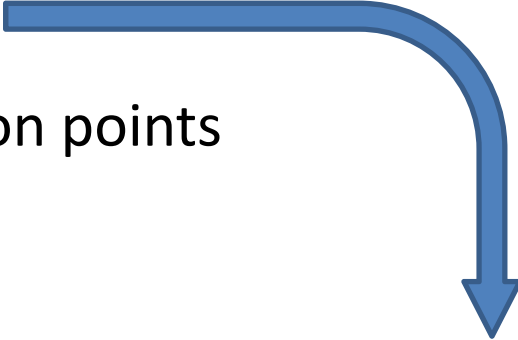


Neutral (usually organic) guests

Guest features

- Lack of strong electrostatic interactions
- Large surface area and volume
- Variety of shapes and interaction points



Dispersion and hydrophobic/solvophobic interaction may become more important than point interactions

Large host are needed to accommodate large guests

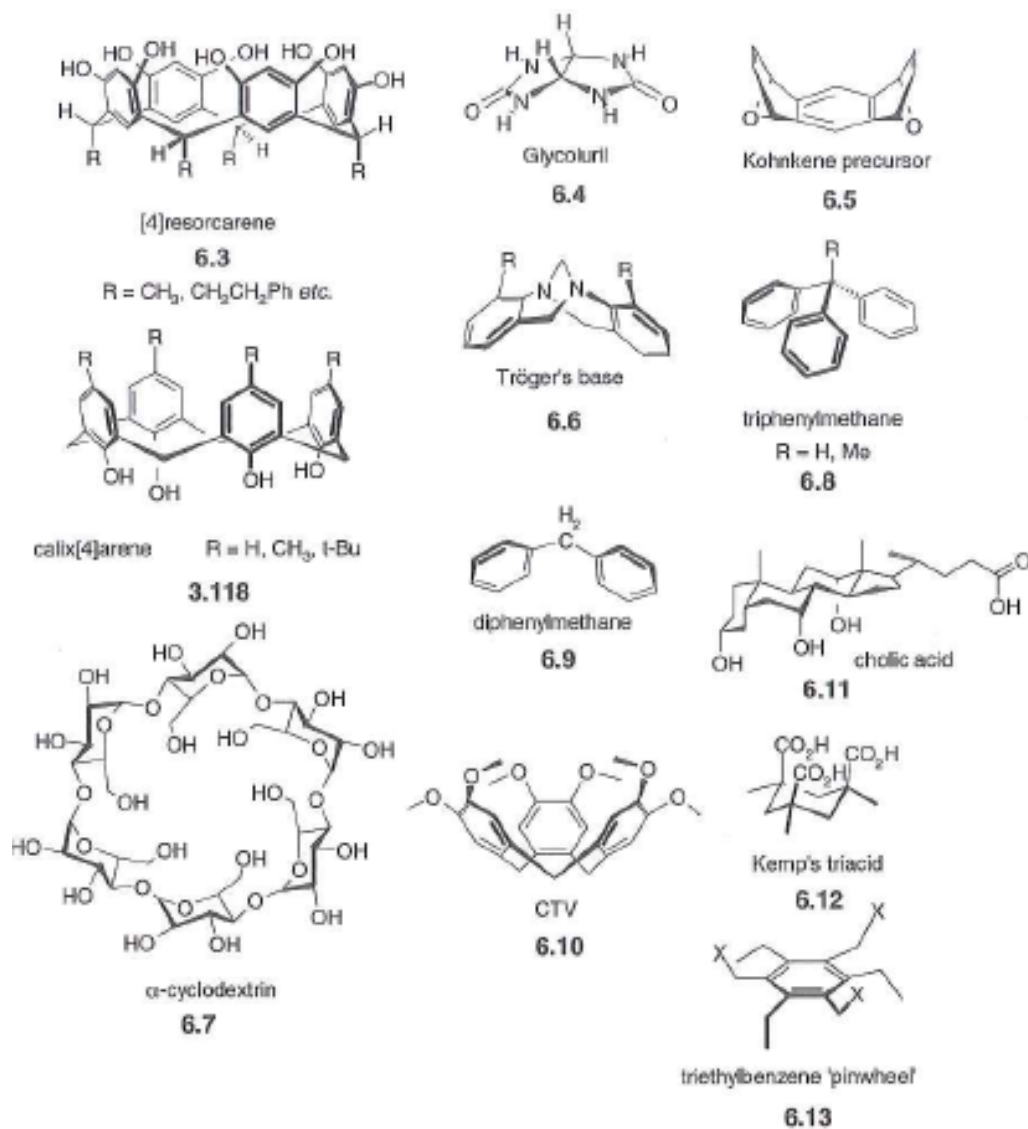


Concave host, with inside curvature, increase the contact area

(if contact between a sphere and a plane is taken as 1, contact with an emispherical cavity is increase by 4, with a cylindrical cavity by 6 and with a sperical cavity by 8

Building blocks

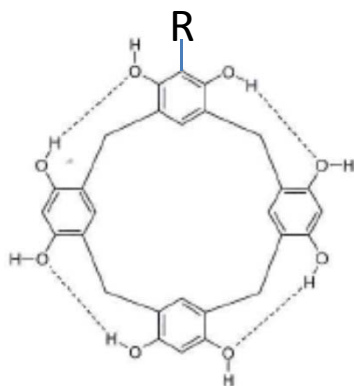
Cavitands



A cavitand is a host molecule possessing an intrinsic cavity capable to act as a container

Calixarenes and resorcarenes

Hydrophobic recognition in water


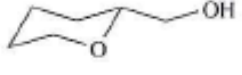

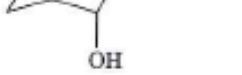
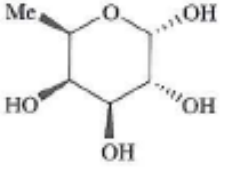
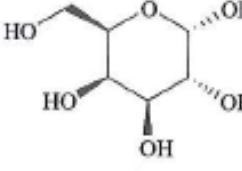


6.20a: R = H

6.20b: R = Me

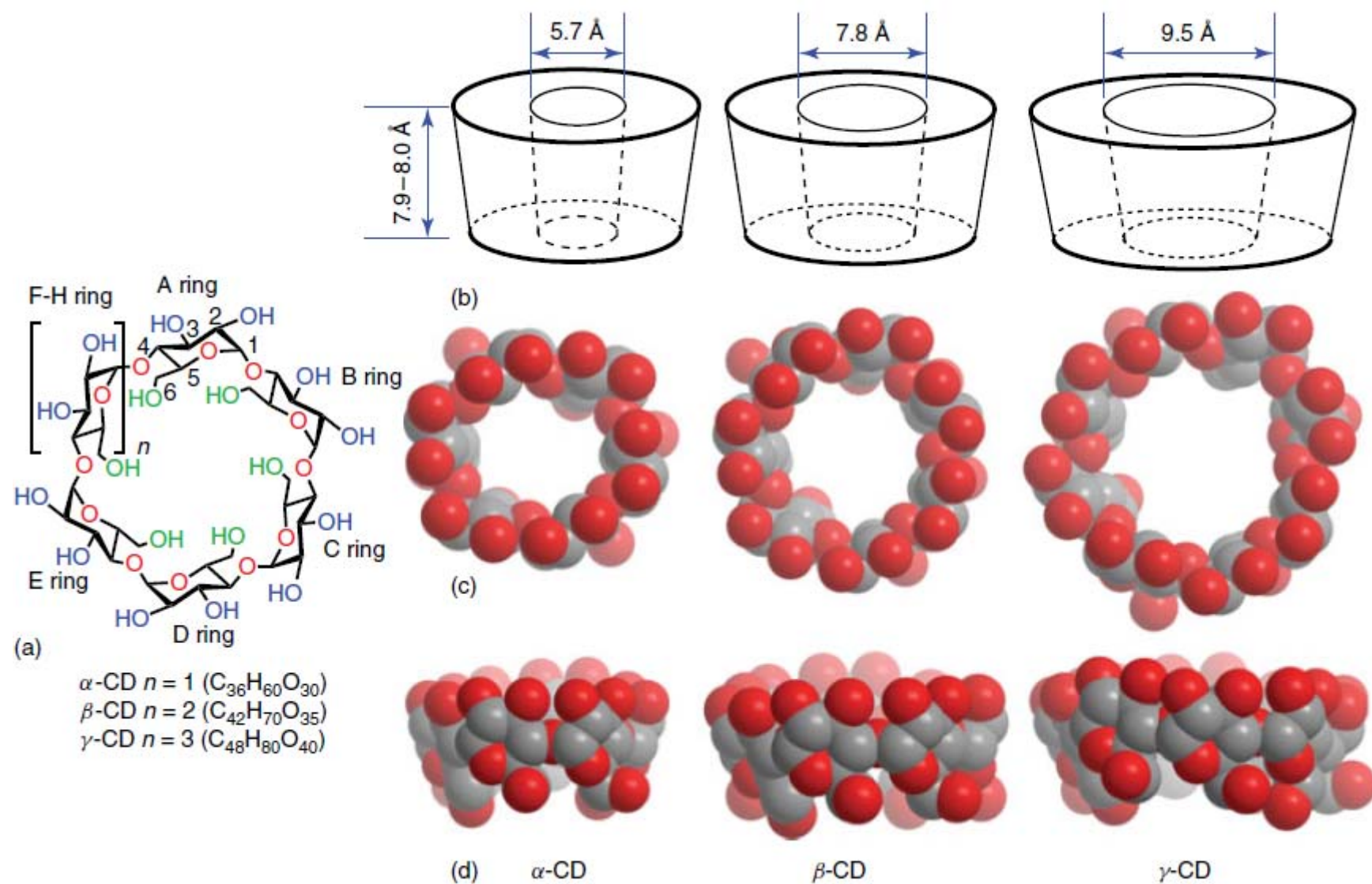
6.20c: R = OH

Table 6.1 Binding constants for sulfonated resorcarenes with various alcohol guests.

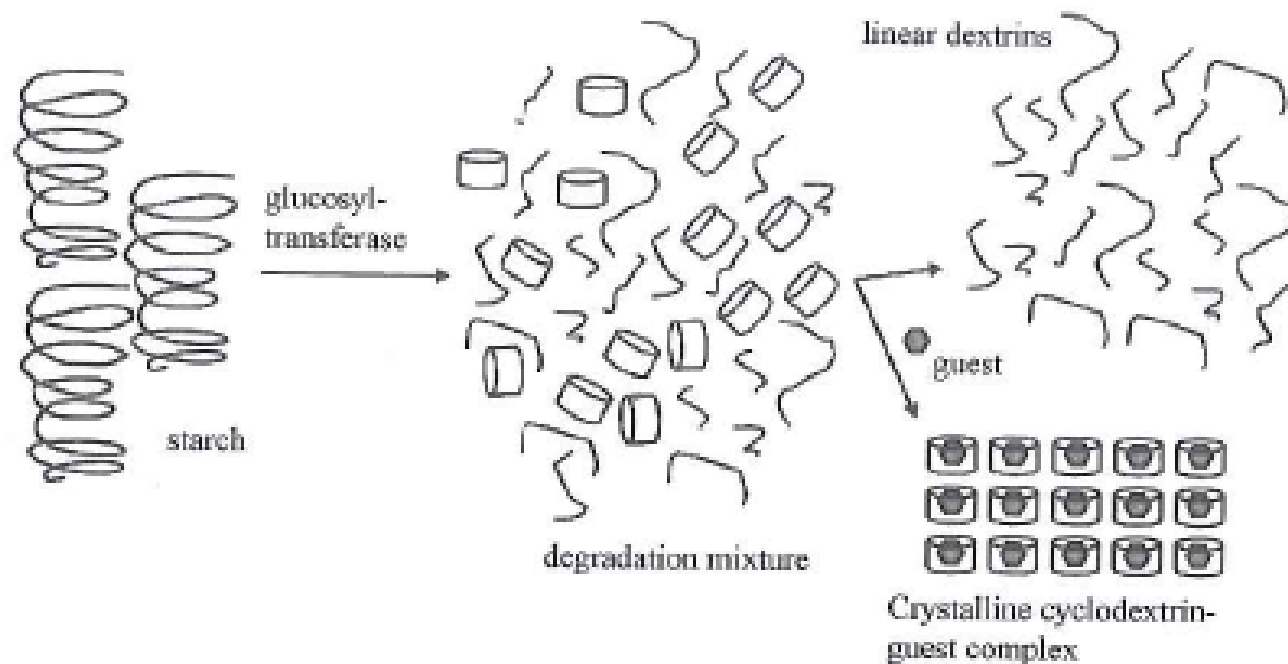
Guest	number	K/M^{-1}		
		6.20a	6.20b	6.20c
Bu ⁿ OH	6.21	4.2	19	24
	6.22	30	200	92
	6.23	29	180	160
	6.24	16	125	64
	6.25	14	80	80
	6.26	1.8	6.0	8.4
	6.27	~0	~0	~0

Water, 25 °C

Cyclodextrins

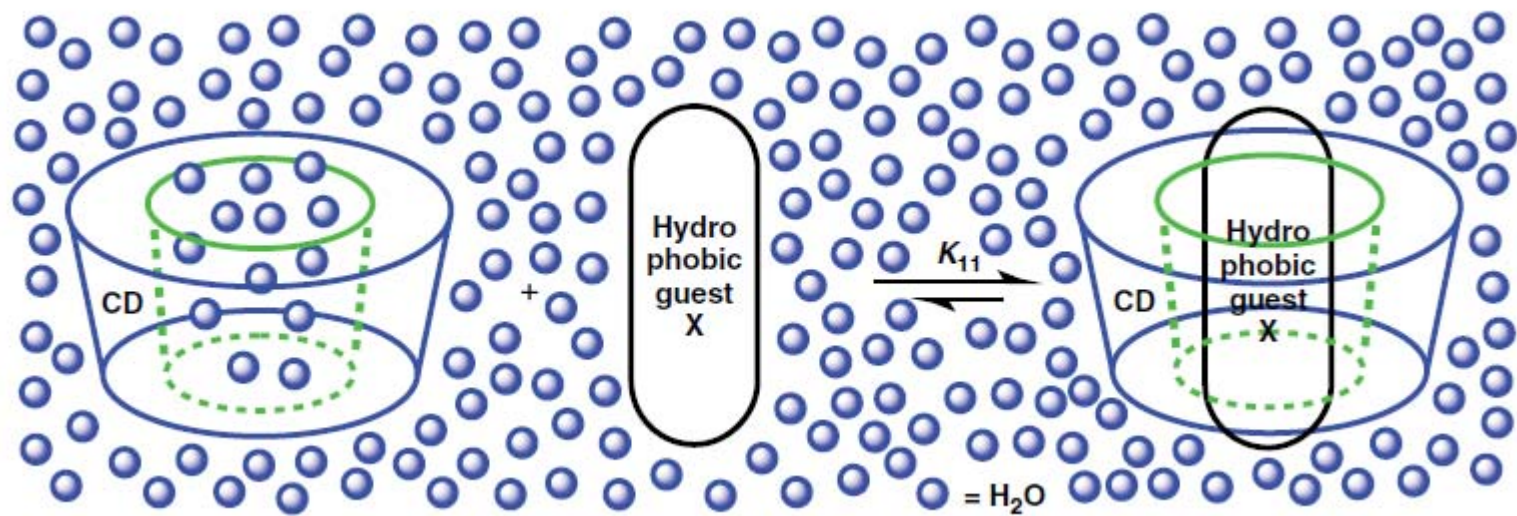


Cyclodextrins: preparation

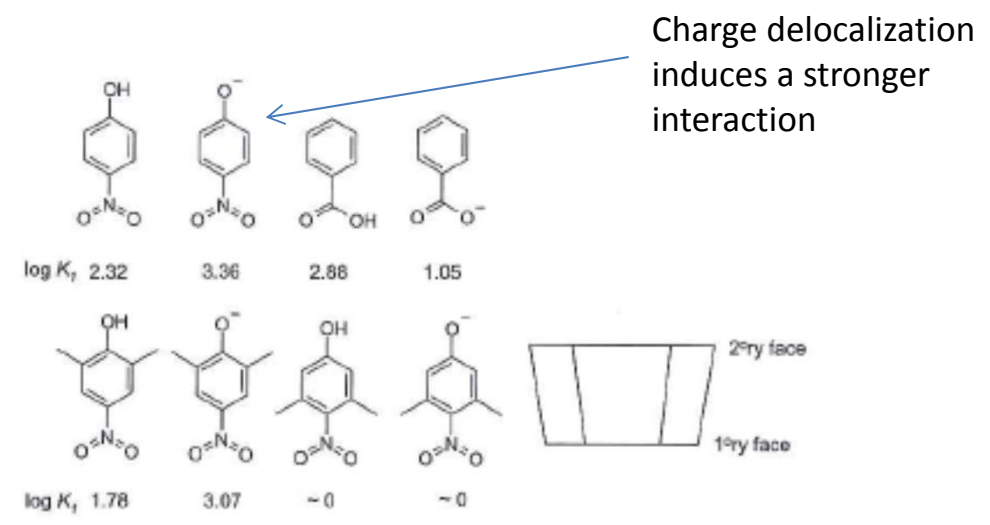


Enzymatic degradation and cyclization of starch followed by selective precipitation of inclusion compounds

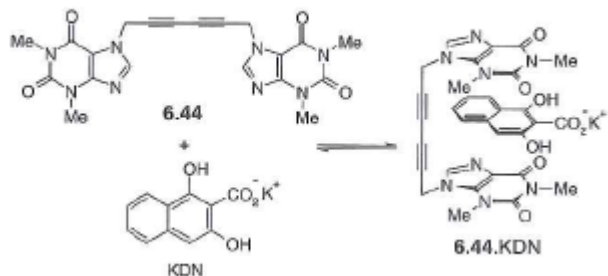
Cyclodextrins: inclusion



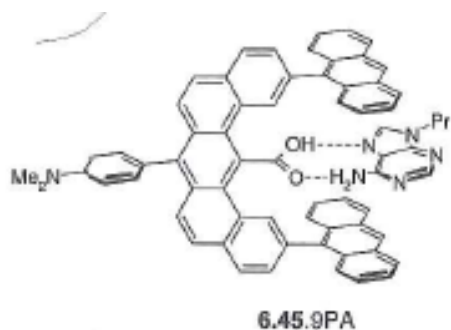
- Steric fit
- Release of high energy water/hydrophobic effect
⇒ non classical (semipolar interior)
- Dispersive interactions
- Dipole-dipole interactions
- H-bonding



Molecular tweezers

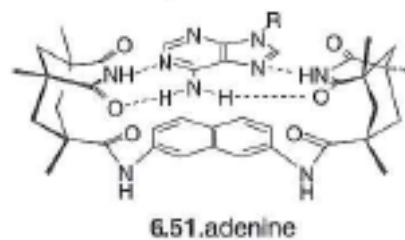
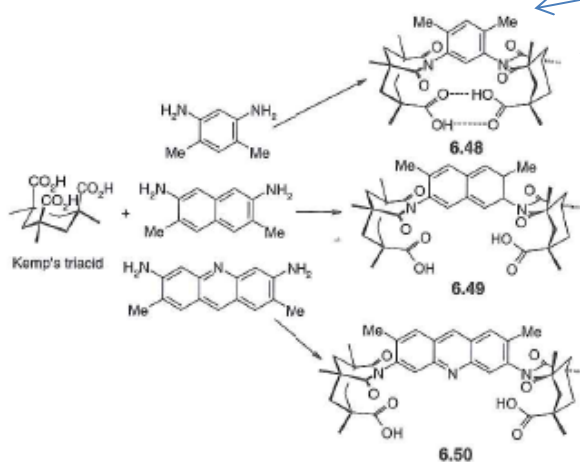


Suggested from the observation that hydrolysis of aspirine in water is inhibited by caffeine



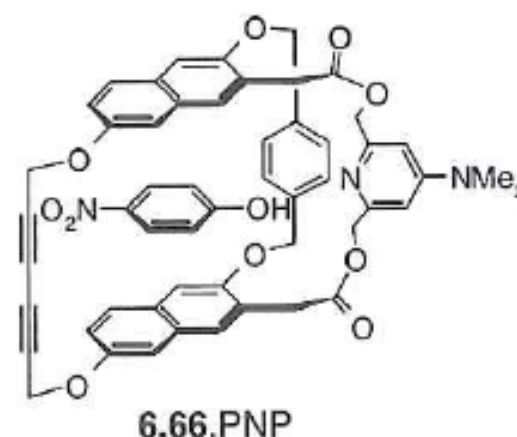
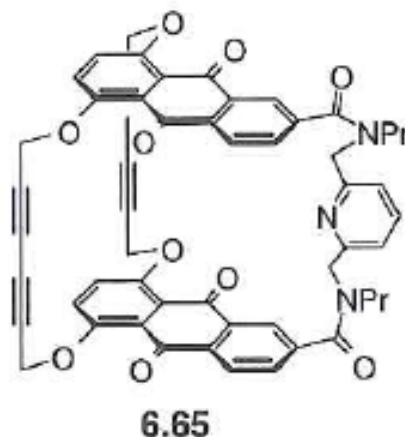
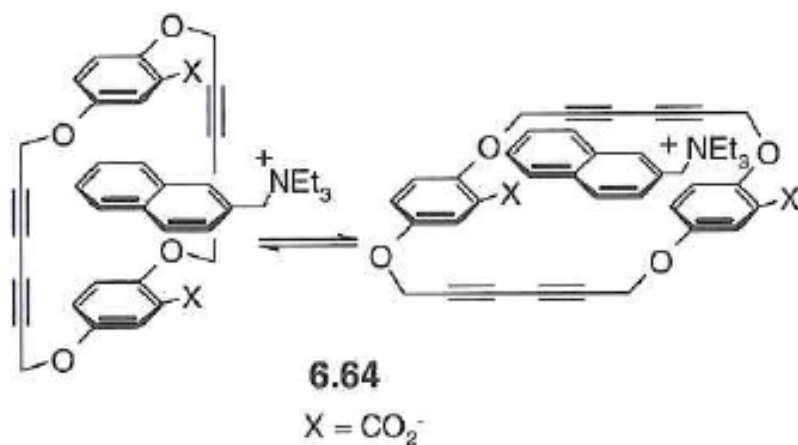
Esterification of the 6.45 carboxylic group or methylation of PA nitrogen dramatically decreases affinity.

Rigidifying groups



Ciclophanes

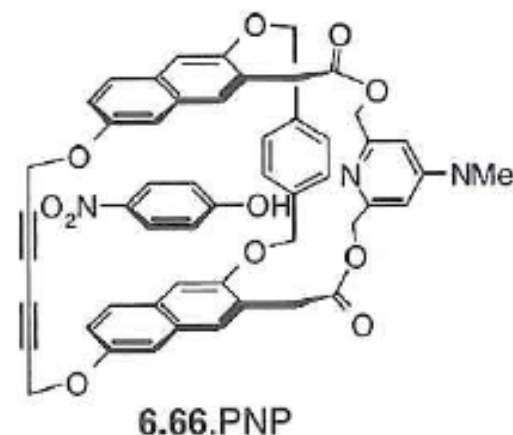
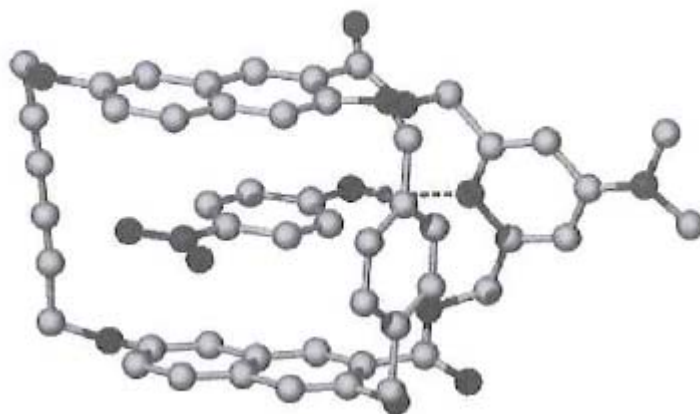
Cyclization of tweezers (cycle of aromatic rings)



- Cyclization of **6.44**
- Additional ion pairing interaction
- $K_{\text{ass}} = 55 \text{ M}^{-1}$ (CDCl₃)
- Cavity is too small
- Open conformation with poor π - π interaction
- More rigid host
- Additional H-bond acceptor
- K_{ass} low with different guests
- Cavity is too large
- Poor π - π interaction
- Smaller cavity
- One shorter bridge
- Additional face-to-edge aromatic interaction
- $K_{\text{ass}} = 9.6 \times 10^4 \text{ M}^{-1}$ (CDCl₃)
- Cavity is too large
- Poor π - π interaction

Ciclophanes

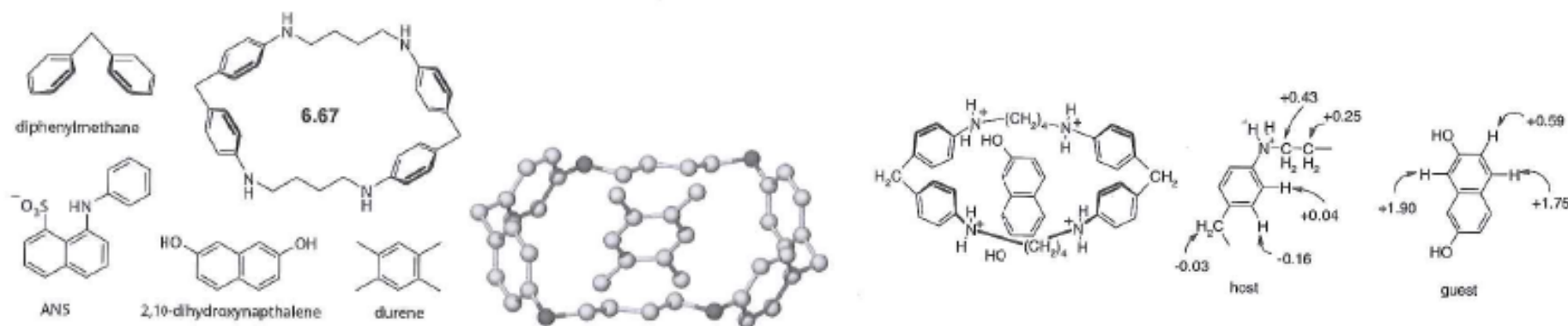
Cyclization of tweezers (cycle of aromatic rings)



- | | | |
|--|--|---|
| <ul style="list-style-type: none"> • Cyclization of 6.44 • Additional ion pairing interaction • $K_{\text{ass}} = 55 \text{ M}^{-1}$ (CDCl_3) | <ul style="list-style-type: none"> • More rigid host • Additional H-bond acceptor • K_{ass} low with different guests | <ul style="list-style-type: none"> • Smaller cavity • One shorter bridge • Additional face-to-edge aromatic interaction • $K_{\text{ass}} = 9.6 \times 10^4 \text{ M}^{-1}$ (CDCl_3) |
| <ul style="list-style-type: none"> • Cavity is too small • Open conformation with poor π-π interaction | <ul style="list-style-type: none"> • Cavity is too large • Poor π-π interaction | <ul style="list-style-type: none"> • Cavity is too large • Poor π-π interaction |

Ciclophanes

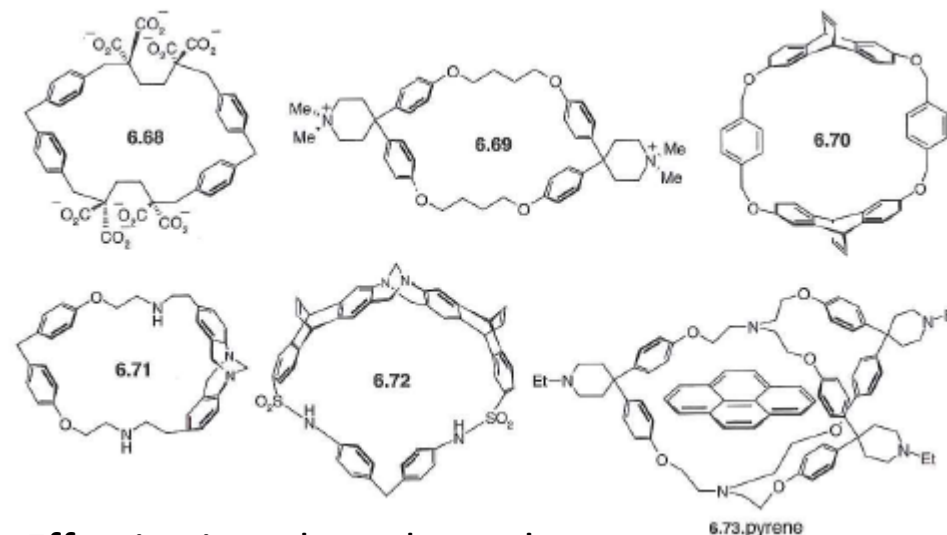
Cyclization of tweezers (cycle of aromatic rings)



- Diphenylmethane as curvature motif
- Soluble in water at pH < 2
- Binds several organic guests
- Crystallized with durene
- Well studied by NMR

Improvements

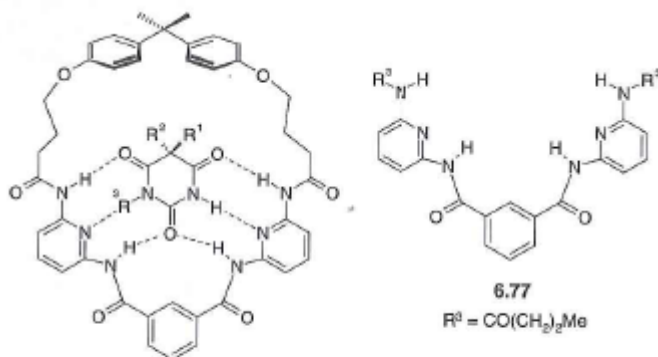
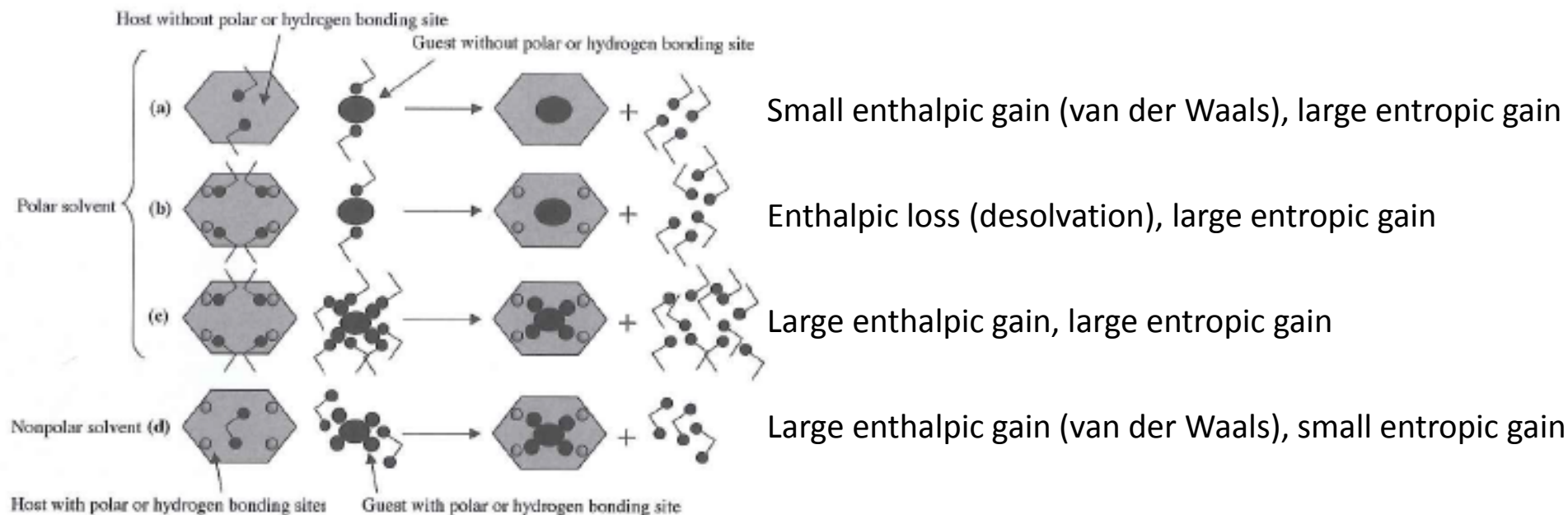
- Alkylation of amines (not shown), water solubility at pH 7
- **6.68-6.69**: charges farther from the cavity
- **6.70-6.72**: more rigid cavity
- **6.73**: 3D cavity



Effective in polar solvents!

Ciclophanes

Binding of polar guests with point interactions



- 6.75 in 6.76
- a $R^1 = R^2 = R^3 = \text{H}$
- b $R^1 = R^2 = \text{Et}, R^3 = \text{H}$
- c $R^1 = \text{Et}, R^2 = \text{Ph}, R^3 = \text{H}$
- d $R^1 = \text{Et}, R^2 = \text{Ph}, R^3 = \text{Me}$

- 6.75b $K_{\text{ass}} = 1.37 \times 10^6 \text{ M}^{-1}$ (CDCl_3)
- 6.75d $K_{\text{ass}} = 6.8 \times 10^2 \text{ M}^{-1}$ (CDCl_3)
- 6.77d $K_{\text{ass}} = 2.8 \times 10^4 \text{ M}^{-1}$ (CDCl_3)

Ciclophanes

Multipoint interactions

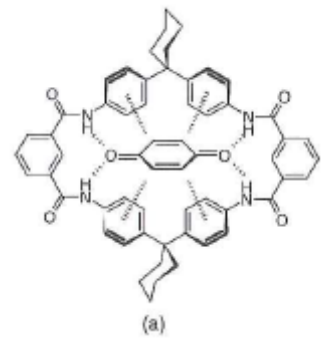
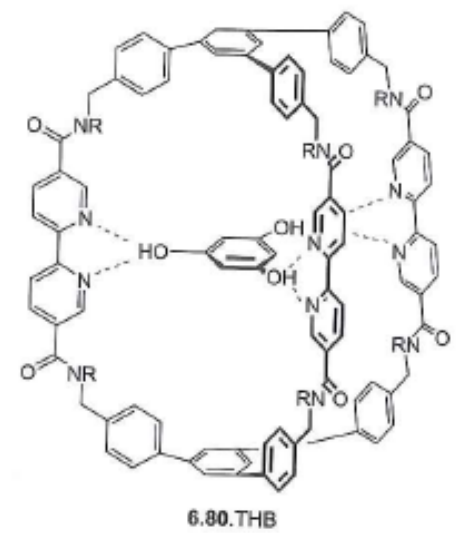
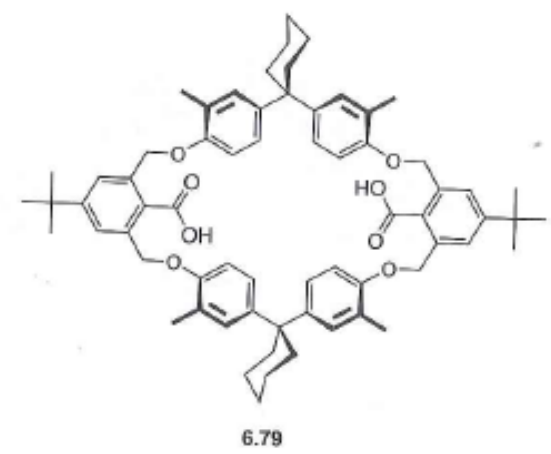


Table 6.6 Binding constants (M^{-1}) of hydrogen-bonding guests by host **6.78** ($R = NMe_2Cl^-$).³⁴

Guest	K (water)	K (chloroform)
	<5	230
	94	850
	71	1.0×10^6
	760	—



$$K_{\text{ass}} = 1.1 \times 10^4 \text{ M}^{-1} (\text{CDCl}_3)$$

