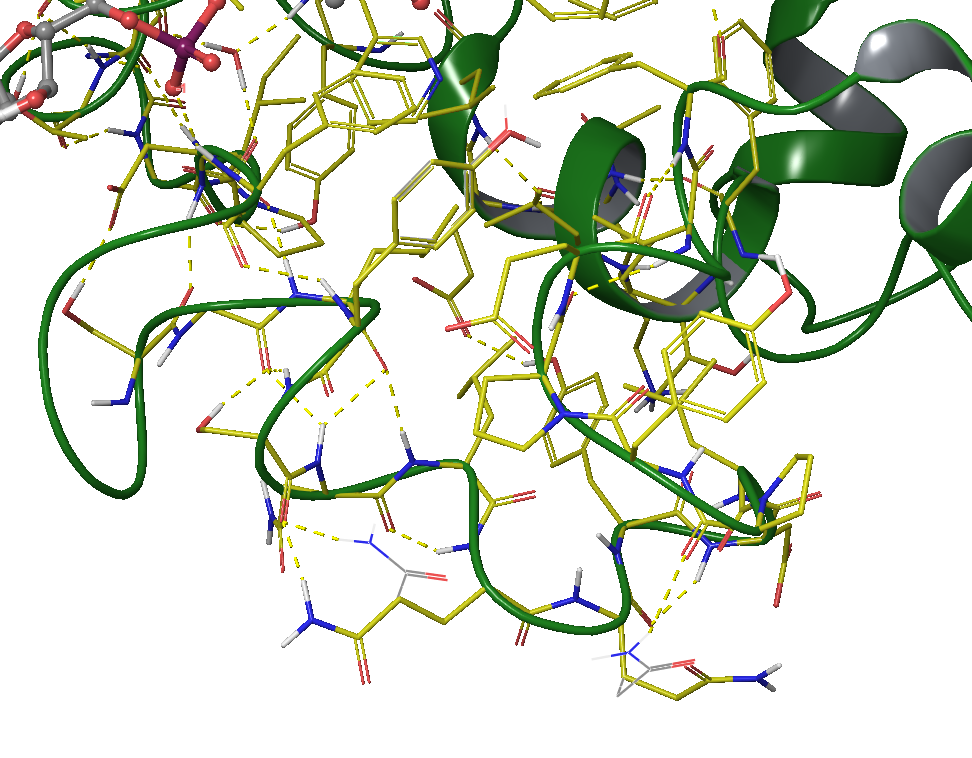
Sidechain prediction for SIRT3/INT/NAM converted from 4FVT with sidechain replacement on residue 155-178 from 4BVG

The structure prepared underwent Prime minimization on the whole system, and it turns out that the default setting for minimization convergence with the system this size can lead to a few kcal/mol in energy difference. (See table below. After round 10, prime minimization seems to have little change in energy, and the structure and energy is used as the reference for sidechain prediction study.)

|  |  |
| --- | --- |
| **Column1** | **Prime Energy of SIRT3/INT/NAM** |
| Prime minimization: round 1 | -12502.8 |
| Prime minimization: round 2 | -12505.4 |
| Prime minimization: round 3 | -12510.8 |
| Prime minimization: round 4 | -12512.6 |
| Prime minimization: round 5 | -12514.9 |
| Prime minimization: round 6 | -12516.2 |
| Prime minimization: round 7 | -12516.7 |
| Prime minimization: round 8 | -12516.8 |
| Prime minimization: round 9 | -12516.8 |
| Prime minimization: round 10 | -12517.0 |

Single-sidechain prediction suggest that TYR165, GLN169, GLN170 can change their sidechain conformation and lower the overall energy by ~ 3kcal/mol.



Prime minimized SIRT3/INT/NAM complex in yellow, sidechain predicted result in green ribbon and C in grey stick.

TYR165

GLN170

GLN169

Multiple residue sidechain prediction using the default option actually leads to higher energy, due to sampling errors that generate some unfavorable sidechain conformation, e.g. SER149, TYR165, GLU177, GLU198, etc. Including CA-CB vector in the option doesn’t help much.

Using Monte Carlo method in sidechain conformation prediction leads to lowering of energy by ~11 kcal/mol. Changes in SER166, ASN167, GLN169 together with the backbone shifting seem to contribute to the better hydrogen interactions that cause the lowering of the energy.



Prime minimized SIRT3/INT/NAM complex in yellow, sidechain predicted result in green ribbon and C in grey stick.

GLN169

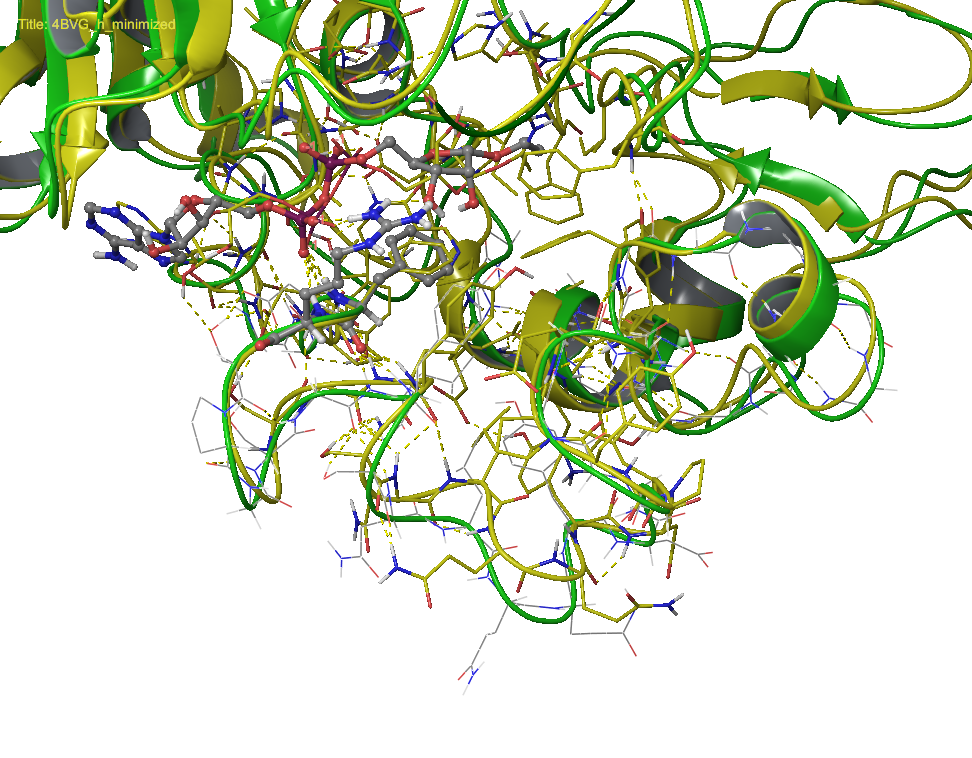
ASN167

SER166

When using the sidechain prediction with backbone sampling, the energy is further lowered, but not by much.

Details of the energies and RMSDs can be found in the EXCEL file 4FVT-INT-NAM-s155-178-set1-DATA.xlsx.

When comparing to 4BVG loop structure, we found that the prepared SIRT3/INT/NAM complex after loop substitution and Prime minimization have shown significant shift in loop backbone.



Prime minimized SIRT3/INT/NAM complex in yellow, 4BVG in green.

RMSD results using 4BVG as reference is in 4FVT-INT-NAM-set1-ref-4BVG.xlsx, replaced loop region and some significant changes are highlighted.

For comparison, I also calculated the energy of SIRT3/INT/NAM converted from 4FVT without loop substitution. It also takes 16 rounds of Prime minimization to reach a stable energy. The loop substituted conformation is favorable in energy by ~11 kcal/mol.

|  |  |
| --- | --- |
| **4FVT-INT-NAM** | **Prime Energy** |
| Prime minimization #1 | -12494.0 |
| Prime minimization #2 | -12496.3 |
| Prime minimization #3 | -12497.2 |
| Prime minimization #4 | -12497.7 |
| Prime minimization #5 | -12498.0 |
| Prime minimization #6 | -12498.2 |
| Prime minimization #7 | -12498.7 |
| Prime minimization #8 | -12499.6 |
| Prime minimization #9 | -12500.3 |
| Prime minimization #10 | -12500.8 |
| Prime minimization #11 | -12500.9 |
| Prime minimization #12 | -12501.4 |
| Prime minimization #13 | -12501.9 |
| Prime minimization #14 | -12502.1 |
| Prime minimization #15 | -12502.3 |
| Prime minimization #16 | -12502.6 |
| Prime minimization #17 | -12502.6 |