Conformational Analysis of Glutathione

Objective

You will use computational chemistry to study different conformations of glutathione: gamma-glutamyl-cystenyl-glycine and alpha-glutamyl-cystenyl-glycine.

Intoduction

Glutathione is an essential tripeptide antioxidant that consists of glutamate, cysteine and glycine. One unique feature of glutathione is that glutamyl fragment forms a peptide bond with cysteinyl by using its side chain carboxy group (gamma-glutamyl-cystenyl-glycine). Glutathione is present in most bacterial, plant and mammal cells. It protects against reactive oxygen species and participates in metabolism of therapeutic drugs and carcinogens. Decreased levels of glutathione have been observed in Parkinson's disease and Alzheimer's disease.

Methods

1. Build the conformations of glutathione shown in the handout (six total).
2. Perform geometry optimizations in the gas phase at PM6 level (semiemiprical method)
3. Save the optimized geometries and record the energies.
4. Perform geometry optimizations in the solution at PM6 level (PCM method, solvent=water). Note: It would be best to start with the optimized structure obtained in the gas phase. Make sure that you save all output files using relevant names (it will help you indentify each structure).
5. Save the optimized geometries and record the energies.
6. Analyze the structural features of glutathione, focusing on differences and similarities (gamma- vs. alpha-glutathione; gas phase vs. solution).
7. Compare the energies between gamma- and alpha-glutathione (make sure that charges are the same).
8. Download the 3-D structure of glutathione synthetase (PBD ID = 2HGS) from the PDB DataBank. Isolate the glutathione, add hydrogens and perform an energy calculation (single point) in the gas phase and solution. Do not perform a geometry optimization on this structure.
9. Compare the energies between gamma- and enzyme-glutathione (make sure that charges are the same). Are there any major structural/energy differences?

Conclusions

Present your results and conclusions in a formal report that follows a journal style format.

1. alpha-glutathione, charge = -1 (aECG-1n)

2. alpha-glutathione, charge = -1, zwitterionic (aECG-1z)

3. alpha-glutathione, charge = 0, zwitterionic (aECG0z)

Structure 1

H_2N—CH—CH_2—CH_2—C(=O)—N(H)—CH—C(=O)—N(H)—CH—C(=O)—OH

with side chains: C(=O) O^- (on first CH), CH_2—SH (on second CH), H (on third CH)

1. gamma-glutathione, charge = -1 (gECG-1n)

Structure 2

$H_3\overset{+}{N}$—CH—CH_2—CH_2—C(=O)—N(H)—CH—C(=O)—N(H)—CH—C(=O)—O^-

with side chains: C(=O) O^- (on first CH), CH_2—SH (on second CH), H (on third CH)

2. gamma-glutathione, zwitterionic, charge = -1 (gECG-1z)

Structure 3

$H_3\overset{+}{N}$—CH—CH_2—CH_2—C(=O)—N(H)—CH—C(=O)—N(H)—CH—C(=O)—O^-

with side chains: C(=O) OH (on first CH), CH_2—SH (on second CH), H (on third CH)

3. gamma-glutathione, zwitterionic, charge = 0 (gECG0z)