Conformational Sampling

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Steps in Project

1. Create library using IBM with benzylic tribromide + peptide chain + thiol. – Completed

2. Use Monte Carlo Multiple Minimum for conformational sampling.

3. Modify format of MCMM output to match Protein Data Bank and overlay cyclic peptides with protein backbones. Find low RMSD values.

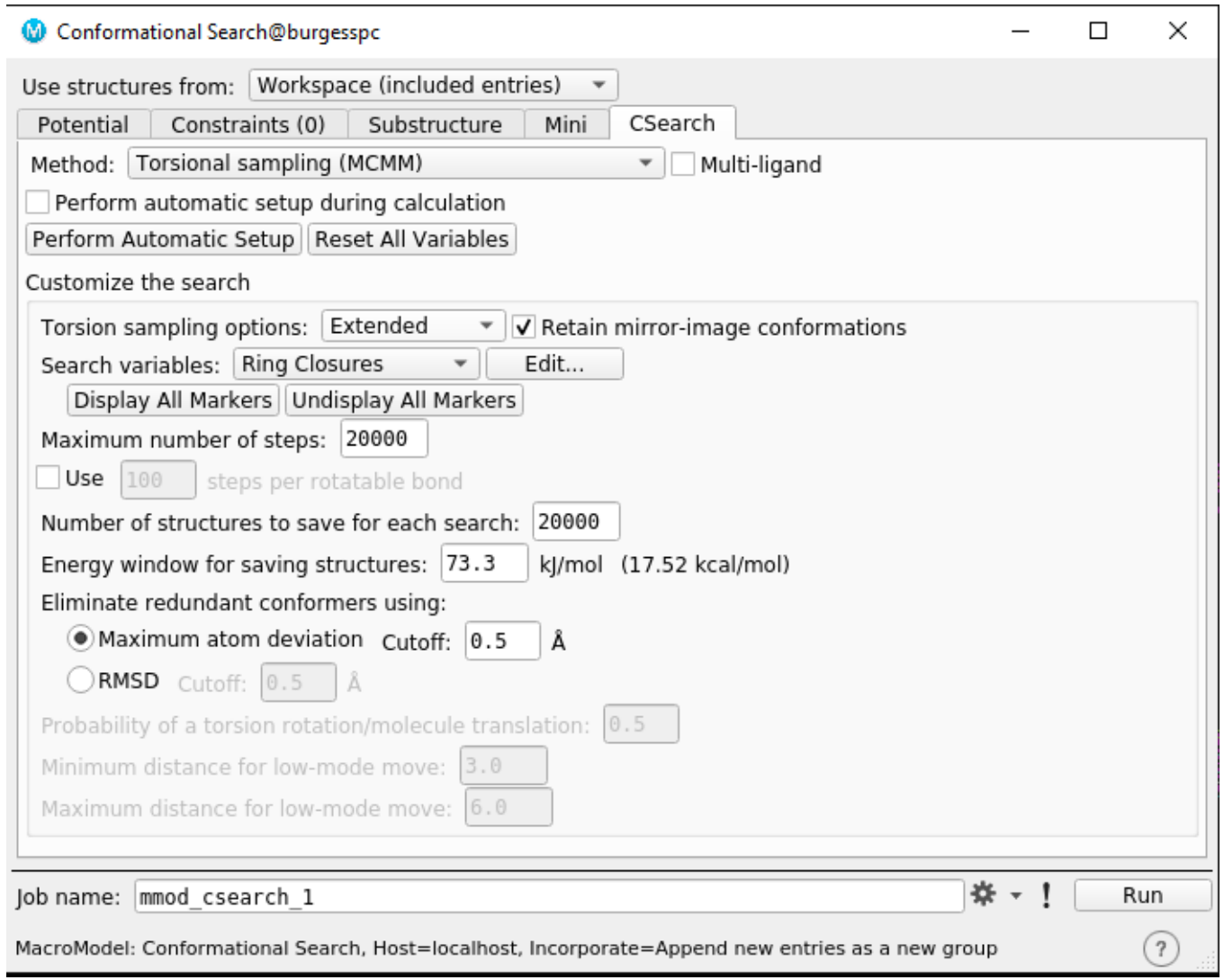
4. Align with Kirtzer hot loops to find possible mimics

Schrodinger Macro model

- The software maestro was used to perform the conformational sampling.
- All the .mols from the library generated in the previous step were loaded into the software. Unique conformers are generated using MCMM.

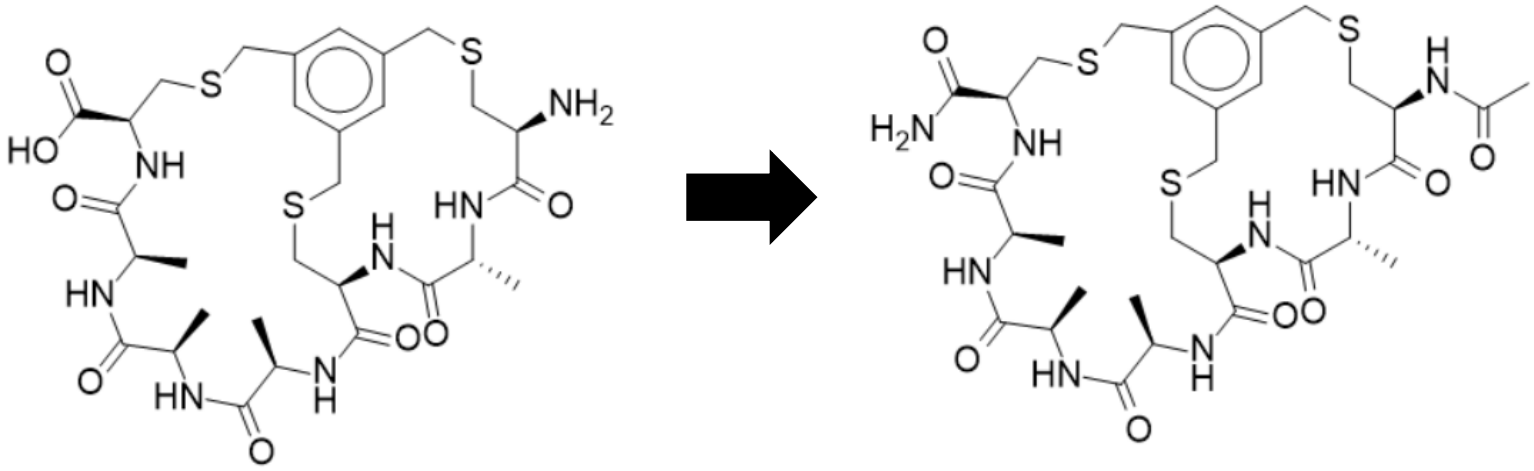
Settings for Conformational Sampling

- Settings including energy to save and max steps/structures to save were based on amount of alanine in structure.
- The minimum energy for smallest ring in the library was 62.8 kJ/mol. For each extra alanine in a ring 2.092 kJ/mol or 0.5 kCal/mol was added to the energy.
- The max steps started at a minimum of 10,000 and 2000 was added per extra alanine.


Conformational Search@burgesspc
Use structures from: Workspace (included entries)
Potential
Constraints (0)
Substructure
Mini
CSearch
Method: Torsional sampling (MCMM)
Multi-ligand
Perform automatic setup during calculation
Perform Automatic Setup
Reset All Variables
Customize the search
Torsion sampling options: Extended
Retain mirror-image conformations
Search variables: Ring Closures
Edit...
Display All Markers
Undisplay All Markers
Maximum number of steps: 20000
Use 100 steps per rotatable bond
Number of structures to save for each search: 20000
Energy window for saving structures: 73.3 kJ/mol (17.52 kcal/mol)
Eliminate redundant conformers using:
Maximum atom deviation Cutoff: 0.5 Å
RMSD Cutoff: 0.5 Å
Probability of a torsion rotation/molecule translation: 0.5
Minimum distance for low-mode move: 3.0
Maximum distance for low-mode move: 6.0
Job name: mmod_csearch_1
Run
MacroModel: Conformational Search, Host=localhost, Incorporate=Append new entries as a new group

Changing Terminal functional group

- Since the compounds after syntheses rarely have free terminal groups, they needed to be modified. The COOH terminus was changed to CONH2 and NH2 terminus was changed to NH-CO-CH3.
- This was done by modifying the script which originally made the library of peptides



Current Progress

- Currently 180/640 tasks are loaded finished.
- All the conformational sampling tasks should be loaded in a few days.