CHM 696-11: Week 3

Instructor: Alexander Wei

Molecular recognition of polar and apolar organic molecules

Catenanes and rotaxanes

π–π, π–cation, and dispersion forces

Enthalpy-entropy compensation

Molecular Recognition of Polar Organic Molecules: Amino Acids (zwitterions)

Some design principles:

- **Increasing the strength of host-guest binding interactions**

- **Multidentate (polytopic) interactions: Size and shape complementarity**

- **Secondary interactions (e.g., surface complementarity)**
  - **α) π–π stacking (aromatic rings)**
  - **b) Charge-transfer or donor-acceptor interactions (induced dipoles)**
  - **c) Van der Waals interactions (London dispersion forces)**
  - **d) Solvophobic interactions**

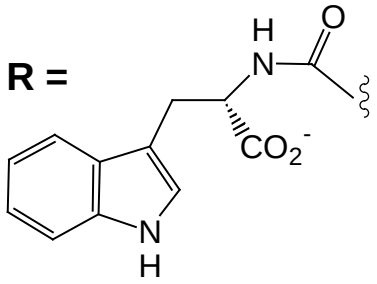
Case Study I: Crown ethers

Ammonium cation receptor

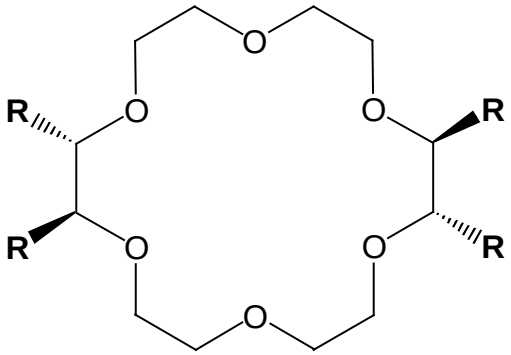
Forms charge-transfer complex (λ_{CT} = 305 nm)

Behr and Lehn, *Chem Commun.*, **1976**, 621

Behr and Lehn, *Helv. Chim. Acta* **1980**, 2112

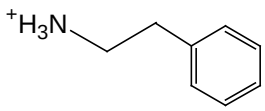
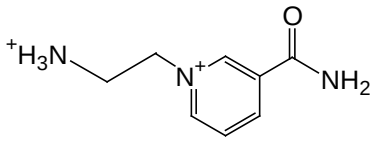
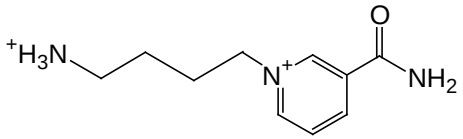


L-Trp

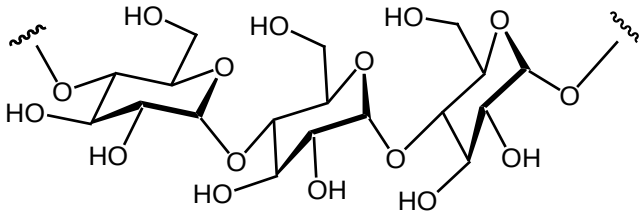


Enthalpic interaction between electron-rich tryptophan (host) and electron-deficient pyridinium (guest)

Sandwich complex possible

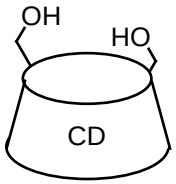
guest	K_S (H_2O, pH 7 buffer)	
	100	**π-π stacking**
	2300	
	400	**H-bonding**

Case Study II: Cyclodextrin Inclusion complex

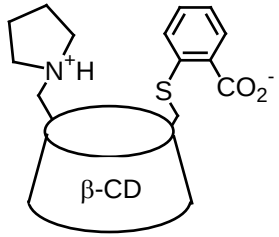


6 glucopyranoside units, linked 1➝4
7 glucopyranoside units, linked 1➝4

≡



α-cyclodextrin (α-CD)
β-cyclodextrin (β-CD)

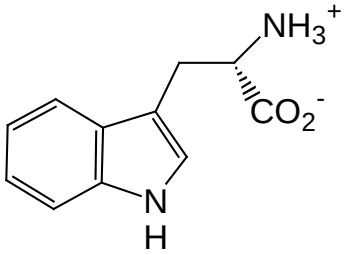


β-CD receptor for D,L-Trp

Chiral recognition studies:

Tabushi et al, *JACS*, **1986**, *108*, 4514
Armstrong et al, *Anal. Chem.,* **1987**, *59*, 2594

guest

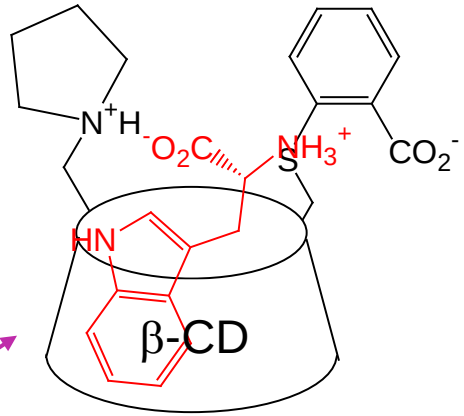


L-Trp

K_s β-CD (H_2O, pH 8.9 buffer, 298 K)

D-Trp: 45-50
L-Trp: 34-42

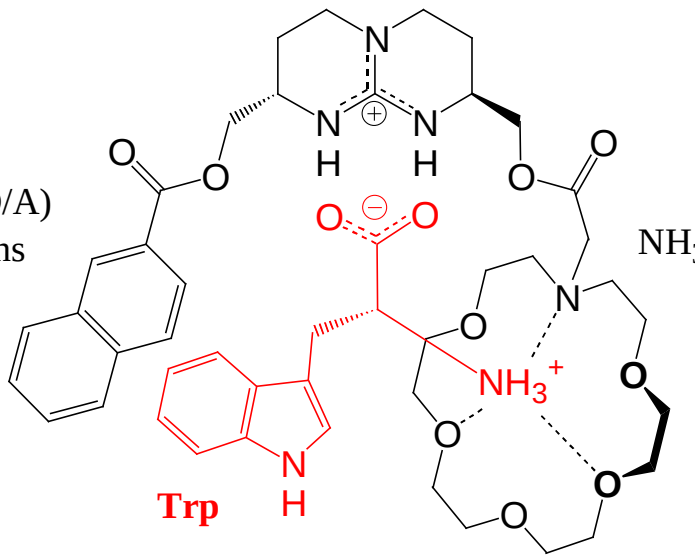
ΔΔG ≤ 0.16 kcal/mol



Hydrophobic pocket;
poor chiral discrimination

Case Study III: Guanidinium receptor

C_2 chiral symmetry
Guanidinium "fork"



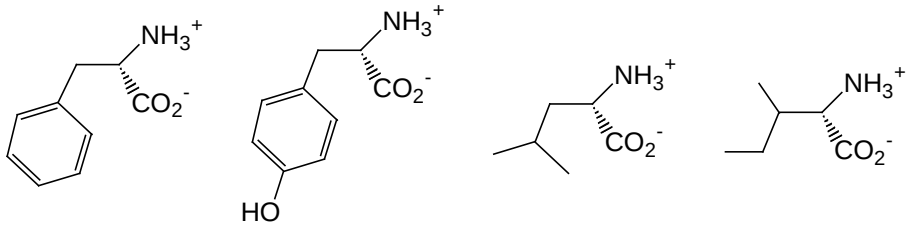
π–π (or D/A) interactions

NH_3^+ receptor

pincer-like aromatic amino acid receptor:
Galan et al, *JACS*, **1992**, *114*, 1511
(see Seel et al, *Topics Curr. Chem*. v.175 for review)

Extraction studies (H_2O/CH_2Cl_2):

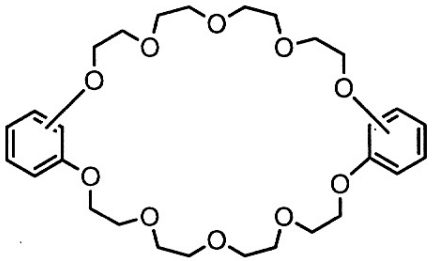
Guest	Partition ratio
L-Phe	100
Trp	**46**
Tyr	17
Leu	28
Ile	11

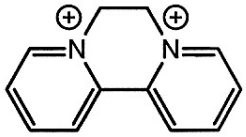


Phe Tyr Leu Ile

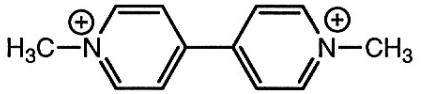
Molecular Recognition of Organic Molecules (cont'd)

1. bis-pyridinium salts (Allwood et al., *Angew. Chem.*, **1985**, *24*, 581; Allwood et al., *J.C.S. Chem. Commun.*, **1987**, 1054-69 (series of papers)





"diquat"

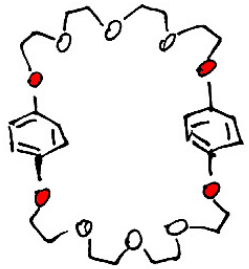


"paraquat"
(methyl viologen)

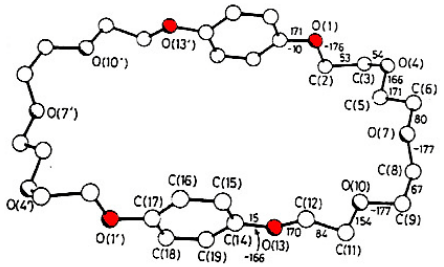
	K_a (acetone-d_6, 298 K)	
Bis-*para*-phenylene 34-C-10	(n/a)	730
Bis-*meta*-phenylene 32-C-10	390	760
Bis-*ortho*-phenylene 30-C-10	17,500	-----

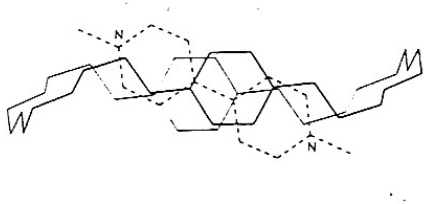
Bis-pyridinium receptors:
J. Fraser Stoddart

Stoddart's bis-pyridinium receptors: X-ray crystal structures (I)

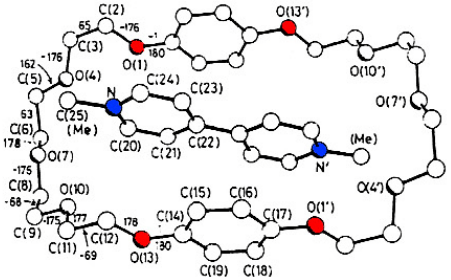


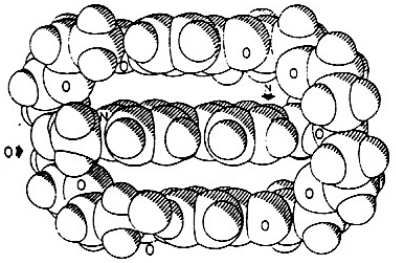
Bis-*para*-phenylene 34-C-10:





paraquat complex vs.
free macrocycle



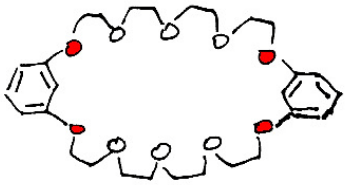


Allwood et al, *Chem. Comm.*, **1987**, 1064

Observations:

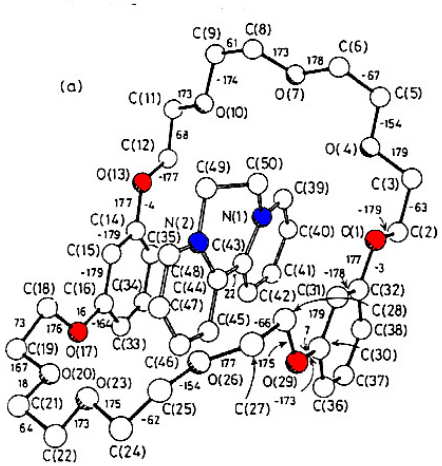
- sandwich complex is favored (Donor|Acceptor|Donor)
- macrocycle size is not critical for complementarity
- modest binding constants for m-, p-substituted macrocycles suggests entropy compensation

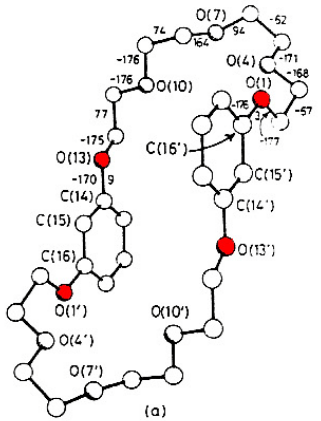
Stoddart's bis-pyridinium receptors: X-ray crystal structures (II)



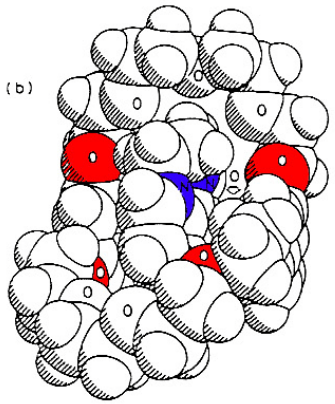
Bis-*meta*-phenylene 32-C-10:

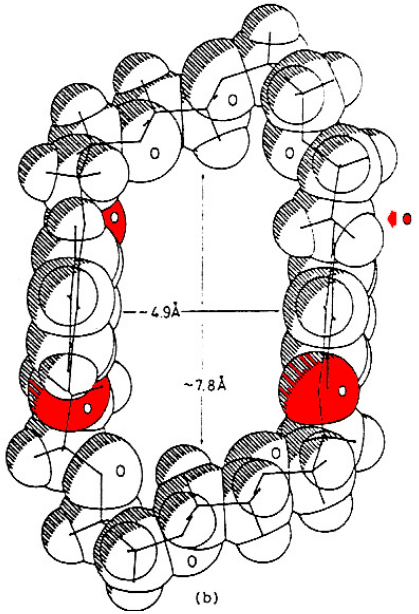
Diquat complex vs. free macrocycle



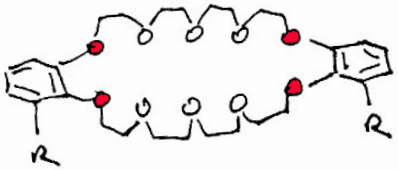


Allwood et al, *Chem. Comm.*, **1987**, 1058





Stoddart's bis-pyridinium receptors: X-ray crystal structures (III)



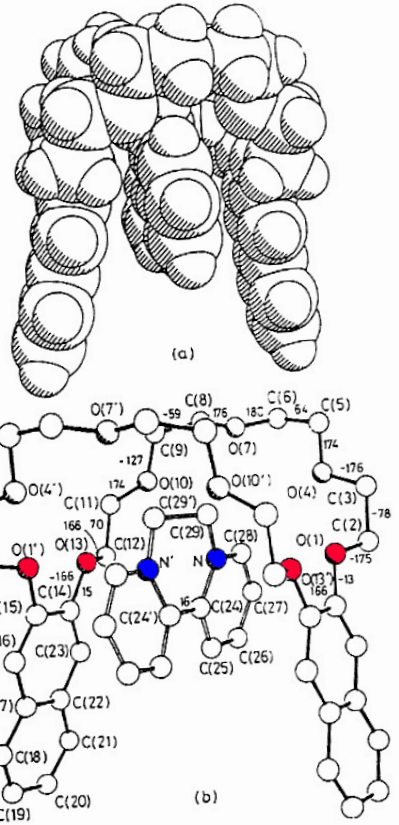
Bis-*ortho*-phenylene 30-C-10:

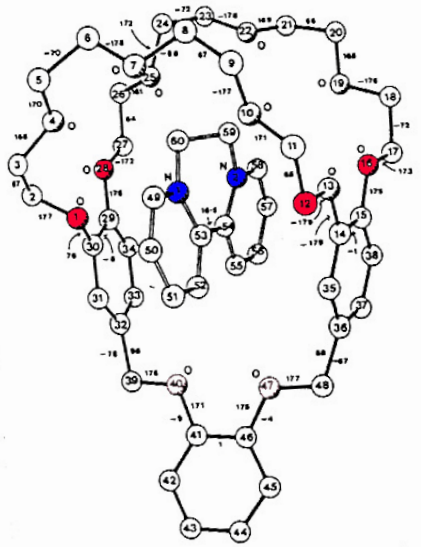
Macrocyclic receptor: R = H

Macrobicyclic receptor: R =

Colquhoun et al, *Chem. Comm.*, **1983**, 1140

Allwood et al, *Angew. Chem.,* **1985**, *24*, 581





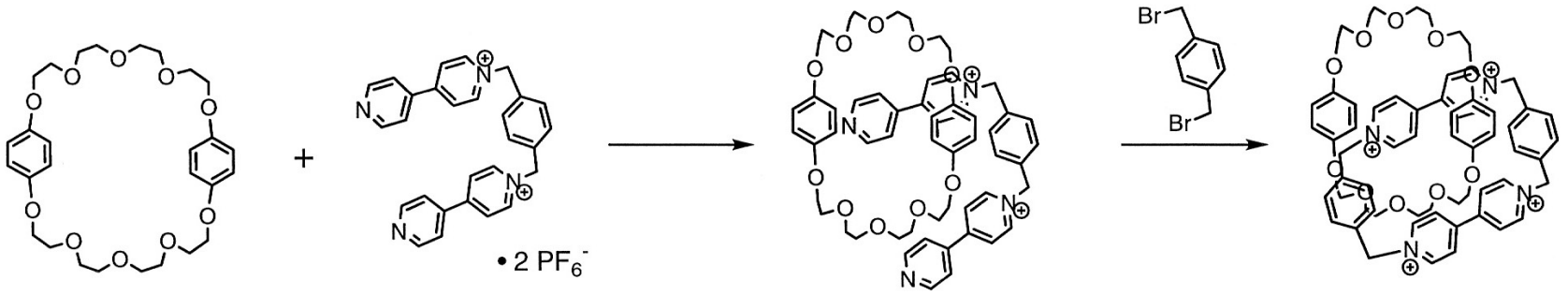
← bis naphthyl derivative

'pincer' complex

Catenanes and Rotaxanes

Ashton et al., *Angew. Chem.*, **1989**, *28*, 1396
Amabilino et al., *Angew. Chem.*, **1994**, *33*, 1286
Anelli et al., *J. Am. Chem. Soc.* **1991**, *113*, 5131

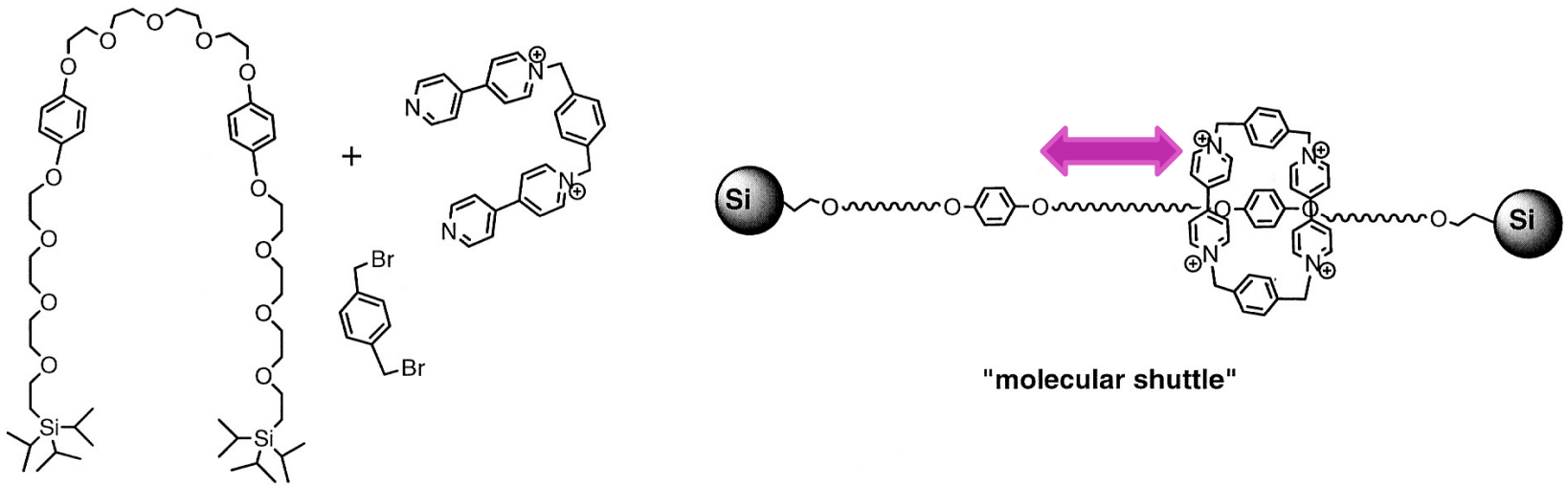
Example of templated synthesis



bis-*para*-phenylene 32-C-10

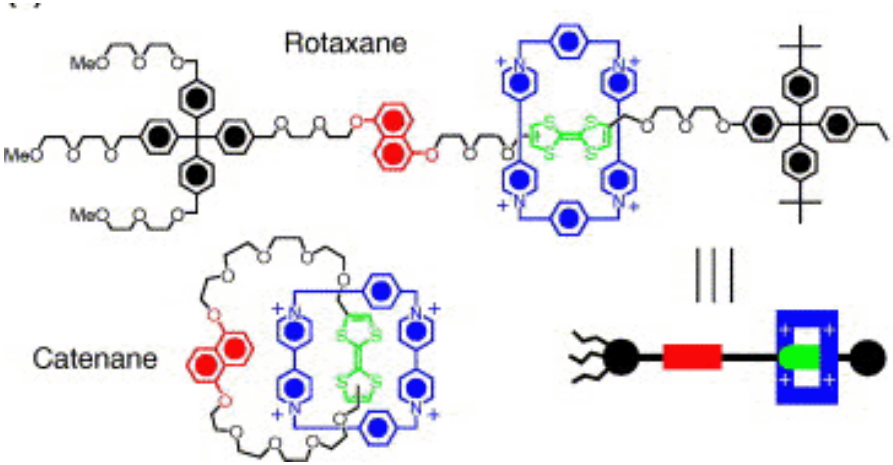
rotaxane

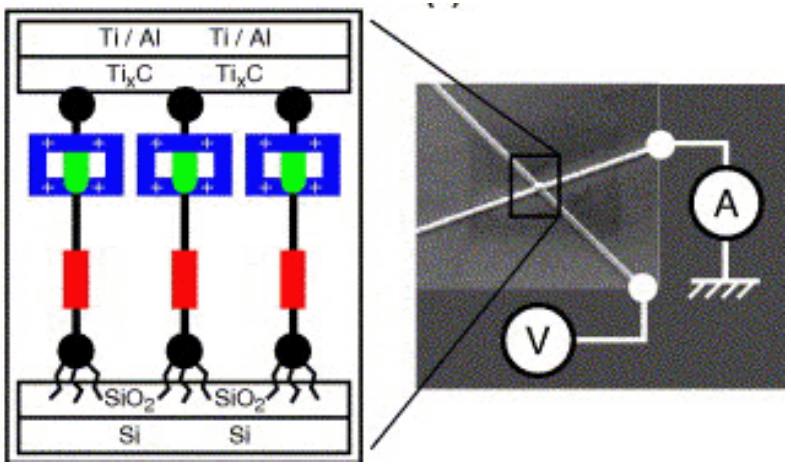
catenane

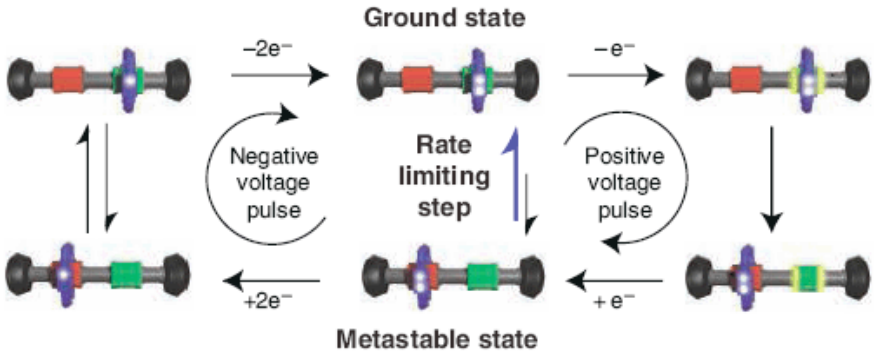


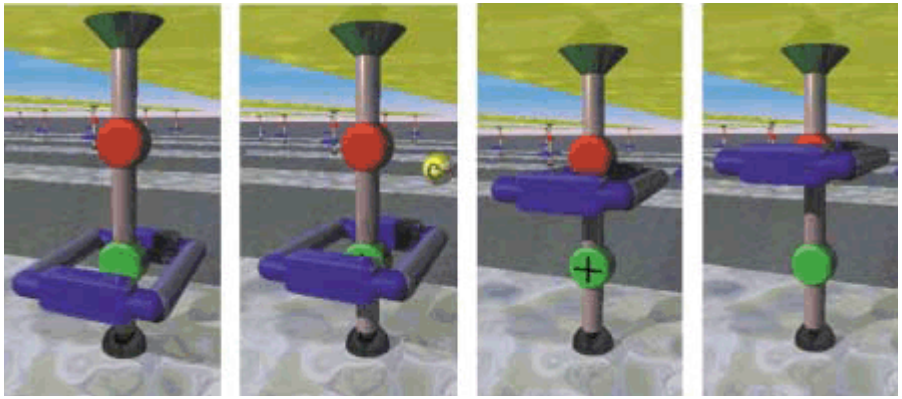
"molecular shuttle"

Catenanes and Rotaxanes: Switches for molecular computing?





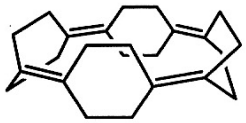


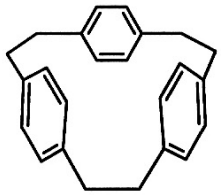


Towards a rational design of molecular switches and sensors from their basic building blocks.
N. N. P. Moonen, A. H. Flood, J. M. Fernández, J. F. Stoddart, *Top. Curr. Chem.* **2005**, *262*, 99-132.

The π-cation effect

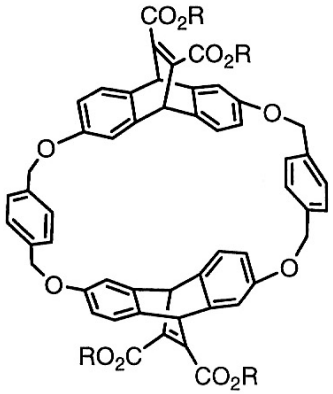
Review: Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303-1324.

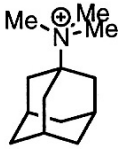
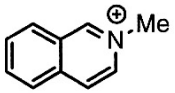
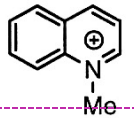
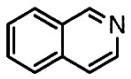
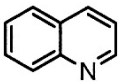




Vögtle, F., "Supramolecular Chemistry," pp. 107-115

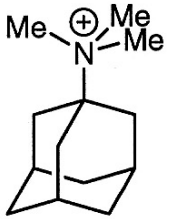
Bridged bis(anthracene) macrocycle: Stauffer and Dougherty, Tetrahedron Lett., **1988**, *29*, 6039

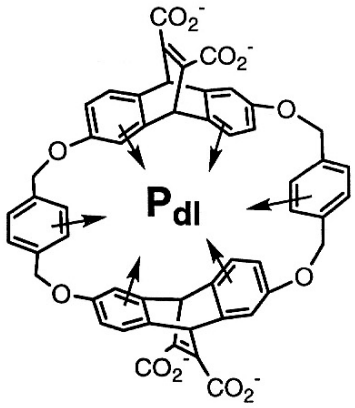


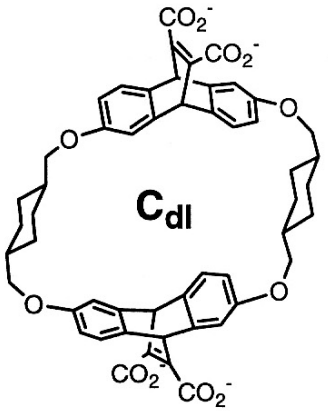
guest molecule	$\Delta G_a°$ (295 K) R=Me ($CDCl_3$)	R=H (D_2O. pD=9)
	2.1	6.7
	2.5	7.2
	3.5	7.6
	0.2	6.3
	0	5.4

The π-cation effect (cont'd)

NMR binding studies: Petti et al., *J. Am. Chem. Soc.*, **1988**, *110*, 6825





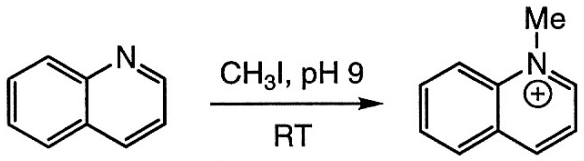


NMR chem. shift data indicates that charged group is most deeply embedded into π-rich macrocycle

ΔG_a°= 6.7 kcal/mol
(295 K, D_2O, pD=9)

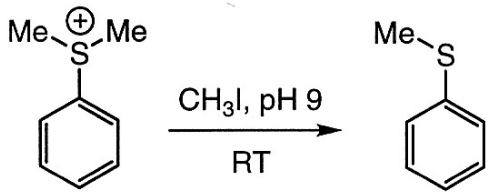
ΔG_a°= 5.4 kcal/mol
(295 K, D_2O, pD=9)

Reaction rate catalysis: McCurdy et al., *J. Am. Chem. Soc.*, **1992**, *114*, 10314



$\frac{k_{cat}}{k_{uncat}} = 80$

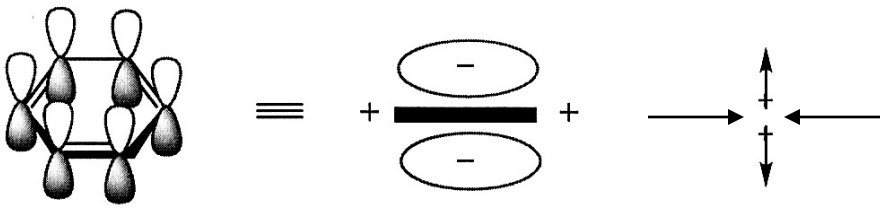
$\frac{k_{cat}}{k_{uncat}} = 20$



$\frac{k_{cat}}{k_{uncat}} = 3.3$

$\frac{k_{cat}}{k_{uncat}} = 9.4$

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