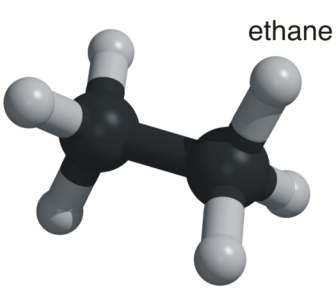
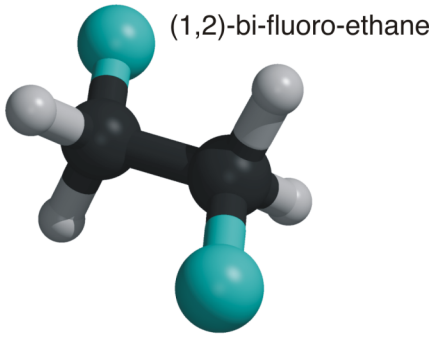
1. Potential energy surfaces

How many dimensions has the potential energy surface of isolated ethane?





Within the molecular mechanics approximation the potential energy of the system is described in terms of intuitive chemical concepts such as bonds, angles, torsions. Electrons are ignored, but their influence is expressed by empirical parameters. For ethane the MM potential energy is given by:

$$V = \sum_{ij}^{n_{\text{bonds}}} k_{ij}^{\text{bonds}}\left[r_{ij} - r_0\right]^2 + \sum_{ijk}^{angles} k_{ijk}^{angle}\left[\theta_{ijk} - \theta_0\right]^2 +$$

$$c_1 \cos\left[\phi_{ijkl}\right] + c_3\left(\cos\left[\phi_{ijkl}\right]\right)^3 + c_5\left(\cos\left[\phi_{ijkl}\right]\right)^5$$

constant	(kJ/mol)
c_1	-12.16
c_2	0.0
c_3	3.06
c_4	0.0
c_5	31.5

where the first sum runs over all bonds and the second over all angles in the molecule. The last sum with the cosine terms is the torsion potential that describes rotation around the C-C bond.

How many (local) minima does the potential energy surface have?

And how many (local) maxima?

Is there a global minimum?

If we now assume the hydrogens to be constrained, that is, their bond length and angles and are fixed at their equilibrium values of 0.1008 nm and 109.4° respectively, can you make a rough sketch of the potential energy surface?

In what follows we futhermore assume that also the carbon-carbon bond is constrained. Thus there is only one degree of freedom left, namely the torsion angle ϕ that describes the rotation of the two CH_3 groups with respect to each other.

We now consider an bi-fluorinated ethane molecule in which the protons on both carbons has been substituted by fluor atoms.

Except for the values of the constants the molecular mechanics forcefield is identical to normal ethane. For the torsion potential function, the values of the constants are listed in the table. We still assume that all bonds and angles are constrained. What are the probabilities of finding the anti conformation ($120 \le \phi \le 240$), and gauche

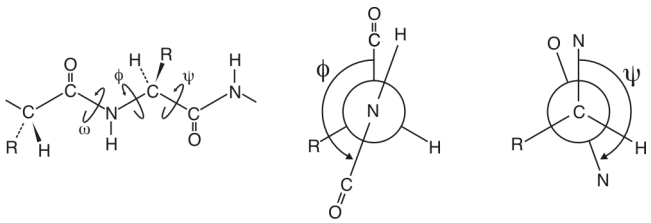
$(0 \leq \phi \leq 120 \wedge 240 \leq \phi \leq 360)$ conformations of this molecule at room temperature (300 K)? The boltzmann factor (Gas contant R) is 0.00831451 $kJmol^{-1}K^{-1}$.

What are these probabilites at 600 K and 1200 K?

Concerning the rate at which anti is converted into guache and vice versa, by what factor is this rate enhanced if the temperature is elevated from 300 to 1200 K?

2. Backbone Conformations / Ramachandran Plot

A protein fold is mainly determined by the configuration of the backbone. The backbone conformation is completely defined by three torsions ϕ, ψ, ω. The definitions of these torsions are shown in the Newman projection below. The direction of the arrow indicates the positive rotation angle.



In glycine the sidechain (-R) is a proton (H). Use your intuition on the relative sizes of the atoms (Van der Waals radii) to sketch a ramachandran plot of a poly-glycine peptide and compare to a typical Ramachandran plot.

Do you expect a difference? If so, why?

Torsion ω is less flexible due to the partial double bond character of the peptide bond.What configurations do you expect for torsion ω?

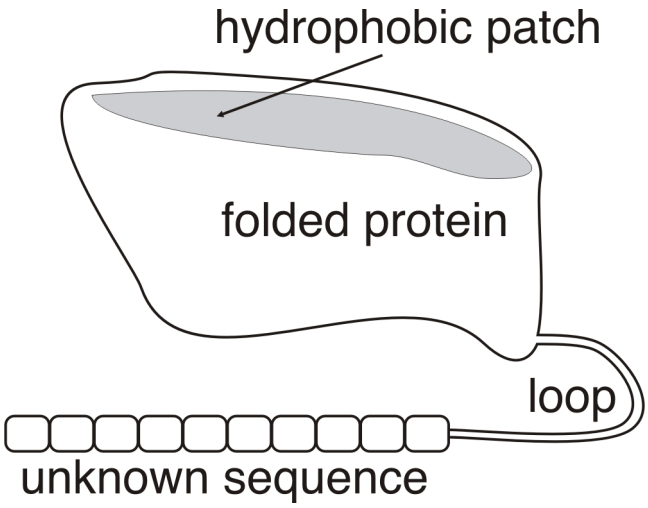
Which configuration is higher in energy?

Where in the Ramachandran plot do you expect proline to be?

What consequences does this have for a poly-proline peptide?

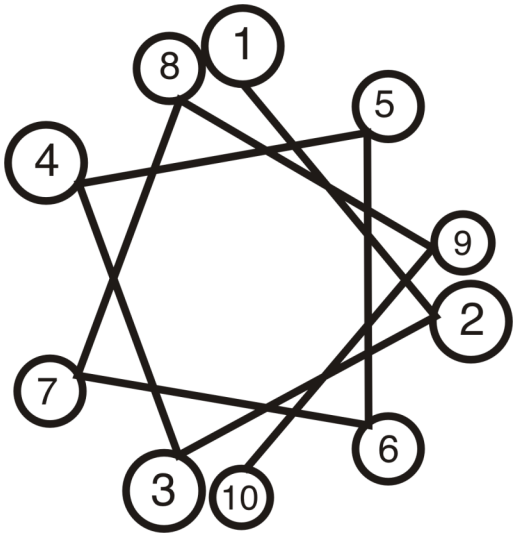
3. Protein Design

The protein shown (schematically) below is only partially folded. There is large hydrophobic patch exposed to the solvent, and 10 residues at the carboxy terminus still need to fold into a alpha helix. Use the hydrophobicity scale of the aminoacids to predict a possible sequence of the helix part, indicated by the open boxes.

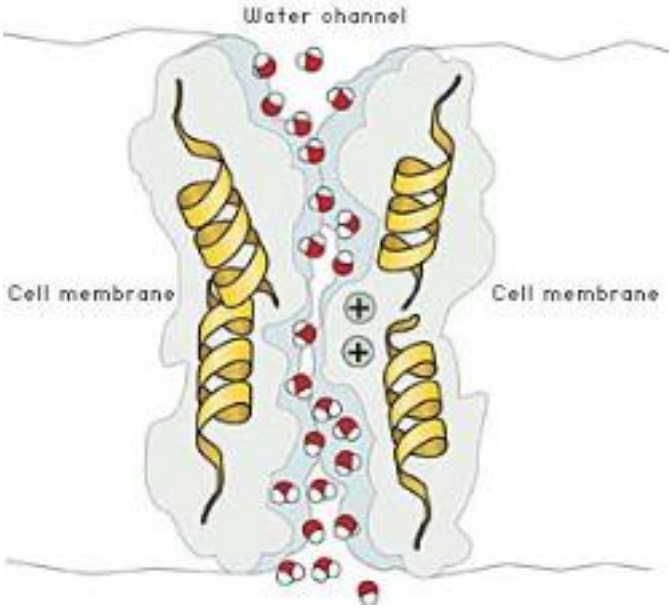


Hints: use the helical wheel representation below, which shows a helix from along the helix axis. For this exercise you can also use an on-line tool @ http://cti.itc.virginia.edu/~cmg/Demo/wheel/wheelApp.html

	non-polar surface area [A^2]	estimated hydrophobic effect [kcal/mol]
Trp	236	4.11
Leu	164	4.10
Ile	155	3.88
Phe	194	3.46
Met	137	3.43
Val	135	3.38
Pro	124	3.10
Lys	122	3.05
Tyr	154	2.81
His	129	2.45
Thr	90	2.25
Arg	89	2.23
Ala	86	2.15
Glu	69	1.73
Gln	66	1.65
Ser	56	1.40
Cys	48	1.20
Gly	47	1.18
Asp	45	1.13
Asn	42	1.05



Use the hydrophobicity scale to design membrane channels for water. Membrane channels are special proteins that span the width of a membrane and allow for small molecules, or water to pass from one side of the membrane to the other. Aquaporin is an example of a water channel protein.



Propose two channel designs. One based on alfa helices and another based on beta sheets.

6. Projects for next week

Prepare an *oral* presentation of about 5-10 minutes on one of the following topics:

- Phase problem in x-ray crystallography
- Protein folding
- Levinthal paradox
- Photosensory proteins
- Photosynthesis
- Membranes
- Computer aided drug design
- ...