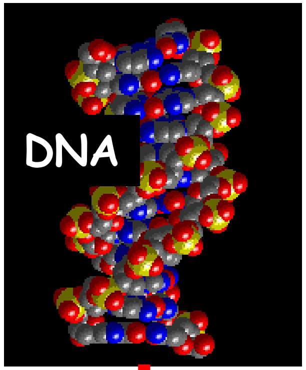
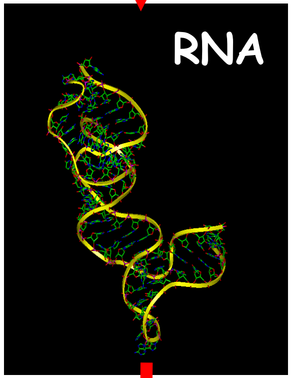
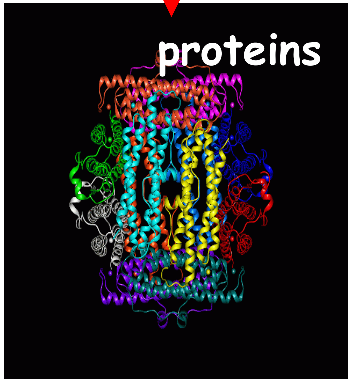
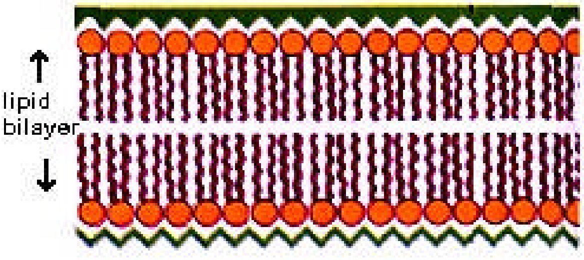
Structural Analysis of Biological Systems

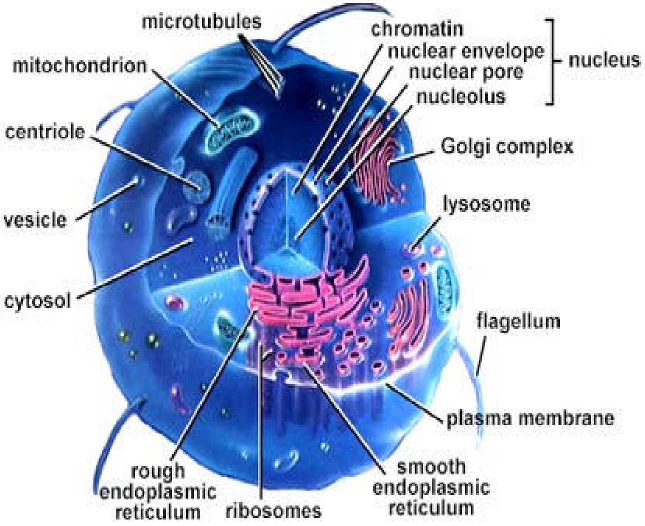




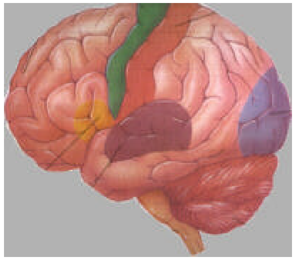




lipids

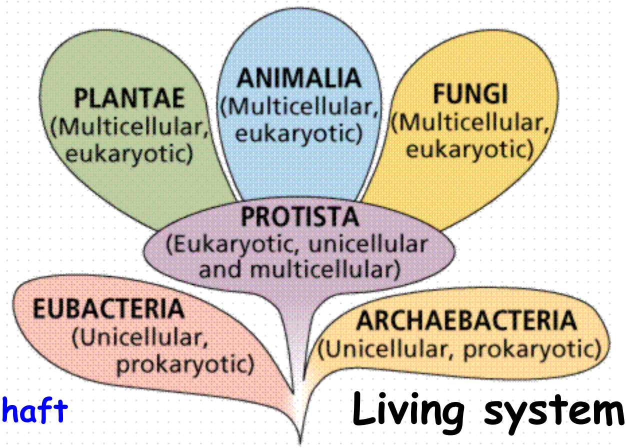


cell



organs

tissues



PLANTAE (Multicellular, eukaryotic)

ANIMALIA (Multicellular, eukaryotic)

FUNGI (Multicellular, eukaryotic)

PROTISTA (Eukaryotic, unicellular and multicellular)

EUBACTERIA (Unicellular, prokaryotic)

ARCHAEBACTERIA (Unicellular, prokaryotic)

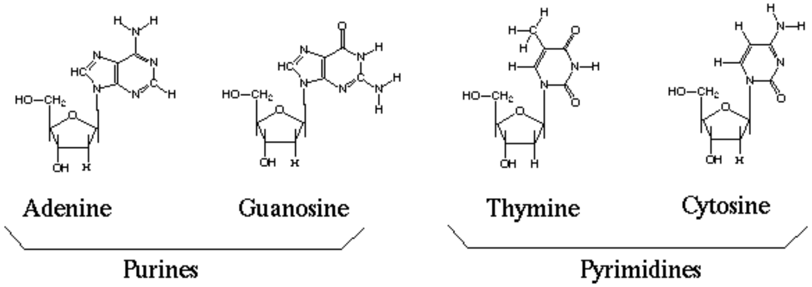
Living systems

Joel Ireta
Fritz-Haber-Institut der Max-Planck-Gesellschaft

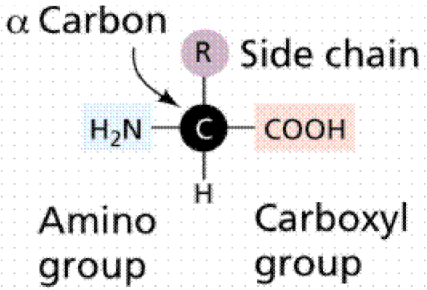
Biological Macromolecules

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

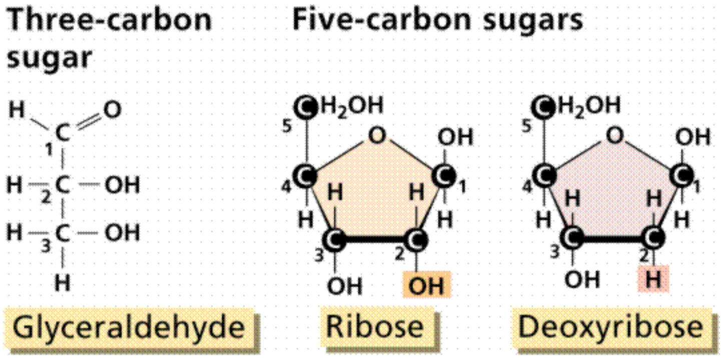
Nucleic Acids



Proteins

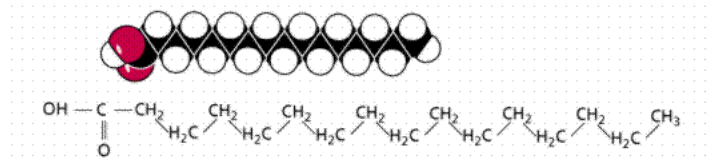


Carbohydrates

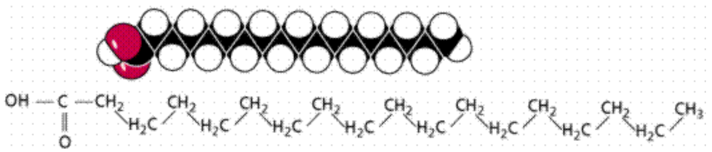


Lipids

(a)Palmitic acid



(b)Stearic acid

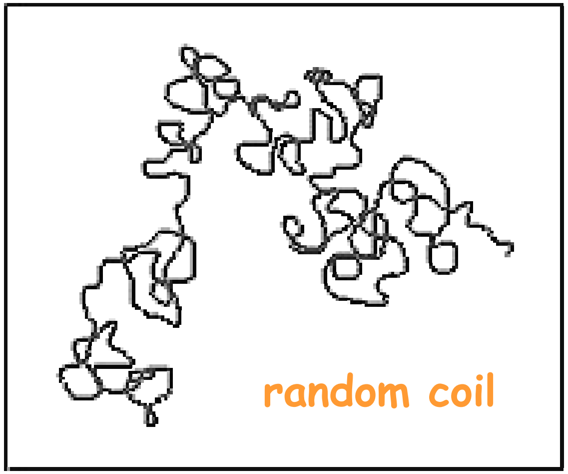


Protein Activity

Native conformation

folding

unfolding (denaturation)



random coil

Conformation → Covalent bonds
weak interactions

Stability → Temperature, Pressure { dynamics
Environment (solvent)

Activity → Charge transfer processes
Mechanical response
{ eletrons
protons

Can DFT help us to find conformation-stability-activity relationships ?

Outline

DFT accuracy ⇒

Weak interactions

Covalent bonds

⇒ **conformation**

a-helix secondary structure ⇒

Hydrogen bonds

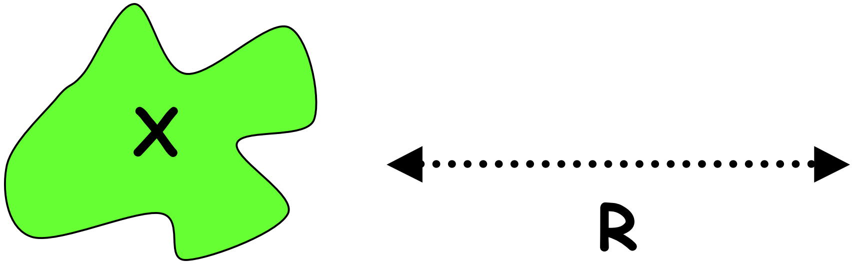
Mechanical response

⇒ **stability**

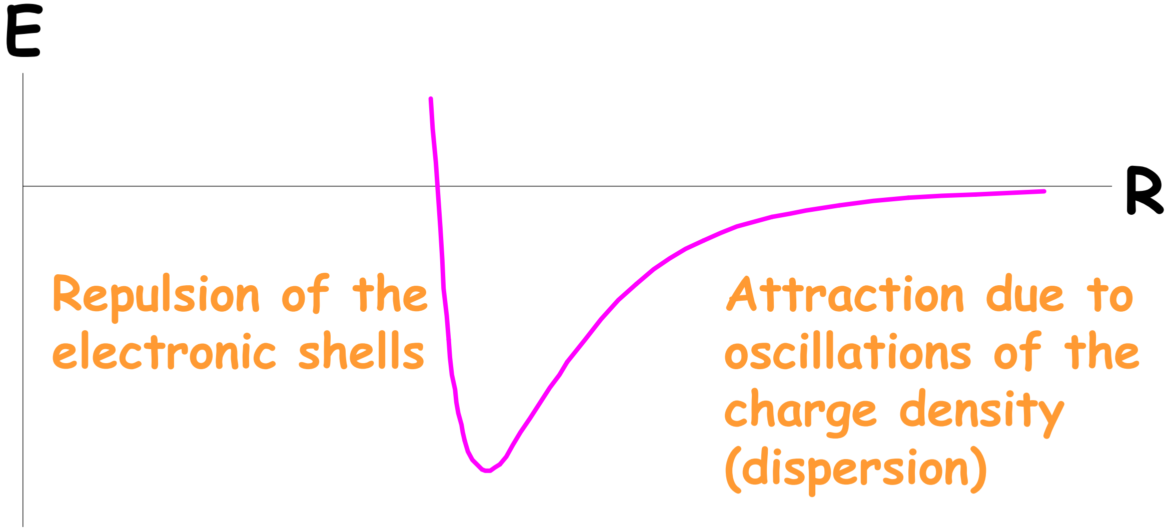
The role and Perspective of Ab Initio Molecular Dynamics in Study of Biological Systems
P. Carloni, U. Rothlisberger and M. Parrinello
Acc. Chem. Res., 35, 455 (2002)

⇒ **activity**

Weak Interactions



Interaction between neutral molecules



Repulsion of the electronic shells

Attraction due to oscillations of the charge density (dispersion)

+ $d^+ \longleftrightarrow d^-$

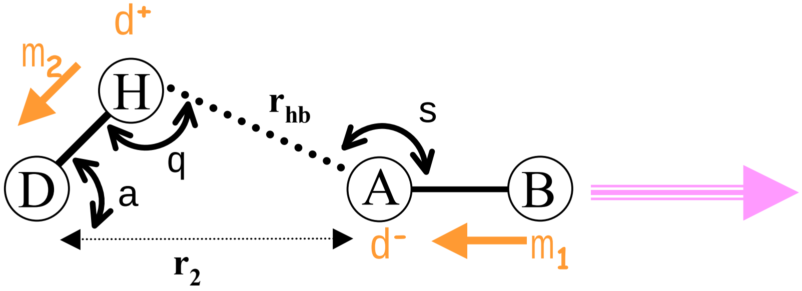
electrostatics

$$E = \frac{A}{R^{12}} - \frac{B}{R^{6}} + \frac{q_x q_y}{R} \Longrightarrow$$

van der Waals (isotropic interaction) **< 2 kcal/mol (0.084 eV)**

DFT can not describe van der Waals interactions !

Weak Interactions



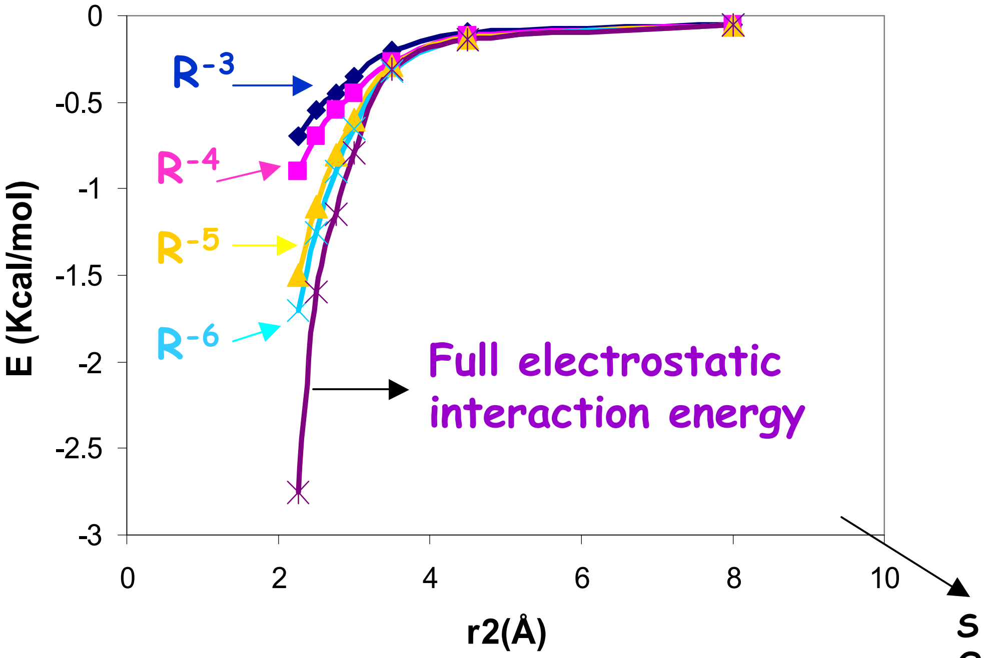
hydrogen bonding interaction

- a) strong > 10 kcal/mol (0.43 eV)
- b) moderate 3 kcal/mol (0.13 eV) to 10 kcal/mol (0.43)
- c) weak < 3 kcal/mol (0.13 eV)

D = donor atom

A = acceptor atom

Hydrogen bonds are predominantly electrostatic interactions. However…



For small r_2 multipole expansion of the electrostatic interaction does not converge properly

Hydrogen bonds are directional :
s usually ranges from 140° to 180°

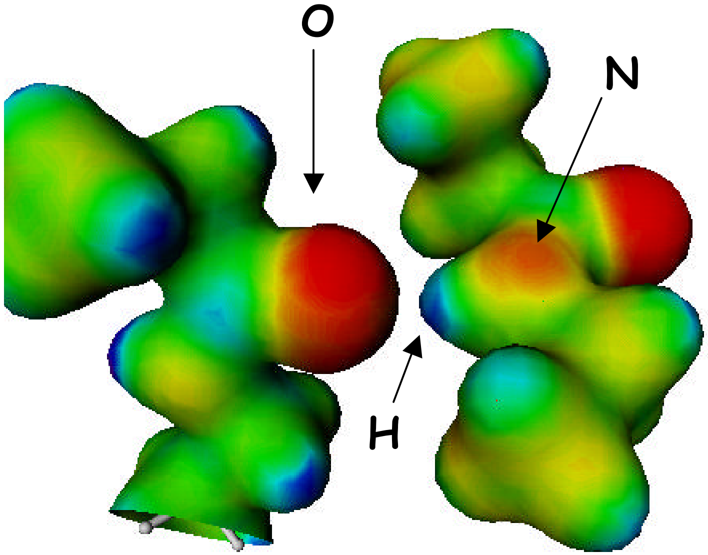
Hydrogen bonds are cooperative: they strongly interact each other modifying its bond strength

S Scheiner, Hydrogen bonding a theoretical perspective Oxford University Press (1997)

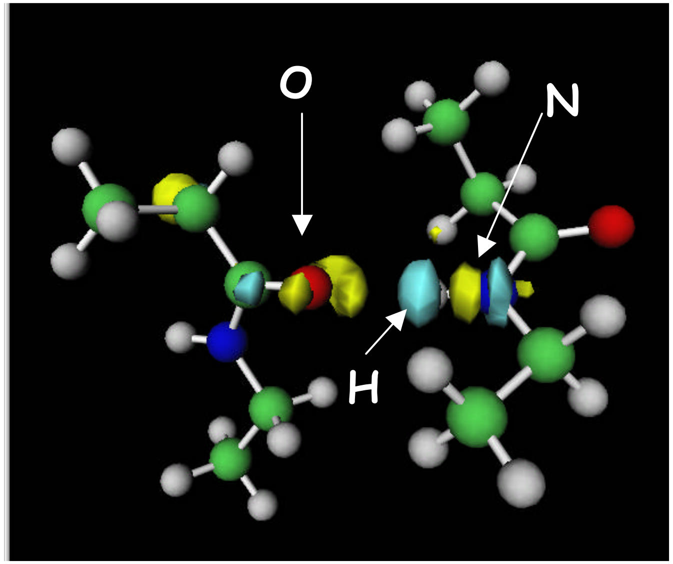
Hydrogen Bond Nature

Attractive part :
electrostatic
induction an dispersion energies
(charge transfer ?)

Repulsion part:
electronic exchange interaction



Projection of the electrostatic potential on a charge density isosurface.
System: alanine peptide dimers forming a hydrogen bond



$$\Delta\rho(r) = \rho_{AB}(r) - \rho_A(r) - \rho_B(r)$$

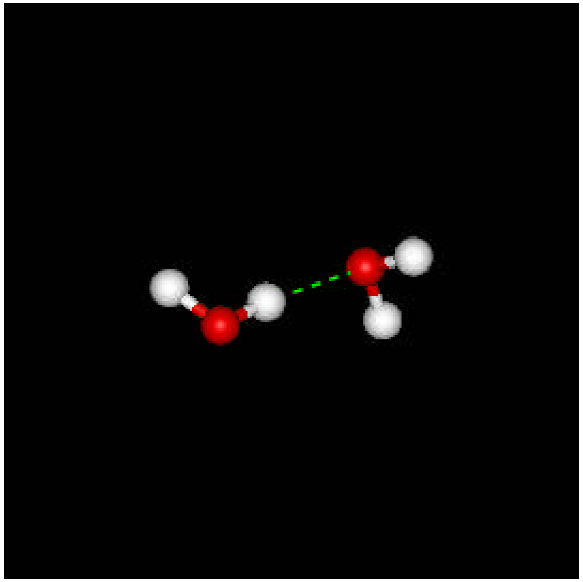
$$\Delta\rho(r) > 0; Yellow$$

$$\Delta\rho(r) < 0; Blue$$

Dispersion energies contributes significantly to the Hydrogen bond energy

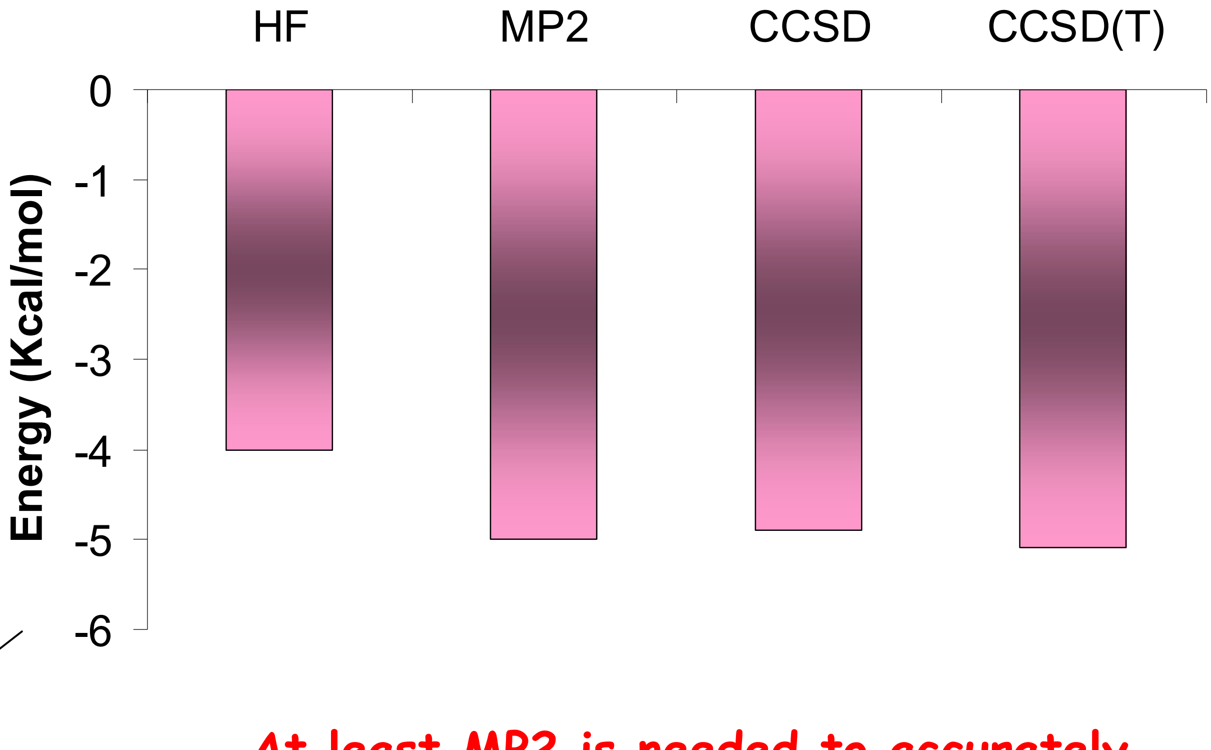
Techniques accounting for the electronic correlation are needed for an accurate description of the hydrogen bonds

Hydrogen Bond Nature



$$A + B \longrightarrow AB$$

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

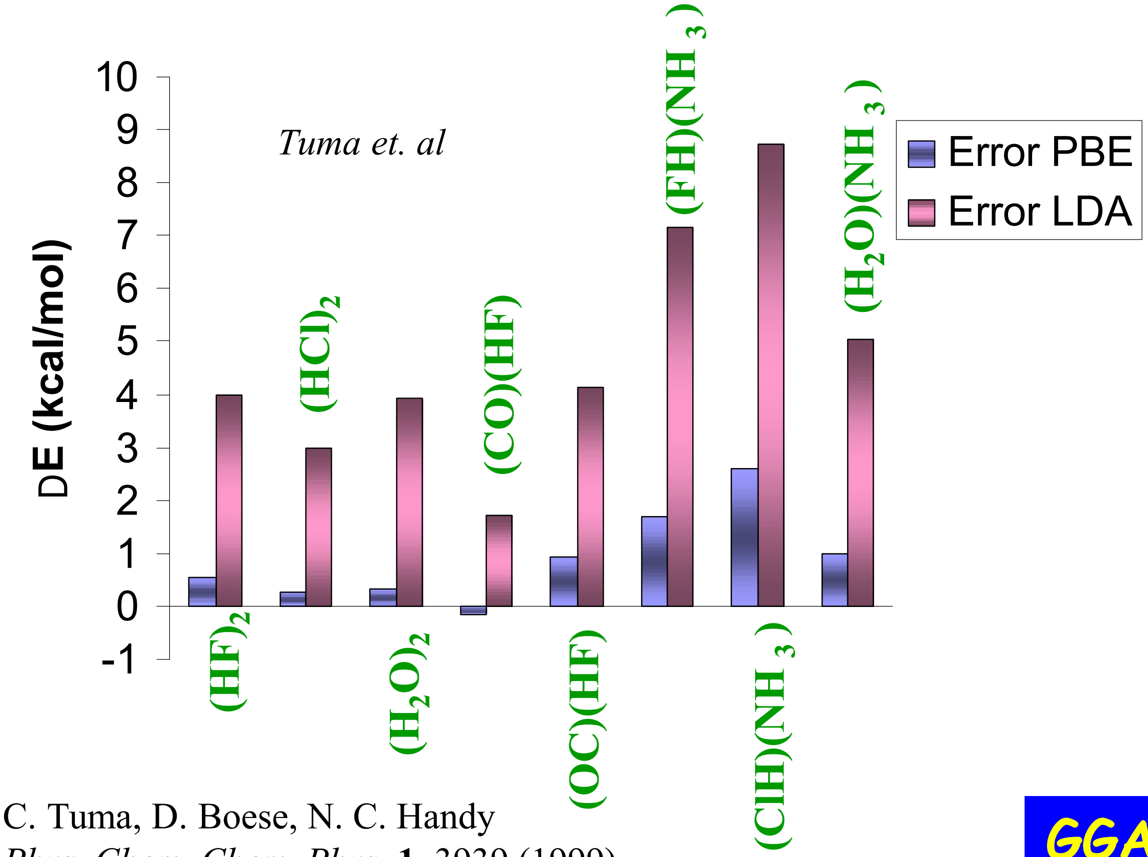


J. E. del Bene, Hydrogen Bonds. Encyclopedia of Computational Chemistry Vol. 2. Schleyer, D. Ed. in Chief.
(John Wiley, Chichester U. K. 1998).

At least MP2 is needed to accurately describe the hydrogen bond interaction

LDA or GGA?

$$\Delta E = E^{hb}_{DFT} - E^{hb}_{best\_ab\_initio} \left\{ \begin{array}{l} \text{Hartree-Fock plus} \\ \text{configuration interaction} \\ \text{or coupled-cluster} \end{array} \right.$$

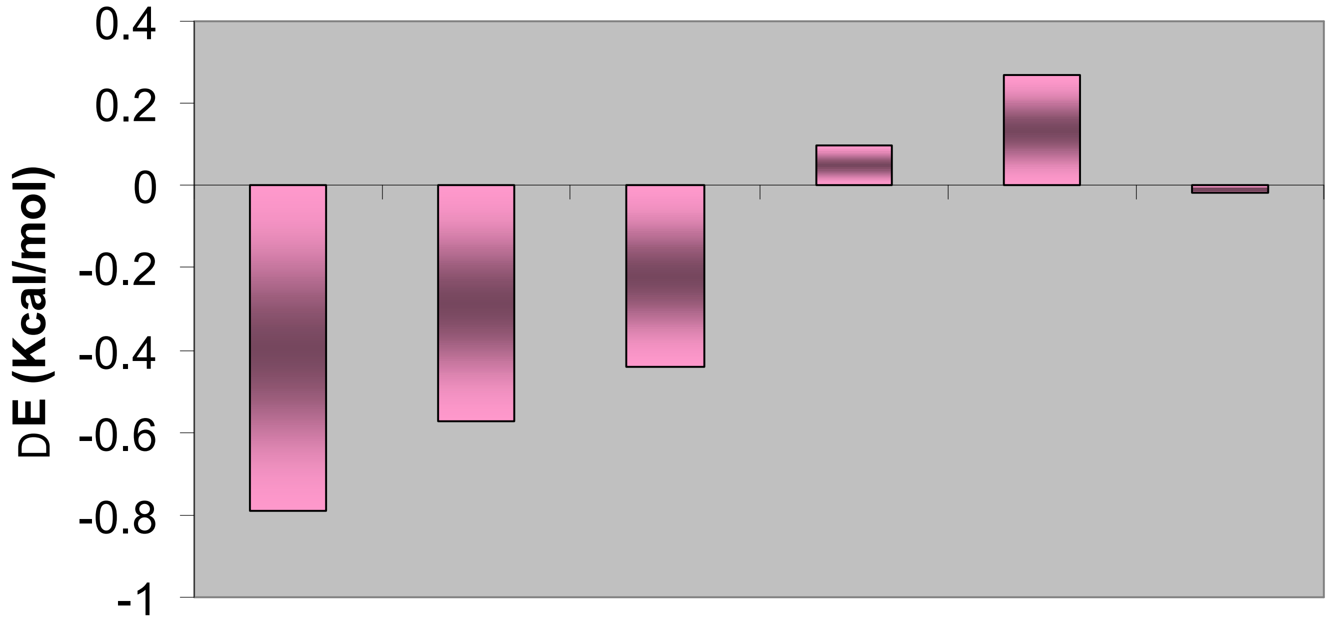


C. Tuma, D. Boese, N. C. Handy
Phys. Chem. Chem. Phys. **1**, 3939 (1999)

GGA is needed !

Accuracy of DFT Plane-wave Pseudopotential Method for the Description of Hydrogen Bonds

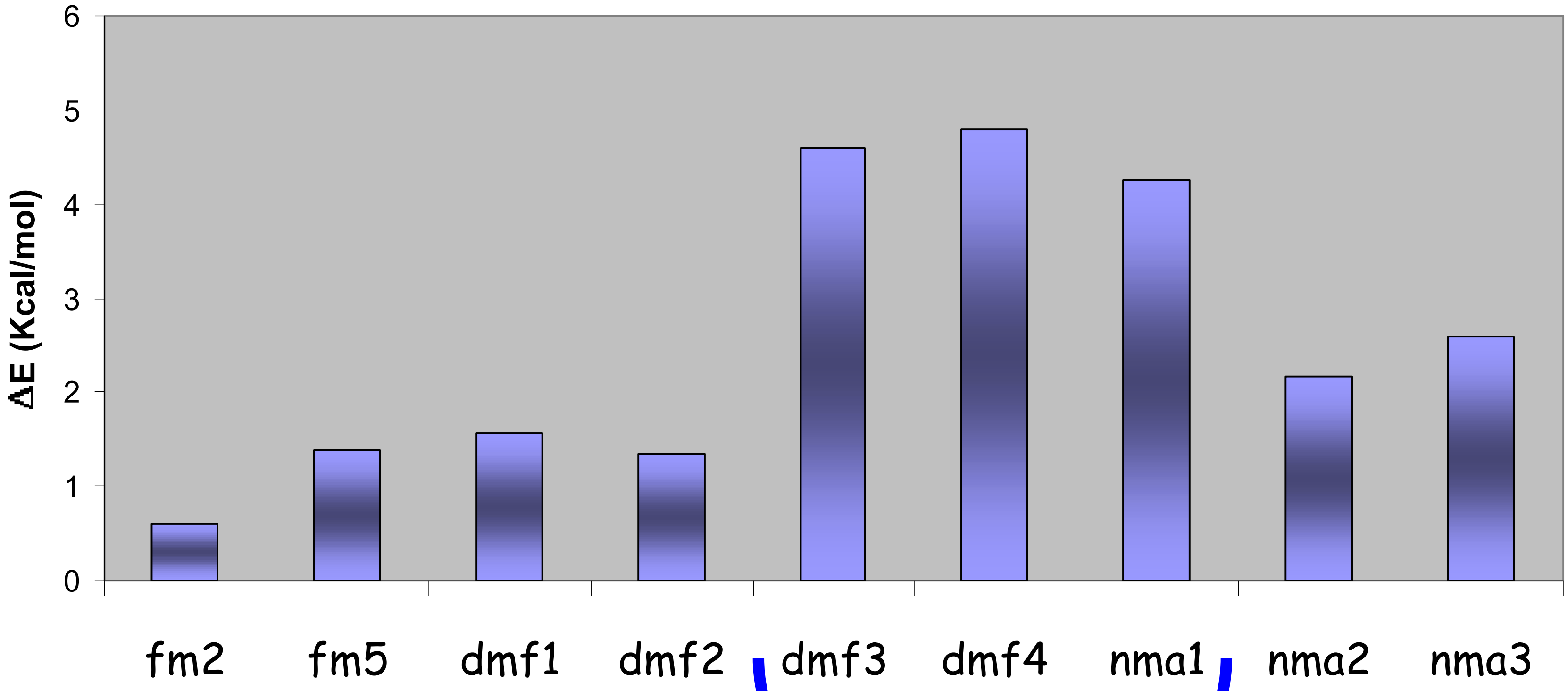
$$\Delta E = E_{DFT}^{hb} - E_{best\_ab\_initio}^{hb} \left\{ \text{CCSD(T)} \right.$$

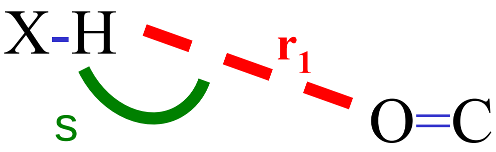


The error bar is less than 1 kcal/mol (0.042 eV)

PBE Accuracy to Describe Hydrogen Bonded Systems: Dependence on the Bond Directionality

$$\Delta E = E^{hb}_{DFT} - E^{hb}_{best\_ab\_initio} \quad \left\{ \text{MP2} \right.$$

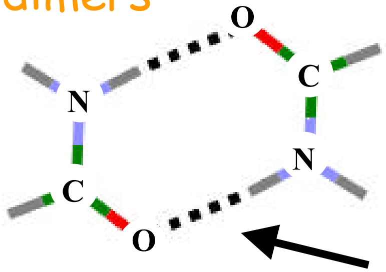




hydrogen bonds are highly bent
.i.e. s < 130°

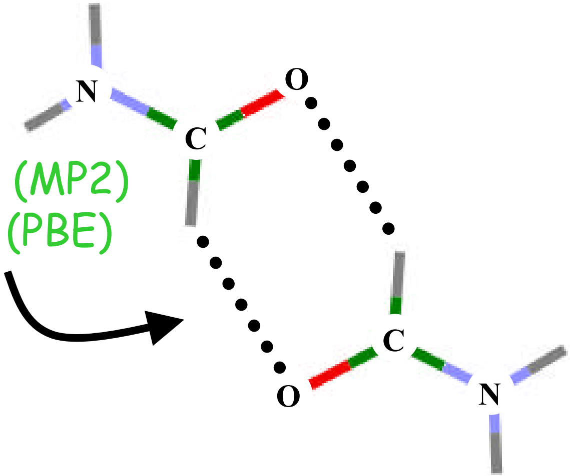
PBE Accuracy to Describe Hydrogen Bond Strength

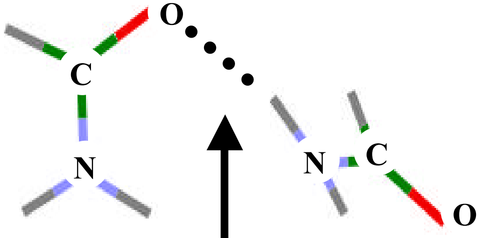
Formamide dimers



-7.2 kcal/mol (MP2)
-7.2 kcal/mol (PBE)

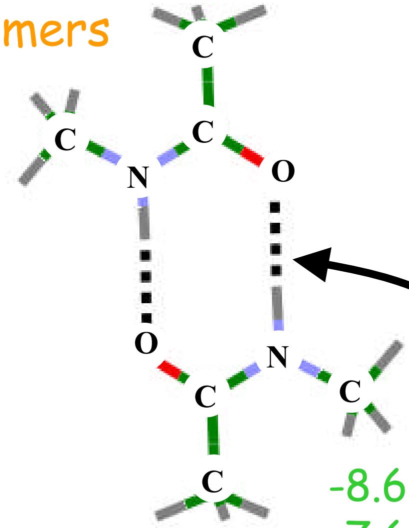
-2.5 kcal/mol (MP2)
-1.8 kcal/mol (PBE)



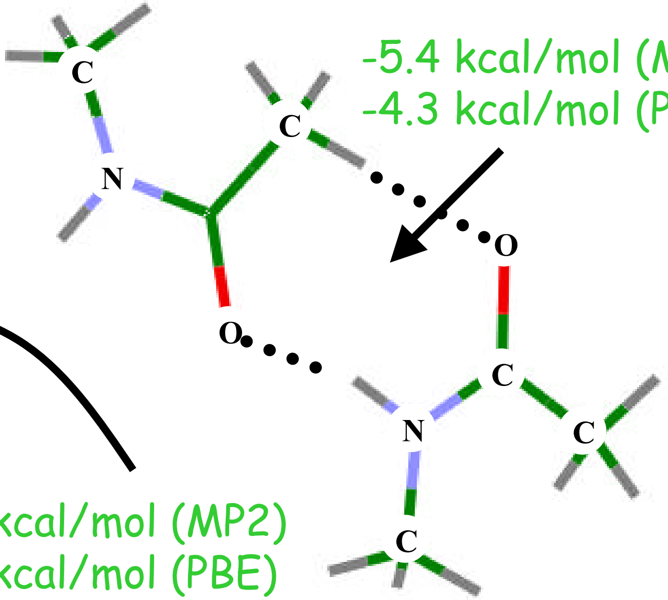


-7.3 kcal/mol (MP2)
-6.8 kcal/mol (PBE)

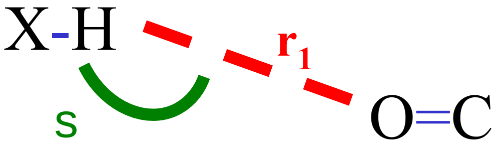
N-Methyl acetamide dimers



-8.6 kcal/mol (MP2)
-7.6 kcal/mol (PBE)



-5.4 kcal/mol (MP2)
-4.3 kcal/mol (PBE)

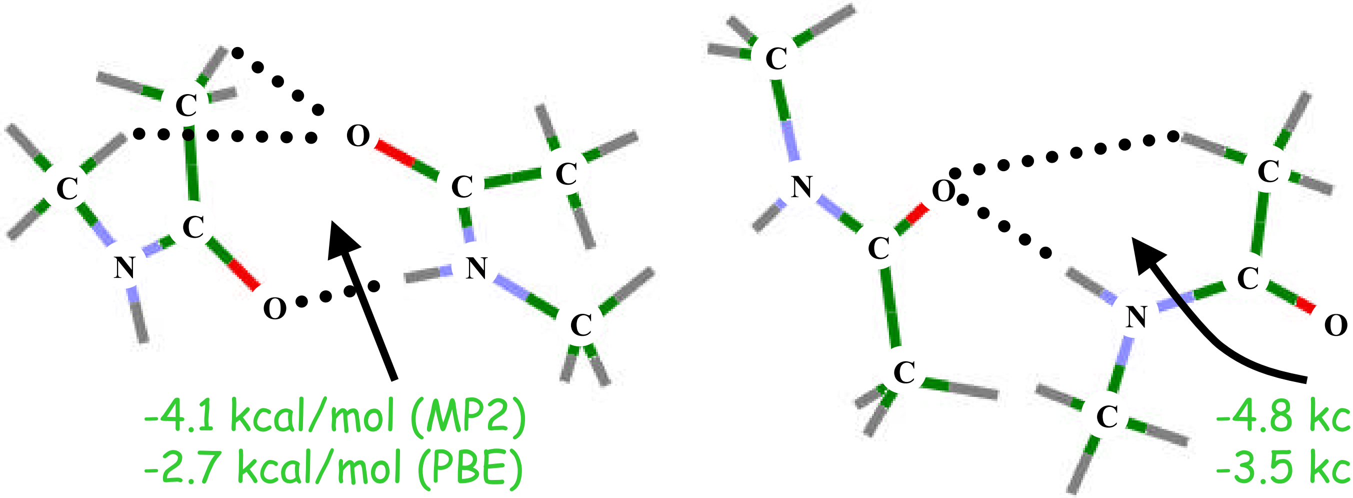


PBE accuracy:
1 kcal/mol per hydrogen bond
with respect to Møller-Plesset (MP2) level of theory if the hydrogen bonds are close to linearity
i.e. s = (130° , 180°)

MP2 results: R. Vargas et al *J. Phys. Chem. A* **105**, 4963, 2001.

PBE Accuracy to Describe Hydrogen Bond Strength

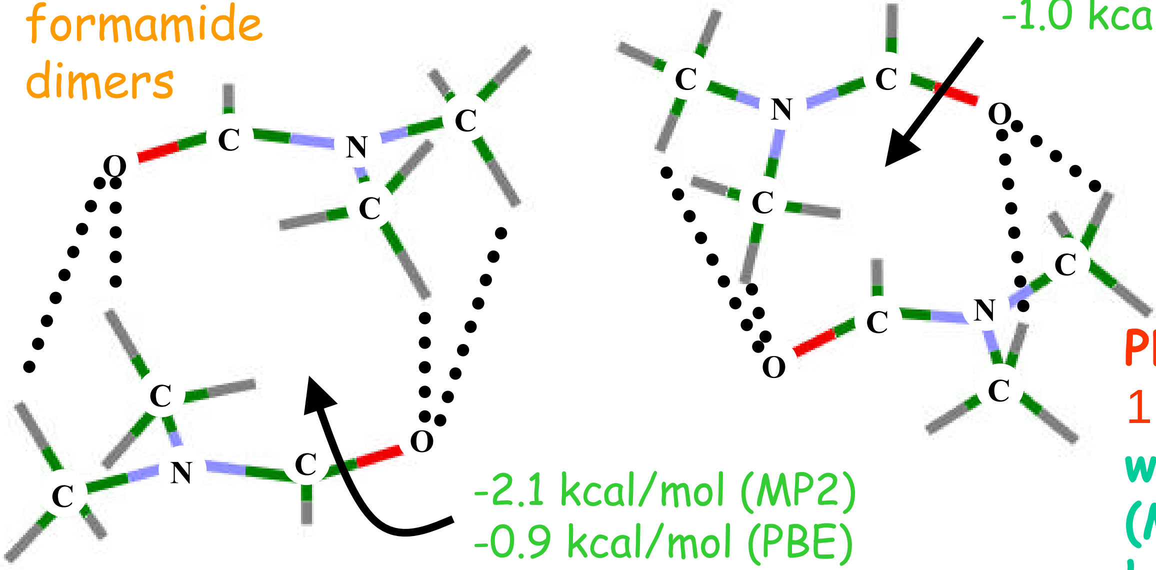
N-Methyl acetamide dimers



-4.1 kcal/mol (MP2)
-2.7 kcal/mol (PBE)

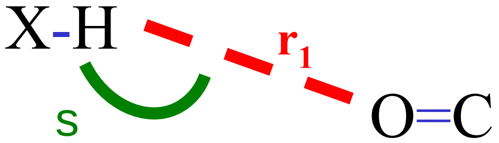
-4.8 kcal/mol (MP2)
-3.5 kcal/mol (PBE)

N, N-dimethyl formamide dimers



-2.2 kcal/mol (MP2)
-1.0 kcal/mol (PBE)

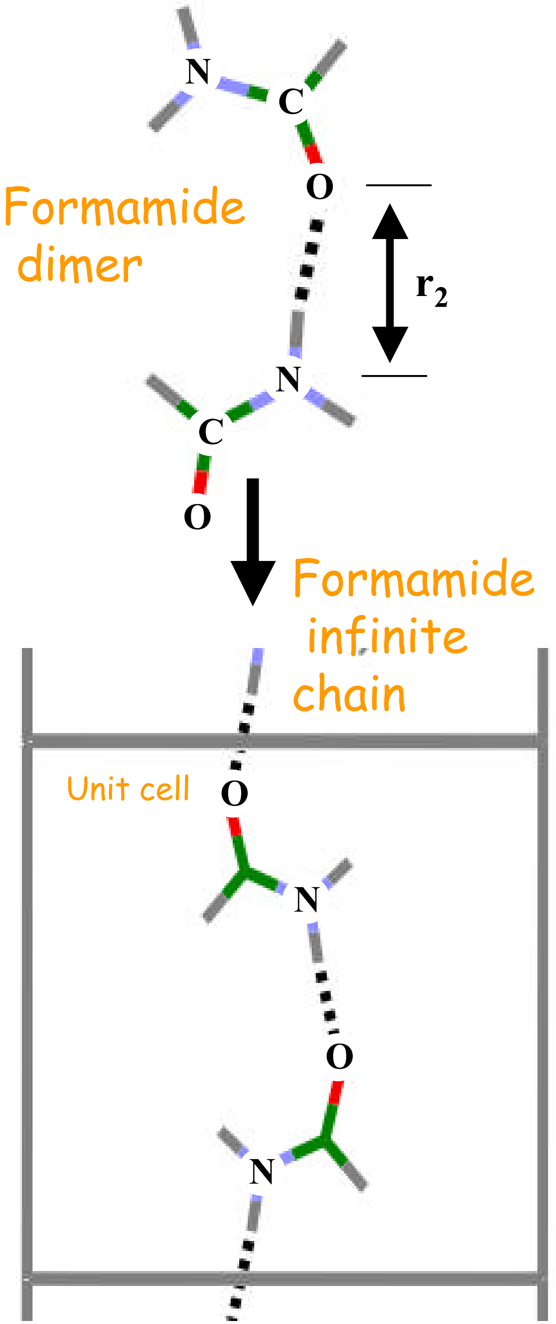
-2.1 kcal/mol (MP2)
-0.9 kcal/mol (PBE)



PBE accuracy:
1.5 kcal/mol per hydrogen bond
with respect to Møller-Plesset (MP2) level of theory if the hydrogen bonds are bent
i.e. s < 130°

MP2 results: R. Vargas et al *J. Am. Chem Soc* **122**, 4750, 2000.
R. Vargas et al *J. Phys. Chem. A* **105**, 4963, 2001.

PBE Accuracy to Describe Hydrogen Bond Cooperativity



Method	hb dimer (kcal/mol)	hb Infinite chain (kcal/mol)	Δhb, cooperativity (kcal/mol)
MP2-tz(2df,2pd)[1]	-5.08	-8.14	-3.06
BLYP-tz(2df,2pd)[1]	-4.39	-7.66	-3.27
BLYP-lno	-5.13	-7.42	-2.29
PBE-lno	-5.91	-8.55	-2.64
PBE-pw	-5.7	-8.3	-2.60

Method	r_2 dimer (Å)	r_2 infinite chain (Å)	Δr_2 (Å)
MP2-tz(2df,2pd)[1]	3.0012	2.8784	-0.1228
BLYP-tz(2df,2pd)[1]	3.0450	2.8516	-0.1934
BLYP-lno	3.05	2.87	-0.18
PBE-lno	3.01	2.83	-0.18
PBE-pw	2.99	2.82	-0.17

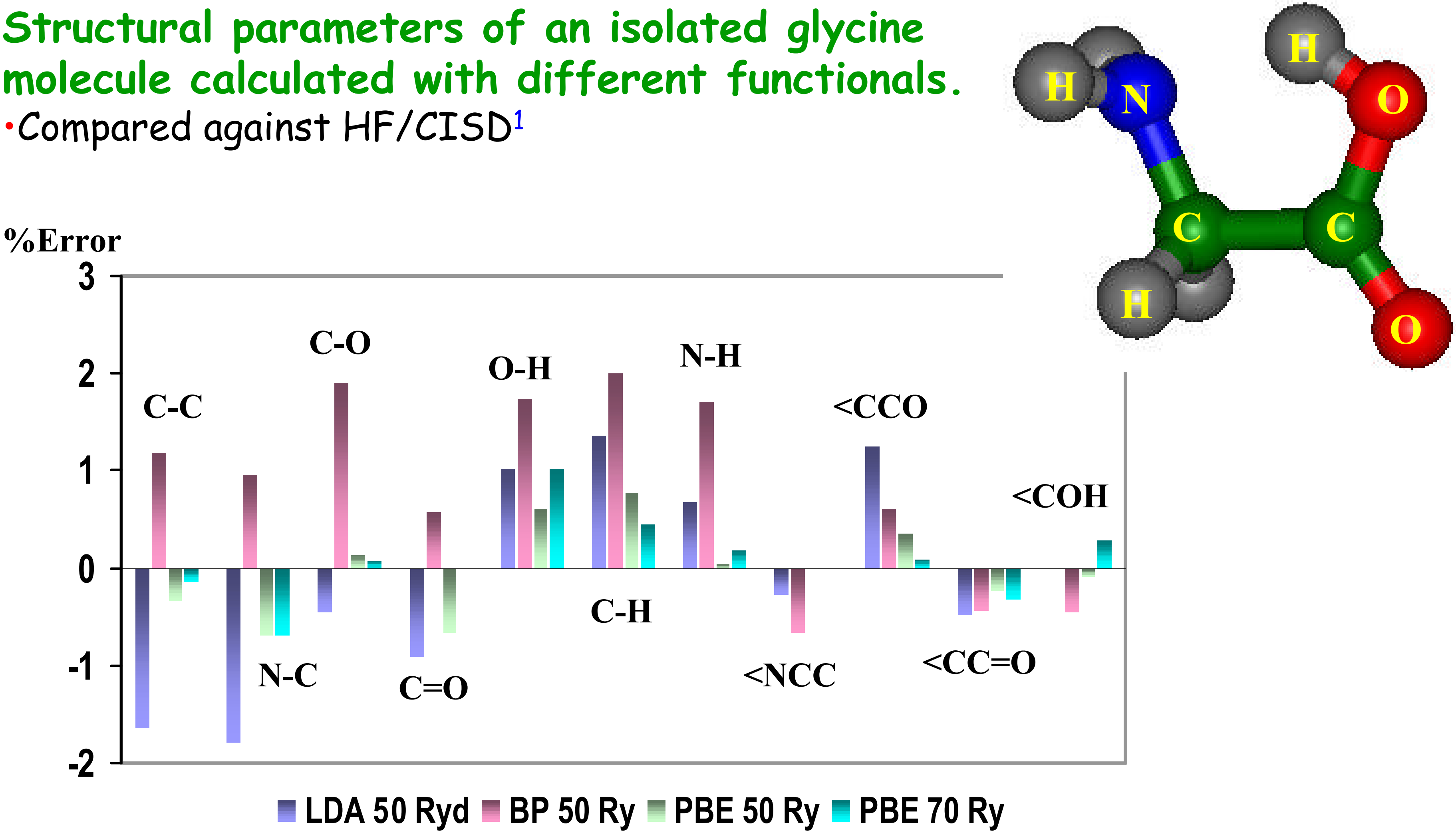
PBE accuracy: 0.05 Å in distance changes
0.5 kcal/mol in hb strength changes

1. S. Suhai, *J. Phys. Chem*. **100**, 3950 (1996)

Accuracy of DFT for Hydrogen Bonded Systems

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

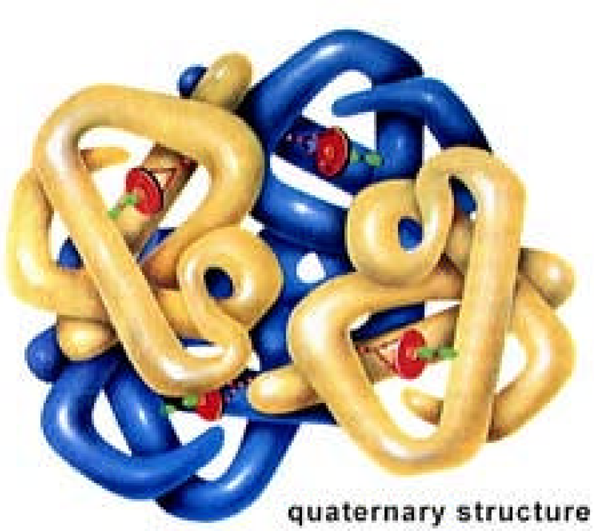
- Compared against HF/CISD[1]



covalent bonds are well described
DFT-PBE gives errors smaller than 1% !

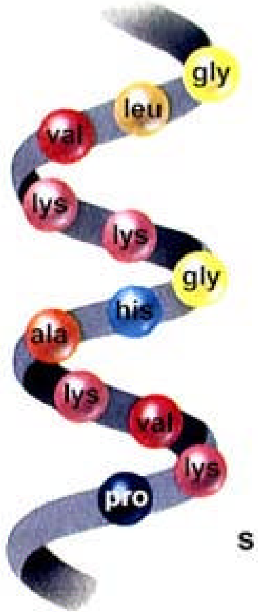
[1]. C.-H. Hu, M. Shen and H. F. Shaefer III, J. Am. Chem. Soc. **115**, 2923 (1993).

Protein Structure

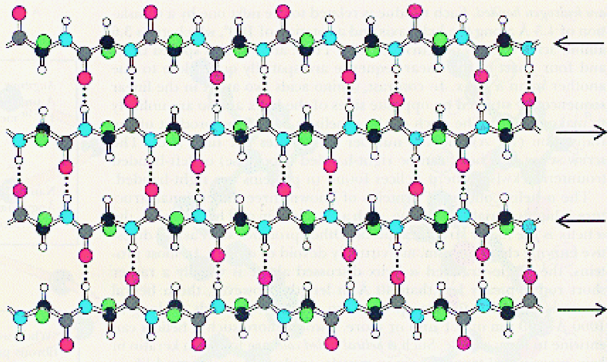


quaternary structure
(aggregation of two or more peptides)

tertiary structure
(folded individual peptide)



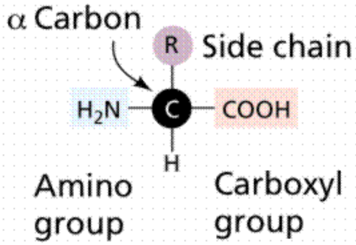
secondary structure
(α-helix)



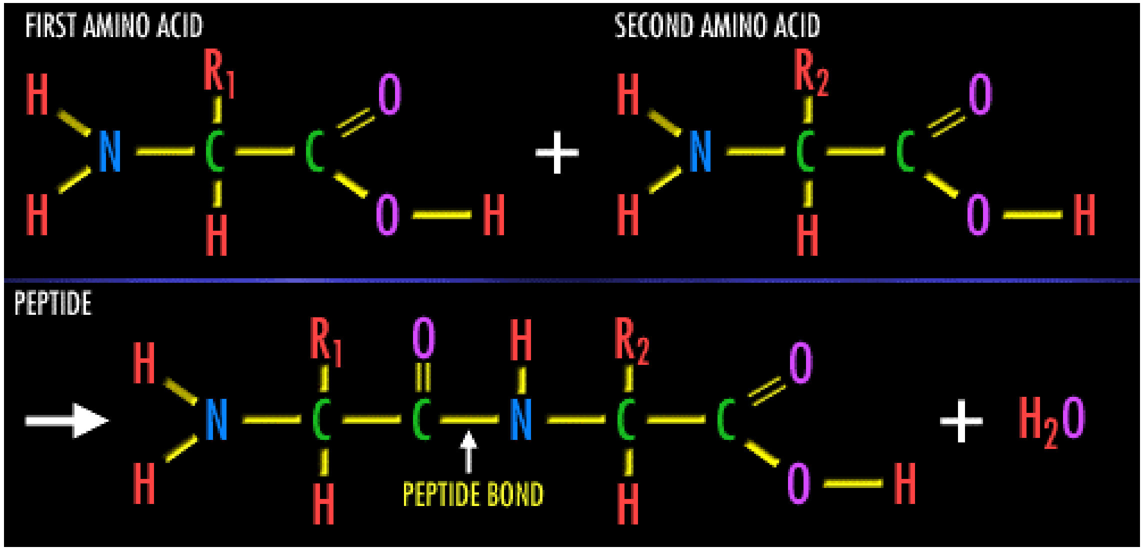
secondary structure
(b-sheet)

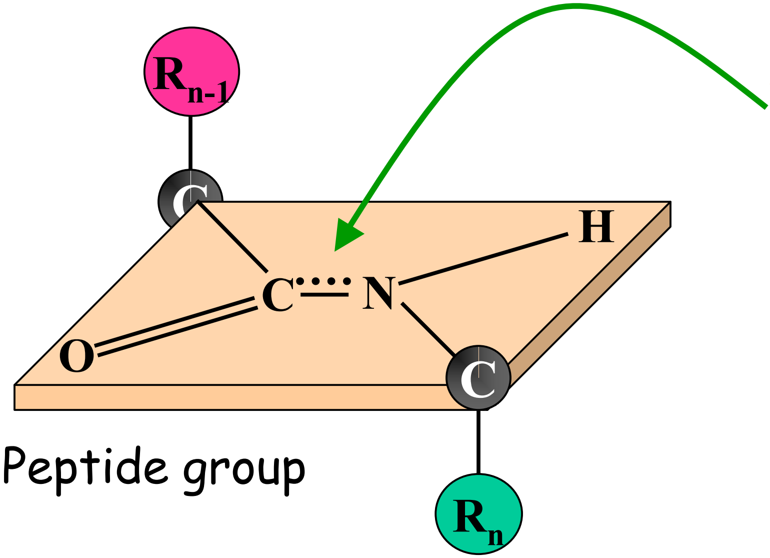
primary structure
(amino acid sequence)

Conventional depiction



The Peptide Bond





Peptide group

The peptide bond has a partial double bond character

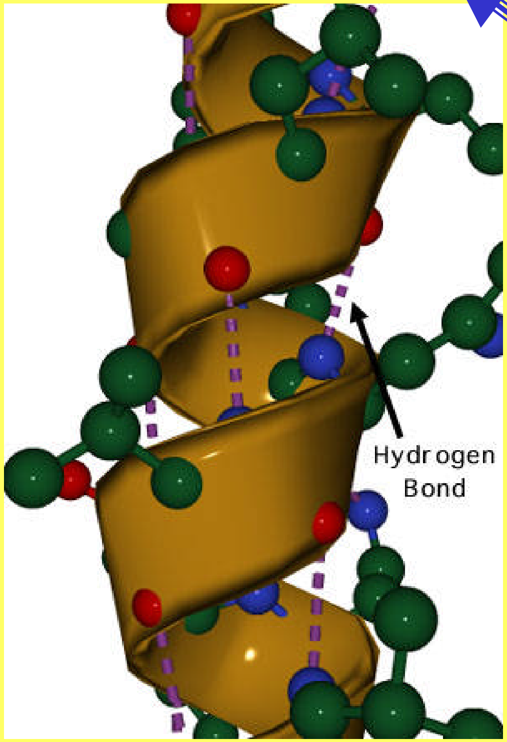
Peptide group characteristics

Planar

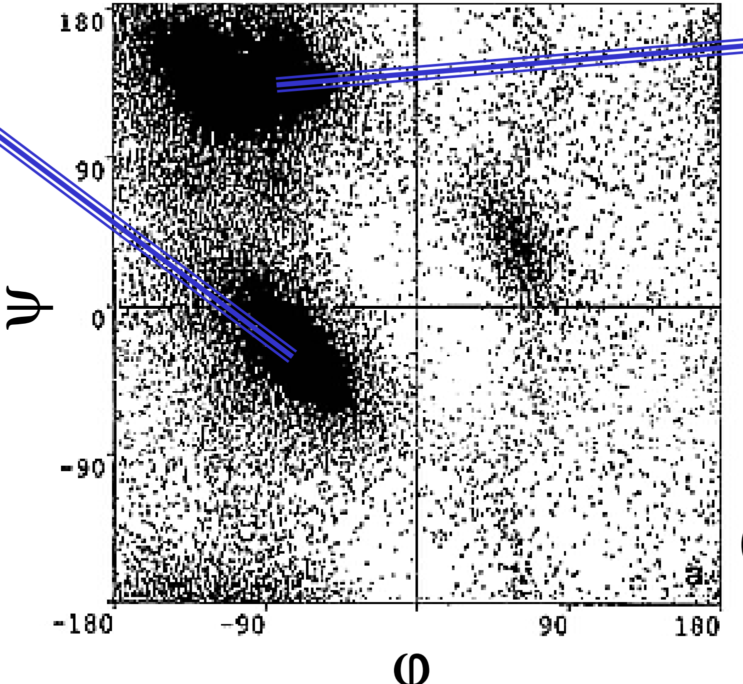
Rigid

Secondary Structure of proteins

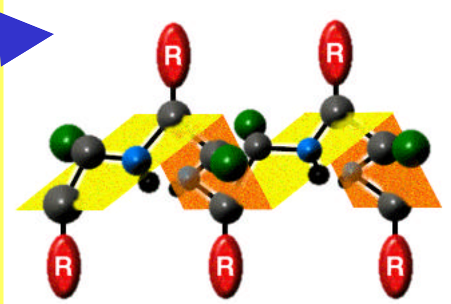
α-Helix

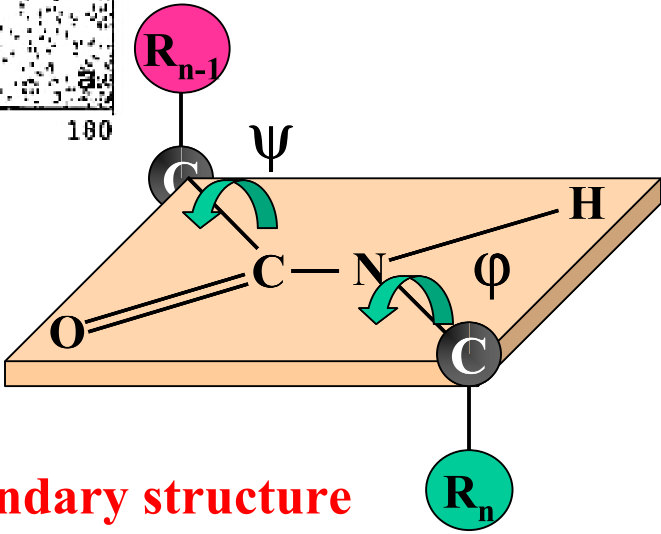


Ramachandran-Diagramm



β-Sheet

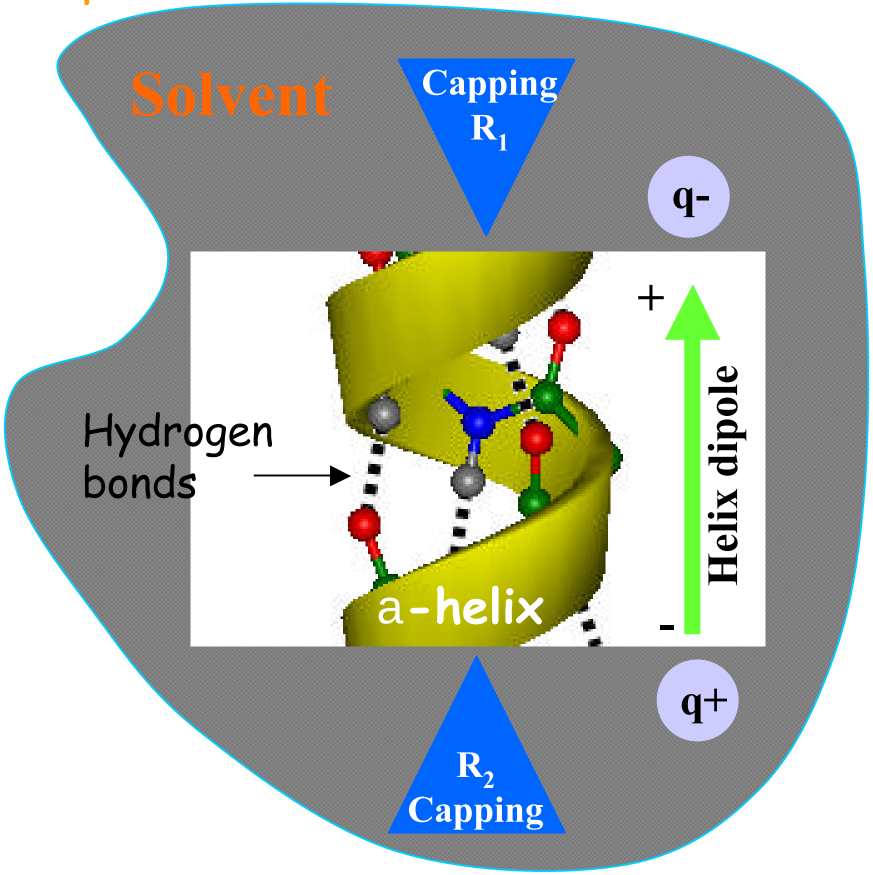




The a-helix conformation is the most common secondary structure

Helix Stability

- a-**helix** is a **prominent secondary structure** in protein conformation

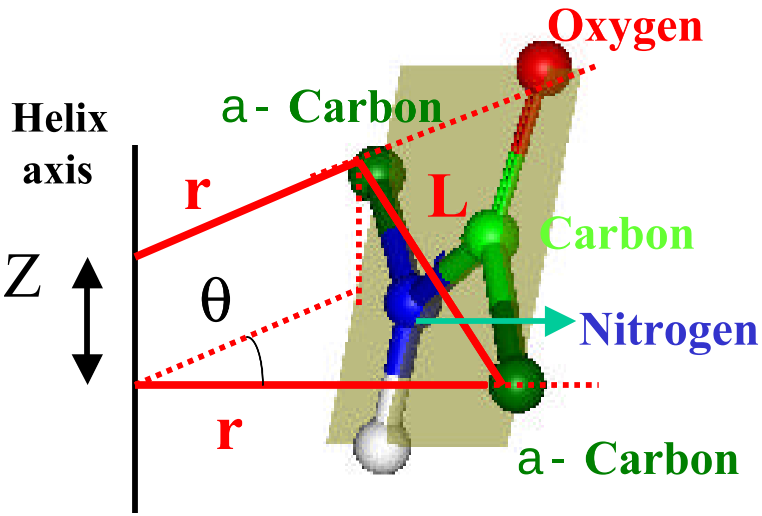


- Several factors are responsible for the α-helix stability
    - **Hydrogen bonds** are considered one of the main interactions stabilizing the α-helix structure
    - **Hydrogen bonds are cooperative**
      The strength of an hb is increased by its interaction with another hb
- **Open questions:**

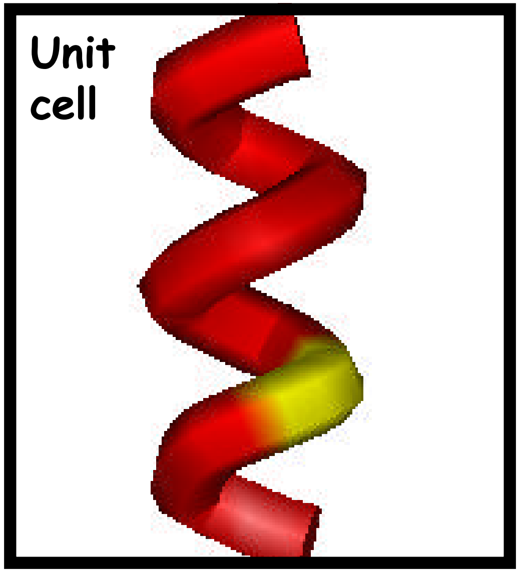
How large is the hydrogen bond strength in an α-helix?

How large is the hydrogen bond cooperativity in an α-helix?

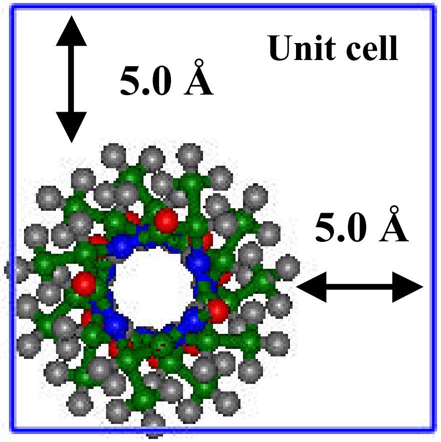
Model



One dimensional crystal



$$R_n = r\cos(qn)e_x + r\sin(qn)e_y + nZe_z$$



$$q = 360^o \, {}^{m}\!/_{N} \rightarrow$$

M turns per unit cell

N peptide units per unit cell

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

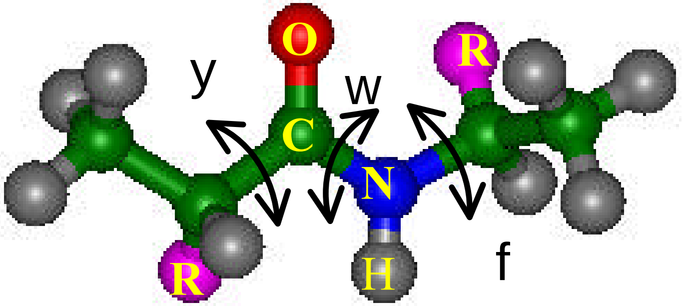
$$q_{\exp} = 99.57^o$$

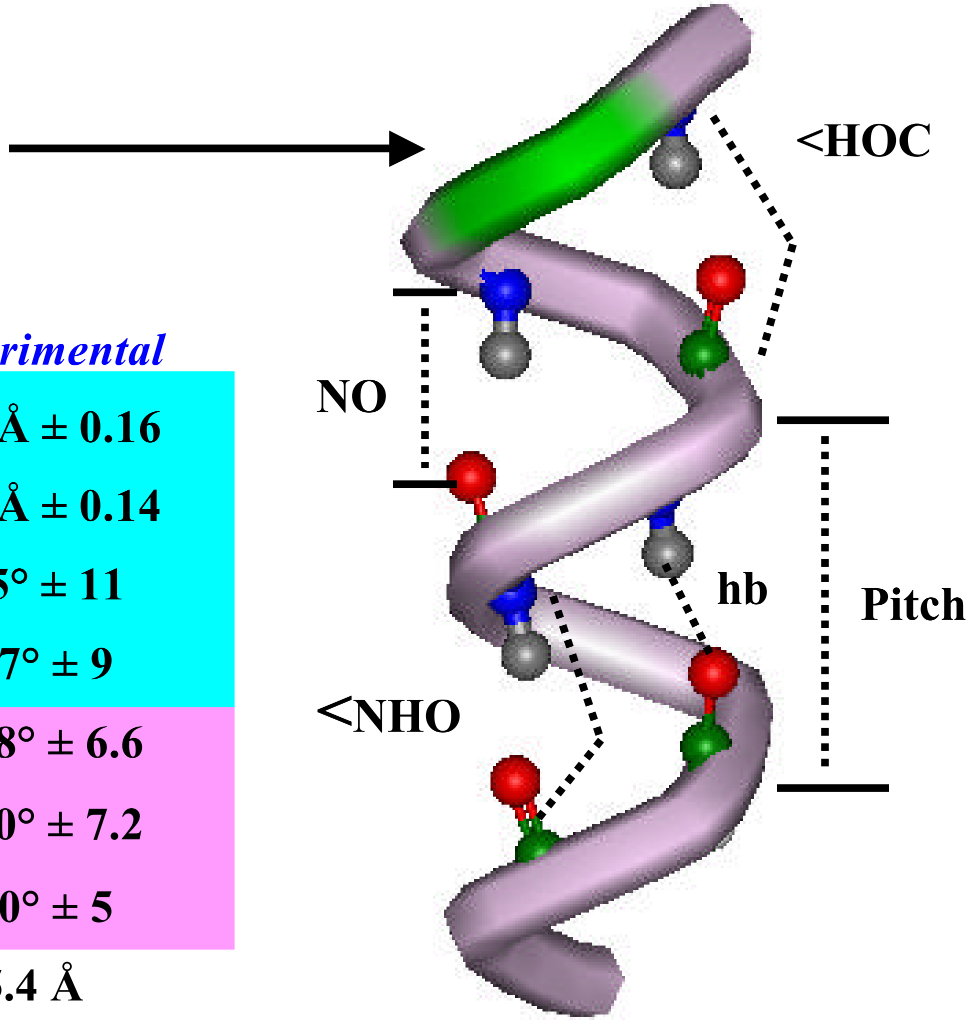
$$q_{\mathrm{mod}\,el} = 98.2^o$$

No ending effects

a-Helix Geometry

Equilibrium structure of the helix



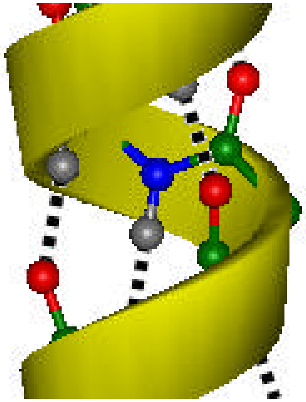


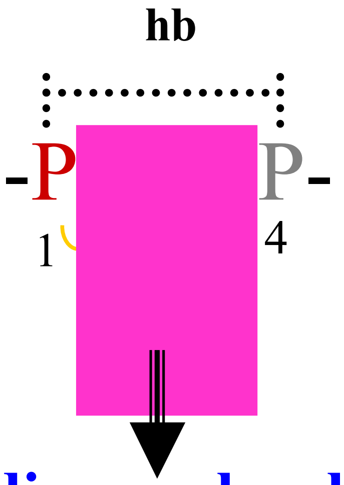
Parameters	*Calculated*	*Experimental*
hb	**1.950 Å ± 0.005**	**2.06 Å ± 0.16**
NO	**2.950 Å ± 0.005**	**2.99 Å ± 0.14**
NHO	**163.6° ± 0.3**	**155° ± 11**
HOC	**147.3° ± 0.5**	**147° ± 9**
f	**-63.5° ± 0.5**	**-63.8° ± 6.6**
y	**-43.0° ± 0.5**	**-41.0° ± 7.2**
w	**177.4° ± 0.7**	**180° ± 5**
Pitch	**5.48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

Good agreement between calculated and experimental parameters!

Hydrogen Bond Strength in a a-helix

a-helix conformation



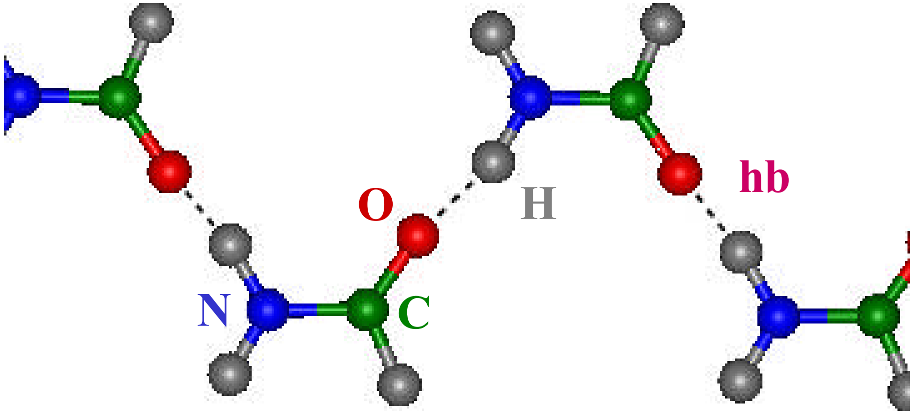


How to extract the hb strength?

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

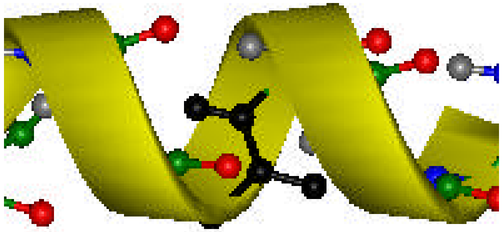


Problem: back bone is not taken into account !

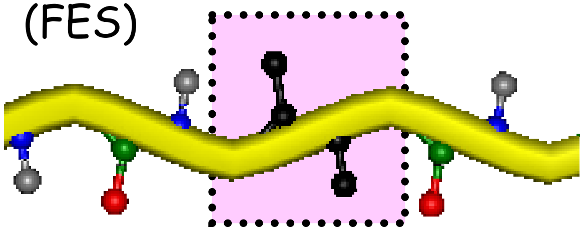
1. S. Suhai, *J. Phys. Chem*. **100**, 3950 (1996)   2. R. Ludwid, F. Weinhold, T. C. Farrar, *J. Chem. Phys*. **107**, 499 (1997).

Hydrogen Bond Strength

α-helix without hb



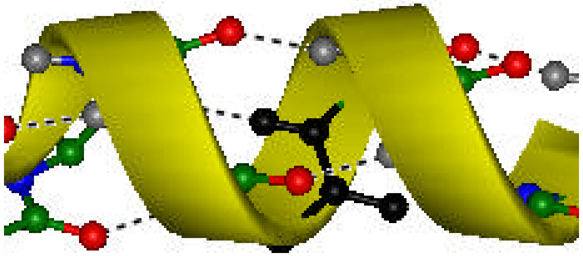
Fully extended structure (FES)



$E_{conformation}$

E_{hb} = Hydrogen bond energy

Stability



α-helix

m = Energy per peptide unit

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

$$E_{conformation} \approx E_{a}^{N} - E_{a}^{N-1} - m_{FES}^{\infty}$$

→ N=3 (α-helices)
N=2 (3_{10}-helices)

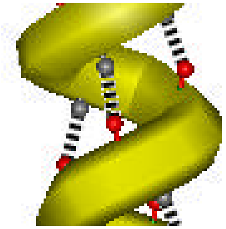
$$E_{hb} = \Delta H_{a}^{N} = E_{a}^{N} - E_{a}^{N-1} - m_{FES}^{\infty} - E_{conformation}$$

→ **finite chain**

$$E_{hb}^{\infty} = m_{a}^{\infty} - m_{FES}^{\infty} - E_{conformation}$$

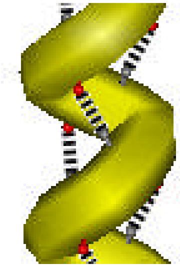
→ **infinite chain**

Hydrogen Bond Strength



α-helix
hbs (i,i+3)

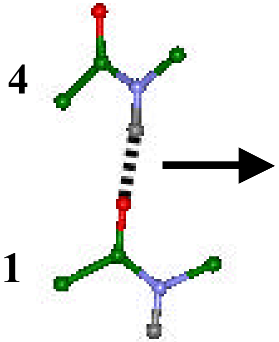
System	$E_{conformational}$	E_{hb} (first turn, i—i+3)	E_{hb} (infinite chain)	ΔE_{hb} (cooperativity)
Polyalanine	5.9 kcal/mol	-3.5 kcal/mol	-8.6 kcal/mol	-5.1 kcal/mol
Polyglycine	7.2 kcal/mol	-4.1 kcal/mol	-9.9 kcal/mol	-5.8 kcal/mol



3_{10}-helix
hbs (i,i+2)

System	$E_{conformational}$	E_{hb} (first turn, i—i+2)	E_{hb} (infinite chain)	ΔE_{hb} (cooperativity)
Polyalanine	5.8 kcal/mol	-4.4 kcal/mol	-8.0 kcal/mol	-3.6 kcal/mol

Hydrogen bond strength as calculated in a cluster approach



-5.9 kcal/mol polyalanine α-helix

-5.9 kcal/mol polyglycine α-helix

The back bone significantly affects the strength of neighboring hb's
Without back bone the hb energy is larger by 50 %

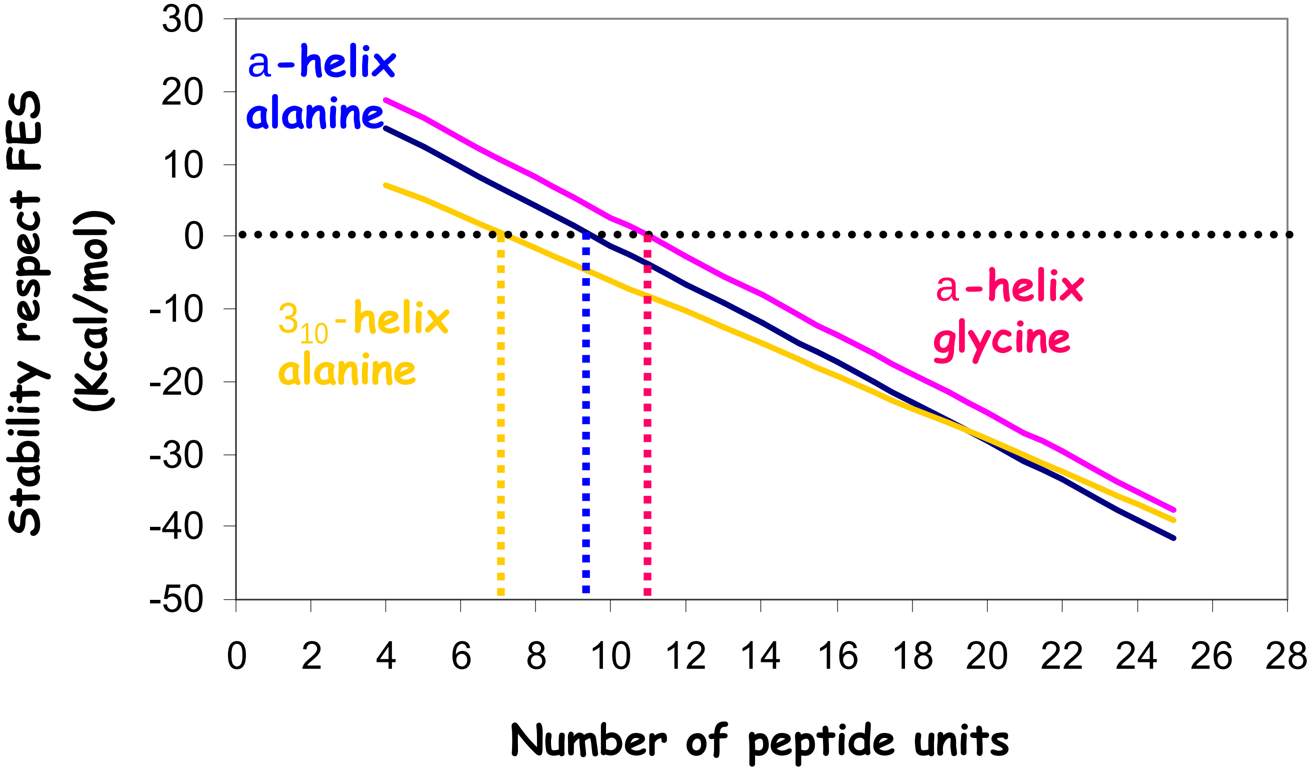
The Importance of Cooperativity

$$NE_{conformation} < -E_{hb}^{\infty}\left(N - A\right)$$

A = 3 for a-helix
A = 2 for 3_{10}-helix

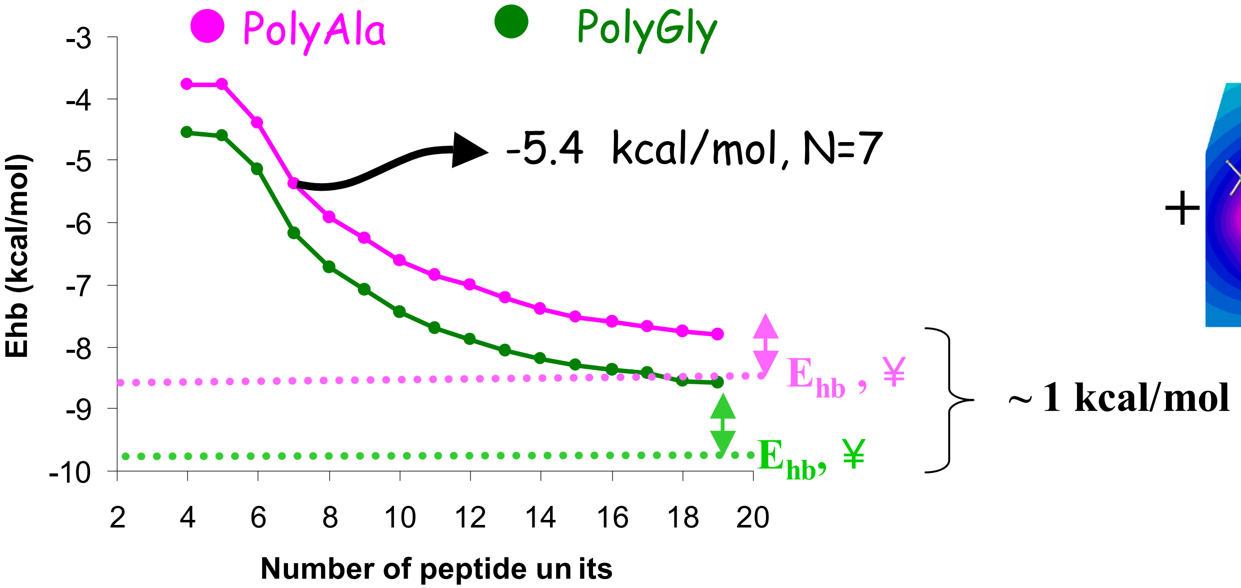
elastic energy

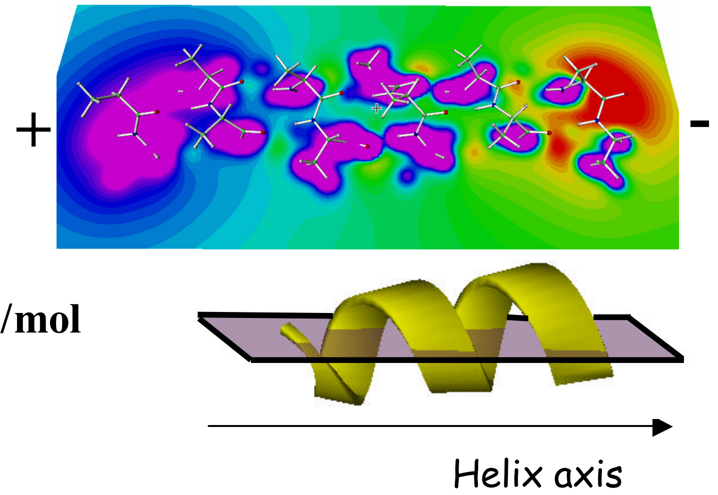
stabilization energy



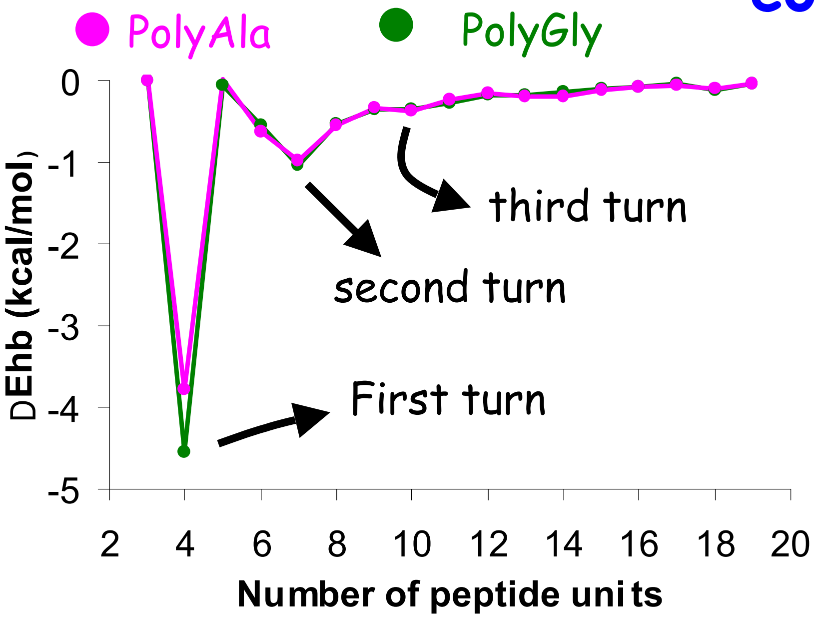
J. Ireta, J. Neugebaure, M. Scheffler, A. Rojo, M. Galván
J. Phys. Chem. B, 107, 1432 (2003)

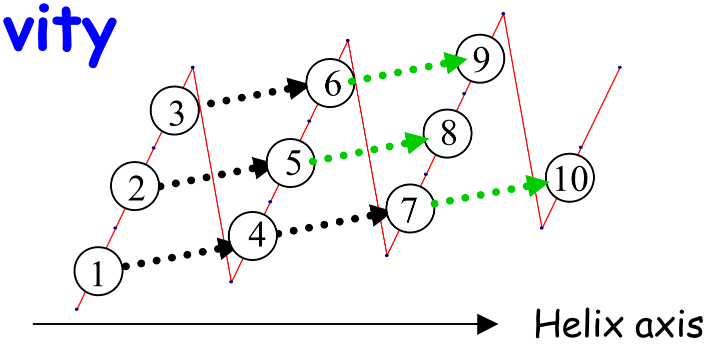
Ending Effects





cooperativity





After the second turn the hydrogen bond strength increases smoothly

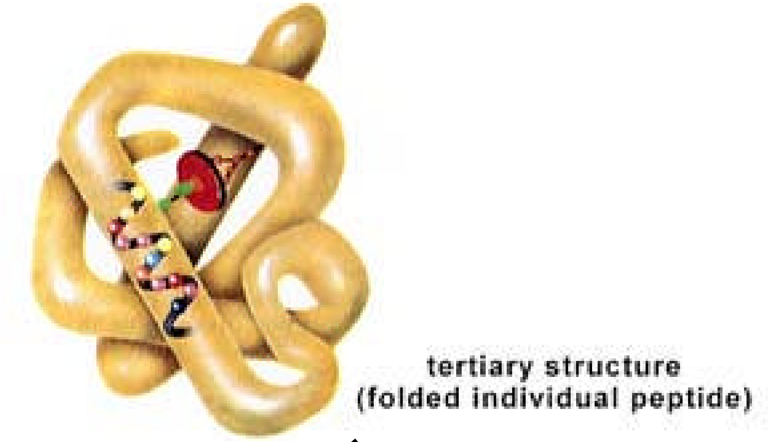
The hydrogen bond strength difference between long finite chains and the infinite one is due to the large electric field at the ends of the finite chains

How does the peptide bond respond to strain ?

Experiment:

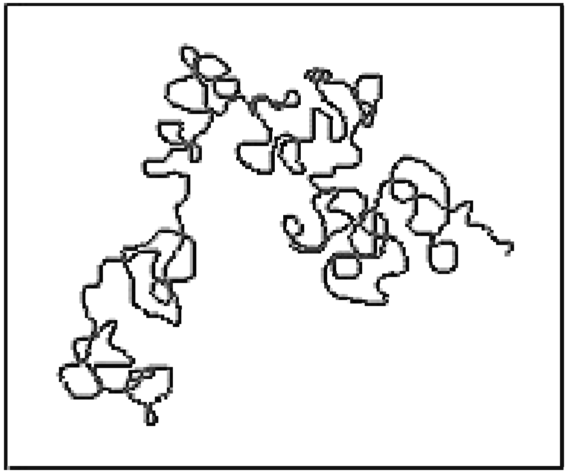
Proteins denaturates when uniaxial compression above 3 GPa is applied (fast ultra shock waves experiments)

a-helix unfolds under tensile load (atomic force microscope experiments)



tertiary structure
(folded individual peptide)

Denaturation
(unfolding)



Random coil

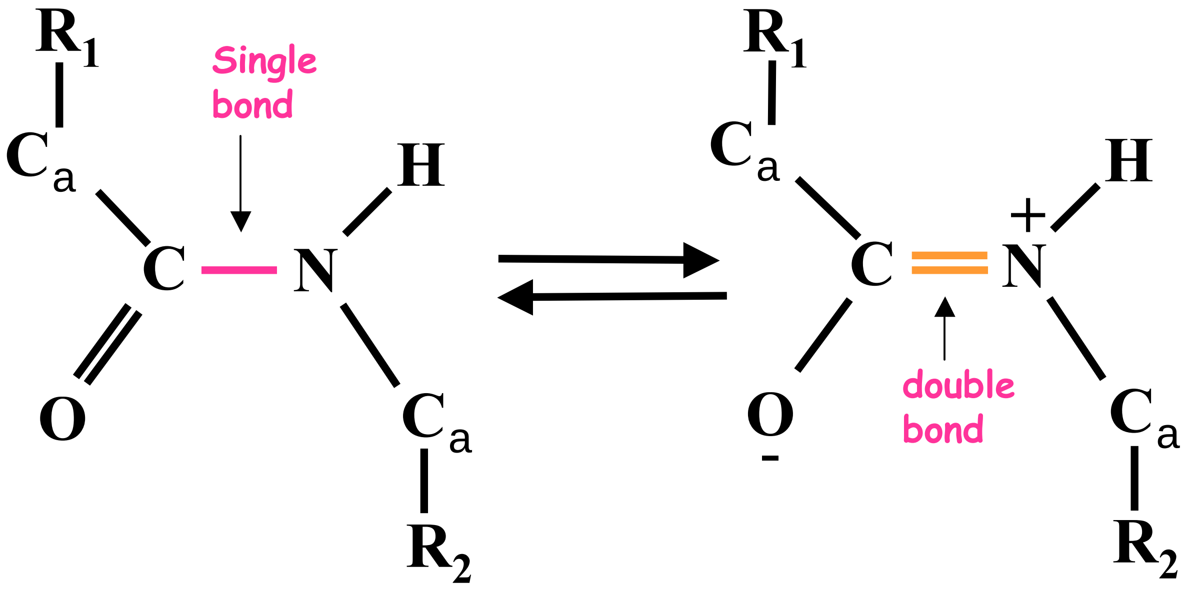
Open questions

How does the helix structure responds to tensile or compressive loads?

How do the hydrogen bonds respond to tensile or compressive loads?

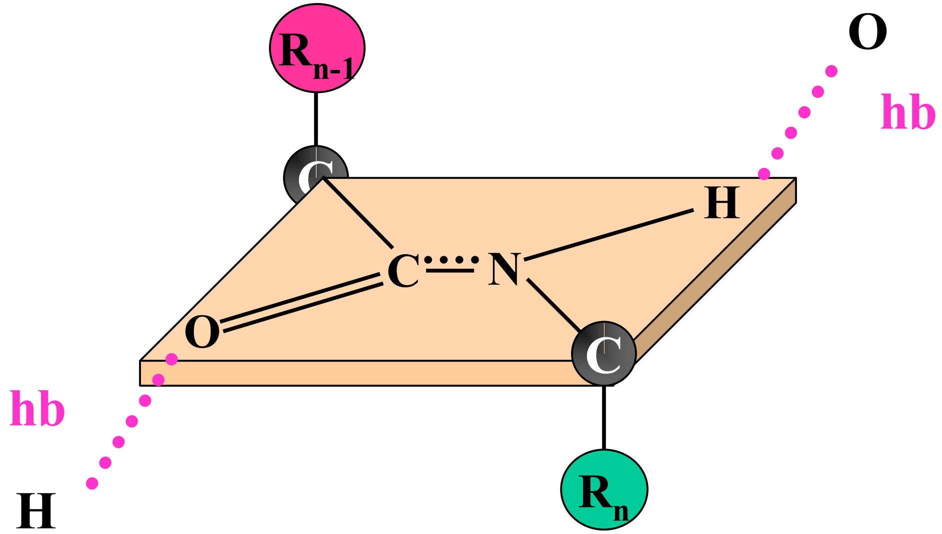
The Resonant Model

Single
bond
state



Double
bond
state
(zwitterion)

Hydrogen bond effect on the peptide group structure



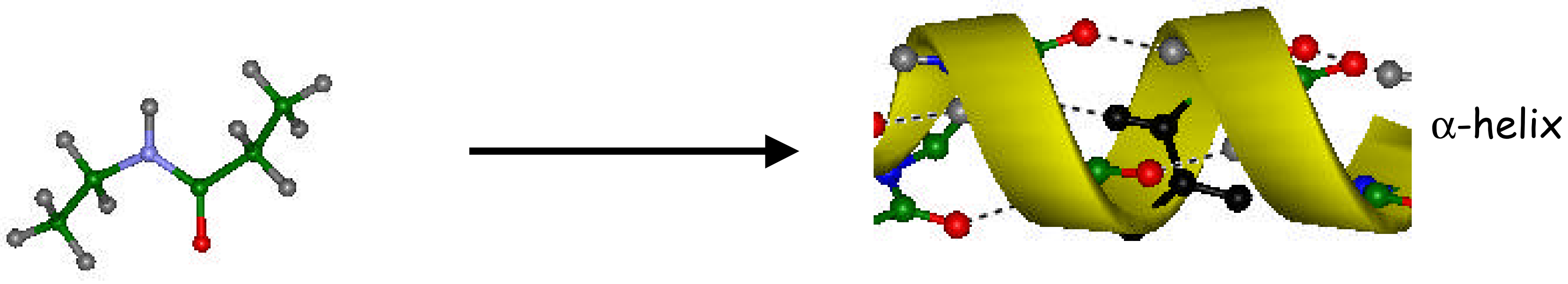
Single
bond

⇌

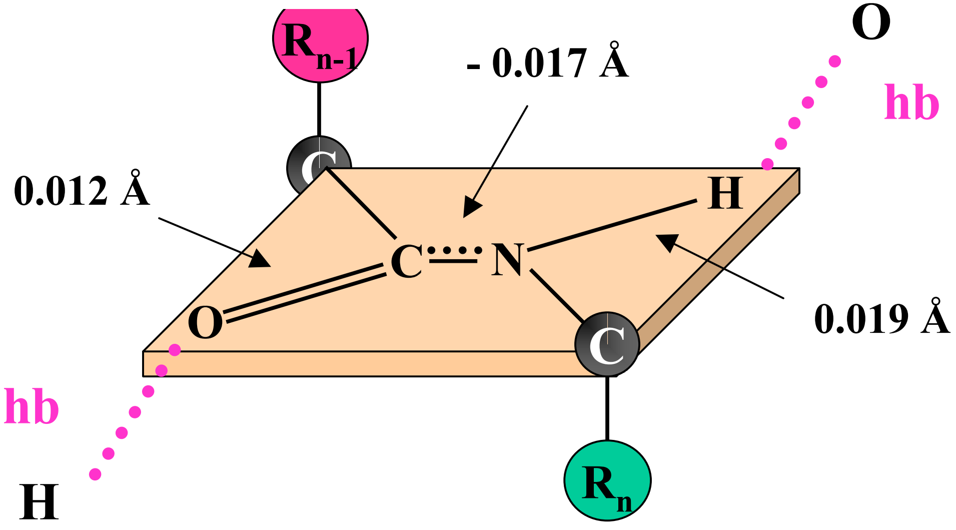
double
bond
(zwitterion)

The hydrogen bonds shifts the equilibrium towards the zwitterion state

Effect of the Secondary Structure on the Peptide Bond

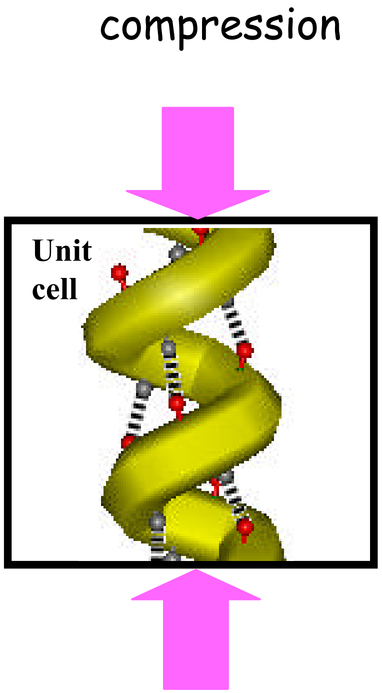


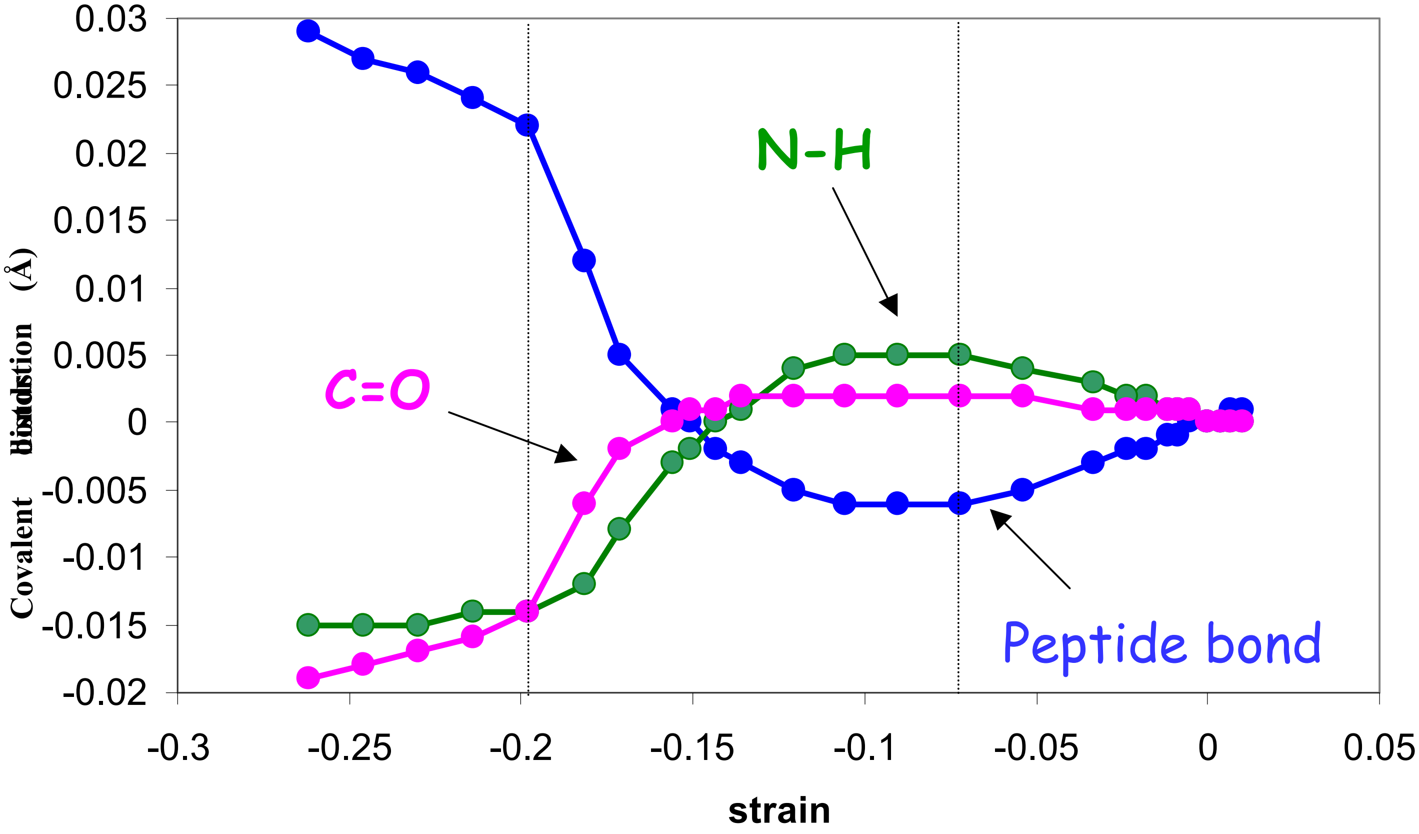
-8.6 kcal/mol per hb



Changes in the peptide bond are modest if they are compared with changes in other systems with hbs of similar strength

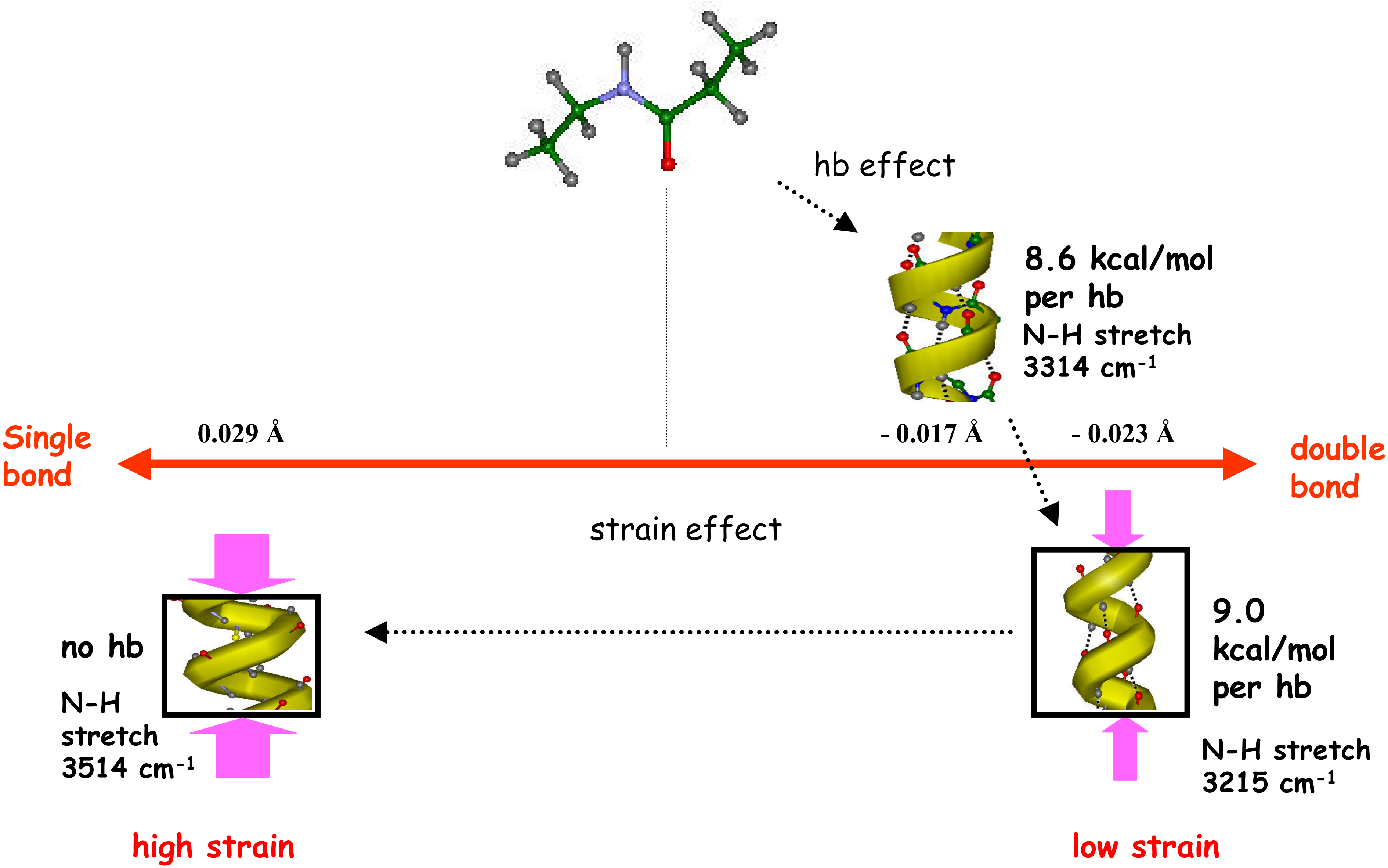
Peptide Bond Response to Strain





peptide bond is compressed by -0.006 Å
N-H bond is elongated by 0.005 Å
C=O bond is elongated by 0.002 Å

Peptide Bond Behavior



hb effect

8.6 kcal/mol per hb

N-H stretch $3314\ cm^{-1}$

Single bond

0.029 Å

- 0.017 Å

- 0.023 Å

double bond

strain effect

no hb

N-H stretch $3514\ cm^{-1}$

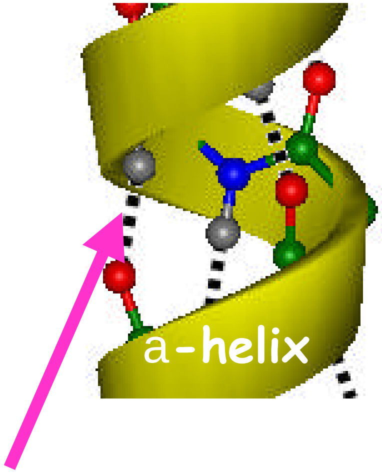
9.0 kcal/mol per hb

N-H stretch $3215\ cm^{-1}$

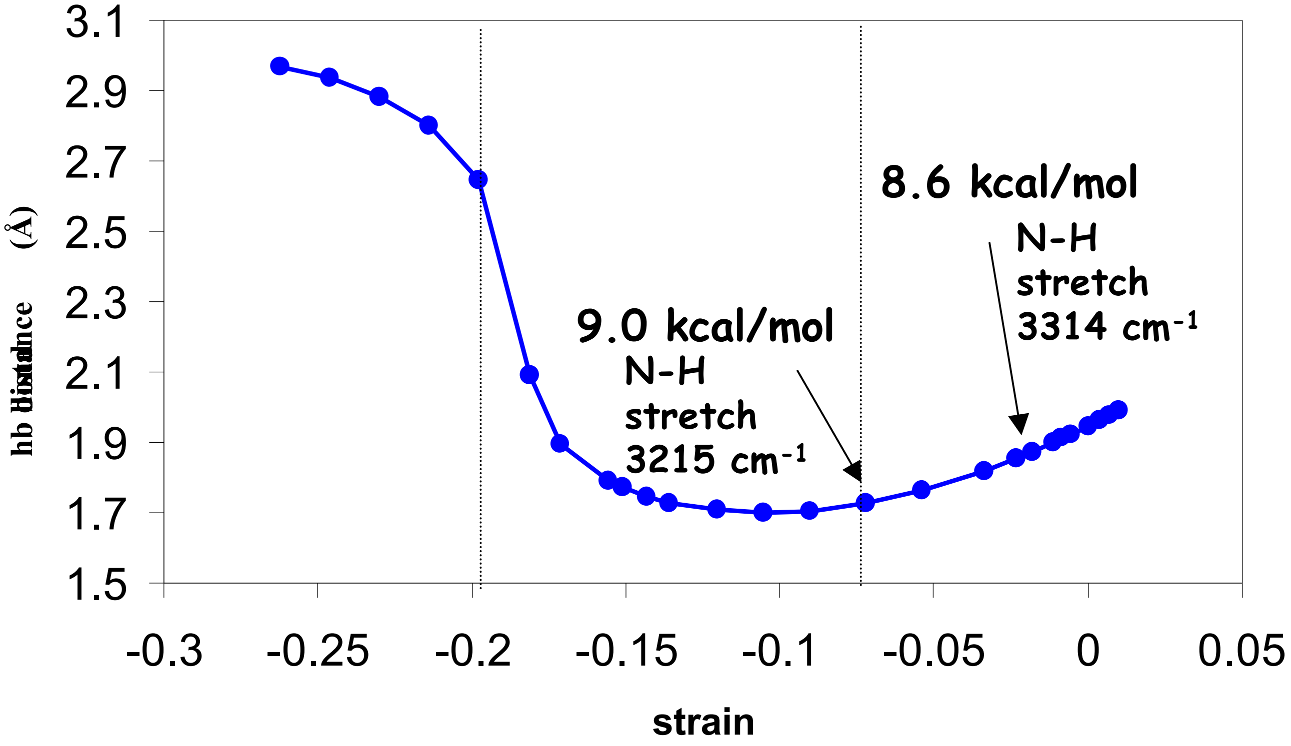
high strain

low strain

Hydrogen Bond Response to Strain

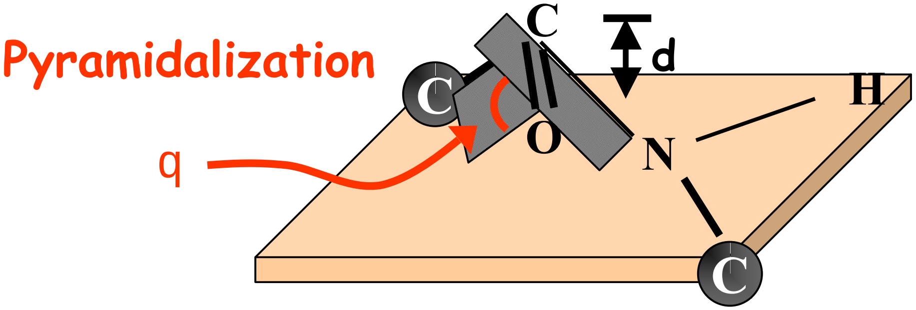


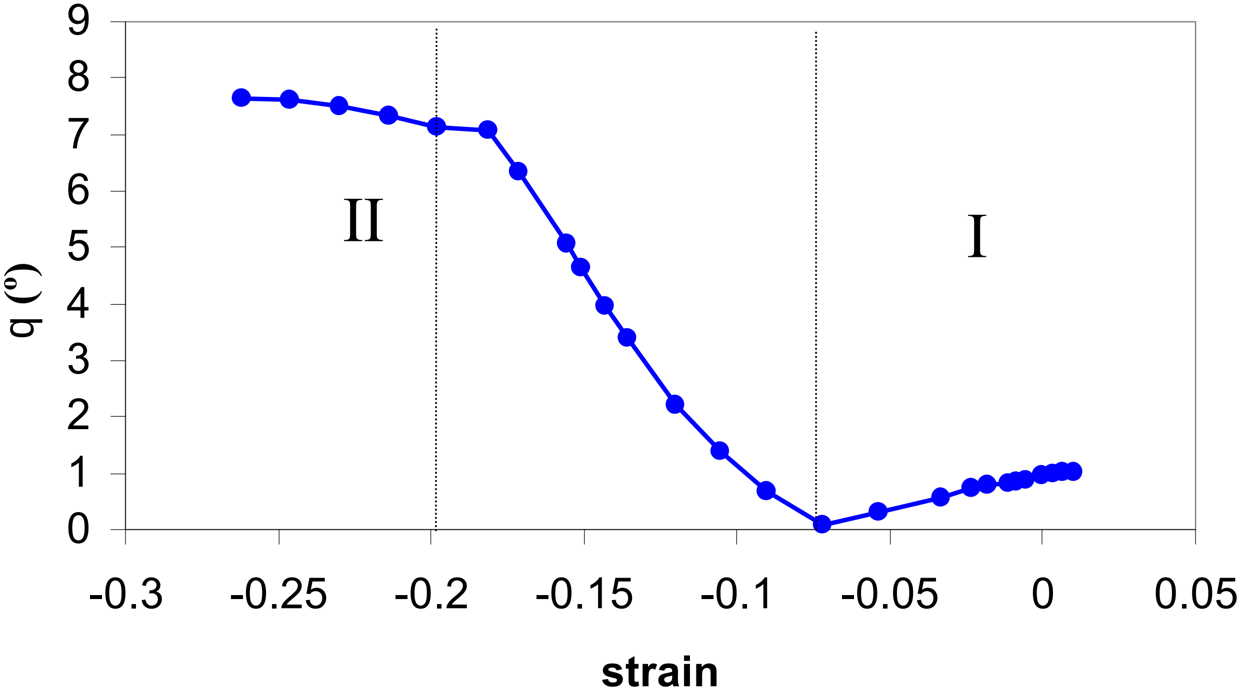
Hydrogen bonds



At high strain the hydrogen bonds are broken

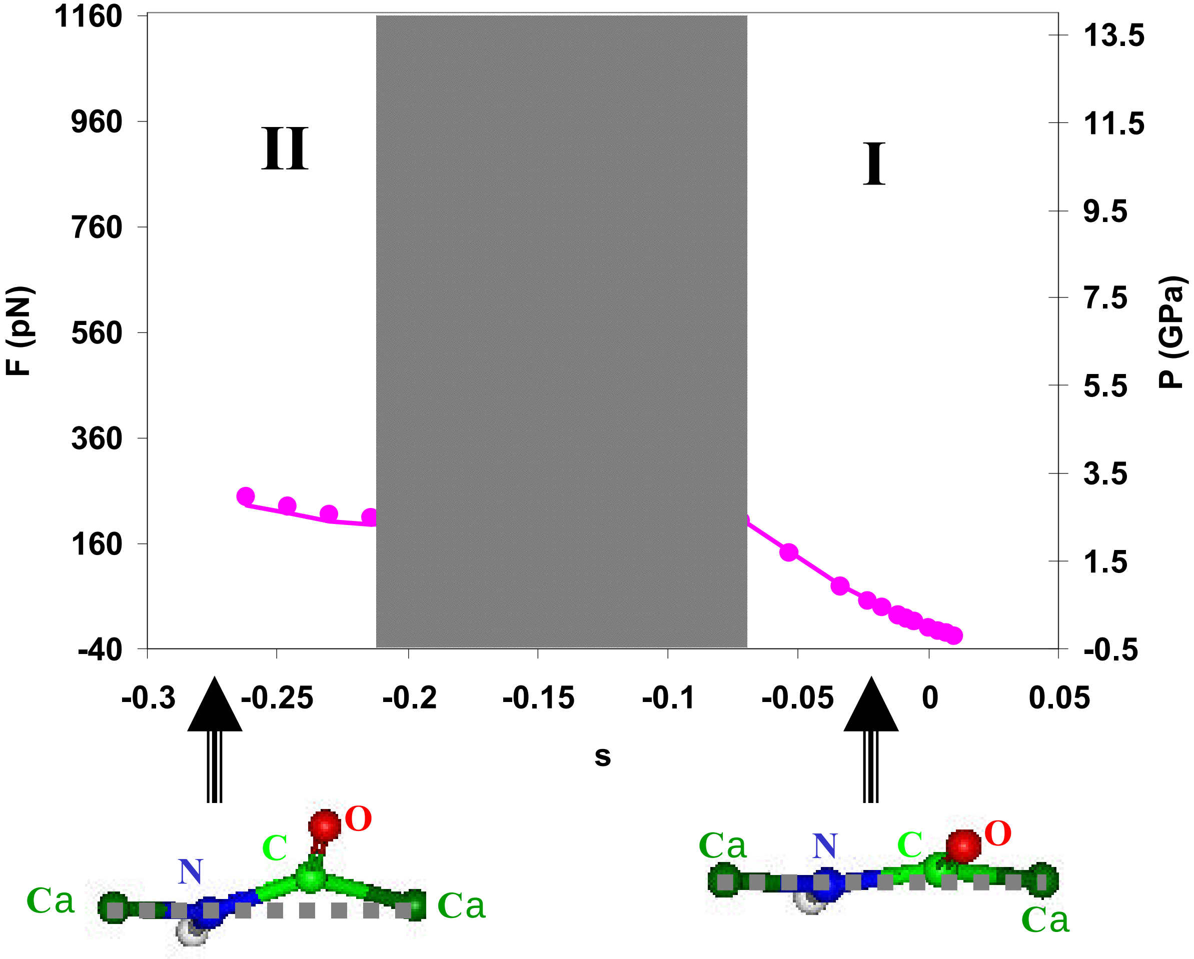
Carbon Pyramidalization





At high strain carbon pyramidalizes

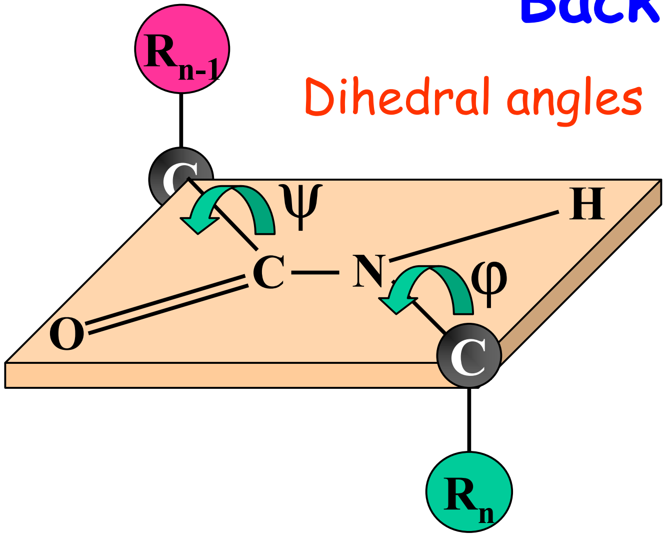
Strain Induced First Order Phase Transition

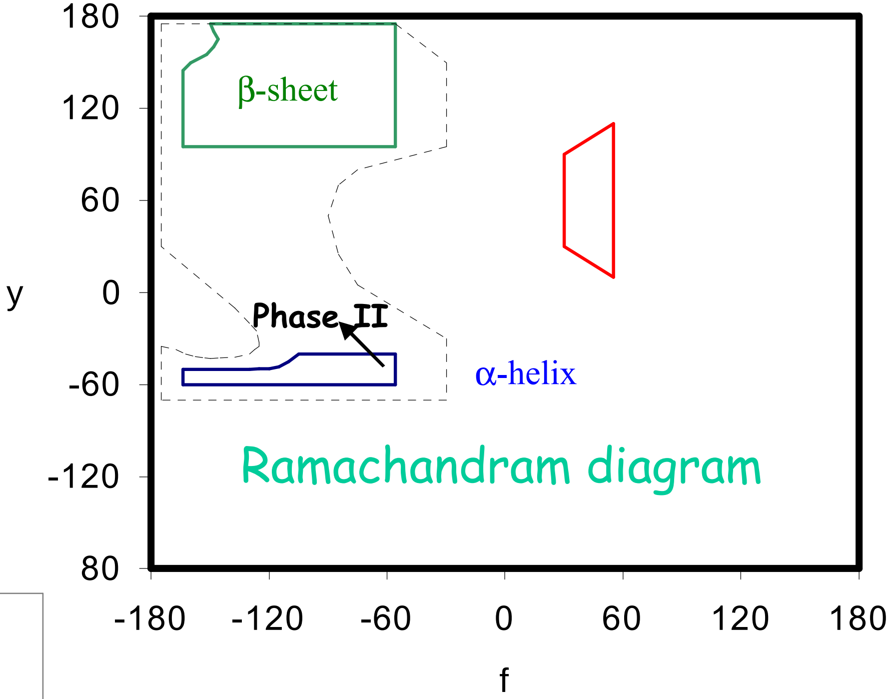


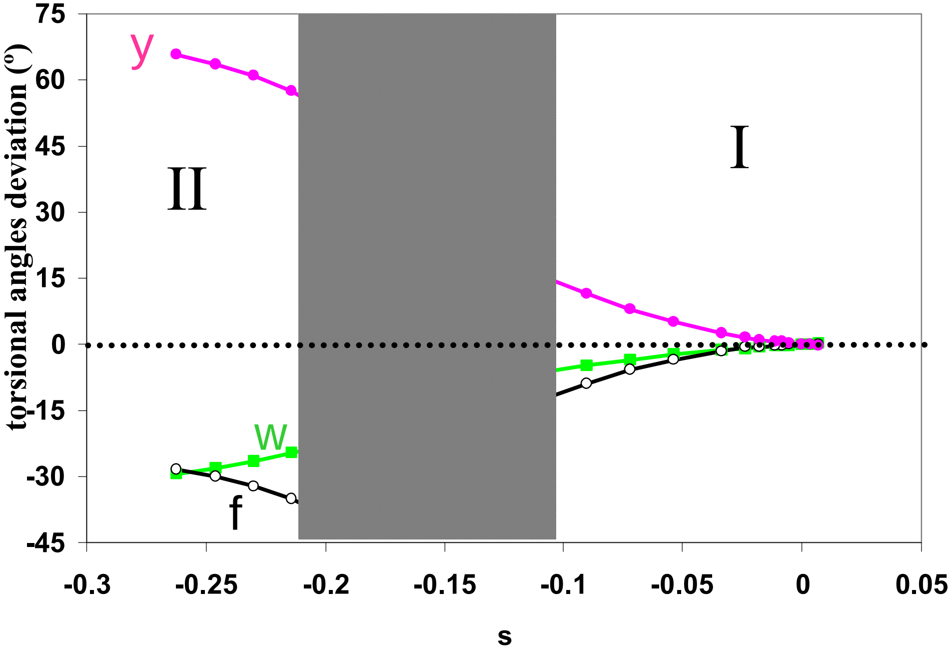
Highly distorted peptide unit
Broken hydrogen bonds
single bond like state

Planar peptide unit
hydrogen bond strength ~ 9 kcal/mol
zwitterionic like state

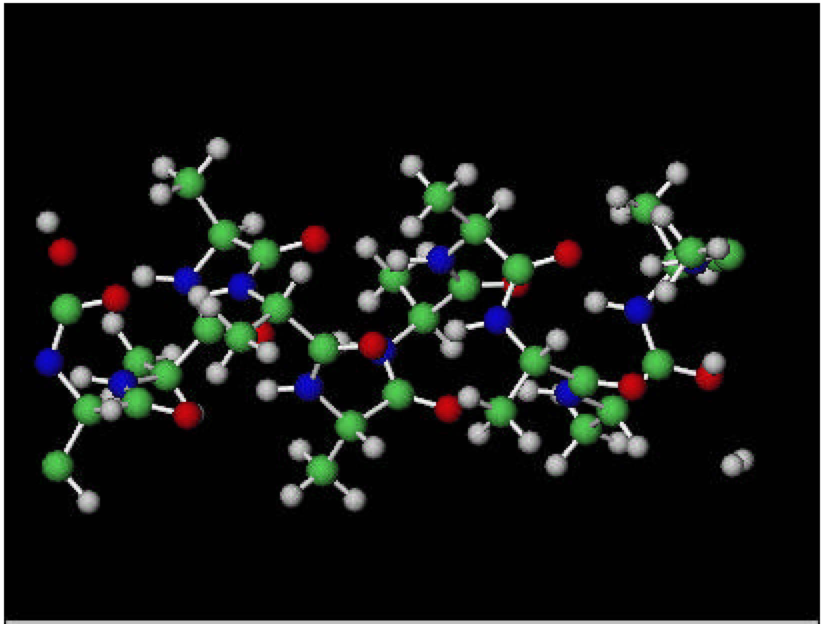
Backbone Response to Strain



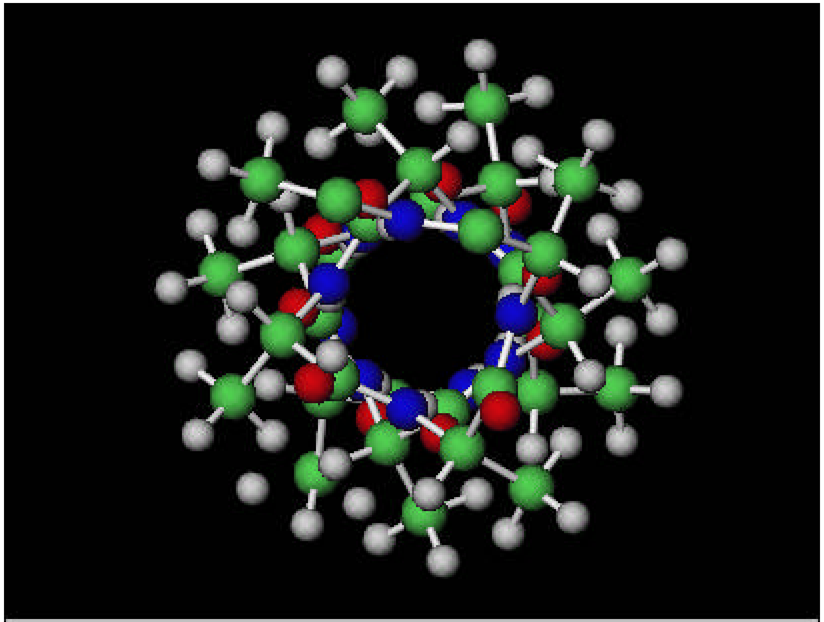




Phase II is out of the helical region in a Ramachandran diagram



nsimu6

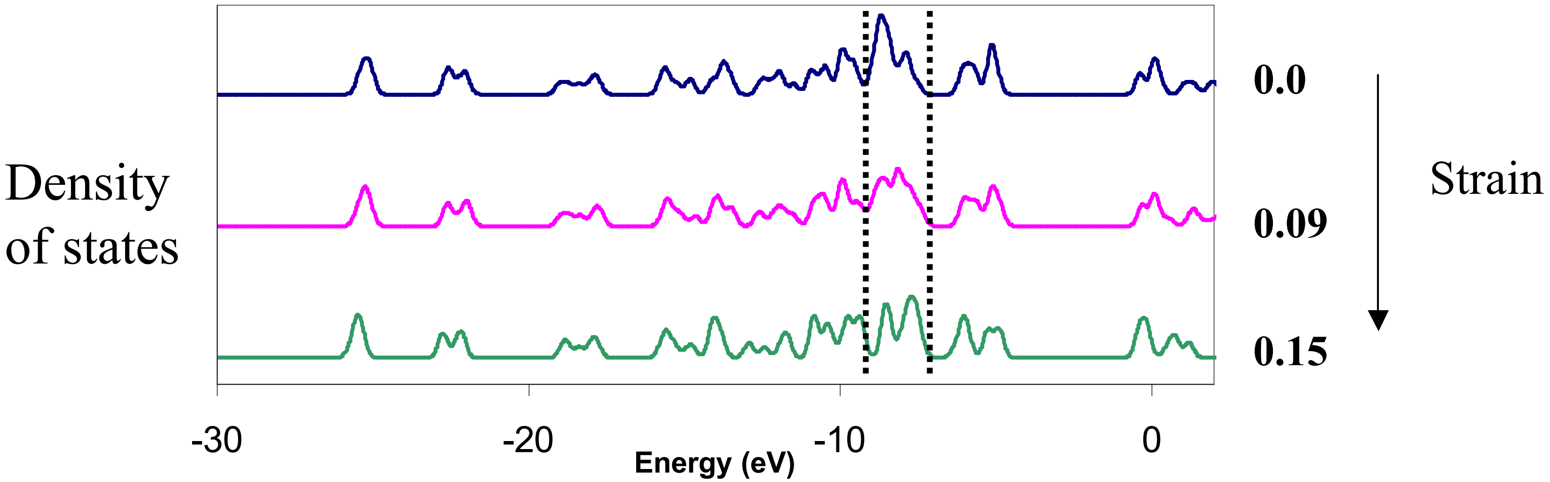


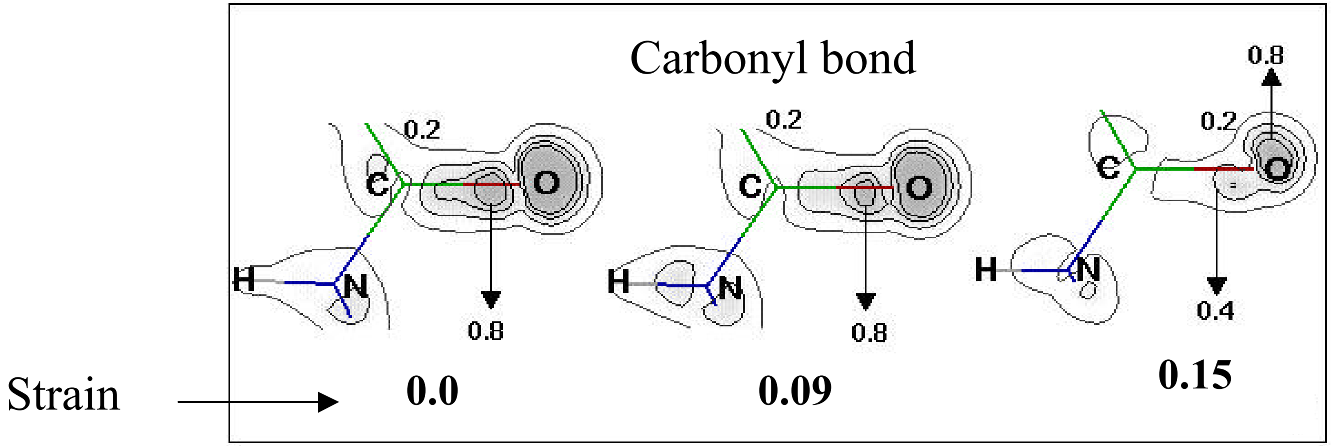
nsimu7

Conclusions

- The DFT plane-wave pseudopotential method is a reliable tool to study biological systems
- PBE describes the hb strength and cooperativity within an error bar of 1 kcal/mol
- Cooperative effects within an infinite a-helix strengthen the hb by a factor of two
- Compressive strain stabilizes the zswitterionic form of a peptide unit
- At high compressive strain helices undergo a first order phase transition
- The interplay between hydrogen bond strength and carbonyl pyramidalization drives the phase transition

Electronic structure response to compression

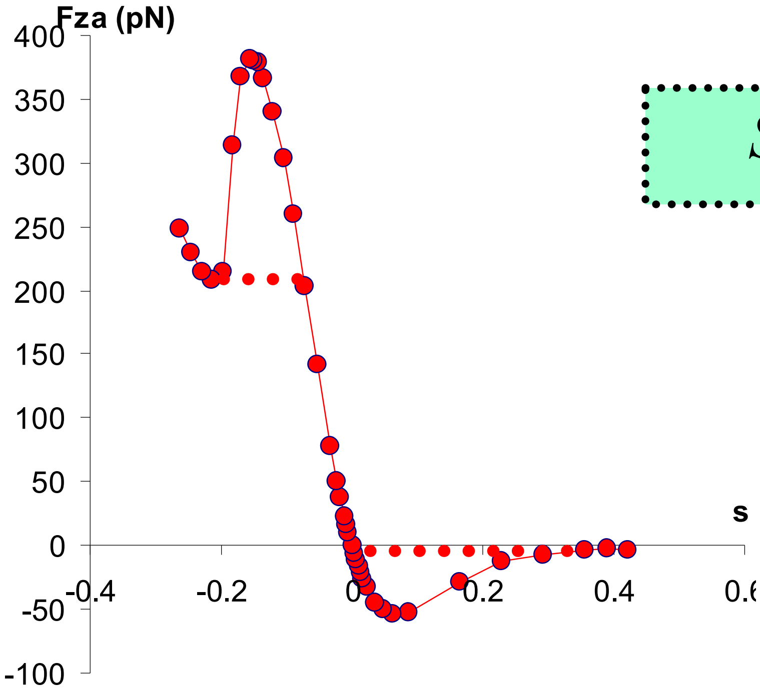




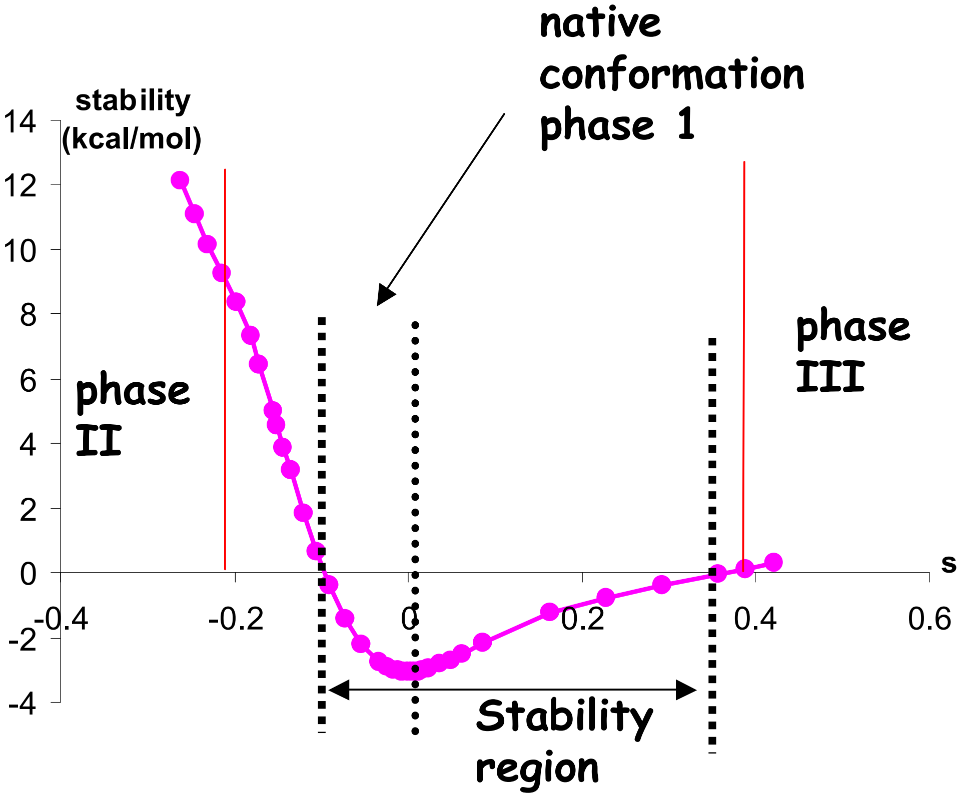
Strain induces a qualitative change in the electronic charge density at the carbonyl bond: (sp^2 Þ sp^3 like hybridization)!

Helix stability

$$Stability = \mu_a - \mu_{FES} = E_{strain} - E_{hb}$$



Under tension
also a phase
transition
is observed



native
conformation
phase 1

phase
II

phase
III

Stability
region