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

Hydrogen bonding

...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*

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

- CH$_3$CO$_2^-$⋯H–OH $\quad -$19
- HO⋯H–N\(\text{H}^+\)–NH\(\text{N}\) $\quad -$14
- HO⋯H–OH $\quad -$6.4
- HO⋯H–SCH$_3$ $\quad -$3.2
- CH$_3$S⋯H–OH $\quad -$3.1

**HB length:**

- \(\text{N}^+\text{H}⋯\text{N/O}\) $\quad$ 1.7–1.9 Å
- \(\text{N}–\text{H}⋯\text{O}\) (carboxylate, \(\text{N}\)-oxide, etc.) $\quad$ 1.93 Å
- \(\text{N}–\text{H}⋯\text{N}\) $\quad$ 1.97–2.0 Å
- \(\text{N}–\text{H}⋯\text{O=C (carbonyl)}\) $\quad$ > 2.0 Å
- \(\text{O}–\text{H}⋯\text{N/O}\) (alcohol) $\quad$
- \(\text{C}–\text{H}⋯\text{O}\) $\quad$
- \(\text{S}–\text{H}⋯\text{O}\) $\quad$

“supporting” HB’s:
Secondary interactions in hydrogen bonding

$$K_a(\text{CDCl}_3, 298 \text{ K}) = 10^4 - 10^5$$

$$K_a(\text{CDCl}_3, 298 \text{ K}) = 1.7 \times 10^4$$

$$K_a(\text{CDCl}_3, 298 \text{ K}) = 170$$

$$K_a(\text{CDCl}_3, 298 \text{ K}) = 90$$

Secondary interactions in hydrogen bonding

ADA-DAD: $K_a(\text{CDCl}_3) = 78$

AAA-DDD: $K_a(\text{CDCl}_3) > 10^5$

AAA-DD$^+D$: $K_a(\text{CDCl}_3) > 5 \times 10^5$

(pK$_a$ = 12.6)

(pK$_a$ = 12.2)


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

Cyclic hydrogen bonding:
DNA base pairs

Antiparallel β-sheet

Parallel β-sheet

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:

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 thermodynamic 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 $N=3$:

$K_3$ (CDCl$_3$) = $8.3 \times 10^5$ M$^{-2}$

$K$ (CDCl$_3$) = $46$ M$^{-1}$

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

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

The G-Quartet

![Image of G-Quartet structure]

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

Isoguanosine tetramer:
Tirumala and Davis, *JACS*, 1997, 119, 2769

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

\[ K_s = 10^9 - 10^{10} \text{ m}^{-3} \text{ in acetone} \]
Examples of self-assembled supermolecules 
($N = 6$)

Encoded self-assembly: Rosette-like structures
Mascal et al, Angew. Chem. 1996, 35, 2204

Characterized by:
VPO (mw 2600 10%; 2511 actual)
GPC (mw > 2200)
X-ray crystallography

Non-coded self-assembly:

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

Packing effect:
secondary van der Waals interactions
Supramolecular rosettes \((N = 6)\)


Melamine units  Barbituric acid unit

\[
\begin{align*}
R &= C_{12}H_{25}, R_1 = C_6H_9 \\
1 & \quad 2
\end{align*}
\]
Self-assembly and statistical entropy


Figure of merit for supramolecular stability: \[
\frac{\text{HB}}{N-1}
\]
Self-assembly in three dimensions

Supramolecular encapsulation of guest molecules

1. Cram’s carcerands: 

![Cram’s carcerands](image1)

2. Rebek’s self-assembling “softballs:”

![Rebek’s self-assembling “softballs”](image2)

Guests: CH₄, H₂C=CH₂, Xe

α-pyrone

HV (254 nm)

- CO₂

encapsulated pyrone

encapsulated CBD -- stable!

Guests: benzene, cyclohexane, p-xylene
Encapsulation of 23a, etc. is entropically driven:

Modest rate acceleration for Diels-Alder reaction:

\[ k_{\text{cat}} \text{ (with softball dimer)} = 1.0 \text{ } \text{mol}^{-1} \text{ d}^{-1} \]

Self-assembly in three dimensions: peptide nanotubes

D/L cyclic peptides:

Enantioselective self-recognition: