Receptor for neutral molecules

Hydrogen bond

Hydrophobic effect

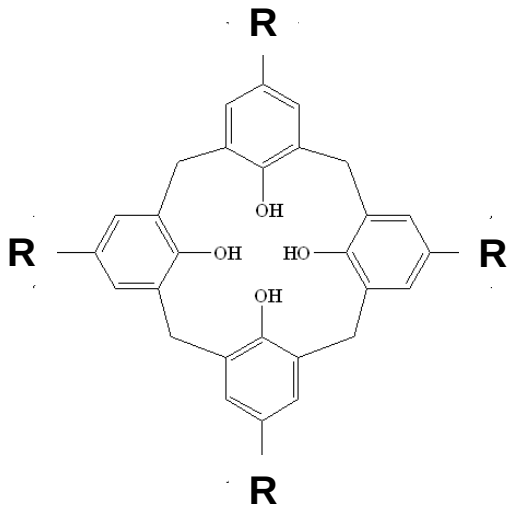
CH-π interactions

π Stacking interactions

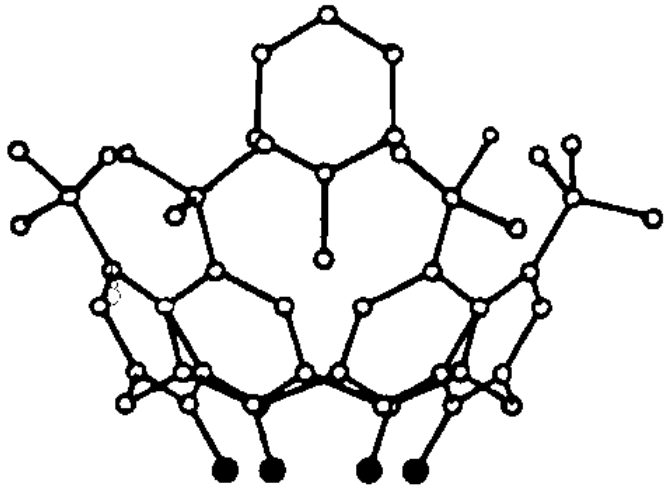
pre organization

Receptor for neutral molecules

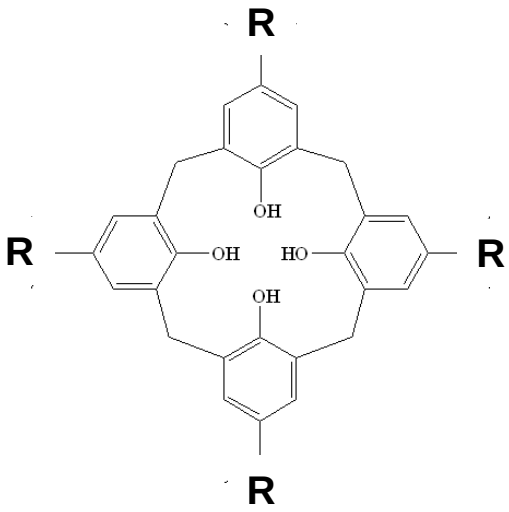
CH-π interactions pre organization (deep and rigid cavities)

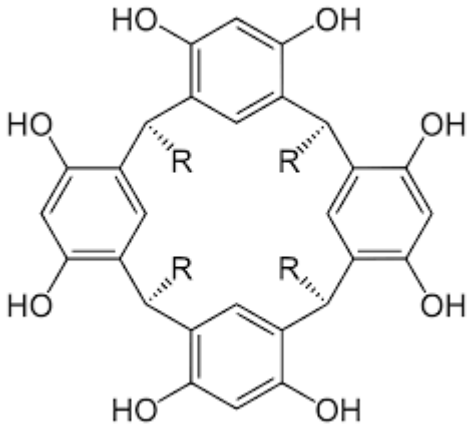


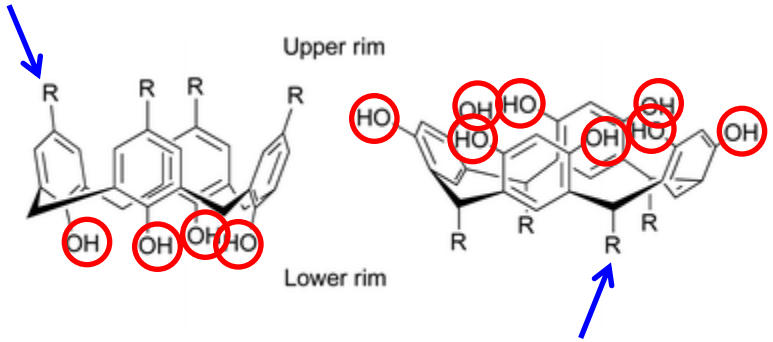
calix[4]arene



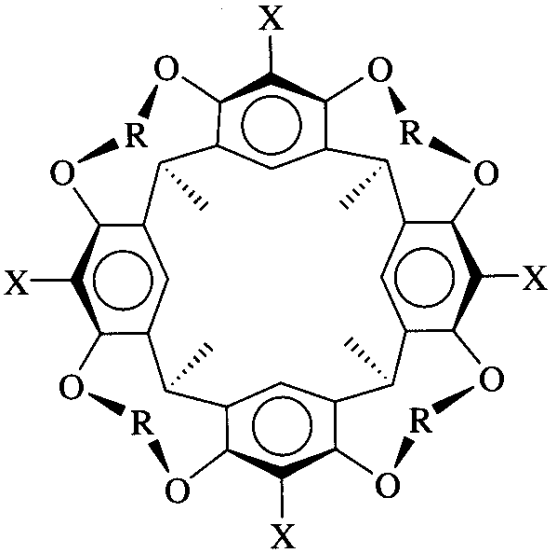
p-tert-Butylcalix[4]arene-toluene inclusion complex

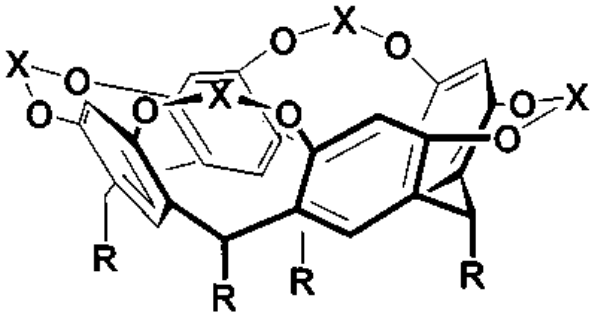

R
R
R
R
OH
OH
HO
OH


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

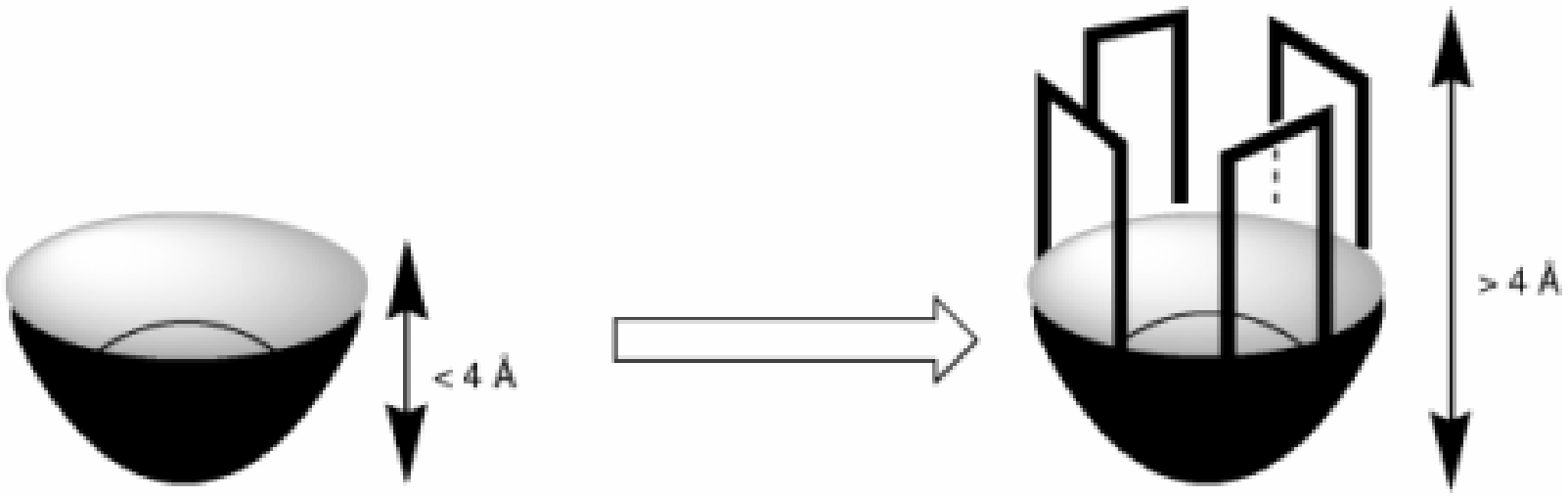
[4] resorcinarene



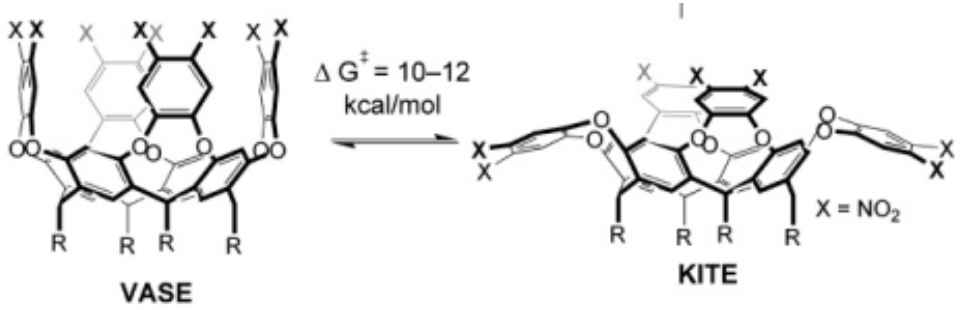


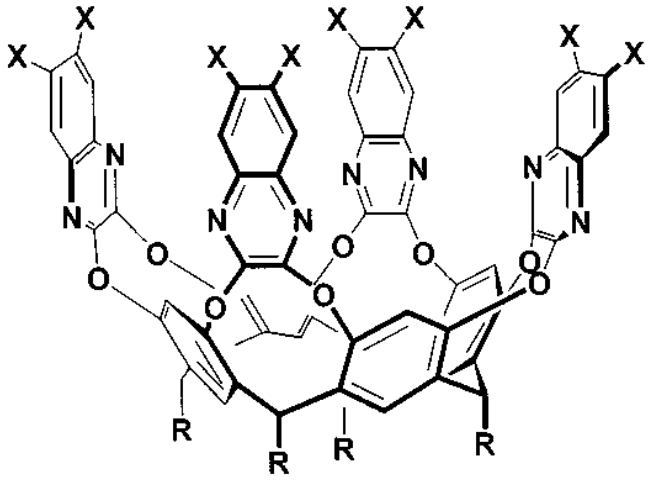
2 R = Alkyl, Ar;
X = $(CH_2)_n$, $SiAlk_2$

Concave cyclophanes ⟹ Cavitands

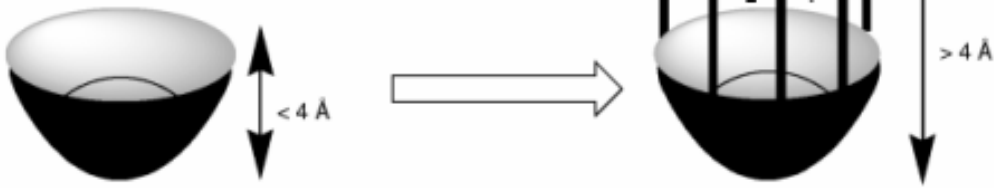


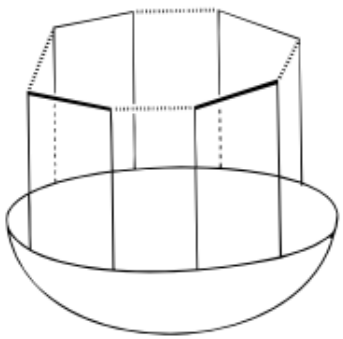
The studies of Cram[13] had established a barrier of some 10 to 12 kcal mol^{-1} for the vase-to-kite interconversion. If this

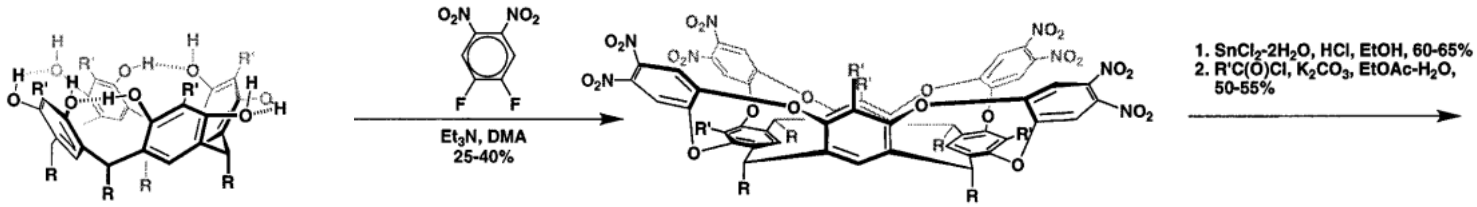


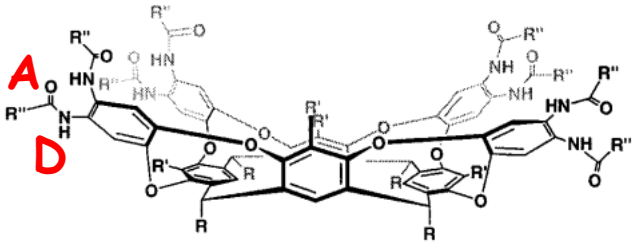


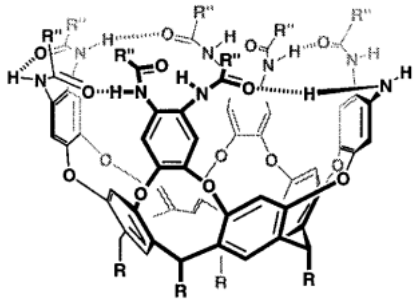
3 R = Alkyl;
X = H, CH_3, Hlg

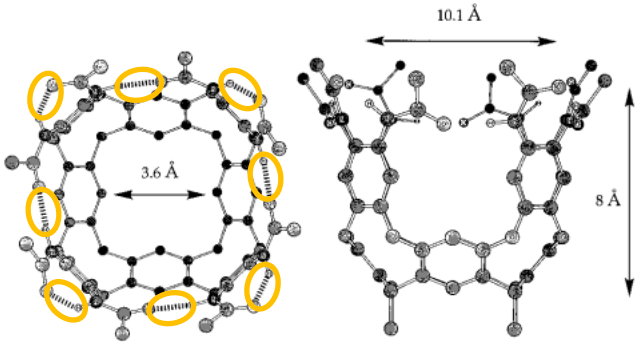

< 4 Å
> 4 Å

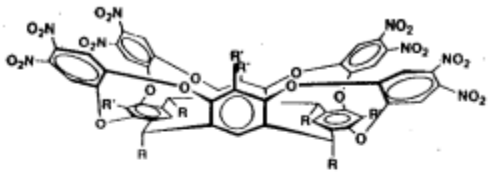



Et3N, DMA
25-40%
1. SnCl2-2H2O, HCl, EtOH, 60-65%
2. R'C(O)Cl, K2CO3, EtOAc-H2O,
50-55%


A
D

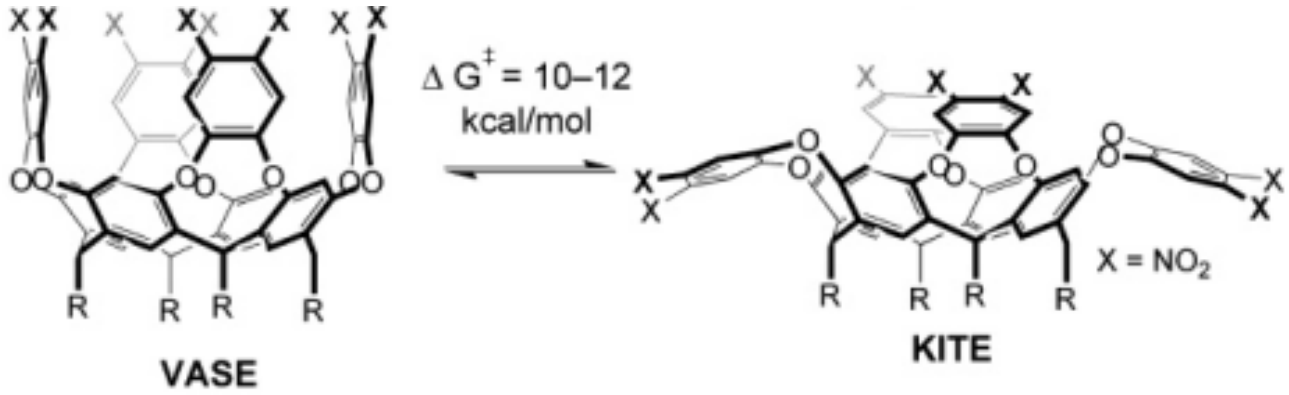


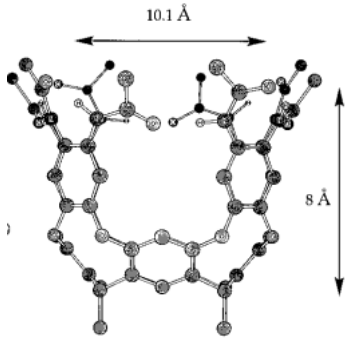

10.1 Å
3.6 Å
8 Å



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

$CDCl_3$, 295 K



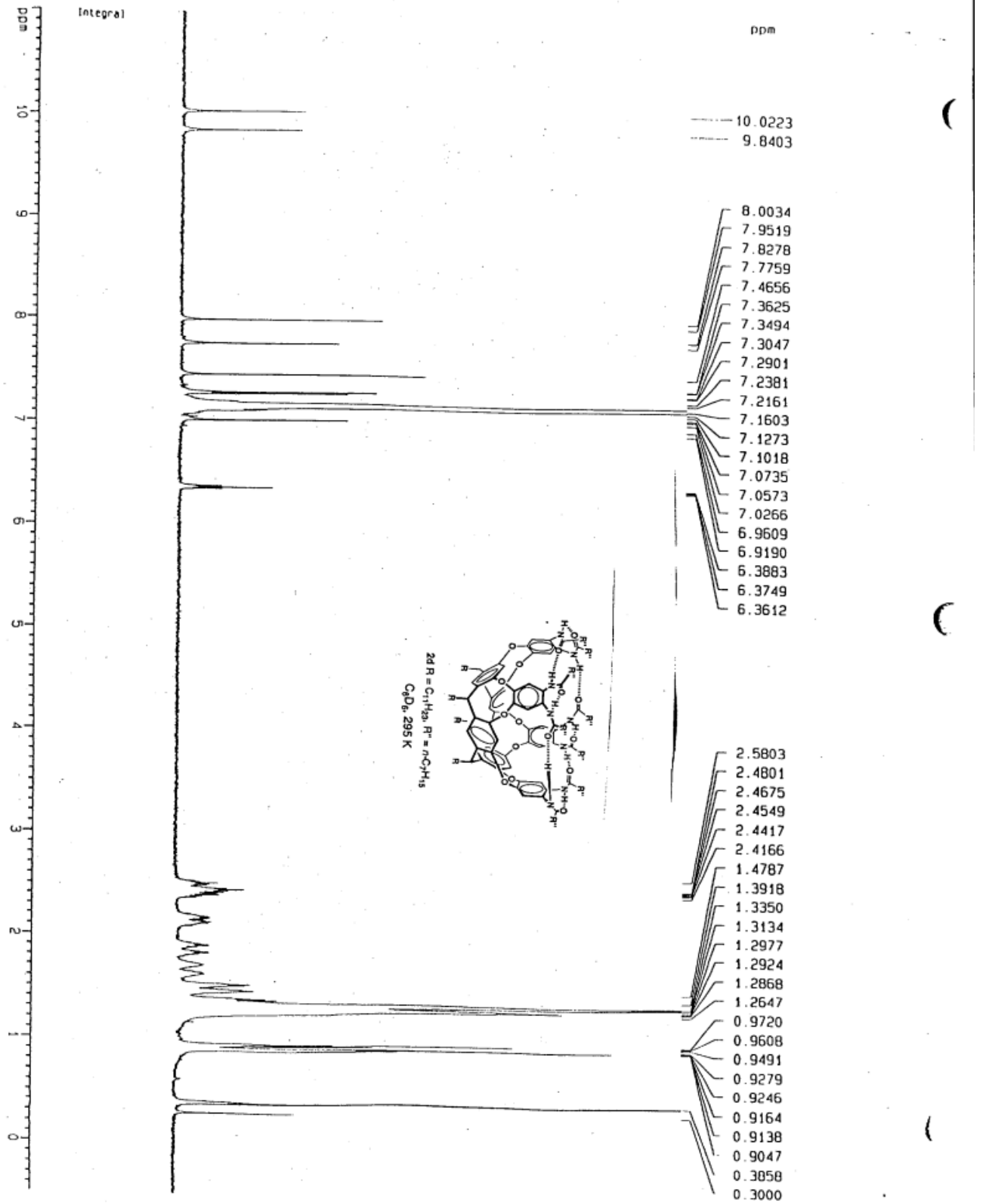


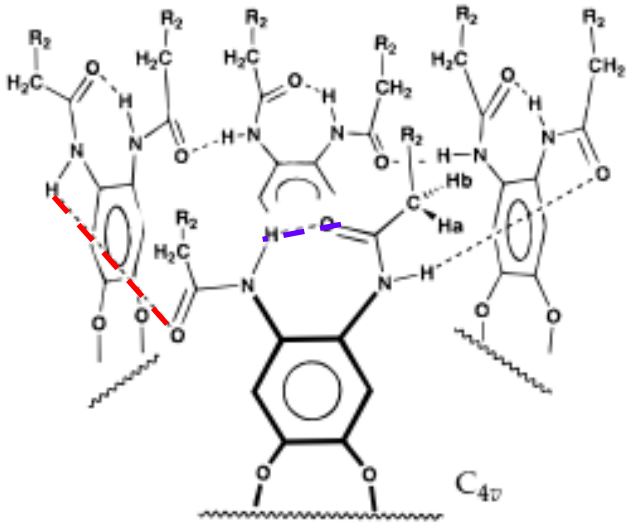
Sharp ^{1}H NMR spectrum
–NH signal shifted dwonfield,

^{1}H NMR spectrum independent from concentration

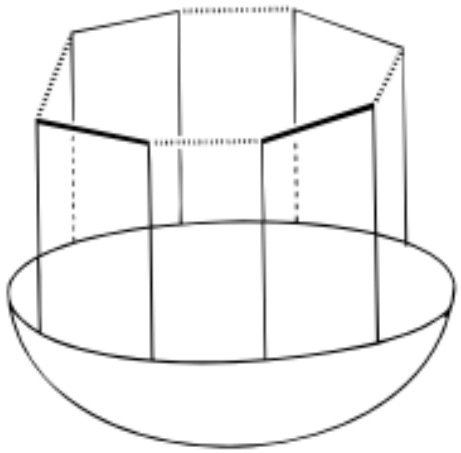
Addition of a competitive solvent (dmso-d_6):
broadening of the signals

Stretching NH (IR)

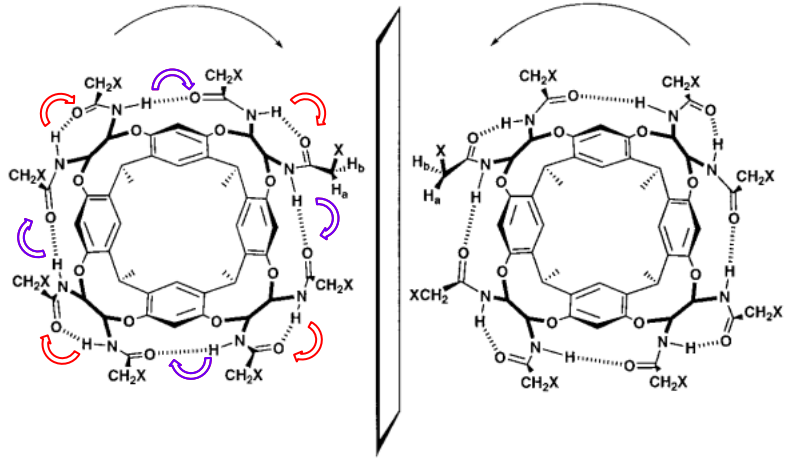

[integral]
ppm
10.0223
9.8403
8.0034
7.9519
7.8278
7.7759
7.4656
7.3625
7.3494
7.3047
7.2901
7.2381
7.2161
7.1603
7.1273
7.1018
7.0735
7.0573
7.0266
6.9609
6.9190
6.3883
6.3749
6.3612
2.5803
2.4801
2.4675
2.4549
2.4417
2.4166
1.4787
1.3918
1.3350
1.3134
1.2977
1.2924
1.2868
1.2647
0.9720
0.9608
0.9491
0.9279
0.9246
0.9164
0.9138
0.9047
0.3058
0.3000
2d R = C11H23, R'' = nC7H15
C6D6, 295 K

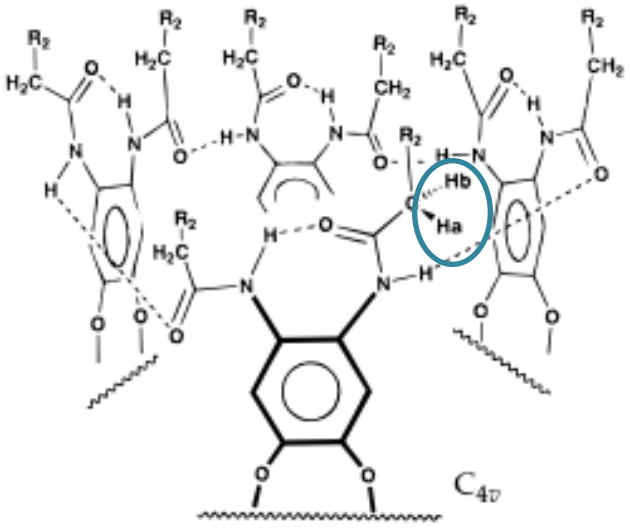


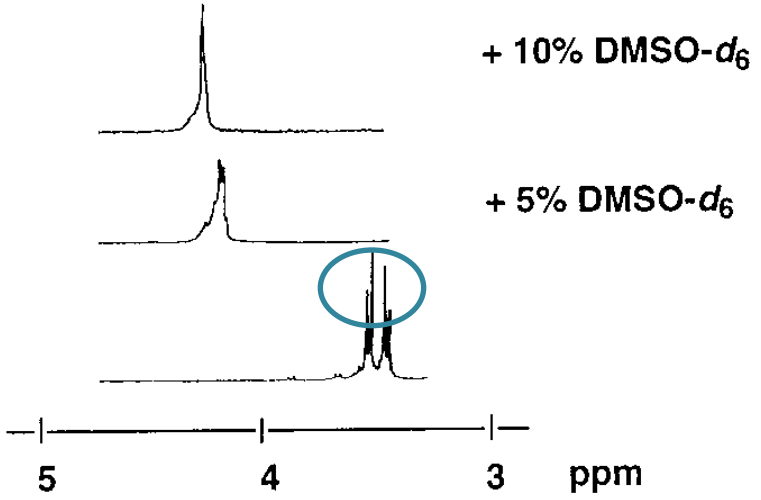
=

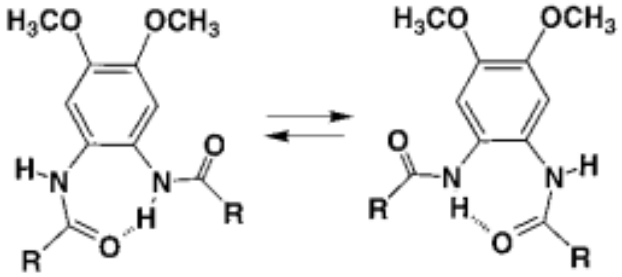


3 $R_1 = C_{11}H_{23}$, $R_2 = C_6H_{13}$



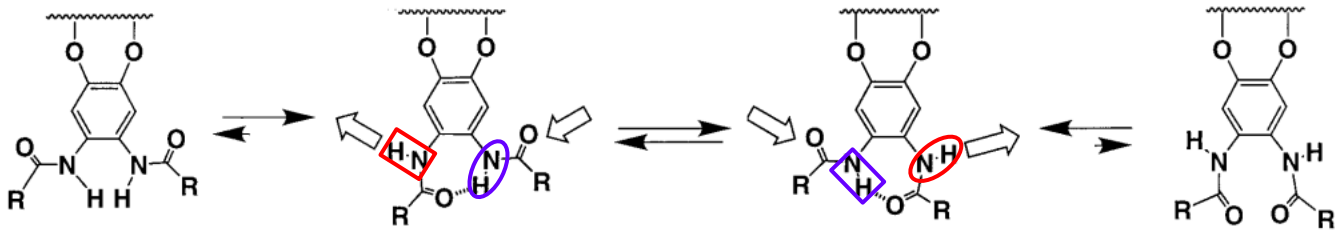

Hb
Ha
C47

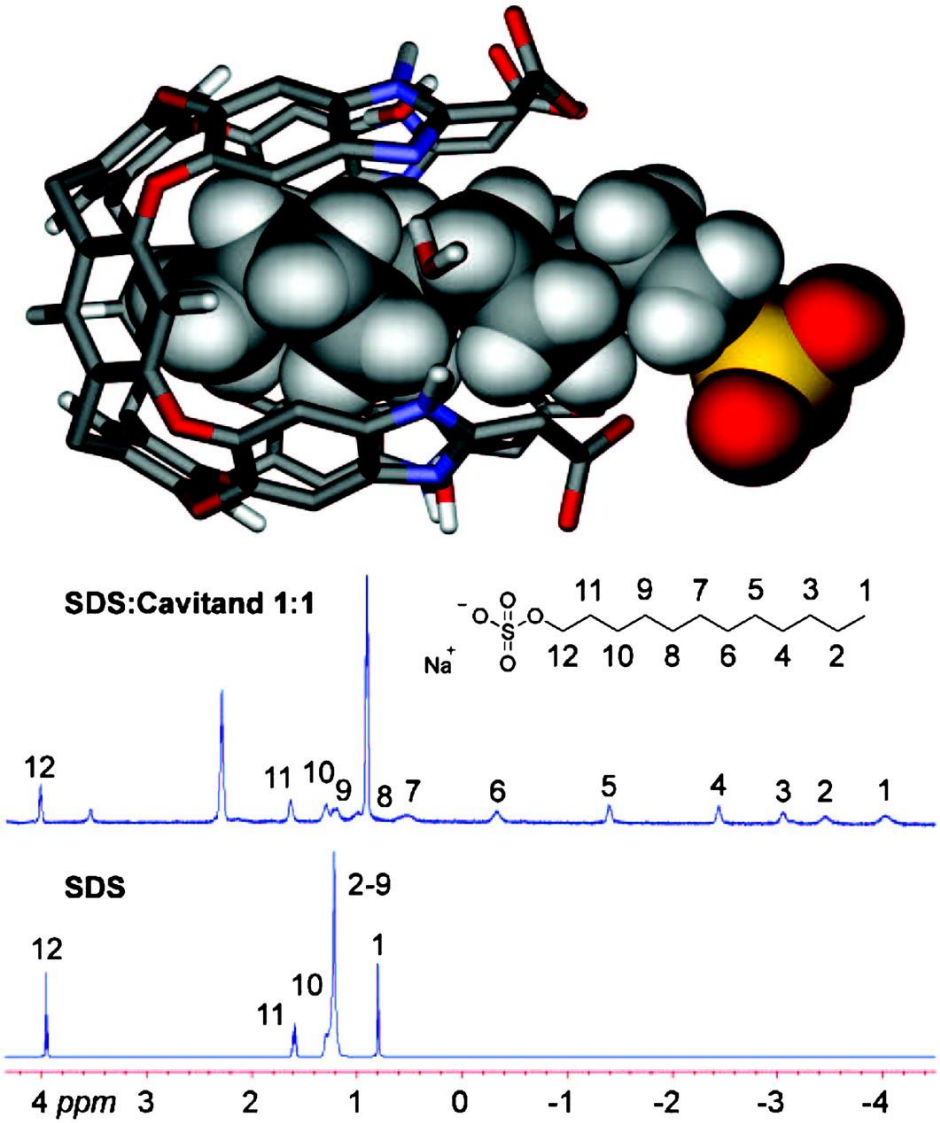

+ 10% DMSO-d6
+ 5% DMSO-d6
5
4
3
ppm

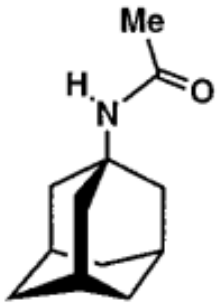


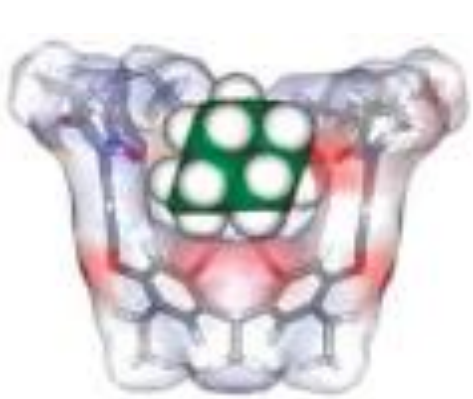
4

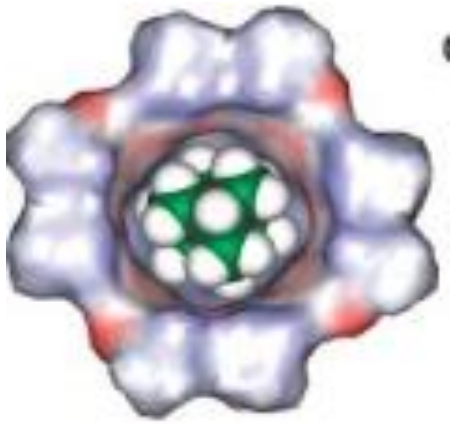
cavitand, four hydrogen bonds need to be broken: those that hold together adjacent rings. The typical costs of such ruptures in organic solvents are roughly 1 to 2 kcal mol^{-1} per hydrogen bond,[17] so the additional 5 to 7 kcal mol^{-1} is quite reasonable for the overall 17 kcal mol^{-1} activation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




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

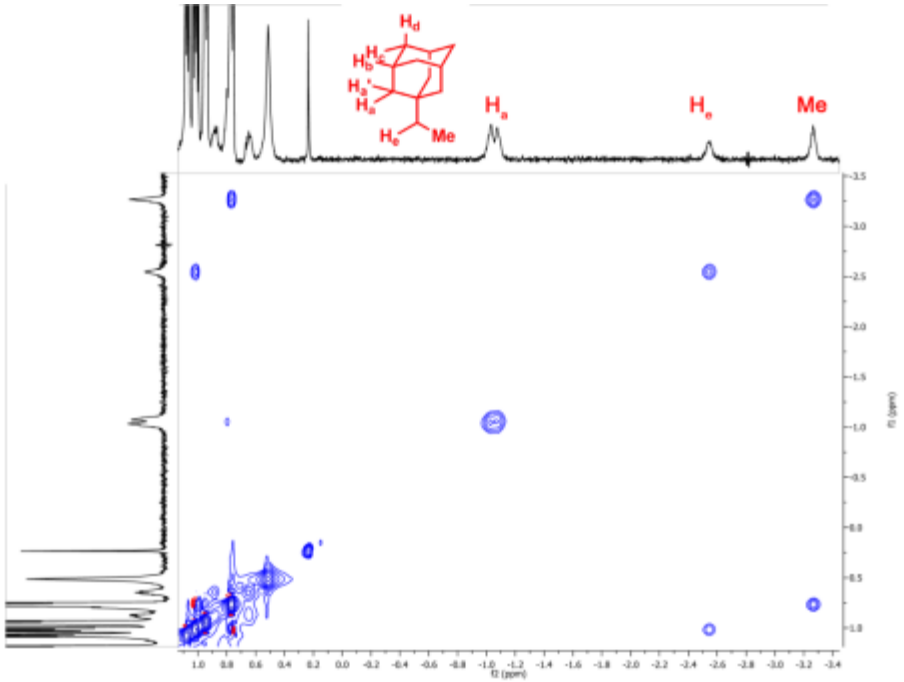




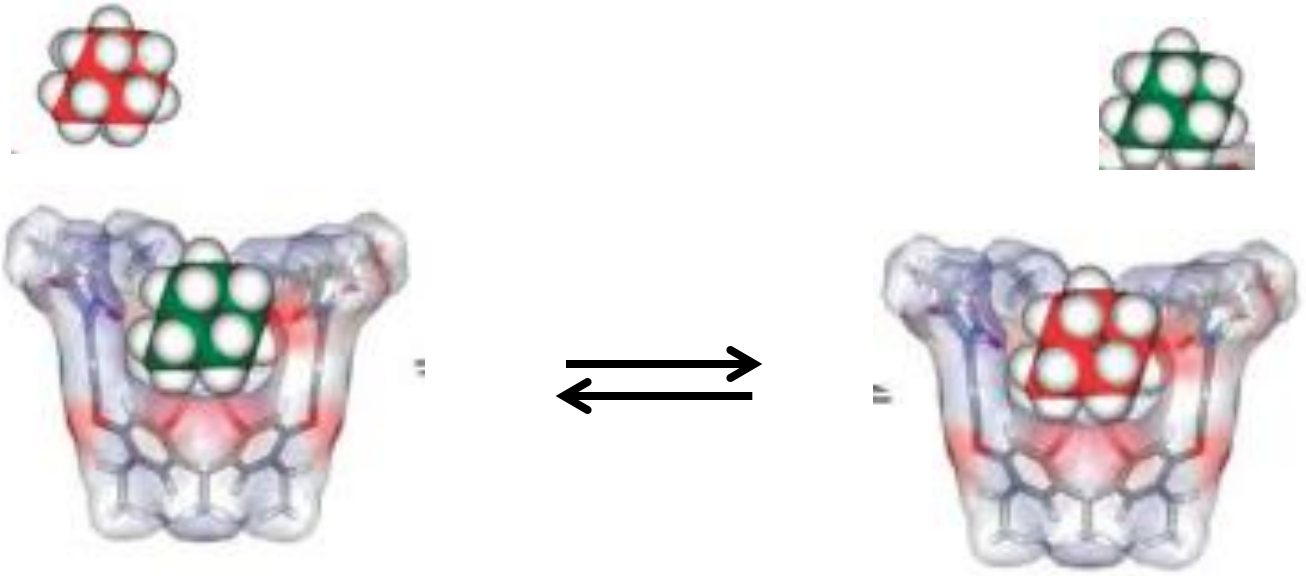


Stability magnitude order: thousands of kcal/mol

2D NOESY cross correlations through space between cavitand and bound guest

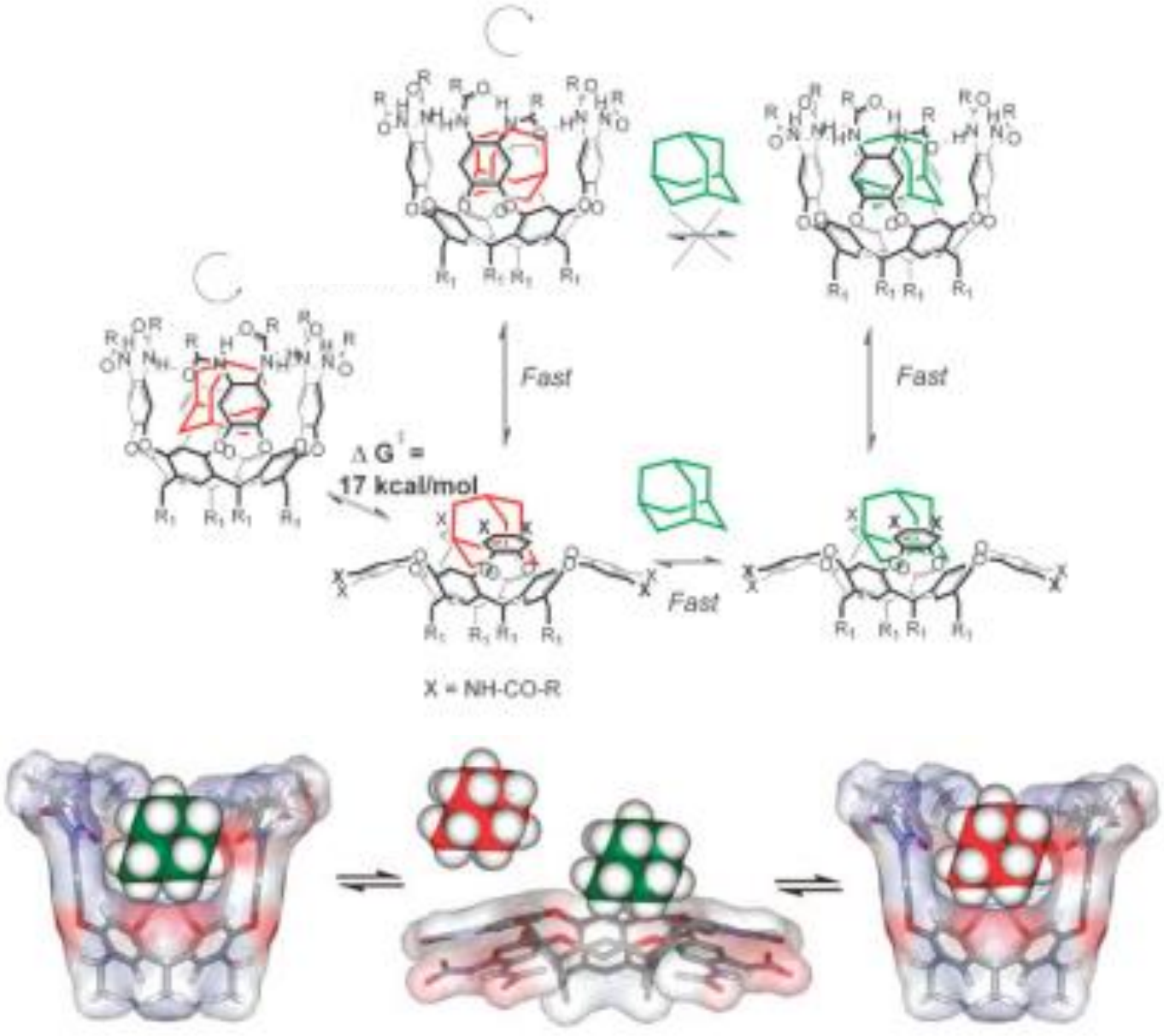


Excess of guest:
distinguished NMR signals for free and bound guest +
evidence of exchange from 2D EXSY

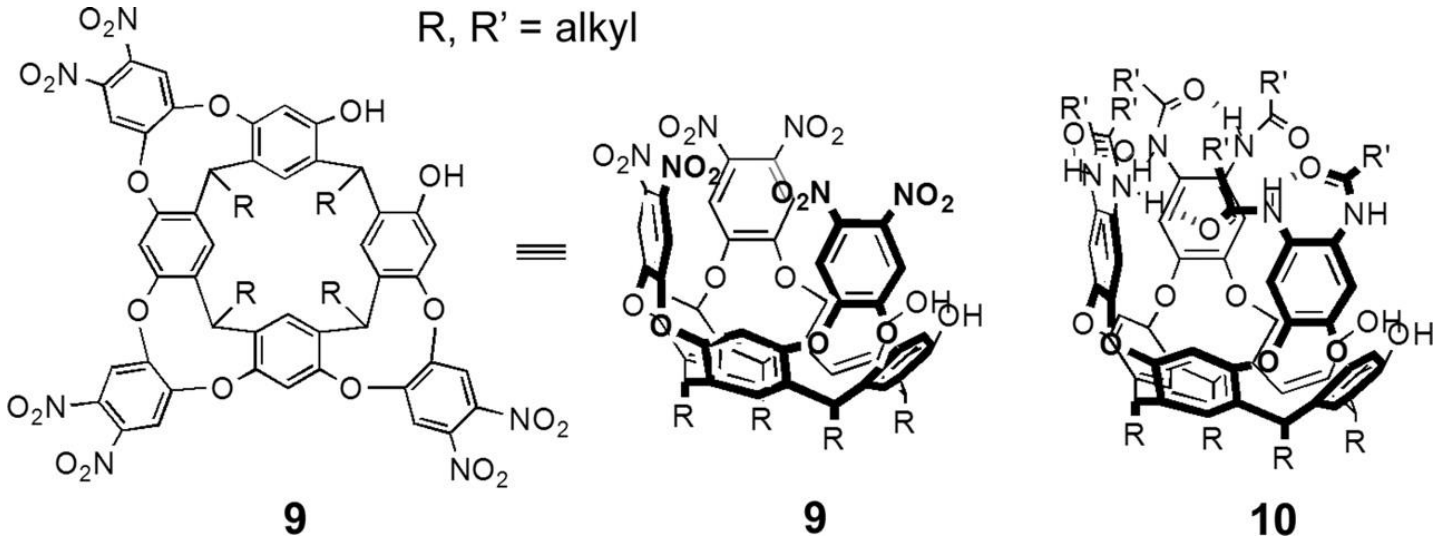


Slow exchange on the NMR time-scale!!

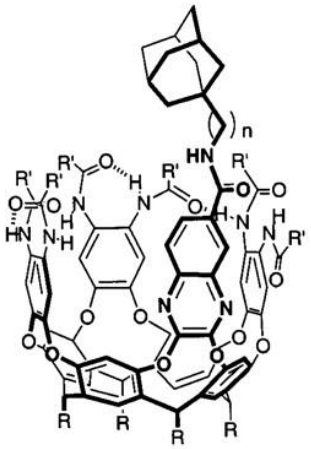
Measure of the exchange kinetic (VT NMR):
Kinetic barrier of *ca.* 17 kcal mol^{-1}



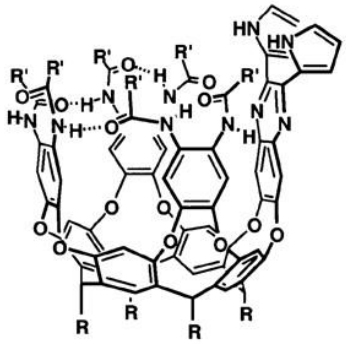
Functional cavitands?



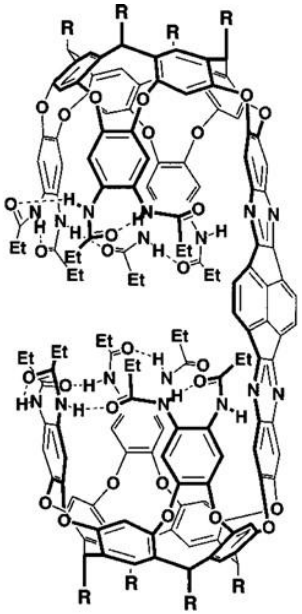
From the hexanitro precursor **9**, encountered as side-product in the preparation of the octanitro derivative, reduction and acylation to obtain hexamide **10**, followed by addition of the fourth wall and reduction to the diamine affords the common precursor to monofunctionalized cavitands.



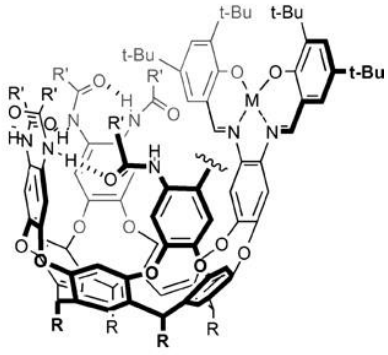
11



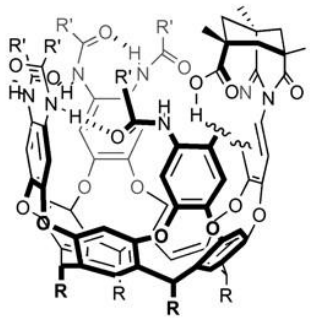
13



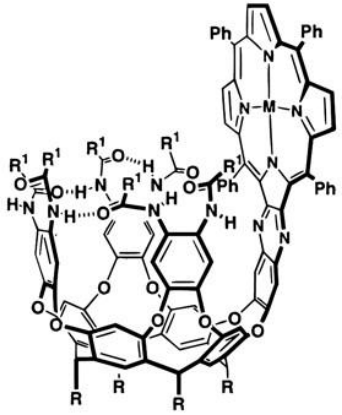
15



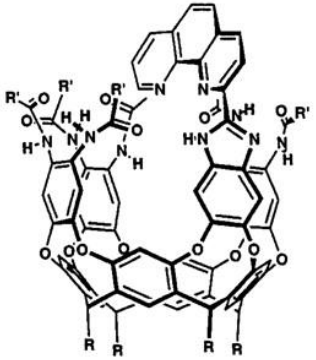
17



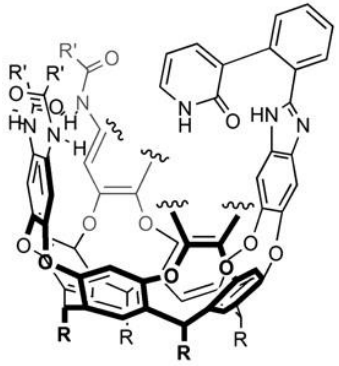
12



14



16



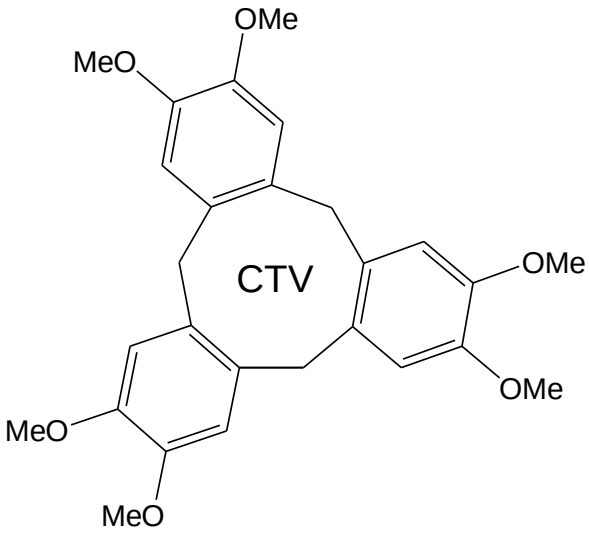
18

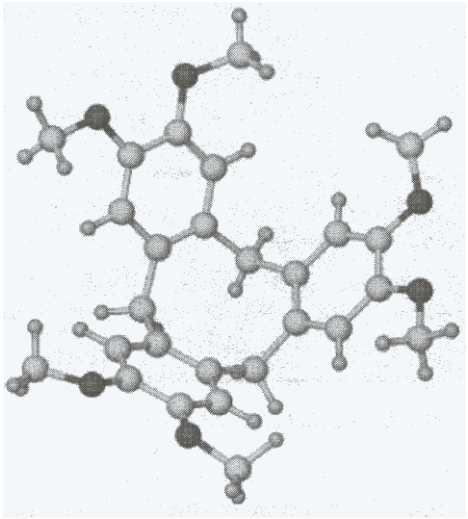
Receptor for neutral molecules

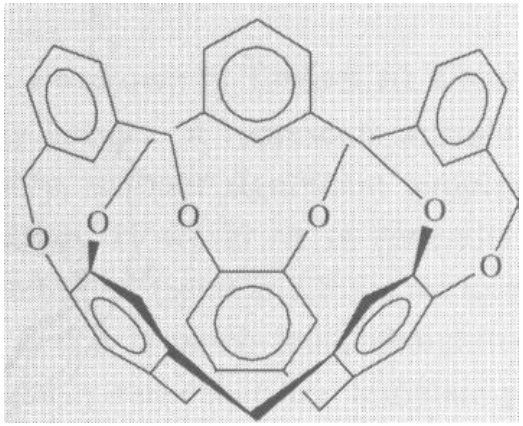
CH-π interactions pre organization (deep and rigid cavities)

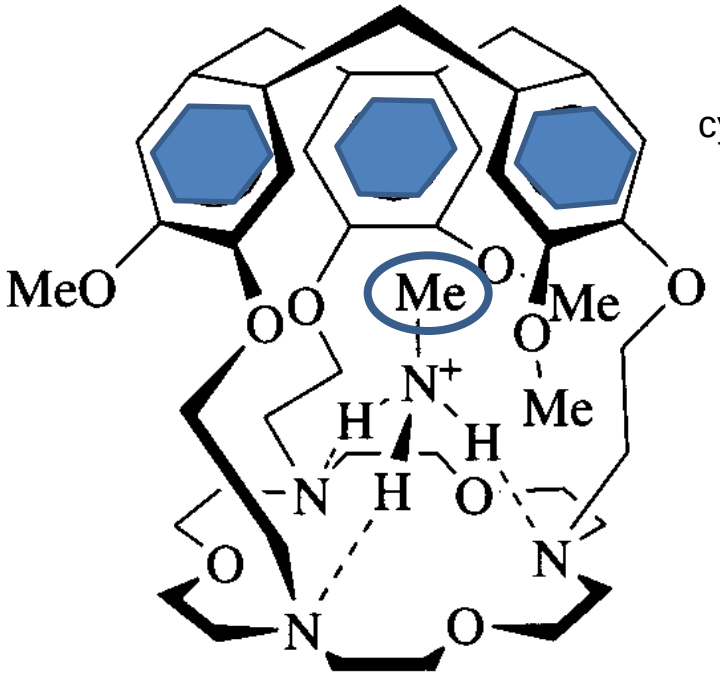
Cyclotriveratrylene CTV

Condensation of 1,2-dimetoxybenzene and formaldheyde in acidic H_2O.









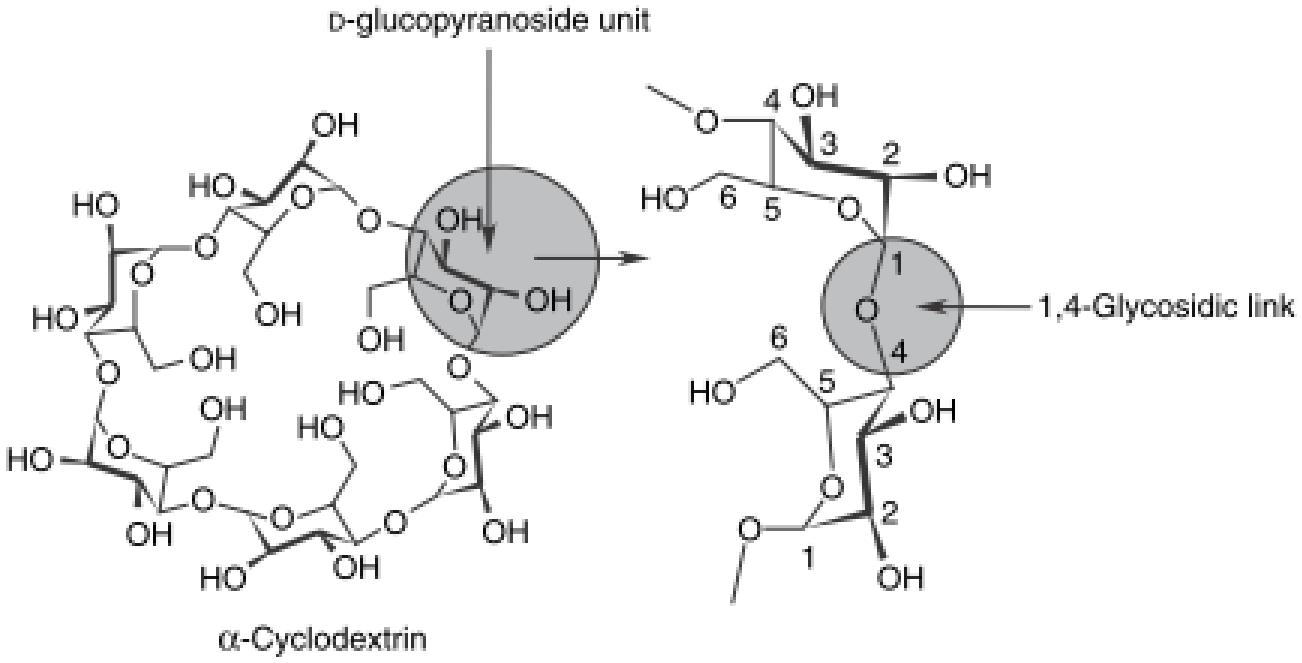
cyclotriveratrylene

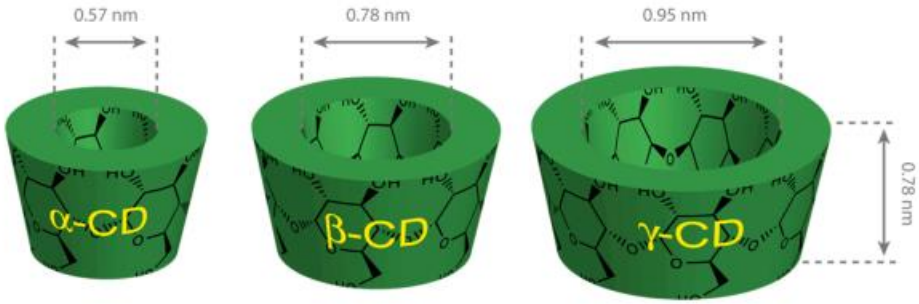
corand

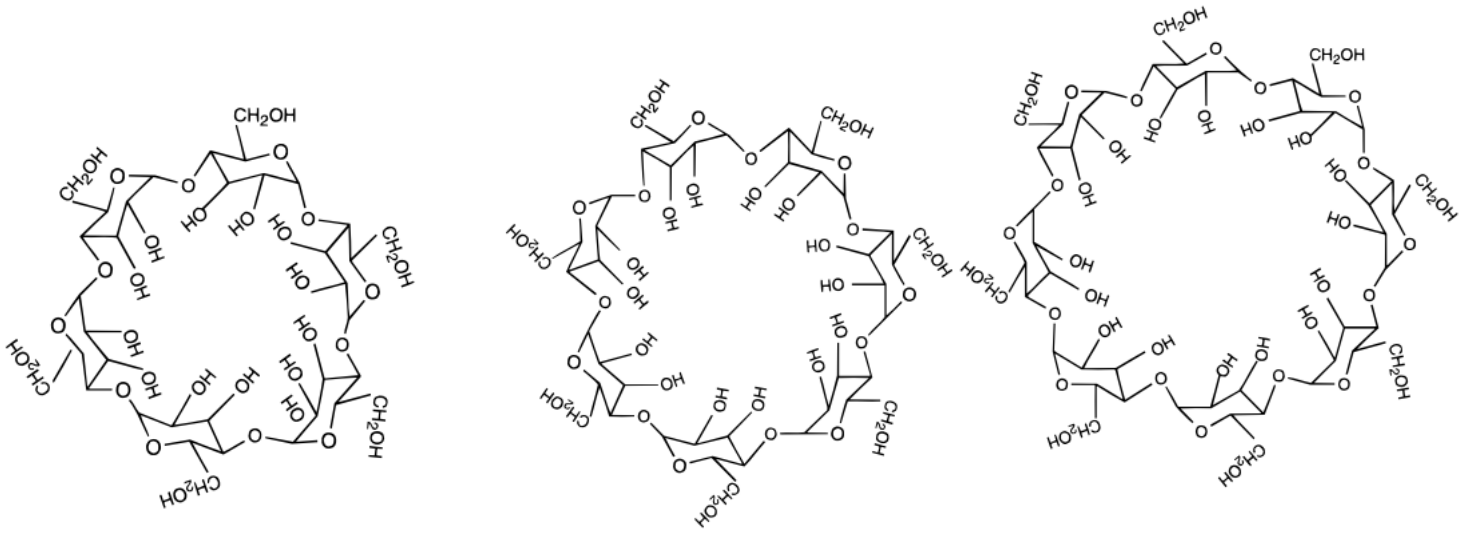
Receptor for neutral molecules

Hydrophobic effect polar exterior (and/or charged) hydrophobic pocket

Cyclodextrines – D-glucopyranoside units (1,4-glycosidic bonds)

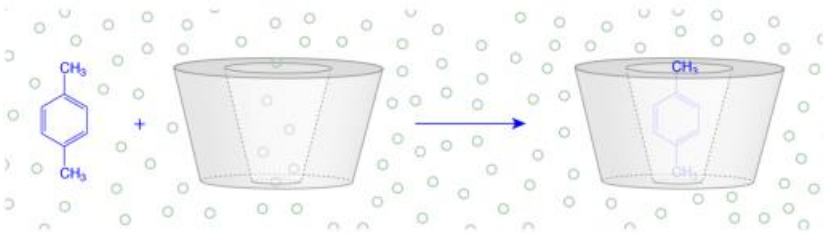



0.57 nm
0.78 nm
0.95 nm
α-CD
β-CD
γ-CD
0.78 nm

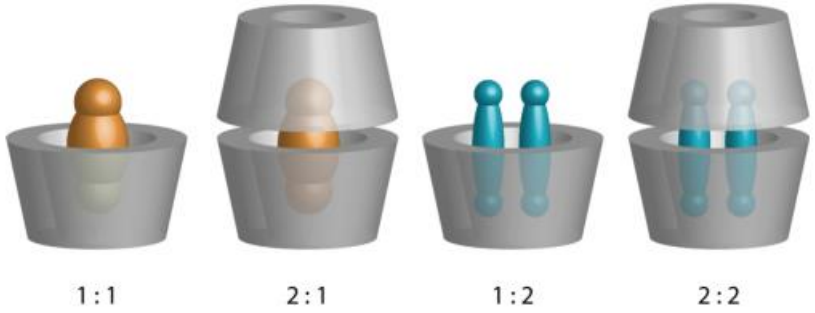


Solubility (H_2O): α 145g/L β 18.5 g/L γ 232 g/L

Size-fit, hydrophobic effect, vdW, dipol-dipol, hydrogen bonds..



1/1 complexes but also alternative stoichiometries



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

non toxic…thermally and air stable…

Production 1000 tons/year

Applications:

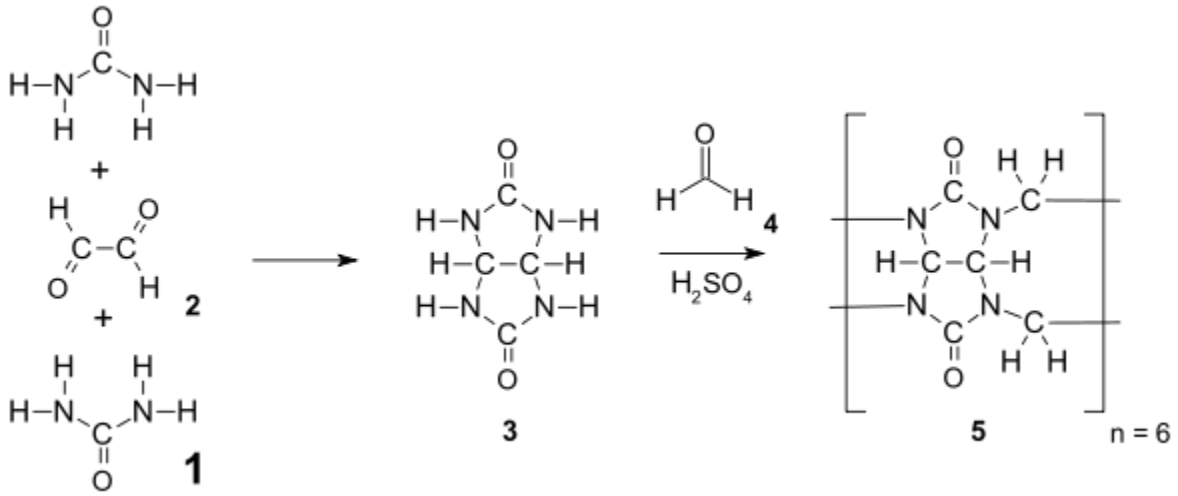
Pharmaceutical: bioavailability – formulation and administering
Food Industry: scents, spices, emulsions, vitamines
Cosmetic: solar lotions, deodorants
Analysis: grafting on polymeric supports for chromatography (chiral HPLC)

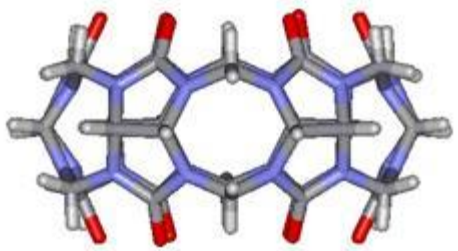
Cyclodextrins News

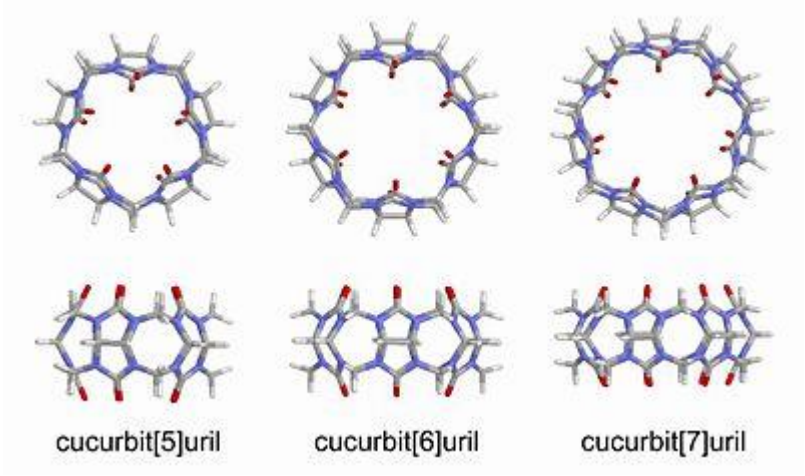
Table 1. Recap of the Main Results of Freudenberg on Schardinger Dextrins

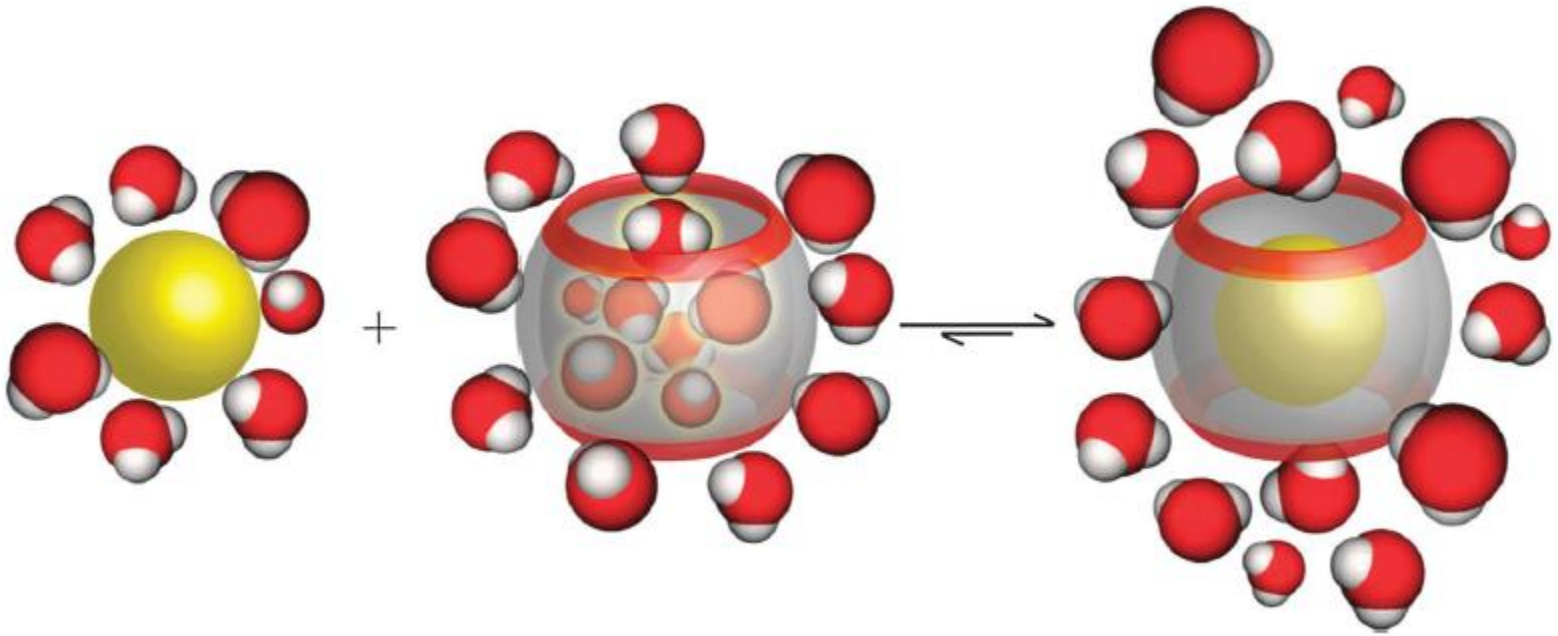
year	result
1922	tosylated dextrins
1930	Schardinger dextrins: laboratory curiosities and/or unwanted byproducts of starch degradation
	Schardinger dextrins: chain molecules intermediate between maltose and starch
1935	the dextrins were lined with a hydrocarbon interior
	synthesis of Schardinger dextrins 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

Cucurbiturils–glycoluril units (methylen bonds)









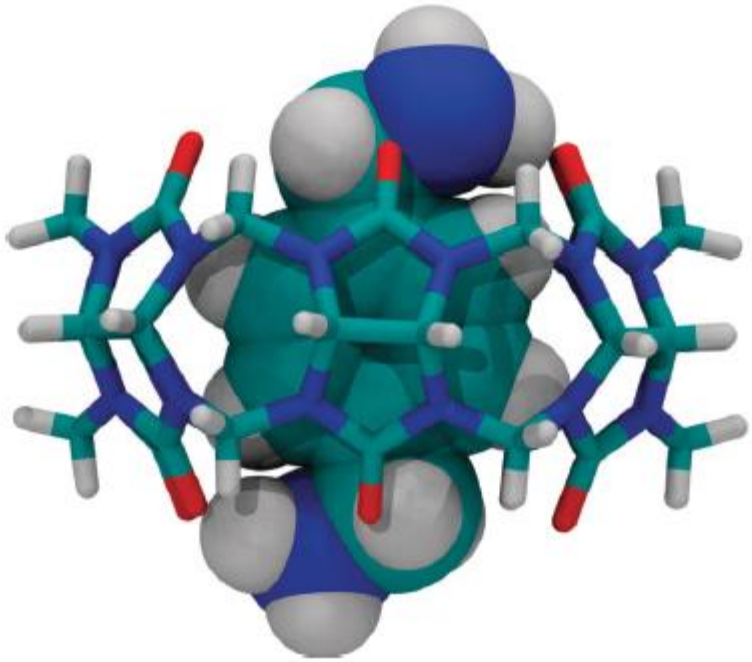


Fig. 13 X-ray structure of the *p*-xylylenediammonium ion encapsulated by CB6, the first X-ray diffraction structure of a CB*n* complex.[127]

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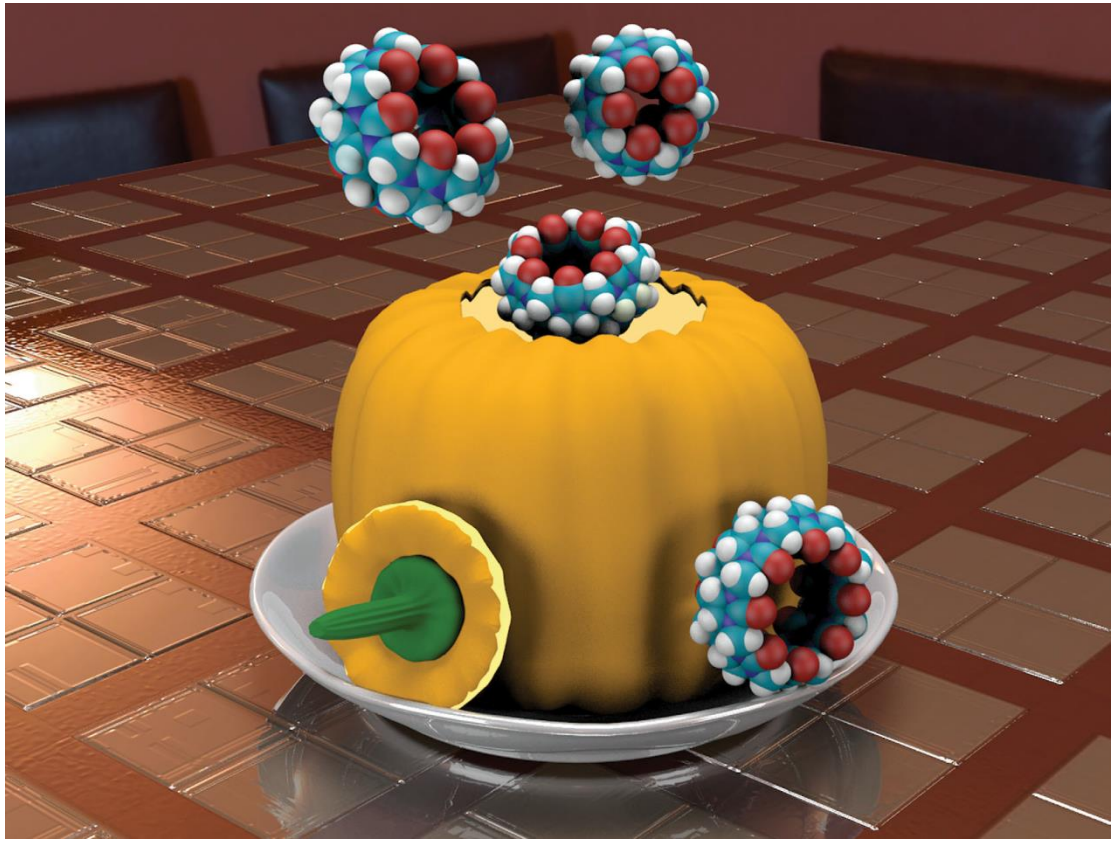
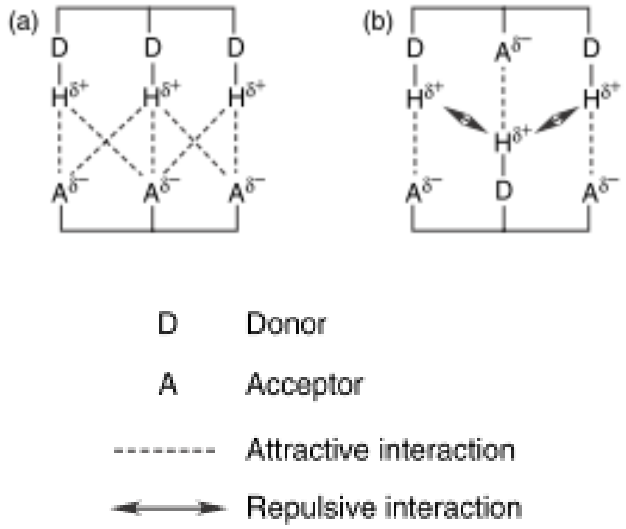
Cucurbiturils: from synthesis to high-affinity binding and catalysis

Khaleel I. Assaf and Werner M. Nau*



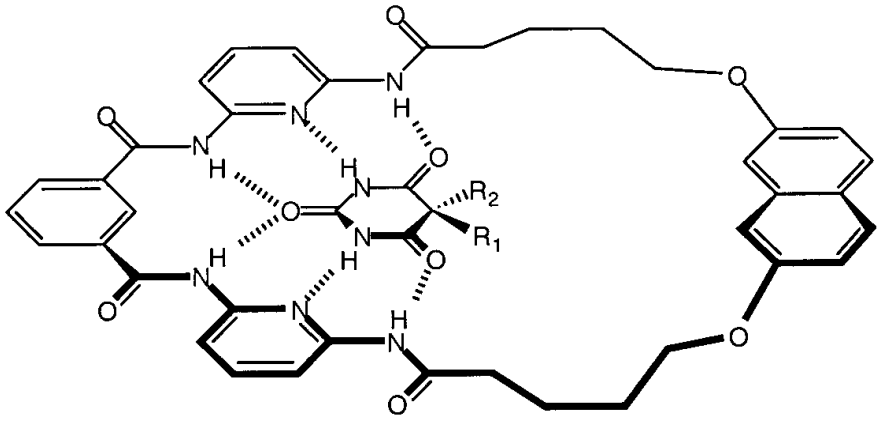
Receptor for neutral molecules

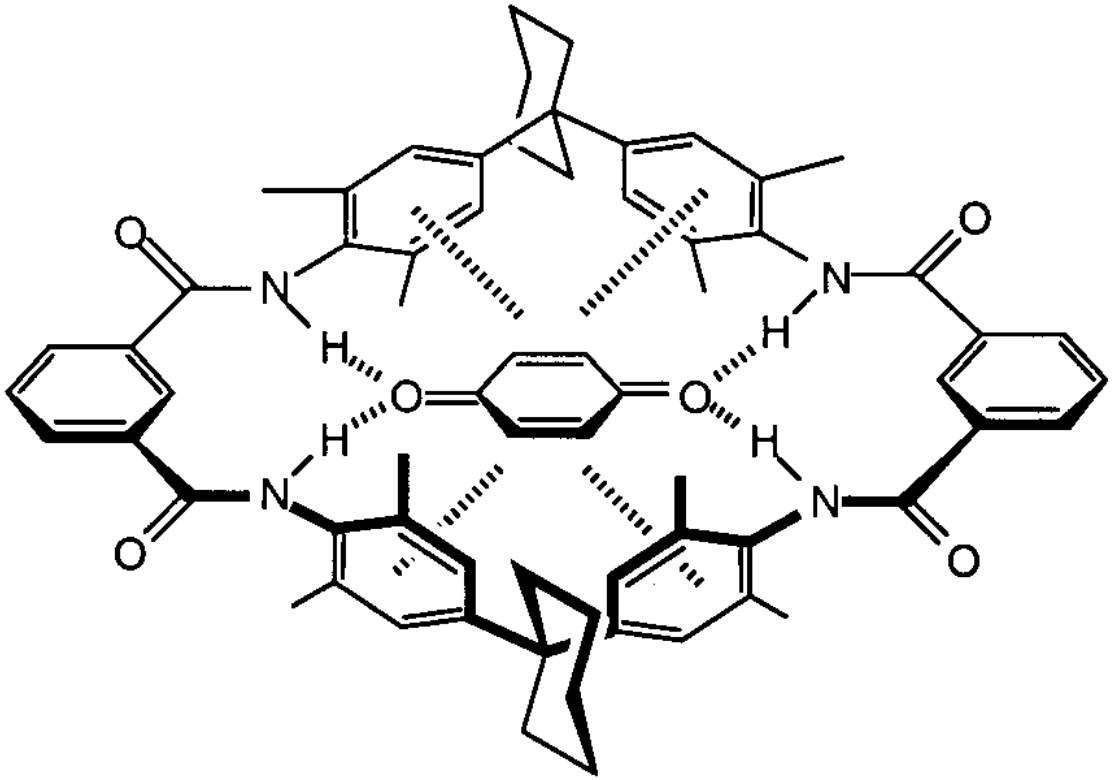
Hydrogen bonds multiple D A sites



Receptor for neutral molecules

Hydrogen bonds pre organization and complementarity (directionality)





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

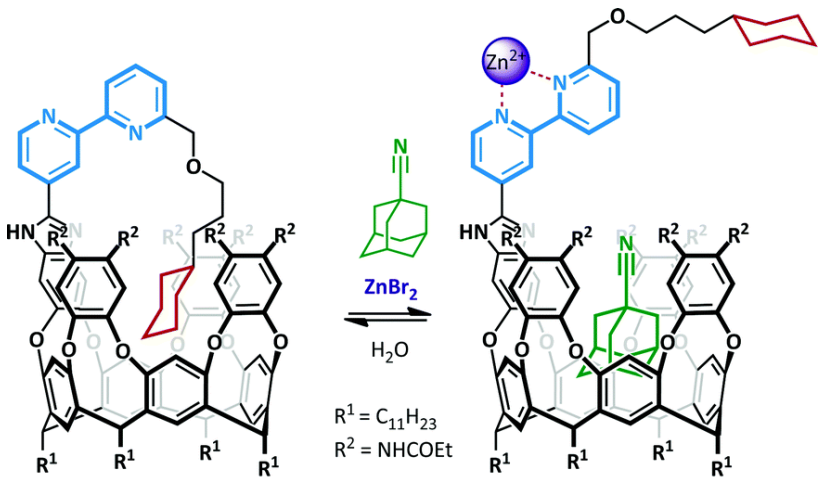
Self-Hosting Cavitand

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



closed-**11** *occupied*-**11**

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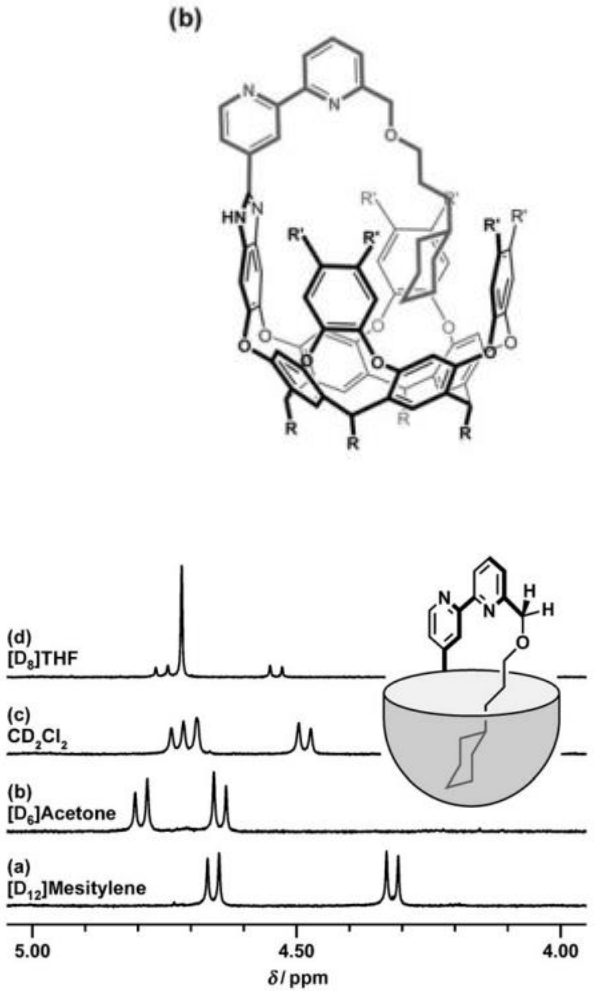
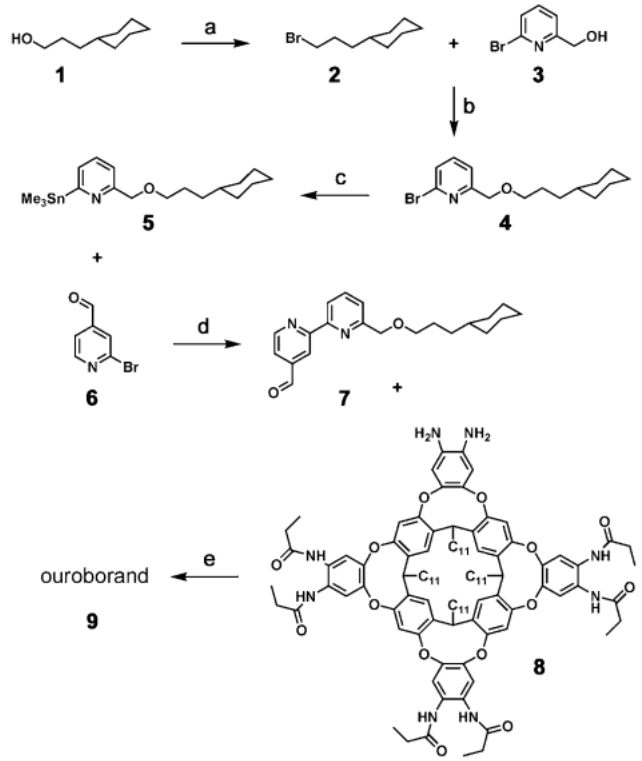
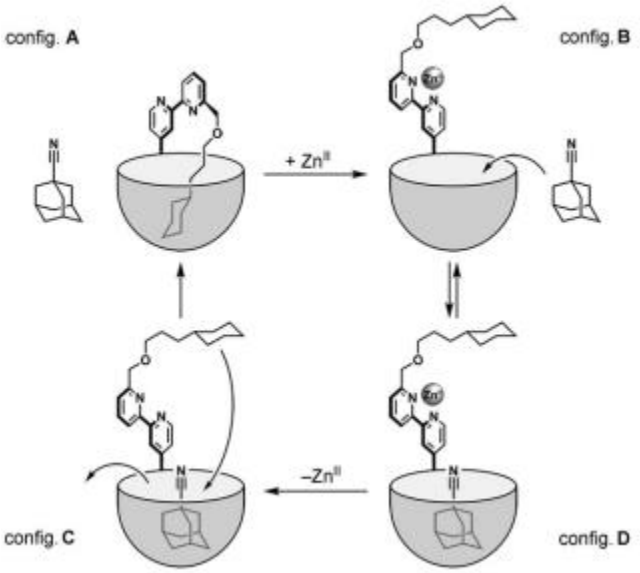
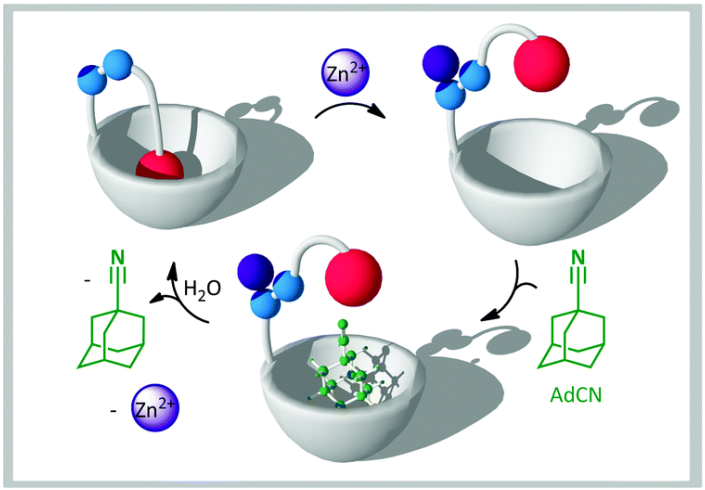
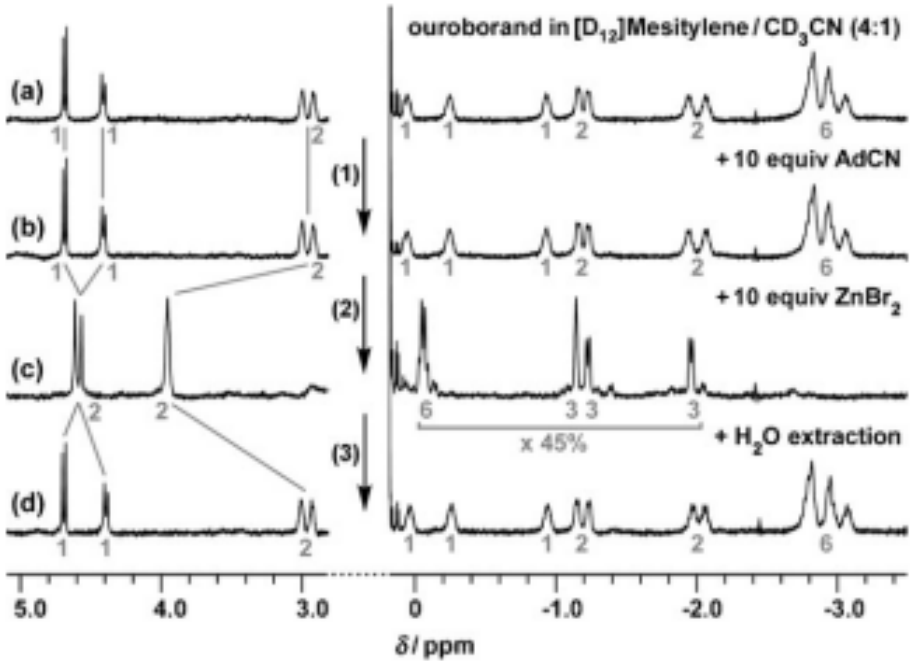




Scheme 3. Synthesis of the ouroborand. a) PBr_3, 0 °C 15 min, RT 2 h, 100 °C 1.5 h, 100%; b) NaH, THF, RT 2 h, 75 °C 16 h, 26%; c) BuLi, toluene, −20 °C, −78 °C 2 h, Me_3SnCl, −78 °C 1 h, RT, 55%; d) [Pd-(PPh_3)$_4$], toluene, 110 °C 48 h, 75%; e) dioxane, RT 30 min, 100 °C 16 h, 67%.


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


Zn^{2+}
N
H$_2$O
AdCN
Zn^{2+}


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