Bioinformatics 2 -- lecture 5

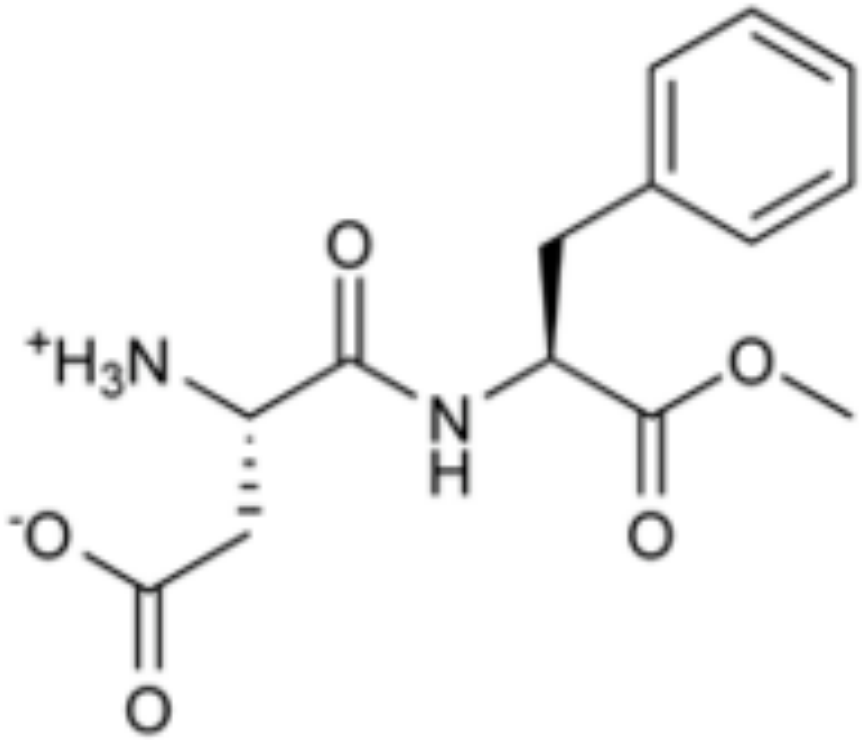
Building a small molecule

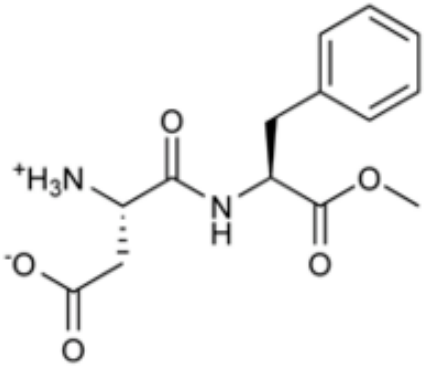
Secondary structure prediction

MOE Exercise 1

5.1 Building a small molecule

Building aspartame





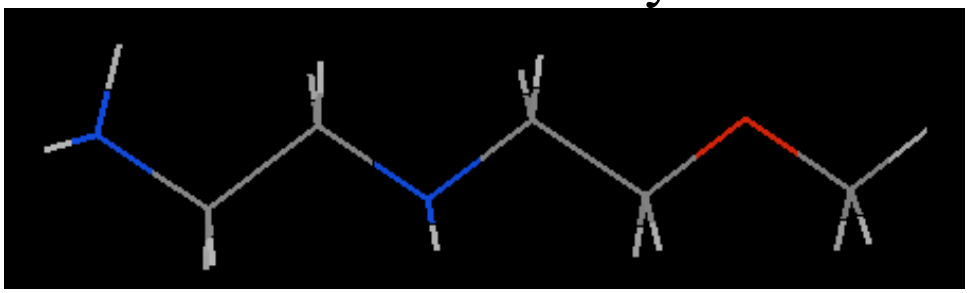
Building aspartame

Starting with an empty Moe window:

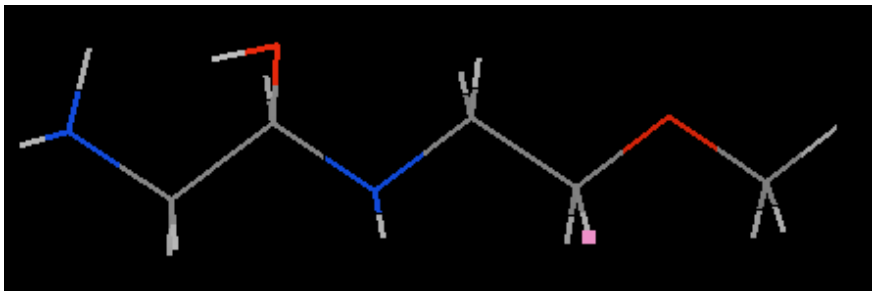
•Edit/Build/Molecule, or use Builder button

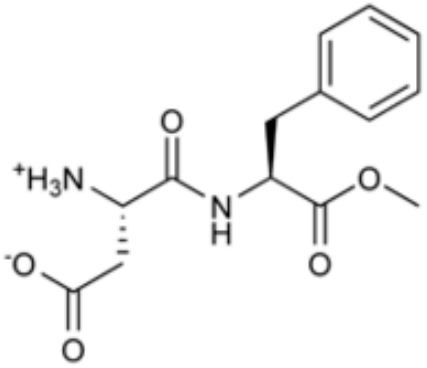
•Create backbone using atoms buttons: N,C,C,N,C,C,O,C

(Notice the chain is made in the fully reduced state.)



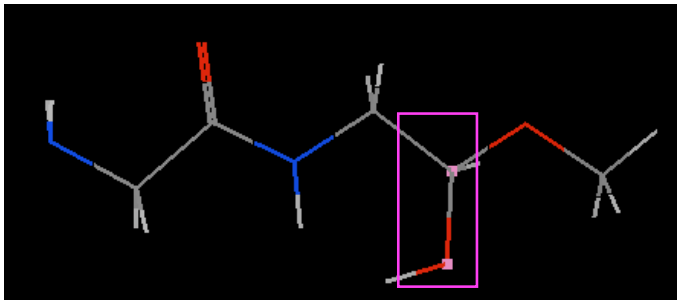
•Add carbonyl oxygens: Select an H, hit O in Builder. the H becomes an O.





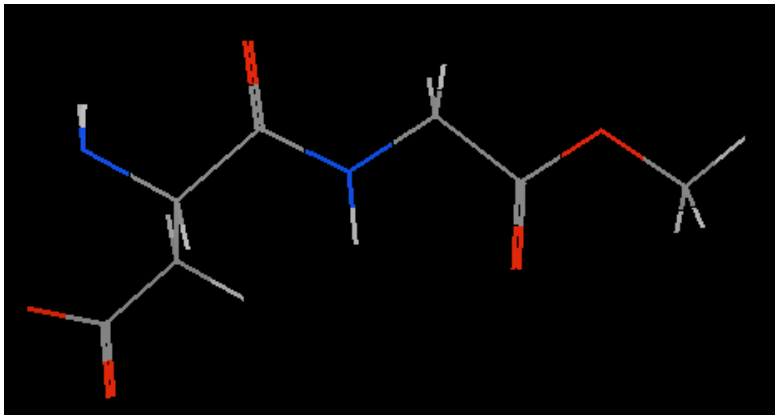
Building aspartame

•Select carbonyl groups. Click double bonds (=)

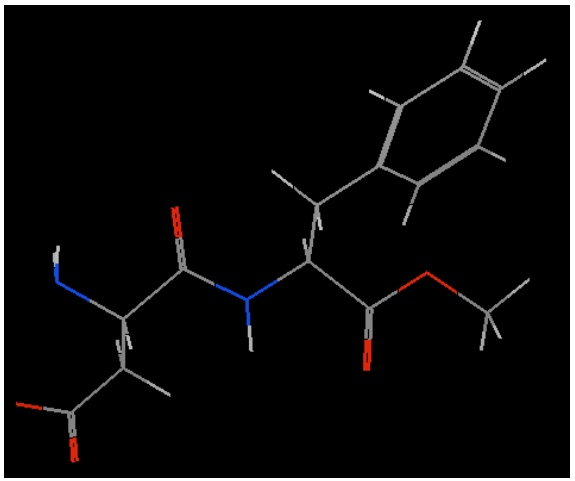


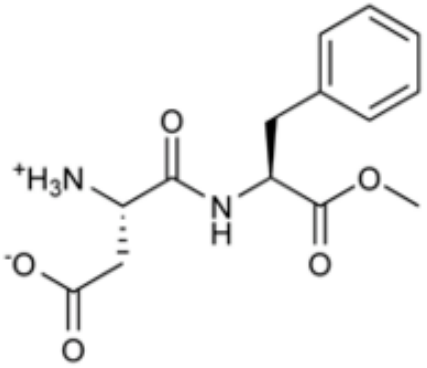
• Add sidechains:

•Select the *back* H on the first alpha-carbon. Click C, then -COO-



•Select the *front* H on the second alpha-carbon. Click C, then benzene.





Building aspartame

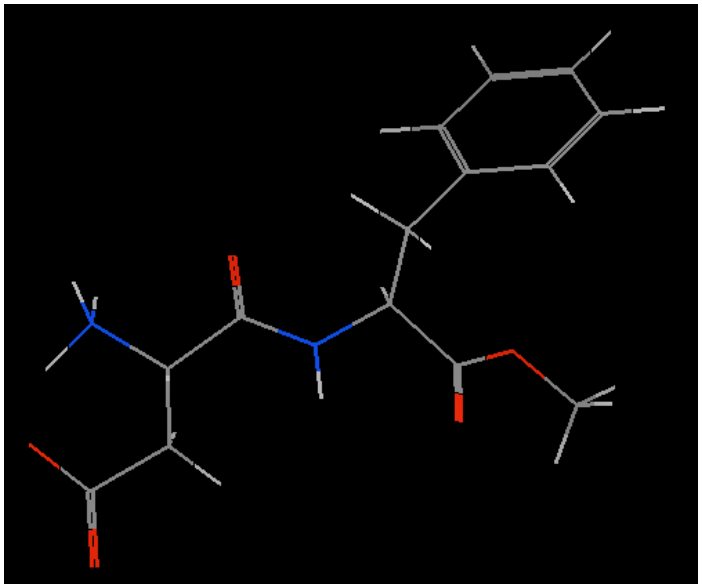
•Fix ionization of NH_3

Select N. In Builder, click "+1" (a proton is added)

•Fix hybridization of NH.

•Double-click second N. Choose Geometry: "sp2". Click "Apply"

•Click "Minimize".



5.2 Energy minimization

What is energy minimization?

- Energy minimization is a **molecular simulation** the leads the system to a **lower potential energy**.
- This is similar to the problem of finding the parameters that minimize a function, but there are generally too many parameters. No **optimal** solution is possible.
- Energy minimization is a **heuristic** method.

How is the energy of a molecular model calculated?

- **Energy** is a function of :
  (1) The coordinates of the atoms.
  (2) Their names.
  (3) Their numbers.

The "names" and "numbers" *tell the program* what **element** the atoms are, how they are **bonded**, and what **oxidation state** they have.

Molecular mechanics energy

An *energy function* is a sum over a set of simple functions. This sum is the so-called “energy” of the system.

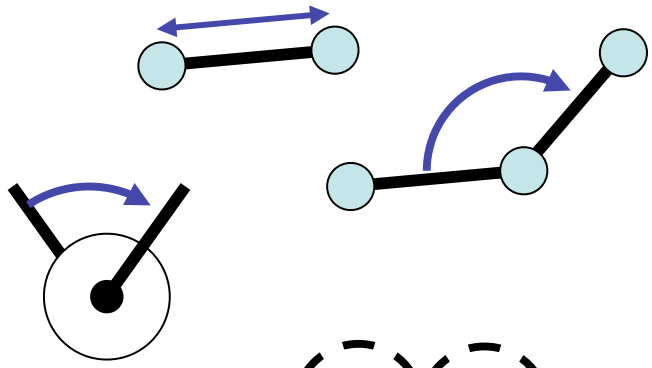
$$E = f(a_1,a_2) + f(a_1,a_3) + f(a_2,a_3) + f(a_1,a_2,a_3) + \text{etc.}$$

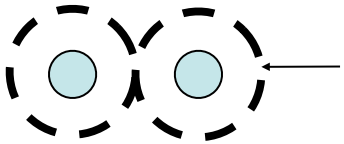
Each simple energy function (f) may have 2,3 or more atoms as parameters: coordinates, names and numbers. Each function uses stored information about each atom name to choose constants within each function. Together the entire set of functions and constants is called a “force field.”

Molecular mechanics

A molecular mechanics energy function includes the following components (and others):

- bonded
  - bond lengths
  - bond angles
  - torsion angles
- non-bonded
  - Lennard-Jones or Vander Waals
  - Coulomb, or electrostatic





van der Waals spheres

charge-charge interaction

constraint/restraint

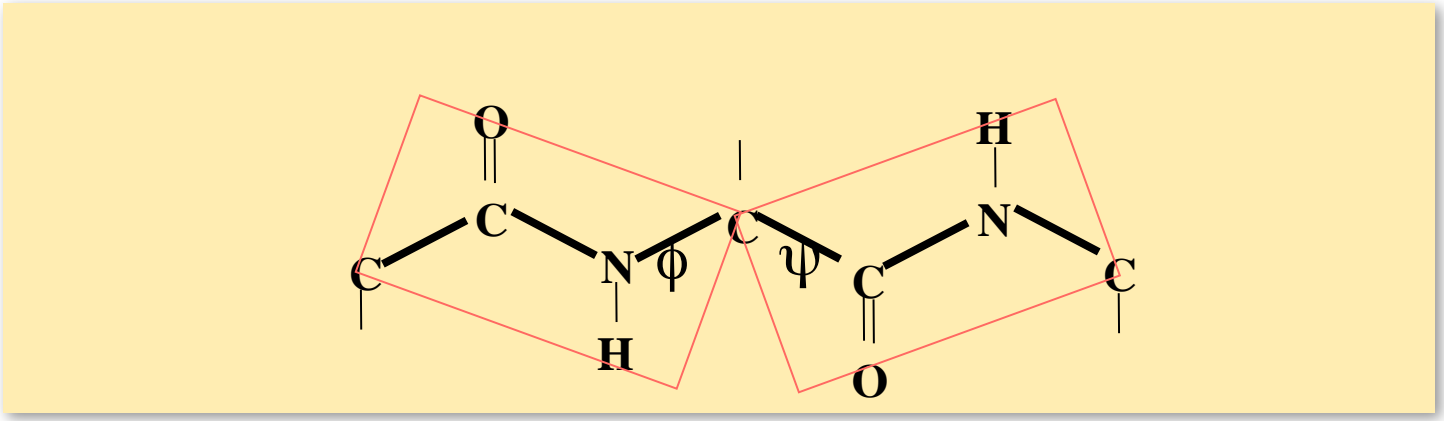
restraint = a function that approaches a minimum as the parameters approach ideal values.

For example, the distance A-B is restrained to 3.8Å using the restraint $E(A,B) = (D_{AB} - 3.8)^2$

constraint = a function that reduces the number of variable parameters in the system.

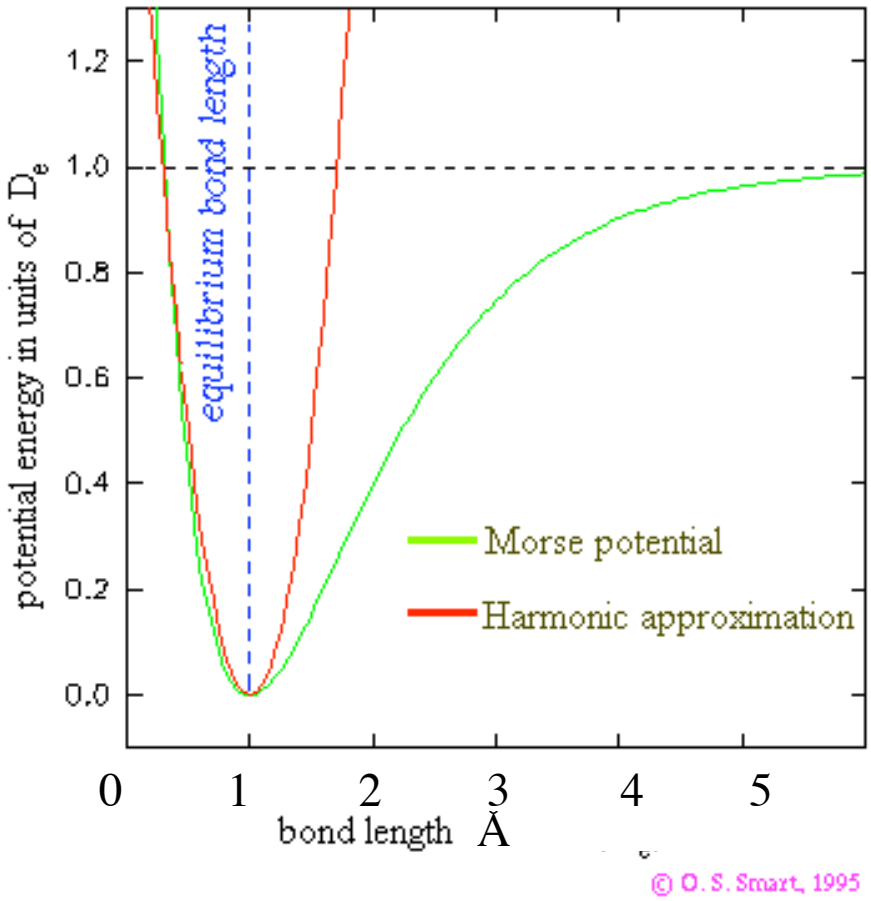
For example, atoms A,B,C and D are constrained to be in the same plane.

Planar groups may be constrained



Distance restraints, harmonic and otherwise

Harmonic and Morse potentials are **restraint** functions.



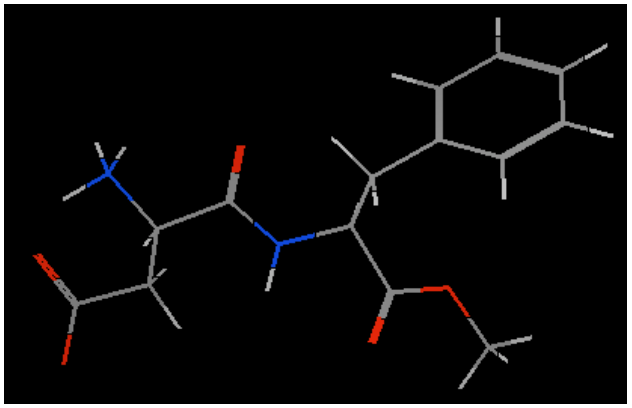
Restraint forces are applied to move the atoms to their ideal distances/angles.

Harmonic potential:

$$E(i,j) = \omega\left(x_{ij} - T\right)^2$$

where x_{ij} is the distance between i and j, and T is the ideal distance between i and j.

Building aspartame the easy way



- Close current system
- Edit-->Build-->Protein
- Click ASP, PHE
- Unselect by clicking in empty space.
- Click "C". a methane appears.
- Select it and use the *meta-middle mouse* to move it close to the -COO group
- Select methane C and one O from the Phe-COO. In Builder, click - (single bond)
- Minimize.

Using distance restraints to make H-bonds

- **Add restraints**

  Edit/Potential/Restrain, distance,

  Target 1.8, 1.8, Weight 100

  Pick H and O. Click Create.

  Target 2.8, 2.8, Weight 100

  Pick N and O. Click Create.

  Cancel/Restrain

- **Energy minimize**

  Compute/Structure preparation

  Checks for missing atoms, assigns energies.

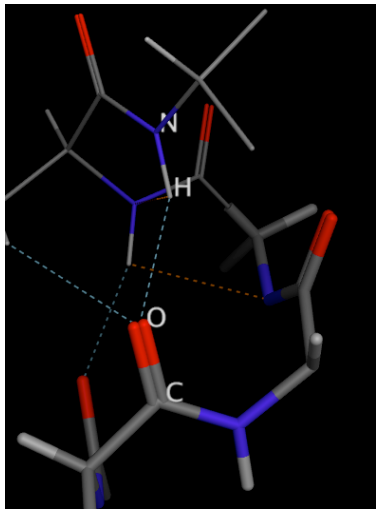
  GizMOE/Minimizer

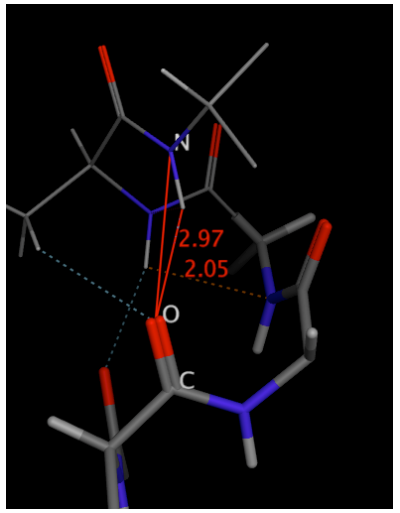
  When finished, Cancel/GizMOE_Minimizer

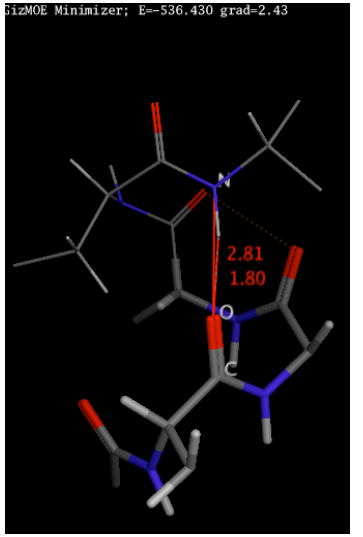
- **To remove or modify restraints**

  Window/Potential setup...

  Restraints. Select a restraint. Delete or modify.







Exercise 5.1

- Make a beta-hairpin