Essential Forces in Protein Folding

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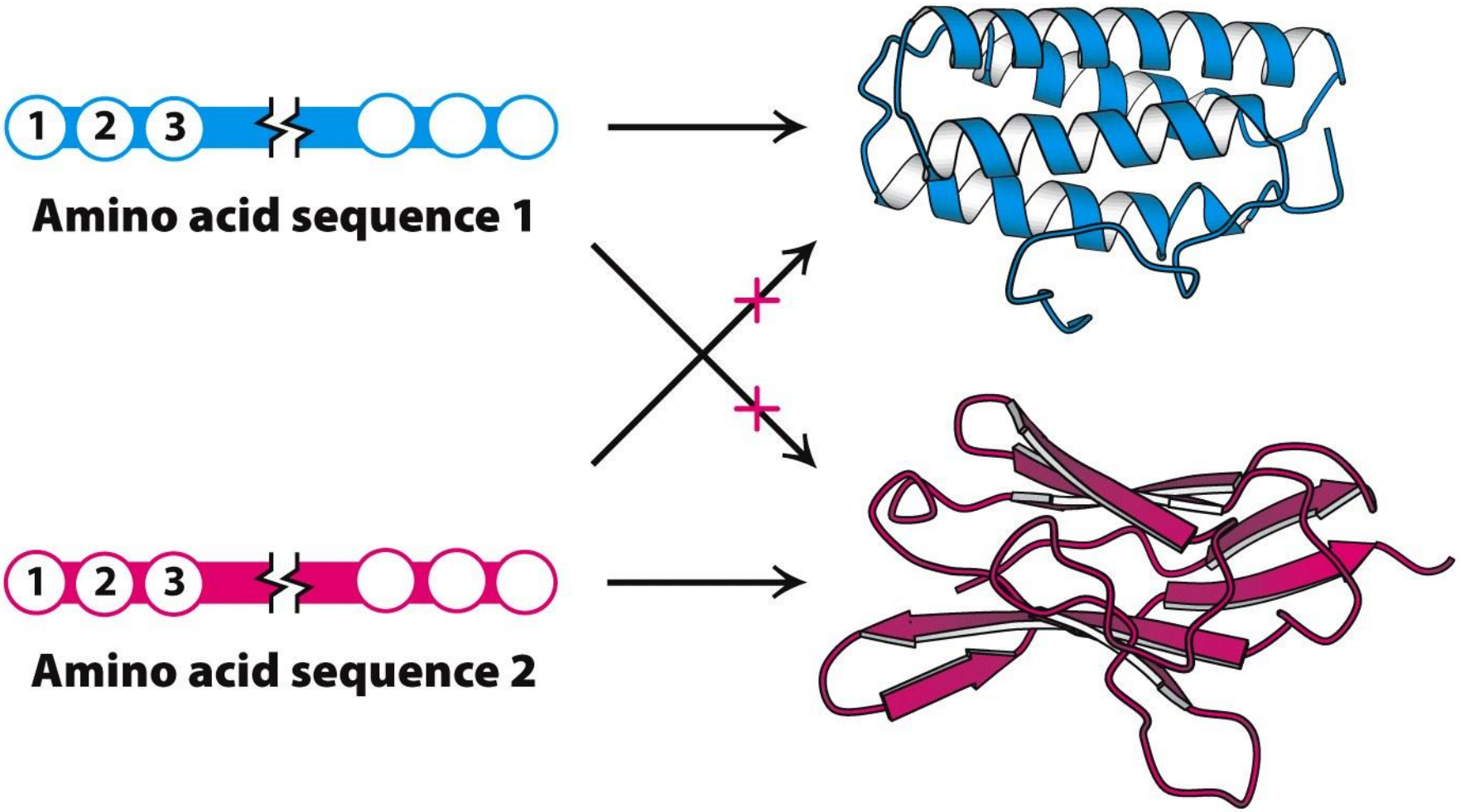
Previously on PHT 426!!

Amino Acid sequence defines the protein conformation

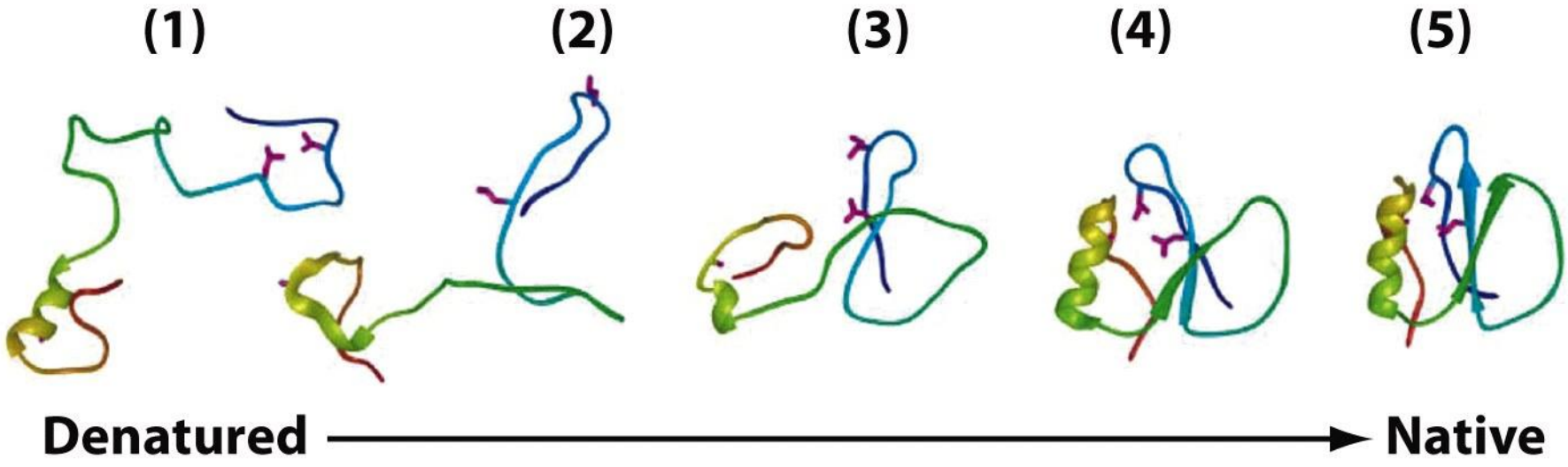


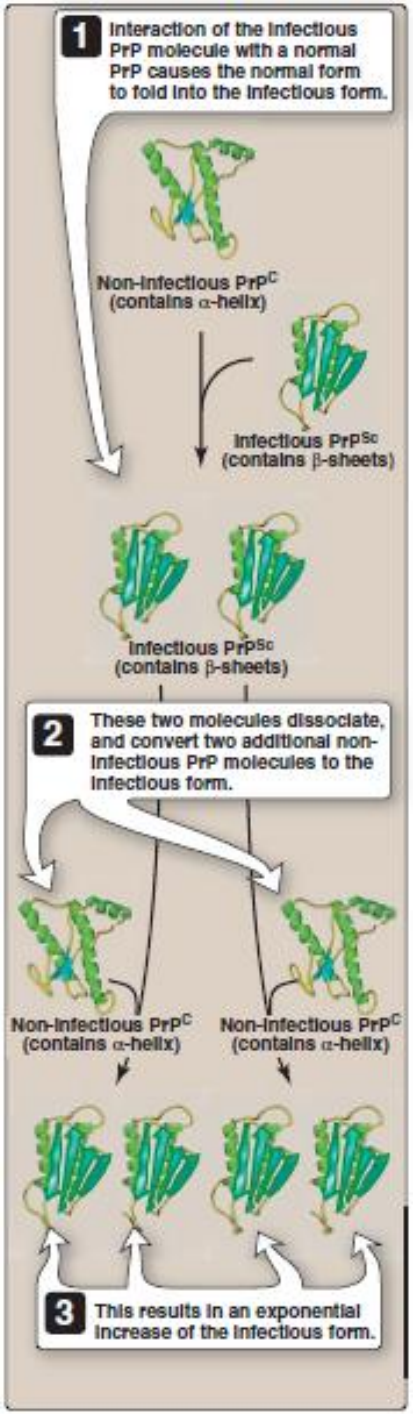
Why do proteins have to fold correctly???

• Proteins become functional only when they adopt a distinct folded state.

• Many physiologically and therapeutically important proteins present their surface for recognition by interacting with molecules such as substrates, receptors, signaling proteins and cell surface adhesion molecules.

• When proteins do not fold correctly (misfolding) there can be serious health consequences, including many well known diseases, such as Alzheimer's, Mad Cow (Bovine spongiform encephalopathy), Creutzfeldt–Jakob disease, Huntington's and Parkinson's disease.

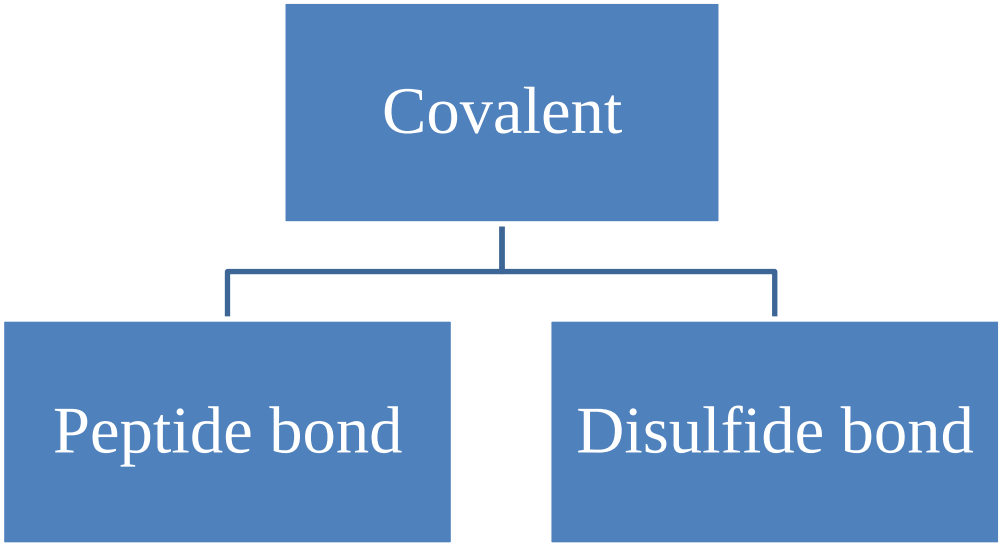




An example of what could happen **<u>"Prion disease"</u>**:

The prion protein (PrP) has been strongly implicated as the causative agent of transmissible spongiform encephalopathies (TSEs), including Creutzfeldt-Jakob disease in humans, and bovine spongiform encephalopathy in cattle (popularly called "mad cow disease"). This infectious protein is designated PrPSc (Sc = scrapie). It is highly resistant to proteolytic degradation, and tends to form insoluble aggregates of fibrils, similar to the amyloid found in some other diseases of the brain. No primary structure differences have been found between the normal and the infectious forms of the protein. **The key to becoming infectious apparently lies in changes in the three-dimensional conformation of PrPC.** It has been observed that a number of α-helices present in noninfectious PrPC are replaced by β-sheets in the infectious form. It is presumably this conformational difference that confers relative resistance to proteolytic degradation of infectious prions, and permits them to be distinguished from the normal PrPC in infected tissue. The infective agent is thus an altered version of a normal protein, which acts as a "template" for converting the normal protein to the pathogenic conformation. The TSEs are invariably fatal, and no treatment is currently available that can alter this outcome.

Essential forces in Proteins folding



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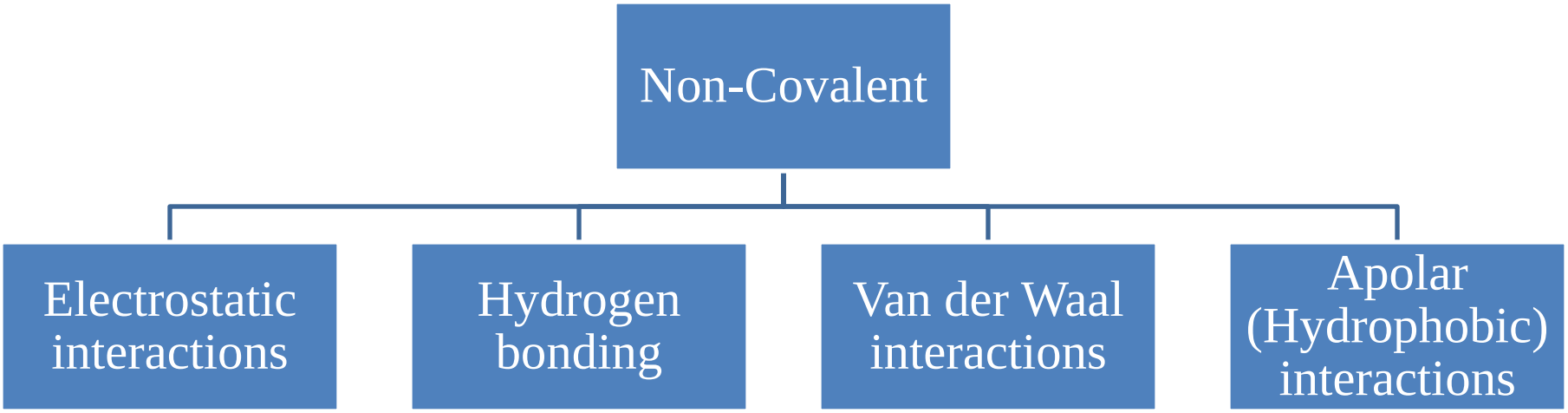
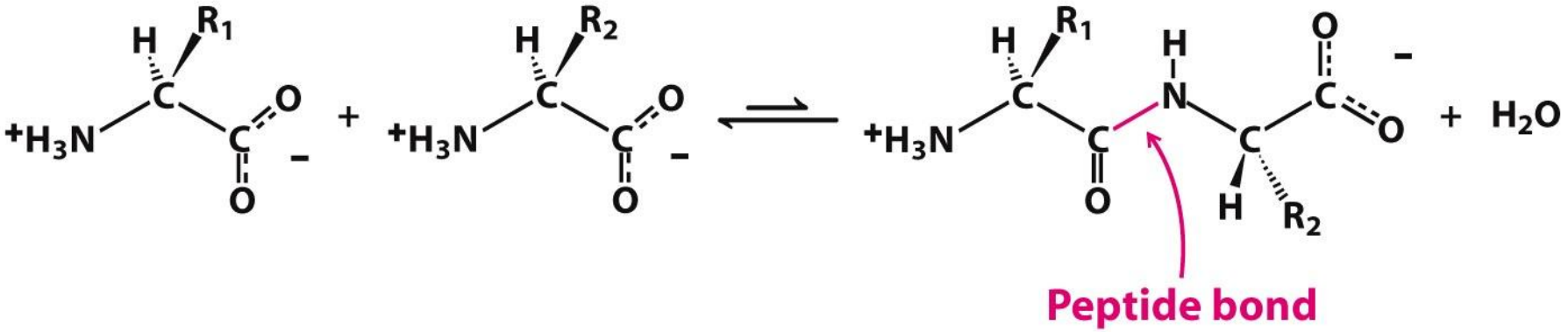
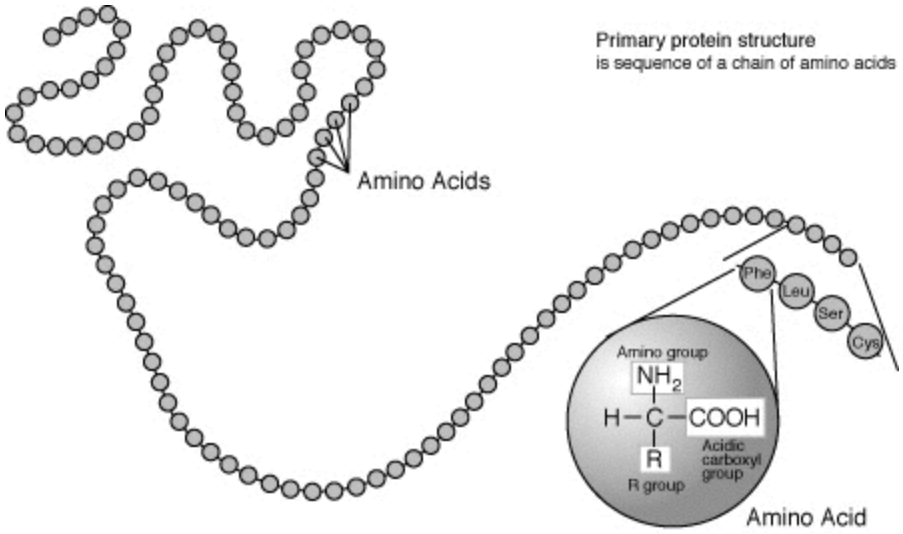


Covalent Interactions

A- Peptide bond:

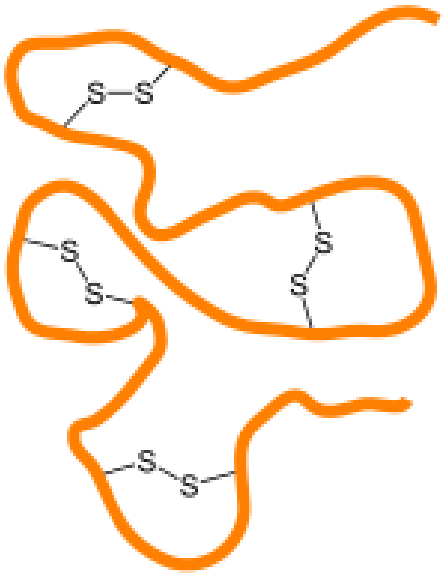


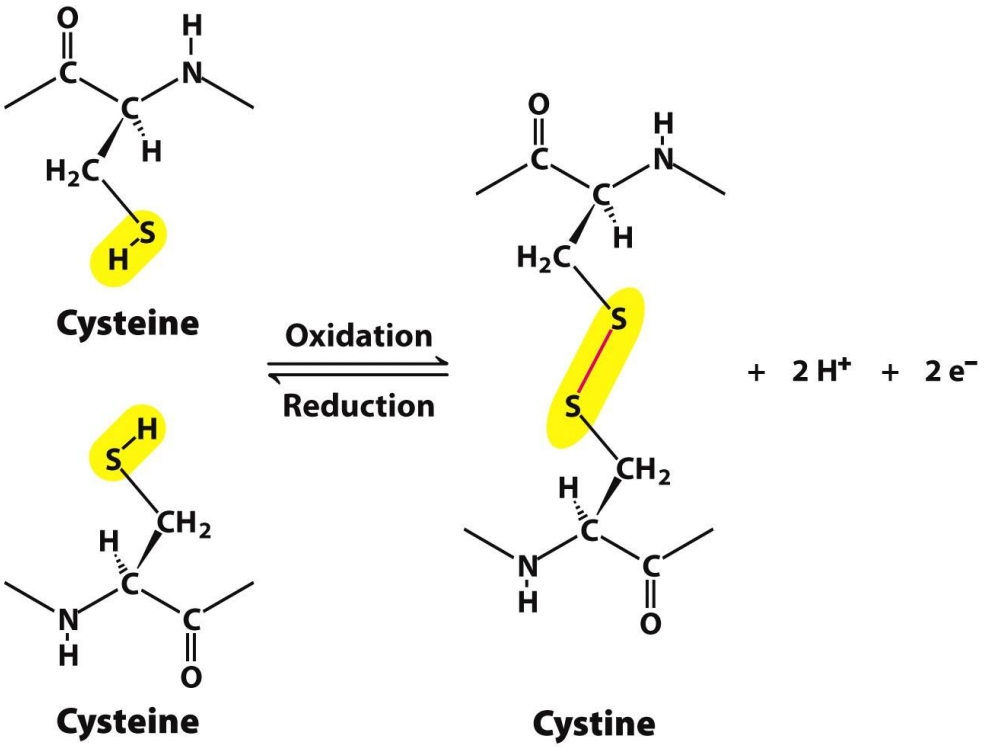


Covalent Interactions

B- Disulfide bond:

- Occurs between two Cysteins
- Reactivity is enhanced by:
  - Basic pH conditions (9-9.5)
  - Oxygen
  - Metal ions (Cu^{2+}, Fe^{2+}, Mn^{2+})





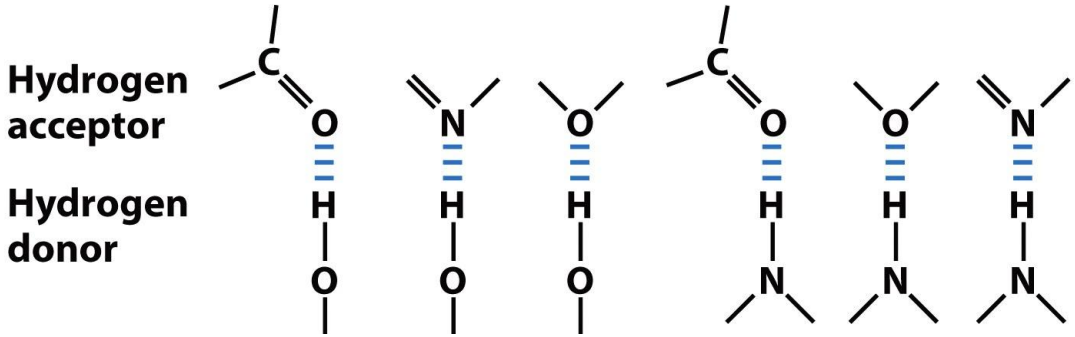
Non Covalent Interactions

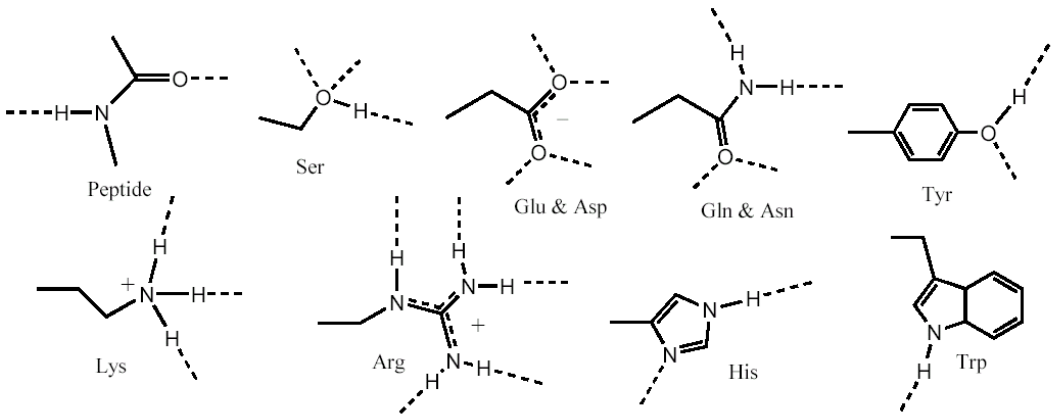
Electrostatic Interactions

A- Hydrogen bonding:

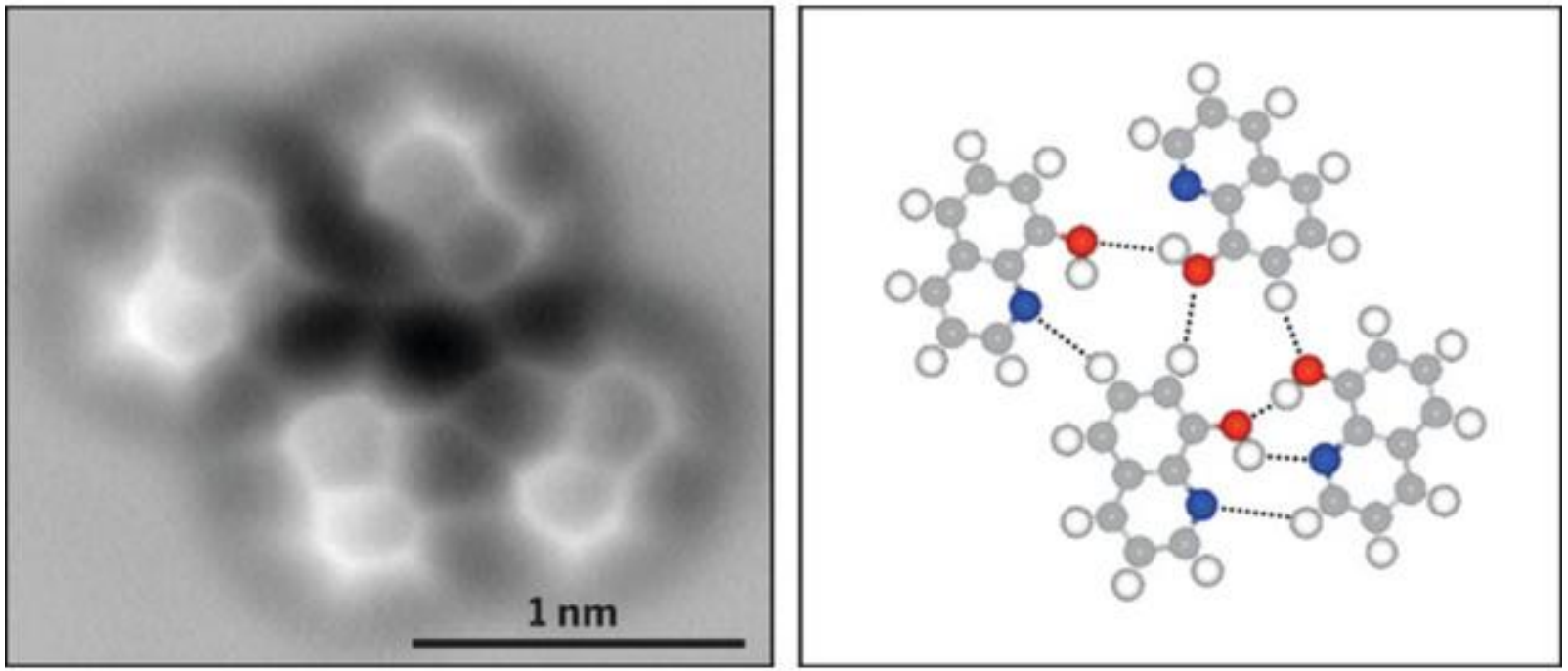
• Occurs when two elecronegative atoms compete for the same hydrogen atom

• The hydrogen atom is covalently bound to one of the atoms (the donor) and interacts favorably with the other (the acceptor).





The Very First Image of a Hydrogen Bond



Atomic Force Microscope (AFM) images of 8-hydroxyquinoline on a copper surface show hydrogen-bonding interactions at low temperature;
C = gray, H = white, O = red, N = blue.
Credit: Science.

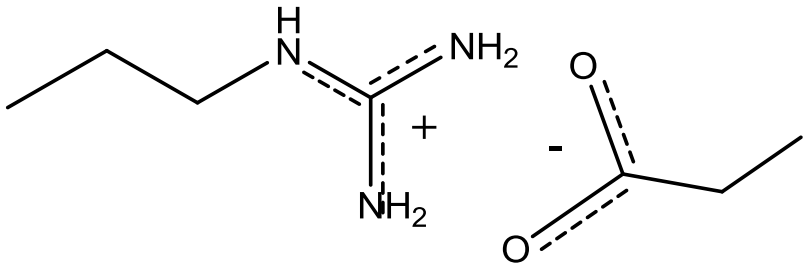
Non Covalent Interactions

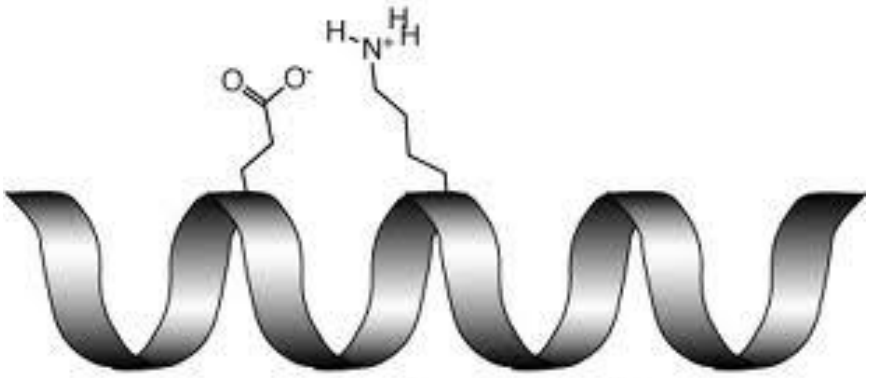
Electrostatic Interactions

B- Charge-Charge interactions (Salt bridges):

• Occurs between Cationic Residues (Arginine/Lysine) and Anionic Residues (Aspartic and Glutamic Acids).

• Usually consist not only of charge-charge interactions, but also of some degree of hydrogen bonding.

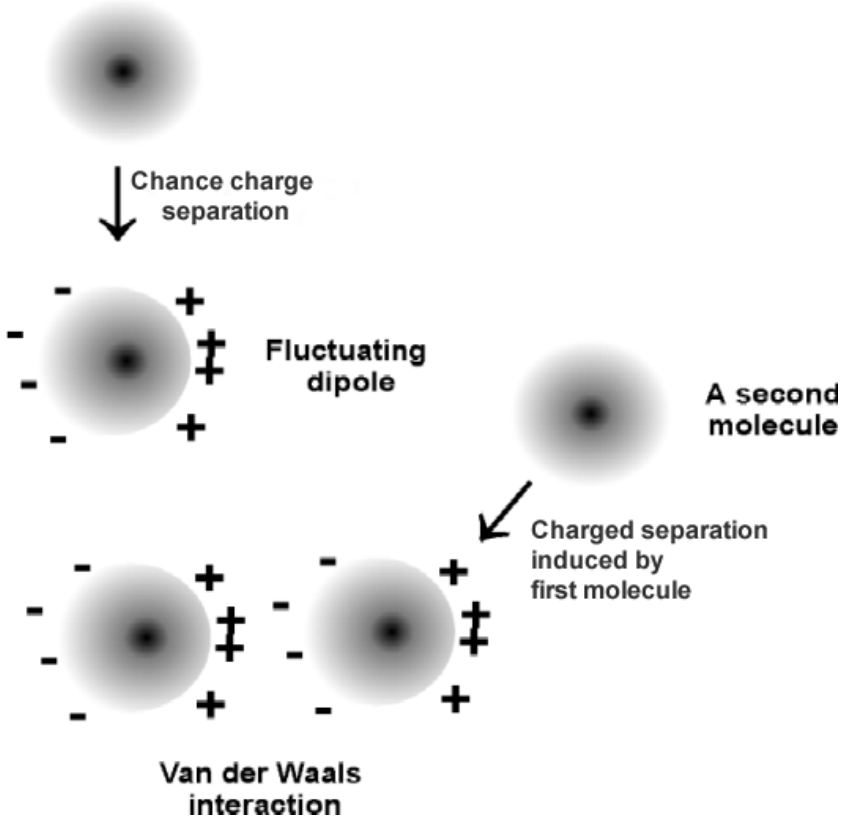


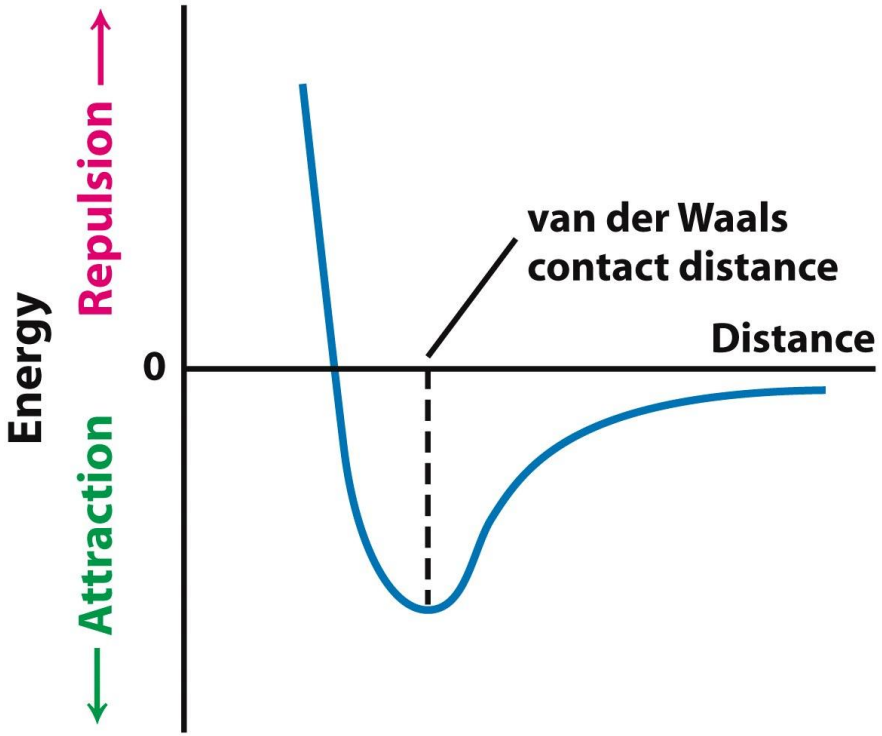


Non Covalent Interactions

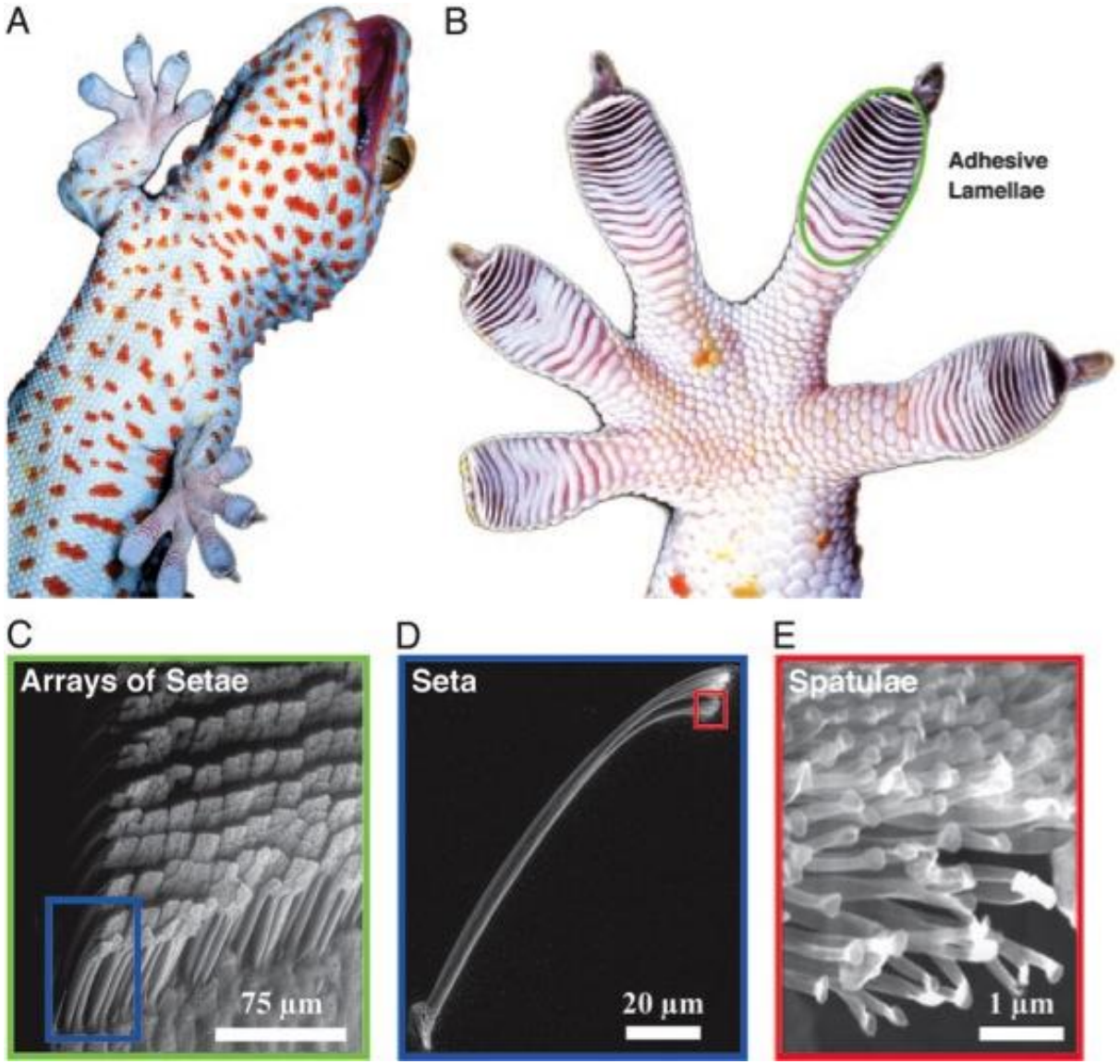
C- Van der Waals interactions:

- Exist between atoms whether they are polar or non polar.
- They arise from the net attractive interactions between fluctuating dipoles.





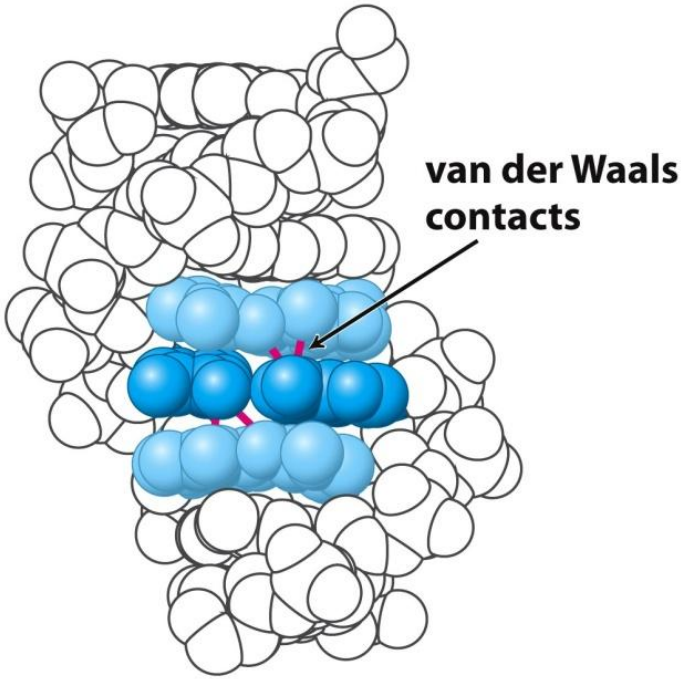
Geckos are sticky because of Van der Waal interactions!!!



Non Covalent Interactions

D- Apolar (Hydrophobic) interactions:

• The tendency of nonpolar groups in water to self-associate and thereby minimize their contact surface area with the polar solvent.
• Reflects the summation of the Van der Waals attractive forces among non-polar groups in the protein interior, which changes the surrounding water structure necessary to accommodate these groups if they become exposed.
• Thus, non-polar groups preferentially reside in the protein interior, while the more polar groups are exposed to the surface and surrounding environment.



Protein forces summary