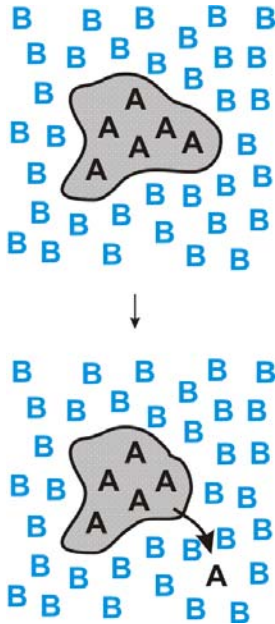# Solvation and Weak Interactions

"Like dissolves like": appropriate, but not sufficient.

Gains:

S_A *entropy of molecular dispersion*

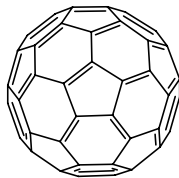K_{AB} *weak interactions between A, B*

Losses:

S_B solvent B is ordered around A

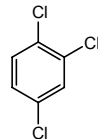K_{AA} broken interactions between A-A

K_{BB} same for B-B

So, specific (often weak) intermolecular interactions responsible for solubility.

Depends on relative magnitudes of K_{AA}, K_{BB}, K_{AB}

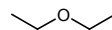# Solvation and Weak Interactions

C_{60} solubility in:

 20 mg/mL

 1.8 mg/mL

 0.037 mg/mL

Not just "like dissolves like";

Specific solvent-solute interactions responsible for solubility differences.

High oxidation potential of C_{60} (E_0 = 0.44 V) means electrons easily donated to electron poor partners (like trichlorobenzene).

Solvent Scales

Table 3.1
Various Solvent Scales*

Solvent	ε	α	β
Formamide	111	0.71	0.48
Water	78	1.17	0.47
DMSO	47	0.00	0.76
DMF	37	0.00	0.76
Acetonitrile	36	0.19	0.40
Methanol	33	0.93	0.66
HMPA	29	0.00	1.05
Ethanol	25	0.83	0.75
Acetone	21	0.08	0.43
Isopropanol	20	0.76	0.84
t-Butyl alcohol	12	0.42	0.93
Pyridine	13	0.00	0.64
Methylene chloride	9	0.13	0.10
THF	8	0.00	0.55
Acetic acid	6	1.12	0.45
Ethyl acetate	6	0.00	0.45
Chloroform	5	0.20	0.10
Diethyl ether	4	0.00	0.47
Benzene	2	0.00	0.10
Carbon tetrachloride	2	0.00	0.10
n-Hexane	2	0.00	0.00

Dielectric constant (ε):

Measure of polarity, polarizability
Values obtained by measuring
capacitance across solvent

Taft α/β:

Measure of proton donating/proton
accepting character

Interesting contrast:
Acetic acid & ethyl acetate
Same dielectric constant, but very
different miscibility with water
*(AcOH infinitely miscible,
EtOAc immiscible)*

(from MPOC text, page 147)

Solvent Scales

Gutmann acceptor/donor numbers (AN/DN): measure of *Lewis* basicity/acidity.

solvent	acceptor number (AN)	donor number (DN)
H_2O	54.8	18
MeOH	41.3	19.1
EtOH	37.1	19.2
1-Propanol	37.7	19.8
2-Propanol	33.8	21.1
t-Butanol	27.1	21.9
DMSO	19.3	29.8
MeCN	18.9	14.1
Nitromethane	20.5	2.7
Diethyl ether	3.9	19.2
CCl$_4$	8.6	0
Benzene	8.2	0
Hexane	0	0
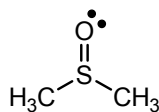
DMSO: Great e⁻ donor,
but poor acceptor
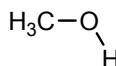
Methanol: Good e⁻
donor, but great e⁻
acceptor (H-donor)

*Point is not importance of this particular
scale, but rather differences in the ways
scales are defined, how solvents and
solutes interact.*

Weak Interactions

- Earlier, discussed strong bonding interactions, BDEs ≈ 50-200 kcal/mol.

- Structures, properties, activities of molecules also depend on weaker, non-bonding interactions. (As does solvent character.)

- Biological molecules, polymer materials, organic molecule/drug design, analyte recognition, all depend on weak interactions.
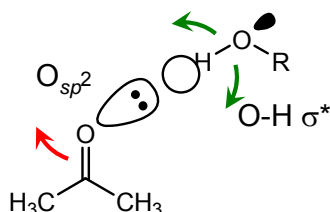
- But…they are much harder to measure and characterize.

Hydrogen Bonding

What you probably already know:
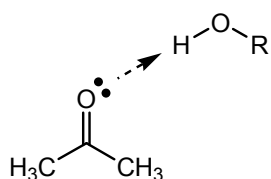
Co-linear arrangement is preferred;

Orbital overlap optimized when O_{sp2} is directed at O-H σ*.

- Other angles about oxygen > 120° are well accommodated (H-bond almost as strong)*

- Other angles about hydrogen are poorly accommodated (weaker H-bond)*

(*see e.g. Morozov, A. V. et al. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 6946.)

Hydrogen Bonding

What you may not know:
"Strength" of H-bond depends on context.
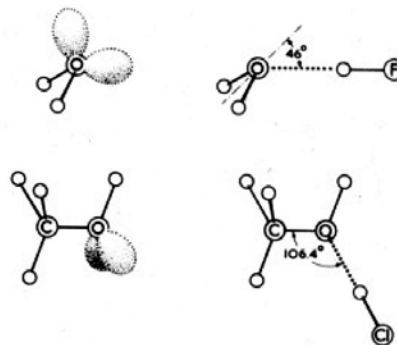
BDEs are measured without context:

$$R_1\text{—}R_2 \;\rightarrow\; R_1 \;+\; R_2 \qquad \Delta H_r = \text{BDE}$$

Typically measured in the gas phase (vacuum):

BDE ($H_2O\cdot HF$) = 8 kcal/mol
BDE ($CH_3OH\cdot HCl$) = 7 kcal/mol

(Geometries from gas-phase spectroscopic measurements. Legon, A. C.; Millen, D. J. *Acc. Chem. Res.* **1987**, *20*, 39-46.)
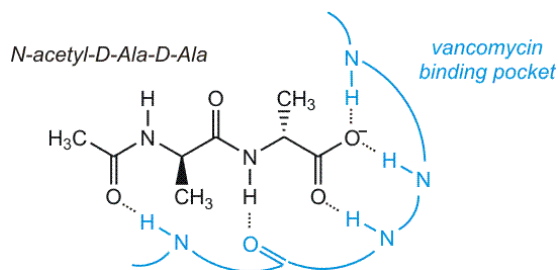

Hydrogen Bonding

What you may not know:
"Strength" of H-bond depends on context.

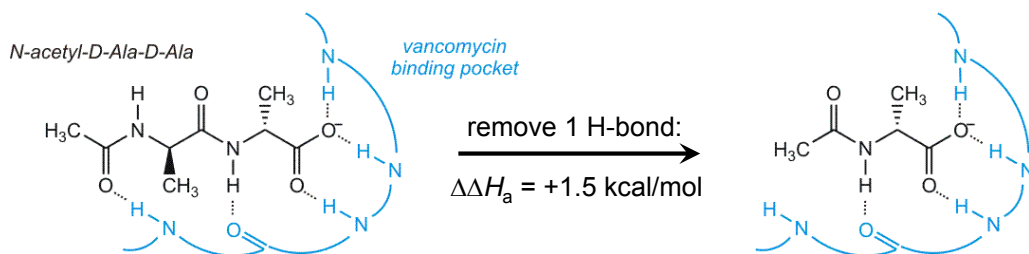What if molecules are dissolved in solvent that can also H-bond (like H_2O)?

Competitive H-bond interactions can make H-bond "worth" much less.

N-acetyl-D-Ala-D-Ala / vancomycin binding pocket

In water, how much is each hydrogen bond between receptor & ligand worth?
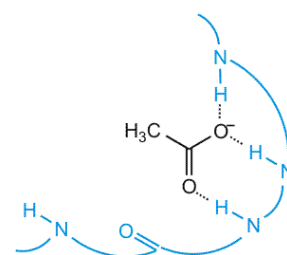
Answer by successively removing H bonds.

Williams, D. H. et al. *J. Chem. Soc. Chem. Commun.* **1994**, 1519.

Hydrogen Bonding

N-acetyl-D-Ala-D-Ala *vancomycin binding pocket*

remove 1 H-bond:

$\Delta\Delta H_a$ = +1.5 kcal/mol

(association of ligand to pocket is 1.5 kcal/mol less favorable)
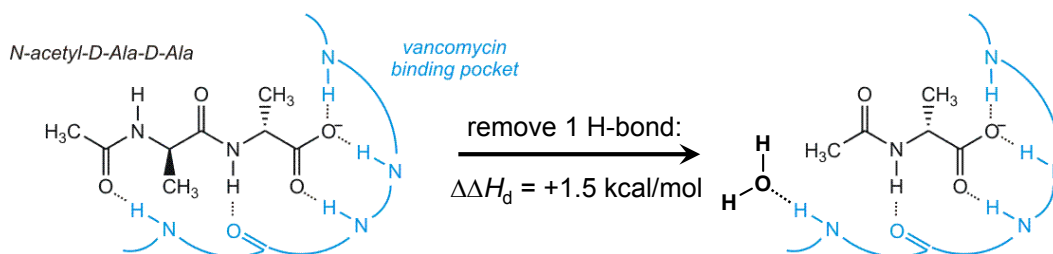
remove another H-bond:

$\Delta\Delta H_a$ = +1.5 kcal/mol

Why were H-bonds so much "weaker" in water than in the gas phase?

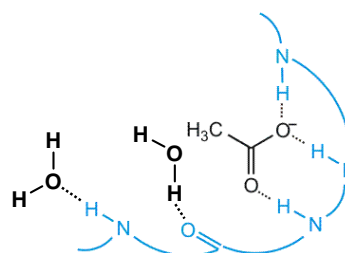Williams, D. H. et al. *J. Chem. Soc. Chem. Commun.* **1994**, 1519.

Hydrogen Bonding

N-acetyl-D-Ala-D-Ala *vancomycin binding pocket*

remove 1 H-bond:

$\Delta\Delta H_d$ = +1.5 kcal/mol

remove another H-bond:

$\Delta\Delta H_d$ = +1.5 kcal/mol

Why were H-bonds so much "weaker" in water than in the gas phase?
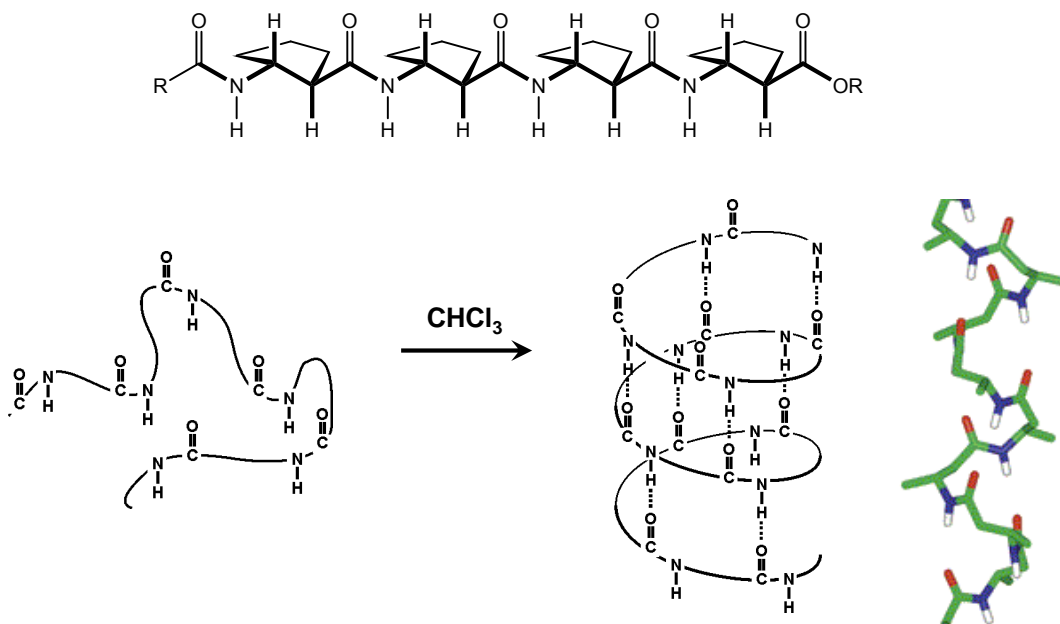
Because H-bonded water recovers much of energy from broken H-bond.

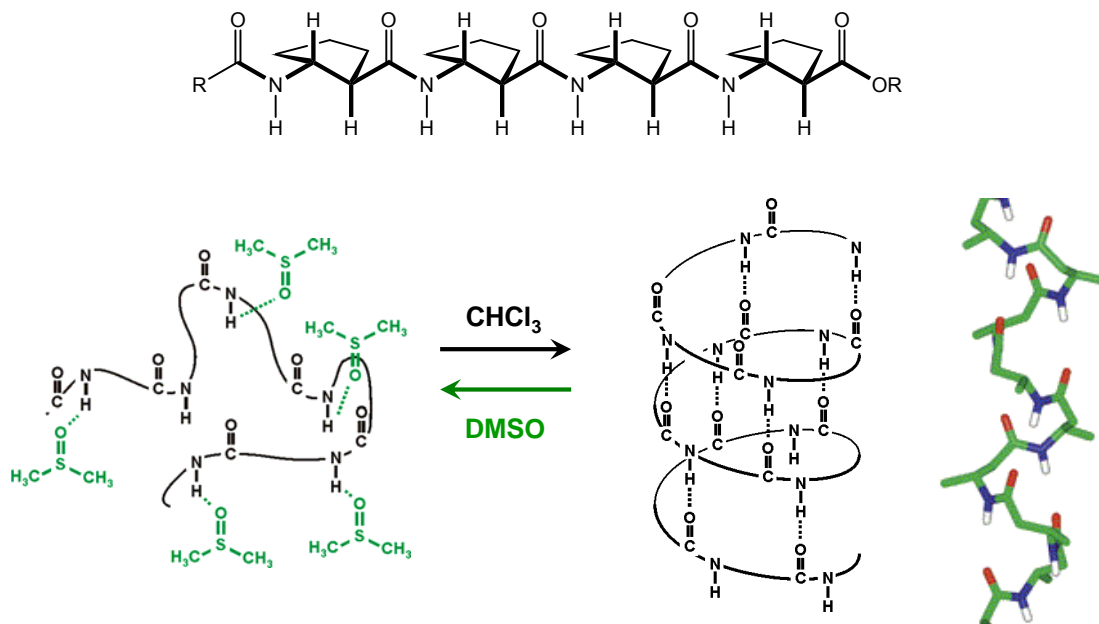Williams, D. H. *J. Chem. Soc. Chem. Commun.* **1994**, 1519.

Hydrogen Bonding

H-bonds to solvent can prevail over H-bonds within a molecule.

Gellman, S. H. et al. *Chem. Rev.* **2001**, *101*, 3219.

Hydrogen Bonding

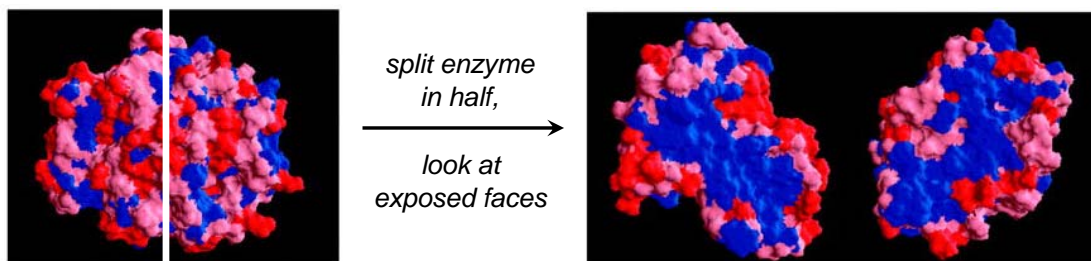*H-bonds to solvent can prevail over H-bonds within a molecule.*

Gellman, S. H. et al. *Chem. Rev.* **2001**, *101*, 3219.

Hydrophobic Effect

If H-bonding solvents (like H_2O) are so good at competing for H-bonds, how do biomolecules stay folded?

The "hydrophobic effect": more accurately *de-solvation* than a weak interaction.

split enzyme in half,

look at exposed faces

BphC enzyme;
hydrophilic residues (K,D,E,R,Q,N) **red**
hydrophobic residues (I,F,V,M,W,C,Y) **blue**

- Exclusion of hydrophobic residues from water important to folding;

- H-bonds "stronger" inside the protein as a result.

Zhou, R. et al. *Science* **2004**, *305*, 1605.
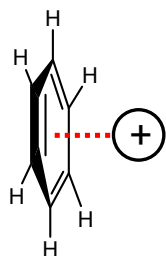
Discussion Question
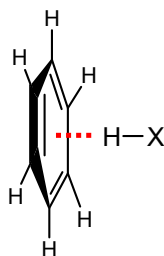
Bases in DNA ("R" is DNA strand):

Assume that you can translate these bases however you want, but you can't rotate them. How can they be paired? (There are more than two possible pairs!)

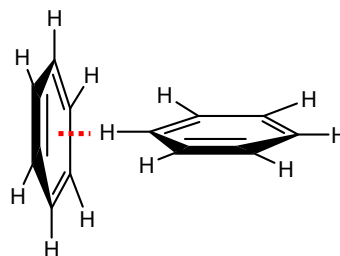If $\Delta G_{H\text{-bond}}$ = 1.2 kcal/mol, how much are these pairs worth?

Sartorius, J.; Schneider, H.-J. *Chem. Eur. J.* **1996**, *2*, 1446.

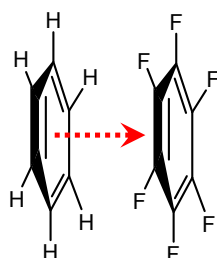# Weak Arene Interactions

arene-cation   *arene-H*   *arene-arene*

ET complex
arene-arene

- Aromatic face can act as electron donor
- Forms interactions with dissociaton energies ~ 1-5 kcal/mol

Review: Diederich, F. et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 1210.
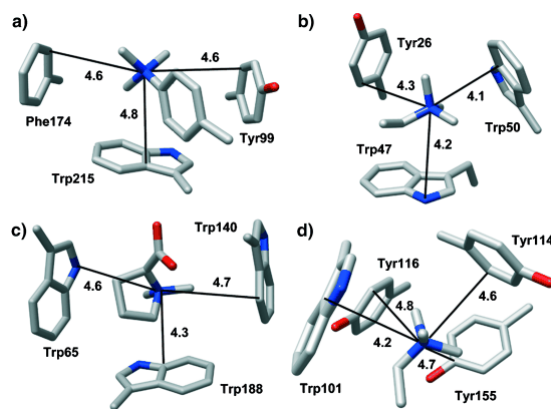

Weak Arene Interactions

How do we know?

Experimental studies…

solvent	ΔG_a (kcal/mol)	ΔH_a (kcal/mol)	$T\Delta S_a$ (kcal/mol)
Water	-9.4	-	-
2,2,2-trifluoroethanol	-7.8	-20.0	-12.2
methanol	-6.4	-12.0	-5.6
ethanol	-6.1	-11.0	-4.9
acetone	-4.3	-6.6	-2.3
dimethyl sulfoxide	-3.9	-6.4	-2.5
N,N-dimethylformamide	-2.9	-3.7	-0.8
tetrahydrofuran	-2.7	-3.0	-0.3
chloroform	-2.3	-3.1	-0.8
benzene	-1.5	-0.8	+0.7

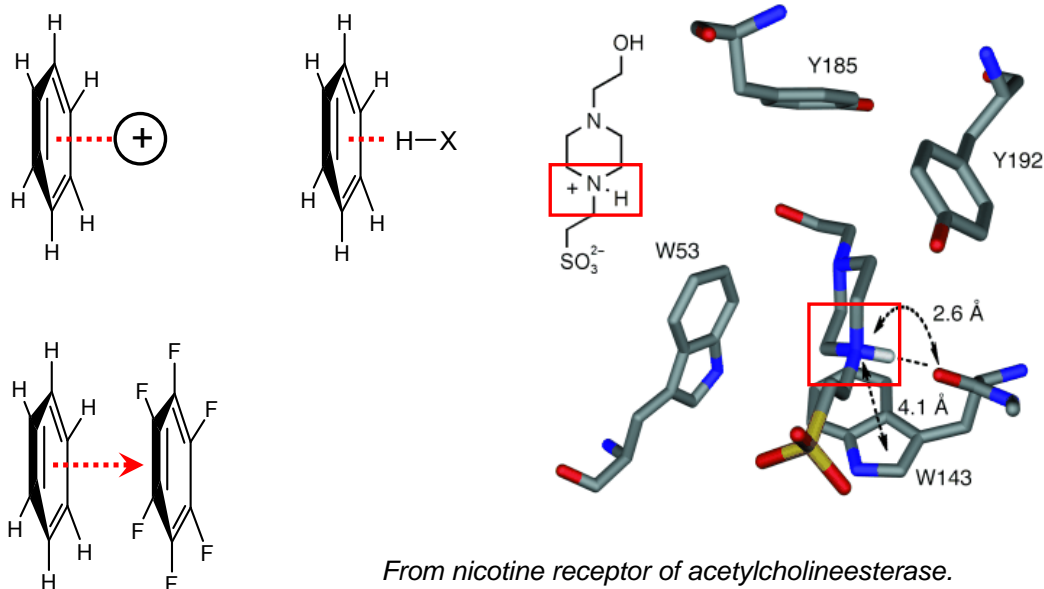**…and crystallographic databases.**

Four examples of arene-(NR_4^+) boxes from Protein Data Bank searching
(Shärer, K. et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 4400.)

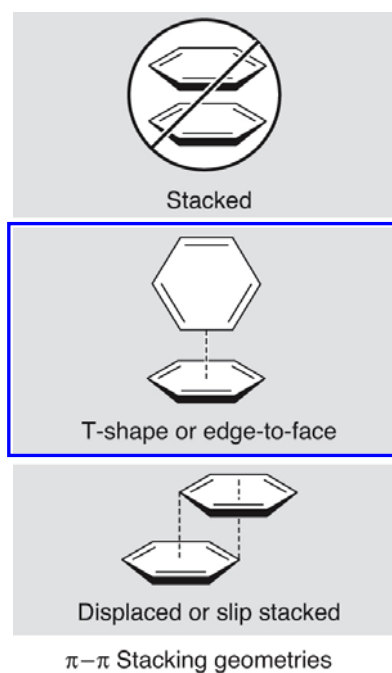Review: Diederich, F. et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 1210.
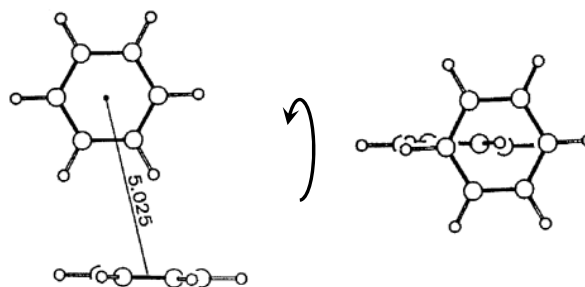
Arene Donor Interactions

From nicotine receptor of acetylcholineesterase.
Cationic ligands (like nicotine) bind aromatic Trp residues

Review: Diederich, F. et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 1210.
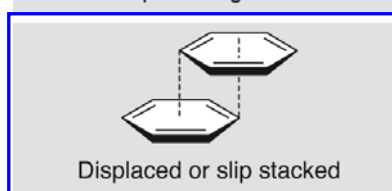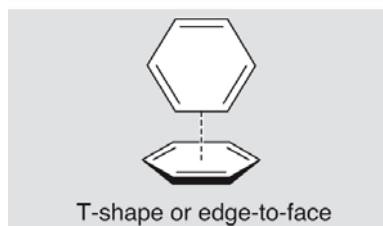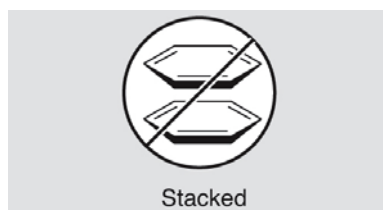
Arene-Arene Interactions

Stacked

T-shape or edge-to-face

Displaced or slip stacked

$\pi-\pi$ Stacking geometries

(MPOC p.184)

Crystal structure of benzene: Rings organized
in herringbone structure (not stacked!)

Arene-Arene Interactions

Stacked

T-shape or edge-to-face

Displaced or slip stacked

$\pi-\pi$ Stacking geometries

(MPOC p.184)

Example: DNA

(From
http://www.bio.cmu.edu/Courses/BiochemMols/
Stacks/bpStacks.htm.
Requires MDL Chime, at http://www.mdli.com)