Development of parameters for modified amino acids to study protein dynamics

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Introduction

- Modified amino acids can be used as probes to study protein dynamics experimentally and computationally
- **RAGTAG** - **R**apid **A**mber **G**pu **T**orsion p**A**rameter **G**enerator is a genetic algorithm that fits MM energies to QM energies to improve conformational dynamics

Goal: To develop parameters for modified amino acids to study protein dynamics

Application 1: Spin label for EPR

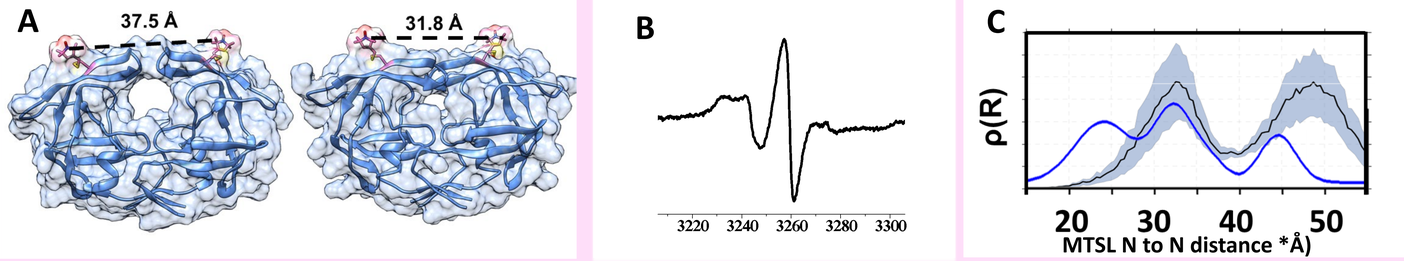


Figure 5: A) MTSL attached to the flaps of HIV-1 protease showing the N to N distance of 37.5 Å (semi-open) and 31.8 Å (closed). B) EPR spectrum. C) Distribution of the N to N distance of MTSL from EPR (blue) and MD (black). Standard Error of the Mean of four MD runs shown in shaded blue.

Partial Charges

$$E = \sum_{i<j} \frac{q_i q_j}{\varepsilon\, r_{ij}}$$

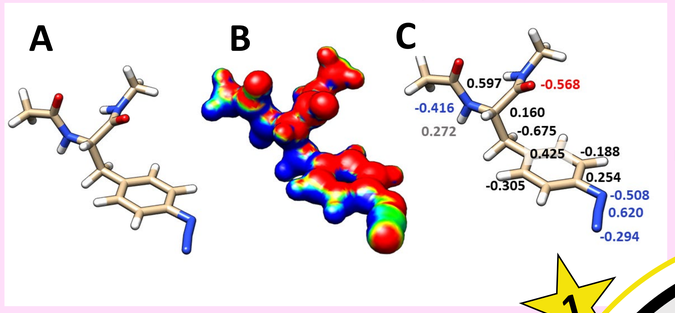


Figure 1: A) Atomic coordinates for azido-phenylalanine. B) Electrostatic potential; negative (red) & positive (blue). C) Restrained electrostatic potential charges.

Lennard-Jones parameters

$$E = \sum_{i<j} \frac{\varepsilon R_{min}^{12}}{r_{ij}^{12}} - \frac{2\varepsilon R_{min}^{6}}{r_{ij}^{6}}$$

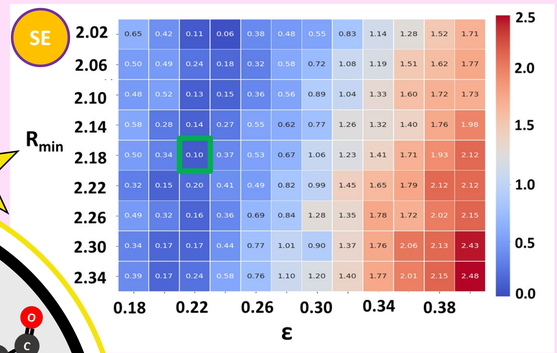


Figure 2: Heatmap showing the RMSE of scanned LJ parameters (Se).

Application 2: FRET Quenchers

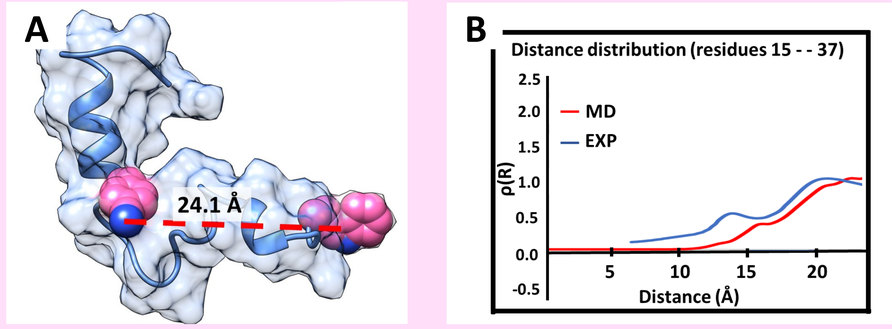
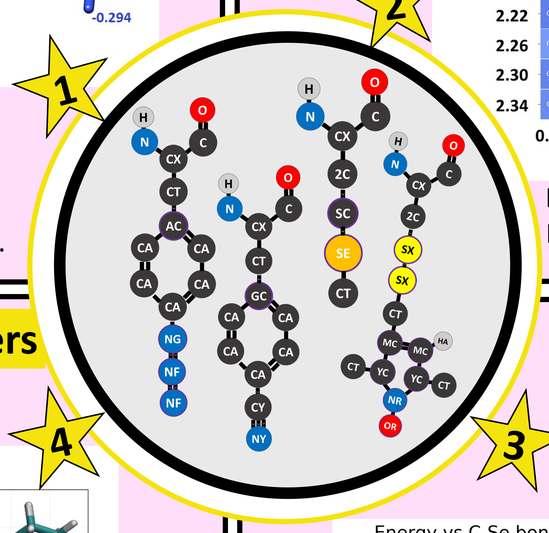


Figure 6: A) distance probed between cyano-Phe15 to Trp37 of IAPP. B) Distribution of distances from FRET and MD simulations.



RAGTAG Dihedral parameters

$$\sum_{dihedrals} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)]$$

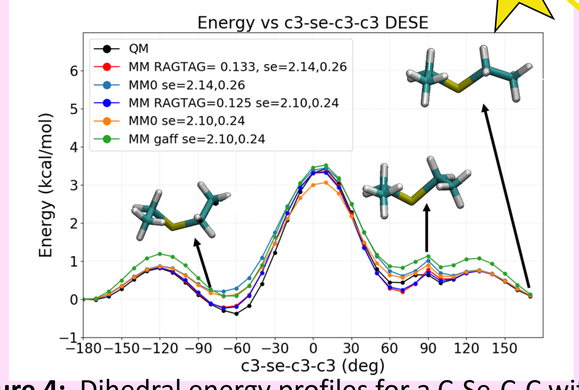


Figure 4: Dihedral energy profiles for a C-Se-C-C with different Se LJ parameters. Black is the QM energy profile used to fit the dihedral parameters.

Bond & Angle parameters

$$E = K_f\left(r - r_{eq}\right)^2$$

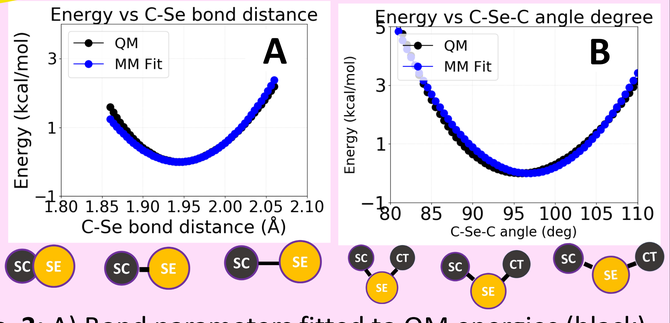


Figure 3: A) Bond parameters fitted to QM energies (black). B) Angle parameters fitted to QM energies. Energies with fitted parameters shown in blue.

Conclusion

- We developed new parameters for 4 modified amino acids to study protein dynamics that describe drug binding and predict secondary structure of intrinsically disordered proteins
- The Average Absolute Error from the RAGTAG Fit ranged from 0.89 – 1.16 kcal/mol
- We added parameters to simulate Selenium compounds

Acknowledgment

sighpc intel NIH National Institutes of Health NSF

Members of the Simmerling Lab

Algorithm: https://github.com/kellonb/RAGTAG

Publication: K. A. A. Belfon; C. Tian; L. Raguette; J. Maier; C. Simmerling. Application of RAGTAG: modified amino acids for comparing MD simulations with FRET/EPR experiments. In Prep, 2020

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