Supramolecular Chemistry

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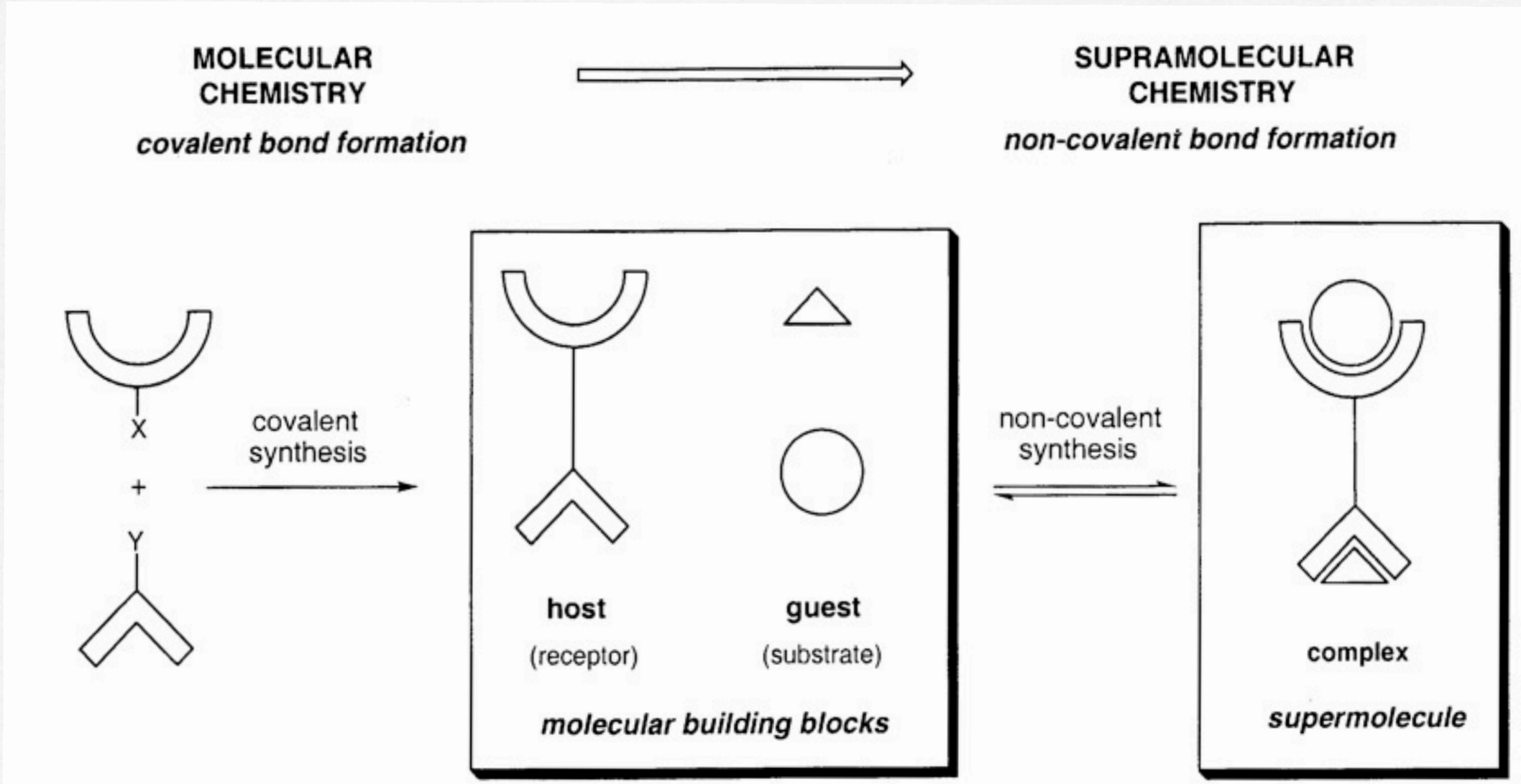


Fig. 1.1 Supramolecular chemistry.

Definitions

"Supramolecular chemistry is the chemistry of the intermolecular bond, covering the structures and functions of the entities formed by the association of two or more chemical species"

J.-M- Lehn

"Supramolecular chemistry is defined as chemistry "beyond the molecule", as chemistry of tailor-shaped inter-molecular interaction. In 'supramolecules' information is stored in the form of structural peculiarities. Moreover, not only the combined action of molecules is called supramolecular, but also the combined action of characteristic parts of one and the same molecule.

F. Vögtle

examples of nature

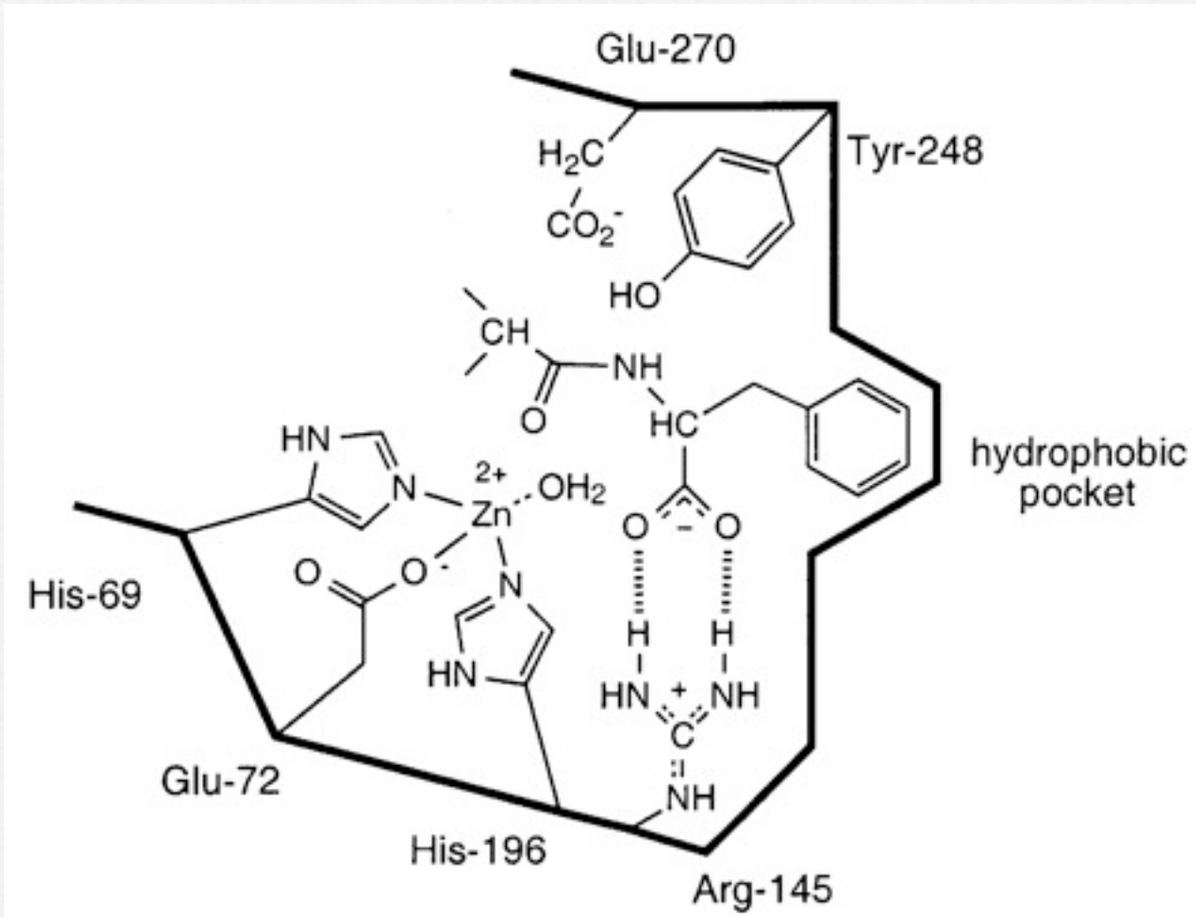
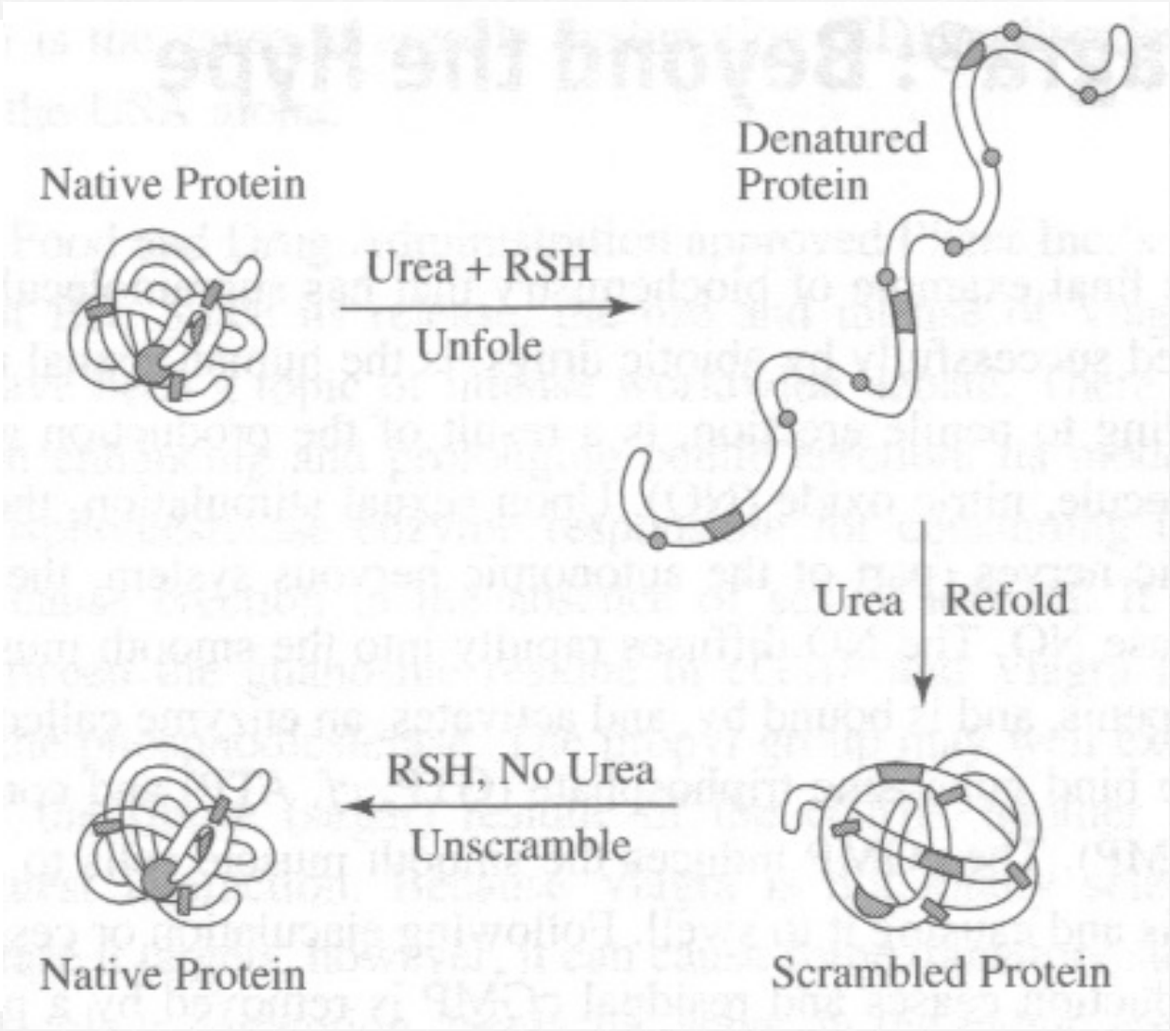
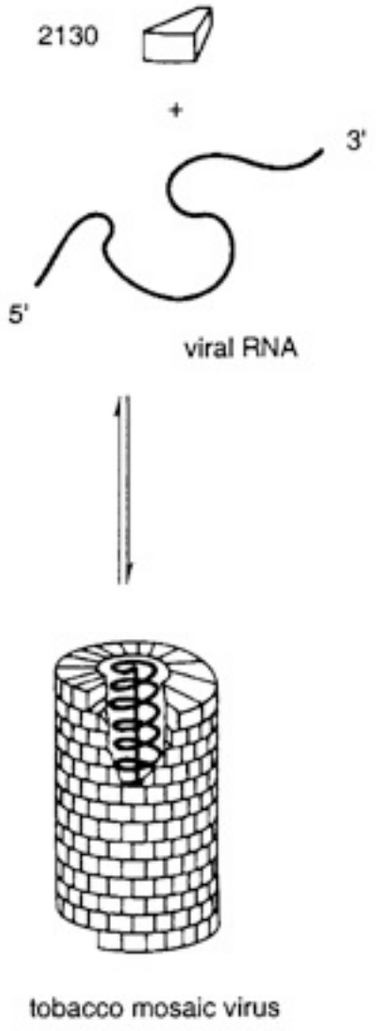


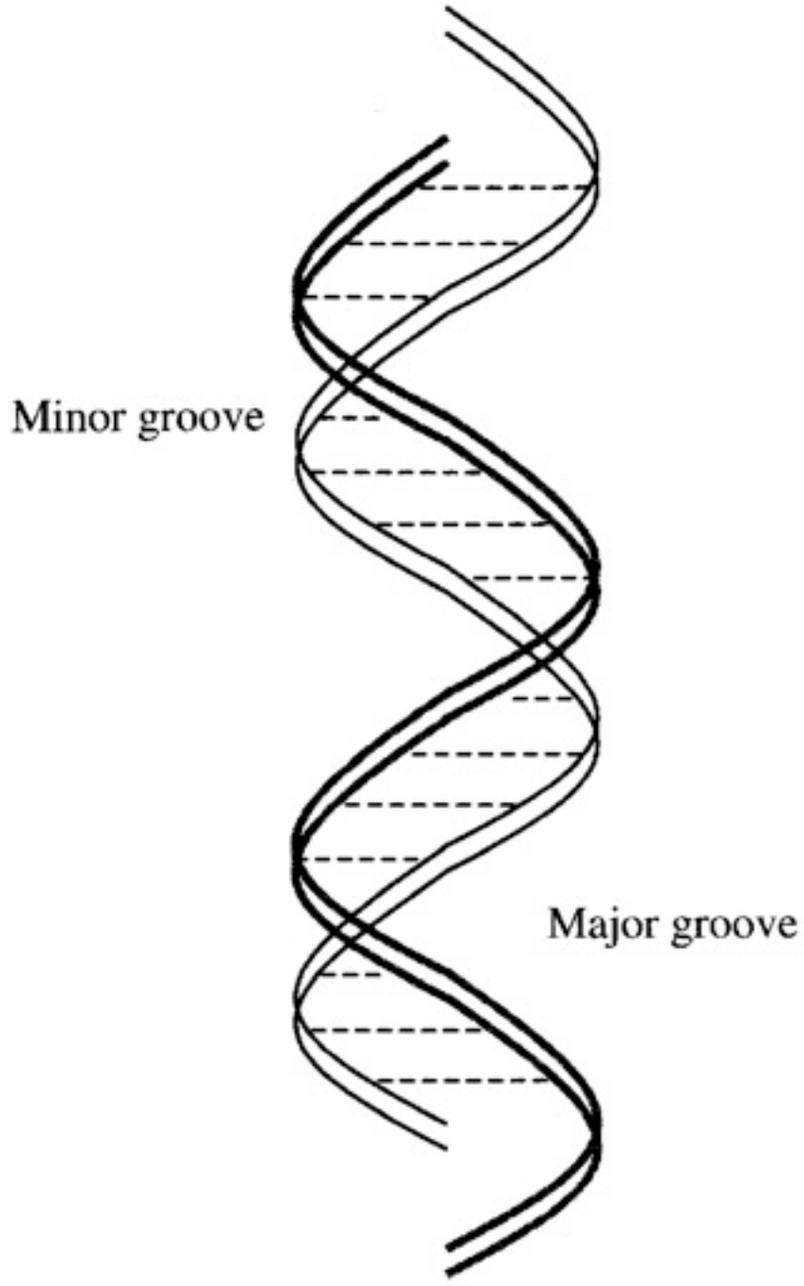
Fig. 1.3 The active site of carboxypeptidase-A with a bound peptide chain.



examples of nature



Scheme 6.1 Self-assembly of the tobacco mosaic virus (reprinted with permission from J.S. Lindsey, New . Chem. 1991, 15, 153. Copyright (1991) CNRS-Gauthier-Villars).



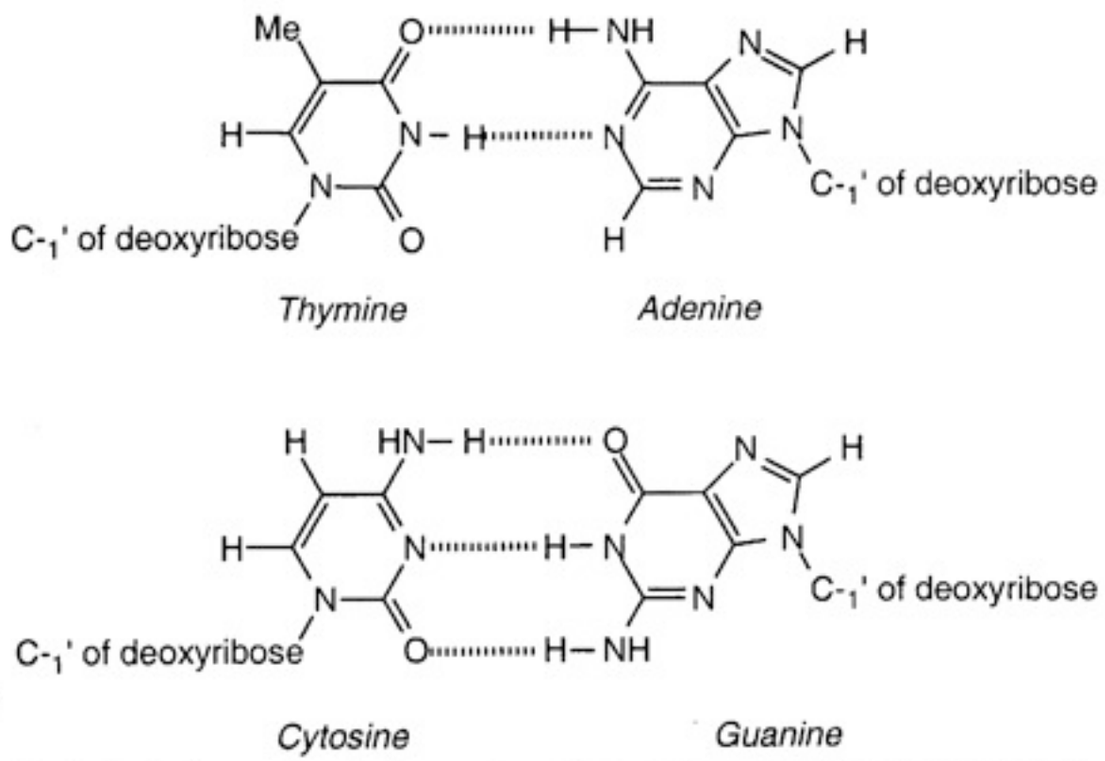
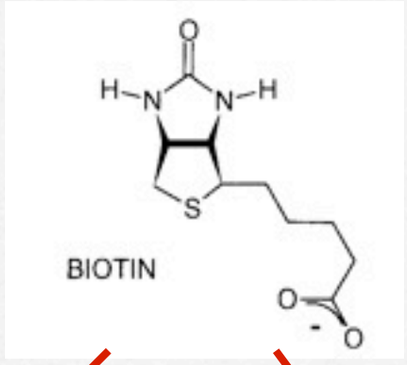


Fig. 1.4 Hydrogen bonded complementary A-T and G-C base pairs in DNA.

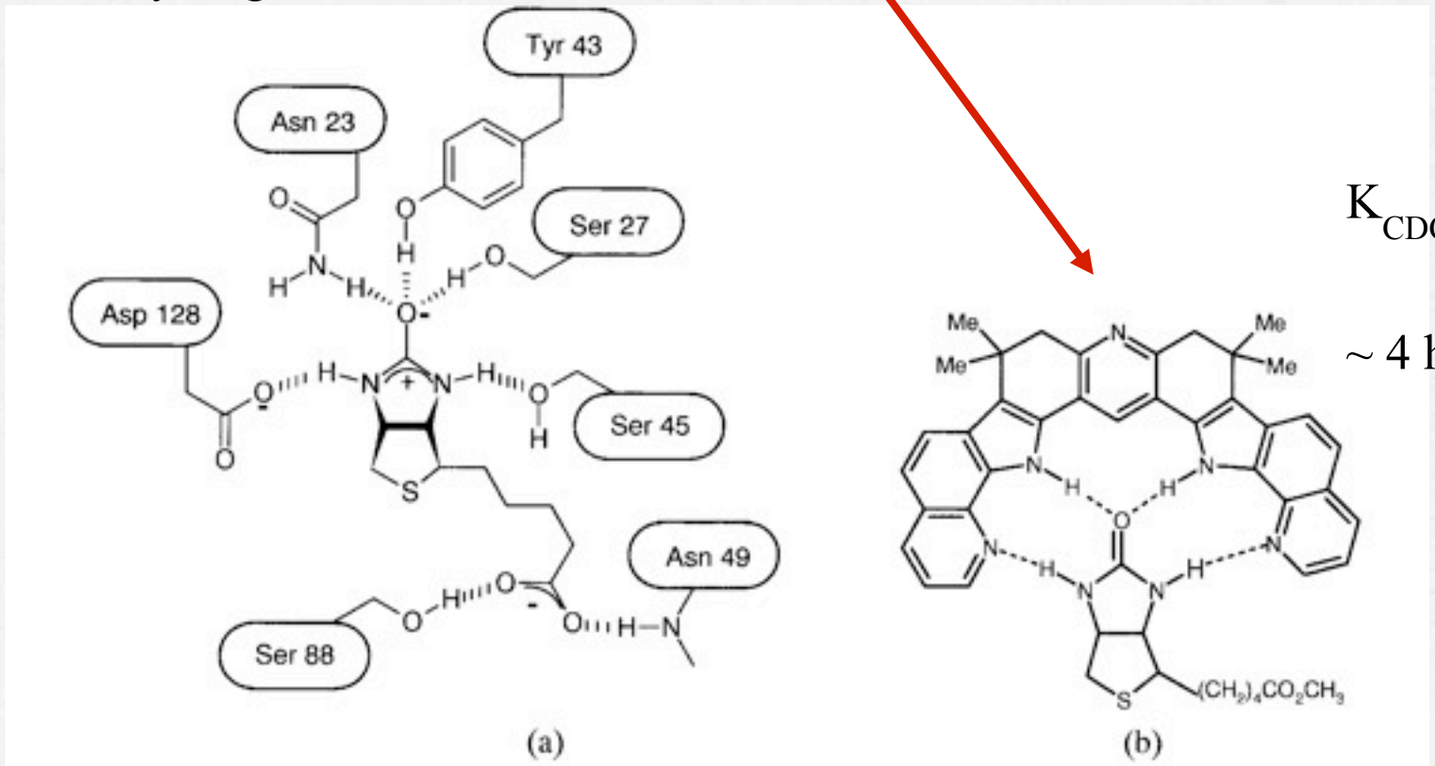
nature vs. synthetic



$K_{water} = 2.5 \times 10^{13}\ M^{-1}$

~ 10 hydrogenbonds

Focus: Supramolecular properties of molecules designed by the chemist – *not by nature*



$K_{CDCl_3} = 9.3 \times 10^{3}\ M^{-1}$

~ 4 hydrogenbonds

Figure A 1. (a) Schematic illustration of biotin binding to streptavidin;[1a] Reprinted with permission from *J. Am. Chem. Soc.*, Hegde *et al.* 1993, **115**, 872. Copyright 1992 American Chemical Society (b) Binding of biotin methyl ester to a synthetic host.[3]

lock-and-key principle

Synonymous terminology used:

host	guest
ligand	metal
enzyme	substrate
receptor	substrate
receptor	drug
antibody	antigen

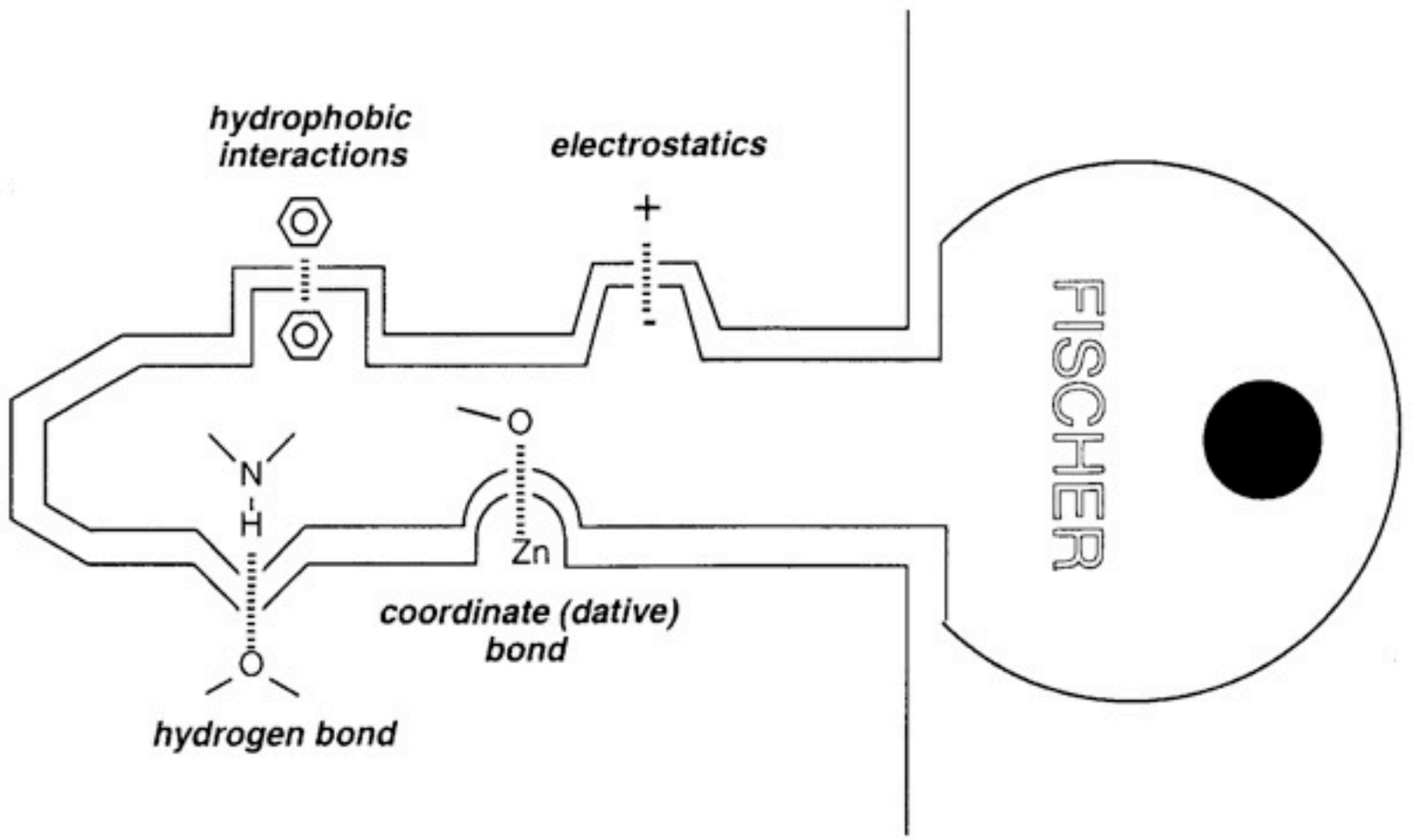


Fig. 1.2 The lock and key principle: receptor sites in the host (lock) are complementary to the guest (key) (see Section 1. 2 for a discussion of these forces in more detail).

lock-and-key principle

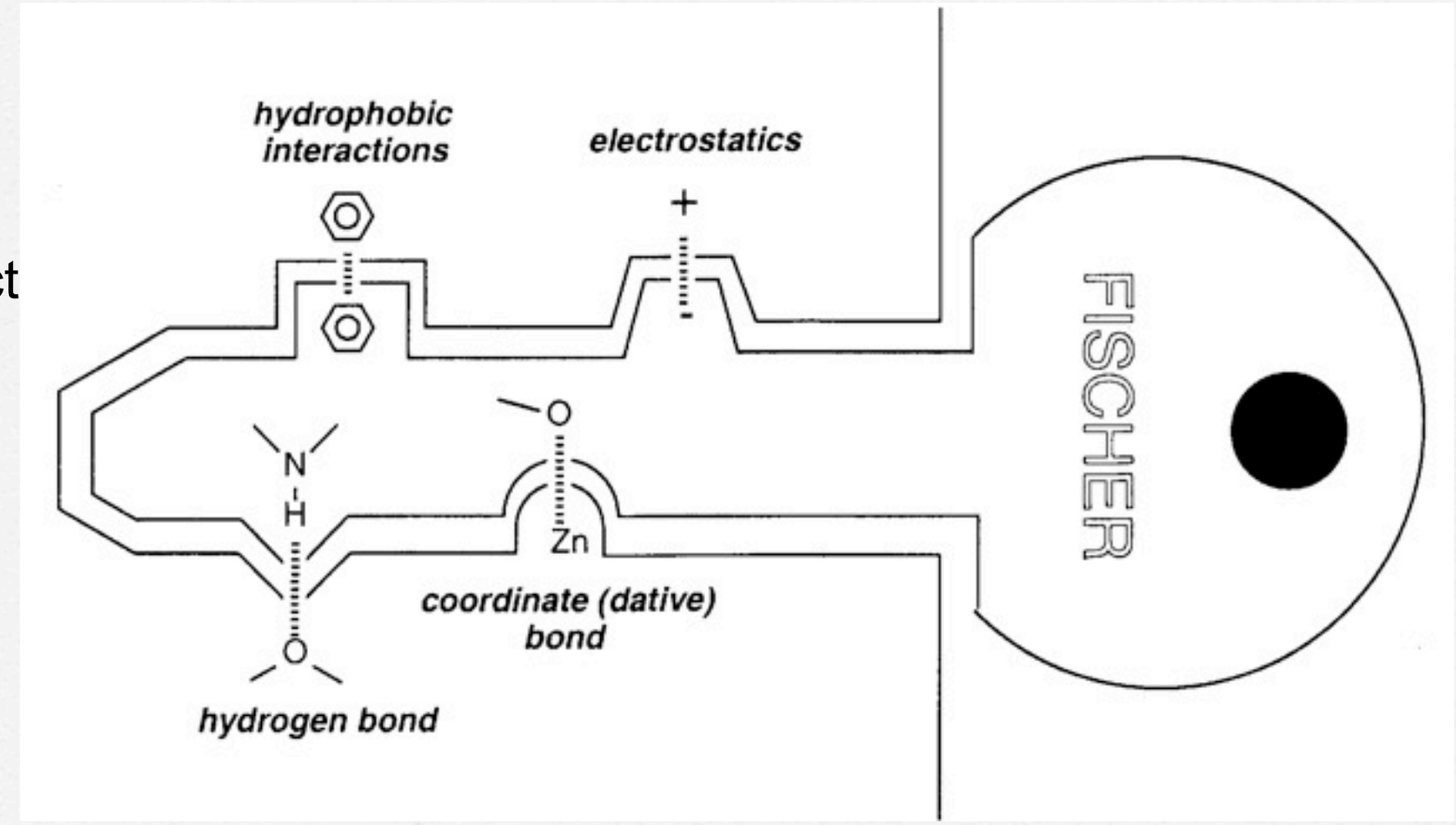
Additivity

Complementarity

- Preorganisation
- Chelate effect
- Macrocyclic effect
- Selectivity

Thermodynamics

Solvent effects



Additivity

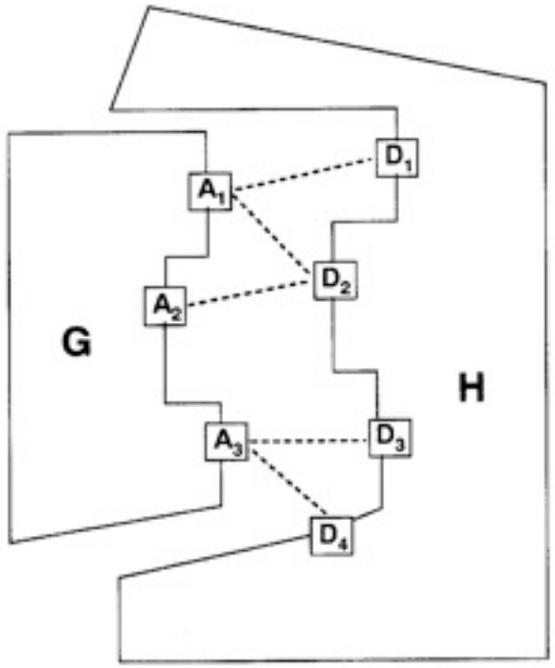


Figure A 2. Schematic illustration of pairwise multi-site host–guest interactions.

$$K_t = K_{11}K_{12}K_{22}\ldots$$

$$\beta_n = K_{11}K_{12}K_{22}\ldots \quad !$$

$$\begin{aligned}
&\text{R–A}_1 + \text{R}'\text{–D}_1 \rightleftharpoons \text{R–A}_1\cdots\text{D}_1\text{–R}' && (K_{11})\\
&\text{R–A}_1 + \text{R}'\text{–D}_2 \rightleftharpoons \text{R–A}_1\cdots\text{D}_2\text{–R}' && (K_{12})\\
&\text{R–A}_2 + \text{R}'\text{–D}_2 \rightleftharpoons \text{R–A}_2\cdots\text{D}_2\text{–R}' && (K_{22})\\
&\text{etc.} && (\text{A 1-1})
\end{aligned}$$

Additivity

Additivity – stepwise vs. overall binding constant

Stepwise Binding Constants:

H (Host)	+ G (Guest)	$\rightleftharpoons$	HG	$K_1 = \frac{[HG]}{[H][G]}$			
HG	+ G	$\rightleftharpoons$	HG_2	$K_2 = \frac{[HG_2]}{[HG][G]}$			
HG_2	+ G	$\rightleftharpoons$	HG_3	$K_3 = \frac{[HG_3]}{[HG_2][G]}$			
HG_{n-1}	+ G	$\rightleftharpoons$	HG_n	$K_n = \frac{[HG_n]}{[HG_{n-1}][G]}$			

Overall Binding Constants:

H	+ G	$\rightleftharpoons$	HG	$\beta_1 = \frac{[HG]}{[H][G]}$			
H	+ 2G	$\rightleftharpoons$	HG_2	$\beta_2 = \frac{[HG_2]}{[H][G]^2}$			
H	+ 3G	$\rightleftharpoons$	HG_3	$\beta_3 = \frac{[HG_3]}{[H][G]^3}$			
H	+ nG	$\rightleftharpoons$	HG_n	$\beta_n = \frac{[HG_n]}{[H][G]^n}$			

Therefore:

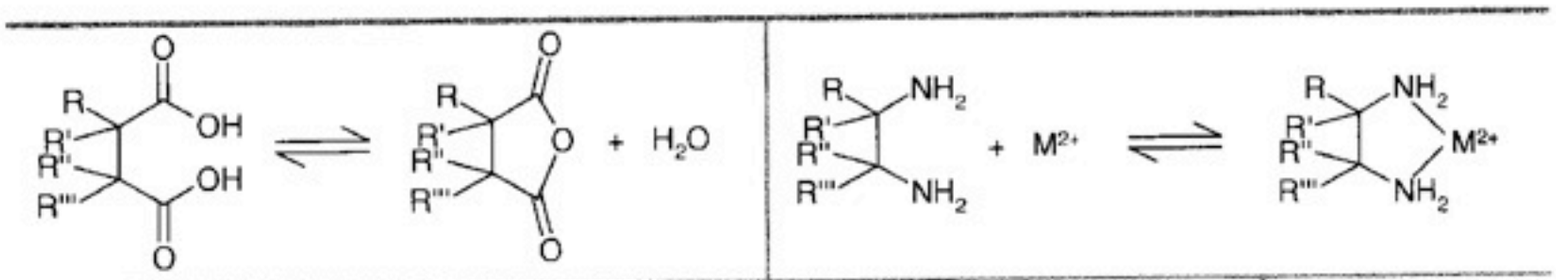
$$\beta_n = \prod_{1}^{n} K_n \qquad [\text{e.g. } \beta_3 = K_1 \times K_2 \times K_3]$$

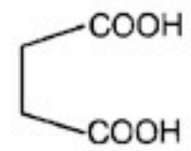
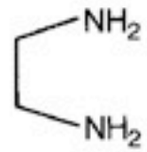
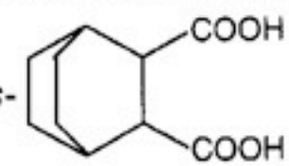
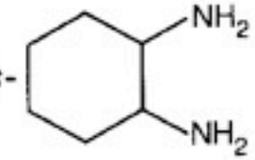
Fig. 1.11 Definition of stepwise (K) and overall (β) binding constants.

$$\Delta G^\circ = -RT \ln \beta$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

Entropy of association



	log K		M^{2+}	logK
	-5.15		Ni^{2+} Cu^{2+} Zn^{2+}	7.35 10.54 5.7
cis- 	-0.52	cis- 	Ni^{2+} Cu^{2+} Zn^{2+}	7.41 10.87 6.08

Scheme A1. Equilibrium constants of cyclic anhydride formation and diamine coordination reactions, from published data.[25,26]

Ridigification enhances host-guest interactions

Low-frequency vibrations (high entropy) in weak interactions can compensate the loss of entropy of internal rotations.

Solvent effects – hydrophobic effect

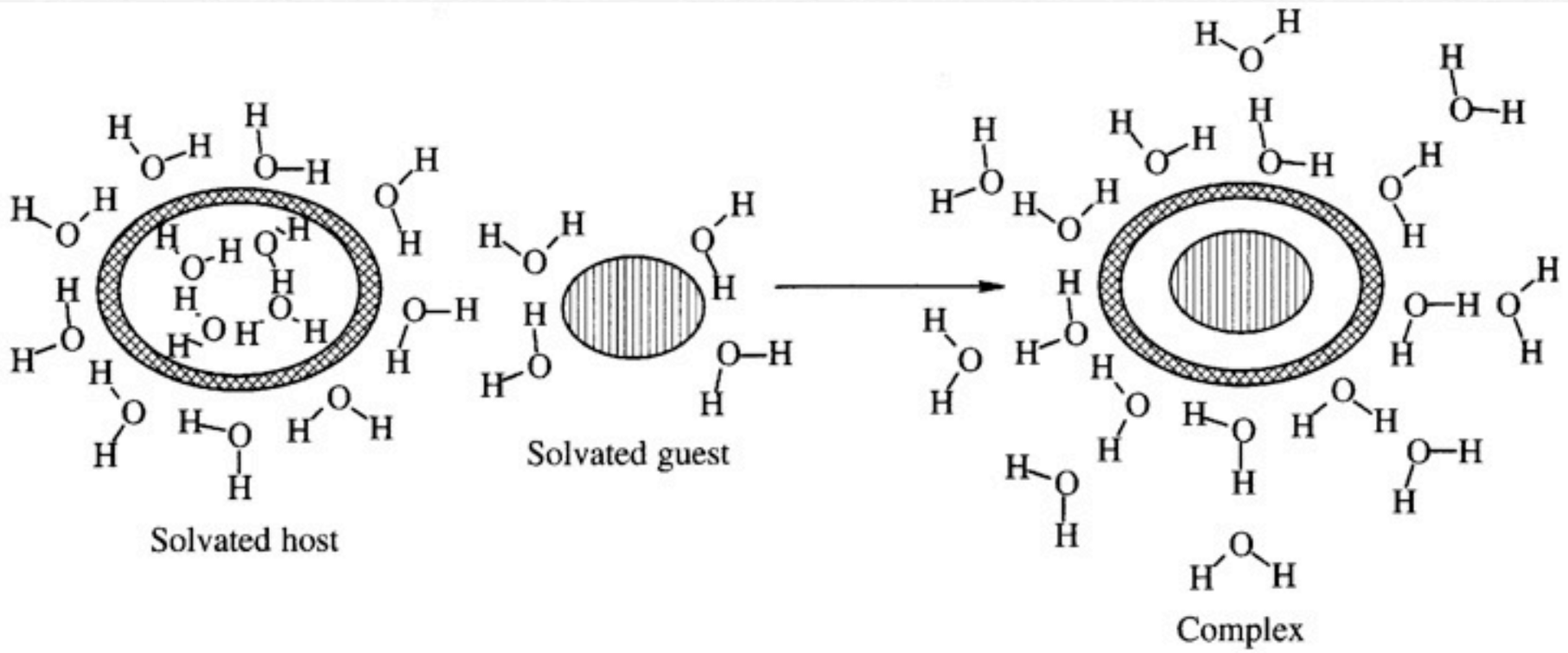


Figure 1.20 Hydrophobic binding of organic guests in aqueous solution.

Release of arranged solvent molecules – favorable ΔS

Optimized hydrogen bonding of previously arranged solvent - favorable ΔH

Solvent effects – competitive solvents

Highly polar solvents, characterized by a large dielectric constant, can interact with charged species.

Solvents which are good hydrogen bond donors/acceptor will compete in hydrogen bonding recognition.

Table 1.2 Gutmann Donor and Acceptor Numbers and dielectric constants for selected solvents (a: donor number for water when measured in bulk solvent).

	Donor number (H-bond acceptor)	Acceptor number (H-bond donor)	Dielectric constant (ε)
H_2O	18.0 (33.0)[a]	54.8	80.1
CH_3SOCH_3	29.8	19.3	46.7
CH_3CN	14.1	18.9	36.6
CH_3OH	19.0	41.5	33.0
CH_3COCH_3	17.0	12.5	21.0
C_4H_8O (THF)	20.0	8.0	7.5
C_6H_{14} (Hexane)	no donor atoms	0.0	1.9

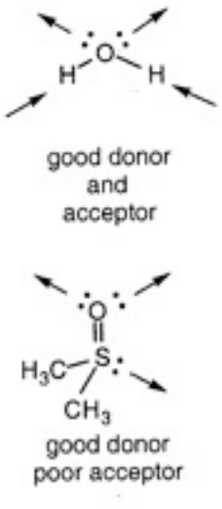


Fig. 1.18 Donor and acceptor properties of solvents.

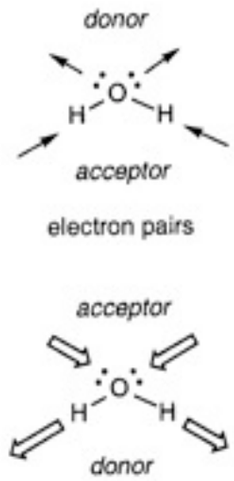


Fig. 1.19 An electron pair donor is hydrogen bond acceptor, and an electron pair acceptor can be a hydrogen bond donor.

Chelate effect

$$[Ni(H_2O)_6]^{2+}_{(aq)} + 6NH_{3(aq)} \rightleftharpoons [Ni(NH_3)_6]^{2+}_{(aq)} + 6H_2O_{(aq)} \quad \log \beta = 8.61$$

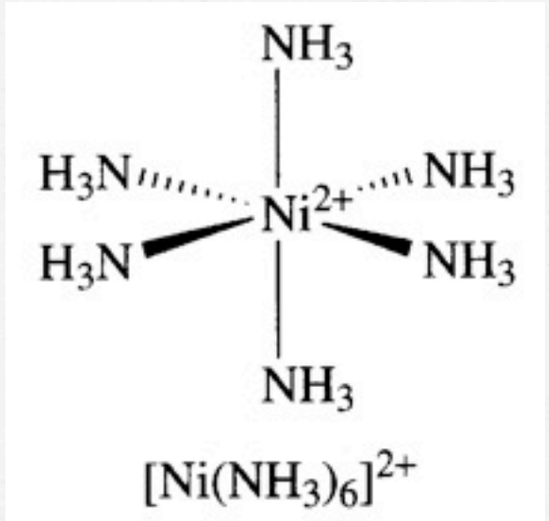
$$[Ni(H_2O)_6]^{2+}_{(aq)} + 3en_{(aq)} \rightleftharpoons [Ni\ en_3]^{2+}_{(aq)} + 6H_2O_{(aq)} \quad \log \beta = 18.28$$

(en = H_2N–NH_2)

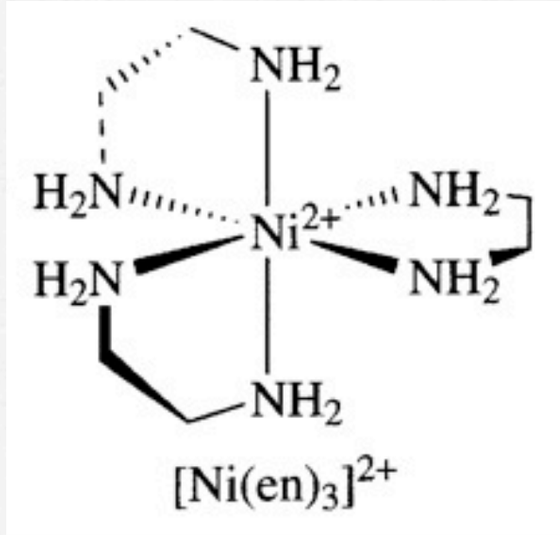
Fig. 1.10 Chelating ligands bind metal ions more strongly.

$$\Delta G^\circ = -RT \ln \beta$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$



$[Ni(NH_3)_6]^{2+}$



$[Ni(en)_3]^{2+}$

Entropy effect: increasing number of independent molecules →

Enthalpy effect: mutual repulsion reduced – disadvantage reduced

Chelate effect - ring size

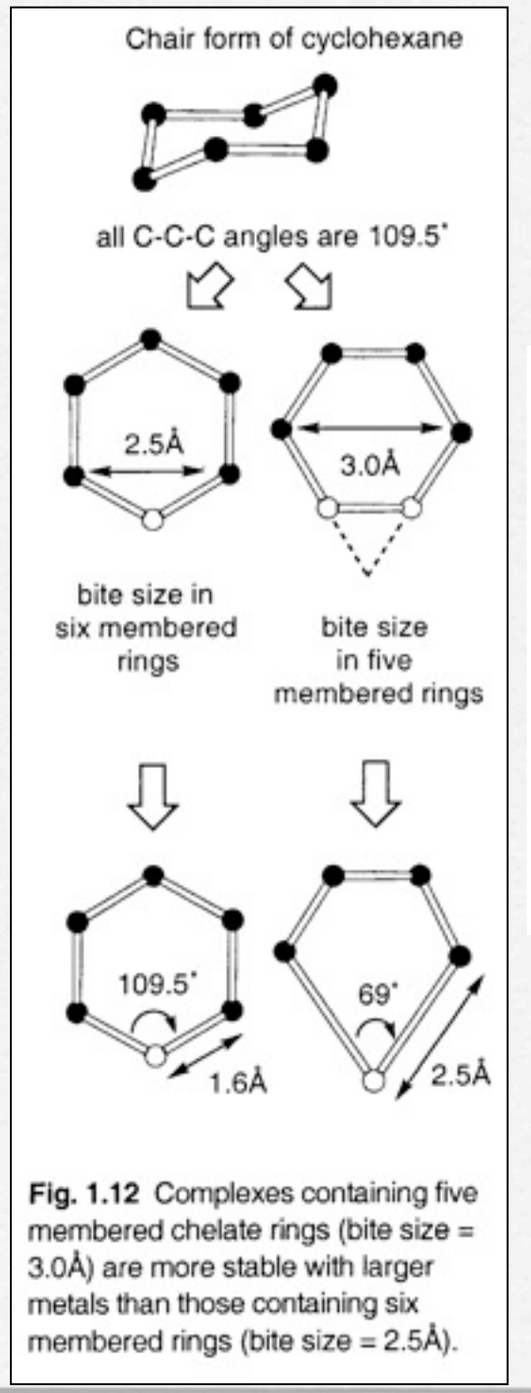
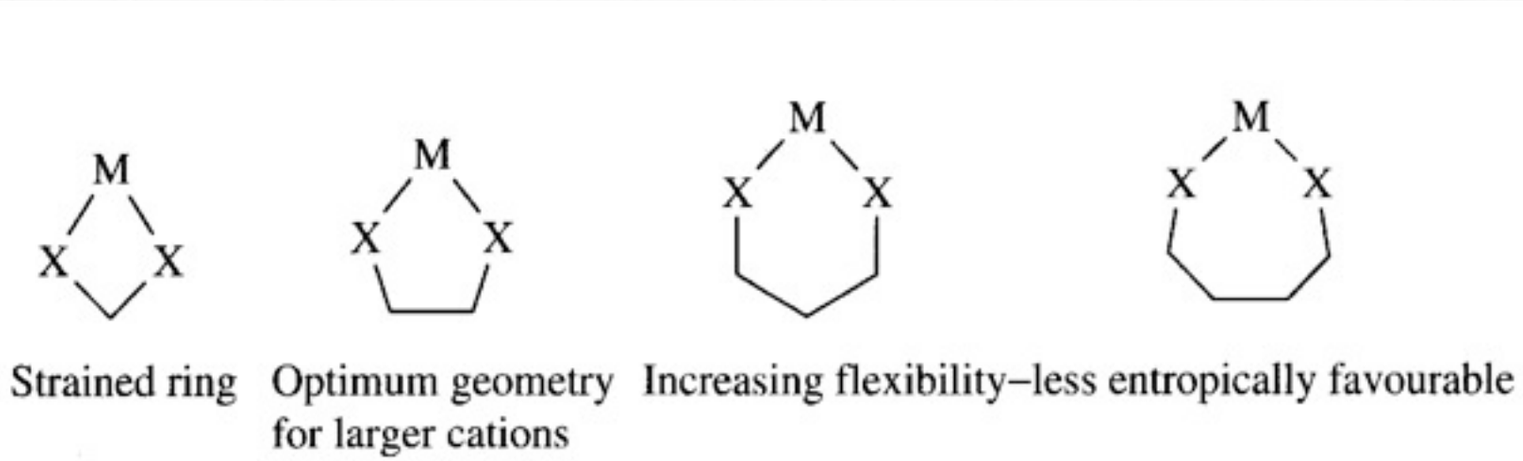


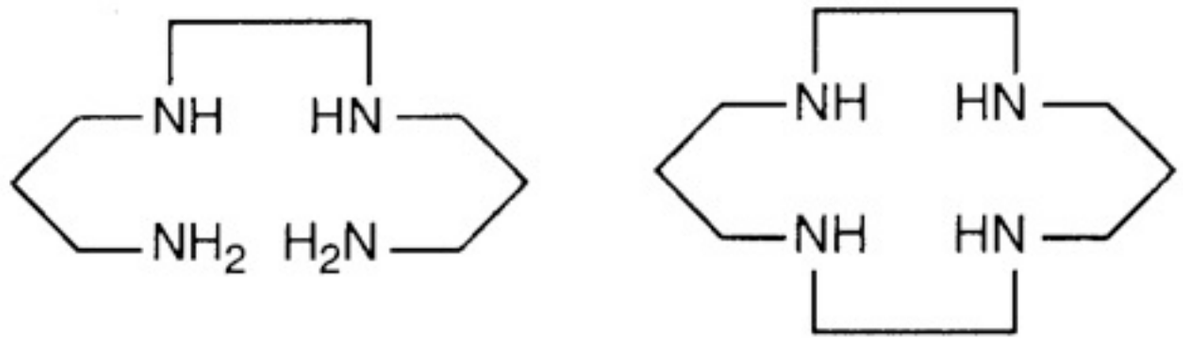
Fig. 1.12 Complexes containing five membered chelate rings (bite size = 3.0Å) are more stable with larger metals than those containing six membered rings (bite size = 2.5Å).



Stabilisation offered by the chelate effect.

macrocyclic effect

Macrocycle: Cyclic molecule containing more than 10 covalent bonds.



1.1 1.2

Fig. 1.13 Acyclic and macrocyclic aza-ligands.

Table 1.1 Thermodynamic parameters for the formation of zinc complexes with macrocyclic and acyclic aza ligands at 25°C.

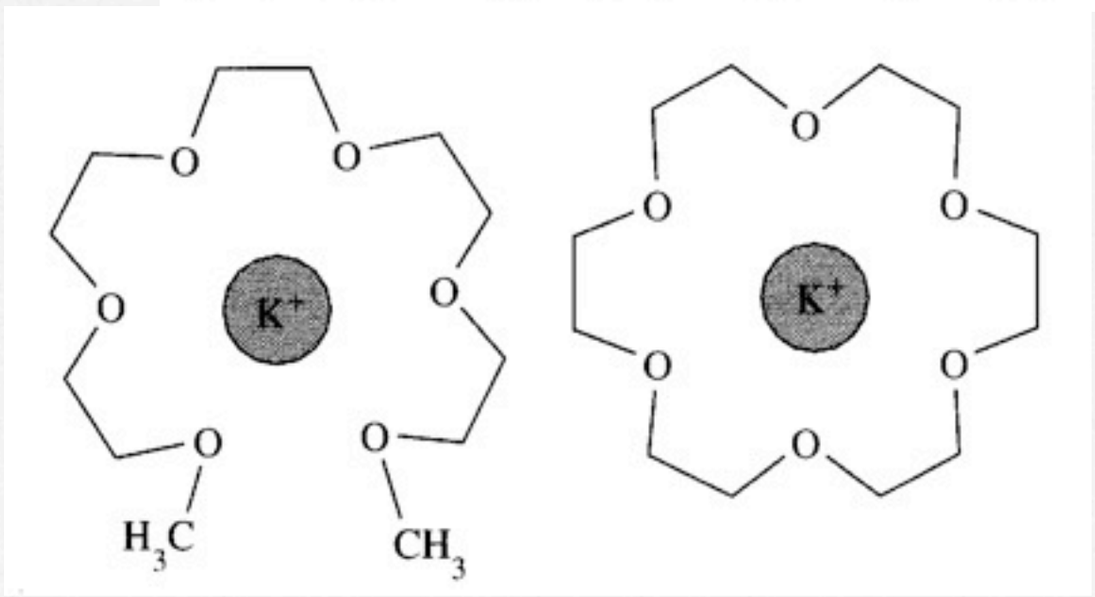
	1.1	1.2
log K	11.25	15.34
$-\Delta H^{\circ}$ ($kJmol^{-1}$)	44.4	61.9
ΔS° ($JK^{-1}mol^{-1}$)	66.5	85.8

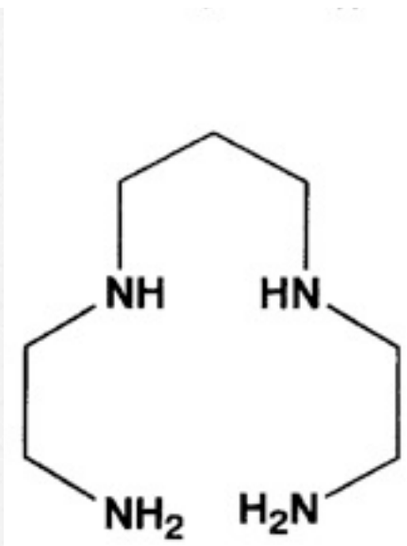
Increased stability (ΔG)
Favorable enthalpy increase
Favorable entropy increase

macrocyclic effect

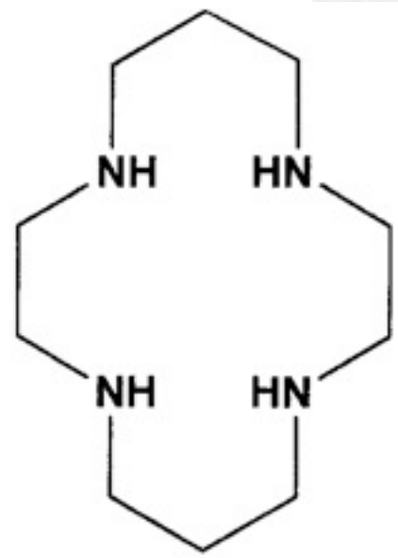
Table A 4. Differences in thermodynamic parameters (kJ mol^{-1}) of complexation with cyclic and acyclic ligands, compiled from published data.[7,35,37d]

Acyclic ligand	*Cyclic ligand*	*Solvent*	*Metal ion*	$\Delta\Delta G$	$\Delta\Delta H$	$T\Delta\Delta S$
Pentaglyme	18-crown-6	MeOH	Na^+	−16.1	−15.5	0.63
			K^+	−23.0	−2.50	20.1
			Rb^+	−19.5	−2.89	16.4
			Cs^+	−15.3	−11.0	3.89
			Ba^{2+}	−25.4	−23.3	2.01
			Pb^{2+}	−27.2	−18.6	8.37
A-10	**A-11**	H_2O	Cu^{2+}	−18.8	−19.7	−0.84
			Ni^{2+}	−15.9	−23.0	−7.11
			Zn^{2+}	−16.3	−12.1	−4.18



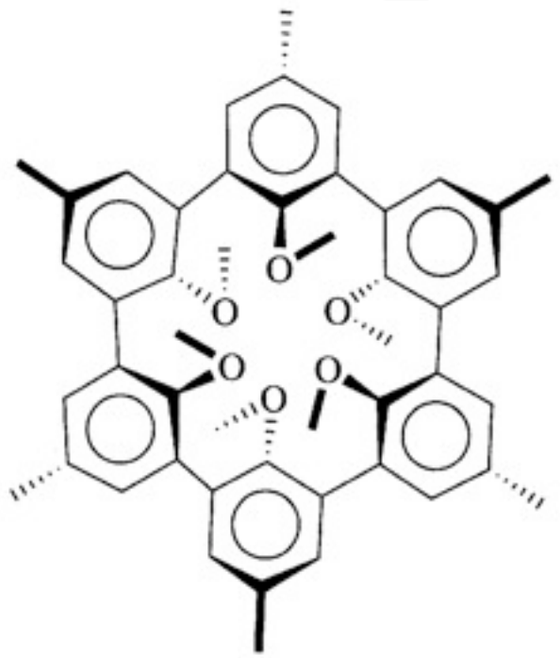


A-10



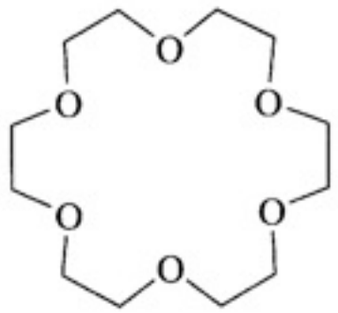
A-11

Preorganization - Spherand



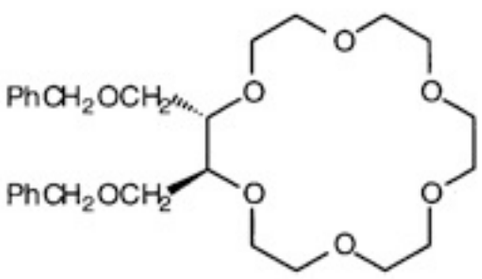
Spherand

(1.10)

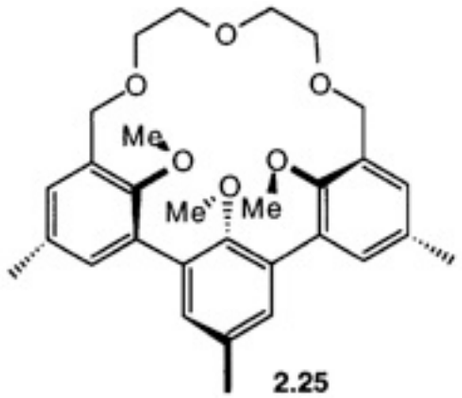


[18]crown-6
Corand

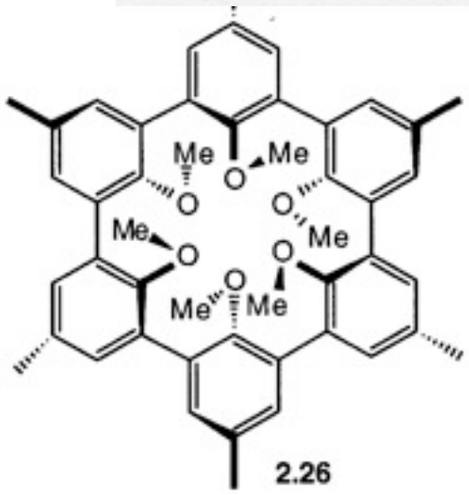
(1.11)



2.24



2.25



2.26

Fig. 2.16 Increasing preorganization from crown ether (**2.24**) to spherand (**2.26**).

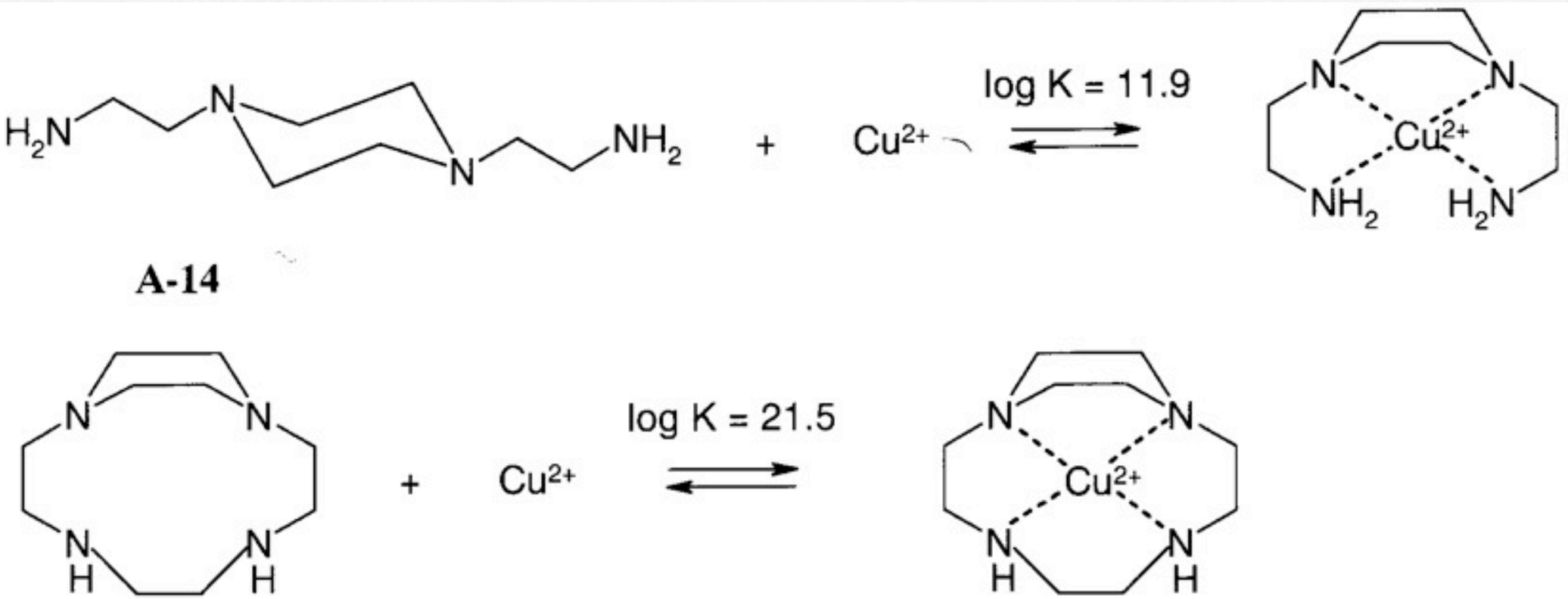
”the more highly hosts and guests are organised for binding and low solvation the more stable will be their complexes”

Donald Cram

Table 2.2 Spherand stability constants (M^{-1}) at 25°C in $CDCl_3$ saturated with D_2O

Host	Li^+	Na^+
2.24	4.1×10^4	1.4×10^6
2.25	1.9×10^5	8.7×10^8
2.26	$>7 \times 10^{16}$	1.2×10^{14}

Preorganization

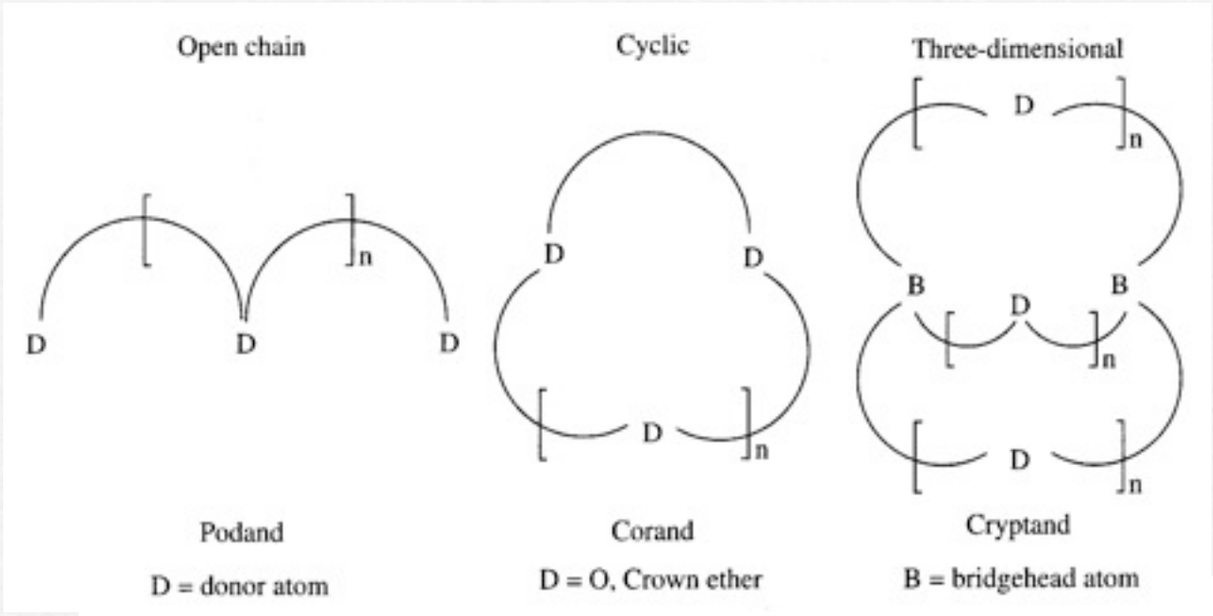


A-14

A-15

Scheme A 4. Coordination equilibria of Cu(II) with acyclic and macrocyclic polyamines derived from piperazine.[37b] **A-15**) Reprinted from *Coordination Chemistry Review*, Vol. 133, Martell *et al.* (Factors affecting stabilities of chelate, macrocyclic and macrobicyclic complexes in solution), pp. 39, copyright 1994 with permission from Elsevier Science.

macrocyclic effect - cryptate

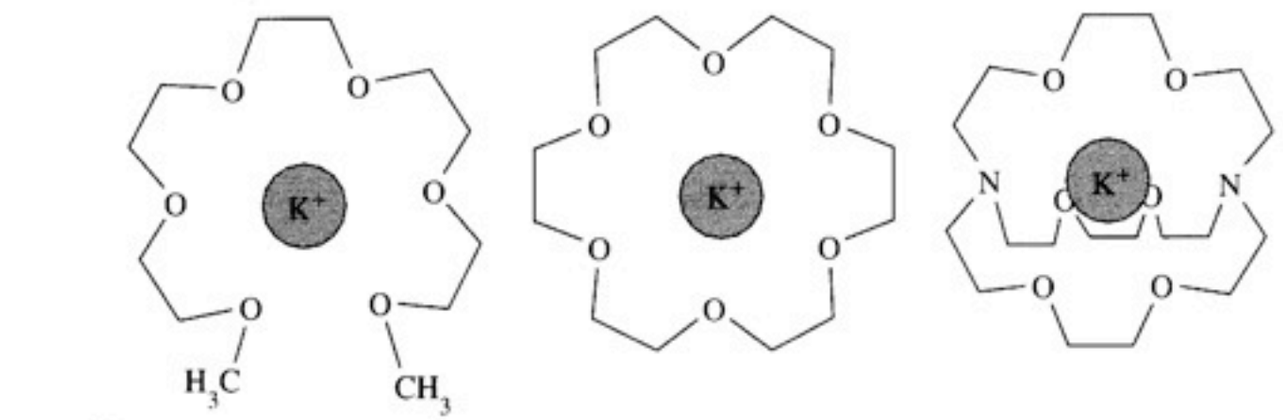


Desolvation of cavity

Reduced flexibility

More favorable contacts – less reorganization

Reduced solvation of complex



	[K⁺-**3.11**]	[K⁺-**3.6**]	[K⁺-**3.23**]
K (MeOH, 25°C)	2.0	6.1	10.0

Figure 3.28 Stabilities of podand (acyclic), crown ether (macrocyclic) and cryptand (macrobicyclic) complexes of K^+.

macrocycles - selectivty

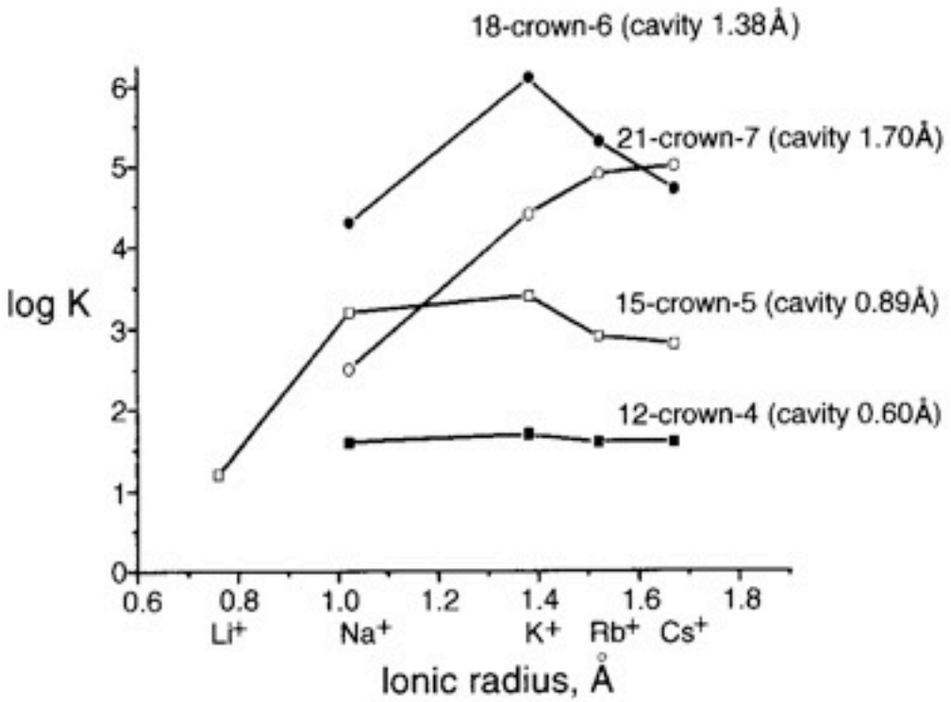


Table 3.3 Comparison of the diameters of different crown ethers with the ionic diameter of various metal cations.

Cation	Diameter (Å)[1]	Crown ether	Cavity diameter (Å)
Li^+	1.36	[12]crown-4	1.20–1.50
Na^+	1.90	[15]crown-5	1.70–2.20
K^+	2.66	[18]crown-6	2.60–3.20
Cs^+	3.38	[21]crown-7	3.40–4.30
Cu^+	1.92		
Ag^+	2.52		
Mg^{2+}	1.44		
Ca^{2+}	2.20		
La^{3+}	2.34		
Lu^{3+}	2.00		
Zr^{4+}	1.72		

[1] Assuming most common coordination number.

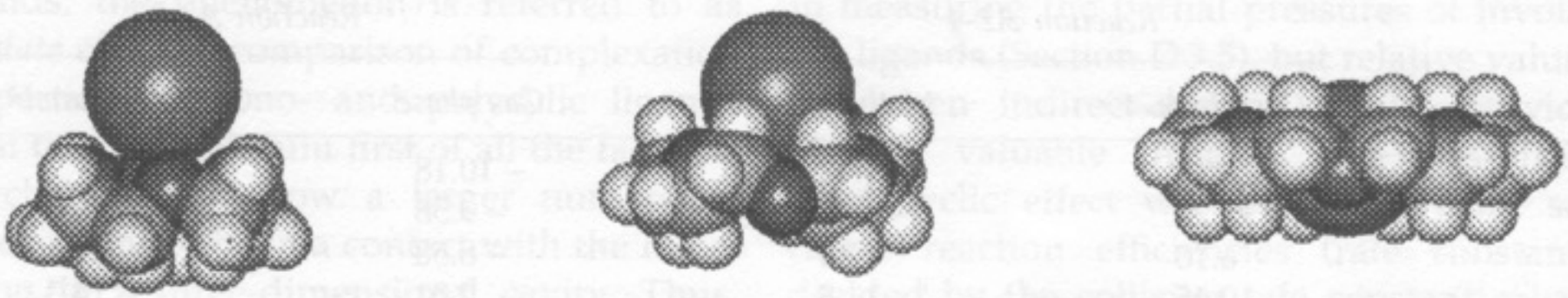


Figure A 7. Structures of K^+ complexes of 12-crown-4, 15-crown-5 and 18-crown-6.

cryptand - selectivty

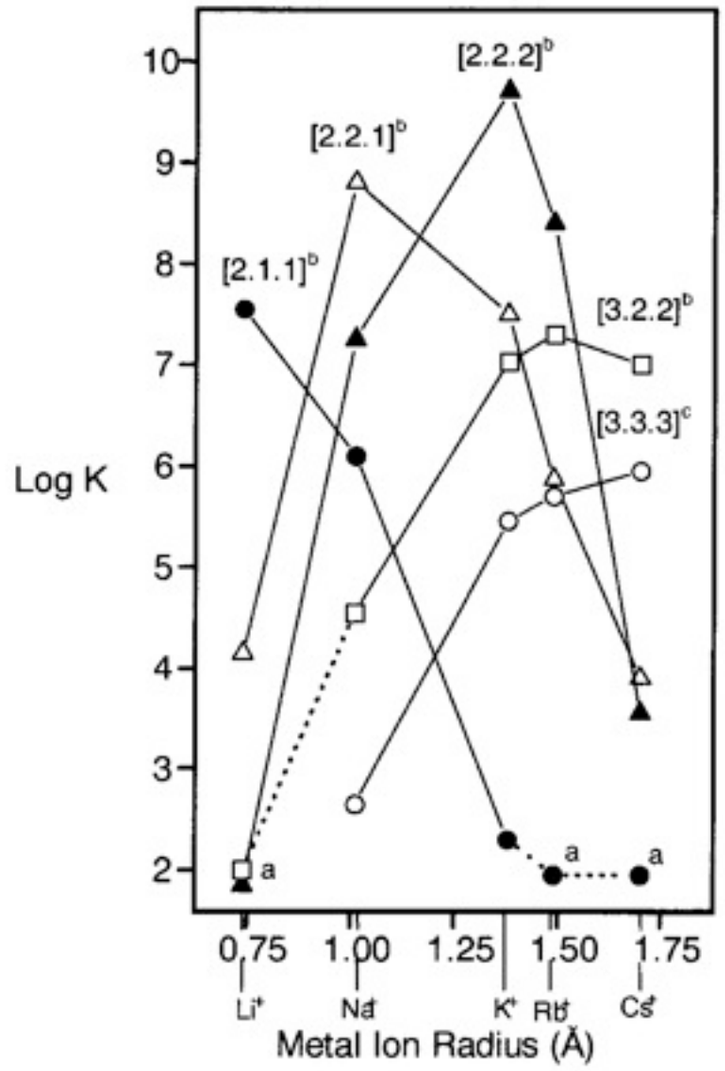
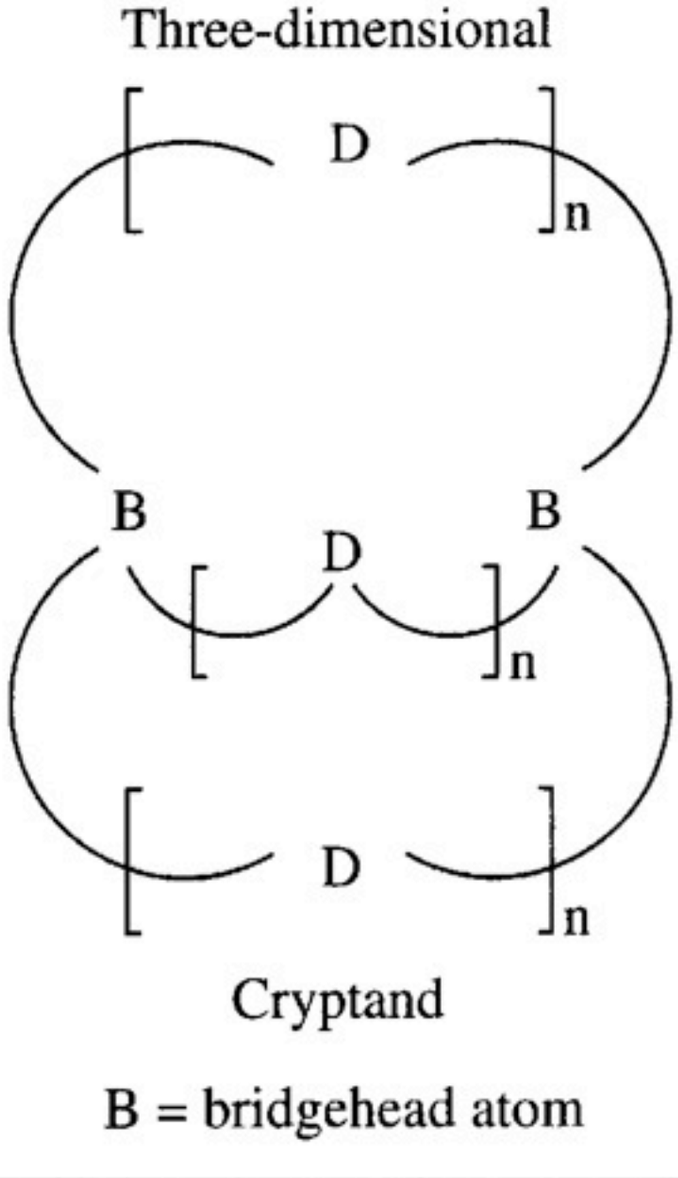
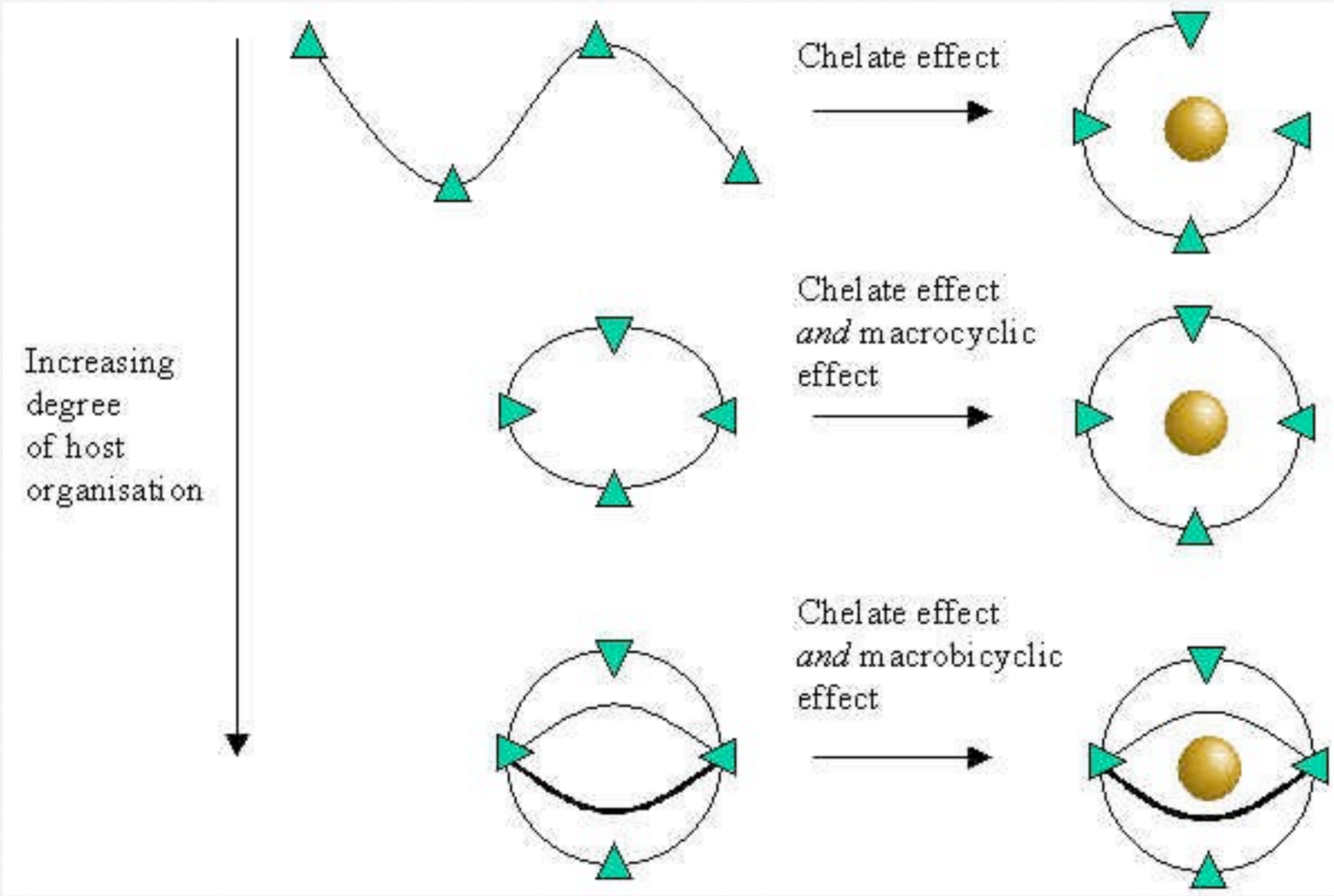


Figure A 6. Size selectivity of cryptands; affinity (lg *K*) *vs.* ion diameters; (a), values with lg $K < 2.0$, (b) in 95% MeOH, (c) in MeOH.[41] Reprinted with permission from *J. Am. Chem. Soc.*, Lehn *et al.*, 1975, **97**, 6700. Copyright 1975 American Chemical Society.



chelate -> cryptate effect



macrocycles in nature

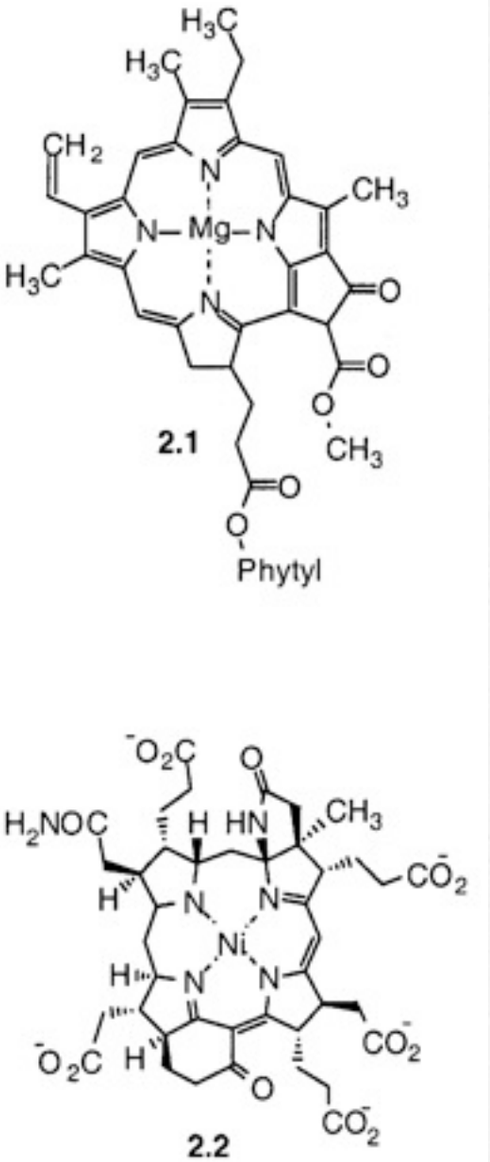
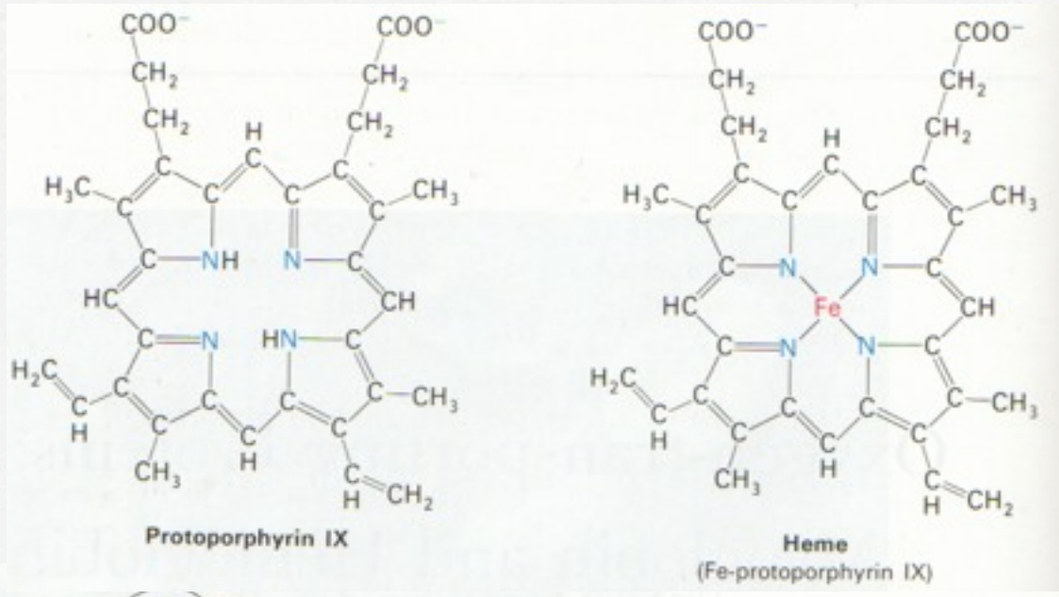


Fig. 2.1 Chlorophyll a **(2.1)** and factor F-430 **(2.2).**



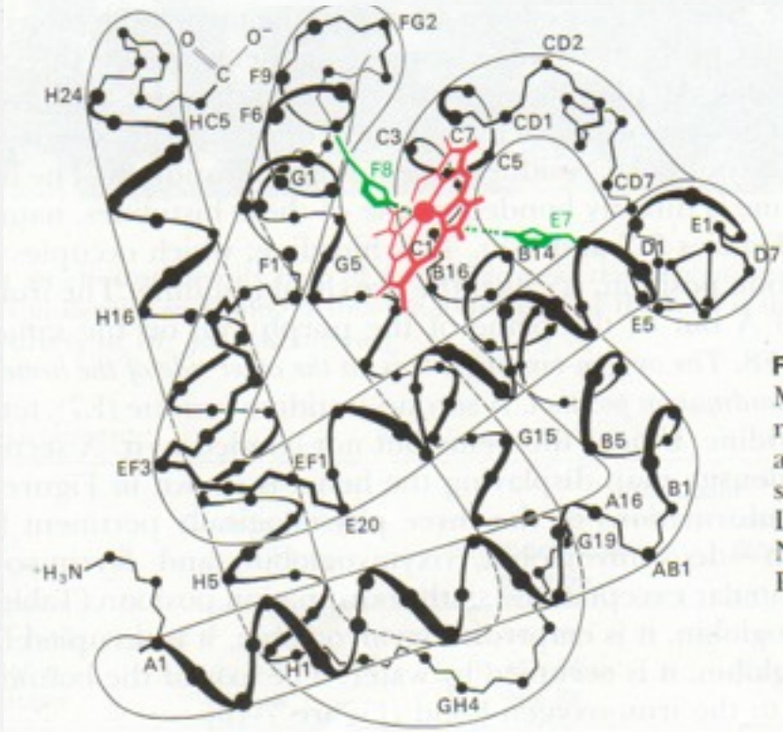
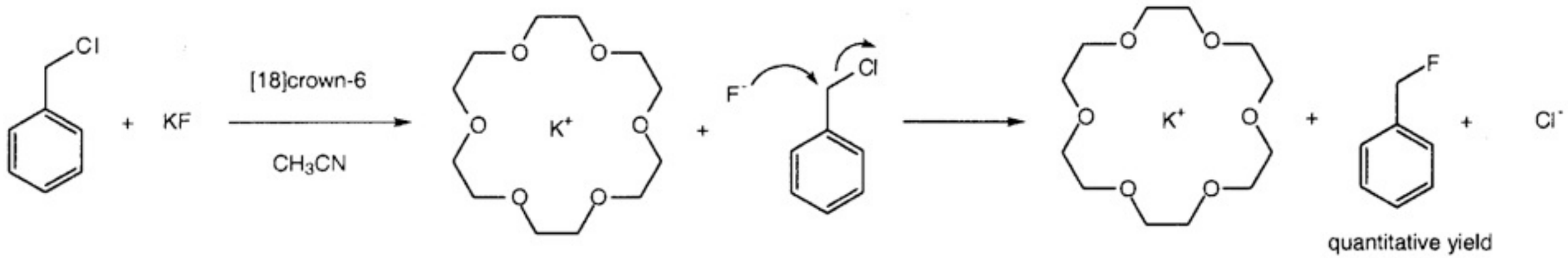


Figure 7-5
Model of myoglobin at high resolution. Only the α-carbon atoms are shown. The heme group is shown in red. [After R. E. Dickerson. In *The Proteins*, H. Neurath, ed., 2nd ed., (Academic Press, 1964), vol. 2, p. 634.]

applications

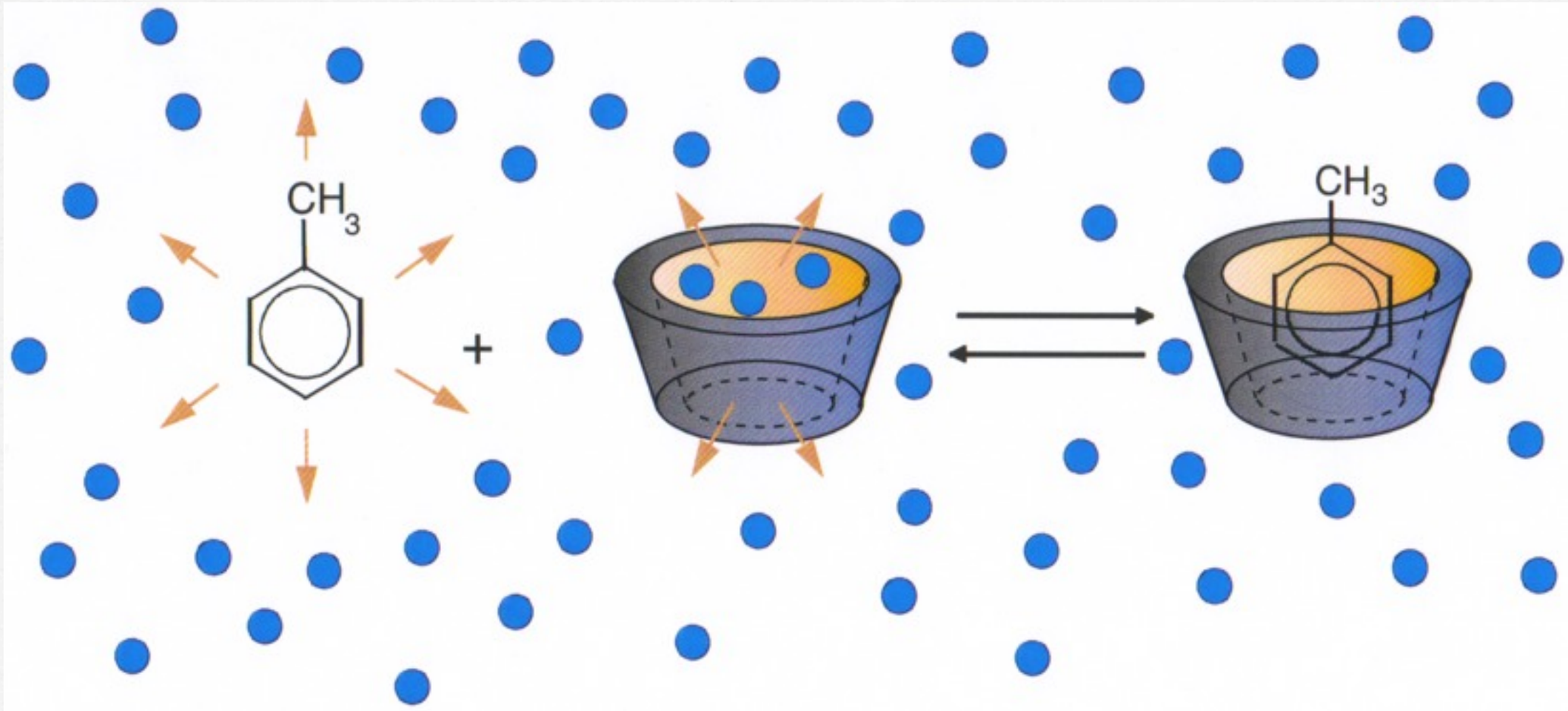
Phase transfer agents



Scheme 7.1 Crown ethers act as phase transfer catalysts for nucleophilic substitutions.

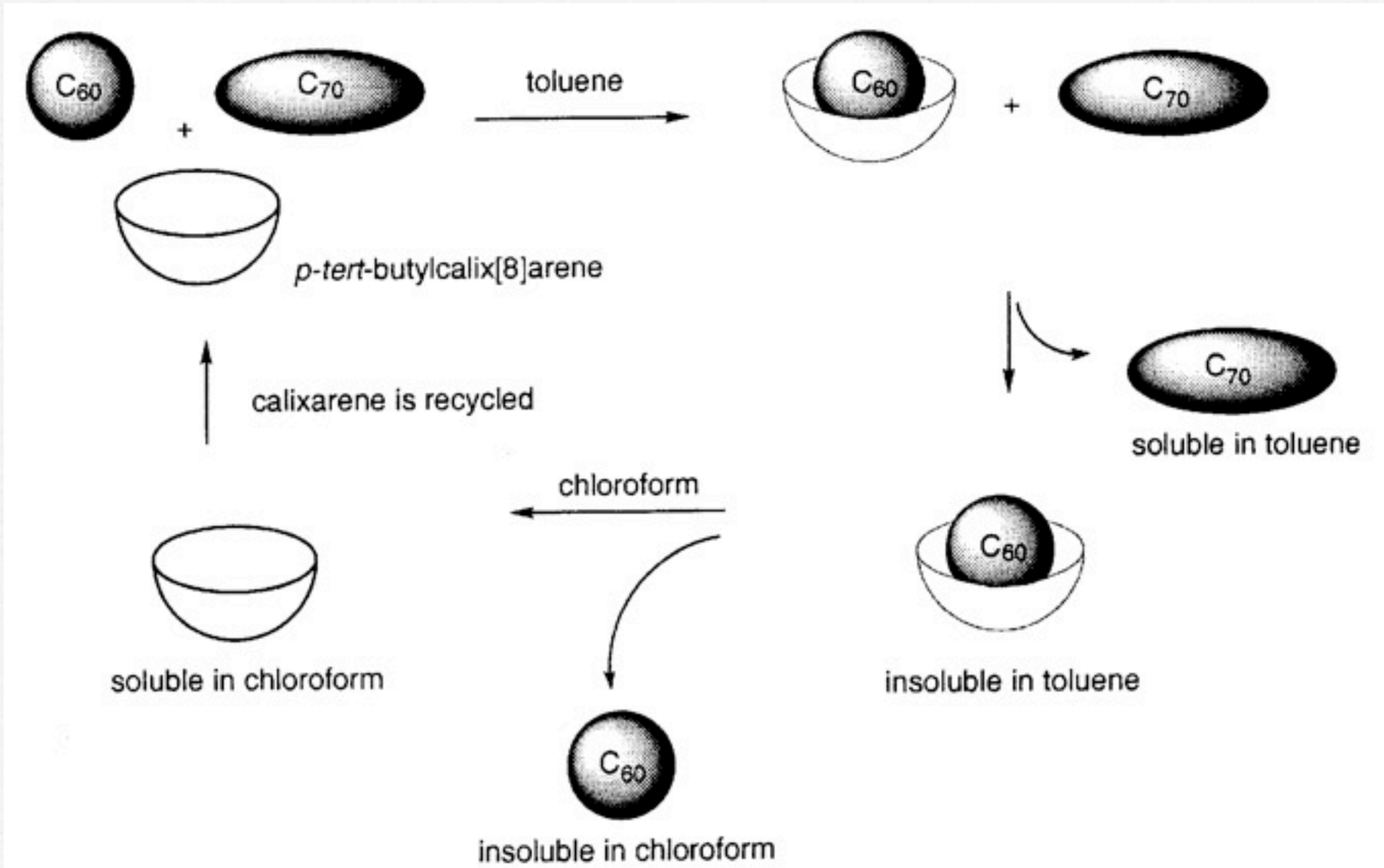
applications

Drug delivery



applications

separations



Scheme 7.4 Purification of a mixture of C_{60} and C_{70} using *p-tert*-butylcalix[8]arene.

applications

molecular switches

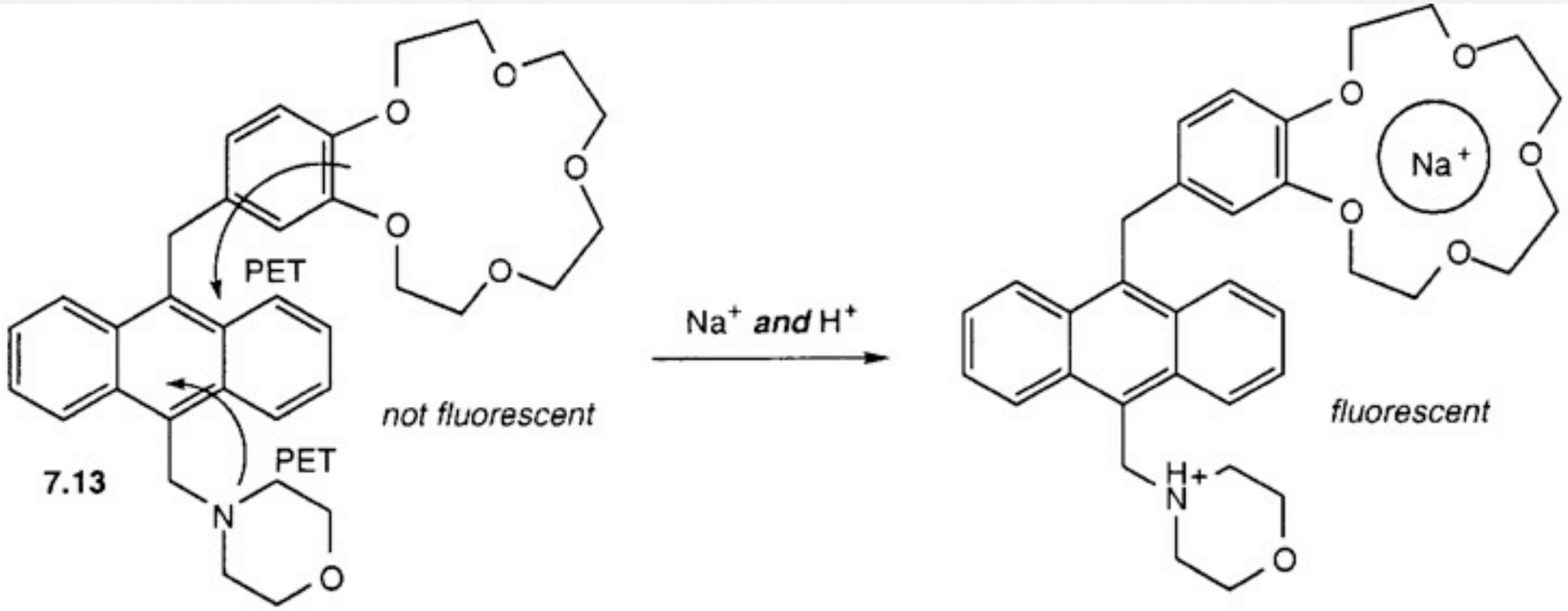


Fig. 7.9 A molecular AND switch: fluorescence is only turned on when both protons *and* sodium cations are present.

applications

catalysts

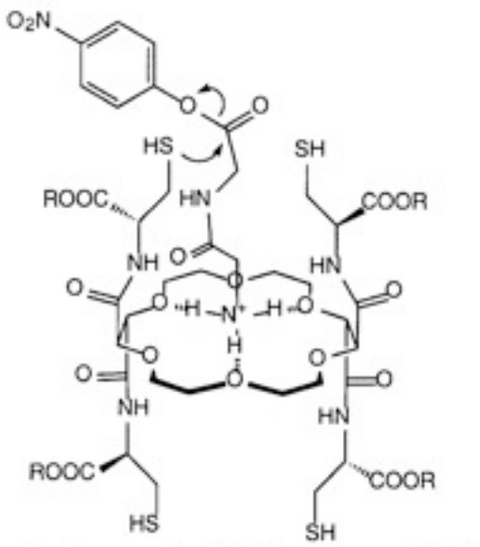
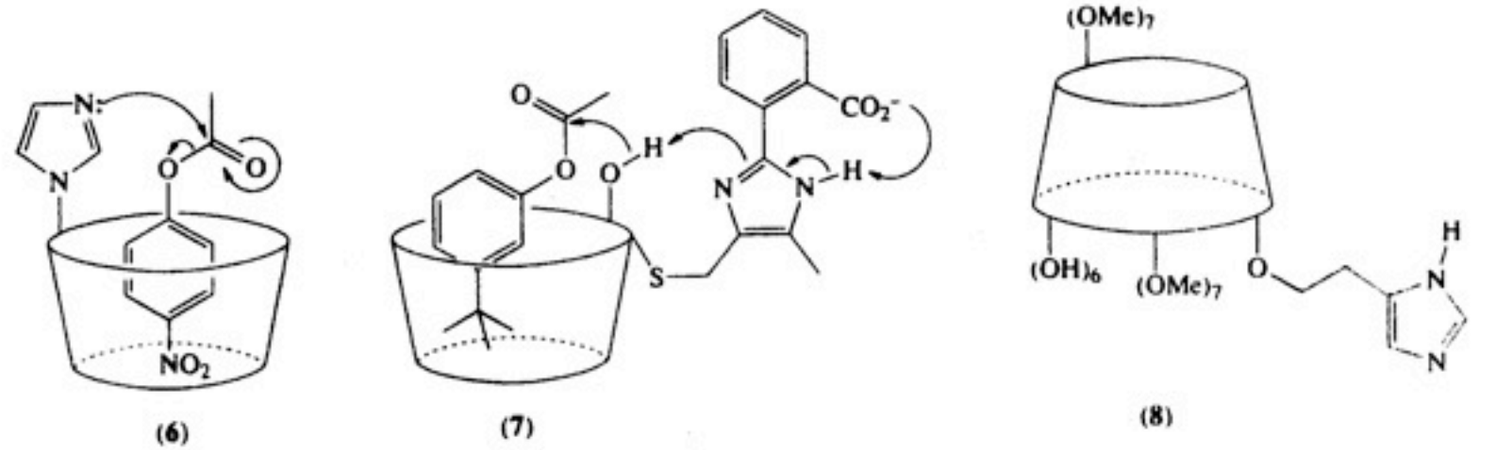
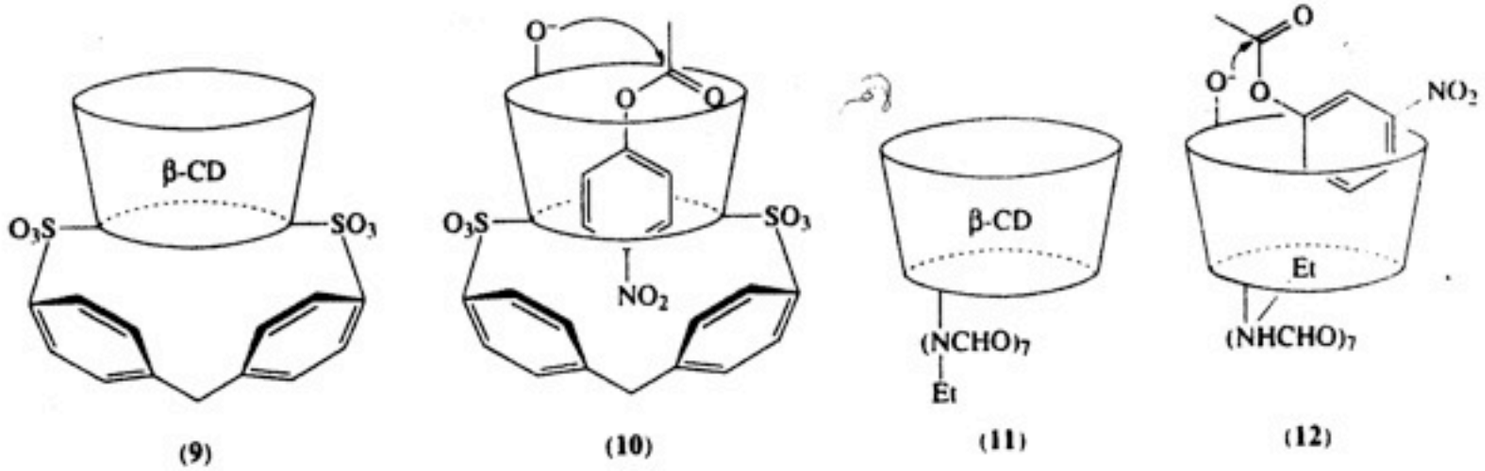


Fig. 7.10 Chiral substituted crown ether (7.14) acts as a catalyst for ester cleavage.

Table 1 Functional groups appended to CDs for hydrolase mimics.

Group	*Enzyme mimic*	*Remarks*	*Ref.*
Imidazole (6)	serine protease	acts as a nucleophile and proton transfer agent	14–17
L- or D-Histidine	serine protease	enantioselective cleavage of nitrophenol esters of phenylalanine derivatives	18
2-Carboxyphenyl-2-imidazolyl (7)	α-chymotrypsin	catalytic triad mechanism with imidazole carboxylate and the CD hydroxy groups	19
2-Carboxyphenyl-2-imidazolyl (7)	α-chymotrypsin	β-CD oxyanion mechanism (denial of triad mechanism)	20
Tripeptide (Ser-His-Asp)	α-chymotrypsin	hydrolysis of *p*-nitrophenyl hexanoate	21
5-Imidazoylethyl and heptakis-2,6-dimethyl (8)	α-chymotrypsin	k_2 value of *p*-NPA comparable to α-chymotrypsin and turnover action	22
Hydroxyamine	α-chymotrypsin	high hydrolysis rate to *p*-NPA	23





directed H-bonding

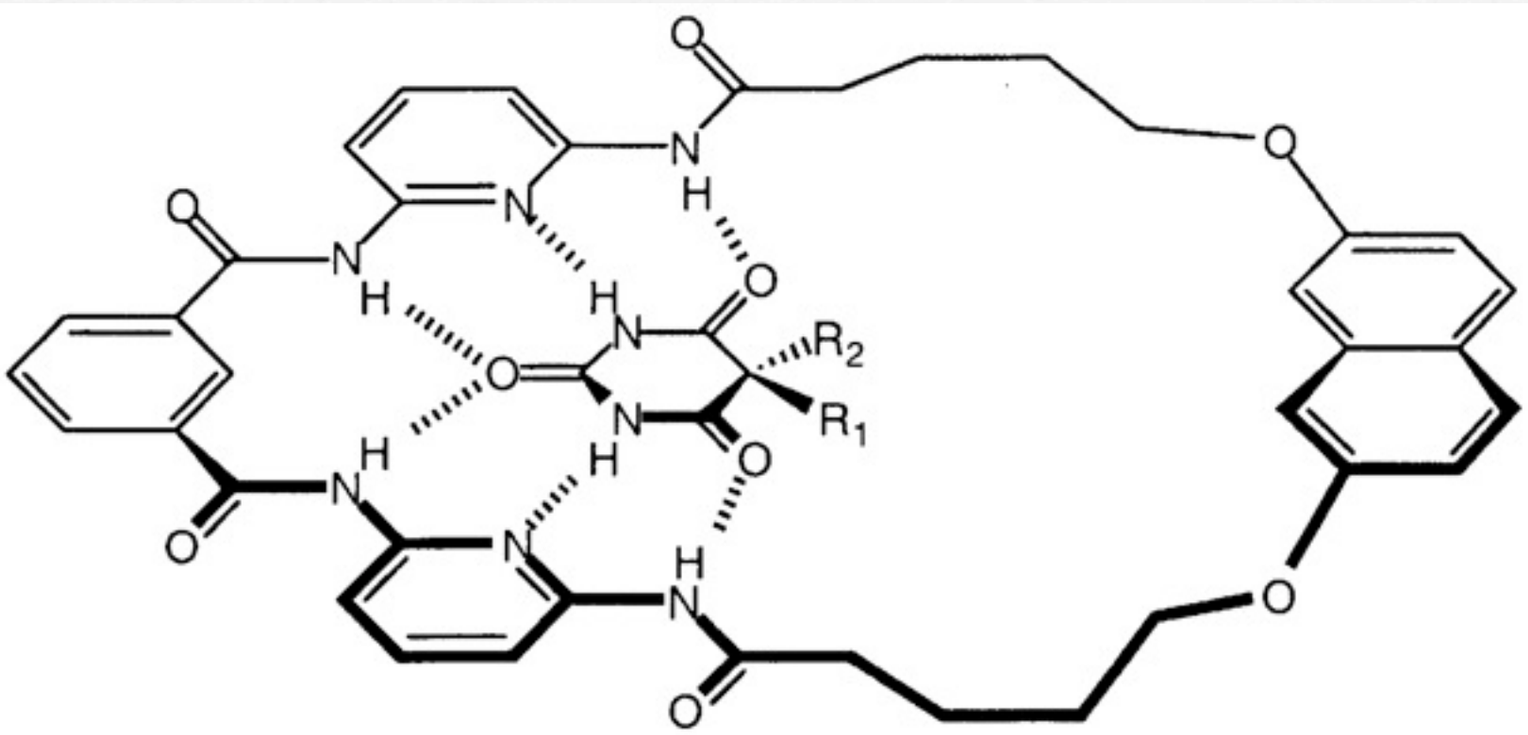
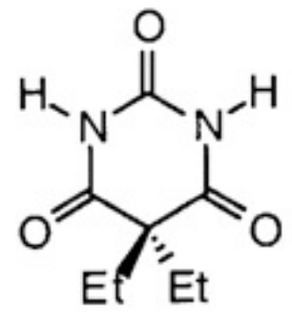
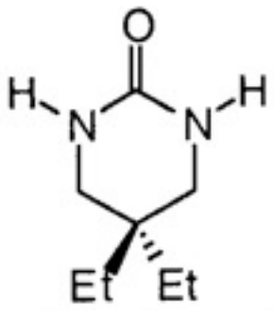
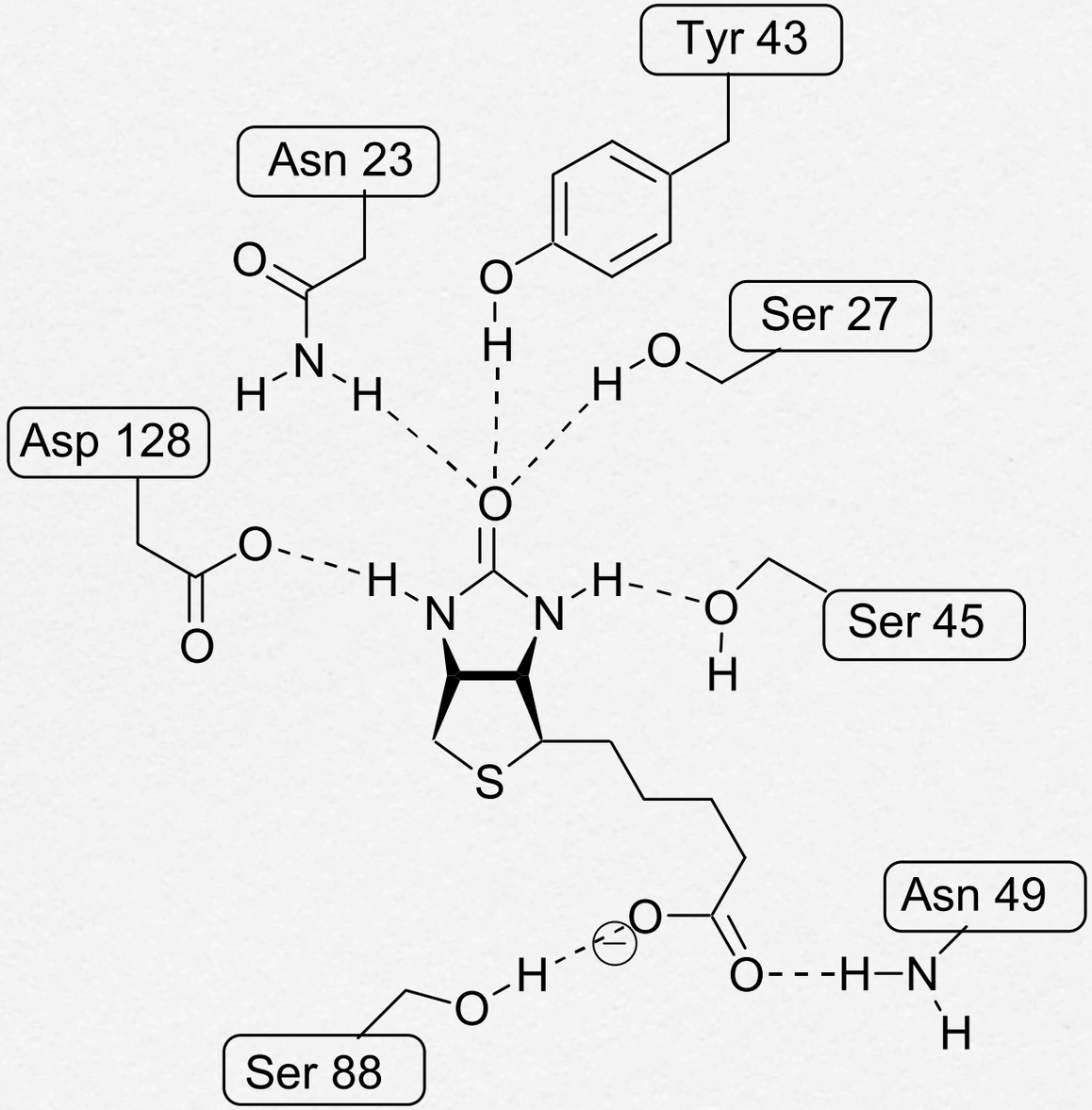


Fig. 5.2 Host-guest complex between receptor **5.3** and a barbiturate guest.

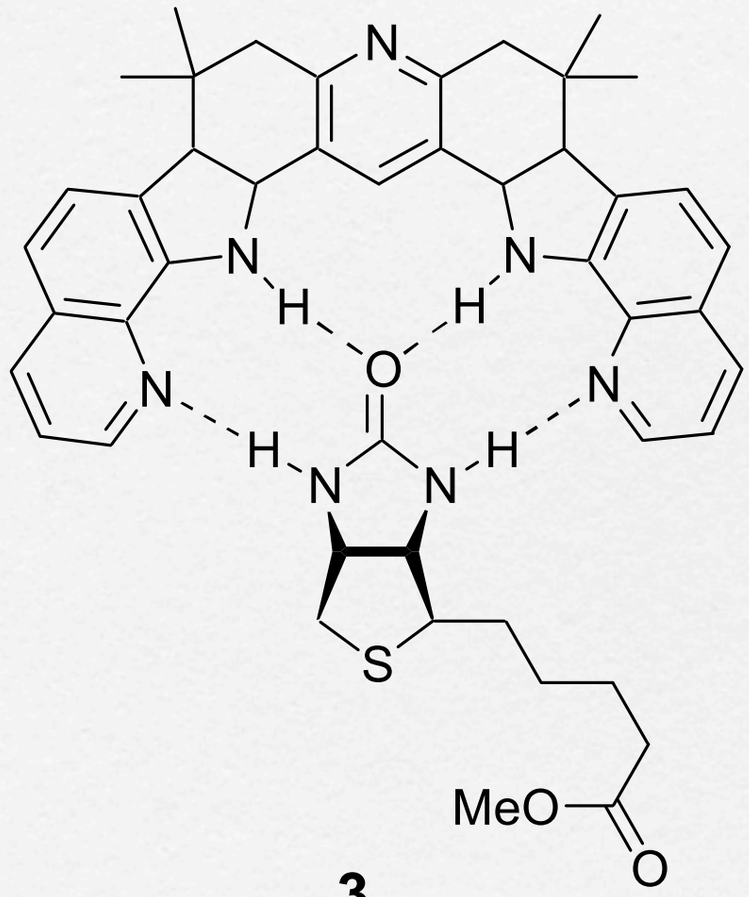
Table. 5.1 Binding data for receptor **5.3**.

Guest	K (M^{-1}) $[CH_2Cl_2]$
	250 000
	400

H-bonding motive

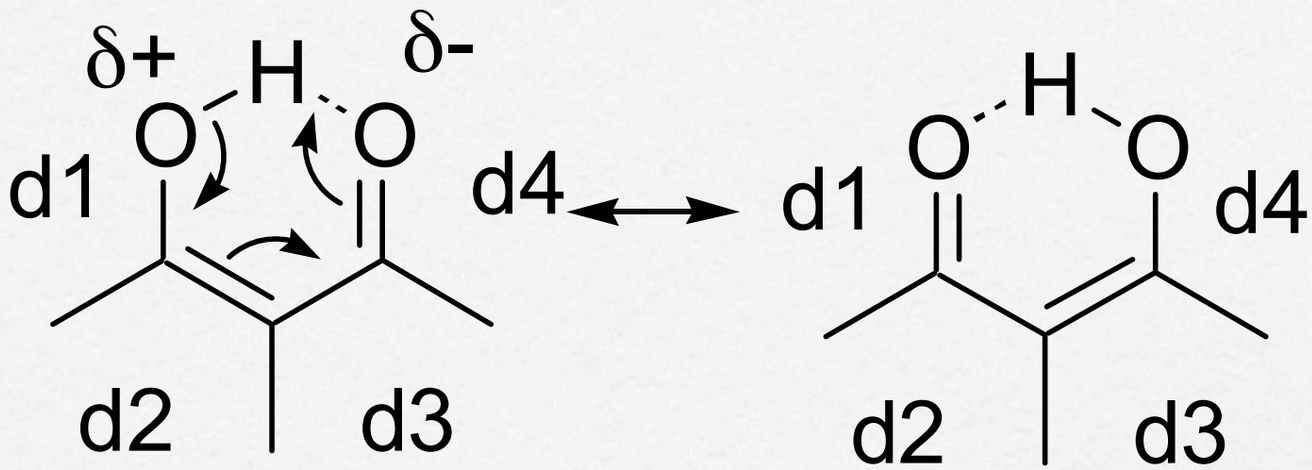


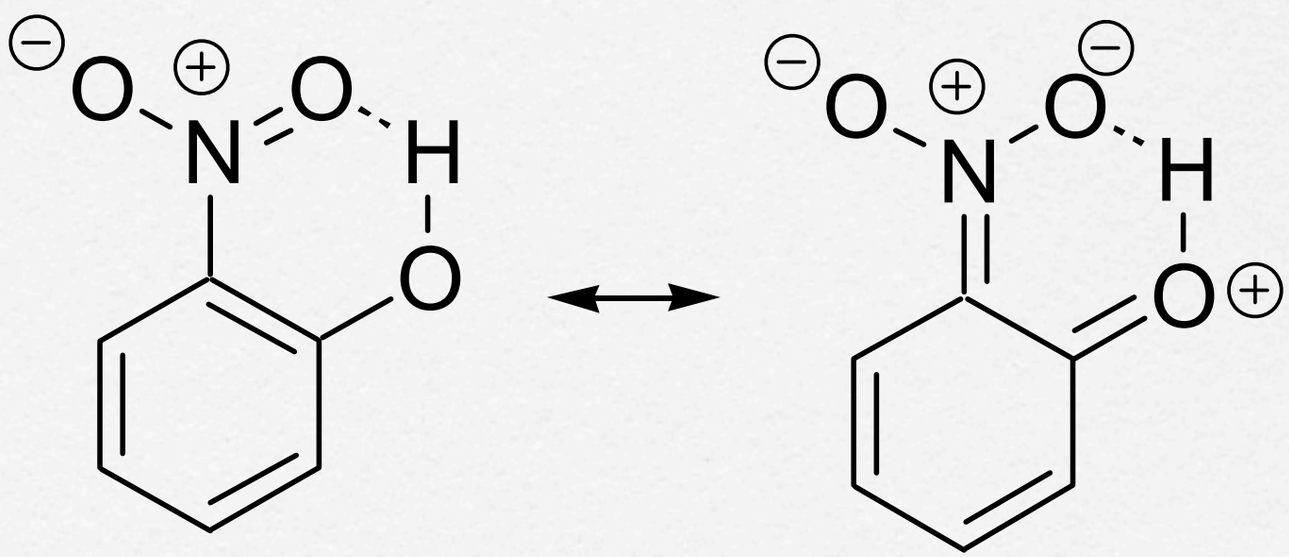
streptavdin - biotin



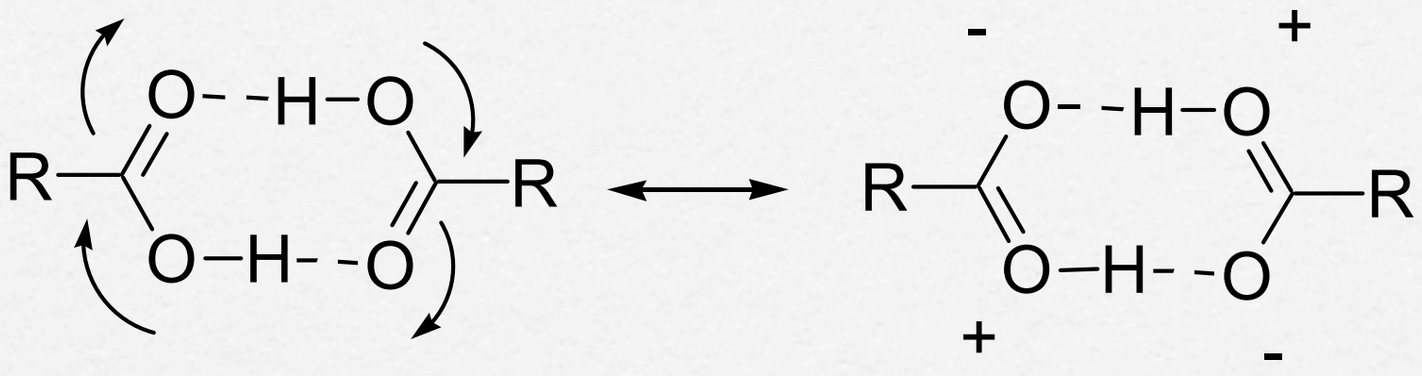
3

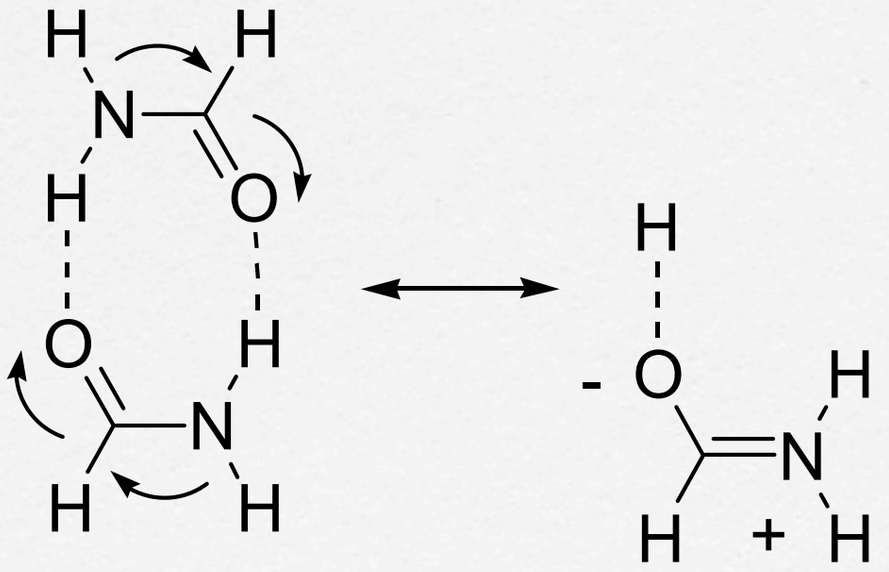
RAHB, Resonance Assisted Hydrogen Bonding

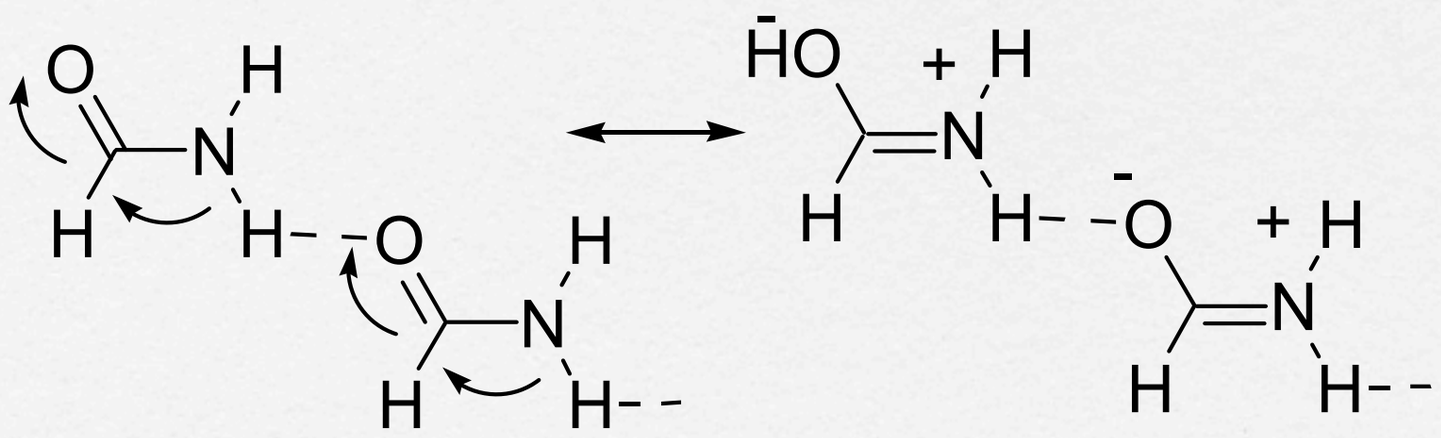




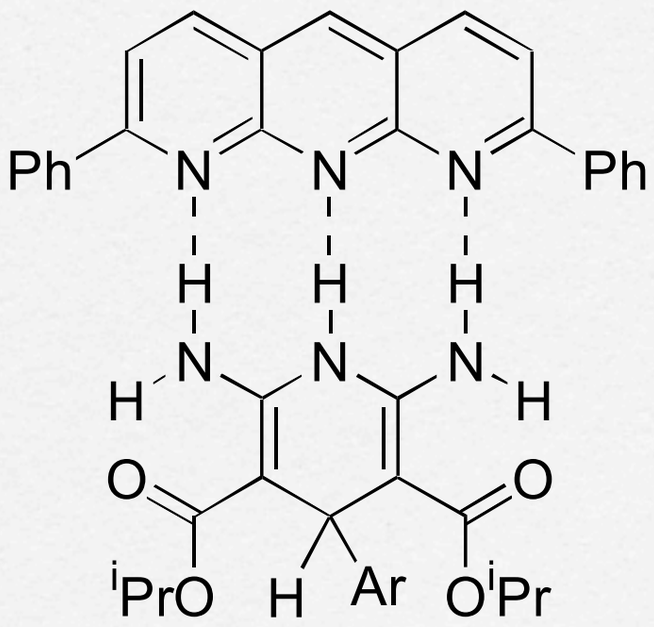
RAHB, Resonance Assisted Hydrogen Bonding



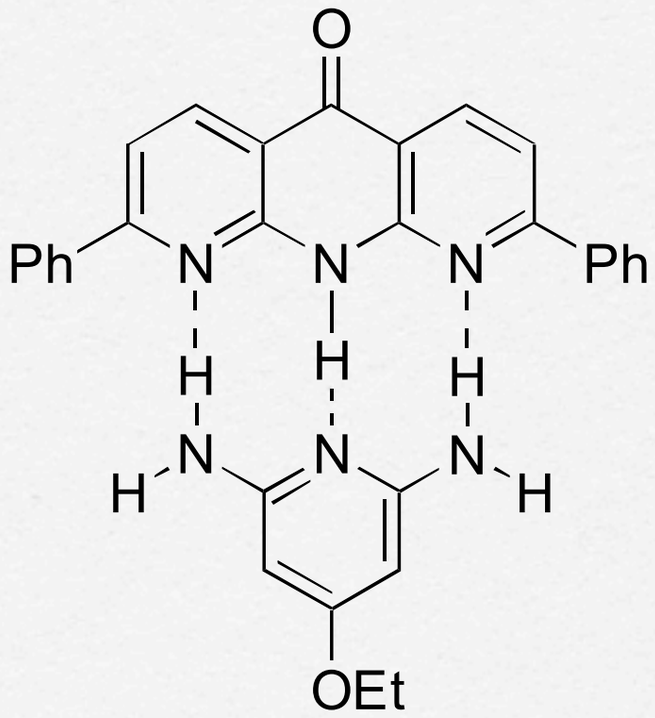




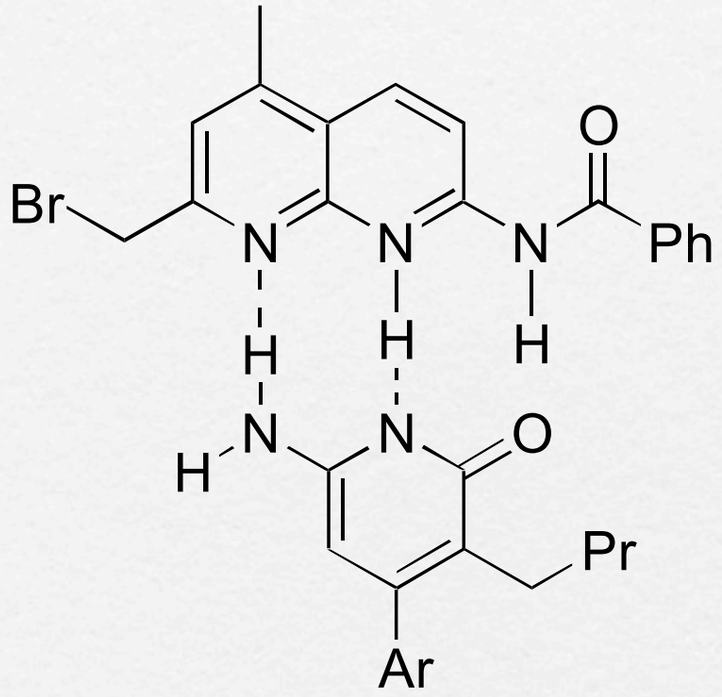
DDD-AAA vs. DAD-ADA



6 K >10^5

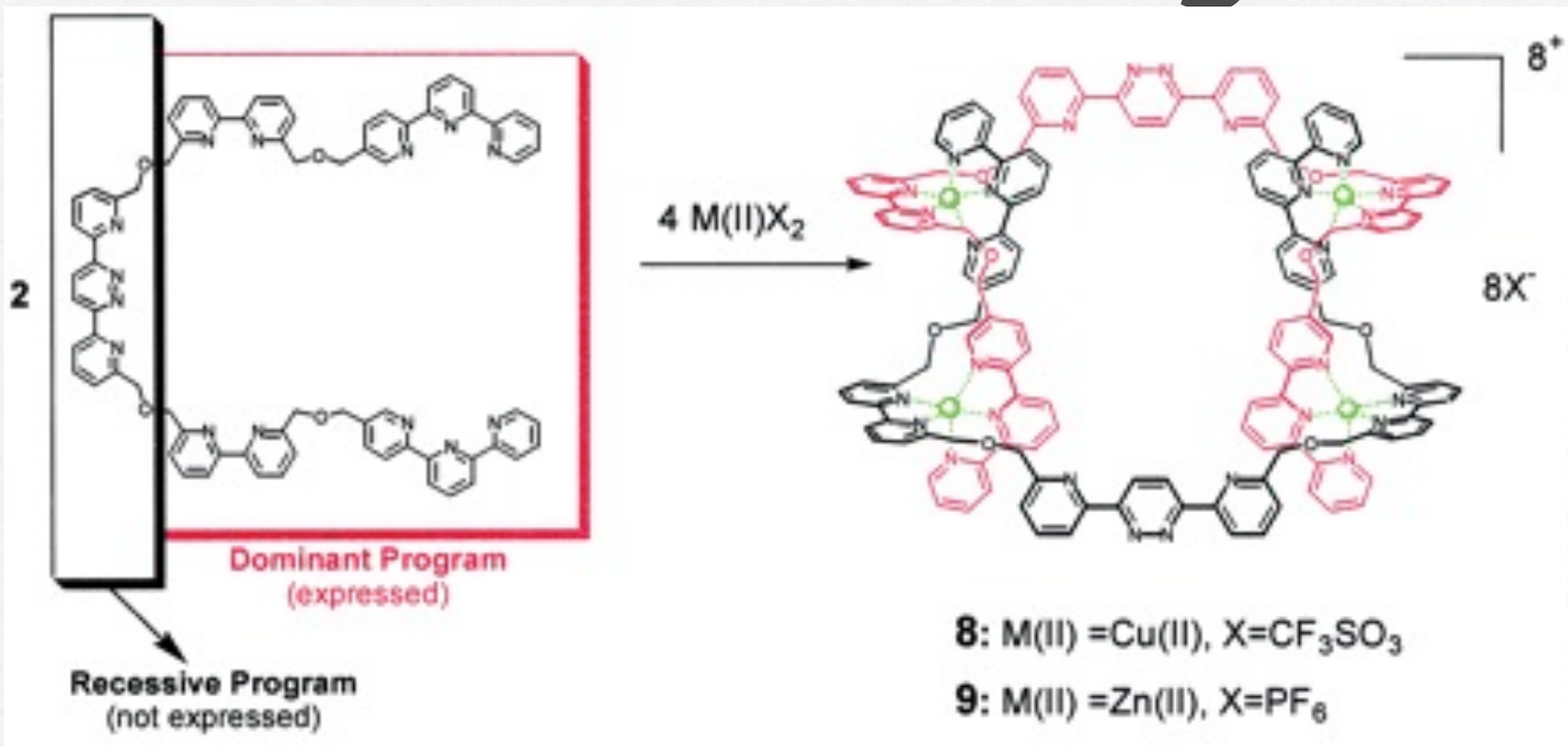


7 K = 70



8 K > 10^4

metal binding

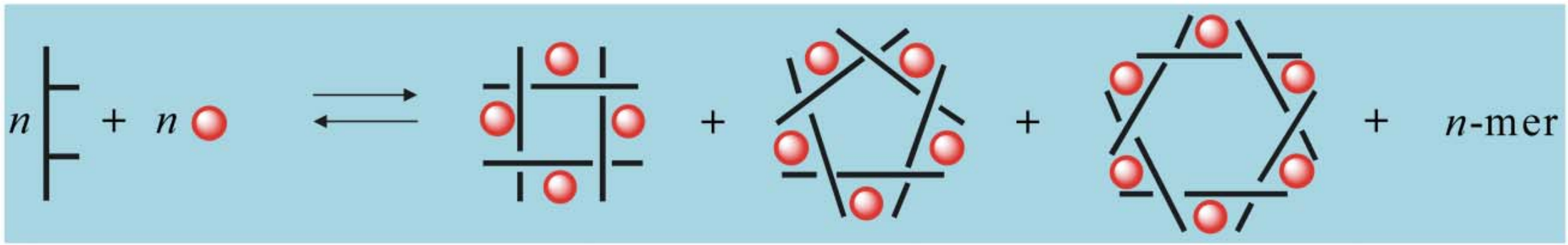


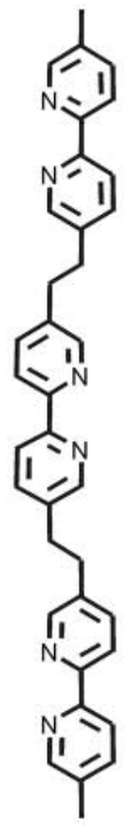
Octahedral coordination center: Co(II), Ni(II)

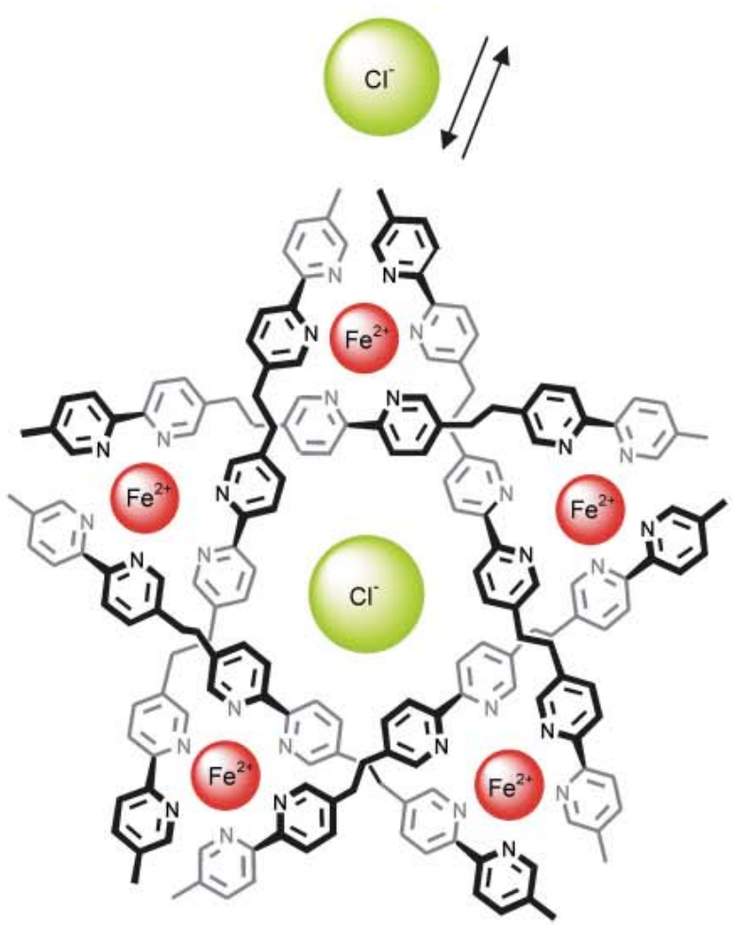
Tetrahedral coordination center: Cu(I)

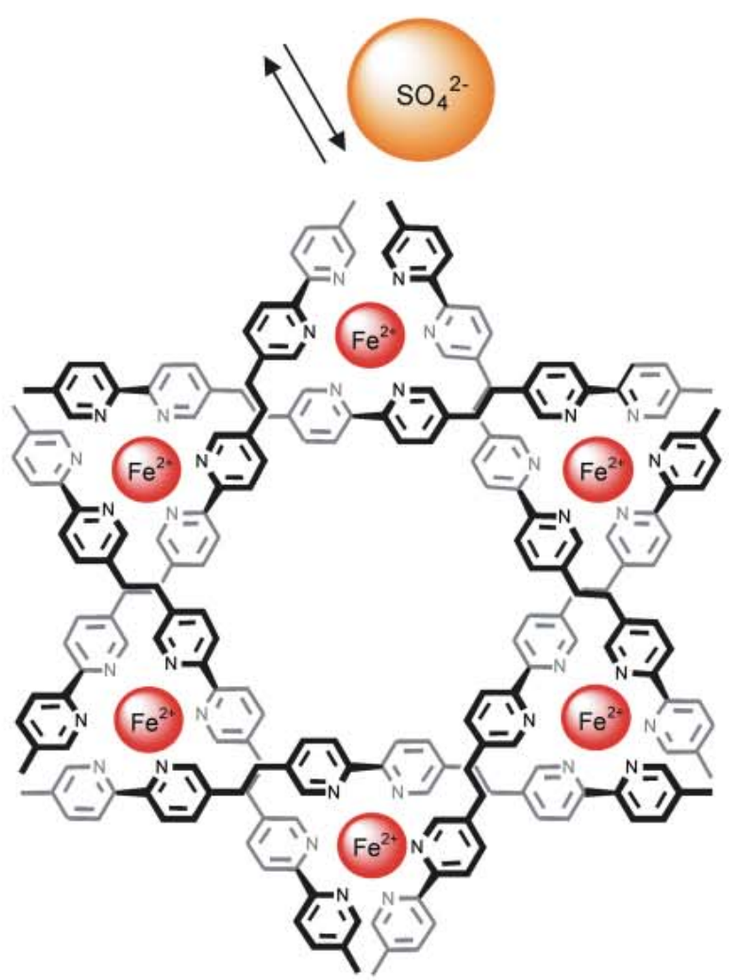
10(Co), **11**(Ni)

dynamic library

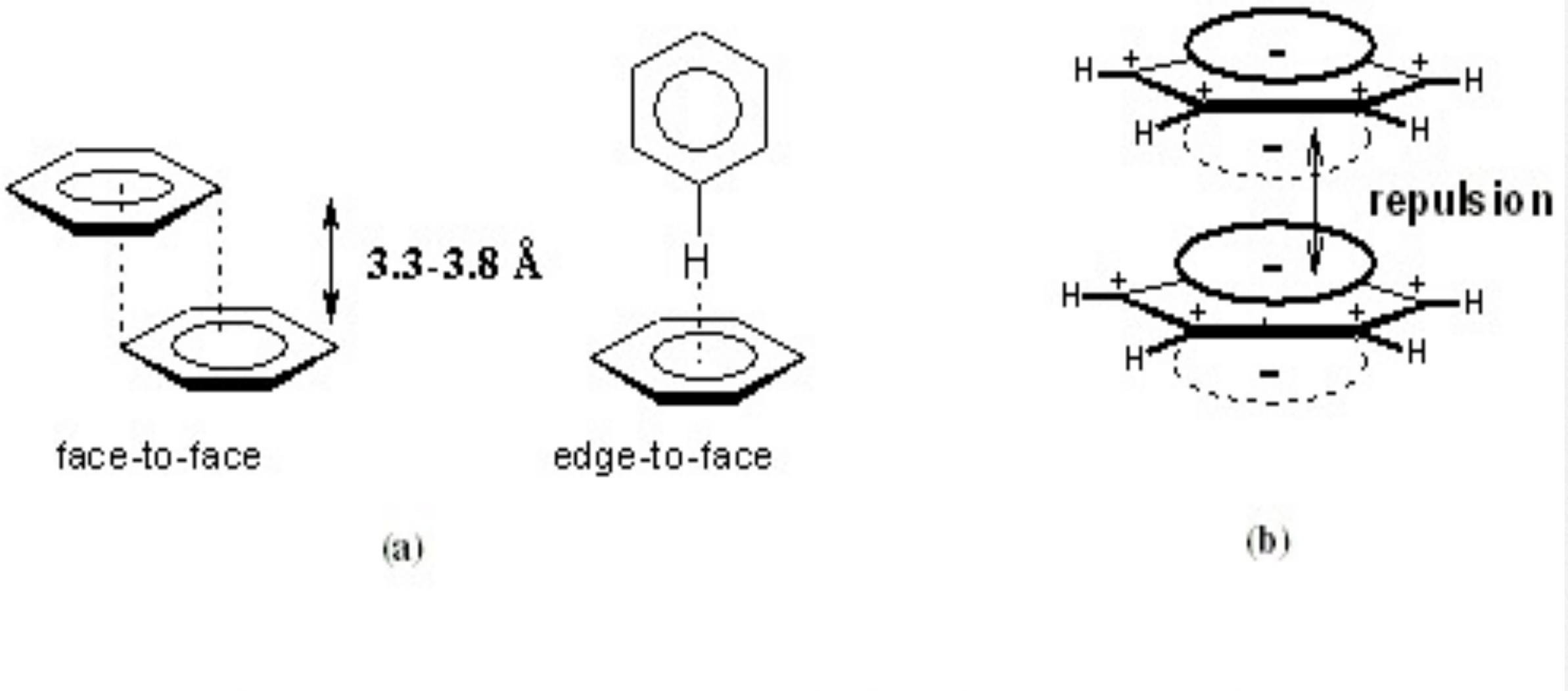




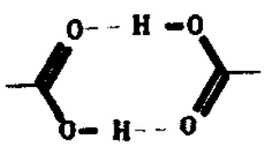




$\pi - \pi$ interactions



H-bonds



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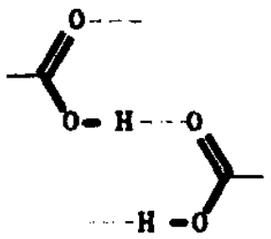

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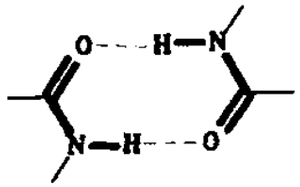

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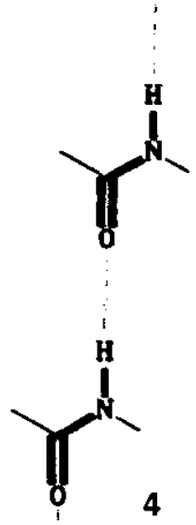

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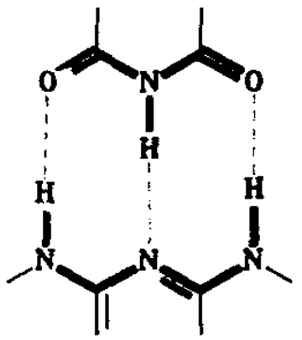

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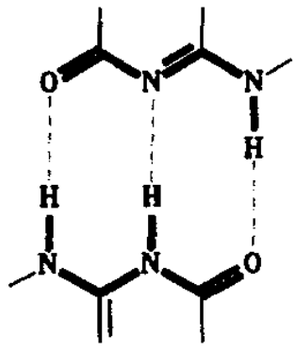

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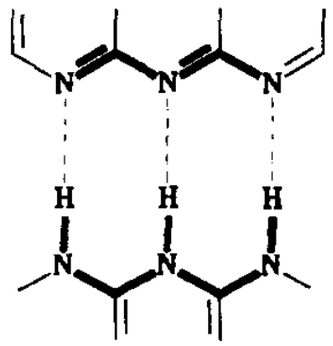

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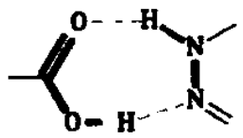

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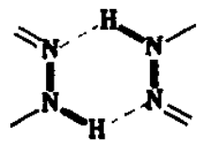

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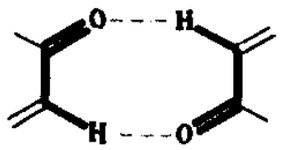

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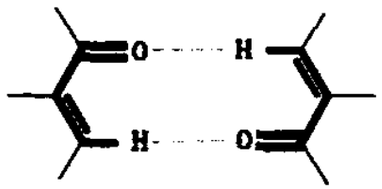

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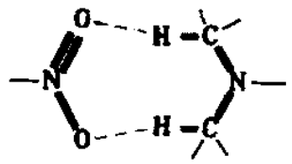

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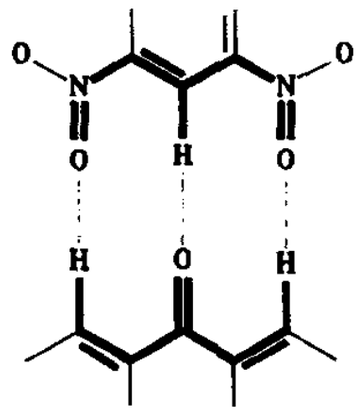

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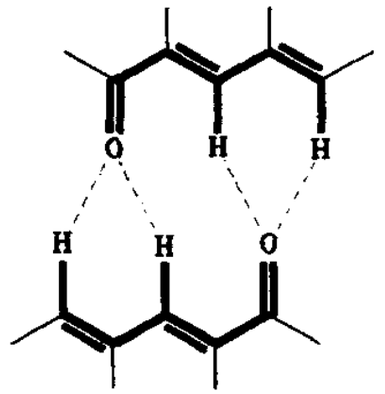

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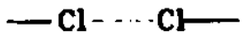

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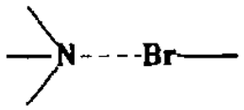

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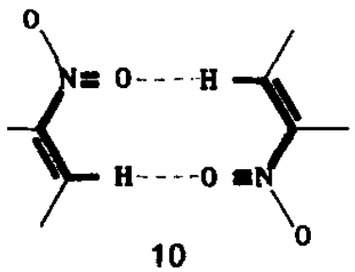
H-bonds



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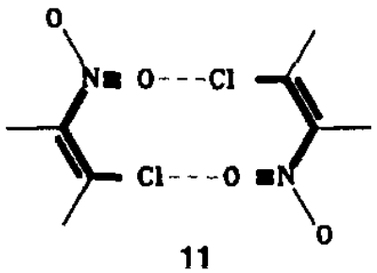

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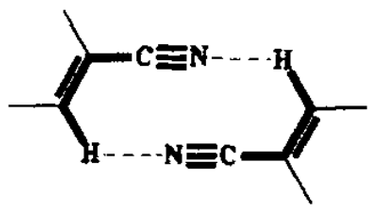

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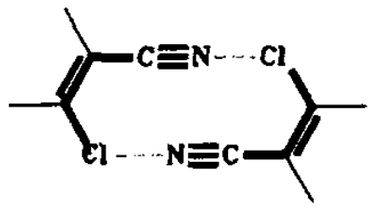

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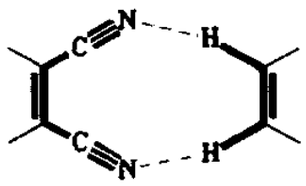

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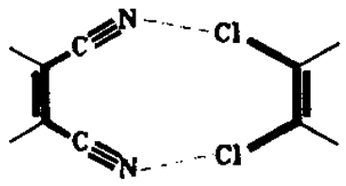

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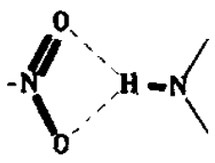

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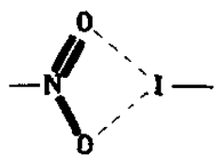

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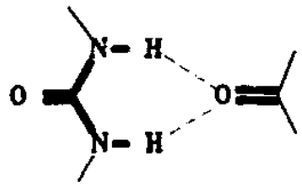

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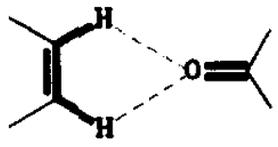

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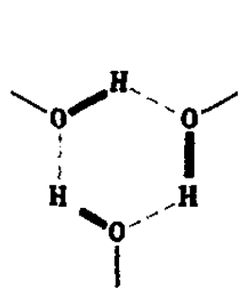

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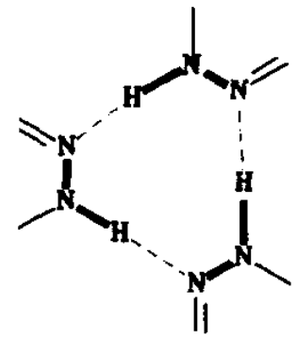

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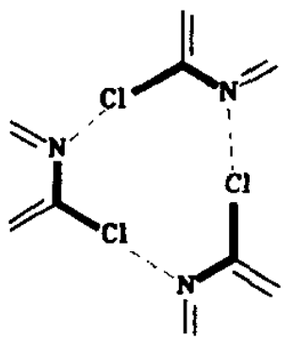

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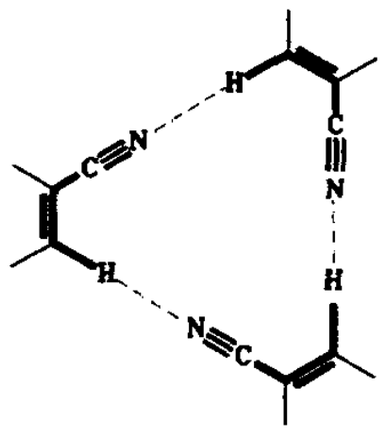

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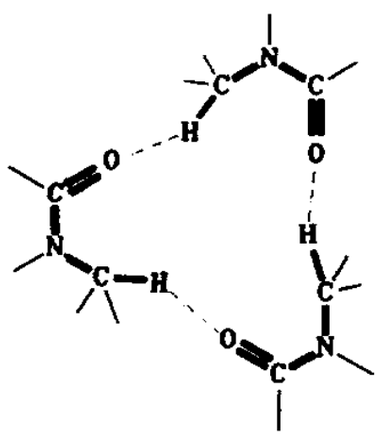

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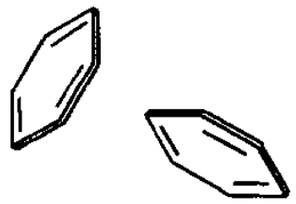

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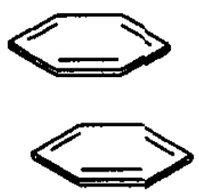

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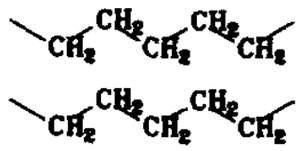

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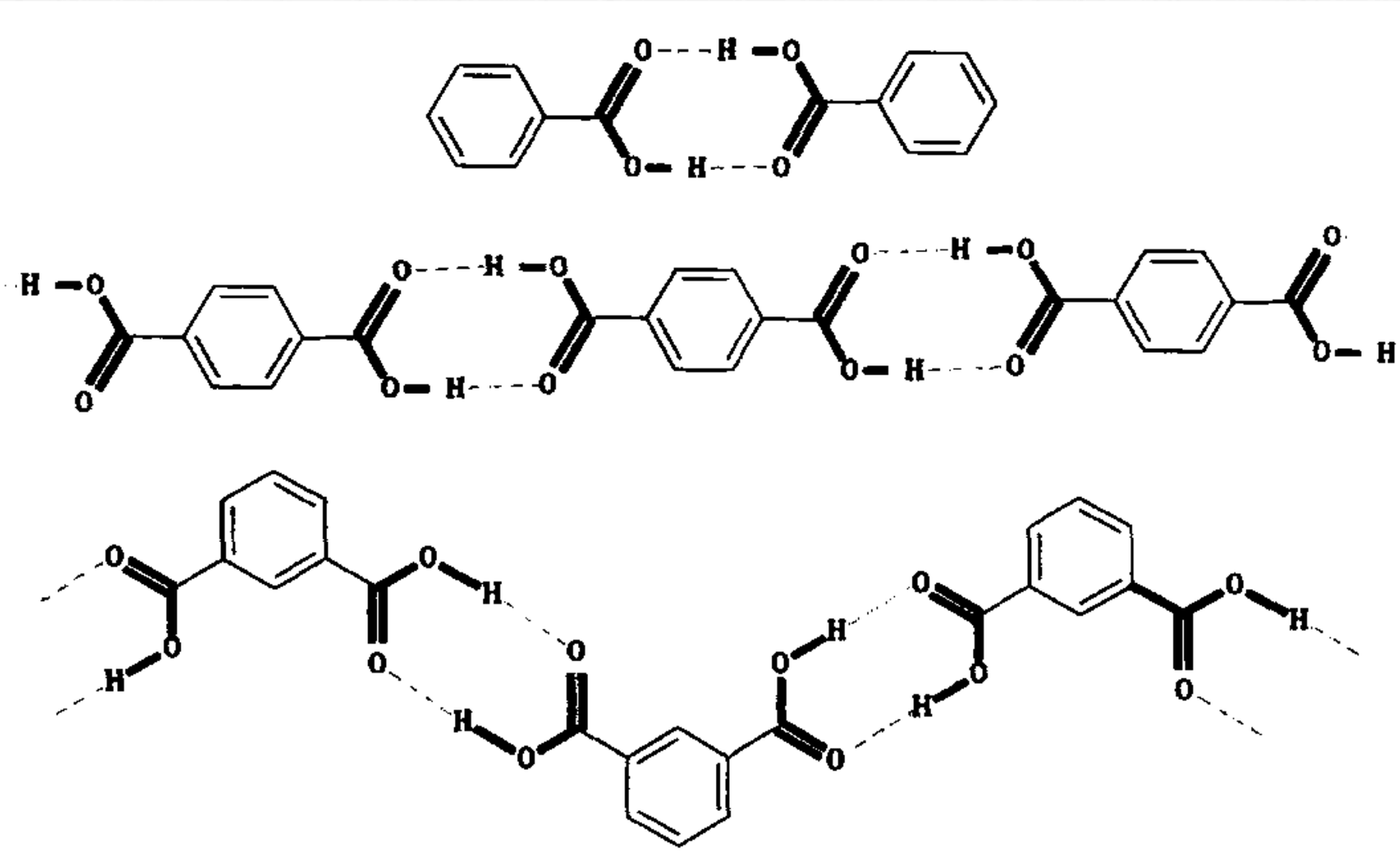
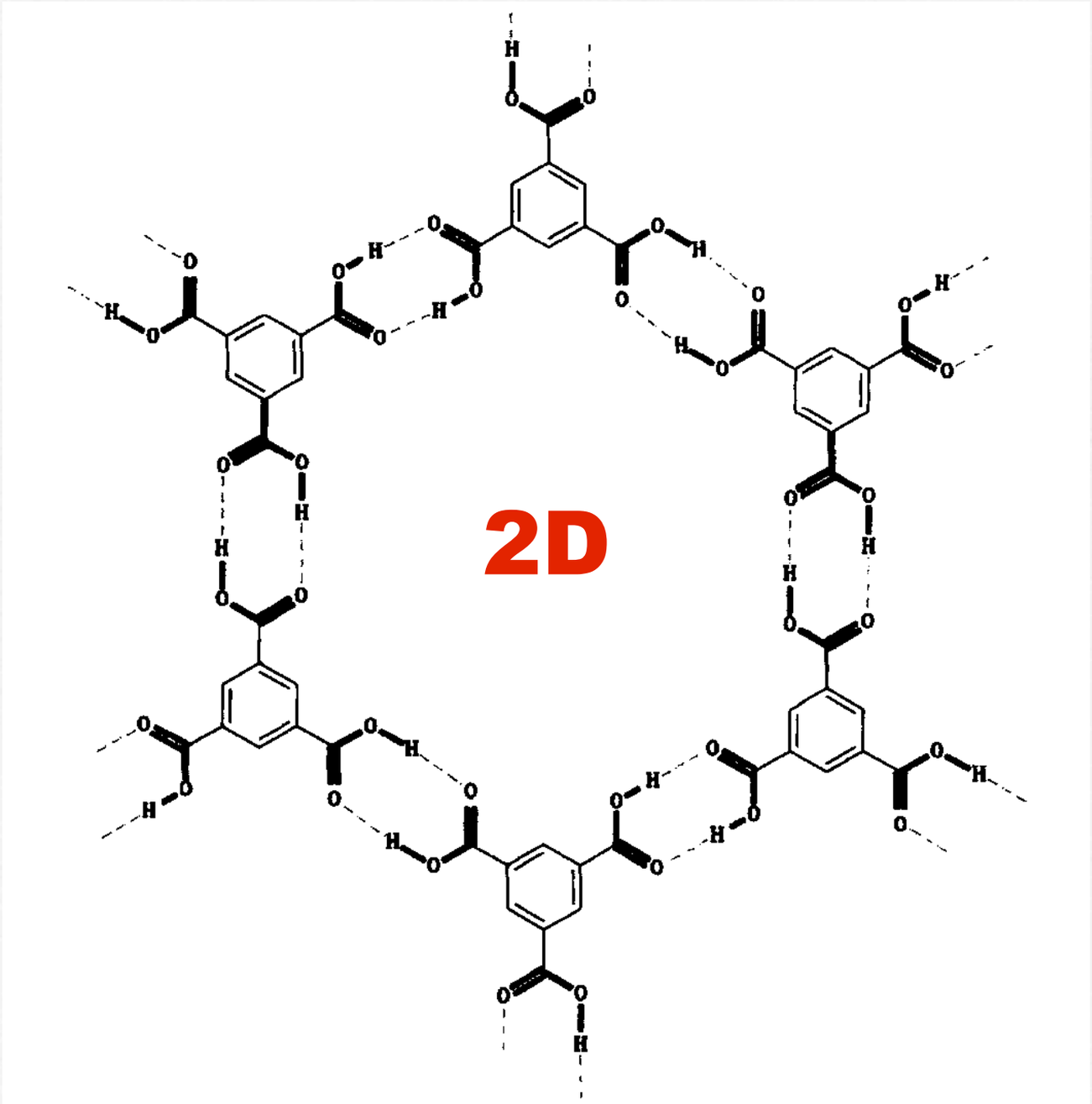
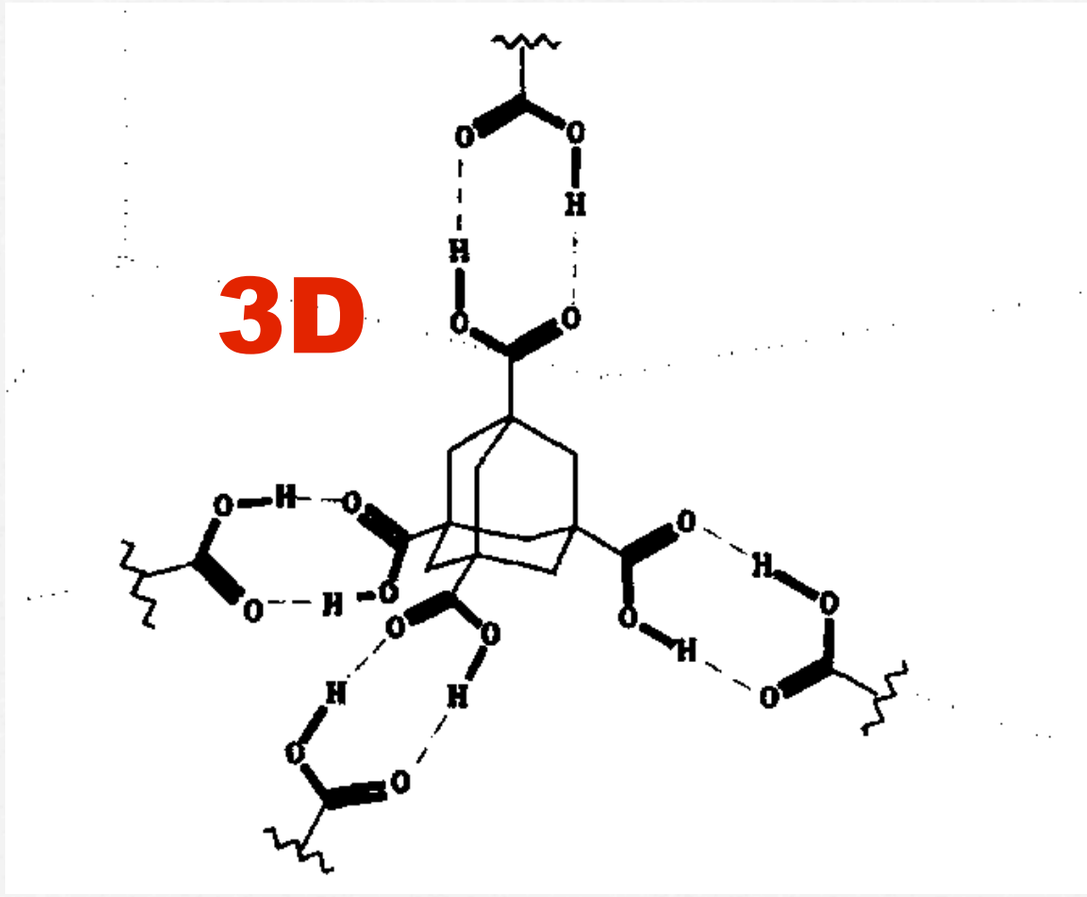
Assembly via H-bonds

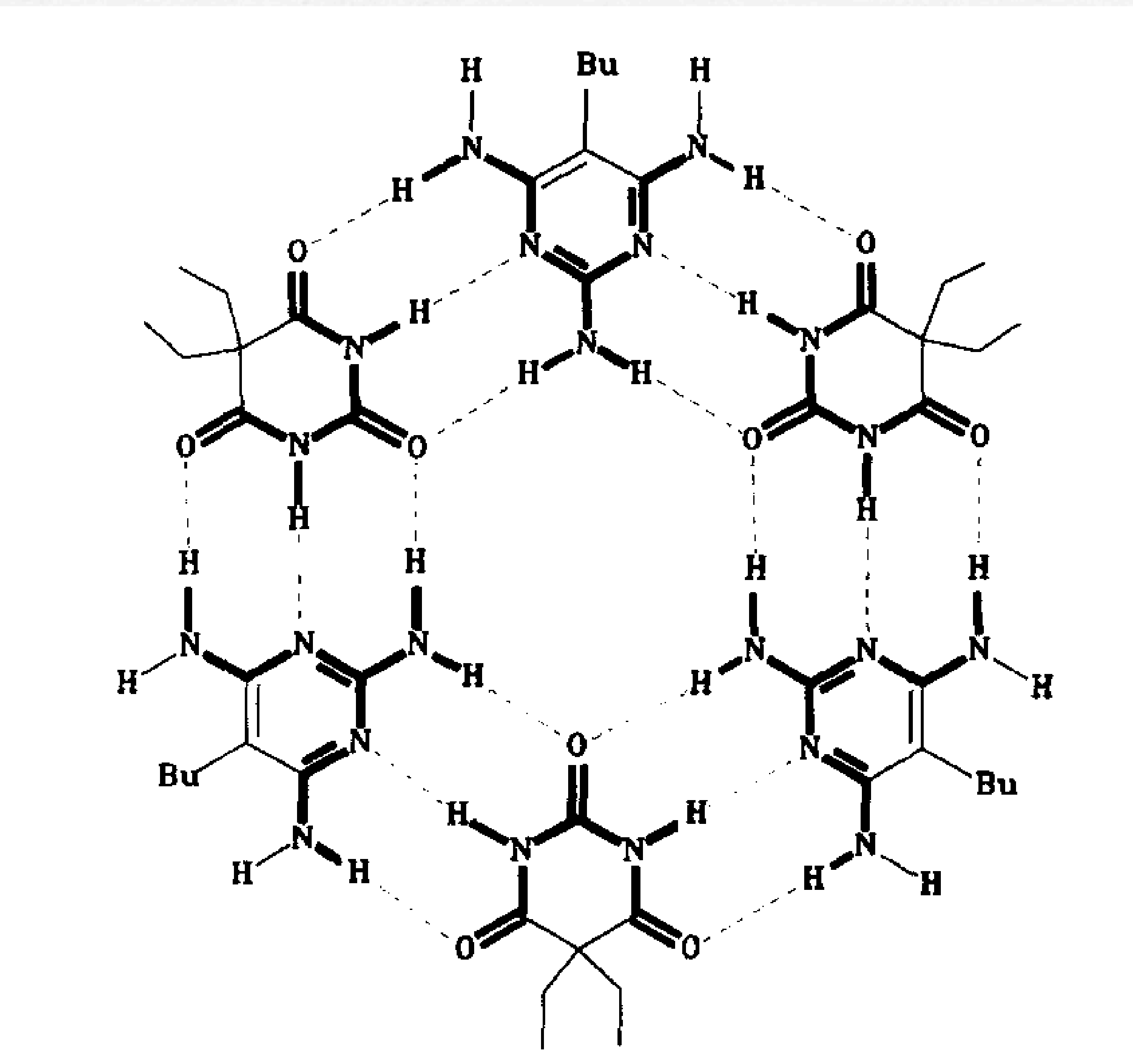


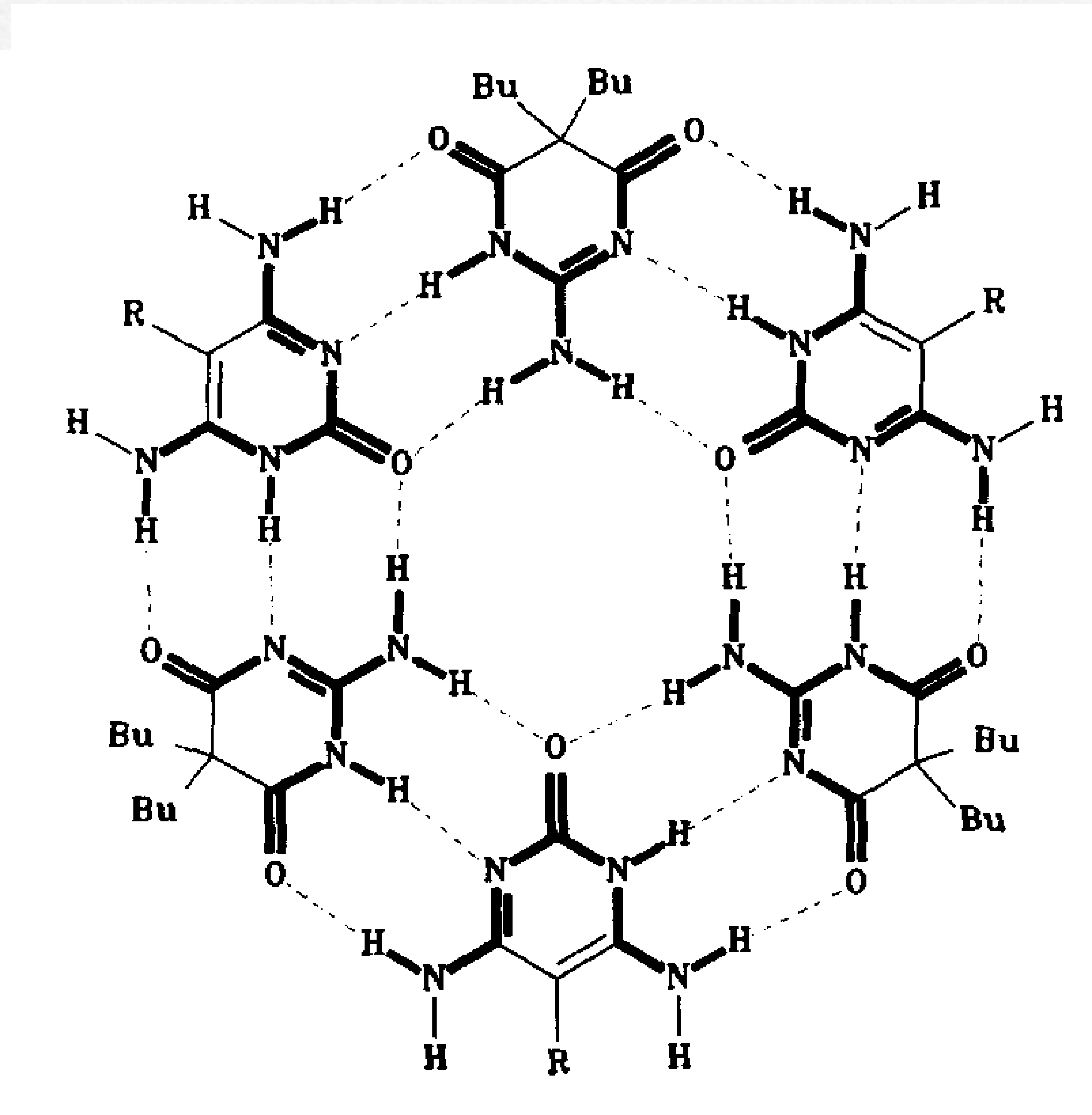
Assembly via H-bonds



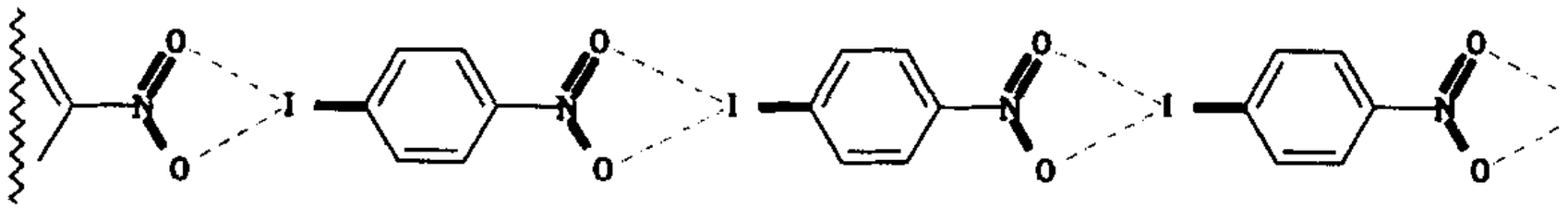


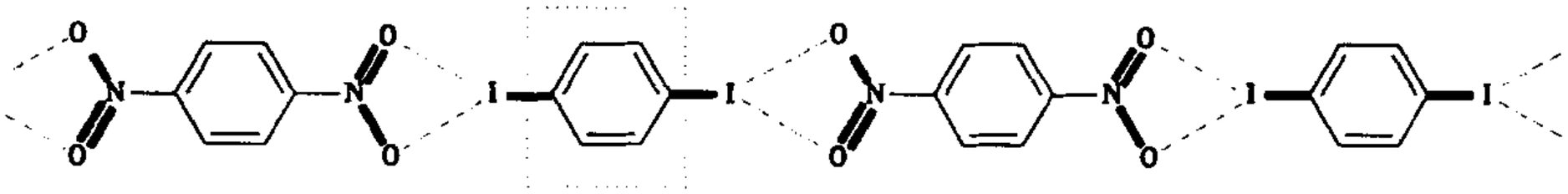
H-bonds

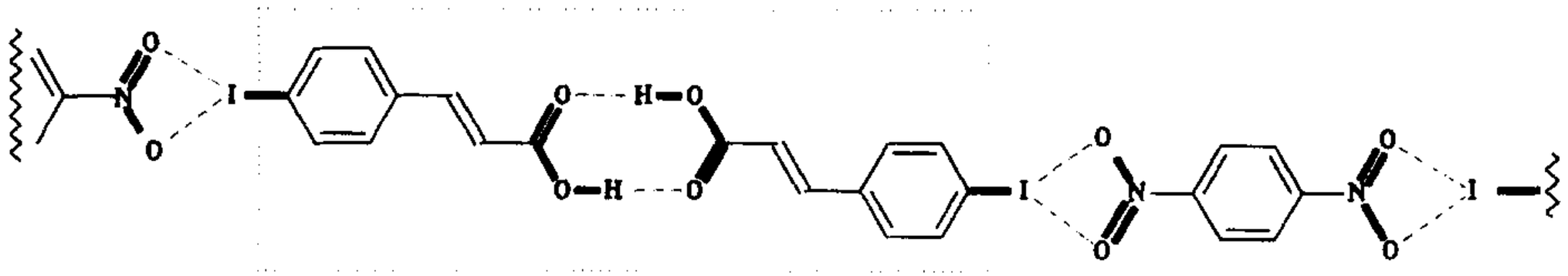




other DA bonds







other DA bonds

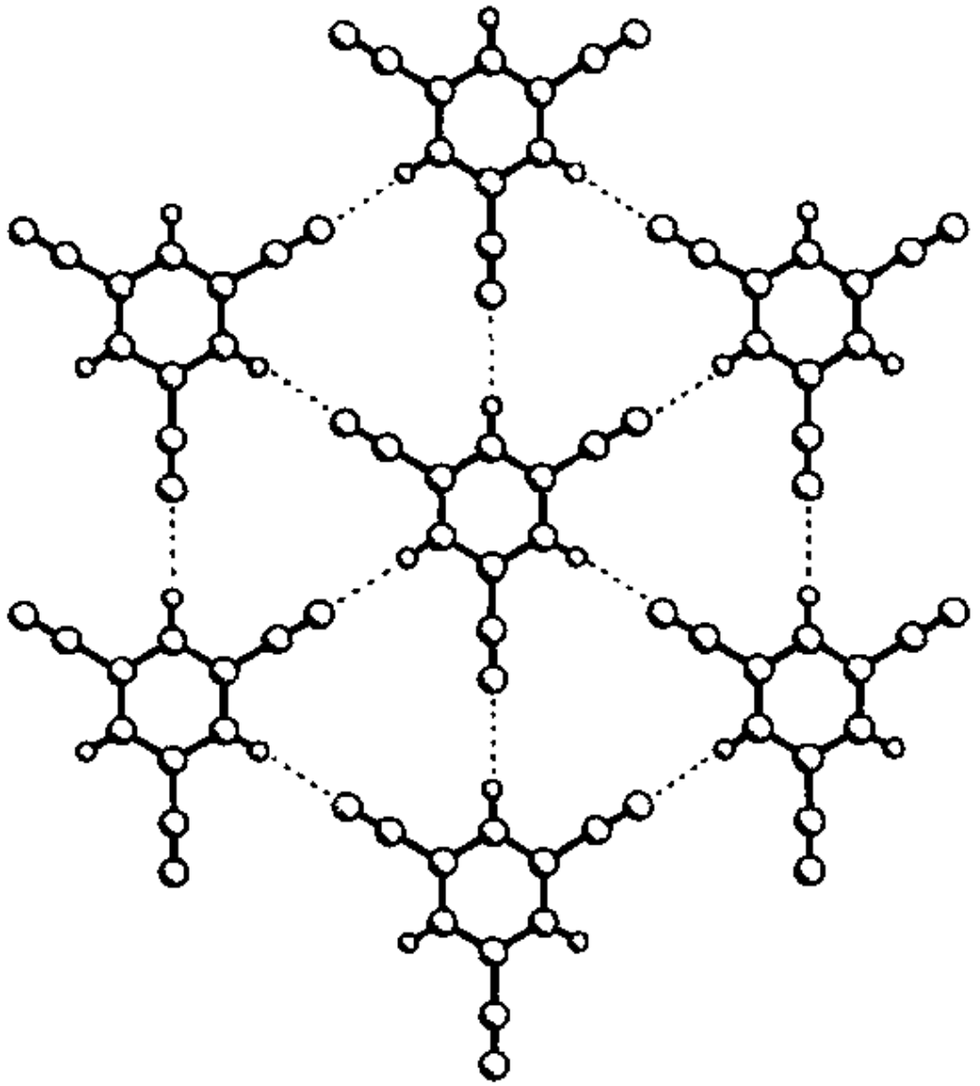


Fig. 8. CH···N network of 1,3,5-tricyanobenzene molecules (synthon **31**) in the crystal structure of the 1:1 complex formed by this substance with hexamethylbenzene. The interleaving hexamethylbenzene network is not shown.

forming polymers

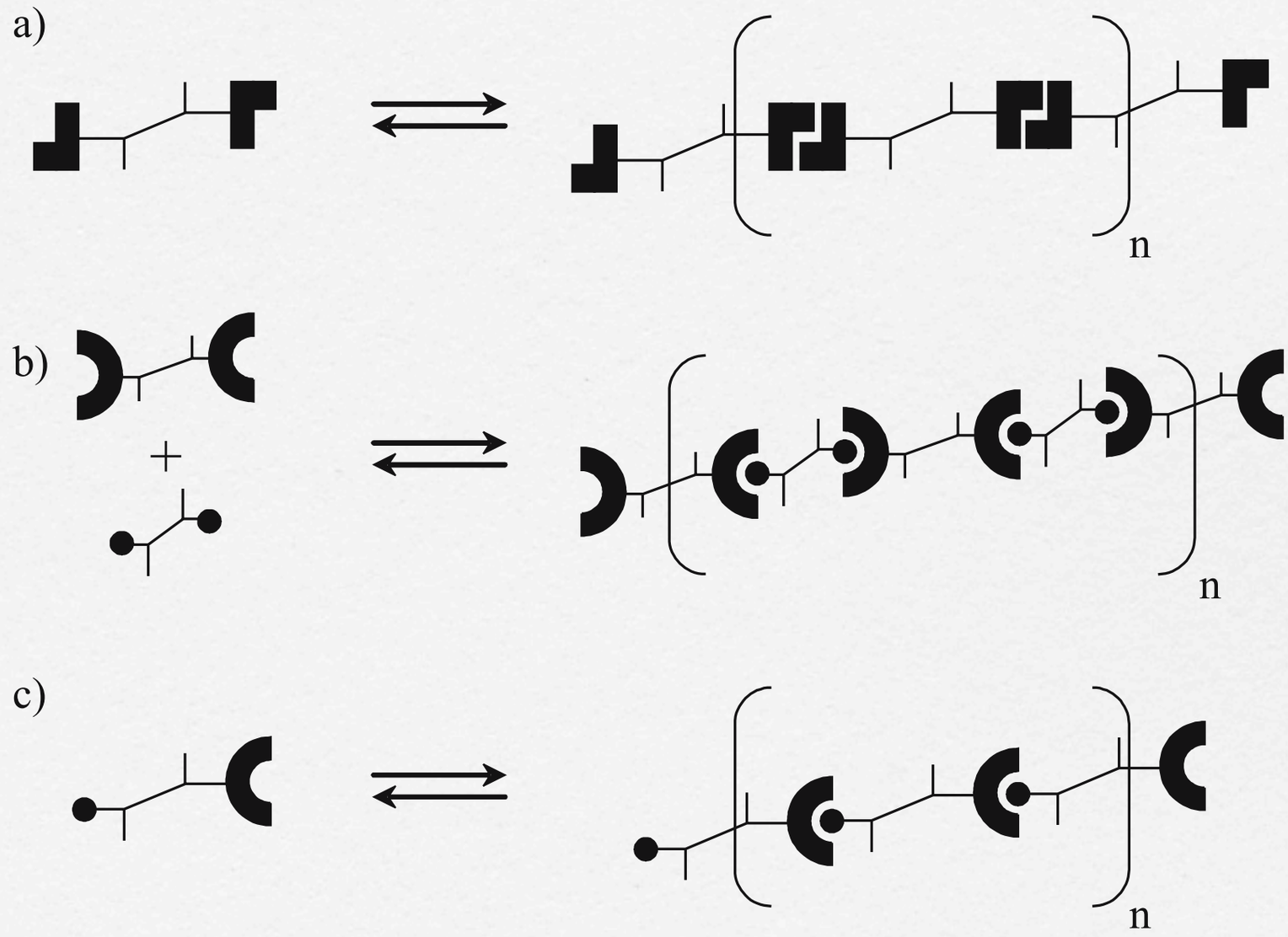


Fig. 1 Schematic representation of supramolecular polymers assembled from self-complementary AA (**a**) or AB (**c**) monomers or complementary A – A + B – B (**b**) monomers

forming polymers

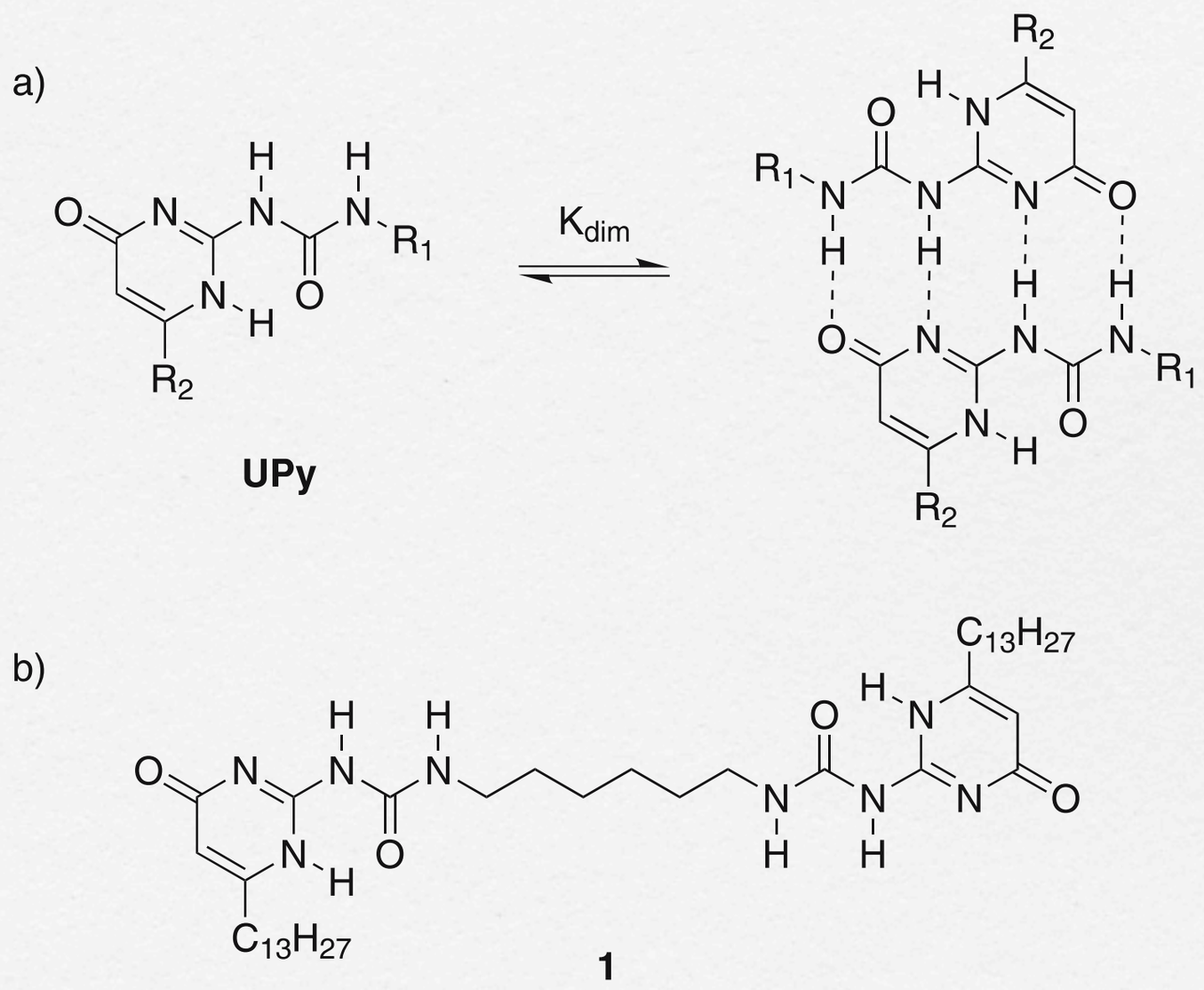
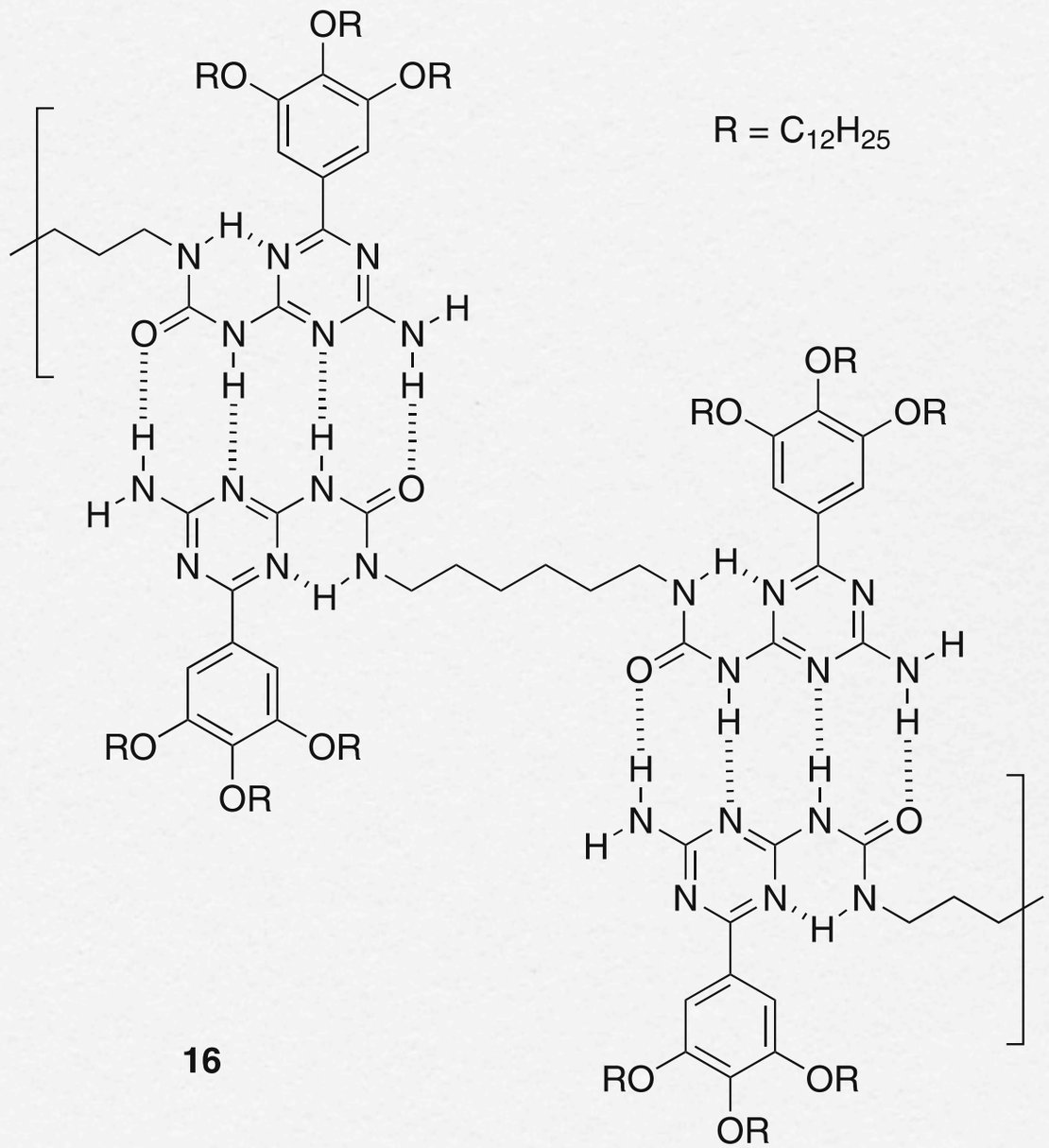


Fig. 2 Structure of UPy dimer (**a**) and monomer 1 (**b**)

forming polymers



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forming polymers

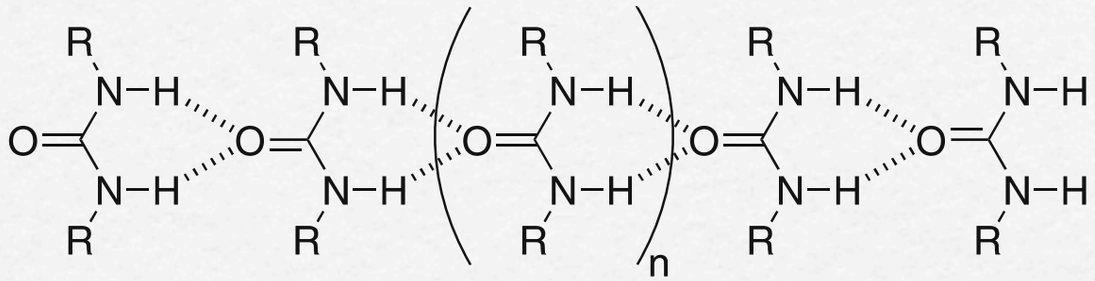


Fig. 23 Hydrogen bonding pattern of dialkyl ureas

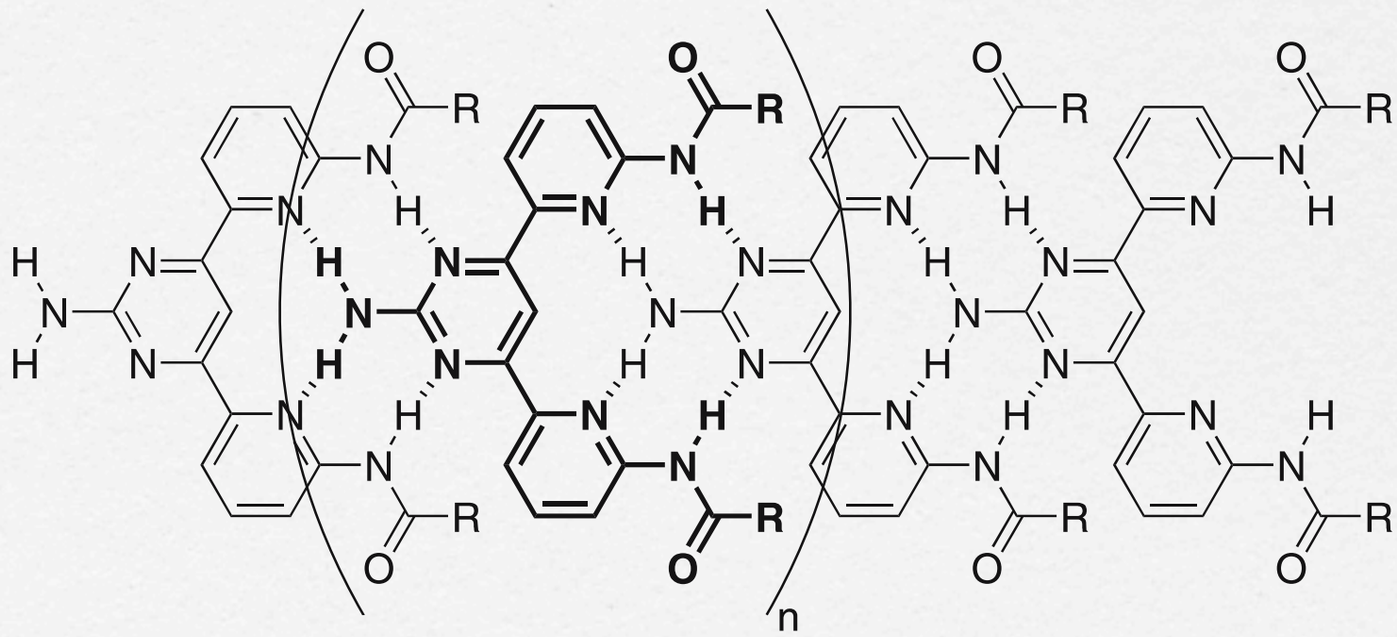
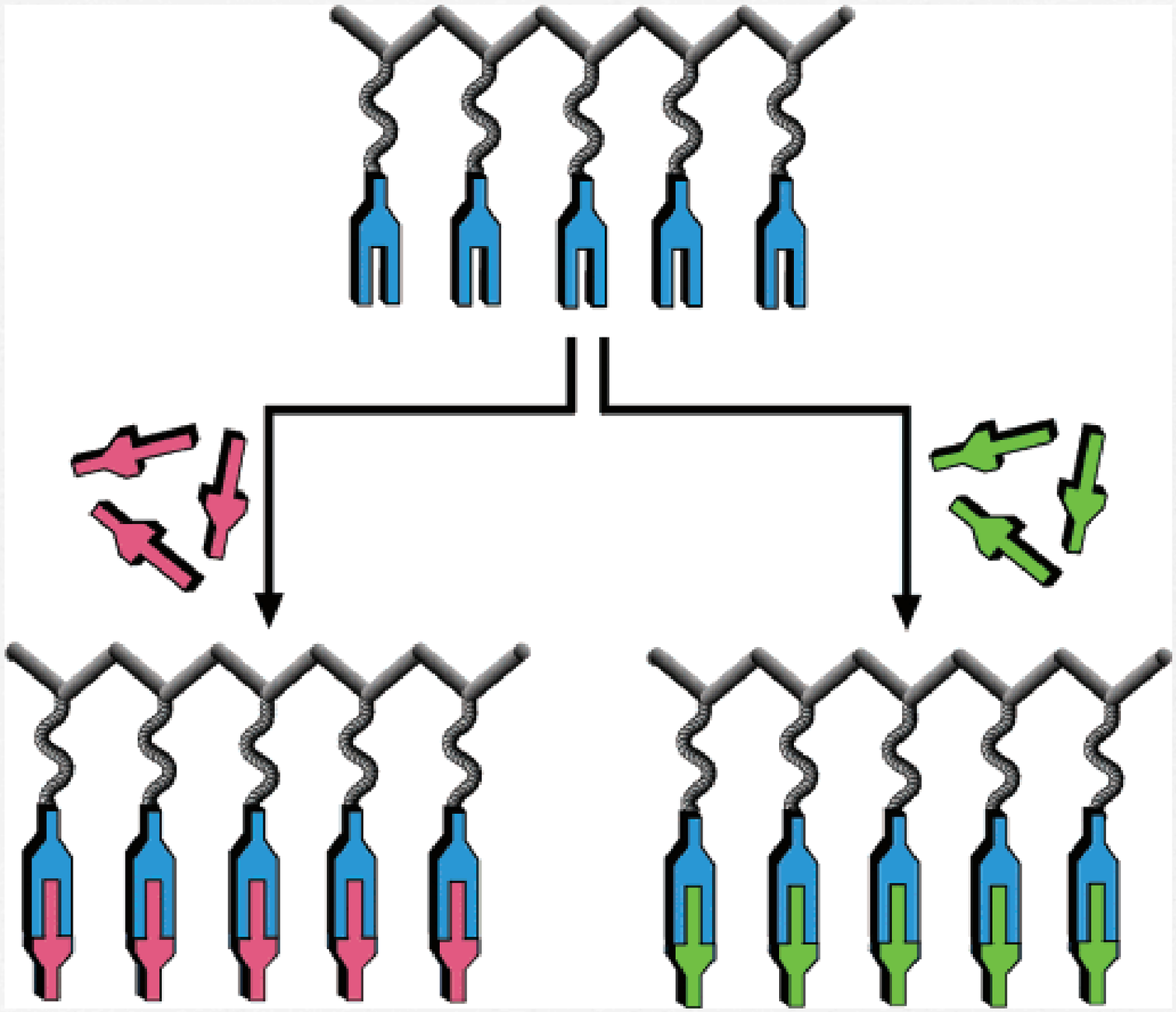
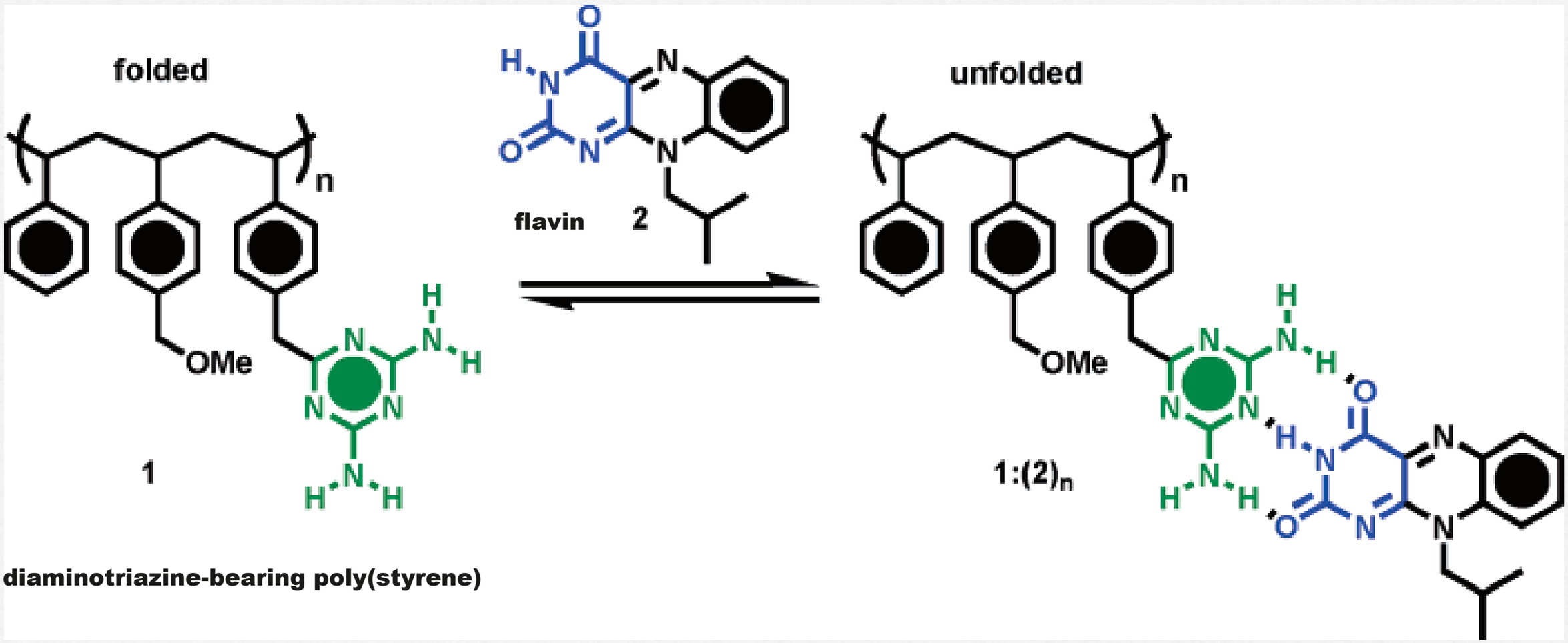


Fig. 24 Hydrogen bonding pattern of supramolecular polymer **19**

functionalization of polymers



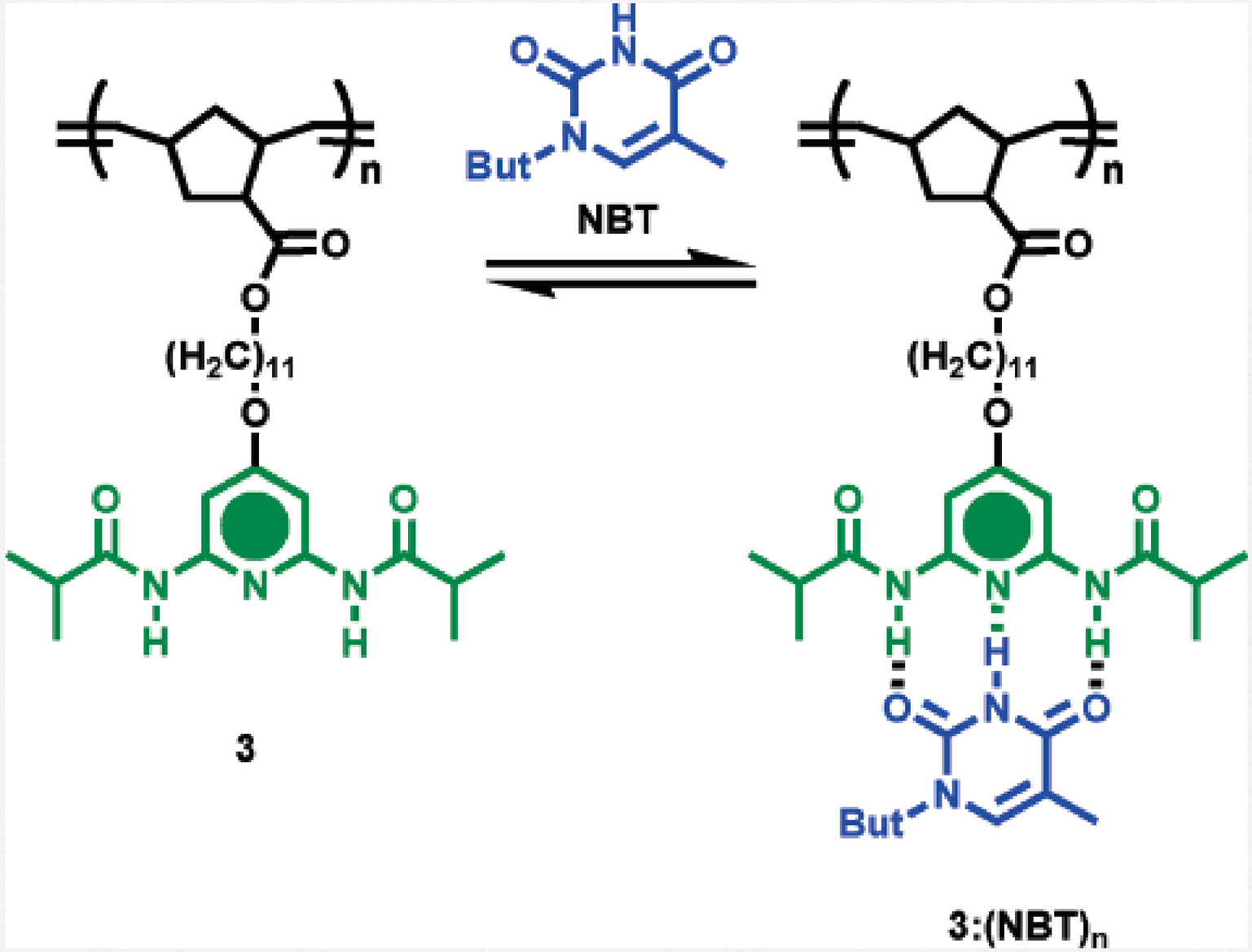
functionalization of polymers



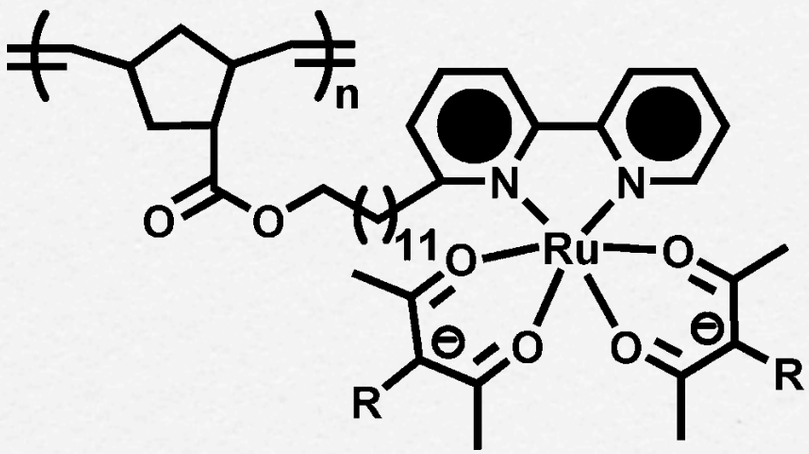
diaminotriazine-bearing poly(styrene)

folded state (due to triazine dimerization)

functionalization of polymers



functionalization of polymers



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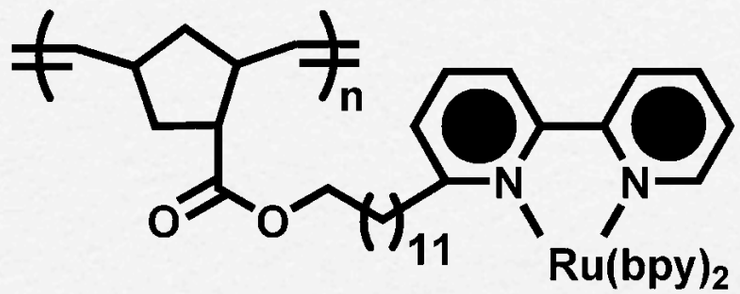

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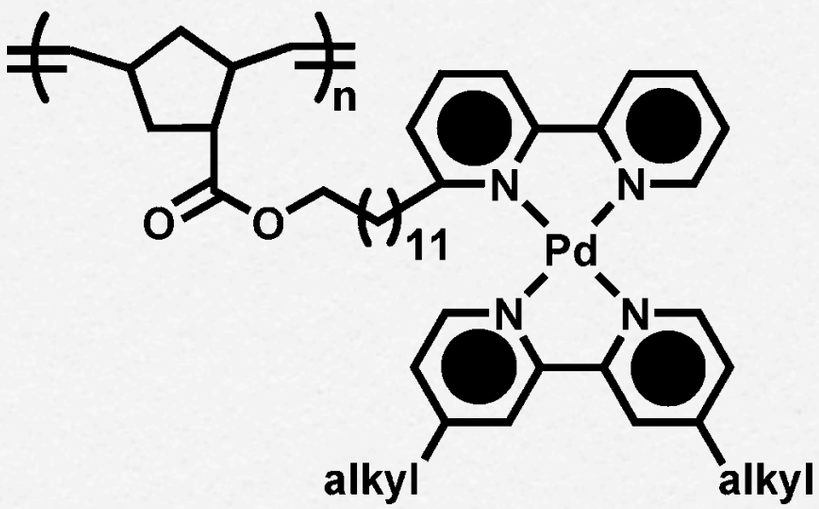

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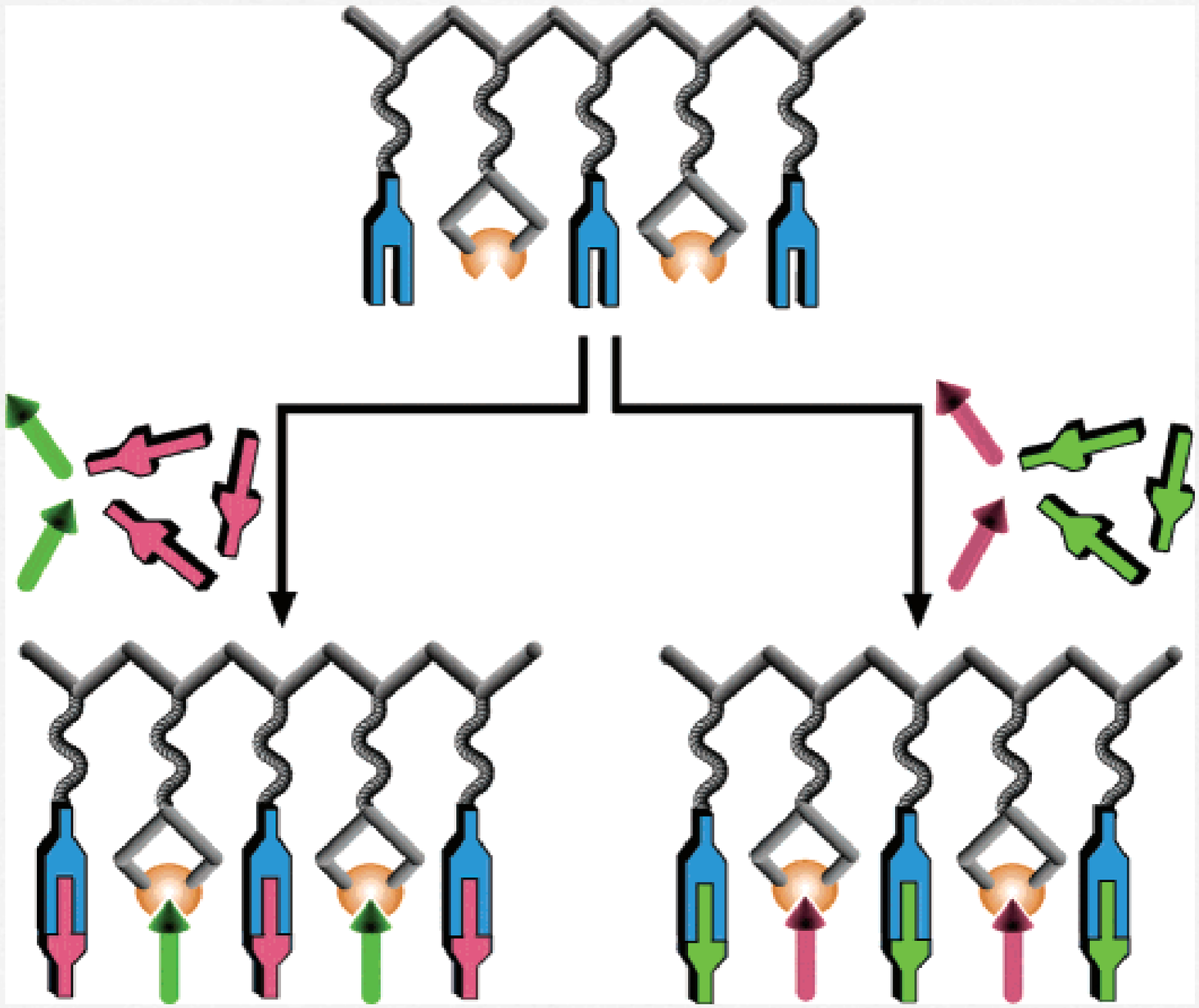
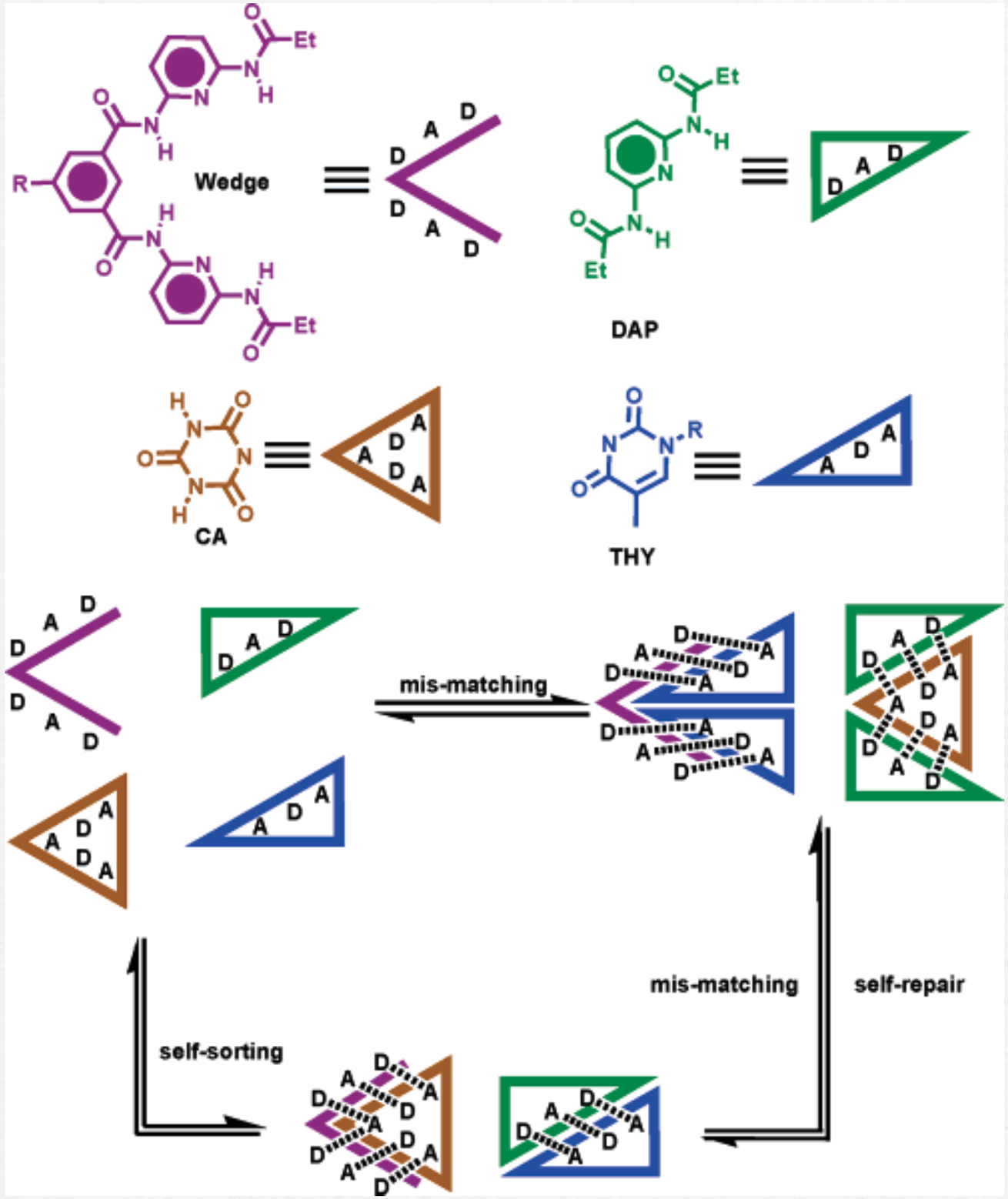
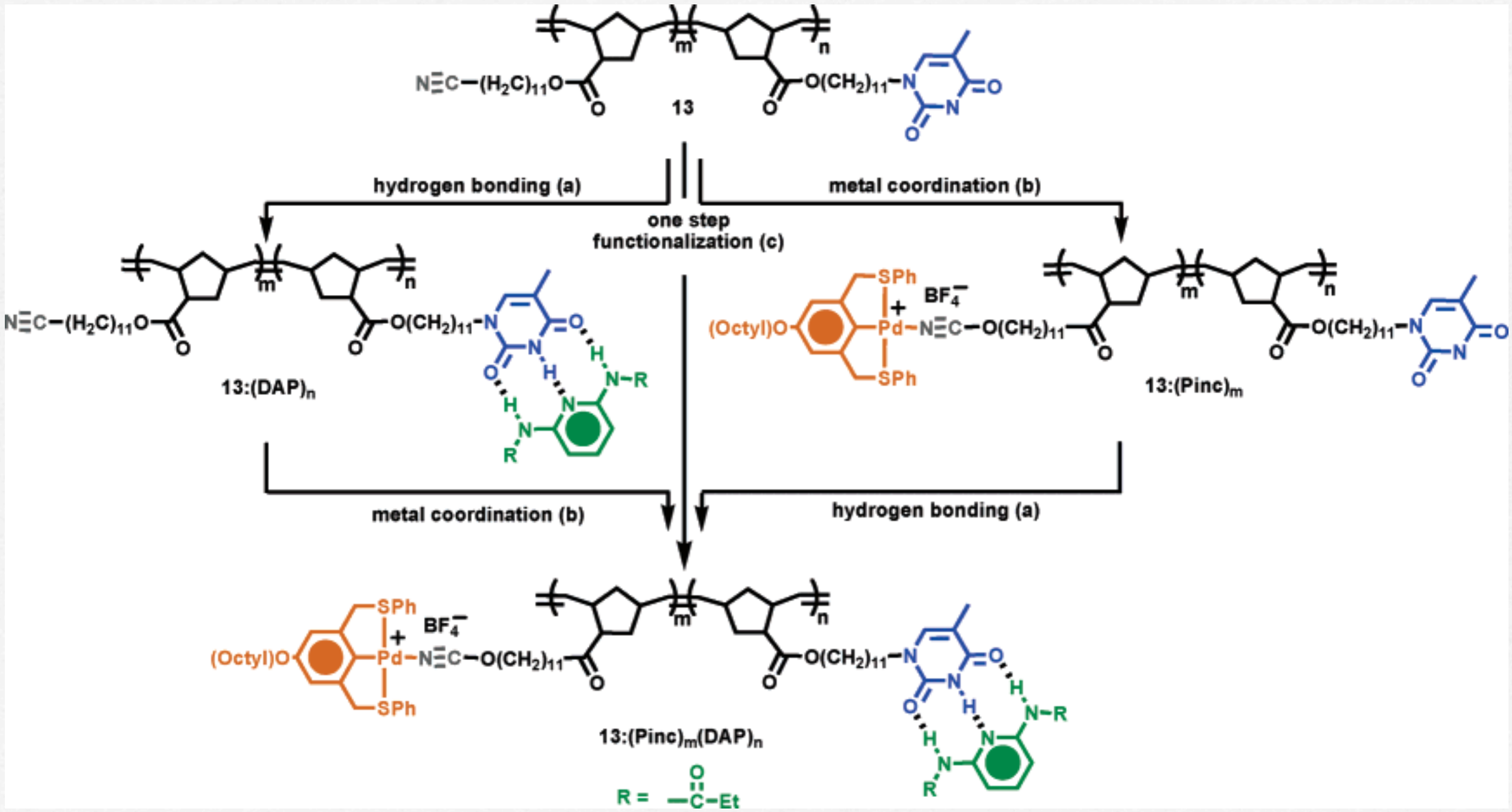
functionalization of polymers



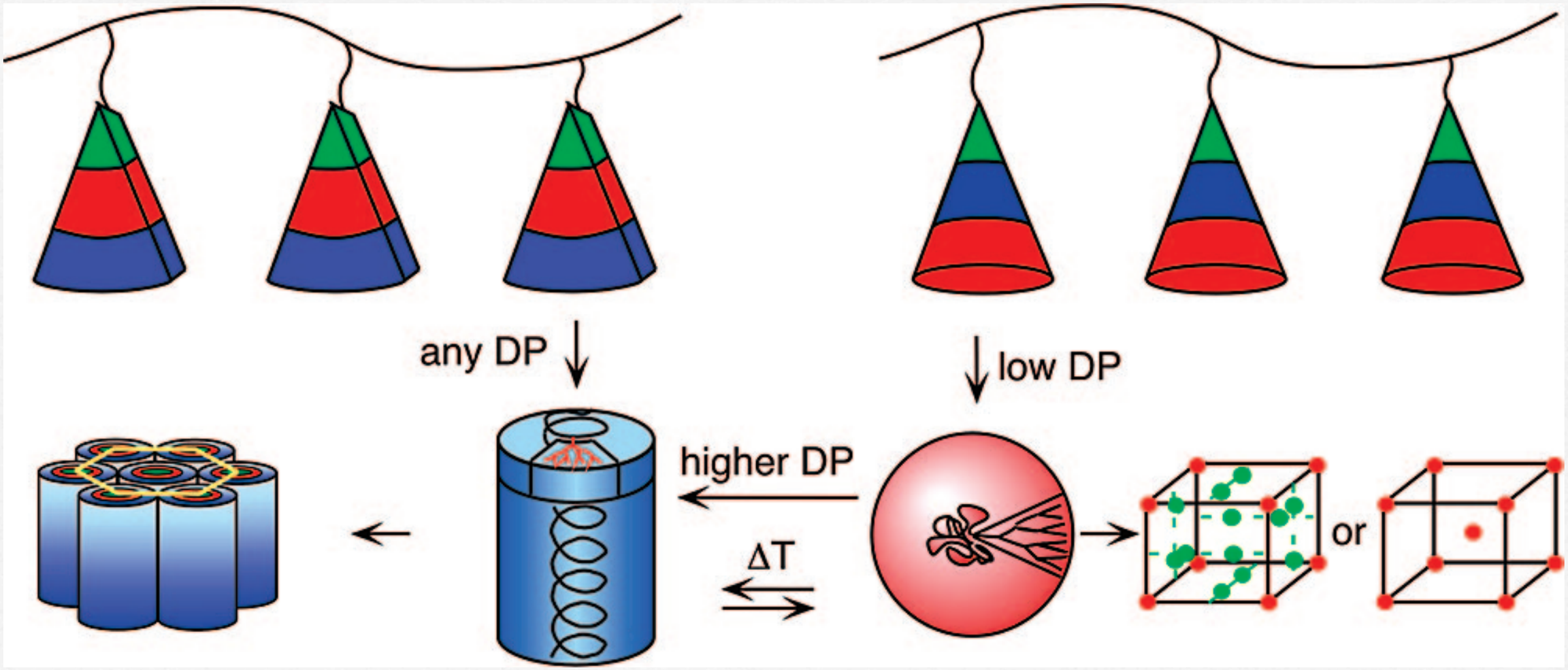
self-sorting



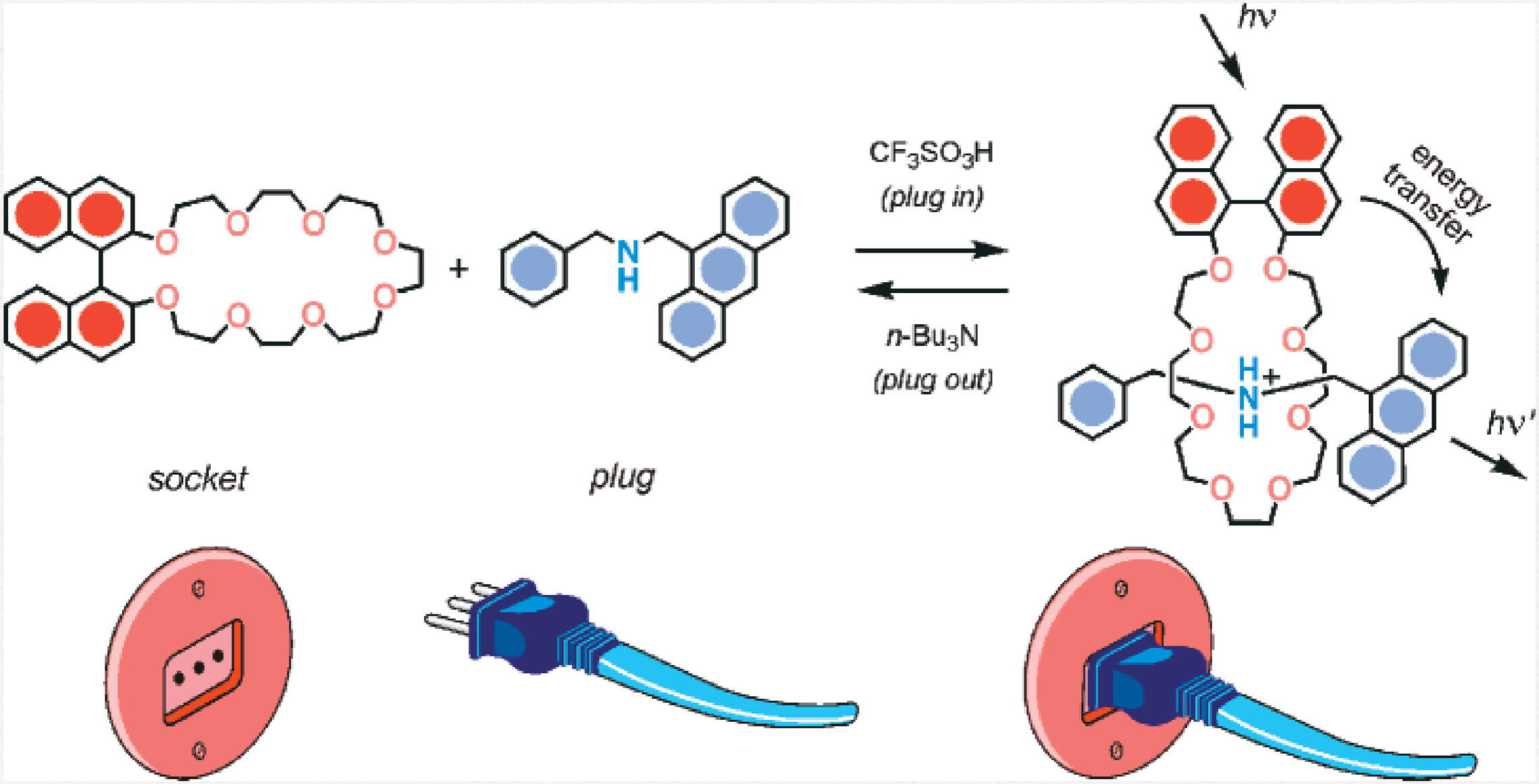
block copolymers



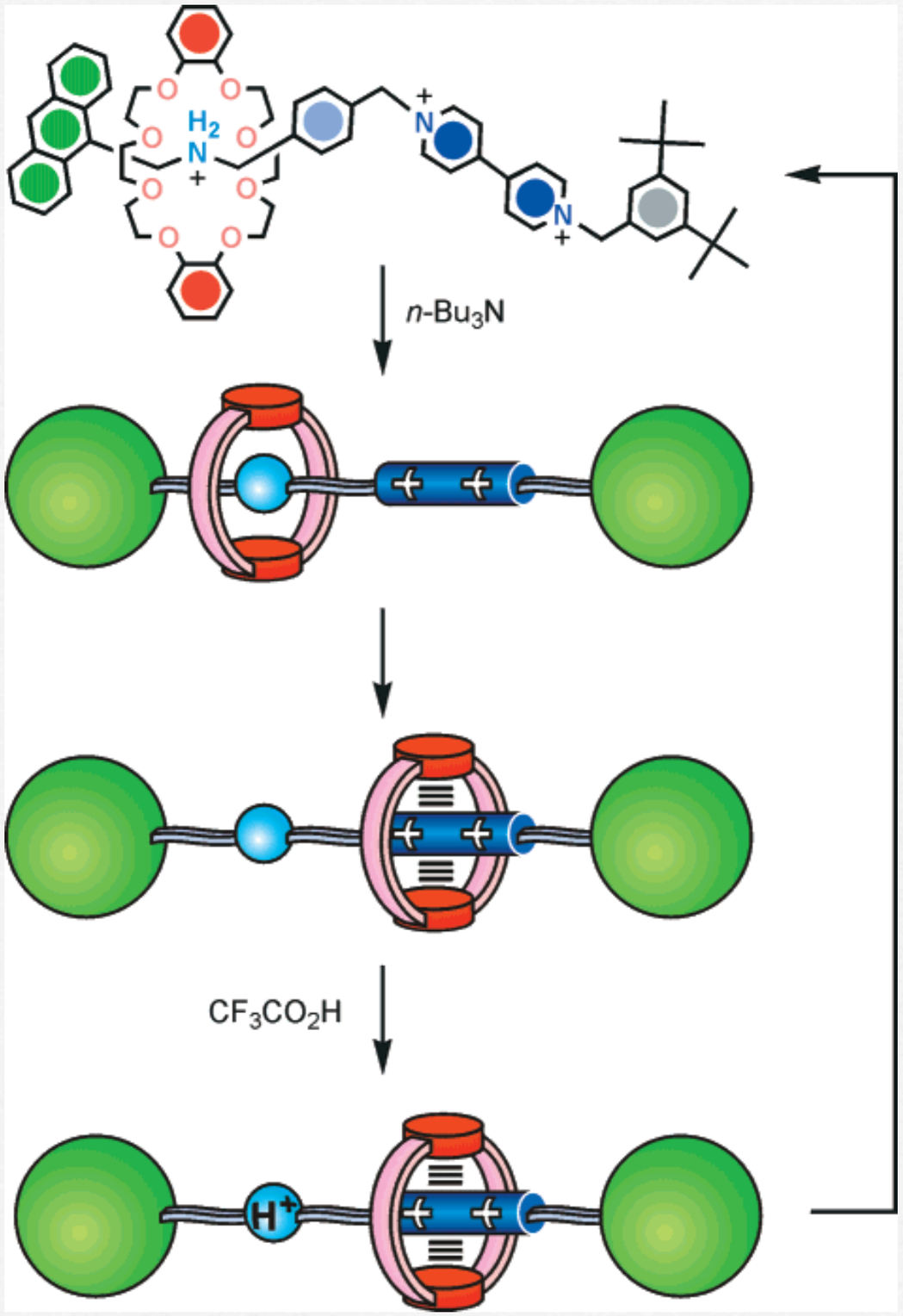
self-organizable polymers



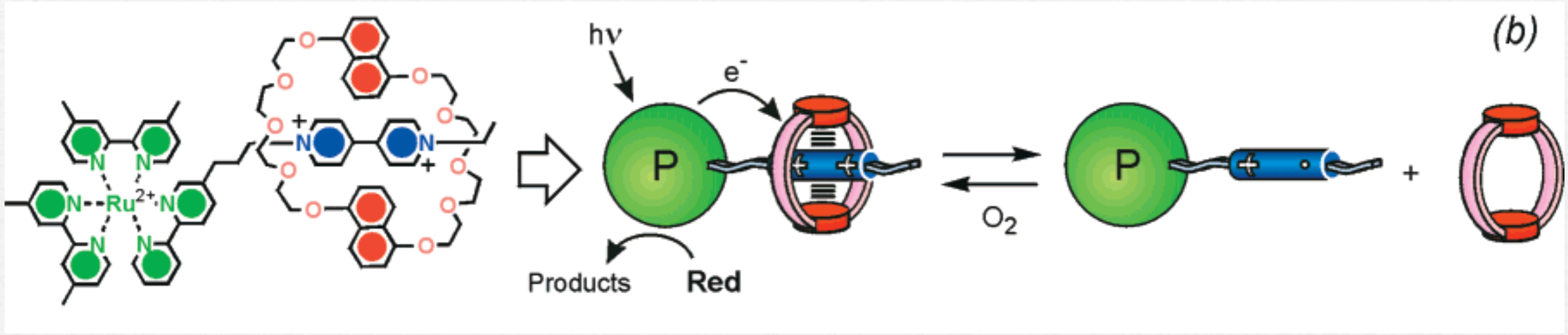
molecular machines?



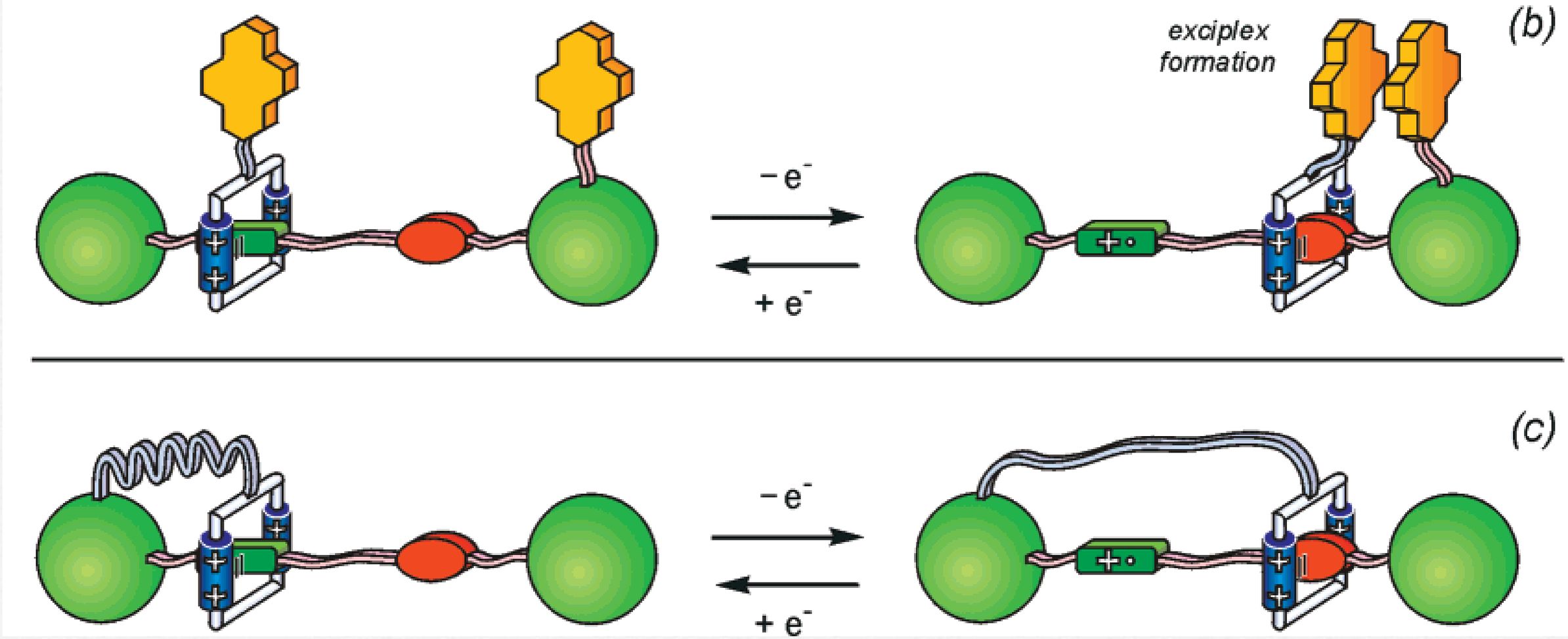
molecular shuttle



light driven dethreading



prospectives



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