Predicting pK_a Values of Flexible Polybasic Pyclen Derivatives

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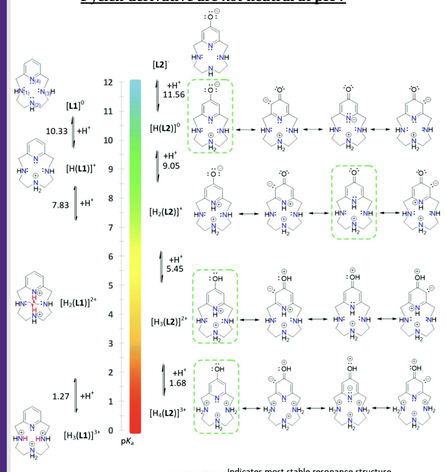
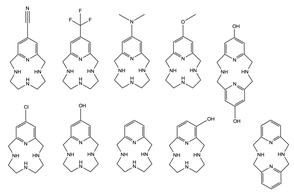
Introduction

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

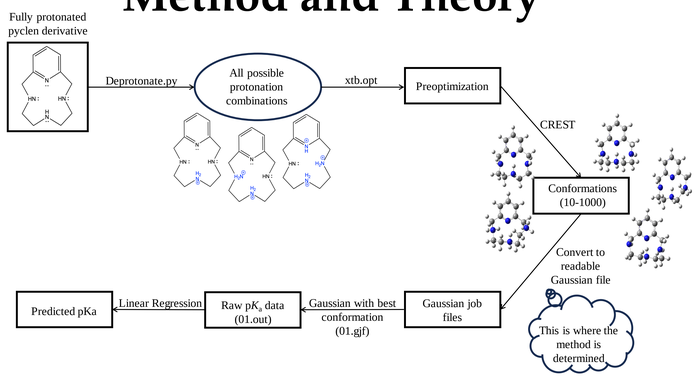
Objectives:

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

Long Term Goal:

- Predict pK_a and other properties with swift accuracy
- Implement workflow as a drug prescreening procedure.

Method and Theory



Accurate pK_a Predictions Require an Appropriate Environment via Solvent Models

H_2O Solvent

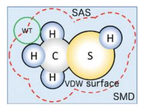
$NaCl \rightarrow Na^+ + Cl^-$

Gaseous

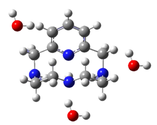
$NaCl \rightarrow Na\bullet + Cl\bullet$

Environment Greatly affects chemical outcomes

Implicit solvent model

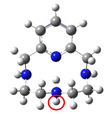
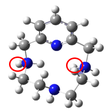
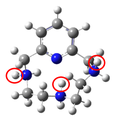


Explicit solvent model



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

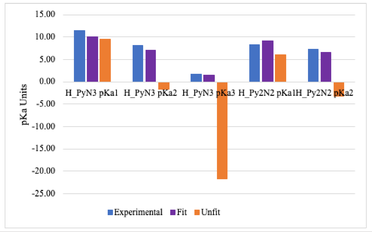
Using CREST conformational analysis, we are able to obtain the lowest energy conformation for the favored protonation state

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

Raw Gibbs Free Energy Data must be Expressed as pK_a

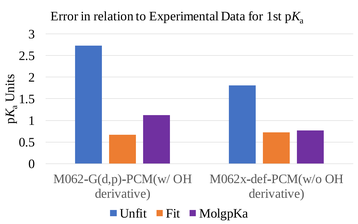
- For charged molecules, Gaussian compensates for this by exaggerating the energy of the molecule
- A linear fit between the experimental pK_a values and computed pK_a is used to estimate an accurate pK_a

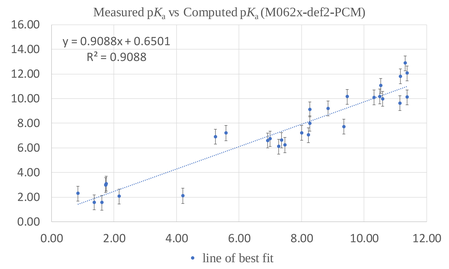
$$pKa = 627.5095 \frac{Hatree}{kcal \cdot mol^{-1}} \times \frac{\Delta G(A^-) - \Delta G(HA) + \Delta G(H^+)}{RT \ln(10)}$$



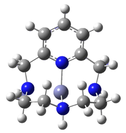
Results

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



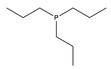


Future Prospects



Metal-binding ligand properties

The versatility of the workflow is exciting, and opens new gateways to expand our understanding of drug candidates in half the time that experiment requires.



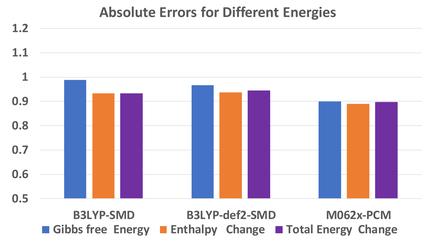
Flexible Molecules

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

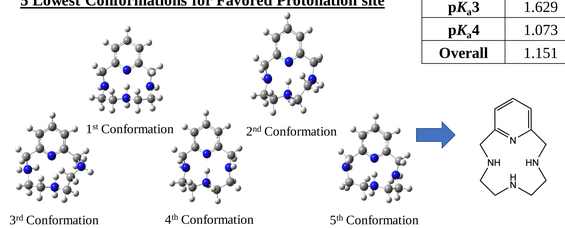


Accounting for Various Conformations in Solution

- 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

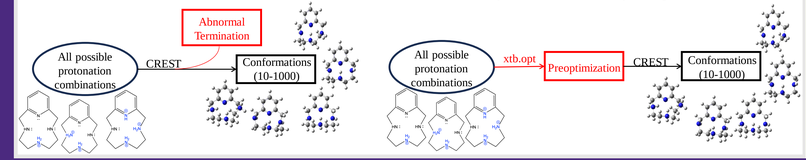
Improving Consistency of Terminations for CREST

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

NIH National Institute of General Medical Sciences

The Welch Foundation

reSEaRCh Science and Engineering Research Center

TCU High-Performance Computing Center and David Freire