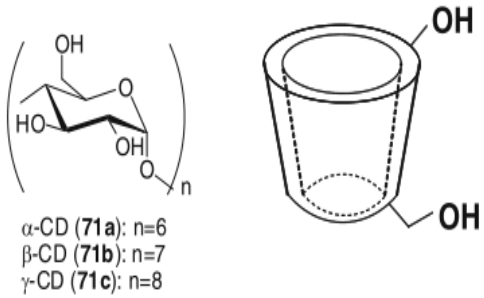

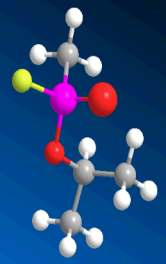

Homeland Security
Science and Technology

SAND2014-16091PE

Development and Investigation of NMR Tools for Chiral Compound Identification

Exploration/Optimization of Enantiomer Identification with Chiral Solvating Agents (CSAs) Using Organo-Fluorophosphate (OFP) Analogs of Chemical Warfare Agents (CWAs)

Vitaliy Dernov

Student Internship Program Presentation at SNL

7/31/14

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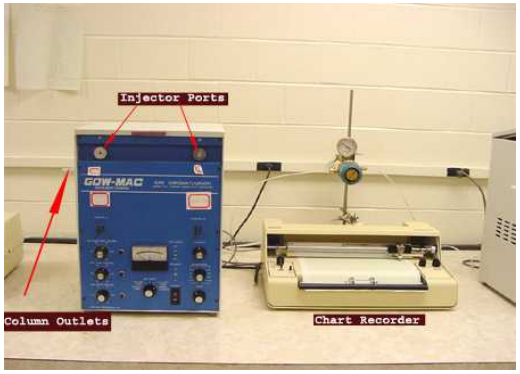
Goals

- Investigate NMR for identification of OFPs enantiomers
- Test several types of CSAs
  - Cyclodextrins
  - High diamagnetic anisotropy
- Electrostatic interactions, Van der Waals forces and H-bonding
- Characterize their binding by calculating $\Delta\delta$ ($\delta_{free} - \delta_{complex}$) and $\Delta\Delta\delta$ ($|R-S|$)

Motivation

- Current major method for chiral recognition of OFPs/OPs is GC
- Chirasil Val Column and Carbowax Column
- Incomplete resolution – VX gas



- DECON optimizations in case of CWA attack
- Development of models correlating chiral compounds and CSA.

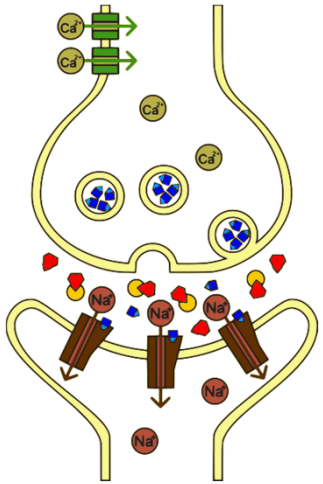
CWAs Background (Sarin)

Sarin:

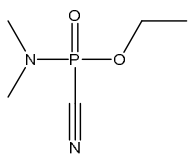
- Developed in Germany at IG Farben – looking for pesticides.
- **S**chrader, **A**mbros, **R**itter and L**in**de
- Sarin is colorless and odorless in pure form.
- 26 times more deadly than cyanide
- Easy to synthesize – but racemic mixture.

Modus Operandi of G-Series CWAs:

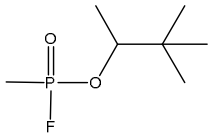
- Acetylcholinesterase (AChE)
- Acetylcholine in CNS and PNS -
  excitatory role at neuromuscular junctions in CNS and PNS.



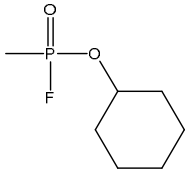
GA - Tabun



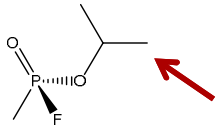
GD - Soman



GF - Cyclosarin

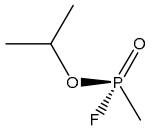


GB - Sarin

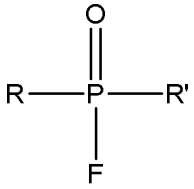


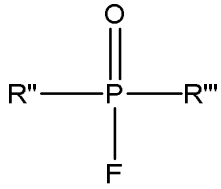
S - enantiomer

Inhibits AChE ~10^4 faster.



R - enantiomer

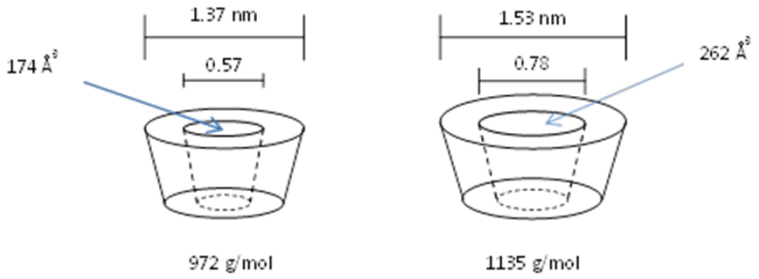


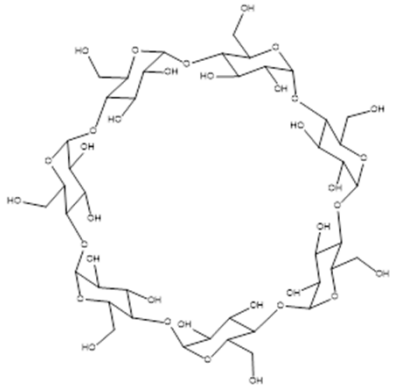


Cyclodextrins

- Discovered in 1891 by Villiers.
- Schardinger clarified bacterial strain as *Bacillus macerans* and knew there were two cyclodextrins.
- From 1911 to 1935, Pringsheim's main contribution was that CDs forms complexes.
- CD inclusion phenomena, pharmaceutical, *etc.*

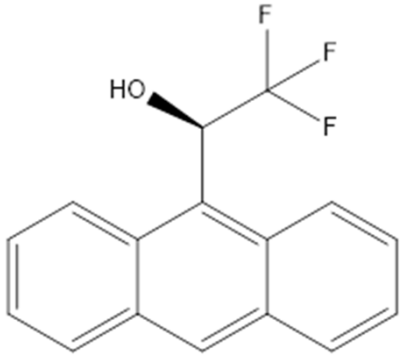
- Cyclic oligosaccharides
- Host/guest complex – guest enters a "donut hole".

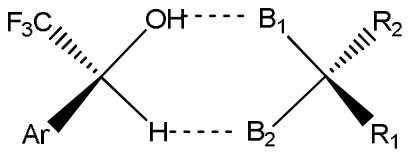


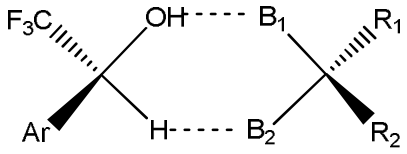


TFAE

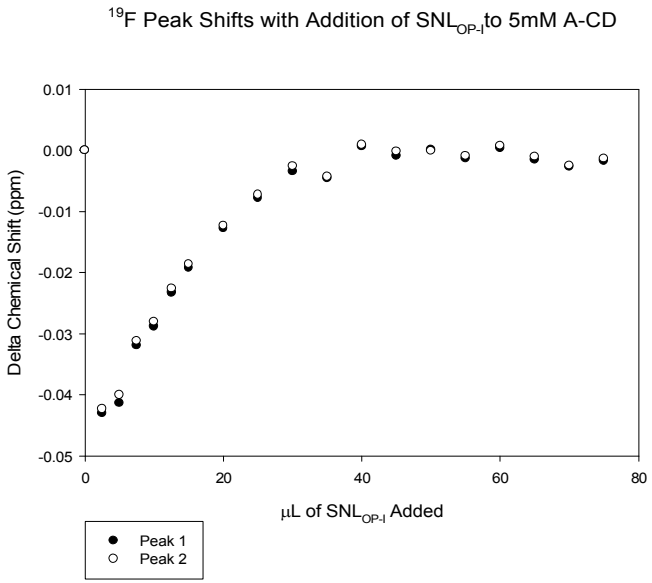
- R-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE)
- Use of TFAE as a CSA in NMR studies reported by Pirkle in 1960s.
- Different from CDs due to high diamagnetic anisotropy of anthracene and lack of CD-type cavity.
- Anisotropy allows for NMR differentiation of enantiomers by causing perturbations of their magnetic environment.

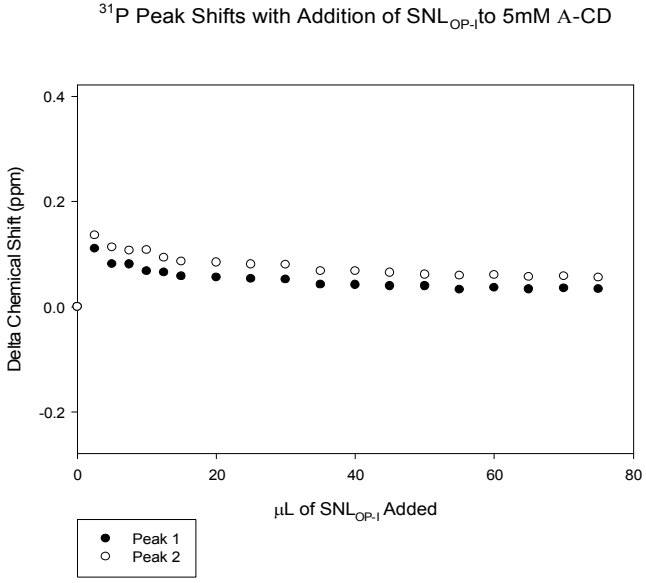


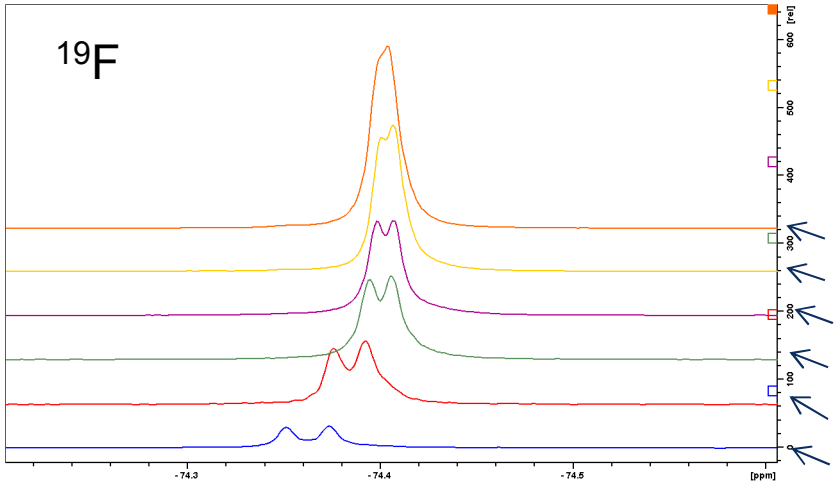


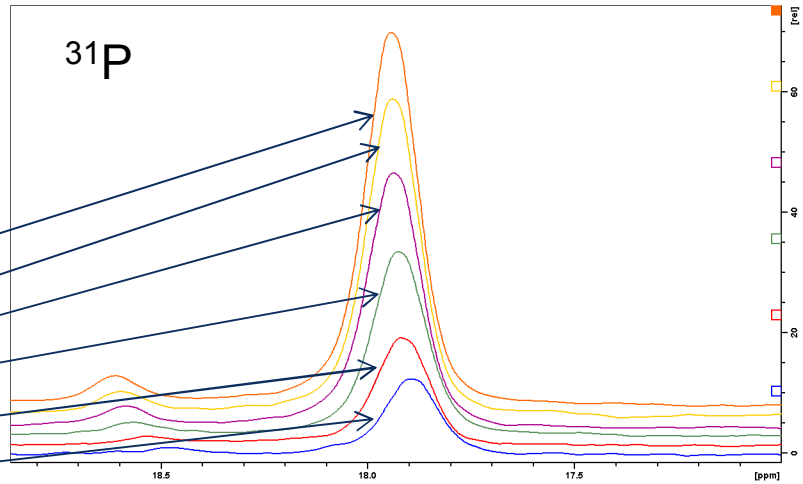


α-CD Results

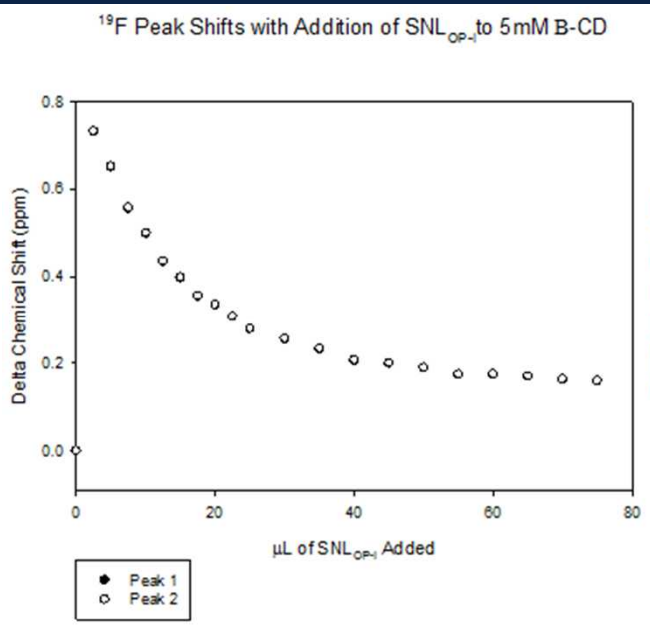

^{19}F Peak Shifts with Addition of SNL$_{OP-I}$ to 5mM A-CD
Delta Chemical Shift (ppm)
0.01
0.00
-0.01
-0.02
-0.03
-0.04
-0.05
0
20
40
60
80
µL of SNL$_{OP-I}$ Added
Peak 1
Peak 2

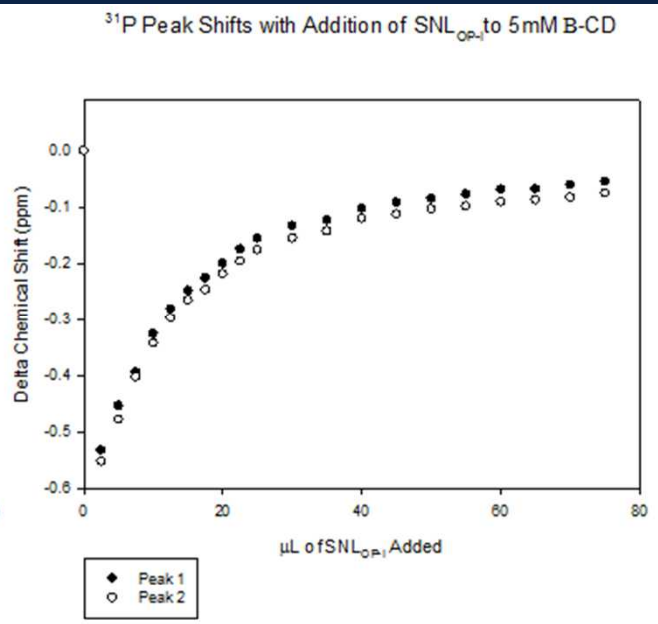

^{31}P Peak Shifts with Addition of SNL$_{OP-I}$ to 5mM A-CD
Delta Chemical Shift (ppm)
0.4
0.2
0.0
-0.2
0
20
40
60
80
µL of SNL$_{OP-I}$ Added
Peak 1
Peak 2

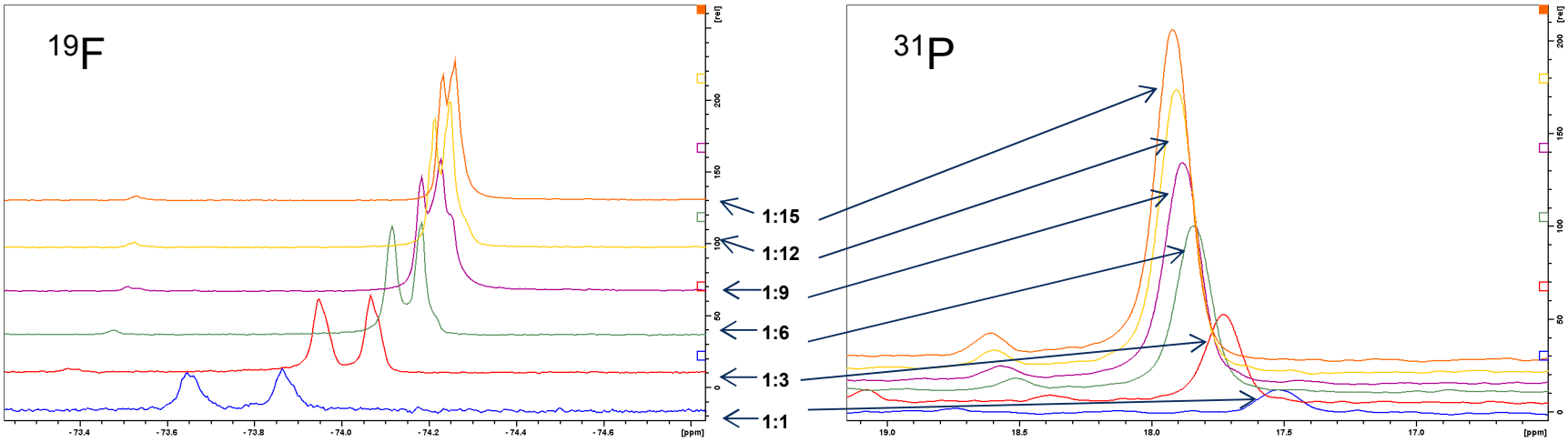

^{19}F
-74.3
-74.4
-74.5
[ppm]
1:15
1:12
1:9
1:6
1:3
1:1


^{31}P
18.5
18.0
17.5
[ppm]

β-CD Results


^{19}F Peak Shifts with Addition of SNL$_{OP-I}$ to 5mM B-CD
Delta Chemical Shift (ppm)
µL of SNL$_{OP-I}$ Added
Peak 1
Peak 2


^{31}P Peak Shifts with Addition of SNL$_{OP-I}$ to 5mM B-CD
Delta Chemical Shift (ppm)
µL of SNL$_{OP-I}$ Added
Peak 1
Peak 2

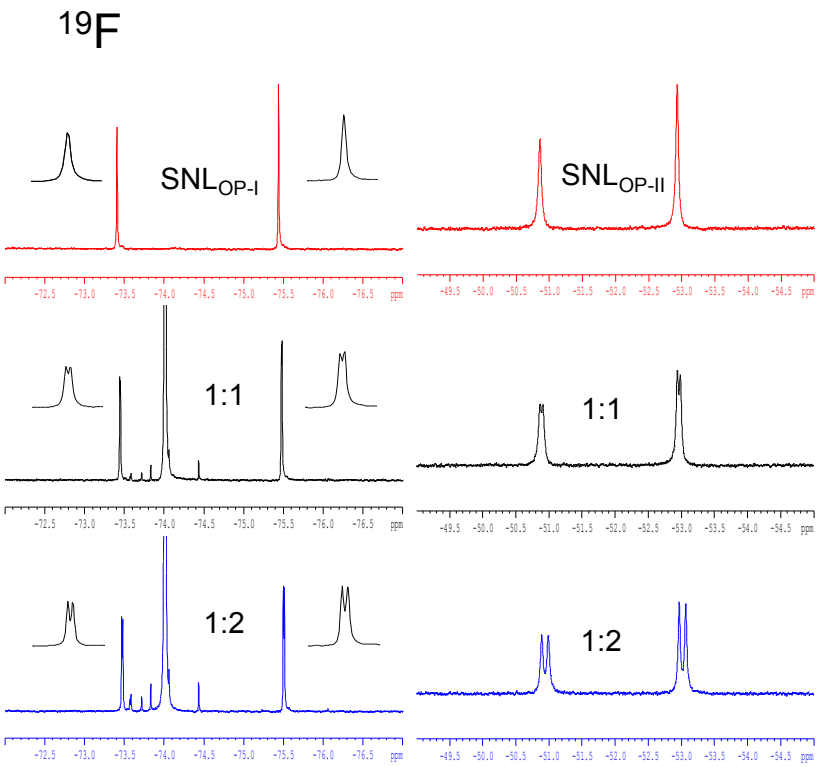

^{19}F
^{31}P
1:15
1:12
1:9
1:6
1:3
1:1
[ppm]

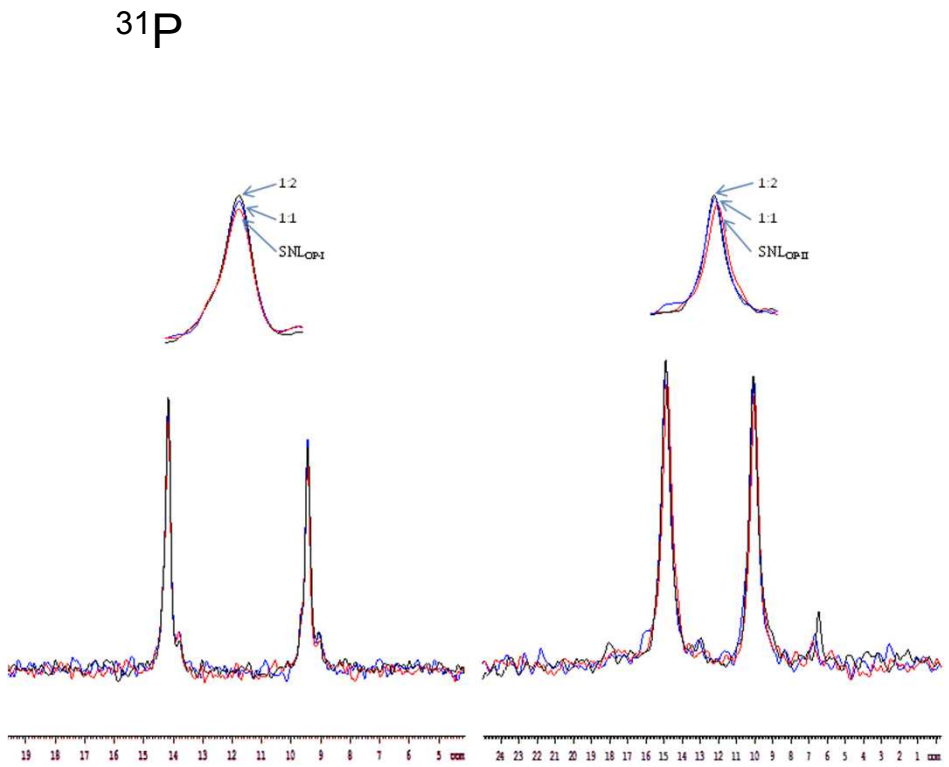
α/β-CD Results

- ΔΔδ could only be calculated from the ^{19}F NMR spectrum.
- Cavity sizes of α-CD (174 Å^3) and β-CD (262 Å^3) sufficient for a G/H interactions with $SNL_{OP\text{-}I}$.

					|R-S| separation		
Compound	CSA	Δδ ^{19}F (ppm)	Δδ ^{31}P (ppm)	Δδ ^{1}H (ppm)	ΔΔδ ^{19}F (ppm)	ΔΔδ ^{31}P (ppm)	ΔΔδ ^{1}H (ppm)
$SNL_{OP\text{-}I}$	α-CD						
1:1		-0.0413	0.0809		0.0221	-	-
1:3		-0.0192	0.0575		0.0164	-	-
1:6		-0.0034	0.0515		0.0113	-	-
1:9		-0.0009	0.0390		0.0084	-	-
1:12		0.0004	0.0361		0.0060	-	-
1:15		-0.0017	0.0332		0.0042	-	-
$SNL_{OP\text{-}I}$	β-CD						
1:1		0.6496	-0.4537		0.2170	-	-
1:3		0.3970	-0.2485		0.1170	-	-
1:6		0.2552	-0.1334		0.0670	-	-
1:9		0.1993	-0.0917		0.0438	-	-
1:12		0.1736	-0.0687		0.0359	-	-
1:15		0.1587	-0.0544		0.0272	-	-

TFAE Results





- As with the cyclodextrins, peak splitting could only be seen within the ^{19}F NMR spectrum.
- The largest chemical shift for $SNL_{OP\text{-}I}$ with one equivalent TFAE was observed in the ^{19}F NMR spectrum.
- However, for $SNL_{OP\text{-}II}$ with one equivalent of TFAE, the largest chemical shift was observed in the ^{31}P NMR spectrum.
- For ^{31}P $\Delta\delta$, less than a hundredth of a ppm for $SNL_{OP\text{-}I}$ and just under a tenth of a ppm for $SNL_{OP\text{-}II}$.

TFAE Results

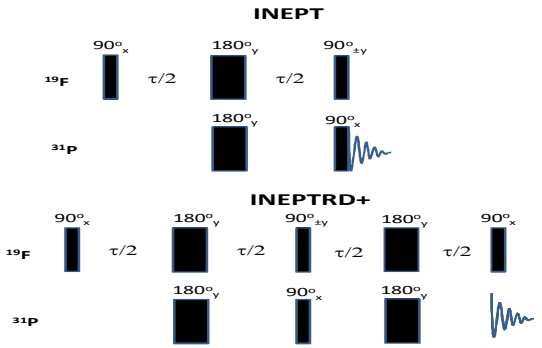
- Overall, SNL_{OP-II} with TFAE had more significant chemical shifts with the addition of a 2nd equivalent of TFAE – 1.7x versus 2.8x in the ^{19}F NMR spectra and 1.5x versus 2.2x in the ^{1}H NMR spectra of SNL_{OP-I} and SNL_{OP-II}, respectively.
- Indication of stronger intermolecular interactions between TFAE and SNL_{OP-II}.
  - Differences in R groups; steric effects.

					|R-S| separation		
Compound	CSA	Δδ ^{19}F (ppm)	Δδ ^{31}P (ppm)	Δδ ^{1}H (ppm)	ΔΔδ ^{19}F (ppm)	ΔΔδ ^{31}P (ppm)	ΔΔδ ^{1}H (ppm)
SNL_{OP-I}	TFAE						
1:1		0.0396	-0.0085	0.0171	0.0074	-	-
1:2		0.0665	-0.0030	0.0252	0.0123	-	-
SNL_{OP-II}	TFAE						
1:1		0.0293	-0.0649	0.0270	0.0404	-	-
1:2		0.0834	-0.0838	0.0592	0.0994	-	-

Discussion/Future Endeavors

Discussion:

- Results show promising leads for future research on optimizing NMR chiral recognition of OFPs.
- Indications that peak splitting by CSAs should be monitored in the ^{19}F spectrum for enantiomeric discrimination.
- Chemical shifts serve as indicators of primary and secondary interactions between CSA and chiral molecule.



Future Endeavors:

- Molecular modeling for elucidation of primary and secondary interactions between our OFPs and CSAs
- Monitoring β-CD – catalyzed hydrolysis of OFPs.
- ^{19}F and ^{31}P INEPT NMR optimizations for ability to assist in the differentiation and quantification of enantiomers.
- Using novel OFPs and other CSA molecules (γ-CD and Mosher's Acid).

References

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