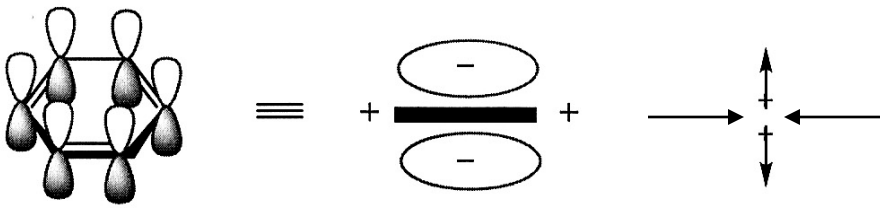
Physical basis for the π-cation effect: an ion- quadrupole interaction



Gas-phase ion studies of benzene-cation complexes:
Sumner, Nishizawa, and Kebarle, *J. Phys. Chem.*, **1981**, *85*, 1814

ion	Li^+	Na^+	K^+	Rb^+	NH_4^+	$N(Me)_4^+$	H_2O	NH_3
$\Delta H_f°$ (benzene-M^+)	38	28	19	16	19	9	1.8	1.4

Computational studies of 2:1 benzene-cation complexes in the gas and aqueous phase:
Kumpf and Dougherty, *Science*, **1993**, *261*, 1708

ion	Li^+	Na^+	K^+	Rb^+
ΔE^{bind}_{gas} (benzene$_2$-M^+)	47.7	38.6	35.4	28.7
G^{sol}_{aq} (M^+)	122	98	81	75
$\Delta\Delta G^{sol}_{aq}$ (benzene$_2$-M^+) (relative to K^+)	30	15.9	0	4.4

$$\Delta\Delta G^{sol}(M_1 \text{ vs. } M_2) = \Delta\Delta E^{bind}_{gas} + \Delta G^{sol}_{aq}(M^+) - \Delta G^{sol}_{aq}(\text{benzene}_2\text{-}M^+)$$

Gas-phase data and computations suggest K^+ ion is selectively (de)solvated by multiple aromatic rings; implication for ion channels and transmembrane transport

Solvent effects on weak intermolecular forces

1. The "classic" hydrophobic effect

$$\mathbf{X}\bullet(H_2O)_m + \mathbf{Y}\bullet(H_2O)_n \longrightarrow \mathbf{X}\bullet\mathbf{Y} + (H_2O)_{m+n}$$

$$\Delta H_a^\circ \gtrsim 0;\ \Delta S^\circ > 0$$

2. Enthalpy-Entropy compensation

$$\Delta G_a^\circ = \Delta G_{complexation} + \Delta G_{solvation}$$

$$\Delta H_a^\circ = \Delta H_{complexation} + \Delta H_{solvation}$$

$\Delta H_{complexation}$ typically < 0

$\Delta H_{solvation}$ $\rightarrow$ $H_s(\mathbf{X}\bullet\mathbf{Y}) + H_{solv\text{-}solv} - H_s(\mathbf{X}) - H_s(\mathbf{Y})$

enthalpy of desolvation (binding sites)

$$\Delta S^\circ = \Delta S_{complexation} + \Delta S_{solvation}$$

$\Delta S_{complexation}$ $\rightarrow$ $S(\mathbf{X}\bullet\mathbf{Y}) - S(\mathbf{X}) - S(\mathbf{Y})$

$\Delta S_{solvation}$ typically > 0

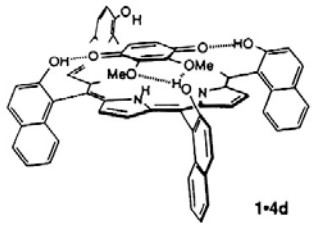
If binding is tight, $|\Delta S_{complex}|$ is large
If binding is loose, $|\Delta S_{complex}|$ is small

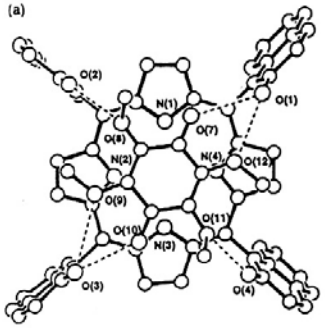
Main source of enthalpy-entropy compensation

Enthalpy-entropy compensation: Case Studies

Case II: Porphyrin hosts with variable guests in nonpolar solutions

Hayashi et al, *JACS*, **1997**, *119*, 7281





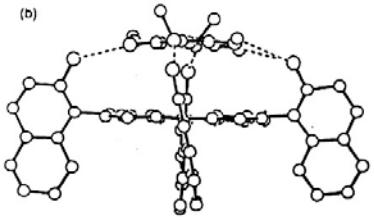


Figure 3. X-ray crystal structure of 1·4f complex. The solvent molecules are omitted for clarity: (a) top view of one molecular structure and (b) side view for one molecular structure.

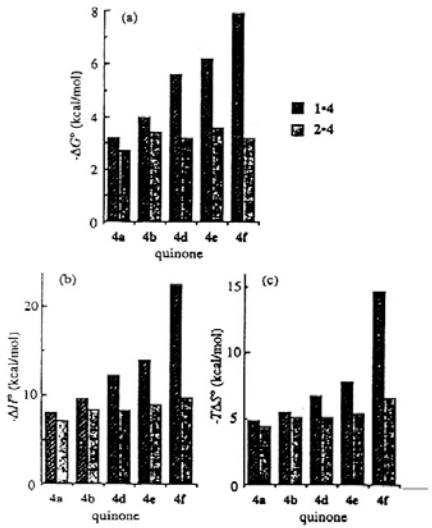
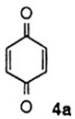
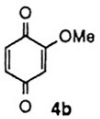
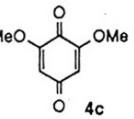
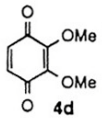
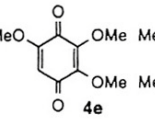
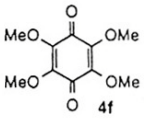


Figure 4. Comparison of thermodynamic parameters between **1**·**4** and **2**·**4** complexation in toluene at 298 K. (a) $-\Delta G°$, (b) $-\Delta H°$, and (c) $-T\Delta S°$.

Table 1. Binding Constants and Thermodynamic Parameters for Porphyrin–Quinone Complex[a] (in toluene)

porphyrin		 4a	 4b	 4c	 4d	 4e	 4f
1 (4 OHs)	K_a (M^{-1})[b]	(2.2 ± 0.1) x 10^2	(8.6 ± 0.1) x 10^2	(3.7 ± 0.1) x 10^3	(1.3 ± 0.1) x 10^4	(3.5 ± 0.1) x 10^4	(6.1 ± 1.1) x 10^5
	$\Delta H°$ (kcal/mol)	-8.1 ± 0.3	-9.6 ± 0.3	-10.7 ± 0.3	-12.2 ± 0.4	-14.0 ± 0.4	-22.7 ± 0.3
	$T\Delta S°$ (kcal/mol)[c]	-4.9 ± 0.3	-5.5 ± 0.2	-5.9 ± 0.3	-6.7 ± 0.4	-7.8 ± 0.3	-14.7 ± 0.3
	$\Delta G°$ (kcal/mol)[b]	-3.2 ± 0.1	-4.0 ± 0.1	-4.9 ± 0.1	-5.6 ± 0.1	-6.2 ± 0.1	-7.9 ± 0.2

2 HB's

2 HB's +
1 bifurcated HB

2 HB's +
2 bifurcated HB

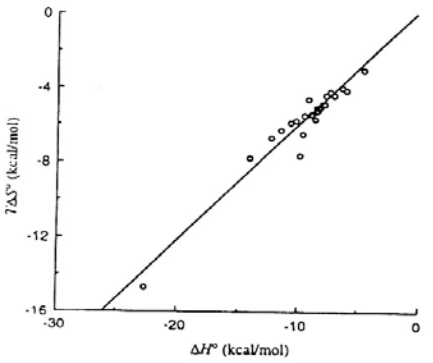


Figure 5. Enthalpy–entropy compensation plot for **1** and **2** with a series of **4** in toluene at 298 K. All plots in the graph refer to the entries in Tables 1 and 2.

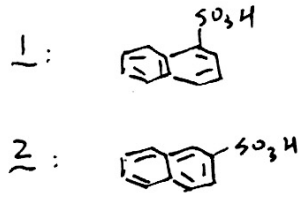
Enthalpy-entropy compensation: Case Studies

Case I: β-Cyclodextrin (*n*=7) with variable guests in aqueous solution

Table I. Complex Stability Constant (K) and Thermodynamic Parameters in kcal/mol for 1:1 and/or 1:2 Inclusion Complex Formation of Naphthalene Derivatives with α-, β-, and γ-Cyclodextrins in Water at 25 °C[a]

host	guest	stoichiometry (n)[b]	log K_n	$-\Delta G$	$-\Delta H$	$T\Delta S$
α	2-naphthalenesulfonate (**2**)	1	2.56 ± 0.01	3.49	0.78 ± 0.07	2.71
α	2,7-naphthalenedisulfonate (**4**)	1	0.98 ± 0.06	1.34	5.99 ± 0.05	−4.65
α	1-naphthaleneacetate (**7**)	1	2.94 ± 0.04	4.01	0.74 ± 0.01	3.27
β	1-naphthalenesulfonate (**1**)	1	3.40 ± 0.06	4.64	1.49 ± 0.05	3.15
β	2-naphthalenesulfonate (**2**)	1	5.37 ± 0.07	7.33	7.01 ± 0.06	0.32
β	2,6-naphthalenedisulfonate (**3**)	1	3.29 ± 0.05	4.49	2.79 ± 0.07	1.70
β	2,7-naphthalenedisulfonate (**4**)	1	2.44 ± 0.02	3.33	6.75 ± 0.08	−3.42
β	2,3,6-naphthalenetrisulfonate (**5**)	1	2.22 ± 0.03	3.03	3.09 ± 0.15	−0.06
β	4-amino-1-naphthalenesulfonate (**6**)	1	1.70 ± 0.03	2.32	2.38 ± 0.04	0.06
β	1-naphthaleneacetate (**7**)	1	4.35 ± 0.05	5.93	1.11 ± 0.06	4.82
γ	2-naphthalenesulfonate (**2**)	1	1.58 ± 0.03	1.58	4.18 ± 0.07	−2.60
		2	2.59 ± 0.07	4.11	5.73 ± 0.06	−1.62
γ	2,7-naphthalenedisulfonate (**4**)	1	2.58 ± 0.02	3.52	0.86 ± 0.01	2.66
γ	4-amino-1-naphthalenesulfonate (**6**)	1	1.31 ± 0.08	1.79	6.70 ± 0.13	−4.91

[a] Determined calorimetrically in buffered aqueous solution at pH 7.20 (0.1 M sodium phosphate); average of more than three independent runs. [b] Guest/host ratio.



Inoue et al, *JACS*, **1993**, *115*, 475

Entropically driven complexation

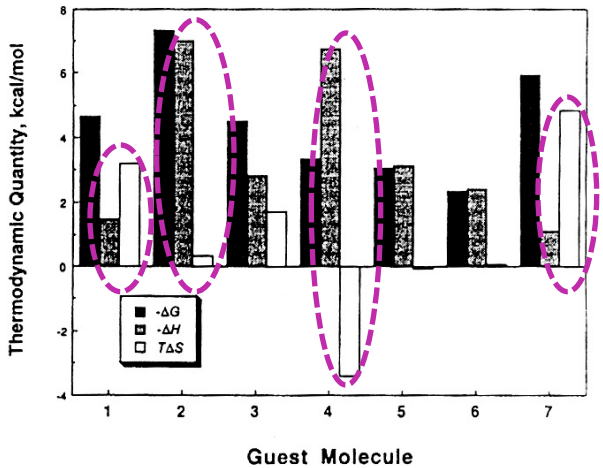


Figure 1. Free energy ($-\Delta G$), enthalpy ($-\Delta H$), and entropy changes ($T\Delta S$) for the inclusion complexation of naphthalene derivatives **1**–**7** with β-cyclodextrin in a buffered aqueous solution (pH 7.20) at 25 °C.

Enthalpically driven complex.

Enthalpy-entropy compensation: Summary

Assuming a constant (linear) relation between ΔS and ΔH:

$$T\Delta S^\circ = \alpha\Delta H^\circ + T\Delta S_0^\circ$$

$$\Delta G^\circ = (1-\alpha)\Delta H^\circ - T\Delta S_0^\circ;$$

$$\boxed{\Delta\Delta G^\circ = (1-\alpha)\Delta\Delta H^\circ}$$

Case I (naphthalenesulfonate-cyclodextrin complexation): $\alpha = 0.90$
Inoue et al., *J. Am. Chem. Soc.*, **1993**, *115*, 475

Case II (porphyrin-quinone complexation): $\alpha = 0.62$
Hayashi et al., *J. Am. Chem. Soc.*, **1997**, *119*, 7281

Enthalpy-entropy compensation: Solvent effects

Case IV: Cyclophane host with pyrene guest in variable solutions:
ΔH_{comp}, ΔS_{comp} remains constant

Smithrud et al, *JACS*, **1991**, *113*, 5420

1

Table II. Enthalpic ($\Delta H°$) and Entropic ($T\Delta S°$) Contributions to the Free Energies of Formation $\Delta G°$ of Complex **1** in Solvents of Different Polarity

run	solvent	$\Delta G°$,[a] kcal mol^{-1}	$\Delta H°$, kcal mol^{-1}	$T\Delta S°$, kcal mol^{-1}
1	2,2,2-trifluoroethanol	−7.8 ± 0.1	−20.0 ± 0.2	−12.2 ± 0.2
2	methanol	−6.4 ± 0.1	−12.0 ± 0.2	−5.6 ± 0.2
3	ethanol	−6.1 ± 0.1	−11.0 ± 0.2	−4.9 ± 0.2
4	*N*-methylacetamide	−5.8 ± 0.1	−9.0 ± 0.2	−3.2 ± 0.2
5	*N*-methylformamide	−5.1 ± 0.1	−5.6 ± 0.1	−0.5 ± 0.1
6	*N*,*N*-dimethylacetamide[b]	−4.4 ± 0.1	−2.0 ± 0.4	+2.4 ± 0.4
7	acetone	−4.3 ± 0.1	−6.6 ± 0.4	−2.3 ± 0.4
8	dimethyl sulfoxide	−3.9 ± 0.2	−6.4 ± 0.2	−2.5 ± 0.2
9	*N*,*N*-dimethylformamide	−2.9 ± 0.2	−3.7 ± 0.2	−0.8 ± 0.2
10	tetrahydrofuran	−2.7 ± 0.2	−3.0 ± 0.2	−0.3 ± 0.2
11	chloroform	−2.3 ± 0.2	−3.1 ± 0.2	−0.8 ± 0.2
12	benzene	−1.5 ± 0.2	−0.8 ± 0.2	+0.7 ± 0.2

[a] The $\Delta G°$ values in runs 8–12 were obtained in deuterated sovlents, whereas all calorimetric data result from protonated solvents. The amounts of 1% (v/v) Me_2SO (in run 1) and 10% (v/v) Me_2SO (in runs 4 and 5) were cosolvents in binding titrations to determine $\Delta G°$, which introduces a nondetermined minor error into the concentrations used to transform measured heats into enthalpies. [b] $\Delta G°$ value from calorimetric titration.

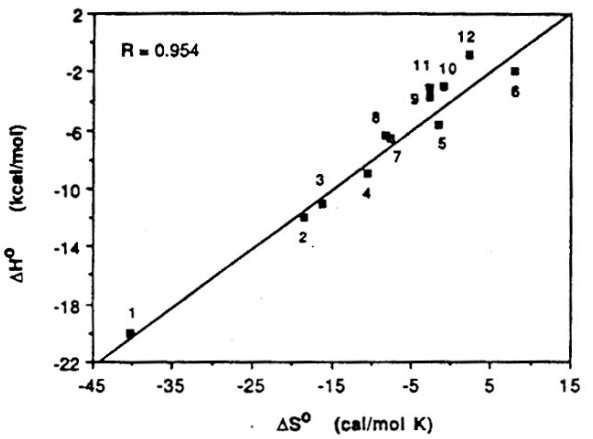


Figure 2. Isoequilibrium relationship between the enthalpy ($\Delta H°$) and the entropy ($\Delta S°$) for the formation of complex **1** at T = 303 K in various solvents. For the numbering of the solvents, see Table II.

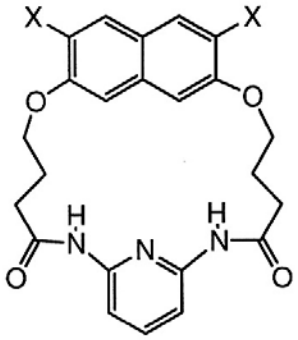
Observations:

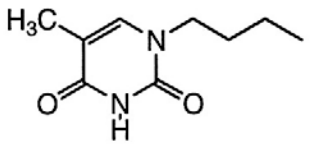
1) host-guest complex formation is enthalpically driven (in most cases)
2) enthalpy-entropy compensation is in effect (α = 0.72)

Cases where $\Delta S^o > 0$: possibly due to release of caged solvent
($\Delta H^o > 0$ as well, due to differences in van der Waals)

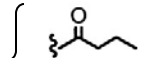
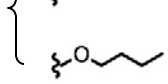
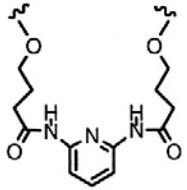
π-π interactions

Alkylthymidine receptor: Hamilton and Van Engen, *J. Am. Chem. Soc.*, **1987**, *109*, 5035
Muehldorf et al., *J. Am. Chem. Soc.*, **1988**, *110*, 6561





due to differences
In binding modes
(see next slide)

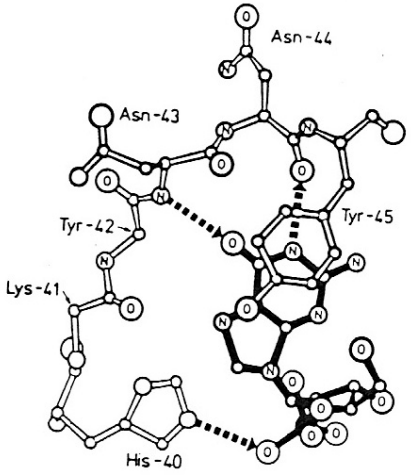
X	$K_s(CDCl_3, 298\ K), M^{-1}$	ΔG°, kcal/mol
H	290	3.35
	570	3.75
	138	2.9
	90	2.7

Electrostatic model for π-π interactions: Hunter and Sanders, *J. Am. Chem. Soc.*, **1990**, *112*, 5525

- aromatic rings have permanent quadrupole moment
- van der Waals interactions favor maximum coplanar overlap, but direct stacking results in electronic repulsion
- π-electrons in aromatic systems are delocalized, but electropositive nuclei (σ-framework) generate local electric field

π–π interactions: X-ray crystal structures

Tyrosine–guanosine stacking complex



Guanosine binding site of ribonuclease T_1. Guanosine is shown in bold

Heinemann & Saenger, Nature, 299, 27 (-82)

Synthetic thymine receptor

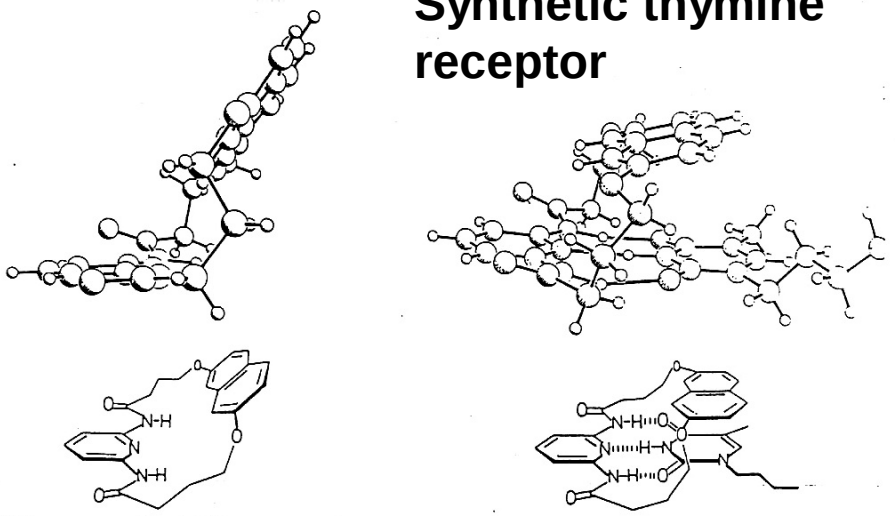
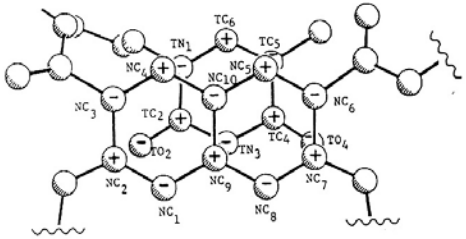
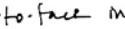


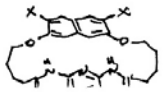
Figure 1. (a) X-ray structure of 1 and (b) X-ray structure of the complex between 1 and 5.

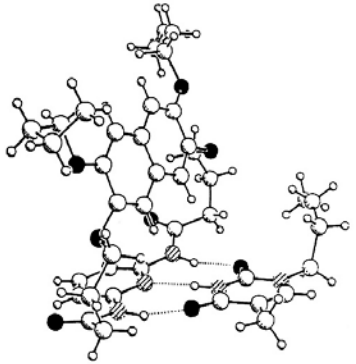
Hamilton and van Engen, *JACS*, **1987**, *109*, 5035
Mueldorf et al, *JACS*, **1988**, *110*, 6561



face-to-face interaction:

x = 





edge-to-face interaction:

X = O

Electron-donating substituents (-OR)
Increase edge-to-face interactions!

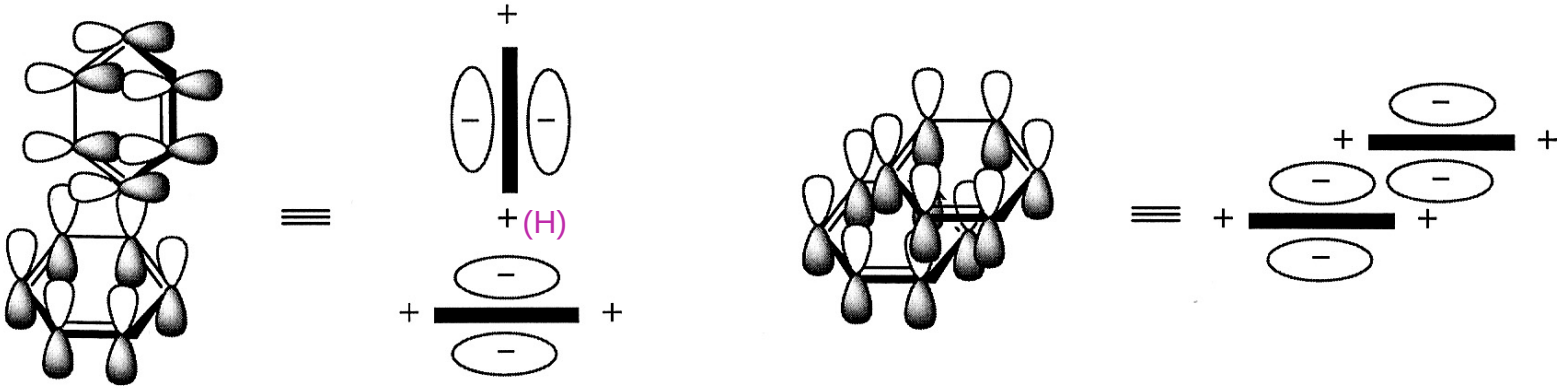
Rules for predicting π-π interactions:

1) π-π orbital repulsion dominates in face-to-face stacking (π–π stacking favored by e-deficient systems)

2) **π–σ orbital attraction dominates in edge-to-face stacking** (i.e., donor-acceptor interactions)

3) π-σ orbital attraction results in an offset stacking

(C–H···π interaction)



Electronic effects:

- π orbital electron density is affected as a function of the substituents, but effect is averaged and has no significant effect on orientation

- σ-framework is polarized by electronegative substituents, with substantial consequences for interacting π systems

Hunter and Sanders, *JACS*, **1990**, *112*, 5525

Hunter–Sanders Rules for π–π interactions

Hunter and Sanders, *JACS*, **1990**, *112*, 5525

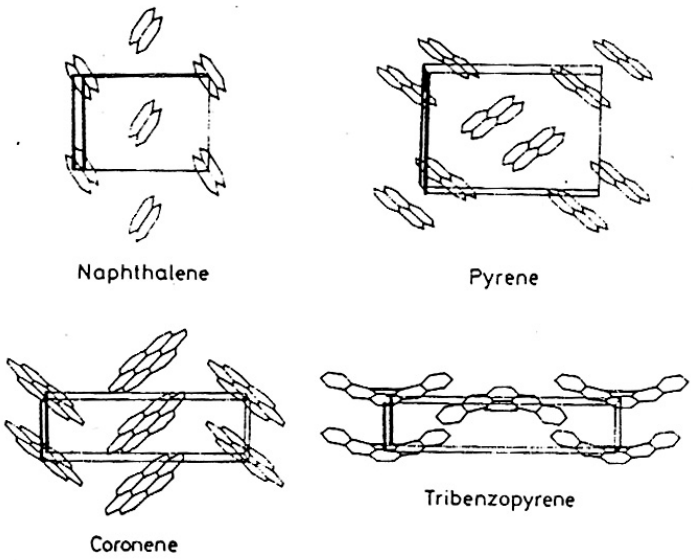


Figure 1. The four basic aromatic crystal packings. The short axes are indicated in each case.

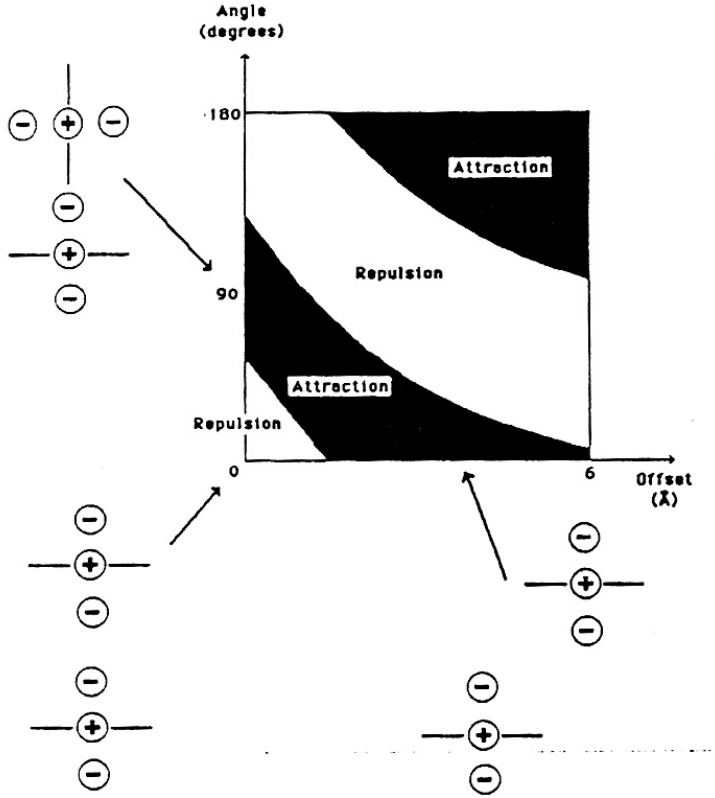
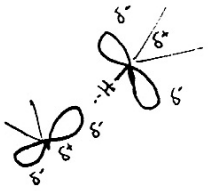
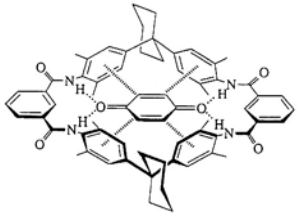


Figure 9. Interaction between two idealized π-atoms as a function of orientation: two attractive geometries and the repulsive face-to-face geometry are illustrated.



Edge-to-face binding interaction

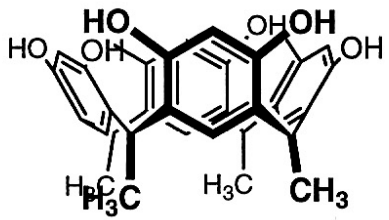
(C–H···π interaction)



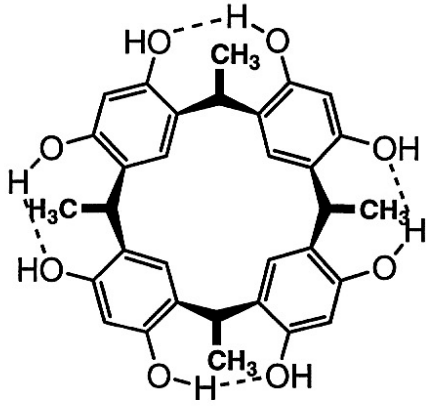
Edge-to-face interactions in a quinone receptor:
Hunter, *Chem. Commun.*, **1991**, 749

Molecular Recognition of Apolar Organic Molecules

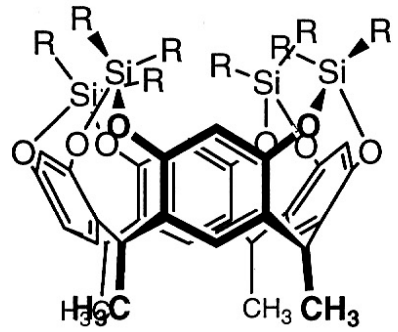
Surface complementarity as a driving force in nonpolar solvents:
Cram et al., *J. Am. Chem. Soc.* **1985**, 2574



calix[4]resorcinarene



Complexation is <u>entropically</u> driven, but stabilized by vdW forces



"cavitand"- cavity-bearing ligand

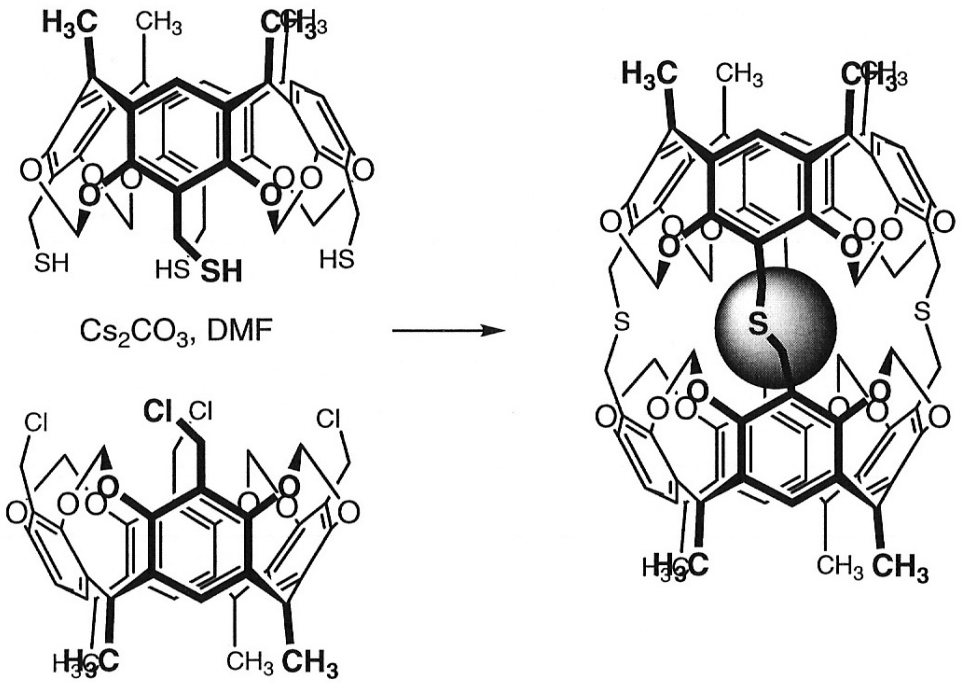
complexation with CS_2:

R	K_a ($CDCl_3$, 250 K)
Me	0.82
Et	8.1
	13.2

Encapsulation of Guest Molecules

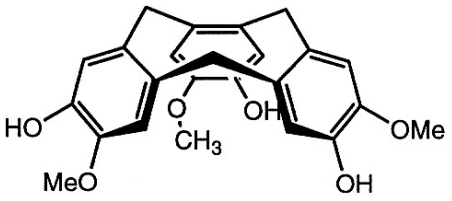
Encapsulation: process by which guest cannot dissociate from host without major changes in conformation of bond restructuring (i.e., entry and exit cannot occur by simple diffusion)

1. "Carcerand" complex of Cs^+ and DMF: Cram et al., *J. Am. Chem. Soc.* **1985**, 2575

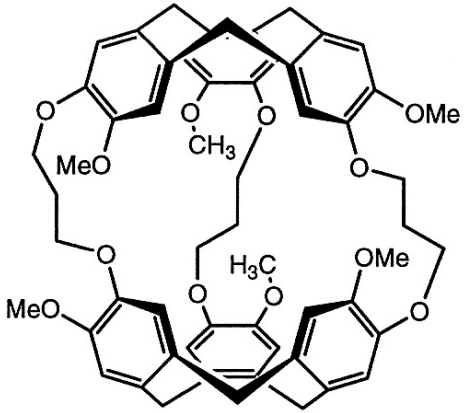


2. "Cryptophane" inclusion complex with halogenated solvent molecules:

Canceill et al., *J. C. S. Chem. Commum.* **1985**, 361;
Canceill et al., *J. Am. Chem. Soc.* **1986**, *108*, 4230;
Canceill et al., *Angew. Chem.* **1989**, *28*, 1246.



cyclotriveratrylene



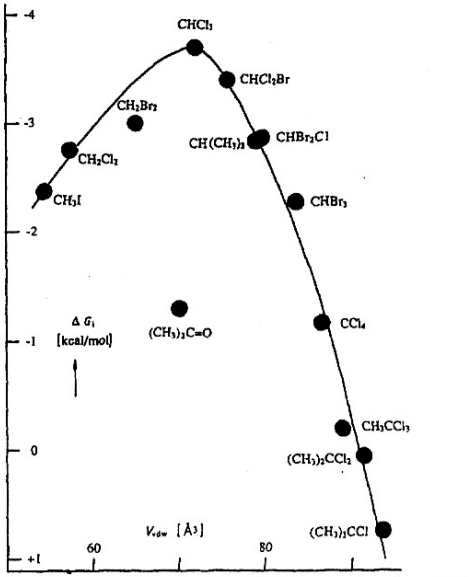


Fig. 2. Free energy of formation (ΔG_i) at 300 K of a series of complexes of I as a function of the size (V_{vdw}) of the guests.

Guest	V_{vdw} [Å^3]	$\Delta\delta$	ΔG_i^* [kcal mol^{-1}] 300 K	330 K	ΔG_i [kcal mol^{-1}] 300 K	ΔH_i [kcal mol^{-1}]	ΔS_i [cal mol^{-1} K^{-1}]
CH_3I	54.5	3.70	13.6		−2.4		
CH_2Cl_2	57.6	4.19	13.3		−2.8	+1.0	+6
CH_2Br_2	65.5	4.18			−3.0		
CH_3COCH_3	70.0	3.44			−1.3		
$CHCl_3$	72.2	4.44	13.3	14.4	−3.7	−6.0	−7
$CHCl_2Br$	76.1	4.42		14.9	−3.4	−5.2	−6
$CH(CH_3)_3$	79.4	4.25 2.95	13.9		−2.8	−3.8	−3
$CHClBr_2$	80.1	4.41		14.8	−2.9	−1.5	+4
$CHBr_3$	84.0	4.35		15.1	−2.3	−1.4	+4
CCl_4	86.8				−1.2		
$C(CH_3)Cl_3$	89.2	3.55			−0.2		
$C(CH_3)_2Cl_2$	91.6	3.45			+0.1		
$C(CH_3)_3Cl$	93.9	3.18			+0.8		