CHM 696-11: Week 4-A

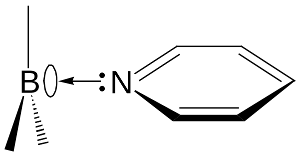
Instructor: Alexander Wei

Hydrogen Bonds & other Directional Motifs

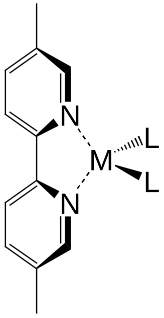
Encoded Self-Assembly

Noncovalent bonds as directing motifs

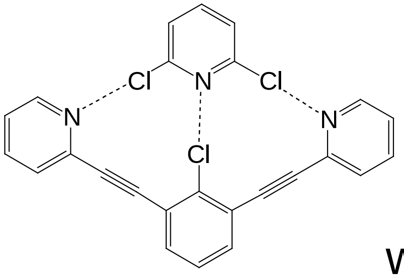
Lewis acid–base interaction (dative bonding)



Metal–ligand coordination



Dipole–induced dipole interactions



weakly directional

Hydrogen bonding

$$\boxed{X_1\text{–}H\cdots X_2}$$

…where X_1, X_2 are more electronegative than H

Directing vs. non-directing hydrogen bonds

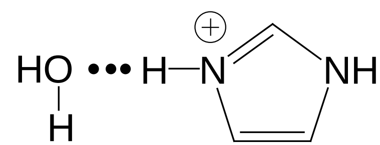
Data from Jeffrey and Saenger, *Hydrogen Bonding in Biological Structures*

	HB length:
N^+–H ··· N/O	1.7–1.9 Å
N–H ··· $^-$O (carboxylate, *N*-oxide, etc.) N–H ··· N	1.93 Å
N–H ··· O=C (carbonyl)	1.97–2.0 Å

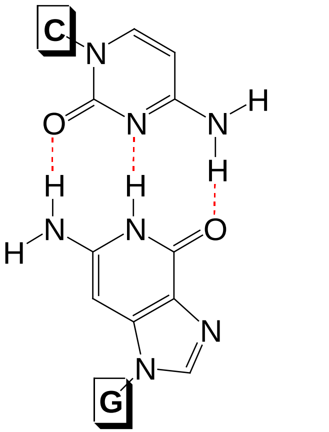
“supporting” HB’s:

N–H ··· OR_2 (ether)	> 2.0 Å
O–H ··· N/O (alcohol)	
C–H ··· O S–H ··· O	

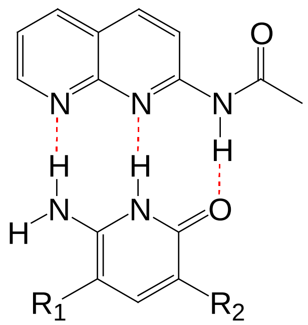
Some gas-phase enthalpies of hydrogen bonds (kcal/mol):

$CH_3CO_2^-$ ···H–OH	–19
	–14
H_2O ••• H–OH	–6.4
H_2O ••• H–SCH_3	–3.2
CH_3SH ••• H–OH	–3.1

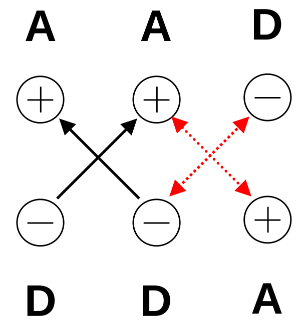
Secondary interactions in hydrogen bonding

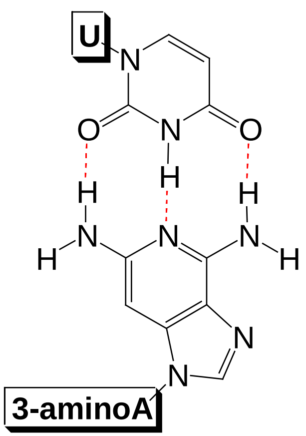


$K_a(CDCl_3, 298\ K) = 10^4\text{-}10^5$

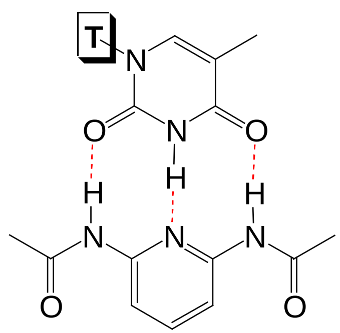


$K_a(CDCl_3, 298\ K) = 1.7 \times 10^4$

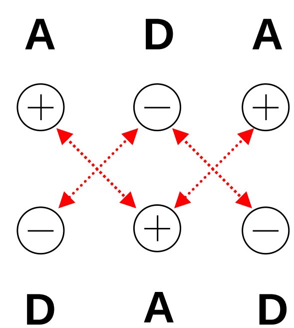




$K_a(CDCl_3, 298\ K) = 170$

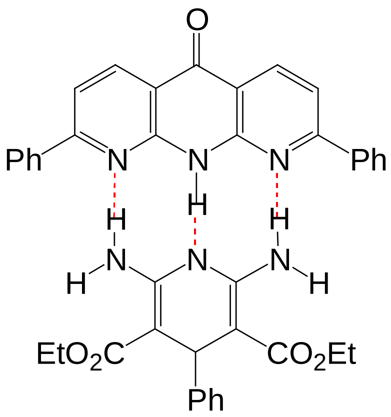


$K_a(CDCl_3, 298\ K) = 90$

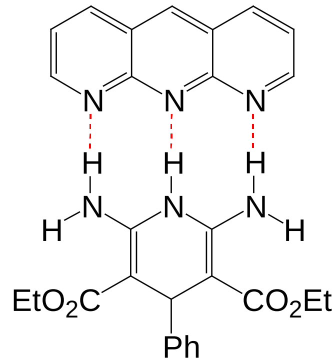


Jorgensen and Pranata, *JACS*, **1990**, *112*, 2008

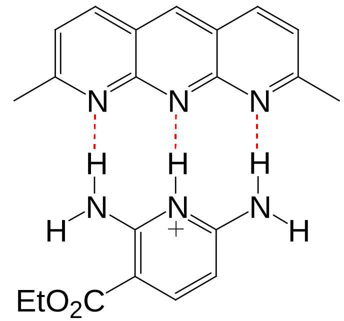
Secondary interactions in hydrogen bonding



ADA-DAD: $K_a(CDCl_3) = 78$



AAA-DDD: $K_a(CDCl_3) > 10^5$!

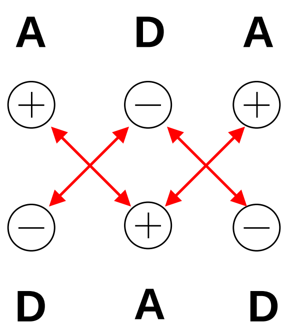


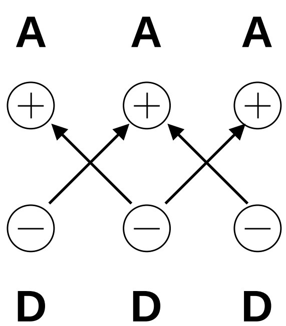
(pK_a = 12.6)

(pK_a = 12.2)

AAA-DD$^+$D: $K_a(CDCl_3) > 5 \times 10^5$

Bell and Anslyn, *Tetrahedron* **1995**, *51*, 7161



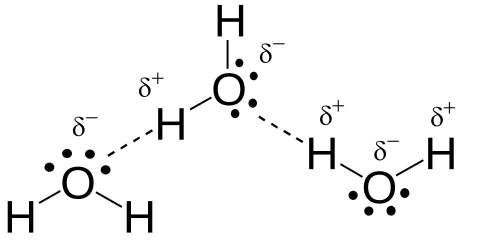


Murray and Zimmerman, *JACS*, **1992**, *114*, 4010

Cooperativity in Hydrogen Bonding

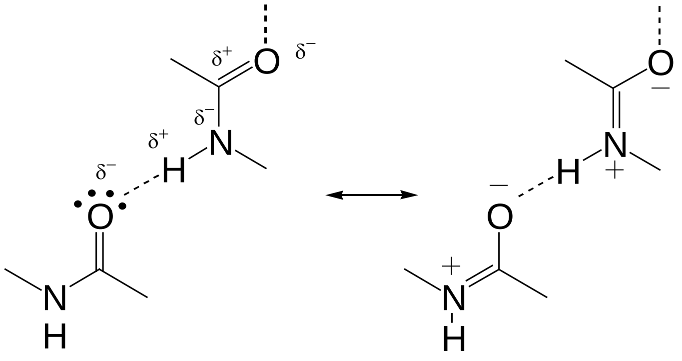
σ-cooperativity

(only σ-bonds involved)



π-cooperativity

("vinylogous" H-bonding)



Connectivity can be *extended* or *cyclic*:

Bulk materials; crystal engineering

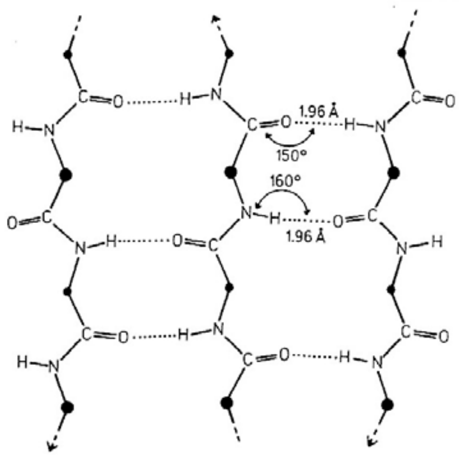
Inclusion complexes, biological motifs

(structures with finite dimensions)

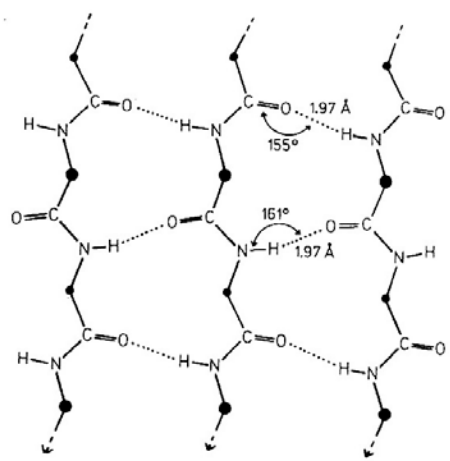
Cooperative hydrogen bonding in x-ray crystal structures

extended HB network: peptide β-sheets

Antiparallel β-sheet

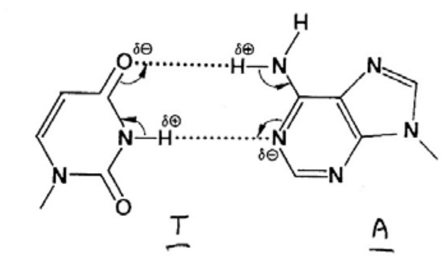


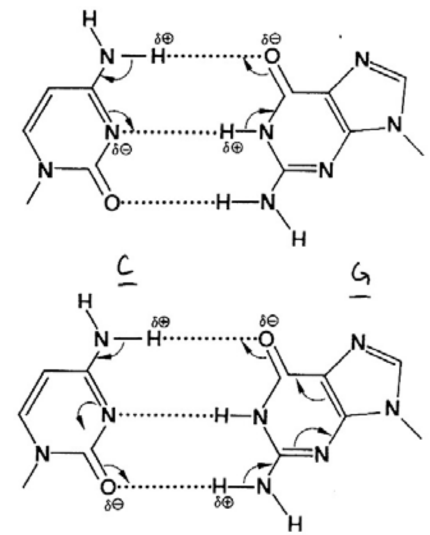
Parallel β-sheet



Cyclic hydrogen bonding:

DNA base pairs





From Jeffrey and Saenger,

Hydrogen Bonding in Biological Structures

SUPRAMOLECULAR SELF-ASSEMBLY

- An extension of molecular recognition
- Thermodynamically driven process; ideally, should produce the lowest energy system (assuming microreversibility)

I. Self-assembled supermolecules (discrete number of programmed components)

II. Supramolecular assemblies: polymolecular arrays with some control over orientation

a. Solid and liquid crystals “by design”

b. Self-assembly of amphiphiles: vesicles and bilayer membranes

Reviews: Lehn’s “*Supramolecular Chemistry*,” Ch. 8-9; Lawrence, Jiang and Levitt, *Chem. Rev.* **1995**, *95*, 2229

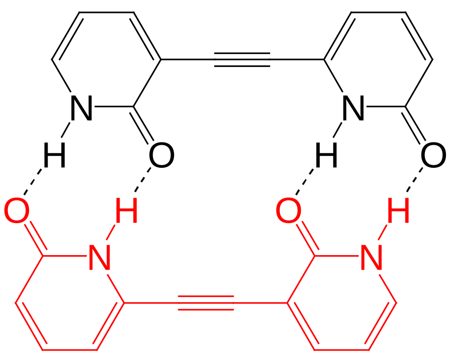
Self-assembly: dimers (N=2)

2 types: Heteromeric (host-guest complexes)

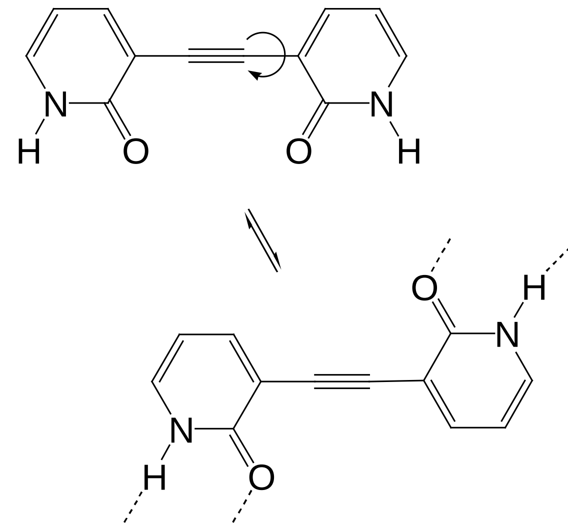
"Homomeric" (self-complementary)

Dimerization easily characterized by NMR, fluorescence, etc.

Molecular geometry is important:



vs.



Ducharme and Wuest, *J. Org. Chem.* **1988**, *53*, 5787

Gallant et al, *J. Org. Chem.* **1991**, *56*, 2284

Self-assembly: N > 2 (aggregates)

More difficult to characterize quantitatively–
“many-bodied problem”

Techniques used to estimate size of aggregate:

- Titration experiments (need to know endpoints)
- Vapor phase osmometry (VPO): estimation of mol. wt.
- Gel permeation or size-exclusion chromatography: based on hydrodynamic volume of aggregate

New thermodyamic issues:

- Enthalpic gain (sum of all molecular interactions)
- Statistical entropy: N subunits form 1 supermolecule; population change = N–1

Cooperativity in self-assembly

Dimer formation: K_2 defined by $2\,A \rightleftharpoons A_2$

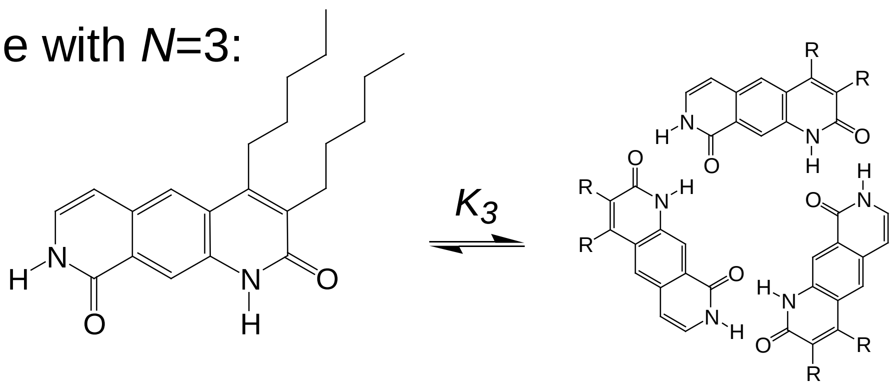
N-aggregate: K_N defined by $N\,A \rightleftharpoons A_N$

Positive cooperativity: $K_N > (K_2)^{N-1}$

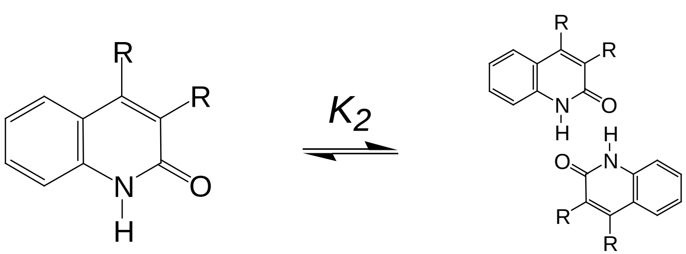
(or K^N, depending on number of interactions)

Negative cooperativity: $K_N < (K_2)^{N-1}$

Example with N=3:

3 

$K_3\,(CDCl_3) = 8.3 \times 10^5\ M^{-2}$

2 

$K\,(CDCl_3) = 46\ M^{-1}$

$K^2 = 2116\ M^{-2}$; $K^3 = 9.7 \times 10^4\ M^{-3}$

Zimmerman and Duerr, *J. Org. Chem.* **1992**, *57*, 2215

Examples of self-assembled supermolecules (*N* = 4)

The G-Quartet

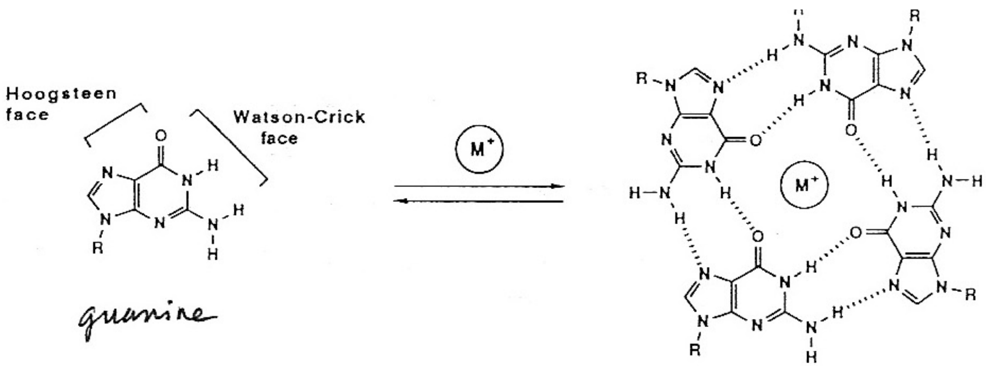
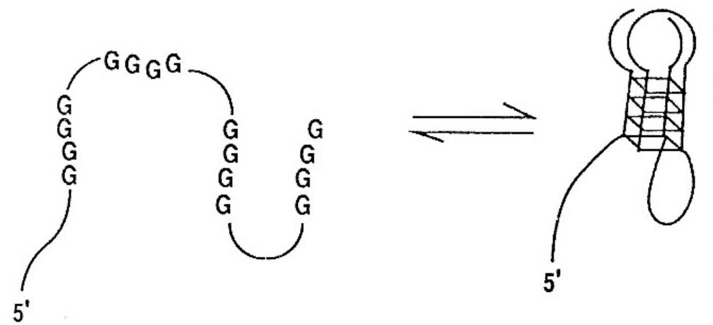


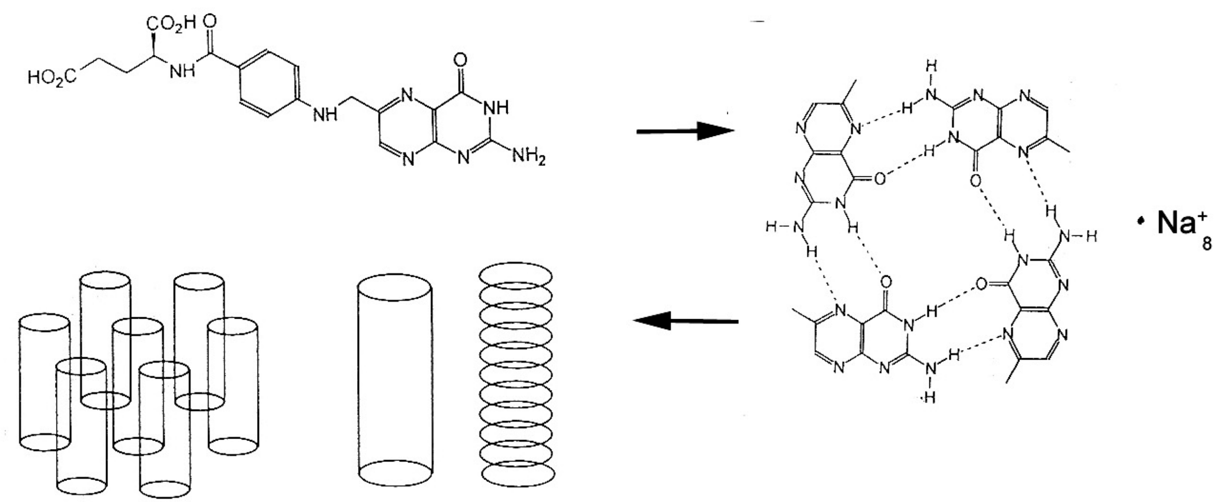
Figure 4. *A self-assembling G-quartet. The subunits interact through hydrogen bonds, although the nucleating metal ion is necessary for this formation.*



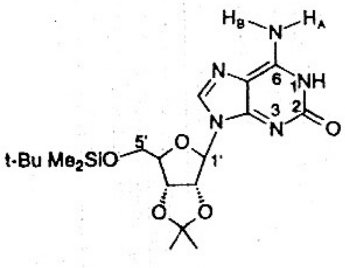
DNA telomeres: “end caps” in chromosomes

Folate tetramer:
Self-assembly into liquid crystal

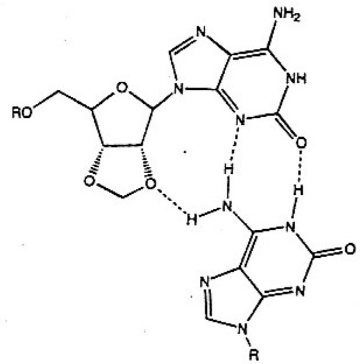
Ciuchi et al, *JACS* **1994**, *116*, 7064
Gottarelli et al, Helv. Chim Acta, **1996**, *79*, 220

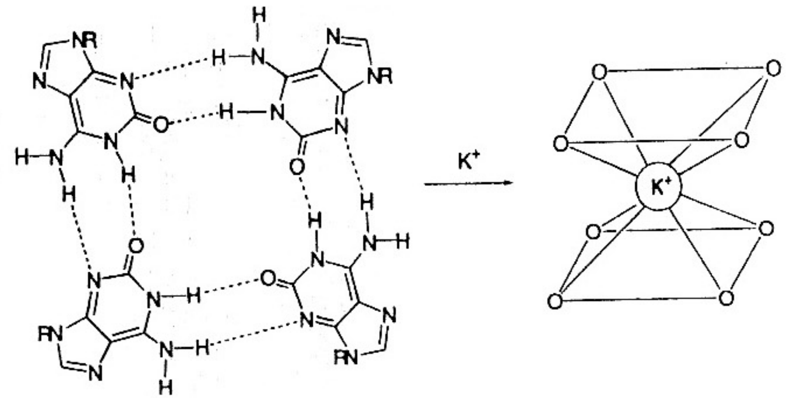


More examples of self-assembled supermolecules (*N* = 4)



IsoG 2





(IsoG)$_4$ 4

(IsoG)$_8$-K$^+$ 5

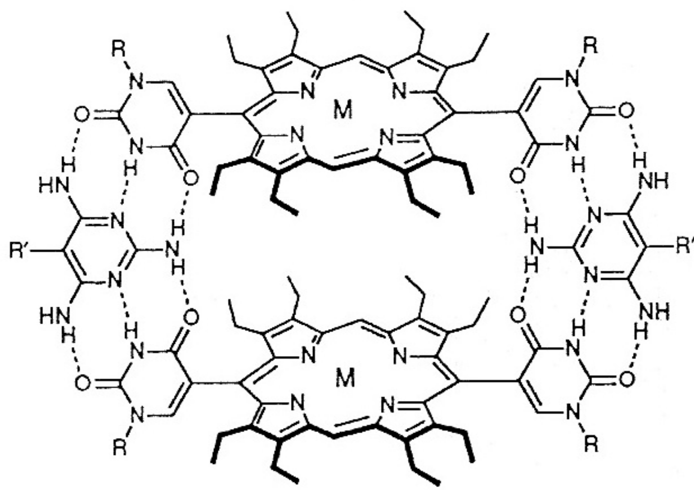
Isoguanosine tetramer:

Tirumala and Davis, *JACS*, **1997**, *119*, 2769

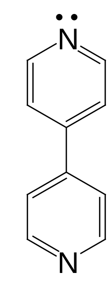
$K_3 = 10^9 - 10^{10}\ M^{-3}$ in acetone

Cooperative [2+2] complex as a supramolecular “host”:

Drain et al, *Chem. Comm.*, **1993**, 243



M = Fe^{II} or Zn^{II}



4,4’-bipyridine (guest)

Examples of self-assembled supermolecules (N = 6)

Encoded self-assembly: Rosette-like structures

Marsh et al, *Chem. Comm.*, **1996**, 1527

Mascal et al, Angew. Chem. **1996**, *35*, 2204

Characterized by:

VPO (mw 2600   10%; 2511 actual)

GPC (mw > 2200)

X-ray crystallography

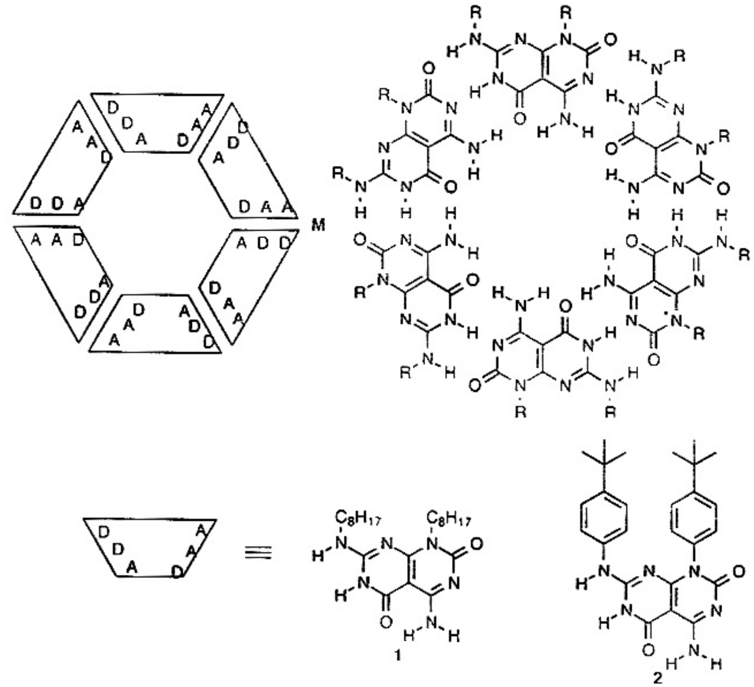
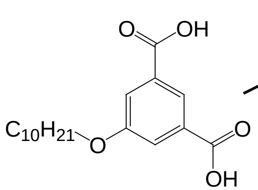
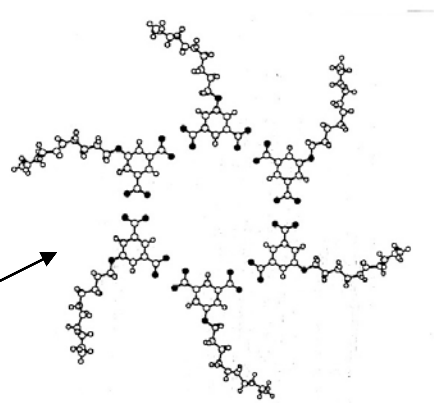


Fig. 1 Proposed self-assembly of the self-complementary heterocycles 1 and 2 into a supramolecular macrocycle M: schematic and structural representation (A/D: hydrogen acceptor–donor site)





Non-coded self-assembly:

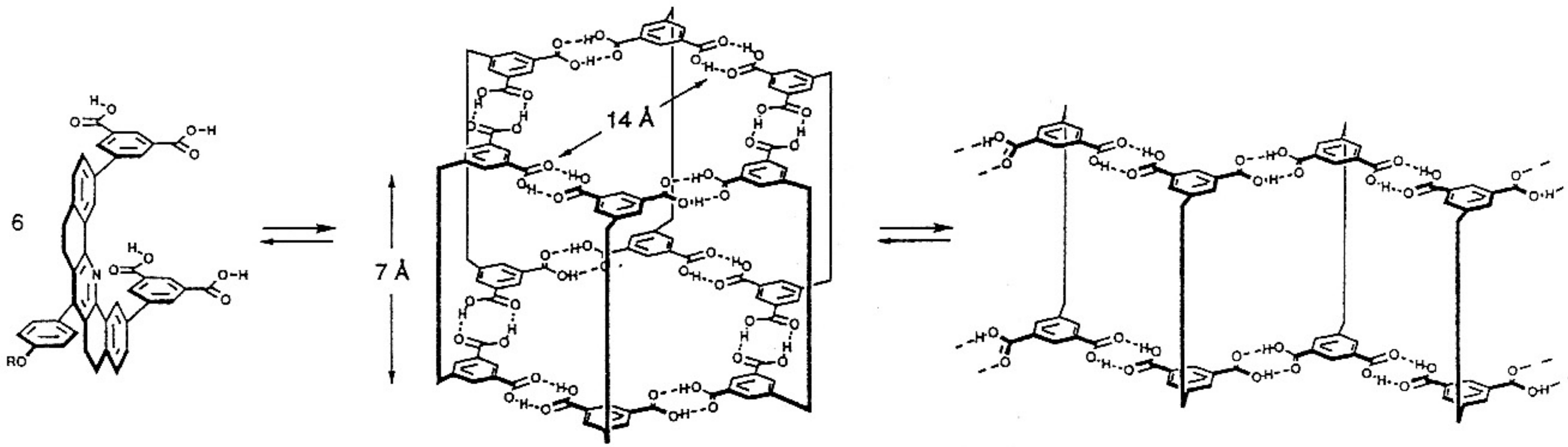
Yang et al, *Tetrahedron Lett.*, **1994**, *35*, 3665

Characterized by VPO for concentrations above 10 mM (mw 4600-4900; 4531 actual)

More examples of self-assembled supermolecules (N = 6)

Surface complementarity in self-assembly: steric effects

Zimmerman et al, *Science* **1996**, *271*, 1095

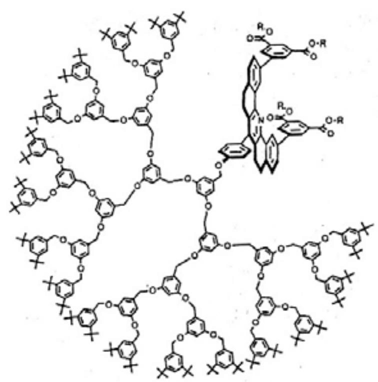


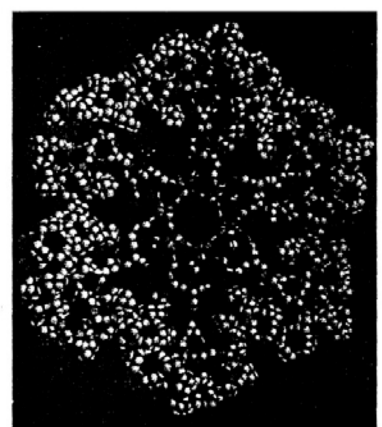
1 2 3

Packing effect:

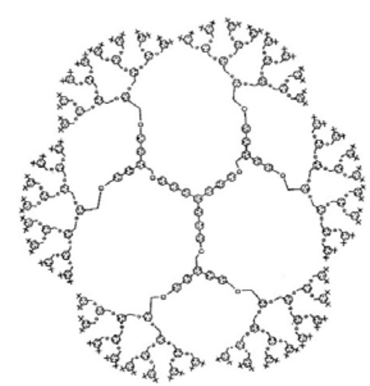
secondary van der Waals

interactions





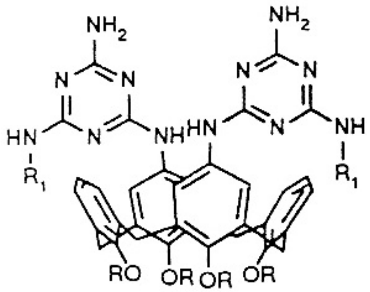
MW = 19,062



MW = 16,932

Supramolecular rosettes (*N* = 6)

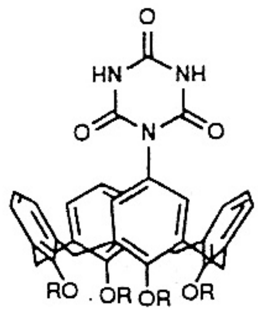
Rosette–calixarene hybrid cage structure: Vreekamp et al, *Angew. Chem.* **1996**, *35*, 1215



1

R = $C_{12}H_{25}$, R_1 = C_4H_9

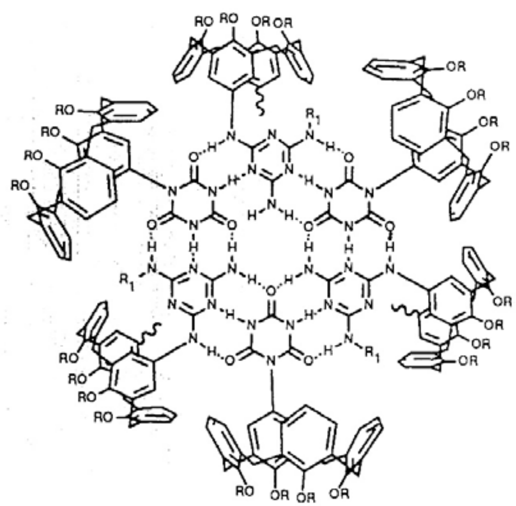
Melamine units



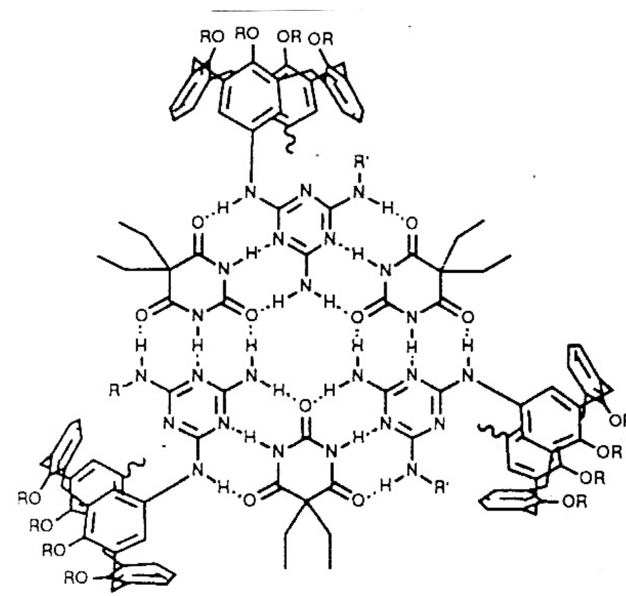
2

R = $C_{12}H_{25}$

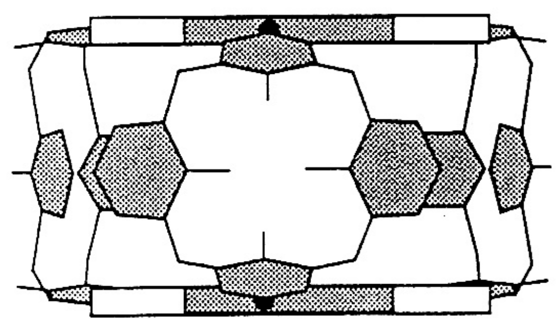
Barbituric acid unit



1 • 2

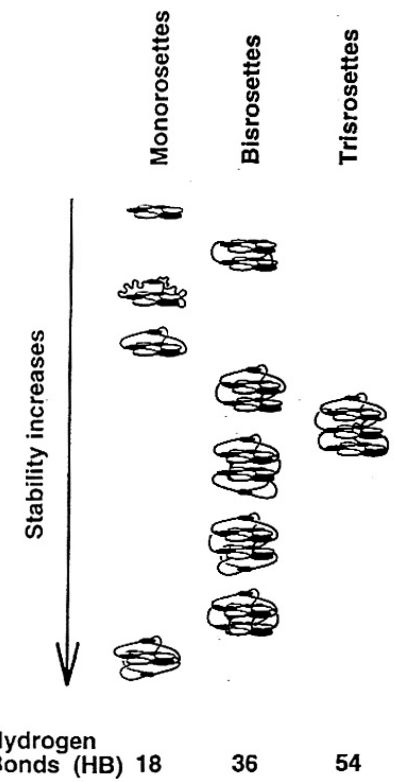


1 • BA

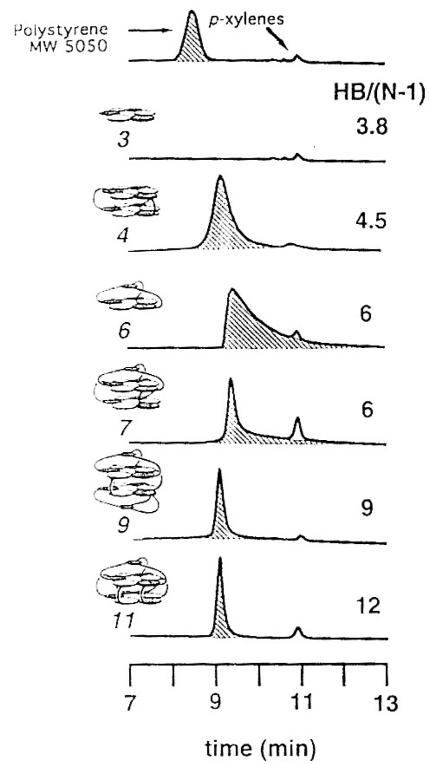


Self-assembly and statistical entropy

Multilevel rosettes: Whitesides et al, *Acc. Chem. Res.* **1995**, *28*, 37



Particles (N)	HB/(N-1)	MW (kDa)	Cmpd. Number
6	3.8	1.2	*3*
9	4.5	4.5	*4*
4	6	2.5	*5*
4	6	2.7	*6*
7	6	4.7	*7*
10	6	6.4	*8*
5	9	5.5	*9*
5	9	5.7	*10*
4	12	4.7	*11*
2	18	4.1	*12*



gpc stability 'indicator'

Conformational preorganization in complex **6**

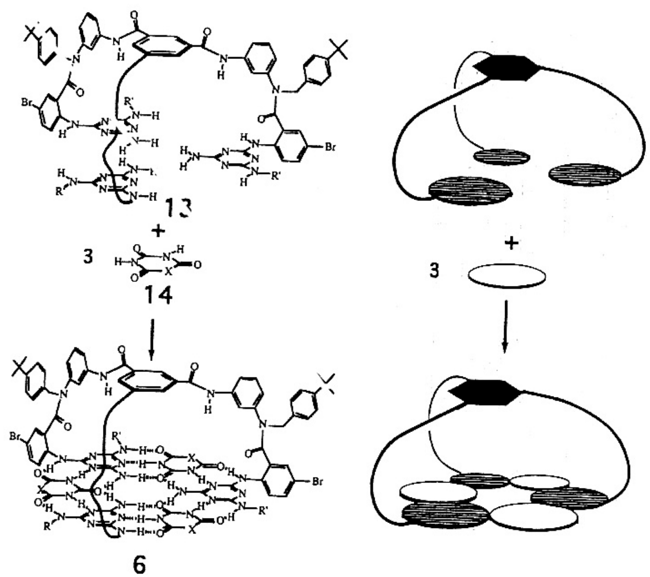
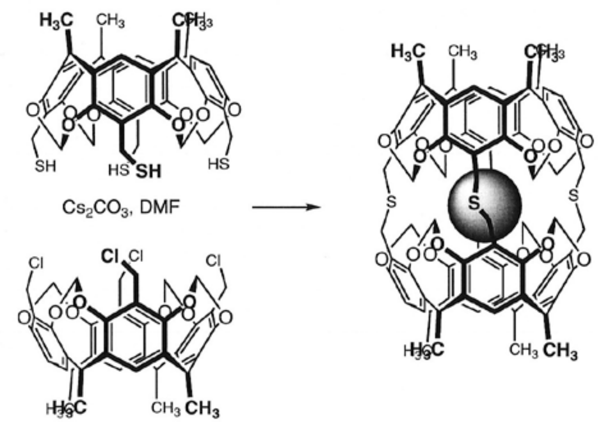


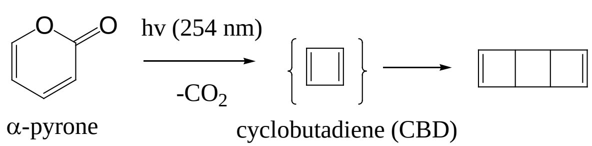
Figure of merit for supramolecular stability: $\dfrac{\mathbf{HB}}{\mathbf{N-1}}$

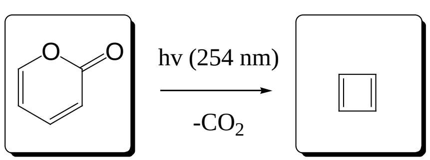
Self-assembly in three dimensions

Supramolecular encapsulation of guest molecules

1. Cram's carcerands:
Nature **1992**, 356, 29.

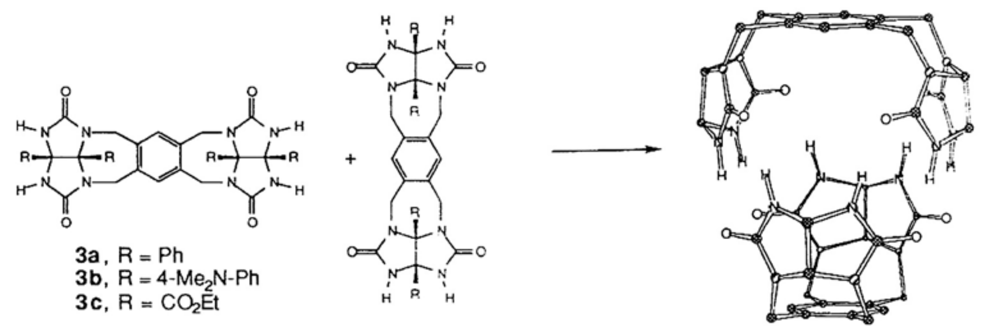




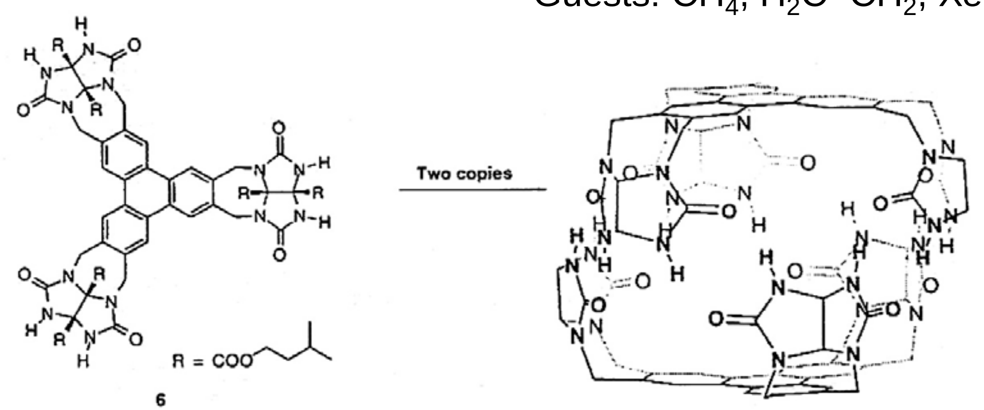


encapsulated pyrone   encapsulated CBD-- stable!

2. Rebek's self-assembling "softballs:"
Acc. Chem. Res. **1999**, 32, 278.

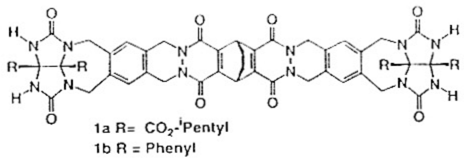


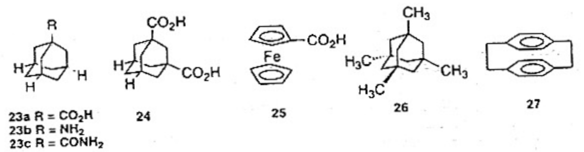
Guests: CH_4, $H_2C{=}CH_2$, Xe



Guests: benzene, cyclohexane, p-xylene

Encapsulation of multiple guests: a nanoreactor?





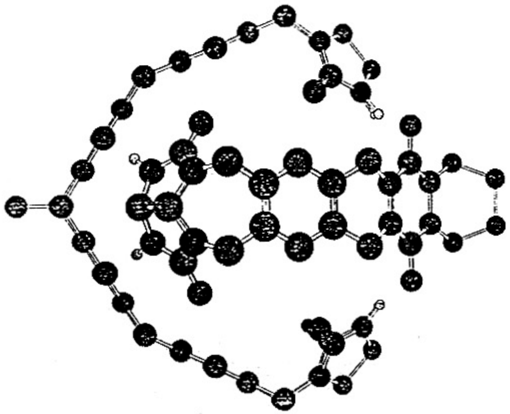
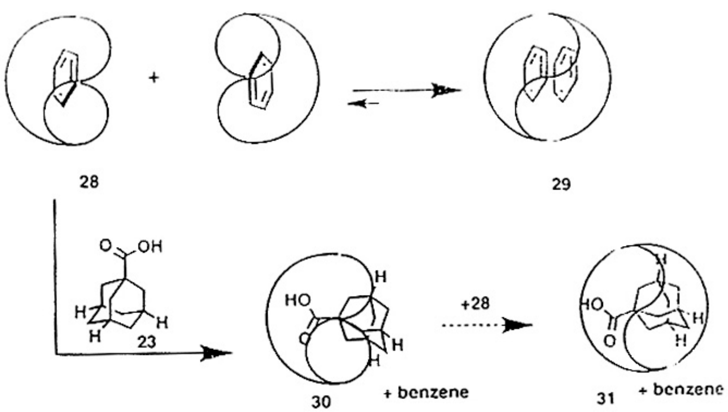


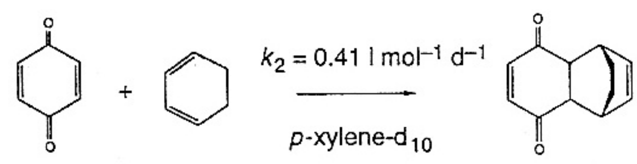
Table 2. Molecular Volumes and Occupancy Factors for Some Guests in the Softball **1b**

guest	molecular vol (Å^3)	occupancy factor
23a	155	0.52
24	185	0.62
23b	137	0.46
26	181	0.60
27	188	0.63
23c	157	0.52
benzene	77	0.26
p-xylene	105	0.35

Encapsulation of **23a**, etc. is entropically driven:



Modest rate acceleration for Diels-Alder reaction:



k_{cat} (with softball dimer) = 1.0 l mol^{-1} d^{-1}

Rebek, *Acc. Chem. Res.* **1999**, 32, 278.

Self-assembly in three dimensions: peptide nanotubes

D/L cyclic peptides:
Granja and Ghadiri, *JACS* **1994**, *116*, 10785

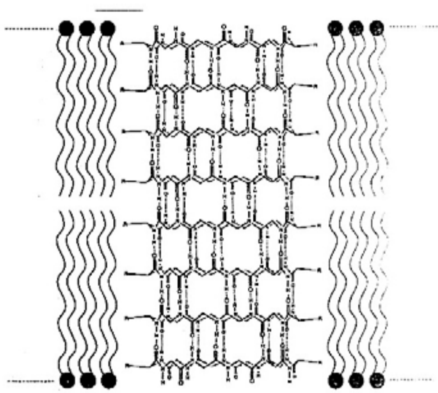
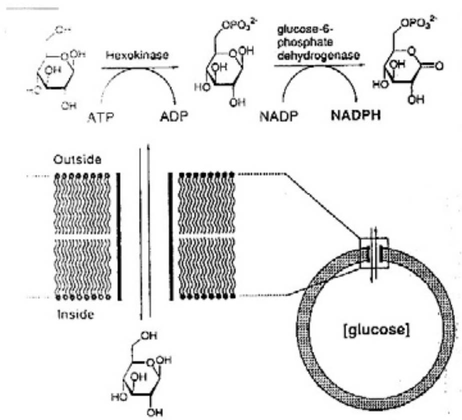
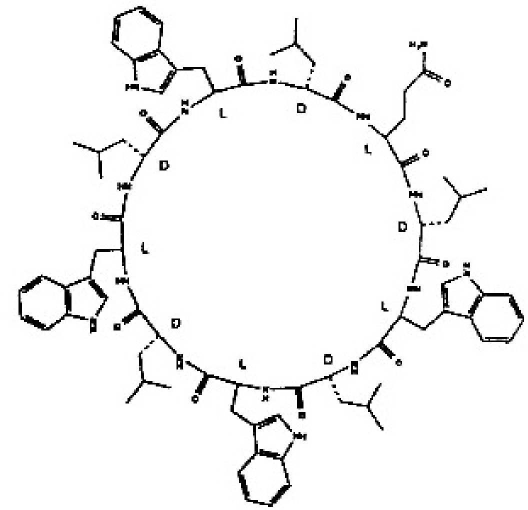


Figure 1. Schematic representation of the self-assembled tubular transmembrane channel structure embedded in a lipid bilayer membrane emphasizing the antiparallel ring stacking, the presence of extensive intersubunit hydrogen-bonding interactions, and side chain–lipid interactions (for clarity, most side chains are omitted). The chemical structure of the peptide subunit is shown on the top (D- or L- refers to the amino acid chirality).





Enantioselective self-recognition:
Ghadiri et al, *Angew. Chem*. **1995**, *34*, 93; 85