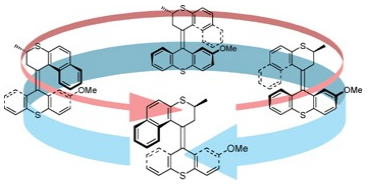
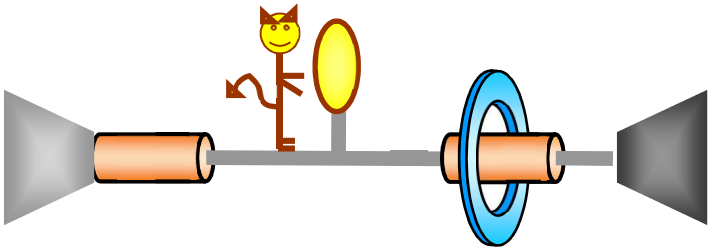
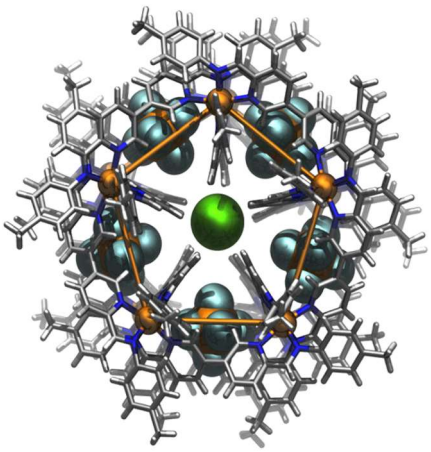
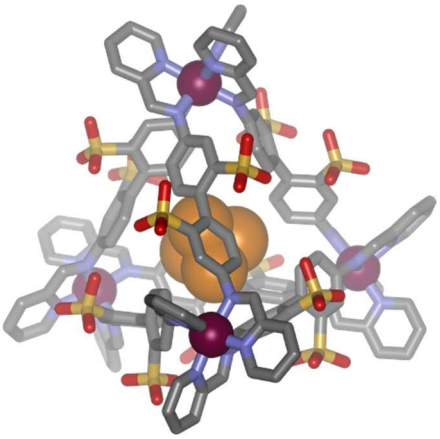
University of Trieste, Autumn 2023

Supramolecular chemistry and self-organisation









Jonathan R. Nitschke

Course Outline

I. Fundamentals

1. Dynamic and Directional Bonds
   - Metal-ligand interactions
   - Dynamic covalent linkages
2. Building up Structural Complexity
   - Helices
   - Squares & cages
   - Larger capsules
   - Tetrahedra & Cubes
   - Chemistry in the ‘Inner Phase’

II. Complexity and Function

3. Molecular topology and entanglements
   - Catenanes, Rotaxanes, Knots
   - The Borromean Rings
4. Molecular machines
   - Rotaxane Shuttling
   - Molecular Elevators
   - Rotary Motion
   - Maxwell’s Demon, summoned
5. Supramolecular catalysis and self-replication: the interface with biology

III. Extra

6. Structural and spectroscopic characterisation methods
   - X-ray crystallography
   - NMR spectroscopy
   - Mass spectrometry
   - Isothermal Titration Microcalorimetry (ITC)
7. Problem sets

General reading

The best book to consult for clarification of fundamentals is *Anslyn & Dougherty* below. Specific references will be found in the handout. For coordination chemistry, see your favourite Inorganic chemistry textbook.

E. V. Anslyn and D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, 2006.

J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, 2nd Edition, Wiley UK, 2009.

J. Hartwig, *Organotransitionmetal Chemistry*, University Science Books, 2010.

J. K. M. Sanders and B. K. Hunter, *Modern NMR Spectroscopy*, 2nd Edition, Oxford, 1993.

1. Dynamic and directional bonds

1.1 Metal-ligand interactions. Some metal-ion properties relevant to supramolecular chemistry and self-assembly

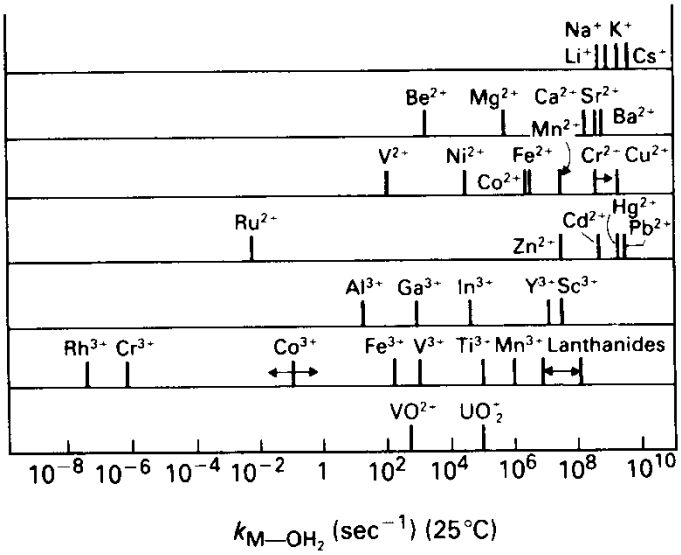
1. Focus on coordination chemistry: we often think of metal ions as 'glue'

2. Structural characterisation:

3. Trends

Kinetics of ligand exchange for the water-exchange reaction:

$M(H_2O)_n^{q+} + H_2O^* \rightleftarrows M(H_2O)_{n-1}(H_2O^*)^{q+} + H_2O$



Group	1	2	3	4	5	6	7	8	9	10	11	12
	Na K	Mg Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
Common oxidation states	1	2	3	3,4	3,4, 5	2,3	2	2,3	2,3	2	1,2	2

Hard-Soft Acid-Base Theory (R.G. Pearson):

Hard Bases	Soft Bases	Borderline Cases
H_2O OH^- F	R_2S RSH RS	$ArNH_2$ C_5H_5N
AcO^- SO_4^{2-} Cl^-	I^- R_3P $(RO)_3P$	N_3^- Br
CO_3^{2-} NO_3^- ROH	CN^- RCN CO	NO_2^-
RO^- R_2O NH_3	C_2H_4 C_6H_6	
RNH_2	H^- R^-	
Hard Acids	**Soft Acids**	**Borderline Cases**
H^+ Li^+ Na^+	Cu^+ Ag^+ Pd^{2+}	Fe^{2+} Co^{2+} Cu^{2+}
K^+ Mg^{2+} Ca^{2+}	Pt^{2+} Hg^{2+} BH_3	Zn^{2+} Sn^{2+} Sb^{3+}
Al^{3+} Cr^{2+} Fe^{3+}	$GaCl_3$ I_2 Br_2	Bi^{3+} BMe_3 SO_2
BF_3 $B(OR)_3$ $AlMe_3$	CH_2 carbenes	R_3C^+ NO^+ GaH_3
$AlCl_3$ AlH_3 SO_3		$C_6H_5^-$
RCO^+ CO_2		
HX (hydrogen-bonding molecules)		

		Ionic radius (6-coordinate)	Optimum Crown size
Group 1	Li^+		
	Na^+		
	K^+		

- Large ionic size, small charge
- Biological roles in

Rather than being specifically

Group 2	Mg^{2+}	0.76 Å
	Ca^{2+}	1.00 Å

Group 8	Fe^{2+}	High spin: 0.78 Å
		Low spin: 0.61 Å
	Fe^{3+}	High spin: 0.65 Å
		Low spin: 0.55 Å
	Ru^{2+}	kinetically inert, octahedral
		binds > but most strongly to softer donors,

Group 9 Co^{2+} forms 4, 5, & 6-coordinate complexes

Co^{3+} virtually always octahedral, relatively inert

Group 10 Ni^{2+} d^8
can be 4-coord tetrahedral or sq. planar

Pd^{2+} 4-coordinate sq. planar, relatively slow

Pt^{2+}

Group 11 $2\ Cu^{I} \rightleftarrows Cu^{II} + Cu^{0}$

Equilibrium may favour either side, depending on

Cu^{+} Tetrahedral, d^{10}, diamagnetic

Cu^{2+} d^9, paramagnetic. Octahedral with

Group 12 Zn^{2+} Filled d shell

always diamagnetic

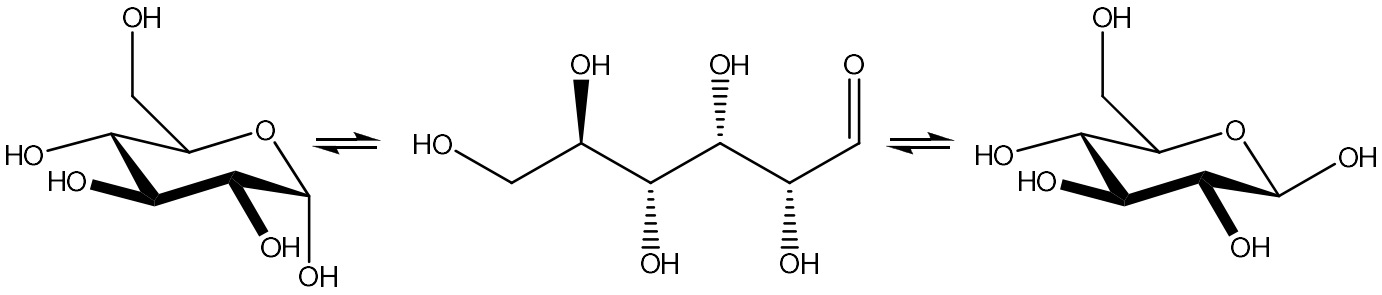
1.2 Dynamic covalent linkages

Angew. Chem. Int. Ed. **2002**, *41*, 898-952.

Up to this point, we have considered only relatively weak linkages as the glue and mortar of supramolecular construction. Weak bonds readily break and reform in dynamic fashion, allowing structures to disassemble and reassemble in minimising the system's free energy.

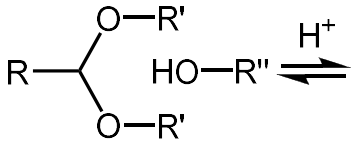
OH···O : C–C :

It is not strictly true, however, that all reversible linkages are weak:

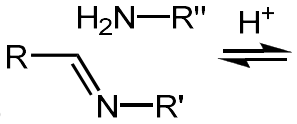


Dynamic covalent chemistry deals with structures that are knit together by bonds that are capable of facile equilibration under a given set of conditions.

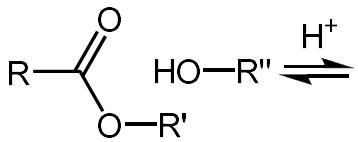
Acetals

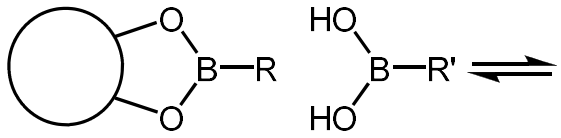


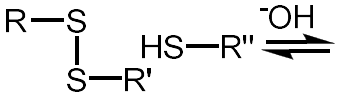
Imines

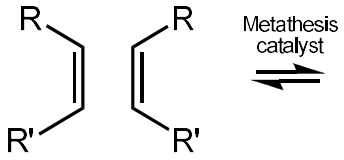


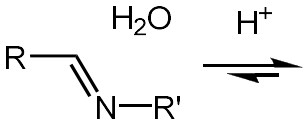
Esters



Boronate Esters 

Disulphides 

Alkenes 

Side reactions can pose problems (i.e., hydrolysis): 

Symmetrical vs. asymmetrical linkages:

$$\begin{matrix} A\rightarrow B & & A\rightarrow B \\ & \Rightarrow & \\ C\rightarrow D & & C\rightarrow D \end{matrix}$$

whereas…

$$A\leftrightarrow B \Rightarrow \quad A\leftrightarrow A \quad B\leftrightarrow B \quad A\leftrightarrow B$$

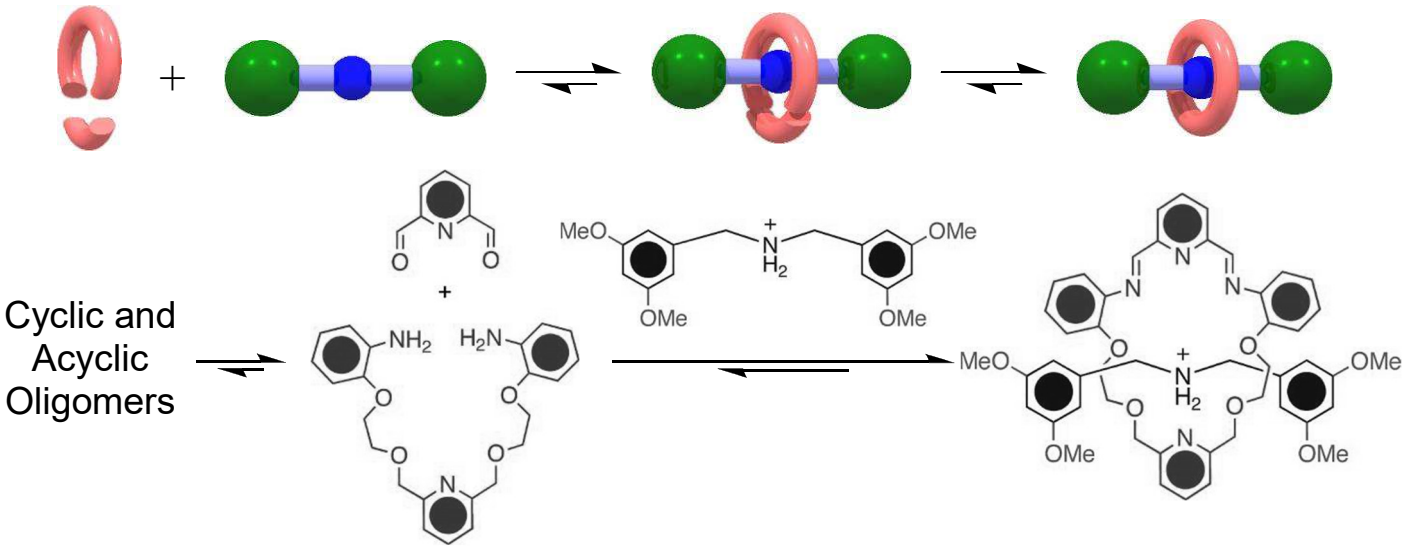
$$\Rightarrow$$

$$C\leftrightarrow D \Rightarrow \quad C\leftrightarrow C \quad D\leftrightarrow D \quad C\leftrightarrow D$$

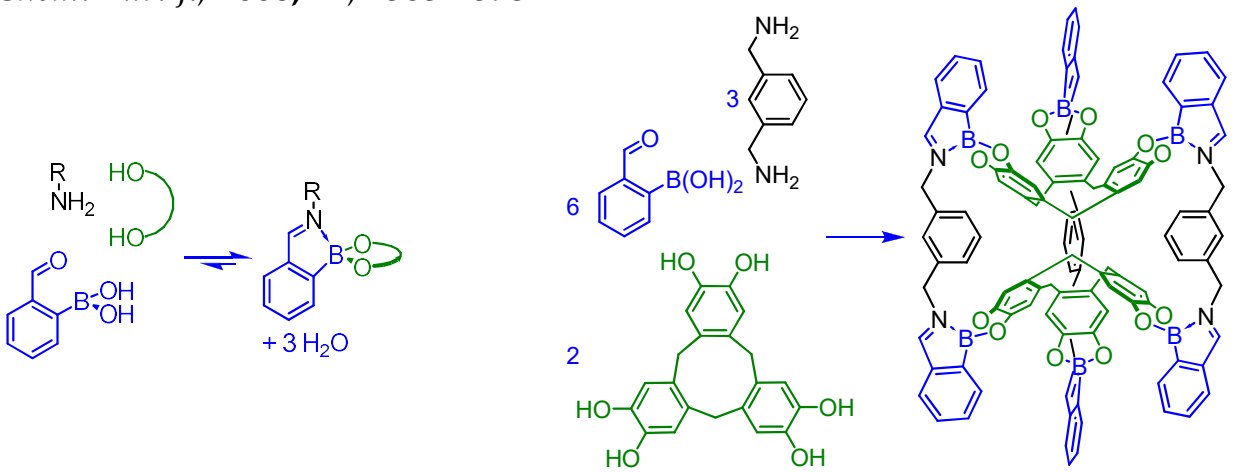
To use dynamic covalent chemistry synthetically, one must be prepared to address chemical problems in new ways: Instead of thinking about a target molecule as a *series* of bonds to be constructed one after another under kinetic control, one must consider bond formations occurring in *parallel*, under thermodynamic control.

Examples:

Angew. Chem. Int. Ed. **2001**, *40*, 1870-1875



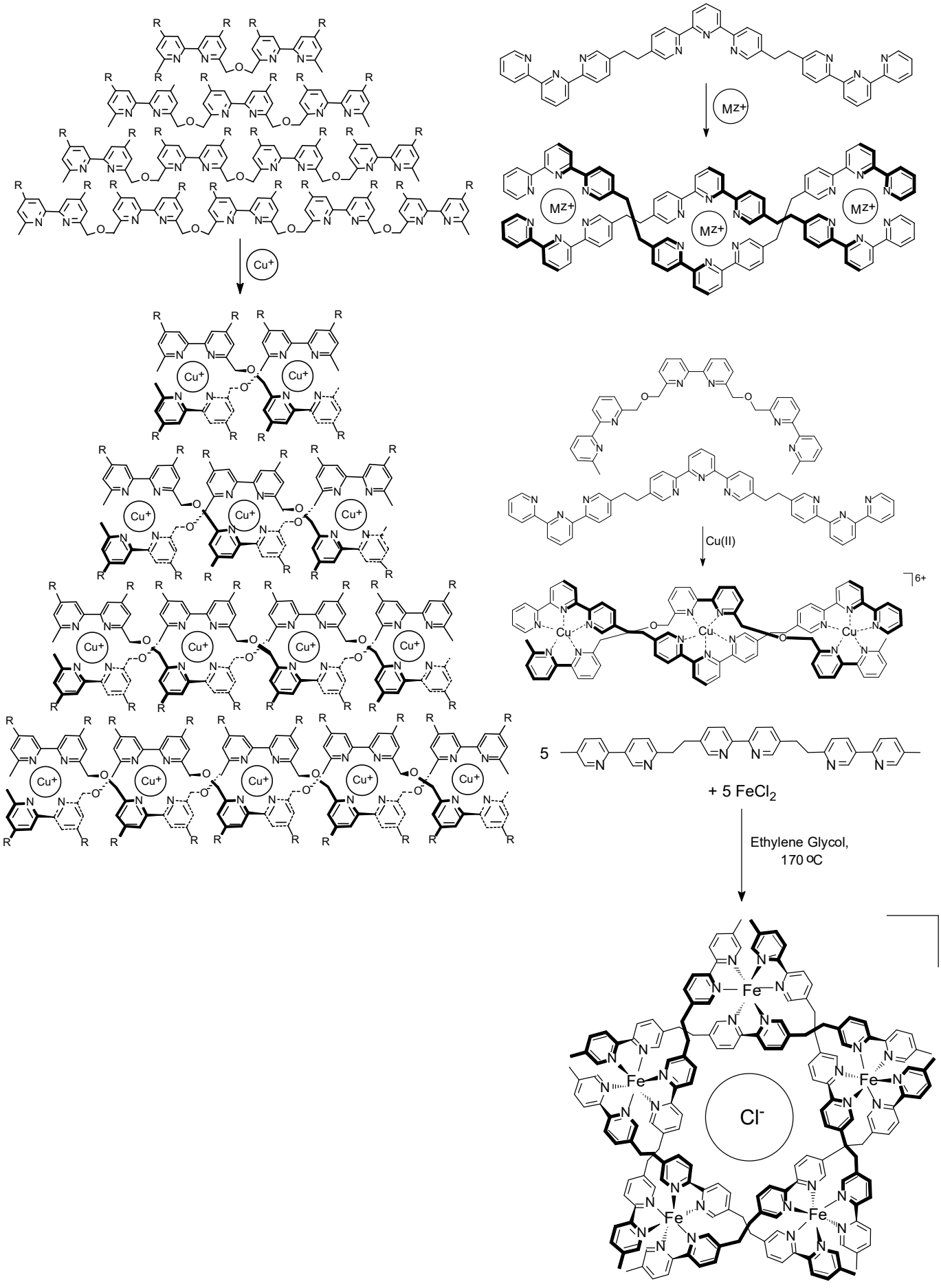
Chem. Eur. J., **2008,** *14*, 4585-4593



2. Building up Structural Complexity

2.1 Helices

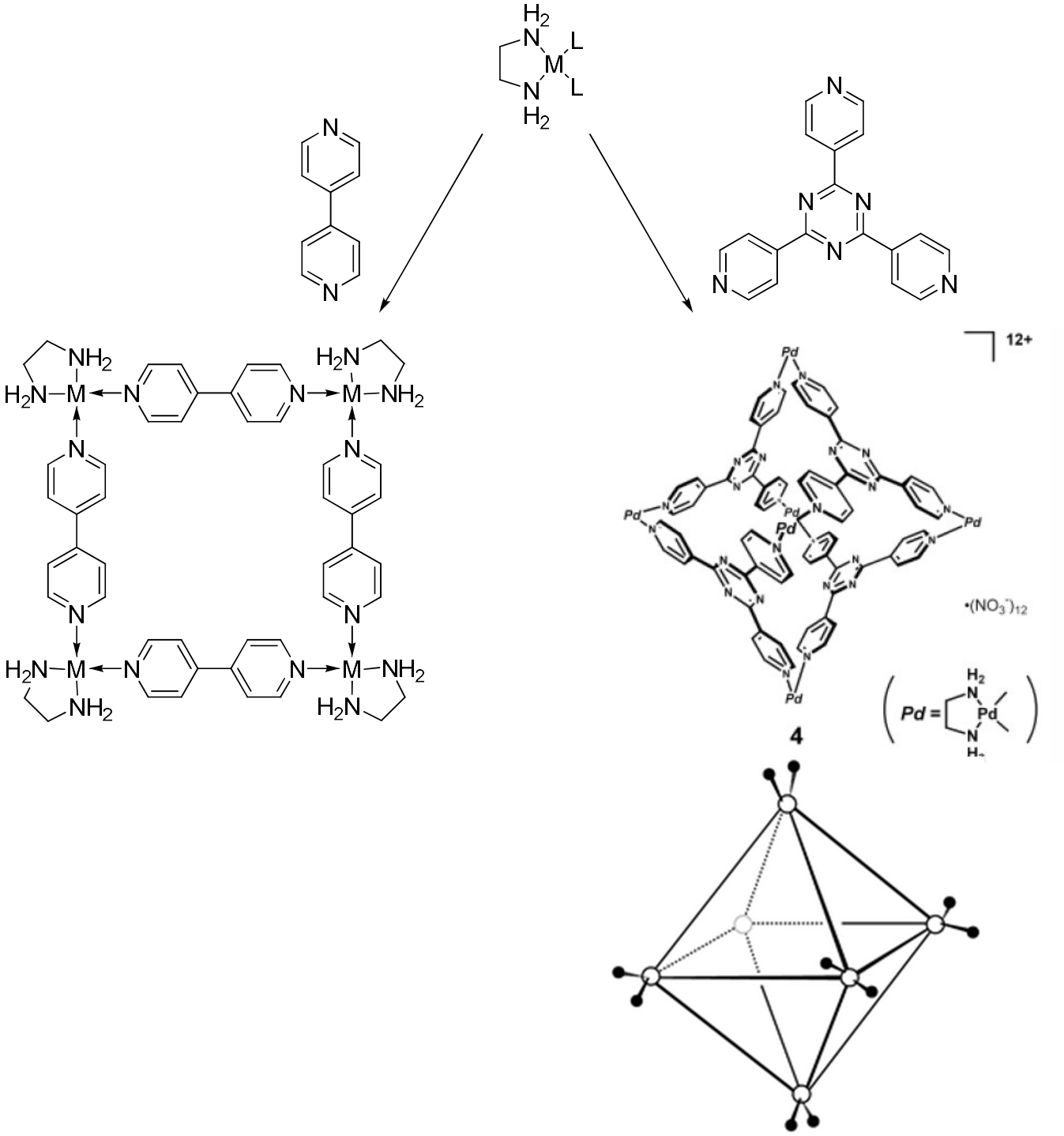
Chem. Rev., 2001, **101**, 3457.

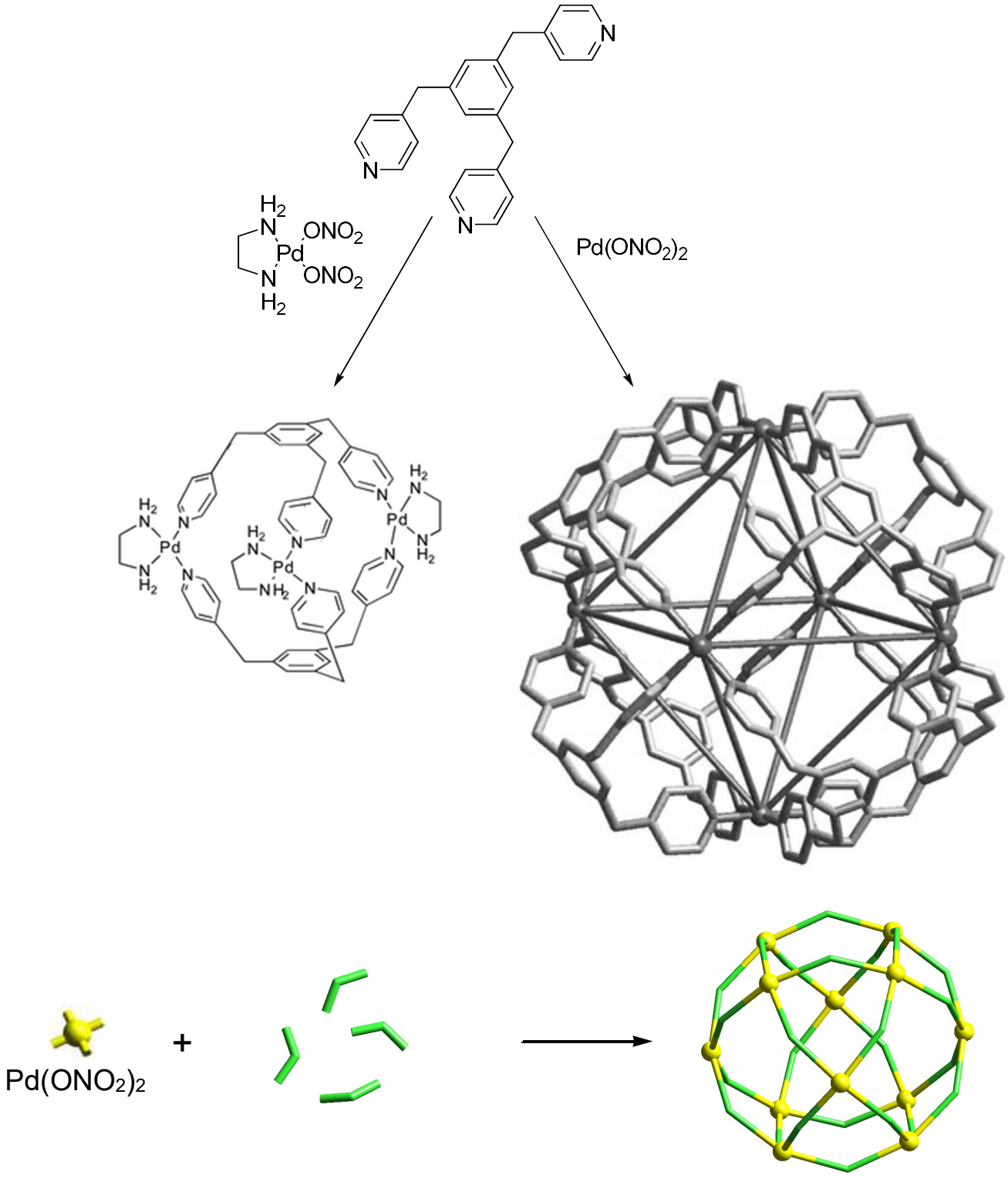


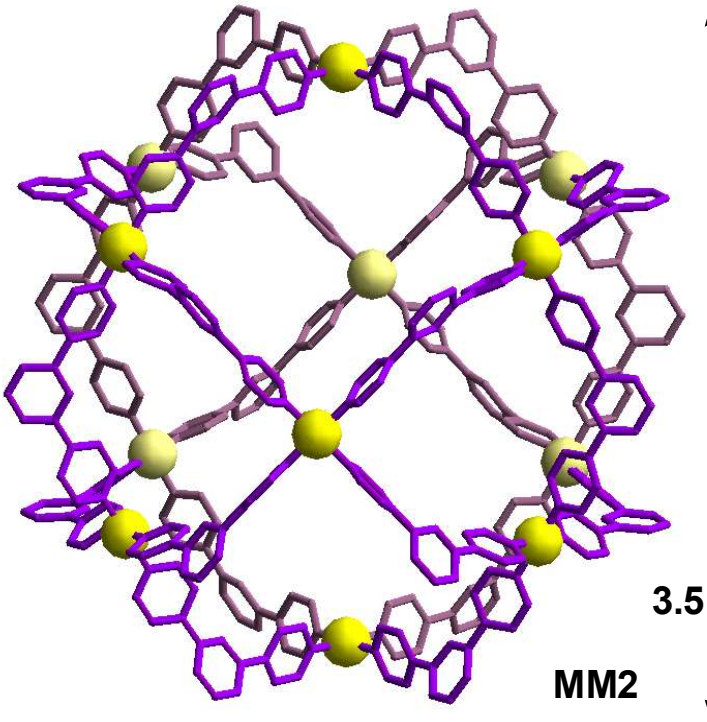
2.2 Squares and Cages

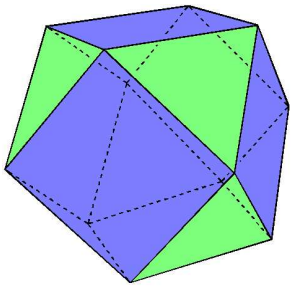
Chem. Commun., 2001, 509; *Chem. Rev.*, 2000, **100**, 853

Angewandte Chemie Intl Edn, 2004, **43**, 5621.




N
N
N
H2
N
ONO2
Pd
N
ONO2
H2
Pd(ONO2)2
Pd(ONO2)2
+



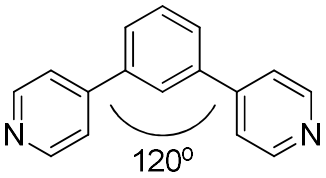


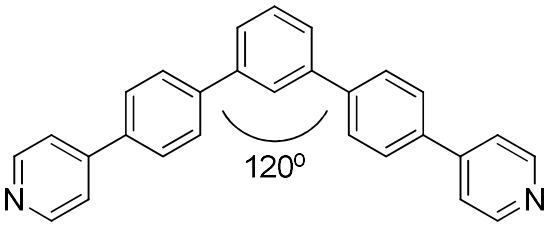
cuboctahedron

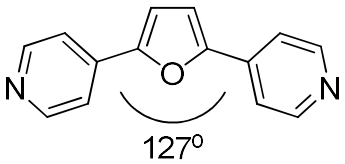
- **12** vertices
- **24** sides

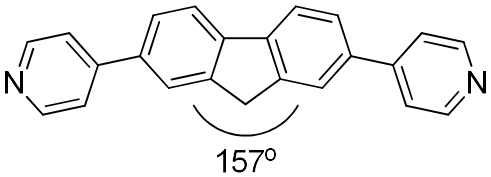
3.5 nm

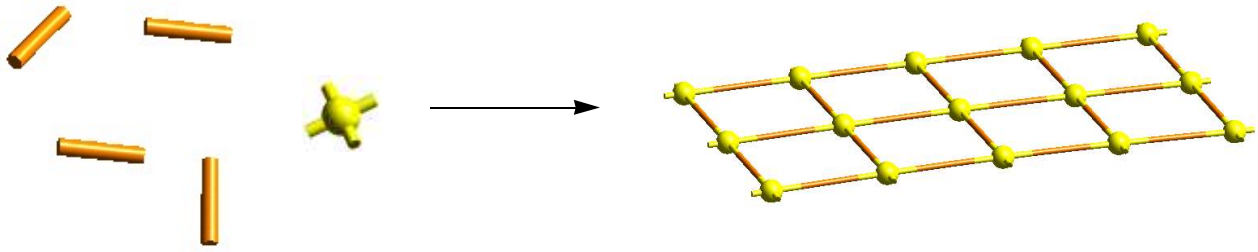
MM2





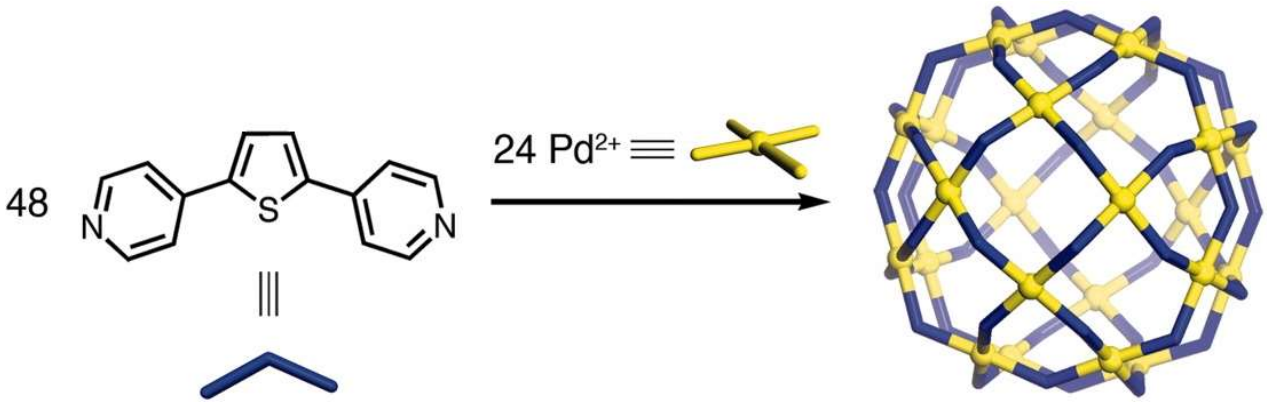






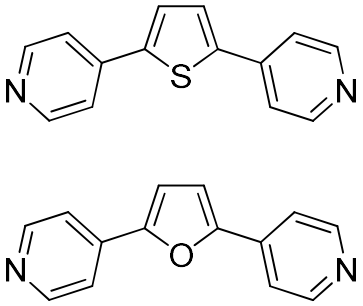
2.3 Larger Capsules

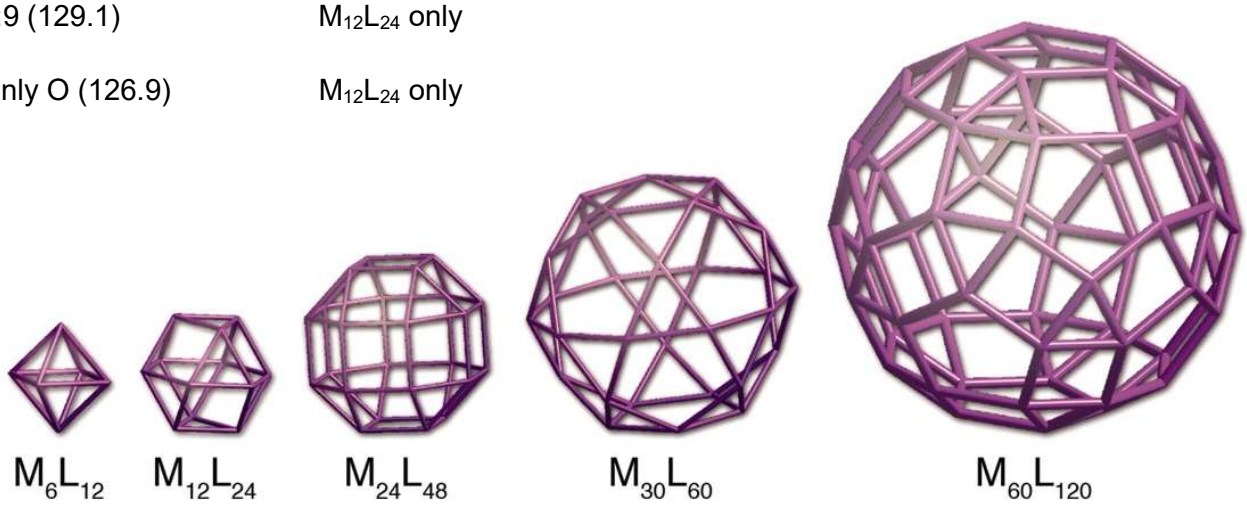
Remarkably, *Science* **2010**, *328*, 1144



Self-organization criticality of dipyridylfuran (O) and dipyridylthiophene (S) mixtures.

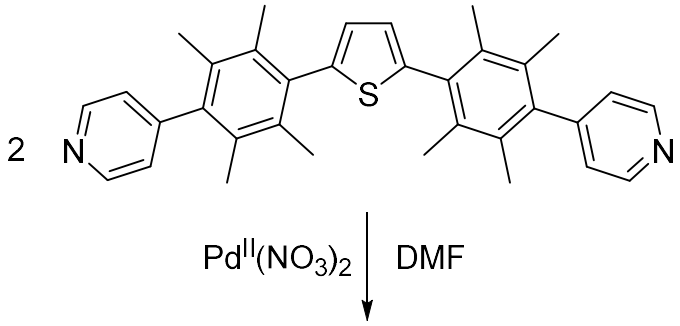
S:O ratio (average angle)	Product
Only S (149.3)	$M_{24}L_{48}$ only
9:1 (147.1)	$M_{24}L_{48}$ only
8:2 (144.8)	$M_{24}L_{48}$ only
7:3 (142.6)	$M_{24}L_{48}$ only
6:4 (140.3)	$M_{24}L_{48}$ only
5:5 (138.1)	$M_{24}L_{48}$ only
4:6 (135.9)	$M_{24}L_{48}$ only
3:7 (133.6)	$M_{24}L_{48}$ only
2:8 (131.4)	$M_{12}L_{24}$ only
1:9 (129.1)	$M_{12}L_{24}$ only
Only O (126.9)	$M_{12}L_{24}$ only

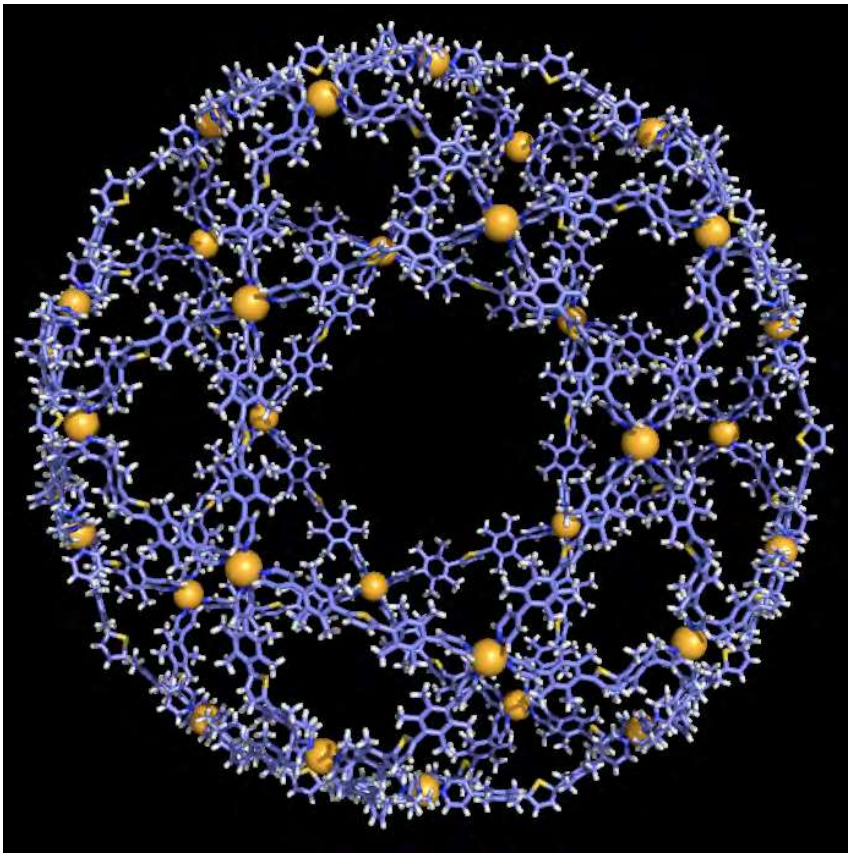


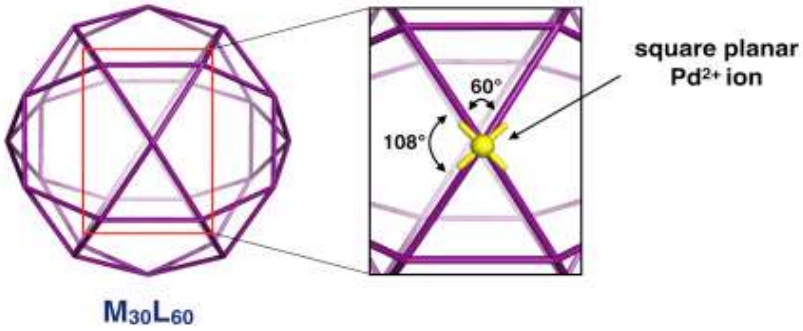


...and now, $M_{30}L_{60}$!

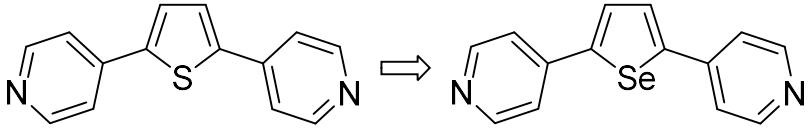
Chem **2016**, *1*, 91



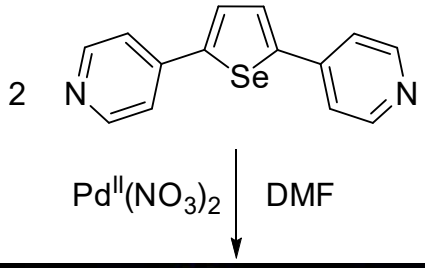


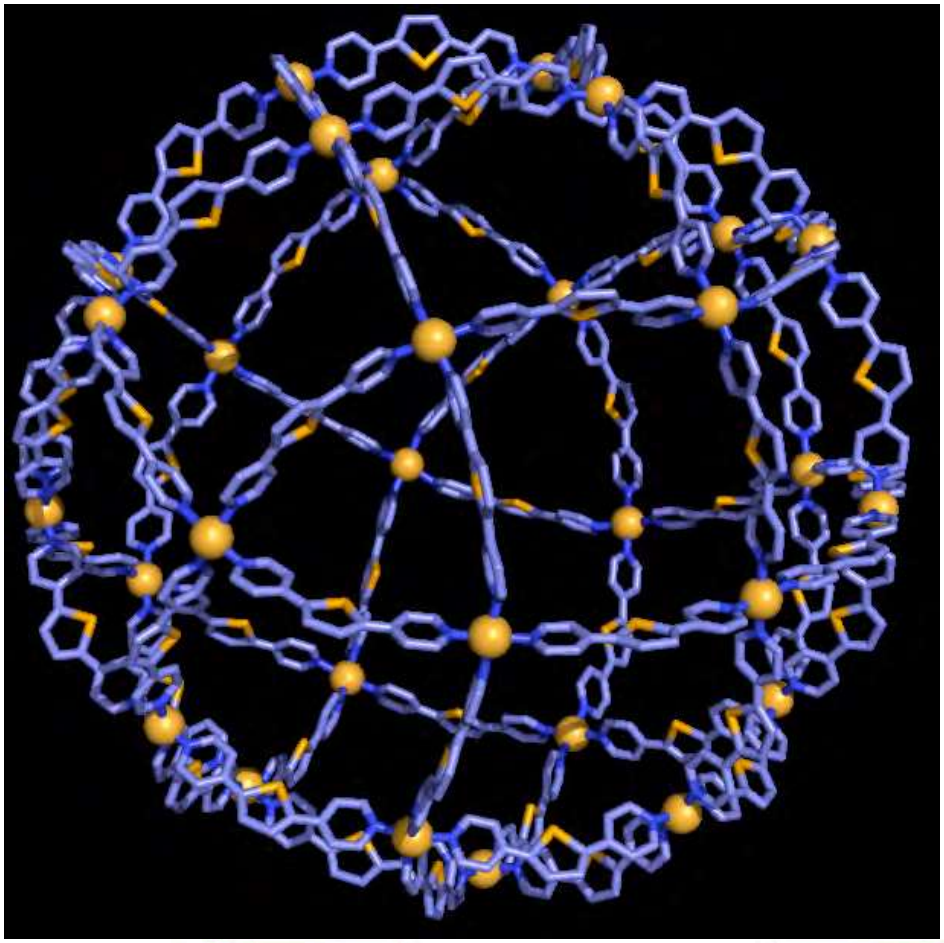


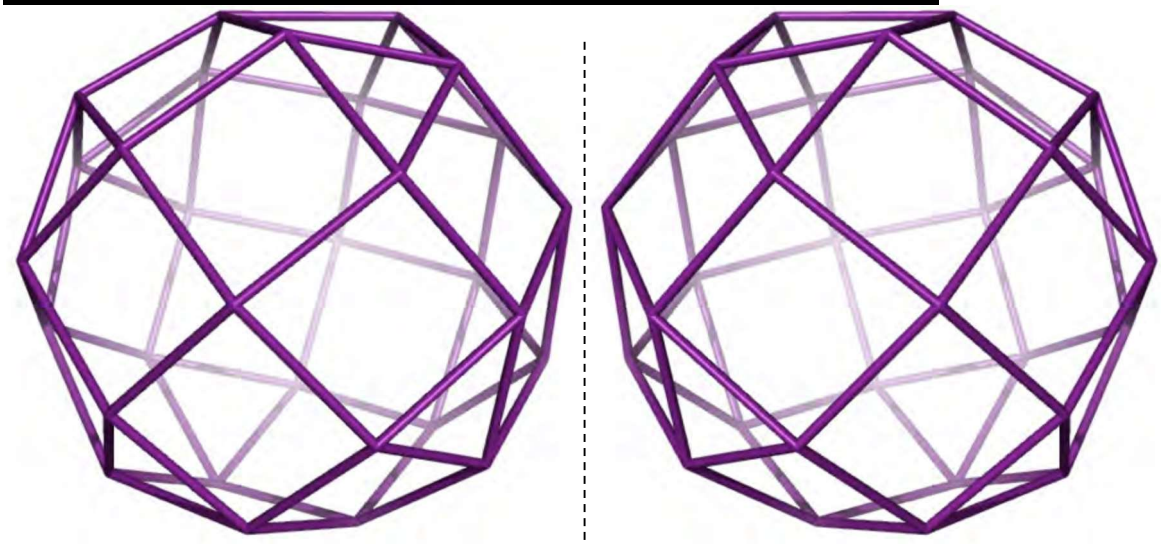
...so how about



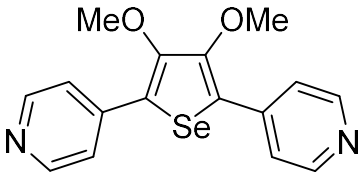
Nature **2016**, *540*, 563

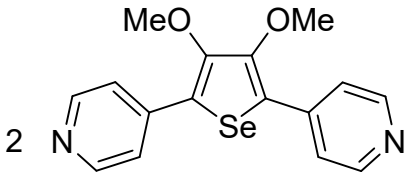




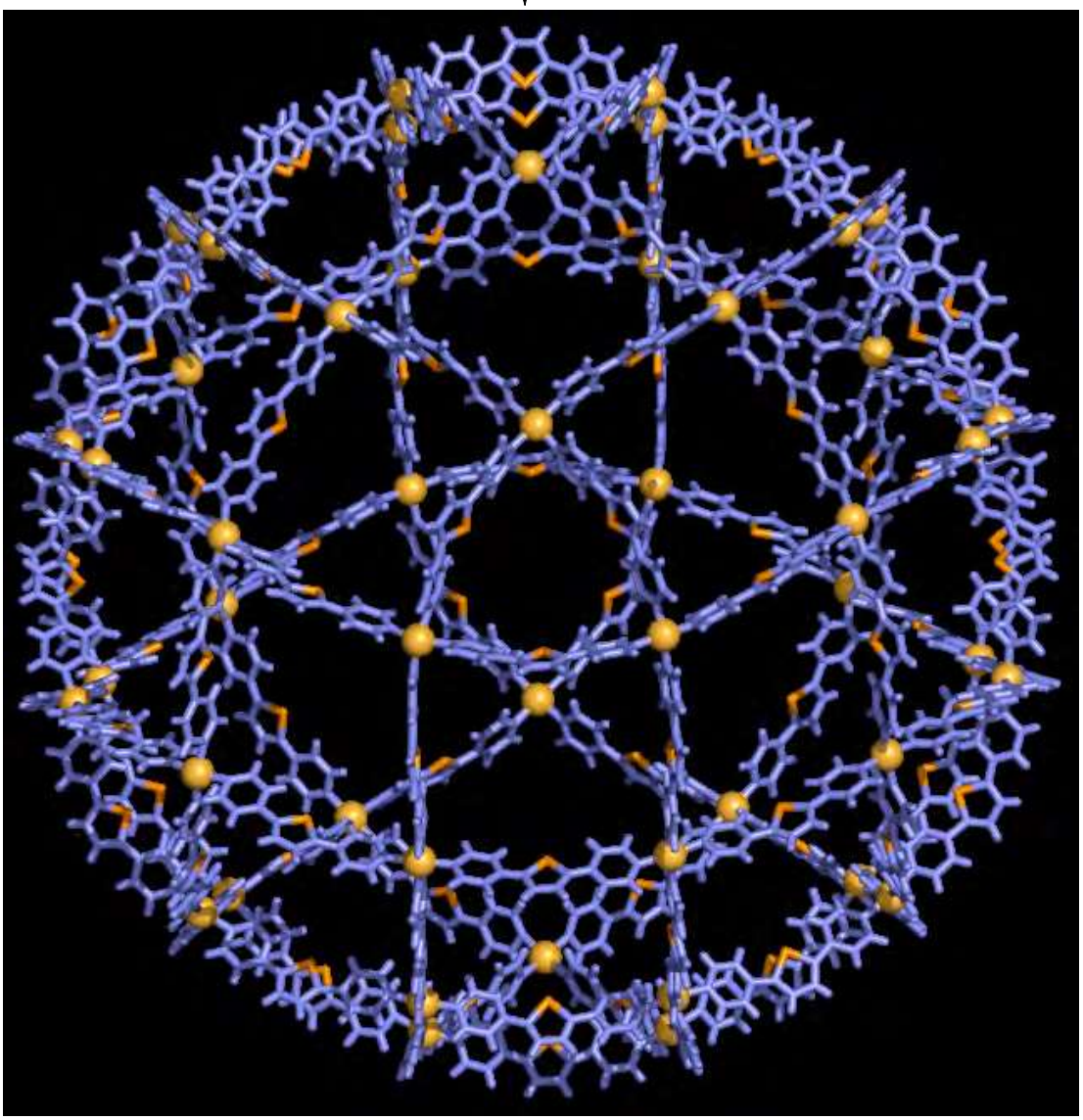


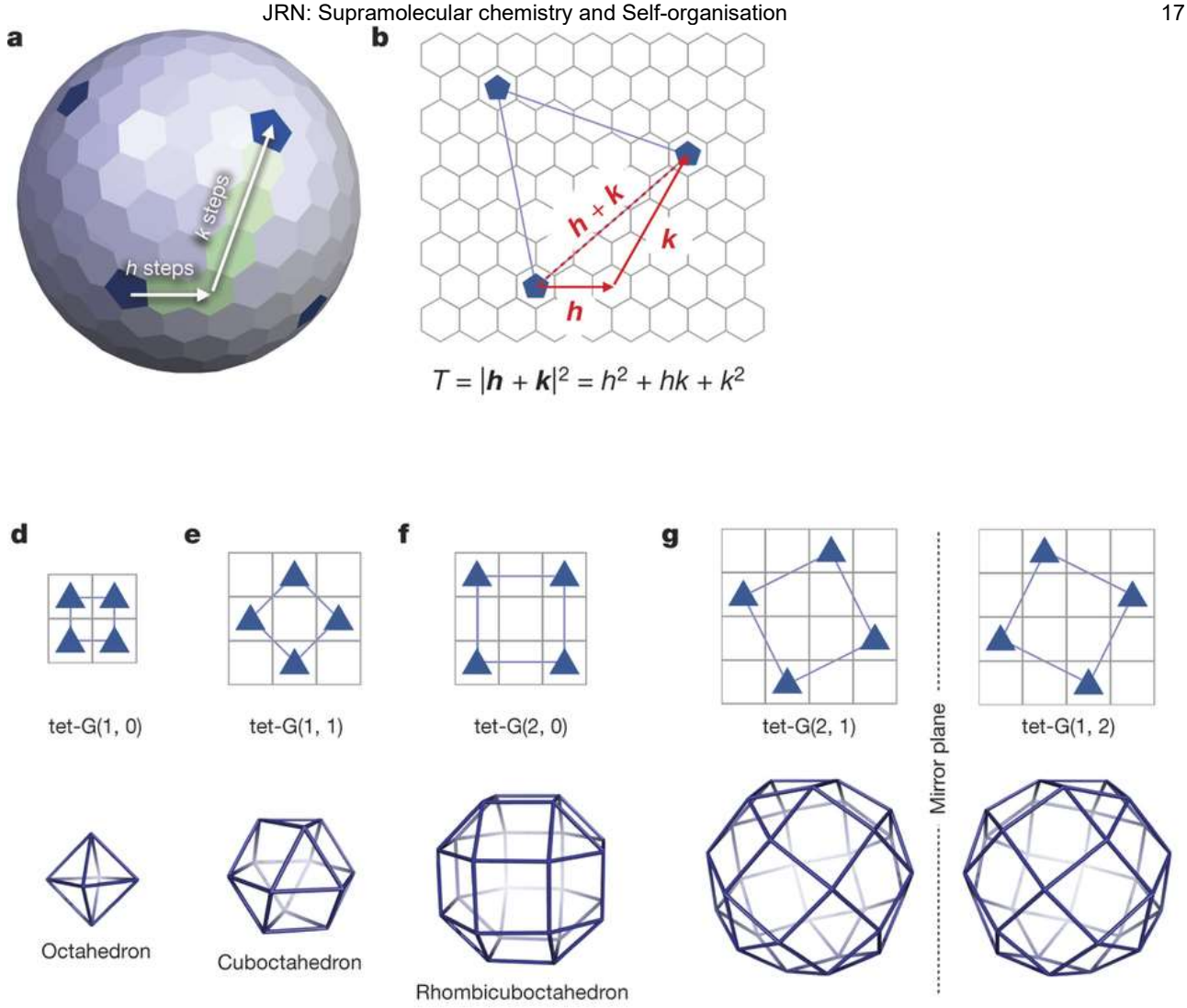
...so how about

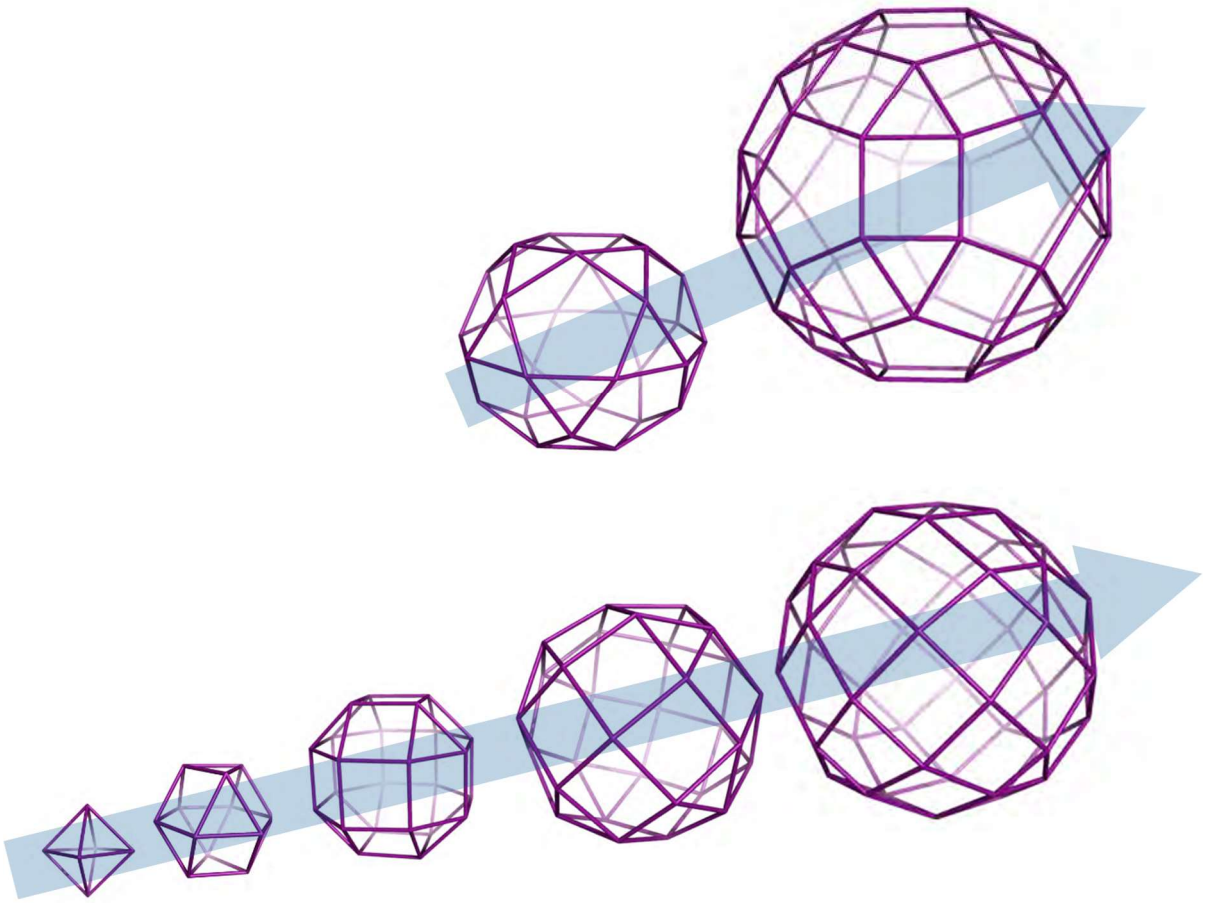


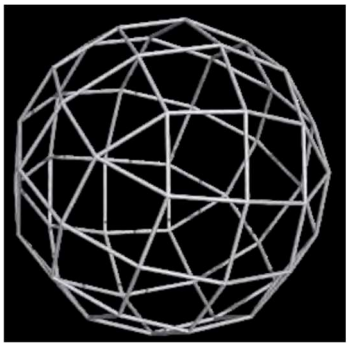


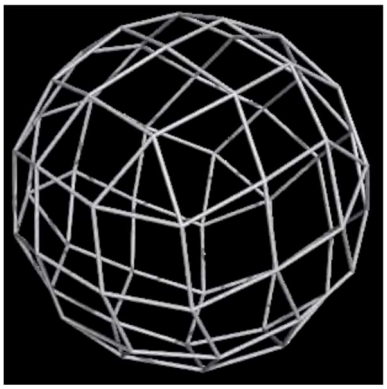
$Pd^{II}(NO_3)_2$ DMF




a
h steps
k steps
b
h + k
k
h
$T = |\boldsymbol{h} + \boldsymbol{k}|^2 = h^2 + hk + k^2$
d
tet-G(1, 0)
Octahedron
e
tet-G(1, 1)
Cuboctahedron
f
tet-G(2, 0)
Rhombicuboctahedron
g
tet-G(2, 1)
tet-G(1, 2)
Mirror plane



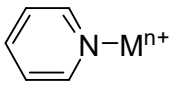


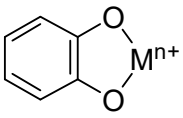


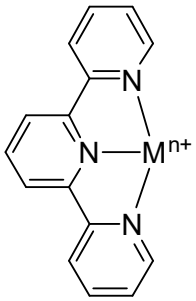
2.4 Tetrahedra & Cubes

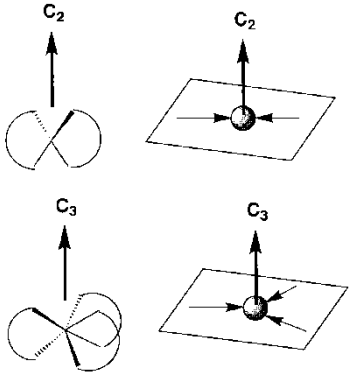
Acc. Chem. Res., 1999, 32, 975

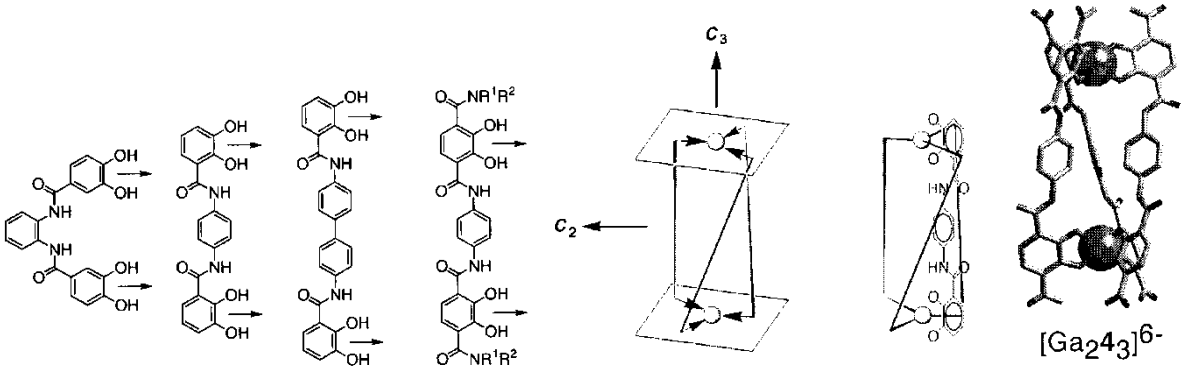
The Coordinate Vector **The Chelate Plane**



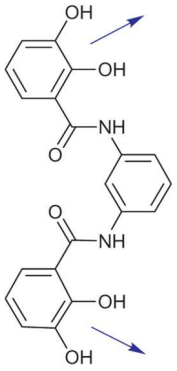


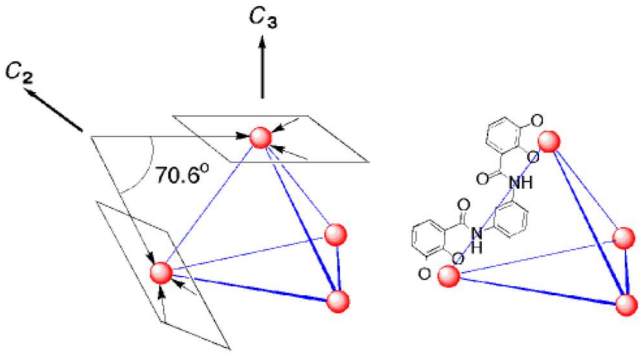


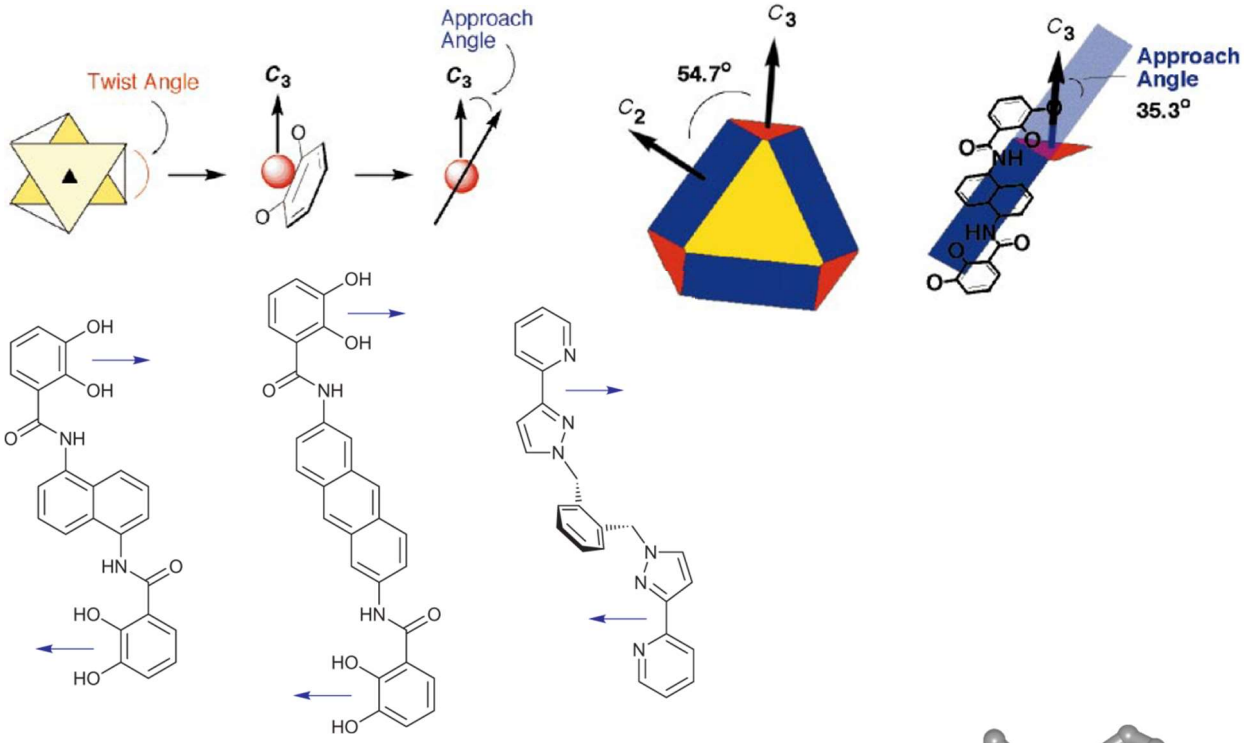




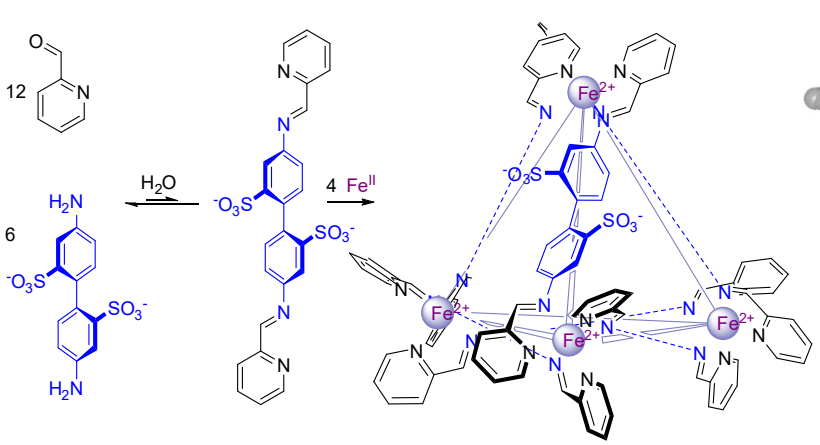
[Ga24 3]6-

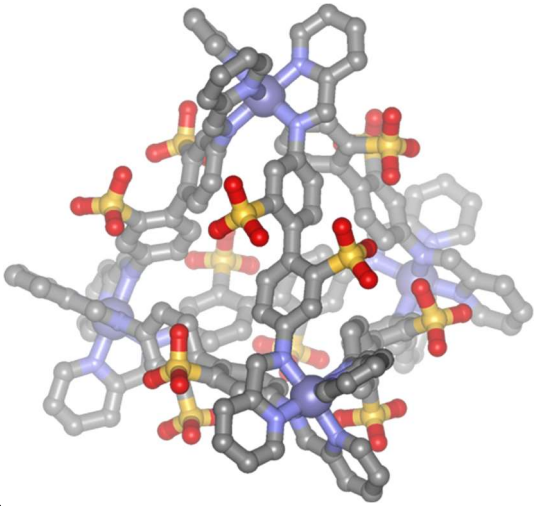






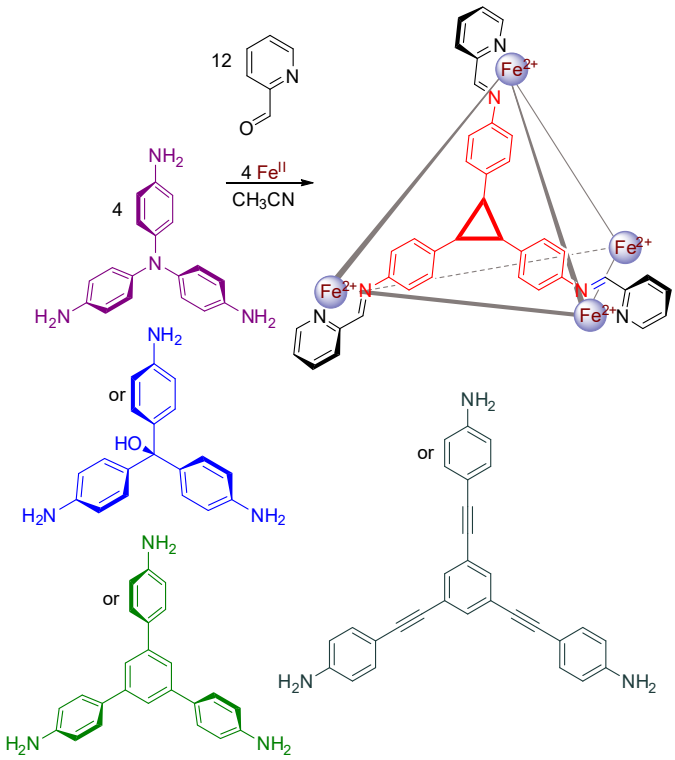
Angew. Chem. Int. Ed. 2008, *47*, **8297**

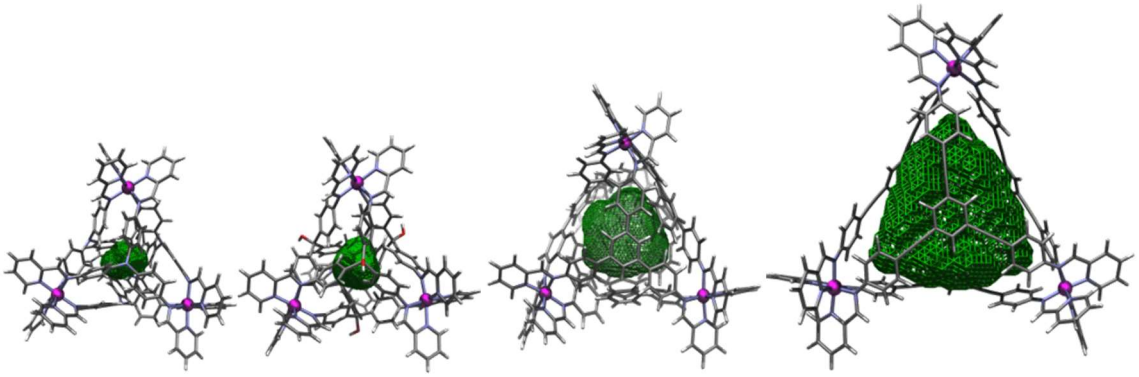




Face-capped tetrahedra

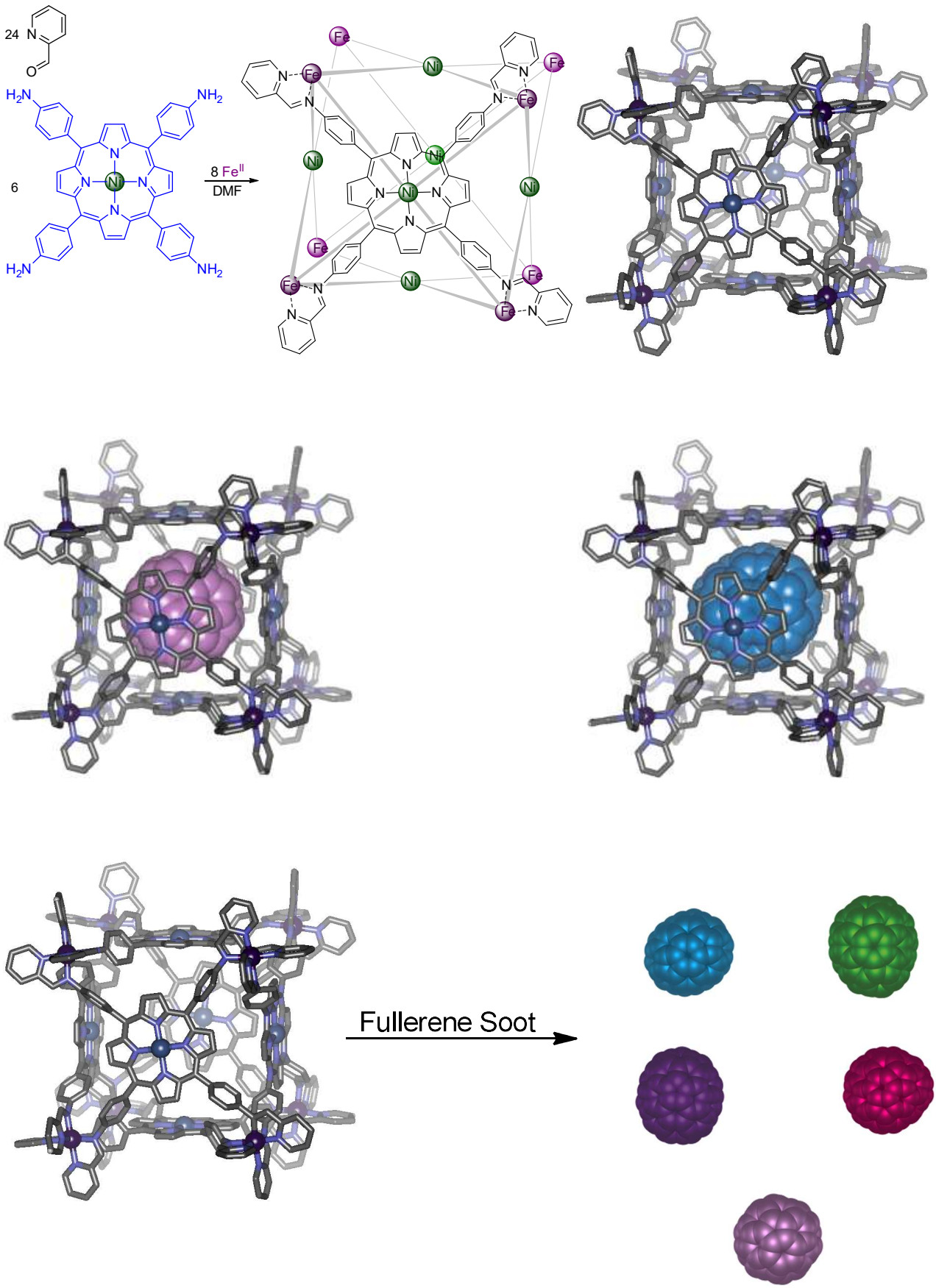
J. Am. Chem. Soc. **2012**, *134*, 5011.





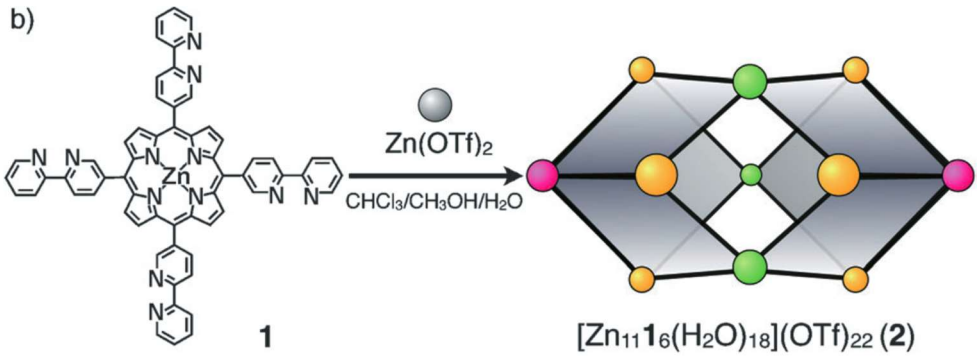
Face-capped cube

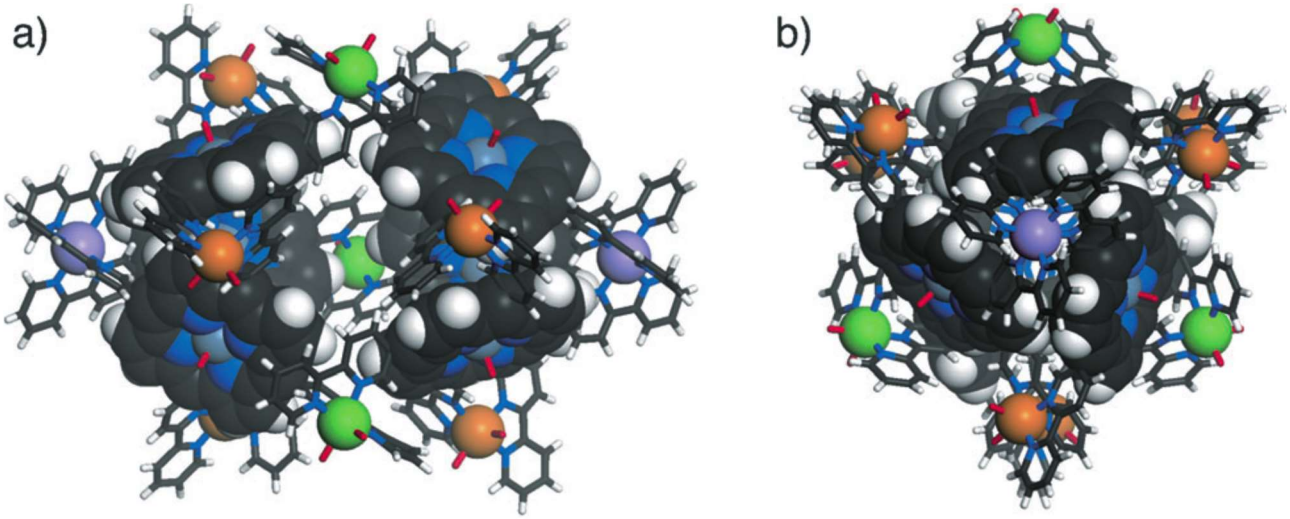
Angew. Chem. Int. Ed. **2011**, *50*, 3479-3483



An interesting non-cube

Angew. Chem. Int. Ed. **2013**, *52*, 720

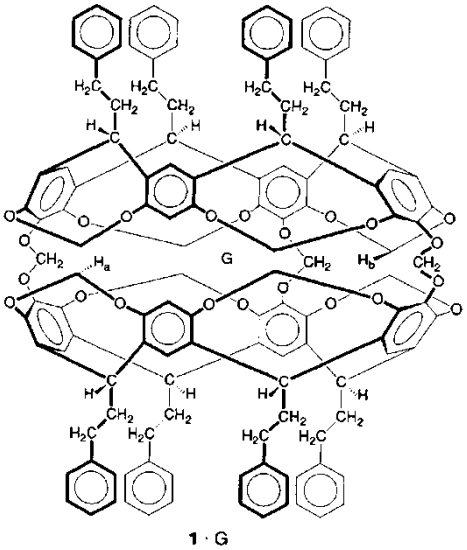




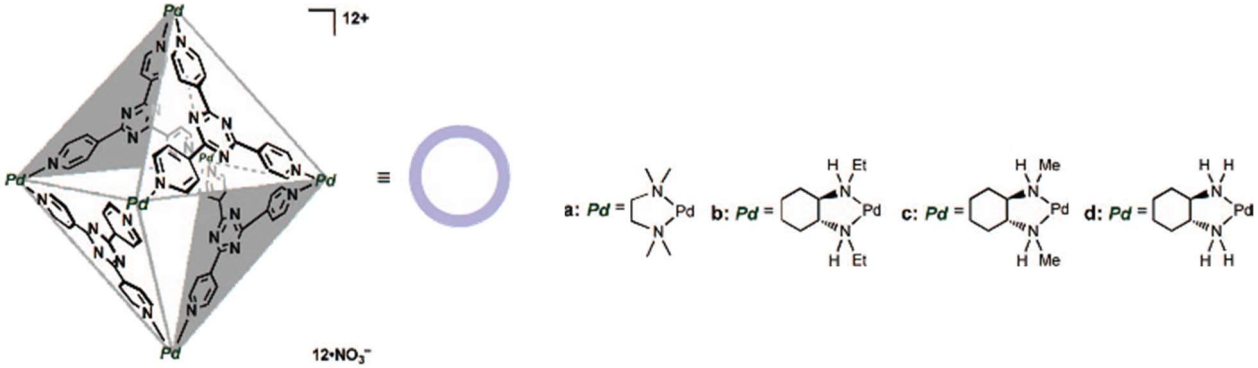
2.5 Chemistry in the 'Inner Phase' of Container Molecules

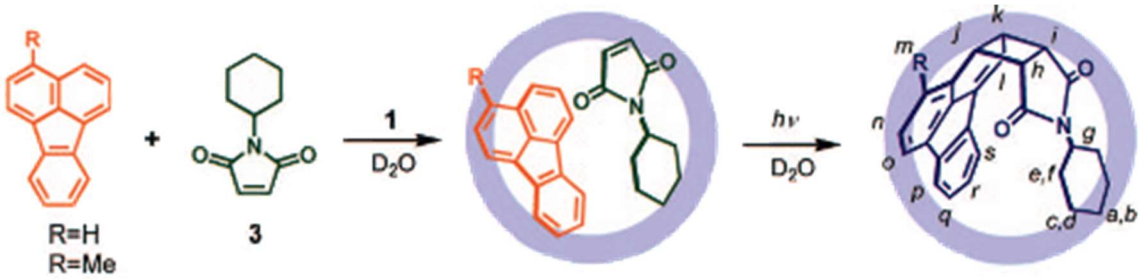
Angew. Chem. Int. Ed. **2002**, *41*, 1488

Angew. Chem. Int. Ed. **1991**, *30*, 1024



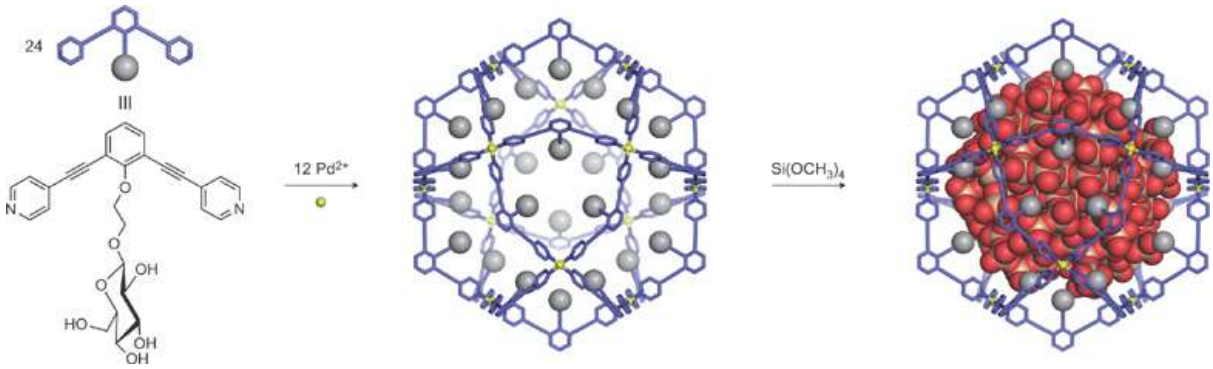
J. Am. Chem. Soc. **2008**, *130*, 8160



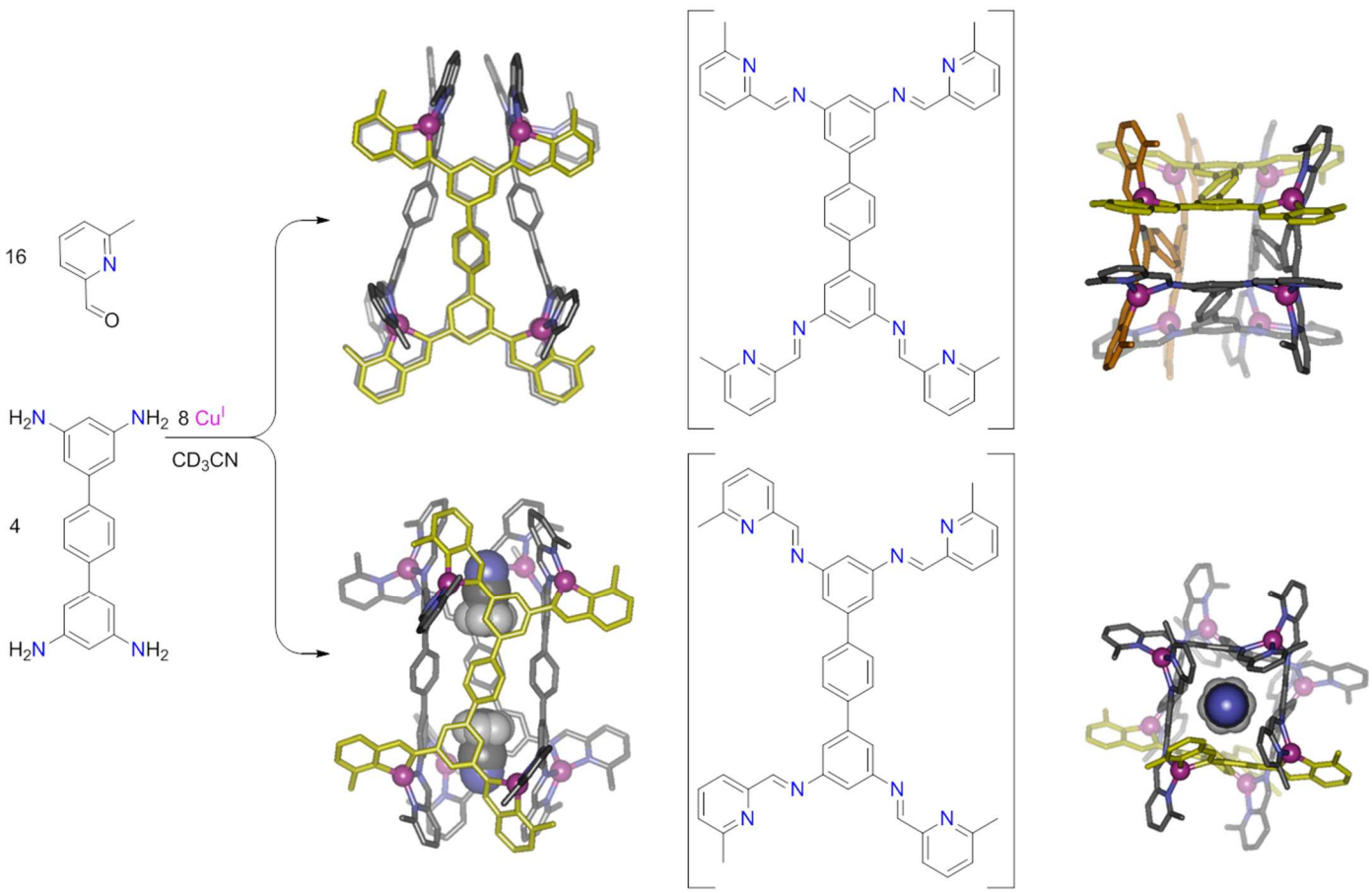


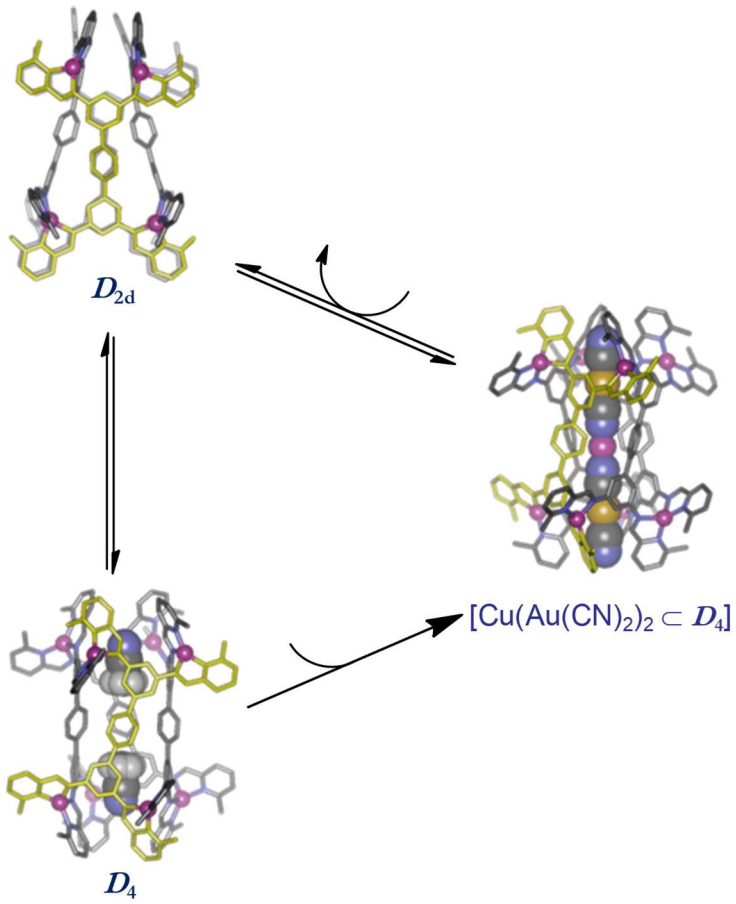
Endo-templation in a capsule *Nature Chem.* **2010**, *2*, 25

$Si(OMe)_4 + 2\ H_2O \rightarrow$

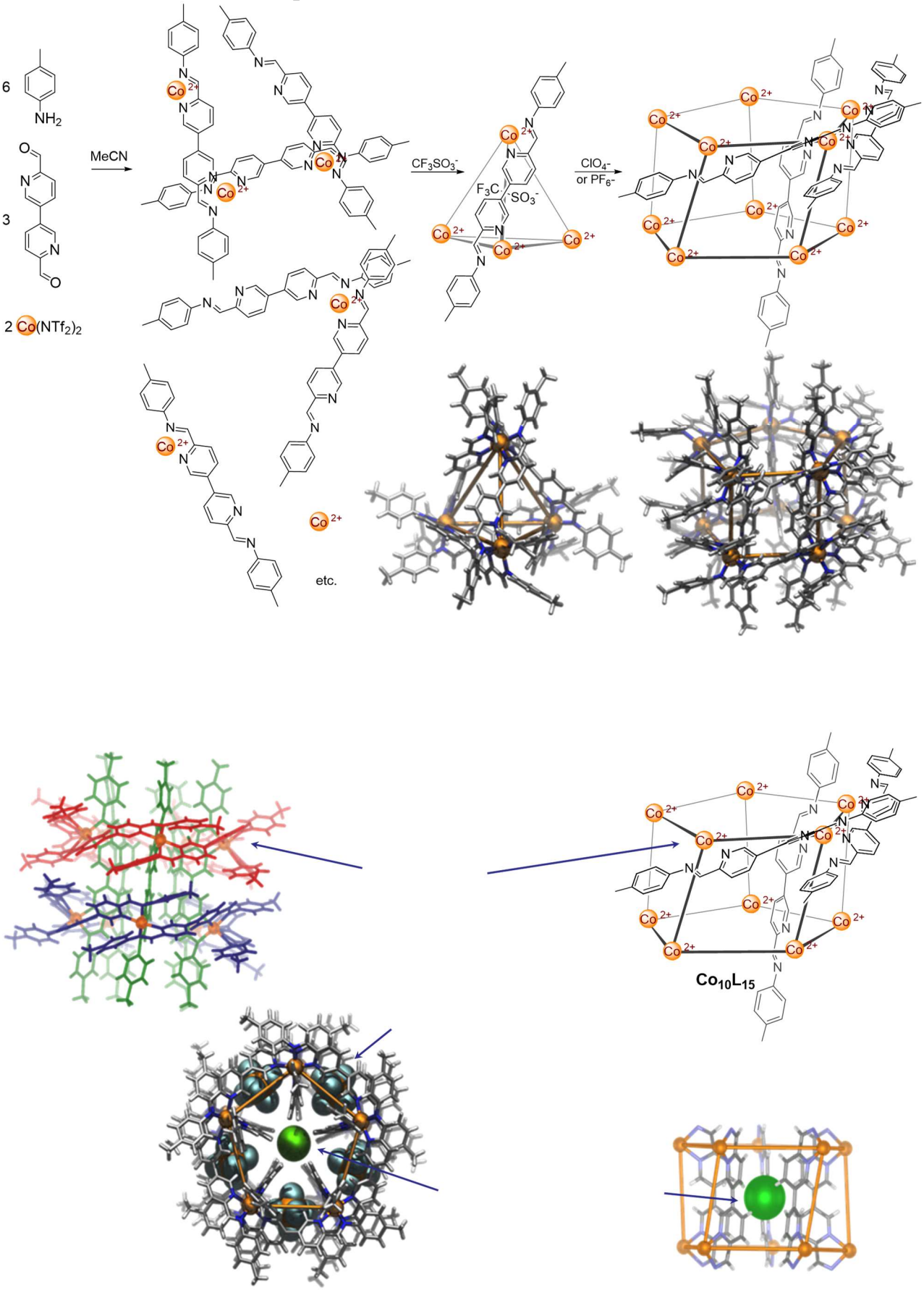


Panning for Gold *Angew. Chem. Int. Ed.* **2012**, *51*, 1881

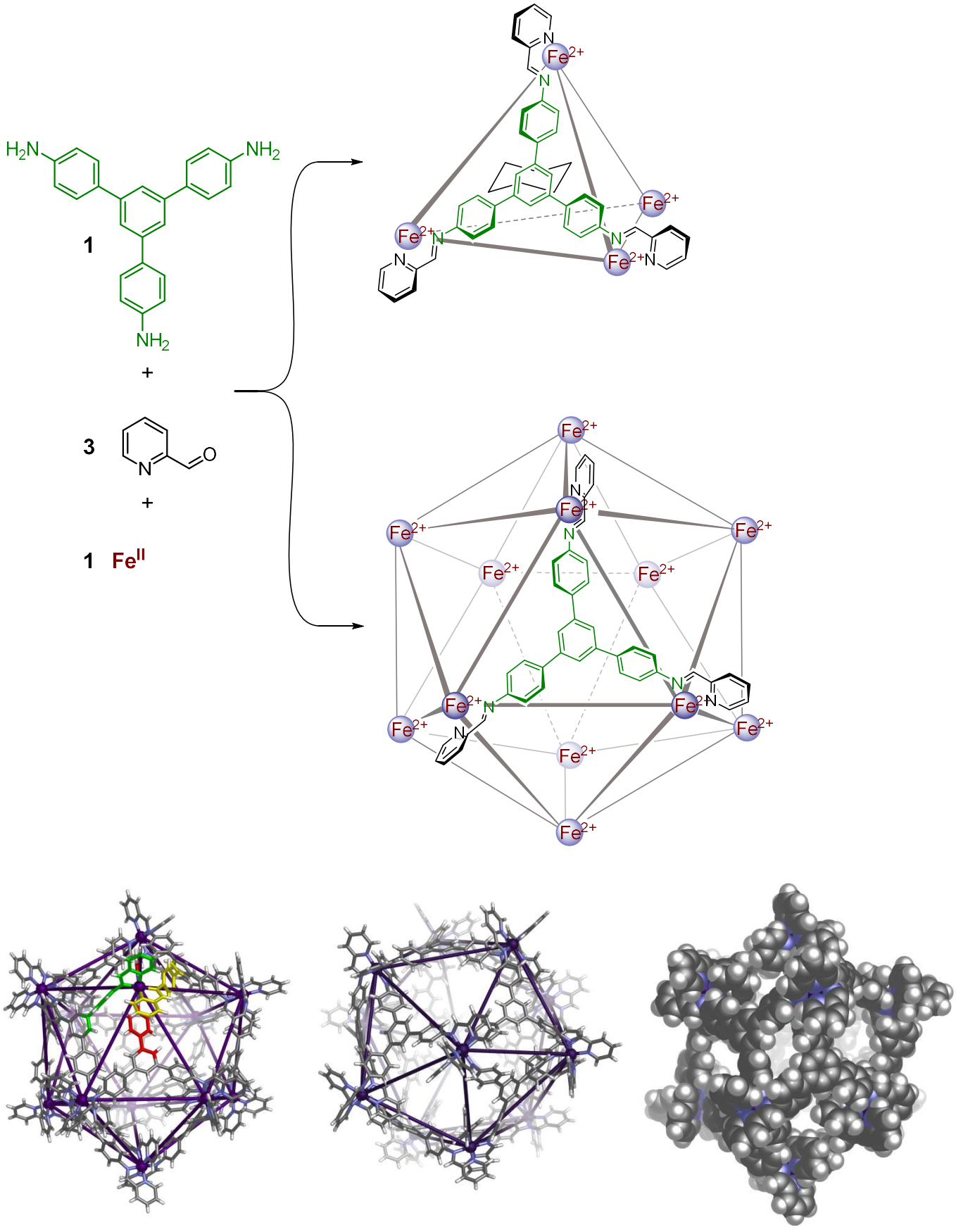



D_{2d}
D_4
$[Cu(Au(CN)_2)_2 \subset D_4]$

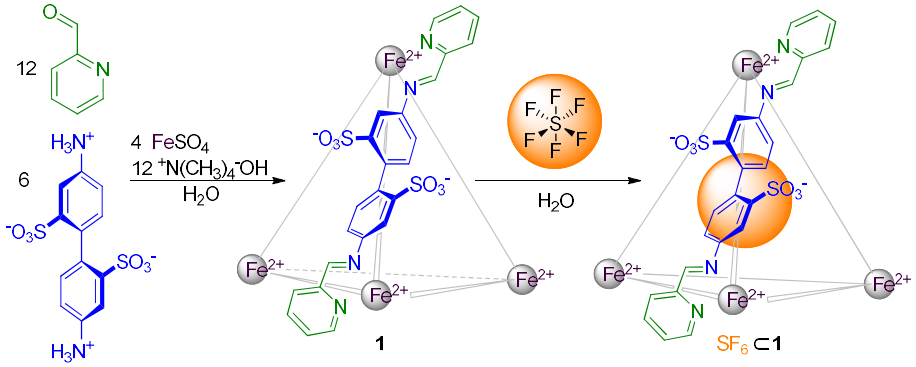
‘Second-order’ Anion Templation *Nature Chem.* **2012**, *51*, 751-756.



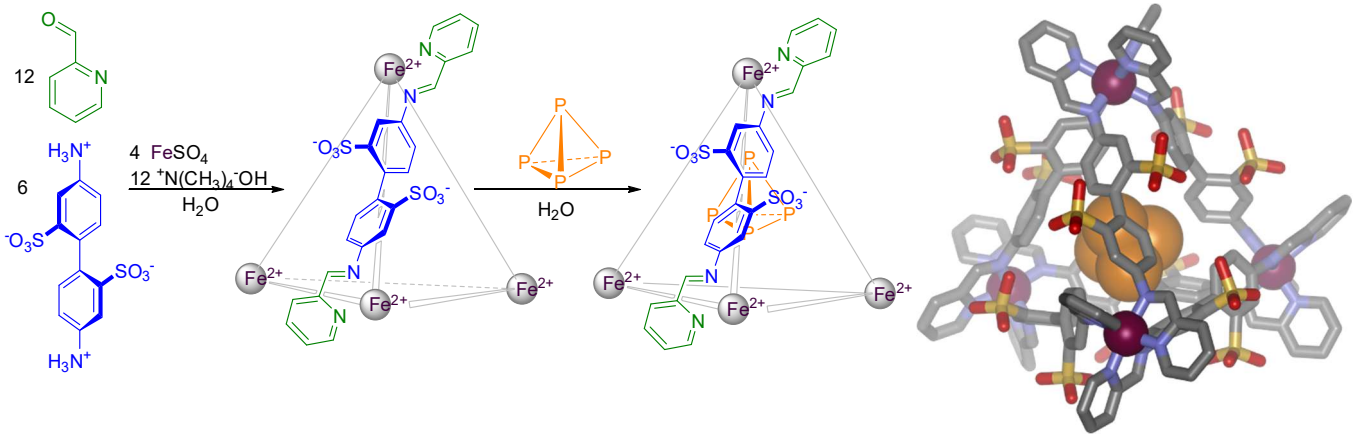
A Pseudo-Icosohedron *Angew. Chem. Int. Ed.* **2013**, *52*, 9027-9030.

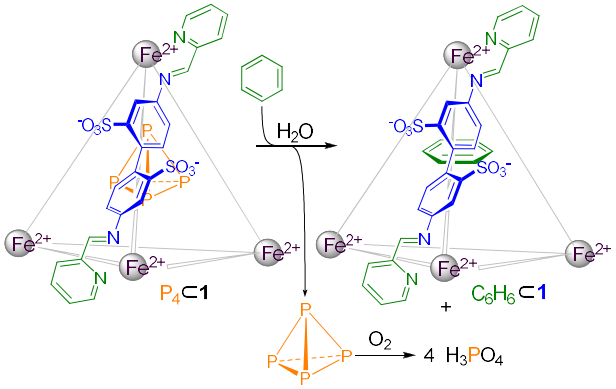


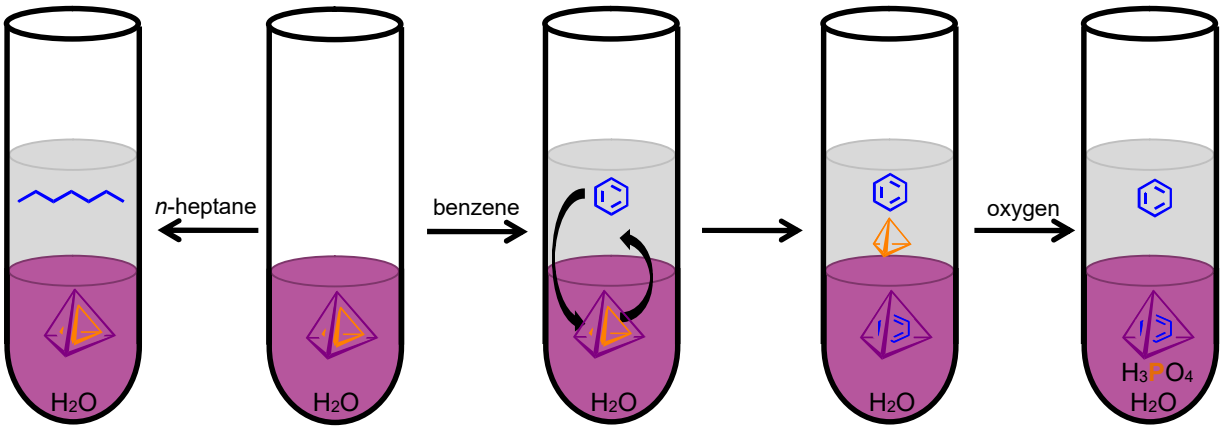
Specific sequestration of SF_6 *Chem. Commun*. **2011**, *47*, 457



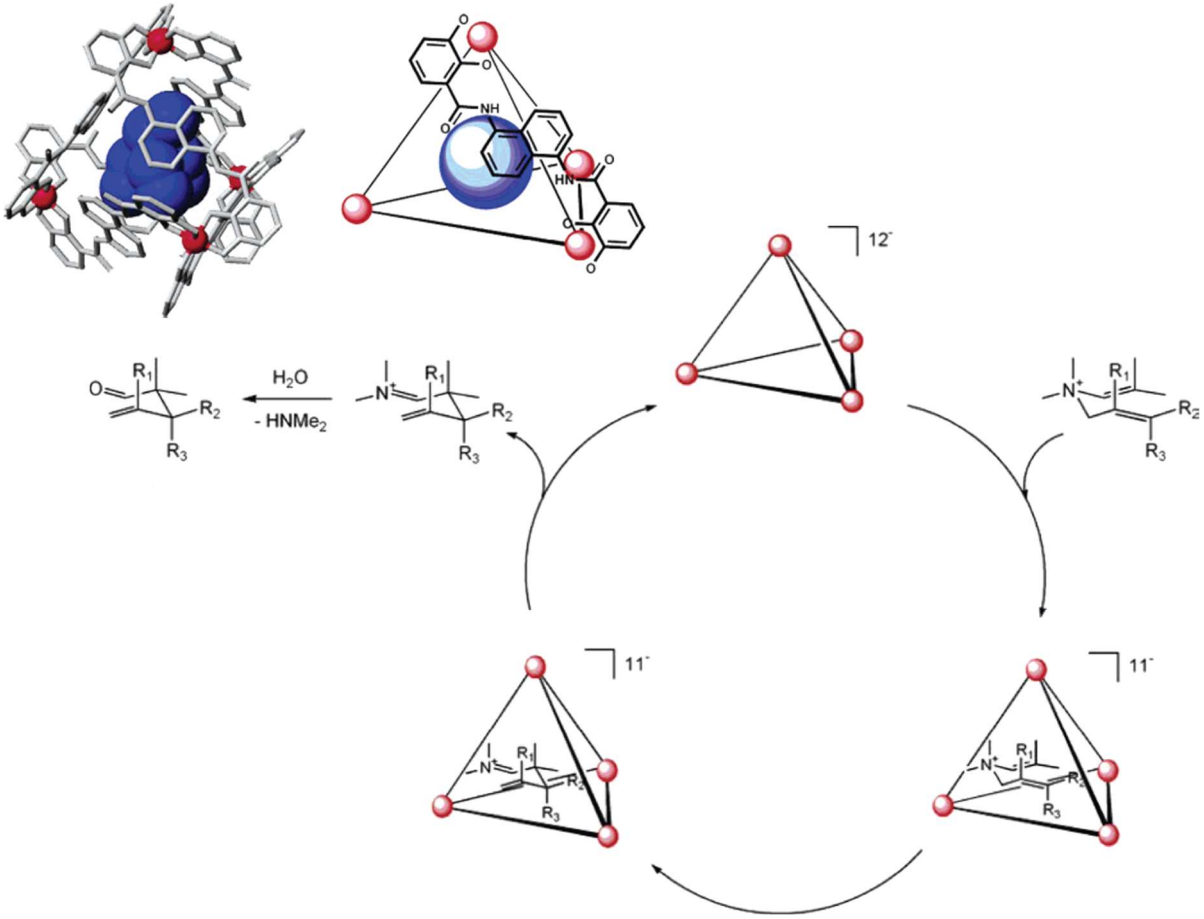
Science **2009**, *324*, 1697



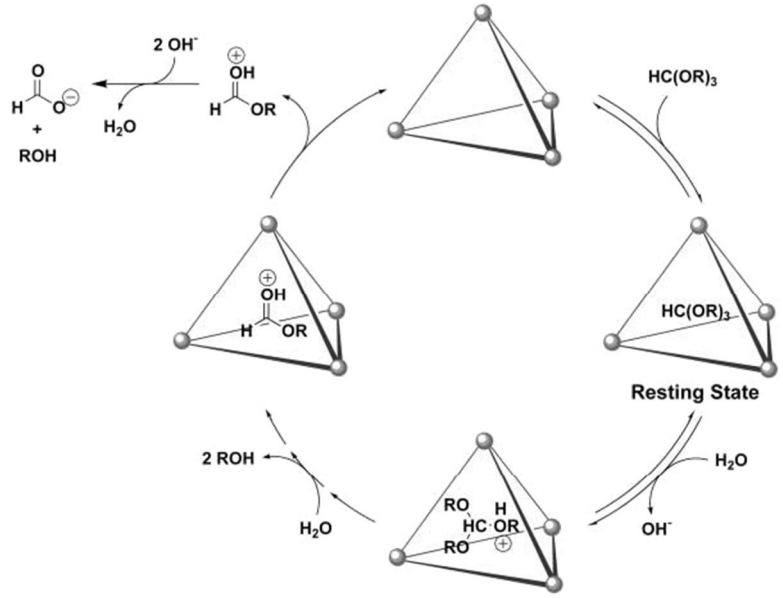




Acc. Chem. Res. **2005**, *38*, 351



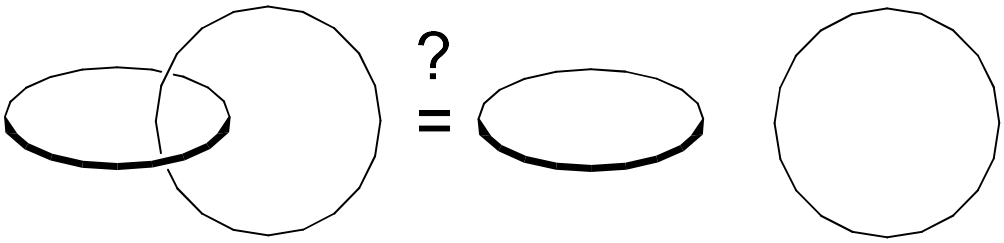
Science **2007**, *316*, 85



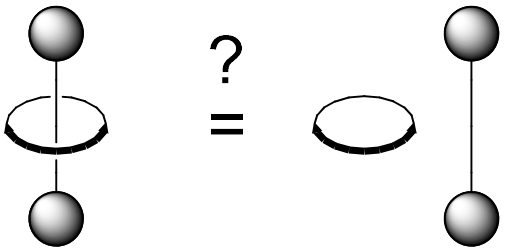
3. Molecular topology

Tetrahedron, 1999, **55**, 5265.
Chem. Eur. J., 1998, **4**, 608.
Chem. Commun., 1998, 723.

Consider a structure consisting of two identical macrocycles, one threaded through the other. Would this structure have the same properties as its constituent rings, unthreaded?

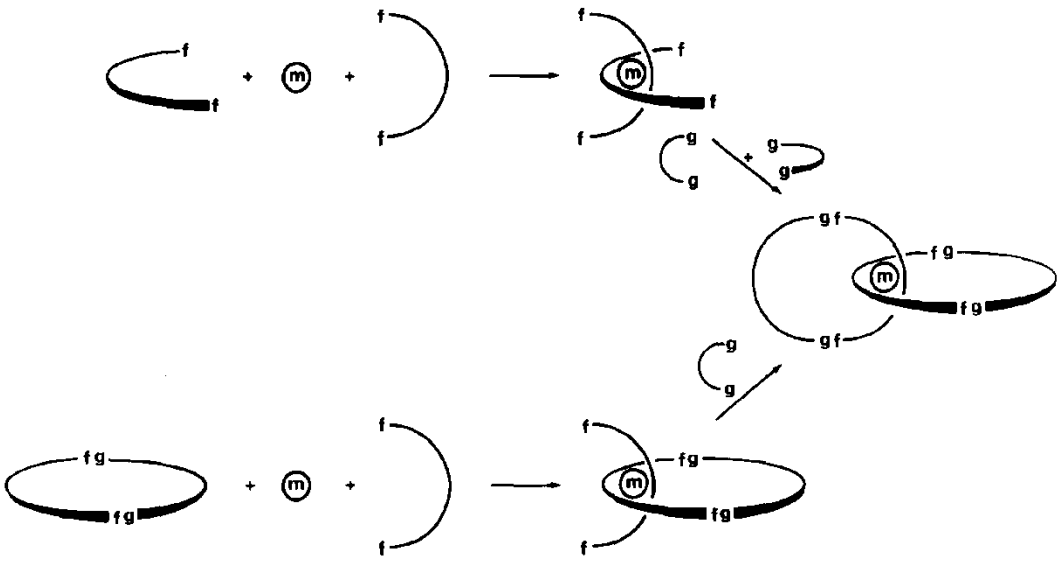


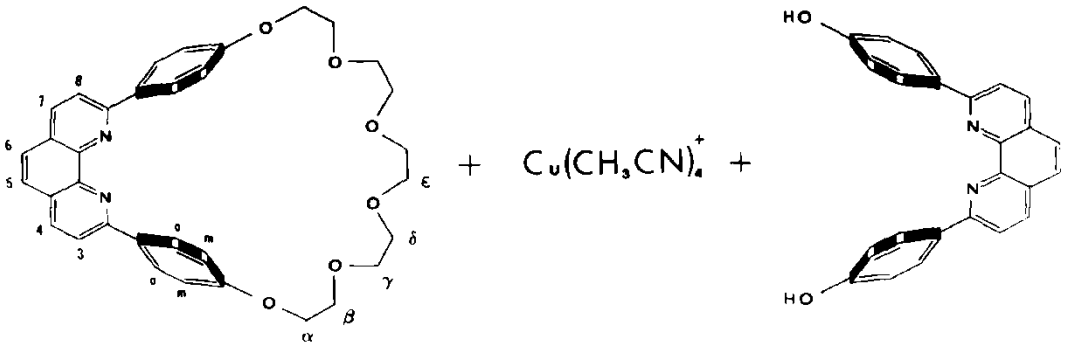
A conceptually similar case is a macrocycle threaded around an axle, the ends of which are both stoppered by bulky groups:

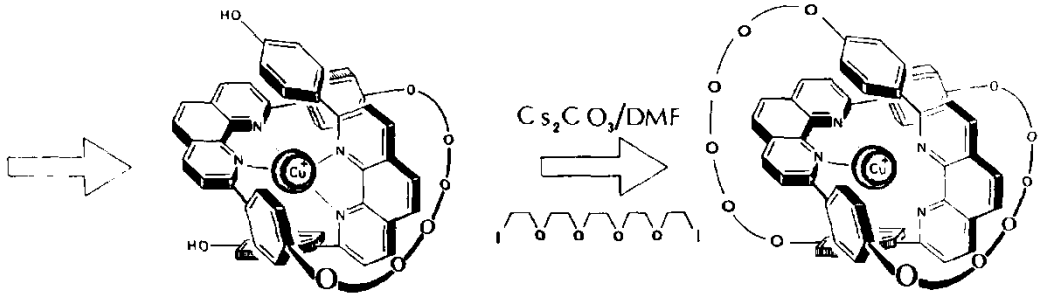


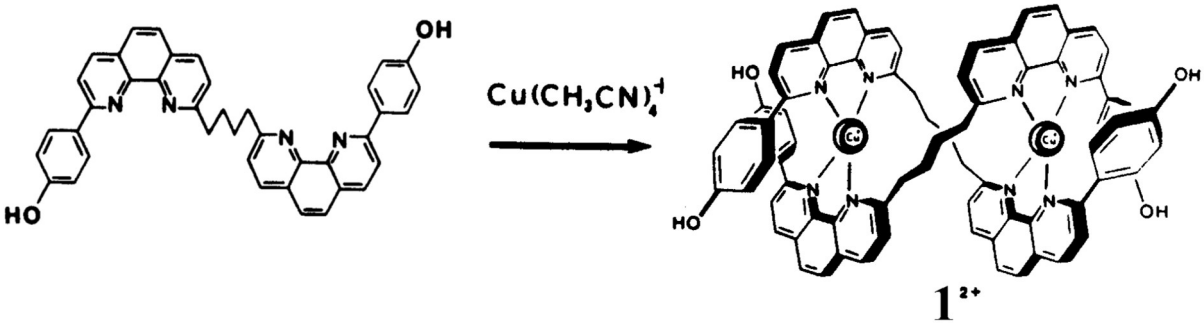
3.1 Catenanes and Knots

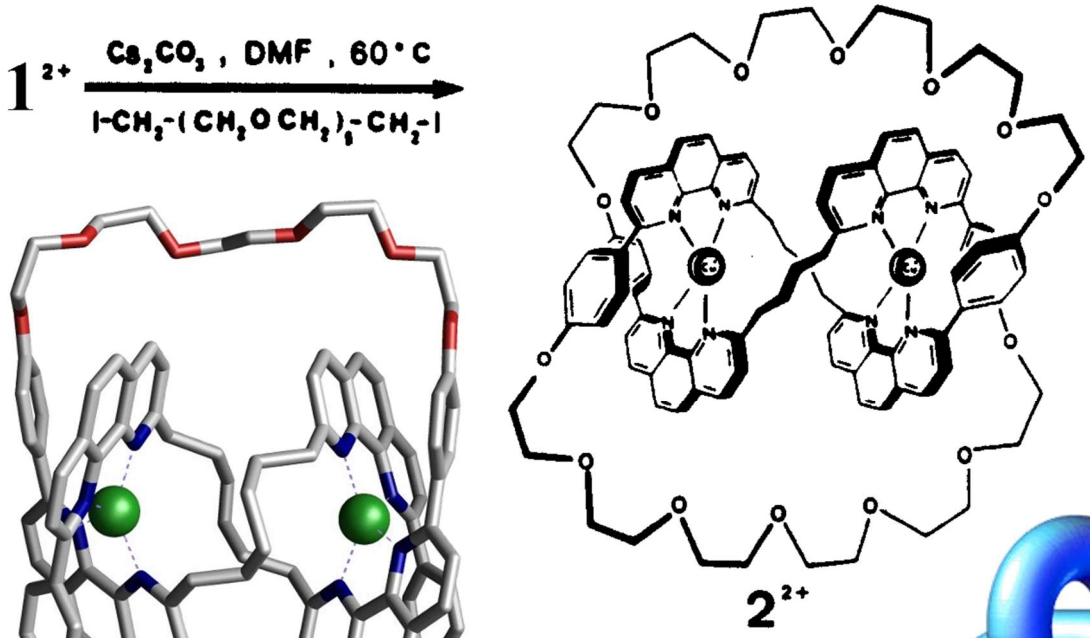
Tetrahedron Lett., 1983, **24**, 5095

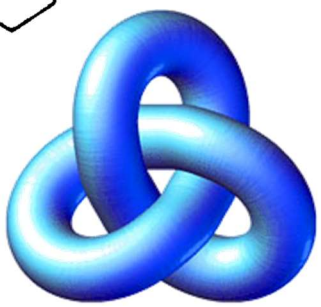




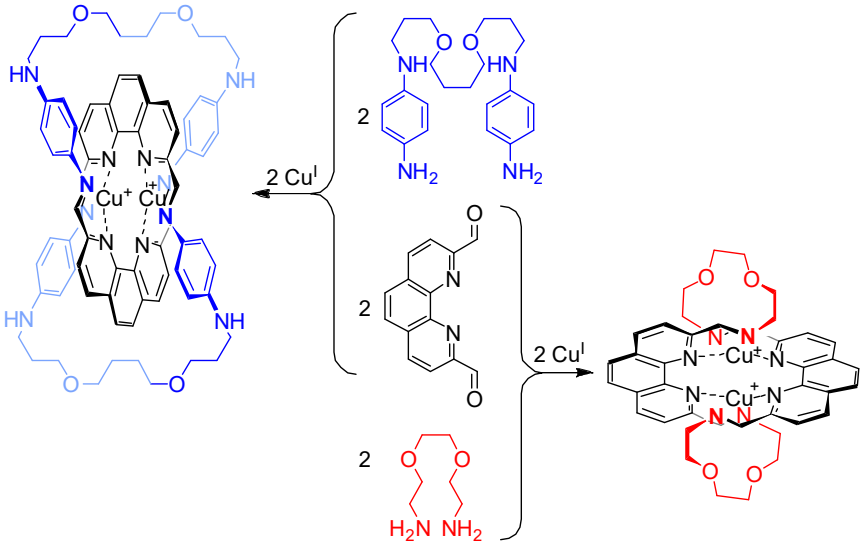

Cs2CO3/DMF


Cu(CH3CN)4+
1 2+

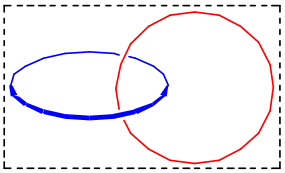

1 2+
Cs2CO3 , DMF , 60°C
I-CH2-(CH2OCH2)5-CH2-I
2 2+

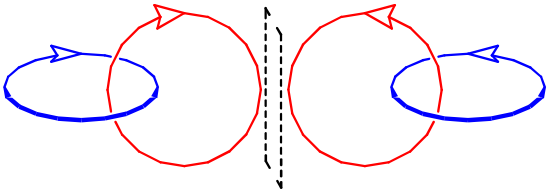


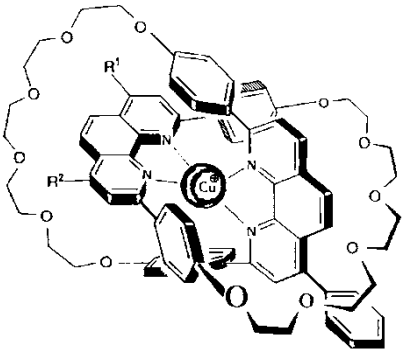
Chem. Eur. J. **2006**, *12*, 4069

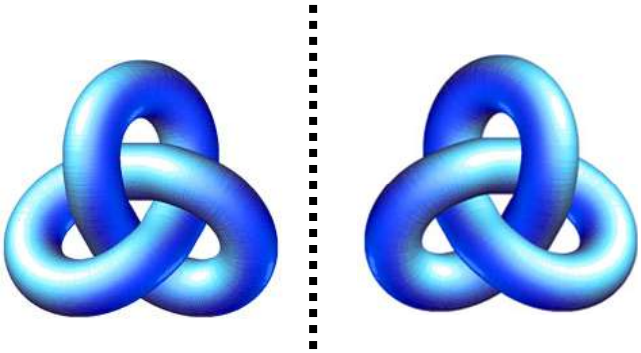


3.2 Topological Chirality



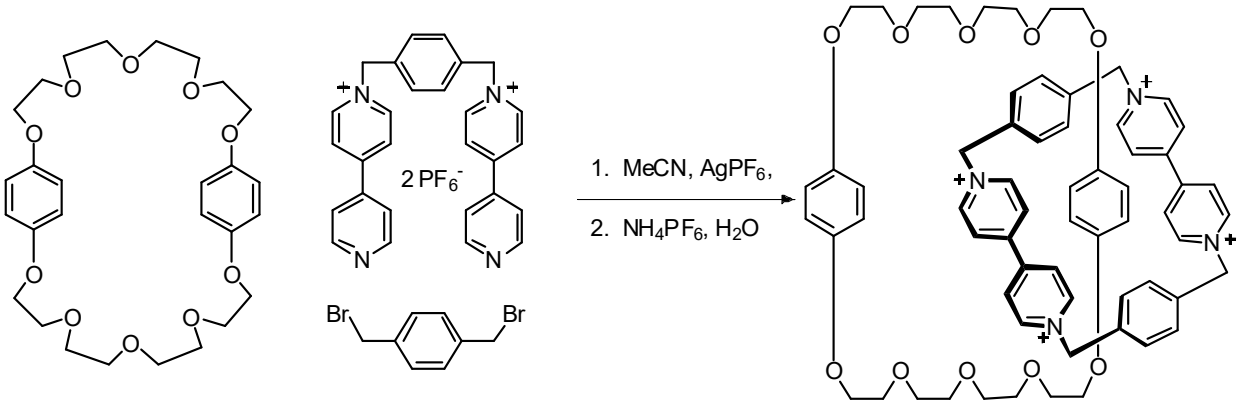


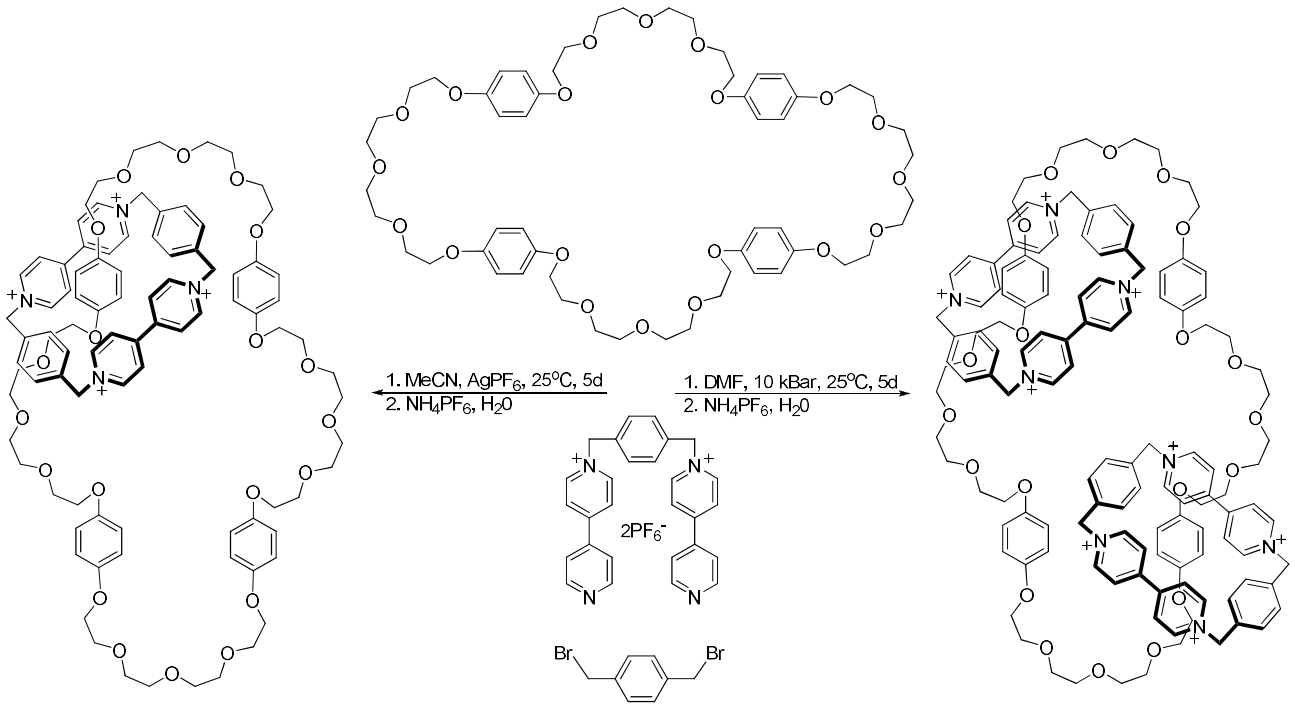


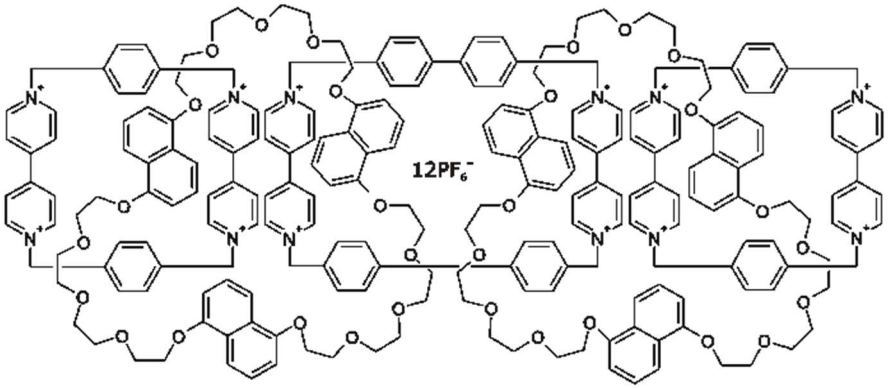


3.3 Donor-acceptor catenanes

Chem. Rev. 1999, **99**, 1643

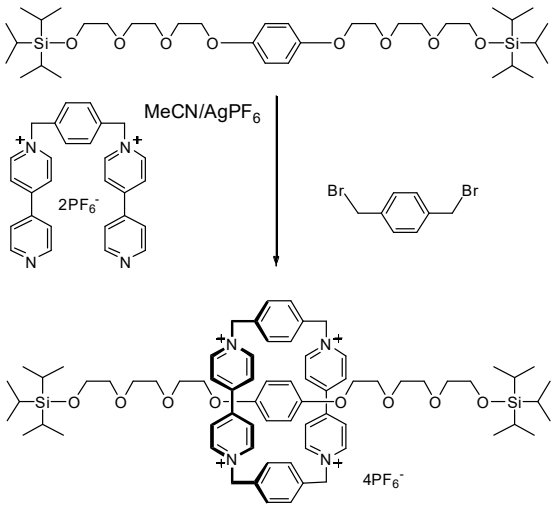


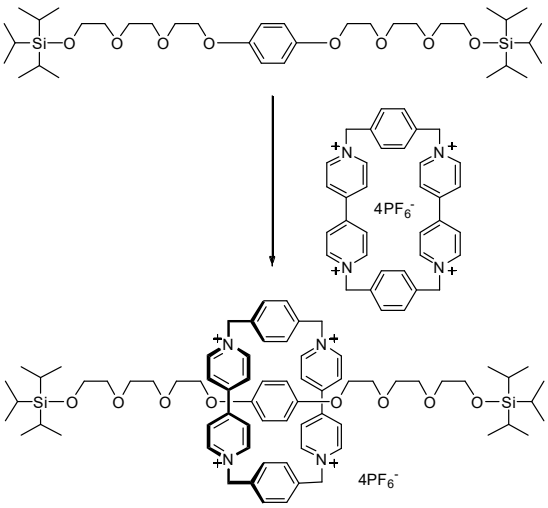


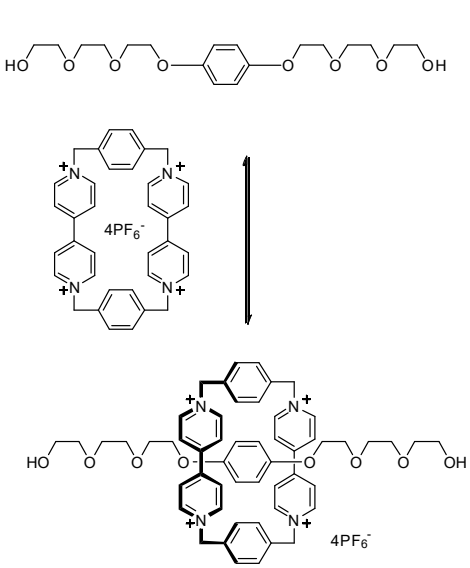


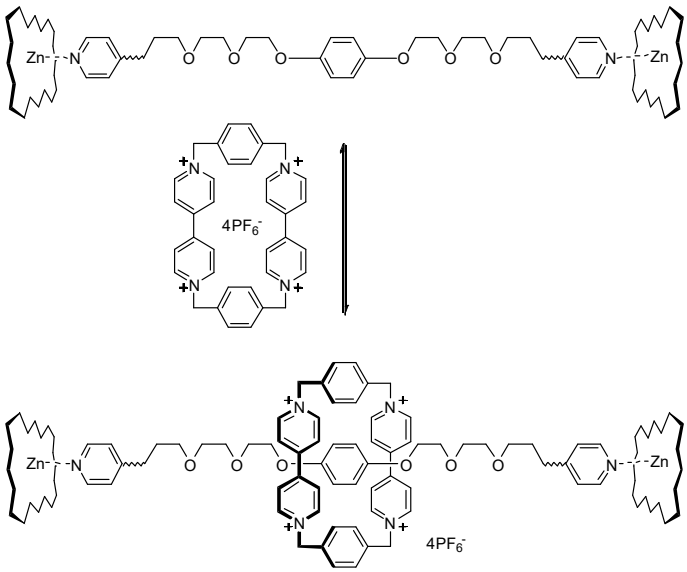
3.4 Rotaxanes

Terminology: Rotaxane vs. Pseudo-rotaxane



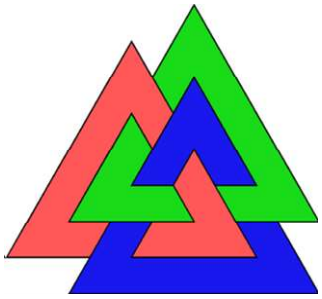


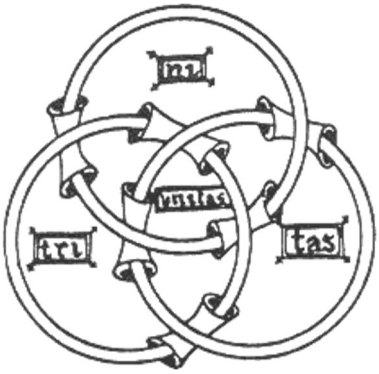


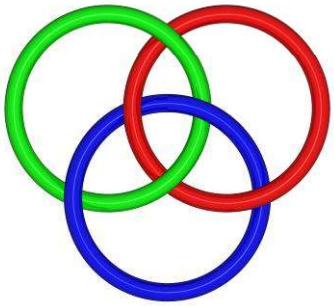


3.5 Borromean Rings

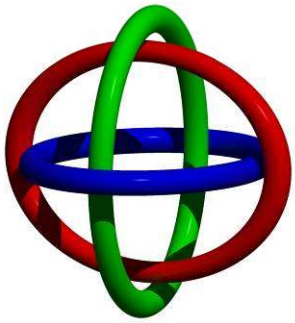
Science **2004**, *304*, 1308



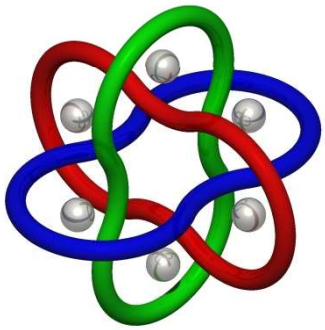




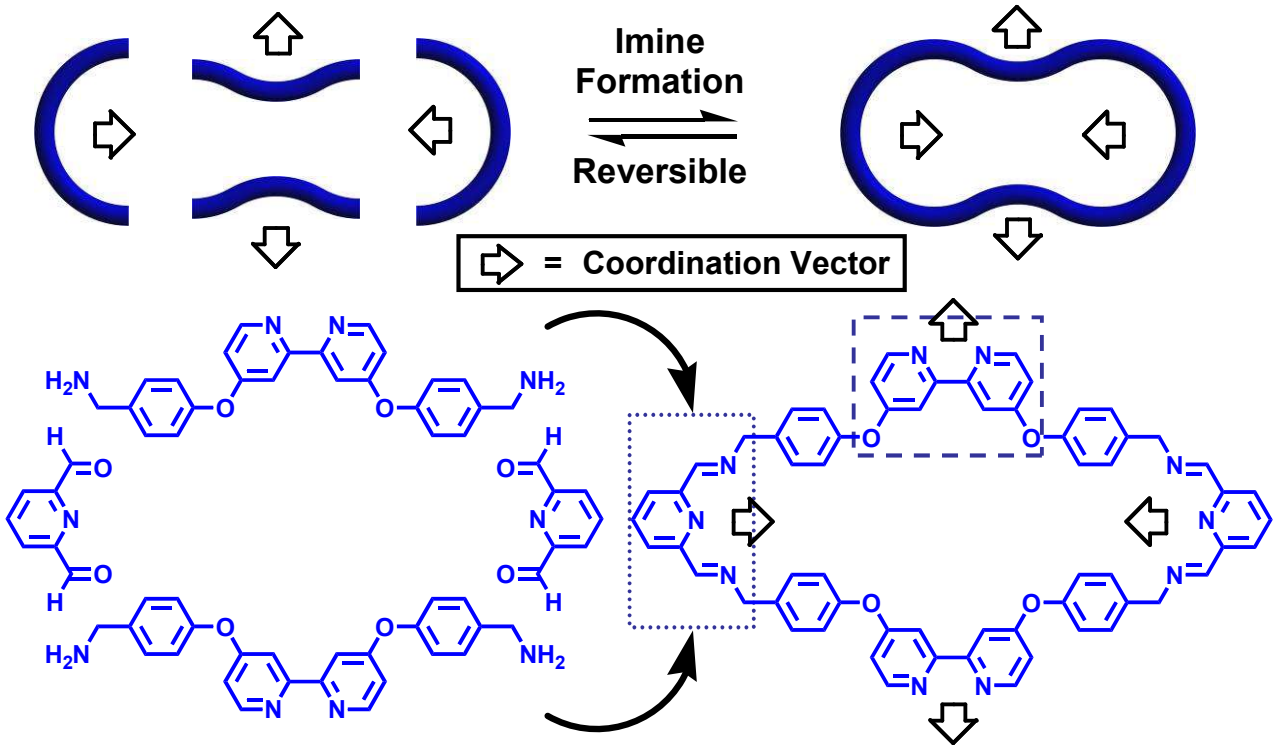
+ / – / + / –
Alternating Nodes

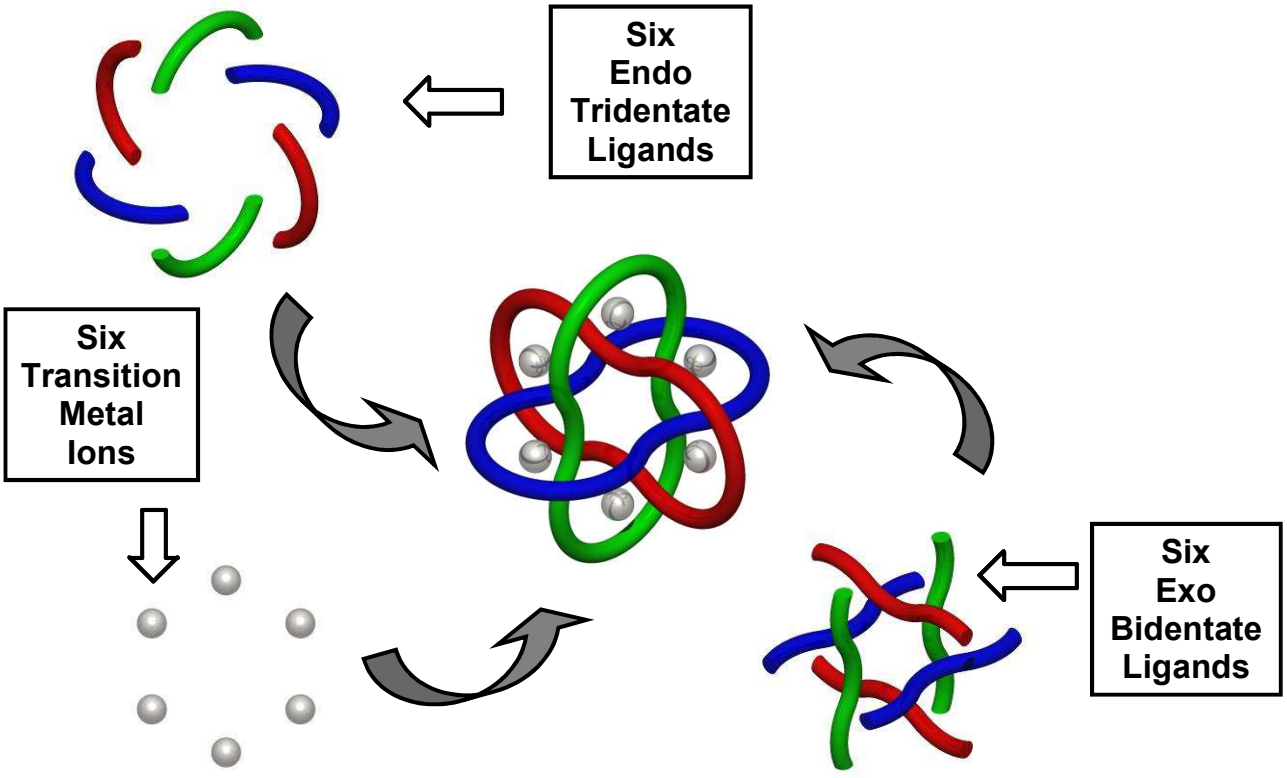


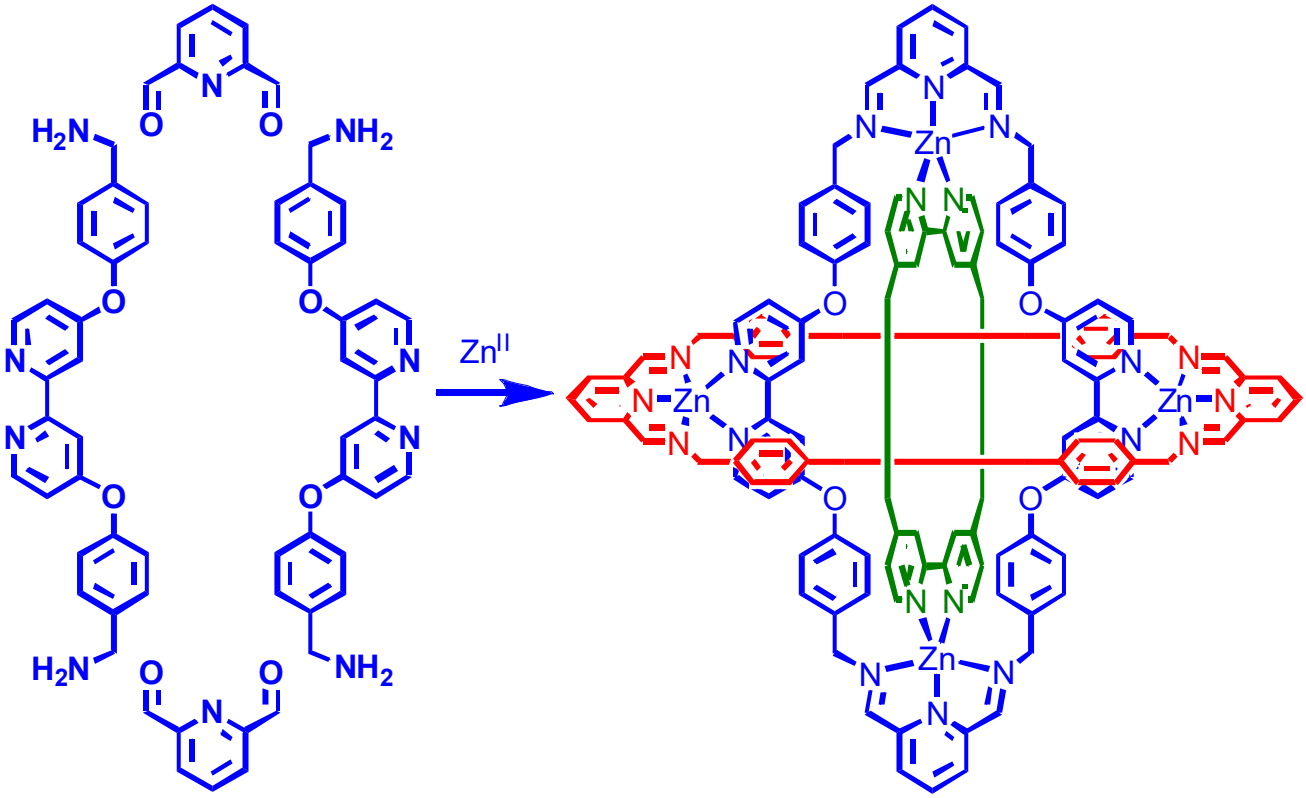
exo* / *endo* / *exo* / *endo
“Binding Sites”

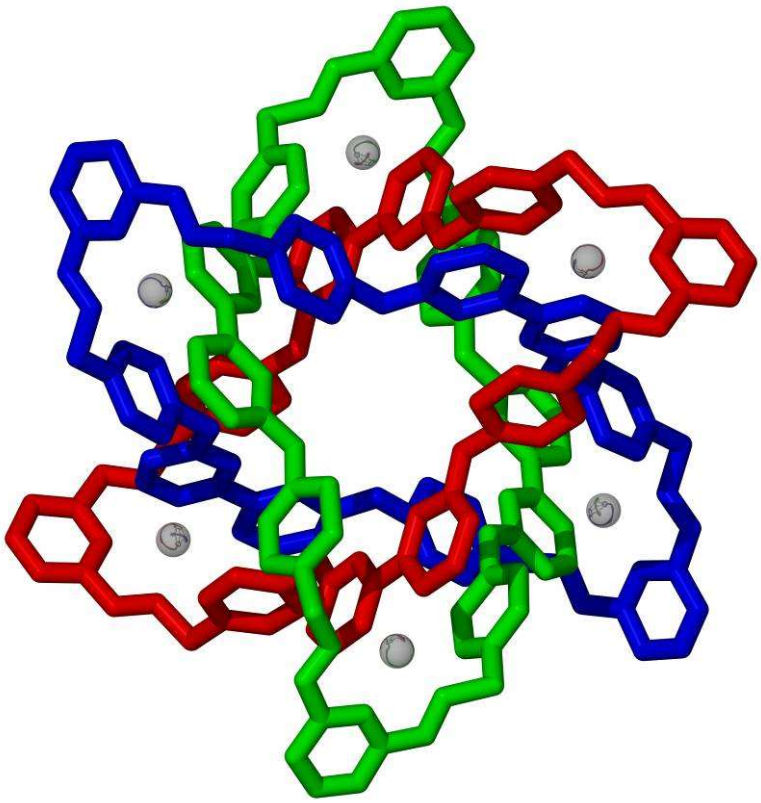


Transition Metals
in the Binding Sites


Imine
Formation
Reversible
= Coordination Vector


Six
Endo
Tridentate
Ligands
Six
Transition
Metal
Ions
Six
Exo
Bidentate
Ligands

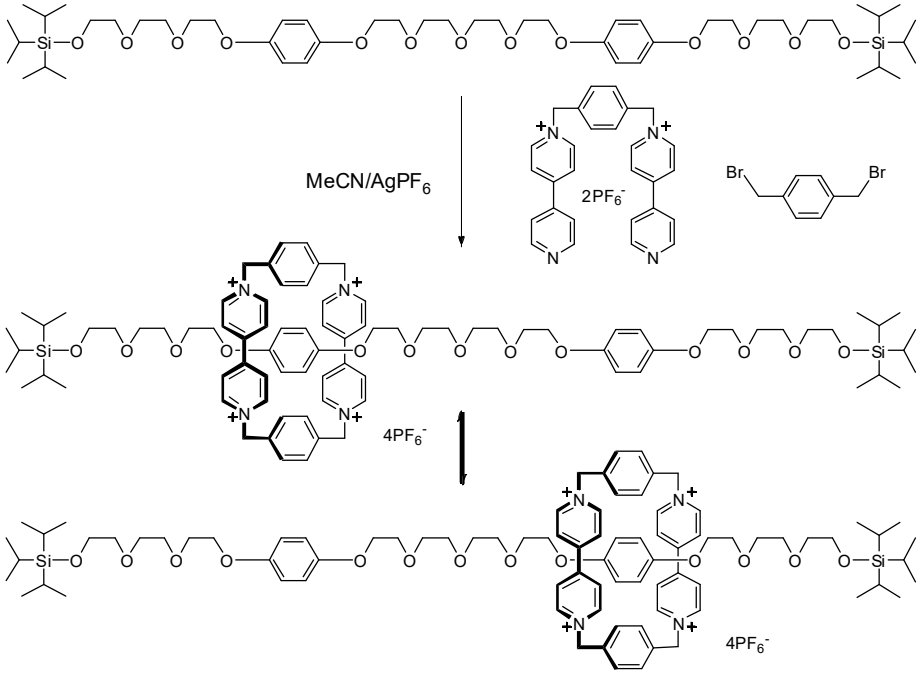

H_2N
NH_2
O
N
Zn^{II}
Zn

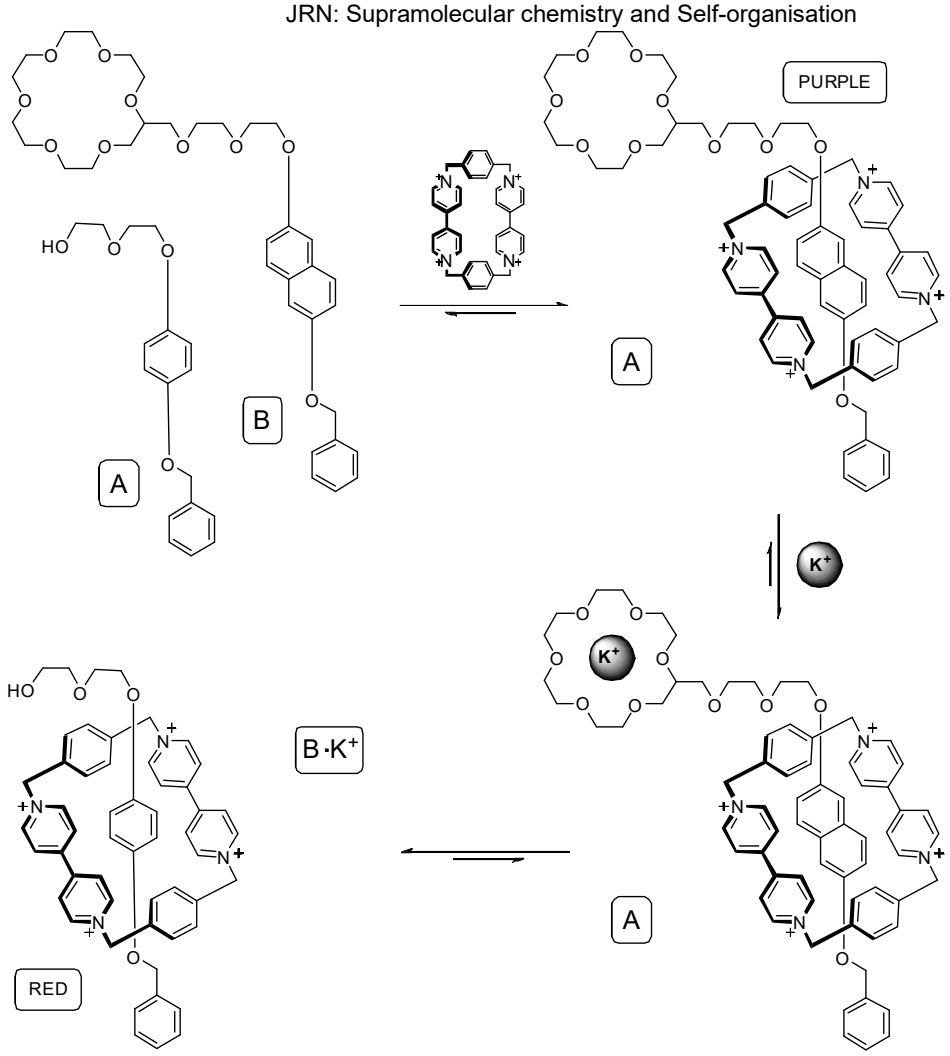


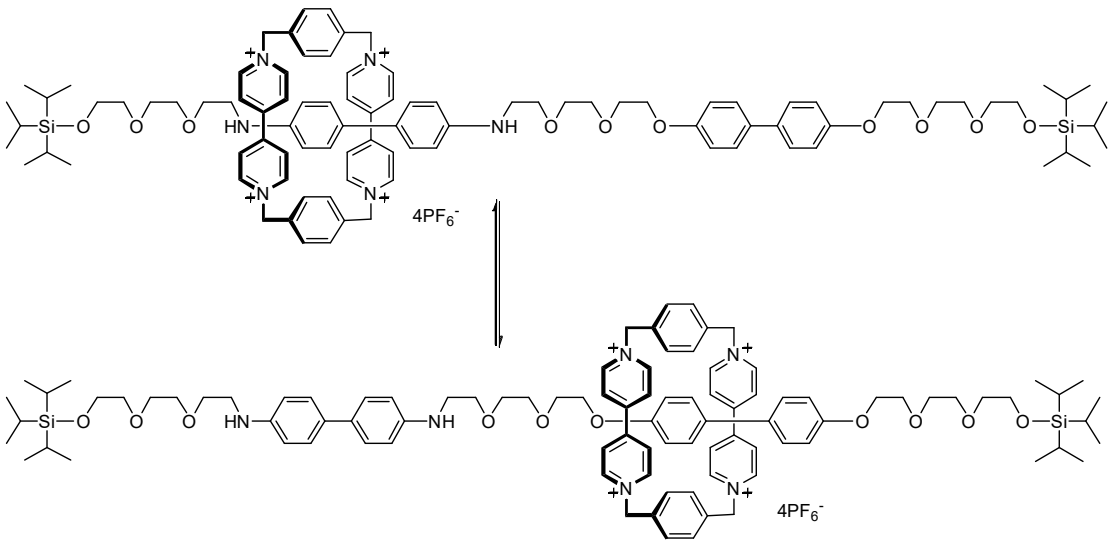
4. Molecular machines

Angew. Chem. Int. Ed. **2007**, *46*, 72

4.1 Rotaxane Shuttling

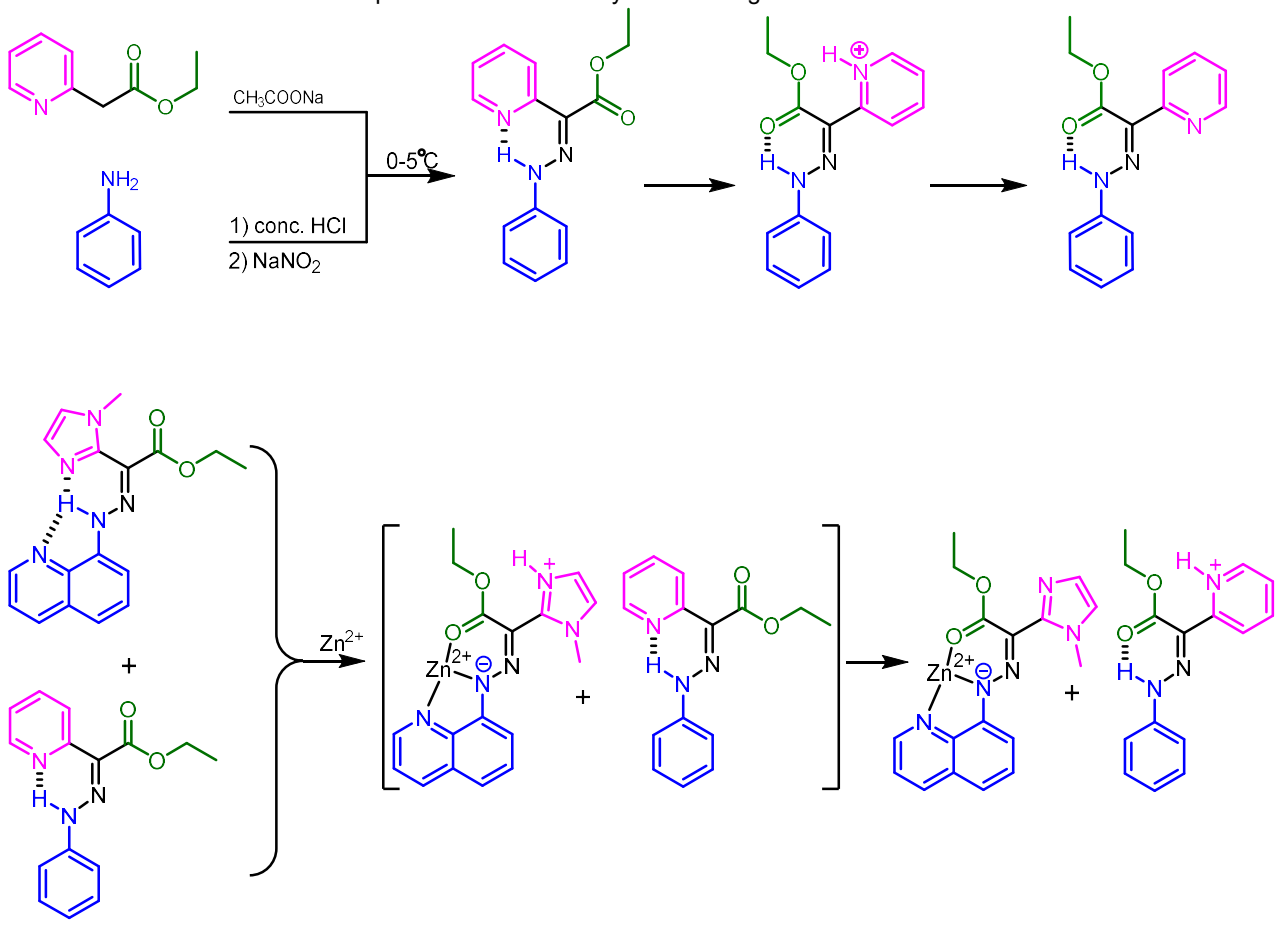






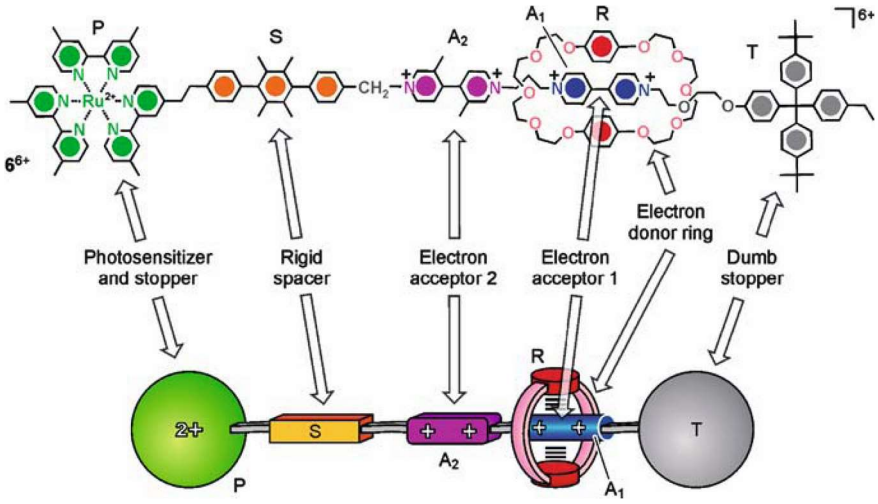
4.2 Hydrazone-based switches

Chem. Soc. Rev. **2014**, *43*, 1963

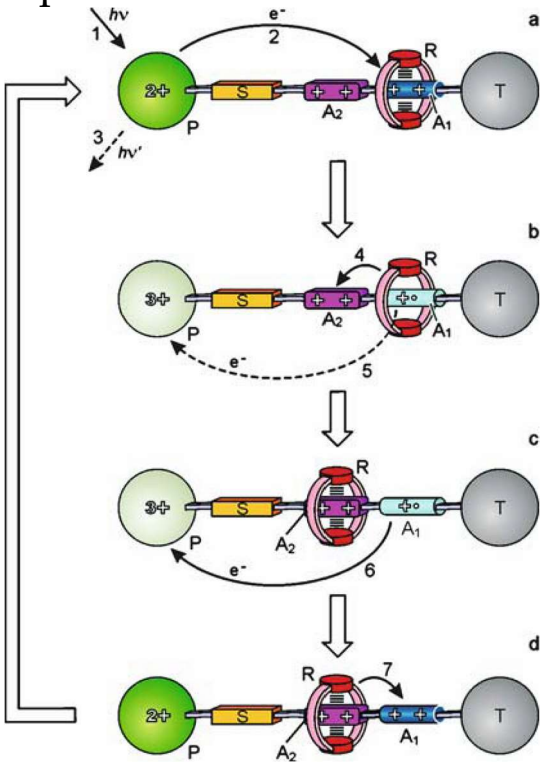

CH3COONa
0-5℃
1) conc. HCl
2) NaNO2
NH2
Zn2+

4.3 A "four-stroke" molecular engine

Chem. Eur. J. **2000**, *6*, 3558

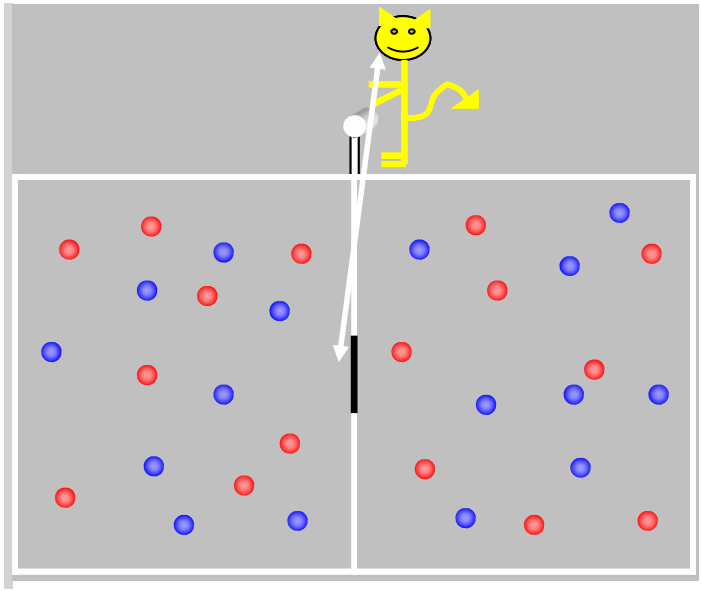


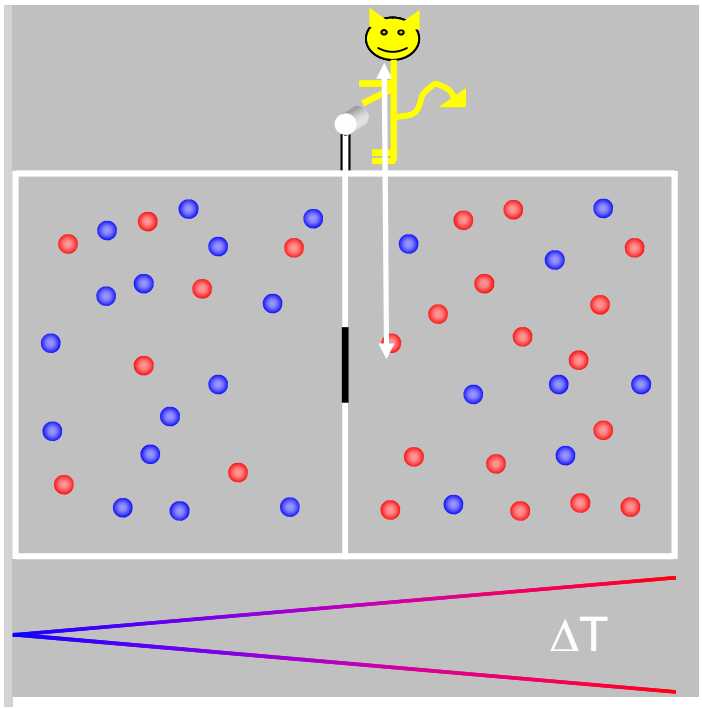
Operation:



4.4 Maxwell's Demon

Nature **2007**, *445*, 523

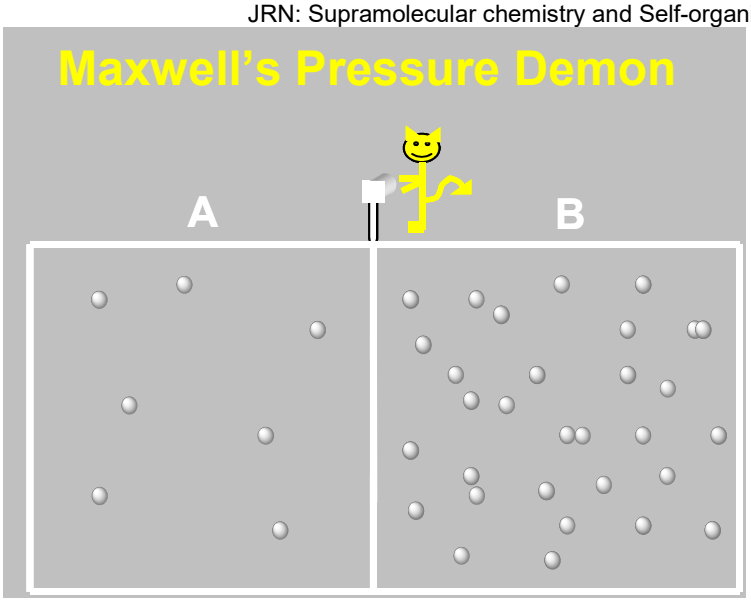


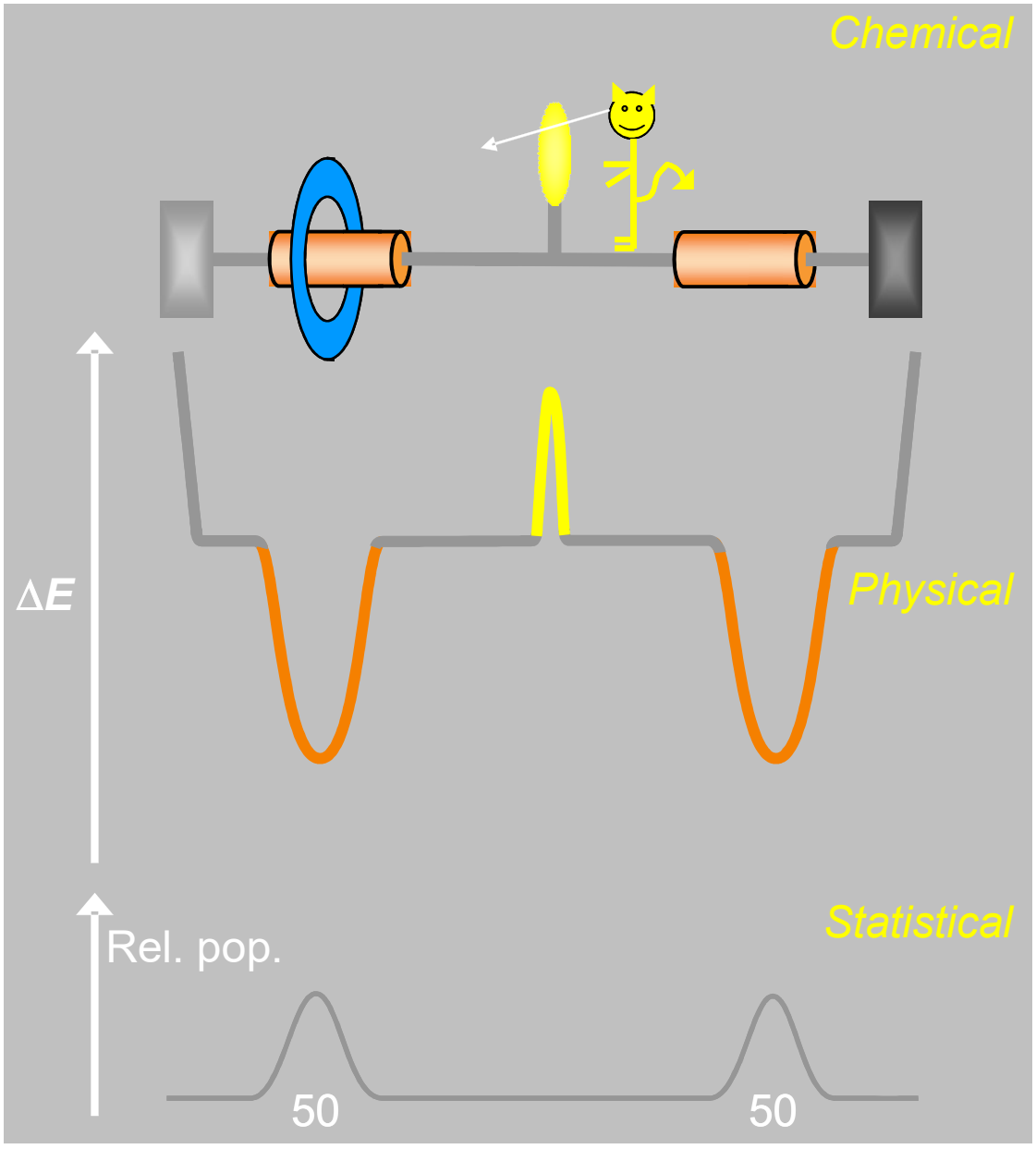


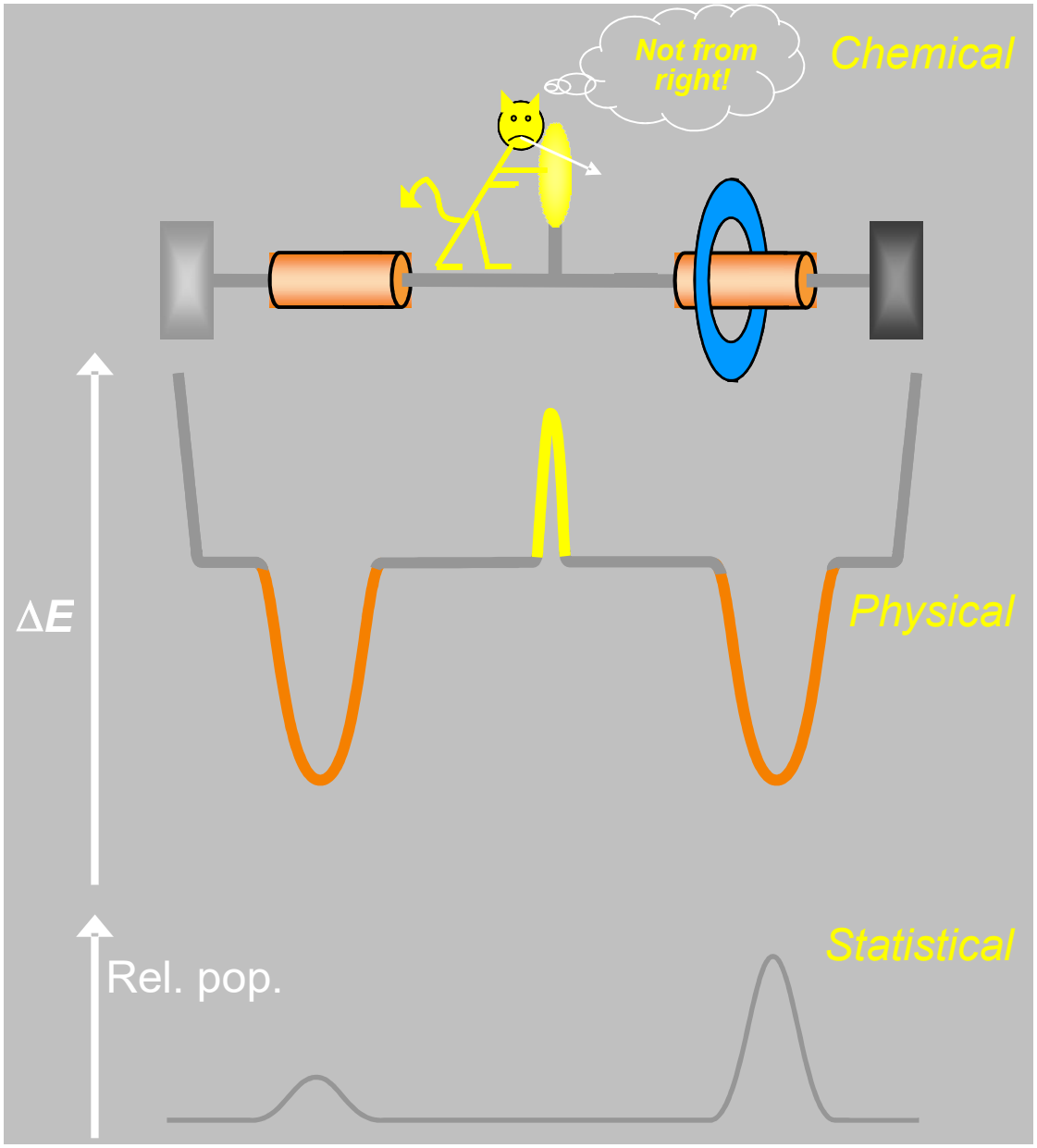
"*Concerning Demons… Is the production of an inequality of temperature their only occupation? No, for less intelligent demons can produce a difference in pressure as well as temperature by merely allowing all particles going in one direction while stopping all those going the other way. This reduces the demon to a valve.*"

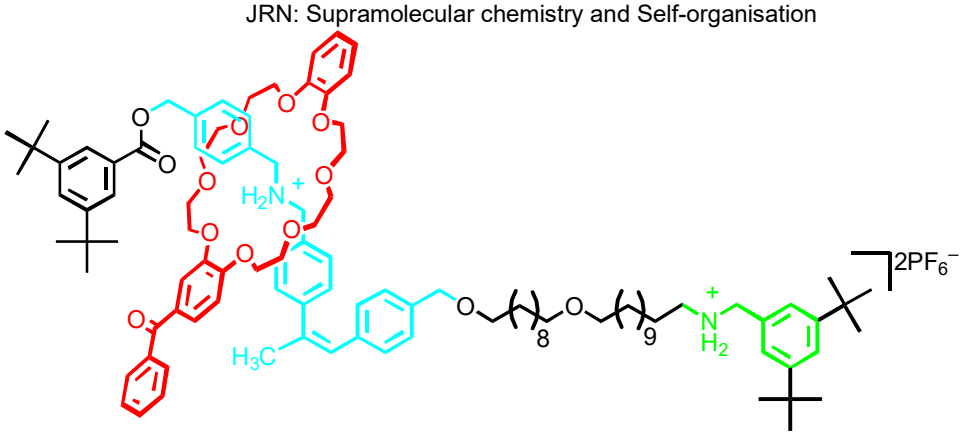
Letter to P. G. Tait, 11 Dec. 1867 (*The Scientific Letters and Papers of James Clerk Maxwell Vol. II 1862-1873* (Ed.: P. M. Harman), Cambridge Univ. Press, Cambridge, **1995**, pp. 331-332.)

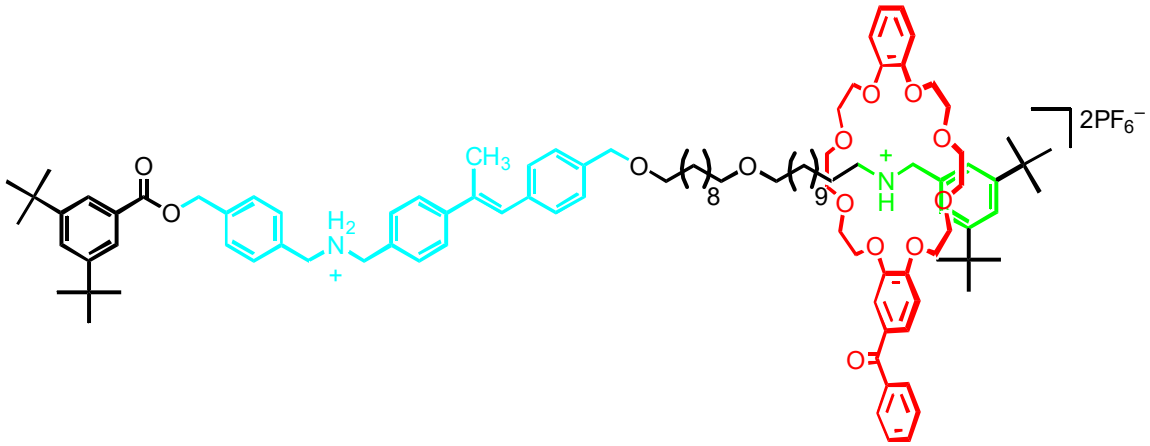
J. C. Maxwell, *Theory of Heat*, Longmans, Green and Co., London, **1871**, Ch. 22.

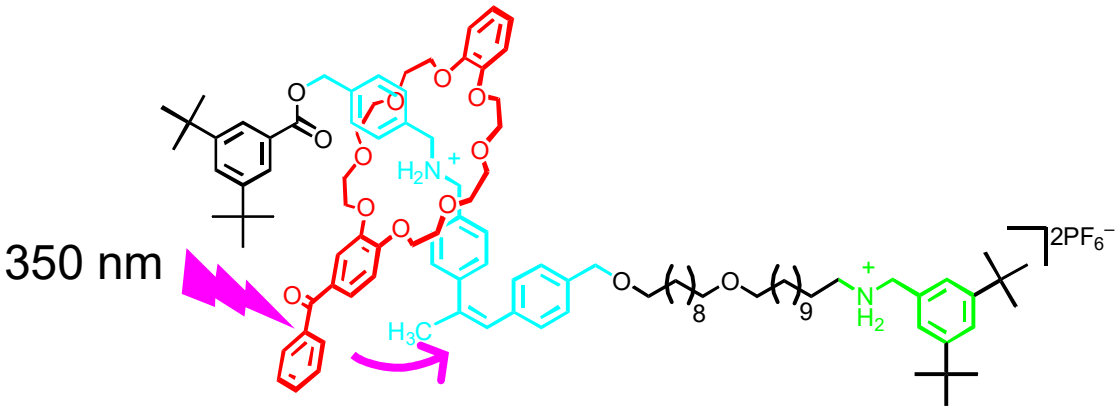

Maxwell's Pressure Demon
A
B

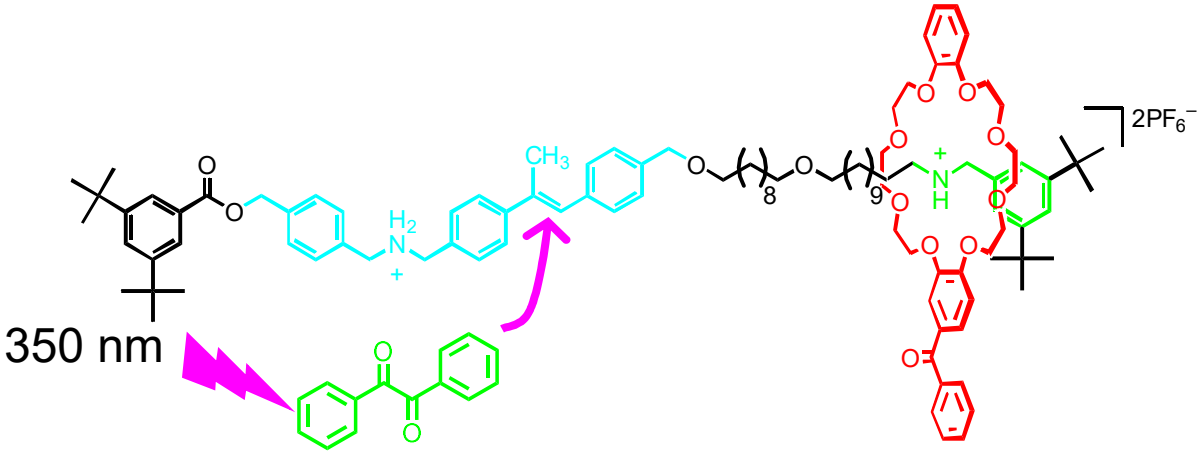

Chemical
Physical
ΔE
Statistical
Rel. pop.
50
50


Not from right!
Chemical
ΔE
Physical
Rel. pop.
Statistical


2PF6−

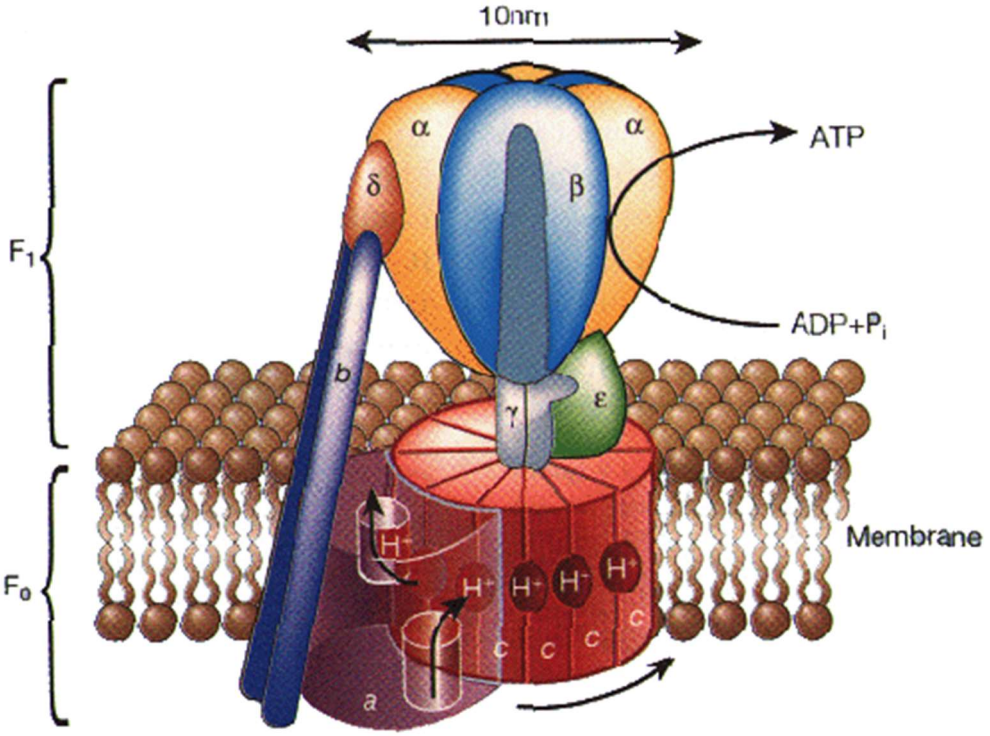

2PF6−

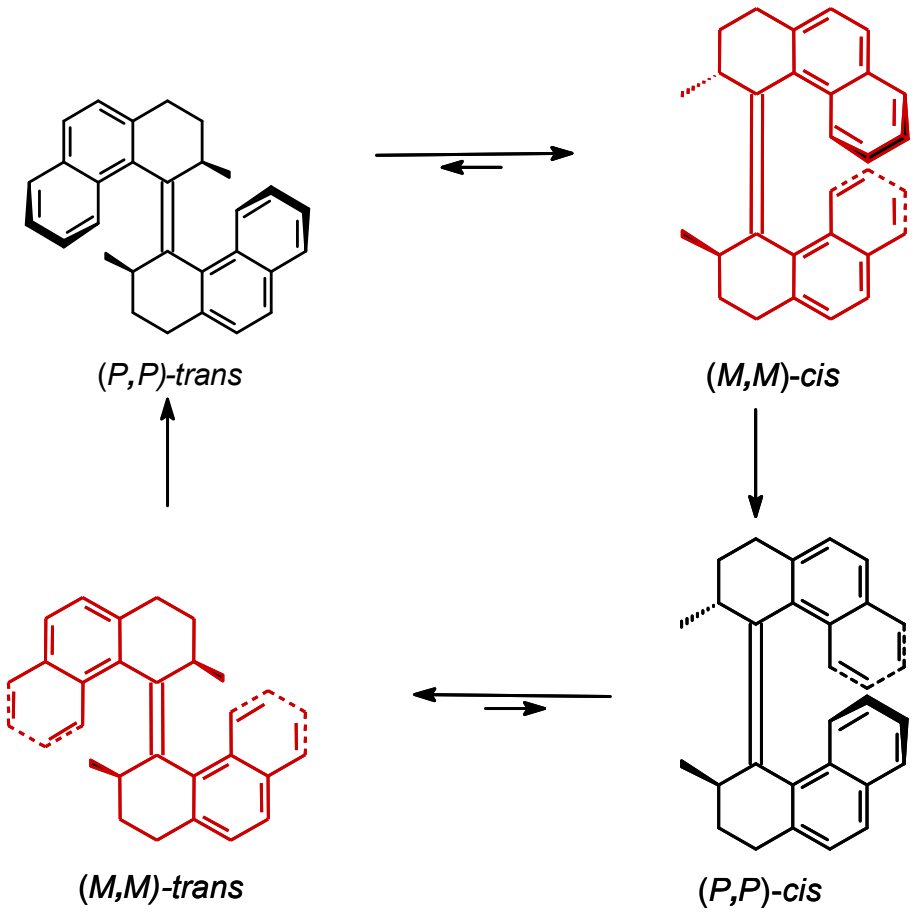

350 nm
2PF6−

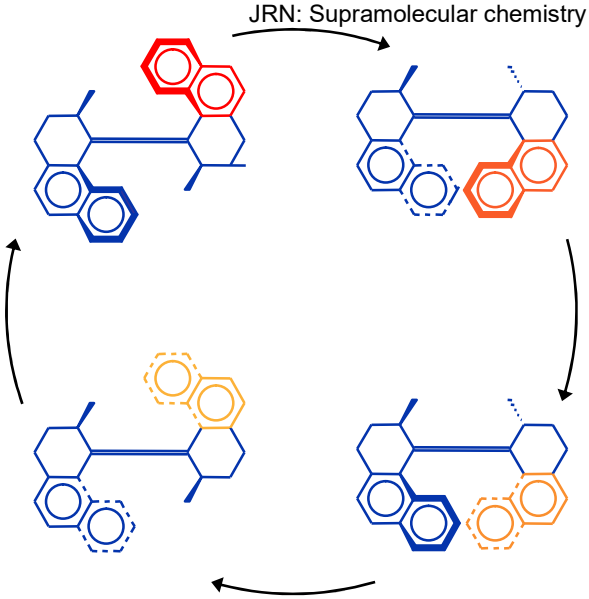

350 nm
2PF6−

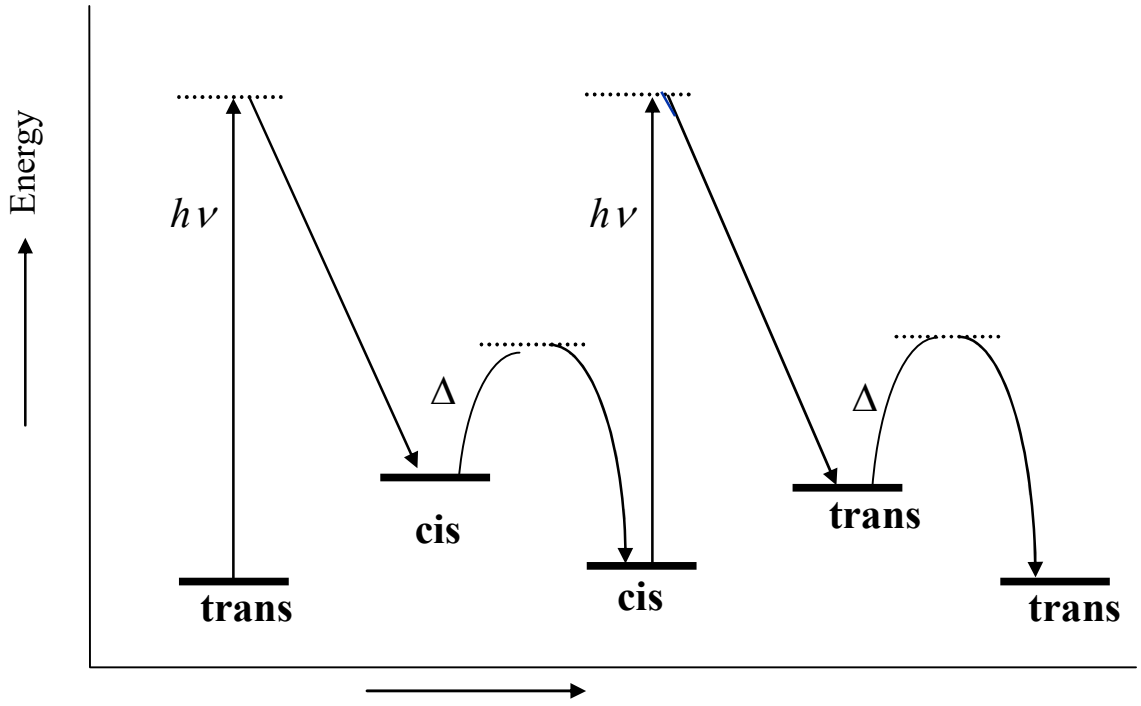
4.5 Molecular Rotary Motor

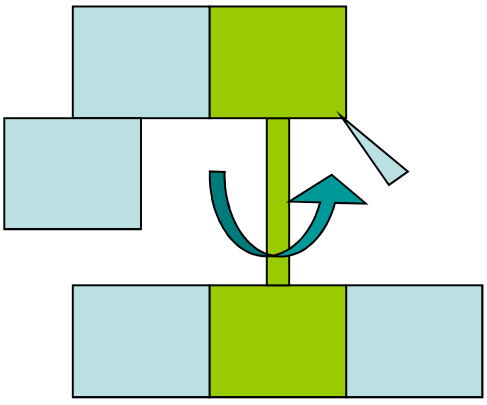
Nature **1999**, *401*, 152

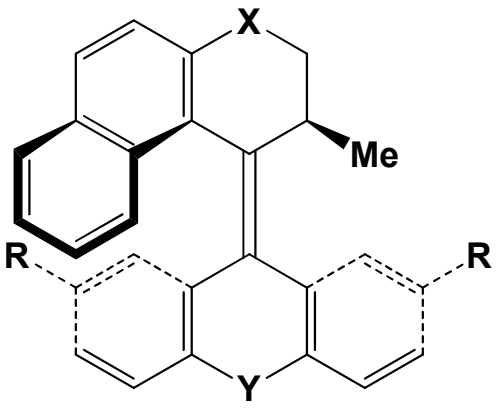


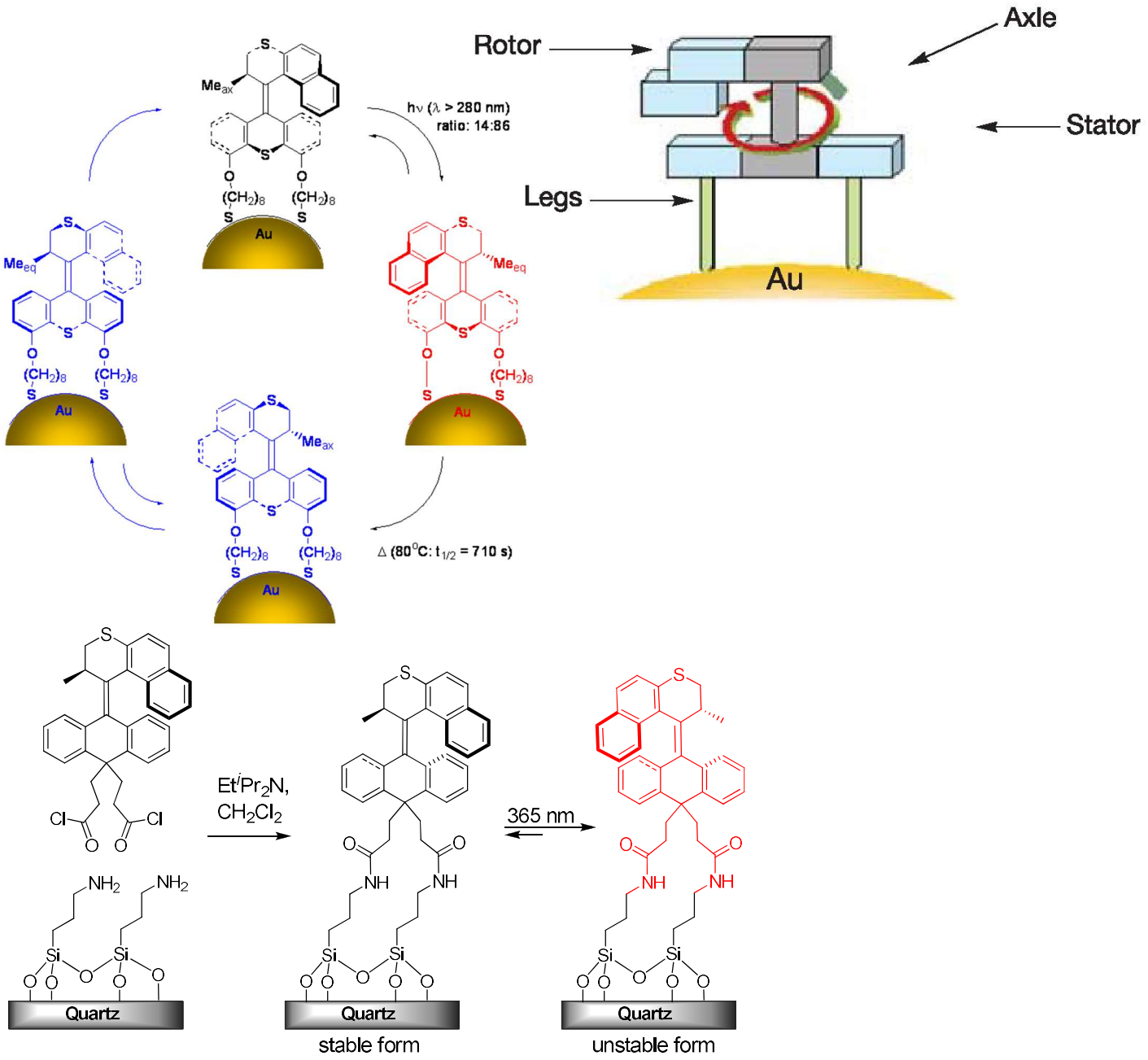




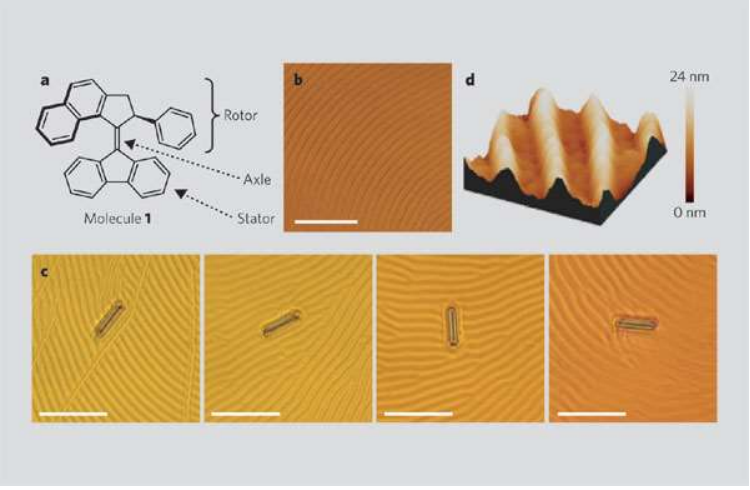

Energy
hν
trans
Δ
cis
hν
cis
Δ
trans
trans



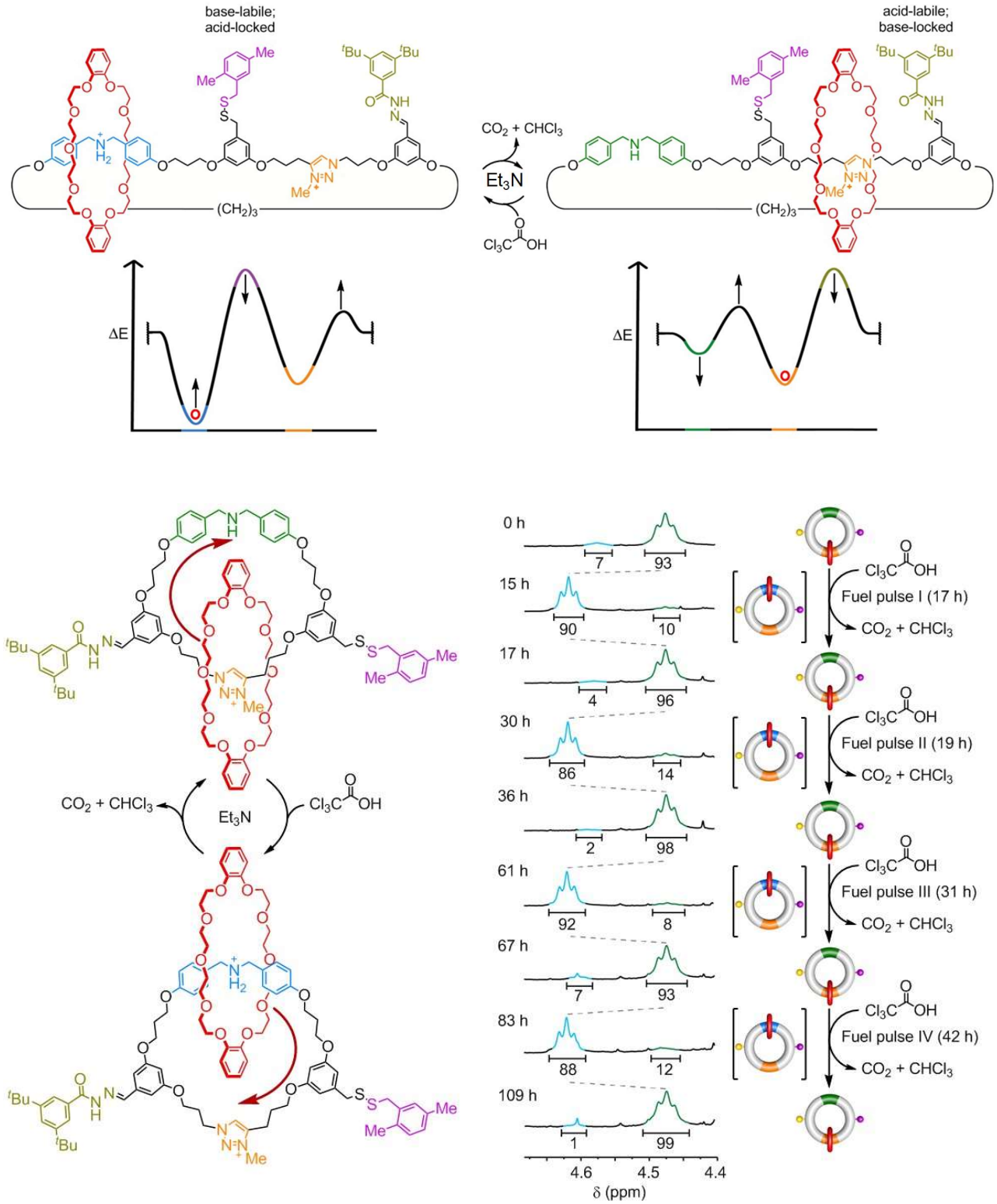

X
Me
R
R
Y



Nature **2006**, *440*, 163



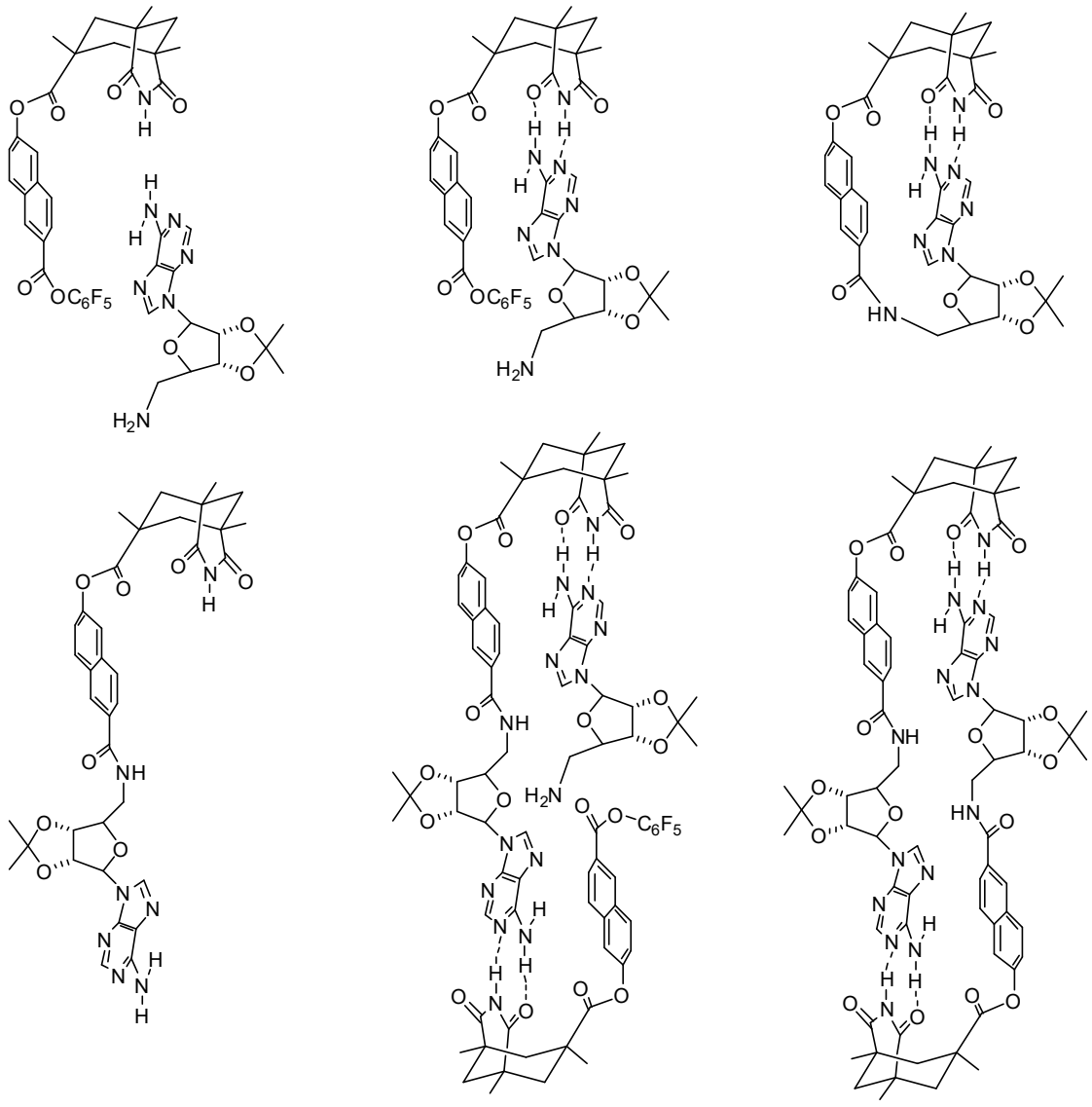
4.6 Fuel-driven Molecular Rotary Motor

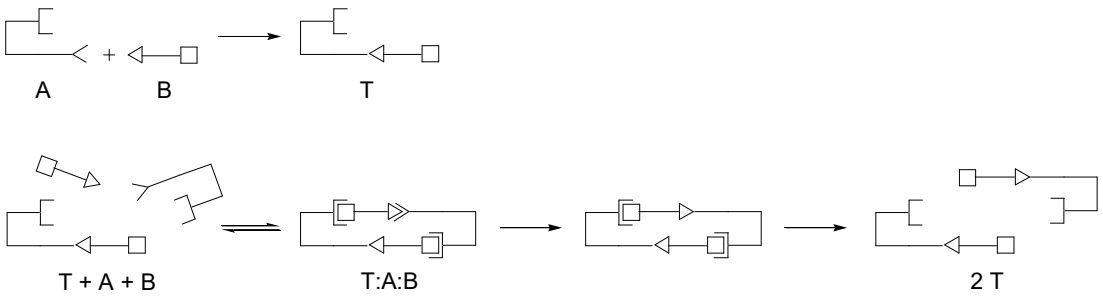


Science **358**, 340-343 (2017)

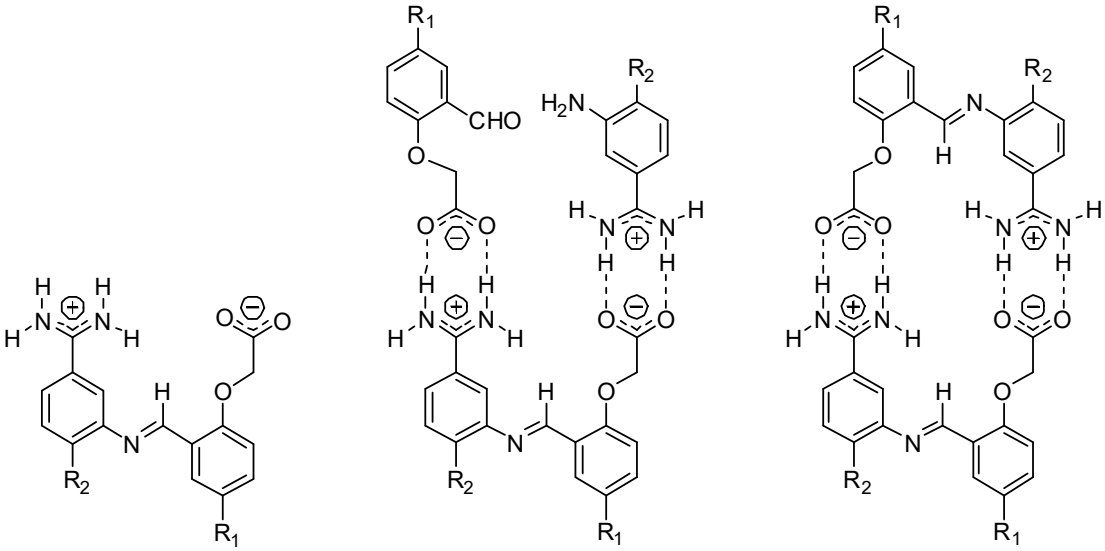
5. Self-replication: the Interface with Biology

J. Am. Chem. Soc. **1990**, *112*, 1249



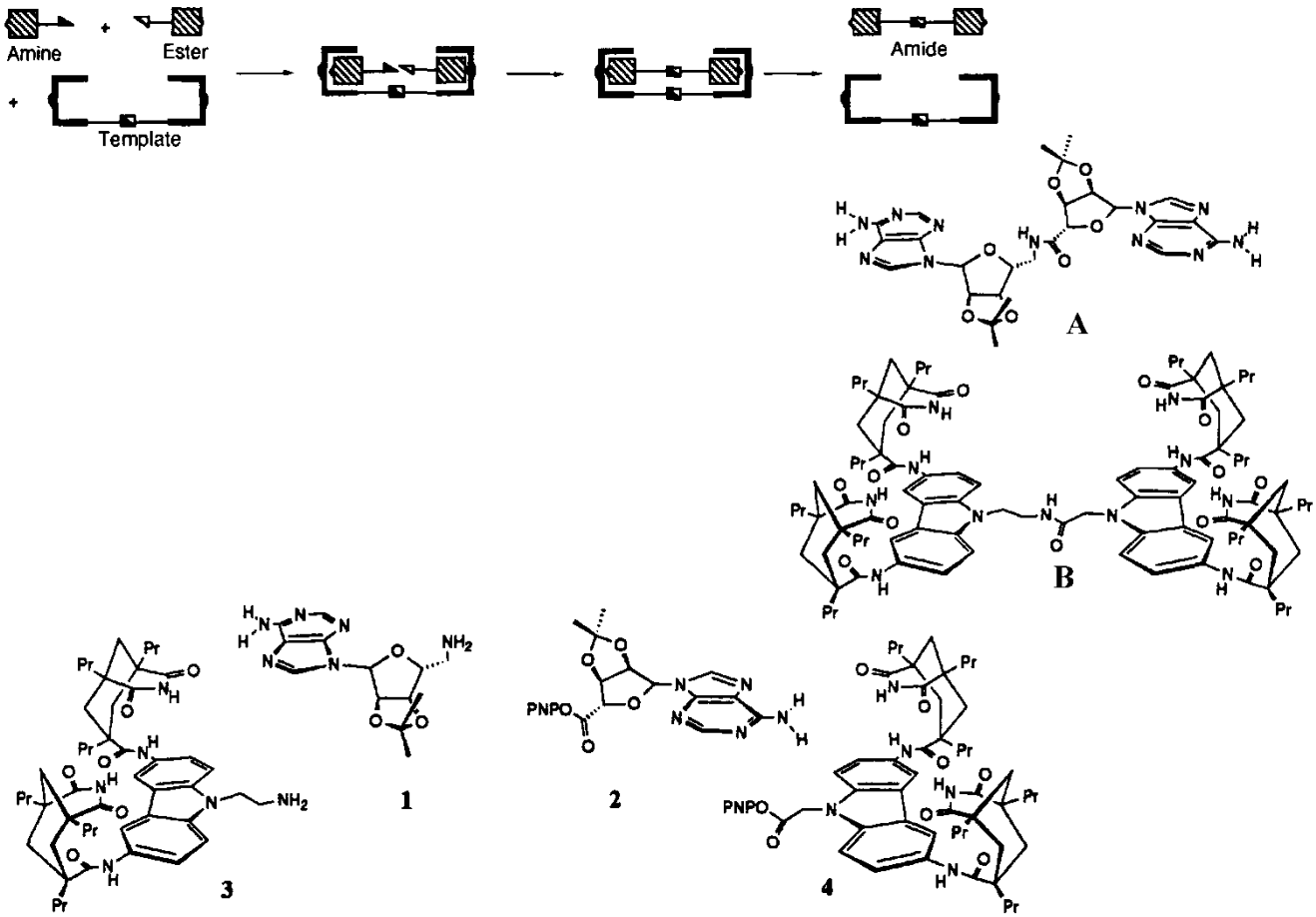


Angew. Chem. Int. Ed. **1992**, *31*, 654

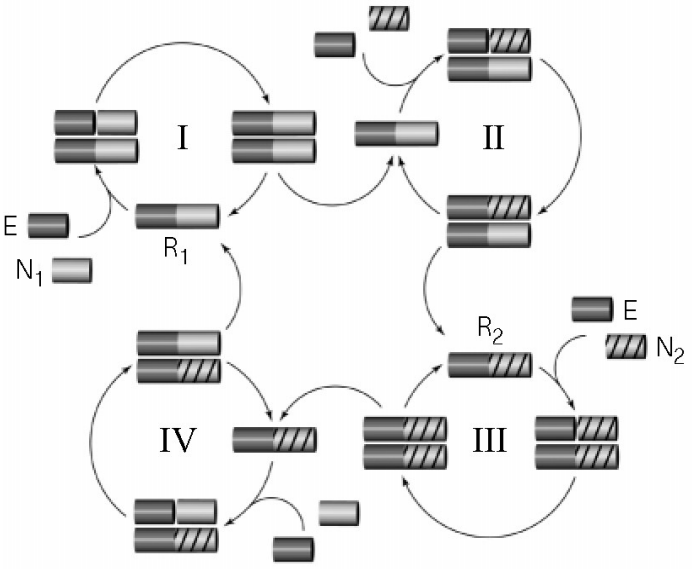


Cross Catalysis & Hypercycles

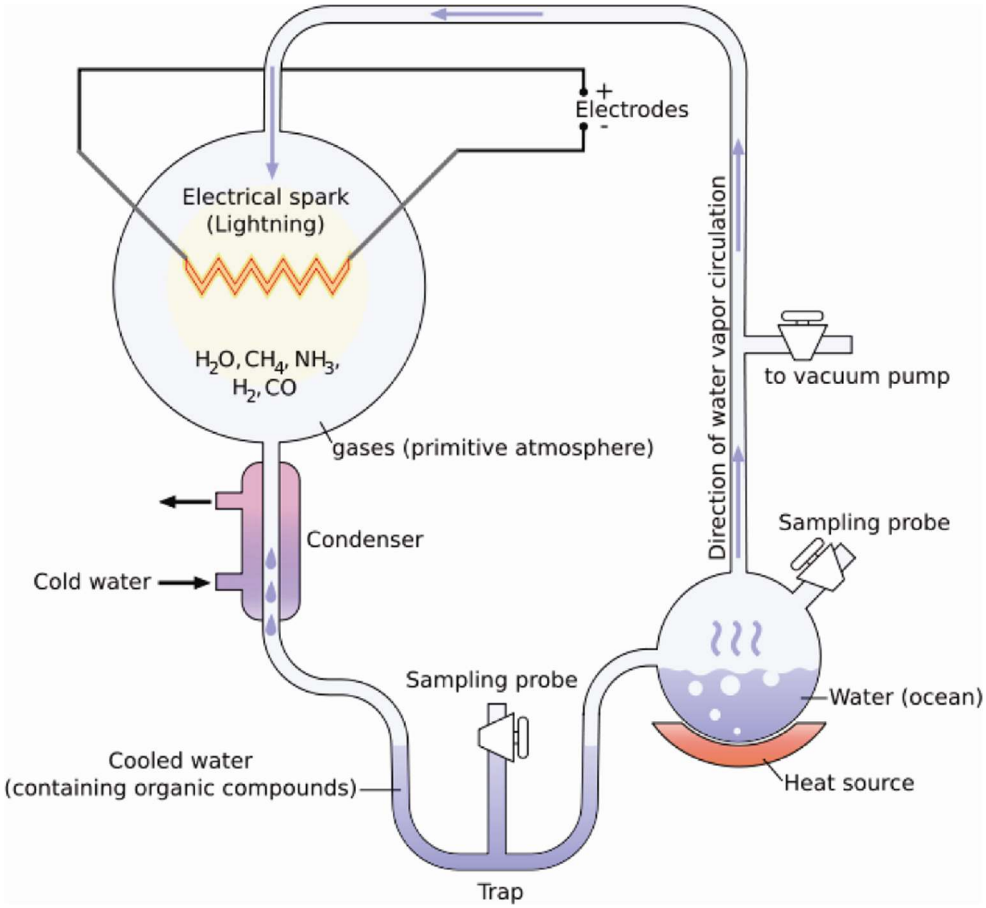
Tetrahedron **1995**, *51*, 485



Nature **1997**, *390*, 591



Curr. Opin. Chem. Biol. **1997**, *1*, 491



Robert Frost, from “West-Running Brook”, 1928

…see how the brook
In that white wave runs counter to itself.
It is from that in water we were from
Long, long before we were from any creature.
Here we, in our impatience of the steps,
Get back to the beginning of beginnings,
…
And even substance lapsing unsubstantial;
The universal cataract of death
That spends to nothingness -- and unresisted,
Save by some strange resistance in itself,
Not just a swerving, but a throwing back,
As if regret were in it and were sacred.
It has this throwing backward on itself
So that the fall of most of it is always
Raising a little, sending up a little.
…
It is this backward motion toward the source,
Against the stream, that most we see ourselves in,
The tribute of the current to the source.
It is from this in nature we are from.
It is most us.

6. Structural and spectroscopic characterization methods

Physical methods are used to determine static structure, dynamics of association and dissociation, and strength of interaction.

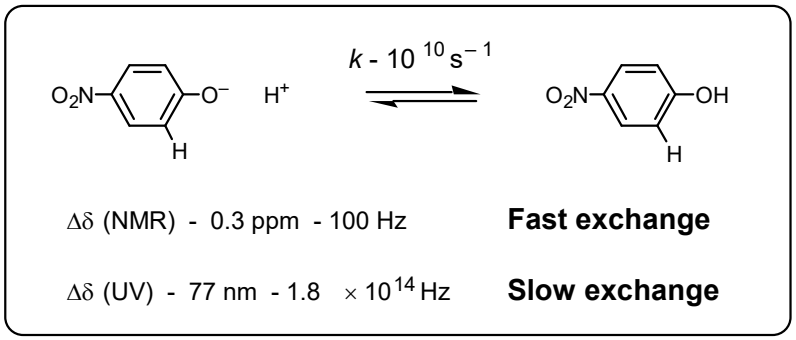
Spectroscopic timescales [See Sanders & Hunter, Chapter 7 for further details]

In any form of spectroscopy the transition from slow exchange (see spectra of both forms simultaneously) to fast exchange (where one observes an average) depends only on

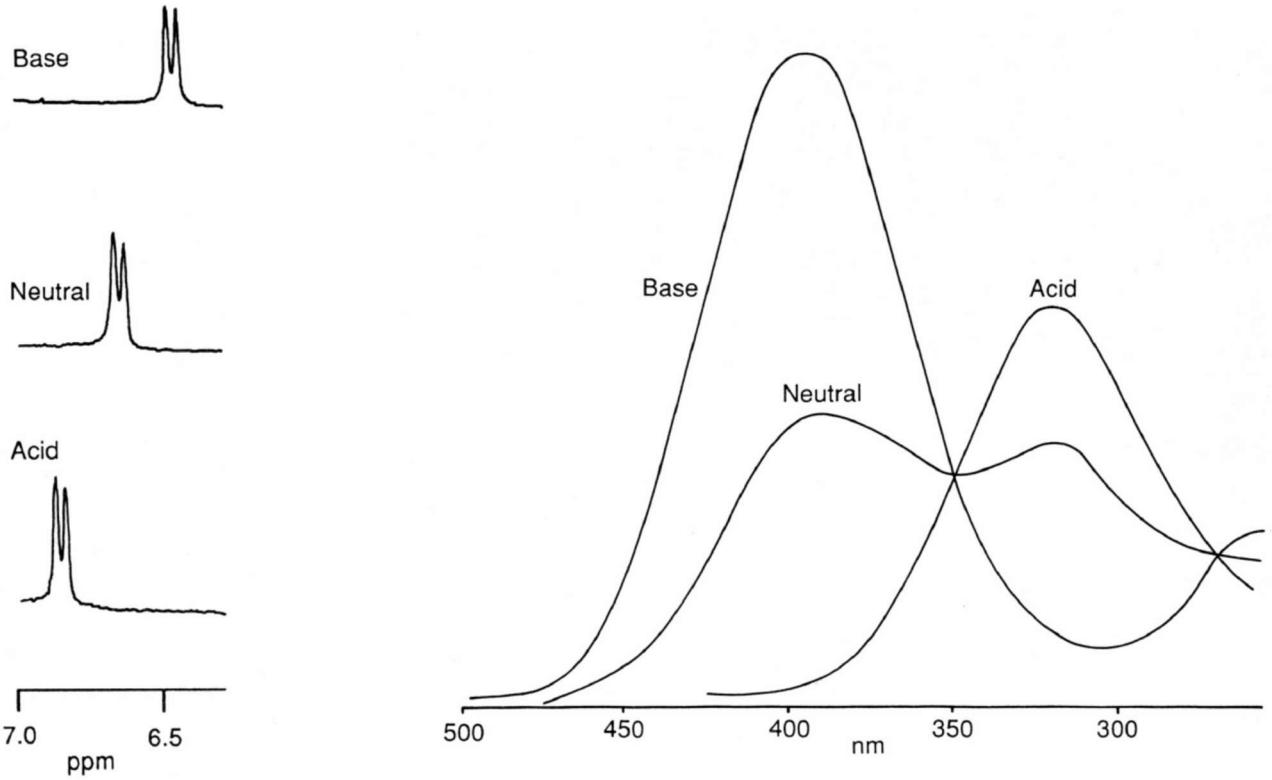
k_{ex}: the rate of exchange between the two states

$\Delta\nu$: the frequency difference *in Hz*

$$k_{ex} = \pi\Delta\nu/\sqrt{2} = 2.22\Delta\nu$$



In each case, a titration can be used to measure the equilibrium constant by varying $[H^+]$

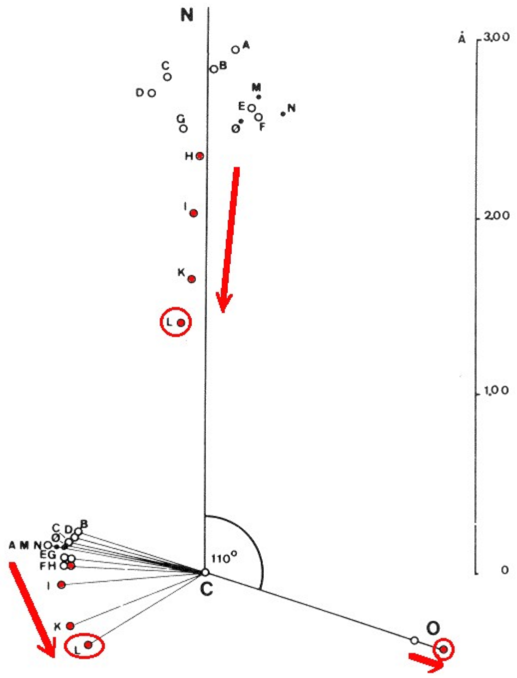


6.1 X-ray crystallography

The ultimate tool for determination of individual structures where it is possible to obtain a single crystal of sufficient quality. Individual crystal structures may also have useful information about inter- or intramolecular non-covalent interactions.

The *Cambridge Structural Database* contains well over 1M structures and powerful search tools for studying them. Statistical analysis allows the identification of very weak interactions that are not obvious in individual structures.

The Bürgi-Dunitz Angle:

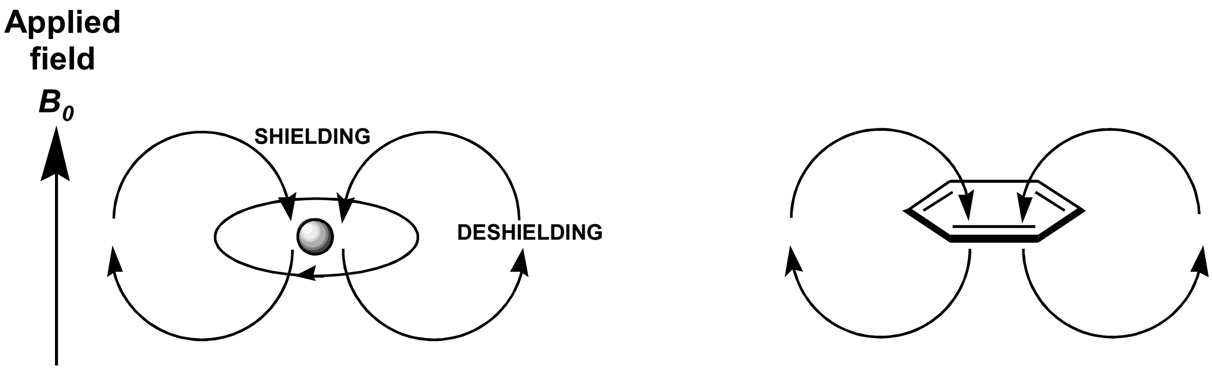


(Bürgi and Dunitz, Acc. Chem. Res. **1983**, *16*, 153-161)

6.2 NMR spectroscopy

Uniquely powerful tool for the study of structure, geometry and kinetics. Without perturbing the system it can provide detailed mechanistic and kinetic information about reactions that are occurring in equilibrium mixtures. The rate constants may be slower than 10^{-2} or faster than 10^{8} s^{-1}. The conformational processes that can be studied range from a single bond rotation to the denaturation and renaturation of a protein molecule, while the accessible chemical reactions range from a simple proton transfer to multistep *in vivo* enzymic pathways.

Chemical shifts

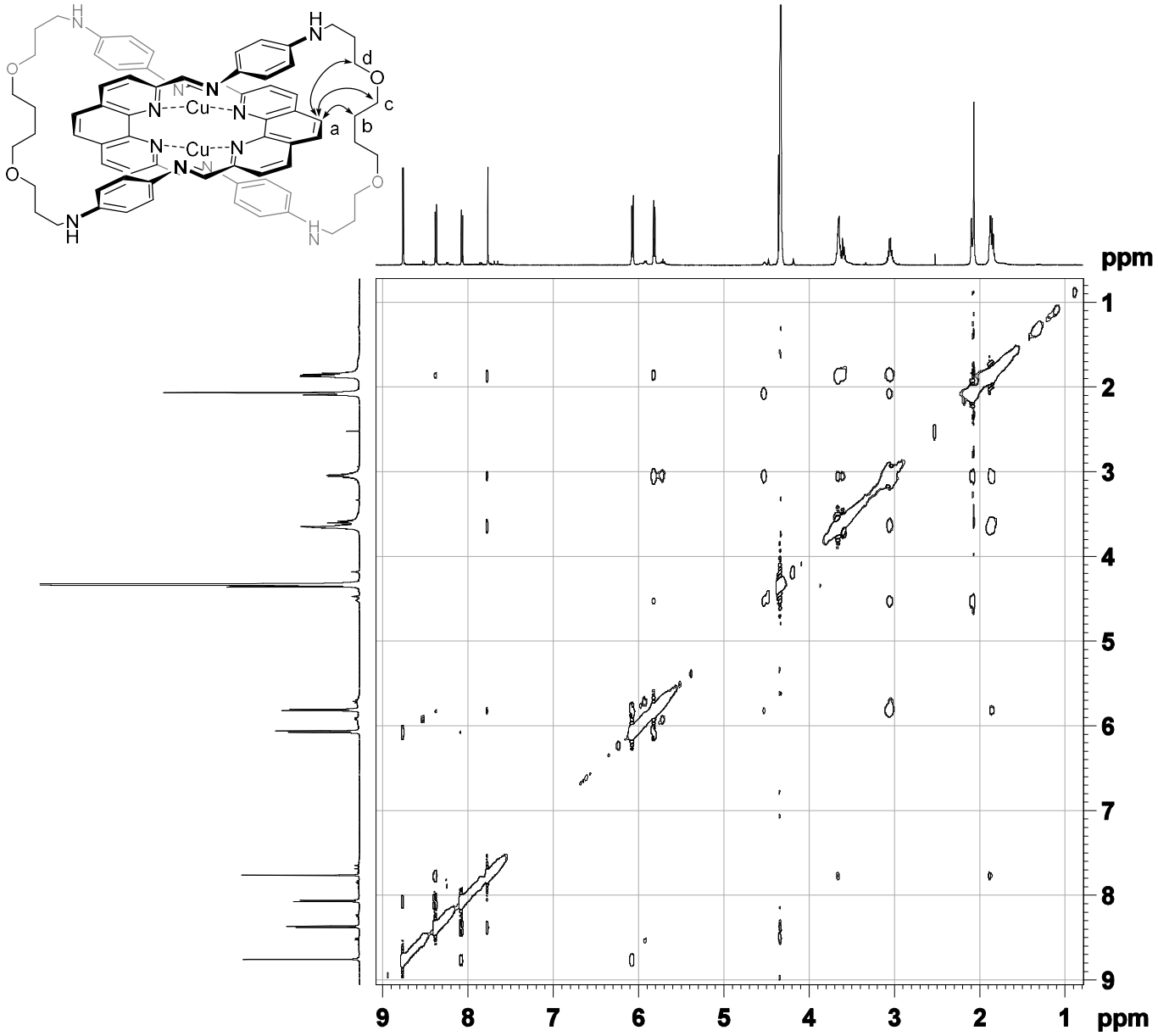


Nuclear Overhauser effect (nOe)

In addition to 'through-bond' J-coupling,
nuclear spins may influence each other through dipolar interactions

The nuclear Overhauser effect leads to magnetisation population transfer, not splitting of signals

Irradiation of one signal leads to a change in the intensity of the other. In a 2D experiment known as NOESY:



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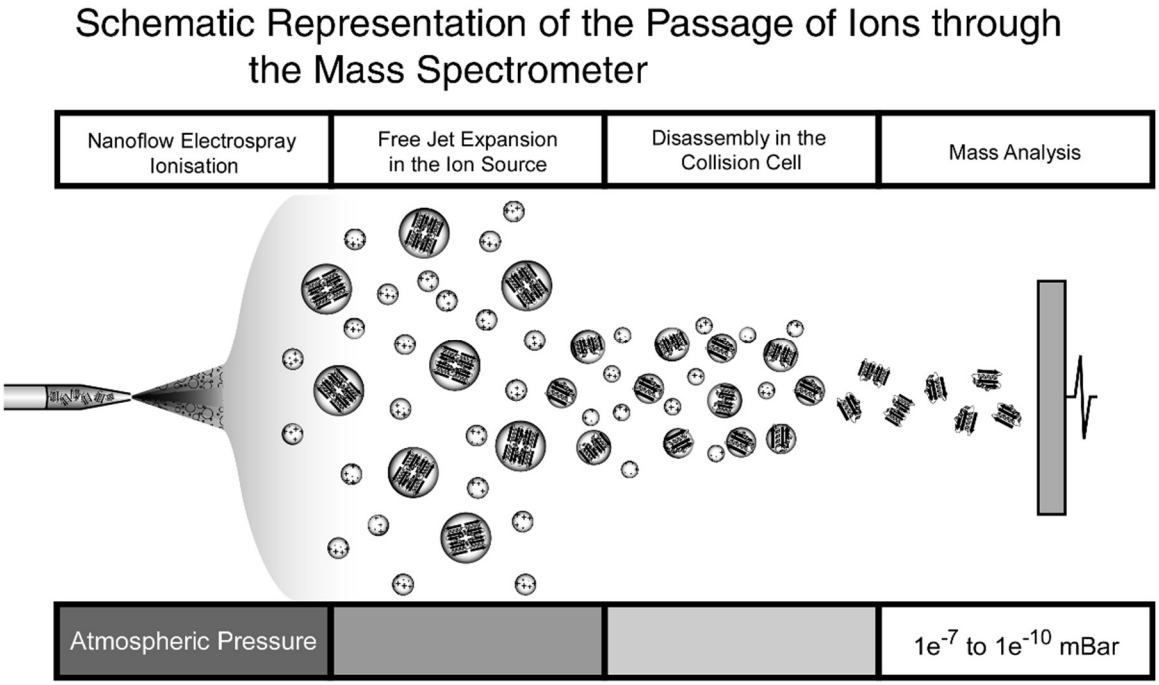
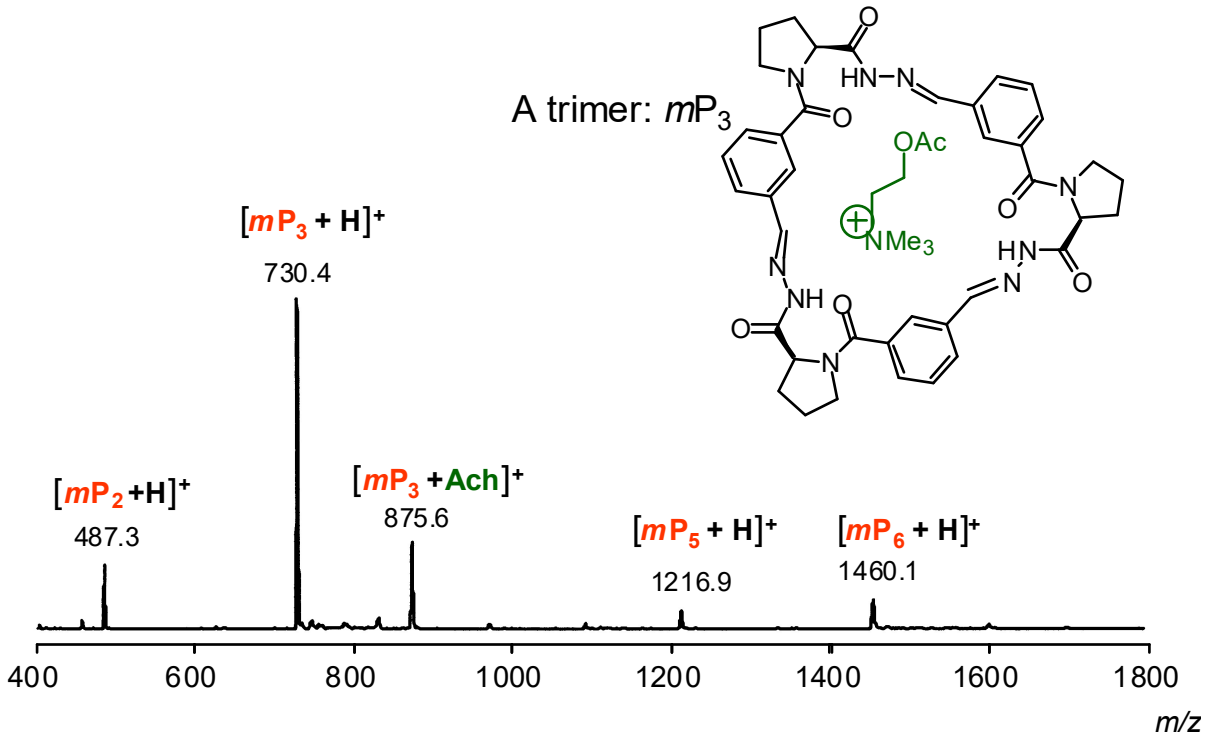
6.3 Mass spectrometry

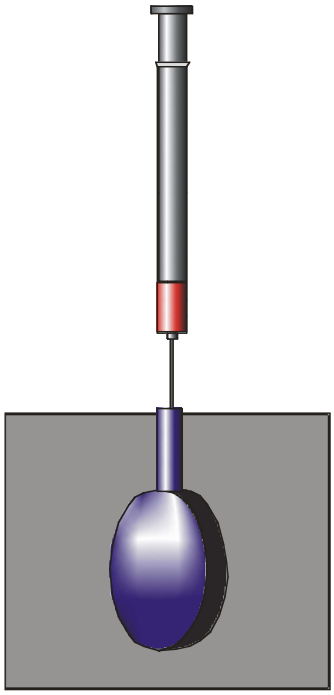
Modern "soft" ionization techniques such as electrospray or Matrix-Assisted Laser Desorption Ionization (MALDI) sometimes allow us to observe non-covalent complexes in mass spectra.

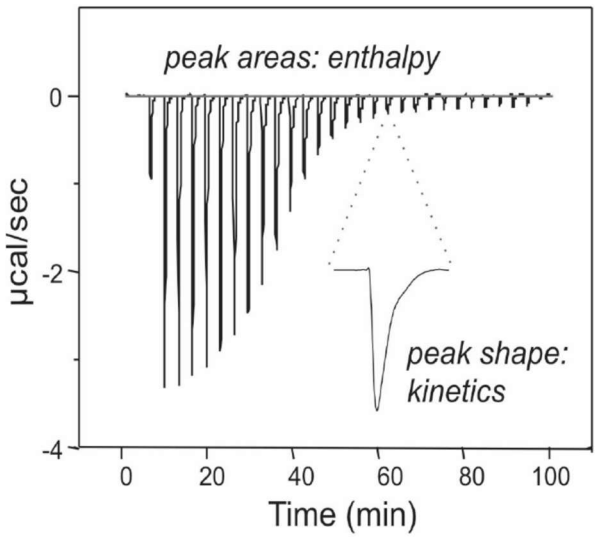


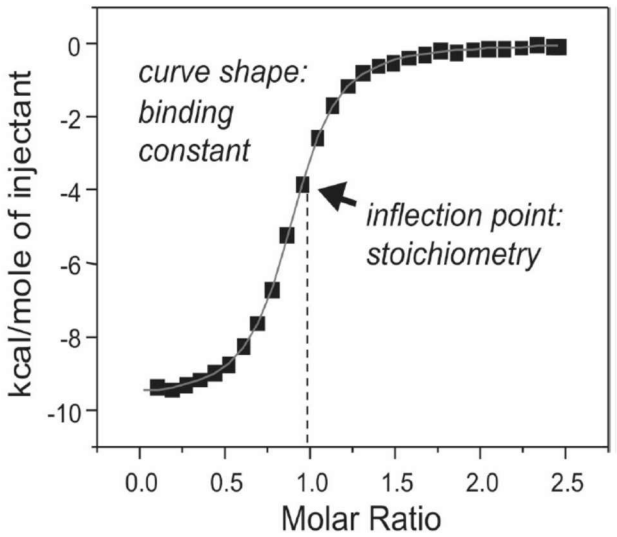


6.4 Isothermal Titration Microcalorimetry (ITC)

This is the most direct method: A solution of one component is titrated into a solution of the other, and the amount of heat given out or taken up is measured.

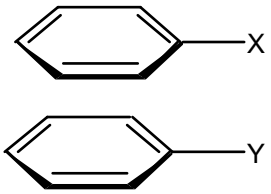




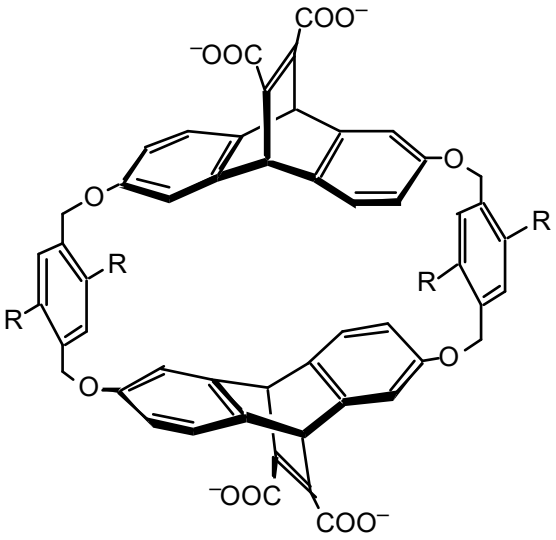


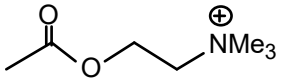
7. Problems

1 Explain why it is energetically unfavourable for two aromatic rings to be stacked vertically above each other as shown. Use your explanation to predict the effect of X and Y substituents on the interaction between the rings. (For example, X and Y may be NO_2 or OMe)



2 In aqueous solution, the host molecule (R = H) shown below left strongly binds the highly hydrophilic acetylcholine within its hydrophobic cavity. Suggest an explanation and predict the effect on binding strength if R = OMe in the host.

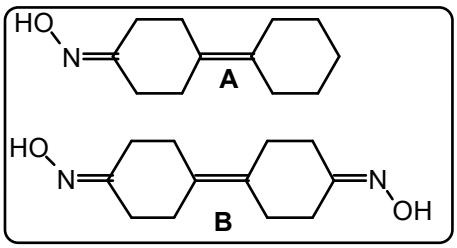




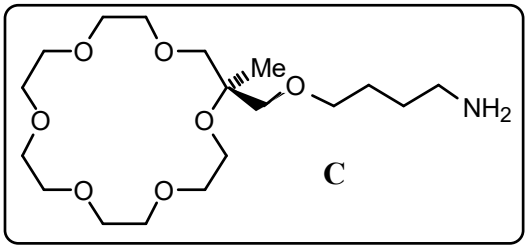
Acetylcholine

$K = 3.6 \times 10^4$ l mol^{-1}

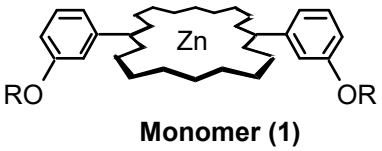
3 Oxime **A** is a normal compound melting at 120° C and soluble in polar or apolar organic solvents, while **B** decomposes on heating to 220° but cannot be melted. Dioxime **B** is only soluble in polar solvents such as DMSO. Explain.



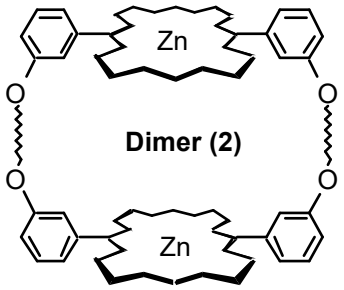
4 The crown ether **C** complexes strongly to K^+ ions in aqueous solutions at high pH, but at low pH no K^+ binding is observed. Why?



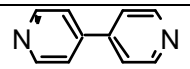
5 The bimolecular binding constants between the two amines shown and porphyrin monomer **1** and dimer **2** were measured in CH_2Cl_2 solution and are summarised in the Table below. Account for the relative binding constants obtained and estimate the effective molarities for the second binding constants within the dimer cavity.



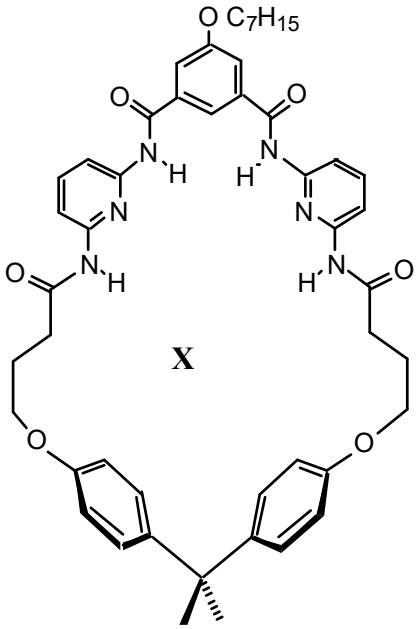
Monomer (1)



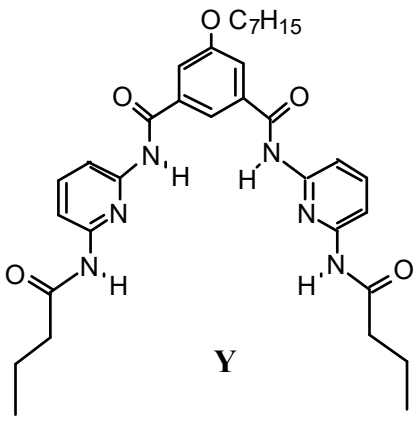
Dimer (2)

	monomer **1**	dimer **2**
	3.0×10^3	2.5×10^7
	1.4×10^4	5.5×10^6

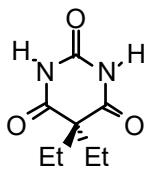
6 In $CHCl_3$ solution at room temperature, $K(XZ) = 1.4 \times 10^6$ M^{-1}, while $K(YZ) = 2.1 \times 10^4$ M^{-1}. What are the complexes formed, and why do they have different stability constants?



X

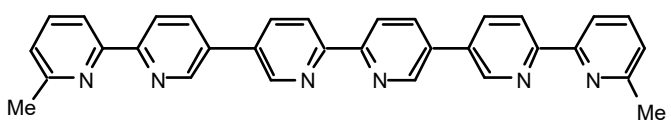


Y

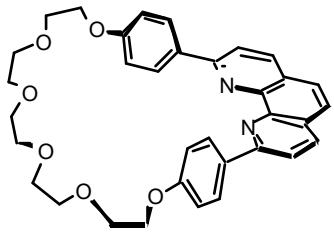


Z

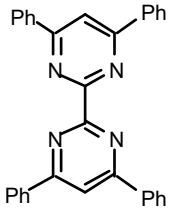
7 Predict the structures of the products obtained in reactions (i) and (ii):



L$_1$



L$_2$

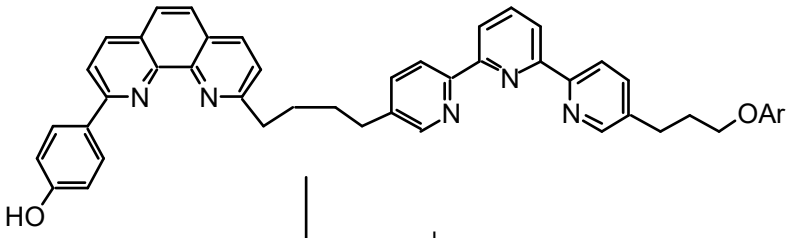


L$_3$

(i) $\mathbf{L_1} + 3\mathbf{L_2} + 3Cu^+ \longrightarrow$ **?**

(ii) $2\mathbf{L_1} + 3\mathbf{L_3} + 6Cu^+ \longrightarrow$ **?**

8 What are the structures of **P**, **Q** and **R** shown below? The oxidation step refers to electrochemical oxidation of Cu^I to Cu^{II}. Explain why the synthesis of **Q** requires the aryl group to be added *after* L and Cu^I, and predict the result of reducing **R**.



(i) **L**, Cu^I

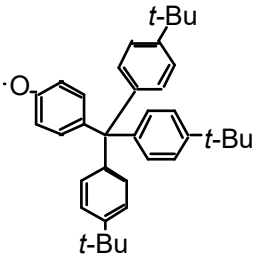
P

(ii) Base

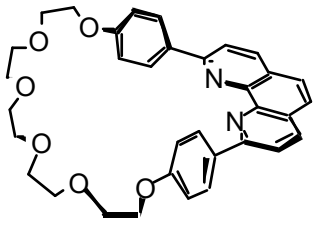
(iii) ICH_2CH_2OAr

Q → Oxidation → **R**

—OAr =

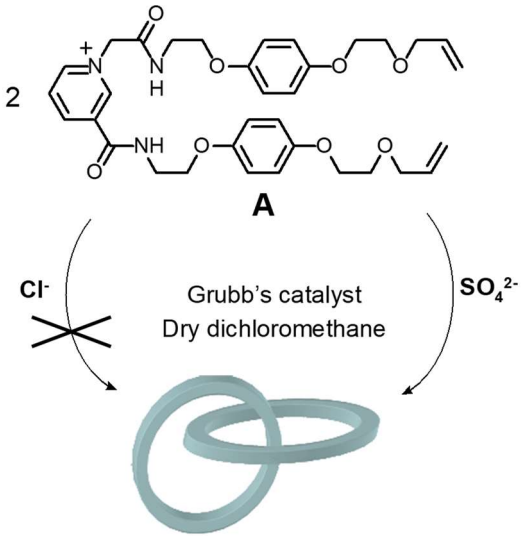


L =



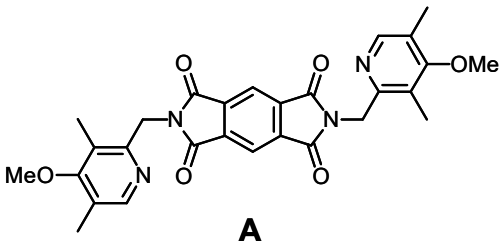
9 When 2 equivalents of **A** react in dry dichloromethane with Grubbs' catalyst in the presence of sulfate anions, a catenane is obtained in 80% yield. The catenane does not form when chloride (or bromide and hexafluorophosphate) is used instead of sulfate.

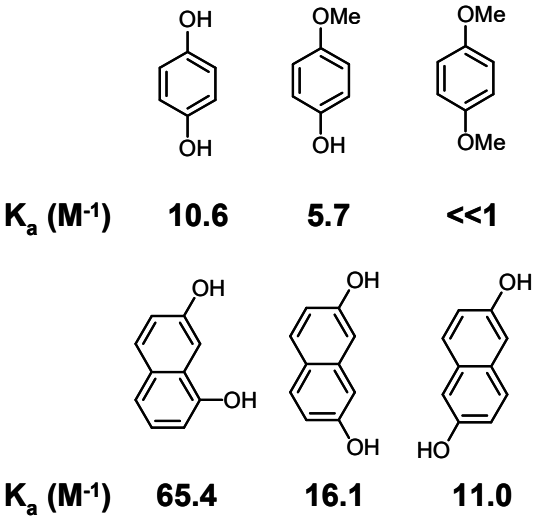
Predict the structure of the catenane and explain why if forms only in the presence of sulfate anions.



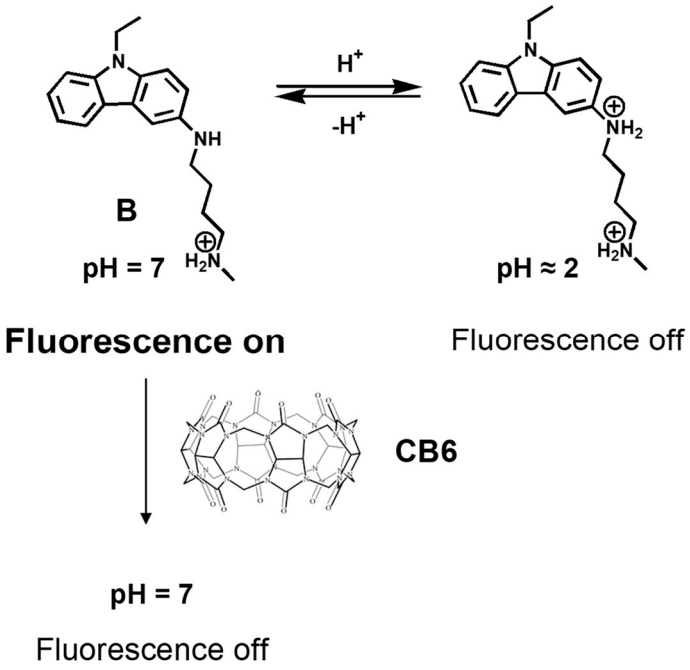
10 Explain the trends observed for the association constants (Ka) measured in $CHCl_3/CH_3CN$ between sensor **A** and the two sets of aromatic diols shown in the picture below.

Which technique/s would you employ to study this system and why?

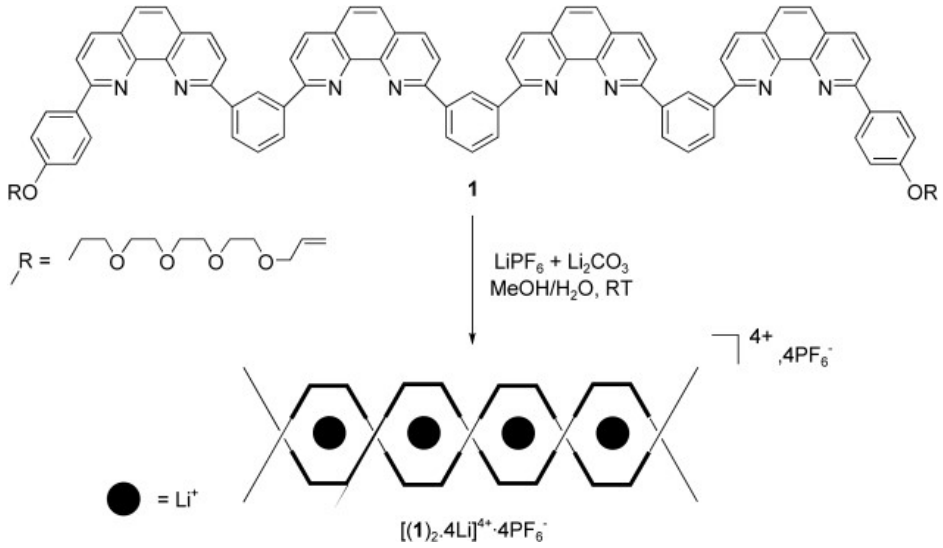




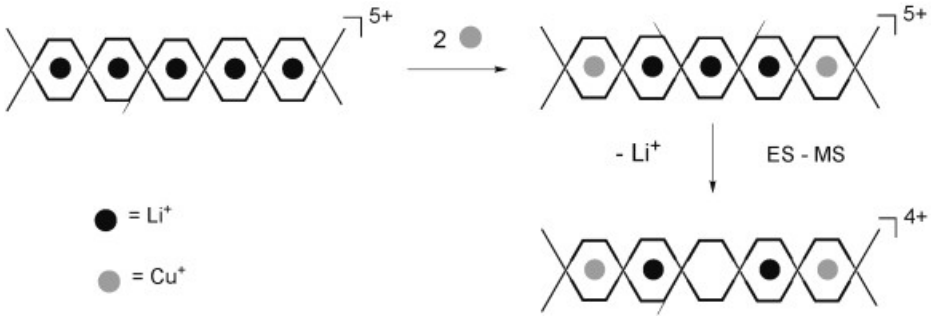
11 The fluorescence emission at 458 nm of carbazole B can be switched off by addition of acid to an aqueous solution of B, decreasing the pH of the solution from 7 to 2. An identical effect was achieved by adding cucurbituril (CB6) to a buffered (pH = 7) solution of B. Explain why.



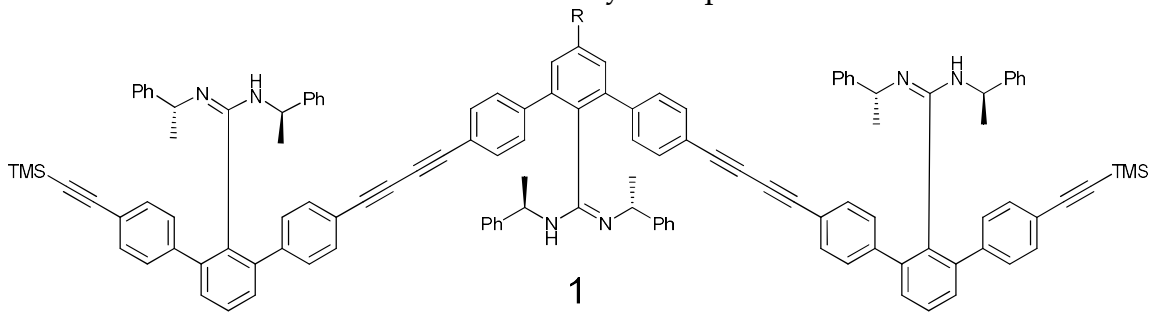
12 a) The helicate shown below formed well when Li^+ was used as the template ion, but intractable, insoluble materials were obtained with Cu^+ (by far the most commonly used template ion for phenanthroline-based structures). Explain.



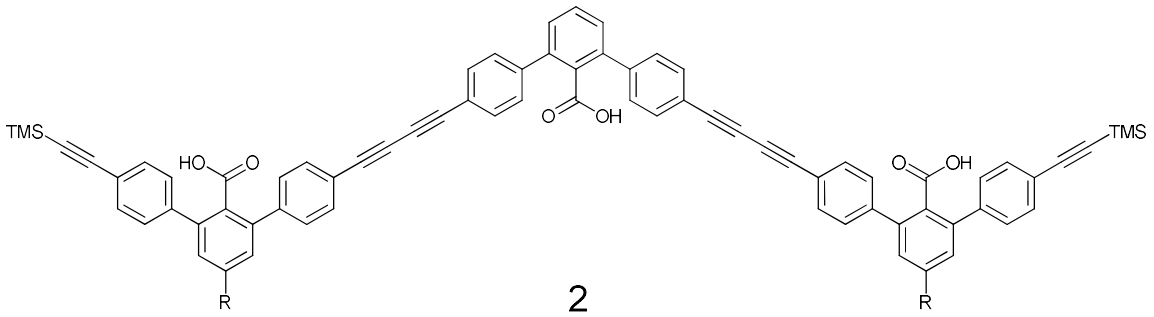
b) The longer double-helicate shown below, prepared from a penta-phenanthroline analogue of the ligand shown above, underwent $Li^+ \rightarrow Cu^+$ metal exchange only at its terminal positions. Explain. In the mass spectrometer, loss of one Li^+ cation was noted, which was postulated to come from the complex's central site. Why would Li^+ loss from this site be favoured?



13 When **1** and **2** are mixed in $CDCl_3$ only one species is formed.



1



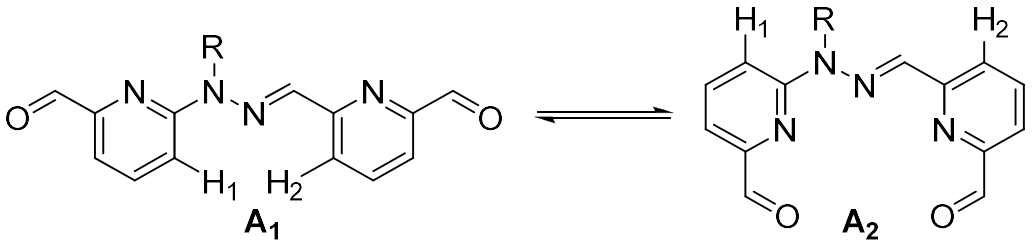
2

R=1-octynyl

a) What is the structure of the species? (schematically)
b) What influence would the chiral residues of **1** have upon the structure?
c) What is the driving force to form this structure?
d) What analytical methods would you use to prove the structure? Describe the information you expect from each method.

14

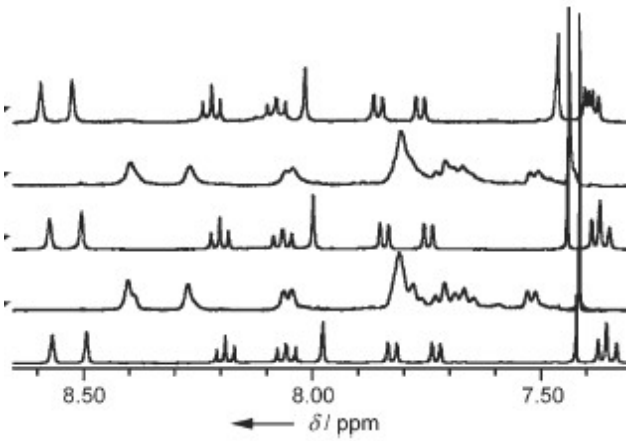
a) The dialdehyde shown below may exist in several conformations; predict which one of the two conformations would be favoured based on the alignment of dipolar functional groups within the molecule. Nuclear Overhauser effect (nOe) NMR correlations can be observed between protons H_1 and H_2: does this support your hypothesis?



b) What products would be observed following the reaction between dialdehyde **A** and 1,4-diaminobutane?

c) To the above reaction what would happen if you added a metal such as Zn^{+2}? Provide a synthetic scheme. What techniques would you use to characterise the final products?

d) The five ^1H NMR spectra shown below document a reversible process involving **A**, 1,4-diaminobutane, Zn^{2+}, and hexacyclen (18-crown-6 in which all oxygen atoms have been replaced with NH groups). Spectrum i) shows the products of the reaction between equimolar amounts of **A**, 1,4-diaminobutane and Zn^{2+}. Spectrum ii) shows the result of subsequent addition of hexacyclen (1 equiv). Spectrum iii) was taken after the addition of one more equivalent Zn^{2+} to the mixture, and iv) and v) show the effects of sequential addition of further hexacyclen and Zn^{2+}, respectively. Describe what is happening.



v) Mixture of iv) + Zn^{2+}

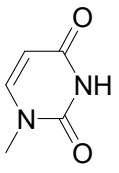
iv) Mixture of iii) + hexacyclen

iii) Mixture of ii) + Zn^{2+}

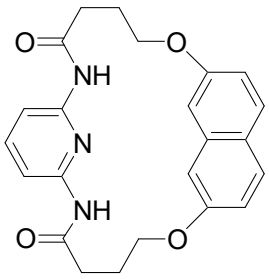
ii) Mixture of i) + hexacyclen

i) **A** + $H_2N(CH_2)_4NH_2$ + Zn^{2+}

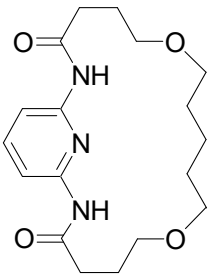
15 Comment on the relative binding of the guest **A**, with the cyclic hosts **B** and **C**, making sure to identify the non-covalent interactions driving the assembly.



A

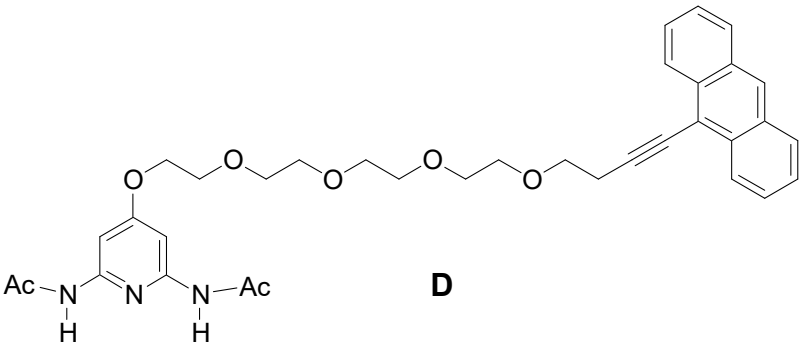


B

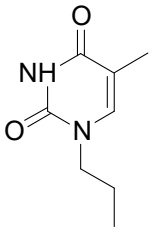


C

16 Describe the nature of the binding between compounds **D** and **E**, and explain why binding increases by a factor of six when sodium is introduced to the system. Point out any notable features in the proton NMR spectrum of the complex that might help assign the structure.

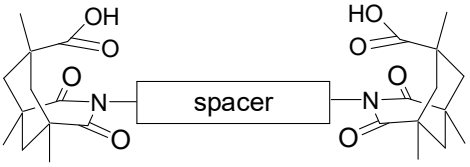


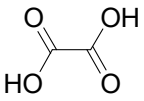
D

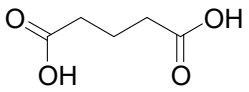


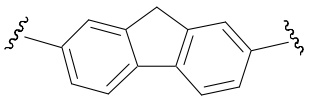
E

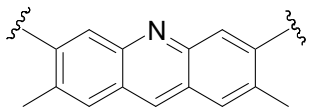
17 Comment on the nature of the interactions, and the efficiency of binding, of the two dicarboxylic acids (below right), to the molecular pincers shown below with the two different aromatic space groups.



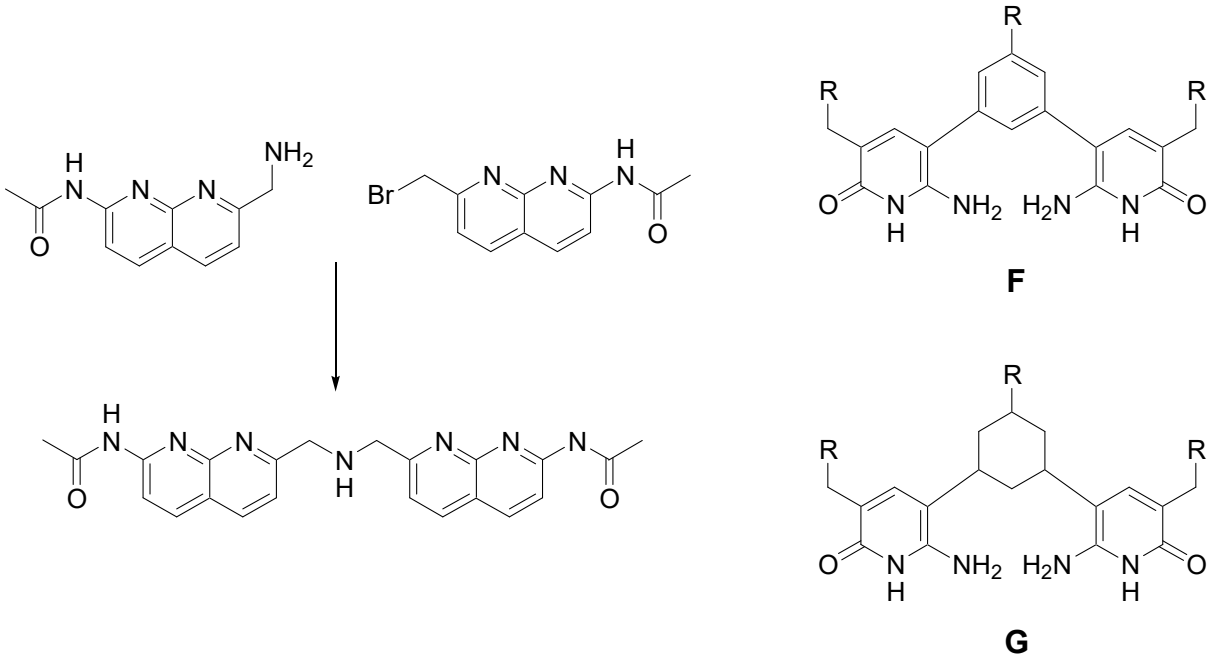








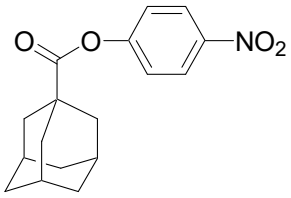
18 Suggest why the following reaction is accelerated by a factor of six in the presence of **F**, but inhibited in the presence of **G**. Comment on the choice of solvent in which you might carry out this study.



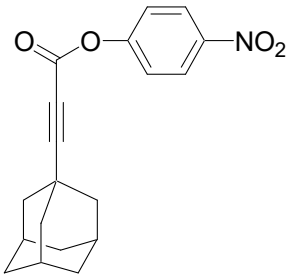
F

G

19 Explain why cleavage of the para-nitrophenyl ester **H** by a functionalised β-cyclodextrin (see p 30 of the notes for comparison), is approximately 10^4 times faster than the ester **I**.

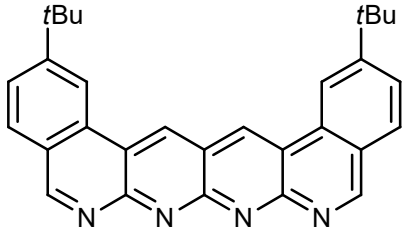


H

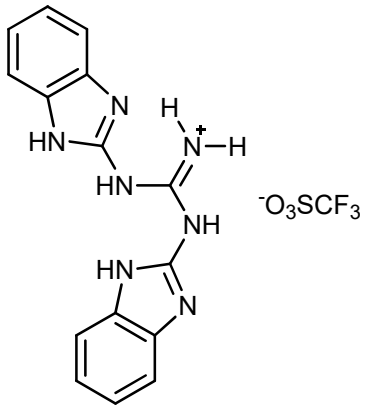


I

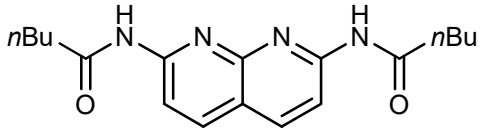
20 Equimolar amounts of compounds **A**, **B**, **C** and **D** below react in solution to form products **1** and **2**.



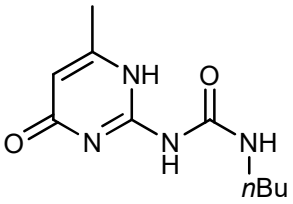
A



B



C



D

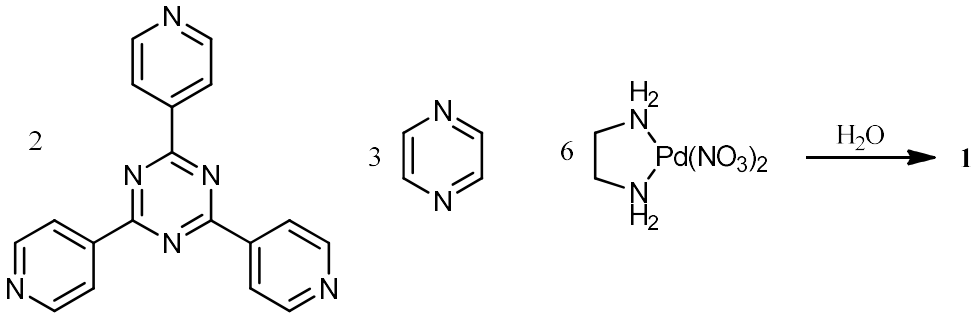
(a) In what solvent would you investigate the formation of **1** and **2**, and why?

(b) What are the structures of **1** and **2**? Explain briefly why these products form.

(c) Compound **1** has a stability constant $K_a > 3 \times 10^{12}$ M^{-1}, whereas **2** has $K_a = 3 \times 10^8$ M^{-1}. Explain this difference briefly.

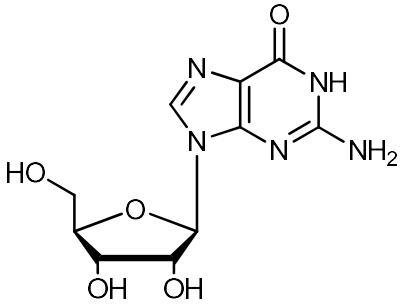
(d) How would you measure these association constants?

21 As shown below, tris(pyridyl)triazine (2 equivalents), pyrazine (3 equivalents) and Pd(ethylenediamine)$(NO_3)_2$ (6 equivalents) are observed to react together in aqueous solution to produce a single product, **1**.

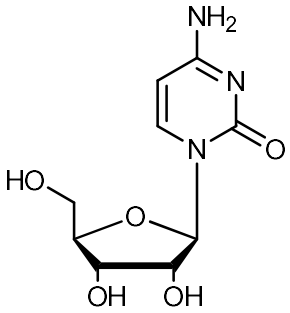


(a) Provide the structure of product **1**.

Nucleobases such as guanosine and cytidine, shown below, form hydrogen-bonded base pairs to a negligible extent in aqueous solution, although the formation of such base pairs is known to hold DNA strands together in double-stranded DNA.



Guanosine



Cytidine

(b) Cite three factors that act either to destabilise the Watson-Crick G-C base pair in aqueous solution, or to stabilise a DNA helix composed of such base pairs.

When **1**, Guanosine and Cytidine were mixed together in aqueous solution, a single new product **2** is observed to form. This product is observed to possess spectroscopic features characteristic of a G-C base pair in aqueous solution.

(c) What is the structure of product **2**? Explain the driving forces that lead to its formation.