Molecular Modeling 2018 -- lecture 5

Building a small molecule

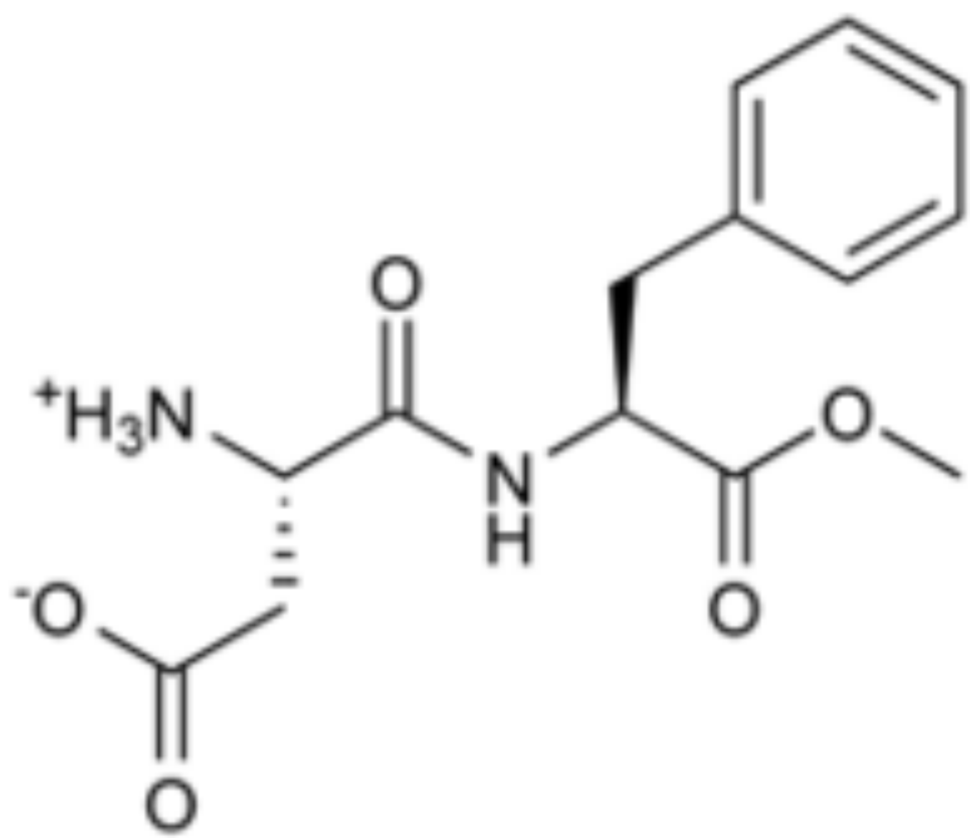
Energy

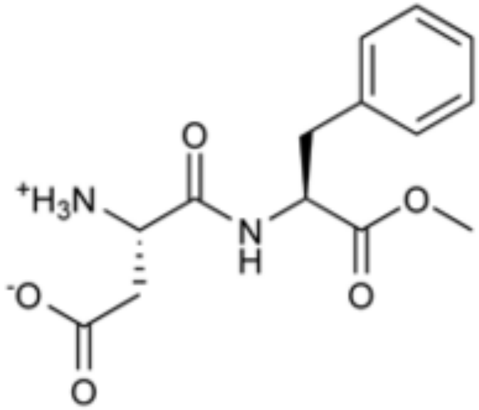
Energy minimization

Make a beta hairpin using restraints

Exercise 4.1 Building a small molecule

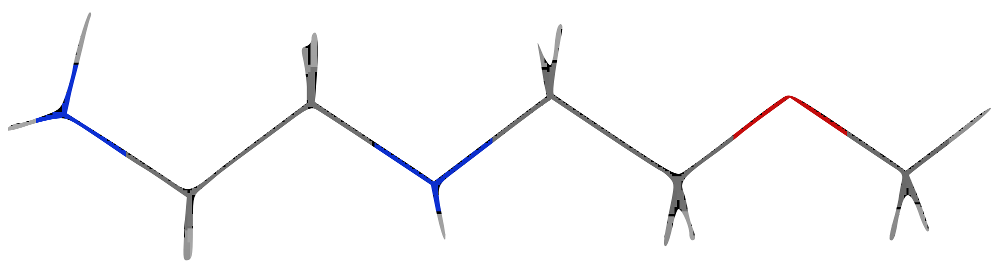
Building aspartame



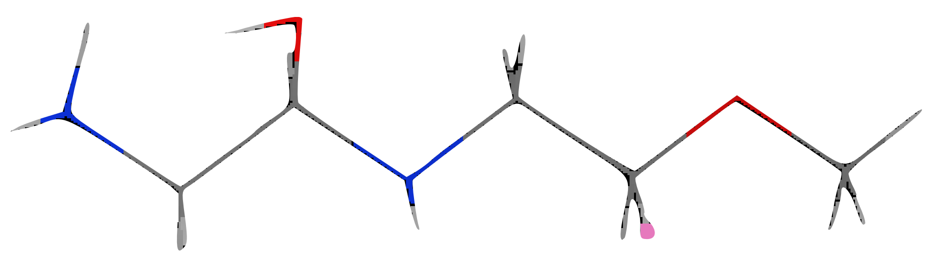


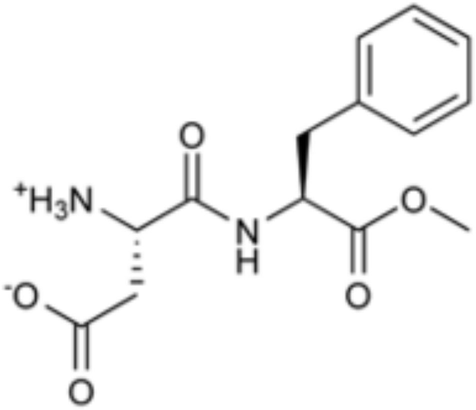
Building aspartame

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.)



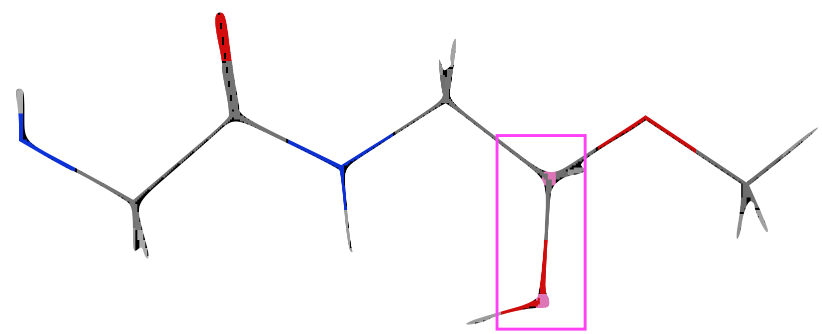
•Add carbonyl oxygens: Select an H, hit O in Builder. the H becomes an O.





Building aspartame

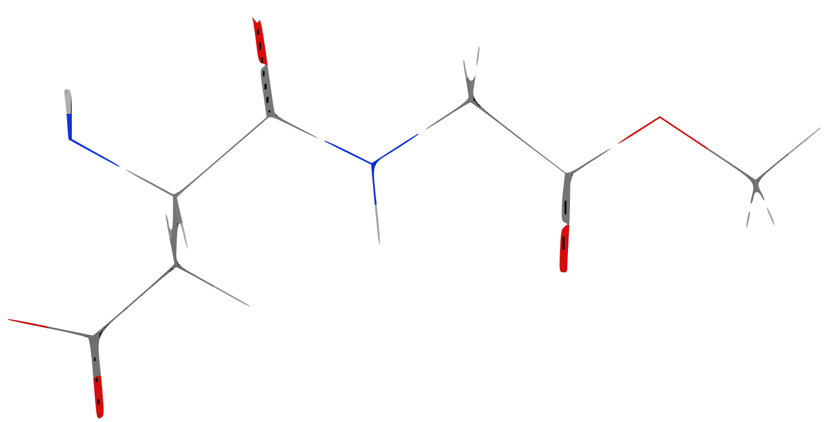
•Select carbonyl groups. Click double bonds (=)

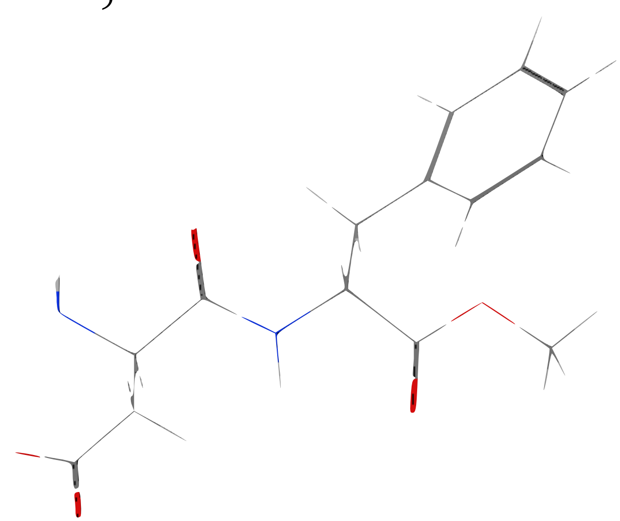


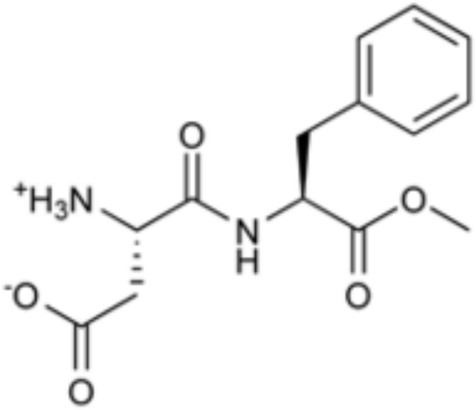
• Add sidechains:

•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.



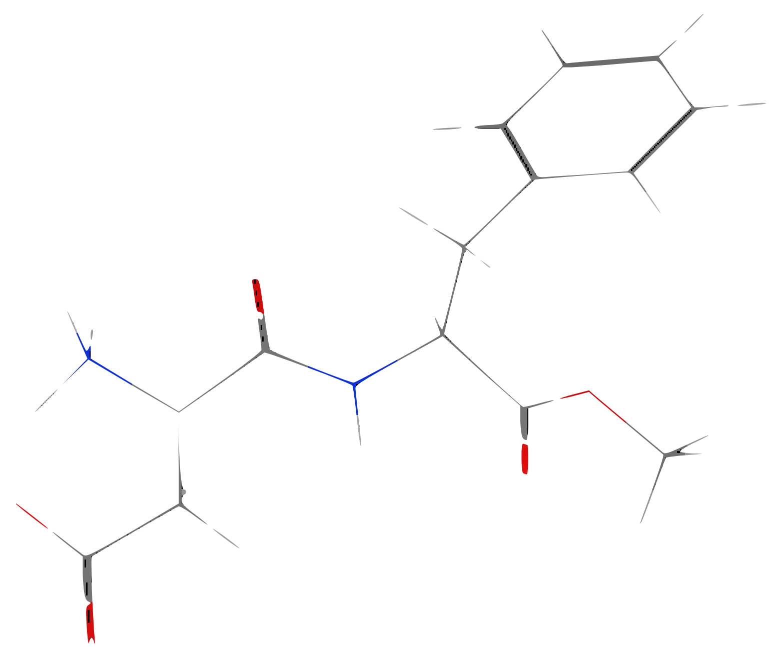




Building aspartame

•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".



What is energy?

- **Energy** (G) is a measure of the **probability** of the **state of the system**. Energy is the **negative log of the probability ratio, times temperature**.
- $\Delta G = -RT \ln (A / \text{not } A)$
  or $-RT \ln(P / (1-P))$, where P = probability.
- The system = <u>the atoms</u>.
- State = <u>where the atoms are</u>.
  (This is a vague definition so we can be flexible about what the energy means.)
- Energy is always relative.
- Energy is measured between two states.
- Energy is expressed in J/mole, or kJ/mole.
- Energy breaks down into enthalpy (H) and entropy (S).
  $\Delta G = \Delta H - T\Delta S$.
- Energy also breaks down to **potential** energy and **kinetic** energy.

What is energy minimization?

- Energy minimization (of proteins & macromolecules) is a **molecular simulation** the leads the system to a **lower potential energy**.
- Energy minimization minimizes the energy as a function of the atom positions.
- In general, no **optimal** solution is possible.
- Therefore, in general, energy minimization is **heuristic**. (i.e. uses short cuts and rules of thumb)

How is the energy of a molecular model calculated?

- **Atom** information includes :
  (1) The coordinates (x,y,z).
  (2) The name (element, oxidation state, hybridization state)
  (3) The residue type and number.
  (bonds, charges, connectivity, flexibility)
  (4) The molecular and chain identifier.

Molecular mechanics

Molecular mechanics is one component of the potential energy, derived from stereochemistry plus pairwise interactions. MM energy (E_{tot}) breaks down into a set of functions E,

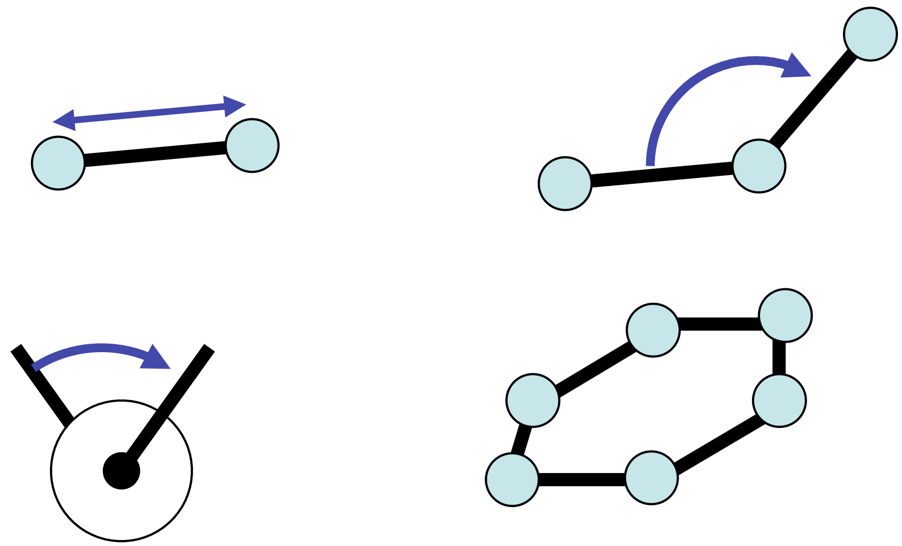
$$E_{tot} = E_1(a_1,a_2) + E_1(a_1,a_3) + E_1(a_2,a_3) + E_2(a_1,a_2,a_3) + \text{etc.}$$

where **a** is an atom.

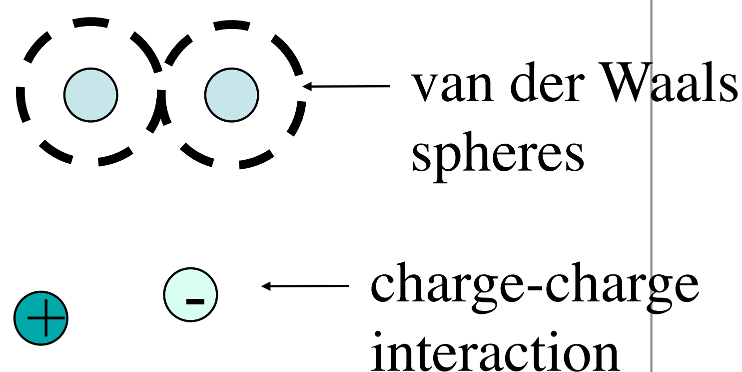
Each simple energy function (E) may have 2,3 or more atoms as parameters: **coordinates**, **names** and **numbers**. Each function uses stored information about each atom name to choose constants within each function. Together the entire set of functions and constants is called a "**force field**."

Molecular mechanics

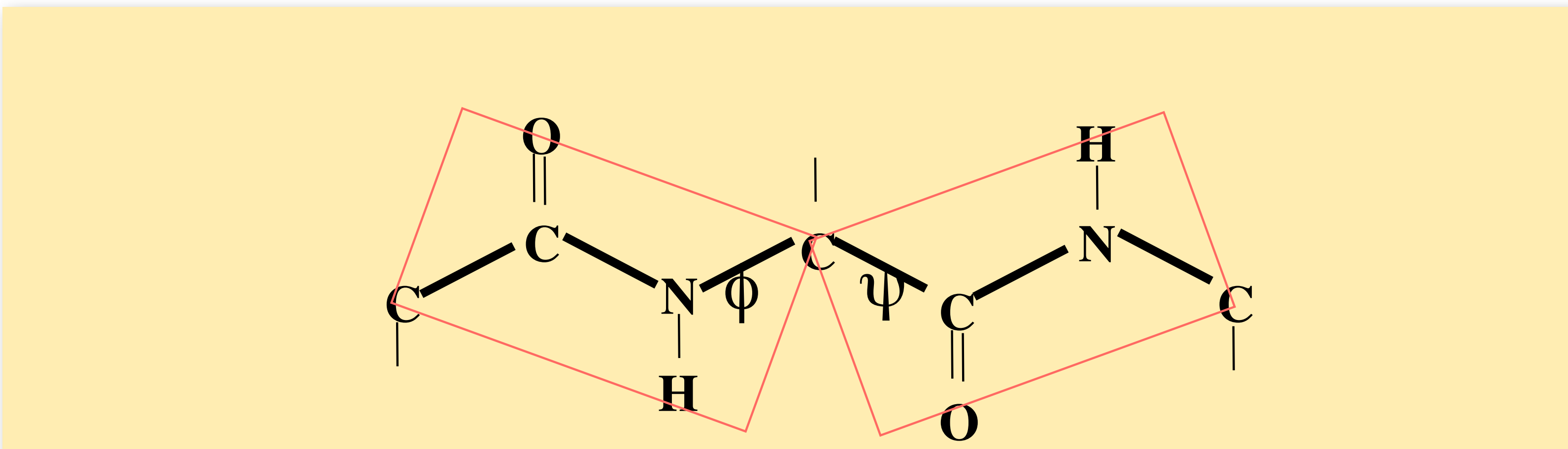
A molecular mechanics energy function includes the following components (and others):



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



Peptide bonds are planar groups



constraints versus restraints

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

For example, the bonded distance A-B is restrained to 1.52Å using the restraint $E(A,B) = (D_{AB} - 1.52)^2$

D_{AB} depends on atoms A and B

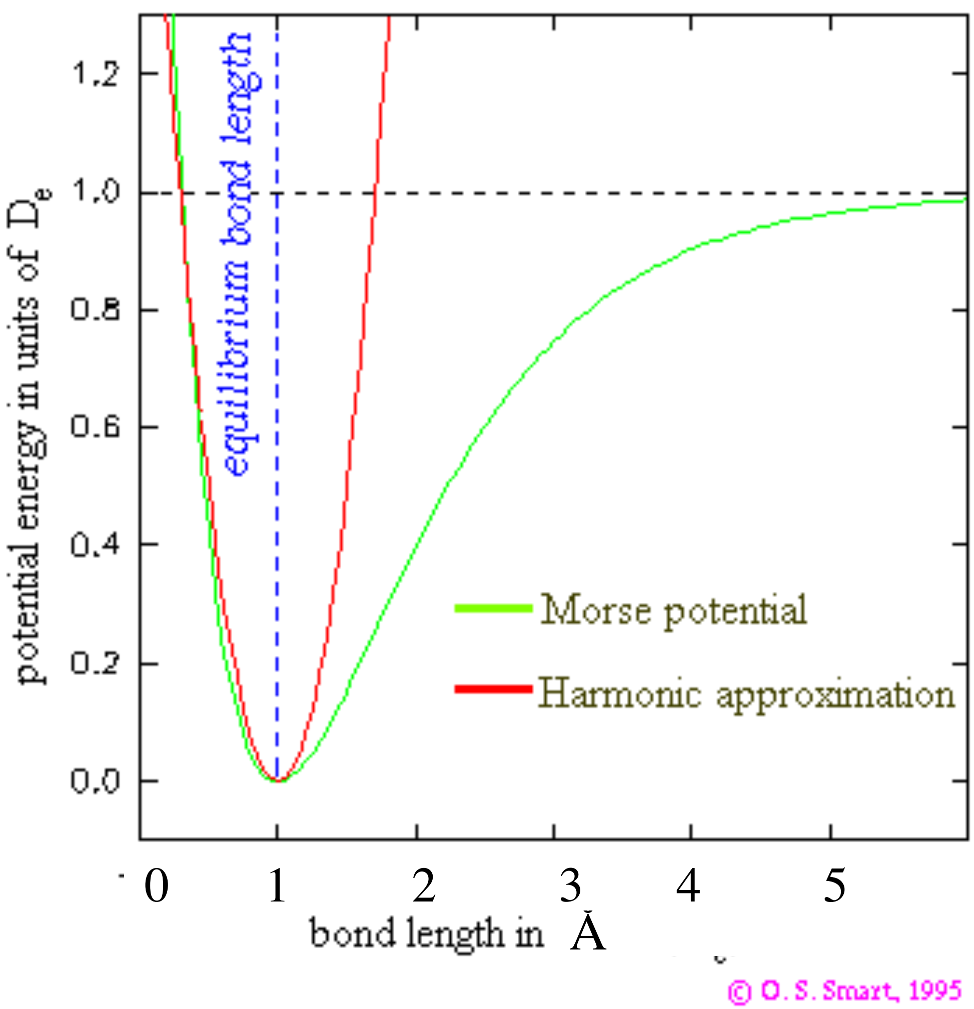
—- versus —-

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. Move atoms, then solve for the constrained atom position.

Harmonic and non-harmonic restraints

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

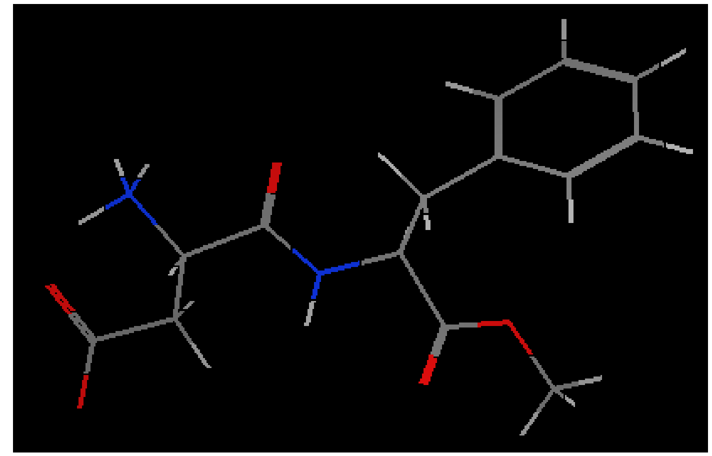


<u>Harmonic potential:</u>

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

where x_{ij} is the current 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.

Real-time energy minimization using GizMOE

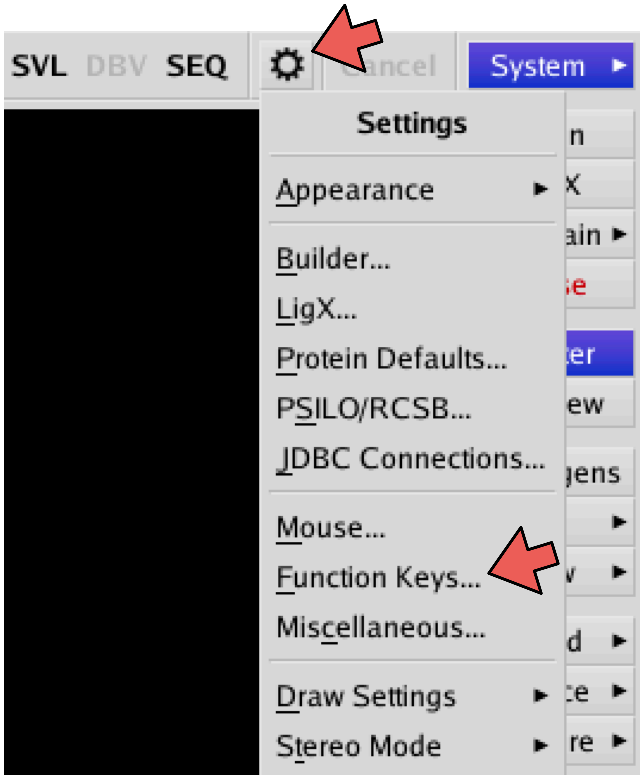
SVL: run ‘gizmin.svl’

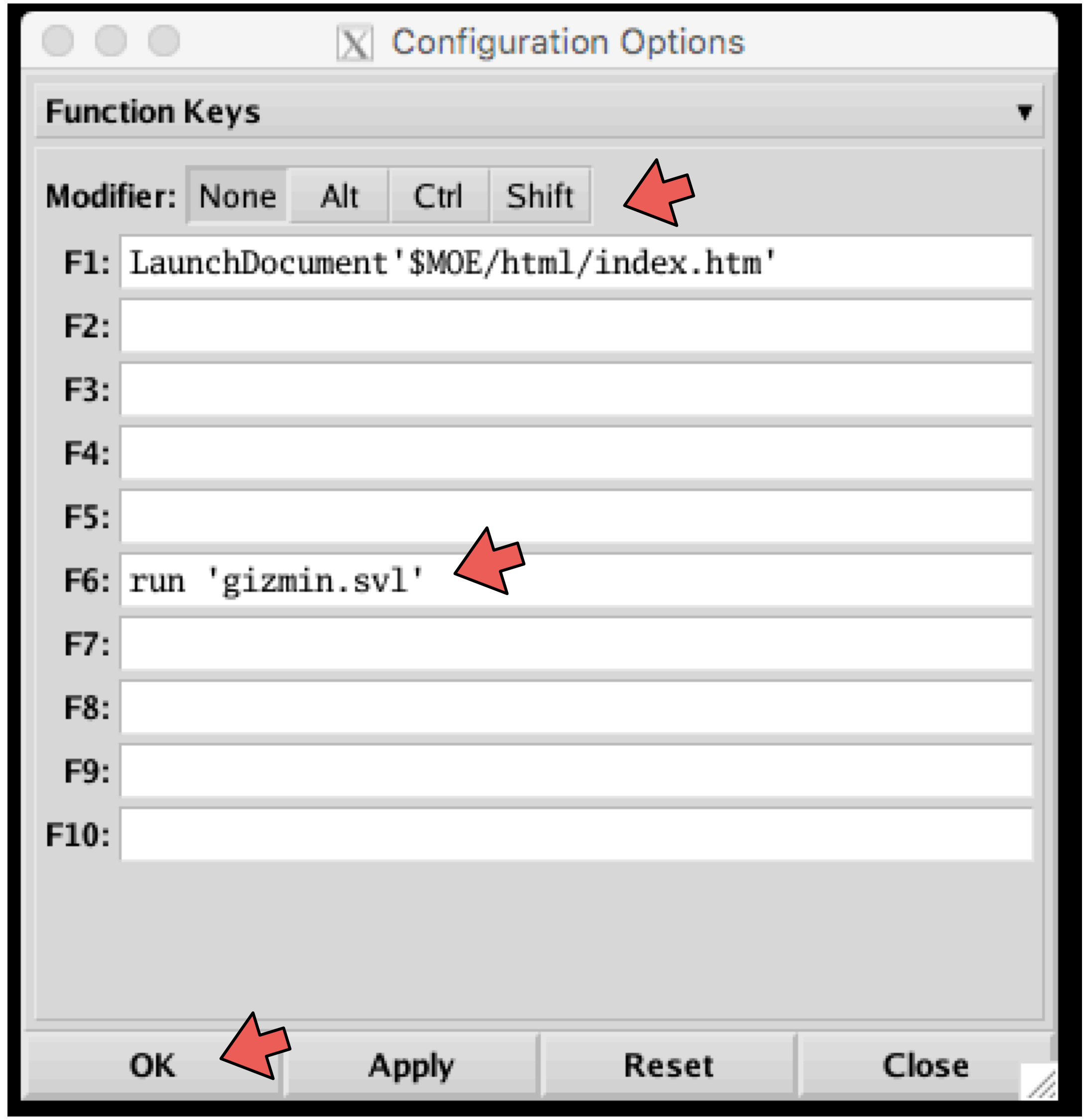
Scientific Vector Language window. You can writer programs for MOE to run.

Runs Minimizer without stopping.

To stop Gizmin, **Cancel/MOE:Giz_minimizer**

..or, make *gizmin* a function key



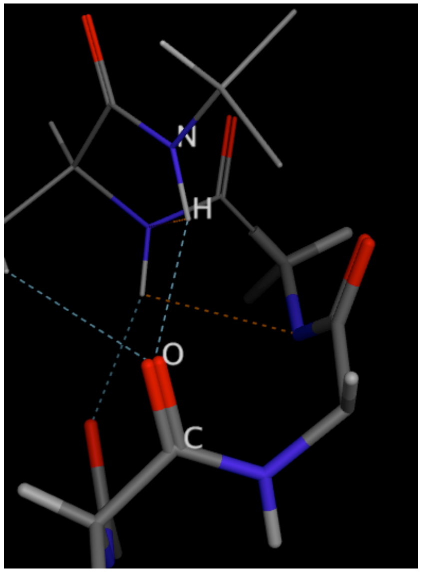


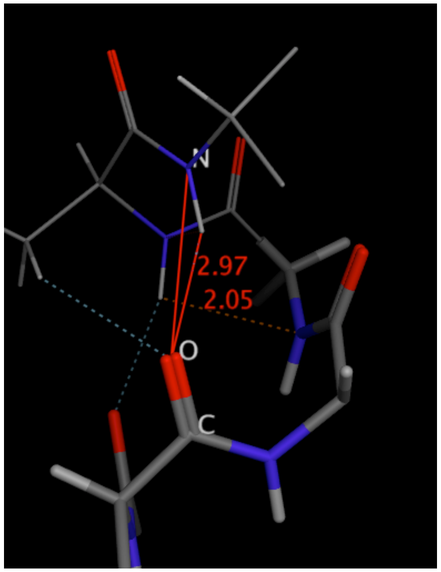
Exercise 4

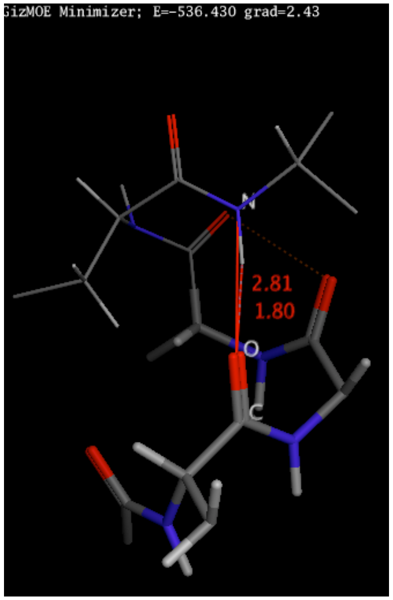
- Make a beta-hairpin
- Read instructions from Exercise4 on course homepage.

How to specifically force hydrogen 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 (or hit esc)
- Energy minimize
  Compute | prepare | Structure preparation
  Checks for missing atoms, assigns energies.
  SVL: run 'gizmin.svl'
  When finished, be sure to **Cancel | GizMOE_Minimizer**
- To remove or modify restraints
  Potential setup (button at far lower left)
  Restraints tab

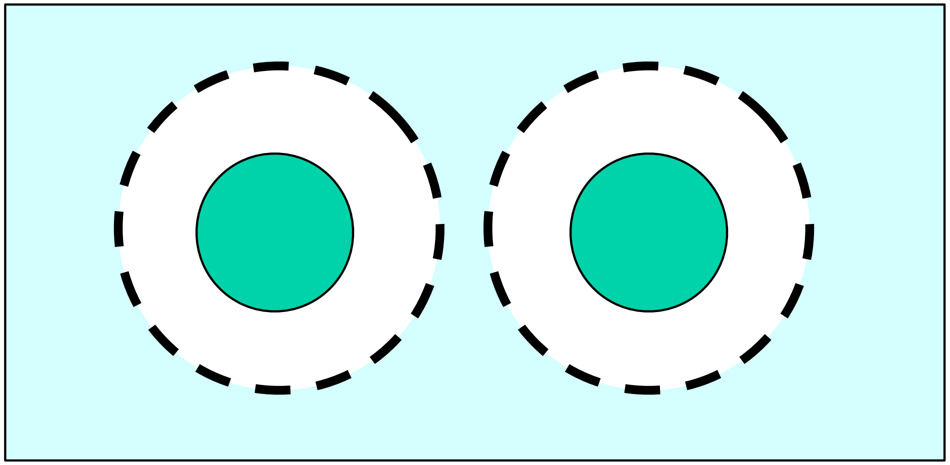




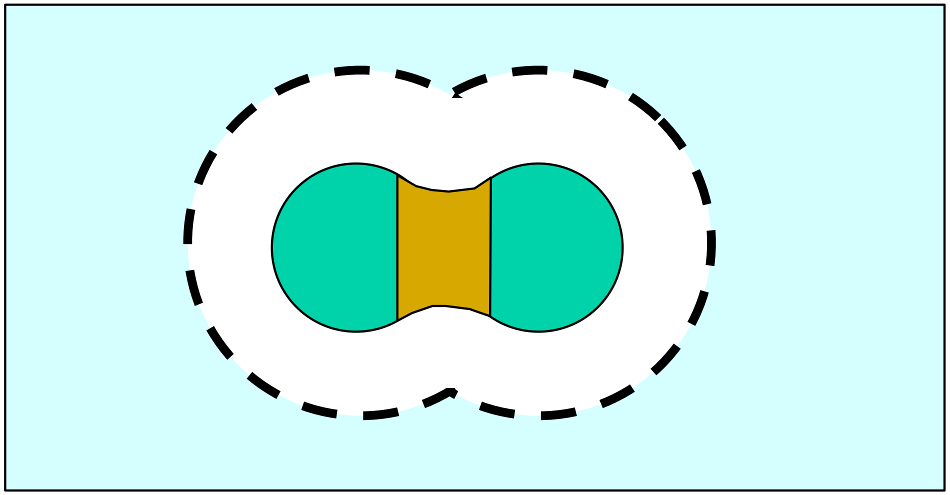


The Hydrophobic Effect

Solvent accessible surface (dashed line) around non-polar atoms contains "high energy waters" because those waters lose H-bonds.



Non-polar atoms come together because it decreases the number of high energy waters. (Even at the cost of creating void space (brown).



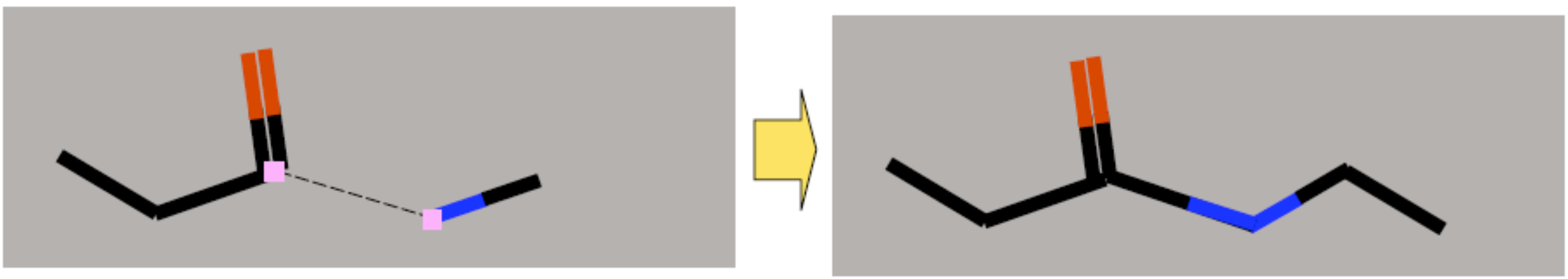
review questions

- What does *sp2* hybridization mean?
- How is energy related to probability?
- What constitutes a “system”?
- What properties of atoms define the state of the system?
- Give an example of a state of a system.
- What changes when we minimize the energy?
- Energy can be broken down into what two components?
- What information is contained in the Atom data structure?
- Name two molecular mechanics component energy functions.
- What is a restraint?
- What is a constraint?
- How do we enforce a hydrogen bond in MOE?

Supplementary slides

Supplementary: How to make a new peptide bond

Zoom in on splice points.



Delete extra oxygen, if present.
Select C, N. **Build | single bond**.
Select N. **Window | Atom manager** (or cntrl-a)
Select the atom. Set geometry to sp2. **Apply**.

Supplementary slides: Pop-up menus in SEQ window. Use meta key or right-mouse.