Structural Analysis of Biological Systems

Joel Ireta

Fritz-Haber Institut der Max-Planck Gesellschaft

Outline

Fundamental concepts:

- **Cell Theory**
- **Cell Composition**
- **Biological (Macro) molecules**
  - **Nucleic Acids**
  - **Proteins**
  - **Lipids**
  - **Carbohydrates**

- **Protein Structure**

- **Hydrogen bonds**
  - **Strength**
  - **Cooperativity**
  - **Biological importance**

Outline

Structural Analysis of proteins using DFT.

Hydrogen bonds:
- Binding energies
- Geometry

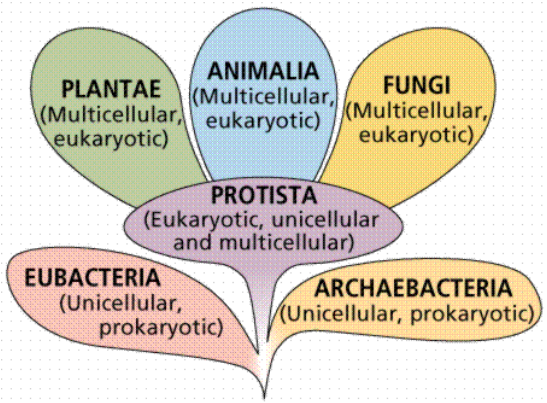
α-helix Stability
- Geometry
- Hydrogen bond strength
- Stabilizing mechanisms

α-helix response to uniaxial strain
- Mechanical response
- Hydrogen bond response
- Electronic Structure response

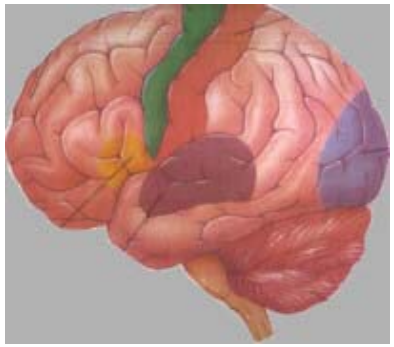
Cell theory

The cell is the fundamental unit of living material

Organism

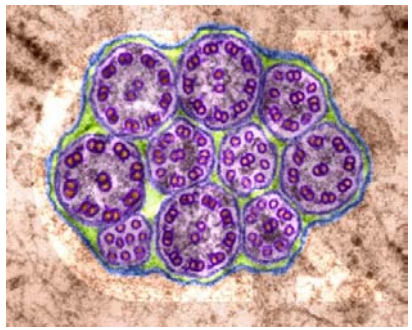


Organs



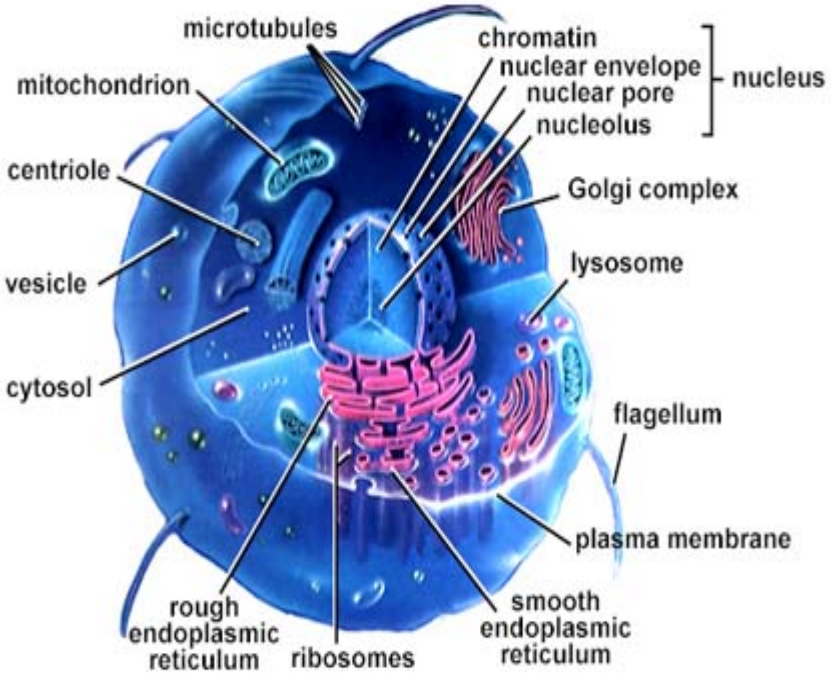
Tissues

Cells



The activity of the organism as a whole is just the sum of the activities and interactions of its individual cells

Cell Structure



http://www.biosci.uga.edu/almanac/bio_103/notes/may_15.html

Organelles:
identifiable structures inside a cell that perform a particular function.

Membrane:
a semipermeable covering that encloses the cellular contents

Composition

90% water

10% The dry weight :

- 50% protein
- 15% carbohydrate
- 15% nucleic acid
- 10% lipid
- 10% miscellaneous

Biological Macromolecules

Composition by element

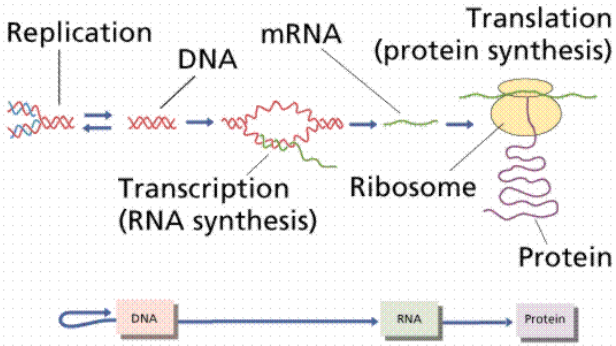
- 60% H
- 24% O
- 10% C
- 5 % N
- 1% → S, P, Ions (Na, K, Ca, Fe), Trace elements

Biological Macromolecules

Nucleic acids

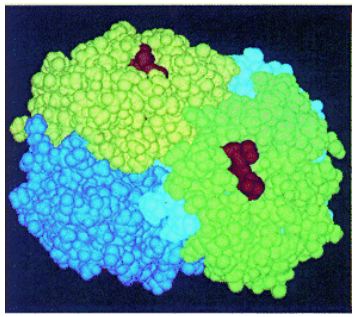
DNA is the major store of genetic information

RNA translate the information stored in the DNA into proteins



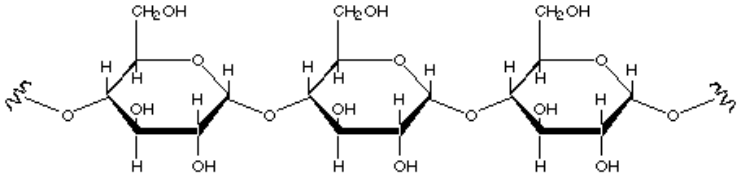
Proteins

Built up from amino acids , they are the working parts of the whole.
Enzymes, receptors …...



Carbohydrates

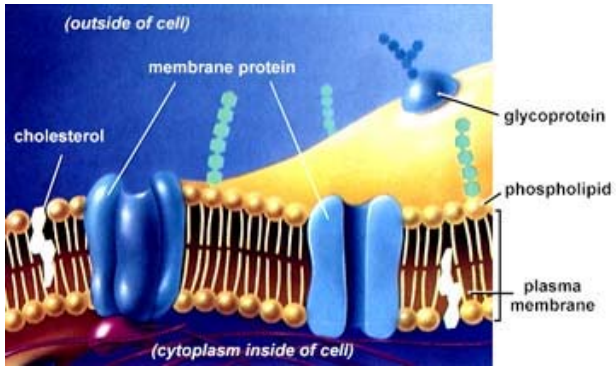
Carbohydrates, the main source of cellular energy, and also structural components of cells.



Amylose
poly(1,4'-O-α-D-glucopyranoside)

Lipids

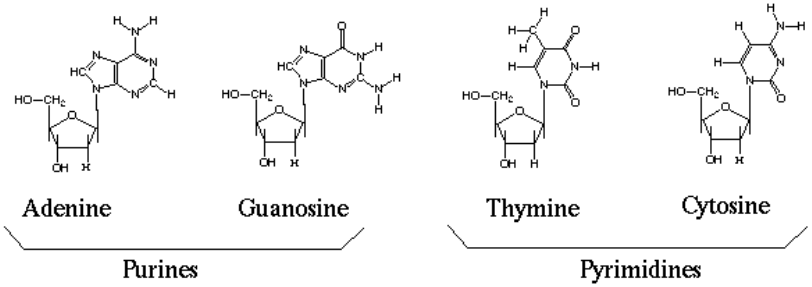
Bipolar molecules whose configuration accounts for many of the biological membrane's properties.



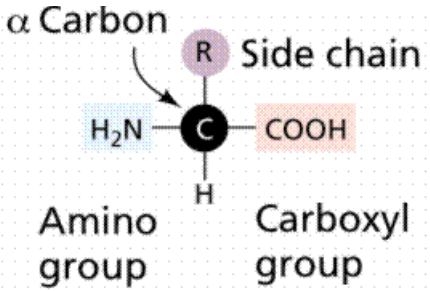
Biological Macromolecules

$-P_A-P_B-P_C-P_D-P_E-$

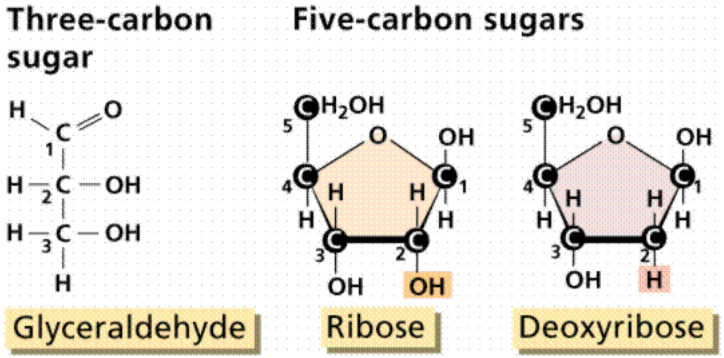
Nucleic Acids



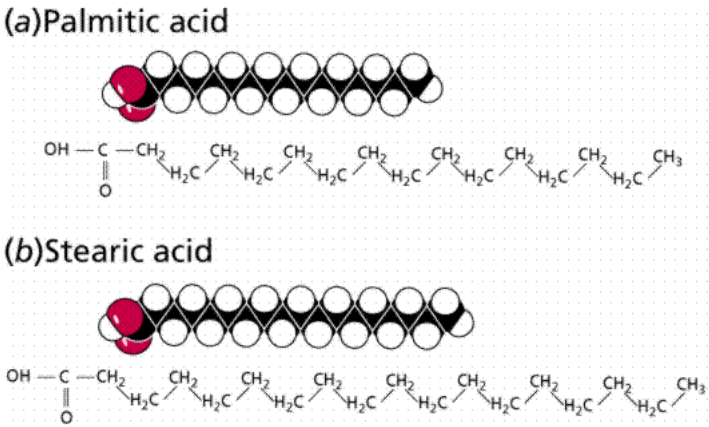
Proteins



Carbohydrates

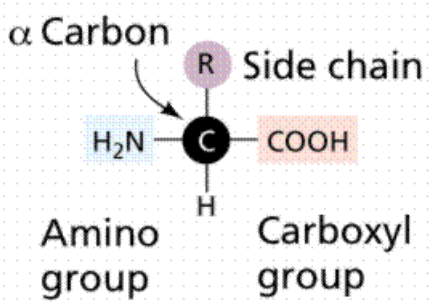


Lipids



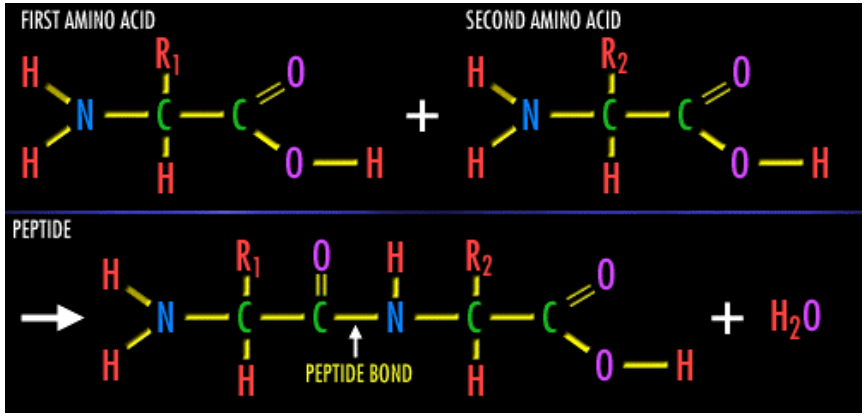
Purves et. Al The science of biology 4th edition, Sinauer associateshttp://gened.emc.maricopa.edu/bio/bio181/BIOBK/BioBookCELL2.html

Protein Structure



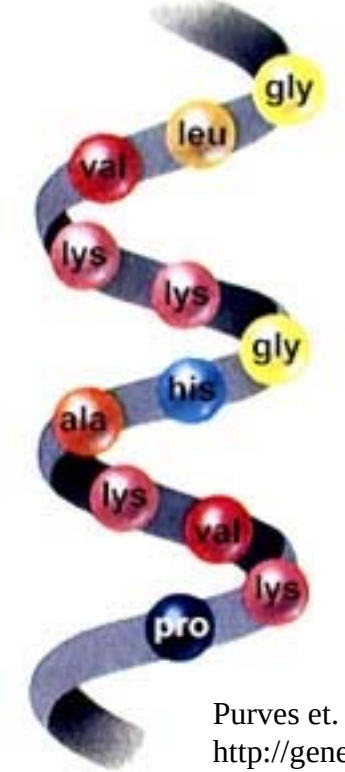
Twenty amino acids found in living systems

Peptide bond



Primary structure

Secondary structure



Tertiary structure

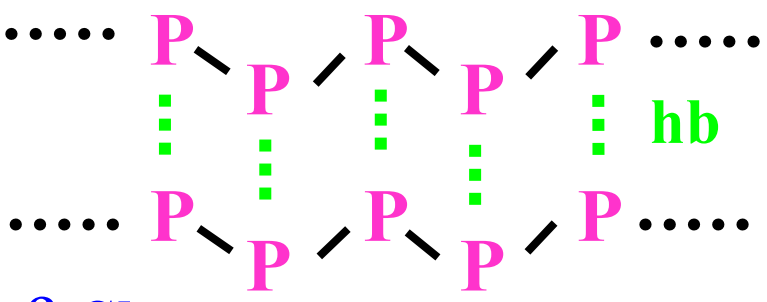
Quaternary structure

Purves et. Al The science of biology 4th edition, Sinauer associates
http://gened.emc.maricopa.edu/bio/bio181/BIOBK/BioBookCELL2.html

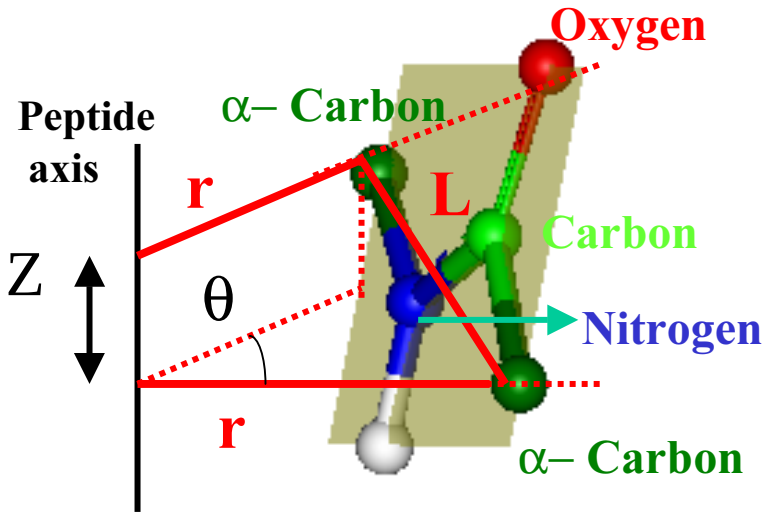
Secondary structure of proteins

Twist (θ)

P – P – P – P – P FES

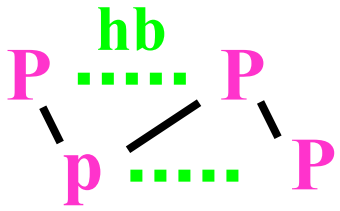


β-Sheet



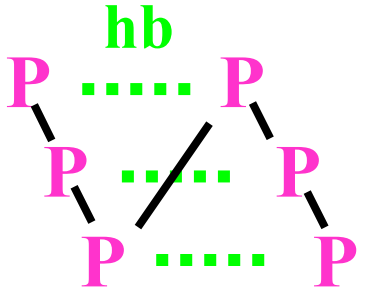
Peptide unit

3_{10}-helix



What is the most stable conformation in proteins?

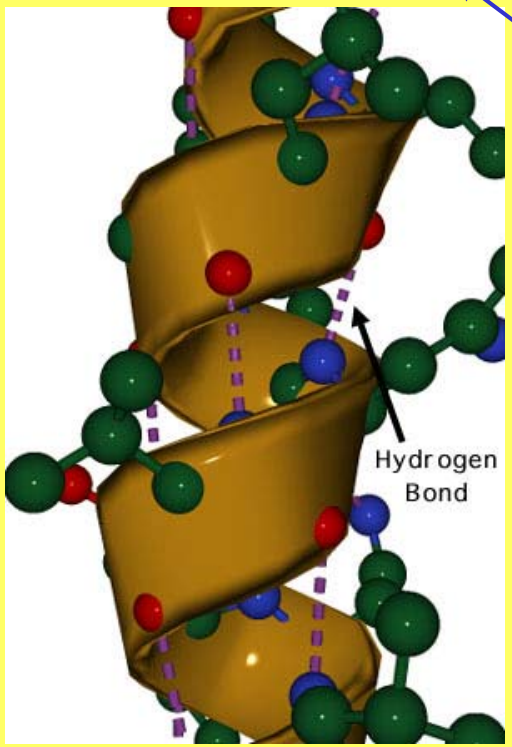
α-helix



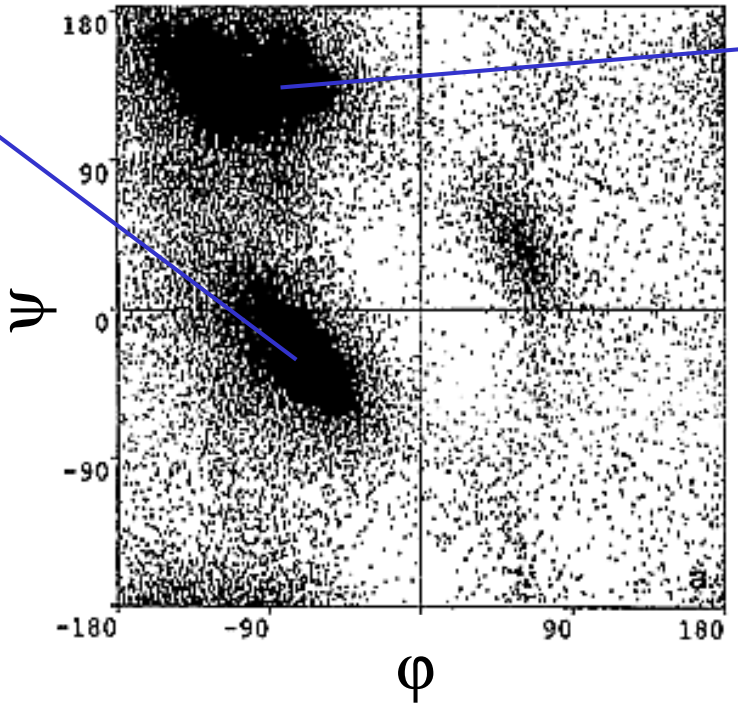
Peptide axis

Secondary Structure of proteins

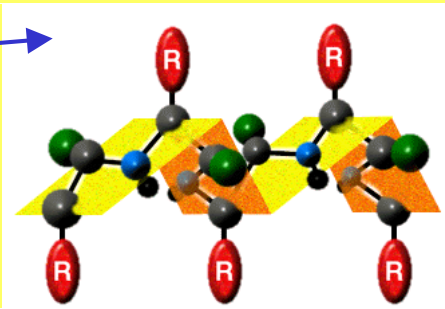
α-Helix

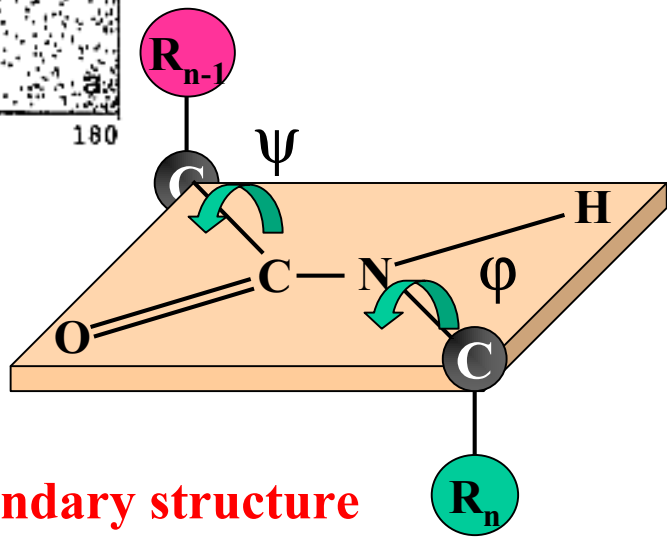


Ramachandran-Diagramm



β-Sheet





The α-helix conformation is the most common secondary structure

Hydrogen bonds

• **An interaction of the form**

A-H ..... **B**

hb

A electronegative atom (donor, N, C, O, F)
B electron-rich atom (aceptor, O, F, N)

•**Strength:** **one oder of magnitude smaller than that of covalewnt bonds**

Strong hb's: 10 -40 kcal/mol (0.4 - 1.7 eV)

Weak hb's: 1 - 10 kcal/mol (0.04 - 0.4 eV)

•**Cooperativity:** **hb strongly interact each other.**

This efect is observed in experiments by changes in:
bond strength
local vibrational modes
dipole moments
Conformation

•**Biological importance**

Stabilization of the structure of proteins

Enzymatic reactions

Molecular recognition

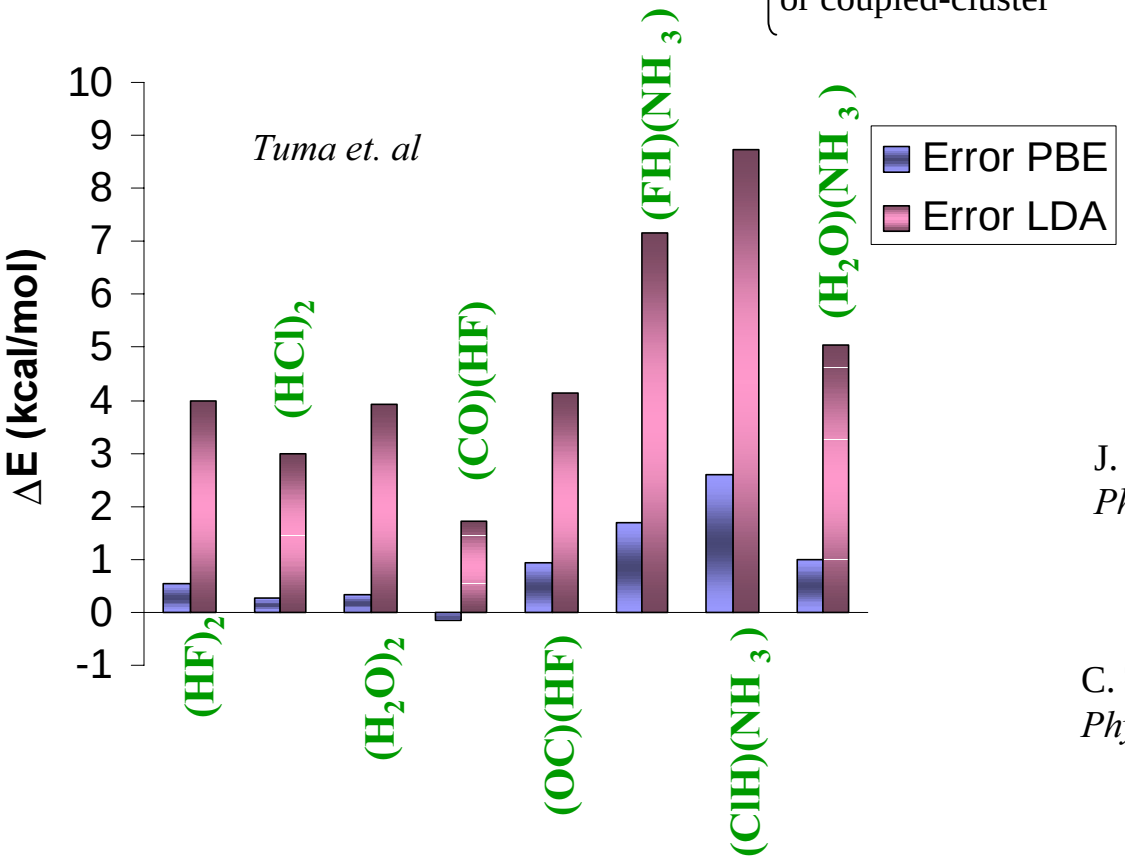
Accuracy of DFT for hydrogen bonded systems

$$A + B \longrightarrow AB$$

$$E^{hb} = E_{binding} = E_{AB} - E_A - E_B$$

$$\Delta E = E^{hb}_{DFT} - E^{hb}_{best\_ab\_initio}$$

Hartree-Fock plus configuration interaction or coupled-cluster



- **GGA is needed**
- **Check the reliability of the employed GGA**
- **PBE functional describes hb's with an accuracy of ~1 kcal/mol**

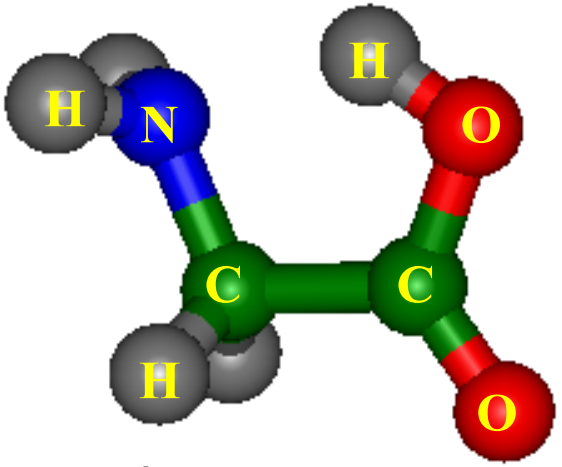
J. Perdew, K. Burke, M. Ernzerhof
Phys. Rev. Lett. **77**, 3865 (1996)

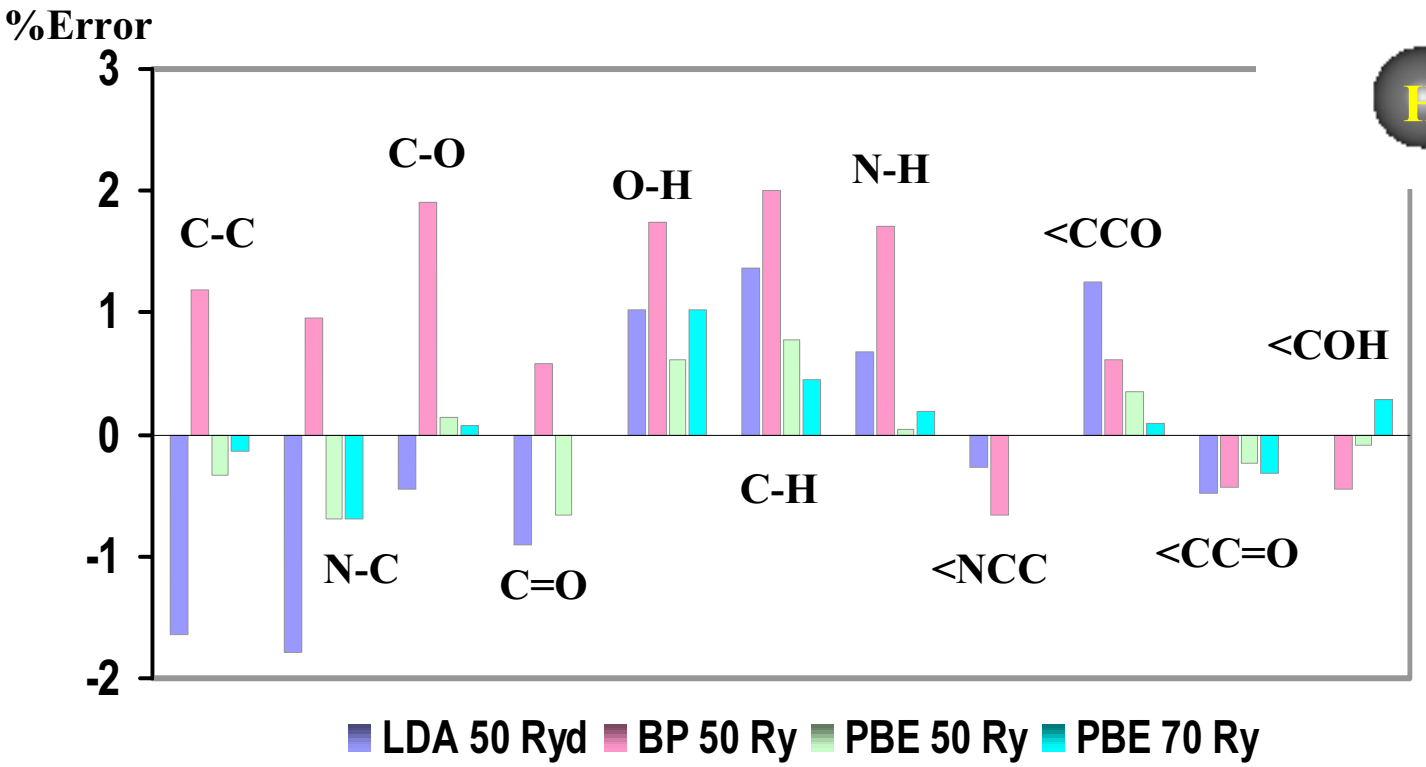
C. Tuma, D. Boese, N. C. Handy
Phys. Chem. Chem. Phys. **1**, 3939 (1999)

Accuracy of DFT for hydrogen bonded systems

Structural parameters of an isolated glycine molecule calculated with different functionals.

•Compared against HF/CISD[1]





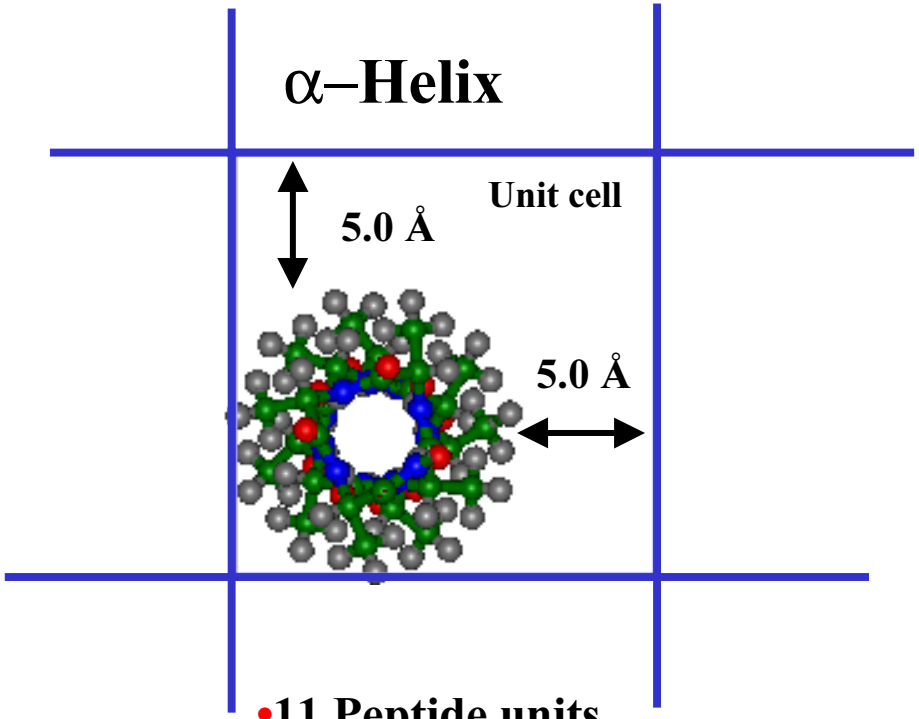
DFT-PBE gives errors smaller than 1% !

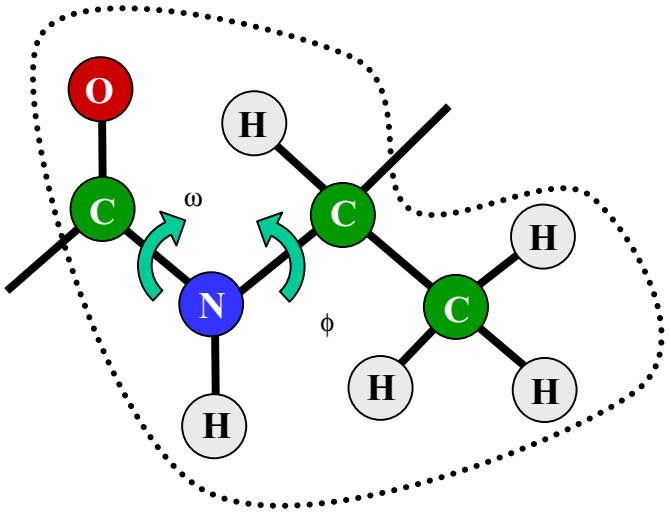
1. C.-H. Hu, M. Shen and H. F. Shaefer III, J. Am. Chem. Soc. **115**, 2923 (1993).

α-helix geometry

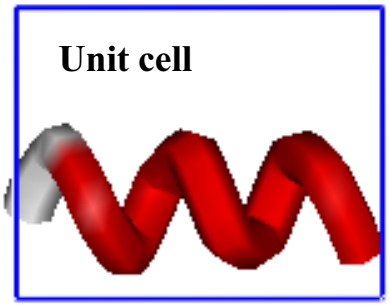
Model: Infinite chain of Polyalanine in α-helical conformation

Finite alanine chains derived from Ethyl acetylamide



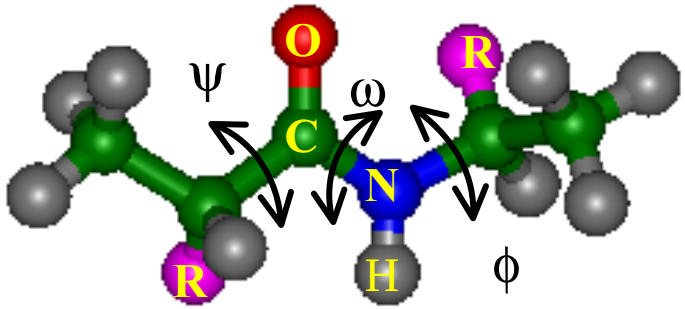


- 11 Peptide units
- 3 turns
- 110 atoms/cell
- 70 Ry cut-off
- Γ Point for sampling Brillouing zone

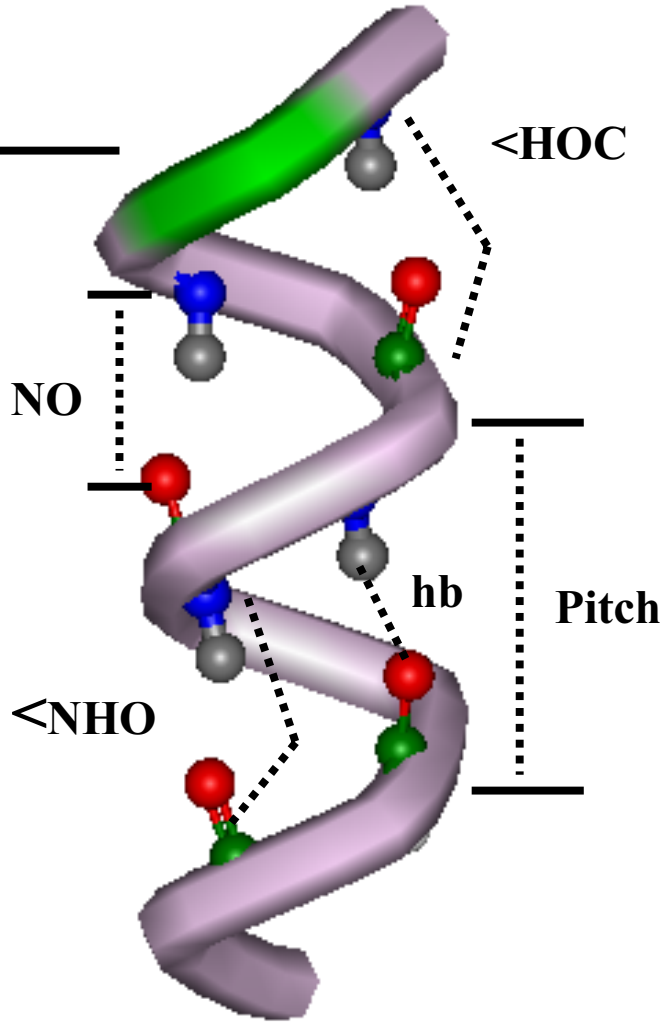


α-helix geometry

Equilibrium structure of the helix



Parameters	*Calculated*	*Experimental*
hb	1.950 Å ± 0.005	2.06 Å ± 0.16
NO	2.950 Å ± 0.005	2.99 Å ± 0.14
NHO	163.6° ± 0.3	155° ± 11
HOC	147.3° ± 0.5	147° ± 9
ϕ	-63.5° ± 0.5	-63.8° ± 6.6
ψ	-43.0° ± 0.5	-41.0° ± 7.2
ω	177.4° ± 0.7	180° ± 5
Pitch	5.48 Å	5.4 Å



Good agreement between calculated and experimental parameters!

α-helix stability

Peptide secondary structure is crucial to understand protein folding and activity

The right-handed helical conformation is the most common secondary structure in proteins

The helical conformation is not stable by itself

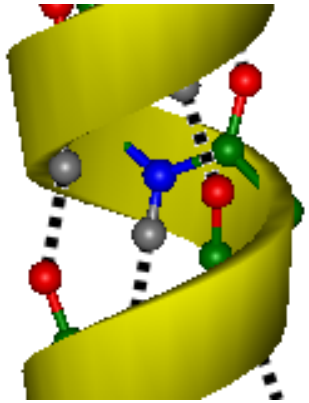
α-helix conformation is not a minimum in the potential energy surface of a dipeptide

Open questions

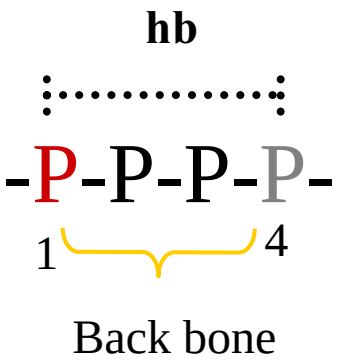
How large is the hydrogen bond strength in a protein?
How large is the cooperativity in proteins?
What is the smallest stable peptide which can form helical conformation?
Are the hydrogen bonds the main interaction stabilizing the secondary structure of proteins?

α-helix stability

α-helix conformation



How to extract the hb strength?

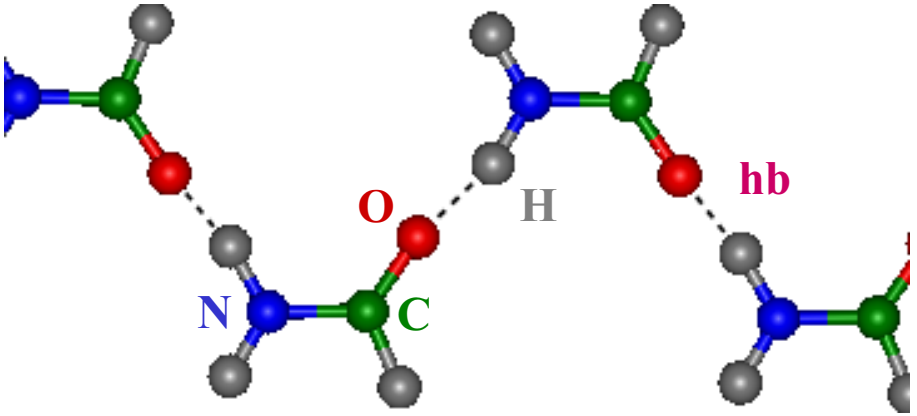


Previous studies: molecular cluster approach:

molecule :

- formamide [1]
  MP2 and DFT calc.
  60-70% cooperativity in an infinite array

- N-methylacetamide [2]
  cluster with five molecules HF calc.
  38-42% cooperativity



Problem: back bone is not taken into account !

1. S. Suhai, *J. Phys. Chem.* **100**, 3950 (1996) 2. R. Ludwid, F. Weinhold, T. C. Farrar, *J. Chem. Phys.* **107**, 499 (1997).

α-helix Stability

Objective:

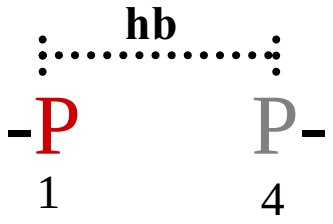
- Calculate the hydrogen bond strength by fully taking into account the back bone of the protein
- Calculate the cooperativity for an infinite α-helix

System:

- Infinite and finite chains of Polyalanine in α-helical and fully extended structures

Idea:

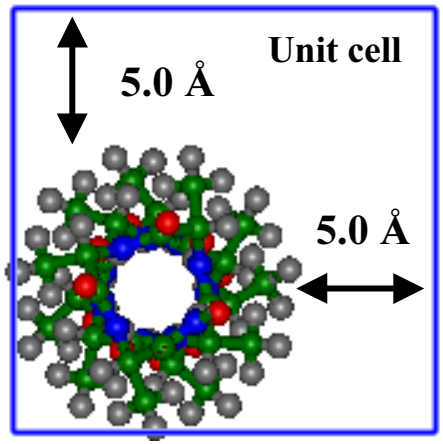
-P-P- Nearest Neighbor peptide-peptide interaction



(N, N+3) Peptide peptide interaction

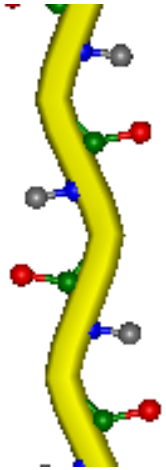
Systems:

α–Helix



- 11 Peptide units
- 3 turns
- 110 atoms/cell
- Γ Point for sampling Brillouing zone

Fully extended structure (FES)



- 2 Peptide units
- 20 atoms/cell
- Two k-Points for sampling Brillouing zone [(0, 0, 0.25),(0, 0, 0.75)]

Finite alanine chains:

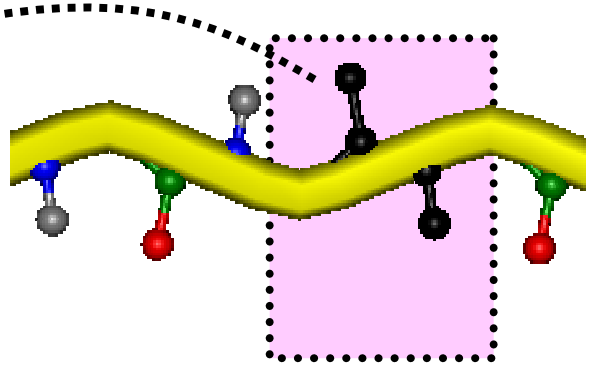
- 1-4 peptide units
- Up to 48 atoms/cell
- Γ Point for sampling Brillouing zone
- Dipole correction [1] to eliminate artificial interaction between neighbor cells in the helix axis direction

1. J. Neugebauer and M. Scheffler, *Phys. Rev. B* **46**, 16067 (1992).

Peptide-Peptide interaction (no hb's)

System: fully extended structure

$$R_1P_{N-1}R_2 + \boxed{P} \rightarrow R_1P_NR_2$$



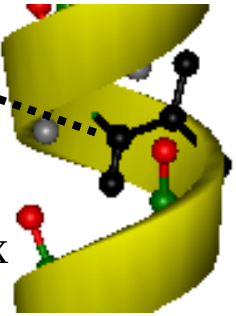
Chemical Reservoir
Infinite polyalanine chain in fully extended conformation (FES)
(no hydrogen bonds)

N	ΔH_{FES} (kcal/mol)
2	0.92
3	0.59
4	0.5
∞	0.0

Peptide-Peptide interaction in FES conformation is nearly zero

hydrogen bond strength of an isolated hb

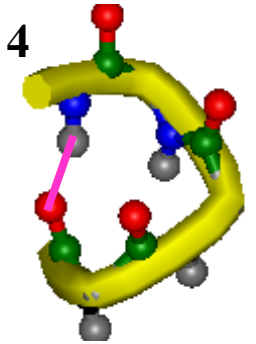
$$R_1P_{N-1}R_2 + P \rightarrow R_1P_NR_2$$



Chemical reservoir
hypothetical α-helix
without hb's

$$\tilde{\mu}_\alpha^\infty = \mu_{FES}^\infty + 5.6\,{}^{kcal}/_{mol}$$

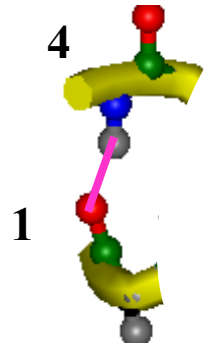
$$-E_{hb} = \Delta H_\alpha^N = E_\alpha^N - E_\alpha^{N-1} - \tilde{\mu}_\alpha^\infty$$



Isolated hb (N=4)

$$E_{hb} = 3.5\,{}^{kcal}/_{mol}\,(0.15eV)$$

Cluster Approach: $E_{hb}^{cluster} = 5.9\,{}^{kcal}/_{mol}\,(0.26eV)$



The back bone significantly affects the strength of neighboring hb's
Without back bone the hb energy is larger by 68 %

Hydrogen bond strength in an infinite α-helix

$$-E_{hb}^{\infty} = \mu_{\alpha}^{\infty} - \tilde{\mu}_{\alpha}^{\infty}$$

$$E_{hb}^{\infty} = 8.6\,{}^{kcal}/_{mol}\,(0.37eV)$$

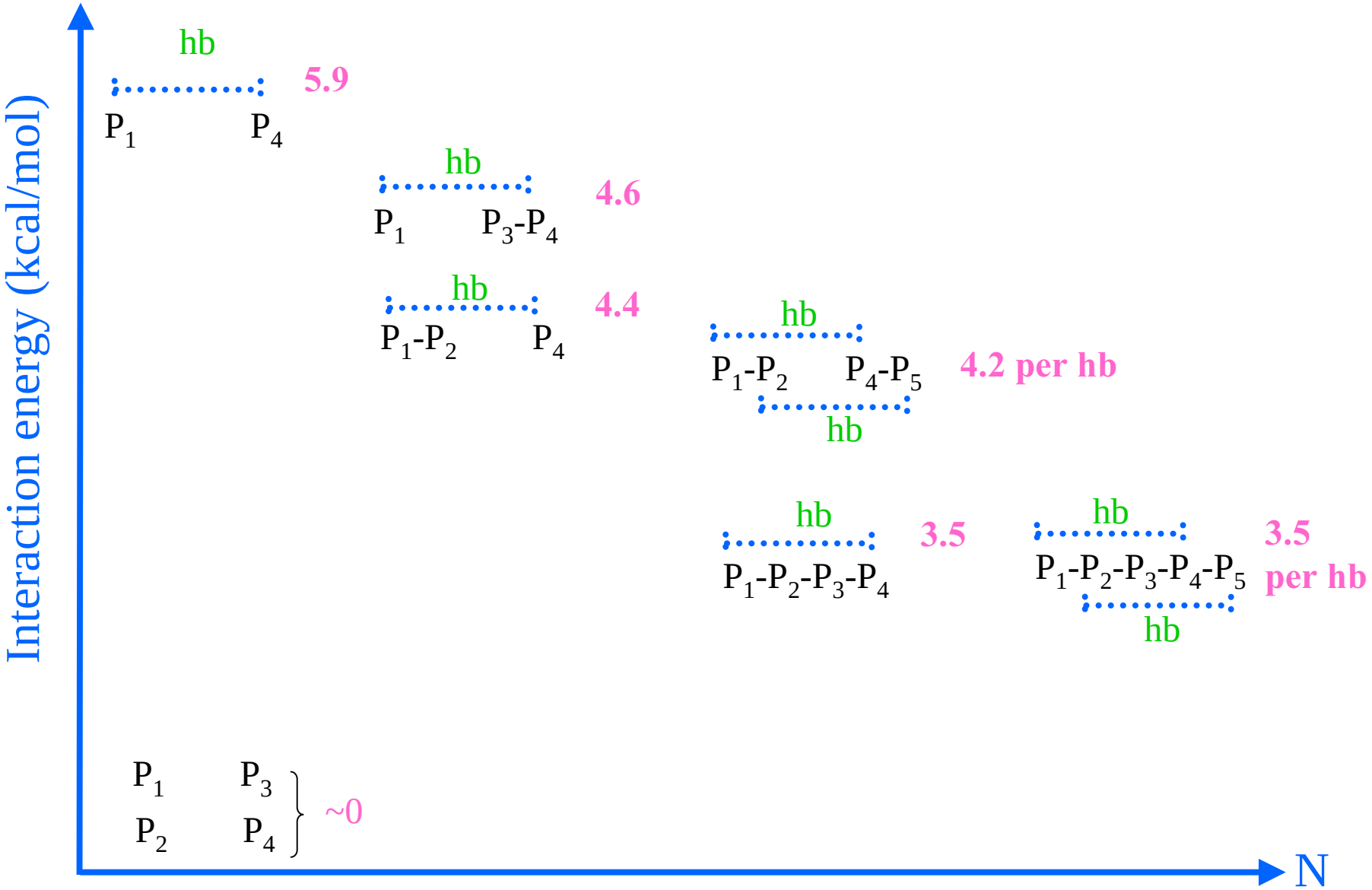
The cooperativity within an infinite network of hb's strengthens each individual bond by more than a factor of two !

The importance of cooperativity

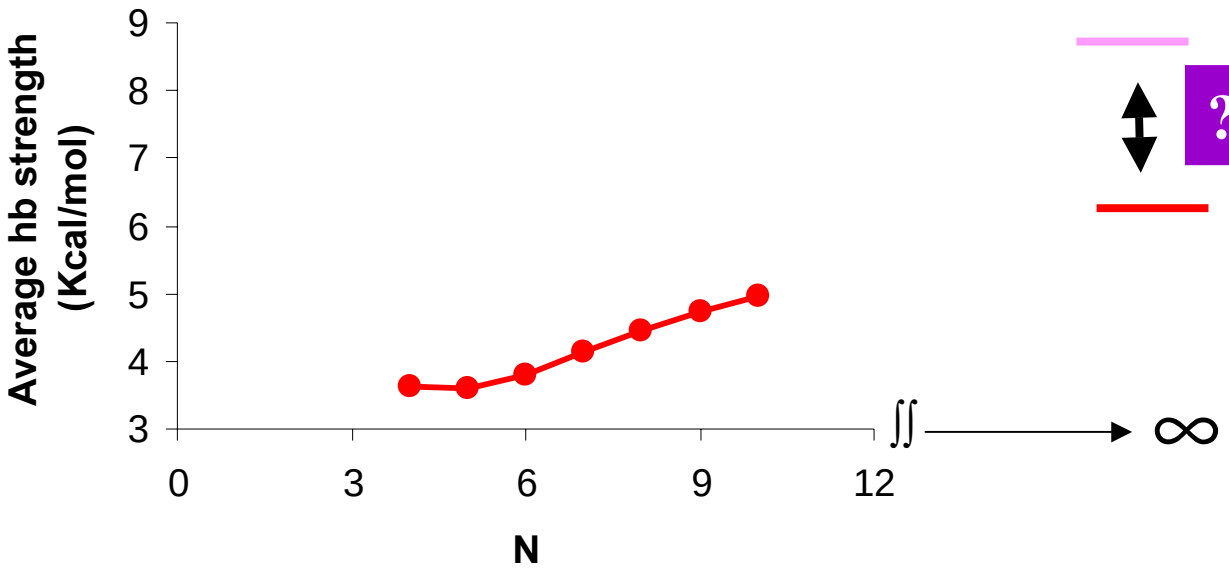
Strain energy **N5.6** < **8.6 (N-3)** Stabilization energy due to hb's

α-helix must consist of at least 9 peptide units to be stable against transformation into the extended structure

Effect of the back bone



α-helix Stability



$E_{hb}^{\infty} = 8.6 kcal/mol$

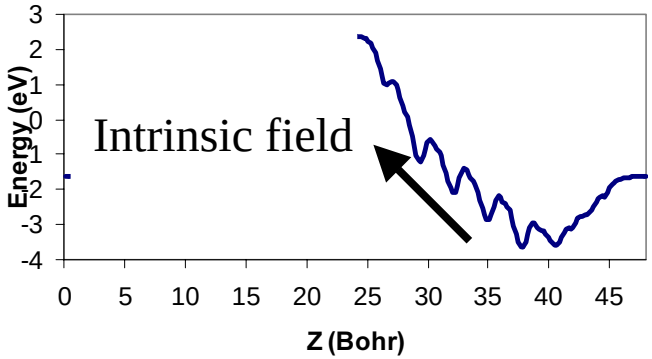
?

$E_{hb}^{N\to\infty} = 6.2 kcal/mol$

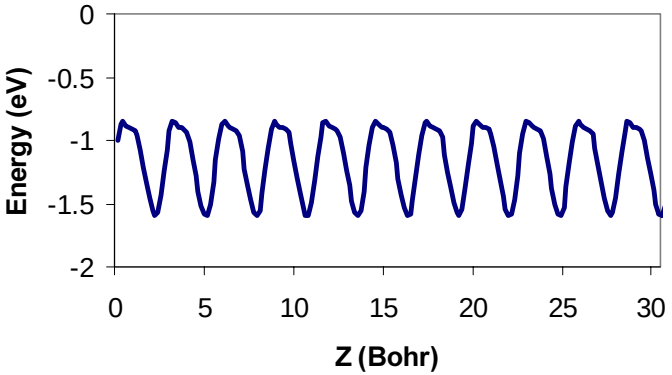
(fitting)

Electrostatic potential (xy-averaged)

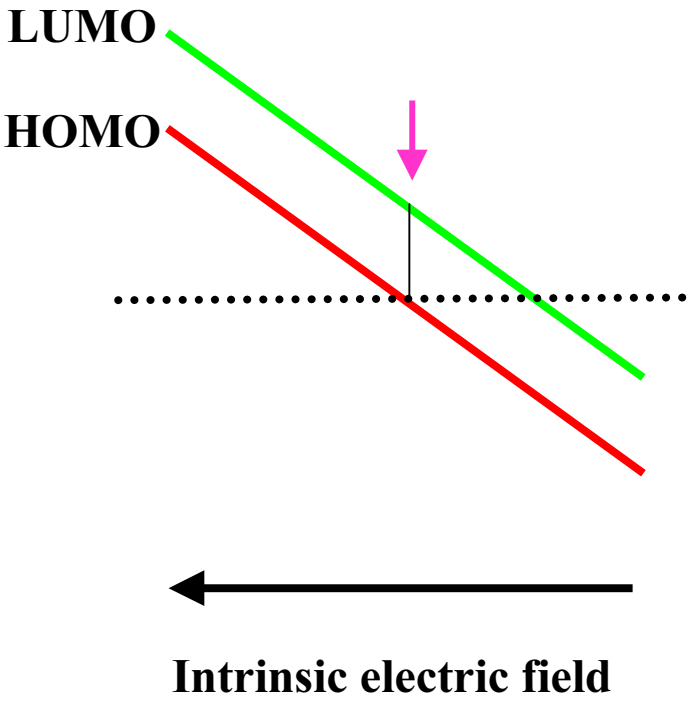
Finite peptide chain (N=4)

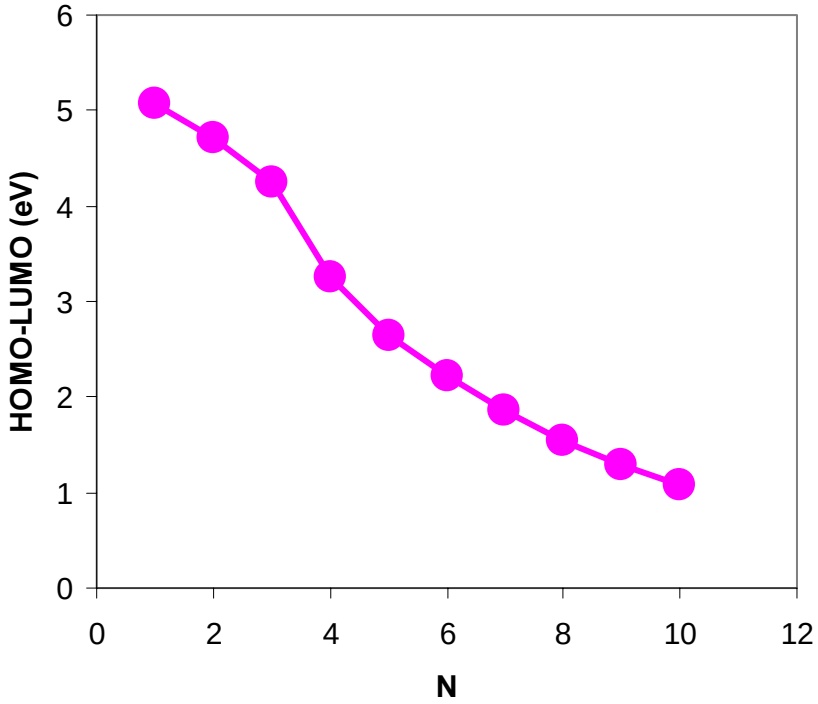


Infinite α-helix



α-helix Stability





For large N, the intrinsic electric field is partially autocompensated by charge transfer. At N=∞, E_{ct}~ 2.4 kcal/mol !

α-helix Stability

$$E^{\infty}_{stab} = \mu^{\infty}_{FES} - \mu^{\infty}_{\alpha}$$

$$E^{\infty}_{stab} = E^{\infty}_{ct} + E^{N\to\infty}_{hb} + E_{PP} + E^{\infty}_{backbone}$$

(negative contribution)

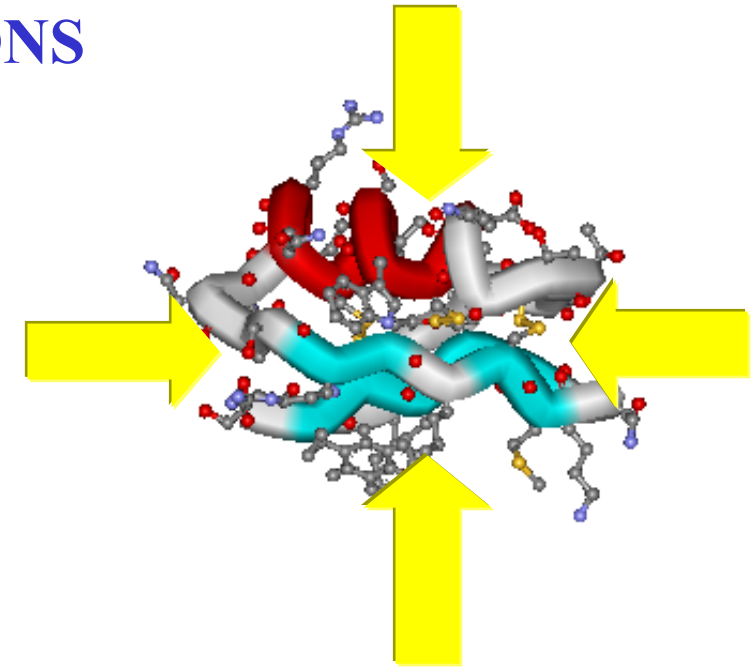
$$E_{ct} \approx 2.4 kcal/mol$$

$$E^{N\to\infty}_{hb} + E^{\infty}_{backbone} \approx 6.2 kcal/mol$$

$$E_{pp} \approx -5.6 kcal/mol$$

Field compensation is crucial to stabilize the helical motif !!

MECHANICAL DEFORMATIONS



LIVING SYSTEMS

- -LARGE COLLECTIVE MOTIONS
- -MEMBRANE PROTEINS

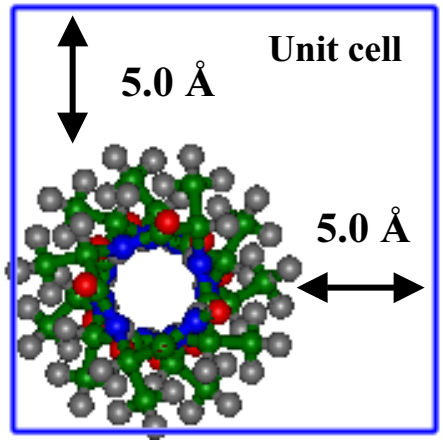
EXPERIMENTS

- -SINGLE MOLECULE MECHANICS
- -DENATURATION BY HYDROSTATIC PRESSURE
- -ULTRAFAST SHOCK WAVES

BIOLOGICAL ACTIVITY ?

- -Electronic transport
- -Proton transport

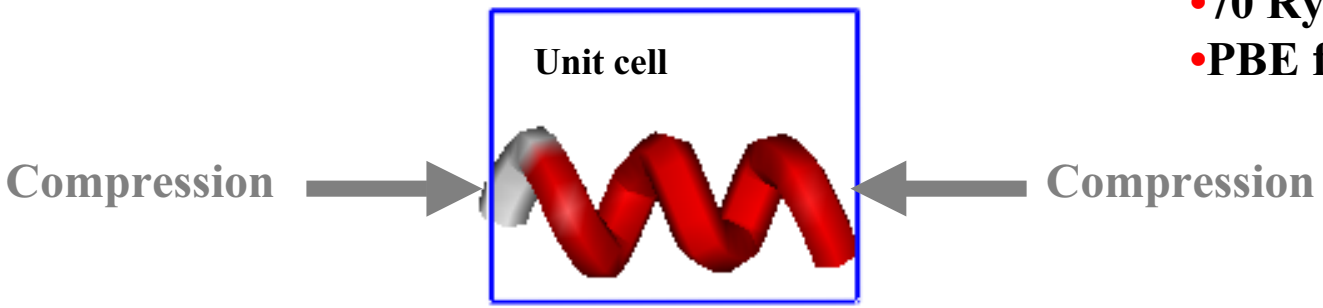
Investigate effect of compression on the conformation of proteins



Infinite polyalanine

(model system for protein alpha-helix)

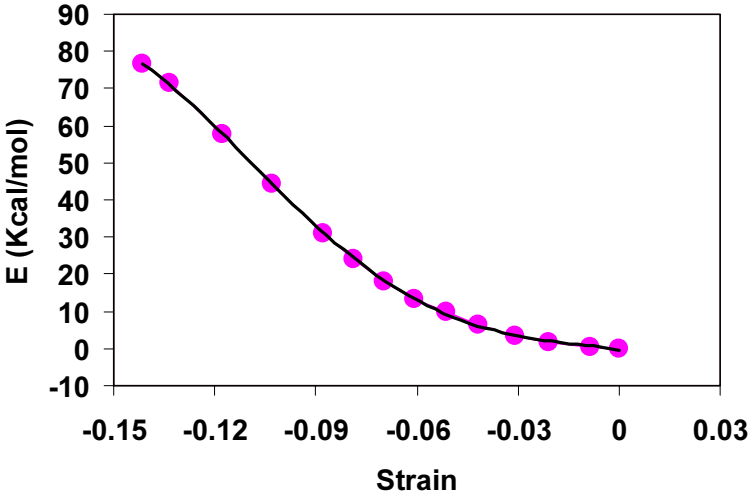
- **11 Residues**
- **3 turns**
- **110 atoms/cell**
- **70 Ry cutoff**
- **PBE functional**



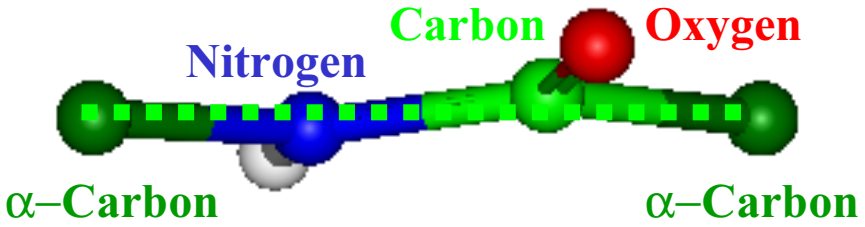
This knowledge is important to understand the molecular basis of the structure and function of proteins

Mechanical response of an alpha helix on uniaxial strain

Energy vs Strain

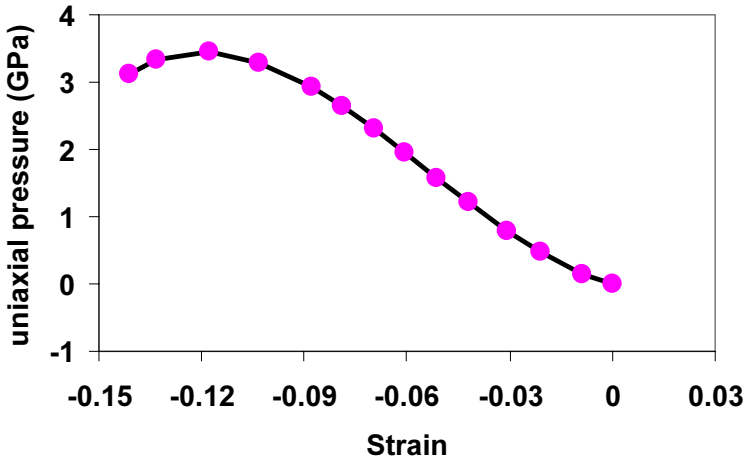


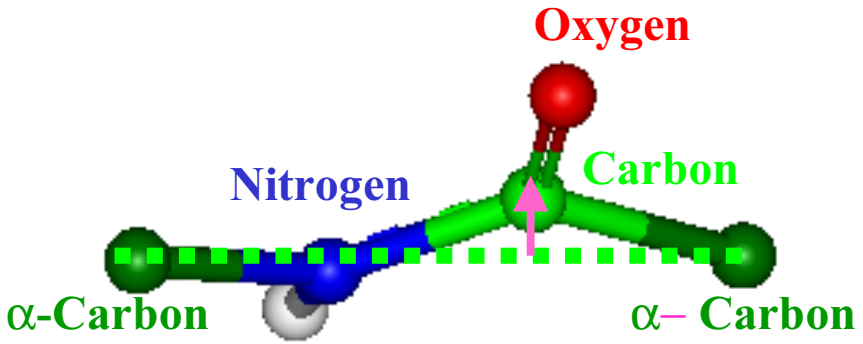
Peptide Unit



low strain: planar structure

Pressure vs Strain

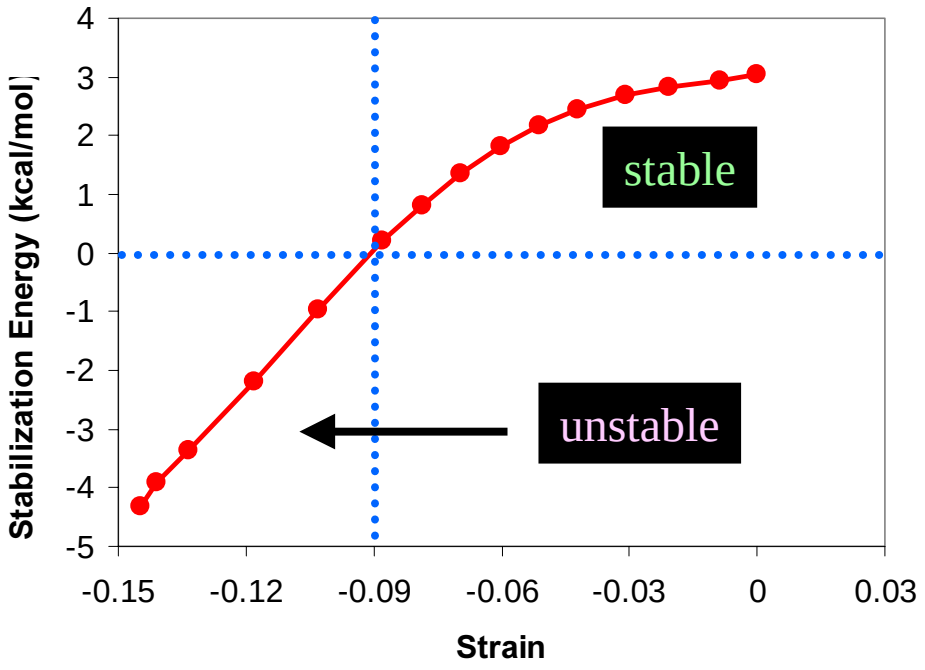




high strain: bent structure

Stabilization energy

$$E^{\infty}_{stab} = \mu^{\infty}_{FES} - \mu^{\infty}_{\alpha}$$



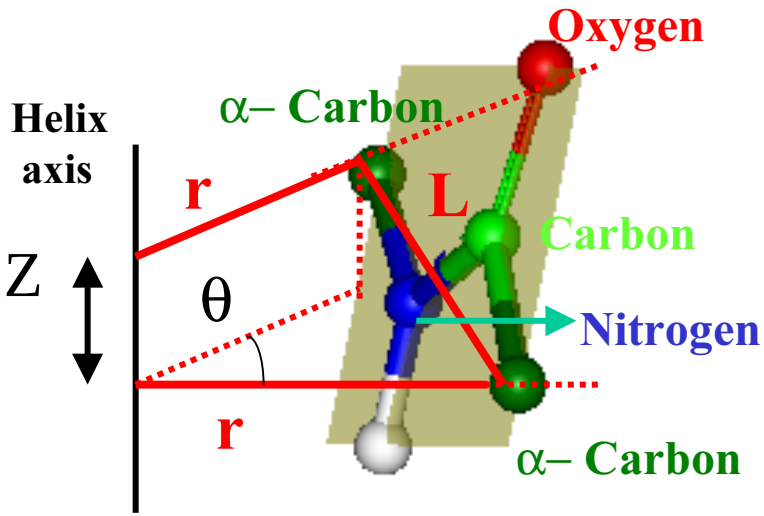
Strain induces destabilization of the secondary motif against transformation into a flat structure. Denaturation-like process !!!

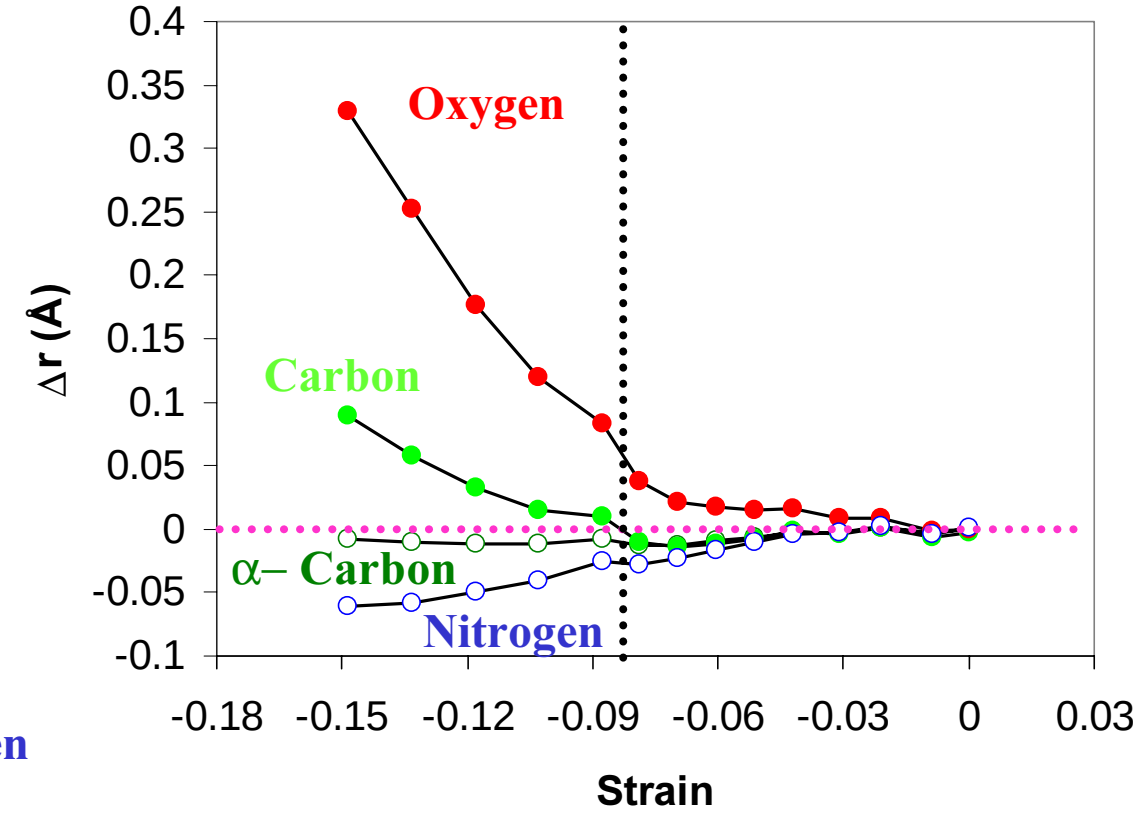
Geometrical response on strain

Peptide unit

$$\Delta r = r - r_{incompressible}$$

for incompressible peptide unit $\Delta r = 0$



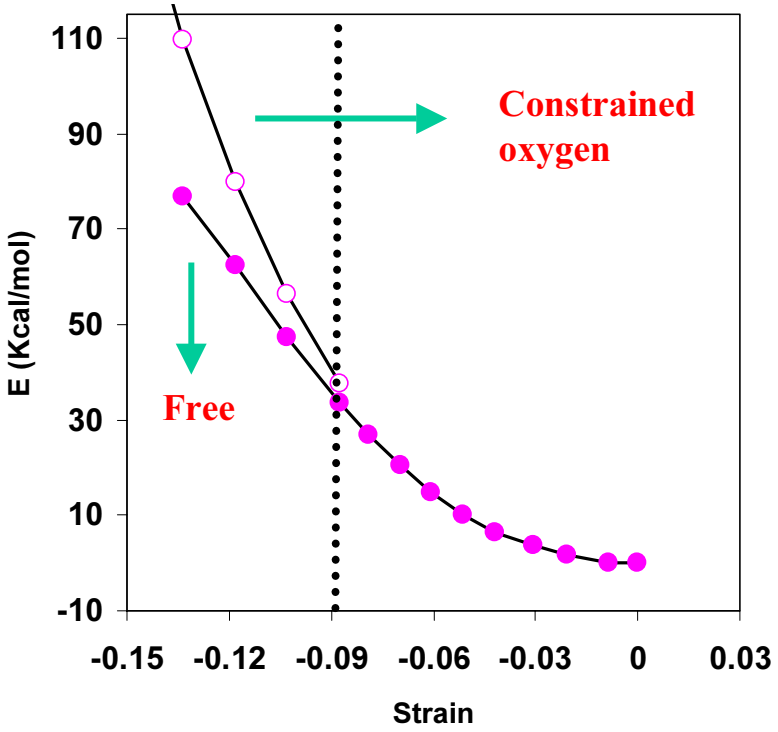


Oxygen shows longer deviation

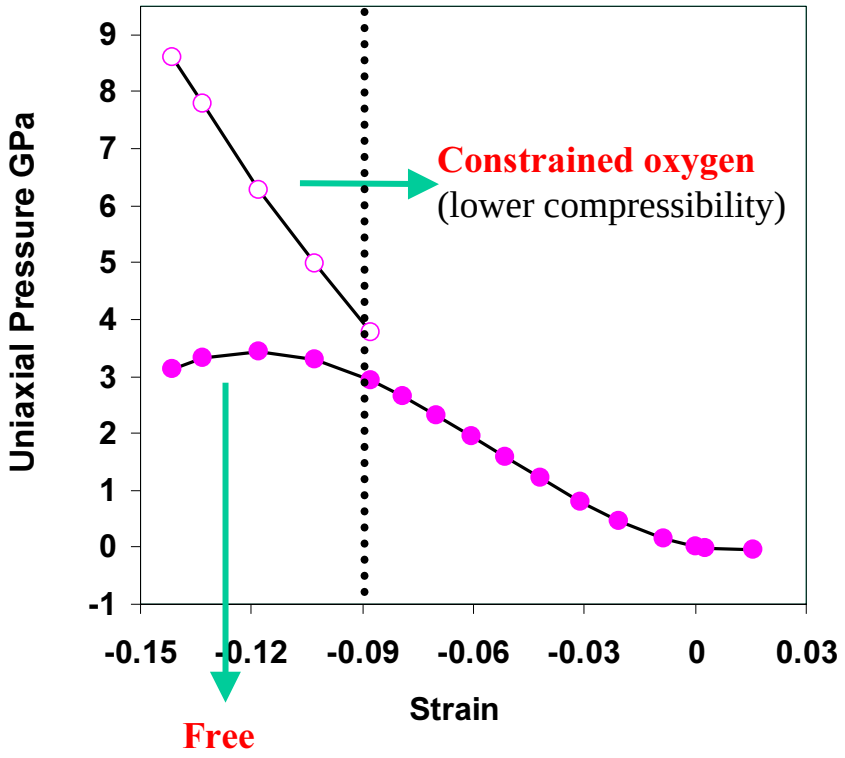
Constrained vs unconstrained relaxation

Constrain: $\Delta r_{oxygen} = 0$

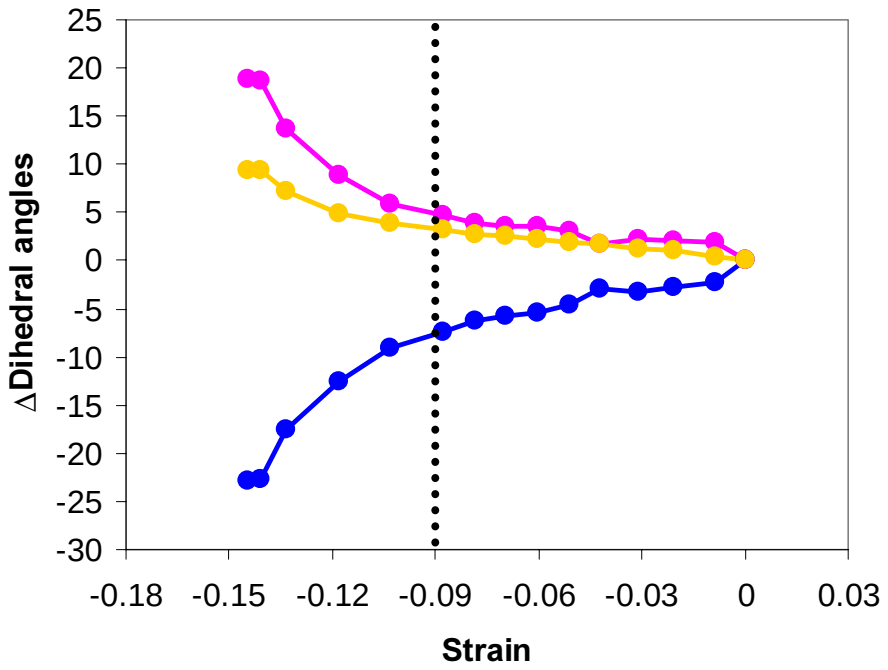
Energy vs Strain



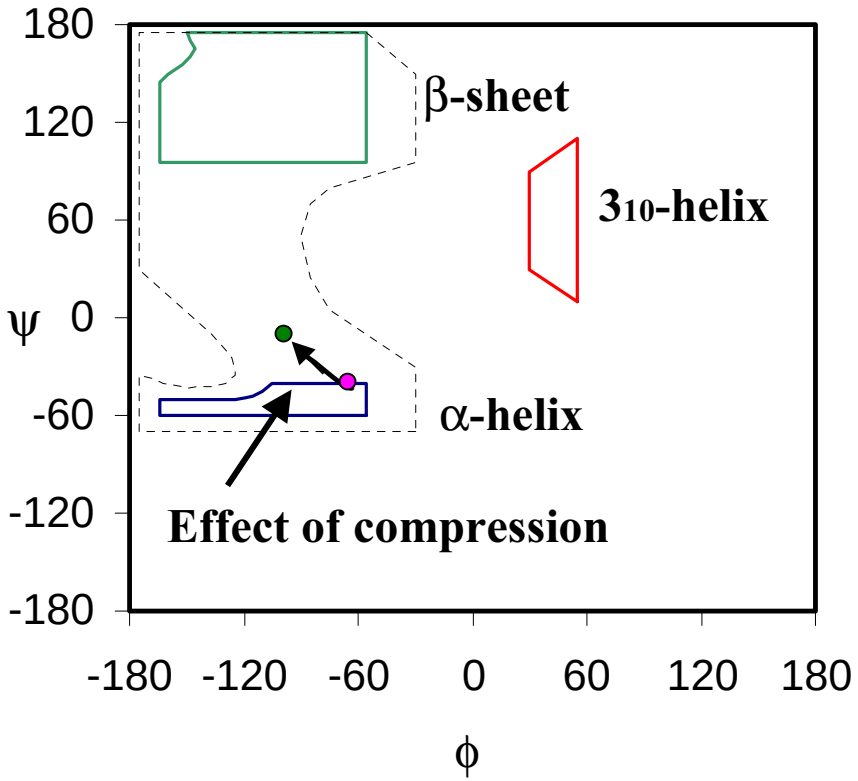
Pressure vs Strain



Secondary structure response



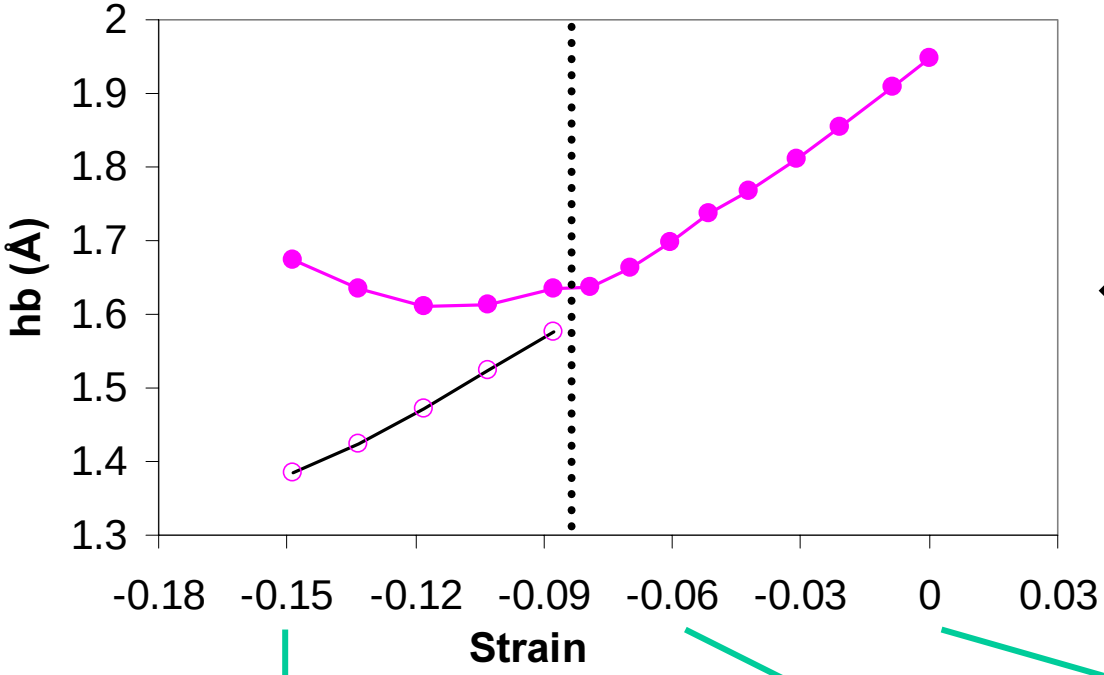
Ramachandran plot

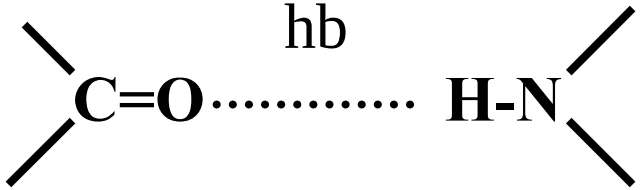


- Zero strain structure
- 0.15 strain structure

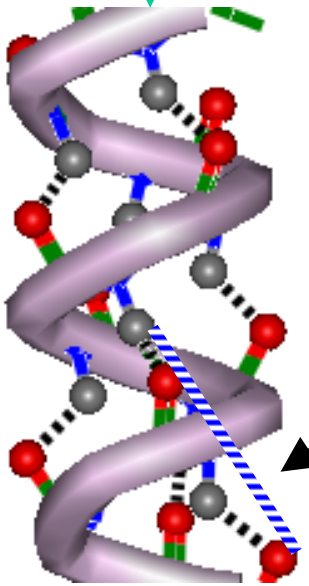
According to the Ramachandran diagram, the strain push out the structure from the helical domain!

Hydrogen-bond distance response on strain

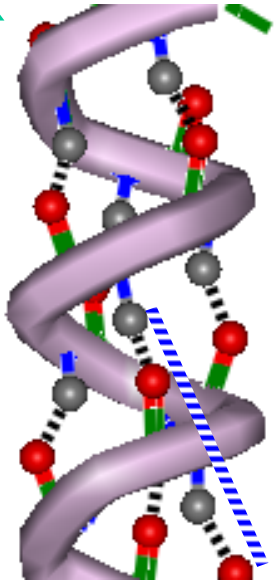


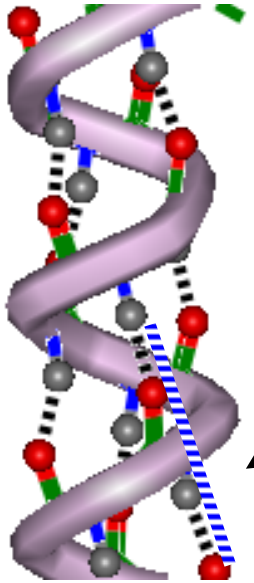


The hydrogen-bond distance can not be smaller than 1.6 Å



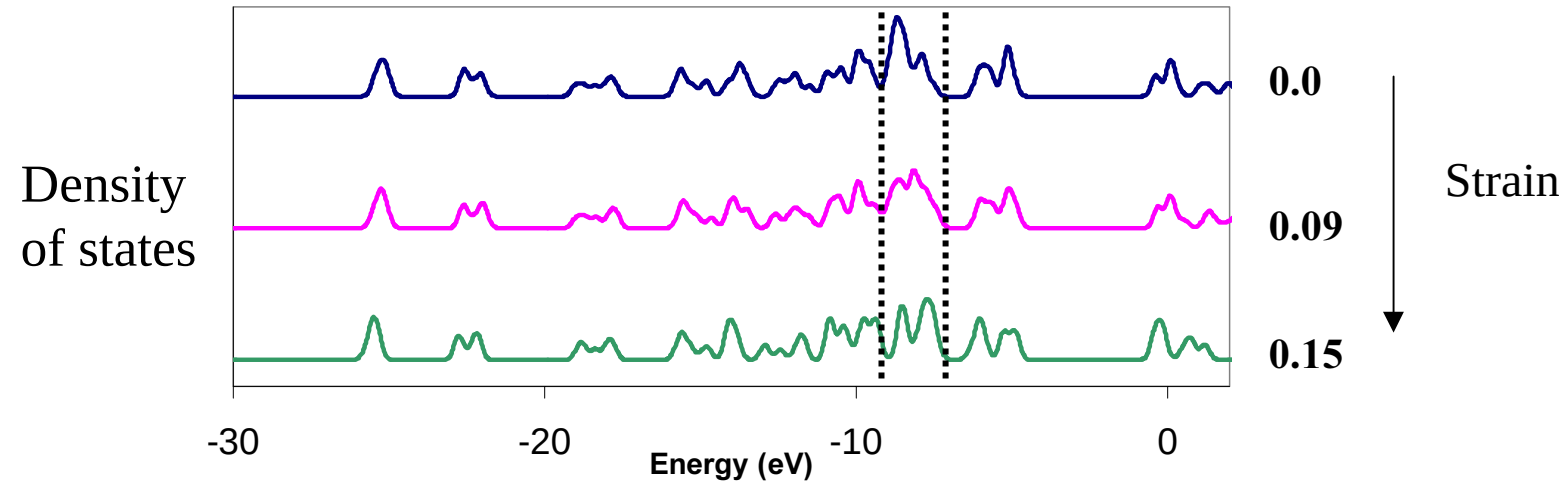
Deviation from alignment of hydrogen-bonds (unconstrained structure)

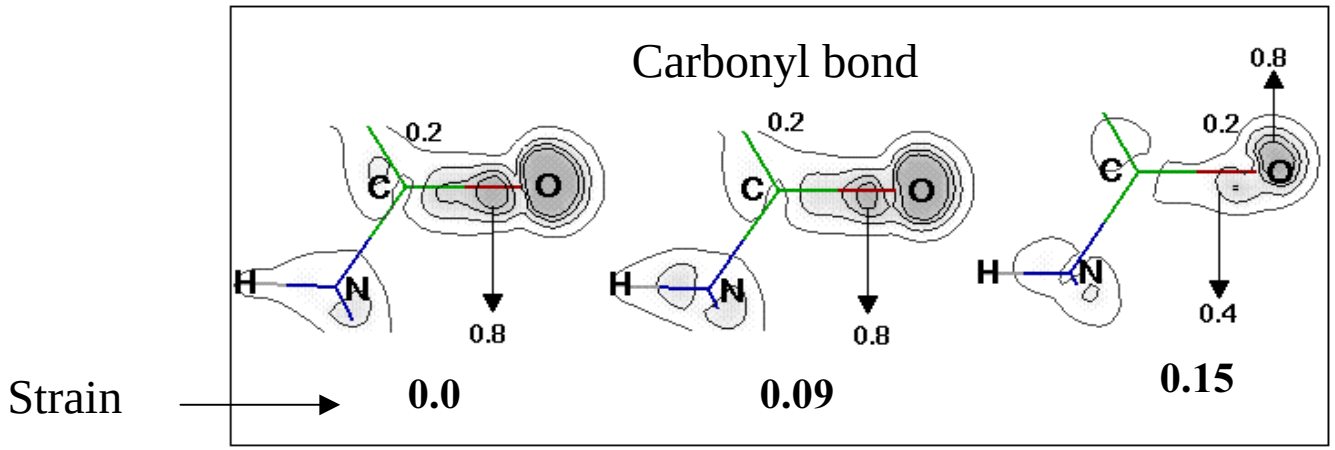




Align hydrogen-bonds

Electronic structure response to compression





Strain induces a qualitative change in the electronic charge density at the carbonyl bond: ($sp^2 \Rightarrow sp^3$ like hybridization)!