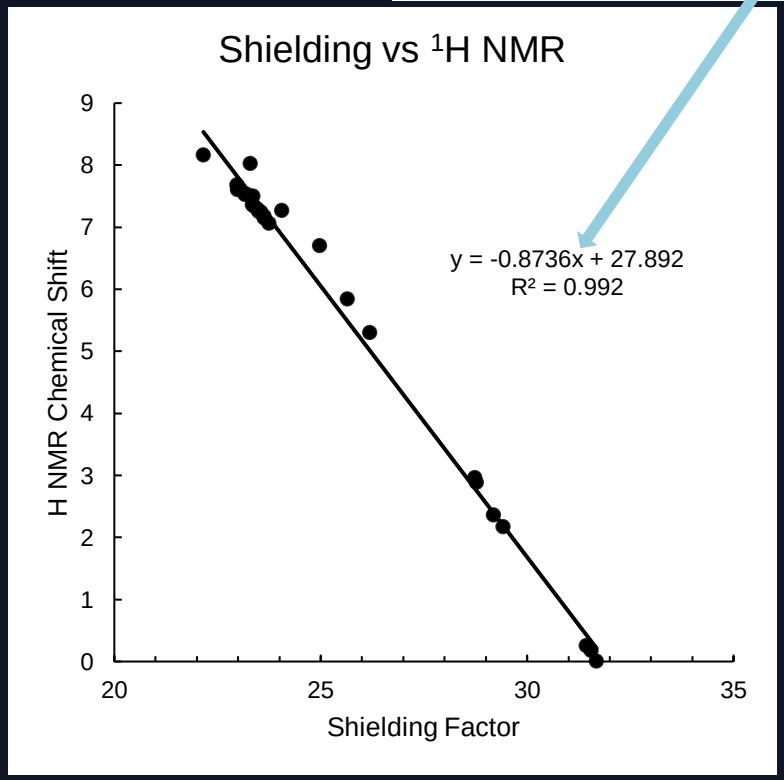


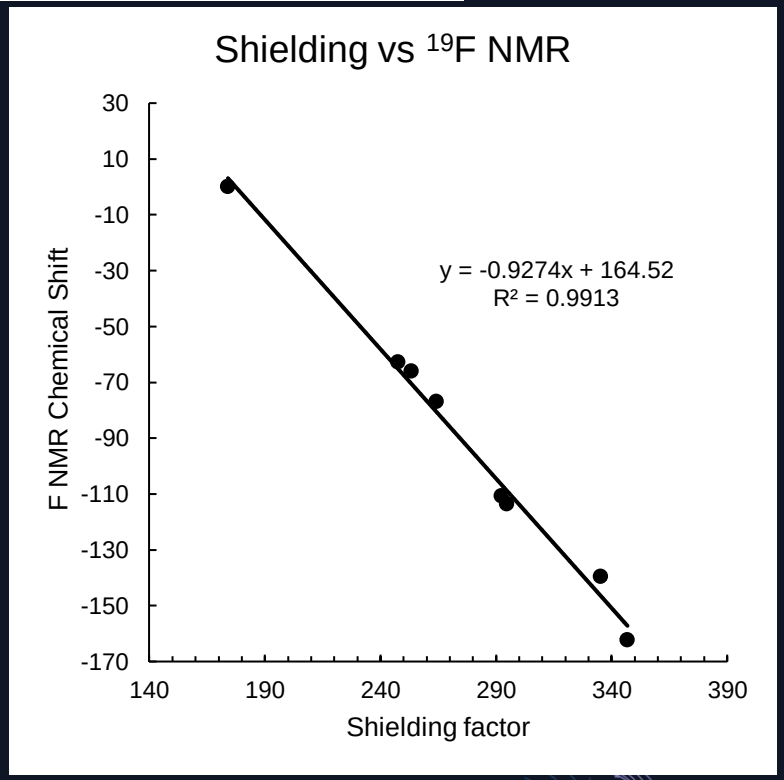
Gaussian calculations do not generate a chemical shift spectrum like this. They calculate the **shielding tensor of each atom, which is scaled differently than chemical shift.**

CAREERS CYBERTEAM

Linear Regressions Generated From Known Reference Compounds

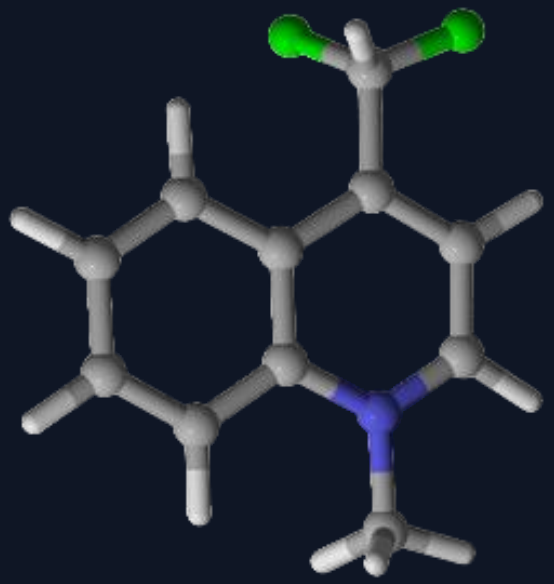
10	H	Isotropic =	24.3707	Anisotropy =	4.2253		
XX=	22.5991	YX=	-1.4226	ZX=	-0.5973		
XY=	-1.6454	YY=	26.1591	ZY=	-1.1677		
XZ=	-3.1934	YZ=	-2.1563	ZZ=	24.3537		



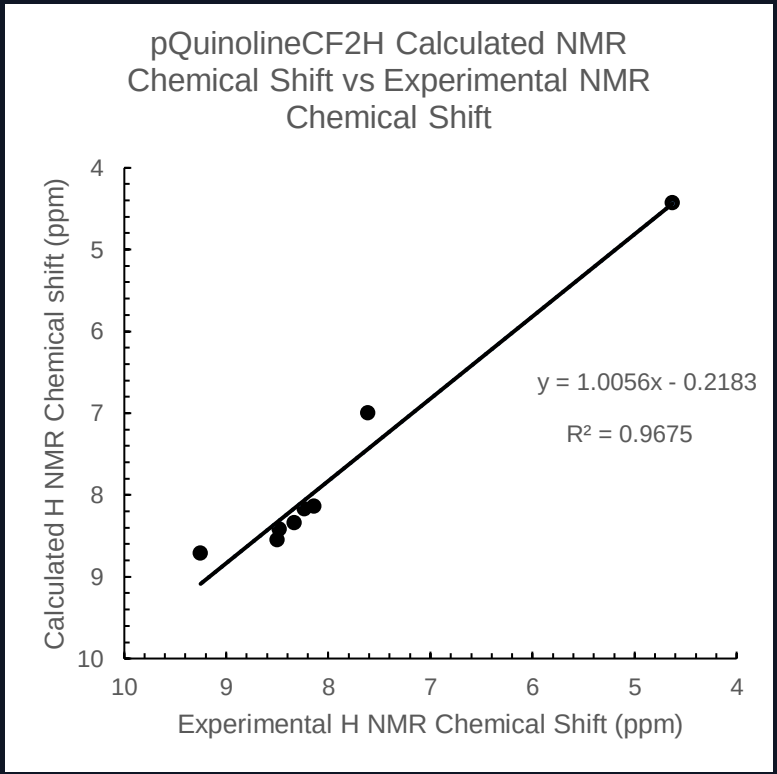


CAREERS CYBERTEAM

Correlation of Calculated NMR with Experimental NMR



Fluorine substituted quinoline molecule



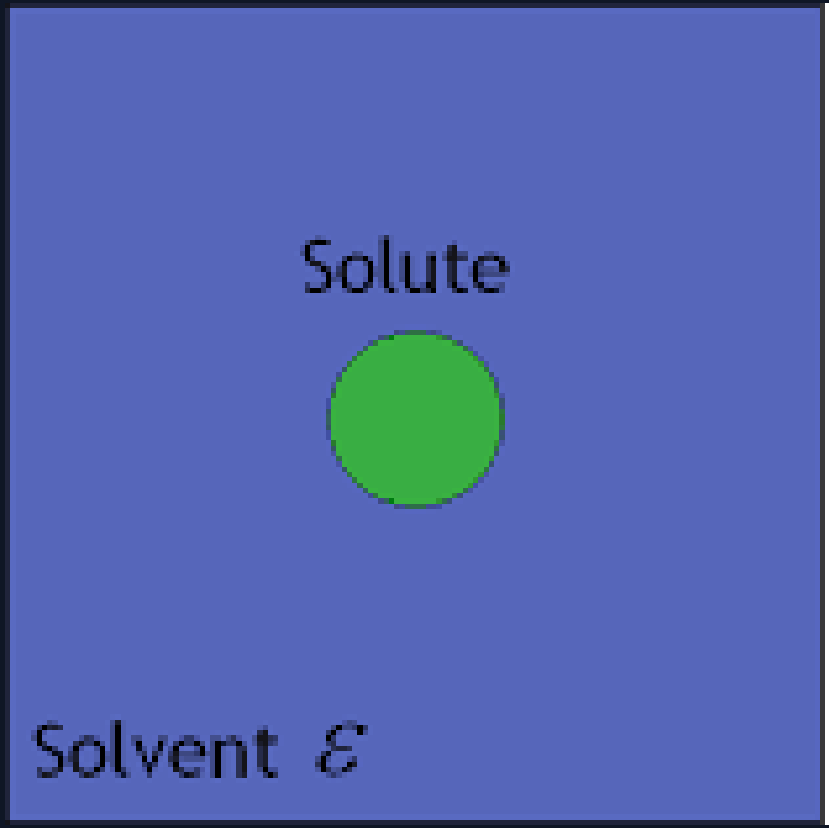
Optimized at the (IEFPCM-Acetonitrile) M06-2X/6-31+G(d,p) level

Correction for Solvent Effects

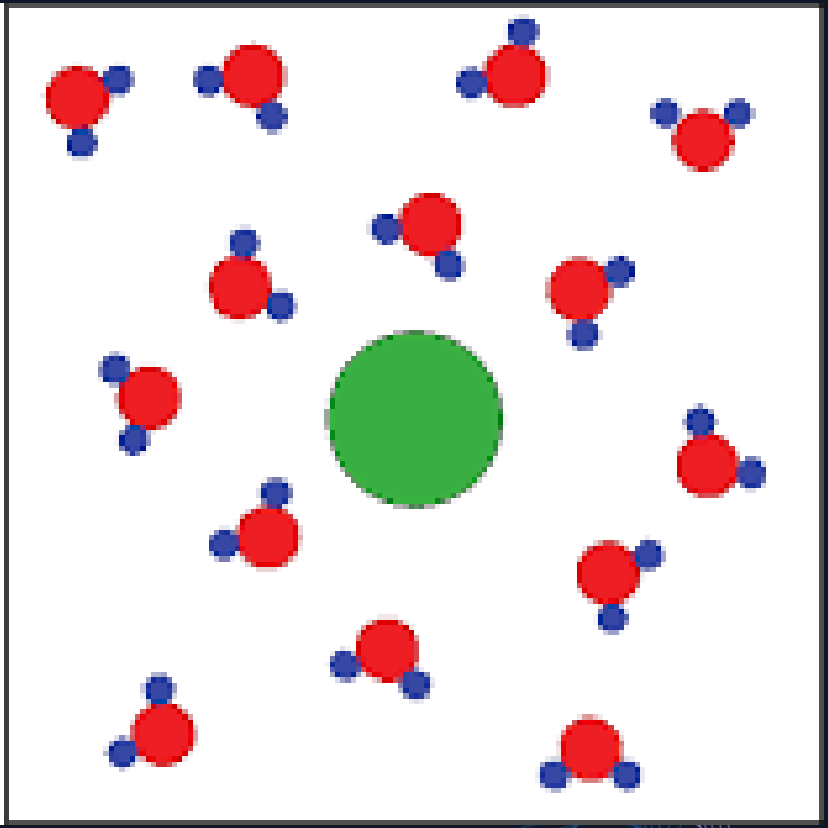
- The Polarizable Continuum Model in Gaussian considers your molecule in the net "field" of the solvent
- Does not account well for actual interaction with individual solvent molecules

Correction for Solvent Effects

Polarizable Continuum Model



Reality (individual solvent molecules)

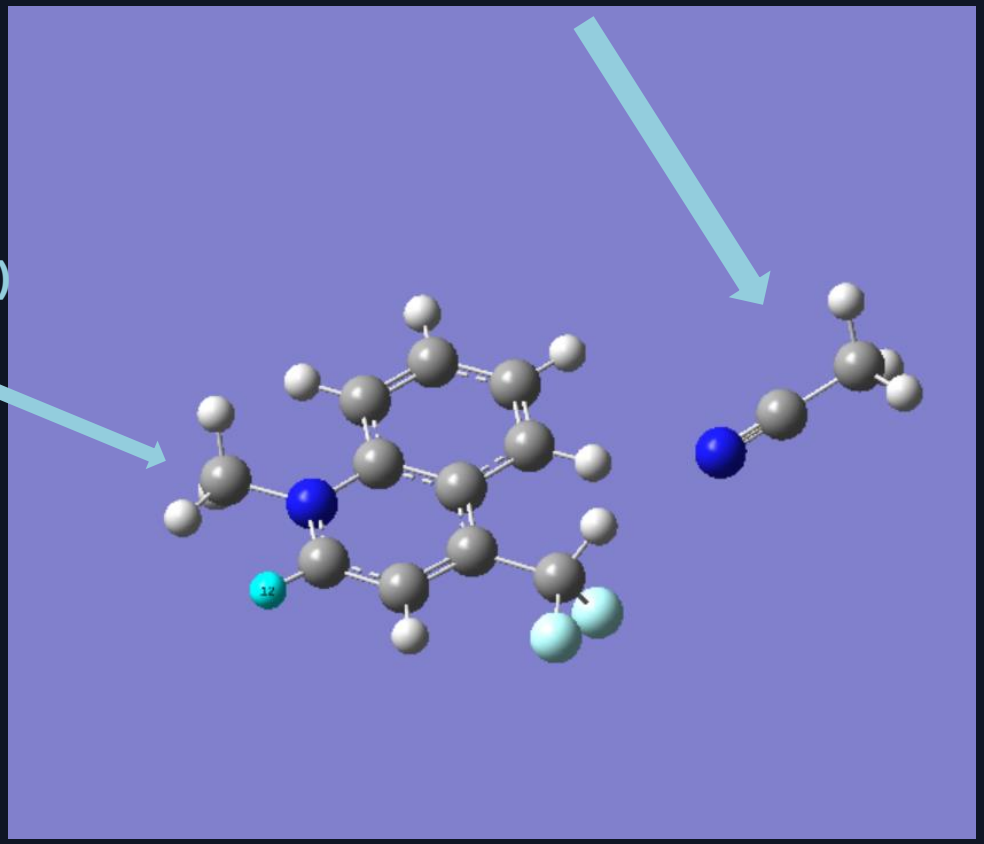


Lima, Telma & Caliri, A. & Barroso da Silva, Fernando Luís & Tinós, Renato & Travieso, Gonzalo & Silva, Ivan & Lopes de Souza, Paulo & Marques, Eduardo & Delbem, Alexandre & Bonatto, Vanderlei & Faccioli, Rodrigo & Brasil, Christiane & Gabriel, Paulo & Tragante, Vinicius & Bonetti, Daniel. (2009). Some Modeling Issues for Protein Structure Prediction Using Evolutionary Algorithms. 10.13140/2.1.3164.6728.

Correction for Solvent Effects

1 explicit solvent molecule (acetonitrile)

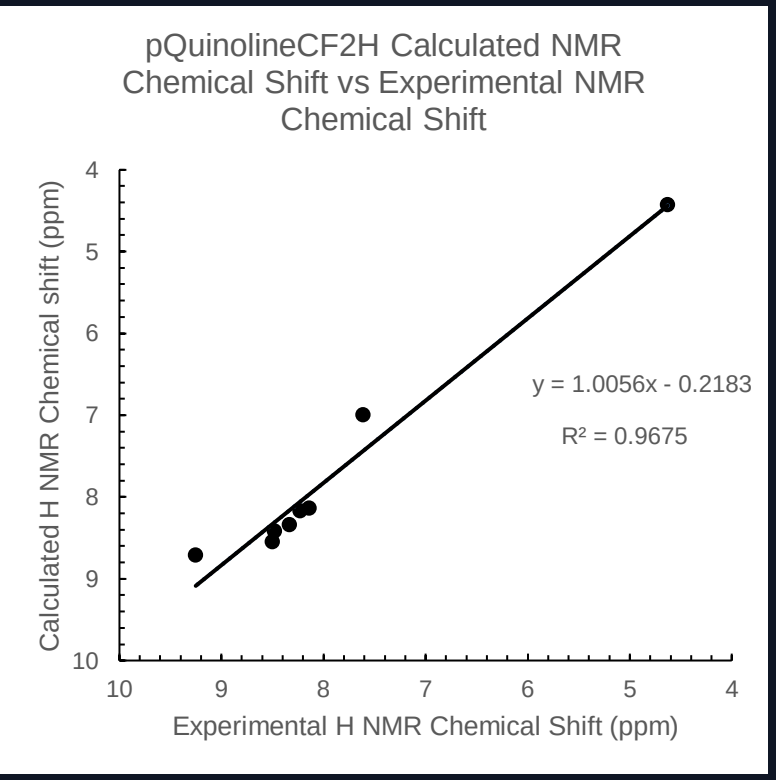
“Solute” (Fluorine substituted quinoline)



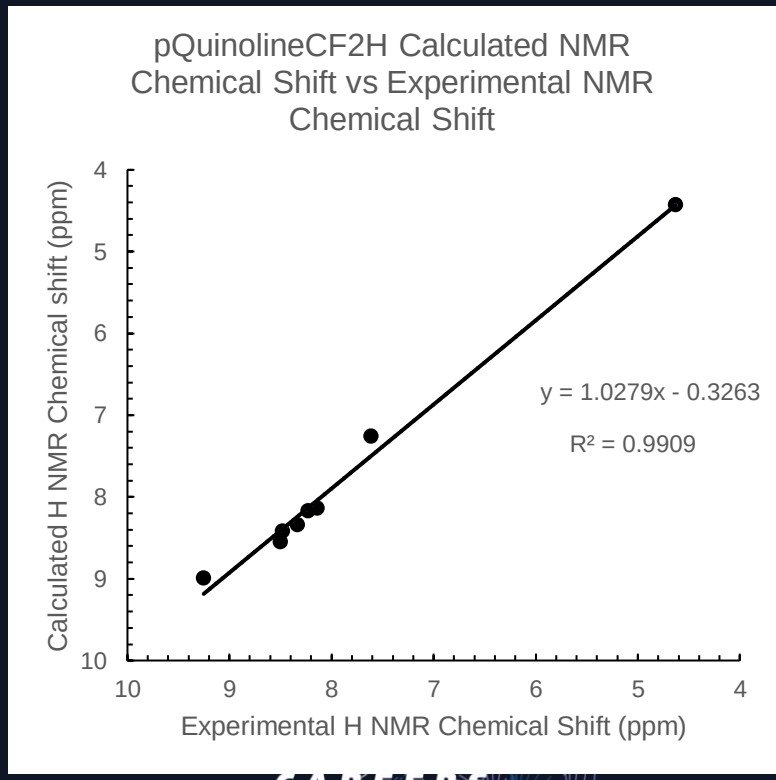
CAREERS CYBERTEAM

Correction for Solvent Effects

No explicit solvent molecule



1 explicit solvent molecule



Quantum Mechanical Simulation of Fluorine-Containing Biomolecules

- Overall Findings
  - Our CF2H substituted molecules so far have hydrogen bonding capabilities (K_a in the range of 125-150 M^{-1})
  - OH functional groups of comparable structure have K_a in the range of 200-250 M^{-1}
  - We can utilize explicit solvation to better simulate H-bonding interactions and increase the accuracy of our theoretical calculations

CAREERS CYBERTEAM

Quantum Mechanical Simulation of Fluorine-Containing Biomolecules

- Lessons Learned
  - Becoming familiar with the HPC system
  - Expanded knowledge of Density Functional Theory
  - Gained insights into how fluorine can function in a molecule to allow hydrogen bonding
  - Data organization
  - Honed skills performing NMR and UV-Vis spectroscopy in the laboratory

CAREERS CYBERTEAM

Publications/Contributions

- The data/findings of this project are being written in a manuscript to be submitted to the Beilstein Journal of Organic Chemistry
- Still some experimental data to collect
- We are targeting to have our manuscript finished early this summer

CAREERS CYBERTEAM

Questions?

Matthew Paolella
University of Rhode Island
mpaolell@uri.edu
fangwang@uri.edu