Predicting pK_a Values of Flexible Polybasic Tetra-aza Macrocycles

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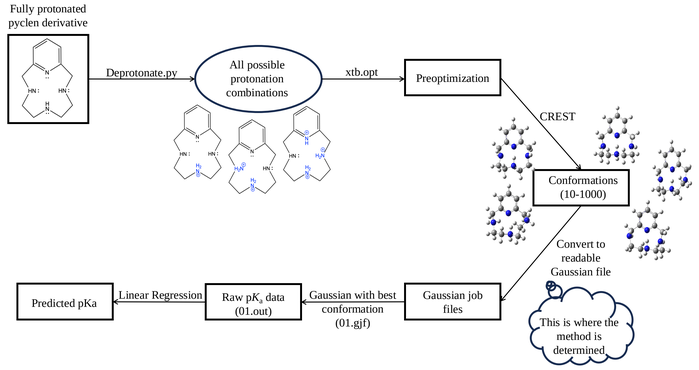
Method and Theory



Accurate pK_a Predictions Require an Appropriate Environment via Solvent Models

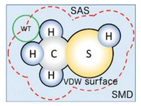
H_2O Solvent

$NaCl \rightarrow Na^+ + Cl^-$

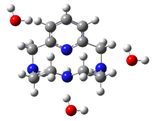
Gaseous

$NaCl \rightarrow Na\bullet + Cl\bullet$

Implicit solvent model



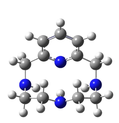
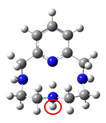
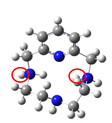
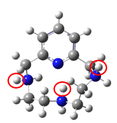
Explicit solvent model



Environment Greatly affects chemical outcomes

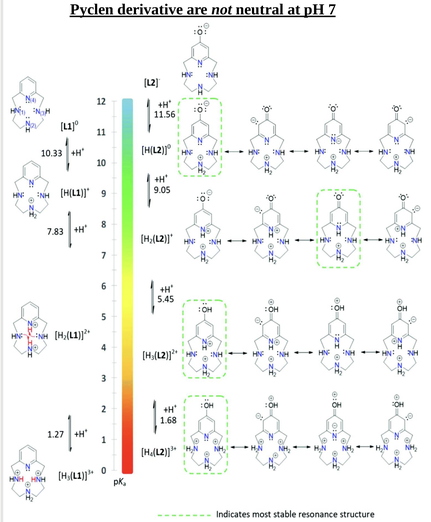
Multiple Conformations of Neutral and Protonated States Must be taken into Account

Using CREST conformational analysis, we are able to obtain the lowest energy conformation for the favored protonation state

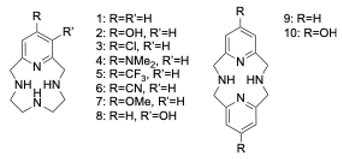
	Neutral	1st Protonation	2nd Protonation	3rd Protonation
H-Pyridine derivative (H_PyN3) using CREST				

Introduction

Pyclen derivative are *not* neutral at pH 7



Characteristics of Testing Set



Antioxidant characteristics:

- Metal binding activity
- Radical Scavenging
- Activation of NRF2 and Grx1 Pathway
- Biocompatibility

Oxidative stress

Free Radicals

Objectives:

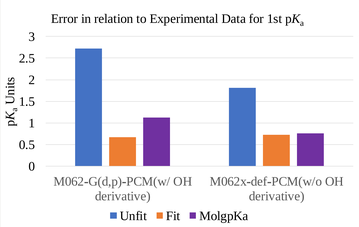
- Validate current workflow with polybasic flexible molecules
- Obtain accuracy across multiple pK_a values
- Optimize workflow

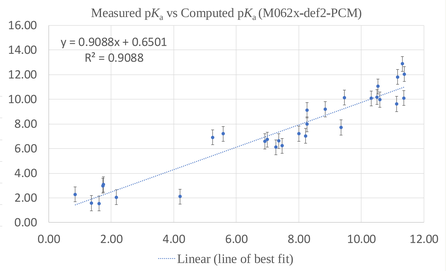
Long Term Goal:

- Predict pK_a of potential neurodegenerative drug candidates within accuracy
- Implement workflow as a drug prescreening procedure.

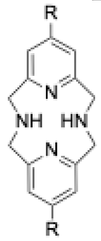
Validating the Workflow

- Current Workflow can achieve an absolute error of .900 pK_a units across all protonation sights





Tetra-aza Macrocycle predictions



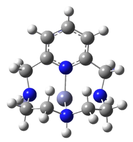
11: R=Cl
12: R=NMe$_2$
13: R=OMe
14: R=CF$_3$

Predicted pK$_a$ values for molecules 1-3		
Molecule	pK$_a$	QM+LEC
11	1	7.72
	2	5.83
12	1	10.04
	2	9.09
13	1	8.51
	2	7.14
14	1	6.66
	2	6.39

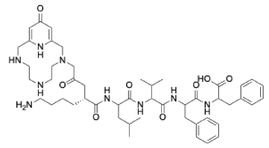
- Novel Tetra-aza macrocycles with unknown experimental pK_a
- Calculated using M062x-def2tzvp with the SMD implicit solvent model
- Results are chemically accurate to changed functional groups

Implementation of Workflow

Metal-binding ligand properties



Predicting pK_a additional potential derivatives



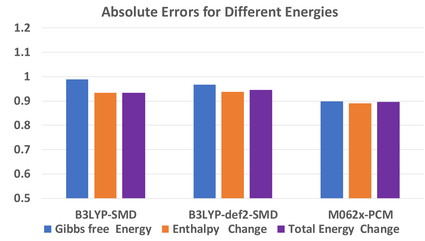
- M062x-def2tzvp with SMD implicit with Liner regression will be used to predict additional tetra-aza macrocycles

Optimizing Workflow

Access to Different Energy Calculations

- Gibb's free energy is the proper energy component to calculate pK_a
- Gaussian is notorious for lacking the ability to account for entropy including in its calculations of Gibb's Free Energy

Absolute Error Overall for all Derivatives			
Methods	Gibbs free Energy	Enthalpy Change	Total Energy Change
B3LYP-SMD	0.989	0.933	0.933
B3LYP-def2-SMD	0.967	0.937	0.945
M062x-PCM	0.899	0.89	0.896

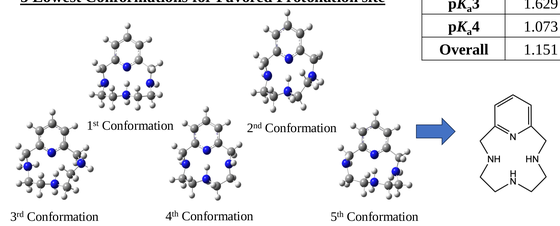


Accounting for Various Conformations in Solution

- In transferring between Gaussian and the CREST conformational analysis tool, measurements of Gibb's Free Energy tend to disagree on the most stable conformer.

Crest Best Free Energy vs 1-5 Output Files Best Free Energies (M062x-SMD)			
	Crest Best	1-5 Output Best	Comparison
pK_a1	0.608	0.776	↑ 0.168
pK_a2	0.950	0.892	↓ 0.058
pK_a3	1.629	1.299	↓ 0.330
pK_a4	1.073	1.599	↑ 0.526
Overall	1.151	1.095	↓ 0.056

5 Lowest Conformations for Favored Protonation site



Averaged Gibbs Free energy from lowest energy conformers

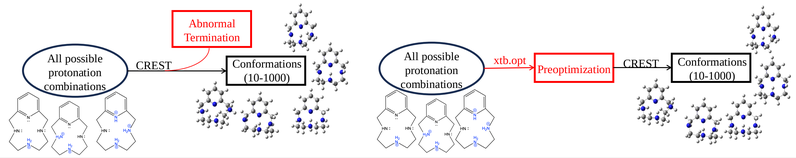
Improving Consistency of Terminations for CREST

Before adding preoptimization:

- Abnormal terminations from coordinate files through CREST
- Lack of reliability, resulting in more work to fix missed calculations

After adding preoptimization:

- Consistent Terminations of CREST
- Reliability and increased efficiency through workflow



Acknowledgements

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