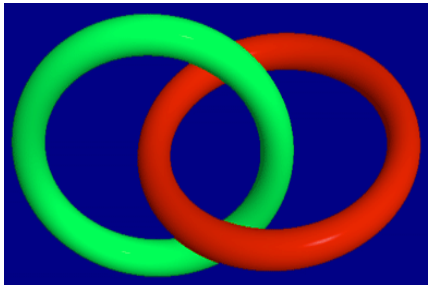
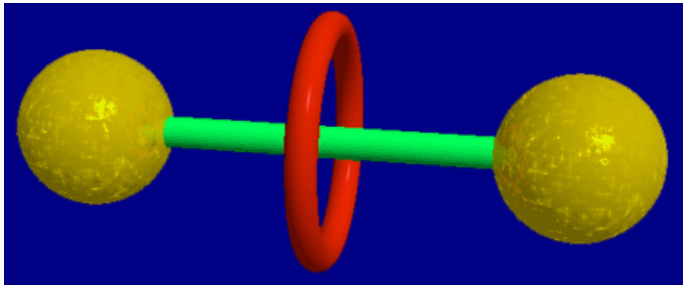
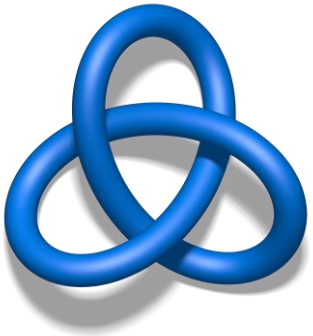
# Catenanes, Rotaxanes and Knots



Catenane
(Hopf Link)



Rotaxane



Molecular Knot

# Masters of Interlocked Molecules

Jean-Pierre Sauvage

nobel lecture

Sir J. Fraser Stoddart

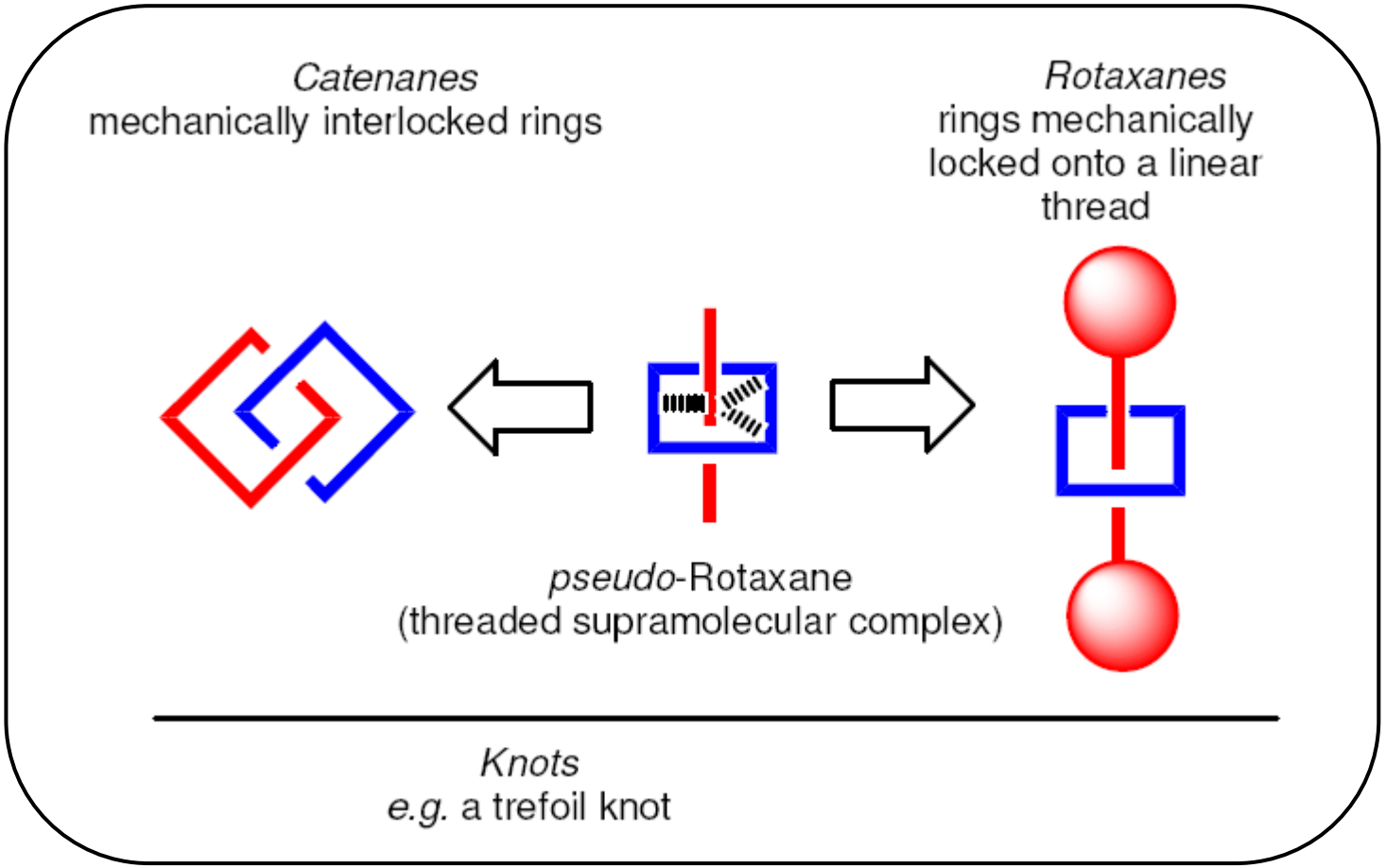
nobel lecture

## Chemistry Noble Prize 2016

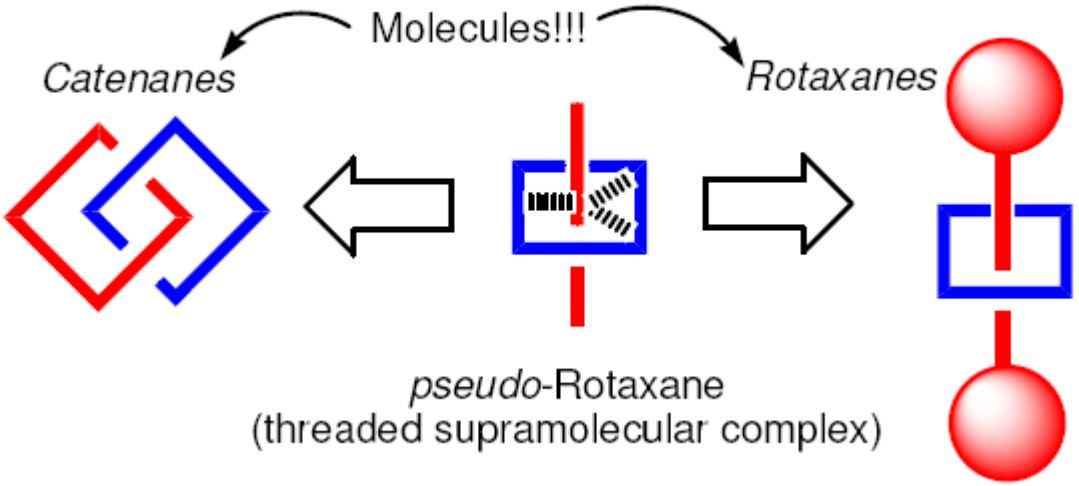
"for the design and synthesis of molecular machines"

# Mechanically Interlocked Molecules

Mechanically interlocked molecular level architectures cover a multitude of types of structures featuring kinetically stable entanglements of covalently bonded backbones.



# Supramolecular Species ?

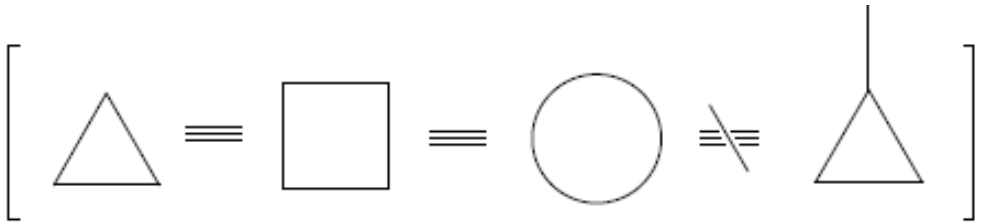



Catenanes, rotaxanes, and knots are molecules NOT supramolecular species!

*A molecule is an assembly of atoms which can only be separated by breaking a covalent bond; a supramolecular complex is an assembly of molecules/ions which can only be separated by breaking noncovalent interactions.*

*Pseudo*-rotaxanes are threaded host-guest complexes – they ARE supramolecular species!

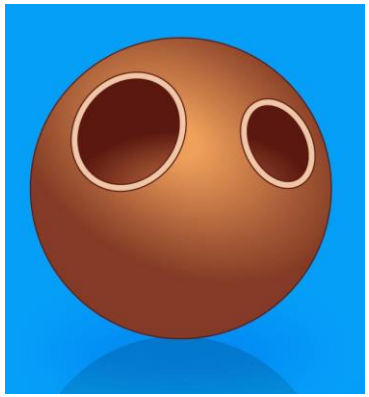
# Topology



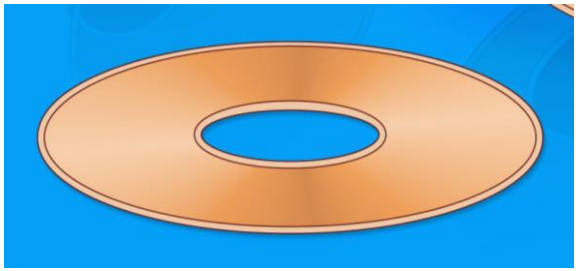
(Topology is the mathematics of connectivity)

# Topology

# Topology

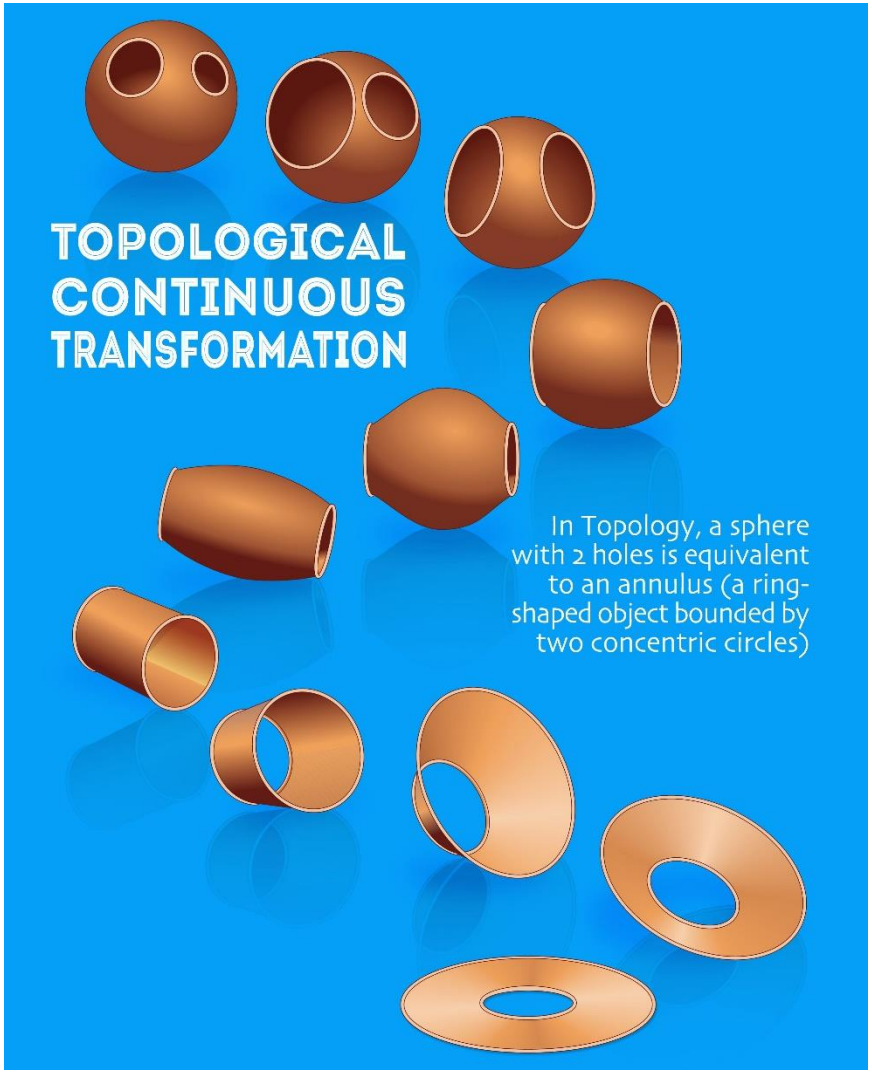


Sphere with two holes

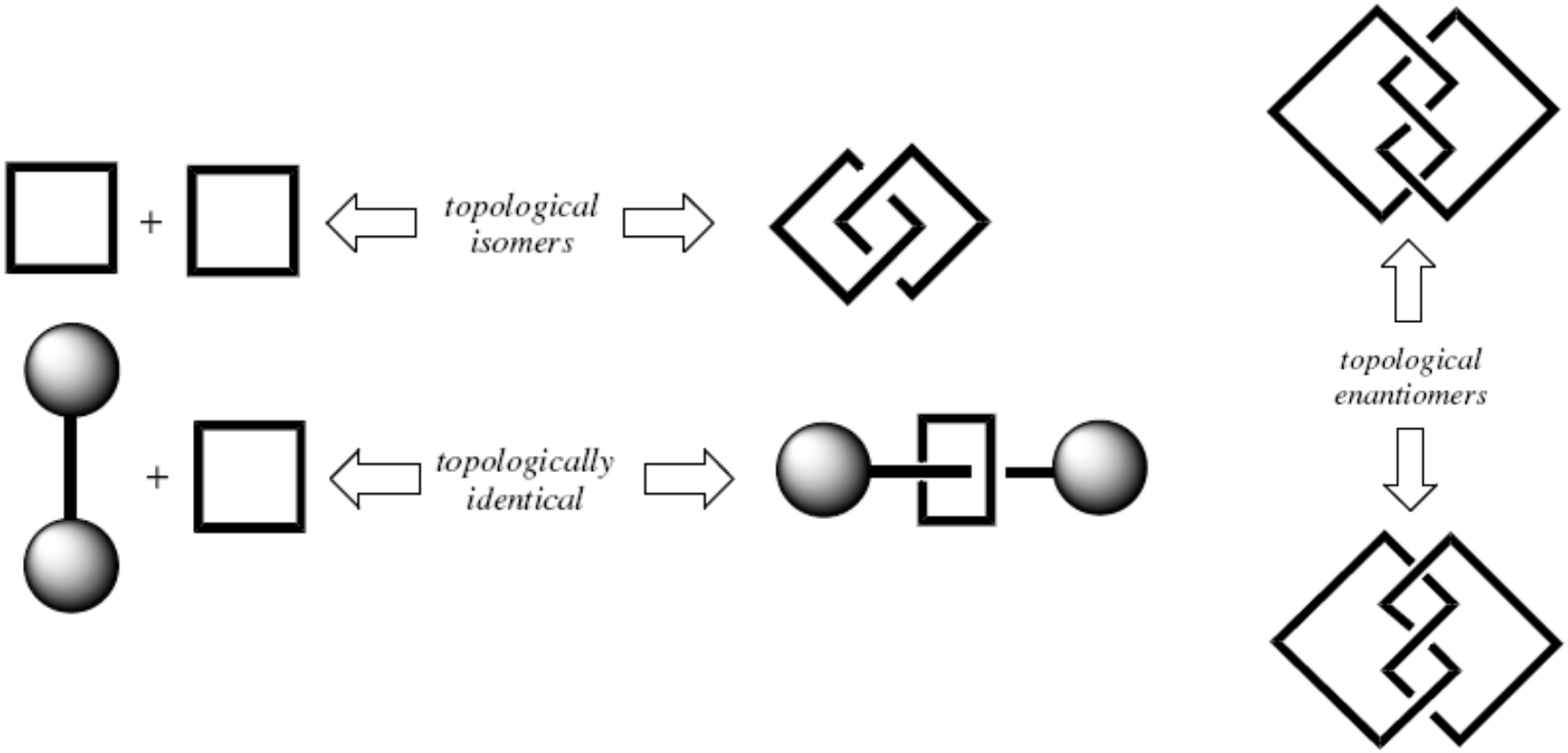


Ring

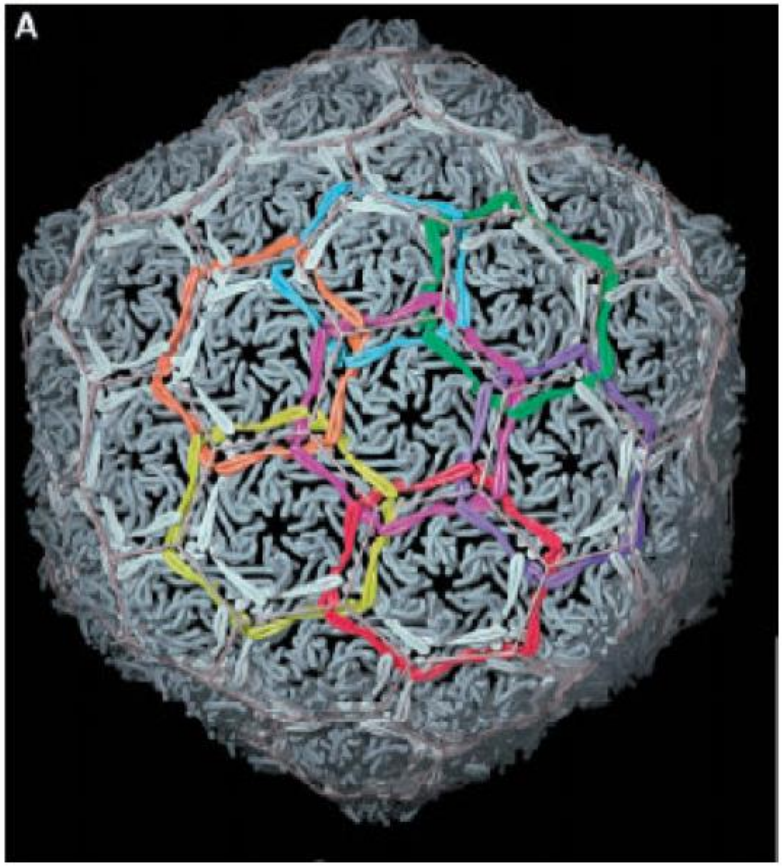
# Topology


TOPOLOGICAL
CONTINUOUS
TRANSFORMATION
In Topology, a sphere with 2 holes is equivalent to an annulus (a ring-shaped object bounded by two concentric circles)

# Topology of Interlocked Compounds



# Mechanically Interlocked Molecules in Nature



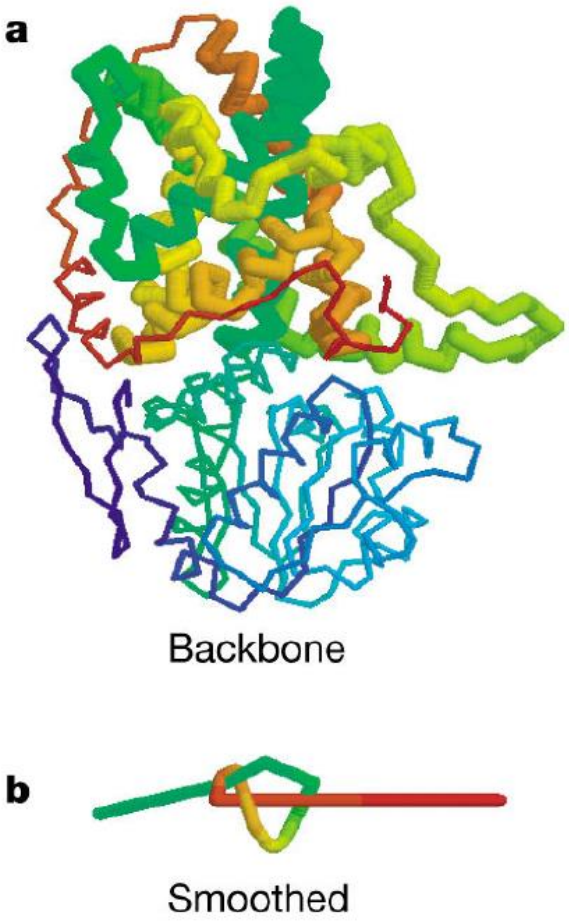

## Topologically Linked Protein Rings in the Bacteriophage HK97 Capsid

William R. Wikoff,[1] Lars Liljas,[1,2] Robert L. Duda,[3] Hiro Tsuruta,[4] Roger W. Hendrix,[3] John E. Johnson[1]*

The crystal structure of the double-stranded DNA bacteriophage HK97 mature empty capsid was determined at 3.6 angstrom resolution. The 660 angstrom diameter icosahedral particle contains 420 subunits with a new fold. The final capsid maturation step is an autocatalytic reaction that creates 420 isopeptide bonds between proteins. Each subunit is joined to two of its neighbors by ligation of the side-chain lysine 169 to asparagine 356. This generates 12 pentameric and 60 hexameric rings of covalently joined subunits that loop through each other, creating protein chainmail: topologically linked protein catenanes arranged with icosahedral symmetry. Catenanes have not been previously observed in proteins and provide a stabilization mechanism for the very thin HK97 capsid.

*Science* **2000**, *289*, 2129.

# Proteins with Knots




## A deeply knotted protein structure and how it might fold

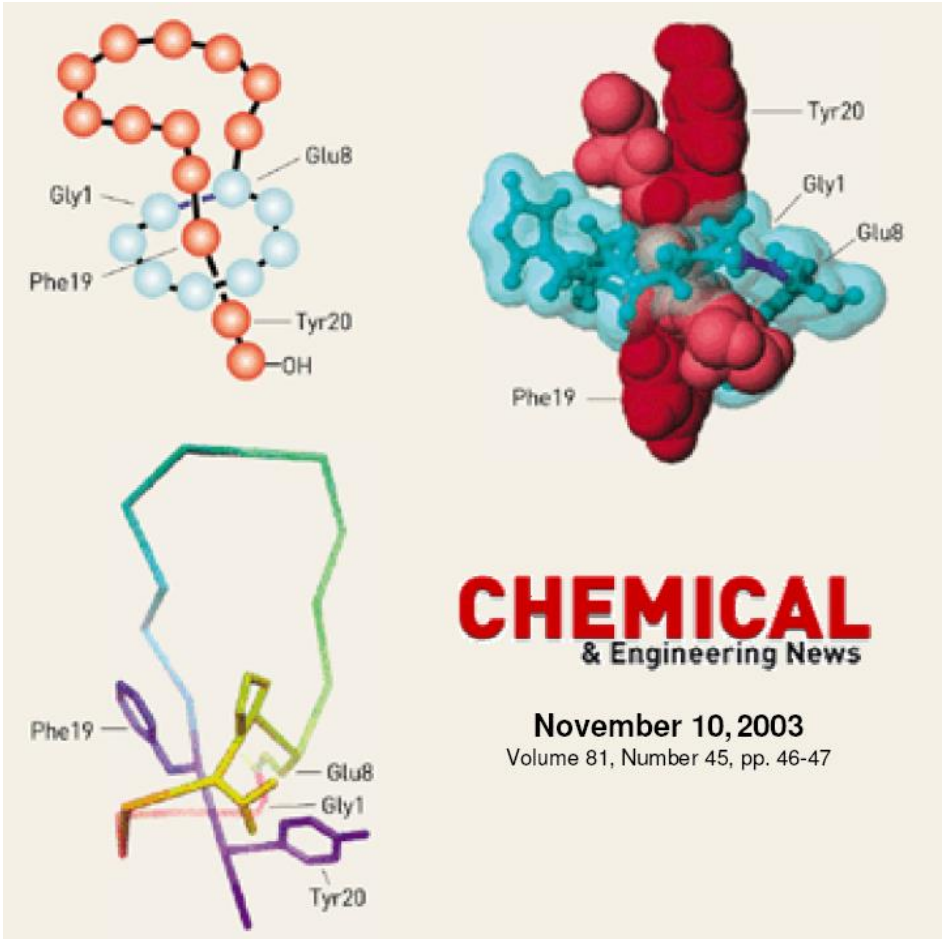
**William R. Taylor**

*Division of Mathematical Biology, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK*

The search for knots in protein has uncovered little that would cause Alexander the Great to reach for his sword. Excluding knots formed by post-translational crosslinking, the few proteins considered to be knotted form simple trefoil knots with one end of the chain extending through a loop by only a few residues[1,2], ten in the 'best' example[3]. A knot in an open chain (as distinct from a closed circle) is not rigorously defined and many weak protein knots disappear if the structure is viewed from a different angle. Here I describe a computer algorithm to detect knots in open chains that is not sensitive to viewpoint and that can define the region of the

*Nature* **2000**, *406*, 916.

# Proteins with ‘Lasso’ Structures



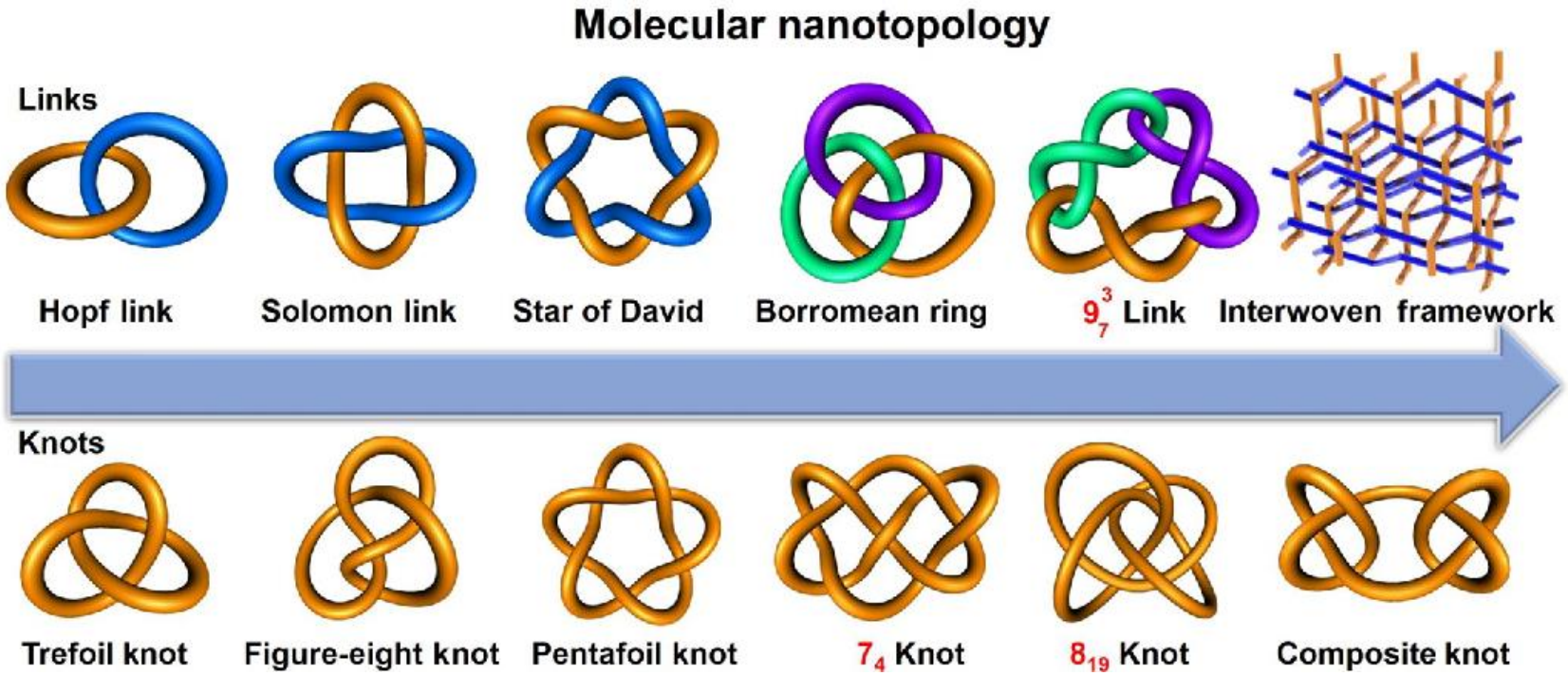

## *NATURE'S NEEDLE AND THREAD*

*Three labs simultaneously report novel lasso structure of RNA polymerase inhibitor*

LOUISA WRAY DALTON, C&EN WASHINGTON

Last month, three separate collaborations unveiled the unusual structure of the same antibacterial peptide, microcin J25, in the same issue of the *Journal of the American Chemical Society* [**125,** 12382, 12464, and 12475 (2003)].

# Molecular Links and Knots



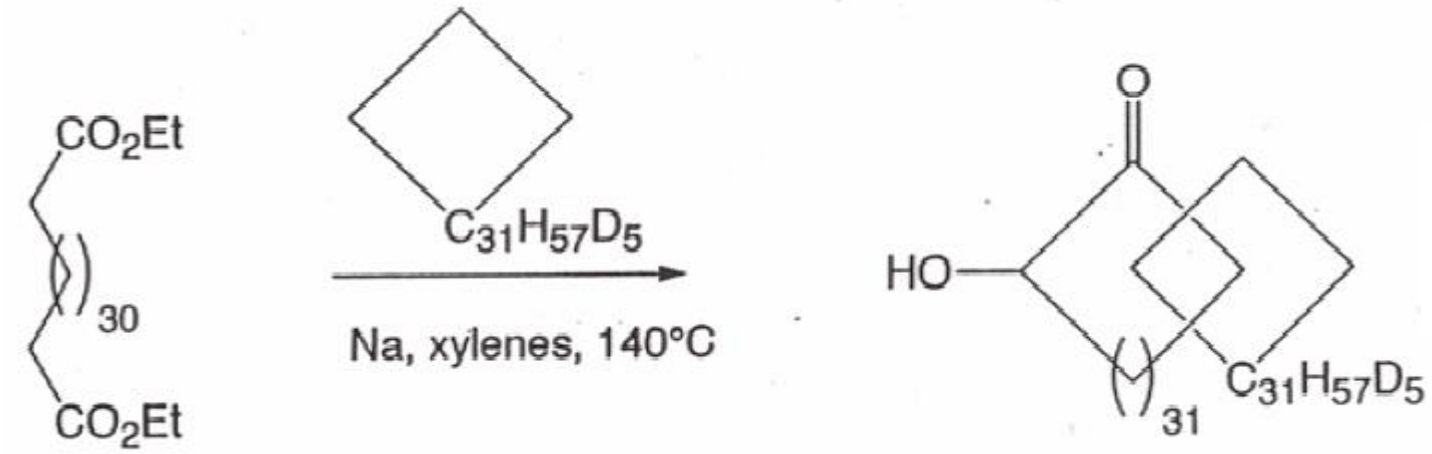

J. F. Stoddart *et al.*, *CCS Chem.* **2021**, *3*, 1542.

# Catenanes

*Catena* (Latin) = chain

prefix = number of interlocked rings, *e.g.* [2]catenane, [3]catenane *etc*

# Catenanes – The Early Years
# Statistical Approach




**Yield: < 1 % !**

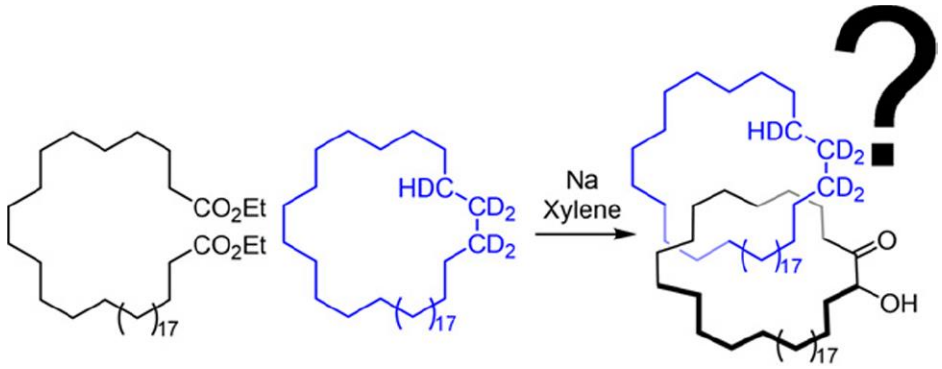
Edel Wasserman, *J. Am. Chem. Soc.* **1960**, *82*, 4433.

# Catenanes – The Statistical Approach

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Article

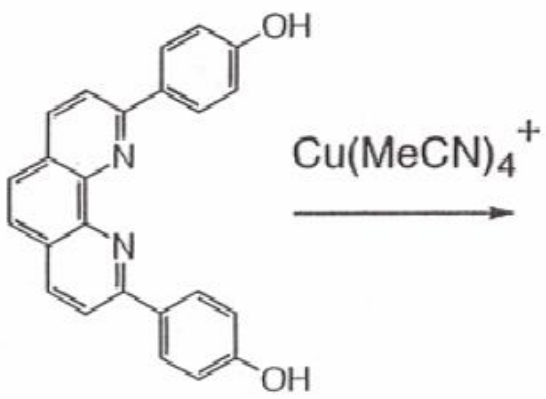
## In Search of Wasserman's Catenane

Andrei S. Baluna, Albano Galan, David A. Leigh,* Gareth D. Smith, Justin T. J. Spence, Daniel J. Tetlow, Iñigo J. Vitorica-Yrezabal, and Min Zhang

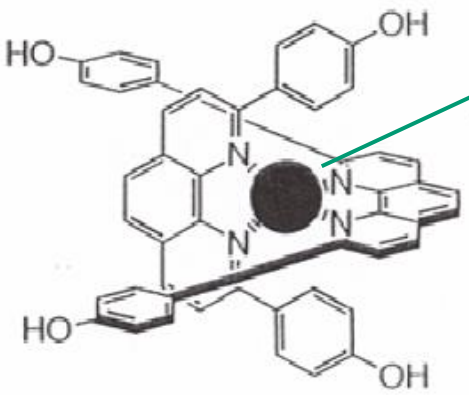



D. Leigh et al., *J. Am. Chem. Soc.* **2023**, *145*, 9825.

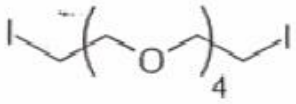
# A [2]Catenane by Cu$^{I}$ Templation




$Cu(MeCN)_4^+$



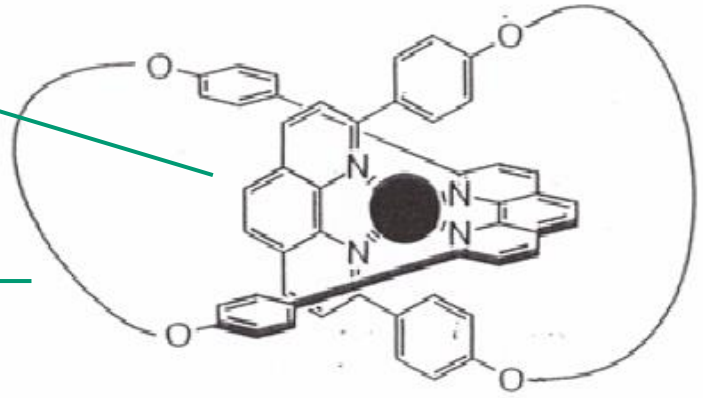

**Cu(I) prefers tetrahedral coordination**




$Cs_2CO_3$

27%

**Most stable Cu(I) complex that exisis with a neutral ligand.**

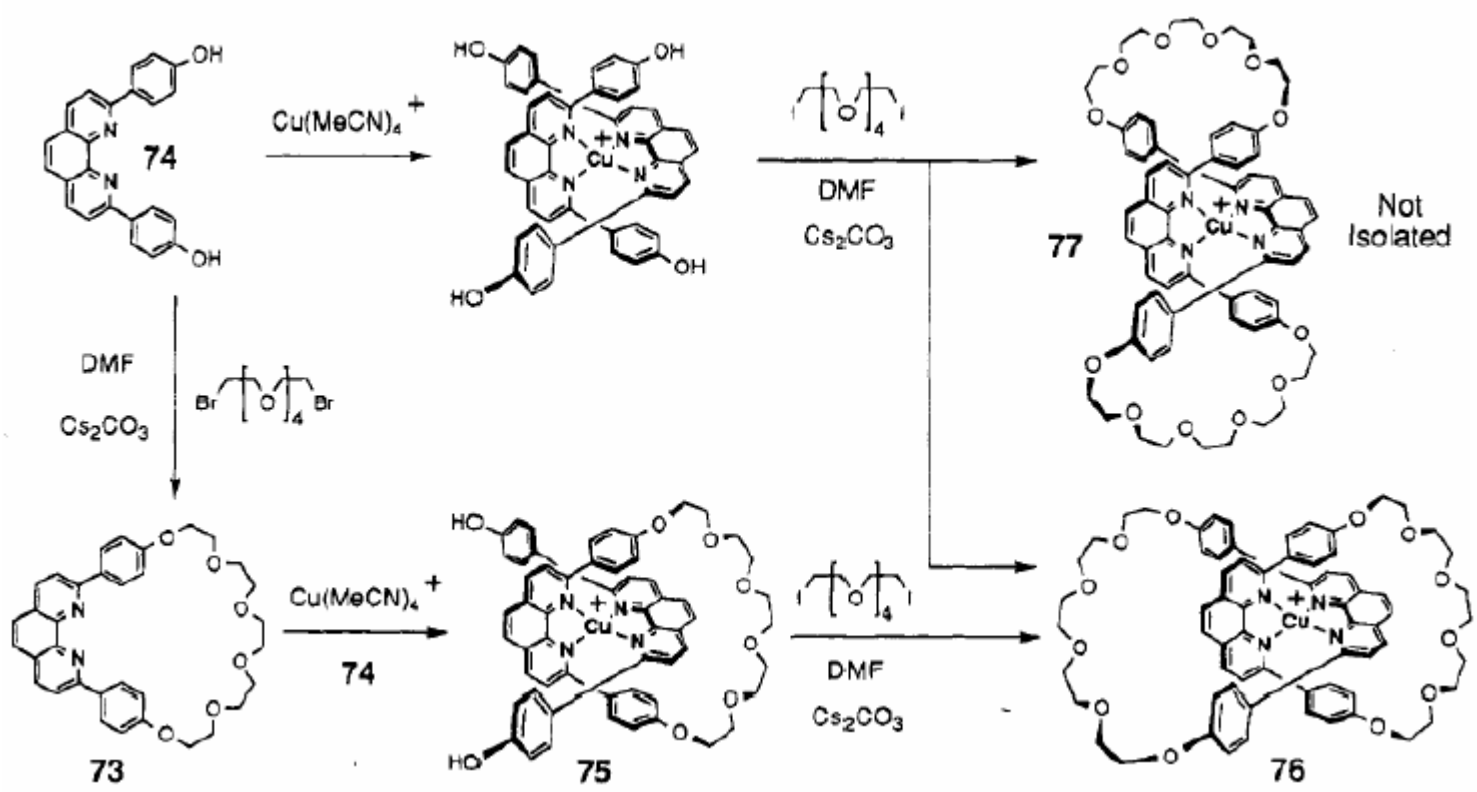



**Cu(I) can be removed with cyanide to give the metal-free [2]catenane.**

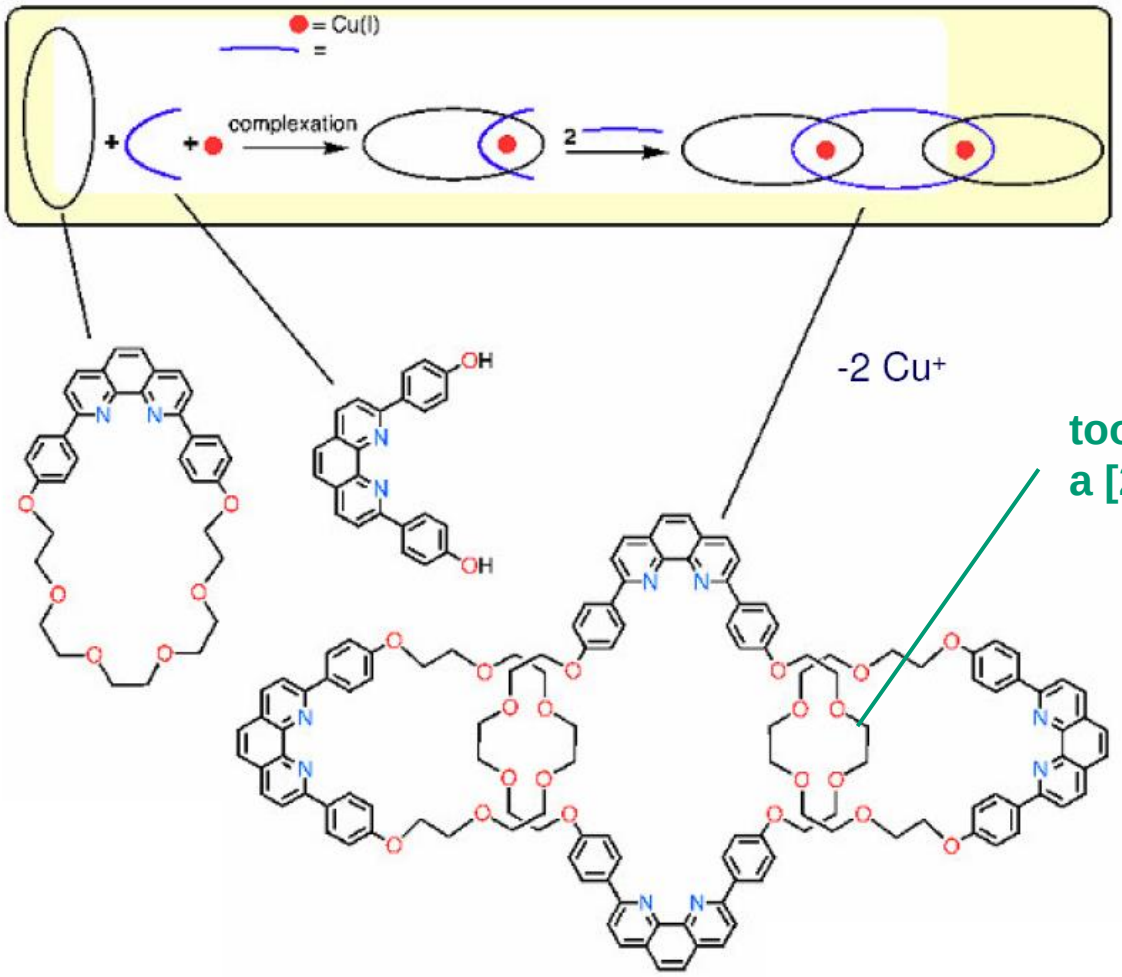
J.-P. Sauvage et al., *J. Am. Chem. Soc.* **1984**, *106*, 3043.

# Different Synthetic Approaches

The final step must proceed by ‘clipping’ – but individual cyclization reactions can either be performed sequentially (more reactions but less possible byproducts) or all in one pot.

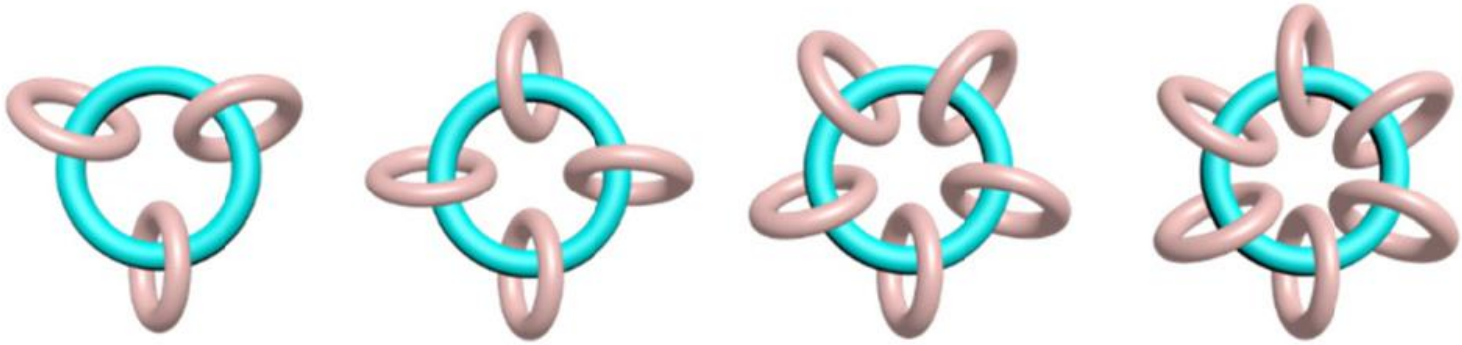


# Formation of a [3]Catenane



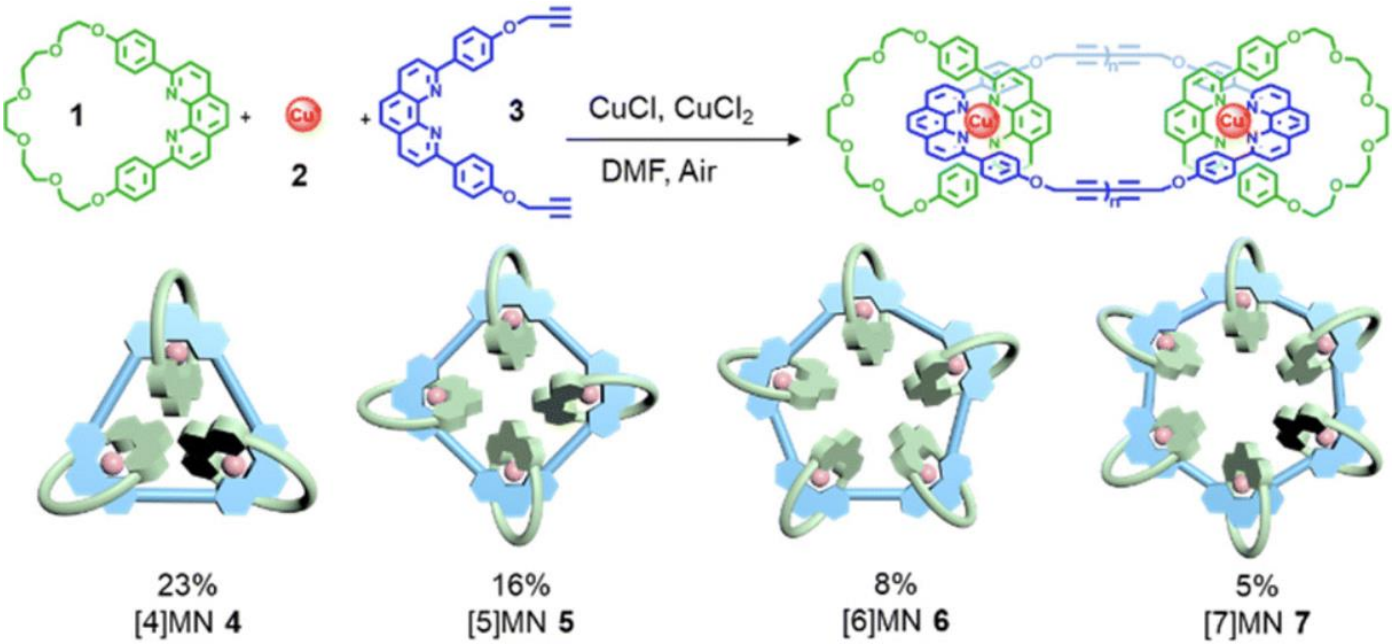

J.-P. Sauvage et al, *J. Am. Chem. Soc.* **1985**, *107*, 6108.

# Molecular Necklaces



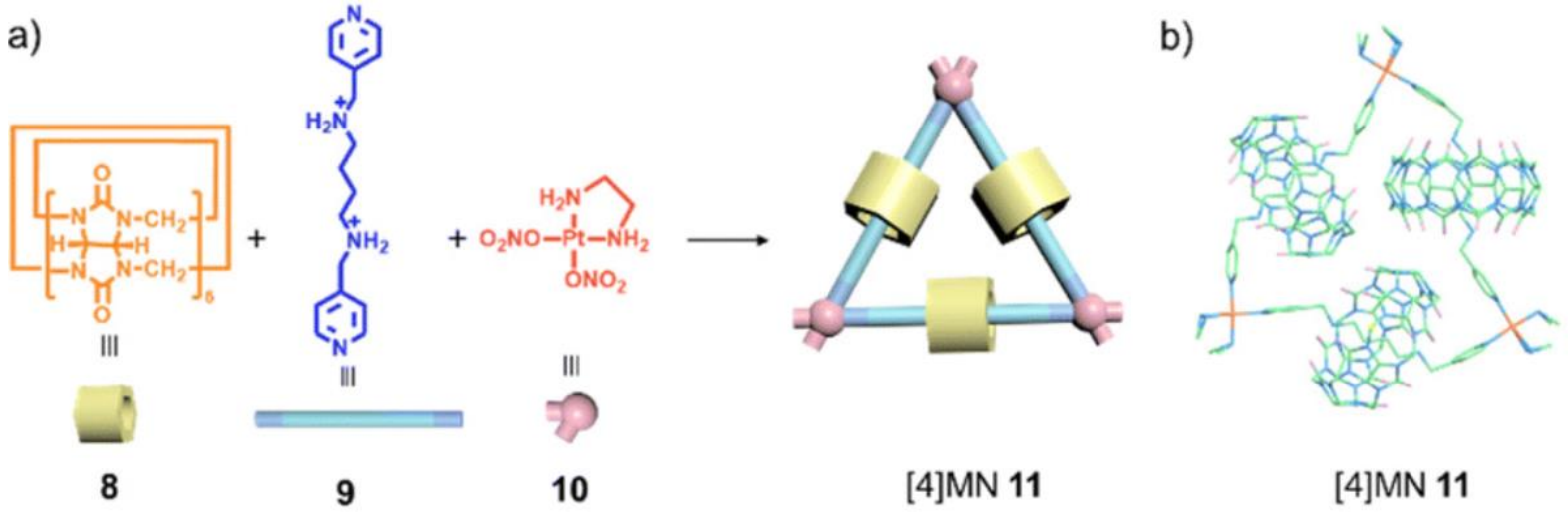
Review: Lin Xu et al., *Dalton Trans.* **2023**, *52*, 2916.

# Molecular Necklaces – Example 1



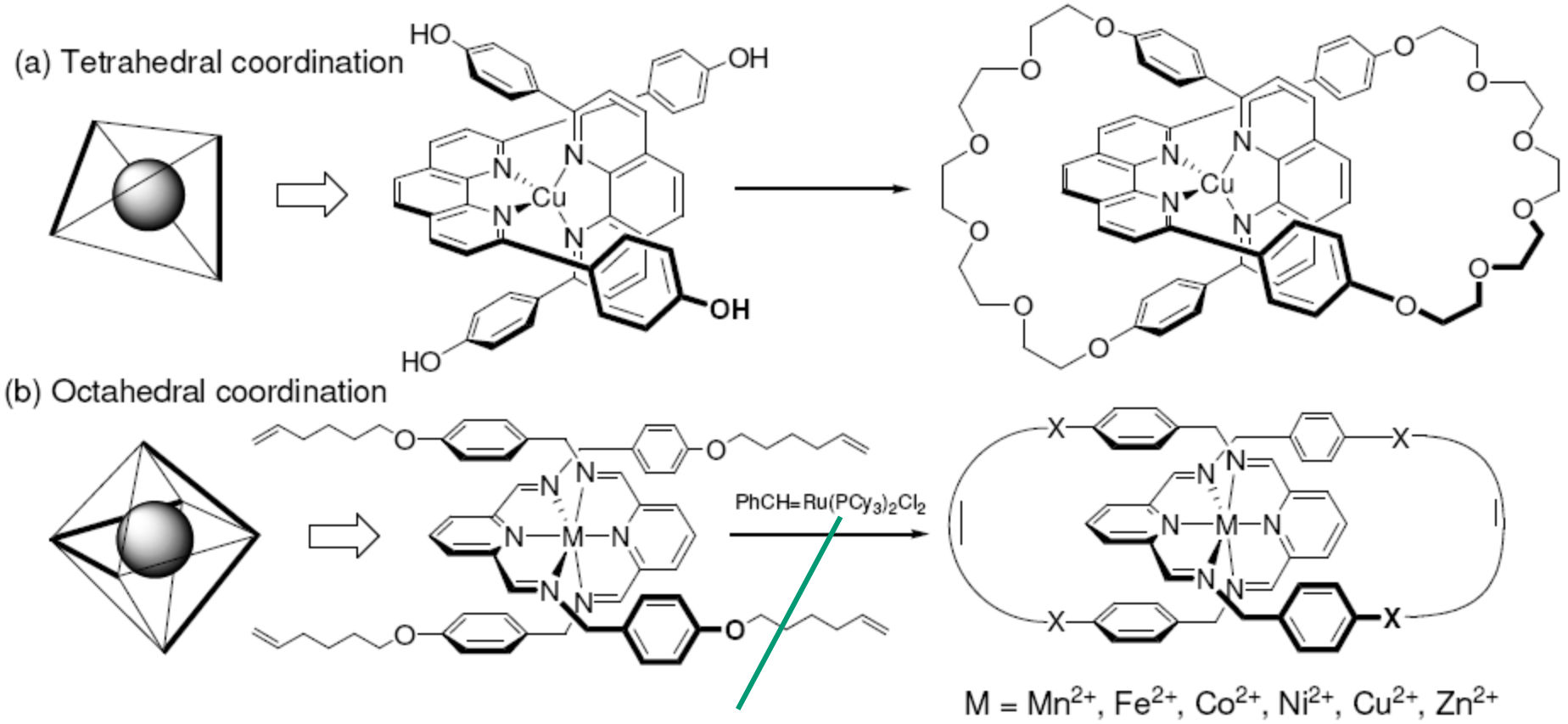

J.-P. Sauvage et al., *J. Am Chem Soc.* **1991**, *113*, 4023.

# Molecular Necklaces – Example 2




K. Kim et al., *J. Am. Chem. Soc.* **1998**, *120*, 4899.

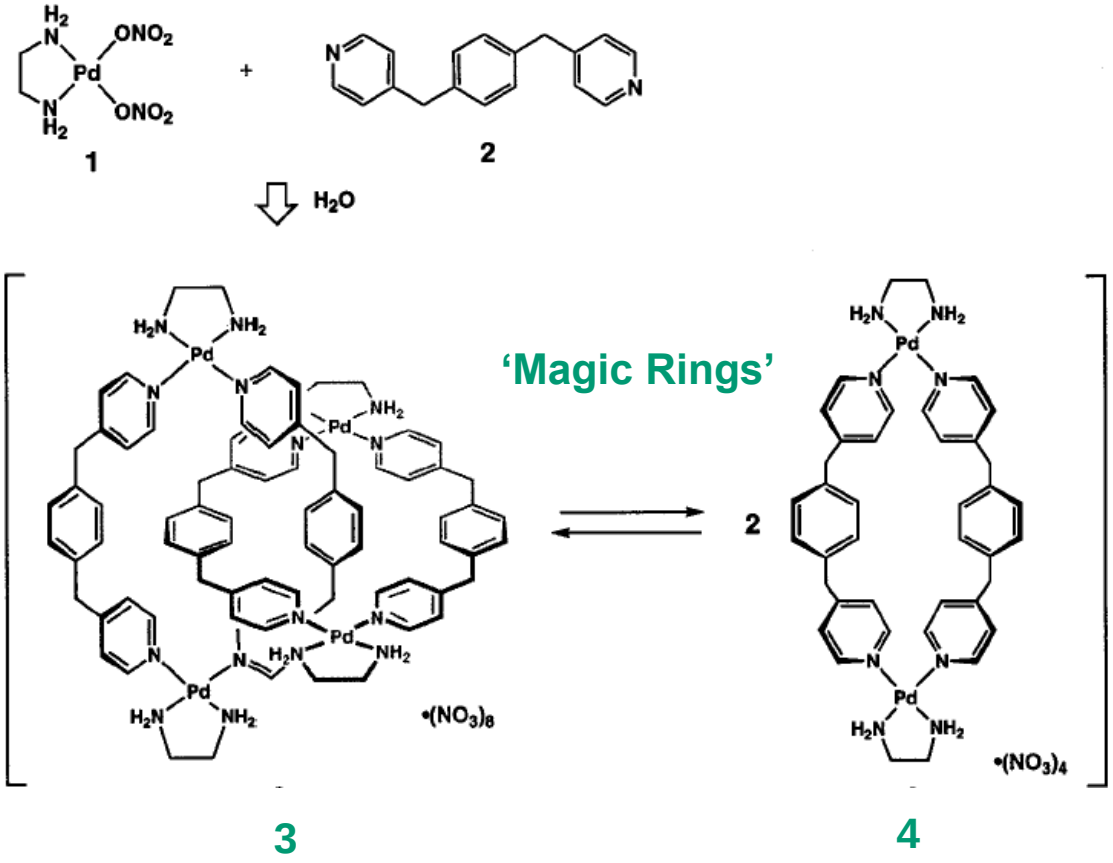
# From Tetrahedral to Octahedral Templates




**Ring closure by olefin metathesis !**

D. Leigh et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 1538.

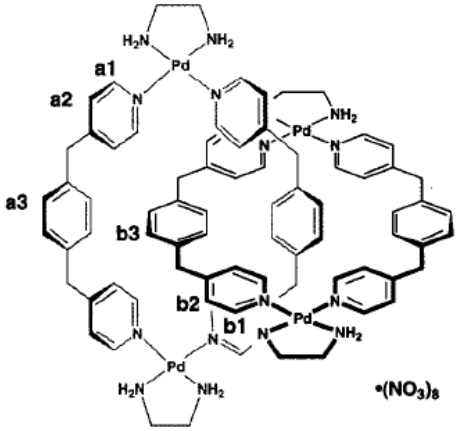
# Formation of a Metallacatenane under Thermodynamic Control

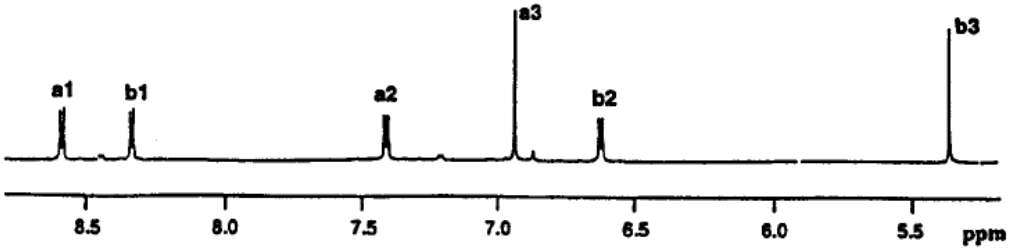



| | 3 | | 4 |
|---|---|---|---|
| 1 mM[b] | <1 | : | >99 |
| 2 mM | 11 | : | 89 |
| 5 mM | 38 | : | 62 |
| 10 mM | 59 | : | 41 |
| 20 mM | 75 | : | 25 |
| 50 mM | 91 | : | 9 |

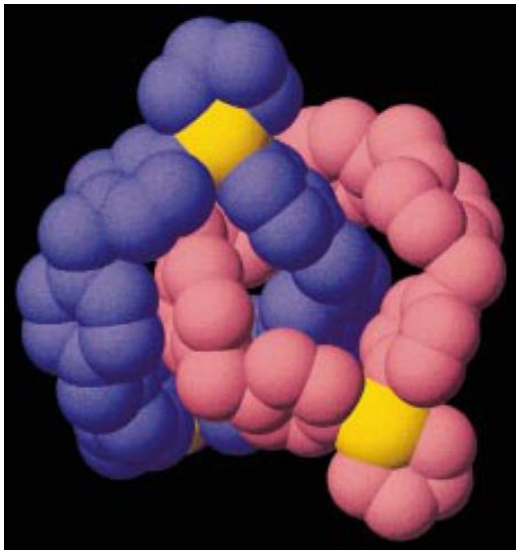
M. Fujita et al, *Nature* **1994**, *367*, 720.

# Characterization of the Metallacatenane




Two inequivalent PyCH2C6H4CH2Py units are observed which are assignable to the inside and outside units of the catenane.



X-ray structure of the Pt(II) analogue.

# Medium Effects

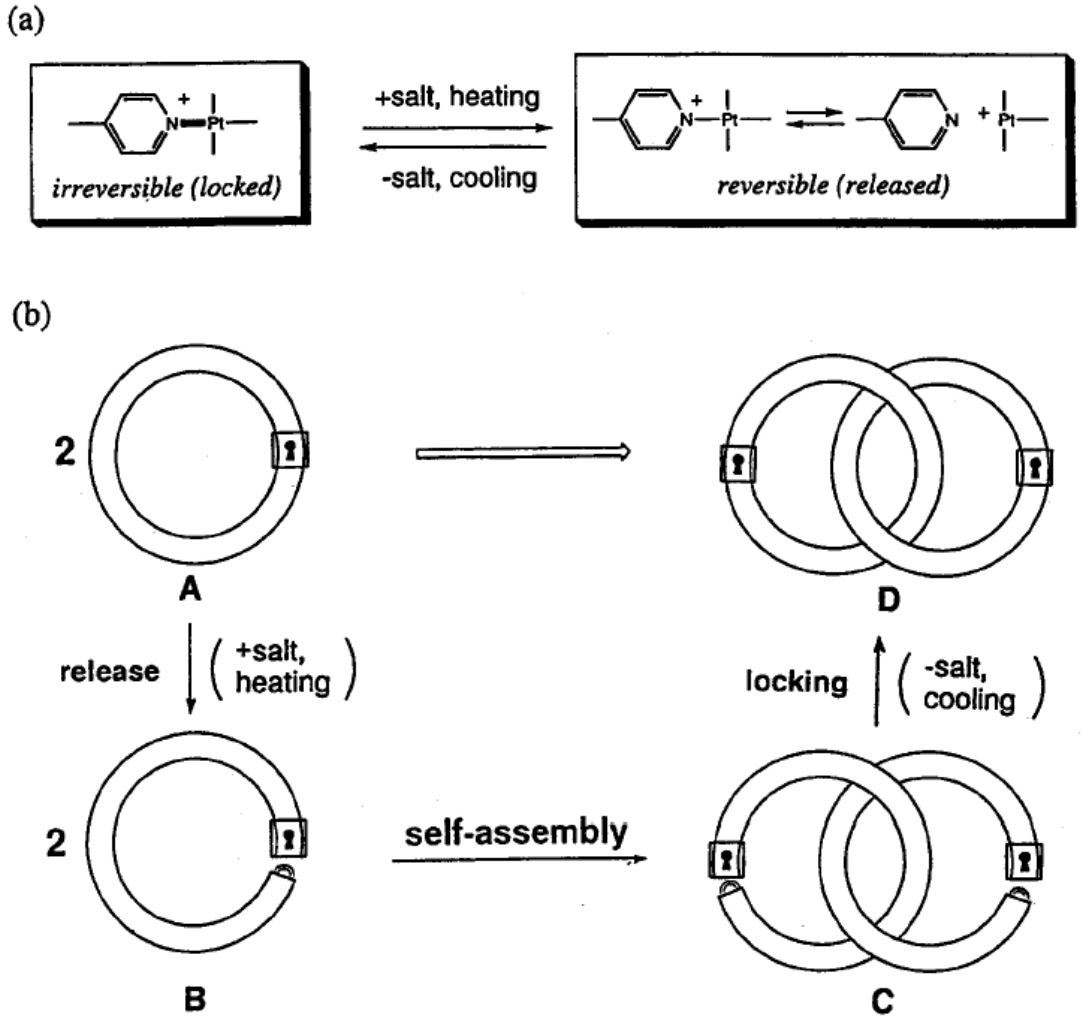
**Medium Effects on the Equilibrium Ratio of 3 and 4[a]**

| medium | guest[b]/mol equiv | **3**:**4** |
|---|---|---|
| 1.0 M $NaNO_3/D_2O$ | | >99:<1 |
| 0.2 M $NaNO_3/D_2O$ | | 95:5 |
| 0.05 M $NaNO_3/D_2O$ | | 86:14 |
| $D_2O$ | | 59:41 |
| $D_2O$ | 0.5 | 27:73 |
| $D_2O$ | 2.0 | 12:88 |
| $D_2O-CD_3OD$ (7:3) | | 9:91 |
| $D_2O-CD_3OD$ (5:5) | | <1:>99 |

[a] Measured at 10 mM, room temperature. [b] Sodium *p*-methoxyphenylacetate.

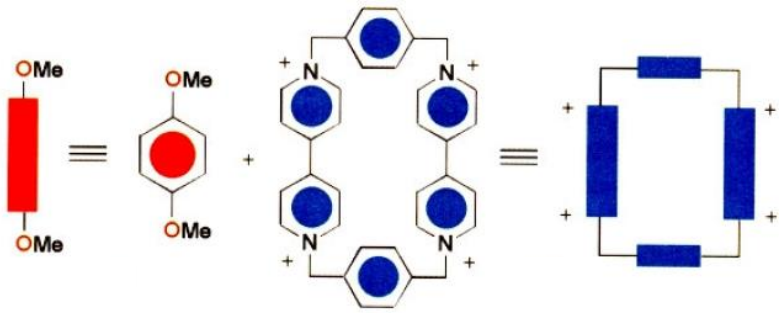
Medium effects enable the modulation of the equilibrium ratio **3**:**4** in the range of >99:1 to <1:99. A more polar medium ($D_2O$ solution of $NaNO_3$) increased the ratio of **3** up to >99% even at low concentrations because of enhanced hydrophobic interactions accompanying the catenane formation. In contrast, the ratio of **3** diminishes in a less polar medium ($CD_3OD$-$D_2O$). Selective stabilization of **4** by adding sodium (*p*-methoxyphenyl)acetate, a specific guest for **4**, also reduces the ratio **3**:**4** .

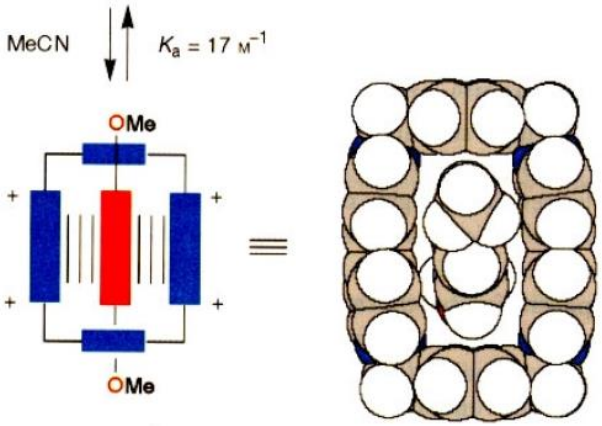
# Locking of Molecular Rings

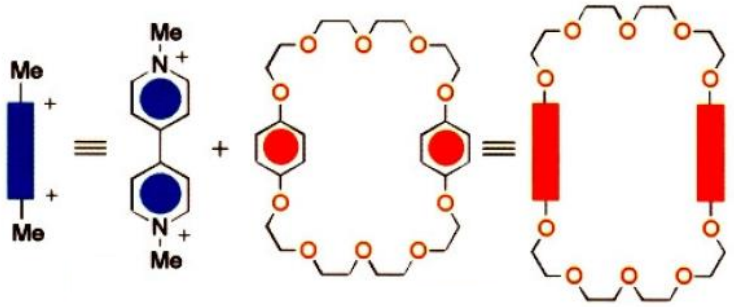


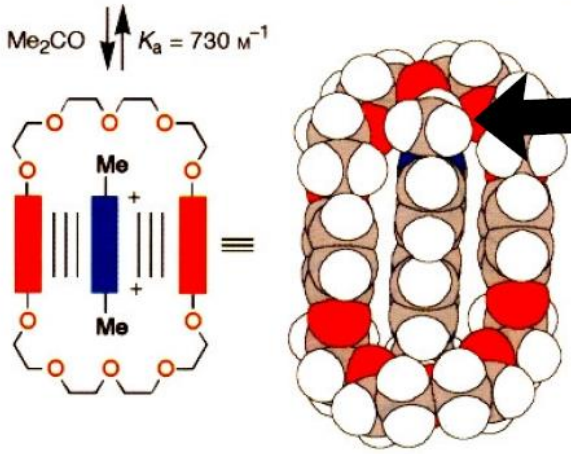

The platinum(II)-pyridine coordinative bond is irreversible ("locked") under the ordinary conditions, but becomes reversible ("released") in highly polar media at elevated temperatures. Incorporation of the molecular lock into a macrocyclic backbone makes it possible to interlock *irreversibly* two molecular rings.

# Paraquat-Based Systems



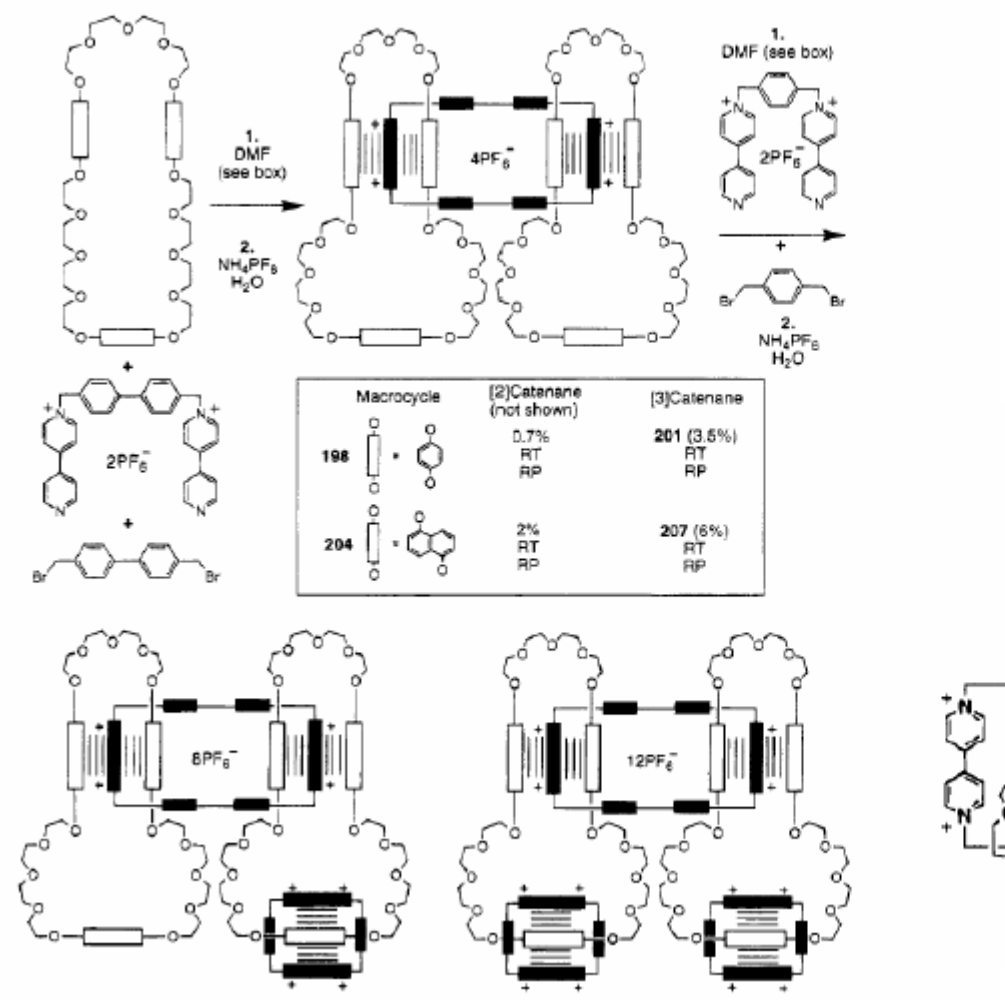



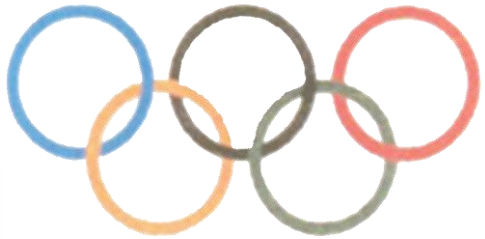



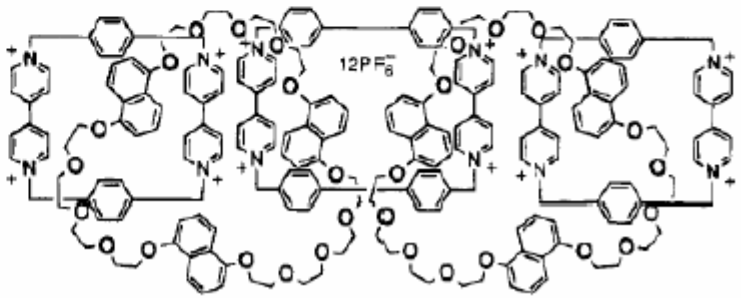




Driving force is really electrostatics and CH···O H-bonding

# Olympiadane

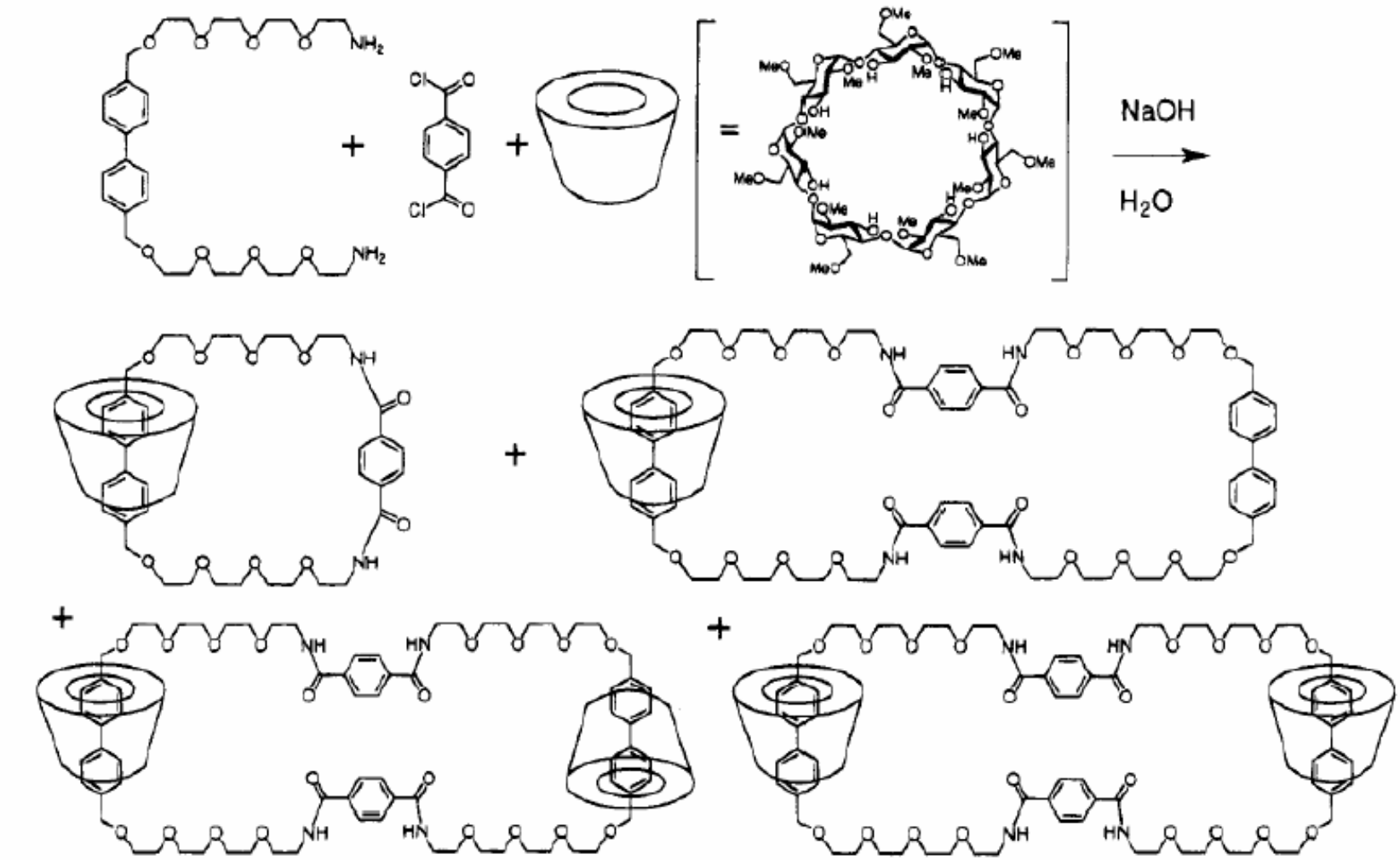


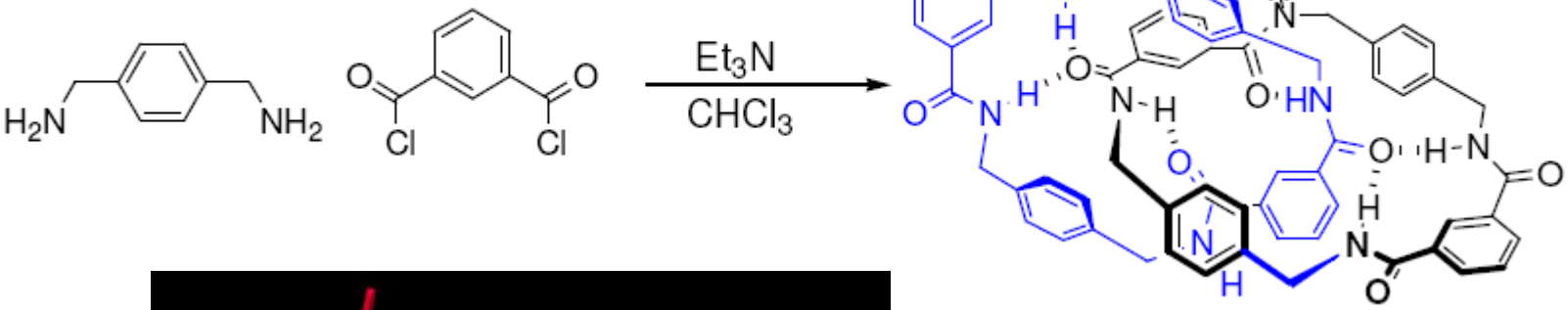


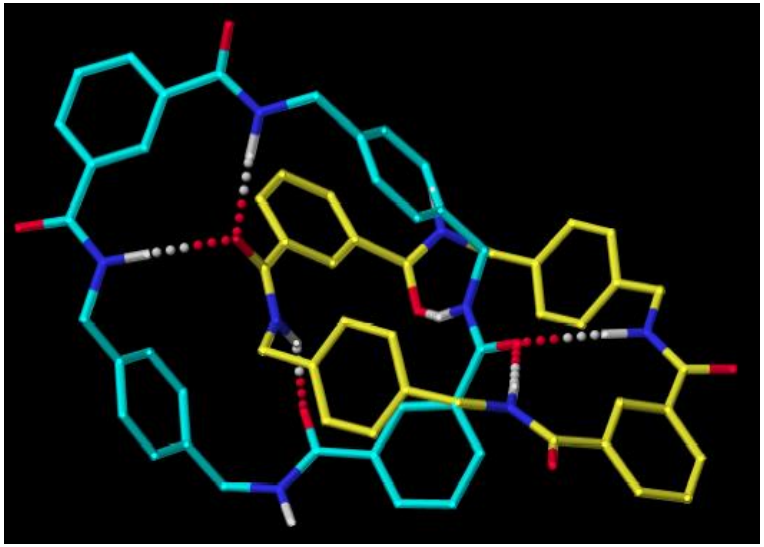

J. F. Stoddart et al., *Angew. Chem. Int. Ed.* **1994**, *33*, 1286.

# Cyclodextrin-Based Catenanes



# H-Bond Directed Catenane Formation

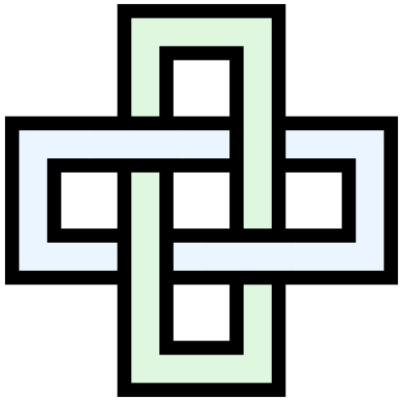


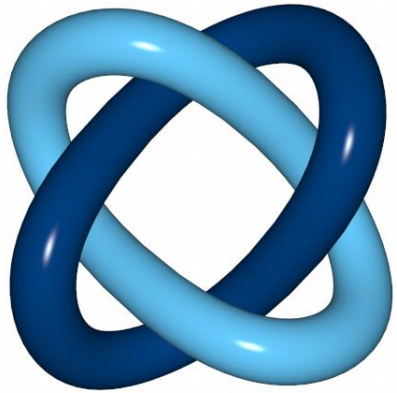



(X-ray)

D. Leigh et al., *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 1209.

# Solomon Link

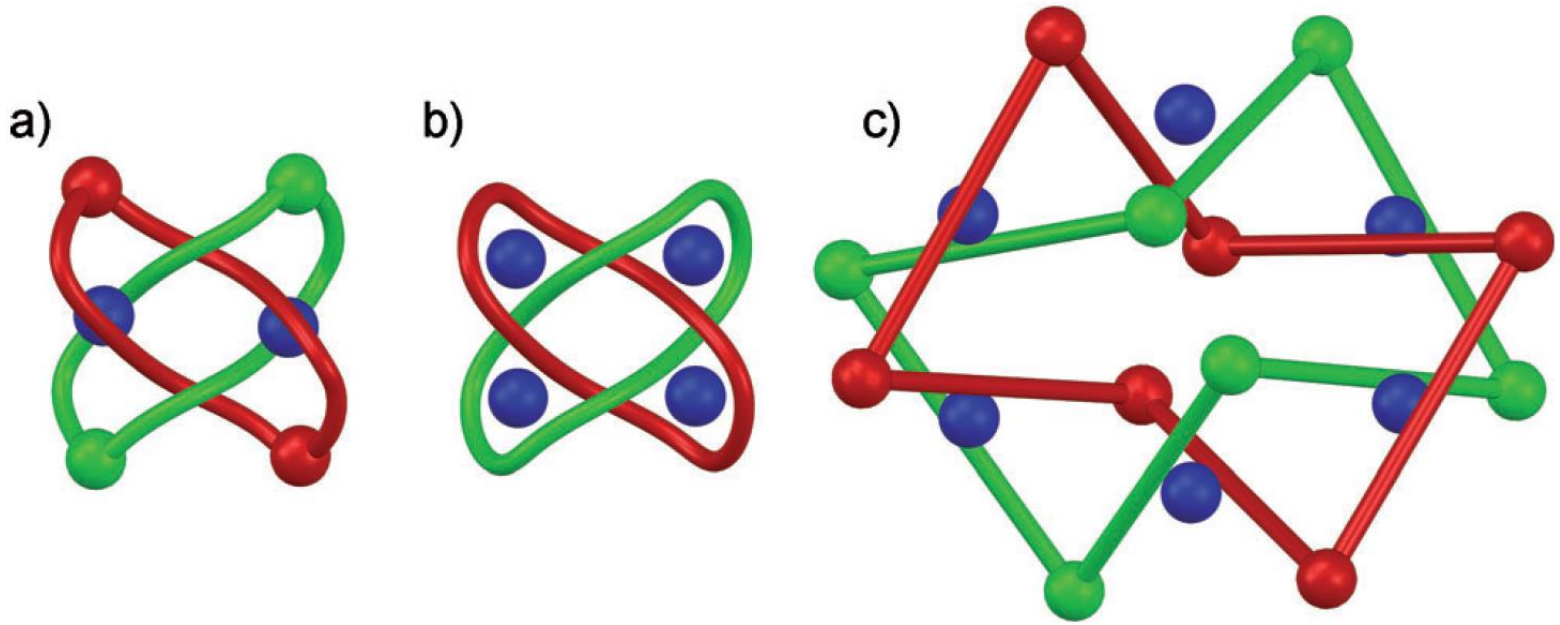




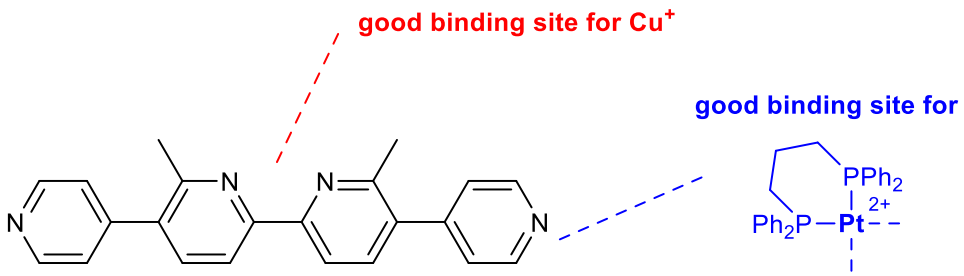
Solomon link: four crossings
[2]Catenane: two crossings

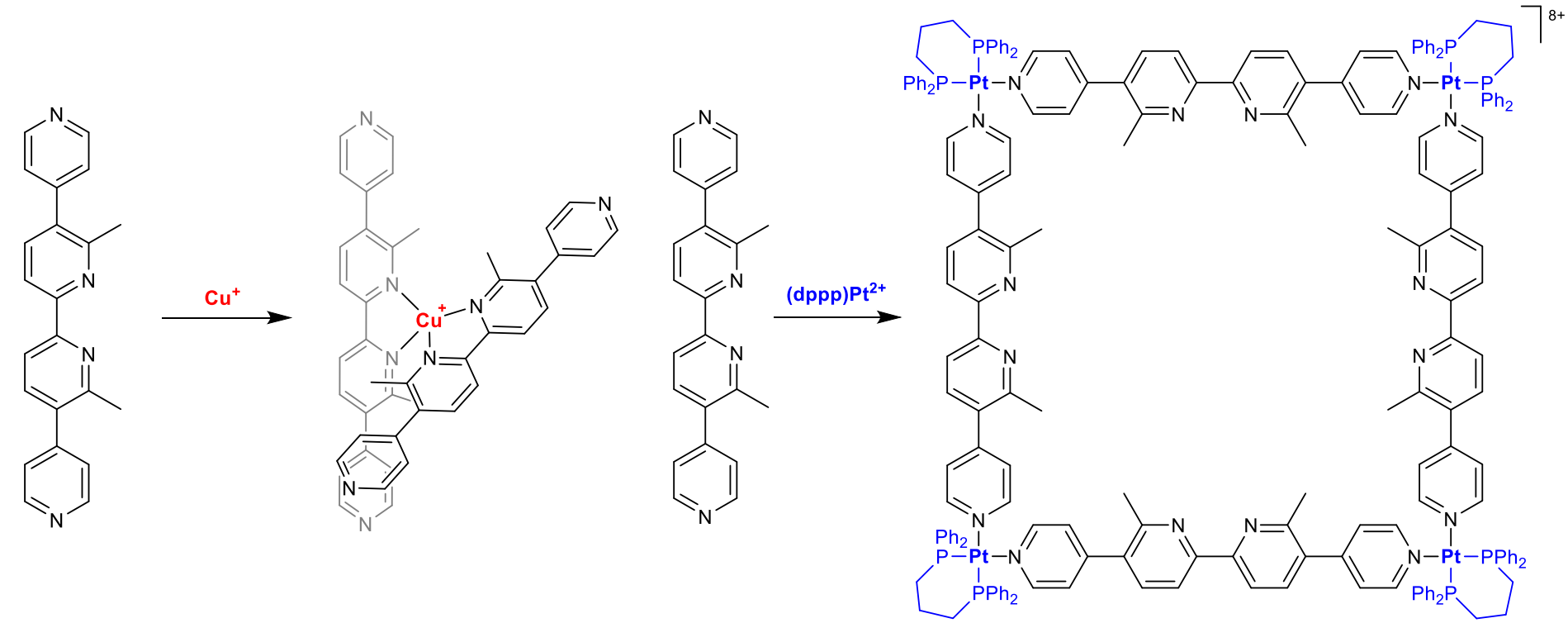
Sometimes referred to as ‘Solomon’s knot’ (e.g. Wikipedia) but technically not correct (= link)

# Molecular Solomon Links

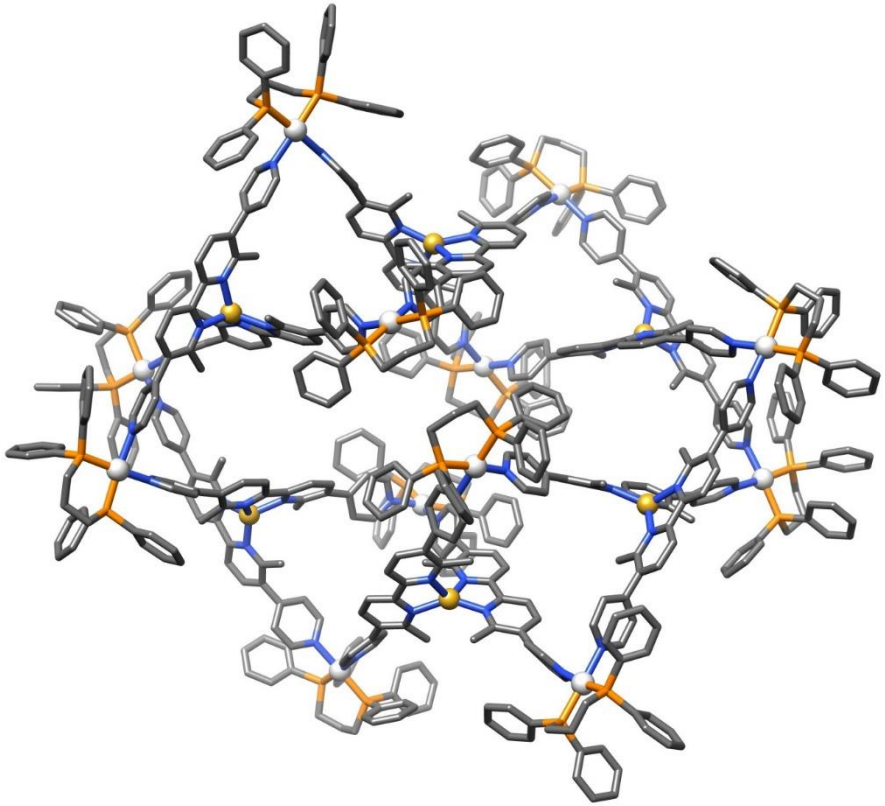


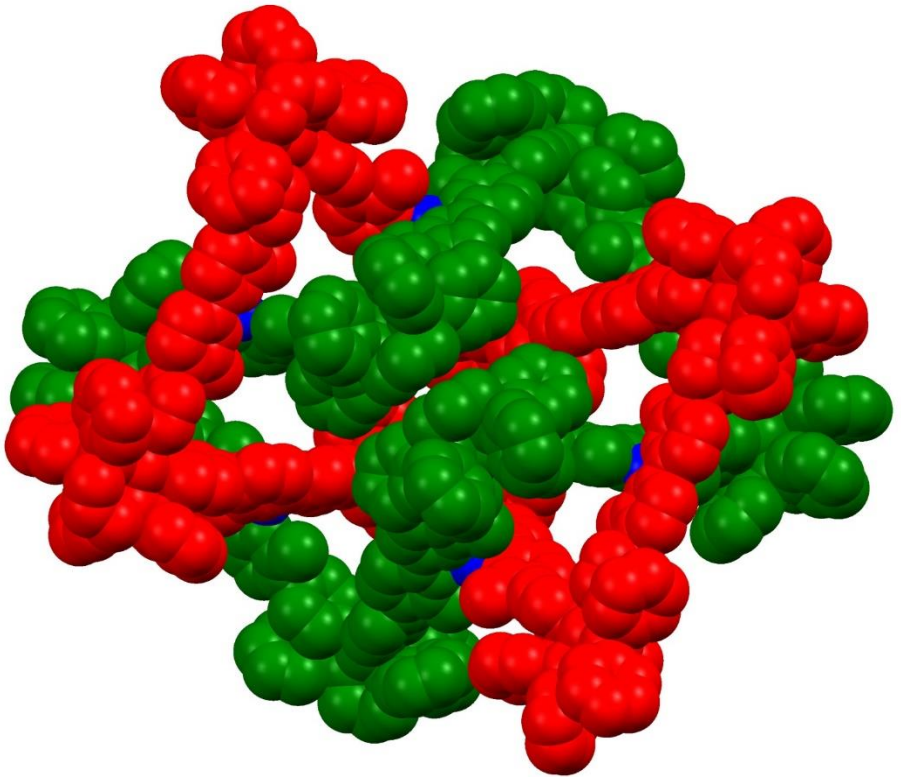
# Orthogonal Metal-Ligand Interactions



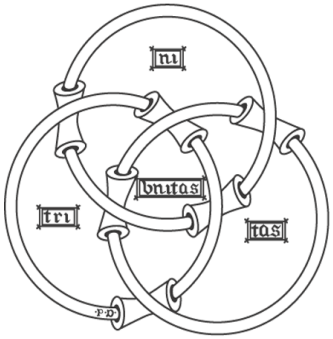
# A Giant Molecular Solomon's Link



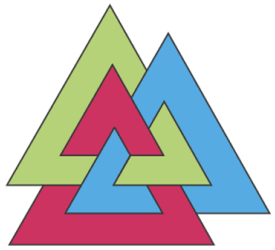


K. Severin *et al.*, *Angew. Chem. Int. Ed.* **2014**, *53*, 11261.

# Borromean Rings




Trinity



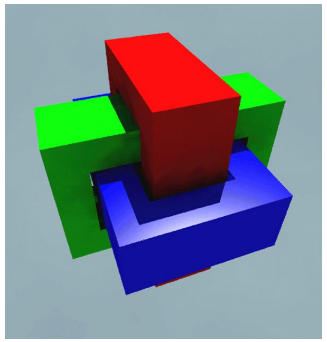
Hrungnir's heart

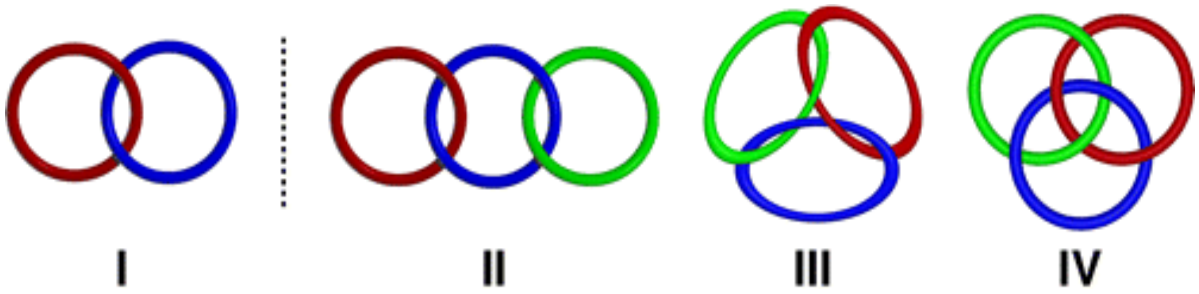
Japanese crest

Isola Bella contains an impressive Baroque palazzo built in the seventeenth century by Vitaliano Borromeo (1620-1690). There are many examples of the famous emblem in the house and the garden.

# Borromean Rings

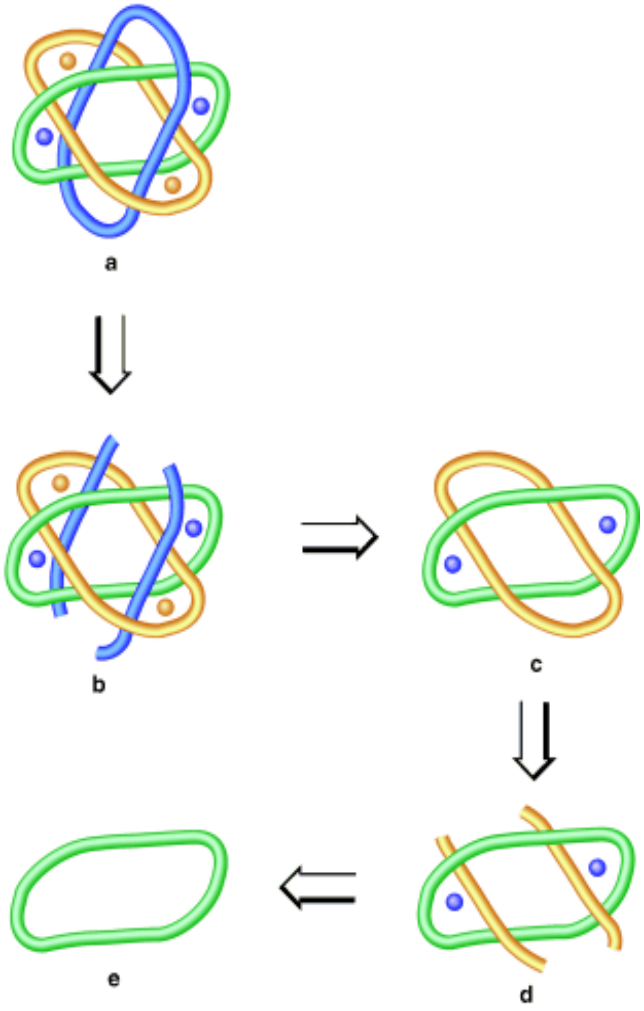
- Three rings figure.
- No two rings are linked.
- Inseparables but fall apart if one of them is broken.
- Highly symbolic figure.





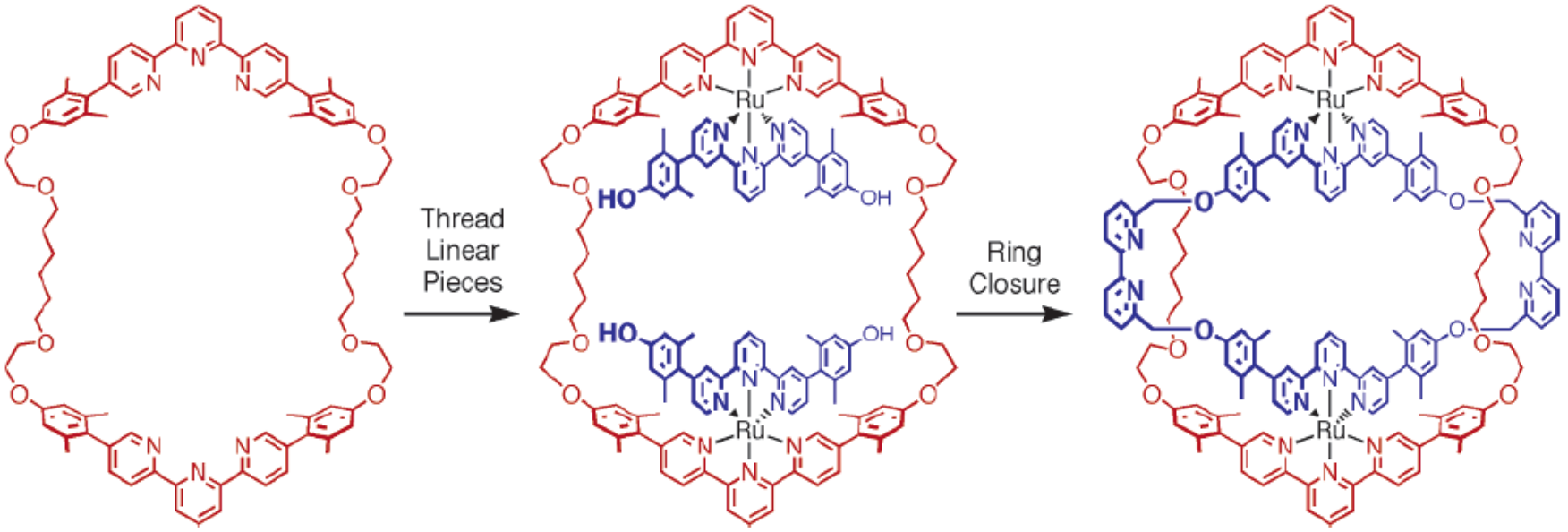

Some nontrivial two- and three-ring links, namely, (**I**) a [2]catenane, (**II**) a linear [3]catenane, (**III**) a cyclic [3]catenane,14 and (**IV**) the Borromean rings.

# Retrosynthetic Analysis



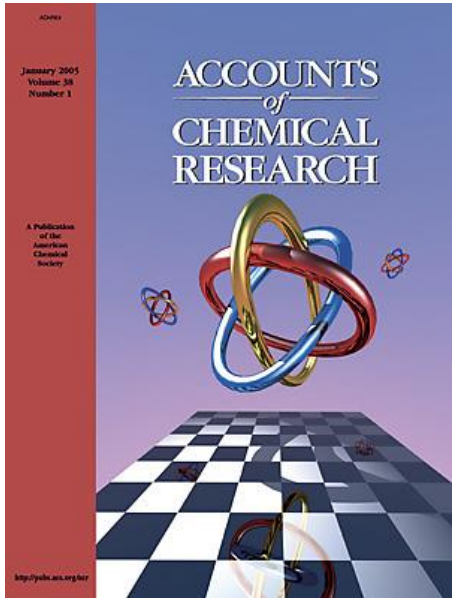

- Metal coordination used as template method.
- Combination of endo- and exo-oriented metal binding sites.
- Orthogonal orientation of rings.

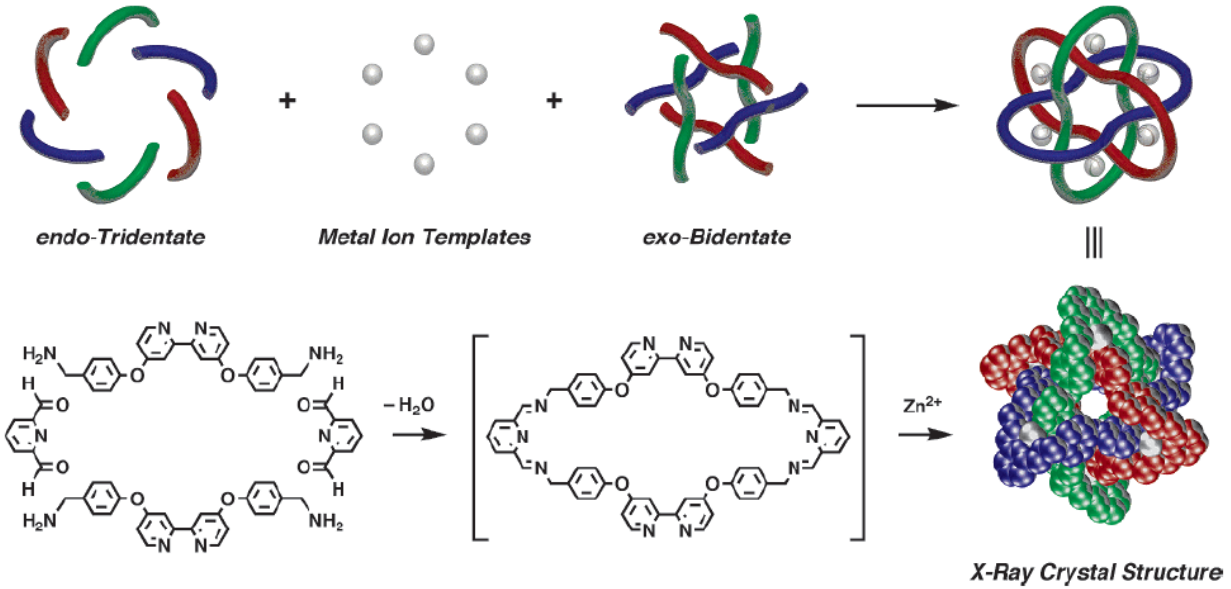
# Synthesis of a Ring in a Ring




J. S. Siegel et al. *Angew. Chem. Int. Ed.* **2003**, 42, 5702.

# Self-Assembly of Borromean Rings



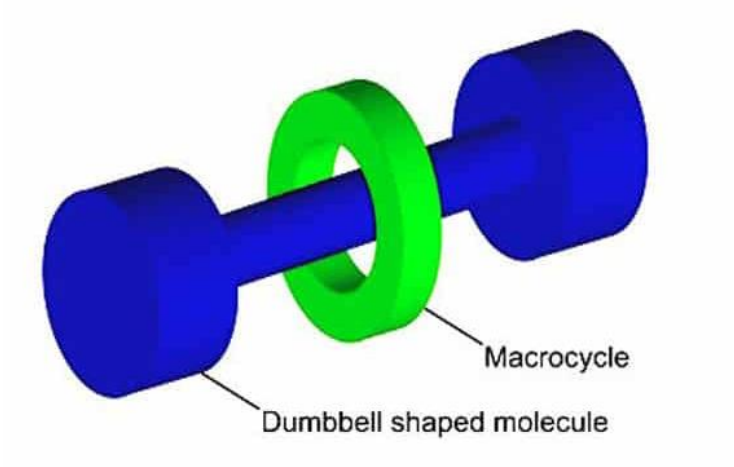



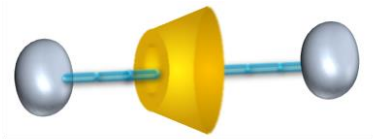

- Template directed self-assembly of 18 components.
- Macrocyclisation via reversible imine formation.
- Two endo-tridentate and two exo-bidentate ligands.
- Synthesis in methanol, 3 days reflux, 90% yield

Stoddart et al, *Science* **2004**, *304*, 1308.

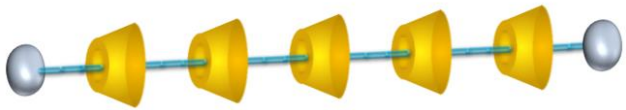
Stoddart et al, *Acc. Chem. Res.* **2005**, 38, 1.

# Rotaxanes



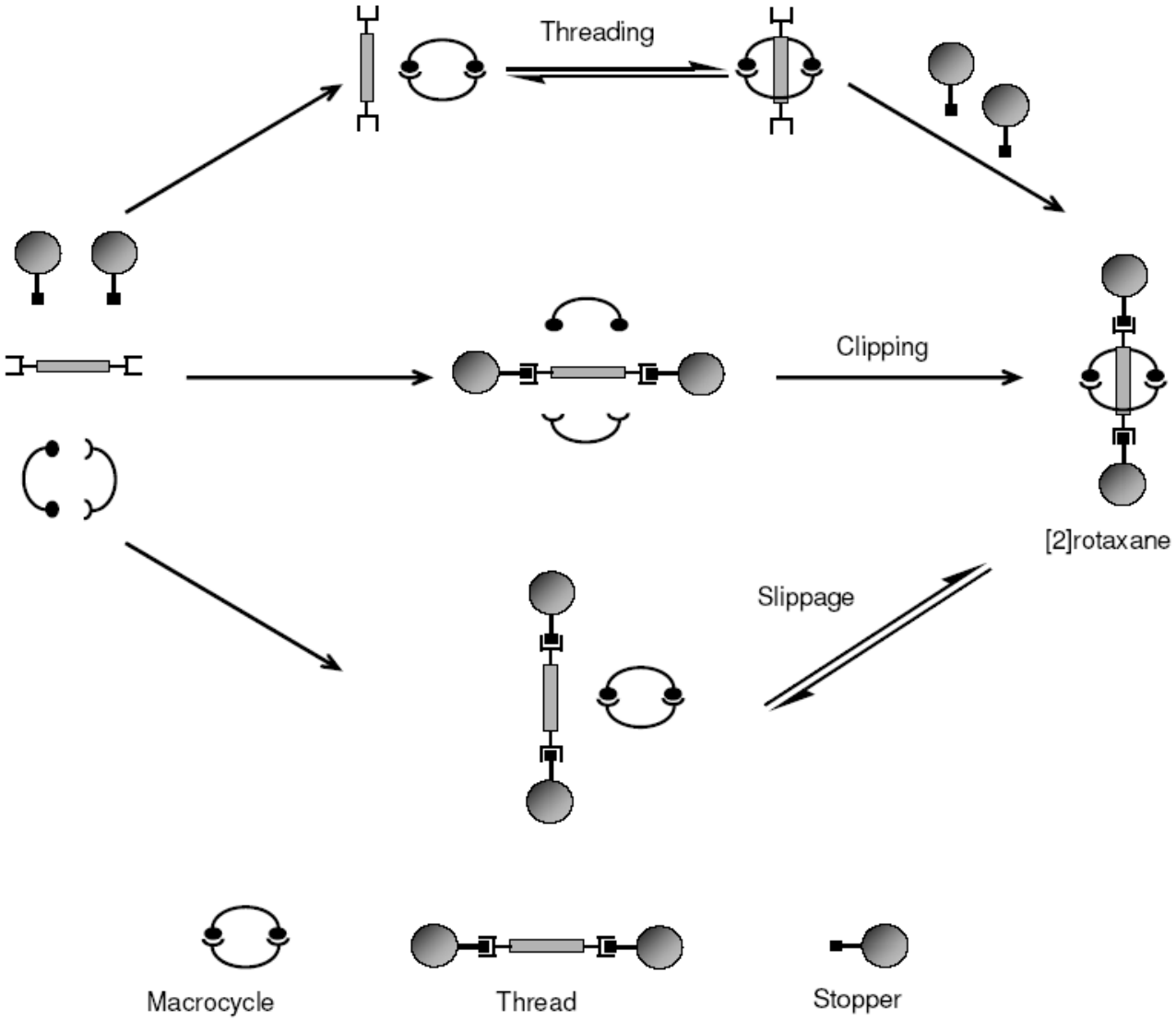



[2]rotaxane

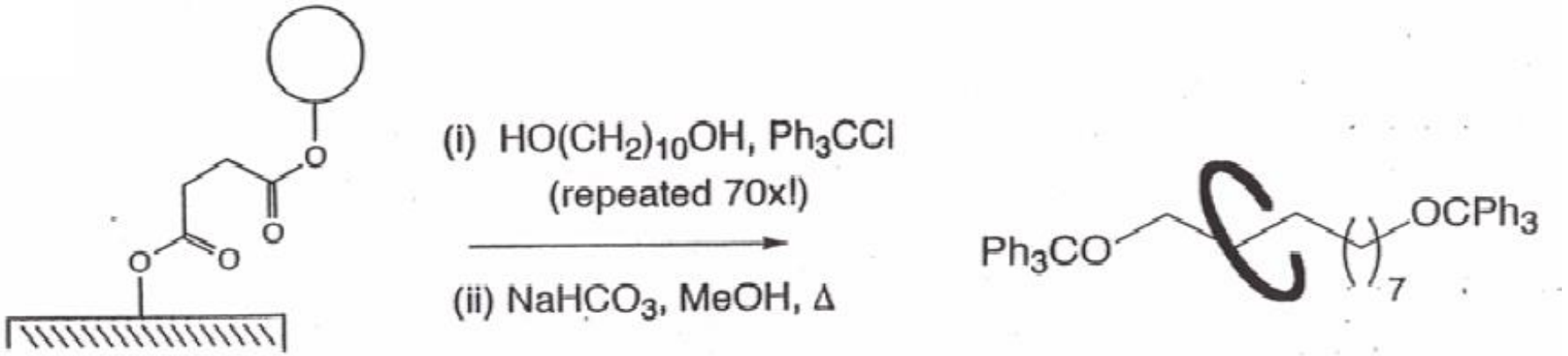


Polyrotaxane

# Strategies for the Synthesis of Rotaxanes



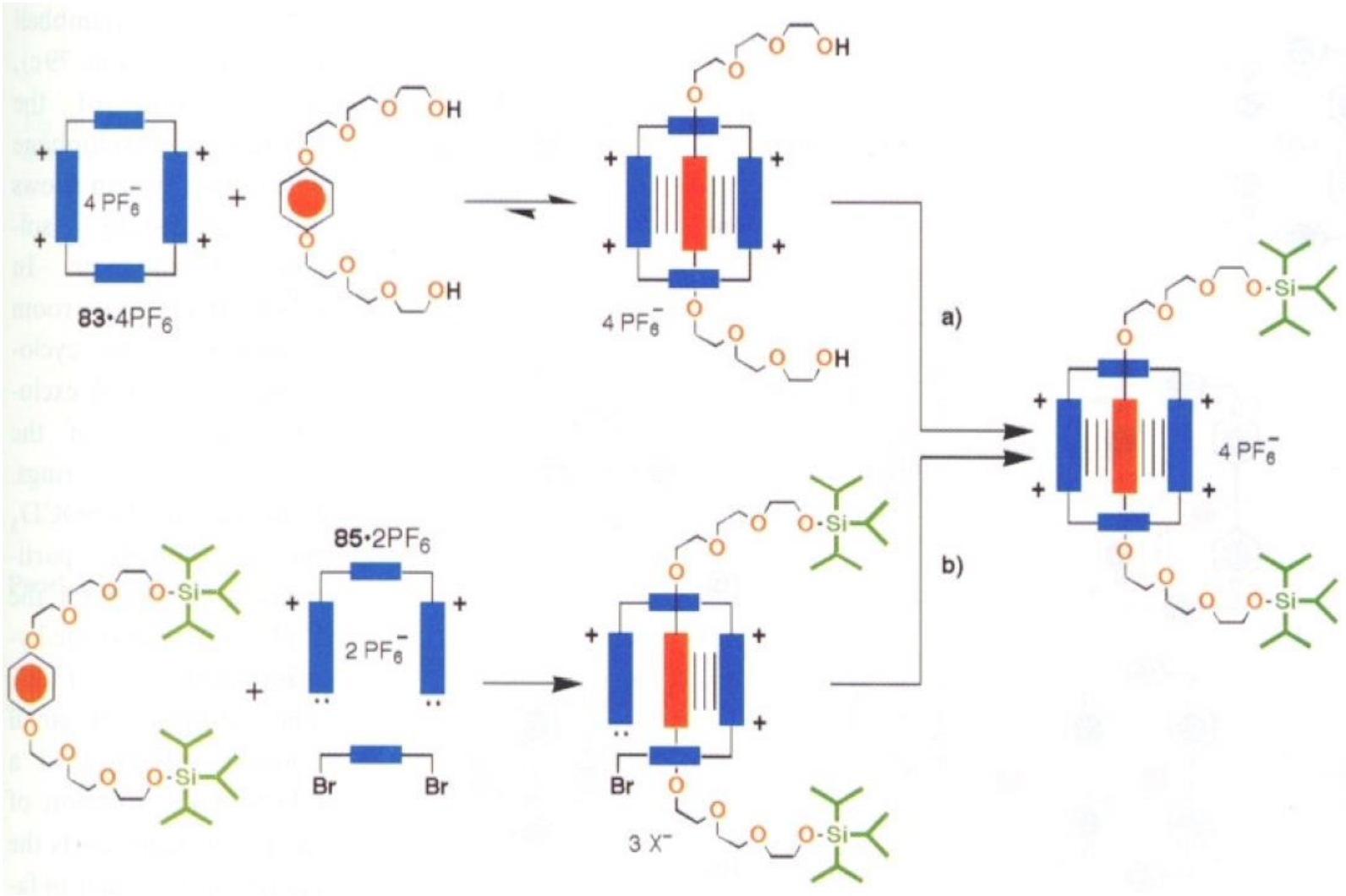
# Rotaxanes – The Early Years
# Statistical Approach



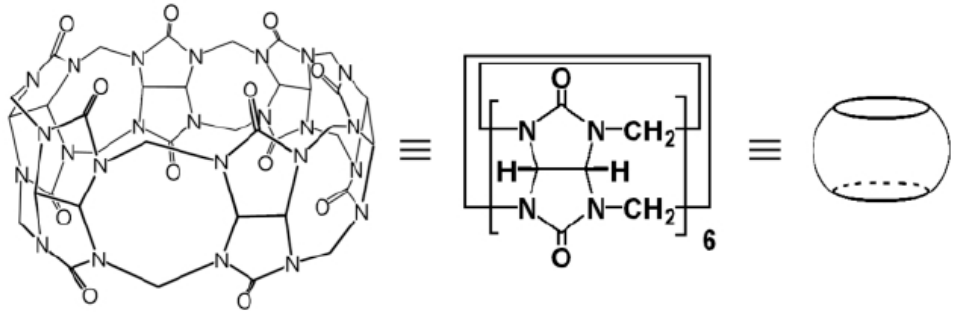

**Yield: 6 % !**

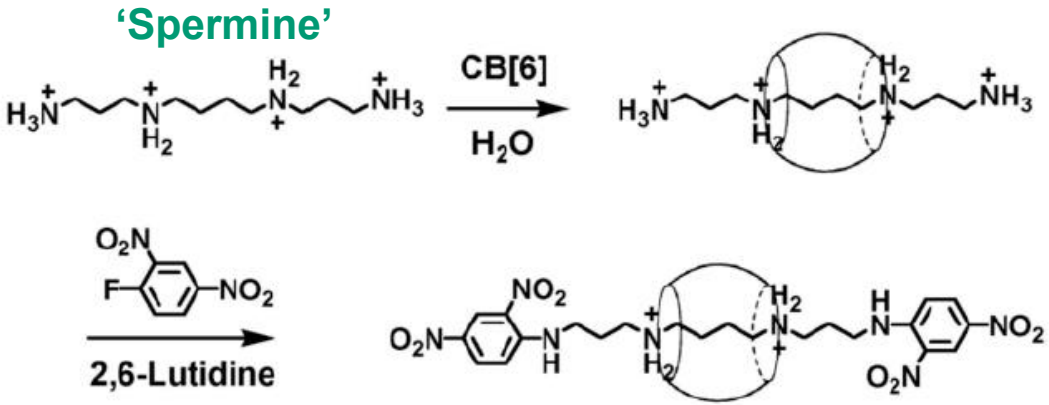
I. T. Harrison and S. Harrison, *J. Am. Chem. Soc.* **1967**, *89*, 5723.

# Paraquat-Based Rotaxanes



# Cucurbituril-Based Rotaxanes




Spermine was chosen as string in this synthesis because it has not only high affinity ($K = 10^7$) toward CB[6], but also terminal amine groups to attach bulky substituents. Interestingly, CB[6] itself is sparingly soluble in water, but the resulting pseudorotaxane is quite soluble in water. The drastically improved solubility upon formation of the pseudorotaxane allows the one-pot, high yield synthesis of the rotaxane.

K. Kim, *Chem. Soc. Rev.* **2002**, *31*, 96.

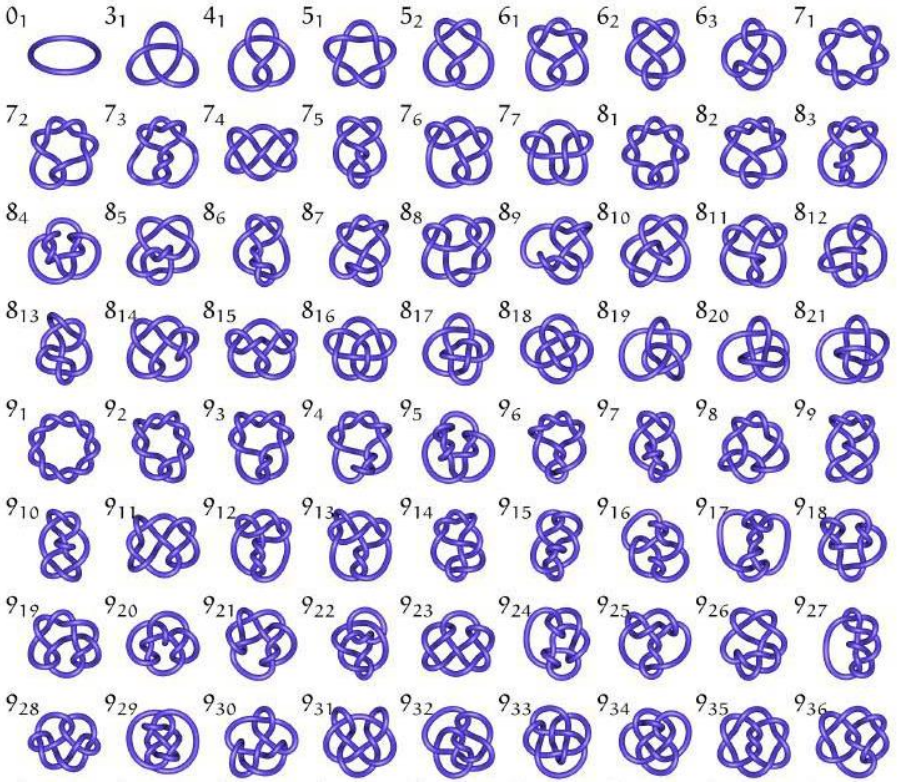
# Knots

a) b)

c) d)

e) f)

In daily life




Mathematical objects

# Molecular Knots

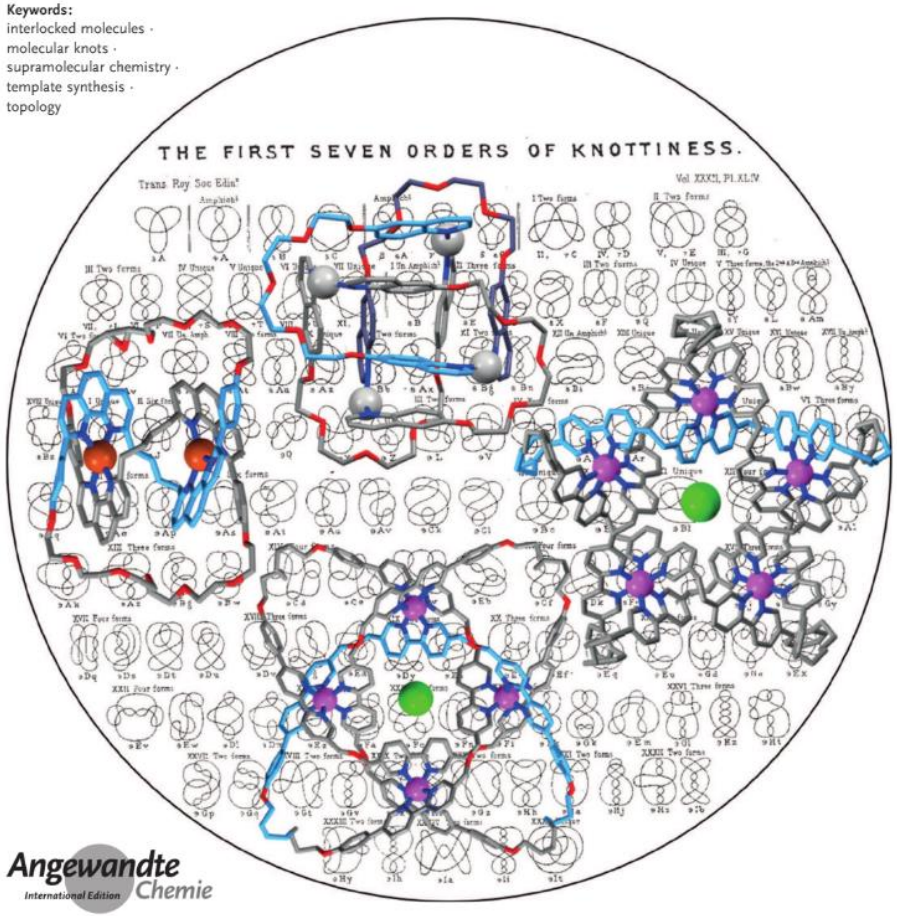
Molecular Topology

International Edition: DOI: 10.1002/anie.201702531
German Edition: DOI: 10.1002/ange.201702531

## Molecular Knots

*Stephen D. P. Fielden, David A. Leigh,* and Steffen L. Woltering*

**Keywords:**
interlocked molecules · molecular knots · supramolecular chemistry · template synthesis · topology

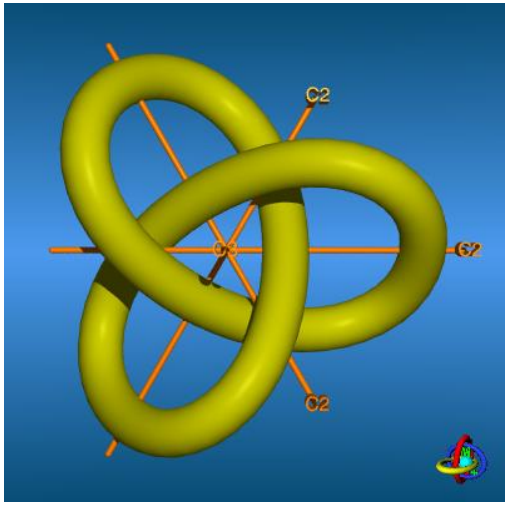


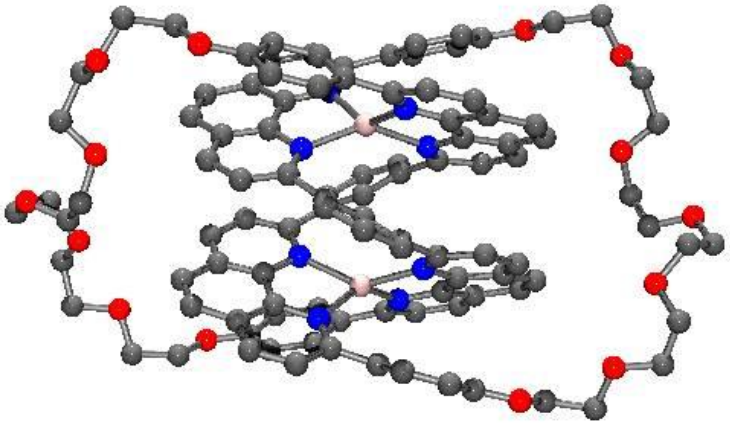

Angewandte International Edition Chemie

Angew. Chem. Int. Ed. **2017**.

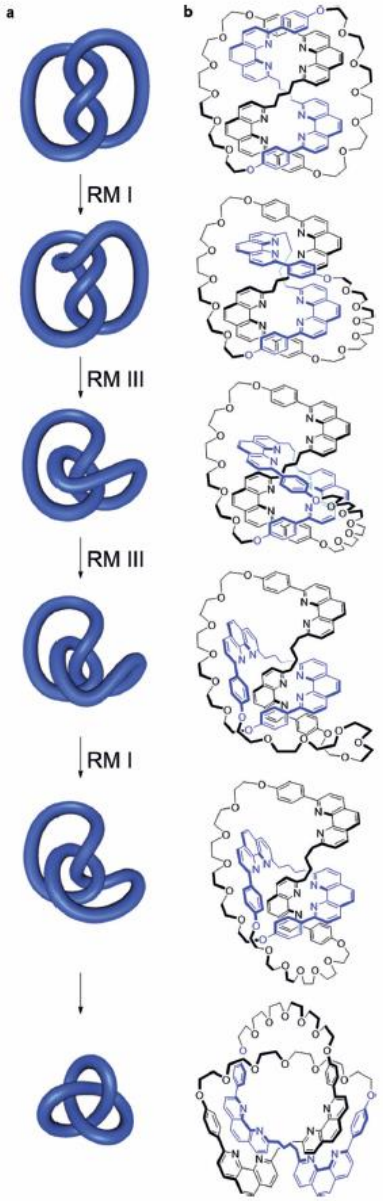
link

# Trefoil Knots

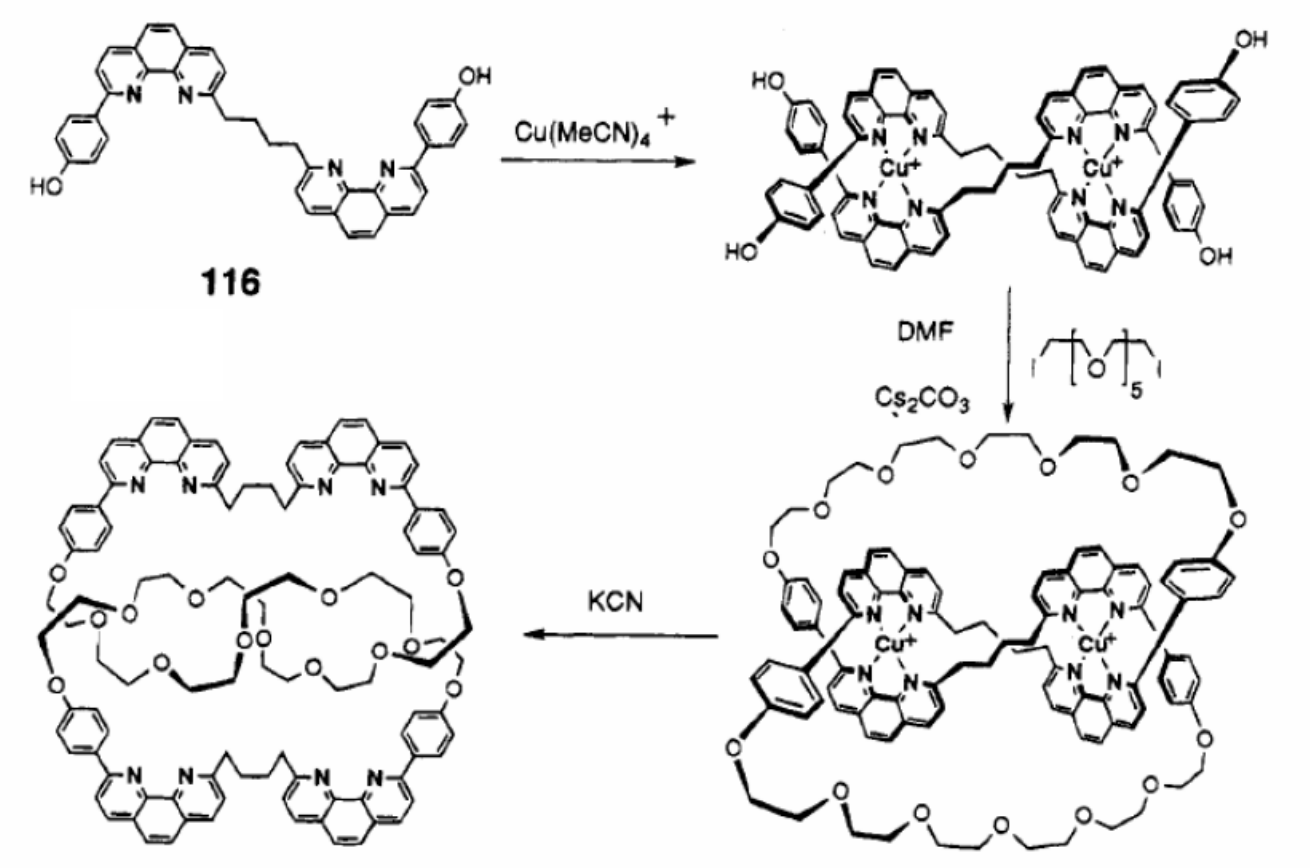


Topologically identical !

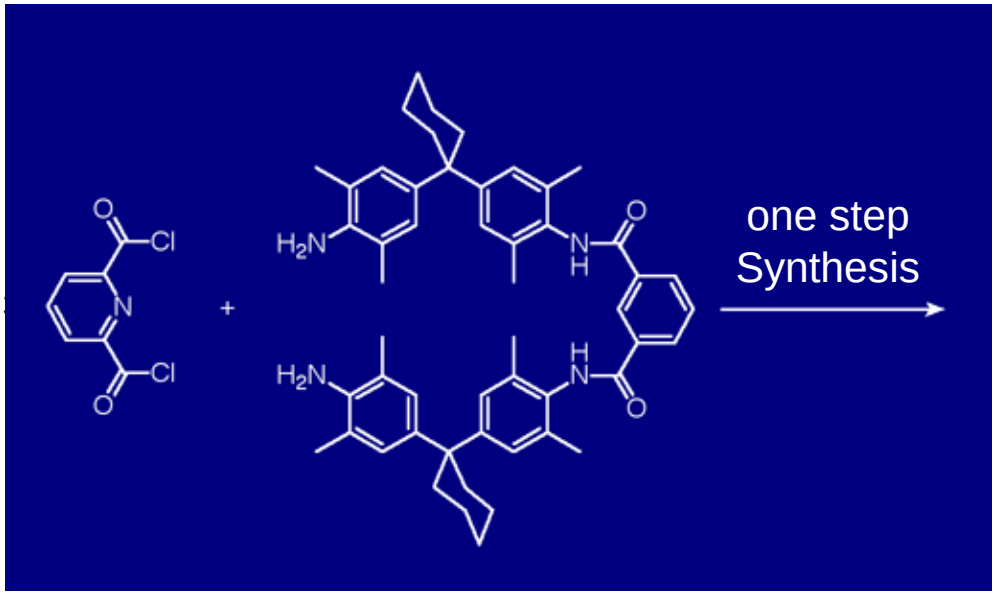


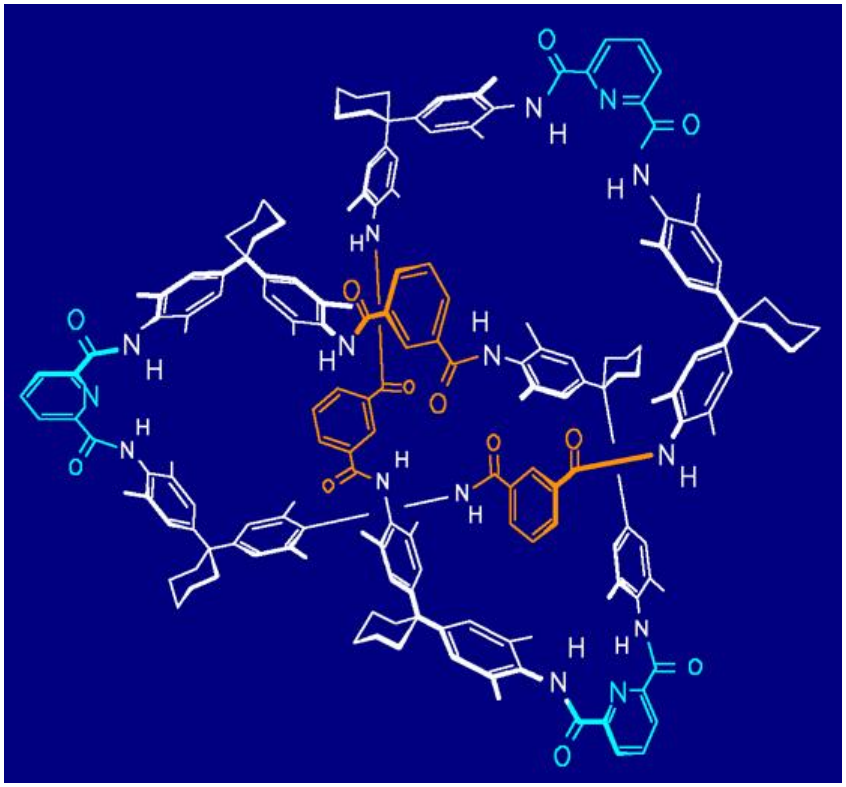
# Synthesis of a Trefoil Knot




- Considered as a major achievement in synthesis.
- Constructed around two Copper(I) centers.
- Double helix around Cu(I) ions.

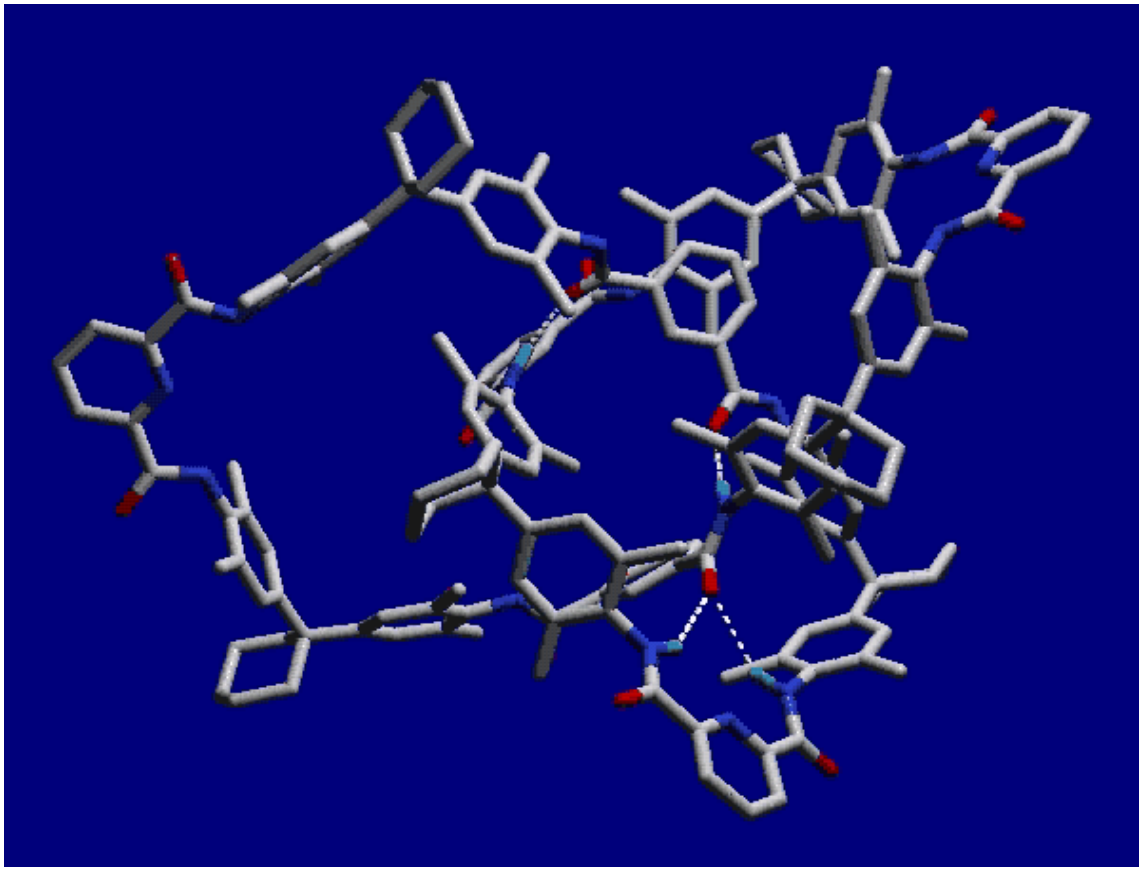
# One-Step Synthesis of a Trefoil Knot



F. Vögtle et al., *Angew. Chem. Int. Ed.* **2000**, *39*, 1616.

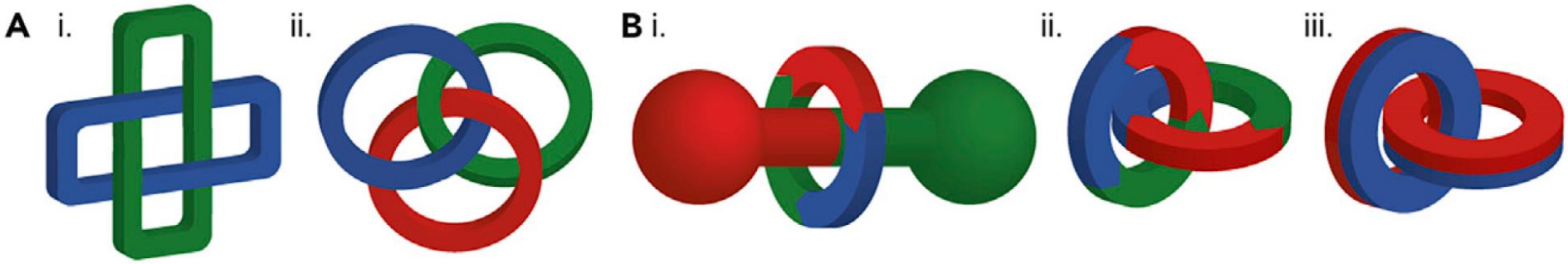
# Trefoil Knots



(X-ray)

Intramolecular hydrogen bonds drive the high-yield formation of the knot.

# Chiral Interlocked Molecules




(A) Unconditional topologically chiral molecules: (i) a Solomon link and (ii) a cyclic [3]catenane. (B) Conditionally mechanically chiral molecules: (i) a mechanically planar chiral [2]rotaxane, (ii) a topologically chiral [2]catenane, and (iii) an axially chiral [2]catenane.

J. R. J. Maynard and S. M. Goldup, *Chem.* **2020**, *6*, 1914.