NEUTRAL GUEST BINDING
Non-covalent interactions available for ligand design:
H-bonding: strongly directional to give specificity.
π-π stacking: between aromatic groups.
Hydrophobic effects: exclusion of non-polar groups or molecules from aqueous solution.

1. Complementarity in H-bonding Principles
   - Host/Receptor has multiple H-bonding groups which are complementary to the guest.
   - H-bonding groups are pre-organized and rigidly held within receptor molecule so that directionality in interaction with guest is retained.
   - Barbital like binding: strength of bonding dependent upon number of H-bonds.

2. π-π stacking Interactions
   - Attraction between negatively charged π-electron cloud of an aromatic system with positively charged π-framework of neighboring aromatic molecule.
   - 2 configurations: a) Face to Face: parallel ring systems separated by ca. 3.5 Å. Aligned so centre of one lies over corner of other.
   - b) Edge to Face: H atom from one ring interlocks in a perpendicular orientation with centre of π-cloud of second ring.

Example: Molecular hinge - π-π stacking of naphthalene with thymine.