A **non-covalent interaction** differs from a covalent bond in that it does not involve the sharing of electrons, but rather involves more dispersed variations ofelectromagnetic interactions between molecules or within a molecule.[1] The chemical energy released in the formation of non-covalent interactions is typically on the order of 1-5 kcal/mol (1000–5000 calories per 6.02 x 10^23 molecules).[2] Non-covalent interactions can be classified into different categories, such as electrostatic,π-effects, van der Waals forces, and hydrophobic effects. Non-covalent interactions [3] are critical in maintaining the three-dimensional structure of large molecules, such as proteins and nucleic acids. In addition, they are also involved in many biological processes in which large molecules bind specifically but transiently to one another (see the properties section of the DNA page). These interactions also heavily influence drug design, crystallinity and design of materials, particularly for self-assembly, and, in general, the synthesis of manyorganic molecules

IONIC INTERACTIONS:

Ionic interactions involve the attraction of ions or molecules with full permanent charges of opposite signs. For example,sodium fluoride involves the attraction of the positive charge on sodium (Na^+) with the negative charge on fluoride (F^-). These bonds are harder to break than covalent bonds because there is a strong electrostatic interaction between oppositely charged ions. However, this particular interaction is easily broken upon addition to water, or other highly polar solvents.

These interactions can also be seen in molecules with a localized charge on a particular atom. For example, the full negative charge associated with ethoxide, the conjugate base of ethanol, is most commonly accompanied by the positive charge of analkali metal salt such as the sodium cation (Na^+).

HYDROGEN BONDING INTERACTIONS:

A hydrogen bond (H-bond), is a specific type of interaction that involves dipole-dipole attraction between a partially positive hydrogen atom and a highly electronegative, partially negative oxygen, nitrogen, sulfur, or fluorine atom (not covalently bound to said hydrogen atom). It is technically not a covalent bond, but instead is classified as a strong non-covalent interaction. It is responsible for why water is a liquid at room temperature and not a gas (given water's low molecular weight). Most commonly, the strength of hydrogen bonds lies between 0 - 4 kcal/mol, but can sometimes be as strong as 40 kcal/moL

VAN DER WAAL'S FORCES:

Van der Waals Forces are a subset of electrostatic interactions involving permanent or induced dipoles (or multipoles). These include the following:

- permanent dipole-dipole interactions, alternatively called the Keesom force
- dipole-induced dipole interactions, or the Debye force
- induced dipole-induced dipole interactions, commonly referred to as London dispersion forces

Note that hydrogen bonding and halogen bonding are typically not classified as Van der Waals forces.

Dipole-dipole

Dipole-dipole interactions are electrostatic interactions between permanent dipoles in molecules. These interactions tend to align the molecules to increase attraction (reducing potential energy). Normally, dipoles are associated with electronegativeatoms, including (but not limited to) oxygen, nitrogen, sulfur, and fluorine.

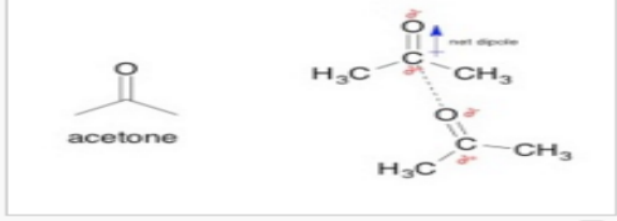

Figure 2. Dipole-dipole interactions between two acetone molecules, with the partially negative oxygen atom interacting with the partially positive carbon atom in the carbonyl.

For example, acetone, the active ingredient in some nail polish removers, has a net dipole associated with the carbonyl (see figure 2). Since oxygen is more electronegative than the carbon that is covalently bonded to it, the electrons associated with that bond will be closer to the oxygen than the carbon, creating a partial negative charge (δ^-) on the oxygen, and a partial positive charge (δ^+) on the carbon. They are not full charges because the electrons are still shared through a covalent bond between the oxygen and carbon. If the electrons were no longer being shared, then the oxygen-carbon bond would be an electrostatic interaction.

Often molecules contain dipolar groups, but have no overall dipole moment. This occurs if there is symmetry within the molecule that causes the dipoles to cancel each other out. This occurs in molecules such as tetrachloromethane. Note that the dipole-dipole interaction between two individual atoms is usually zero, since atoms rarely carry a permanent dipole.

Dipole-induced dipole

A dipole-induced dipole interaction (Debye force) is due to the approach of a molecule with a permanent dipole to another non-polar molecule with no permanent dipole. This approach causes the electrons of the non-polar molecule to be polarized toward or away from the dipole (or "induce" a dipole) of the approaching molecule. Specifically, the dipole can cause electrostatic attraction or repulsion of the electrons from the non-polar molecule, depending on orientation of the incoming dipole. Atoms with larger atomic radii are considered more "polarizable" and therefore experience greater attraction as a result of the Debye force.

London dispersion forces

London dispersion forces are the weakest type of non-covalent interaction. They are also known as "induced dipole-induced dipole interactions" and present between all molecules, even those which inherently do not have permanent dipoles. They are caused by the temporary repulsion of electrons away from the electrons of a neighboring molecule, leading to a partially positive dipole on one molecule and a partially negative dipole on another molecule. Hexane is a good example of a molecule with no polarity or highly electronegative atoms, yet is a liquid at room temperature due mainly to London dispersion forces. In this example, when one hexane molecule approaches another, a temporary, weak partially negative dipole on the incoming hexane can polarize the electron cloud of another, causing a partially positive dipole on that hexane molecule. While these interactions are short-lived and very weak, they can be responsible for why certain non-polar molecules are liquids at room temperature.

π-π interaction

π-π interactions are associated with the interaction between the π-orbitals of a molecular system.[1] For a simple example, a benzene ring, with its fully conjugated π cloud, will interact in two major ways (and one minor way) with a neighboring benzene ring through a π-π interaction (see figure 3). The two major ways that benzene stacks are edge-to-face, with an enthalpy of ~2 kcal/mol, and displaced (or slip stacked), with an enthalpy of ~2.3 kcal/mol.[1] Interestingly, the sandwich configuration is not nearly as stable of an interaction as the previously two mentioned due to high electrostatic repulsion of the electrons in the π orbitals.

Figure 3. Various ways that benzene can interact intermolecularly. Note, however, that the sandwich configuration is not a favorable interaction compared to displaced or edge-to-face

Cation-π interactions involve the positive charge of a cation interacting with the electrons in a π-system of a molecule. This interaction is surprisingly strong (as strong or stronger than H-bonding in some contexts), and has many potential applications in chemical sensors. For example, the sodium ion can easily sit atop the π cloud of a benzene molecule, with C_6 symmetry.

Anion-π interactions are very similar to cation-π interactions, but reversed. In this case, an anion sits atop an electron-poor π-system, usually established by the placement of electron-withdrawing substituents on the conjugated molecule

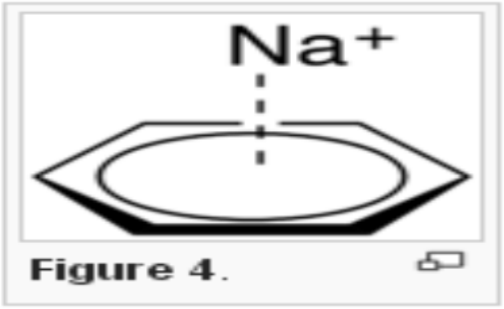

Figure 4.

HYDROPHOBIC INTERACTIONS:

The hydrophobic effect is the desire for non-polar molecules to aggregate in aqueous solutions in order to separate from water. This phenomenon leads to minimum exposed surface area of non-polar molecules to the polar water molecules (typically spherical droplets), and is commonly used in biochemistry to study protein folding and other various biological phenomenon. The effect is also commonly seen when mixing various oils (including cooking oil) and water. Over time, oil sitting on top of water will begin to aggregate into large flattened spheres from smaller droplets, eventually leading to a film of all oil sitting atop a pool of water.

DNA – DRUG INTERACTIONS:

DNA has two main functions

1. *Transcription:* Information is retrieved from the DNA by ribonucleic acid, RNA, and utilized to synthesize proteins in the body. Proteins are involved in all body processes and play many roles. e.g. as hormones, enzymes, carriers, structural proteins, receptors, regulators etc.
2. *Replication:* DNA is responsible for its own regeneration, i.e., DNA self replicates.

DNA is present in the body in the form of a double helix, where each strand is composed of a combination of four nucleotides, adenine (A), thymine (T), guanine (G) and cytosine (C). Within a strand these nucleotides are connected via phosphodiester linkages. The two strands are held together primarily via Watson Crick hydrogen bonds where A forms two hydrogen bonds with T and C forms three hydrogen bonds with G (Figure2).

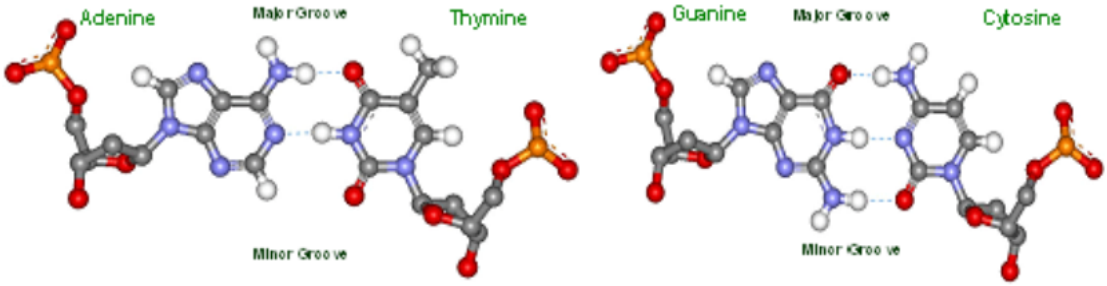

Fig.2 Watson Crick Base pairing, A-T and G-C base pairing

Specific recognition of DNA sequences by proteins/ small molecules is achieved via the combination of hydrogen bond acceptor/donor sites available on the major groove or minor groove. e.g. the A-T base pair offers a hydrogen bond acceptor, N7, a donor N6, and an acceptor, O4 on the major groove side.

DNA-Drug Interaction

Transcription and replication are vital to cell survival and proliferation as well as for smooth functioning of all body processes. DNA starts transcribing or replicating only when it receives a signal, which is often in the form of a regulatory protein binding to a particular region of the DNA. Thus, if the binding specificity and strength of this regulatory protein can be mimicked by a small molecule, then DNA function can be artificially modulated, inhibited or activated by binding this molecule instead of the protein. Thus, this synthetic/natural small molecule can act as a drug when activation or inhibition of DNA function is required to cure or control a disease (Table 1).

DNA activation would produce more quantities of the required protein, or could induce DNA replication; depending on which site the drug is targeted. DNA inhibition would restrict protein synthesis, or replication, and could induce cell death. Though both these actions are possible, mostly DNA is targeted in an inhibitory mode, to destroy cells for antitumor and antibiotic action.

Drugs bind to DNA both covalently as well as non-covalently.

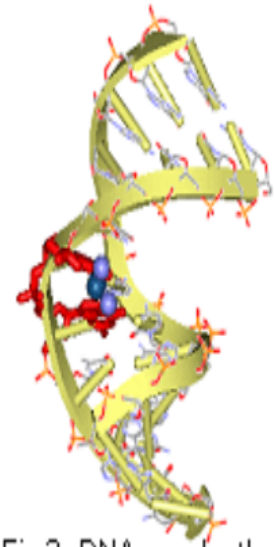

Fig.3. DNA covalently bound to cisplatin.(PDBID: 1AU5)

Covalent binding in DNA is irreversible and invariably leads to complete inhibition of DNA processes and subsequent cell death. Cis-platin (cis-diamminedichloroplatinum) is a famous covalent binder used as an anticancer drug, and makes an intra/interstrand cross-link via the chloro groups with the nitrogens on the DNA bases.

Non-covalent binders mostly fall under the following two classes:

1. *Minor groove binders*- Minor groove binding drugs are usually crescent shaped, which complements the shape of the groove and facilitates binding by promoting van der Waals interactions. Additionally, these drugs can form hydrogen bonds to bases, typically to N3 of adenine and O2 of thymine. Most minor groove binding drugs

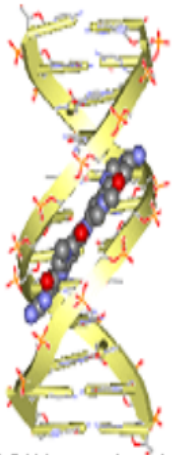

Fig.4 DNA complexed with netropsin, a minor groove binder.(PDB ID: 121D)

bind to A/T rich sequences. This preference in addition to the designed propensity for the electronegative pockets of AT sequences is probably due to better van der Waals contacts between the ligand and groove walls in this region, since A/T regions are narrower than G/C groove regions and also because of the steric hindrance in the latter, presented by the C2 amino group of the guanine base. However, a few synthetic polyamides like lexitropsins and imidazole-pyrrole polyamides have been designed which have specificity for G-C and C-G regions in the grooves.

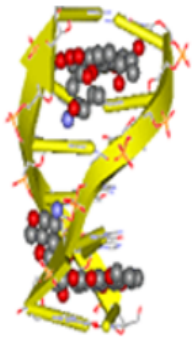

Fig.5 DNA complexed with actinomycinD, an intercalator. (PDB ID: DSC)

2. *Intercalators*- These contain planar heterocyclic groups which stack between adjacent DNA base pairs. The complex, among other factors, is thought to be stabilized by π-π stacking interactions between the drug and DNA bases. Intercalators introduce strong structural perturbations in DNA.

Non-covalent binding is reversible and is typically preferred over covalent adduct formation keeping the drug metabolism and toxic side effects in mind. However, the high binding strength of covalent binders is a major advantage.
Proteins are large molecules and bind quite strongly to the DNA, with binding constants in the nanomolar range. It has been difficult to achieve similar specificity and affinity using small non-covalent binders, and remains a major challenge to the design of drugs for DNA.