Recettori per molecole neutre

Legami idrogeno

Effetto idrofobico

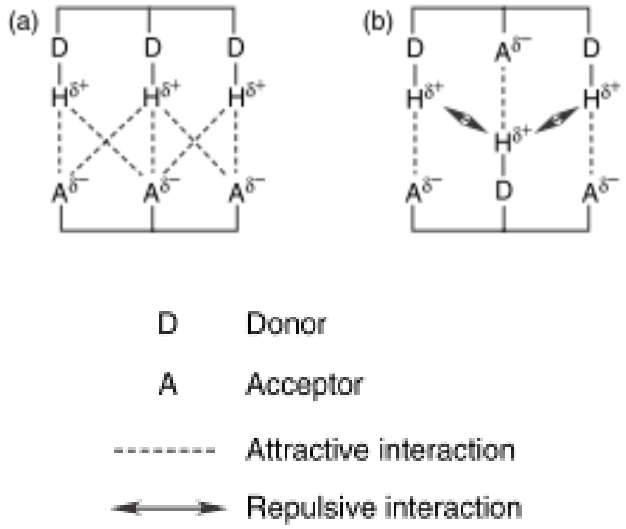
Interazioni CH-π

Interazioni π stacking

pre organizzazione

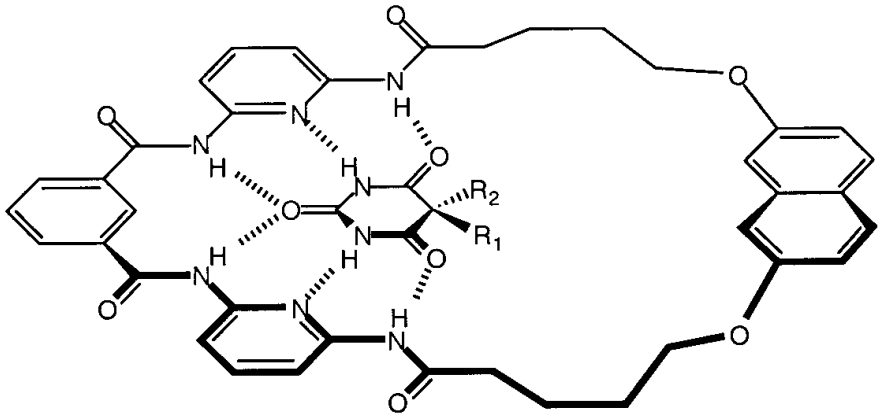
Recettori per molecole neutre

Legami idrogeno siti D A multipli



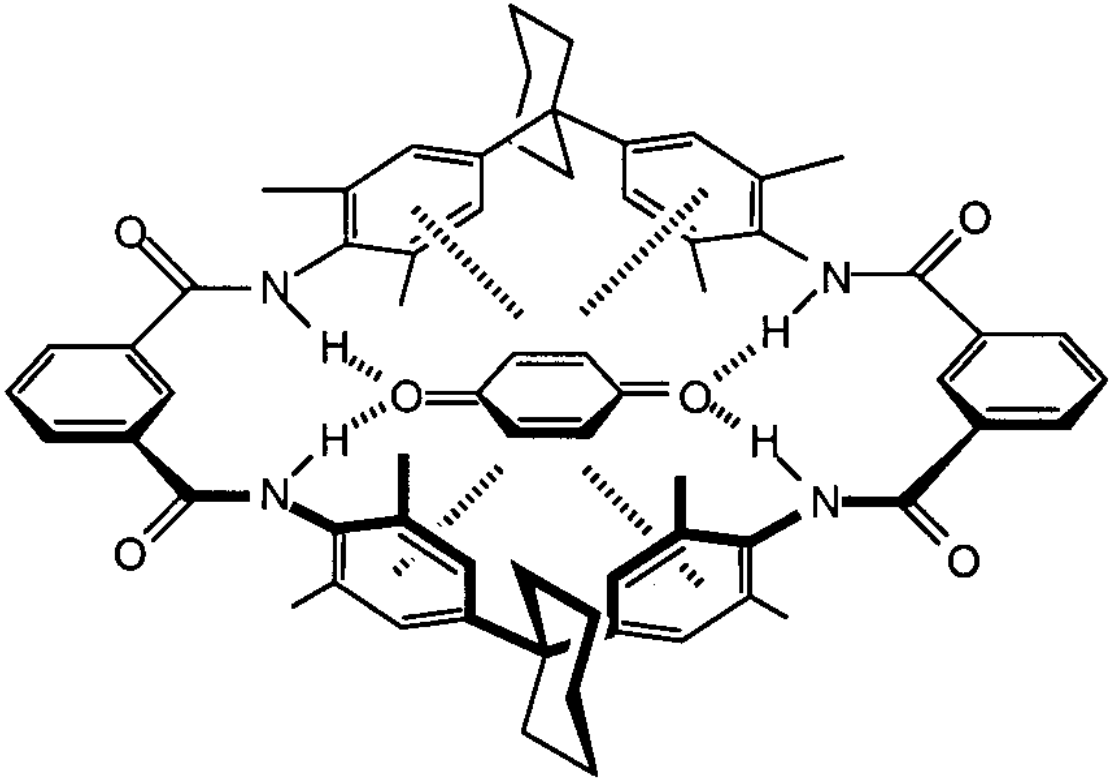
Recettori per molecole neutre

Legami idrogeno preorganizzazione e complementarietà (direzionale)



Barbiturato ($CHCl_3$) K ca. 25×10^4

Interazioni cooperative



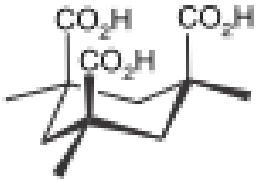
Receptor for benzoquinone which alters the electronic properties of the guest.

Recettori per molecole neutre

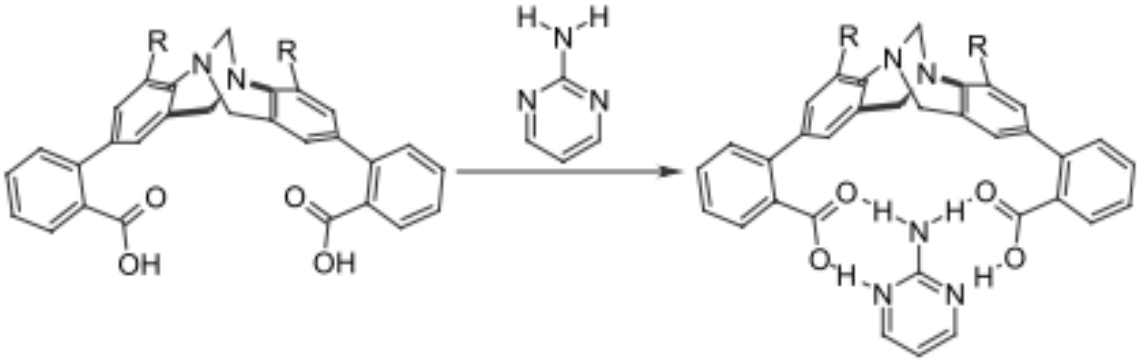
Legami idrogeno Guest con DA; recettori "ad hoc"

Pinze Molecolari

Tröger's base

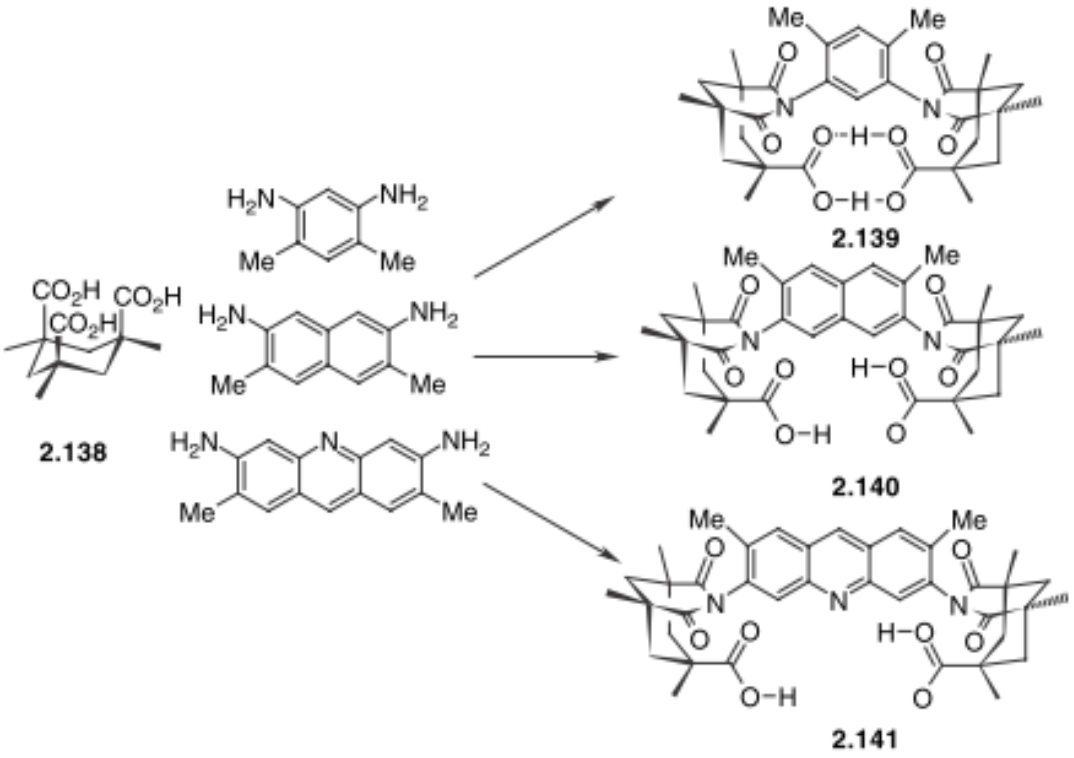


Kemp's triacid



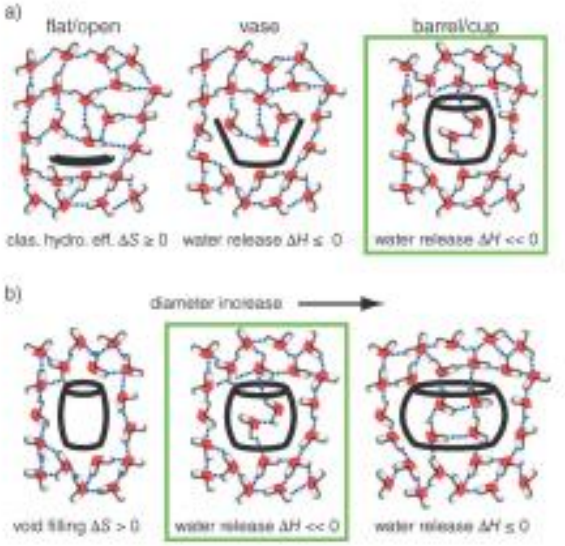
92 – 104°

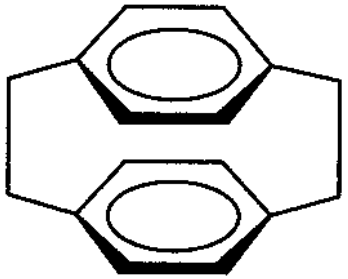
K (CH_2Cl_2) = 2.4 x 10^4 M^{-1}


CO2H
CO2H
CO2H
2.138
H2N
NH2
Me
Me
H2N
NH2
Me
Me
H2N
N
NH2
Me
Me
Me
Me
O
N
O
O
O
O
O-H-O
O-H-O
2.139
Me
Me
O
N
O
O
O
O
H-O
O
O-H
2.140
Me
Me
O
N
O
N
O
O
O
O
H-O
O
O-H
2.141

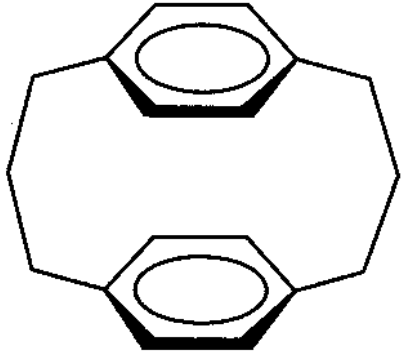
Recettori per molecole neutre

Effetto idrofobico esterno polare (e/o carico) tasca idrofobica

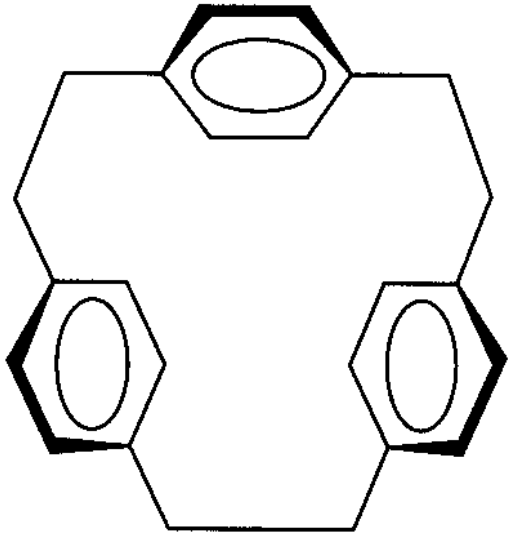




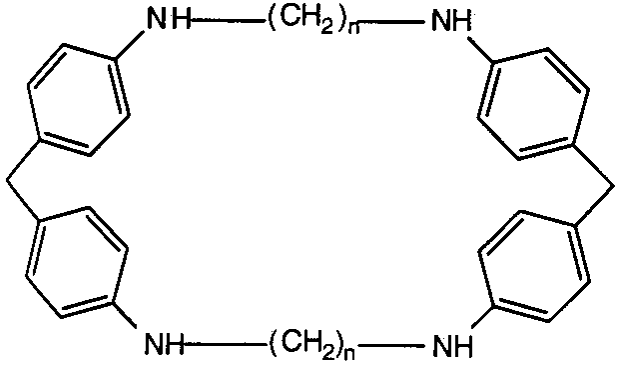
[2.2]Paracyclophane

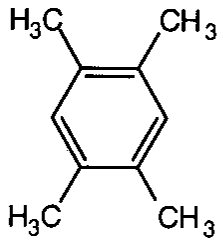


[3.3]Paracyclophane

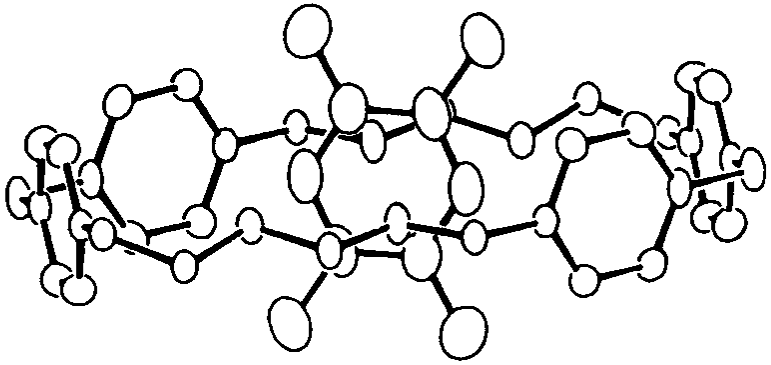


[2.2.2]Paracyclophane





durene

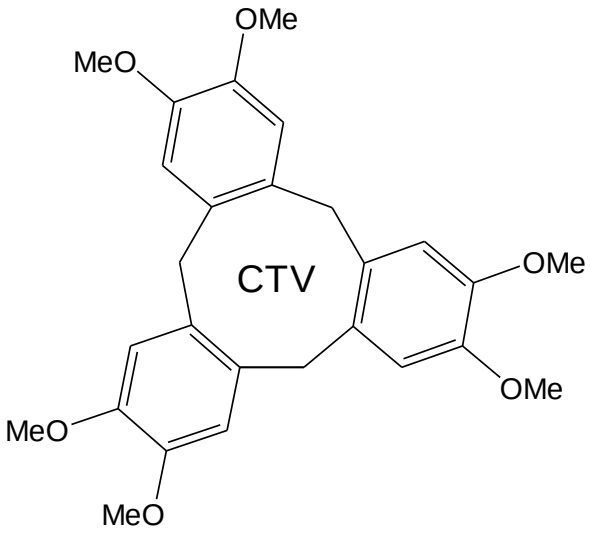


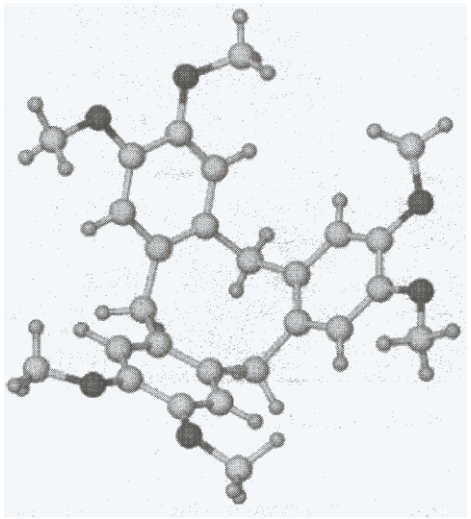
Recettori per molecole neutre

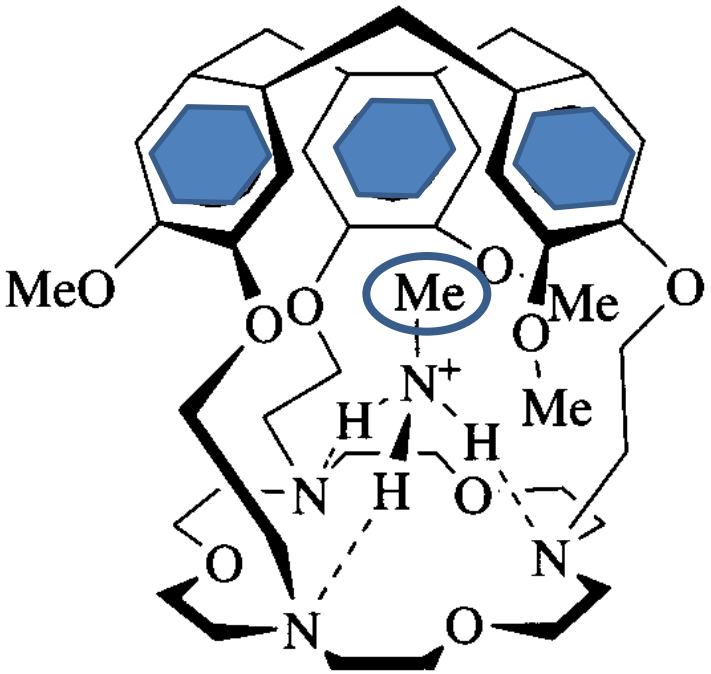
Interazioni CH-π pre organizzazione (cavità profonde e rigide)

Ciclotriveratrilene CTV

condensazione 1,2-dimetossi benzene e formaldeide, H_2O acida; scaffold: ciclononatrene.

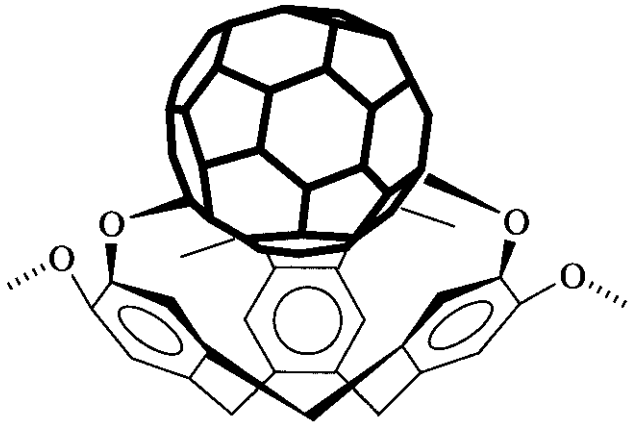


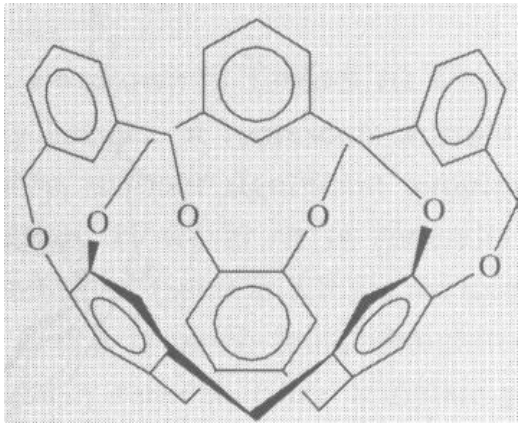


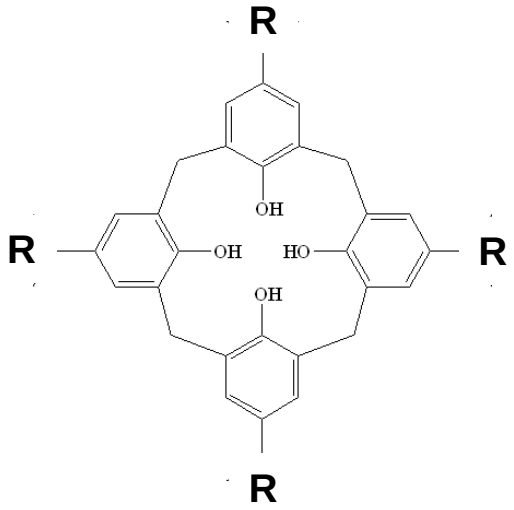


ciclotriveratrilene

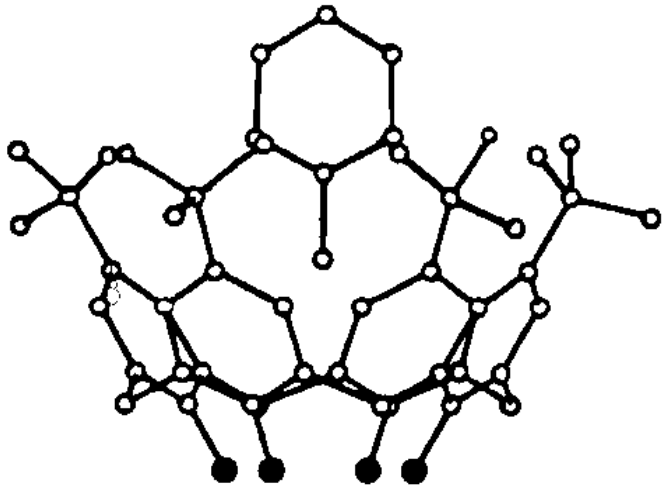
corando


O
O
O
O

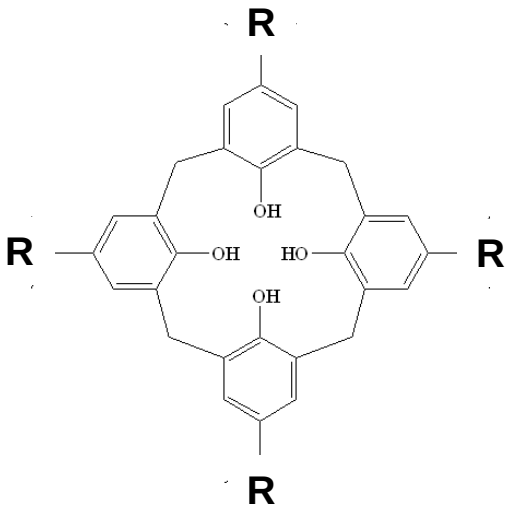

O
O
O
O
O
O

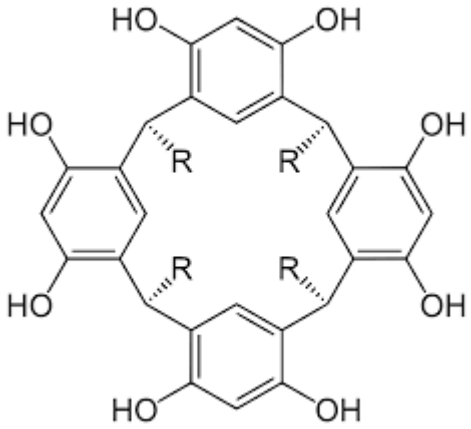


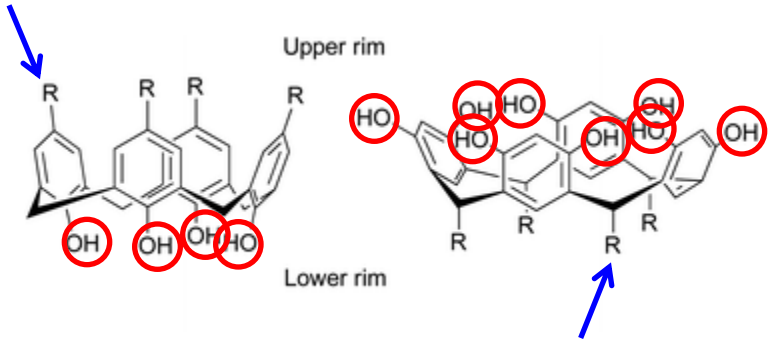
calix[4]arene



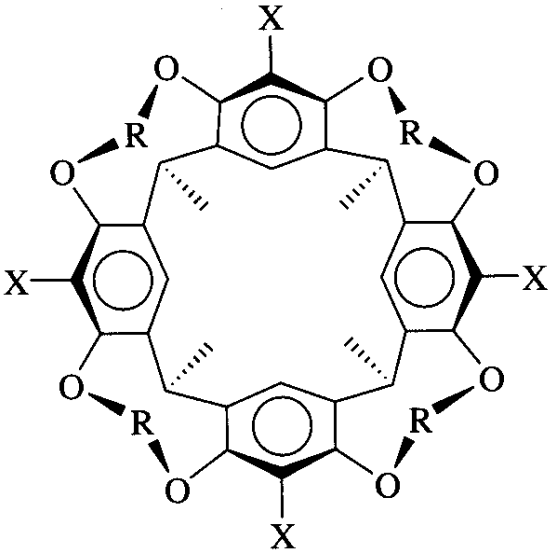
p-tert-Butylcalix[4]arene-toluene inclusion complex

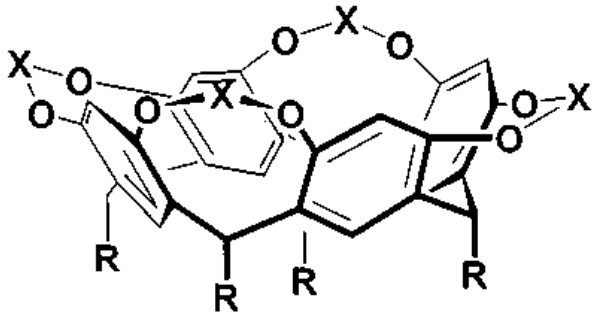

R
R
R
R
OH
OH
HO
OH


HO
OH
HO
OH
R
R
R
R
HO
OH
HO
OH


Upper rim
Lower rim
R
R
R
R
OH
OH
OH
HO
HO
OH
HO
OH
HO
OH
R
R
R
R

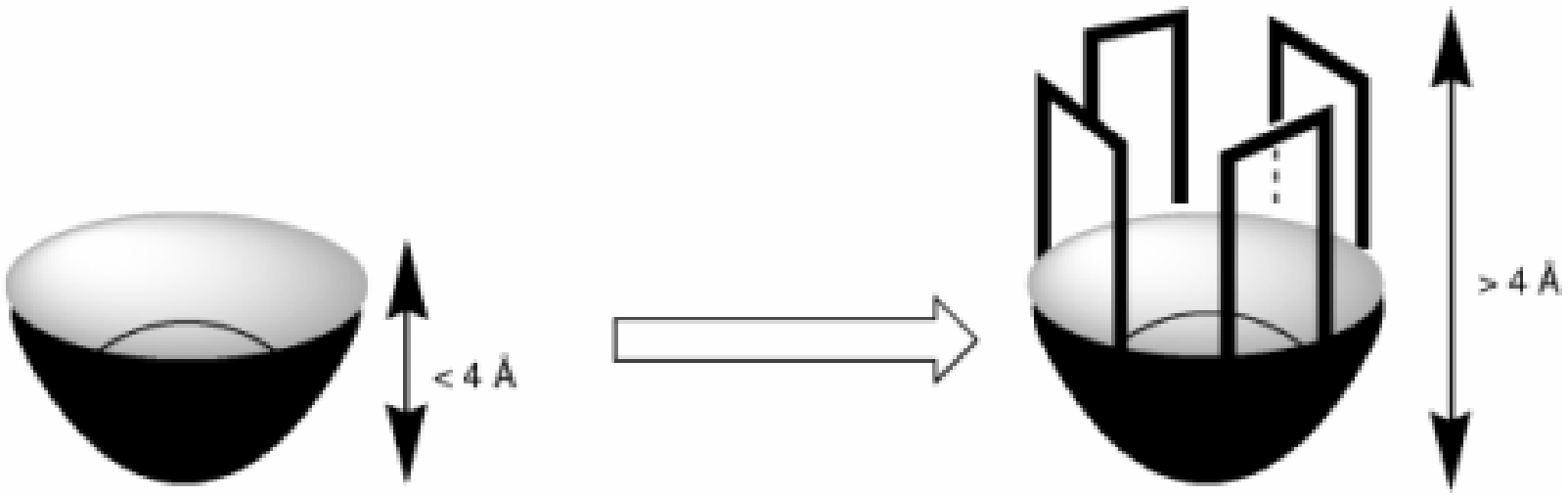
[4] resorcinarene



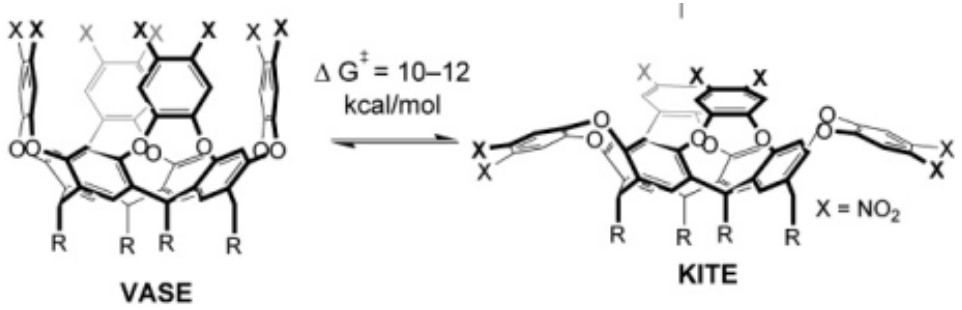


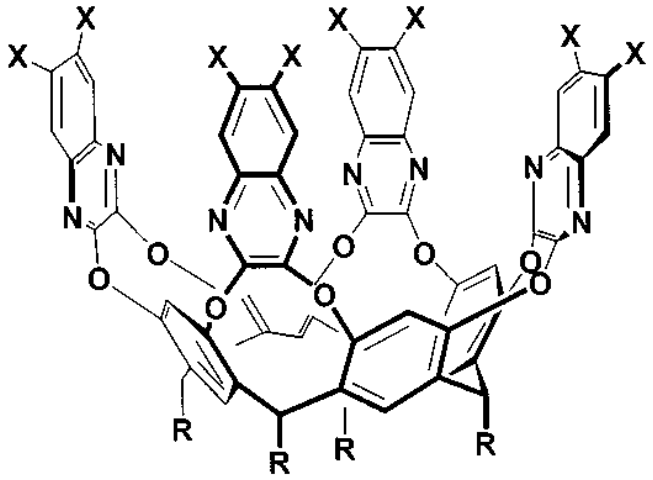
2 R = Alkyl, Ar;
X = $(CH_2)_n$, $SiAlk_2$

Ciclofani concavi ⟹ Cavitandi

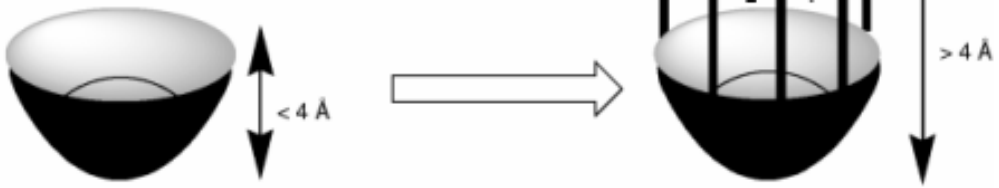


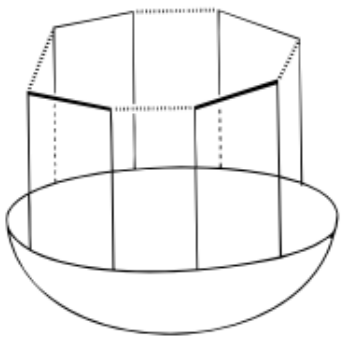
The studies of Cram[13] had established a barrier of some 10 to 12 kcal mol^{-1} for the vase-to-kite interconversion. If this

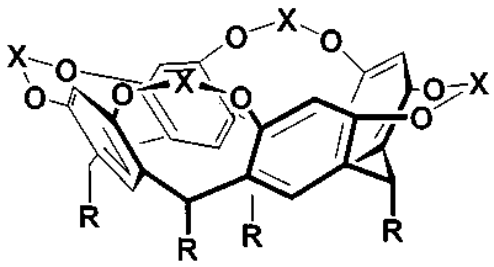




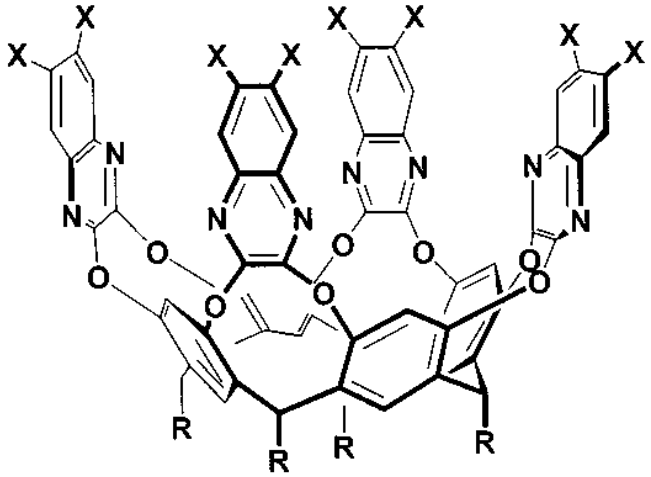
3 R = Alkyl;
X = H, CH_3, Hlg


< 4 Å
> 4 Å

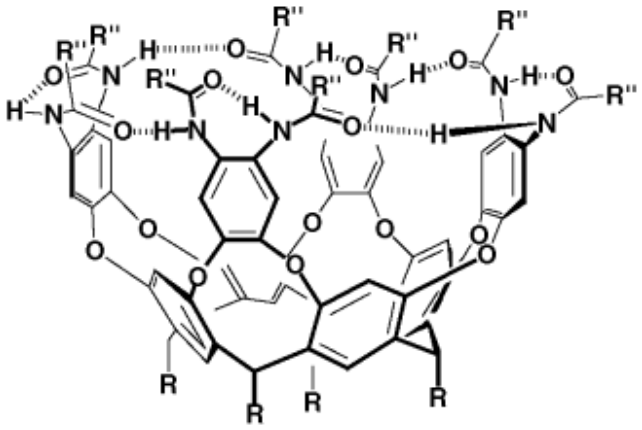


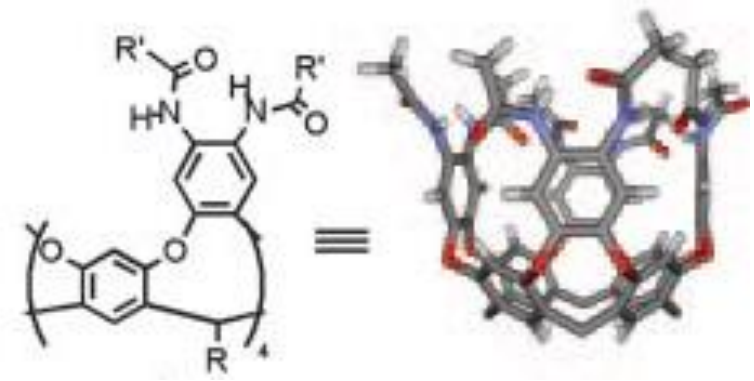


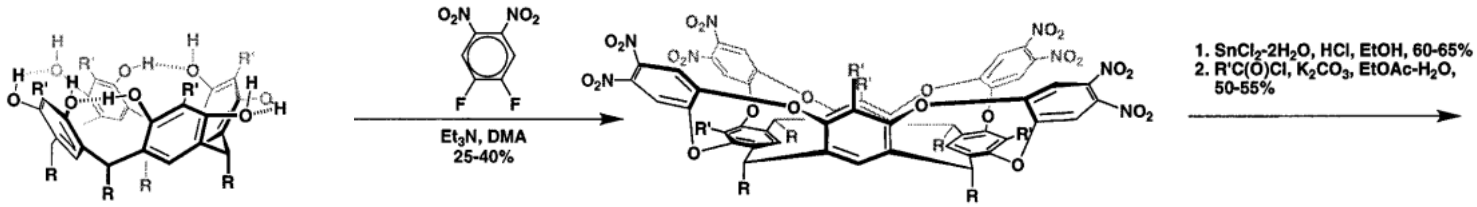
2 R = Alkyl, Ar;
X = $(CH_2)_n$, $SiAlk_2$

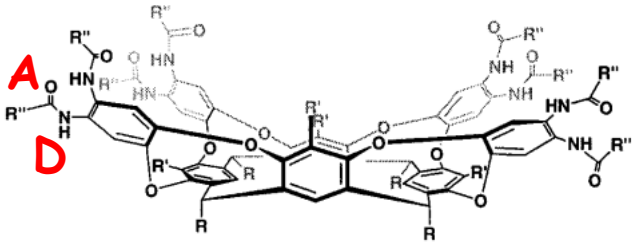


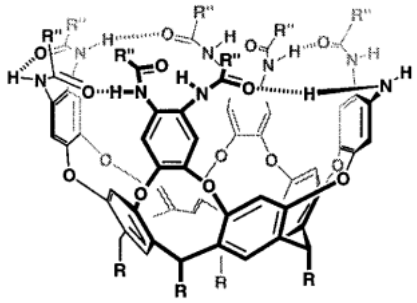
3 R = Alkyl;
X = H, CH_3, Hlg

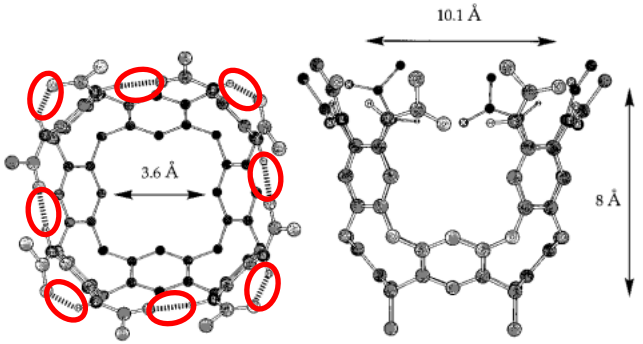


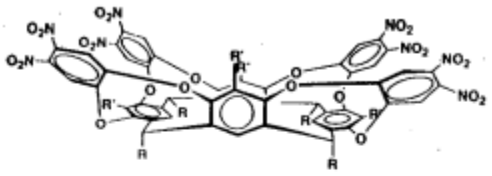



Et3N, DMA
25-40%
1. SnCl2-2H2O, HCl, EtOH, 60-65%
2. R'C(O)Cl, K2CO3, EtOAc-H2O,
50-55%


A
D

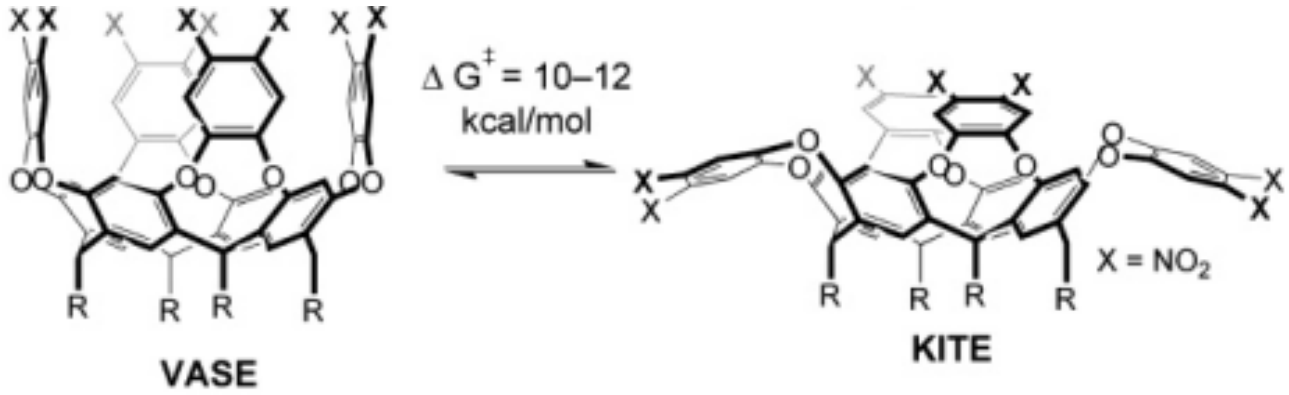


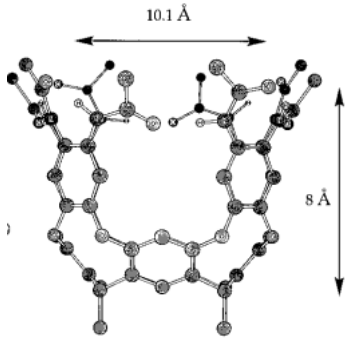

10.1 Å
3.6 Å
8 Å



4 c R = $C_{11}H_{23}$, R' = H

$CDCl_3$, 295 K





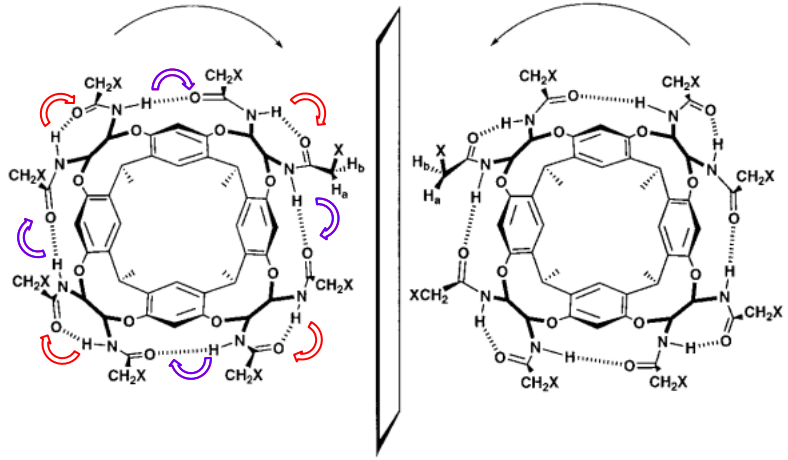
Spettro ^{1}H NMR affilato

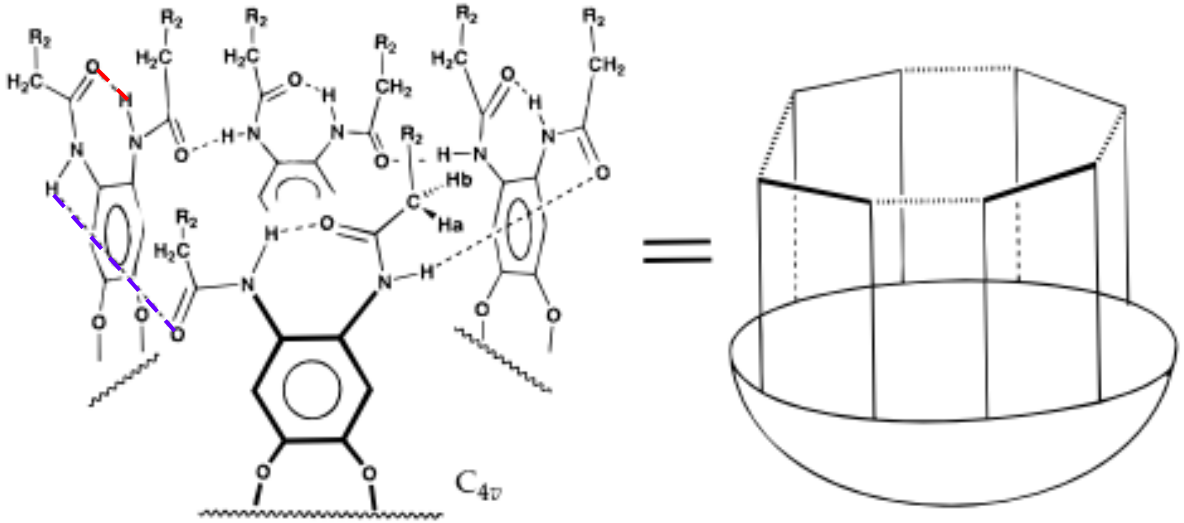
Segnale –NH spostato a campi bassi e sdoppiato in due risonanze della stessa intensità

Spettro ^{1}H NMR non varia con la concentrazione

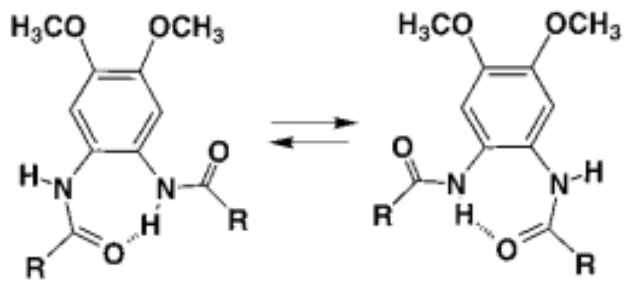
Aggiunta solvente competitivo (dmso-d_6): allargamento dei segnali

Stretching NH (IR)



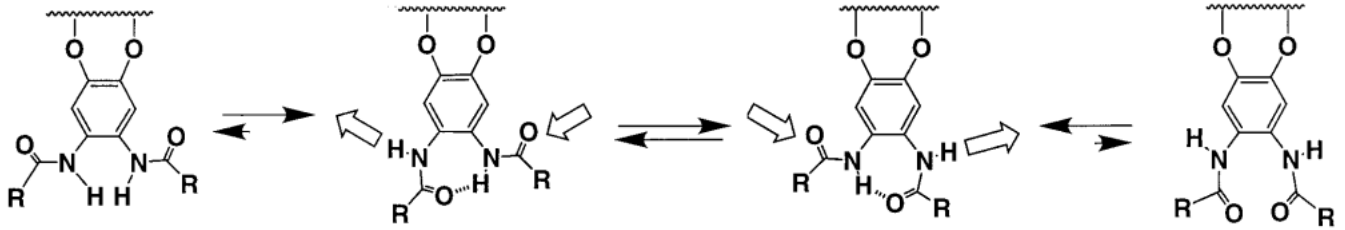


3 $R_1 = C_{11}H_{23}$, $R_2 = C_6H_{13}$

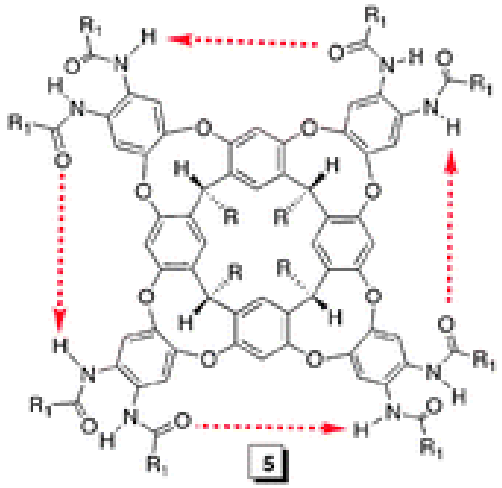


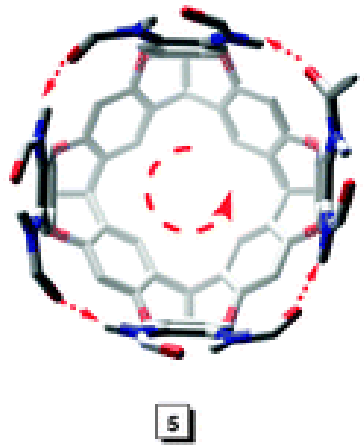
4

cavitand, four hydrogen bonds need to be broken: those that hold together adjacent rings. The typical costs of such ruptures in organic solvents are roughly 1 to 2 kcal mol^{-1} per hydrogen bond,[17] so the additional 5 to 7 kcal mol^{-1} is quite reasonable for the overall 17 kcal mol^{-1} activation barrier to racemization.

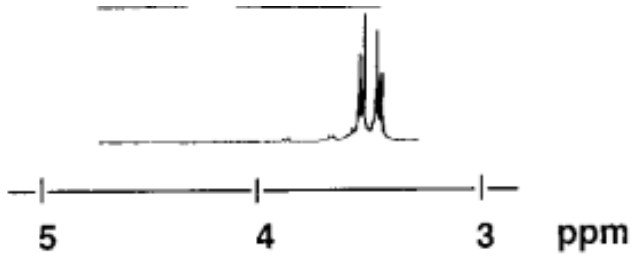


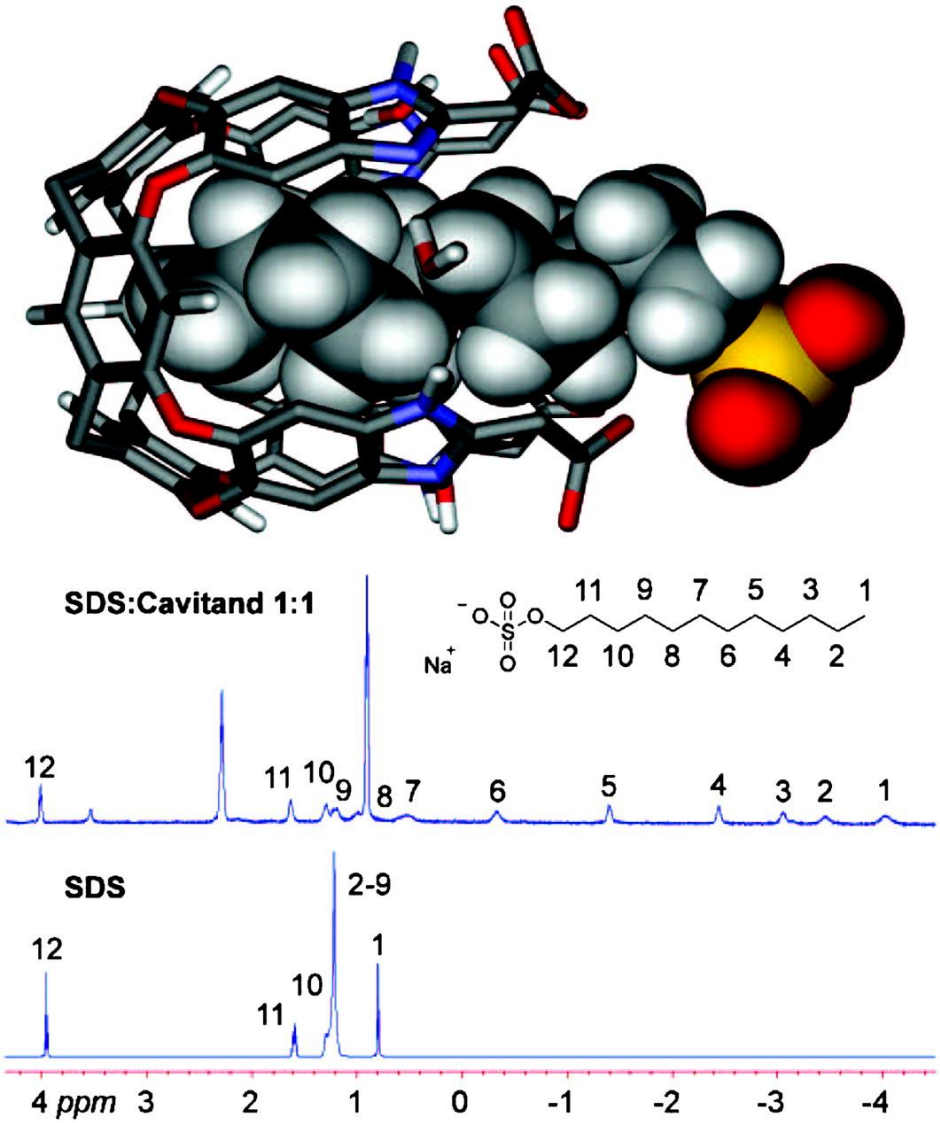
(B)

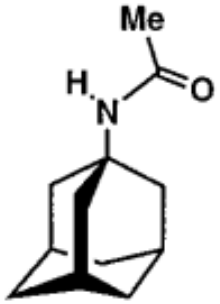


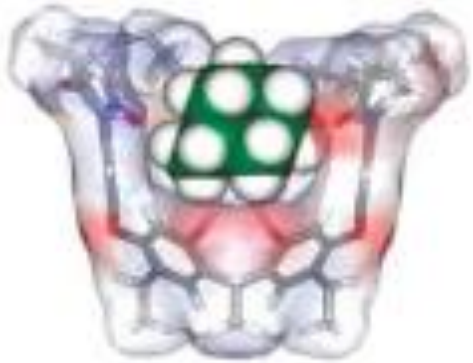


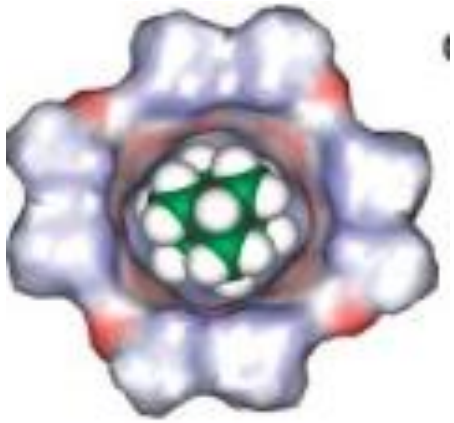
(C)



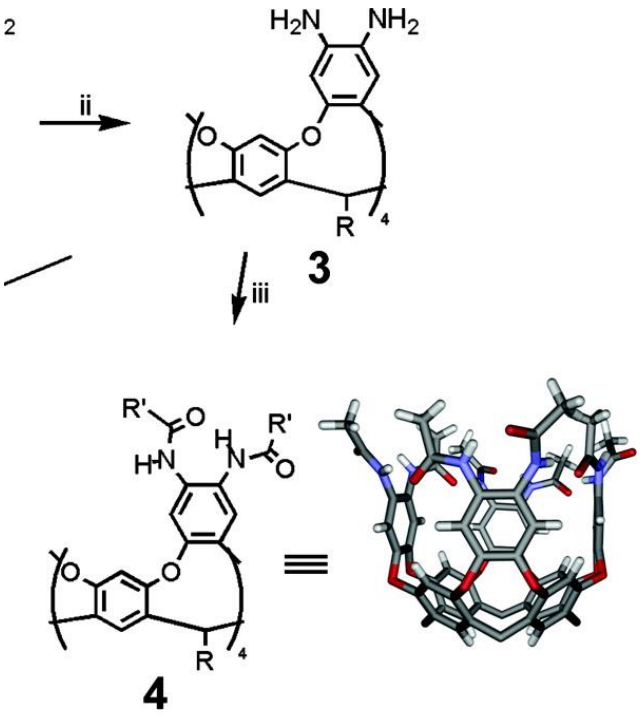

SDS:Cavitand 1:1
11 9 7 5 3 1
12 10 8 6 4 2
Na+
12
11 10 9 8 7 6 5 4 3 2 1
SDS
2-9
12
1
10
11
4 ppm 3 2 1 0 -1 -2 -3 -4


Me
H
N
O





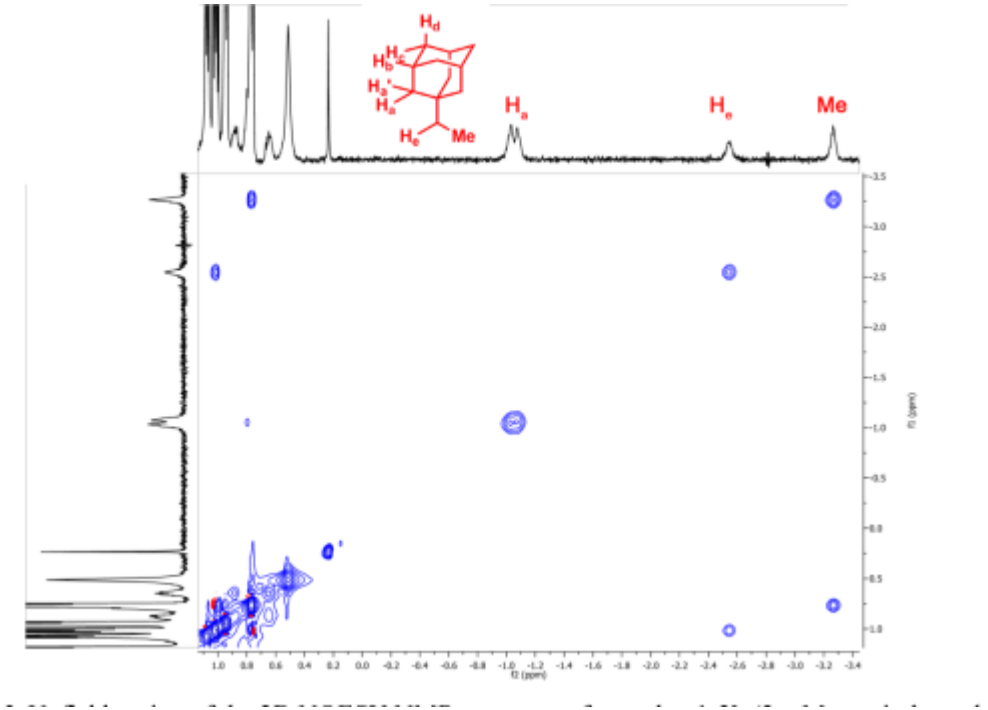
Preorganizzazione aumenta stabilità



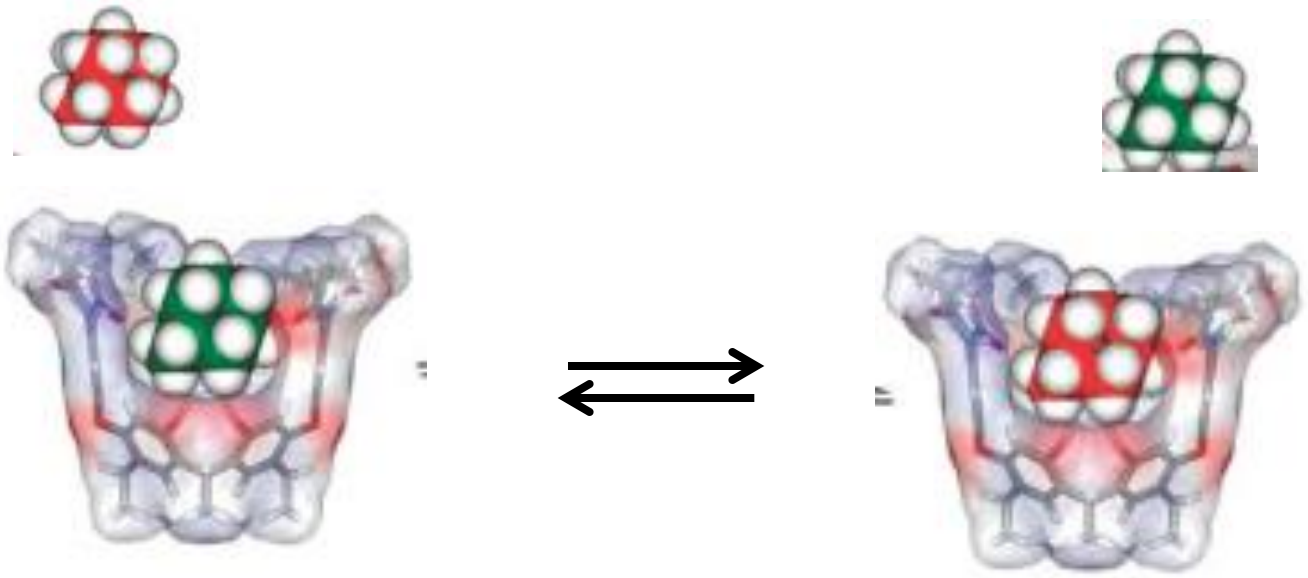
Stabilità migliaio di kcal/mol

Scambio lento nella scala dei tempi NMR!!

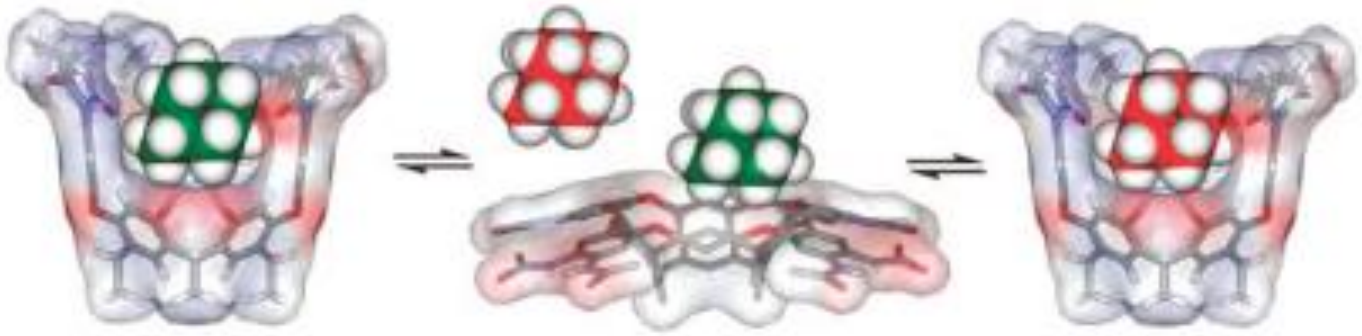
2D NOESY/EXSY/ROESY accoppiamenti di vicinanza spaziale (sia tramite legame che non) e informazioni su SCAMBIO CHIMICO



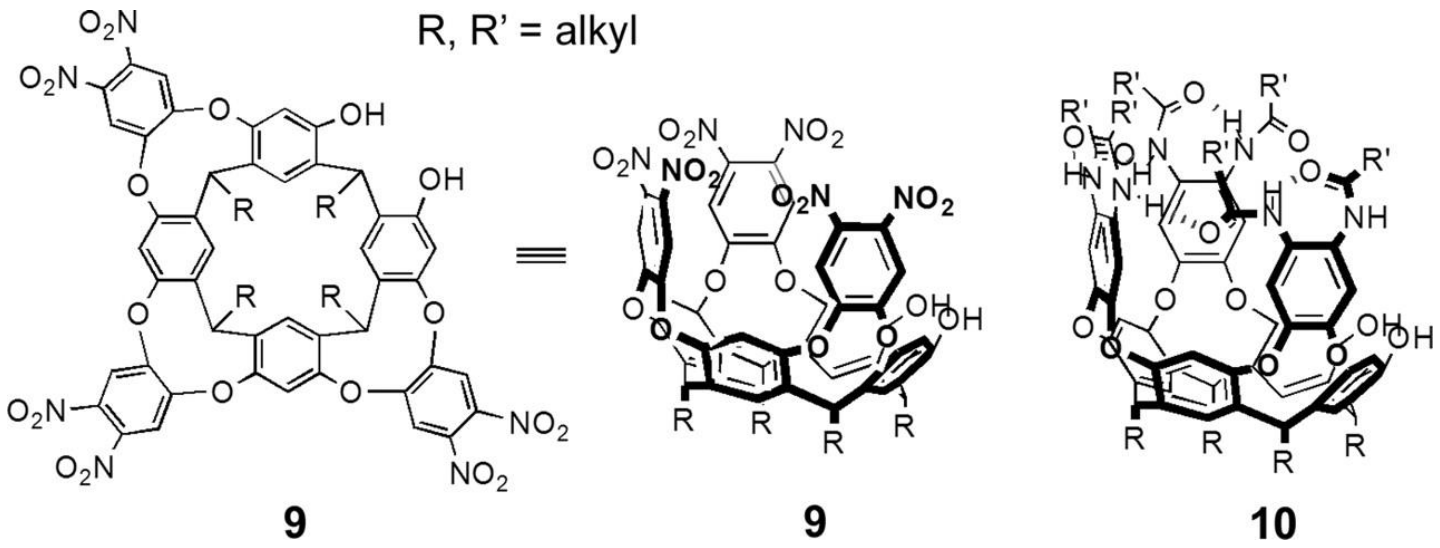
Segnali NMR distinti, misura della cinetica di scambio (VT NMR)

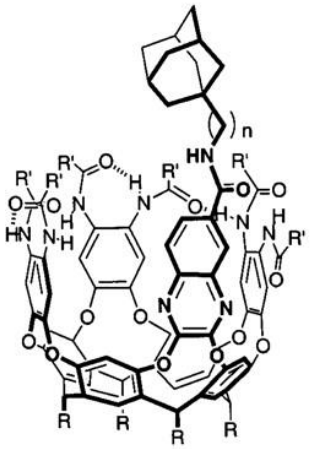


Barriera cinetica di scambio di *ca.* 17 kcal mol^{-1}



Cavitandi funzionali?





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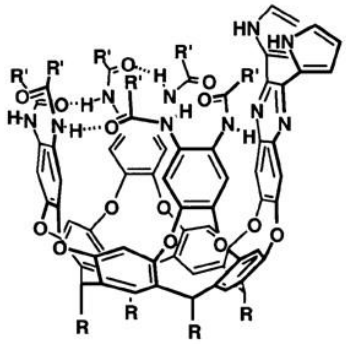

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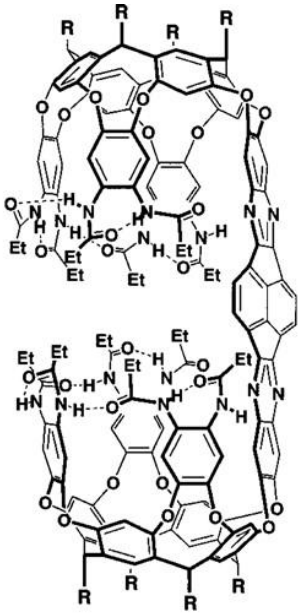

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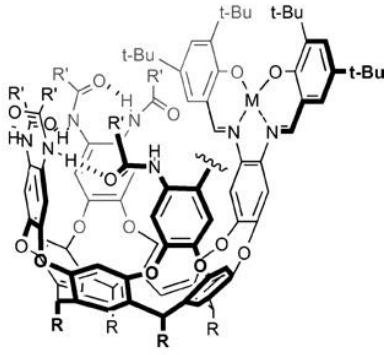
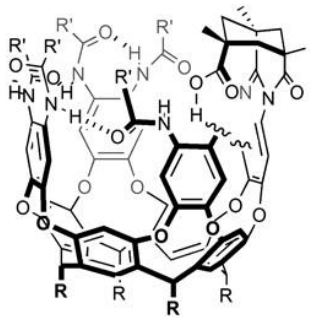


17



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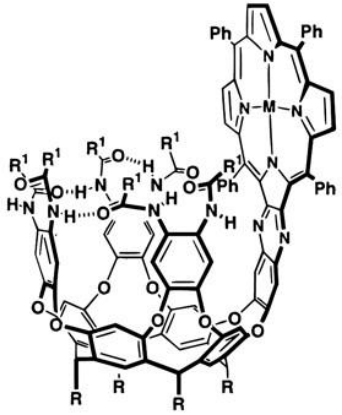
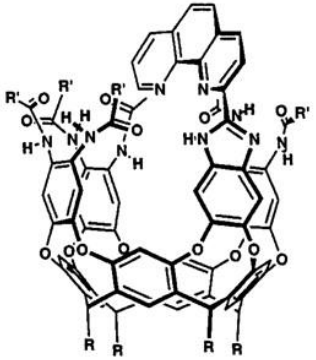


14



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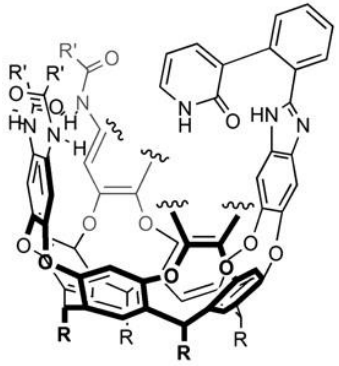

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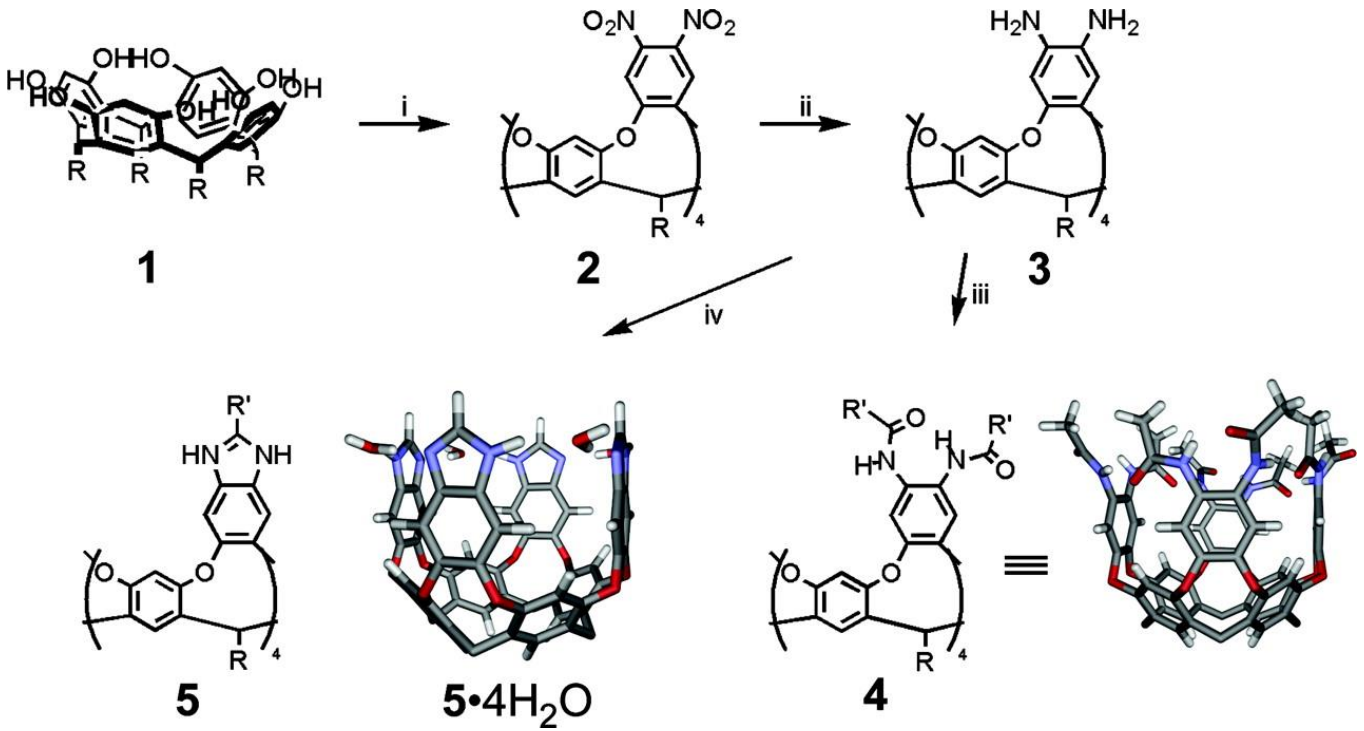


Fig. 1. The synthesis of deep cavitands from a resorcinarene platform. 1, 1,2-difluoro-4,5-dinitrobenzene, Et_3N, DMF, Δ. 2, $SnCl_2$, HCl, EtOH, Δ; or H_2, Raney Ni, toluene. 3, acyl chloride, K_2CO_3, EtOAc, H_2O; or acyl chloride, Et_3N, toluene. 4, ortho ester, DMF/CH_2Cl_2; or imidate, EtOH; or aldehyde, $C_6H_5NO_2$. The model structure of **5** has been minimized by using the AMBER force field, whereas that of **4** is truncated from the crystal structure (51). The R groups have been removed or truncated for viewing clarity.

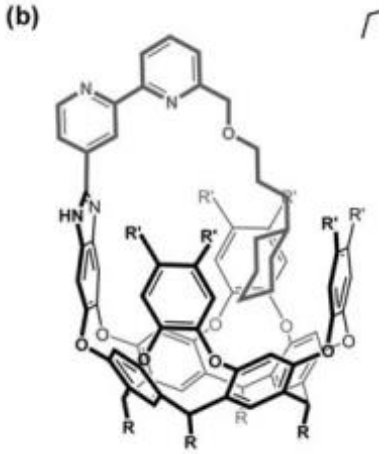
Self-Hosting Cavitand

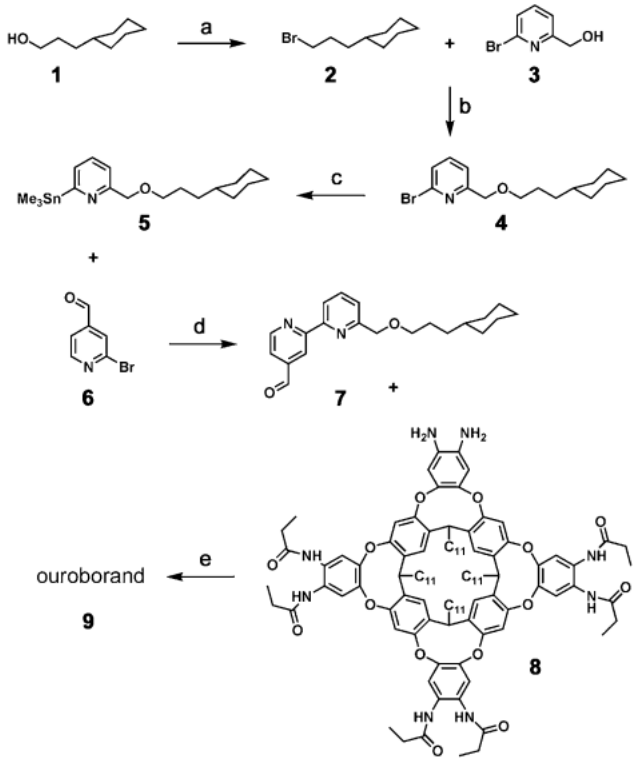
DOI: 10.1002/anie.200906753

The Ouroborand: A Cavitand with a Coordination-Driven Switching Device**

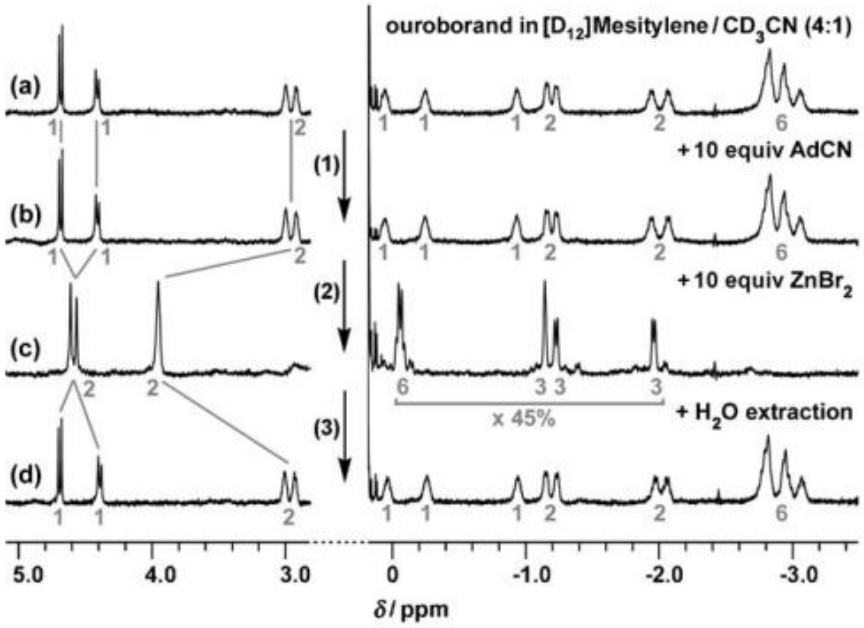
*Fabien Durola and Julius Rebek, Jr.**

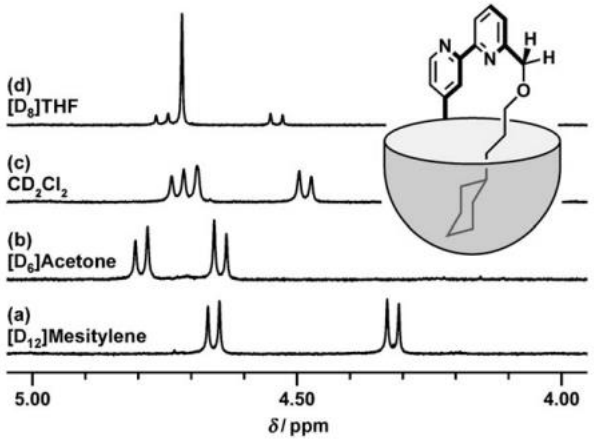
Angew. Chem. Int. Ed. **2010**, *49*, 3189–3191

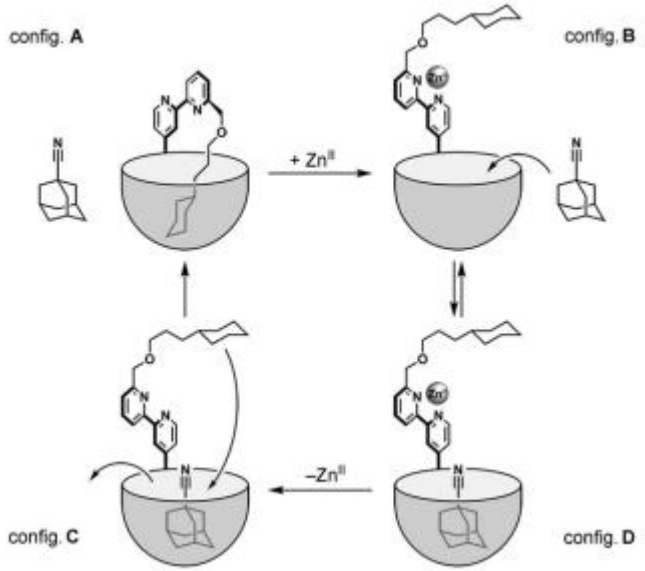


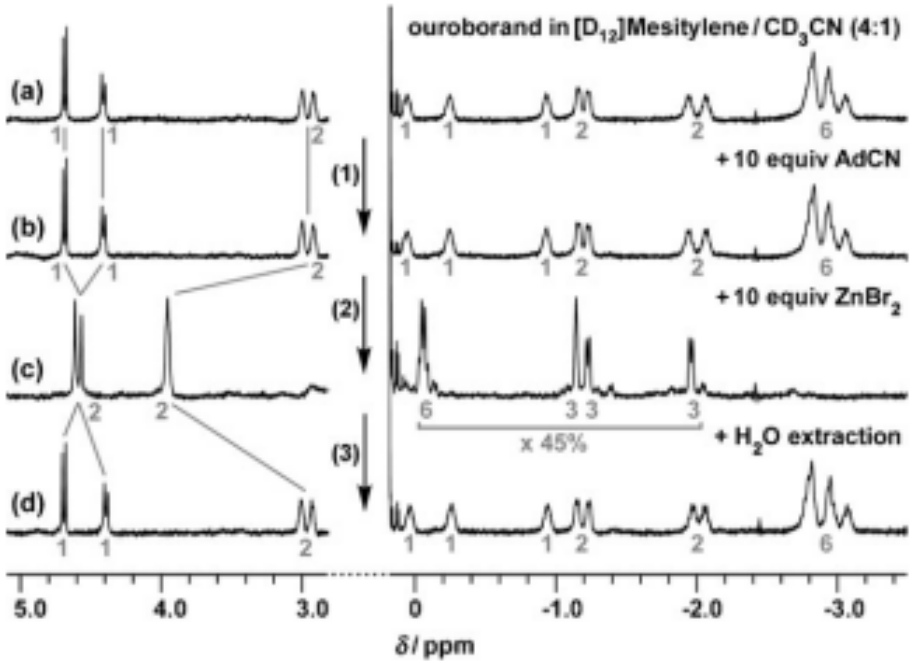


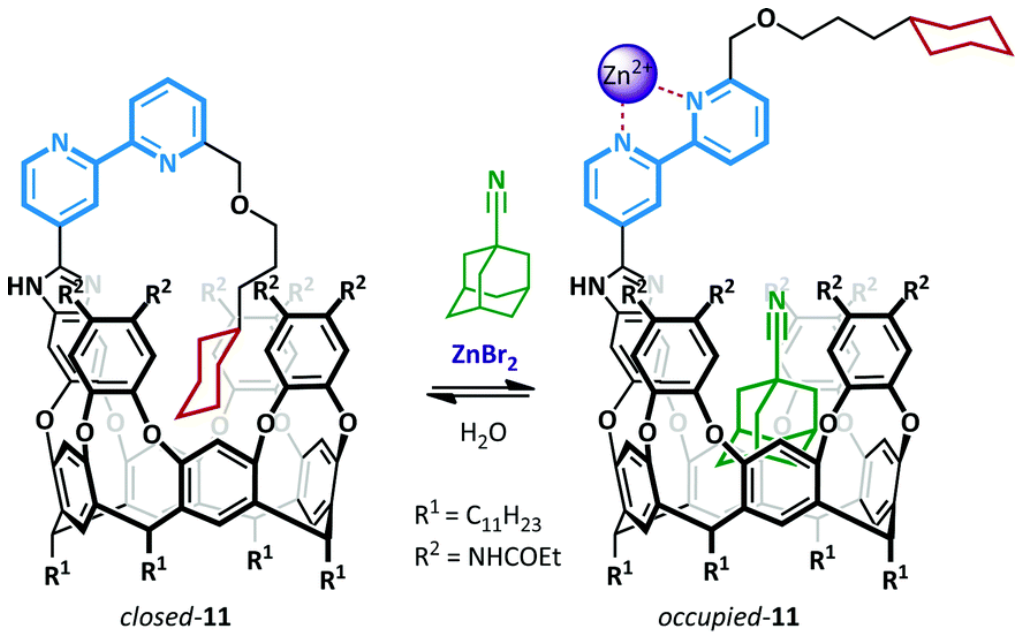
Scheme 3. Synthesis of the ouroborand. a) PBr_3, 0 °C 15 min, RT 2 h, 100 °C 1.5 h, 100%; b) NaH, THF, RT 2 h, 75 °C 16 h, 26%; c) BuLi, toluene, −20 °C, −78 °C 2 h, Me_3SnCl, −78 °C 1 h, RT, 55%; d) [Pd-(PPh_3)$_4$], toluene, 110 °C 48 h, 75%; e) dioxane, RT 30 min, 100 °C 16 h, 67%.

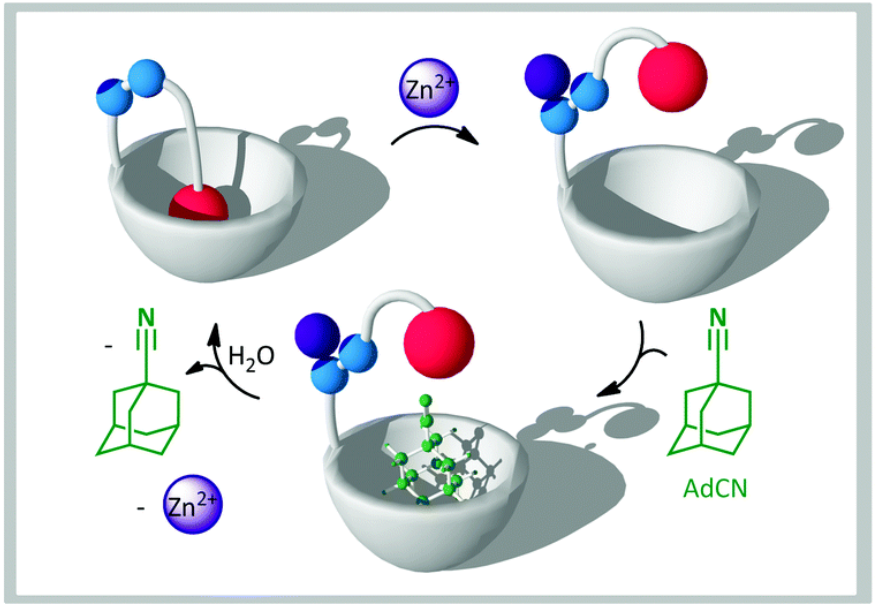

ouroborand in [D12]Mesitylene / CD3CN (4:1)
(a)
(b)
(c)
(d)
(1)
(2)
(3)
+10 equiv AdCN
+10 equiv ZnBr2
+ H2O extraction
x 45%
5.0
4.0
3.0
0
-1.0
-2.0
-3.0
δ / ppm


(d)
[D8]THF
(c)
CD2Cl2
(b)
[D6]Acetone
(a)
[D12]Mesitylene
N
N
H
H
O
5.00
4.50
4.00
δ / ppm


config. A
config. B
config. C
config. D
+ Zn^{II}
–Zn^{II}


ouroborand in [D$_{12}$]Mesitylene / CD$_3$CN (4:1)
(a)
(b)
(c)
(d)
(1)
(2)
(3)
+ 10 equiv AdCN
+ 10 equiv ZnBr$_2$
+ H$_2$O extraction
x 45%
5.0
4.0
3.0
0
-1.0
-2.0
-3.0
δ / ppm


ZnBr2
H2O
R1 = C11H23
R2 = NHCOEt
closed-11
occupied-11

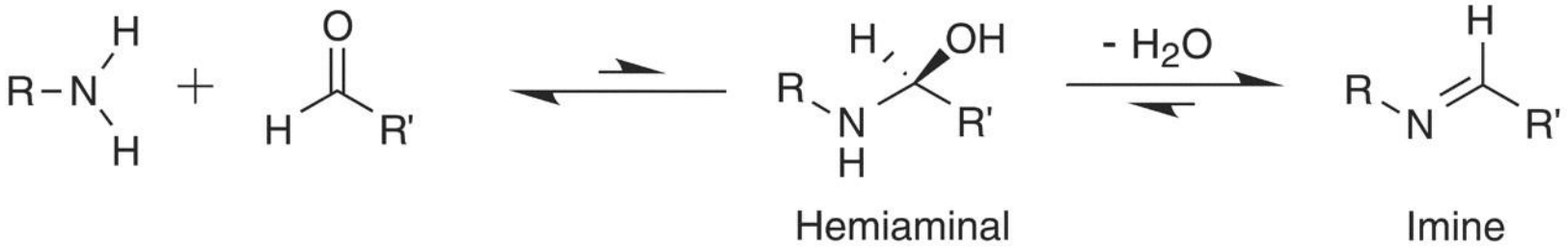

Zn2+
H2O
AdCN

Stabilization of Labile Carbonyl Addition Intermediates by a Synthetic Receptor

Tetsuo Iwasawa, *et al.*

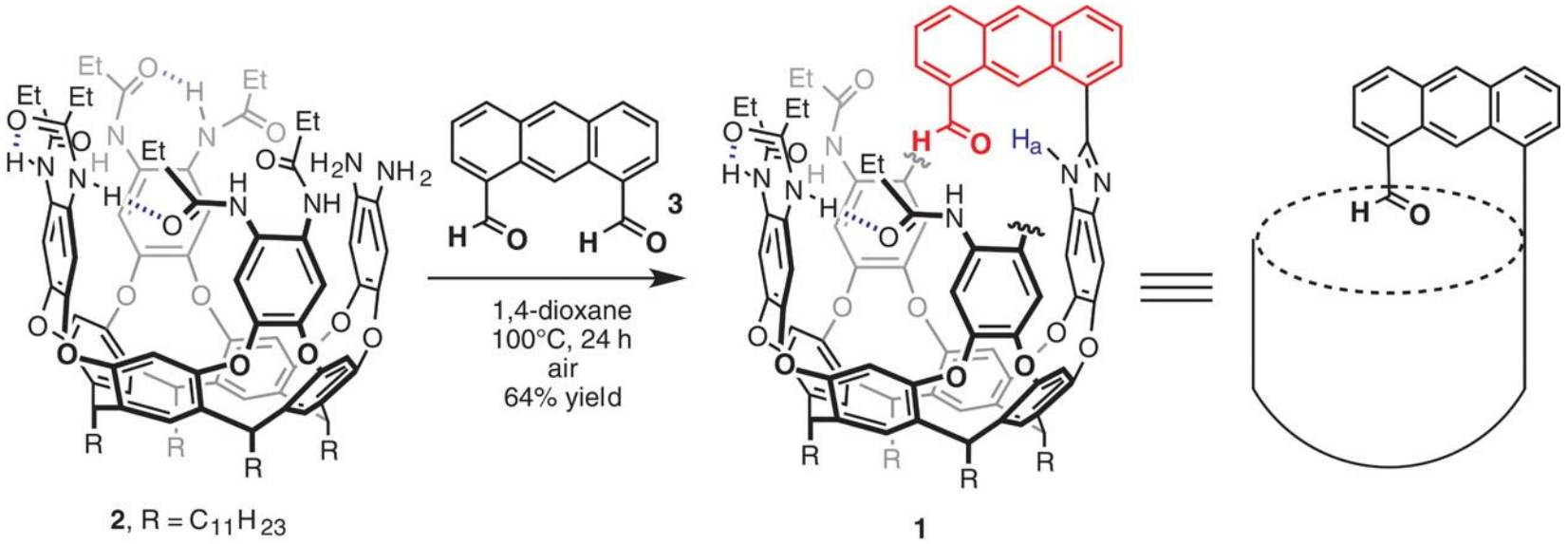
Science **317**, 493 (2007);
DOI: 10.1126/science.1143272

Fig. 1. Mechanism of imine formation from a primary amine and aldehyde.



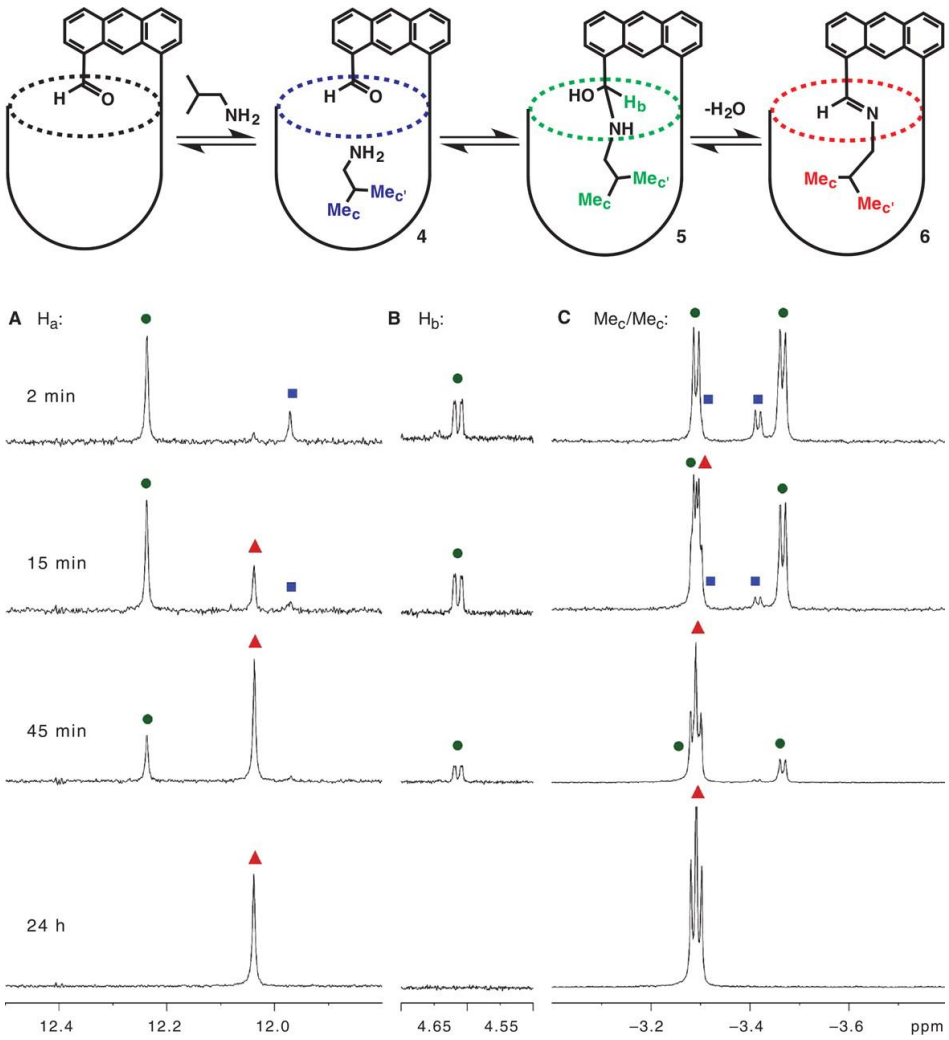
T Iwasawa et al. Science 2007;317:493-496

Fig. 2. Synthesis of cavitand 1.



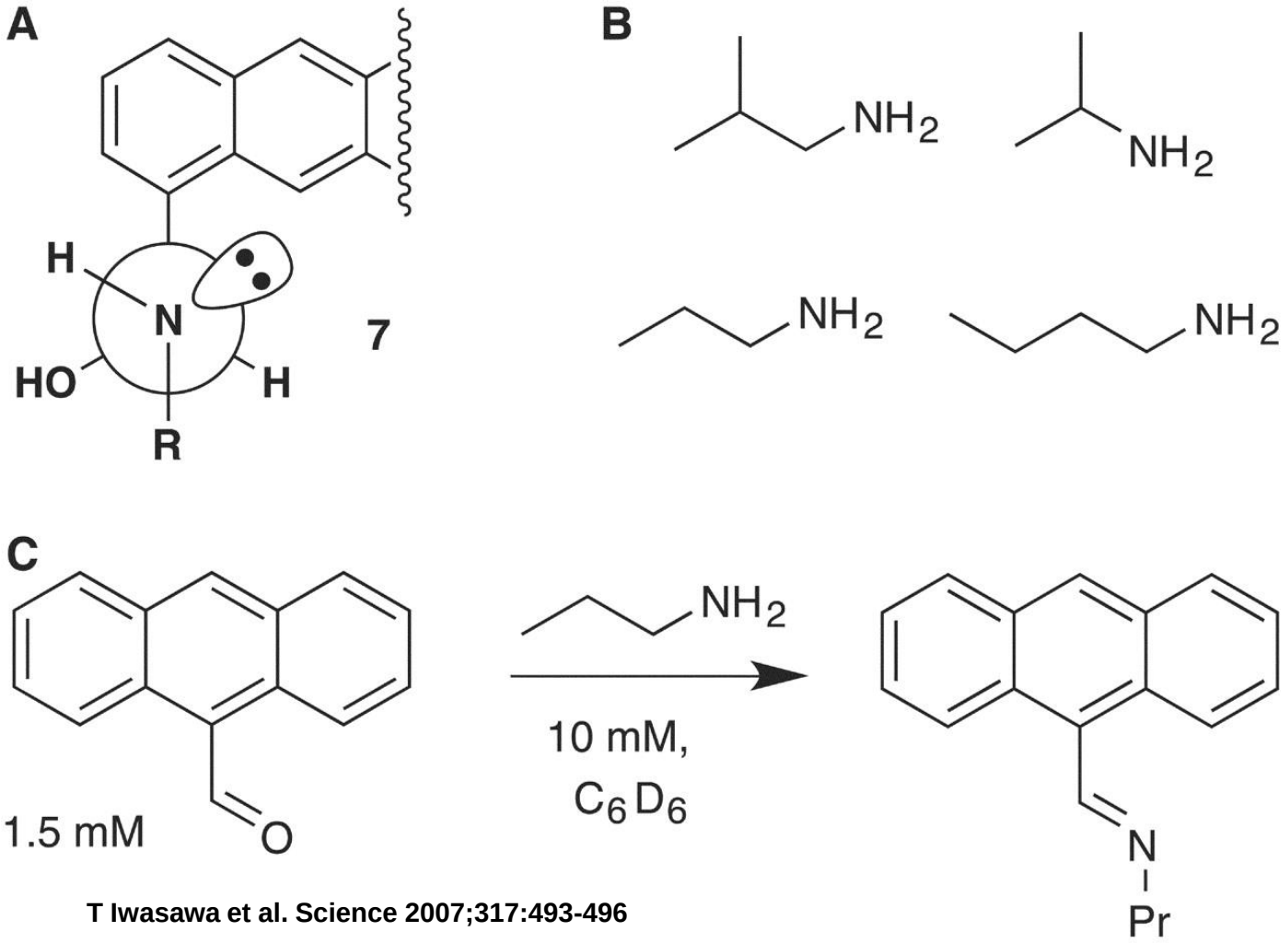
T Iwasawa et al. Science 2007;317:493-496

Fig. 3. The reaction in the cavitand.



T Iwasawa et al. Science 2007;317:493-496

Fig. 4. (A) Conformation of the hemiaminal stereocenter inside the complex as viewed down the newly formed N-C bond (one of two possible enantiomers is shown); (B) other amines for which hemiaminal formation is observed; (C) representation of the cavitand-free control reaction.



T Iwasawa et al. Science 2007;317:493-496

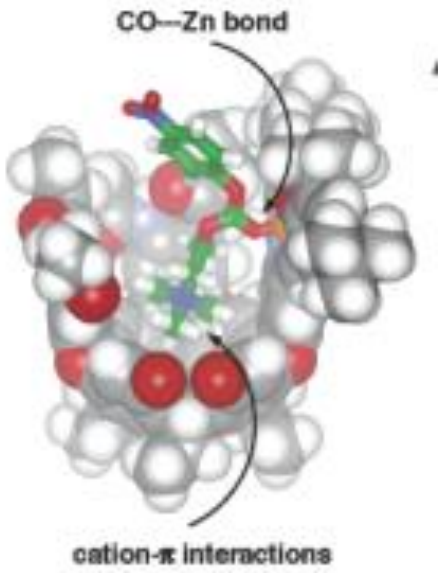
J|A|C|S
COMMUNICATIONS

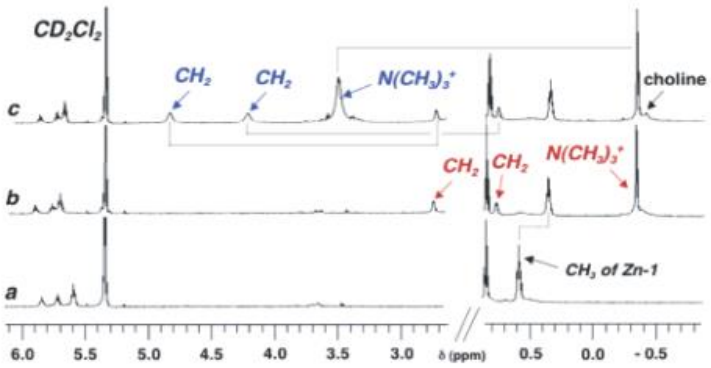
Published on Web 11/24/2004

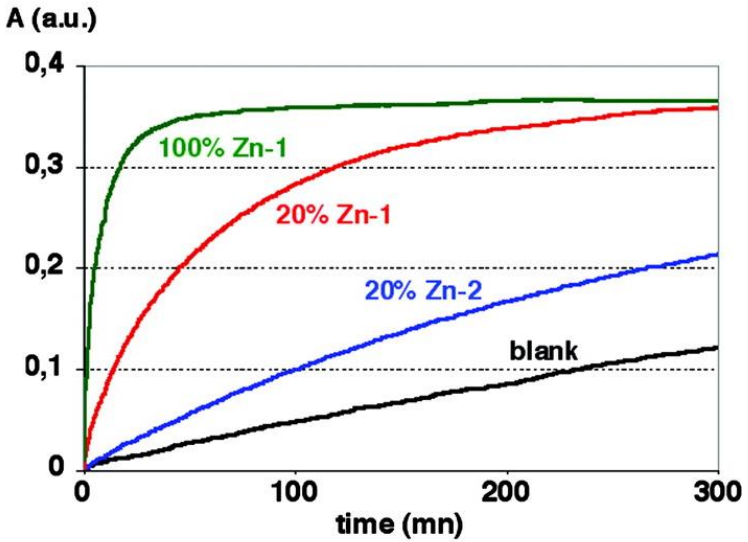
J. AM. CHEM. SOC. 2004, *126*, 16280−16281

Catalysis by a Synthetic Receptor Sealed at One End and Functionalized at the Other

Sébastien Richeter and Julius Rebek, Jr.*

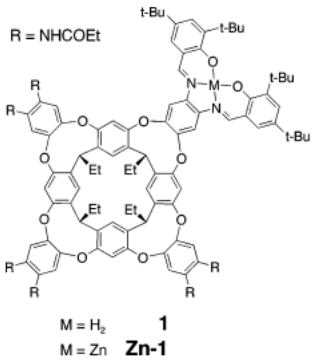


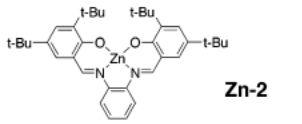


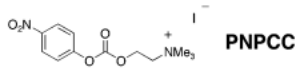


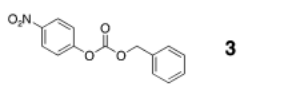
$\lambda_{max} = 405$ nm

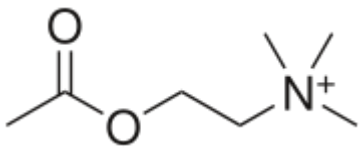
entry	catalyst (mole %)	k_{obsd} (10^{-3} mn^{-1})	$t_{50\%}$ (mn)	k_{obsd}/k_{uncat}
1	– (0)	1.6	>300	1
2	**Zn-1** (10)	10.3	85	6.4
3	**Zn-1** (20)	19.1	38	11.9
4	**Zn-1** (50)	43.7	9	27.3
5	**Zn-1** (100)	84.7	4	52.9
6	**Zn-2** (20)	3.6	230	2.3
7	**1** (20)	1.6	>300	1
8	**Zn-1** (20)[b]	3.9	173	2.4

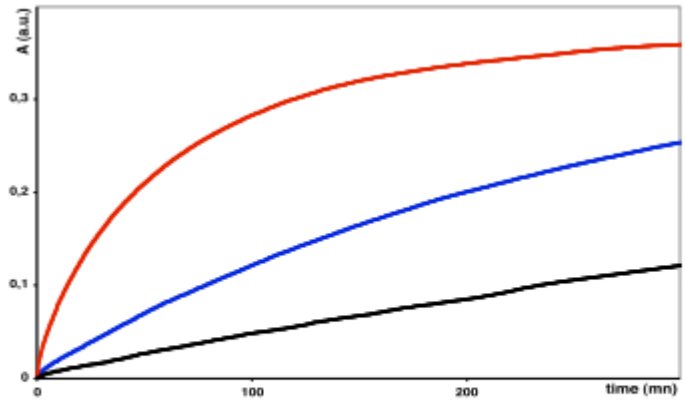




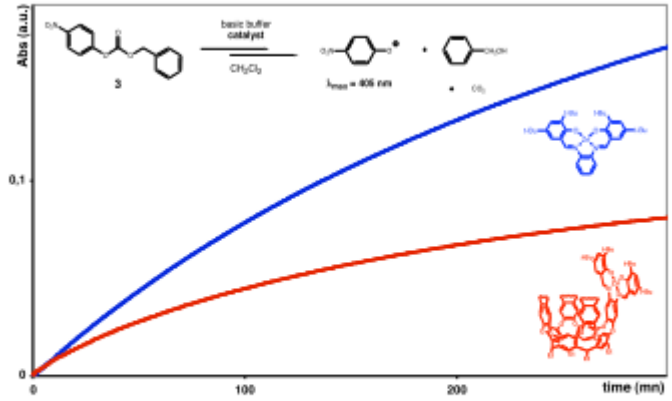






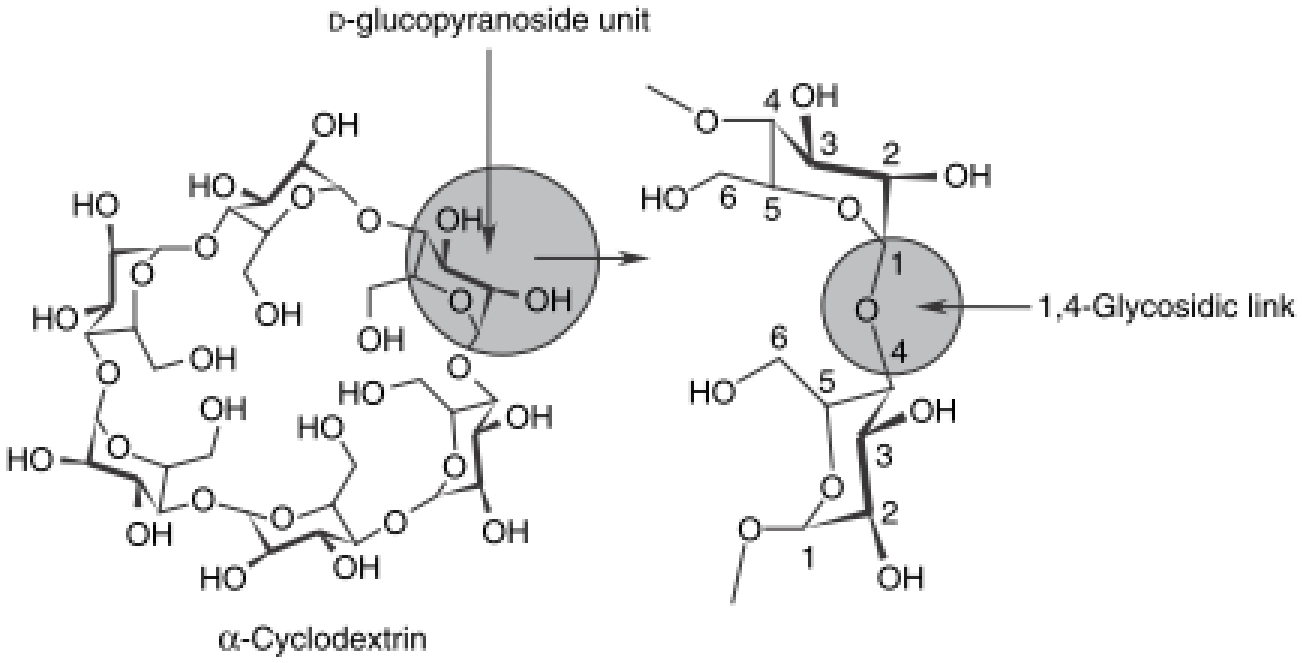


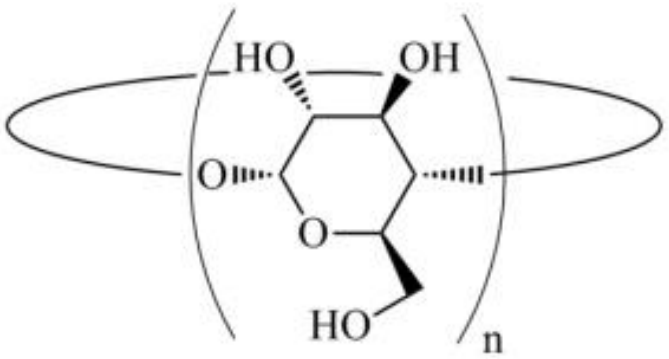
Red : 20% of the cavitand **Zn-1**
Blue : 20% of the cavitand **Zn-1 + 65 µM acetylcholine chloride**
Black : no catalyst (blank reaction)

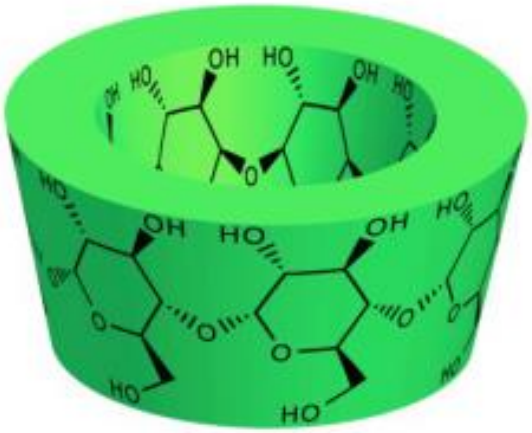


Red : 20% of the cavitand **Zn-1**
Blue : 20% of the cavitand **Zn-2**

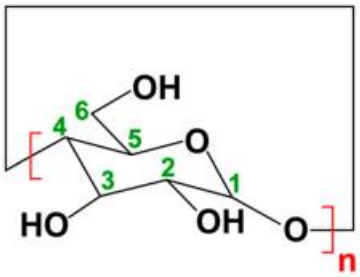
Ciclodestrine – unità D-glucopiranosidiche (legami 1,4-glicosidici)

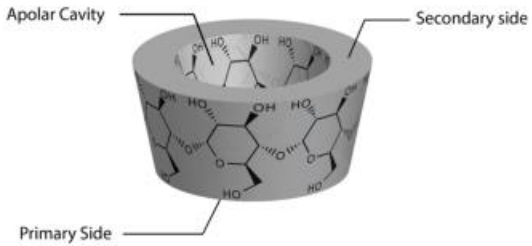


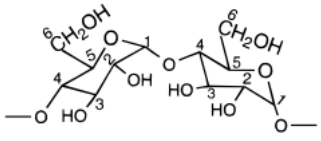


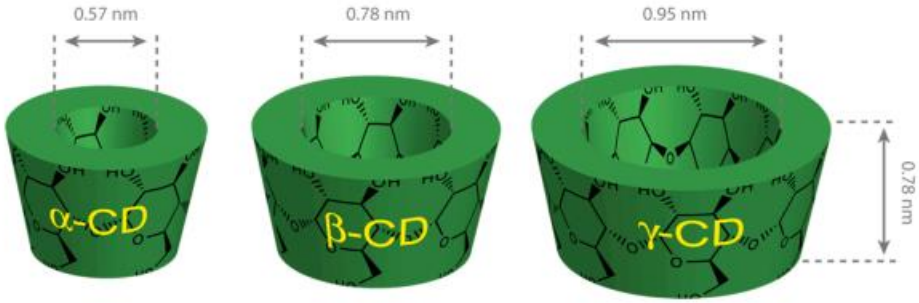


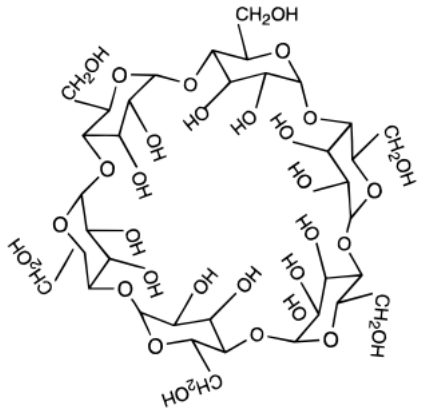
n=6 α-cyclodextrin
n=7 β-cyclodextrin
n=8 γ-cyclodextrin

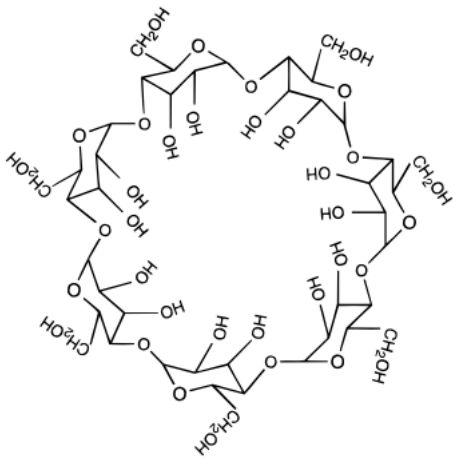

OH
6
4
5
O
3
2
1
HO
OH
O
n

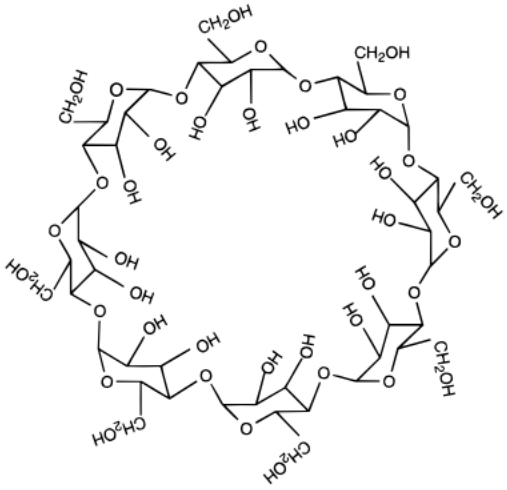

Apolar Cavity
Secondary side
Primary Side




0.57 nm
0.78 nm
0.95 nm
α-CD
β-CD
γ-CD
0.78 nm







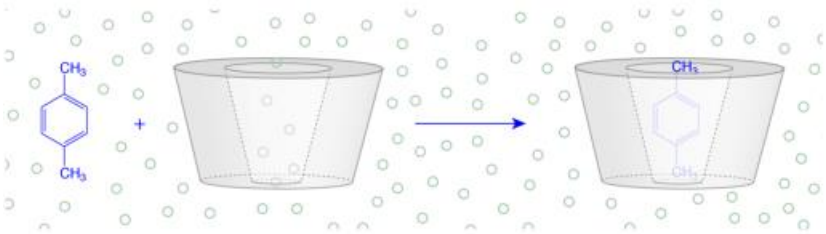
Schardinger was the first researcher to describe the fundamental properties of these dextrins, and he is also acknowledged as being the first to lay down the basis of their chemistry, including their ability to form complexes. Indeed, he became known as the "Founding Father" of cyclodextrin chemistry. He also hypothesized that the crystalline substances were cyclic "polysaccharides"; this was taken up again 30 years later by Freudenberg who came to the conclusion that they were cyclic oligosaccharides.[18] Schardinger in fact never managed to elucidate their structure, and it was only in the late 1940s that the first X-ray analyses confirmed his hypothesis.[19] The major discovery of Schardinger was to isolate the microorganism able to synthesize the enzyme that catalyzes the degradation of starch into cyclodextrins. This was identified a few years later as cyclodextrin glucosyltransferase, which more exactly attacked amylose, the linear component of starch. It can be noted that even today the most frequently used source of enzyme for the production of CDs is *Bacillus macerans*. The terms crystalline α-dextrin and crystalline β-dextrin were indeed used for the first time by Schardinger, which is why for many years cyclodextrins were called Schardinger dextrins in his honor (almost up to the 1970s) even though their discovery is still attributed to Professor Antoine Villiers. Professor Franz Schardinger decided to stop his research into dextrins in 1911, and as a conclusion[15] he wrote: "I realize that still very many questions remain unsolved; the answer to these I must leave to another, who, owing to more favorable external conditions, can deal with the subject more intensively."

Table 1. Recap of the Main Results of Freudenberg on Schardinger Dextrins

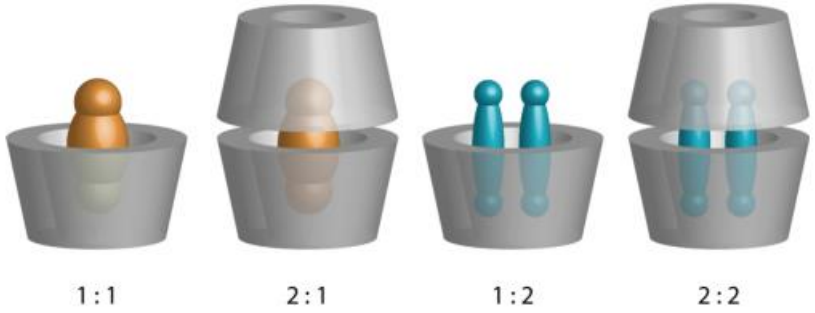
year	result
1922	tosylated dextrins
1930	Schardinger dextrins: laboratory curiosities and/or unwanted byproducts of starch degradation
	Schardinger dextrins: chain molecules intermediate between maltose and starch
1935	the dextrins were lined with a hydrocarbon interior
	synthesis of Schardinger dextrins with high purity
	determination of molecular weights (five for α-dextrin and six for β-dextrin)
	solubility differences of the dextrins
	chemical modification of dextrins (acetylation, methylation, saponification reactions)
1936	studies on the nature of the glycosidic bonds
	hypothesis on the cyclic nature
1938	cyclic chemical structure of dextrins
	hydrophobicity of the inner surface of the dextrins
	ability to form inclusion complexes
	Foundation of the Research Institute for the Chemistry of Wood and Polysaccharides
1939	description of the mechanism of action for *Bacillus macerans*
1943	cyclic structure composed of maltose units bound together by $\alpha(1\rightarrow 4)$ glycosidic linkages
1947	the first scheme for the isolation of pure fractions
1948	discovery of γ-dextrin
	Freudenberg and Cramer demonstrated their conclusions on cyclic structure using optical activity data
	the first indication of the existence of dextrins comprising more than 8 glycosyl units
1950	structure of γ-dextrin
	involvement of hydrophobic forces in the formation of the complexes
	possible existence of dextrins with 9 or 10 units of glucose
1953	first patent concerning applications in pharmaceutical formulations

Solubilità (H_2O): α 145g/L β 18.5 g/L γ 232 g/L

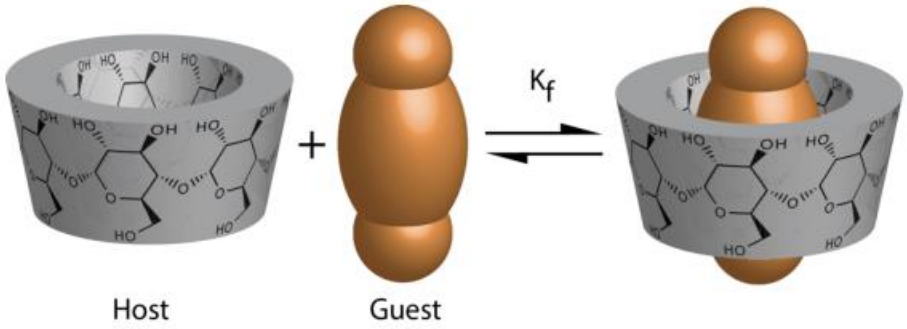
Size-fit, effetto idrofobico, vdW, dipolo-dipolo, legami a idrogeno..

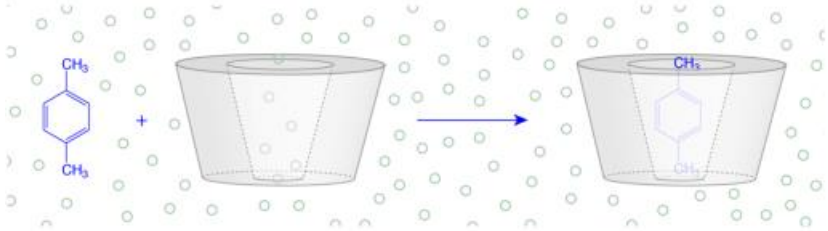


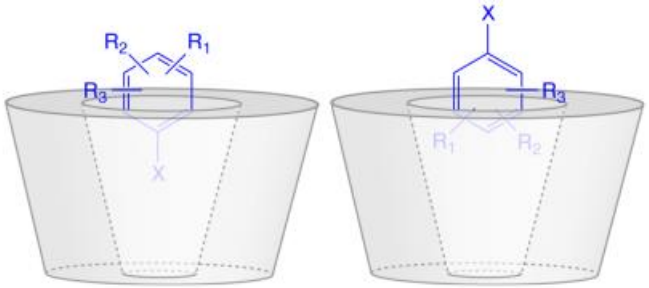
Complessi 1/1 o con varie stechiometrie



Derivatizz tramite gruppi OH:
alkyl/hydroxyalkyl/carboxyalkyl/ester/thiol/tosyl/…


K_f
Host
Guest


CH3
CH3
+
CH3


R2
R1
R3
X
X
R3
R1
R2

non toxic…termostabili..airstable…

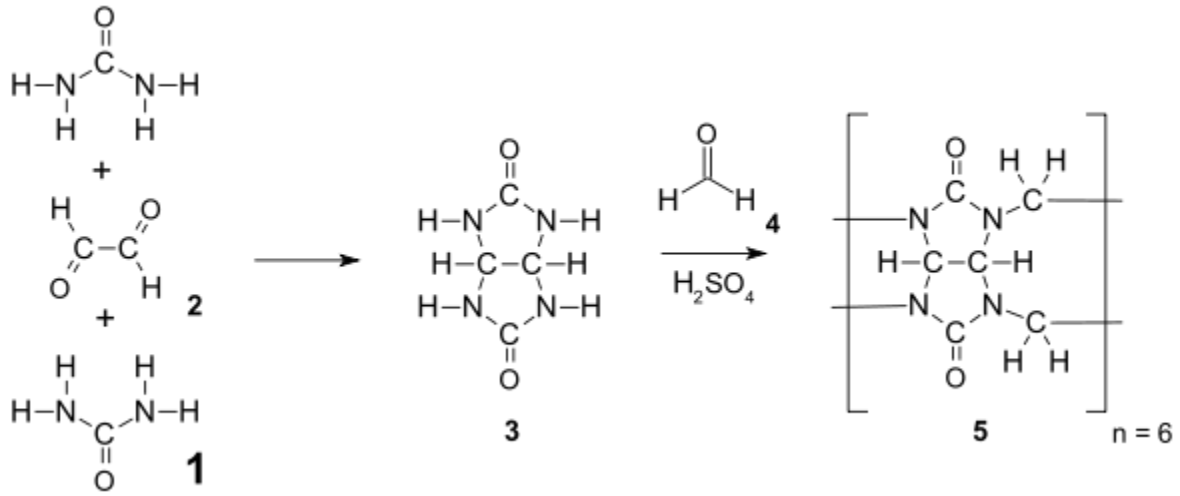
Production 1000 tons/year

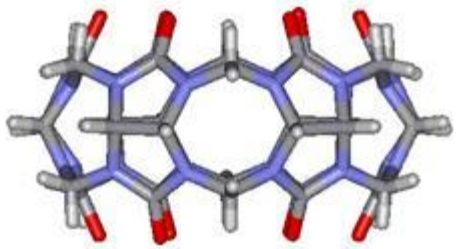
Settori applicativi:

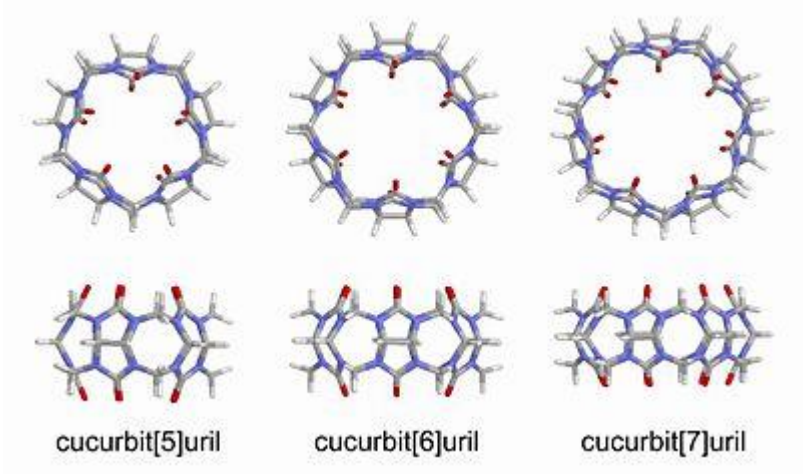
Farmaceutico: stabilità (luce aria). Biodisponibilità, formulazione, somministrazione..
Alimentare: aromi, spezie, emulsioni, colesterolo, vitamine
Cosmetico: lozioni solari
Analitici: grafting su supporti polimerici x cromatografia (HPLC chirale)

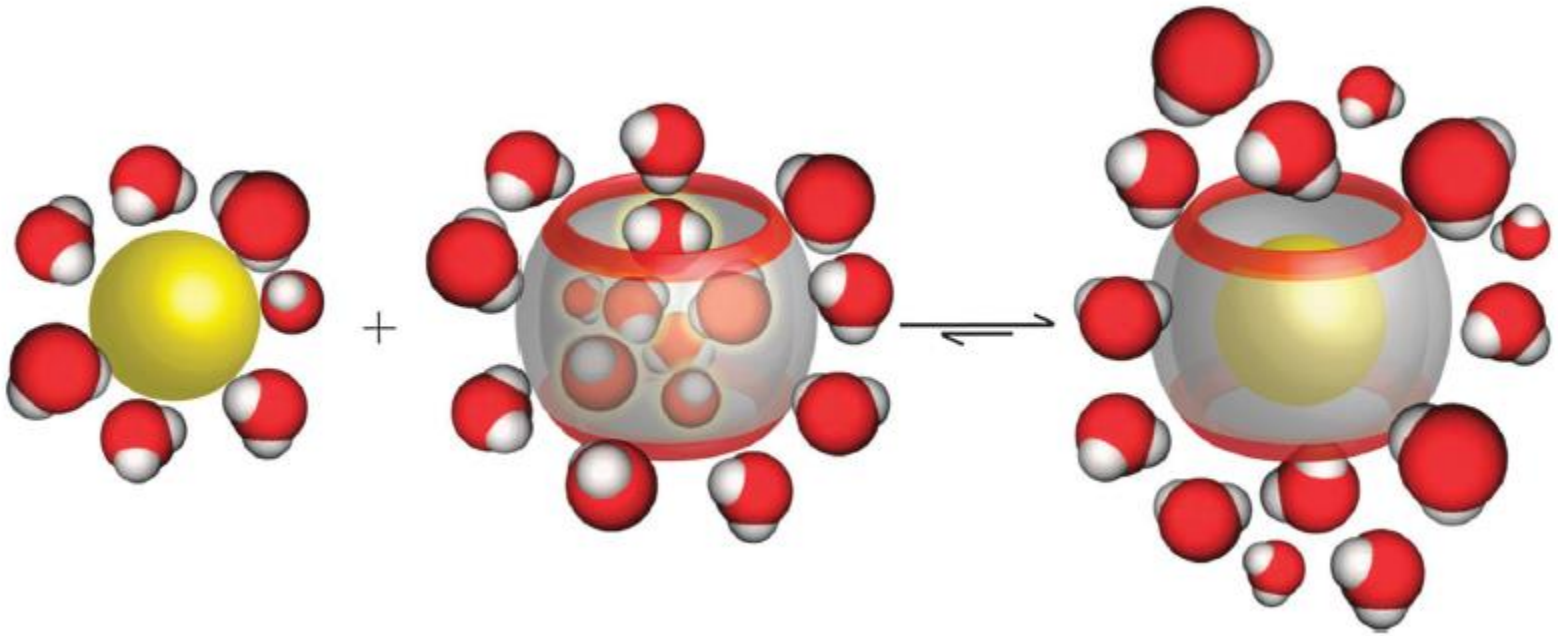
Cyclodextrins News

Cucurbiturili– unità glicolurile (legami metilenici)









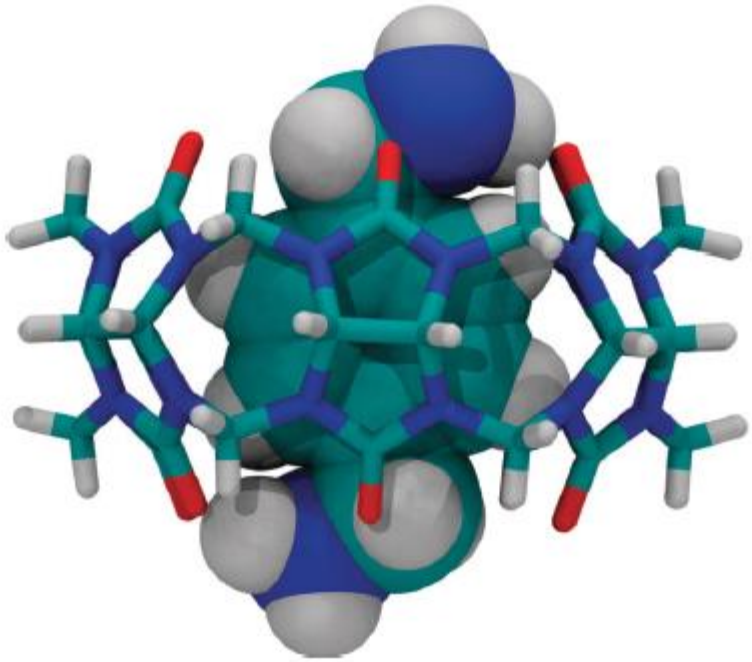


Fig. 13 X-ray structure of the *p*-xylylenediammonium ion encapsulated by CB6, the first X-ray diffraction structure of a CB*n* complex.[127]

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Cucurbiturils: from synthesis to high-affinity binding and catalysis

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