

# Molecular Interactions

(Noncovalent Interactions)

and the Behaviors of Biological Macromolecules

[ww2.chemistry.gatech.edu/~lw26/structure/molecular\\_interactions/mol\\_int.html](http://ww2.chemistry.gatech.edu/~lw26/structure/molecular_interactions/mol_int.html)

Loren Dean Williams

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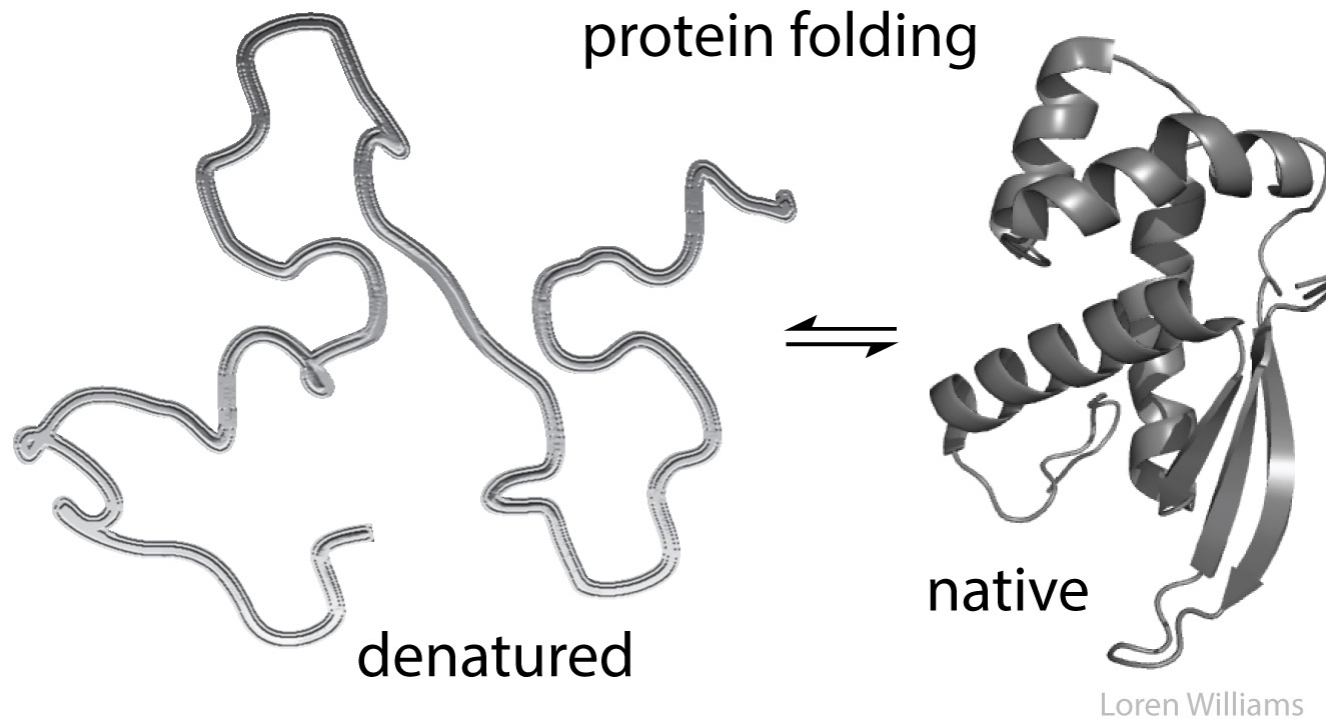
## TABLE OF CONTENTS

- A** [Introduction](#)
  - A1** [What are molecular interactions?](#)
  - A2** [Folding and assembly of biological macromolecules](#)
  - A3** [Note on van der Waals interactions](#)
- B** [Short range repulsion](#)
- C** [Electrostatic interactions](#)
  - C1** [Ion Pairs in Proteins](#)
- D** [Dipolar interactions](#)
  - D1** [Electronegativity and molecular dipoles](#)
  - D2** [Dipole-dipole interactions](#)
  - D3** [Dipole-induced dipole interactions](#)
  - D4** [Charge-dipole interactions](#)
- E** [Fluctuating dipoles \(London Dispersion\)](#)
- F** [Cation- \$\pi\$  interactions](#)
- G** [Hydrogen bonding](#)
  - G1** [Anatomy of a hydrogen bond](#)
  - G2** [Geometry](#)
  - G3** [Water](#)
  - G4** [Ammonia](#)
  - G5** [Cooperativity](#)
  - G6** [Molecular recognition and assembly](#)
  - G7** [Template-directed catalysis](#)
- H** [Water - the liquid of life](#)
  - H1** [The biochemistry of water](#)
  - H2** [Molecular structure of water in the crystalline state](#)
  - H3** [Molecular structure of water in the liquid state](#)
  - H4** [Empirical description of the hydrophobic effect](#)
  - H5** [Molecular basis of the hydrophobic effect](#)
  - H6** [Thermodynamic basis of the hydrophobic effect](#)
- I** [Base stacking and base pairing](#)
- J** [Counterion release from nucleic acids](#)
- K** [Biological Polymers](#)
- L** [About this document](#)

# Molecular Interactions

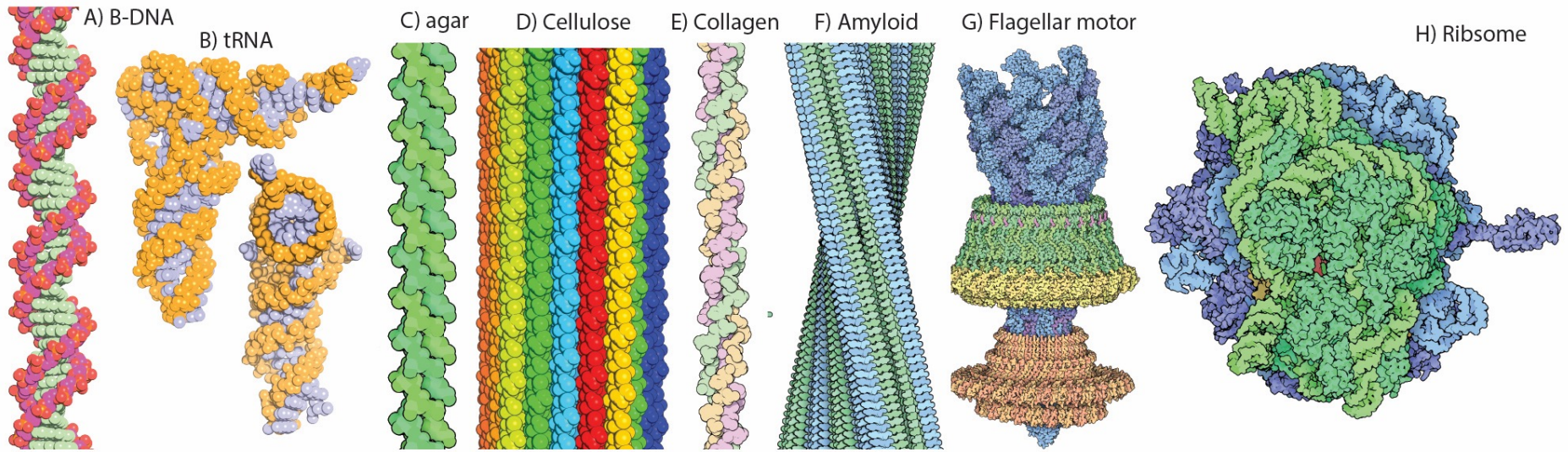
Molecular Interactions are attractive or repulsive forces *between molecules* and between non-bonded atoms. The processes of melting, boiling, sublimation, unfolding, strand separation and disassembly involve changes in molecular interactions.





Protein folding is the conversion from a denatured state (a random coil) to a native state. On the right-hand side the arrows are  $\beta$ -strands and the coils are  $\alpha$ -helices.

Huge numbers of molecular interactions within a protein native state are opposed by huge numbers of intermolecular interactions in the denatured state (with surrounding water molecules).



**Molecular interactions drive assembly of biopolymers assemblies.** A) DNA, a double-helical polydeoxy-ribonucleotide. B) tRNA, a folded polyribonucleotide. C) Agar, a triple-helical polysaccharide. D) Cellulose, a polysaccharide assembly composed of many strands. E) Collagen, a triple-helical polypeptide that forms fibers. F) A helical assembly of  $\beta$ -sheet polypeptide. G) A flagellar motor, which is an assembly of five distinct types of polypeptide chains. H) The ribosome, a large assembly of around 50 polypeptide chains and over 3,000 deoxyribonucleotides. Some of these images were produced by David S. Goodsell and the RCSB PDB

# Types of Molecular Interactions

- Short range repulsion<sup>a,b</sup>
- Electrostatic interactions (between species with formal charge)
- Dipolar interactions (between species with partial charge)
  - Dipole-dipole interactions<sup>b</sup>
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  - Charge-dipole interactions
- Fluctuating dipoles (London Dispersion)<sup>a,b</sup>
- Cation- $\pi$  interactions
- Hydrogen bonding<sup>b</sup>

a) In all liquids and solids

b) In liquid and solid water

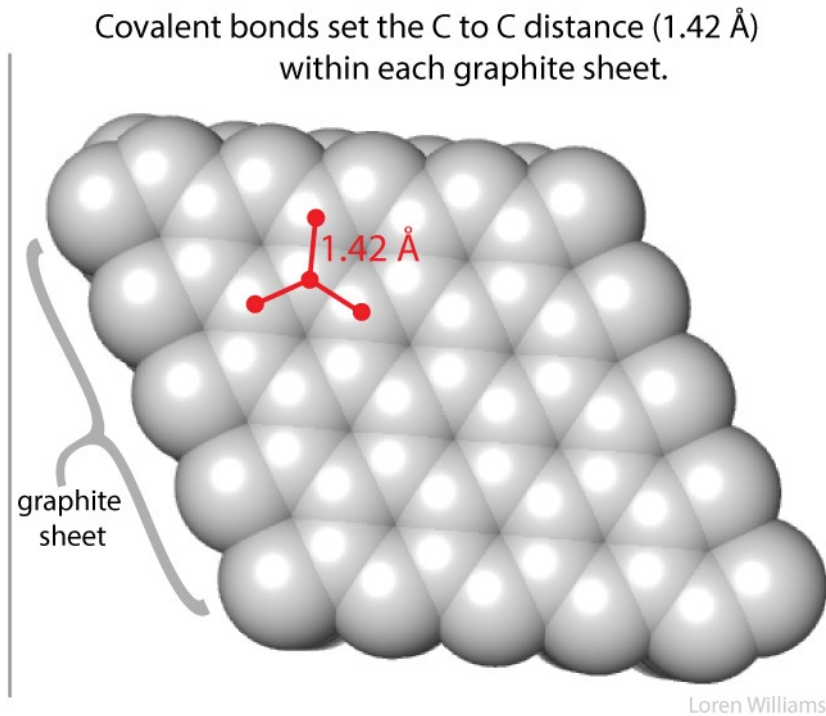
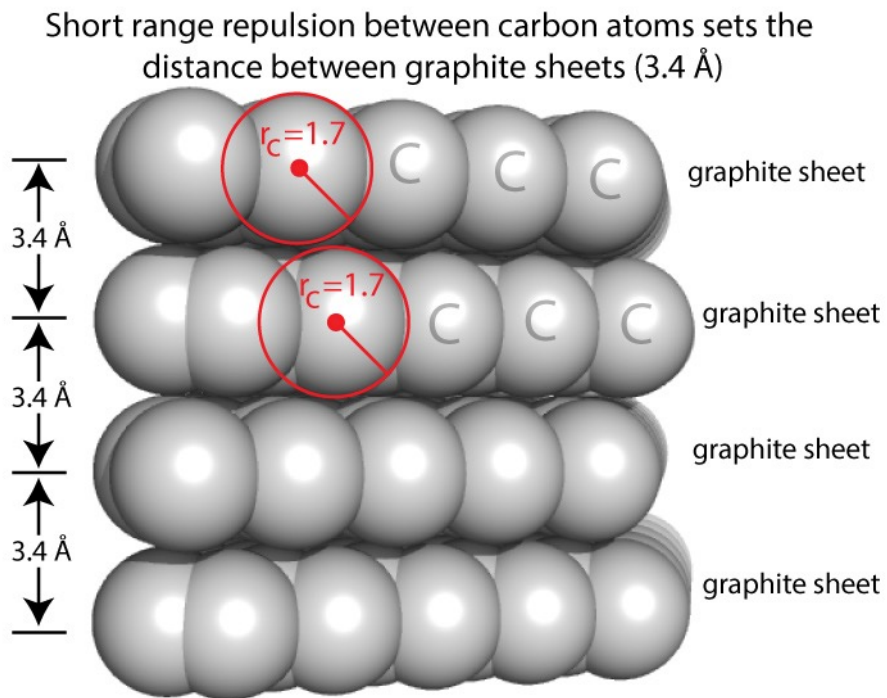
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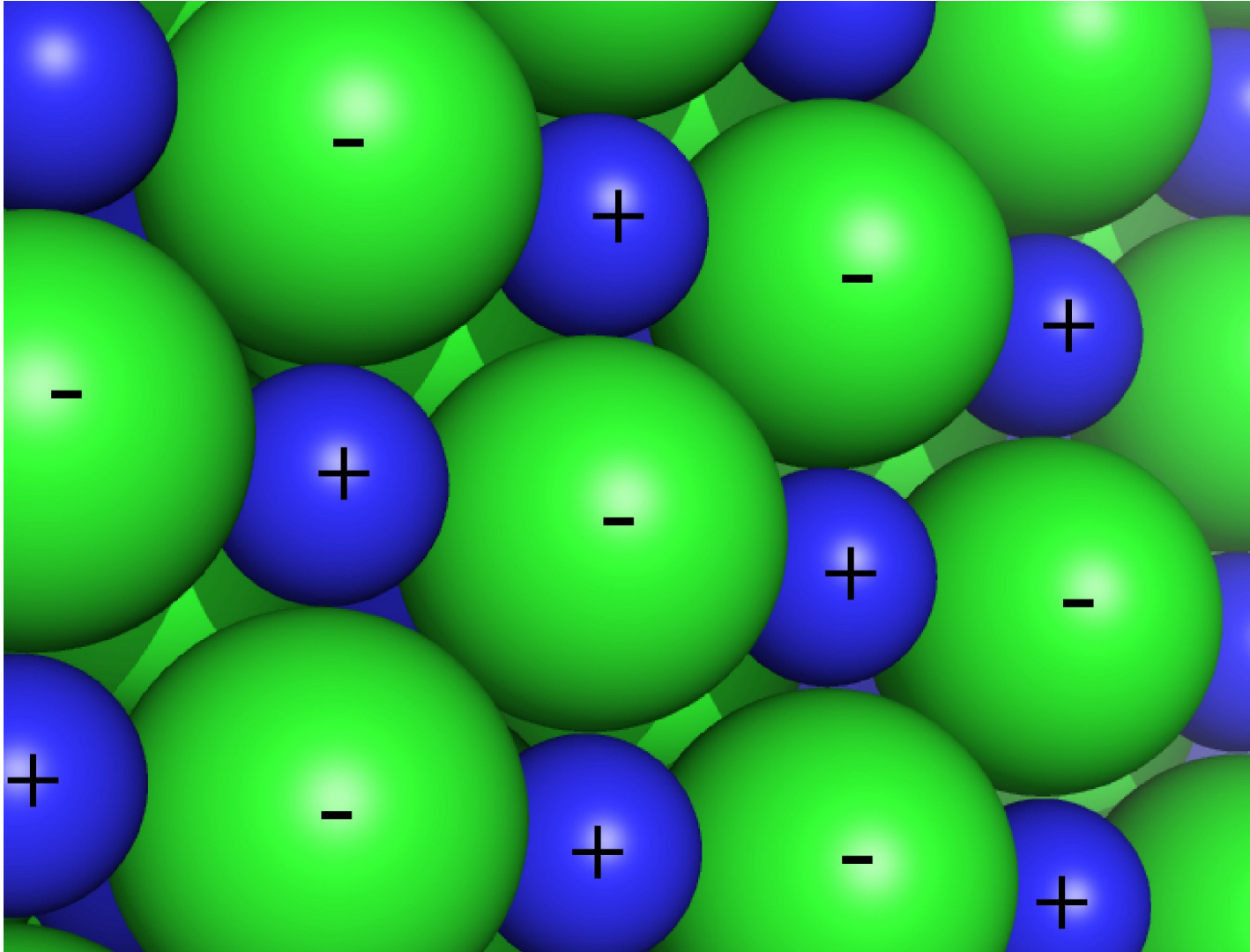
Short range repulsion sets the distance of 3.4 Å between sheets in graphite. If two non-bonded atoms are separated by a distance of less than the sum of their VDW radii, short range repulsion forces them apart.

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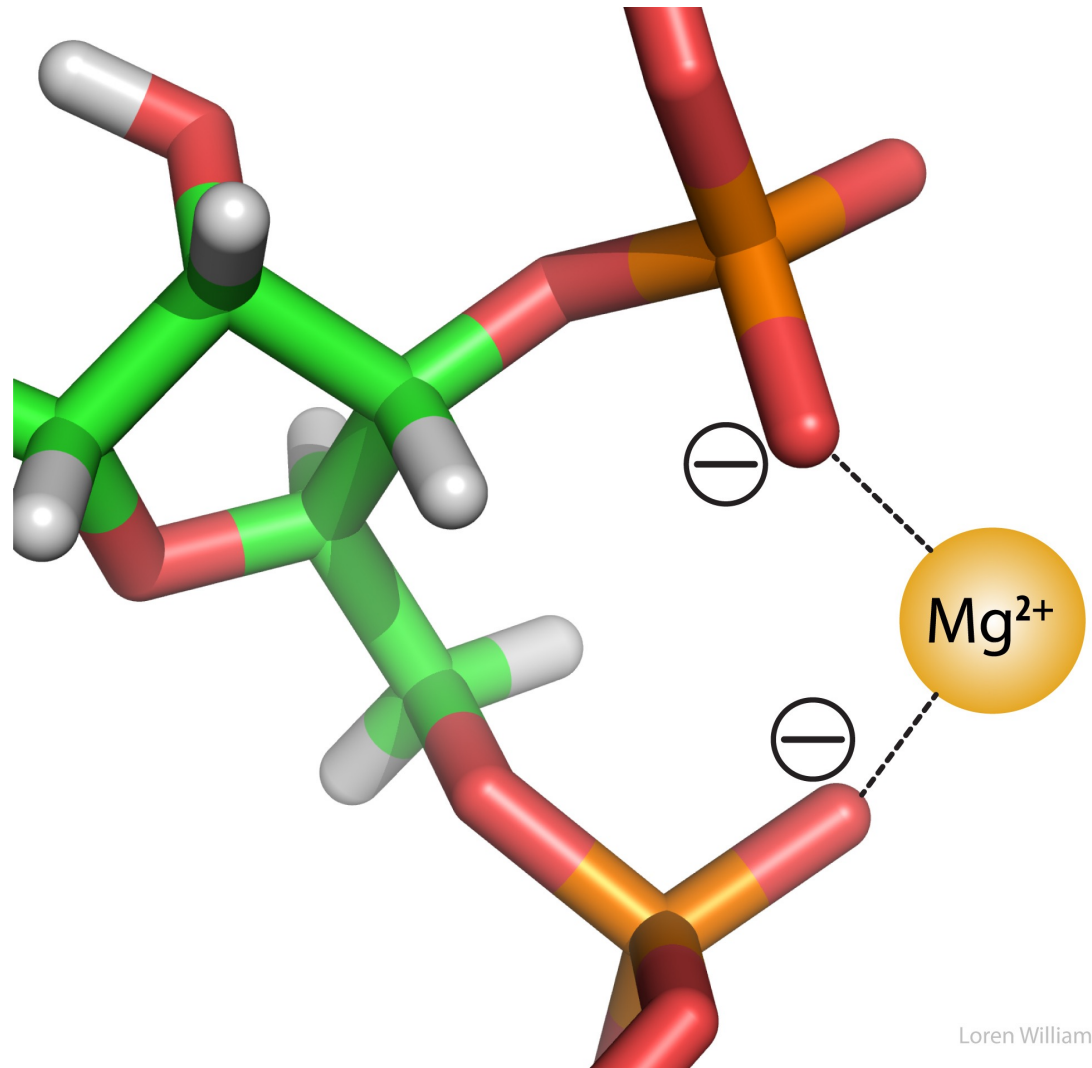
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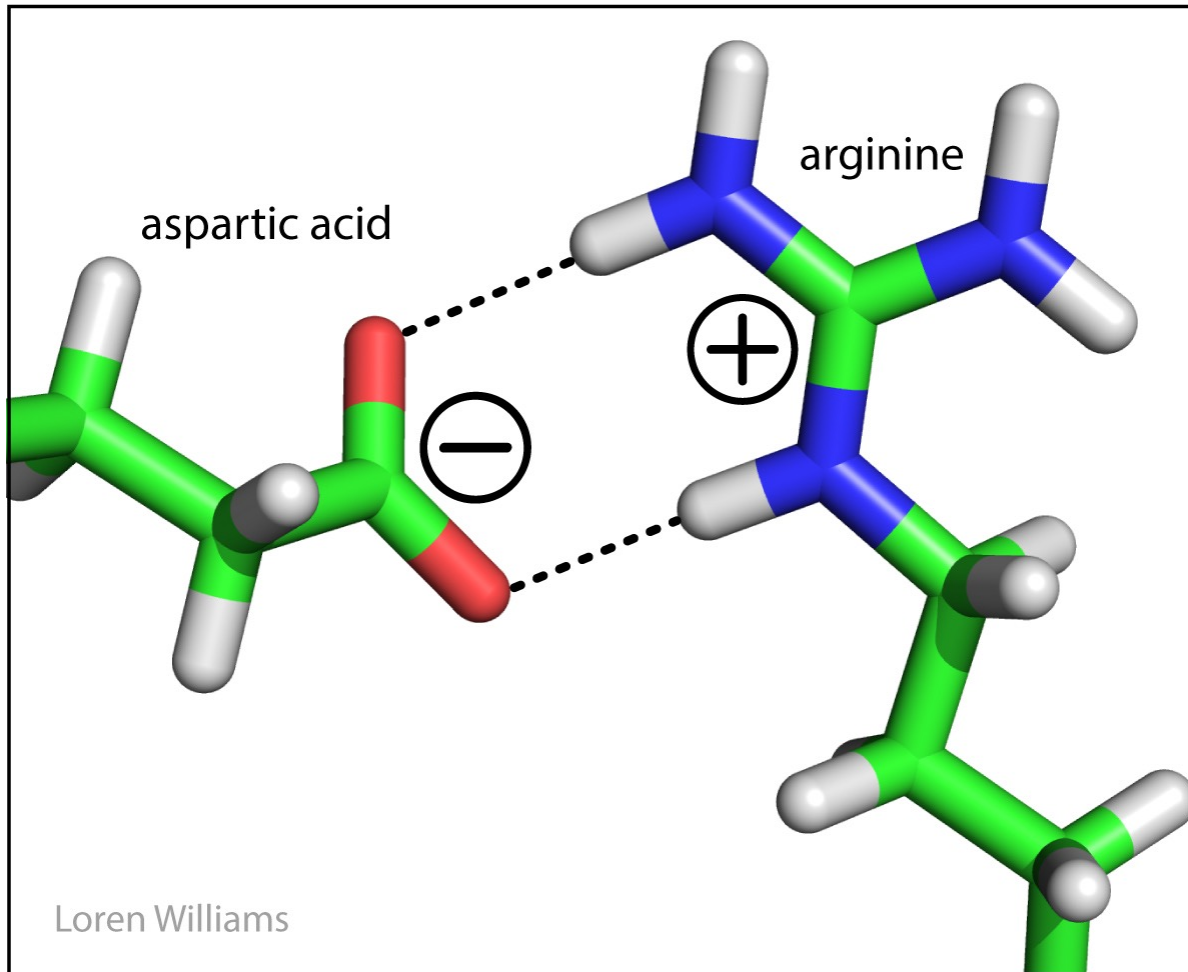
b) In liquid and solid water



Electrostatic interactions in a solid are shown in a cross section of an NaCl crystal. Each sodium cation experiences strong electrostatic attraction with adjacent chloride anions. The ionic radius of a sodium cation is less than that of a chloride anion.

Electrostatic interactions in solution effect RNA (for example in the ribosome). Anionic phosphate oxygens (charge = -1) engage in attractive electrostatic interactions with cationic magnesium ions (charge = +2). Two phosphate groups can 'clamp' onto the  $Mg^{2+}$  ion. The O to  $Mg^{2+}$  distance is 2.1 Å. The dashed lines represent favorable electrostatic interactions.





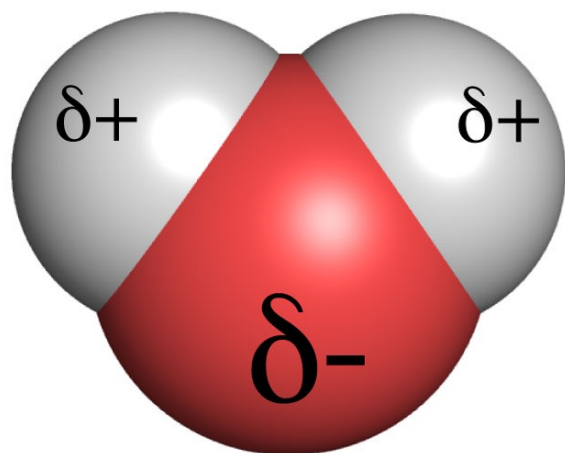
This is an ion pair within a folded protein. An anionic aspartic acid (charge = -1) engages in attractive electrostatic interactions with cationic arginine (charge = +1). The two amino acids also interact via hydrogen bonds. The dashed lines represent hydrogen bonds.

# Types of Molecular Interactions

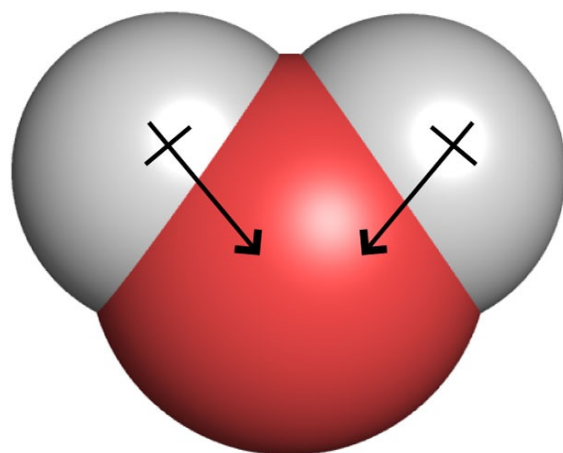
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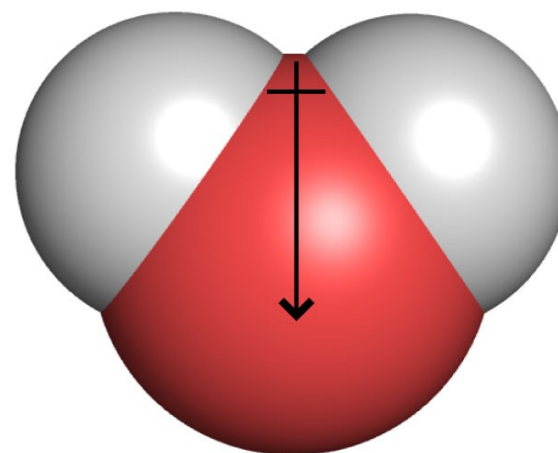
b) In liquid and solid water



partial charges



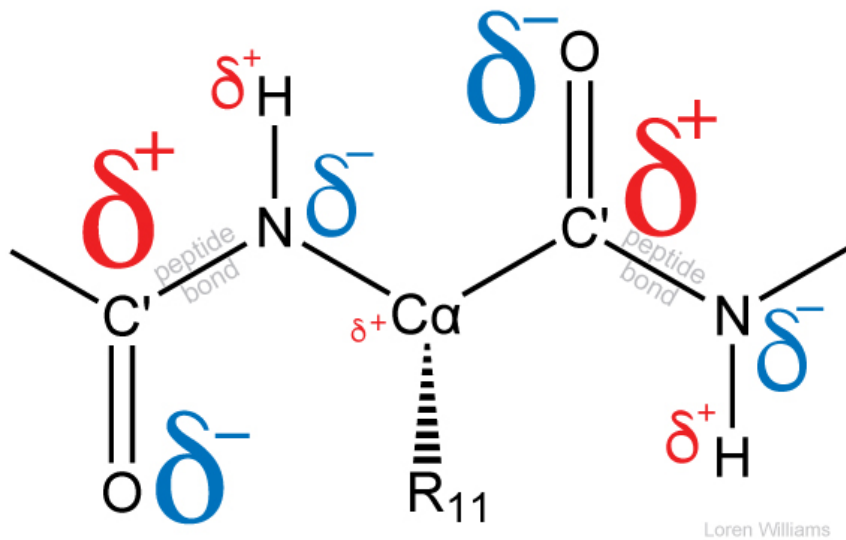
bond dipoles



net dipole

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This figure shows the partial charges and dipole moment of a water molecule. The electronegative oxygen atom pulls electron density away from the hydrogen atoms. The oxygen carries a partial negative charge and the hydrogen atoms carry partial positive charges. The net charge remains as zero. Bond dipoles (center) and molecular dipoles (right) can be represented as vectors. The arrows point from positive partial charge to negative partial charge.



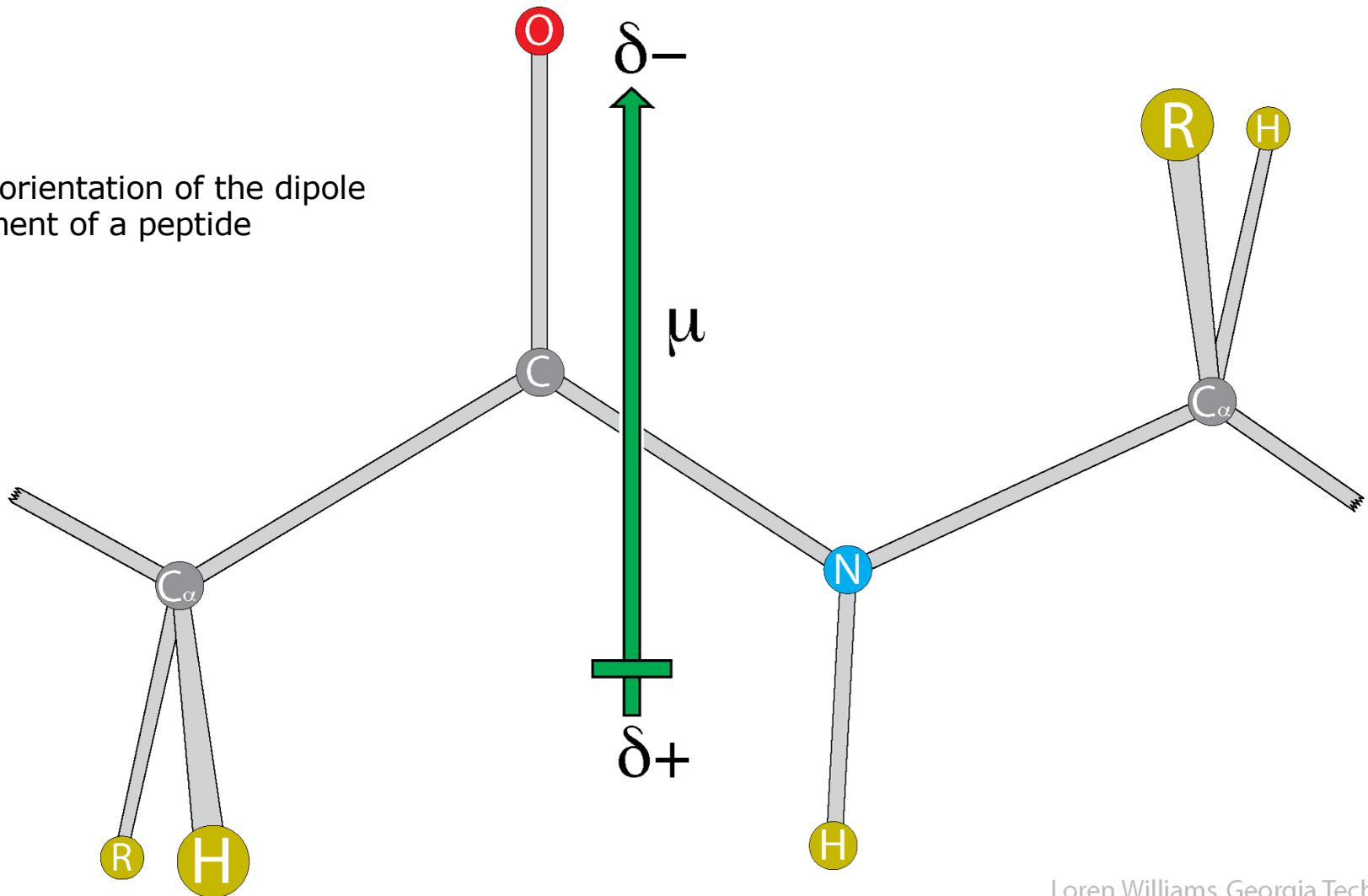
-- Partial Charges on the Atoms of a Peptide --

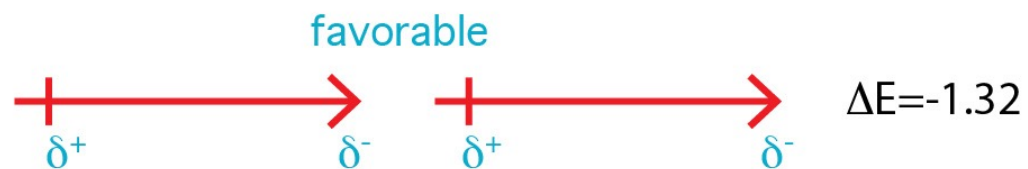
Atom	partial charge (e <sup>-</sup> )
N	-0.42
HN	+0.27
Cα	+0.12
C'	+0.60
O	-0.57

This figure shows the partial charges of a polypeptide. The symbol size ( $\delta$ ) is scaled to the magnitude of the partial charge. Oxygen atoms are the most electronegative and have the greatest negative partial charge.



The orientation of the dipole moment of a peptide





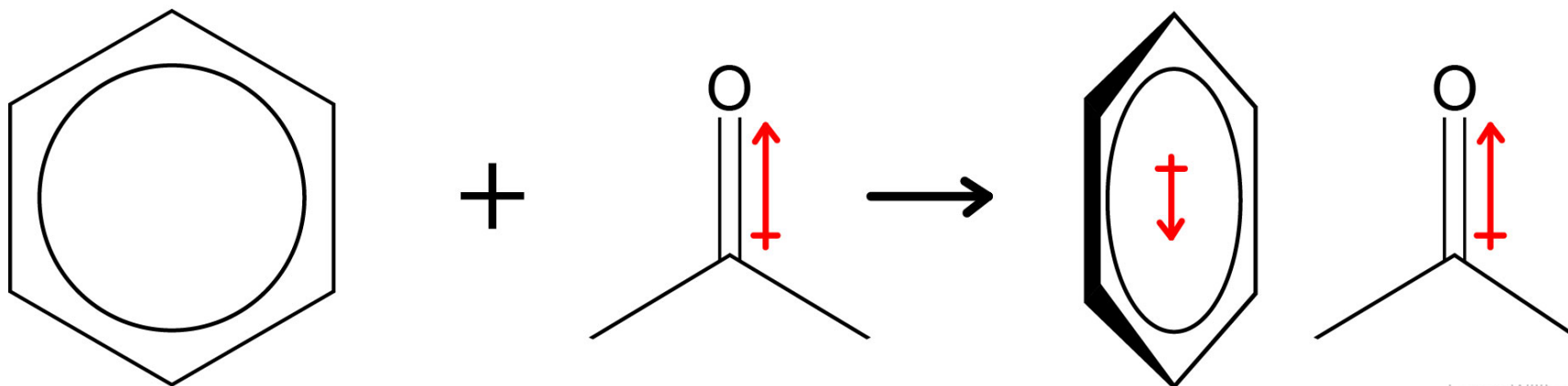
Dipole-dipole interactions depend on the orientations of the dipoles. Dipole-dipole interactions can be attractive or repulsive.

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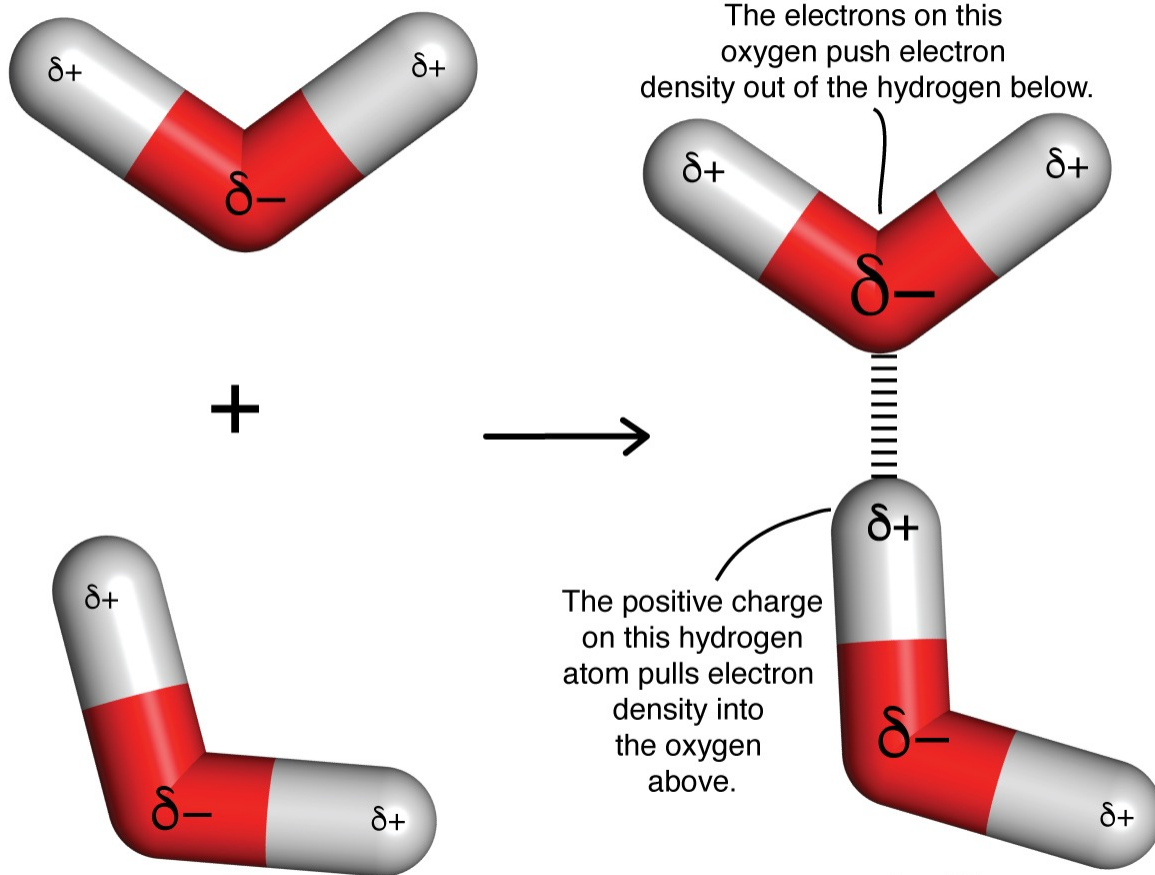
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**Dipole-Induced Dipole.** A permanent dipole can induce a dipole in an adjacent molecule. When two isolated molecules (left) come together in a liquid or solid (right), the static dipole 'polarizes' the adjacent molecule.  $\pi$  Electrons are more polarizable (more easily perturbed by an electric field) than  $\sigma$  electrons. The strength of a dipole-induced dipole interaction depends on the size of the dipole moment of the first molecule and on the polarizability of the second molecule.

A polarizable molecule tumbling in a solution of polar molecules is like a wind sock buffeted by shifting winds. The electron density of a polarizable molecule is shifted and deformed by the electric fields of the surrounding polar molecules.



## Polarization of Water by H-Bonding



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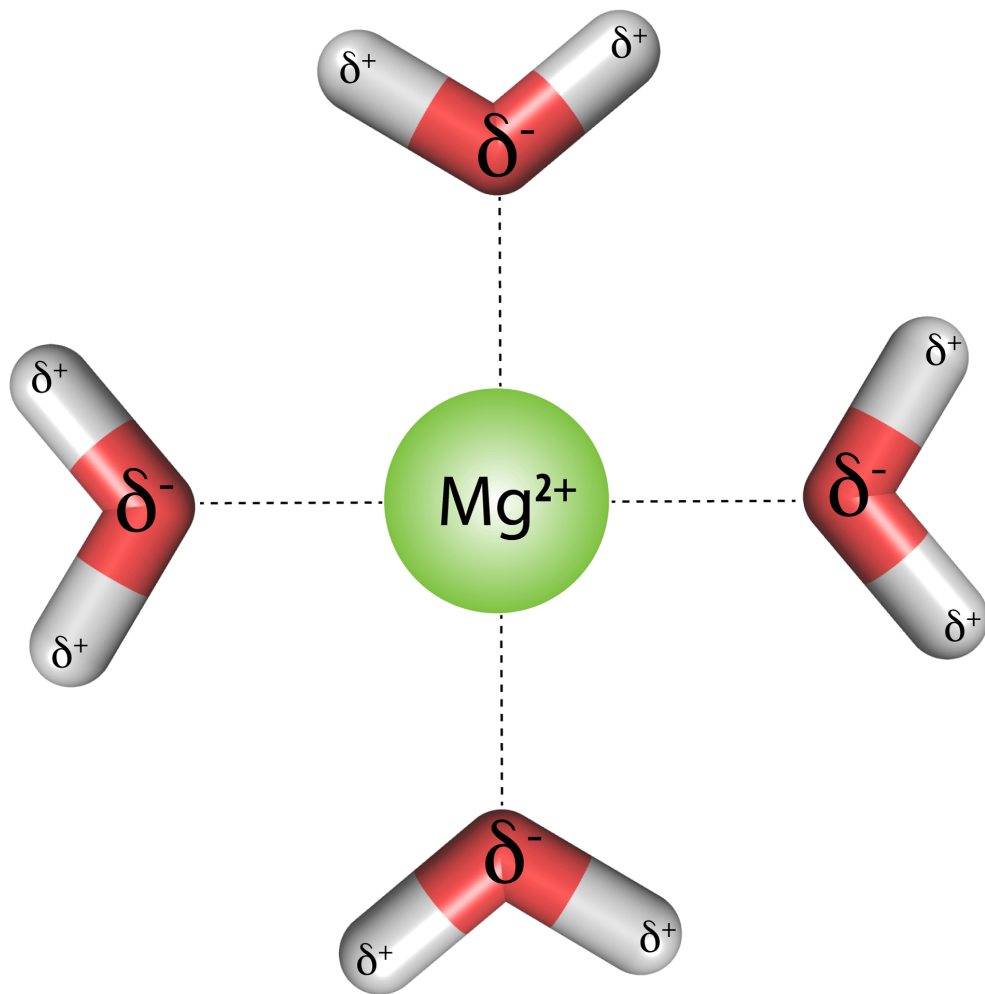
Water molecules polarize each other in liquid water. Each water molecule polarizes neighboring water molecules and increases neighboring dipole moments. When the two water molecules approach each other and form a hydrogen bond as shown here, the partial negative charge on the oxygen of the top water molecule is increased in magnitude, and the partial positive charge on the proton of the bottom water molecule is also increased. Here the symbol size is scaled to the magnitude of the partial charge.

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Charge-dipole Interactions. Four water molecules (which are polar) are shown interacting favorably with a magnesium dication. The negative ends of the water dipoles are directed toward the positively charged magnesium ion. Six water molecules coordinate magnesium in solution. Two are omitted for clarity.

For an anion like chloride, the water molecules switch direction and direct the positive ends of their dipoles toward the anion.

Here the dashed lines do not represent hydrogen bonds. There are no hydrogen atoms between the  $Mg^{2+}$  cation and the water oxygen atoms.

# Types of Molecular Interactions

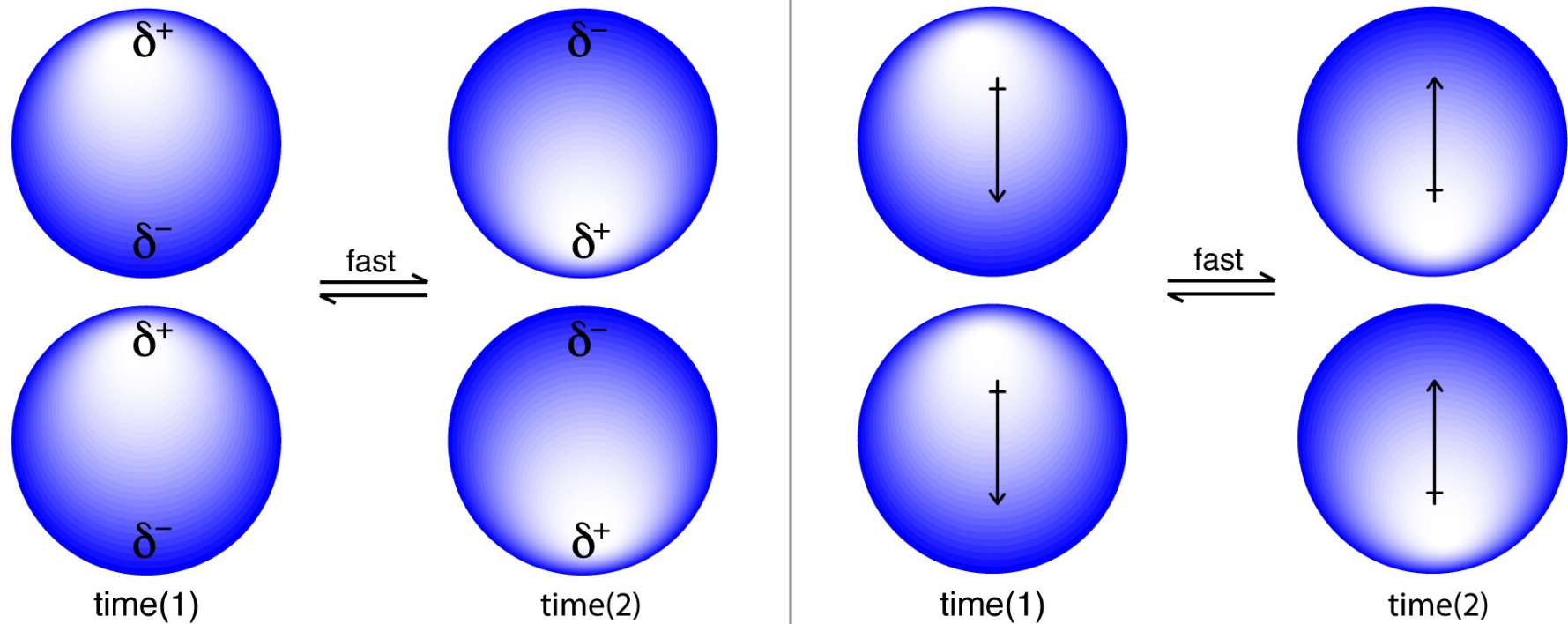
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### London Dispersion Interactions in Xe (liq)



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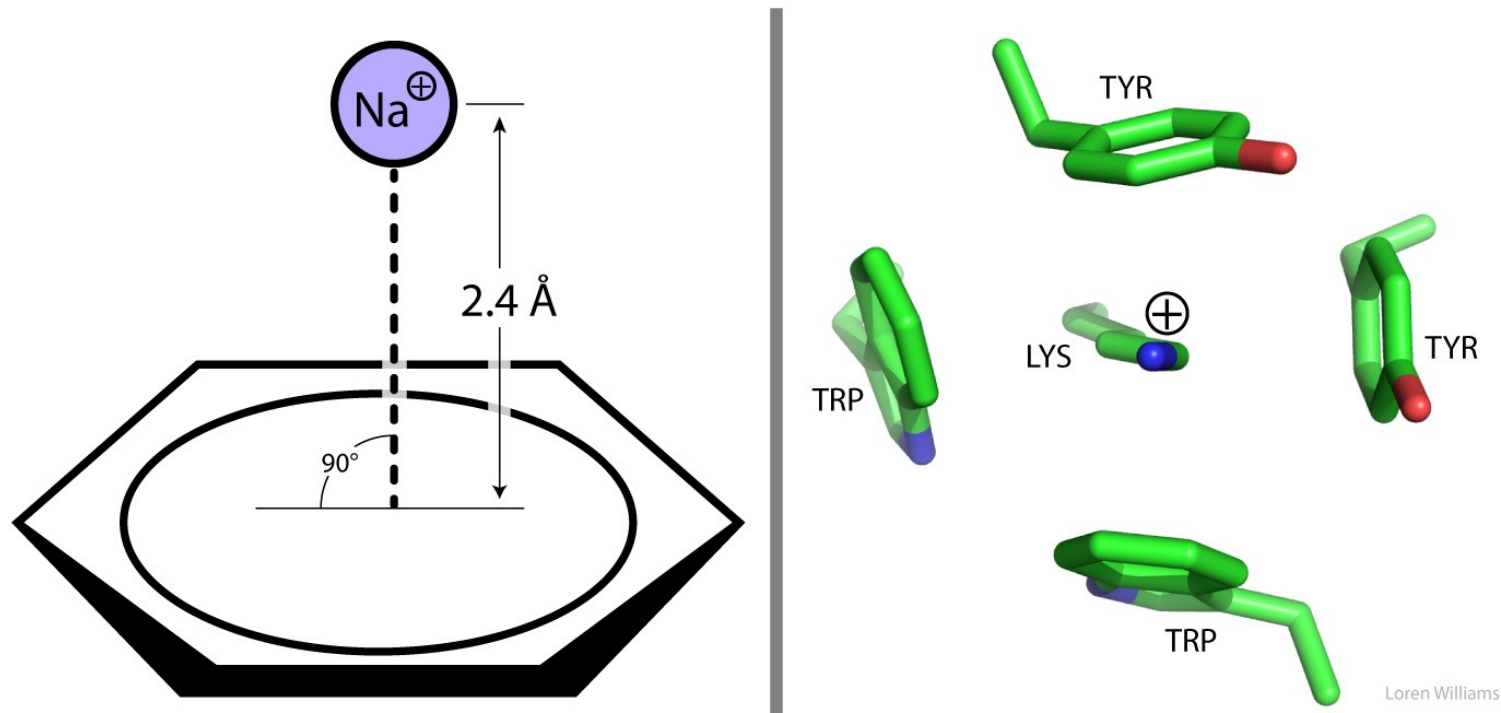
Dispersive interactions in liquid Xenon (or Helium or Neon, etc) are attractive interactions between coupled fluctuations of dipoles. Darker blue indicates higher electron density. The fluctuations are correlated and are very fast, on the femtosecond ( $10^{-15}$  second) timescale. Adjacent Xenon atoms experience electrostatic attraction from the transient dipoles. All molecules experience Dispersive Interactions in solid or liquid phases.

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The optimal geometry for a cation- $\pi$  interaction between a  $\text{Na}^+$  cation and a benzene. The distance from the  $\text{Na}^+$  to the center of the ring is 2.4 Å (ionic radius of  $\text{Na}^+$  = 0.9 Å, vdw radius of C ( $r_C$ ) = 1.7 Å). (Right)

The  $\epsilon\text{-NH}_3^+$  of a lysine engages in cation- $\pi$  interactions with two tryptophan sidechains and two tyrosine sidechains in a protein (glucoamylase, PDB ID 1GAI).

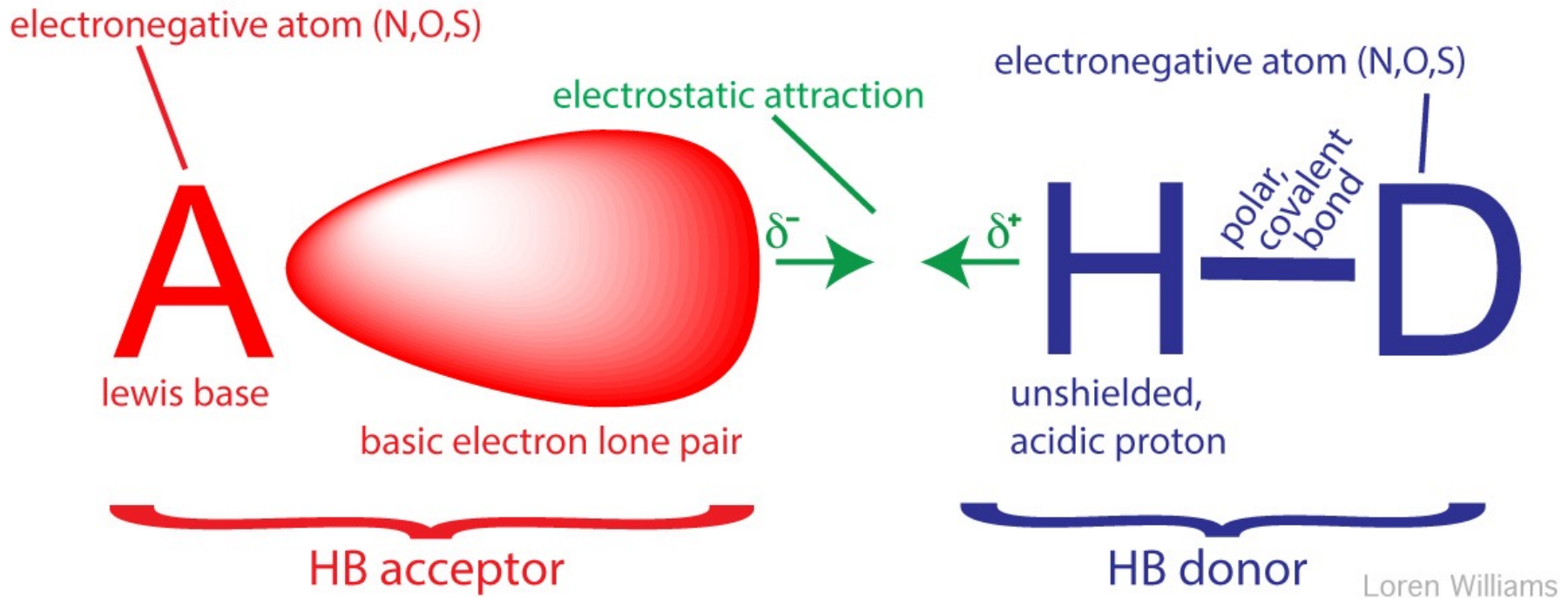
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# Anatomy of a Hydrogen Bond

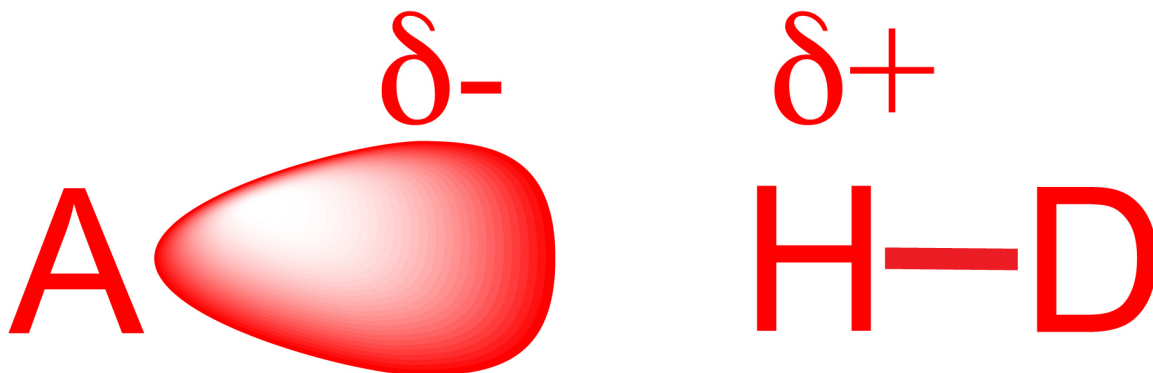


This image illustrates the elements of a hydrogen bond, including the HB acceptor and HB donor, the basic electron lone pair and the acidic proton. N, O, S are the predominant hydrogen bonding atoms (A & D) in biological systems.

The unshielded face of the proton is exposed, attracting the partial negative charge of an electron lone pair.

Three different styles for representing a hydrogen bond. Atom A is the Lewis base (for example the N in NH<sub>3</sub> or the O in H<sub>2</sub>O) and the atom D is electronegative (for example O, N or S).

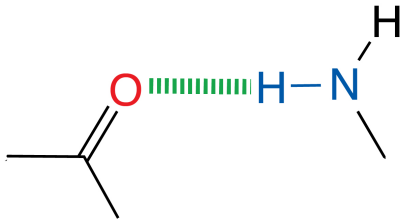
The nomenclature can be confusing: a hydrogen bond is not a covalent bond.



## Hydrogen Bonding in Biological Systems



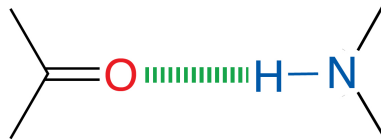
*DNA*  
(base pairing)



*DNA*  
(base pairing)



*protein*  
( $\alpha$ -helix,  $\beta$ -sheet)



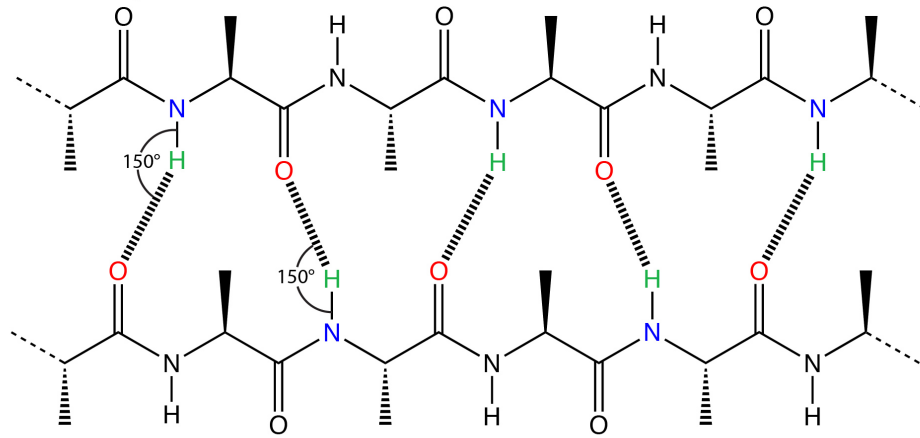
*cellulose*  
(crystalline assemblies)



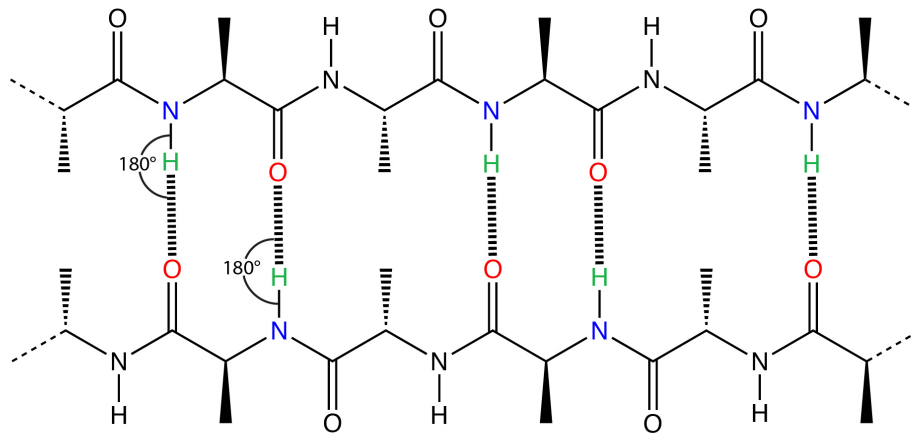
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The most common hydrogen bond acceptors and donors of biological macromolecules.

### Parallel $\beta$ -sheet

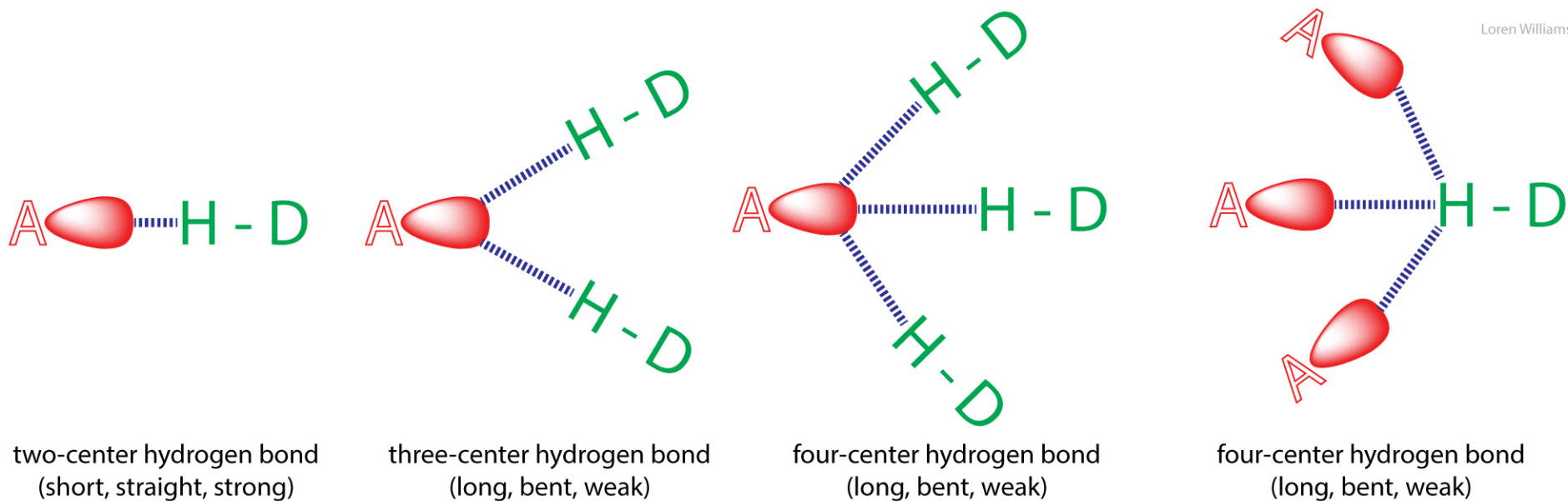


### Antiparallel $\beta$ -sheet



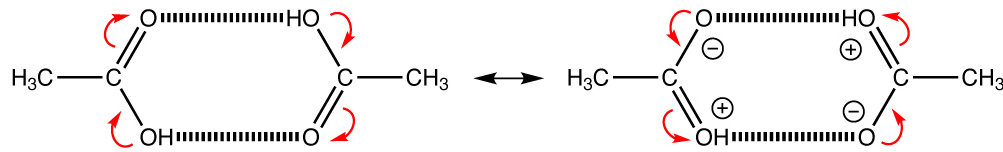
The non-linearity of parallel  $\beta$ -sheet hydrogen bonds and the linearity of antiparallel  $\beta$ -sheet hydrogen bonds.





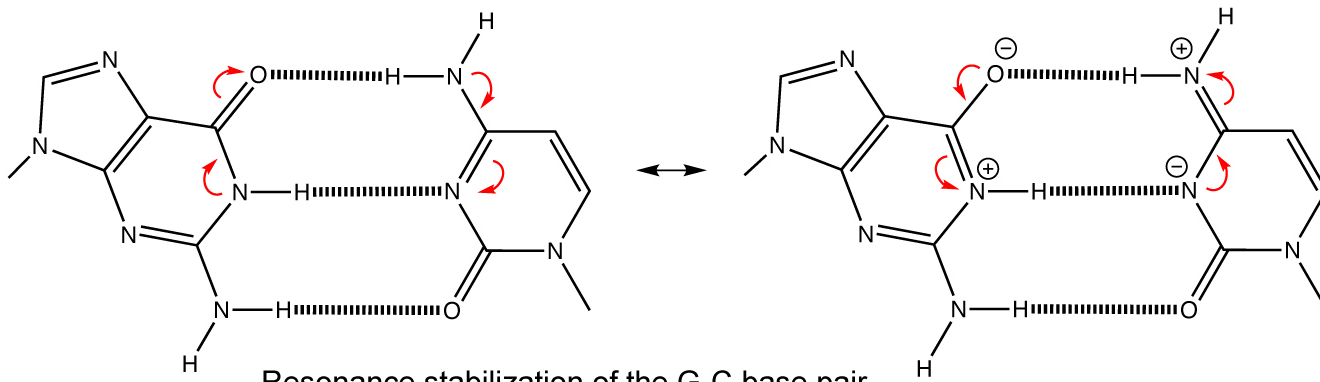
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Two-, three- and four-center hydrogen bonds. The two-center hydrogen bond is an 'ideal' hydrogen bond, and is stronger than the other types. The four-center hydrogen bonding scheme on the right is observed in crystalline ammonium, where one acceptor lone pair has to accommodate three donors.



Resonance stabilization of the acetic acid dimer

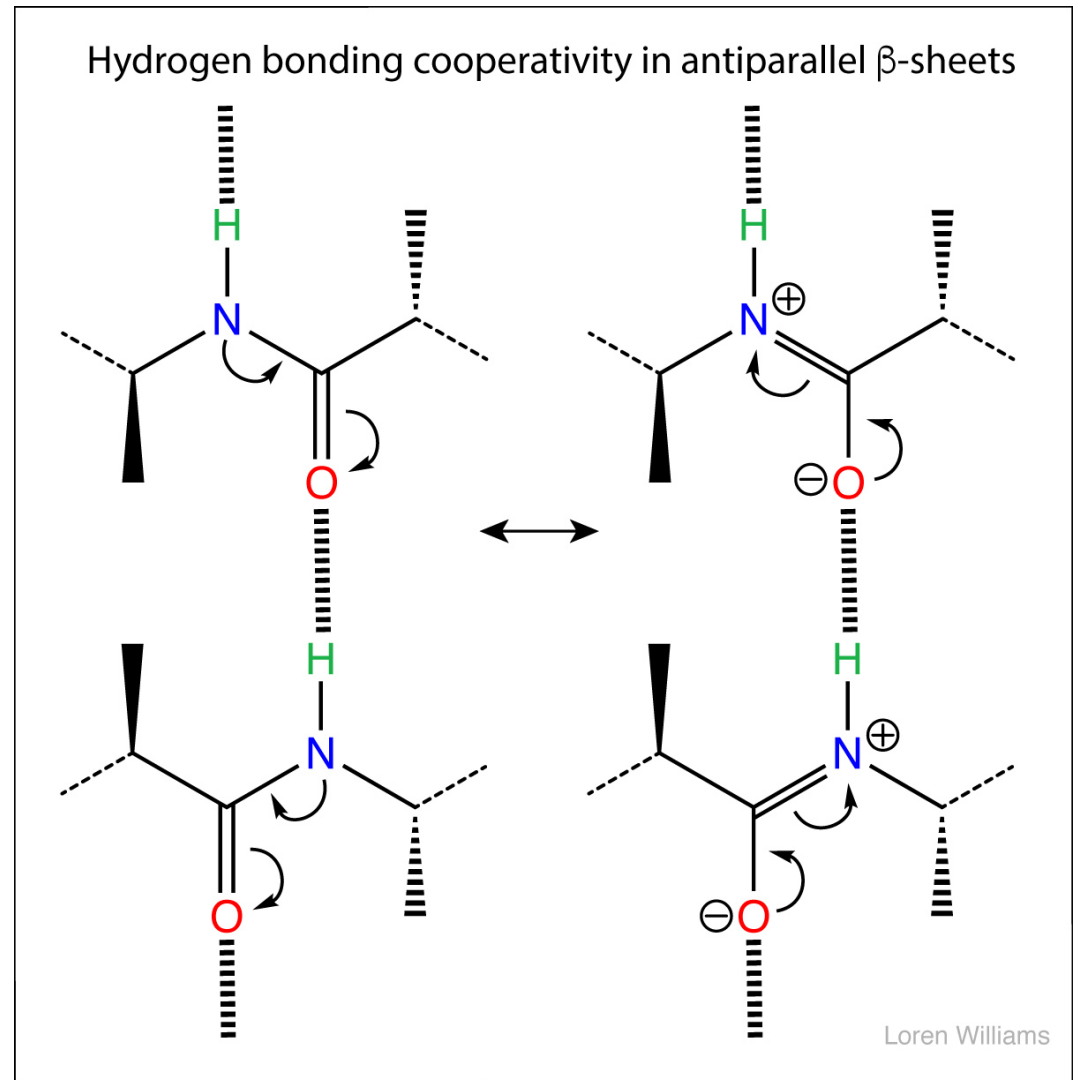
Cooperativity via resonance of the hydrogen bonds of an acetic acid dimer (top) and of a G-C base pair (bottom).



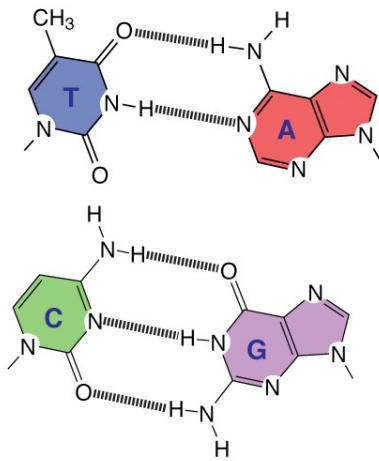
Resonance stabilization of the G-C base pair

One hydrogen bond increases the stability of the adjacent hydrogen bond (and vice versa).

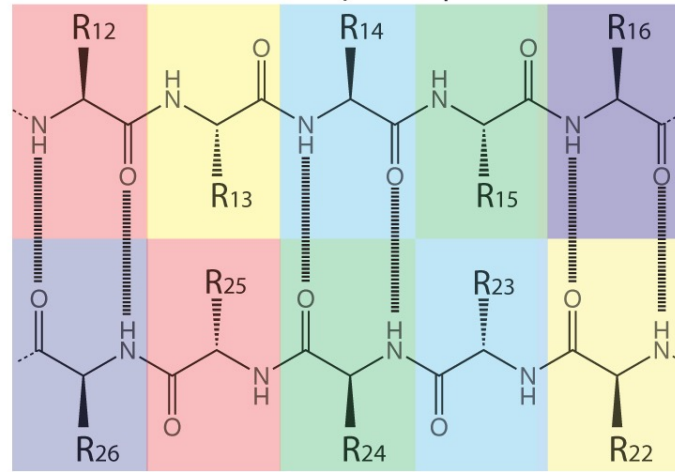
Cooperativity via resonance of the hydrogen bonds of an anti-parallel  $\beta$ -sheet.



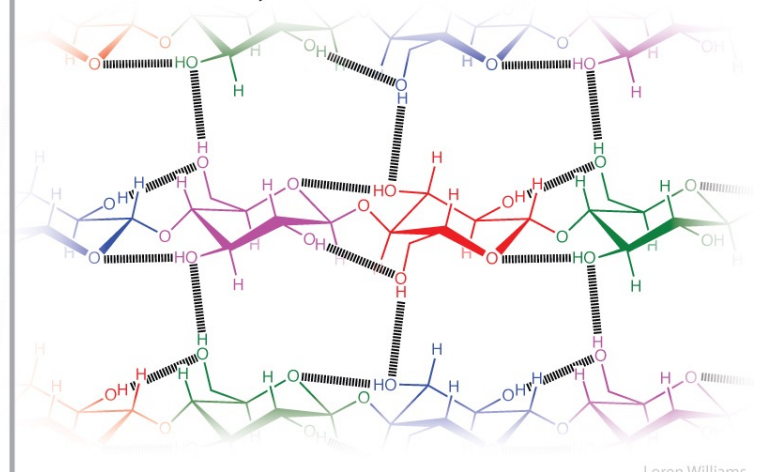
DNA: Watson-Crick base pairs



Protein: antiparallel  $\beta$ -sheet



Polysaccharide: cellulose



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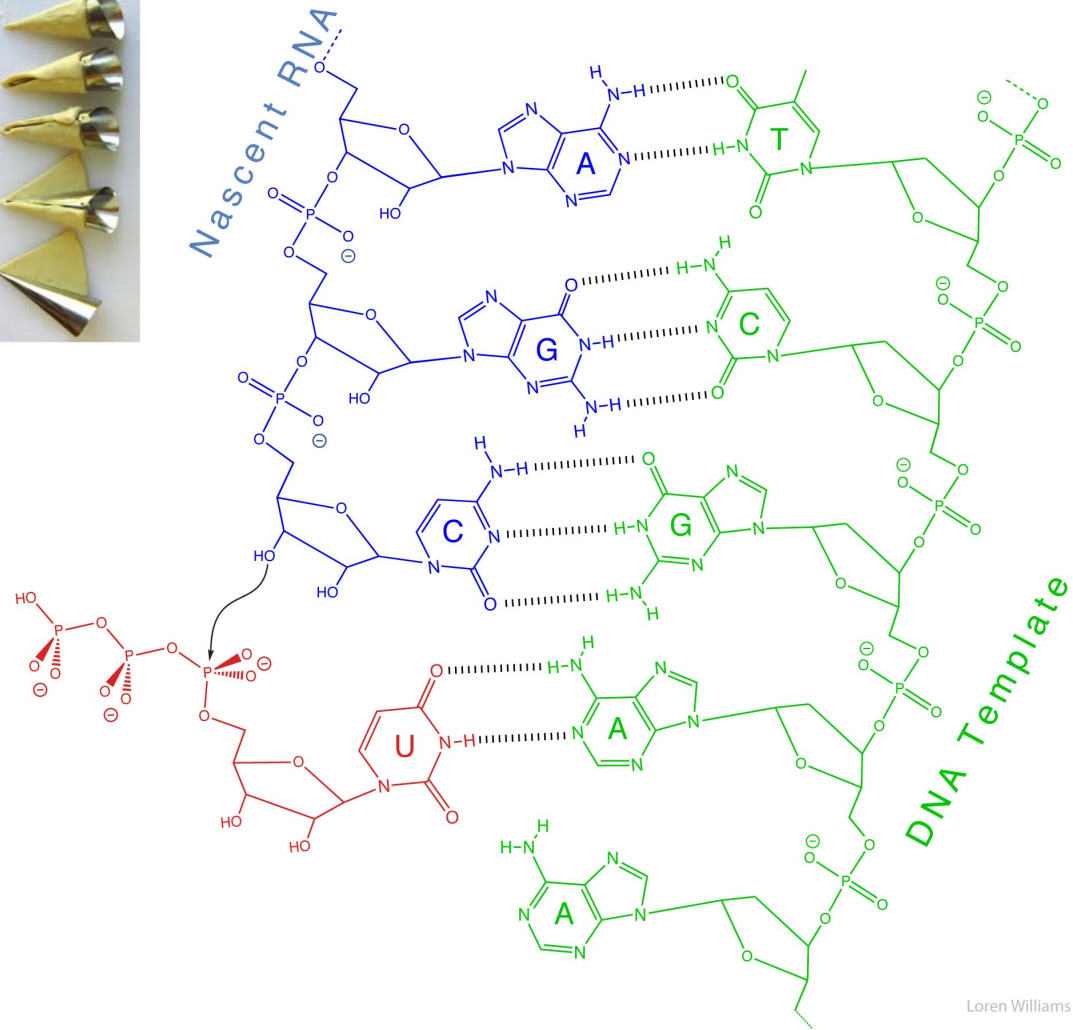
The self-assembly of biological macromolecules is a function of complementary hydrogen-bonding interactions. (Left) Base pairing between complementary hydrogen bond donors and acceptors on the sidechains of nucleic acids.

(Center) Backbone assembly between self-complementary hydrogen bond donors and acceptors of the protein backbone to form anti-parallel  $\beta$ -strands in a  $\beta$ -sheet, and

(Right) Self-complementary hydrogen bond donors and acceptors in carbohydrate, between glucose moieties within cellulose.

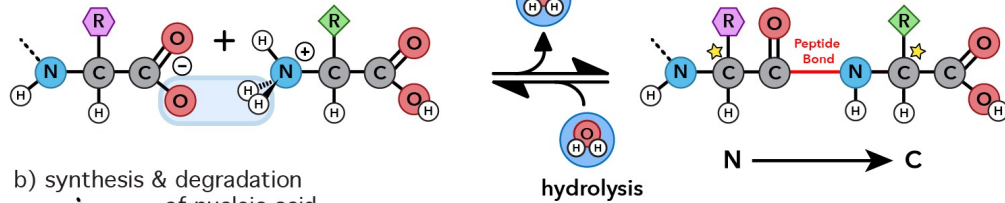
A pastry template (top left) directs and controls the shape of a pastry.

A molecular template (a DNA molecule), that directs synthesis of a molecule of RNA. The DNA template strand is green, the nascent (growing) RNA strand is blue and the incoming nucleotide is red.

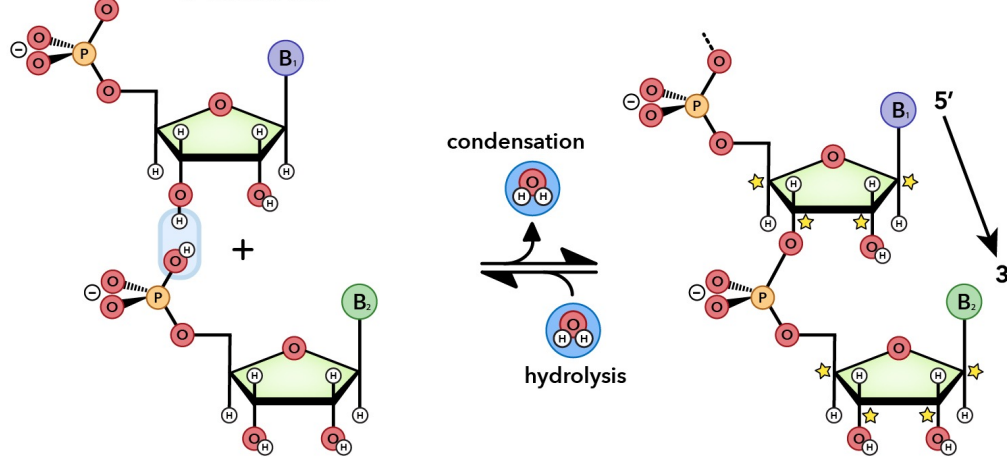


Water

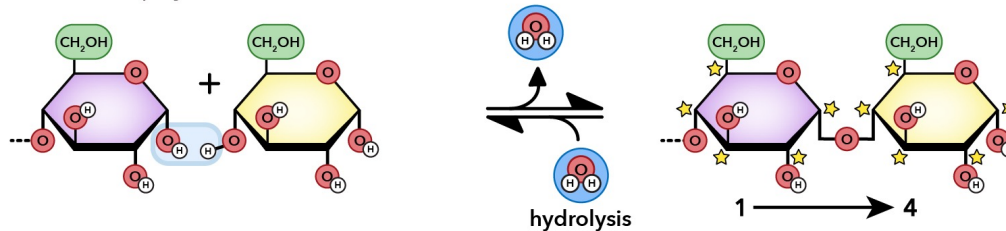
a) synthesis & degradation of protein



b) synthesis & degradation of nucleic acid



c) synthesis & degradation of polysaccharide

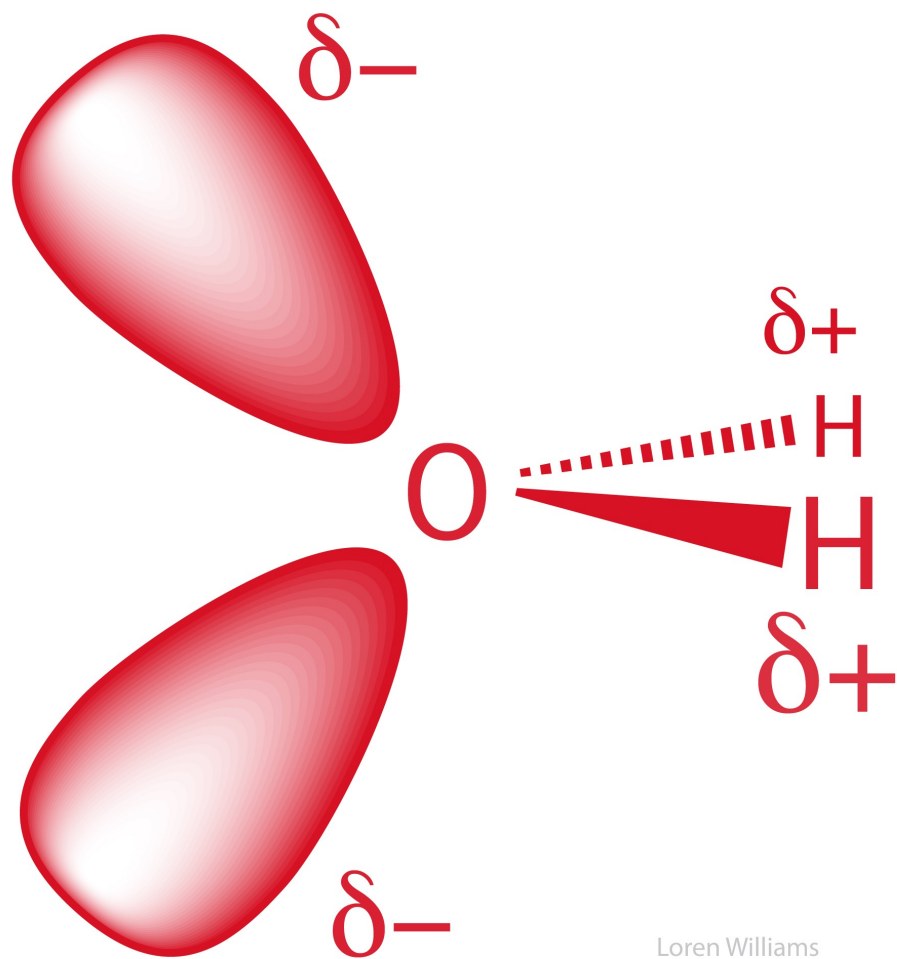


Water is a biochemical reagent.

Net reactions for biopolymer formation by condensation dehydration and biopolymer degradation by hydrolysis.

- a) Protein.
- b) RNA.
- c) Polysaccharide.

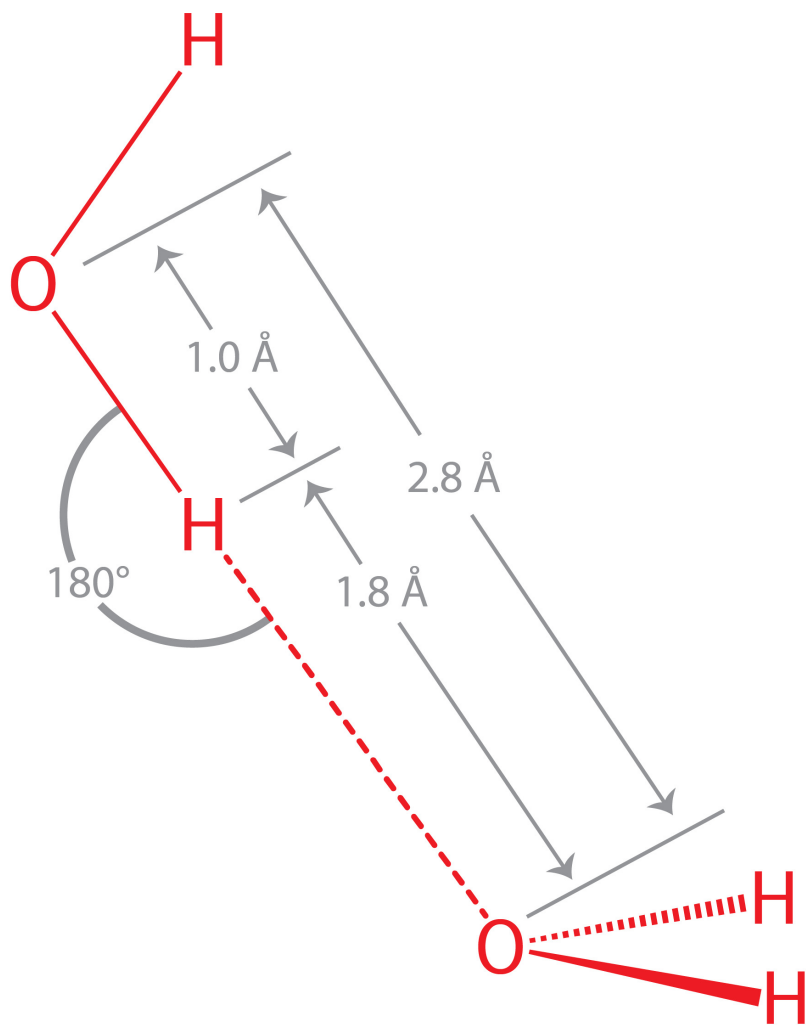
All biopolymers are chiral and directional with distinctive ends. Chiral centers (stars, shown in polymers only) and strand directionalities (arrows) are indicated. Blue boxes indicate (in toto) the atoms involved in the synthesis/degradation reactions.



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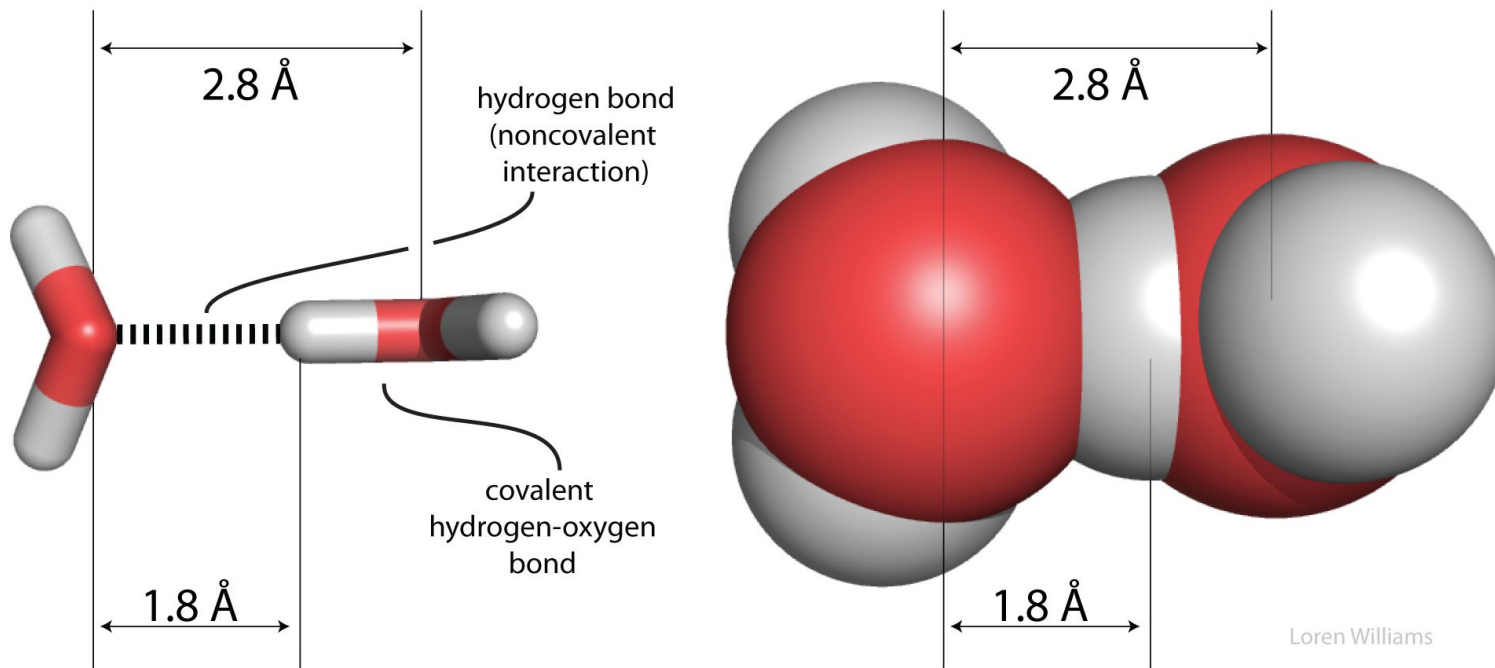
The two lone electron pairs and the two bonding electron pairs of a water molecule form a slightly distorted tetrahedron. The non-bonding electron pairs take up a little more space than the bonding electron pairs.





Hydrogen bonding between two water molecules as observed in liquid water or ice. The hydrogen bonds are short, linear and strong. This is a two-center hydrogen bond. Although each water molecule in liquid water and in ice forms four hydrogen bonds, only one hydrogen bond is shown here.

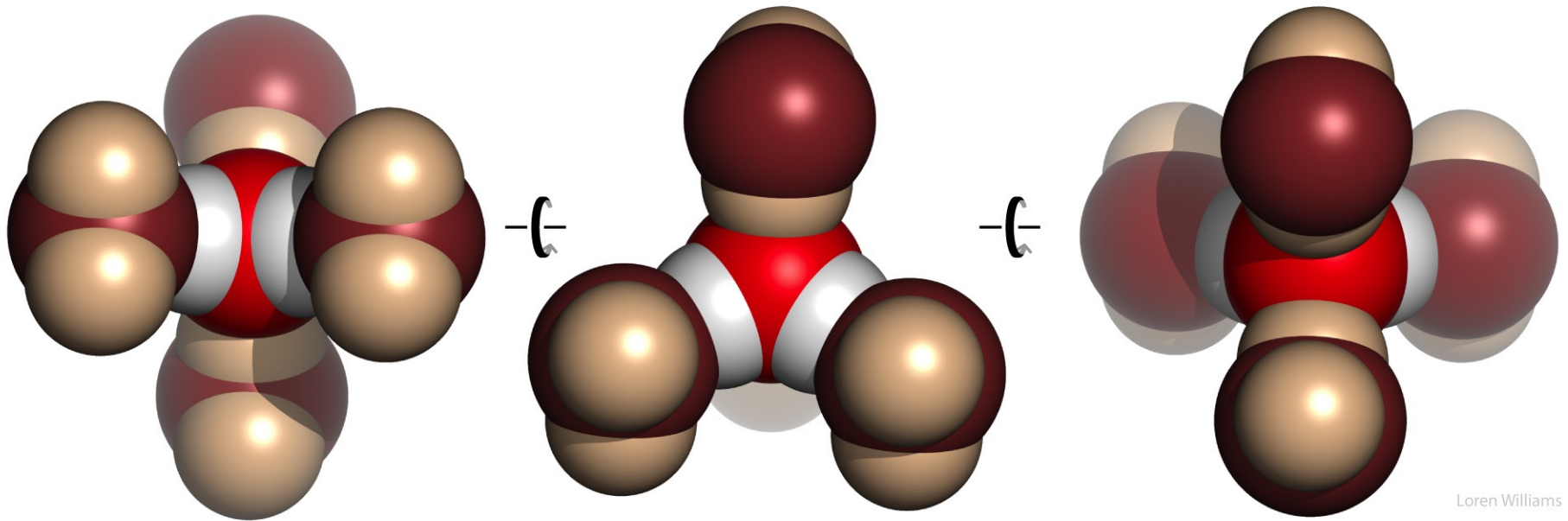
## Hydrogen bonding between two water molecules



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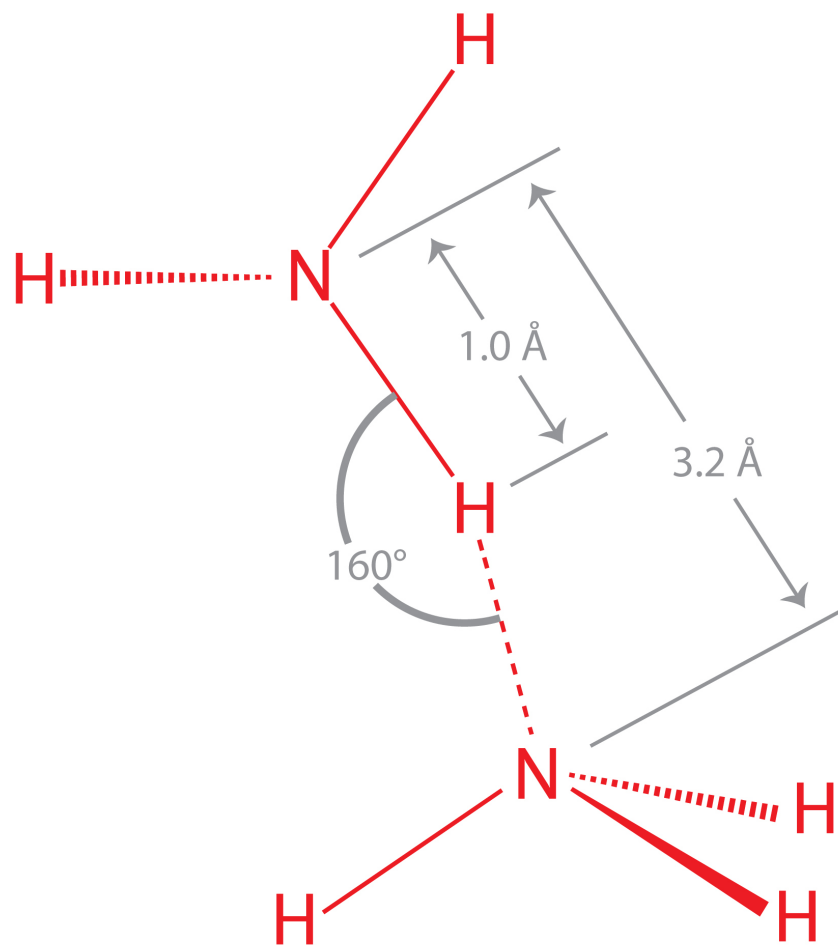
This image shows how hydrogen bonds link two water molecules and illustrates the difference between a covalent bond, linking an oxygen atom to a hydrogen atom, and a hydrogen bond, also linking an oxygen to a hydrogen. A hydrogen bond is a non-covalent molecular interaction. Oxygen atoms are red and hydrogen atoms are white. The space filling representation on the right shows how hydrogen bonding causes violations of van der Waals surfaces.

Five water molecules in a hydrogen-bonded cluster. The central water molecule forms four hydrogen bonds.



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The central water molecule here is donating two and accepting two hydrogen bonds. In liquid water the total number of hydrogen bond donors equals the total number of hydrogen bond acceptors. All hydrogen bonding donors and acceptors are satisfied. Water is self-complementary.



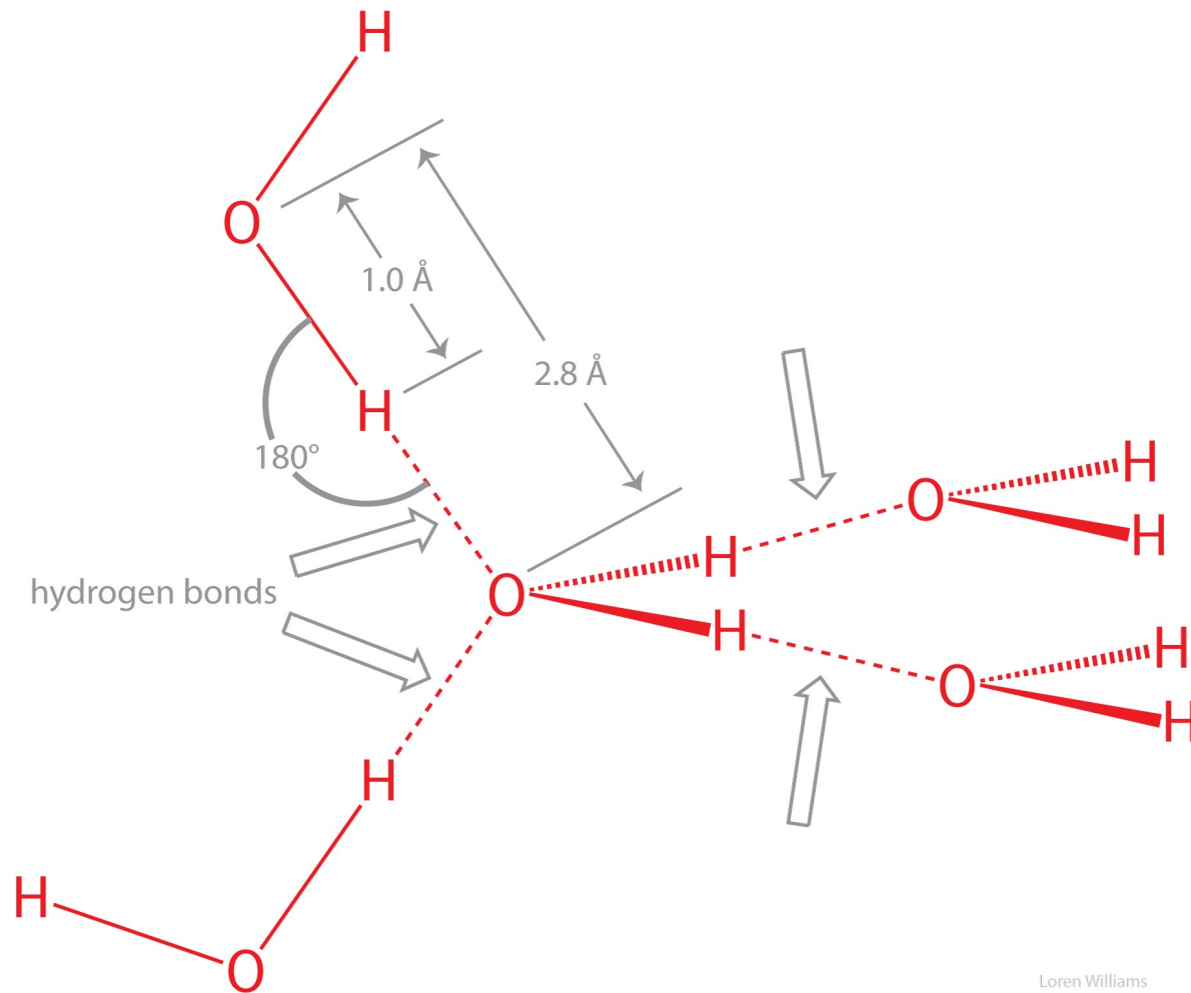
Loren Williams

The boiling point of ammonia is 130 °C less than that of water, meaning that cohesive interactions of ammonia are much weaker than those of water. Why?

Ammonia is unbalanced. It contains more HB donors than acceptors (3:1). Unlike water, ammonia is not self-complementary.

The hydrogen bonds of crystalline ammonia are longer than those in ice and are non-linear and are multi-centered.

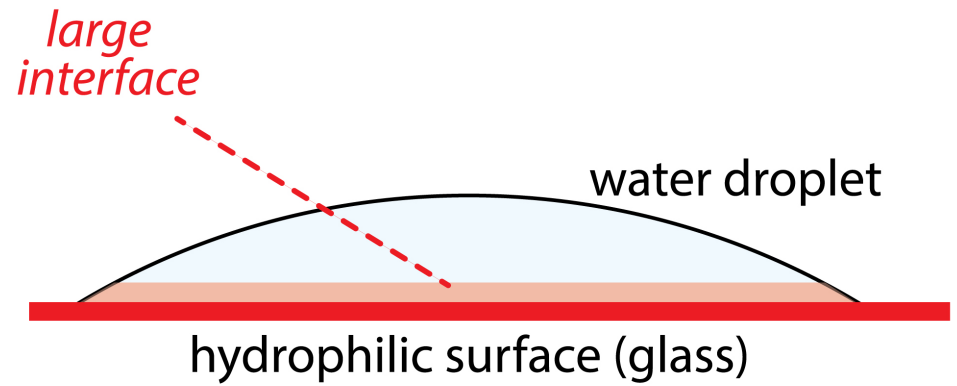
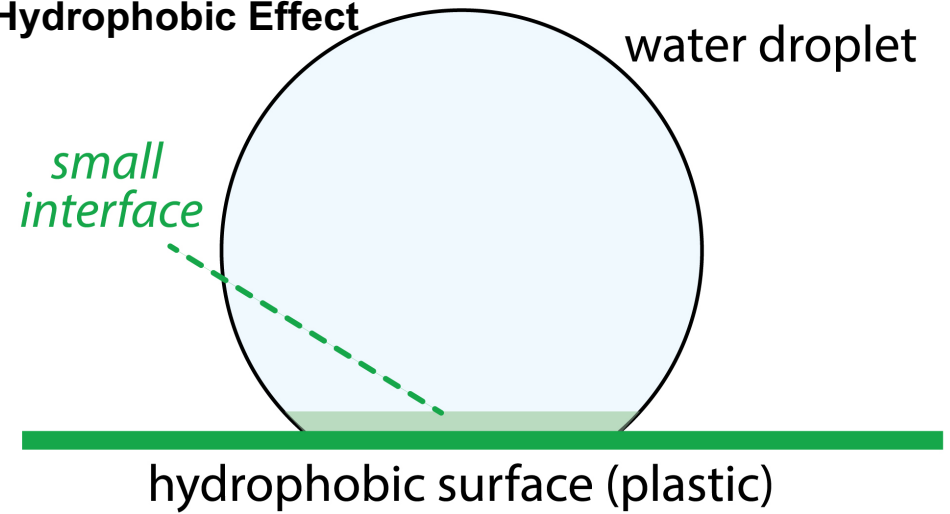
Each ammonia molecule forms hydrogen bonds with six neighbors in the crystal, only two ammonia molecules are shown here.



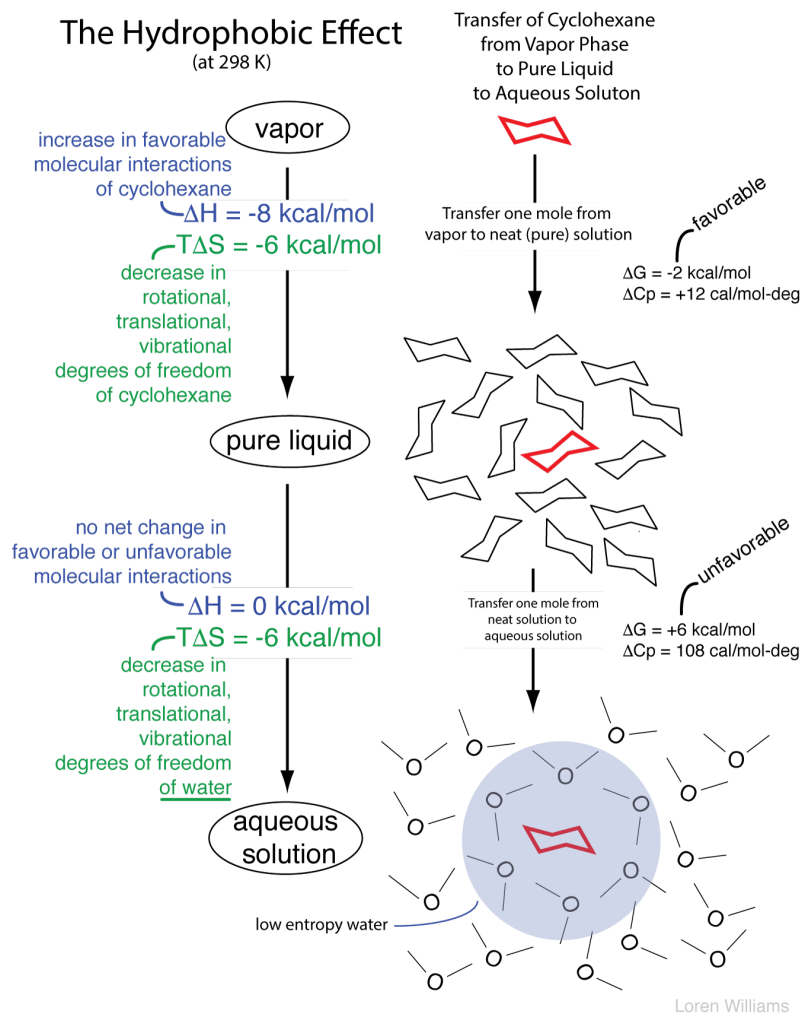
The hydrogen-bonding interactions of one water molecule with four others. A water molecule can donate two hydrogen bonds and accept two hydrogen bonds.



## The Hydrophobic Effect



## The Hydrophobic Effect (at 298 K)

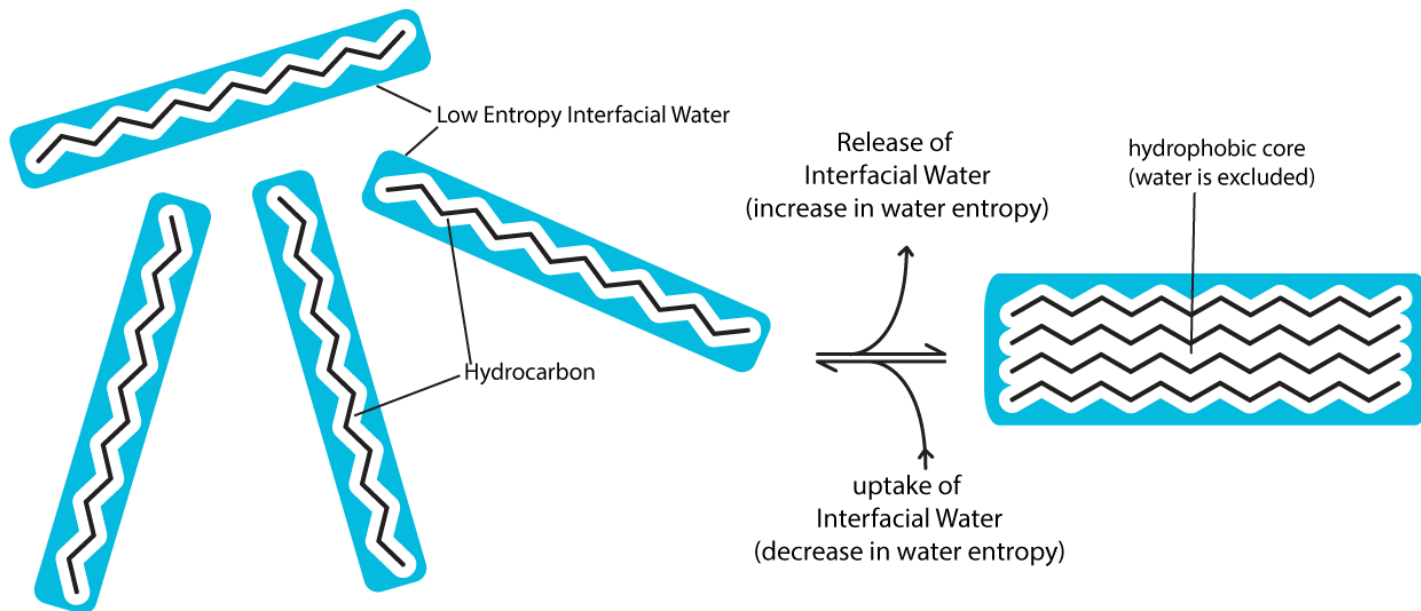


What happens when a hydrophobic substance (cyclohexane in this case) is converted from vapor to neat liquid to aqueous phase.

In the first step, condensation from vapor phase to neat liquid, there is an increase in intramolecular interactions and a decrease in rotational and translational degrees of freedom. Therefore sees a favorable enthalpy contribution (negative  $\Delta H$ ) and an unfavorable entropy contribution (negative  $T\Delta S$ ) for the condensation.

In the second step, going from neat liquid to dilute aqueous solution, the change in stability contributed from intramolecular interactions is a wash, no gain or loss. The enthalpy of transfer is near zero. The entropy of the cyclohexane does not change much either

But water loses entropy. Water is more highly ordered in the vicinity of a cyclohexane molecule than in pure water. Therefore, for this step,  $\Delta H$  is zero,  $T\Delta S$  is negative and  $\Delta G$  is positive ( $\Delta G = \Delta H - T\Delta S$ ).



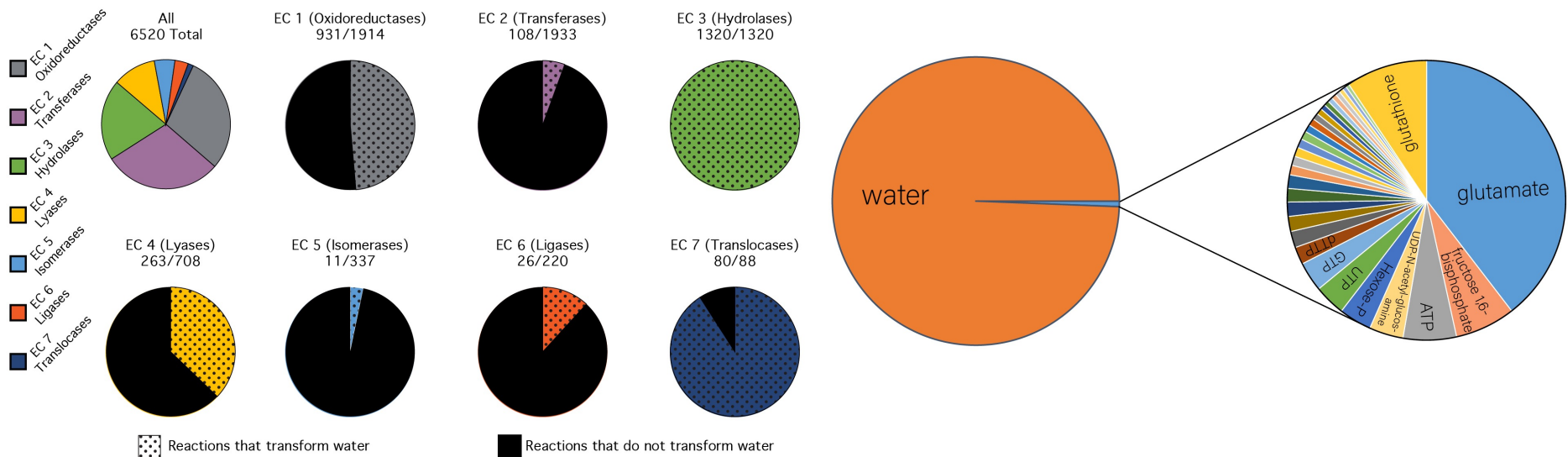
The aggregation of hydrocarbon molecules causes the release of interfacial water molecules. Therefore the system gains entropy (positive  $T\Delta S$ ) upon hydrocarbon aggregation. Release of low entropy interfacial water molecules into the bulk solution drives hydrocarbon aggregation. The bottom panel illustrates that there is more interfacial water on the left hand side of the equation than on the right hand side.



When the hydrocarbon aggregates the amount of interfacial water decreases.

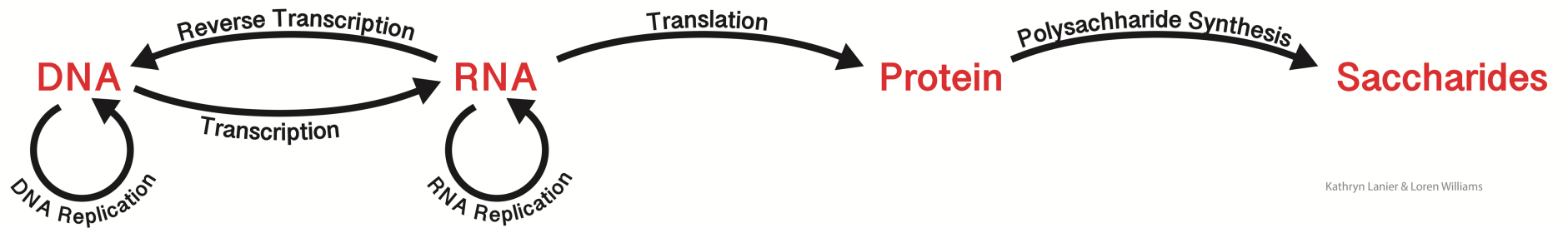






- The unusual physical properties of water as a solvent are coupled with frequent participation in diverse chemical transformations during the life of a cell.
- Water is never absent or physically separated from biological macromolecules, organic cofactors, and metals, but readily combines with, withdraws from, and intercedes in their transformations. In biological systems, water is fully integrated into processes of bond making and bond breaking.
- We do not have a language to describe water in biology. The distinction between medium and chemical participant is so blurred as to be devoid of meaning.

# Polymers



Kathryn Lanier & Loren Williams

The Central Dogma of Molecular Biology describes the flow of information in biological systems. The arrows indicate allowed pathways of information flow. Carbohydrates are included here in an extended version of the Central Dogma; oligomers of various sugars store and transmit information. For example carbohydrates provide cell-cell communication through cell surface interactions.

Spectacular fibers of protein or carbohydrate. Spider web is made from protein. Tree branches, such as those supporting this spider web, are made mostly from carbohydrate (cellulose is polymerized glucose). The spider web ratio of strength to density can exceed that of steel. Wood, which contains polycellulose and other fibers, is strong, lightweight and flexible. Photo courtesy of Mary Ellen St. John, Newark, Ohio.

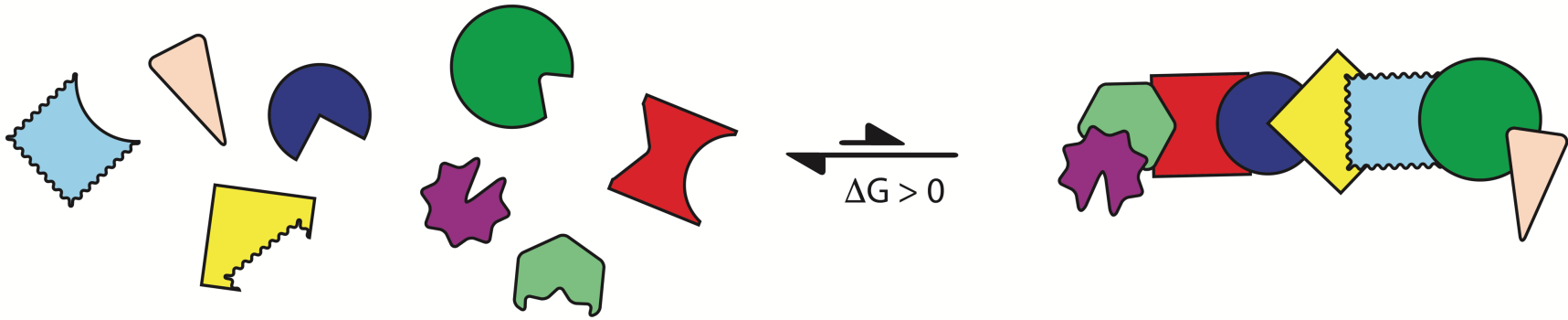


# Emergence

The extraordinary molecular interactions observed in biological systems are *emergent* upon polymerization.

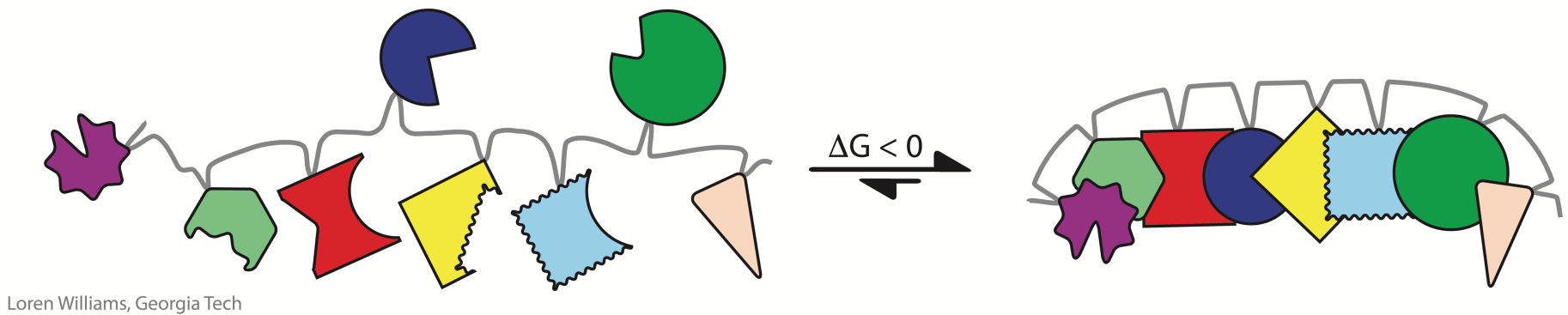
Emergent properties are those of a sum (the polymer) that the parts (the monomers) do not have.

It is not possible to predict the properties of biopolymers from the properties of their monomers.

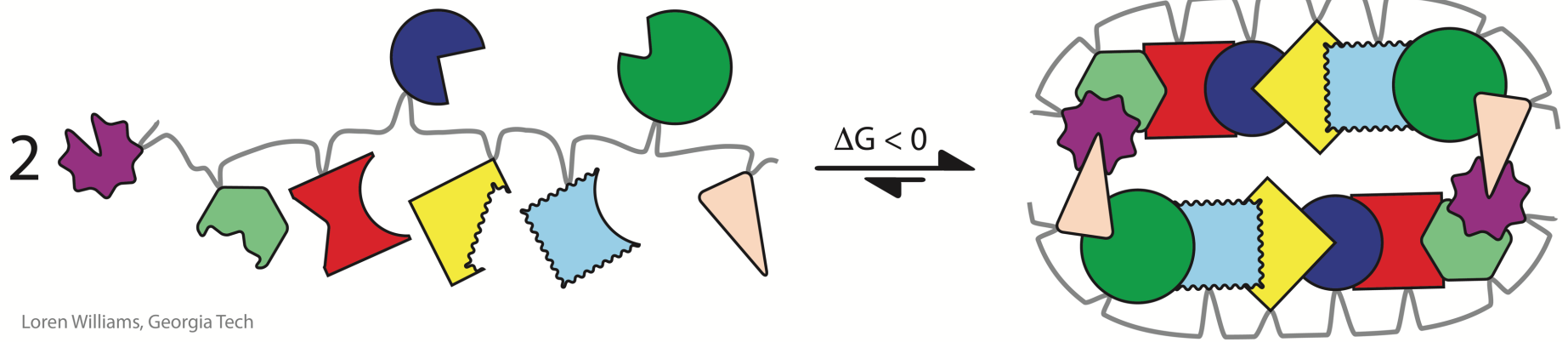


Loren Williams, Georgia Tech

A large entropy loss (and unfavorable free energy) for specific assembly of a complex mixture of monomer types. The number of states of disassembly and incorrect assembly is very large compared to the number of states of correct assembly. Imagine all the different ways those monomers on the left side can be arranged in solution.

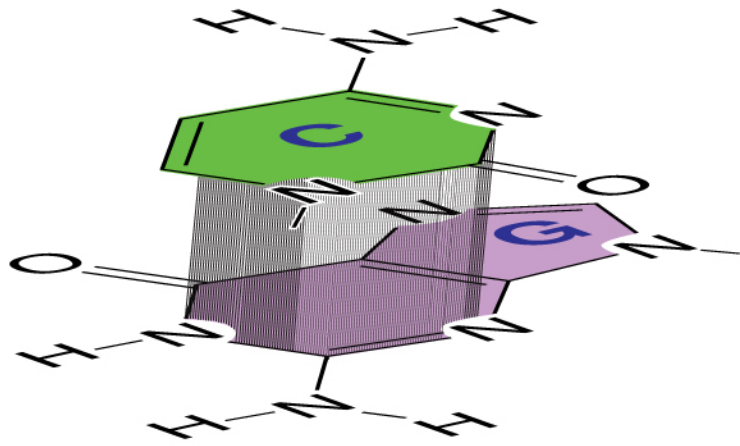


a more modest entropy loss (and more favorable free energy) for folding of polymer compared to assembly of monomers. The monomers lose many accessible states of disassembly during polymerization (paid for by ATP hydrolysis and billions of years of evolution). Therefore the loss of entropy during folding of the biopolymer is small.

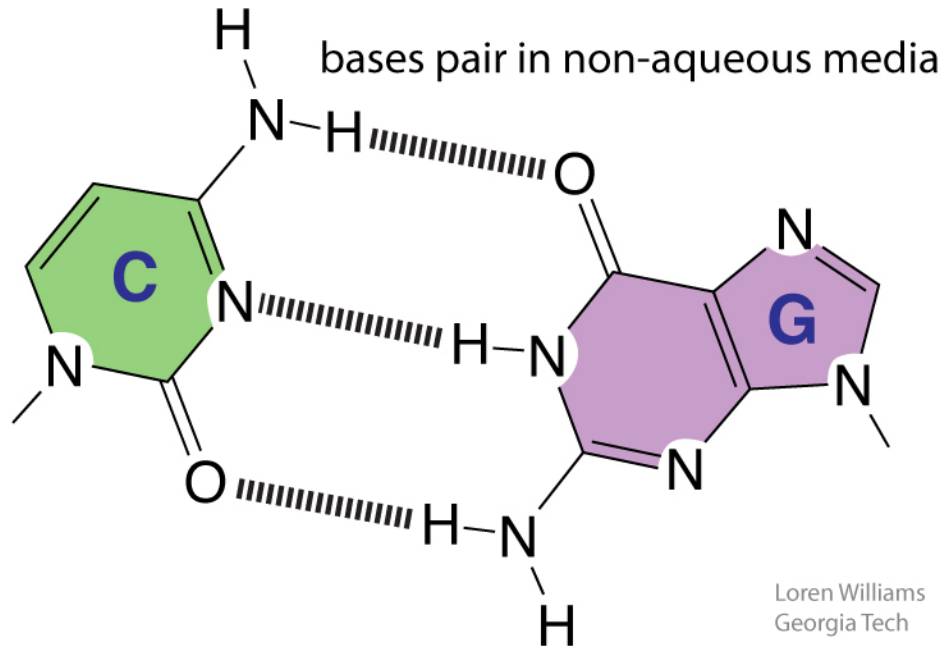


Folded polymers, with pre-organized functional groups can form complex assemblies.





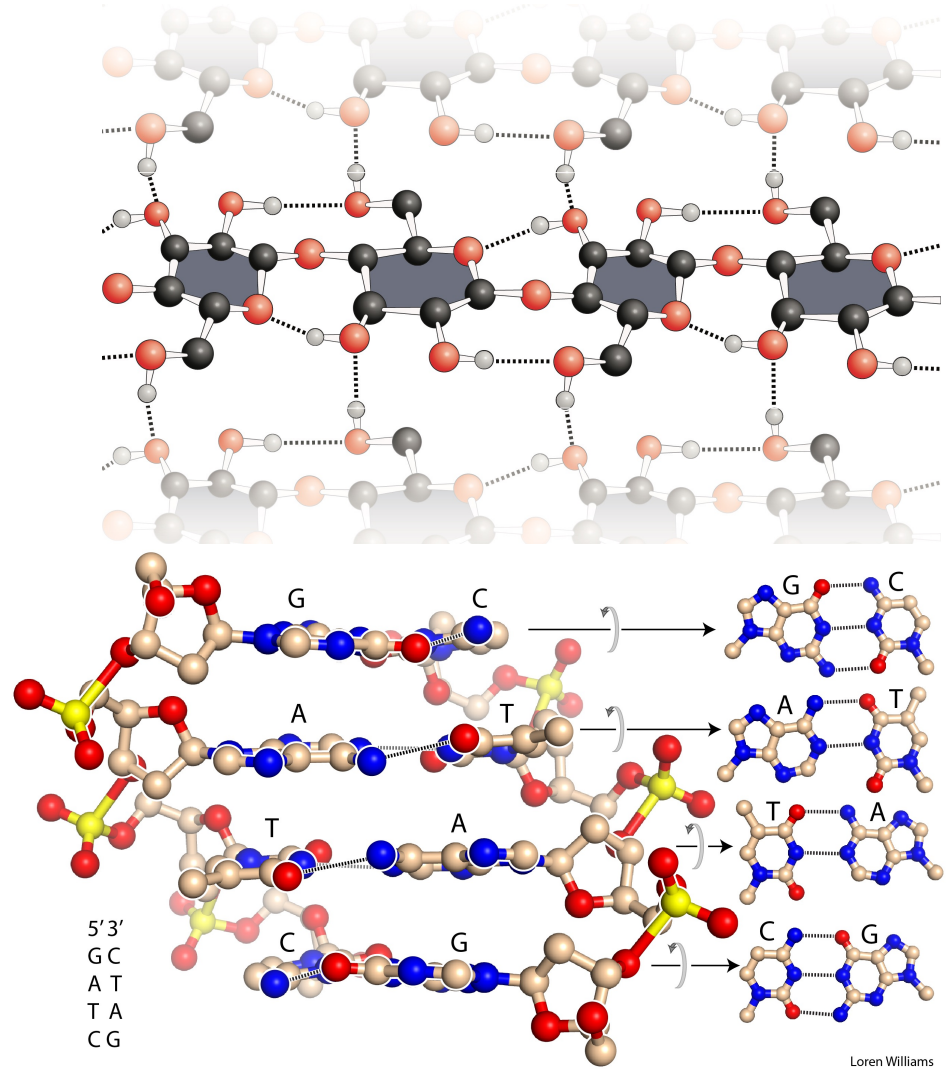
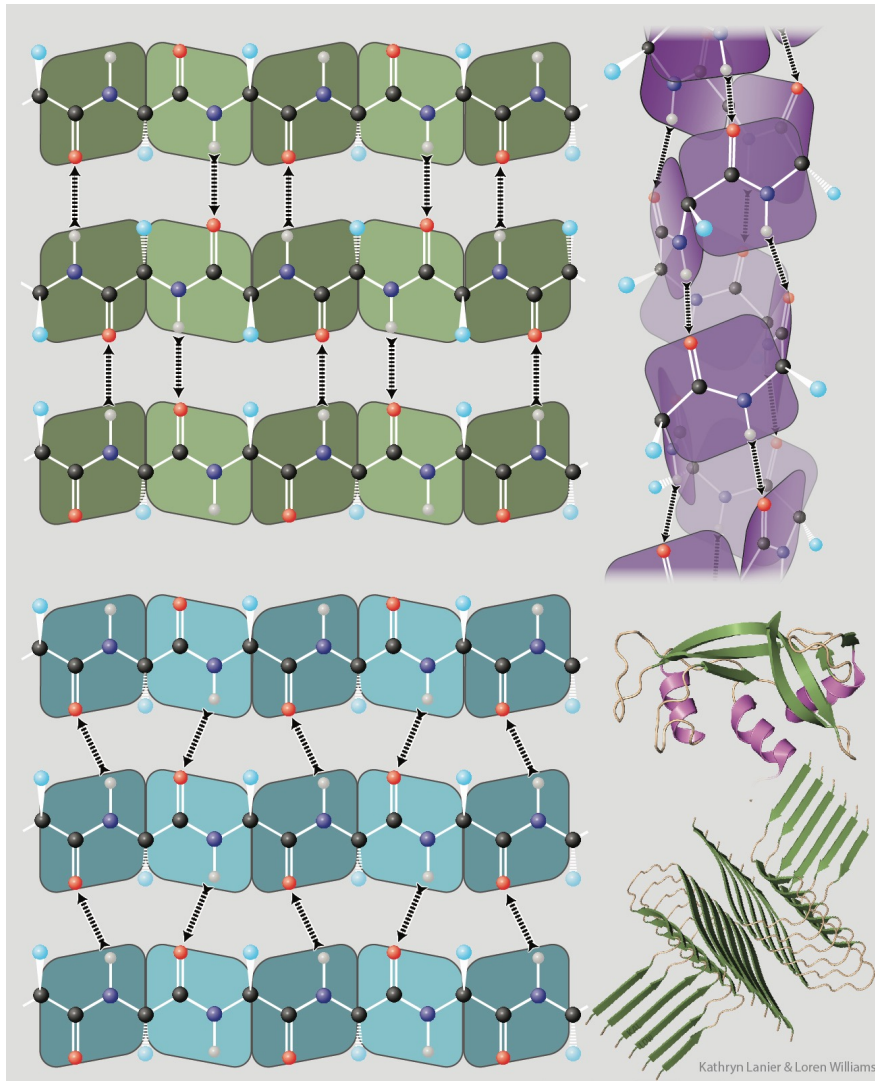
bases stack in aqueous media

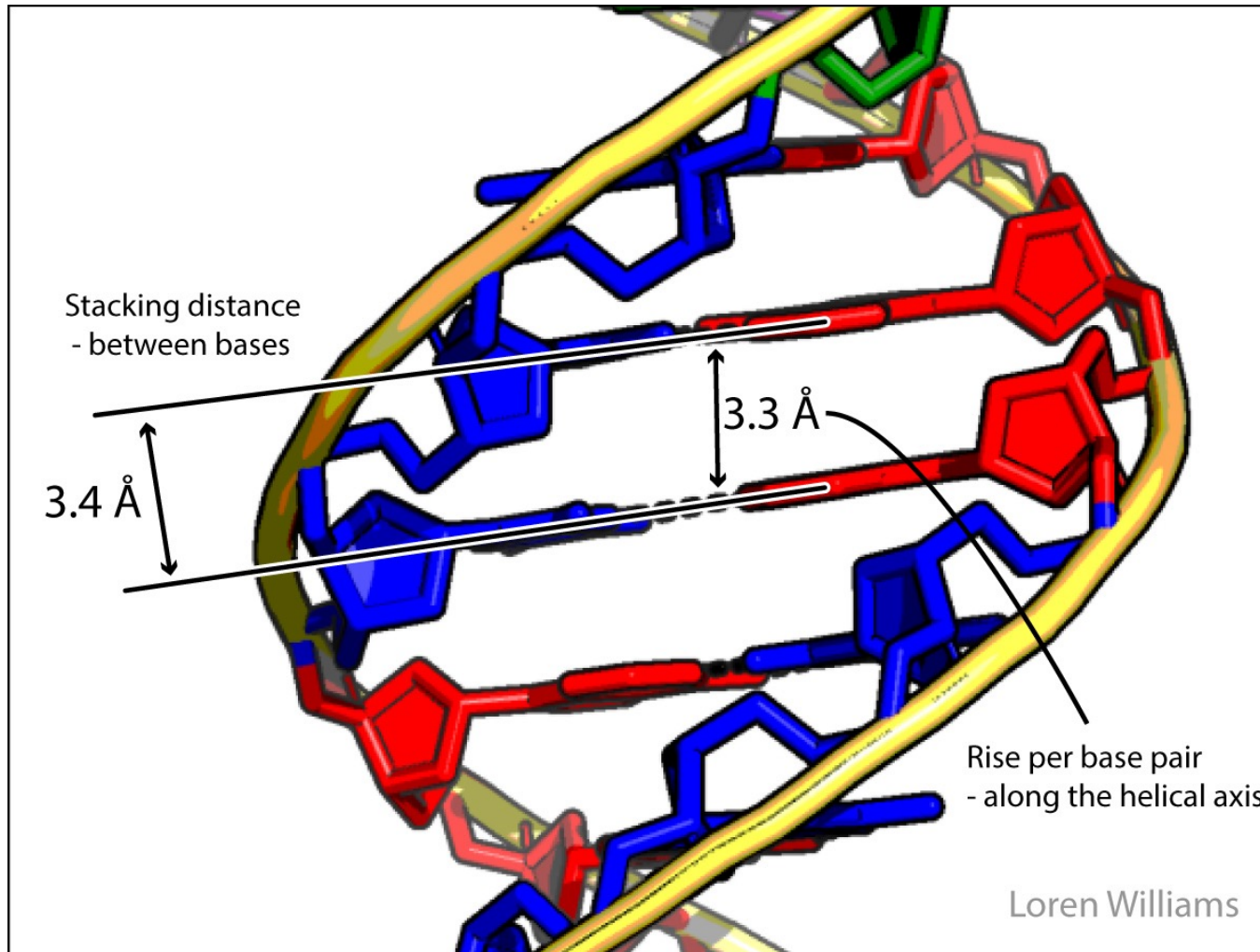


Loren Williams  
Georgia Tech

Figure 34 shows how the bases of mono-nucleosides stack in water and do not pair.

Bases of mono-nucleosides pair in non-aqueous media (like chloroform) and do not stack.





Base stacking in B-DNA. Short range repulsion sets a distance of 3.4 Å between base pairs. The helical rise is 3.3 Å/base pair.

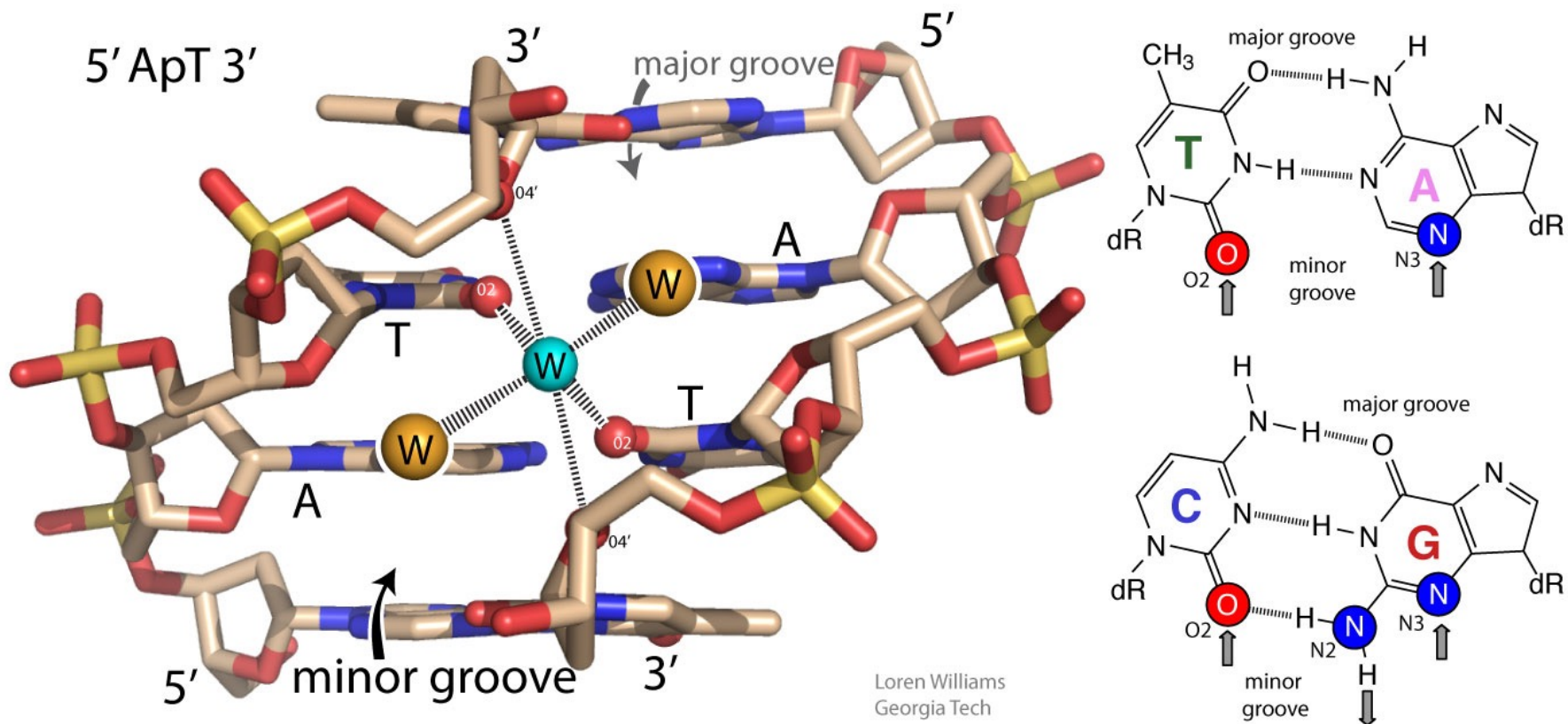
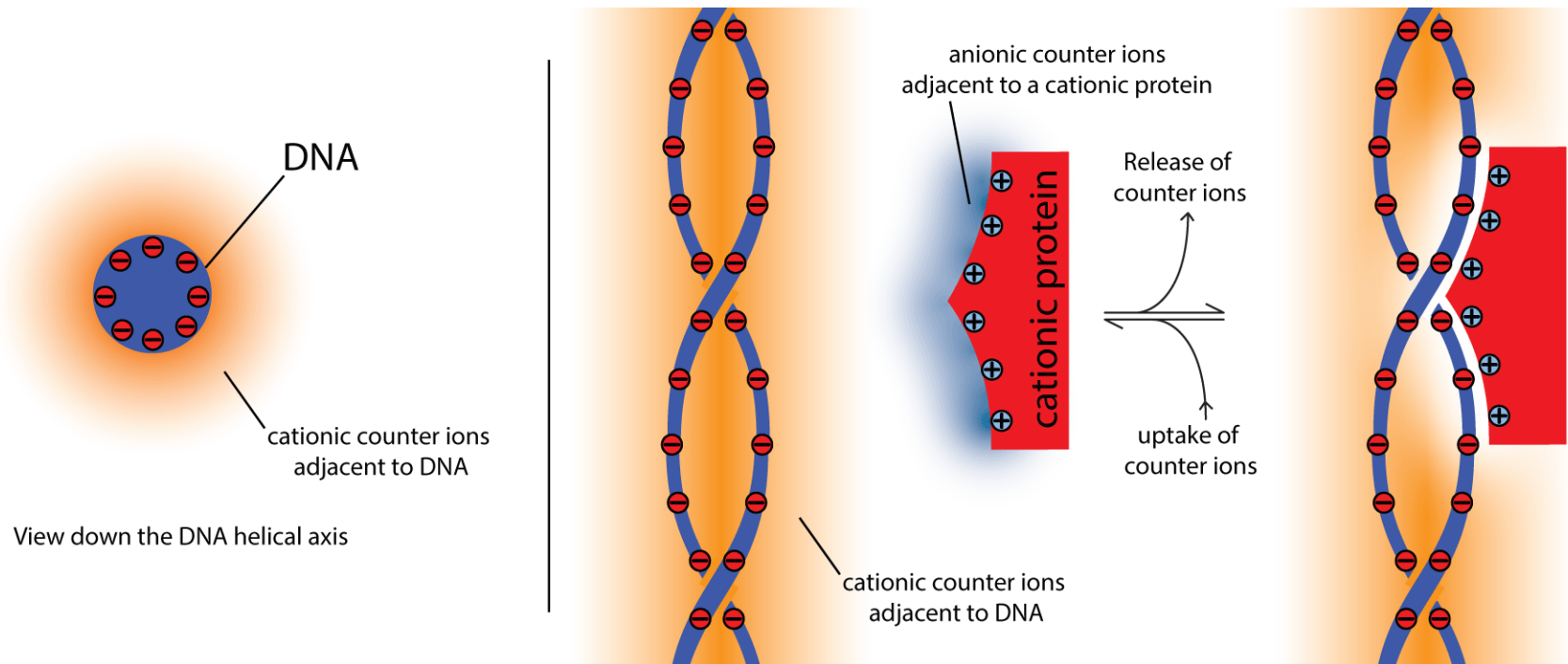


Figure 35 shows how AT-base pairs can cause water molecules to lose entropy. Hydrogen bonding interactions localize a water molecule (cyan) in the minor groove of an ApT step. Two keto oxygens (O2) and two O4' oxygens accept hydrogens from the water molecule, which accepts hydrogen bonds from two additional water molecules. Hydrogen atoms are not shown. GC base pairs have a wider minor groove and more polymorphic hydrogen bonding.



Loren Williams

An axial view of DNA, represented as an anionic cylinder. Cationic counterions (orange shading) surround the cylinder. The concentration of cations decreases with distance from the surface of the cylinder. The deeper orange shading indicates more concentrated cations. The panel on the right illustrates how both anionic counterions (blue) associated with a cationic protein, and cationic counterions (orange) associated with anionic DNA, are released to bulk solution when the protein binds to DNA. This release of counterions drives the association (by contributing  $+T\Delta S$ ).