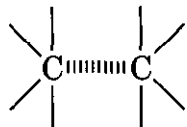



Table 1.1 Types of Intermolecular Forces

| Bond Type | Bond Strength (kcal/mol) | Example |
|--------------------------|-----------------------------|--|
| 1. Covalent | 40-140 | CH ₃ CH ₂ O-H |
| 2. Ionic (Electrostatic) | 5 | $R_4\overset{+}{N} \cdots \overset{-}{O} - \overset{O}{\parallel} C -$ |
| 3. Hydrogen | 1-10 | $-NH \cdots \underset{H}{O} - H$ |
| 4. Dipole-dipole | 1 | $R_3N: \cdots C=O$ |
| 5. van der Waals | 0.5-1 |  |
| 6. Hydrophobic | 1 |  |

In the broadest sense, these "bonds" would include covalent, ionic, hydrogen, dipole-dipole, van der Waals, and hydrophobic interactions. Most drug-receptor interactions constitute a combination of the bond types listed in Table 1.1, most of which are reversible under physiological conditions.

Covalent bonds are not as important in drug-receptor binding as noncovalent interactions. Alkylating agents in chemotherapy tend to react and form an immonium ion, which then alkylates proteins, preventing their normal participation in cell divisions. Baker's concept of active site directed irreversible inhibitors was well established by covalent formation of Baker's antifolate and dihydrofolate reductase (46).

Ionic (electrostatic) interactions are formed between ions of opposite charge with energies that are nominal and that tend to fall off with distance. They are ubiquitous and because they act across long distances, they play a prominent role in the actions of ionizable drugs. The strength of an electrostatic force is directly dependent on the charge of each ion and inversely dependent on the dielectric constant of the solvent and the distance between the charges.

Hydrogen bonds are ubiquitous in nature: their multiple presence contributes to the sta-

bility of the α helix and base-pairing in DNA. Hydrogen bonding is based on an electrostatic interaction between the nonbonding electrons of a heteroatom (e.g., N, O, S) and the electron-deficient hydrogen atom of an -OH, SH, or NH group. Hydrogen bonds are strongly directional, highly dependent on the net degree of solvation, and rather weak, having energies ranging from 1 to 10 kcal/mol (47, 48). Bonds with this type of strength are of critical importance because they are stable enough to provide significant binding energy but weak enough to allow for quick dissociation. The greater electronegativity of atoms such as oxygen, nitrogen, sulfur, and halogen, compared to that of carbon, causes bonds between these atoms to have an asymmetric distribution of electrons, which results in the generation of electronic dipoles. Given that so many functional groups have dipole moments, ion-dipole and dipole-dipole interactions are frequent. The energy of dipole-dipole interactions can be described by Equation 1.8, where μ is the dipole moment, θ is the angle between the two poles of the dipole, D is the dielectric constant of the medium and r is the distance between the charges involved in the dipole.

$$E = 2\mu_1\mu_2\cos\theta_1\cos\theta_2/Dr^3 \quad (1.8)$$