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Engineering®**

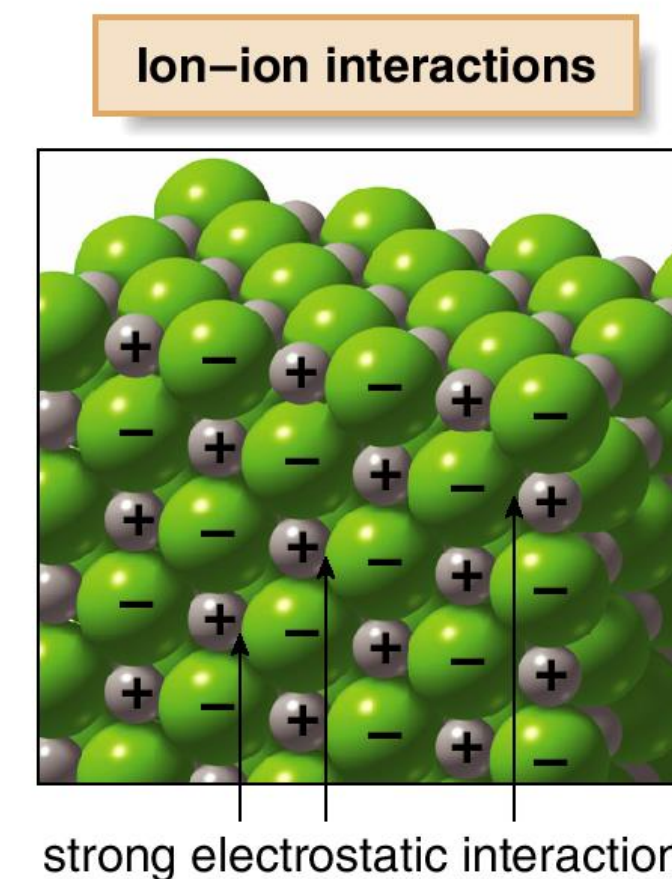
*Go, change the
world*

Computational Chemistry

UNIT-II**Computational Chemistry****08 Hrs**

Scope, cost and efficiency of computational modeling. Stabilizing interactions: Bonded and non-bonded interactions. Molecular topology, topological matrix representation, topological indices, QSAR/QSPC concept for insilico prediction of properties. 3D co-ordinate generation for small molecules, geometry optimization.

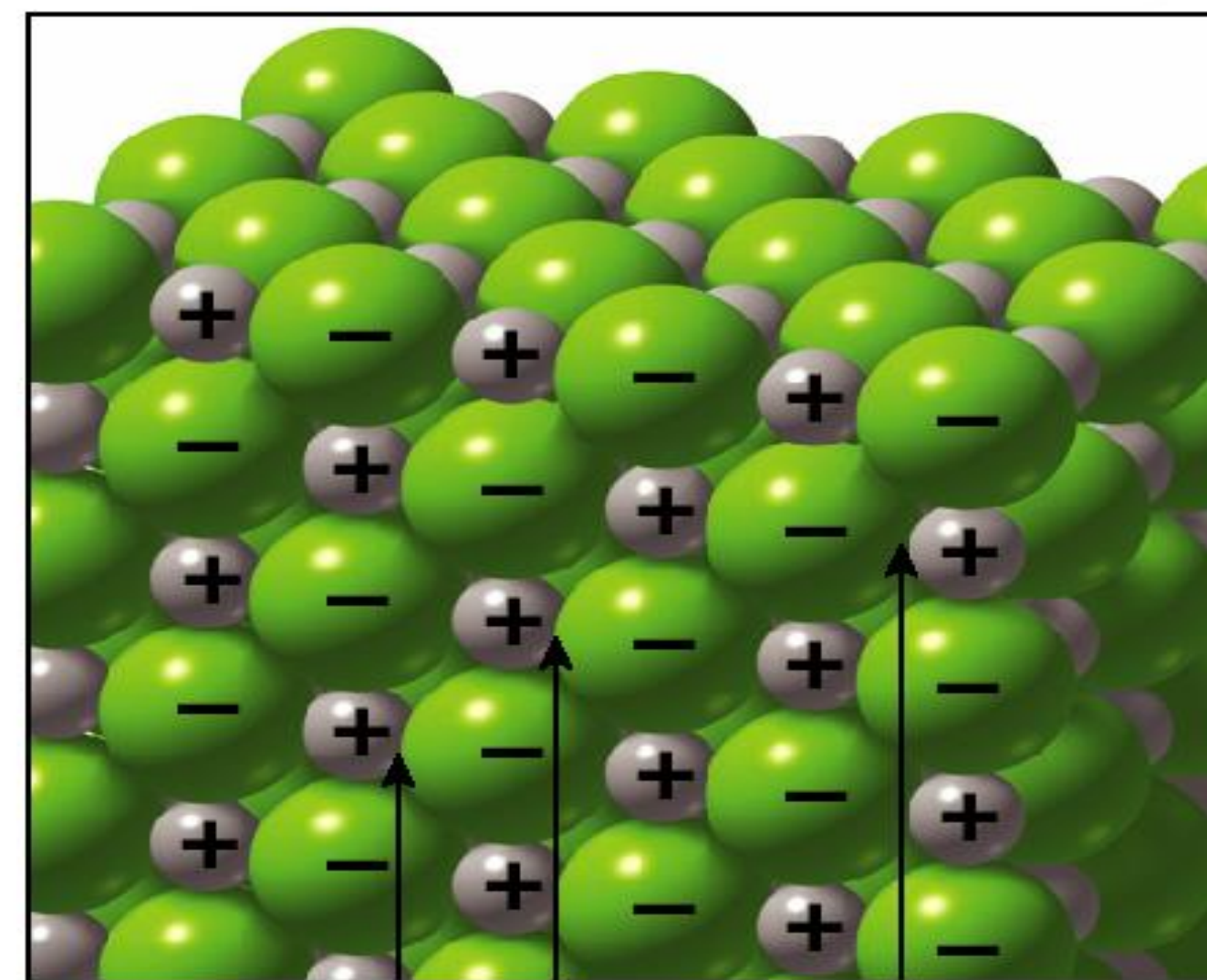
- Intermolecular forces are interactions that exist between molecules. Functional groups determine the type and strength of these interactions.
- There are several types of intermolecular interactions.
- Ionic compounds contain oppositely charged particles held together by extremely strong electrostatic interactions. These ionic interactions are much stronger than the intermolecular forces present between covalent molecules.
- Covalent compounds are composed of discrete molecules.
- The nature of the forces between molecules depends on the functional group present. There are three different types of interactions, shown below in order of increasing strength:
 - van der Waals forces
 - dipole-dipole interactions
 - hydrogen bonding



- Intermolecular forces are interactions that exist between molecules. Functional groups determine the type and strength of these interactions.
- There are several types of intermolecular interactions.
 - Ionic interactions occur between cations and anions.
 - These bonds are non-directional
 - These ionic inter-actions are much stronger than the intermolecular forces present between covalent molecules.
 - Strength depends on the distance of separation (r) according to $1/r^2$. Strength also depends on the medium (dielectric constant), and is less in polar than nonpolar solvents.

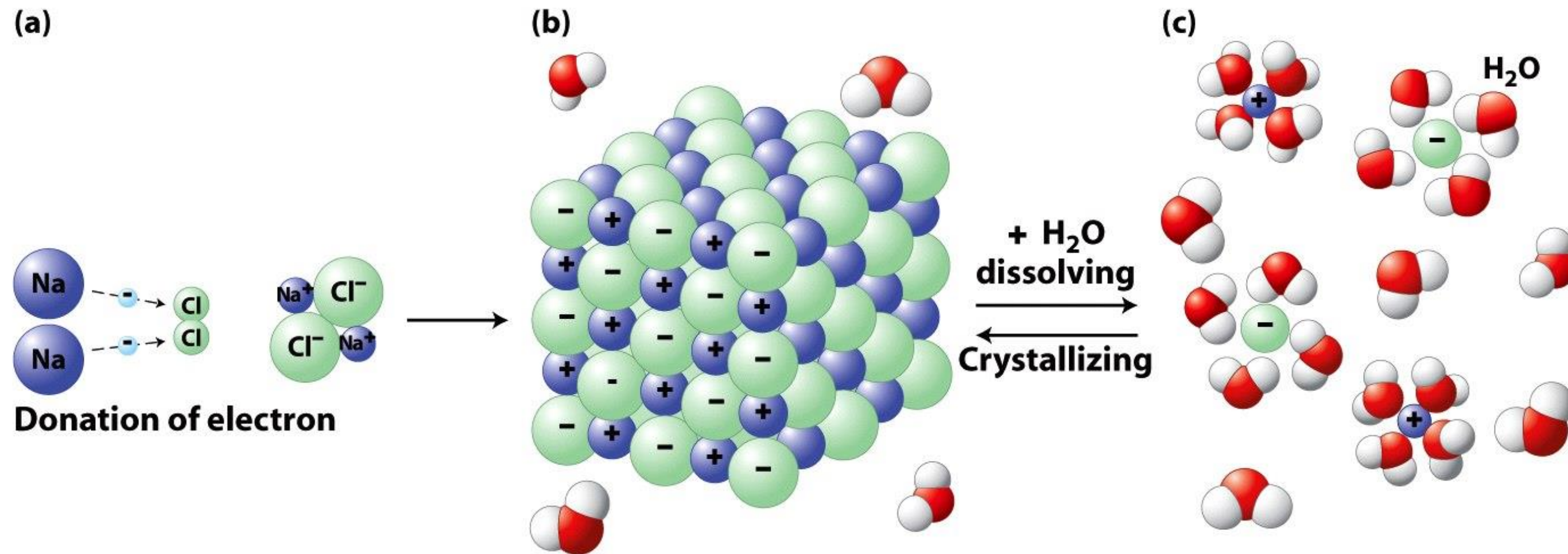
Ionic compounds such as NaCl are readily dissolved in water. Solvation spheres of water molecules surround ions in solutions. Water molecules orient so that the negative ends of their dipoles contact cations and the positive ends contact anions in solution.

Ion-ion interactions



strong electrostatic interaction

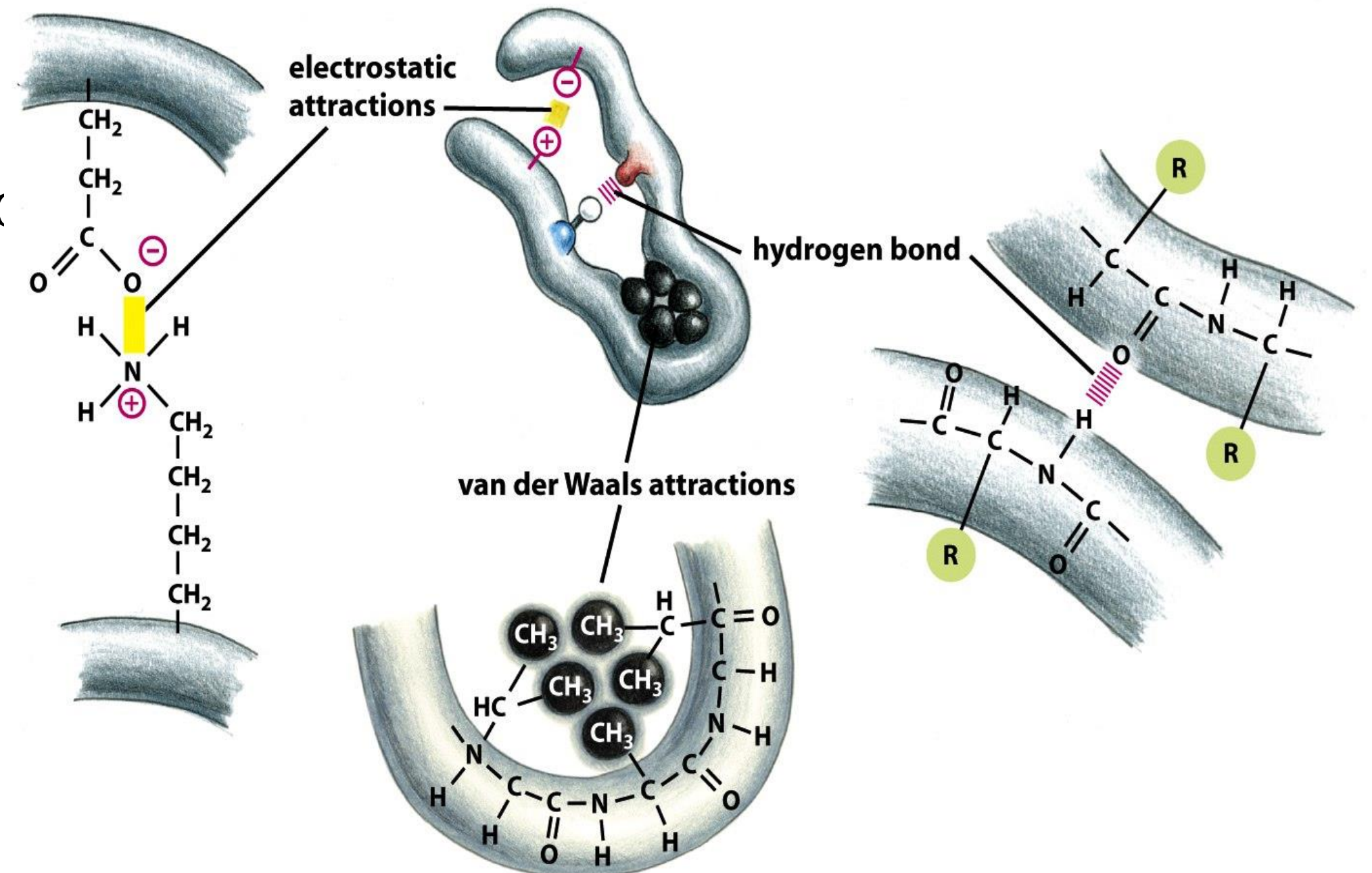
Ionic compounds such as NaCl are readily dissolved in water. Solvation spheres of water molecules surround ions in solutions. Water molecules orient so that the negative ends of their dipoles contact cations and the positive ends contact anions in solution.



Favorable electrostatic interactions cause the vapor pressure of sodium chloride and other salts to be very low. If you leave crystals of table salt (NaCl ; Na^+ =cation, Cl^- =anion) on a hot pan, how long does it take before they vaporize and sublime away? A very very long time; electrostatic interactions are very very strong. The electrostatic interactions within a sodium chloride crystal are called ionic bonds. But when a single cation and a single anion are close together, within a protein, or within a folded RNA, those interactions are considered to be non-covalent electrostatic interactions.

Noncovalent interactions determine protein structure

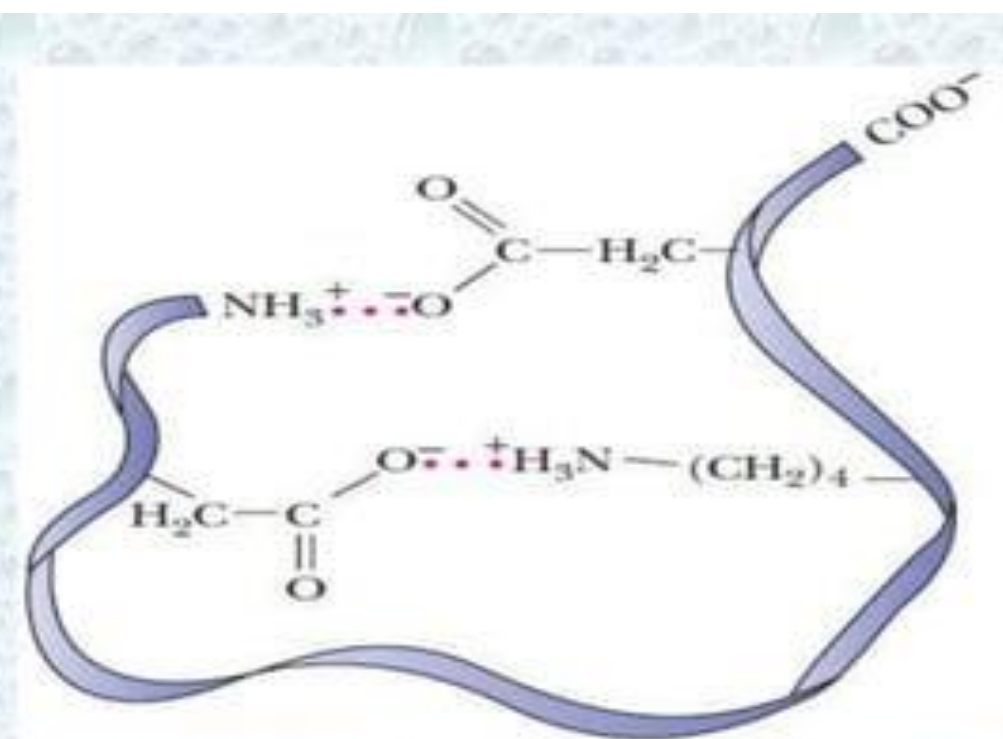
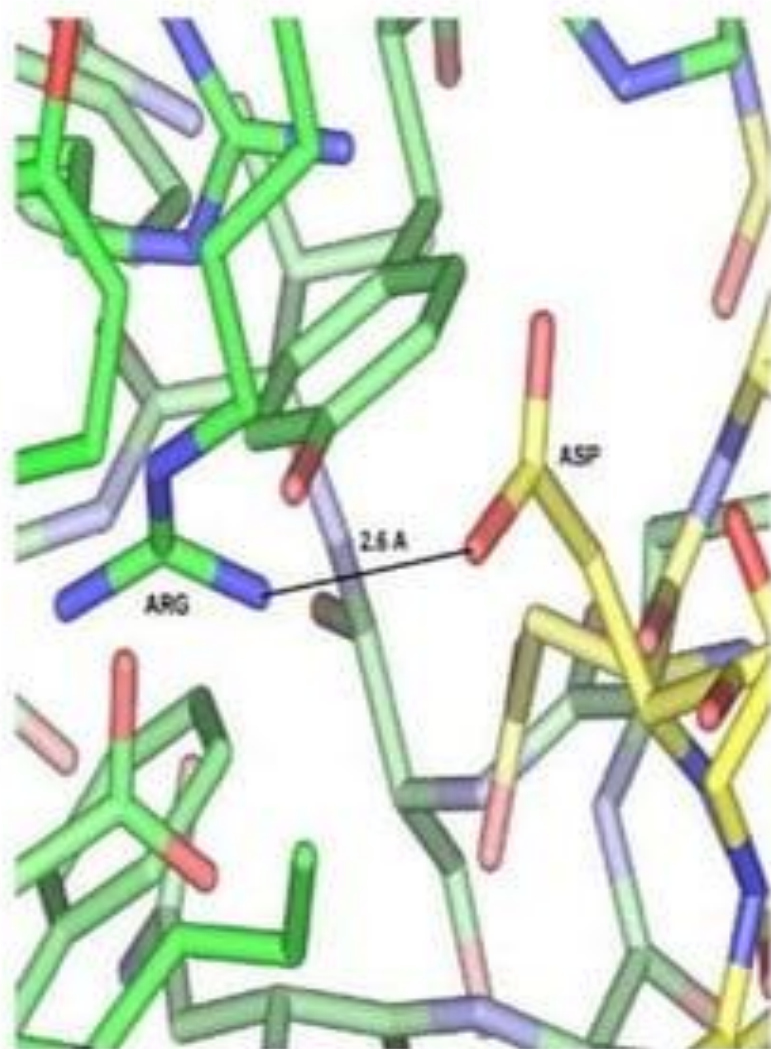
- Amino acids are connected by *covalent* bonds called peptide bonds.
- *noncovalent* interactions between amino acids affect protein structure



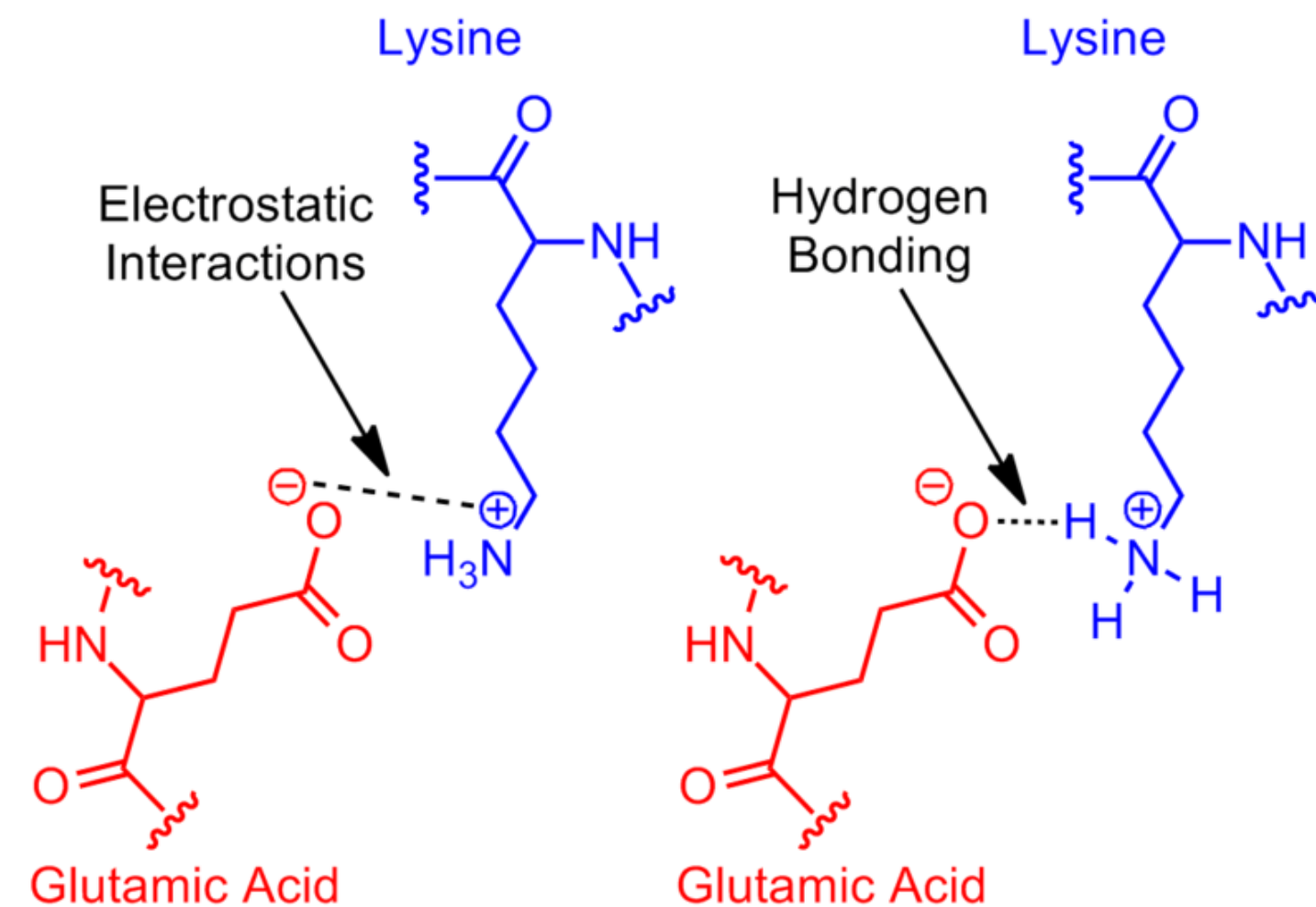
A salt bridge is a *non-covalent interaction between two ionized sites*. It has two components: a hydrogen bond and an electrostatic interaction. Salt bridges in proteins are bonds between oppositely charged residues that are sufficiently close to each other to experience electrostatic attraction.

Salt Bridges

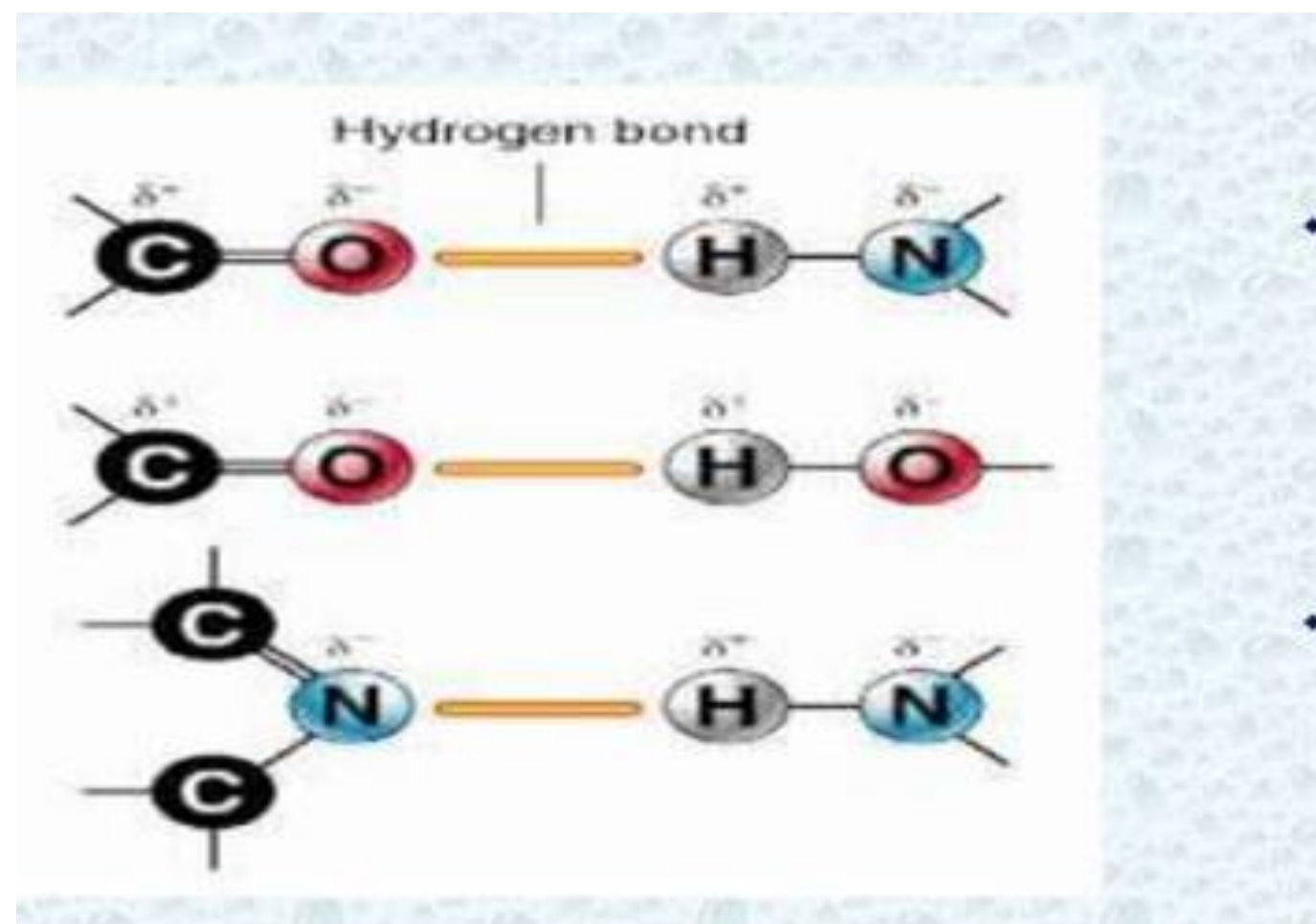
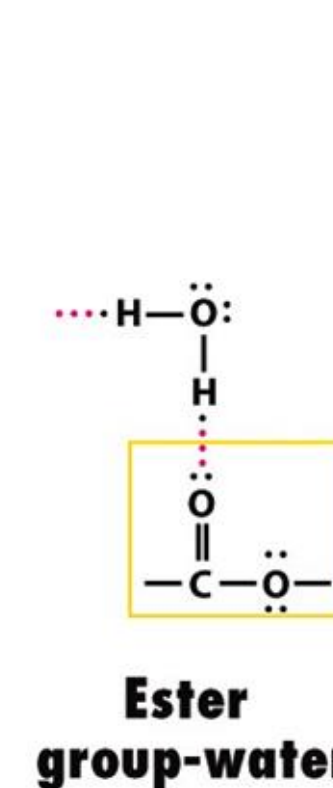
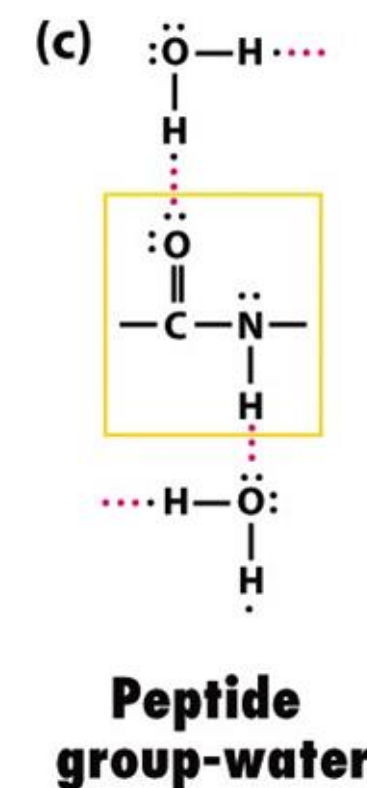
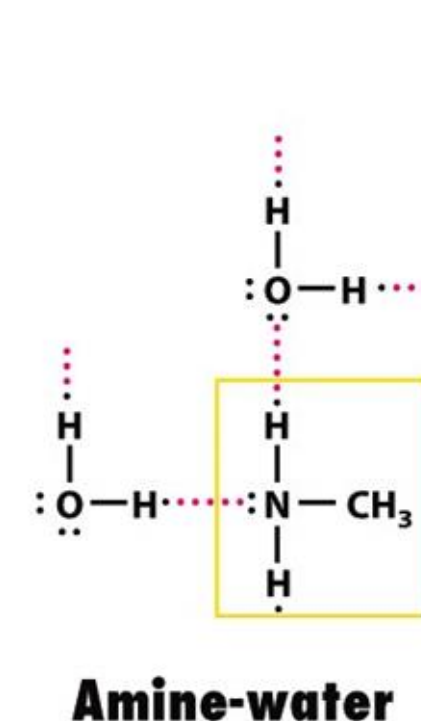
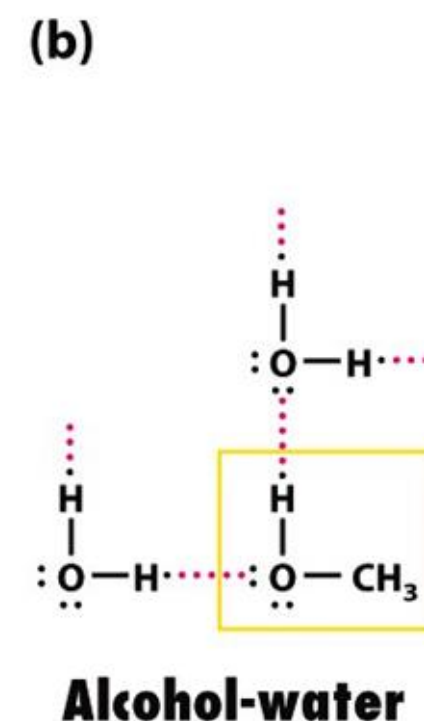
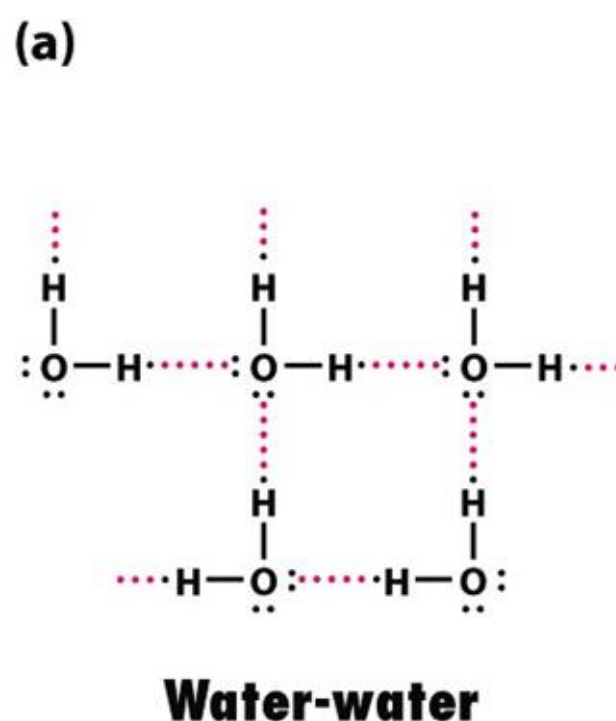
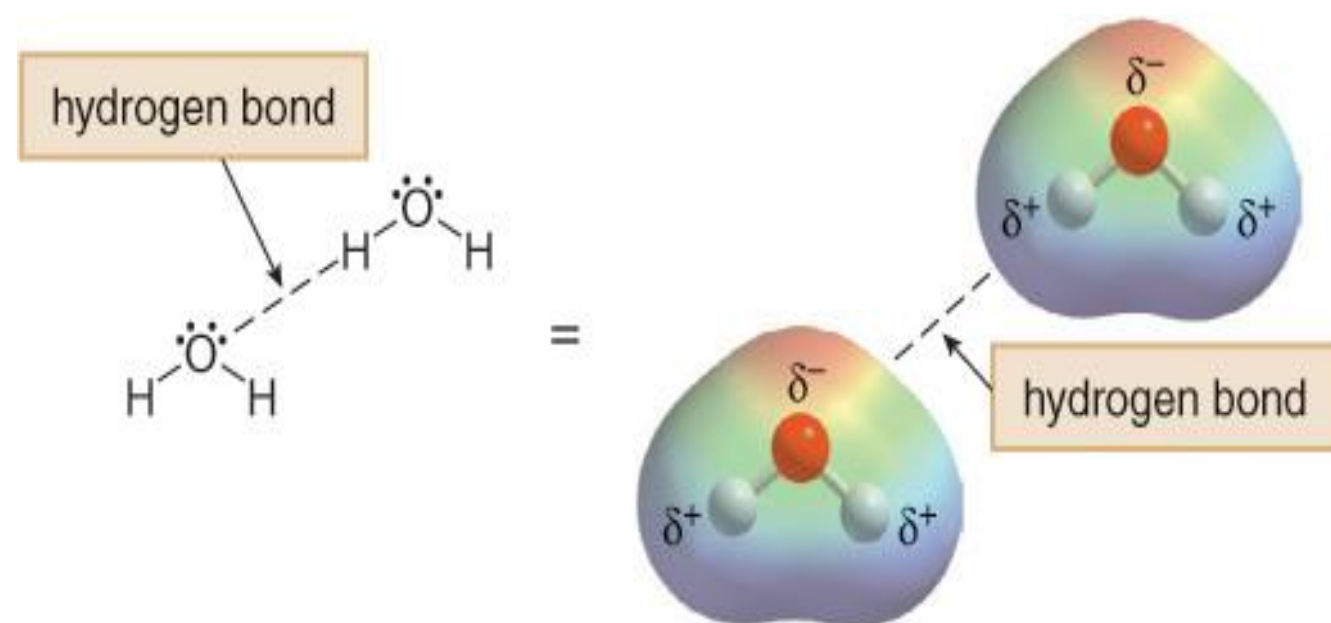
- Salt bridges are electrostatic bonds between oppositely charged groups
- The strength is usually 4-7 kcal/mol



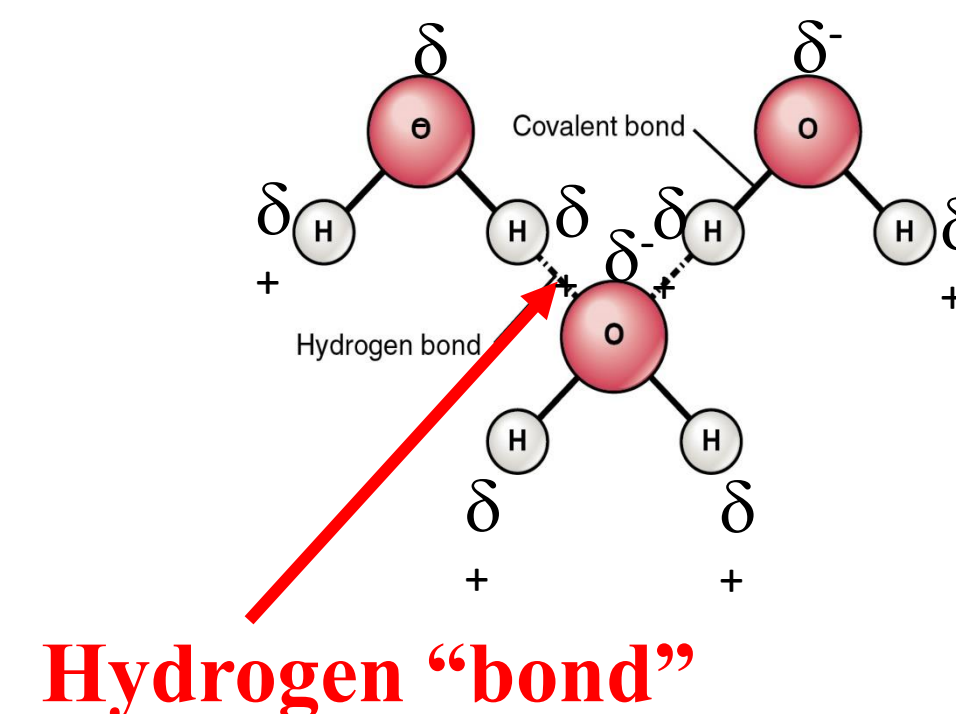
- Ions on R groups form salt bridges through ionic bonds.
- NH_3^+ and COO^- areas of the protein attract and form ionic bonds.

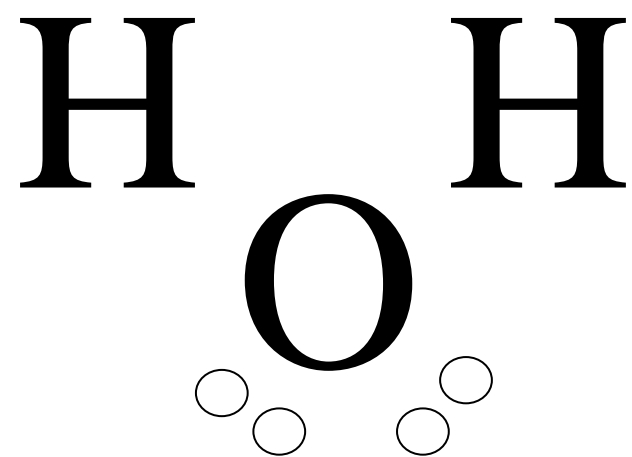


Hydrogen bonding typically occurs when a hydrogen atom bonded to O, N, or F, is electrostatically attracted to a lone pair of electrons on an O, N, or F atom in another molecule.



- ❖ H bonds are weak which allows to be broken and reformed easily.
- ❖ Allows structural change and produces 'functional' molecules

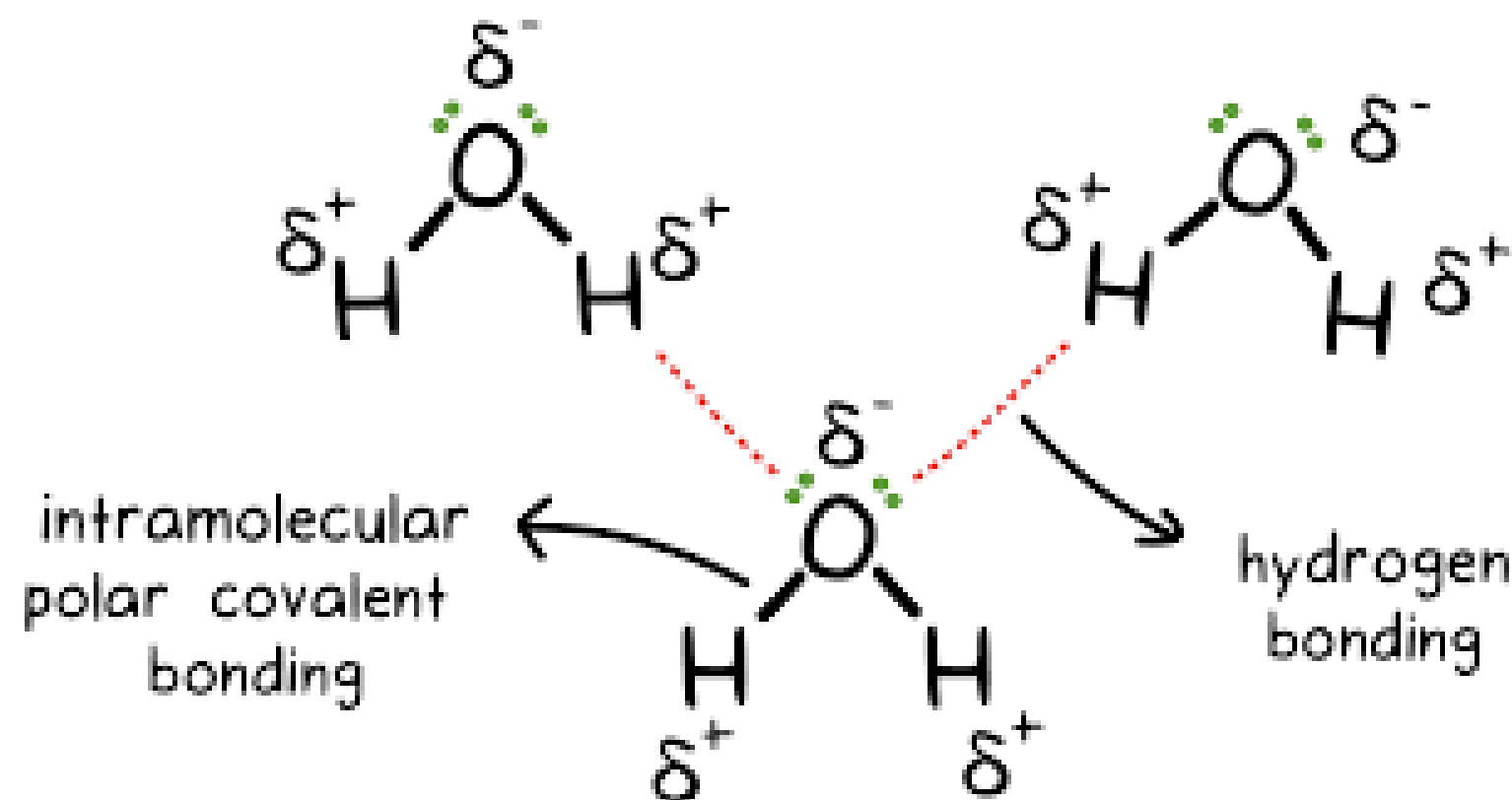




Water is a **POLAR** molecule, there are unshared pairs of electrons on the central atom.

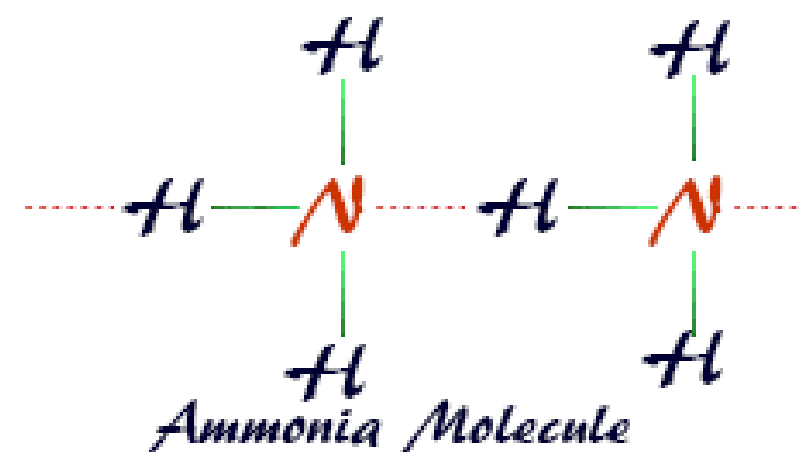
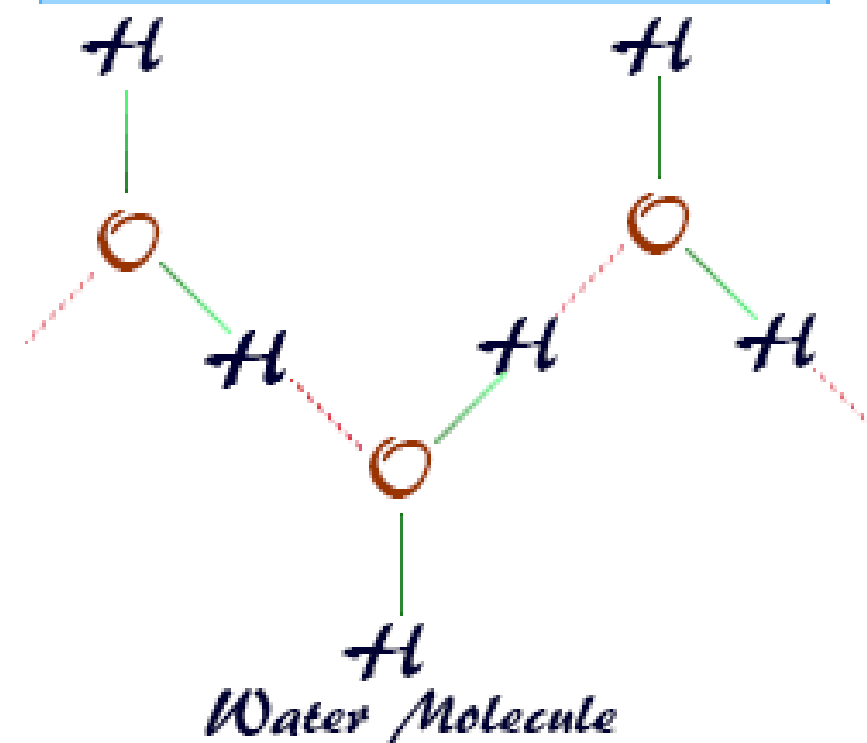
More on *inter*molecular forces Hydrogen “Bonding”

STRONG *inter*molecular force Like magnets
Occurs *ONLY* between **H** of one molecule and **N, O, F** of another molecule

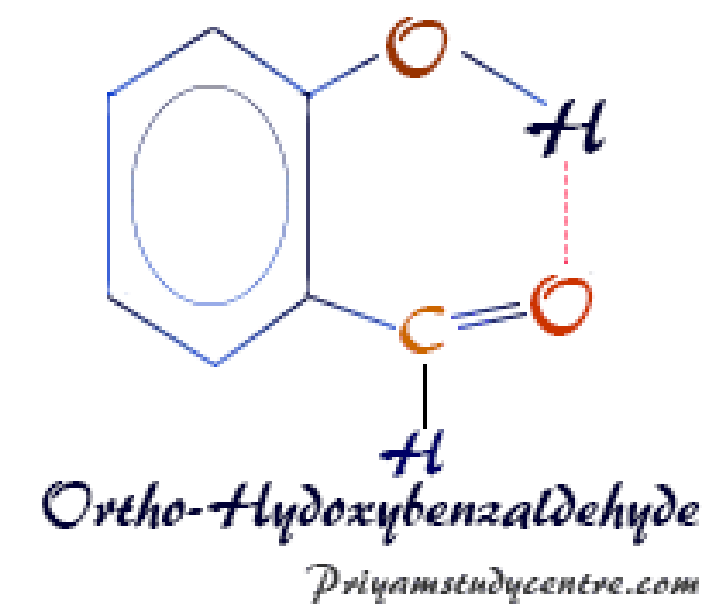
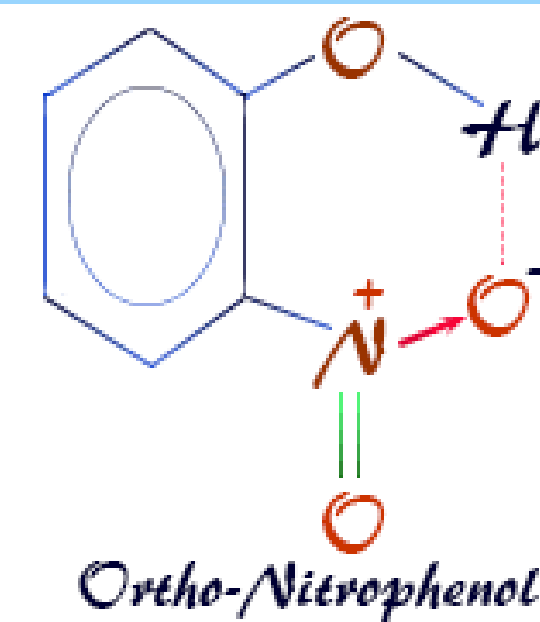


Hydrogen Bonding

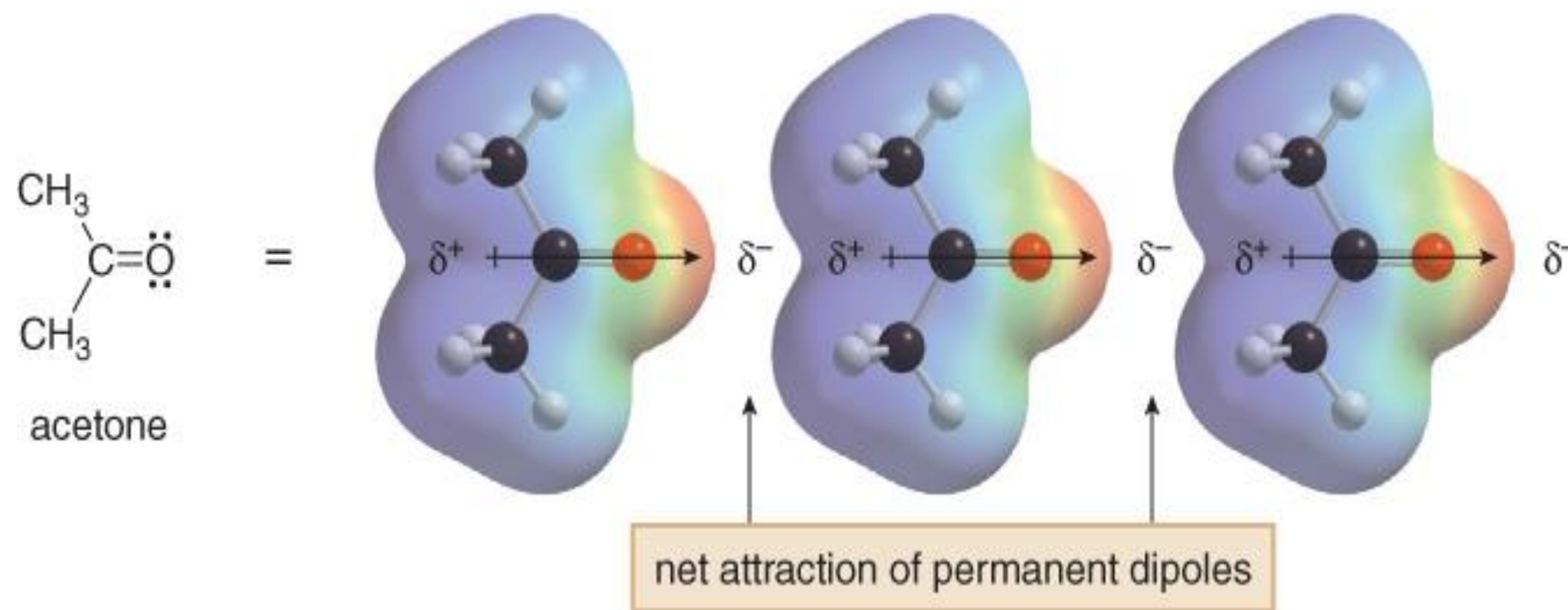
Intermolecular H-Bonding



Intramolecular H-Bonding



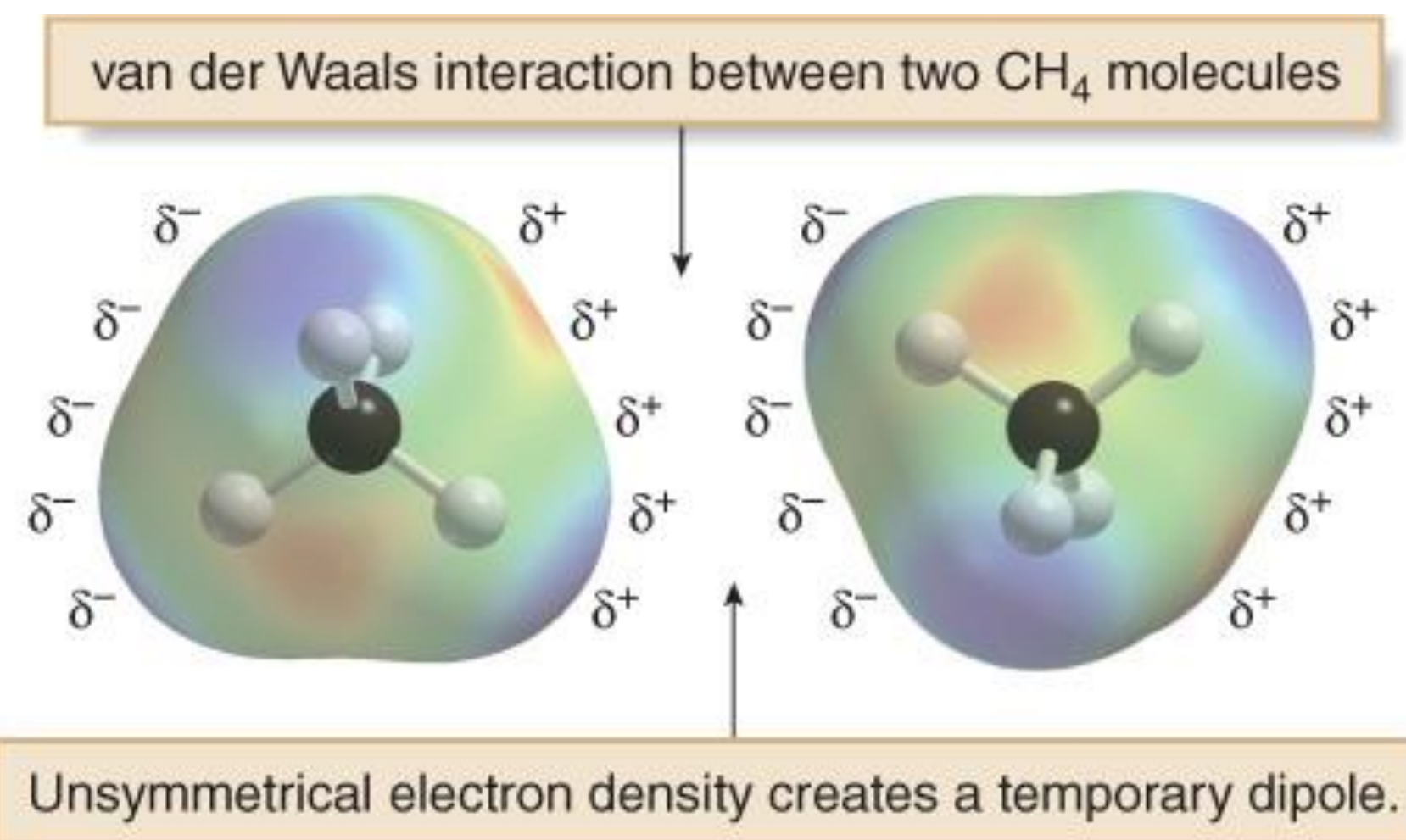
Dipole—dipole interactions are the attractive forces between the permanent dipoles of two polar molecules.



- Consider acetone. The dipoles in adjacent molecules align so that the partial positive and partial negative charges are in close proximity. These attractive forces caused by permanent dipoles are much stronger than weak van der Waals forces.

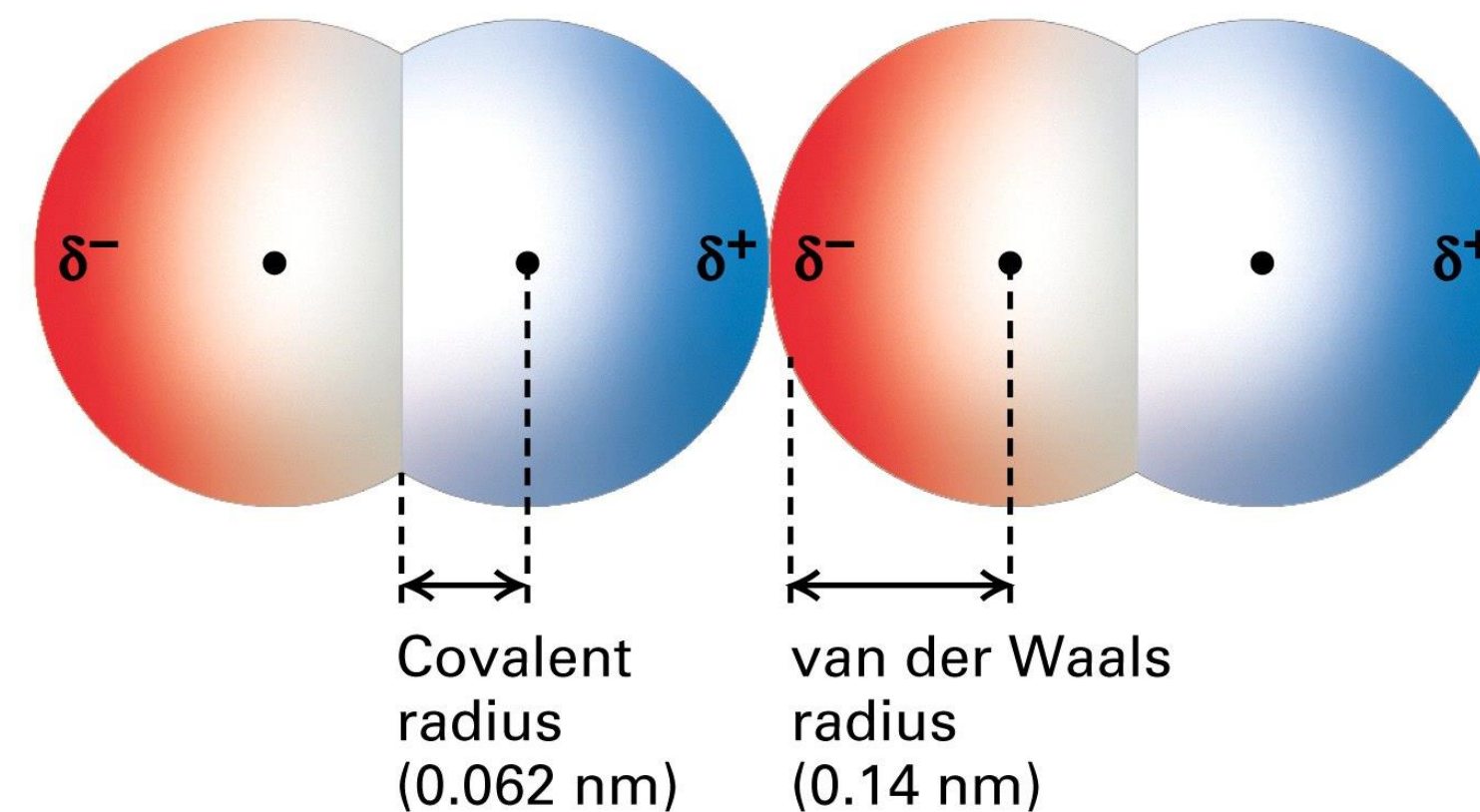
- Van der Waals forces are also known as London forces.
- They are weak interactions caused by momentary changes in electron density in a molecule.
- They are the only attractive forces present in nonpolar compounds.
- All compounds exhibit van der Waals forces.
- The surface area of a molecule determines the strength of the van der Waals interactions between molecules. The larger the surface area, the larger the attractive force between two molecules, and the stronger the intermolecular forces

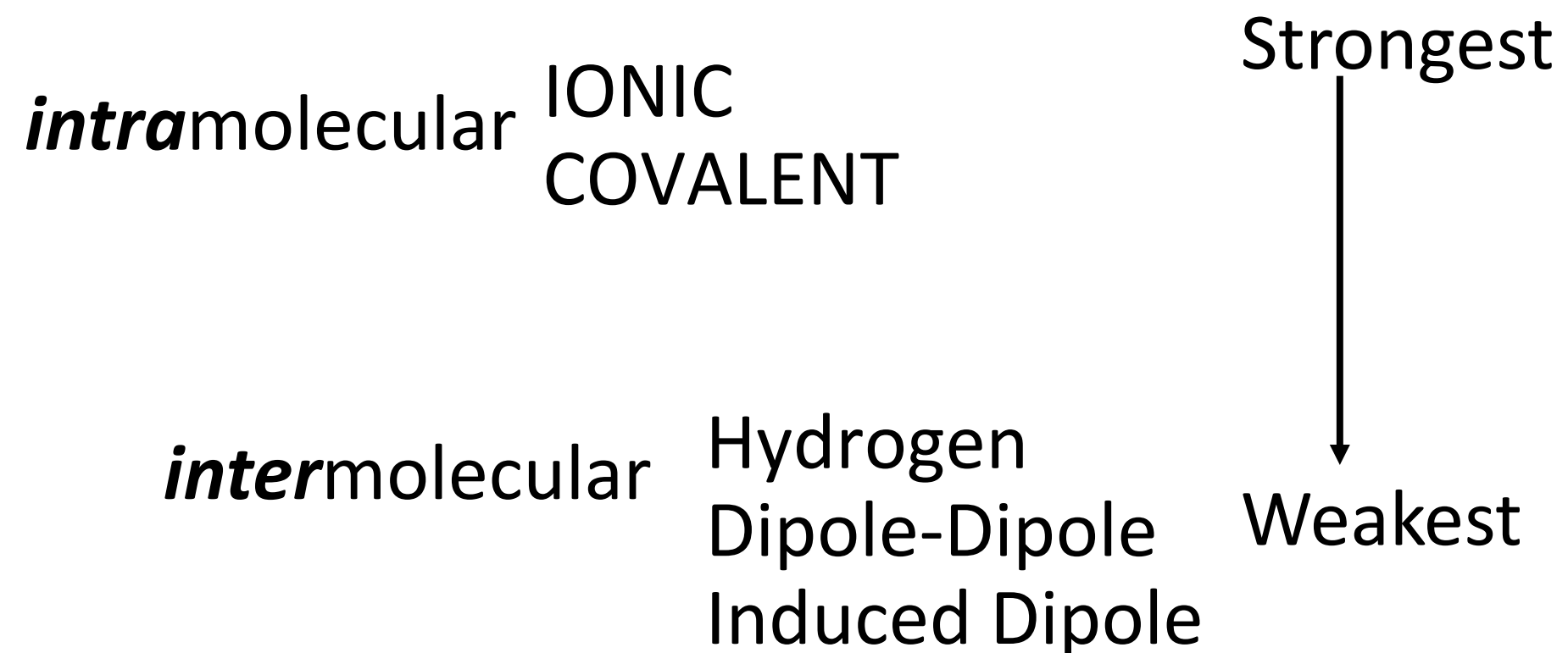
Even though CH_4 has no net dipole, at any one instant its electron density may not be completely symmetrical, resulting in a temporary dipole. This can induce a temporary dipole in another molecule. The weak interaction of these temporary dipoles constitutes van der Waals forces.



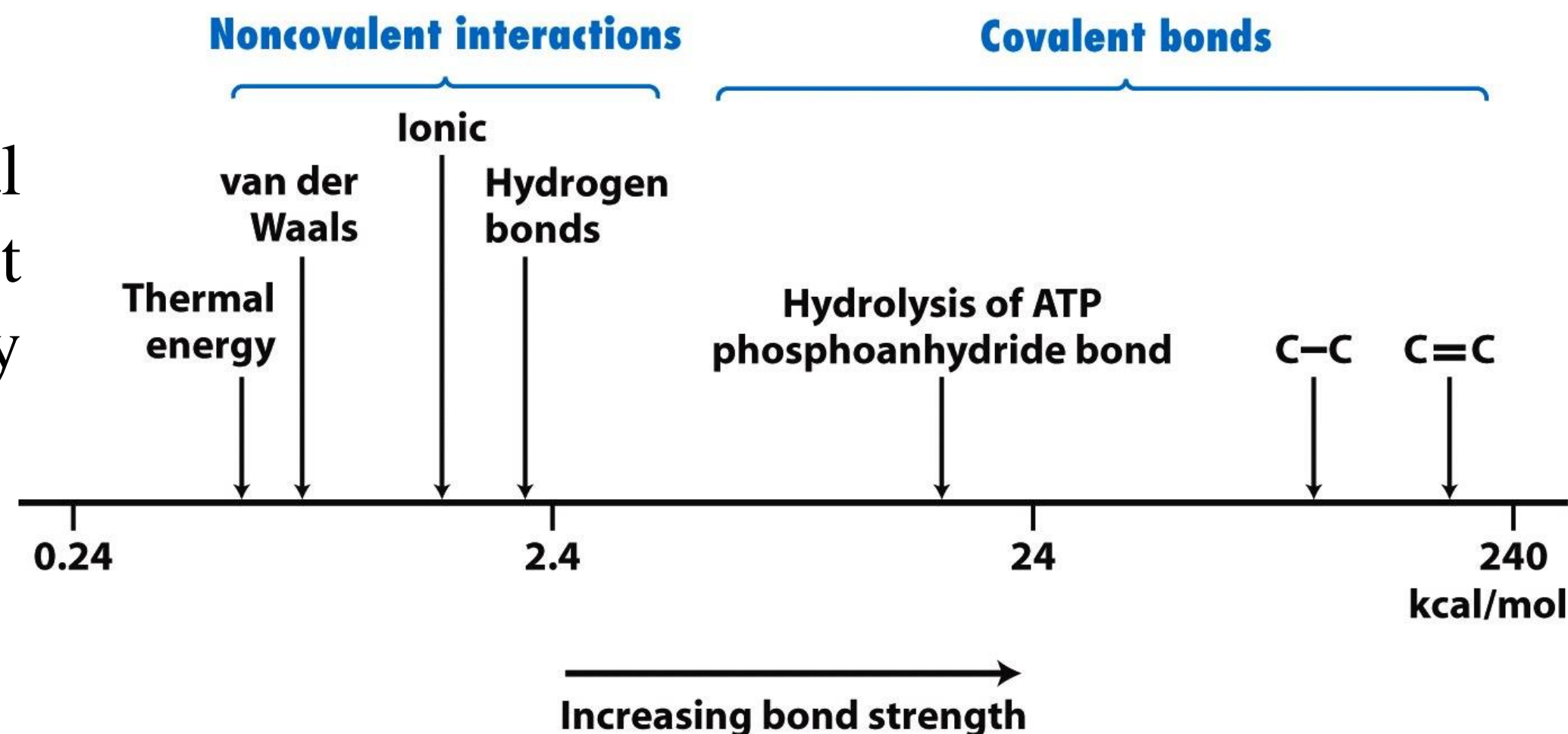
Force two atoms together and they will push back. When two atoms are close together, the occupied orbitals on the atom surfaces overlap, causing electrostatic repulsion between surface electrons. This repulsive force between atoms acts over a very short range, but is very large when distances are short.

van der Waals interactions are bonds between fluctuating, induced dipoles within the electron clouds of interacting molecules. These bonds can occur between nonpolar or polar molecules. van der Waals bonds are extremely dependent on the distance of separation between molecules, and are significant only when the electron clouds of the molecules are just touching. van der Waals interactions are demonstrated for two O_2 molecules and the covalent and van der Waals radii are shown.





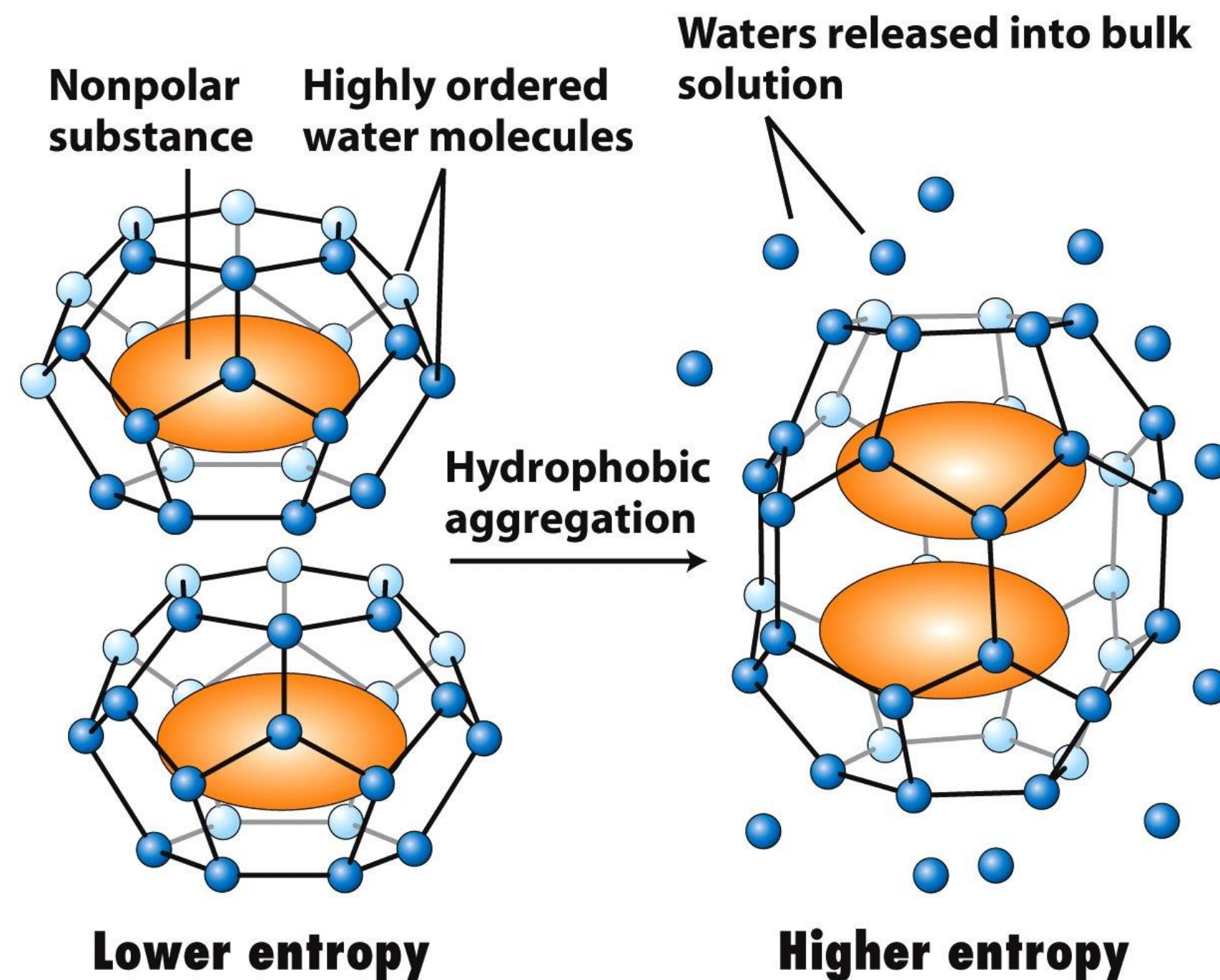
Noncovalent interactions are weak electrical bonds between molecules. Noncovalent interactions (1-5 kcal/mol) are typically ~100-fold weaker than covalent bonds



The Hydrophobic Effect

The hydrophobic effect refers to the entropy-driven aggregation of nonpolar molecules in aqueous solution that occurs to minimize the ordering of water molecules with which they are in contact. This is not an attractive force, but rather a thermodynamically driven process.

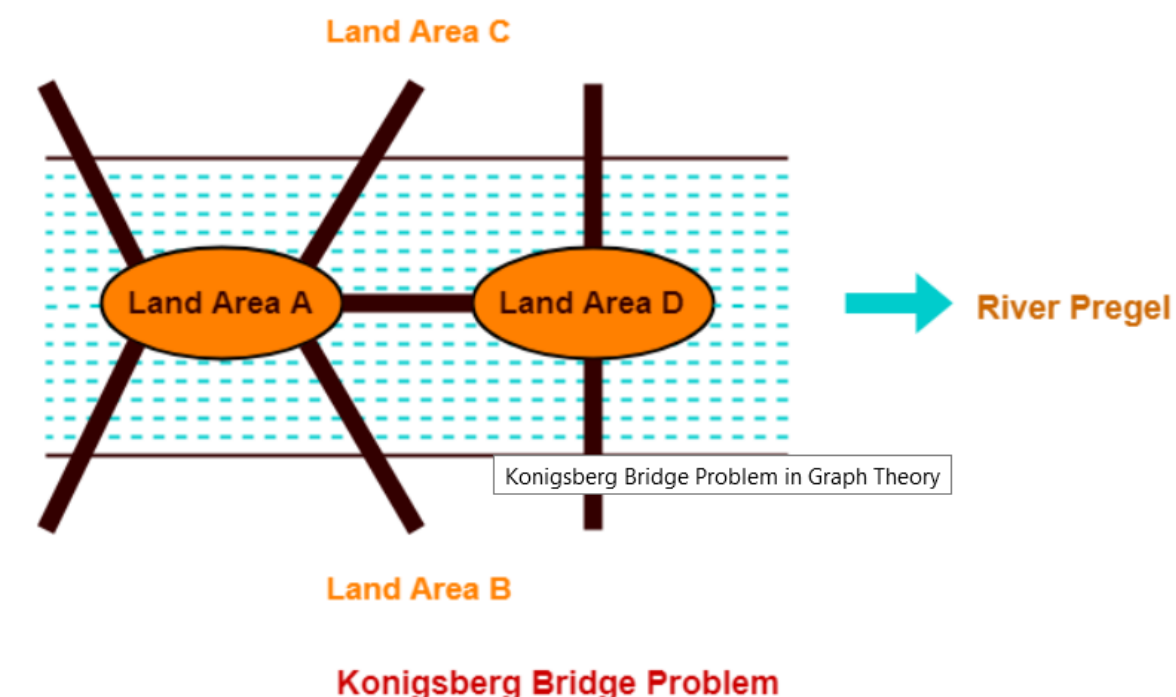
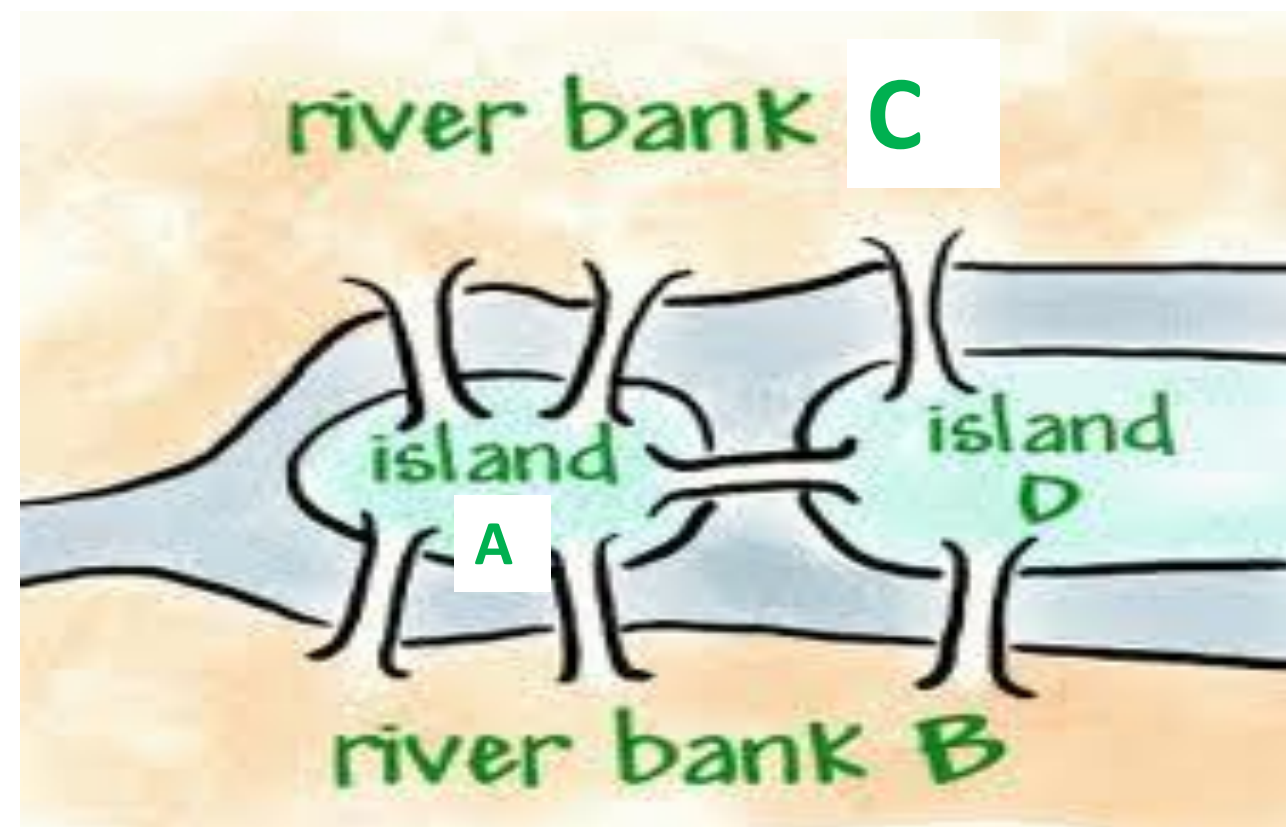
The cage-like structures formed by water molecules surrounding a nonpolar solute.





Molecular Topology

Seven Bridges of Königsberg



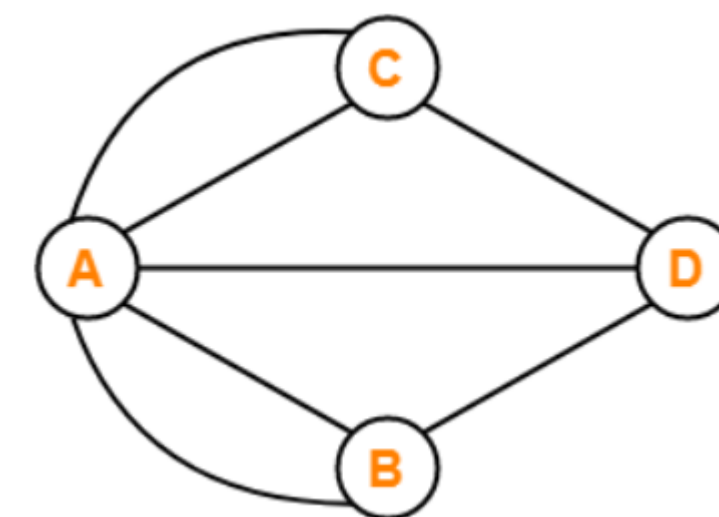
“Starting from any of the four land areas A, B, C, D, is it possible to cross each of the seven bridges exactly once and come back to the starting point without swimming across the river?”

In 1735, A Swiss Mathematician Leonhard Euler solved this problem.

- He provided a solution to the problem and finally concluded that such a walk is not possible.

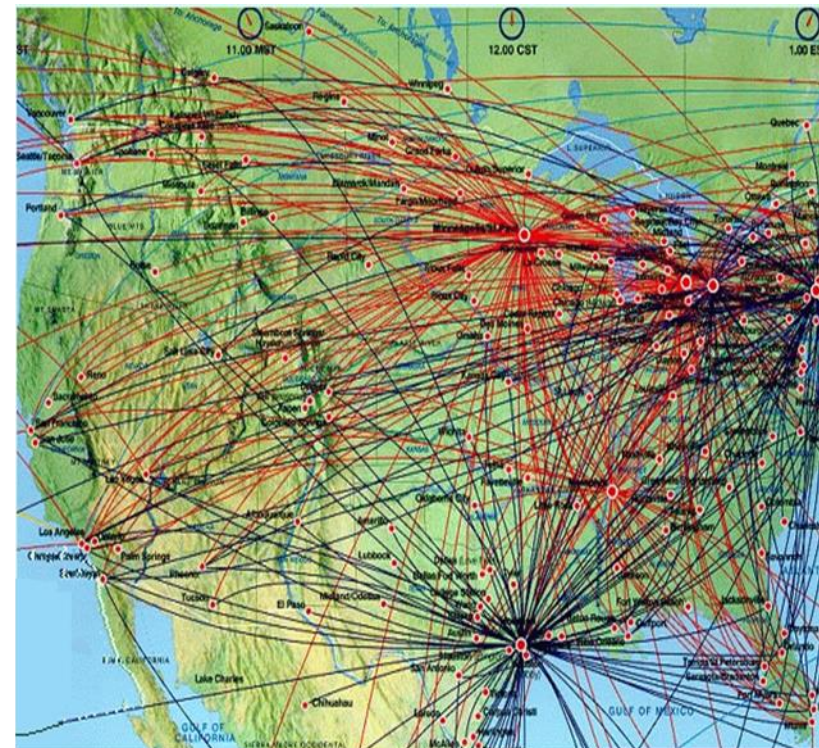
Euler found that only those networks are traversable that have either-

- No odd vertices (then any vertex may be the beginning and the same vertex will also be the ending point)
- Or exactly two odd vertices (then one odd vertex will be the starting point and other odd vertex will be the ending point)

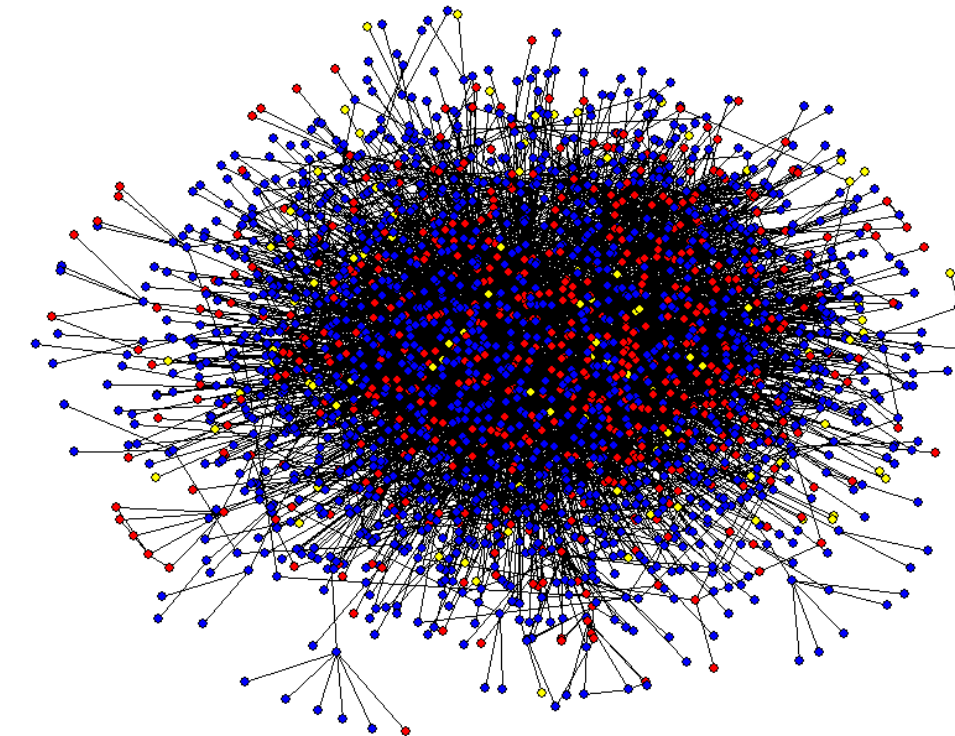


What is a Network?

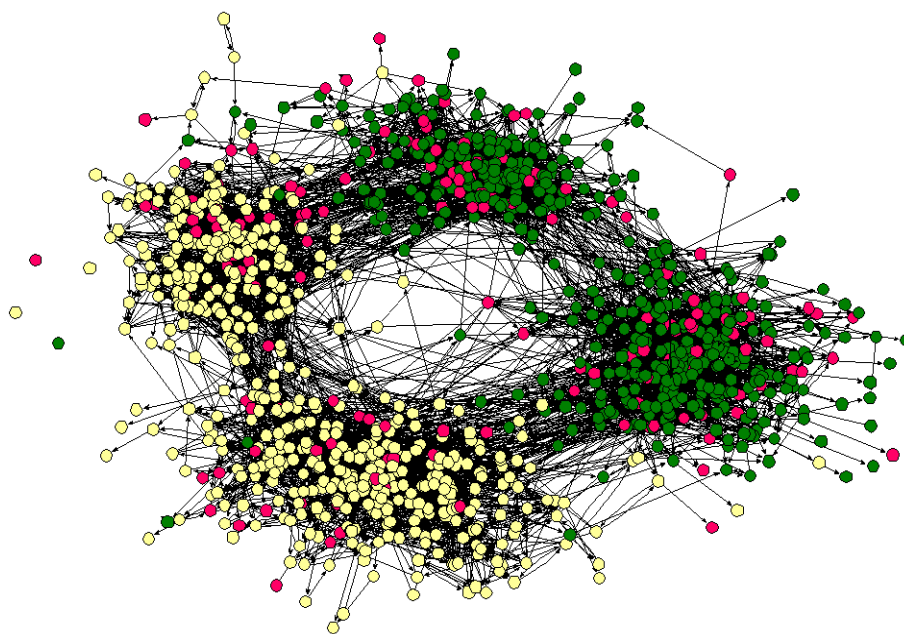
Transportation



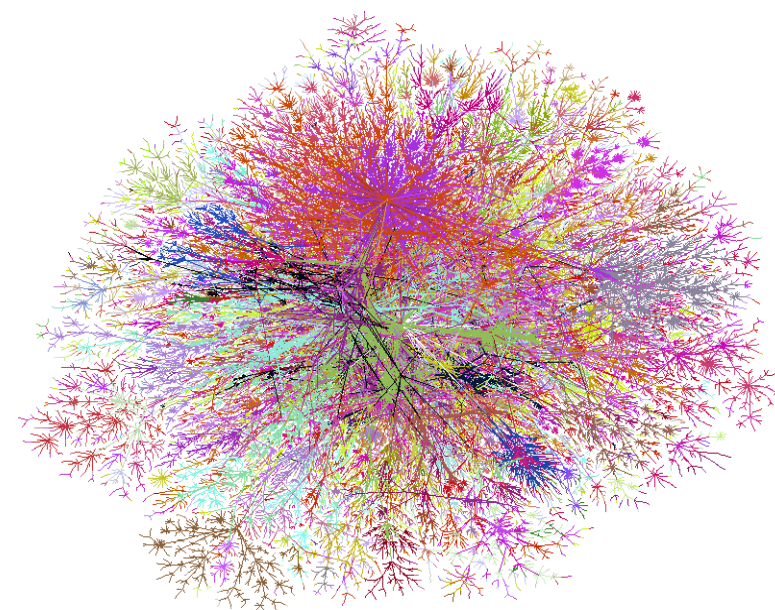
Protein-Protein Interaction



Friendship



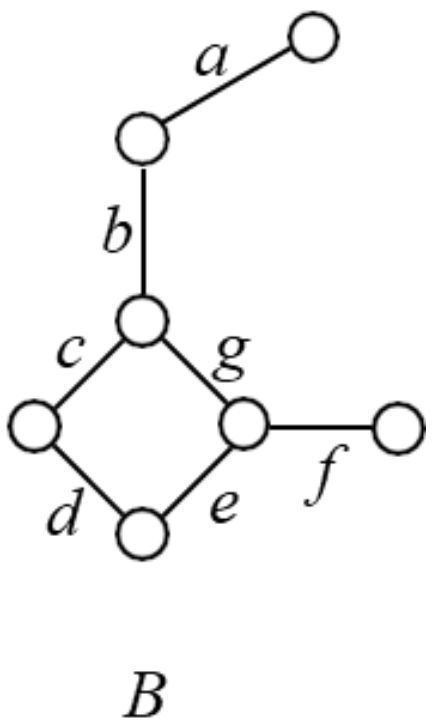
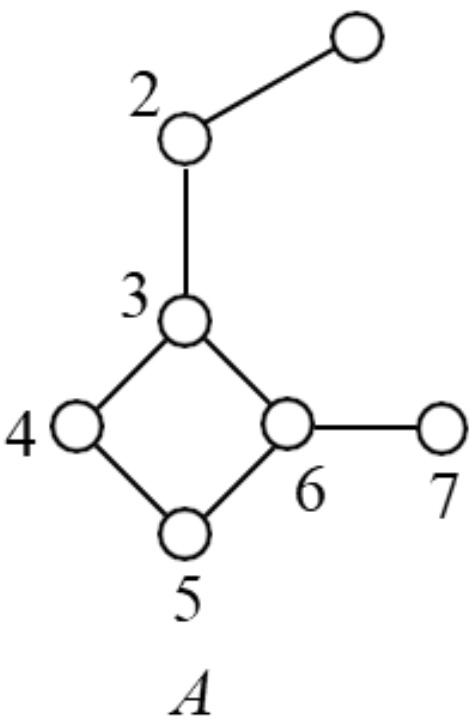
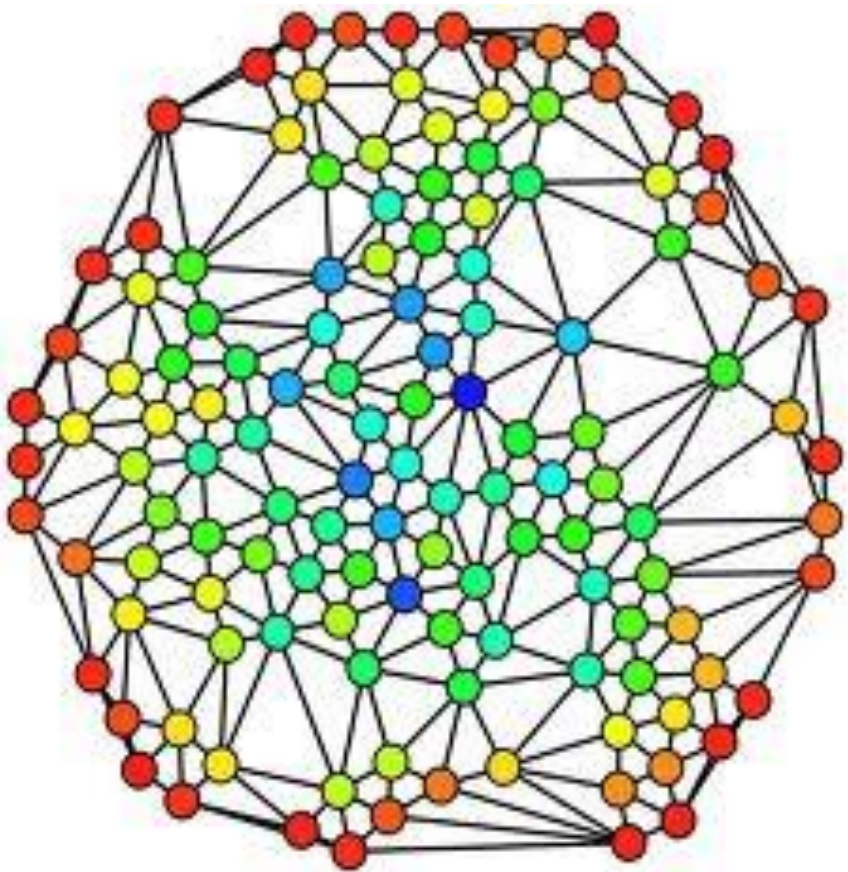
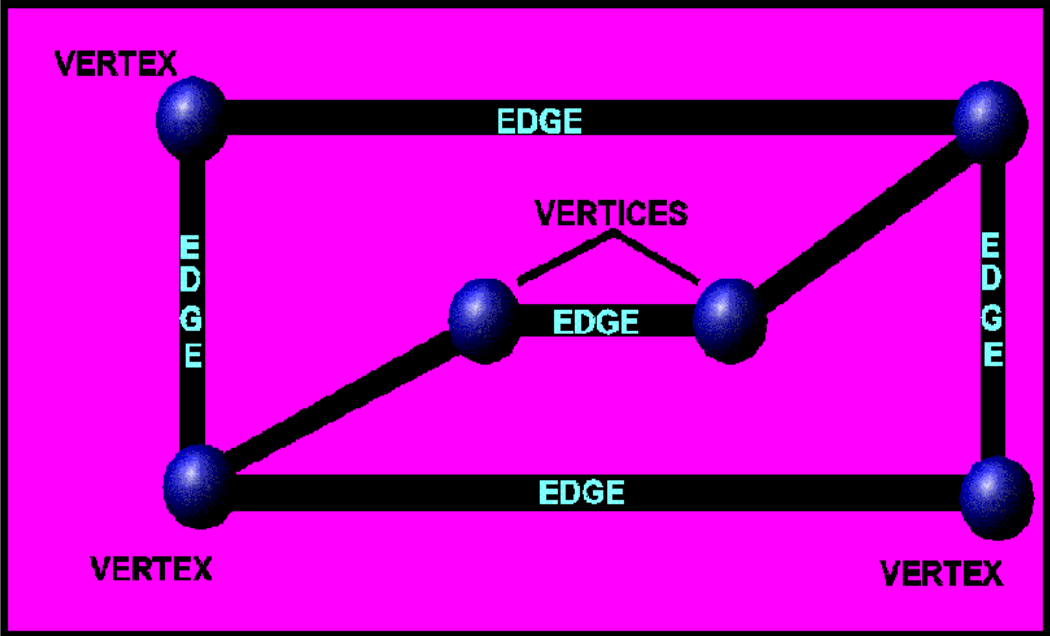
Internet



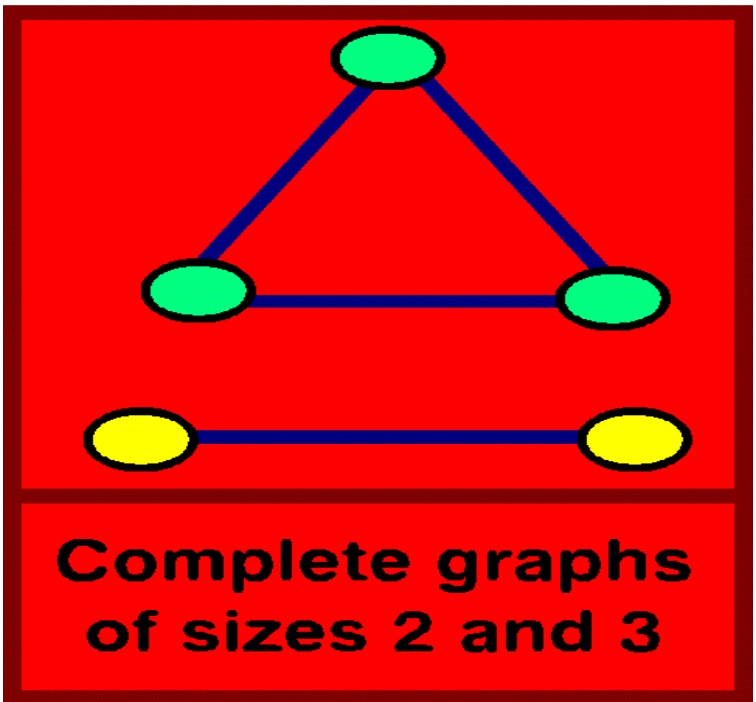
- Network = Graph
- Informally a *graph* is a set of nodes joined by a set of lines or arrows.

What is a graph?

Graph is a pair $G = (V, E)$,
where V is the Vertex set and E is the Edge set



Vertex-labeled (A) and edge-labeled (B) graph G

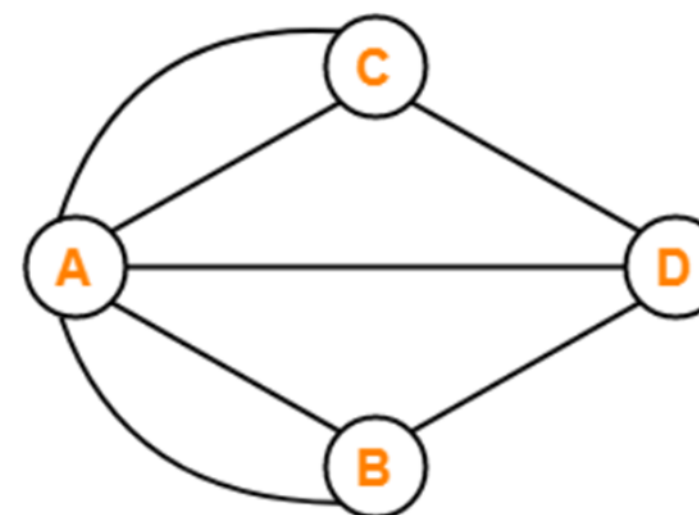
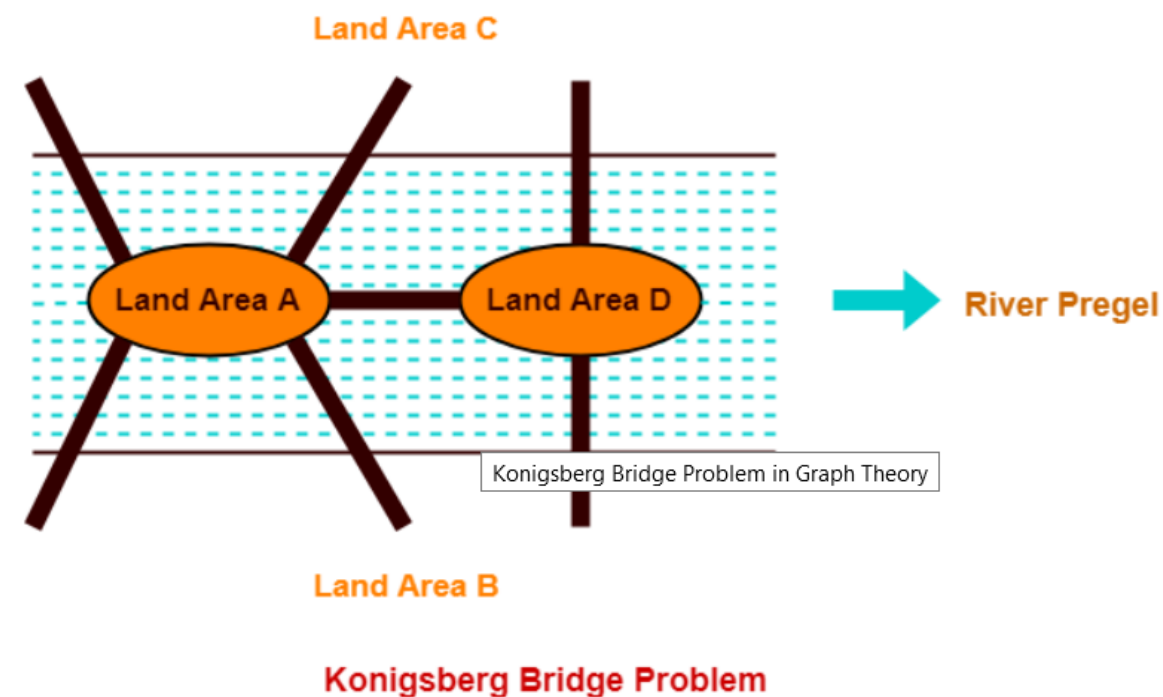


Graph-Based Representations

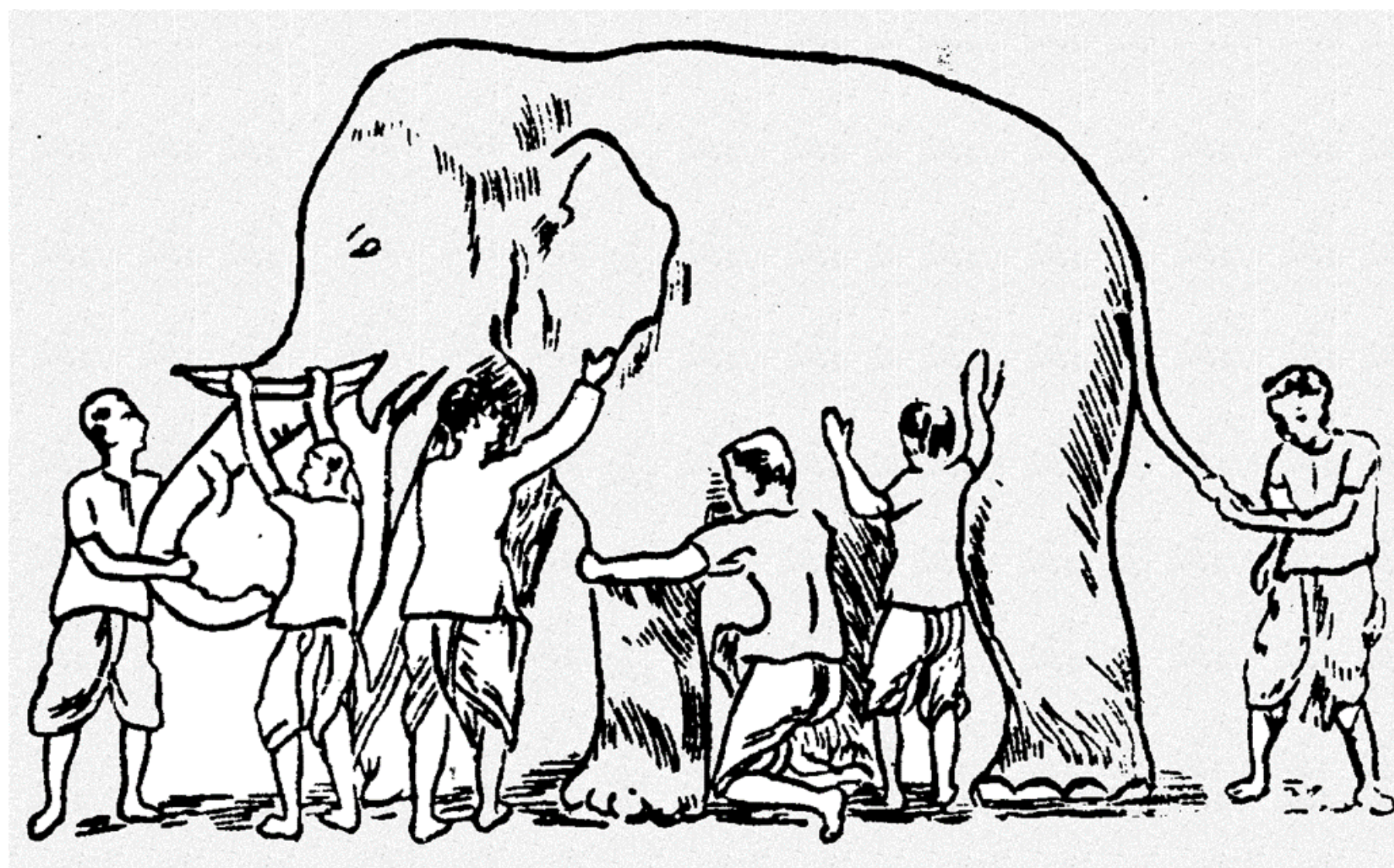
- Representing a problem as a graph can provide a different point of view
- Representing a problem as a graph can make a problem much simpler
 - More accurately, it can provide the appropriate tools for solving the problem

What makes a problem graph-like?

- There are two components to a graph
 - Nodes and Edges
- In graph-like problems, these components have natural correspondences to problem elements
 - Entities are nodes and interactions between entities are edges
- Most complex systems are graph-like



- “Similarity” can have quite different meanings in chemical approaches.
- Molecular Similarity does not just mean similarity of structural features.
- Similarity in a chemical context must include additional properties.



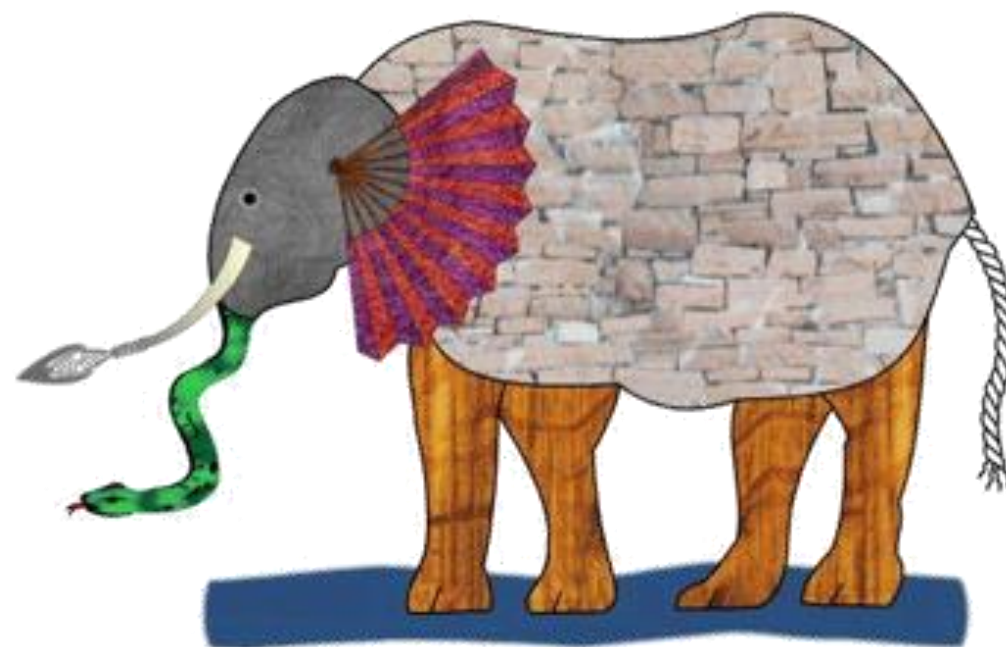
It's an Elephant

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind

The First approached the Elephant,
And happening to fall
Against his **broad and sturdy side**,
At once began to bawl:
“God bless me! but the Elephant
Is very like a **wall**!”

The Second, feeling of the **tusk**,
Cried, “Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a **spear**!”

The Third approached the animal,
And happening to take
The squirming **trunk** within his hands,
Thus boldly up and spake:
“I see,” quoth he, “the Elephant
Is very like a **snake**!”



The Fourth reached out an eager hand,
And felt about the **knee**.
“What most this wondrous beast is like
Is mighty plain,” quoth he;
“ ‘Tis clear enough the Elephant
Is very like a **tree**!”

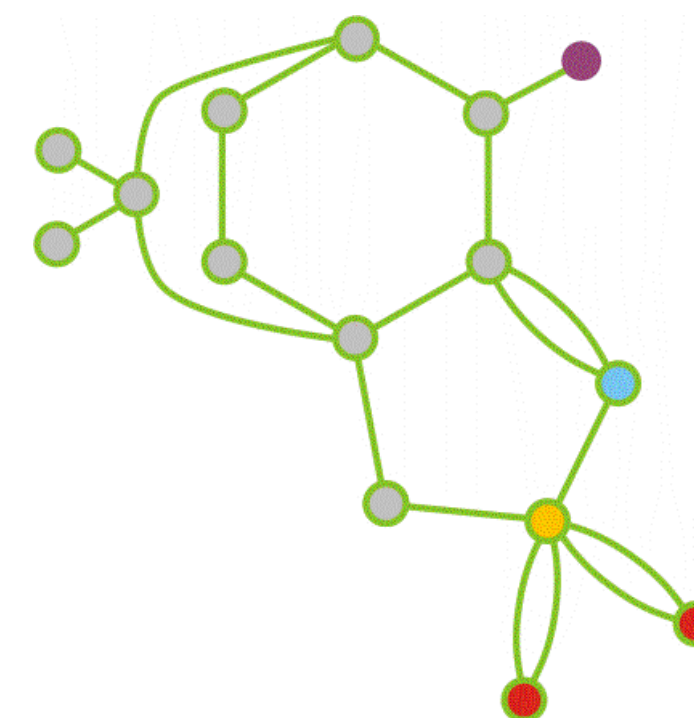
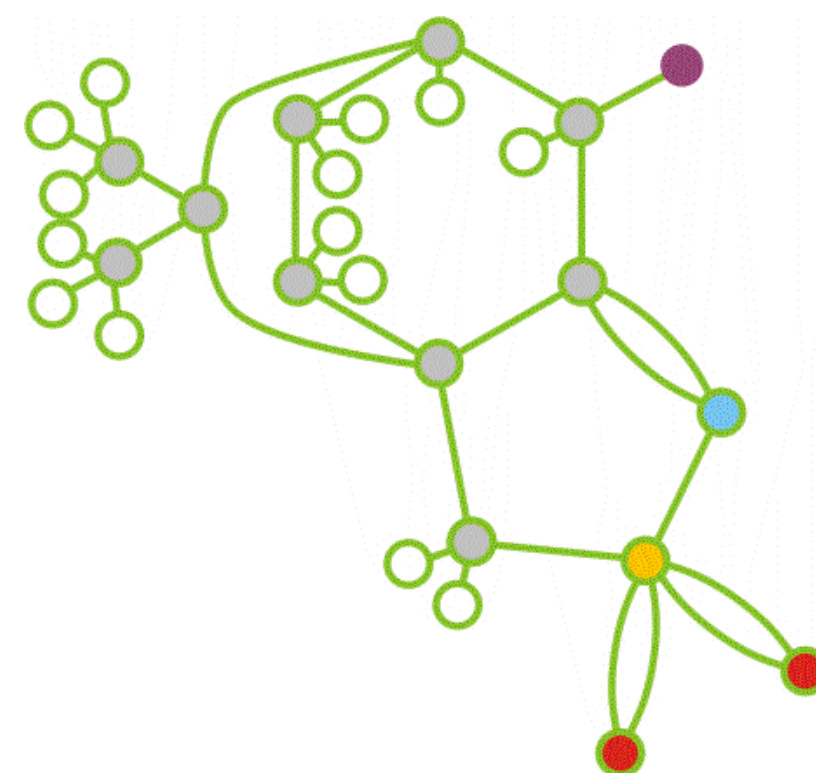
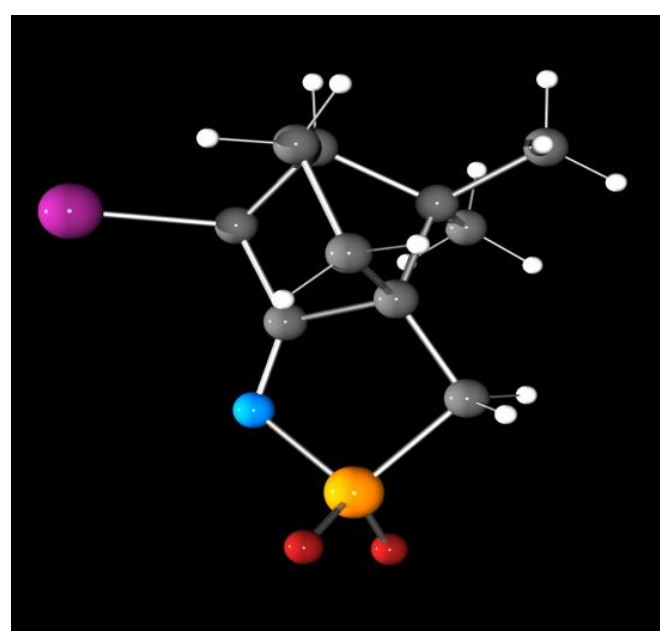
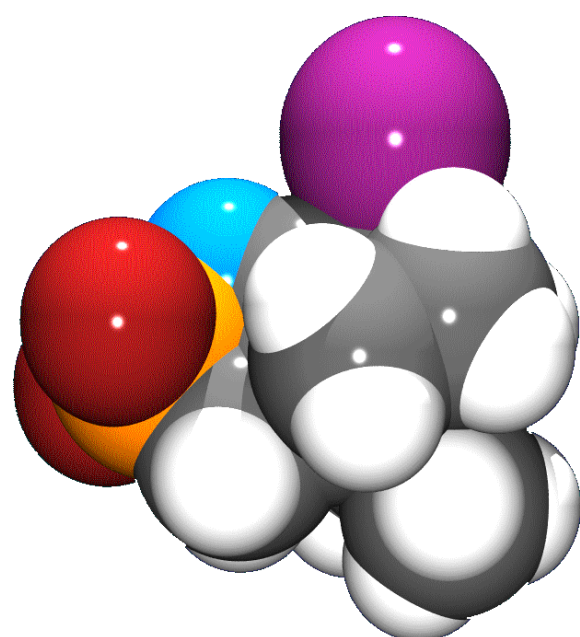
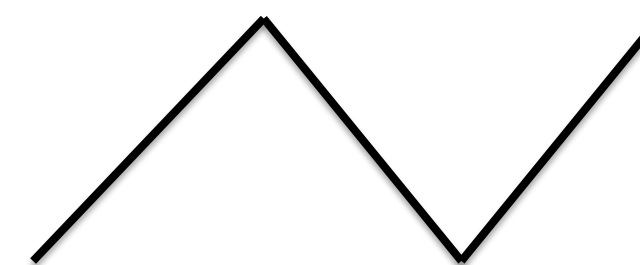
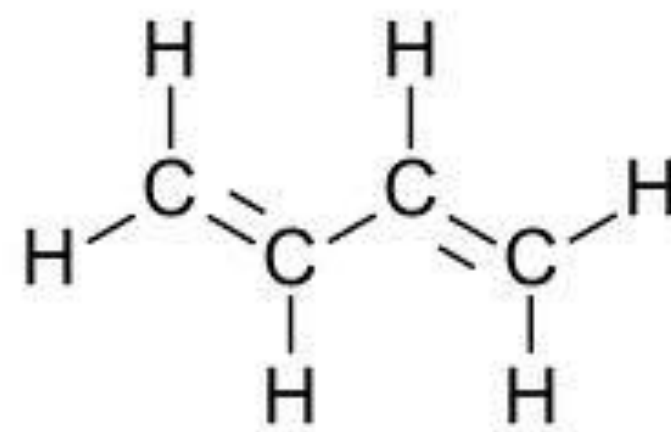
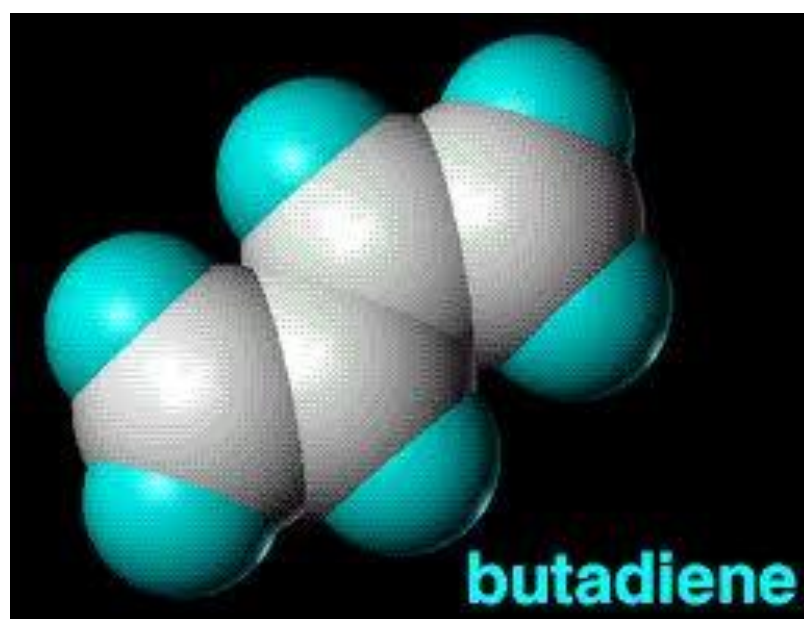
The Fifth, who chanced to touch the **ear**,
Said: “E’en the blindest man
Can tell what this resembles most;
Deny the fact who can
This marvel of an Elephant
Is very like a **fan**!”

The Sixth no sooner had begun
About the beast to grope,
Than, seizing on the **swinging tail**
That fell within his scope,
“I see,” quoth he, “the Elephant
Is very like a **rope**!”

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!

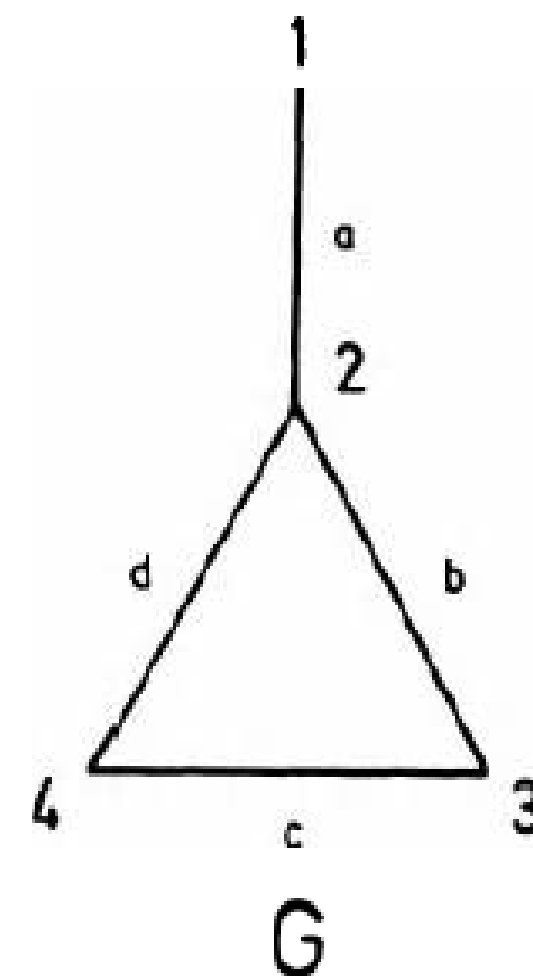
- John Godfrey Saxe (1816-1887)

- molecular (structural) graphs (often: hydrogen-suppressed)
- degree of a vertex = valence of atom

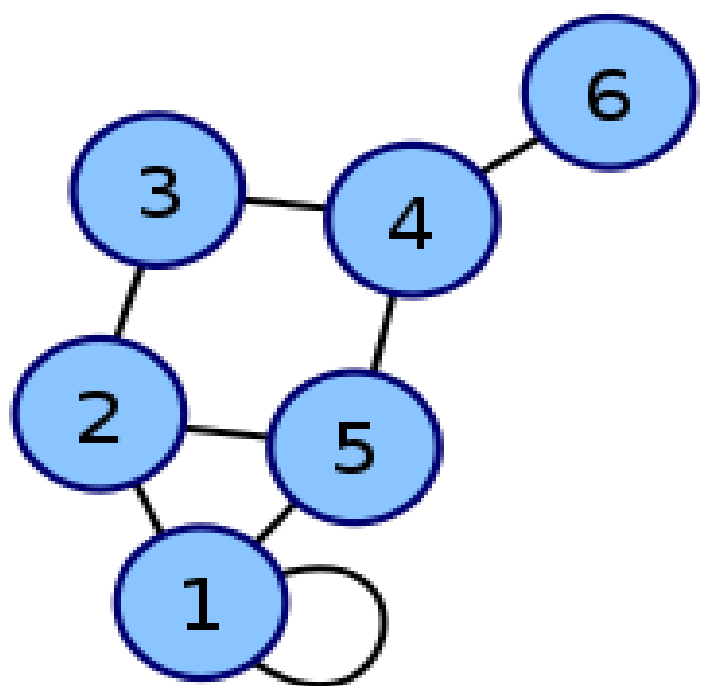


The *vertex-adjacency matrix*, denoted by A , of a vertex-labeled connected simple graph G with V vertices is a square $V \times V$ matrix, which is determined by the adjacencies of vertices in G

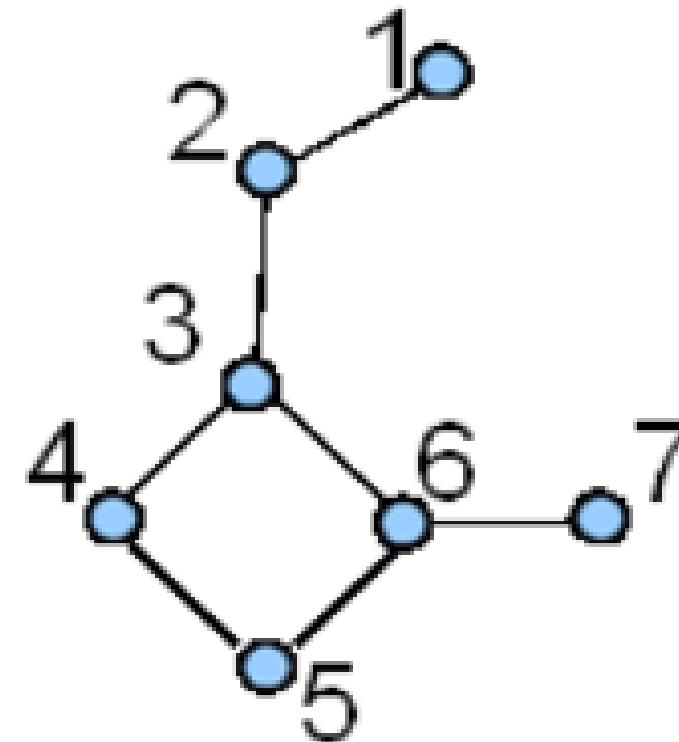
$$[A]_{ij} = \begin{cases} 1, & \text{if vertices } i \text{ and } j \text{ are adjacent} \\ 0, & \text{otherwise} \end{cases}$$



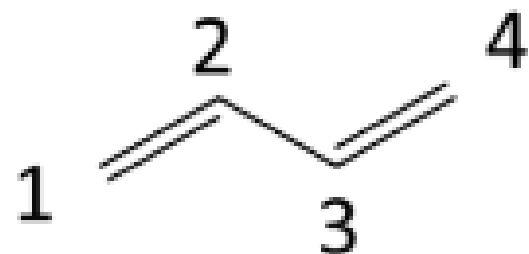
$$A(G) = \begin{matrix} & \textcircled{1} & \textcircled{2} & \textcircled{3} & \textcircled{4} \\ \begin{matrix} \textcircled{1} \\ \textcircled{2} \\ \textcircled{3} \\ \textcircled{4} \end{matrix} & \begin{bmatrix} 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix} \end{matrix}$$



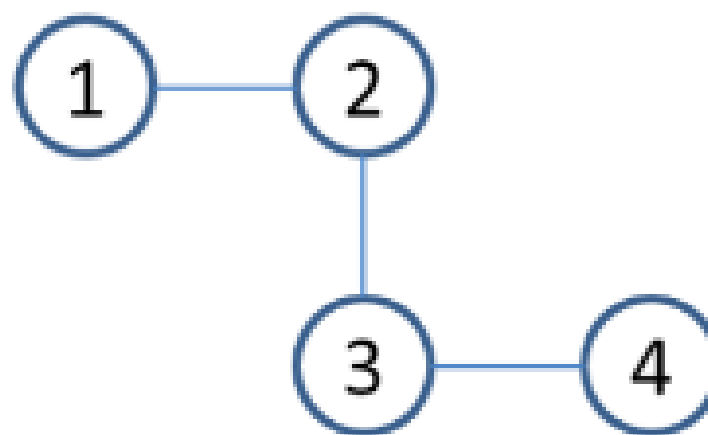
$$\begin{pmatrix} 1 & 1 & 0 & 0 & 1 & 0 \\ 1 & 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 1 & 1 \\ 1 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \end{pmatrix}$$



$$\begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}$$



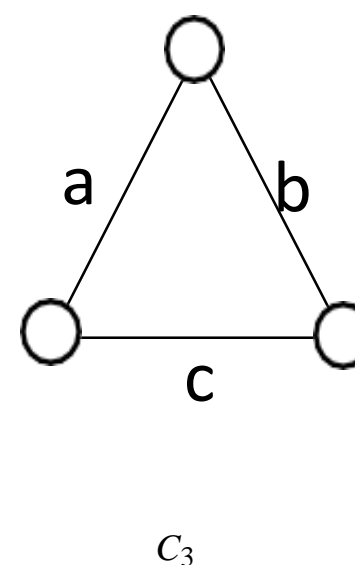
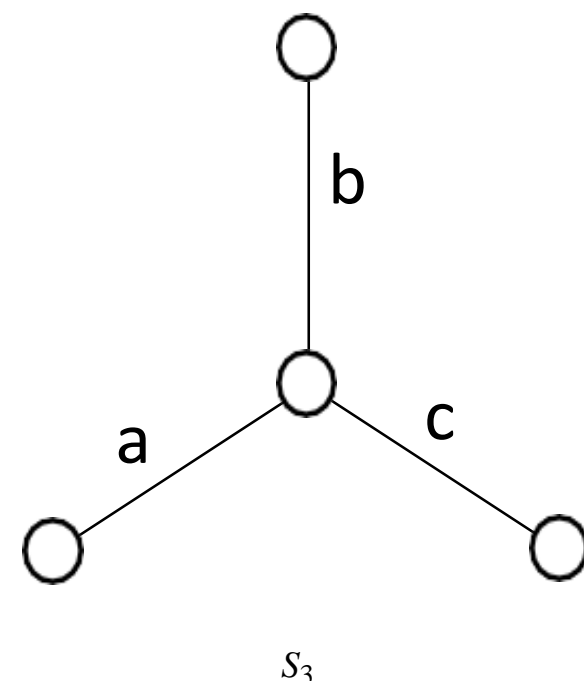
molecule



graph

$$\mathbf{A} = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 \end{bmatrix}$$

adjacency matrix

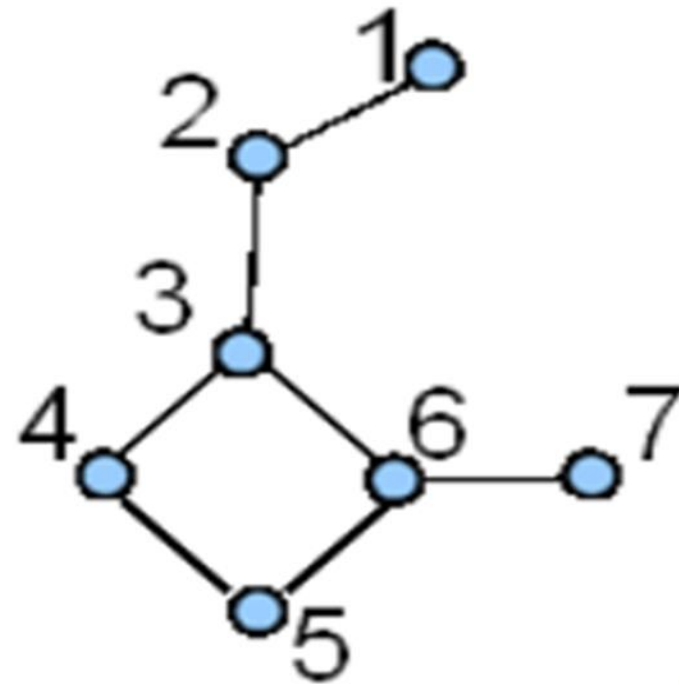


$$[E] = \begin{bmatrix} 0 & 1 & 1 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \end{bmatrix}$$

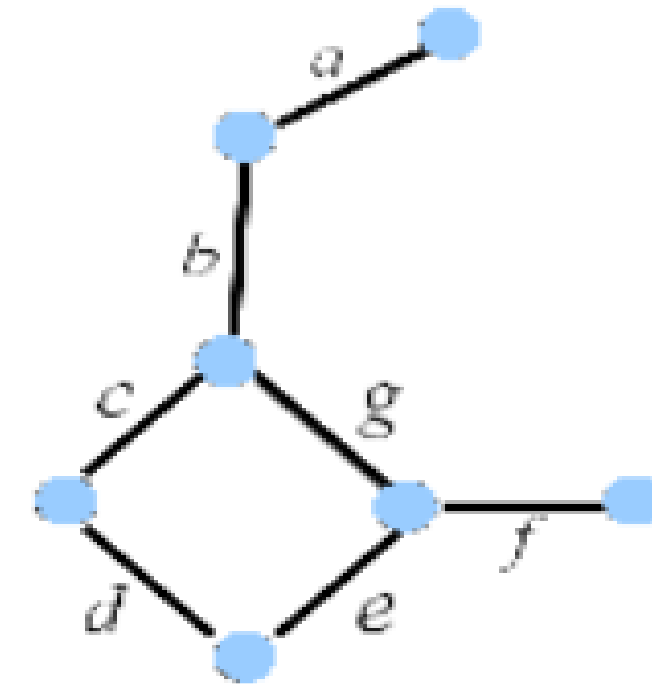
The *edge-adjacency matrix*, denoted by \mathbf{E} , of an edge-labeled connected graph G is a square $E \times E$ matrix which is determined by the adjacencies of edges

$$[E]_{ij} = \begin{cases} 1, & \text{if edges } i \text{ and } j \text{ are adjacent} \\ 0, & \text{otherwise} \end{cases}$$

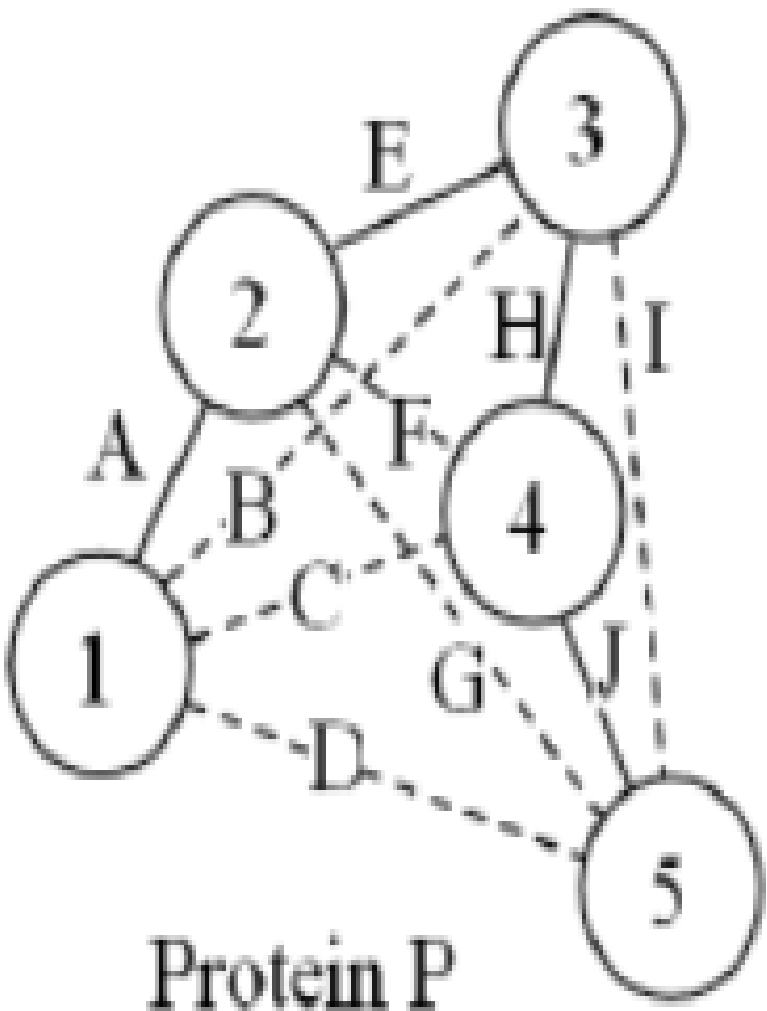
It should be noted that the vertex-adjacency matrix *uniquely* determines a graph, but the edge-adjacency matrix *does not*, that is, there are known graphs with *identical* edge-adjacency matrices. A pair of nonisomorphic graphs – the three-point star S_3 and the cycle on three vertices C_3 – possessing identical edge-adjacency matrices.



$${}^v\mathbf{A}(G_1) = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}$$

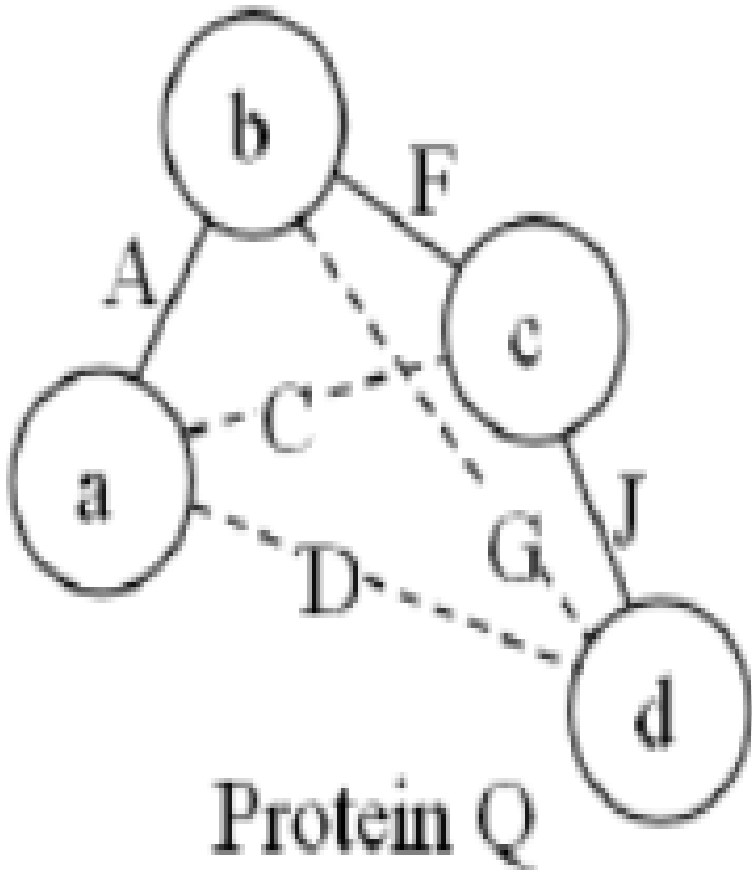


$${}^e\mathbf{A}(G_1) = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 1 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 & 0 & 1 \\ 0 & 1 & 1 & 0 & 1 & 1 & 0 \end{bmatrix}$$



	1	2	3	4	5
1	0	A	B	C	D
2	A	0	E	F	G
3	B	E	0	H	I
4	C	F	H	0	J
5	D	G	I	J	0

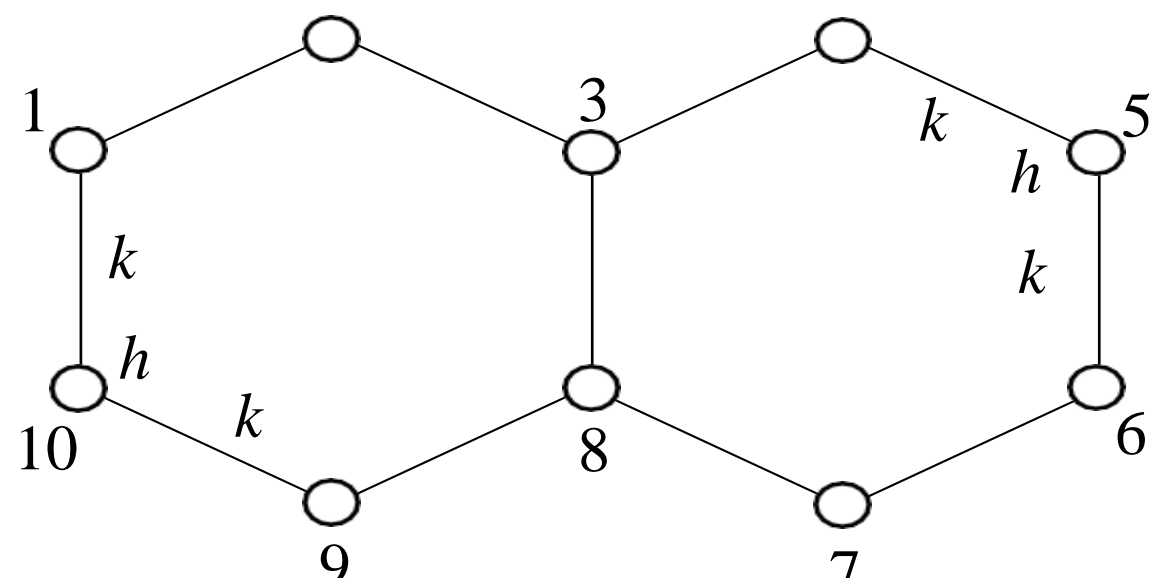
Distance matrix of P



	a	b	c	d
a	0	A	C	D
b	A	0	F	G
c	C	F	0	J
d	D	G	J	0

Distance matrix of Q

Vertex-Adjacency Matrix of Weighted Graphs



The parameters h and k depend, respectively, on the chemical nature of the corresponding atoms and bonds in a molecule. Some people select for them the values of the Hückel parameters for heteroatoms and heterobonds.

$$[A] = \begin{cases} k & \text{if the edge } i-j \text{ is weighted} \\ 1 & \text{if the edge } i-j \text{ is not weighted} \\ h & \text{if the vertex } i \text{ is weighted} \\ 0 & \text{otherwise} \end{cases}$$

$$[A] = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k \\ 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & k & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & k & h & k & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & k & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & k \\ k & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k & h \end{bmatrix}$$

A topological index, sometimes also known as a graph-theoretic index, is a numerical invariant of a chemical graph, some examples of topological indices include the Balaban index, Harary index, molecular topological index, and Wiener index.

Unless otherwise stated, hydrogen atoms are usually ignored in the computation of such indices

The topological index of a graph is defined by $TI = |A + D|$

where A is the adjacency matrix, D is the graph distance matrix, and $|A + D|$ denotes the determinant of the matrix addition

Zagreb Index Z one counts the connections from each vertex (node, carbon).

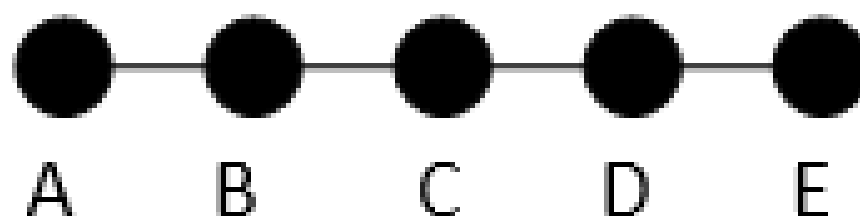
The first Zagreb index $M_1(G)$ is equal to the sum of squares of the degrees of the vertices

The second Zagreb index $M_2(G)$ is equal to the sum of the products of the degrees of pairs of adjacent vertices of the underlying molecular graph

Method of calculation: If δ_i is the degree of vertex i then

$$M_1 = \sum_{i=1}^n \delta_i^2$$

$$M_2 = \sum \delta_i \delta_j$$



$$M_1 = 1^2 + 2^2 + 2^2 + 2^2 + 1^2 = 1 + 4 + 4 + 4 + 1 = 14$$

$$M_2 = 1 \times 2 + 2 \times 2 + 2 \times 2 + 2 \times 1 = 2 + 4 + 4 + 2 = 12$$

Zagreb group indices were introduced to characterize branching

Wiener Number W is the total distance between all carbon atoms (sum of the distances between each pair of carbon atoms in the molecule, in terms of carbon-carbon bonds).

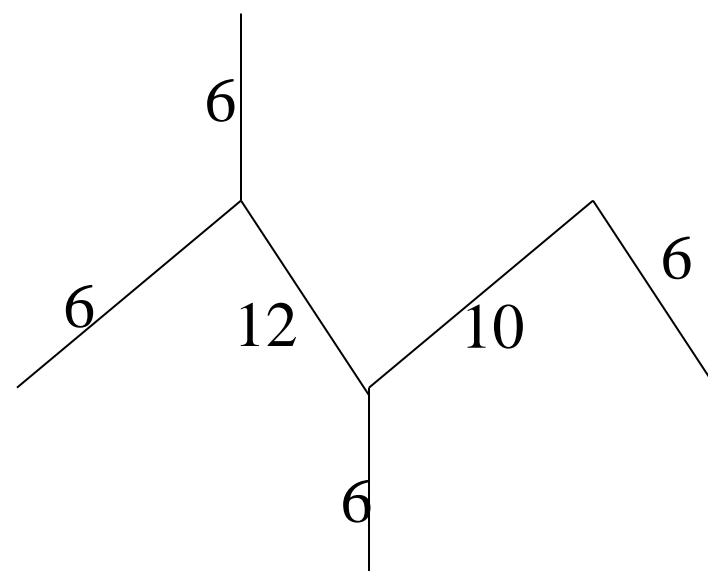
The smaller this number, the larger is the compactness of the molecule.

Method of calculation: Multiply the number of carbon atoms on one side of any bond by those on the other side; W is the sum of these two values for all bonds.

W can also be obtained by simply adding all the elements of the graph distance matrix above the main diagonal.

Or This topological index is defined as the half-sum of the elements of the distance matrix.

$$W = 6 + 6 + 12 + 6 + 10 + 6$$

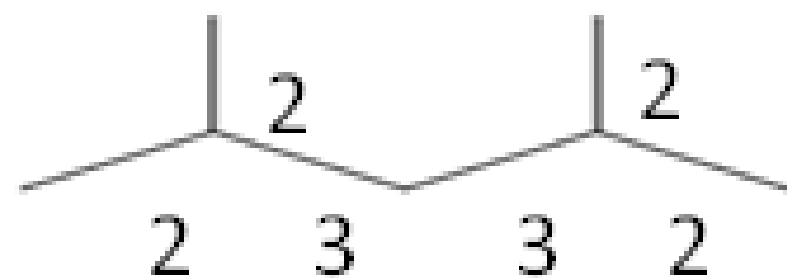


Weiner showed that the index value is closely correlated with the *boiling point of a series of alkanes*, also observed that it is correlated with other physical properties such as *density, surface tension and viscosity*.

Platt Number F Is equal to the total sum of edge-degrees in a graph G. The *edge-degree* of an edge e , $D(e)$, is the number of its adjacent edges. This index was named the *Platt number*.

Method of calculation: The Platt number of a graph G is defined by

$F(G) = \sum_{i=1}^M D(e_i)$, The Platt number, thus represents the first neighbors sum.



2, 4 di-methyl pentane chemeddon.com

$$F = 2 + 2 + 3 + 3 + 2 + 2 = 14$$




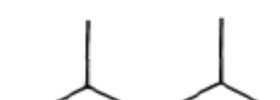




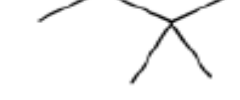
Predicting physical parameters (molar volumes, boiling points, heats of formation, heats of vaporization) of alkanes

Largest Eigenvalues x_i is equal to the highest eigenvalues of the characteristic polynomial

Method of calculation:

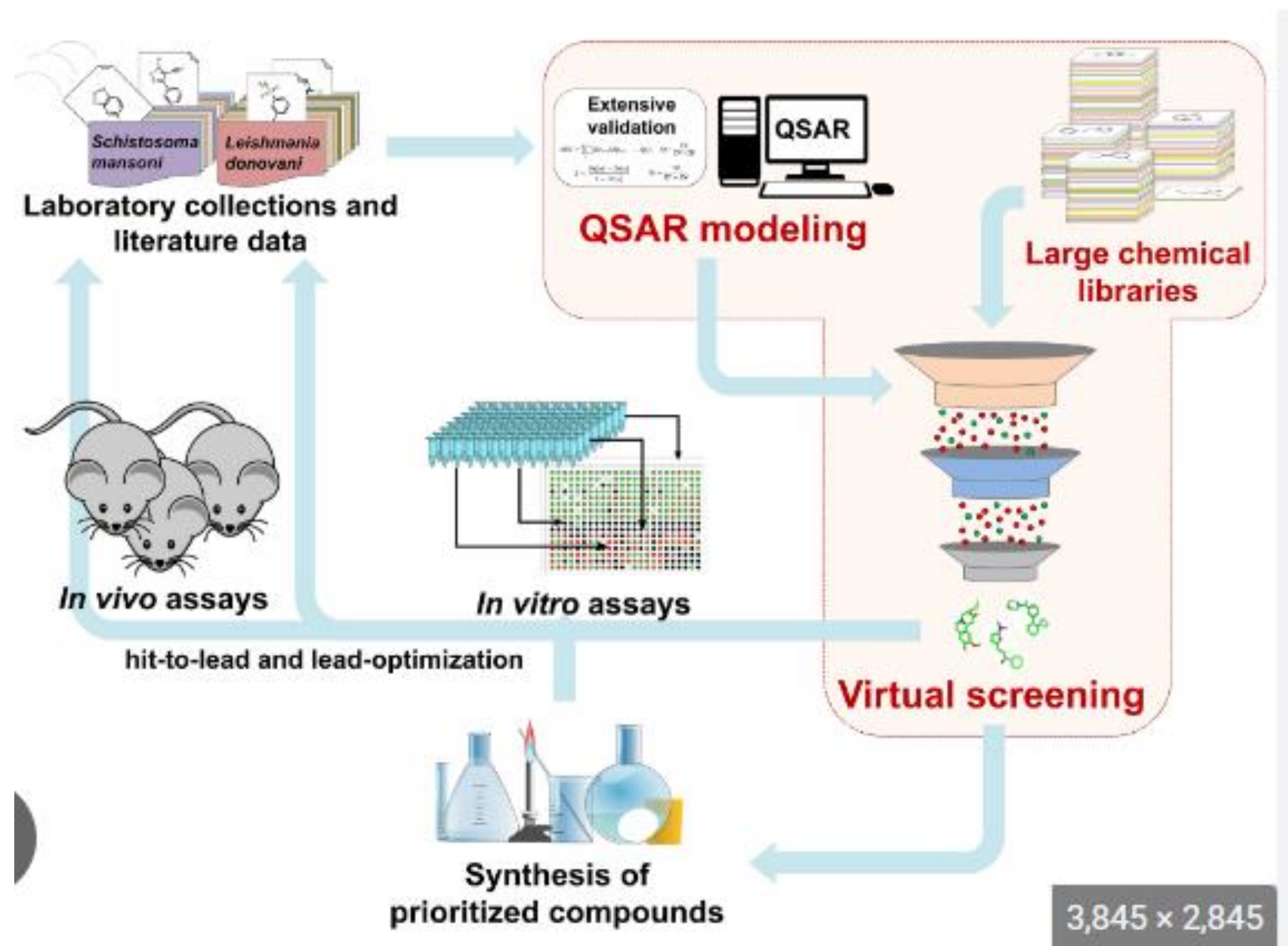
$$P(G;x) = \det |xI - A| \quad \text{or} \quad \det |A - xI|$$

solve the characteristic polynomial $P(G;x) = 0$

Alkane Tree	x_i
	1.848
	1.932
	1.970
	2.000
	2.000
	2.053
	2.101
	2.136
	2.175

Quantitative Structure Activity Relationship (QSAR)

Quantitative Structure Property Relationship (QSPR)





Drug Discovery Today

1. Quantitative relationship between the structure and physiochemical properties of substances and their biological activity are being used as the foundation stone in search of new medicines. The mathematical and statistical analysis helps us to predict the drug activity.
2. QSAR makes it easy now to reach the conclusion for any of the congener that still not in process, in way that whether it will optimal and profitable or not.
3. To quantitatively correlate and recapitulate the relationships between trends in chemical structure alterations and respective changes in biological endpoint for comprehending which chemical properties are most likely determinants for their biological activities.
4. To optimize the existing leads so as to improve their biological activities.
5. To predict the biological activities of untested and sometimes yet unavailable compounds.

Hansch analysis

- The biological activity of most drugs is related to a combination of physico-chemical properties.
- In such cases, simple equations involving only one parameter are relevant only if the other parameters are kept constant.
- In reality, this is not easy to achieve and equations which relate biological activity to more than one parameter are more common.
- These equations are known as Hansch equations and they usually relate biological activity to the most commonly used physicochemical properties ($\log P$, electronic, and a steric factor).

Hansch Analysis

- Hansch and Fujita combined different physico-chemical parameters in one equation.

$$\log 1/C = k_1 \log P + k_2 \sigma + k_3$$

- Where, C – Molar concentration
k₁, k₂, k₃, – Coefficients determined by least squares procedure



Thank you