The Importance of Cooperative Interactions In Hydrogen-Bonding Interactions

What are Hydrogen Bonds?

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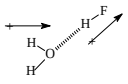
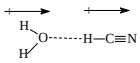
Are Hydrogen Bonds Electrostatic?





Water and HCN form a H-bonding dimer that is consistent with a dipole-dipole electrostatic interaction

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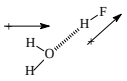
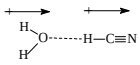
Water and HF form a H-bonding dimer which is non planar. This cannot be explained by a dipole-dipole electrostatic interaction





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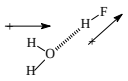

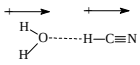

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Electrostatic interactions cannot explain all H-bonding

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Materials:
- Crystals
- Aggregates
- Proteins

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Computer experiments
- Can do experiments with computer that would be impossible in laboratory.

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Peptides are like solid as the H-bonds have fixed orientations

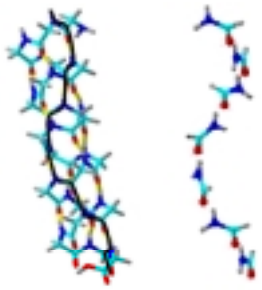
Cooperativity in H-Bonded Systems Modeling Elements of the Secondary Structure of Proteins

Hydrogen bonds are among the strongest interactions of non-covalent nature. They play an important role determining conformations and binding in many biological systems. An understanding of the quantitative aspects of the hydrogen bonding may lead to the building of more precise models for the processes of biological importance.

In this study we present data that reveals a high degree of cooperativity for hydrogen bonding

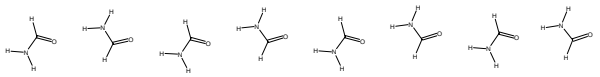
- in formamide aggregates that mimic the H-bonding in helices and antiparallel β-sheets
- in the various 3_{10}- and α-helical structures
- In models of β-sheets

H-bonding chains in the



One of the three H-bonding chains in an α-helix. The H-bonding chains turn in the opposite direction to the covalent bonds in the polypeptide because there are 3 H-bonding chains

H-Bonding Formamide Chains



1 2 3 4 5 6 7 8 ...

•The repeating unit is two formamides

•We shall define the numbering scheme from the left:

the terminal NH_2 is formamide number 1

Kobko, N.; Paraskevas, L.; del Rio, E.; Dannenberg, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 4348

Kobko, N.; Dannenberg, J. J. *J . Phys . Chem. A* **2003**, *107*, 10389.

Methods

Geometric optimization of all the formamide aggregates was conducted at the B3LYP/D95** level using GAUSSIAN98 suite. Full CP-optimizations were performed for the flat chains of up to five formamides.

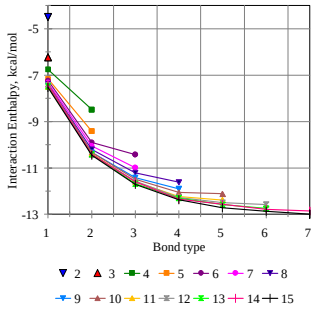
The H-bond interaction energy for each H-bond within an aggregate of N formamides was calculated according to the following equation:

$$E_{inter} = E_N - (E_m - E_{(n-m)}) + ZPVE + BSSE$$

where m and (n-m) are the sizes of the two smaller aggregates that remain after the H-bond is broken; ZPVE and BSSE are the corrections for one H-bond.

Kobko, N.; Dannenberg, J. J. *J . Phys . Chem. A* **2003**, *107*, 10389

H-bonding enthalpies for flat formamide chains



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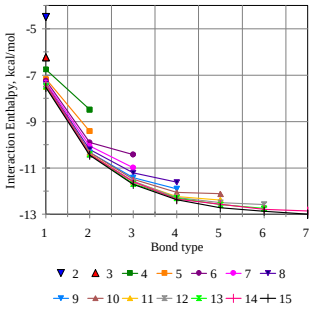

The H-bonds become significantly stronger as the chain becomes longer

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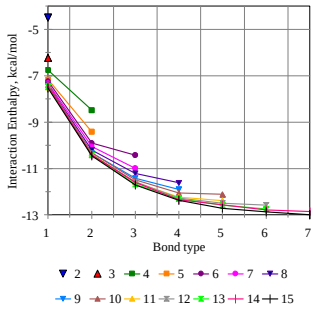

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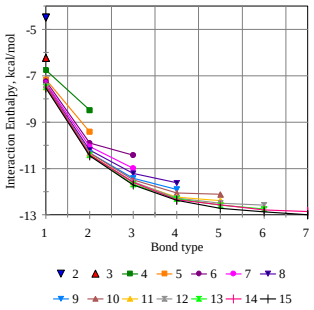

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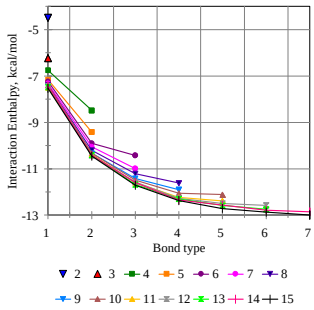

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Cooperativity is not primarily electrostatic

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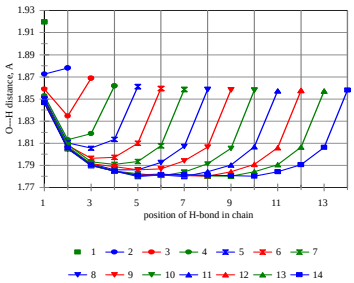
H-bonding distances in flat formamide chains



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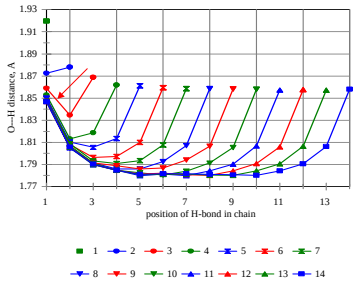

There are pairs of H-bonds that have the same energies but different O…H distances

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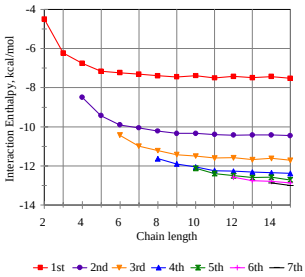

Interaction enthalpies for H-bonds organized by chain length for H-bond types (k) indicated by the symbols.

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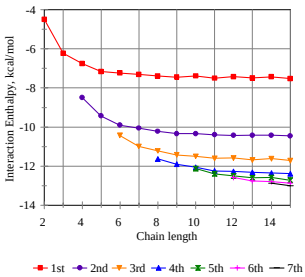

The energies of each type of H-bond reach individual asymptotic limits

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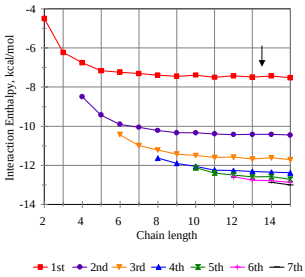

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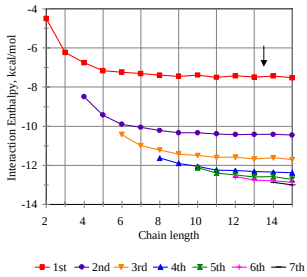

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They are most obvious when the H-bond energy is close to its limiting value

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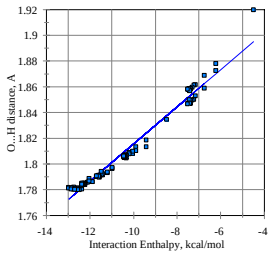
H-bonding distances vs. interaction energies of the terminal and middle hydrogen bonds in flat formamide chains



H-bonding distances vary with the calculated H-bond energies in a regular quasi-linear manner.

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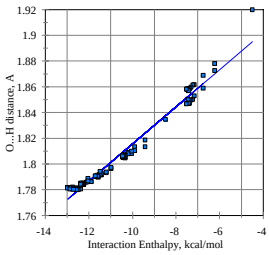

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We should also note that there can be two non-equivalent H-bonds that have the same enthalpy but different length.

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Helical Peptides

Conformers of glycine polypeptide

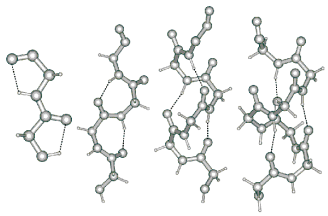

Fig.2 Ref.12b Schematic drawing of the conformers of glycine

1. repeating unit of the C5 conformer (flat);

2. two repeating units of the C7 conformer;

3. two repeating units of the 3_{10} helix conformer;

4. one repeating unit of the α-helix (or 4_{13} helix) conformer (seven residues).

Hydrogen bonds are shown by dotted lines.

ONIOM Method

•System is divided into up to three levels (high, medium and low). We use only two.

Morokuma and Frisch

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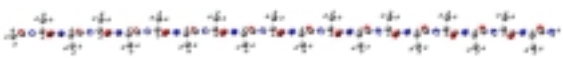
•ONIOM energy is equal to the entire system calculated at low level with the polyglycine calculated at the high level substituted for the low-level

Morokuma and Frisch

Comparison of secondary structures of acetyl(ala)$_N$NH$_2$ as a function of N

β-Strand of acetyl(ala)$_{18}$NH$_2$

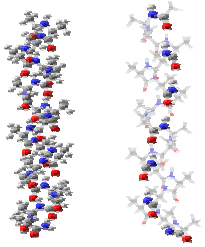


Wieczorek, R.; Dannenberg, J. J. **2004**, *126, 14198-205.*

α-Helix of acetyl(ala)$_{18}$NH$_2$

Wieczorek, R.; Dannenberg, J. J. **2004**, *126, 14198-205.*

α-Helix of acetyl(ala)$_{18}$NH$_2$



Chain 1

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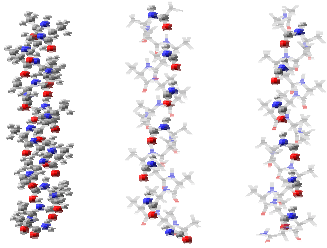

Chain 1 Chain 2

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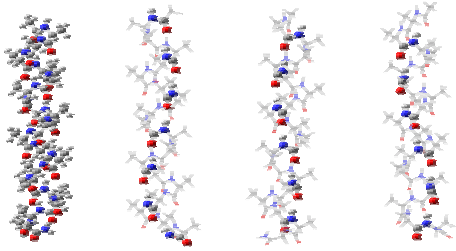
α-Helix of acetyl(ala)$_{18}$NH$_2$



Chain 1 Chain 2 Chain 3

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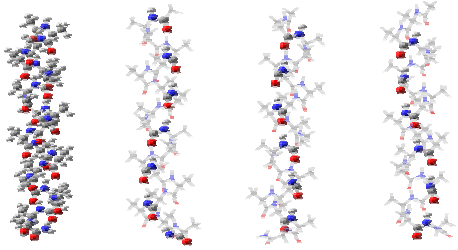
α-Helix of acetyl(ala)$_{18}$NH$_2$



	Chain 1	Chain 2	Chain 3
H-bonds:	6	5	5

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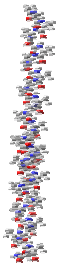
3_{10}-Helix of acetyl(ala)$_{18}$NH$_2$



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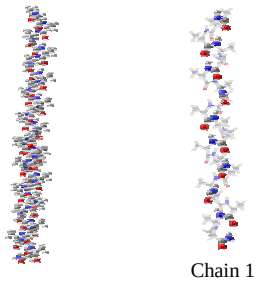
3_{10}-Helix of acetyl(ala)$_{18}$NH$_2$



Chain 1

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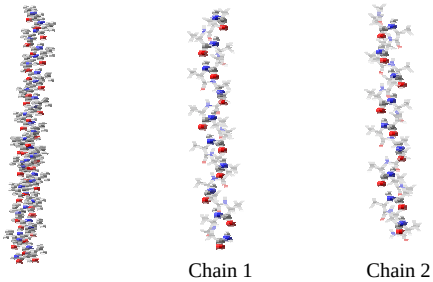
3_{10}-Helix of acetyl(ala)$_{18}$NH$_2$



Chain 1 Chain 2

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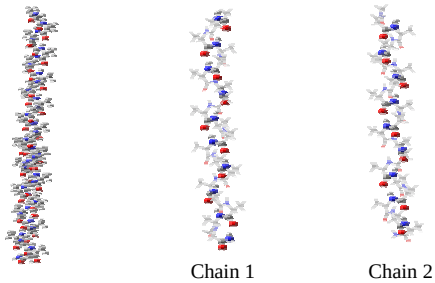
3_{10}-Helix of acetyl(ala)$_{18}$NH$_2$



H-bonds Chain 1 Chain 2
9 8

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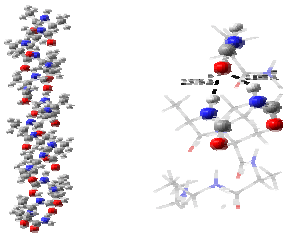
α-Helix of acetyl(ala)$_{18}$NH$_2$



Bifurcated H-bonds at acetyl end

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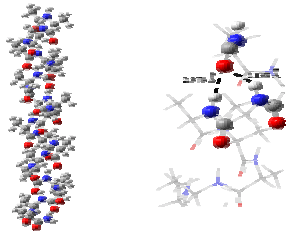
α-Helix of acetyl(ala)$_{18}$NH$_2$



Bifurcated H-bonds at acetyl end

1 α-helical

1 3_{10}-helical

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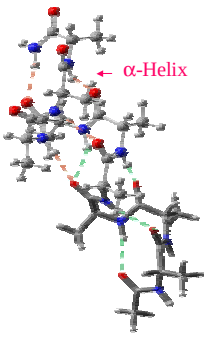
For acetyl(ala)$_N$NH$_2$:

α-helices are only stable for N=8,10 and 12 or greater

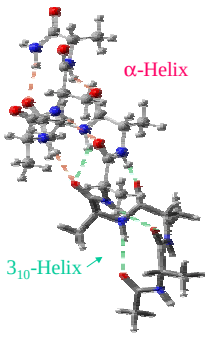
N=6,7,9,11 are mixed helices

Helix of acetyl(ala)$_9$NH$_2$



Wieczorek, R.; Dannenberg, J. J. **2004**, submitted for publication.

Helix of acetyl(ala)$_9$NH$_2$



Wieczorek, R.; Dannenberg, J. J. **2004**, submitted for publication.

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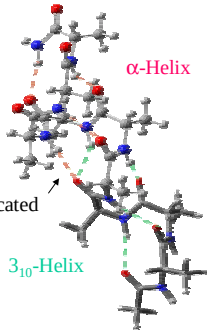


Wieczorek, R.; Dannenberg, J. J. **2004**, submitted for publication.

Relative energies of capped polyalanines in different secondary structures

Relative energies of capped polyalanines in different secondary structures

Acetyl(ala)$_N$NH$_2$

N varies from 2 to 18

Relative energies of capped polyalanines in different secondary structures

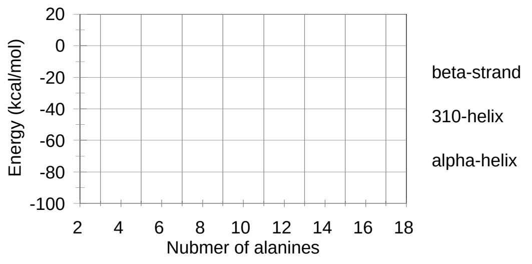
Acetyl(ala)$_N$NH$_2$

N varies from 2 to 18

We calculate the energy of polymerization for each of three secondary structures using the following relationship:

$$E_{polymerization} = E_{peptide} - E_{CH_3COOH} - E_{NH_3} - NE_{alanine} - (N+1)E_{H_2O}$$

Energies of Reaction



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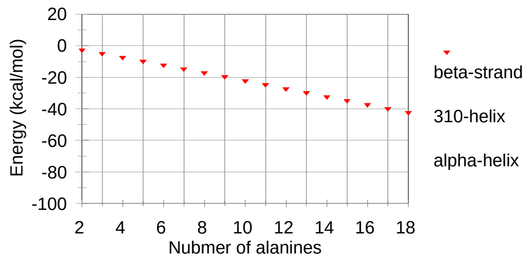
Energies of Reaction



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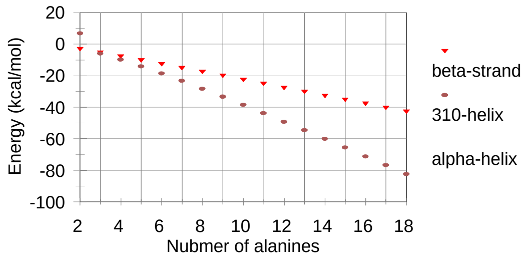
Energies of Reaction



Wieczorek, R.; Dannenberg, J. J., *J. Am. Chem. Soc.* **2004,** *126*, 14198-205

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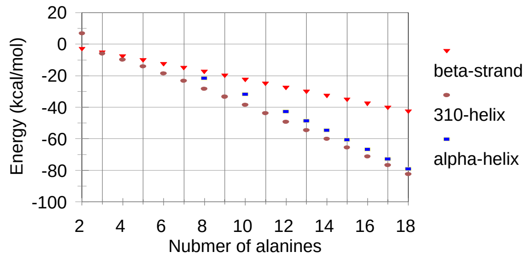
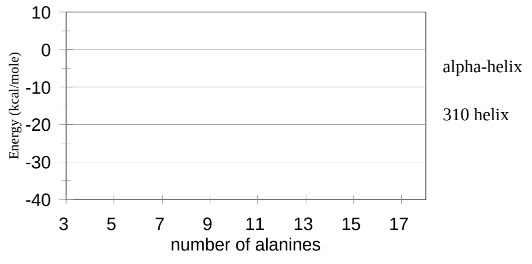


Wieczorek, R.; Dannenberg, J. J., *J. Am. Chem. Soc.* **2004,** *126*, 14198-205

Energy vs beta-strand



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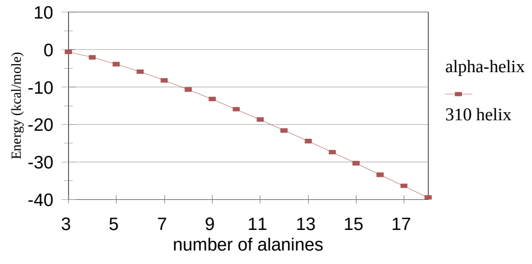

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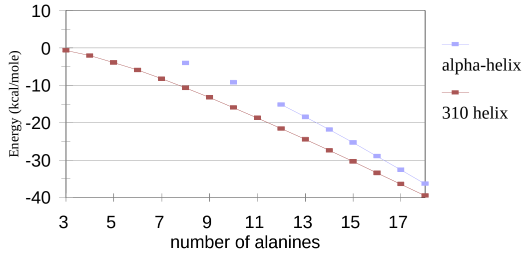

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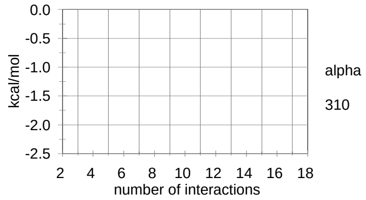
Energy per Peptide Interaction

relative to beta-strand



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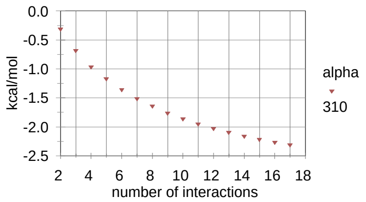

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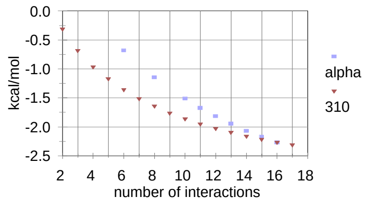

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Incremental Stabilities

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Incremental Stabilities

The difference in the $E_{polymerization}$ between $Ac(ala)_NNH_2$ and $ac(ala)_{N-1}NH_2$

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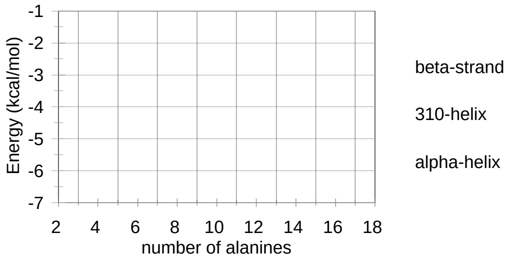
Incremental stabilities



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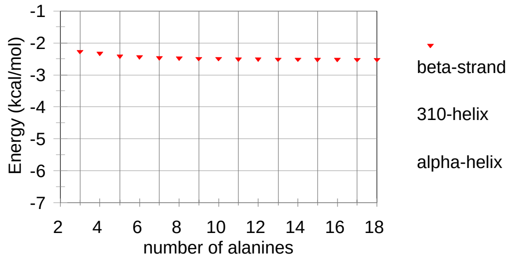

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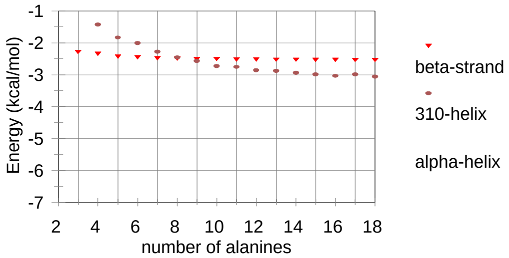

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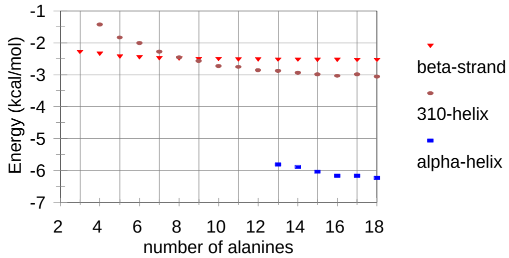

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Helical strain per H-bond

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Helical strain per H-bond

Peptide backbone must accommodate the H-bonds

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Peptide backbone must accommodate the H-bonds

This induces 'helical' strain

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Peptide backbone must accommodate the H-bonds

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We calculate the helical strain as follows:

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1) We estimate the interaction energies of each H-bonding chain of the helix from the formamide chains of the same lengths

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3) We make an approximate vibronic correction
4) We divide by the number of H-bonds in the system

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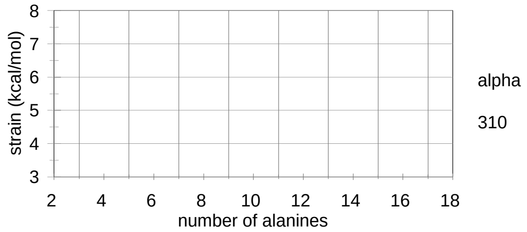
Helical Strain

Per H-Bond



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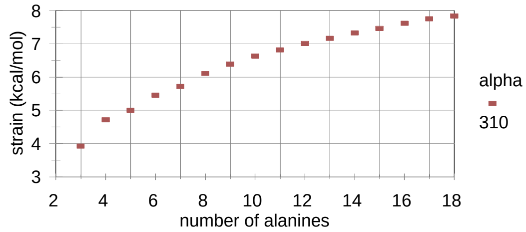
Per H-Bond



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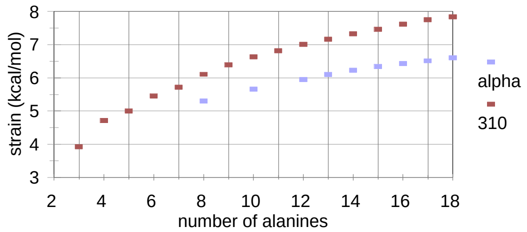
Per H-Bond



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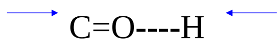
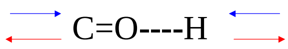
Stronger H-bond

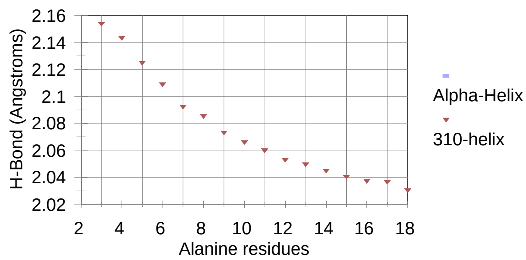


Stronger H-bond



More strain

Average O...H Distance



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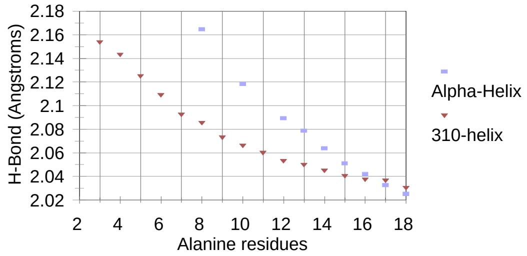

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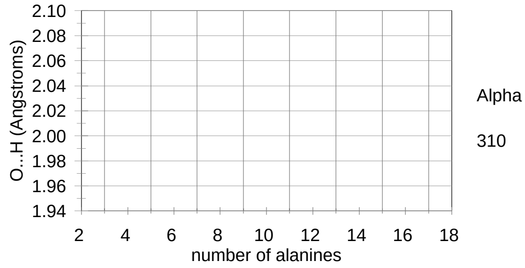
Minimum O...H Distances in Helices



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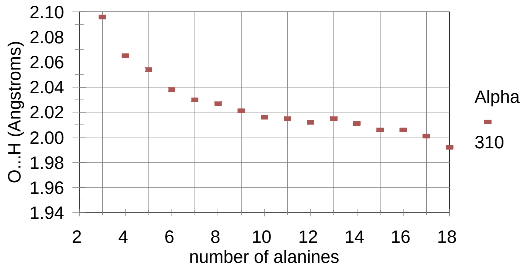

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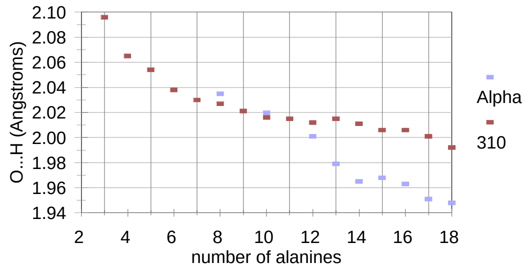

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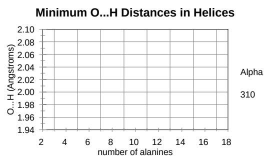

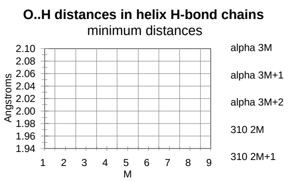

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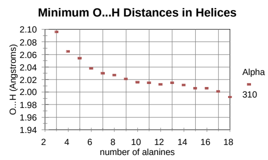

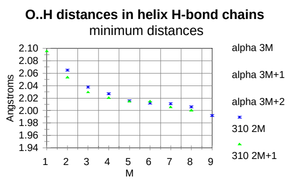

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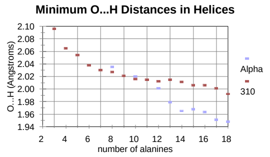

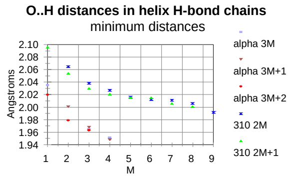

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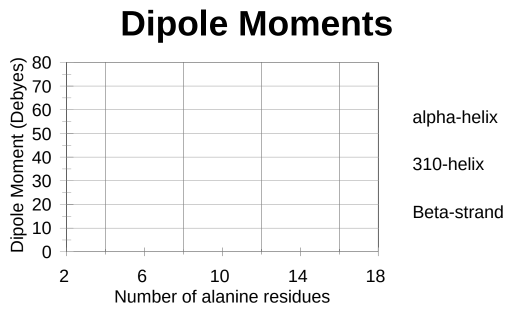

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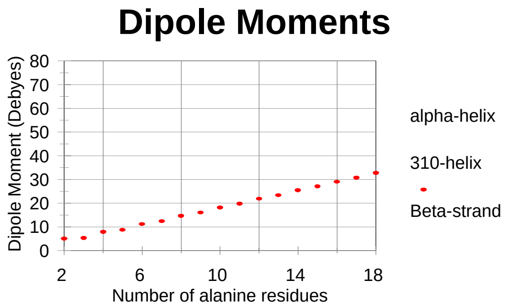

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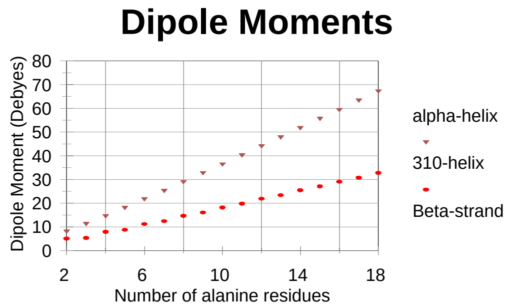

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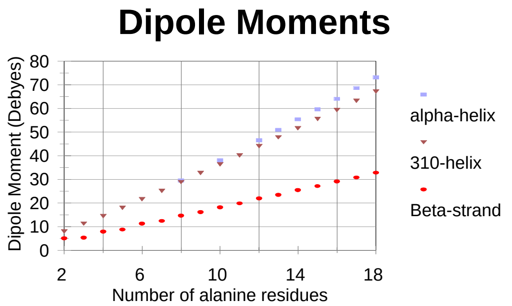

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Why are H-bonds in α-helices more cooperative?

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All of these factors interact with each other

Protonation of Peptides

Small peptides are zwitter ionic

Protonation of Peptides

Small peptides are zwitter ionic

Are helical peptides zwitter ions?

Protonation of Peptides

Small peptides are zwitter ionic

Are helical peptides zwitter ions?

If so, they should protonate most easily on NH_2

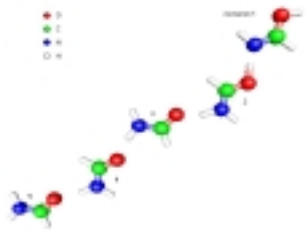
Protonation of Peptides

Models:

Formamide chains

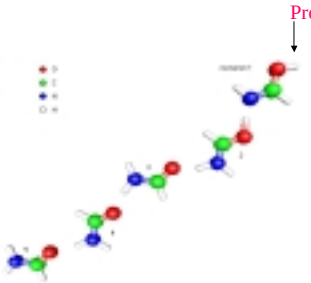
α-helices

Protonated Formamide Chains



Moisan, S.; Dannenberg, J. J. *J . Phys . Chem . B* **2003**, *107*, 12842

Protonated Formamide Chains



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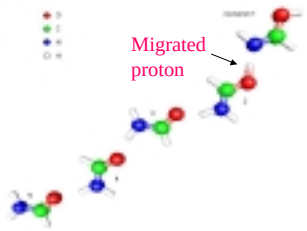

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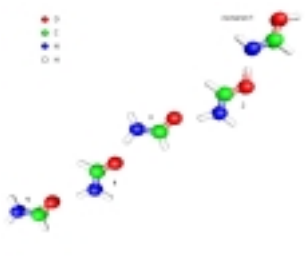

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Protonation at NH2 breaks H-bond between protonated and next formamide

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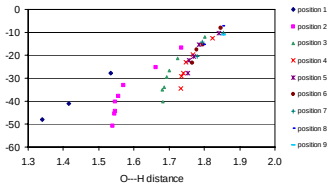
H-bond enthalpies at 298 K as a function of O...H distance for protonated formamide chains.



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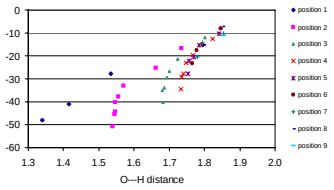

The relationship between O…H and H-bond strength is no longer linear

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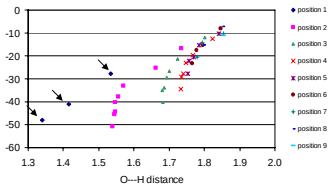

The relationship between O…H and H-bond strength is no longer linear

The O…H distance for position 1 decreases markedly until the proton migrates

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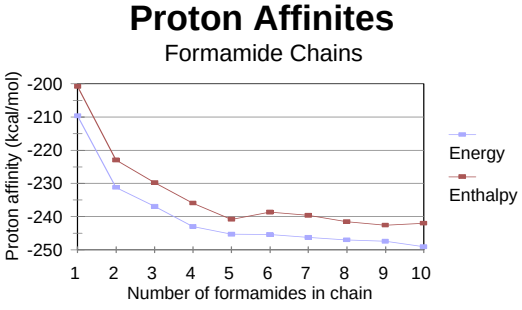
Protonated Formamide Chains



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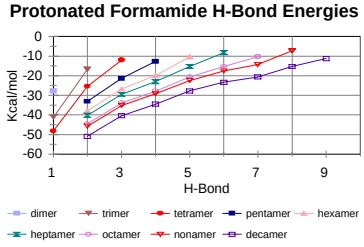
H-Bond Energies in Protonated Formamide Chains



Proton in first H-bond is transferred to second formamide in aggregates with five or more monomers

Moisan, S.; Dannenberg, J. J. *J . Phys . Chem . B* **2003**, *107*, 12842

Protonation of Peptides

Models:

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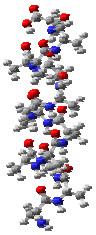
Proton affinities of ala_{14}



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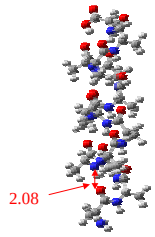

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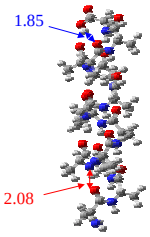

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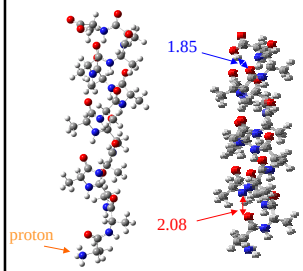

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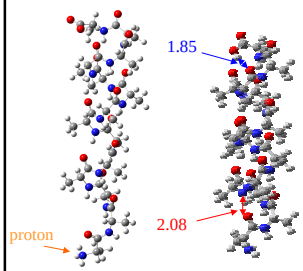

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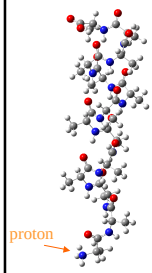

243.1

Wieczorek, R.; Dannenberg, J. J., *J. Am. Chem. Soc.* **2004,** *126,* 12278-9

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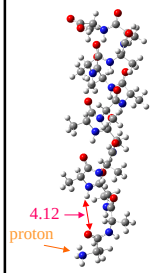

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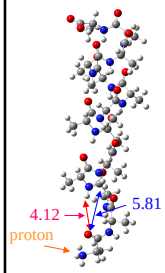

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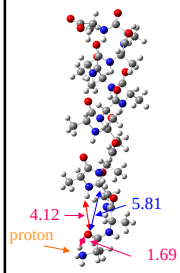

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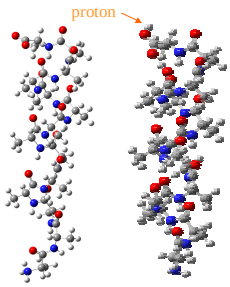

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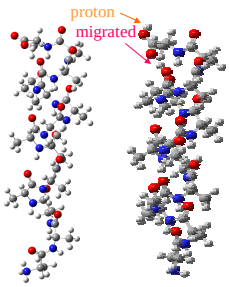

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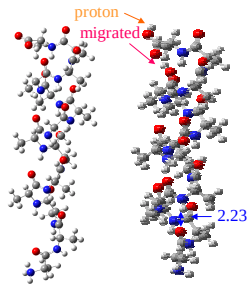

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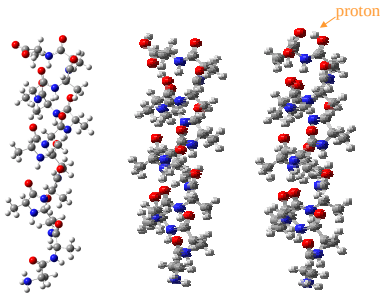

243.1 259.1 259.4

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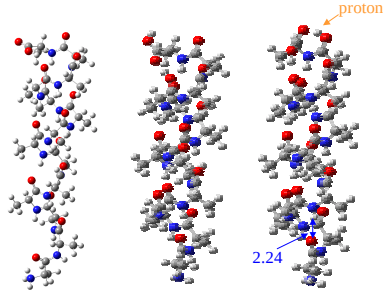

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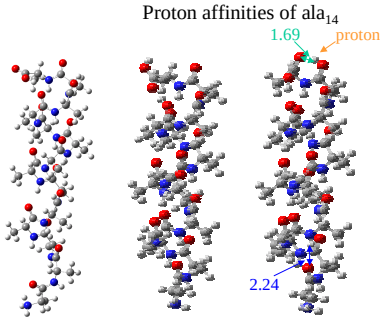

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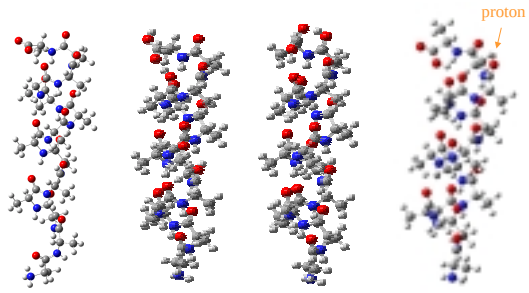

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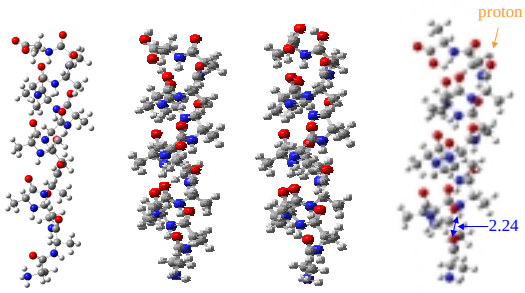

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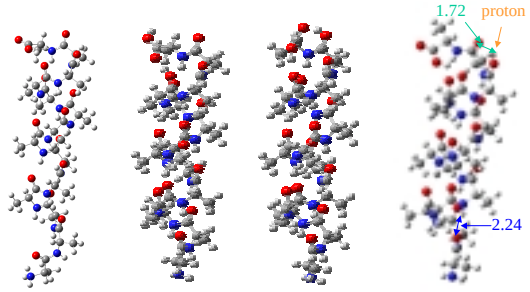

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Comparison of proton affinities of ala_{14} and ala_{17}

kcal/mol

Ala's	COOH	1st C=O	2nd C=O	NH_2
8	259.1	259.3	258.5	243.1
14	272.3	274.0	274.7	212.6
17	276.5	278.0	279.0	202.5

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β-Sheets

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β-strands that are models of two glycines

β-Sheets

β-strands that are models of two glycines, four glycines

β-Sheets

β-strands that are models of two glycines, four glycines and two glycines with a CH_2CH_2 spacer

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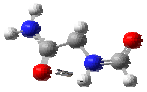
Two and four stranded sheets

β-Sheets

β-strands that are models of two glycines, four glycines and two glycines with a CH_2CH_2 spacer

Two and four stranded sheets that maintain a center of symmetry (C_{2H})

β-Sheets of polyglycines



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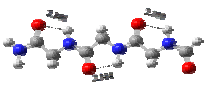

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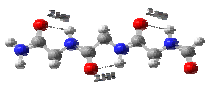

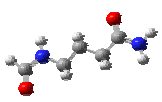

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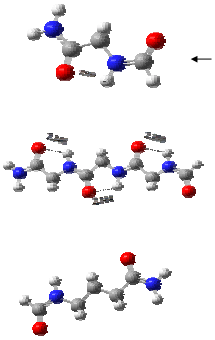

GLY2

GLY4

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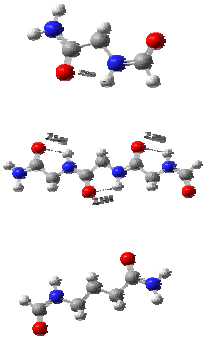

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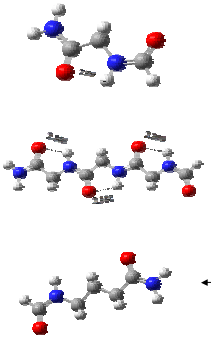

GLY2

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GLY2C

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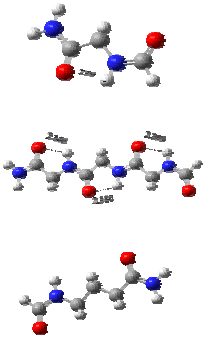

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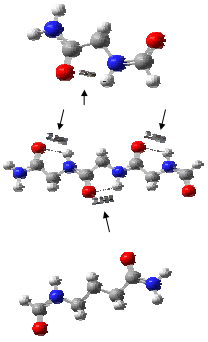
β-Sheets of polyglycines

C5 H-bonds:
GLY2
GLY4
Not GLY2C



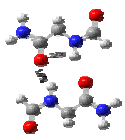
GLY2

GLY4

GLY2C

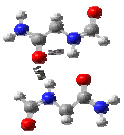
Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

Dimers of GLY2



Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

Dimers of GLY2



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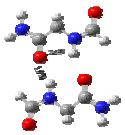
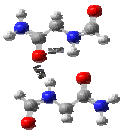
Dimers of GLY2

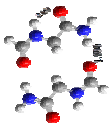


ΔH: -4.85 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

Dimers of GLY2

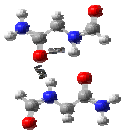


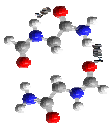


ΔH: -4.85 kcal/mol -13.99 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

Dimers of GLY2





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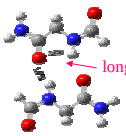

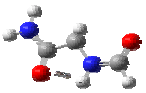

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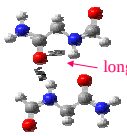

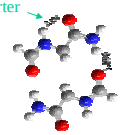

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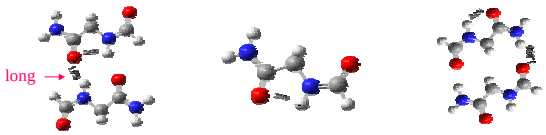

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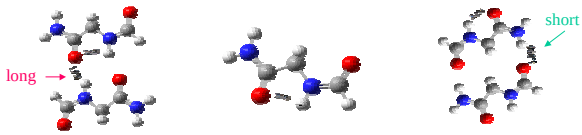

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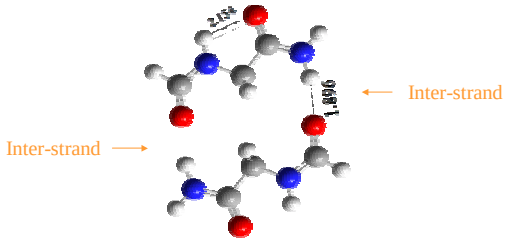

Cyclic H-bonding chain with 4 H-bonds

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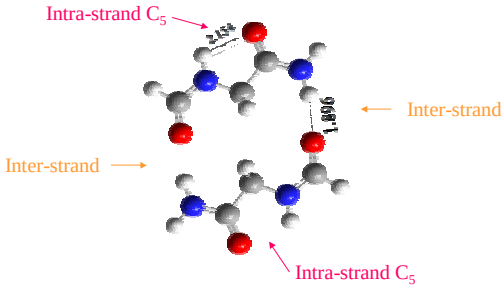
Dimers of GLY2



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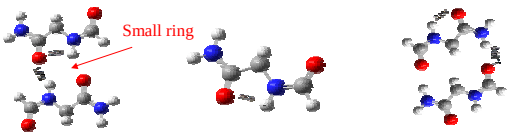

ΔH: -4.85 kcal/mol -13.99 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

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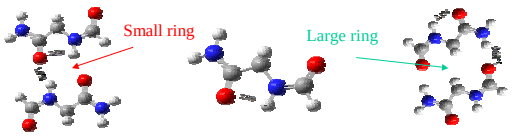

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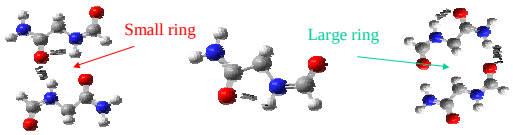
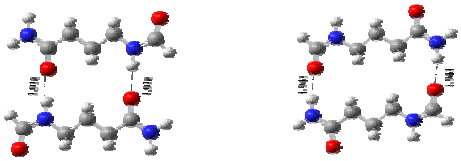


ΔH: -4.85 kcal/mol -13.99 kcal/mol

Difference in ΔH = ~9 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

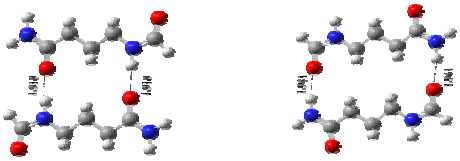
Dimers of GLY2C



ΔH: -7.38 kcal/mol -9.18 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

Dimers of GLY2C



ΔH: -7.38 kcal/mol -9.18 kcal/mol

Difference in ΔH = 1.8 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

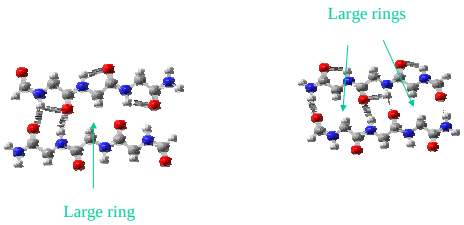
Dimers of GLY4

ΔH: -12.96 kcal/mol 22.91 kcal/mol

Difference in ΔH = ~9 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

Dimers of GLY4



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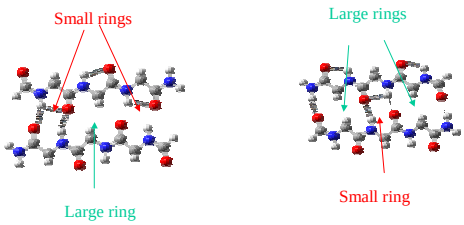
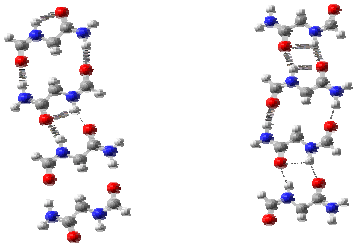


ΔH: -12.96 kcal/mol 22.91 kcal/mol

Difference in ΔH = ~9 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

Tetramers of GLY2



ΔH:	-36.74 kcal/mol	-27.13 kcal.mol
Cooperativity:	3.91 kcal/mol	3.44 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

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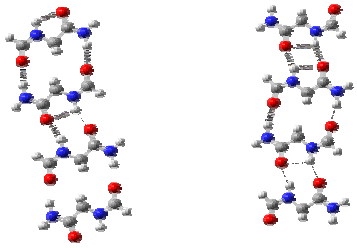

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Difference in ΔH = ~9 kcal/mol

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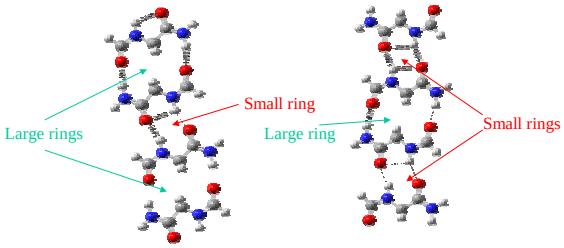
Tetramers of GLY2



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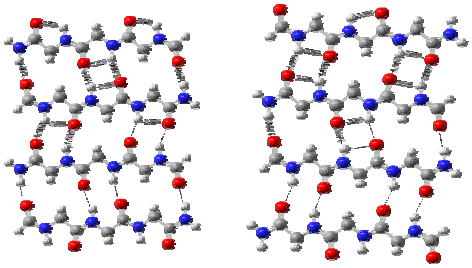
Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

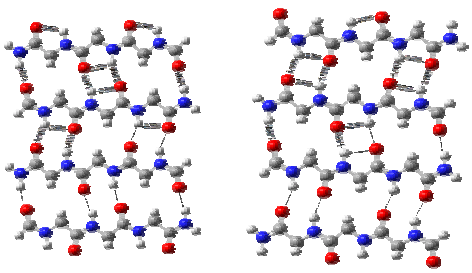
Tetramers of GLY4



ΔH:	-58.98 kcal/mol	-46.37 kcal.mol
Cooperativity:	0.20 kcal/mol	-2.46 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

Tetramers of GLY4

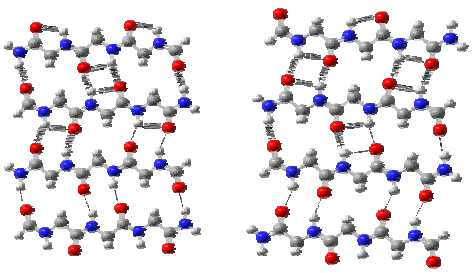


ΔH:	-58.98 kcal/mol	-46.37 kcal.mol
Cooperativity:	0.20 kcal/mol	-2.46 kcal/mol

Difference in ΔH = ~12 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

Tetramers of GLY4

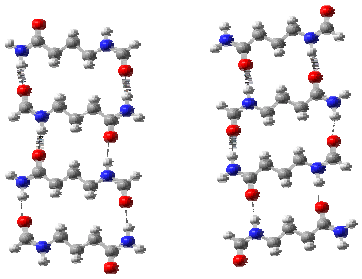


ΔH:	-58.98 kcal/mol	-46.37 kcal.mol
Cooperativity:	0.20 kcal/mol	-2.46 kcal/mol

Difference in ΔH = ~12 kcal/mol or ~-9 without cooperativity

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J . Phys. Chem. A* **2004,** *108*, 9205-12.

Tetramers of GLY2C



ΔH:	-32.35 kcal/mol	-31.19 kcal.mol
Cooperativity:	6.61 kcal/mol	7.25 kcal/mol

Viswanathan, R.; Asensio, A.; Dannenberg, J. J., *J. Phys. Chem. A* **2004,** *108*, 9205-12.

Little or no Cooperativity apparent in β-sheets

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Due to the weakening and strengthening of intra-strand C5 H-bonds

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Many proteins have only 2-stranded β-sheets

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Many proteins have only 2-stranded β-sheets

Why do others have extended β-sheets?

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Implications for amyloid diseases:

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Why do others have extended β-sheets?

Implications for amyloid diseases:

Which sequences will allow H-bond cooperativity?

Summary

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Chains of amide H-bonds are highly cooperative

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Cooperativity is manifest in 3_{10}-, α-helices and β-sheets

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α-helices are not zwitter ions (at least in gas phase)

Understanding H-bond cooperativity is essential for predicting protein folding

Coworkers

Nadya Kobko
Robert Wieczorek
Pedro Salvador
Raji Viswanathan
Amparo Asensio
Sandy Moisan
Artem Masunov
Midas Tsai

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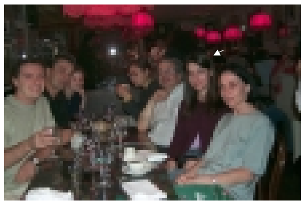

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