Chimica Supramolecolare

4 cfu: 16 lezioni frontali, 32 ore
+ 2 cfu laboratorio, 24 ore

Prof. Francesco Peri

AA 2020-2021

Argomenti del corso (2021)

- Introduzione alla chimica supramolecolare: host-guest, autoassembly, chimica supramolecolare in natura
- Costanti di binding, termodinamica di binding
- Misura dei parametri di binding con metodi spettroscopici UV, NMR, fluorescenza, ITC ed altre tecniche)
- Selettività ed affinità
- Natura delle interazioni supramolecolari
- Hosts in soluzione:
- 1) crown ethers, criptandi, sferandi, complessazione cationi, esempi di interesse biologico
- 2) calixareni
- 3) cucurbiturili
- 4) ciclodestrine
- 5) ciclofani, criptofani, carcerandi, emicarcerandi
- Per tutti gli hosts sopra citati collegamenti con self-assembly e machine molecolari, esempi biologici: enzimi artificiali, canali ionici, siderofori
- Autoassemblaggio: catenani e rotaxani
- Molecular devices: elettronica molecolare (circuiti, interruttori molecolari), fotochimica supramolecolare. Semiochimica, machine molecolari (muscoli molecolari)
- Sistemi BIOMIMETICI: catalisi supramolecolare ed altri sistemi descritti durante il corso

Dal Syllabus

- **D1 - CONOSCENZA E CAPACITÀ DI COMPRENSIONE**

- Al termine di questa attività formativa, lo studente dovrà dimostrare di essere in grado di leggere un articolo scientifico che tratti della sintesi e caratterizzazione di sistemi supramolecolari (chimica host-guests, sensori, sistemi autoassemblanti e biomimetici, macchine molecolari). Per raggiungere questo scopo durante il corso vengono analizzati una serie di articoli molto recenti che spiegano ed esemplificano gli argomenti trattati. Il corso fornisce allo studente conoscenze specifiche nei seguenti ambiti:

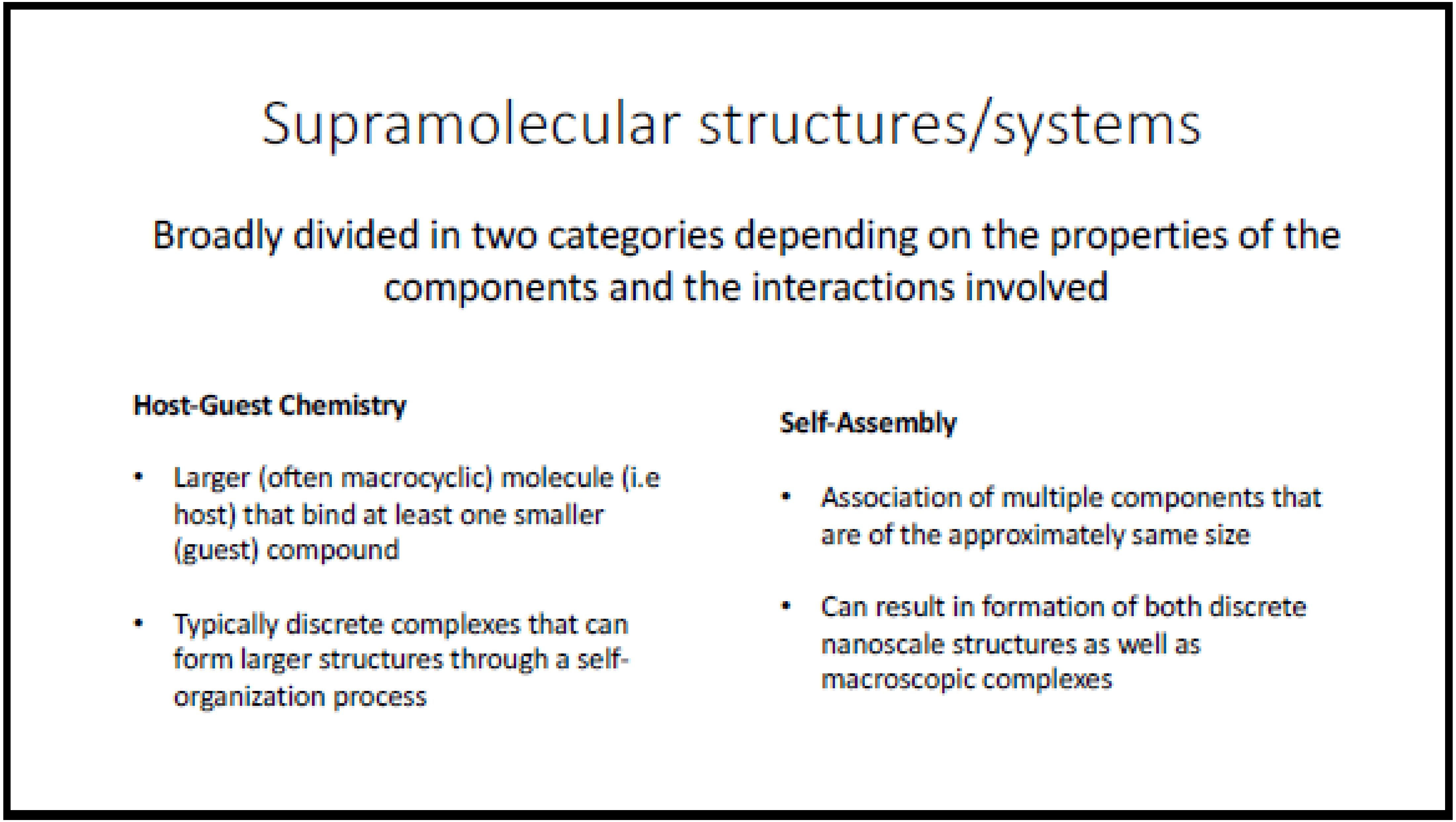
- 1 **Metodi spettroscopici** (NMR, **FLUORESCENZA**, UV, IR, microcalorimetria, Surface Plasmon Resonance, Massa) per la determinazione delle interazioni molecolari
- 2 **Metodi di sintesi dei principali sistemi host** (cavitandi, sferandi, macrocicli)
- 3 **Principali applicazioni della chimica host-guest**

- D2 - CAPACITÀ DI APPLICARE CONOSCENZA E COMPRENSIONE
- Al termine di questa attività formativa, lo studente dovrà dimostrare di essere in grado di:
- 1 Disegnare una molecola host dato un guest
- 2 Immaginare sistemi host-guest in diversi ambiti applicativi
- 3 Immaginare la tecnica analitica più indicata a studiare un sistema host-guest

- D3 - AUTONOMIA DI GIUDIZIO
- Al termine di questa attività formativa, lo studente dovrà dimostrare di essere in grado di leggere criticamente un articolo scientifico, analizzarne i contenuti, giudicare eventuali debolezze e punti di forza dell'articolo, prevedere possibili limitazioni sperimentali ed applicative, immaginare in modo creativo ulteriori sviluppi della tecnica presentata dall'articolo. Il docente stimola la discussione critica degli articoli presentati in classe in modo da abituare lo studente a questo tipo di analisi della letteratura scientifica.
- Alcuni studenti potranno presentare approfondimenti di argomenti specifici che sono poi discussi insieme in classe.

Lesson 1

- Introduzione al corso ed alla chimica supramolecolare
- La chimica supramolecolare in natura, e la chimica supramolecolare biomimetica
- Laboratori didattici



Supramolecular structures/systems

Broadly divided in two categories depending on the properties of the components and the interactions involved

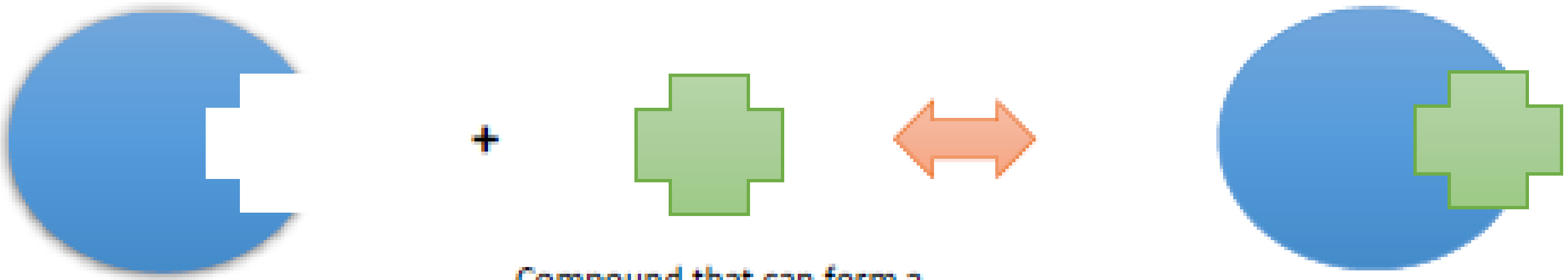
Host-Guest Chemistry

- Larger (often macrocyclic) molecule (i.e host) that bind at least one smaller (guest) compound
- Typically discrete complexes that can form larger structures through a self-organization process

Self-Assembly

- Association of multiple components that are of the approximately same size
- Can result in formation of both discrete nanoscale structures as well as macroscopic complexes

Host-Guest Chemistry – the terminology



"Host"
(Receptor, Ligand)

Compound capable of recognizing and binding a guest in defined confinement by means of non-covalent interactions, e.g: crown ether or enzyme.

"Guest"
(Substrate)

Compound that can form a complex with a host E.g. :

- Metal ion
- Co-factor
- Hormone

Supramolecule

The complex formed can also be referred to as:

- "Host-guest komplex"
- "Inclusion komplex"
- "Clathrate komplex"

Libri consigliati:

An Introduction to Supramolecular Chemistry

Peter J. Cragg

Supramolecular Chemistry

Steel, Atwood

Wiley

C’e’ in biblioteca

Introduction

The development of supramolecular chemistry dates back to 1987 when Lehn, Cram, and Pedersen won the Nobel Prize on account of their leading discoveries in the host−guest systems.1 Ever since its discovery, the concept of supramolecular chemistry has attracted lots of attention from chemists, biologists, and material scientists, where they utilize the noncovalent interactions, including hydrogen-bonding interaction, π−π stacking interaction, electrostatic interaction, van der Waals force, and hydrophobic/hydrophilic attraction, to explain the systems from easy to complicated

Jean-Marie Lehn, premio Nobel 1987 per il concetto di chimica supramolecolare

SUPRAMOLECULAR CHEMISTRY – SCOPE AND PERSPECTIVES MOLECULES - SUPERMOLECULES -MOLECULAR DEVICES

Nobel lecture, December 8, 1987 by JEAN-MARIE LEHN

.

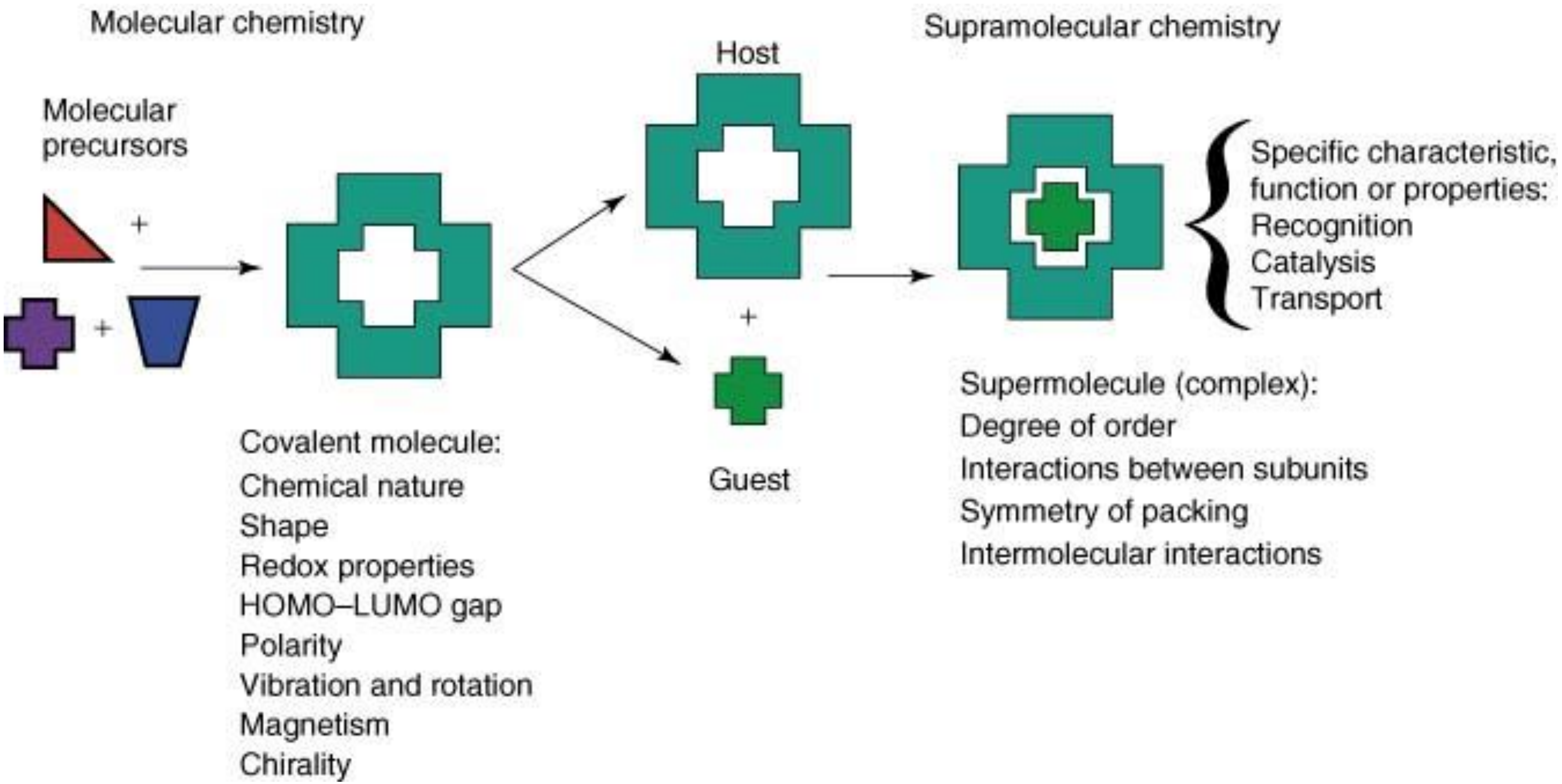
Supramolecular chemistry is the chemistry of the intermolecular bond, covering the structures and functions of the entities formed by association of two or more chemical species.

Molecular chemistry, the chemistry of the covalent bond, is concerned with uncovering and mastering the rules that govern the structures, properties and transformations of molecular species.

Supramolecular chemistry may be defined as “chemistry beyond the molecule”, bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces. Its development requires the use of all resources of molecular chemistry combined with the designed manipulation of non-covalent interactions so as to form supramolecular entities, supermolecules possessing features as well delined as those of molecules themselves. One may say that supermolecules are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond.

Jean Marie Lehn, Nobel lecture, 1987

Molecular (synthetic) vs supramolecular chemistry

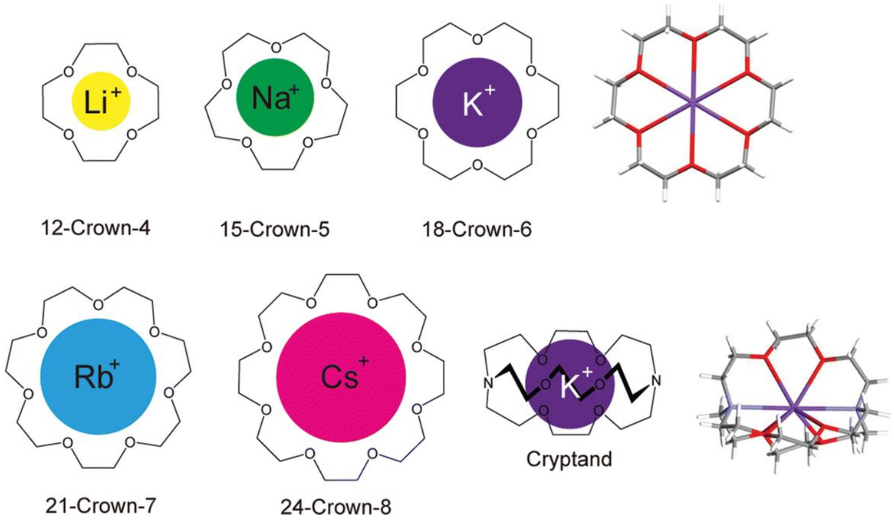


Covalent molecule:
Chemical nature
Shape
Redox properties
HOMO–LUMO gap
Polarity
Vibration and rotation
Magnetism
Chirality

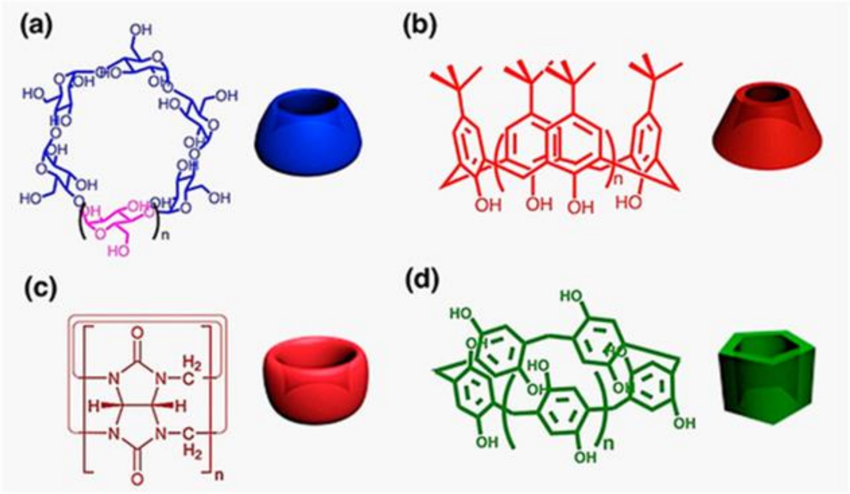
Specific characteristic, function or properties:
Recognition
Catalysis
Transport

Supermolecule (complex):
Degree of order
Interactions between subunits
Symmetry of packing
Intermolecular interactions

Definizione di host e guest



Crown ethers hosts e ioni metallici guests

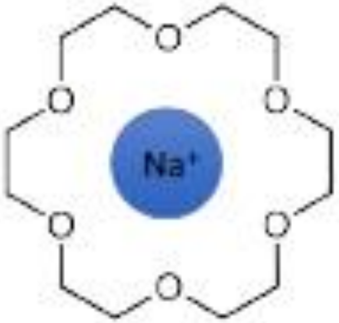


Altri hosts: ciclodestrine (CD), calixareni, cucurbiturili (CB),

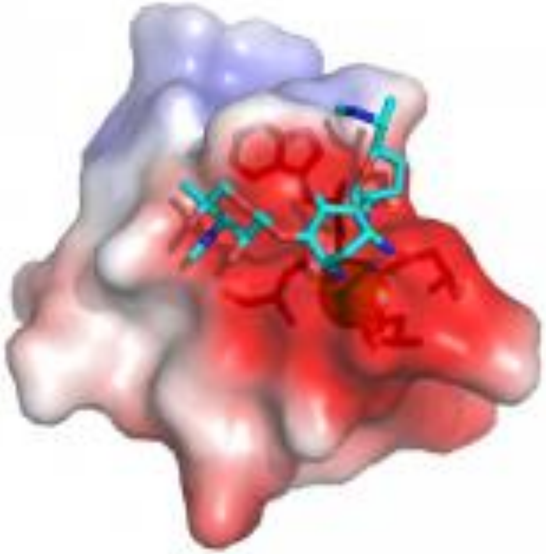
- Una molecola host lega una molecola guest formando un complesso host.guest
- L'host è una molecola organica (inclusi gli enzimi)in genere un macrociclo con una cavità centrale
- Più formalmente l'host è una molecola con binding sites convergenti (donatori di Lewis, legami ad idrogeno), il guest con binding sites divergenti (catione o acido di Lewis sferico, oppure na accettore di legame ad idrogeno)

… for example

Host: 18-crown-6
Guest: Na^+



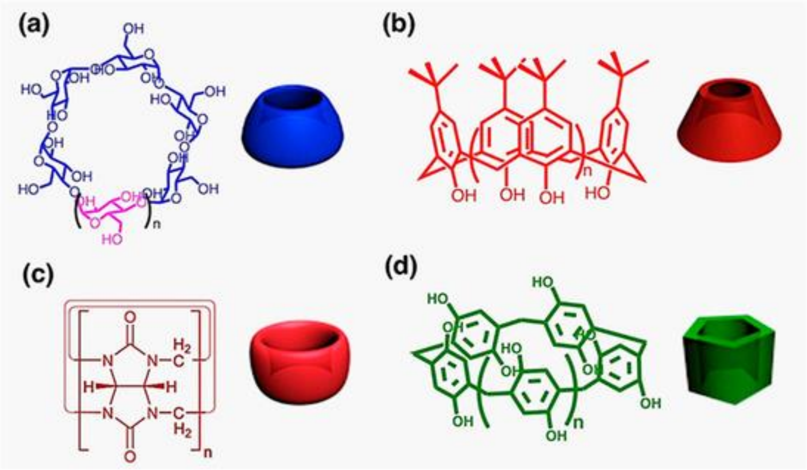
Host: Protein receptor
Guest: drug



(not drawn to scale)

Hosts that bind cations, anions and neutral molecules

- Crown ethers
- Podands and lariat ethers
- Cryptands
- Organometallic receptors
- Spherands
- Calixarenes and resorcinarenes
- Cucurbiturils
- Cyclodextrins
- Molecular clefts and tweezers
- Cyclophanes
- Carcerands and hemicarcerands
- Molecular cages and metallamacrocylces



Dynamic hosts

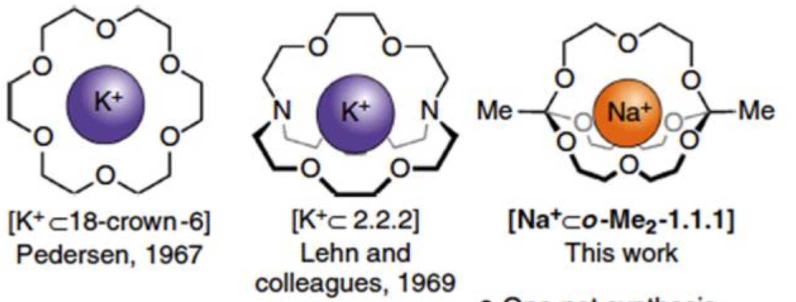
Increasing dimensions of the guest, from static to dynamic host/guest chemistry

- From alkali metals to anions to neutral molecules to proteins

cryptands

statics

dynamics



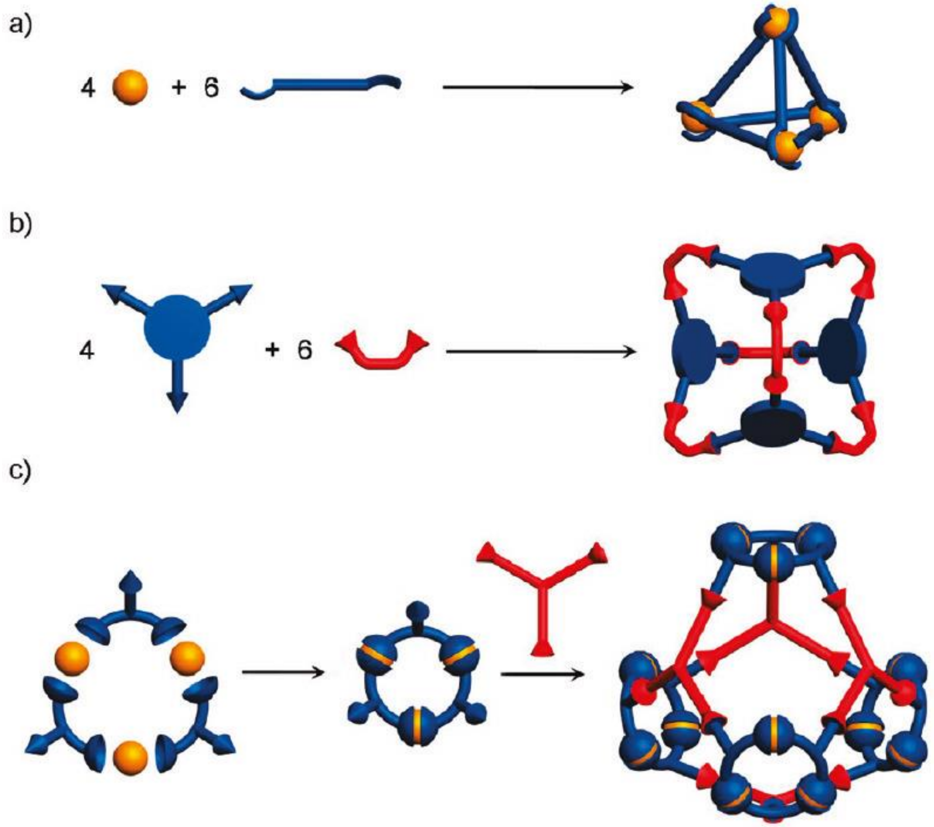
$[K^+ \subset 18\text{-crown-6}]$
Pedersen, 1967

$[K^+ \subset 2.2.2]$
Lehn and colleagues, 1969

$[Na^+ \subset o\text{-}Me_2\text{-}1.1.1]$
This work

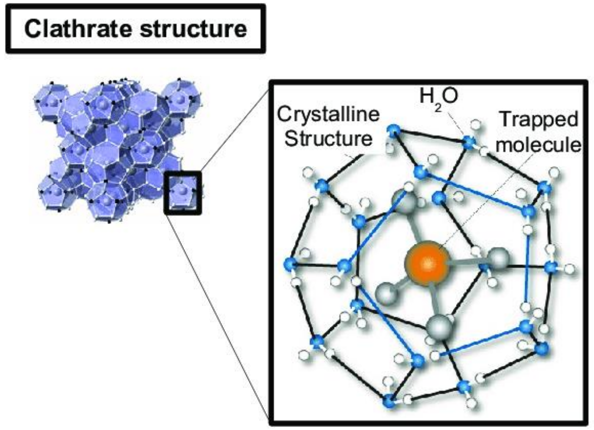
- One-pot synthesis
- Constitutionally dynamic
- Controlled guest release

Dynamic cages

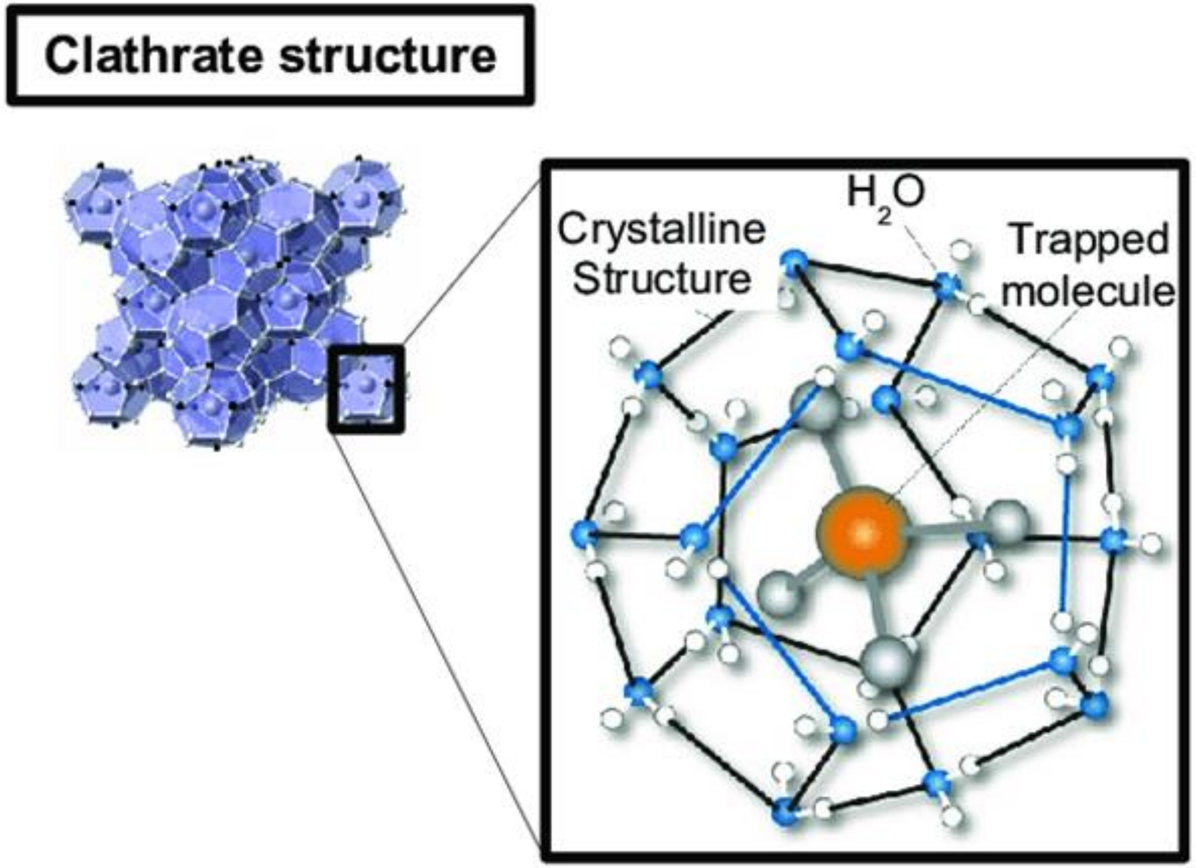


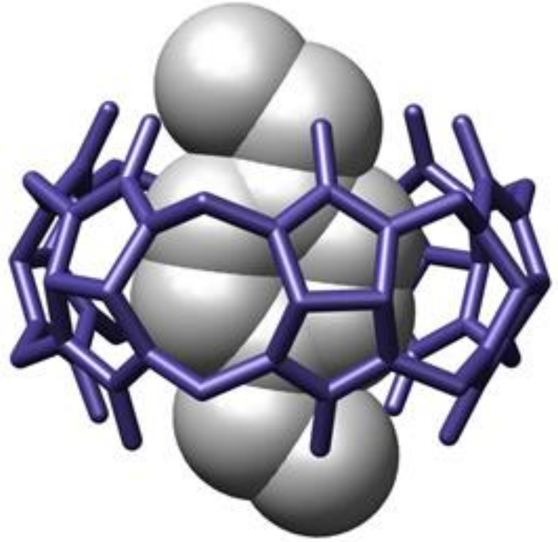
Gli hosts inorganici

- L'host può essere inorganico (host-guest dello stato solido):
- Zeoliti
- Poliossometallati
- Questi hosts sono clatrati, cioè il guest viene ospitato in uno spazio intermolecolare
- I clatrati ono stabili allo stato solido cristallino ma si dissociano in soluzione (inclusion chemistry)
- Gli hosts organici funzionano allo stato solido ma anche in soluzione



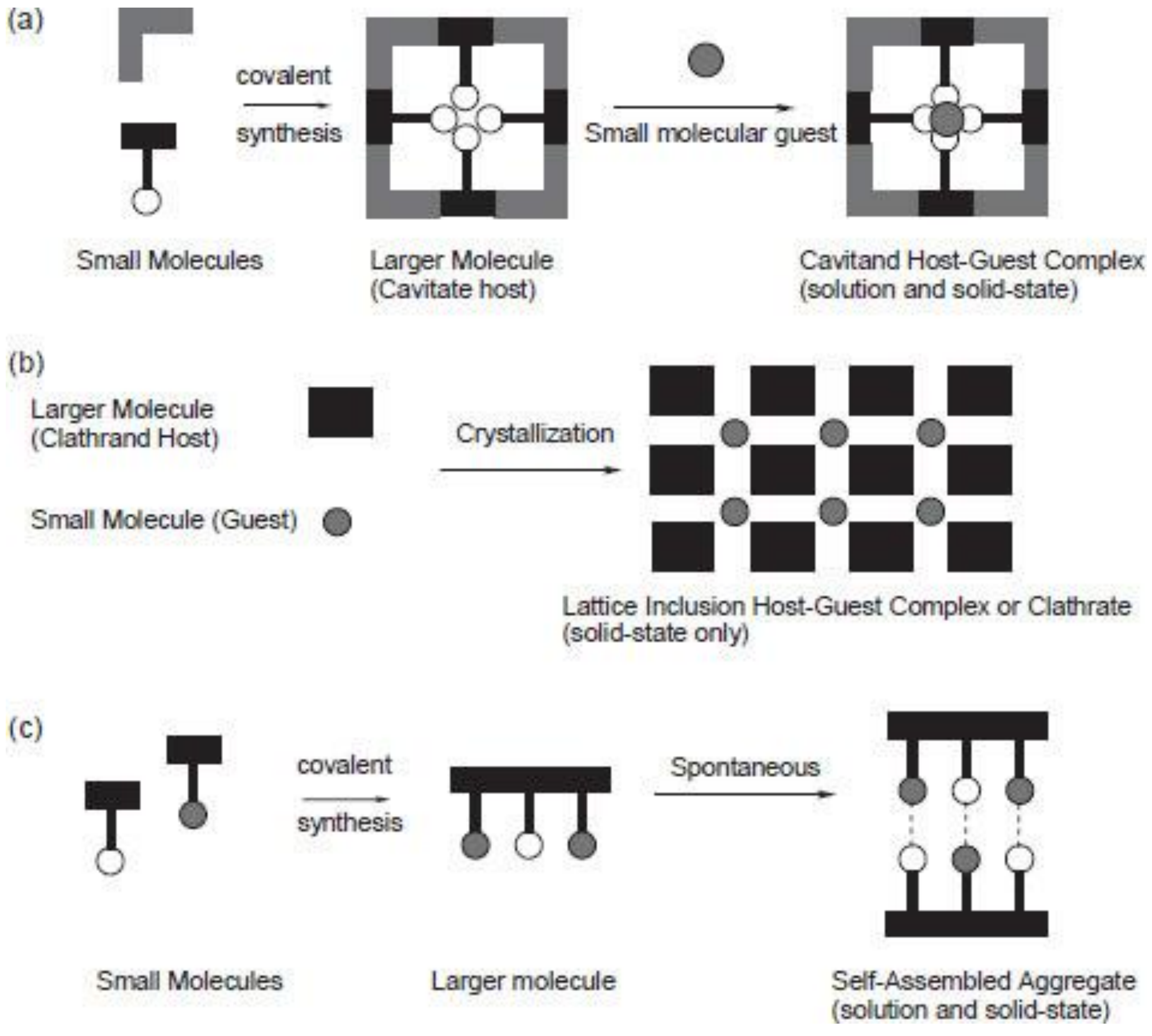
Soldi phase vs solution phase H-G chemistry





Host-guest complex in solution: Cucurbituril + organic guest

1) Definition of supramolecular chemistry host/guest (cavitands, clathrates, templates)

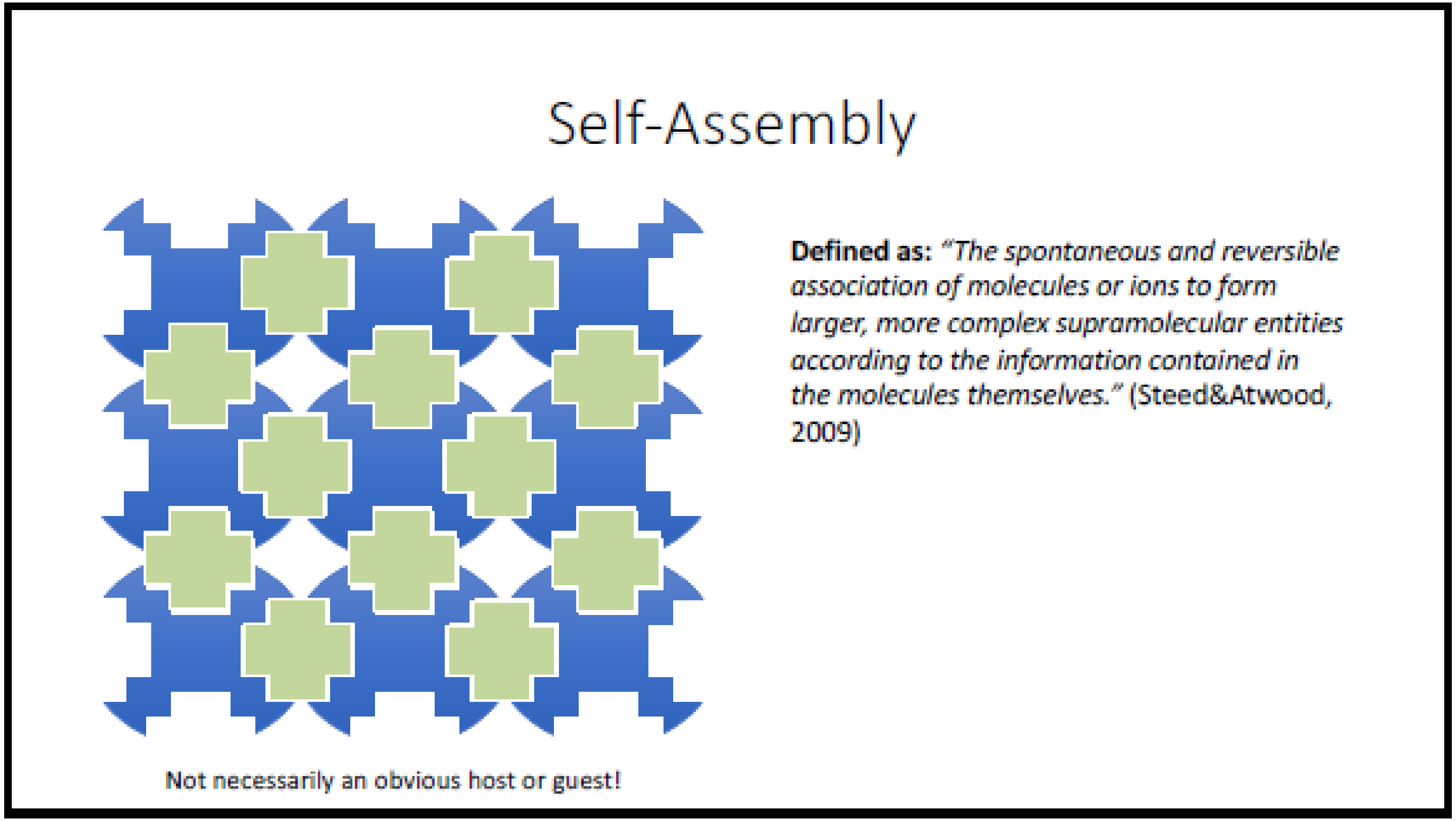


SOLUTION and solid state

SOLID-STATE only

SELF-ASSEMBLY

Self-assembly



Self-Assembly

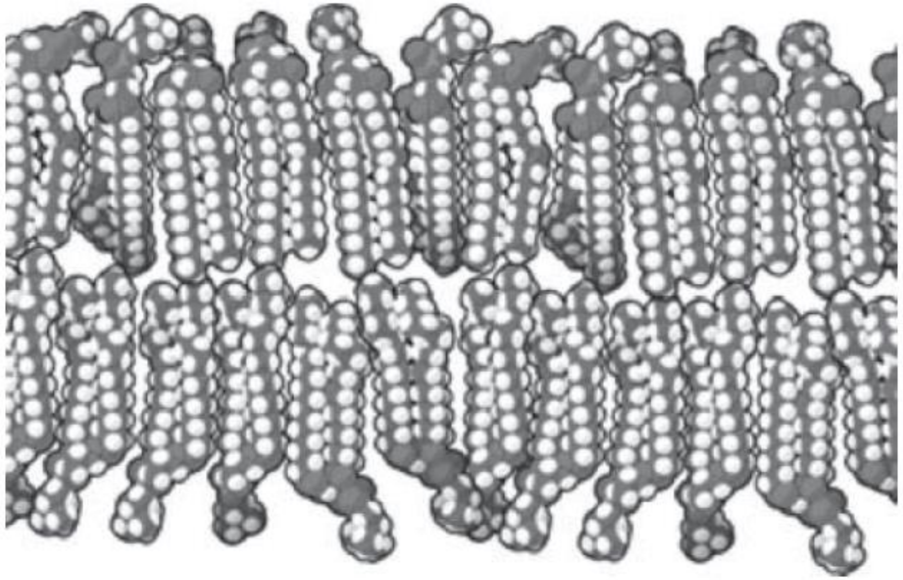
Defined as: *"The spontaneous and reversible association of molecules or ions to form larger, more complex supramolecular entities according to the information contained in the molecules themselves."* (Steed&Atwood, 2009)

Not necessarily an obvious host or guest!

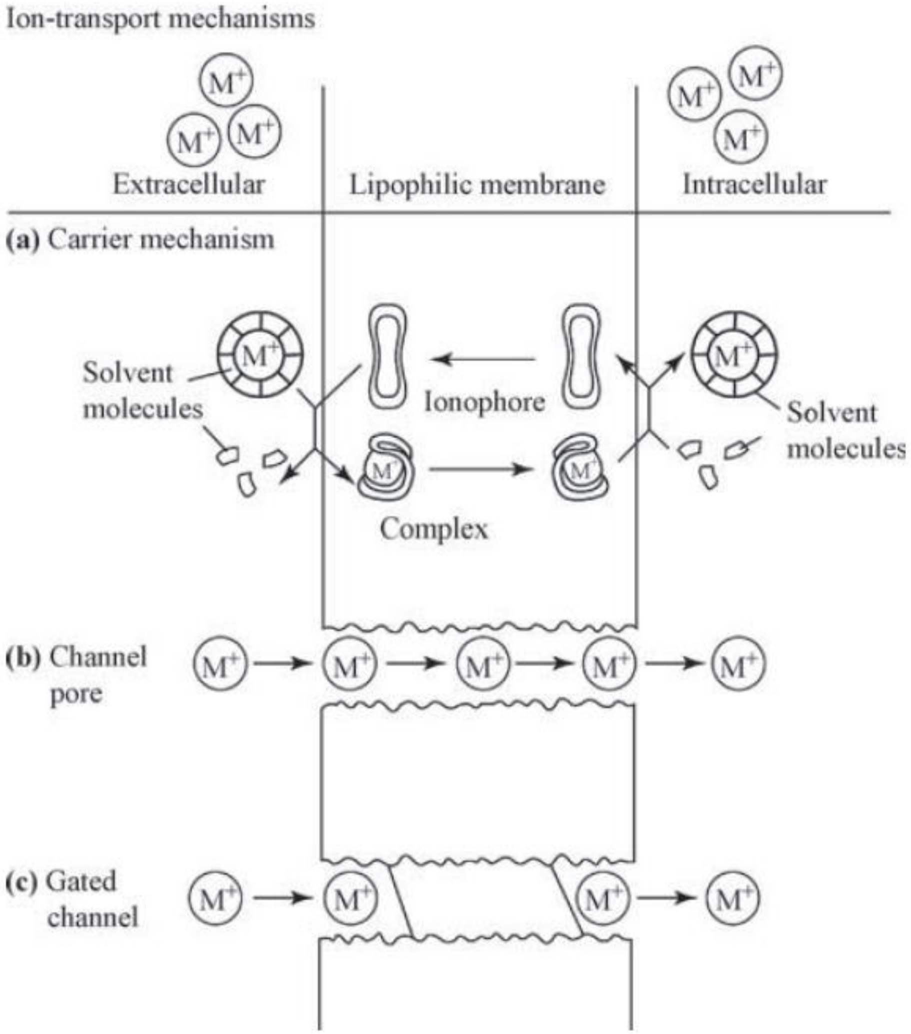
La chimica supramolecolare in natura…ed i sistemi supramolecolari biomimetici

- Sistemi host-guest: canali ionici, trasportatori di ioni, enzimi/substrati recettori/ligandi
- Sistemi autoassemblanti: DNA, proteine, capsidi dei virus
- Sistemi che producono movimento: actina e miosina nelle fibre muscolari
- Sistemi che rispondono a stimoli esterni: cellule
- Sistemi che si rigenerano: tessuti
- Le molecole della vista: switch molecolari indotti dalla luce
- I chimici supramolecolari imitano la natura e talvolta cercano di migliorarla
- I sistemi host-guest si autoassemblano: emergono nuove proprietà

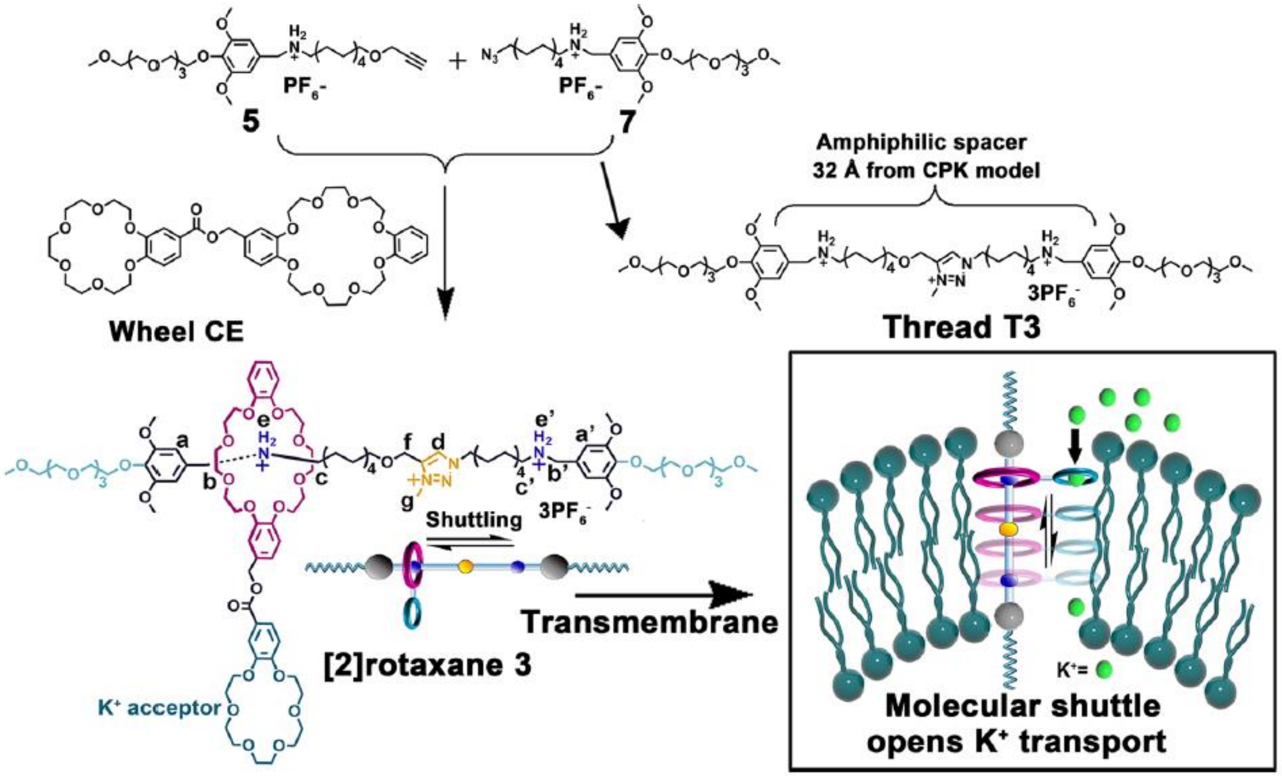
Trasporto di ioni e molecole attraverso la membrana cellulare



hematic diagram of a phospholipid biological membrane (5–6 nm in width).



Trasportatori di ioni attraverso membrane ottenuti artificialmente con la chimica supramolecolare

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Article
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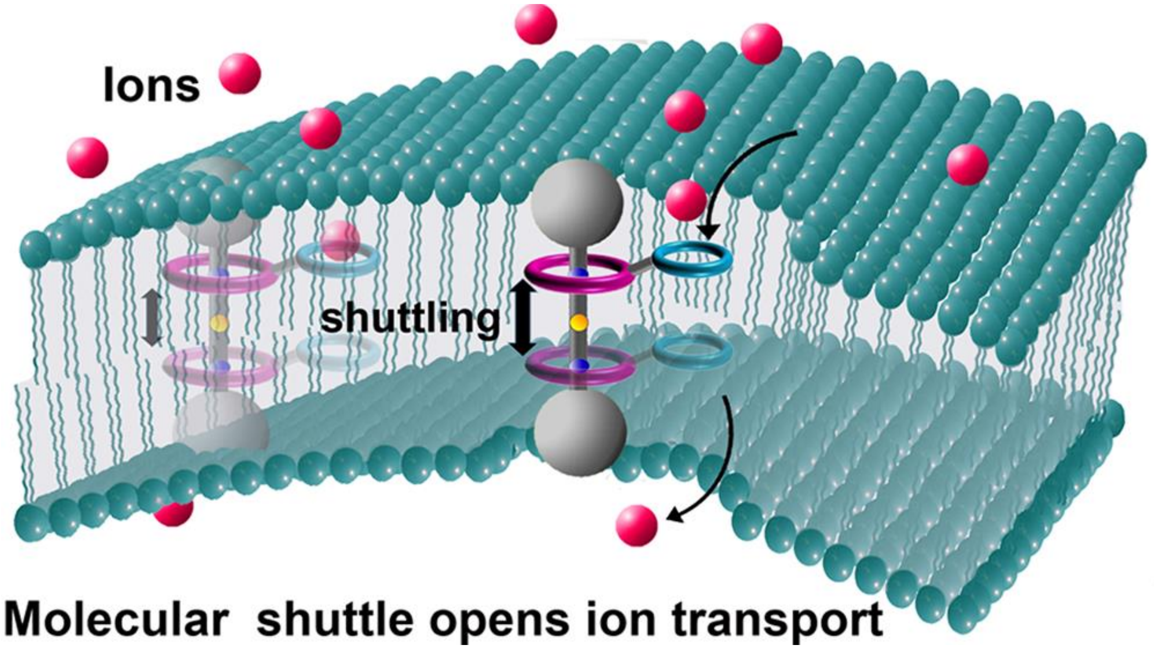
An Artificial Molecular Shuttle Operates in Lipid Bilayers for Ion Transport

Sujun Chen,[†,‡] Yichuan Wang,[†,‡] Ting Nie,[†] Chunyan Bao,*[,†] Chenxi Wang,[†] Tianyi Xu,[†] Qiuning Lin,[†] Da-Hui Qu,*[,†] Xueqing Gong,[†] Yi Yang,[§] Linyong Zhu,*[,†] and He Tian[†]



Calixarenes as ion channels

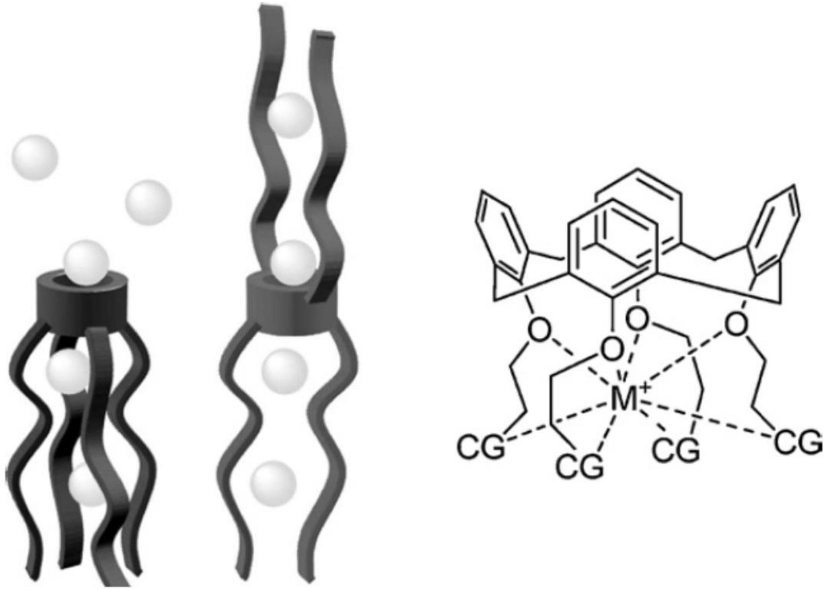
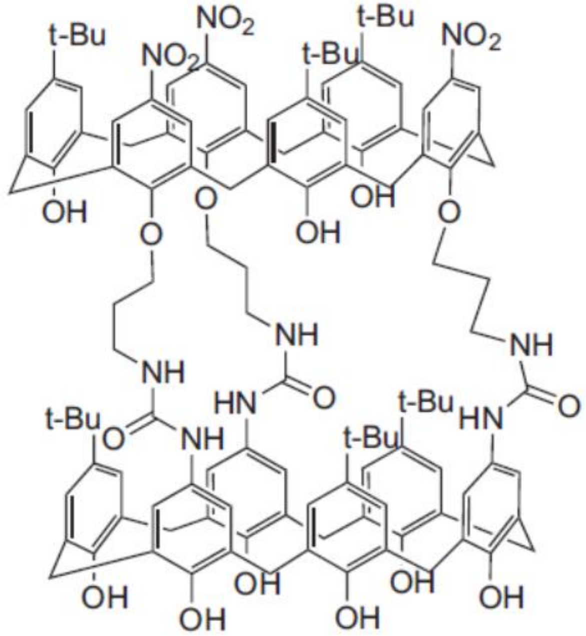


Fig. 3. Two possibilities of how calixarenes can span phospholipid bilayers (left, image reprinted with permission from Ref. [15]) and most common binding motif of calixarene based ion channels (right, CG = coordinating group).



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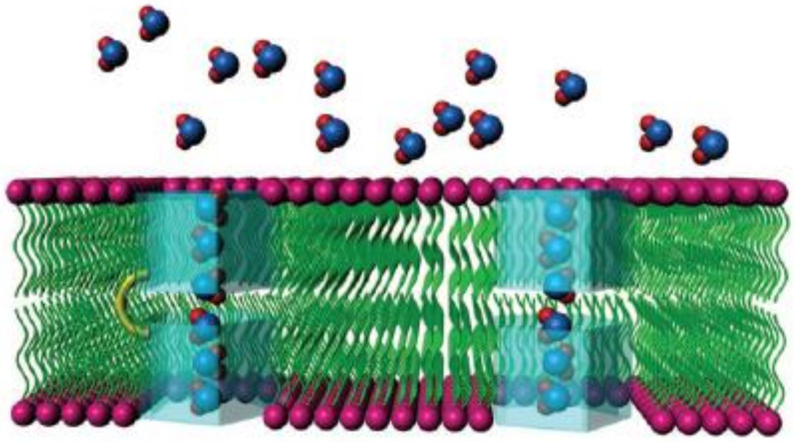
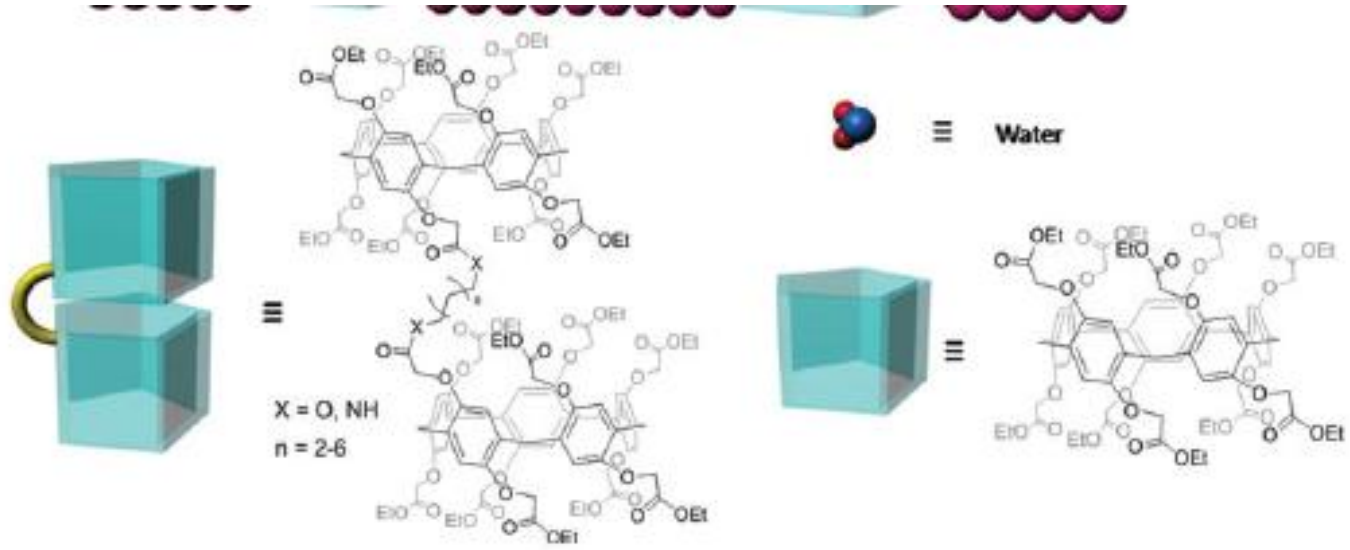
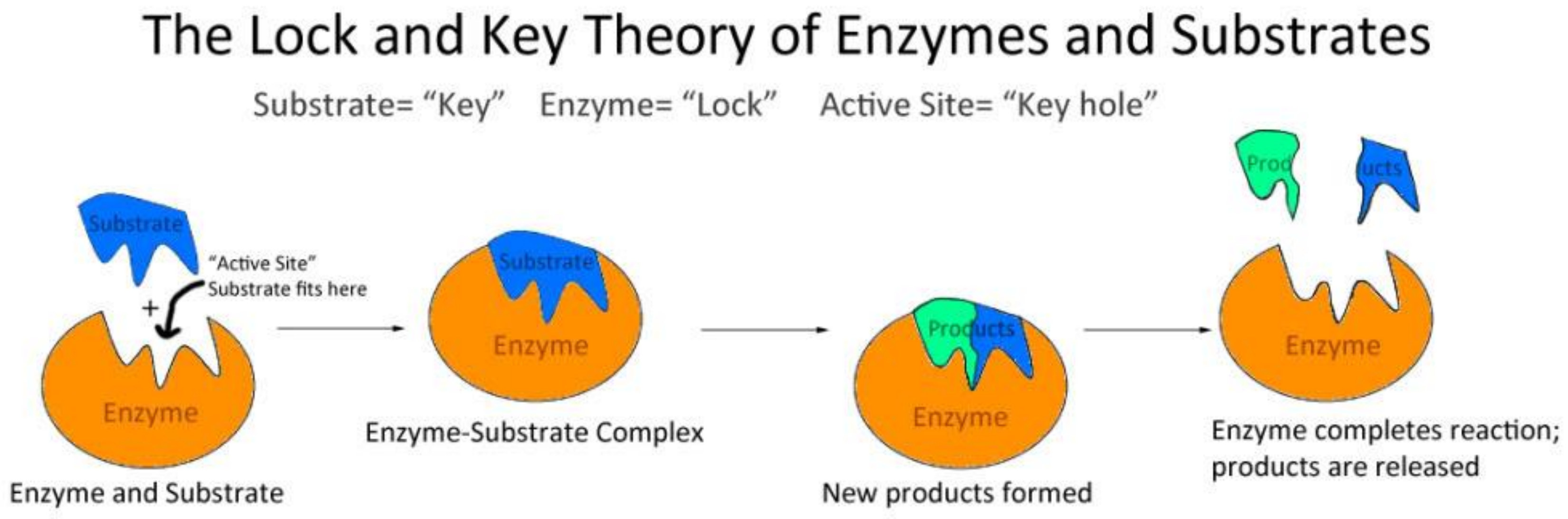
Pillar(5) arenes to build water channels



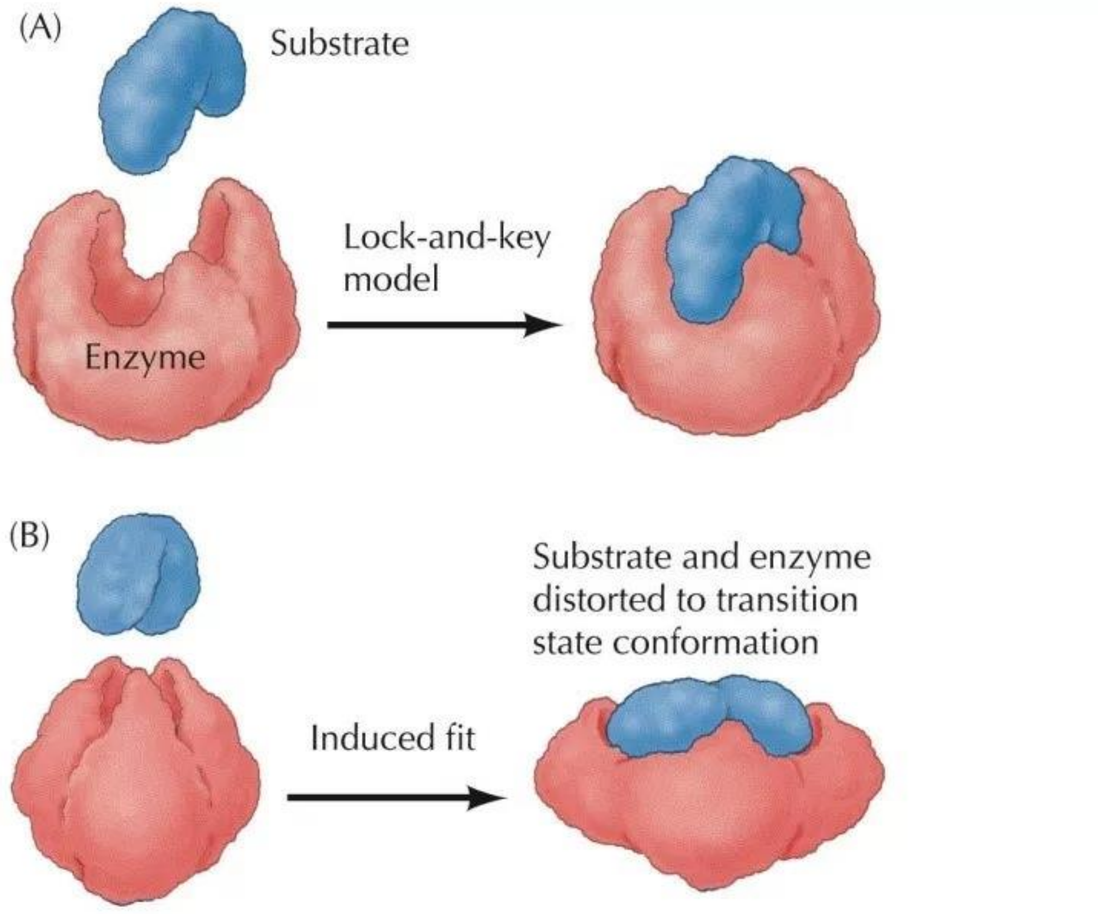


Enzyme/substrate and receptor/ligand interactions



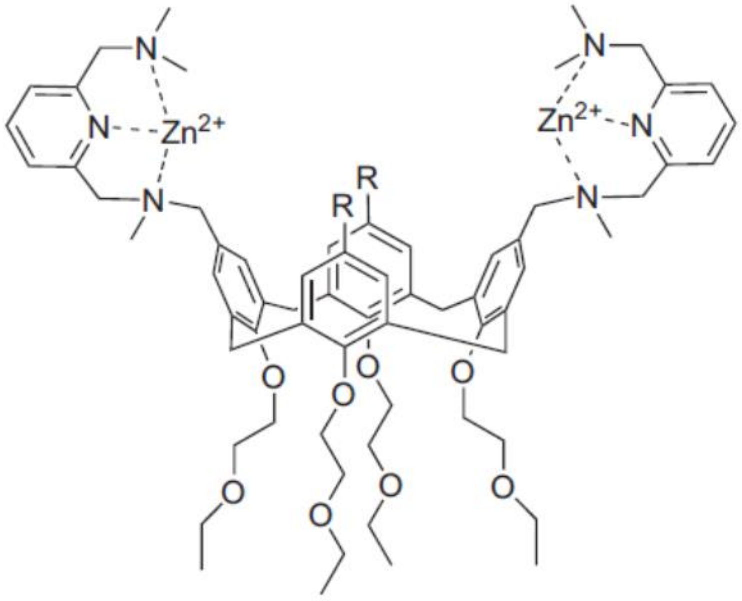
- P. Ehrlich: concept of drug as ligand and proteins as targets
- E. Fischer: lock and key «static» model, the basis of the «molecular recognition» concept

Daniel Koshland: the «induced fit» model

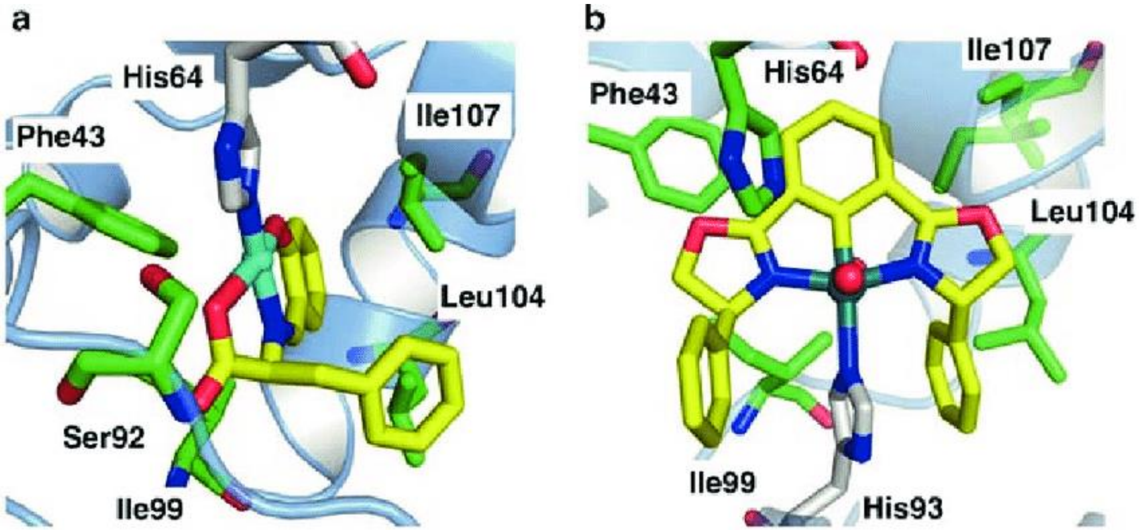


THE CELL, Fourth Edition, Figure 3.3 © 2006 ASM Press and Sinauer Associates, Inc.

Calixareni come mimetici di metallo-enzimi



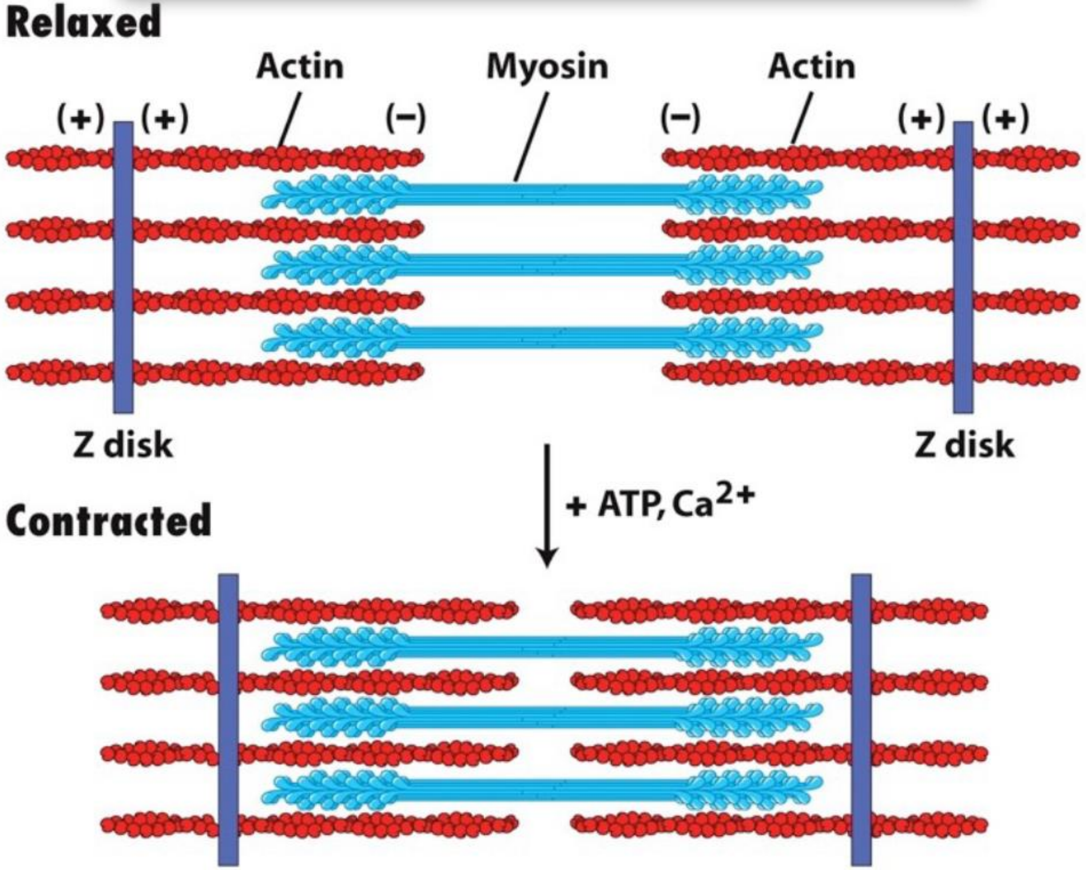
14a R = H, k_{rel} = 23000
14b R = CH_2NMe_2, k_{rel} = 7400



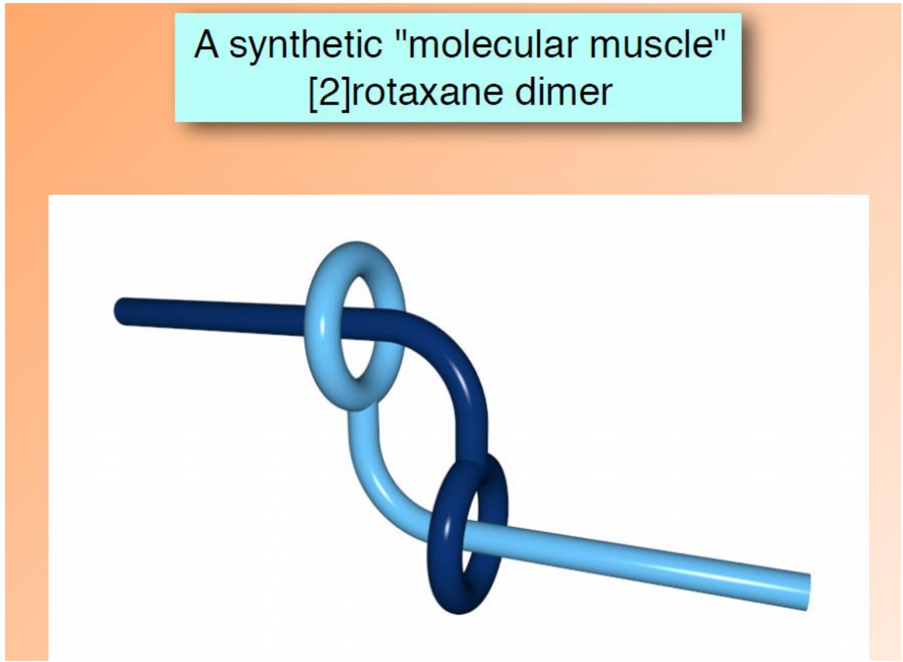
Struttura ai raggi X di un metalloenzima:
Ammino acidi che coordinano il metallo
Cavità tipo host

Miosina ed actina: le molecole del movimento muscolare. I muscoli artificiali fatti da dimeri rotaxanici

contraction and extension of a sarcomere
(elemental unit of the striated muscle)



A synthetic "molecular muscle"
[2]rotaxane dimer



Towards Synthetic Molecular Muscles: Contraction and Stretching of a Linear Rotaxane Dimer**

M. Consuelo Jiménez, Christiane Dietrich-Buchecker,
and Jean-Pierre Sauvage*

In memoriam Olivier Kahn

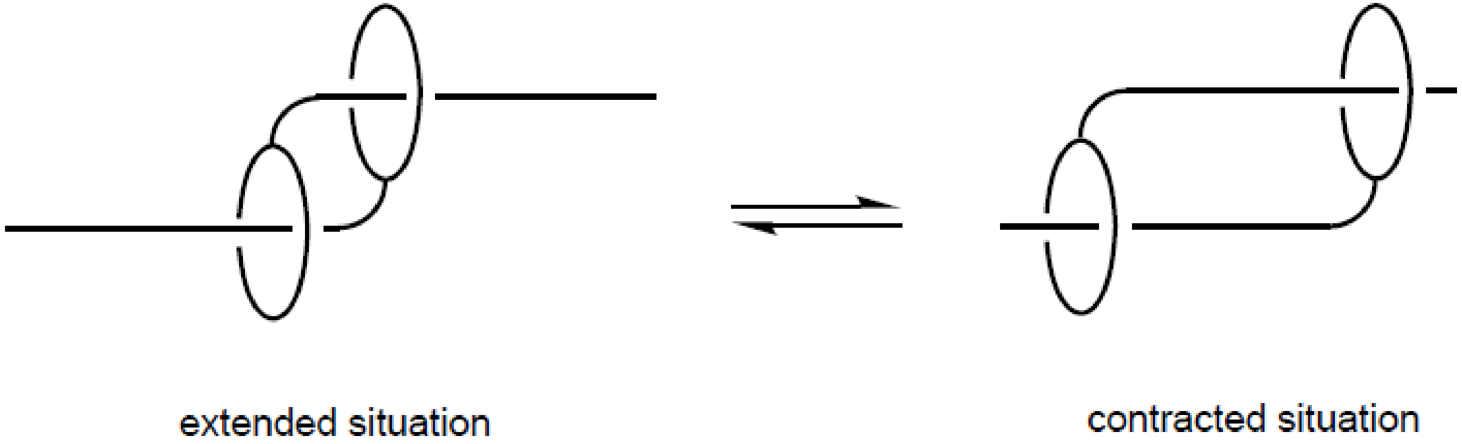
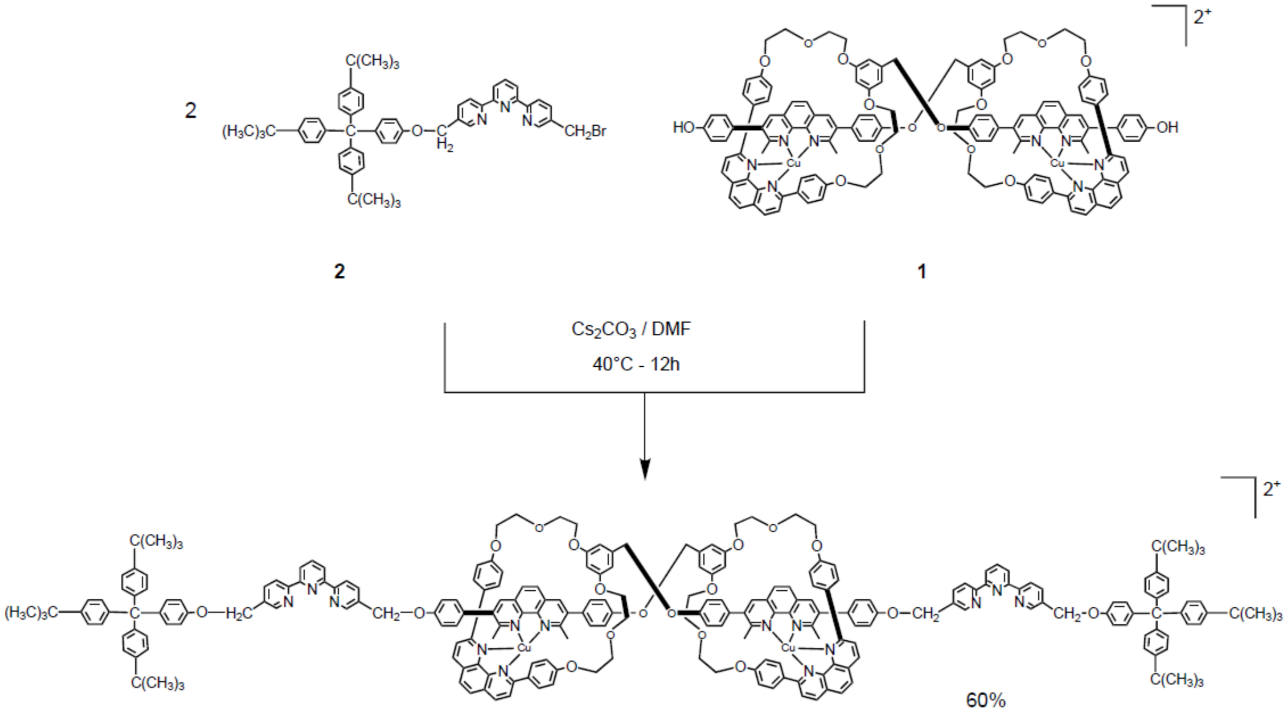
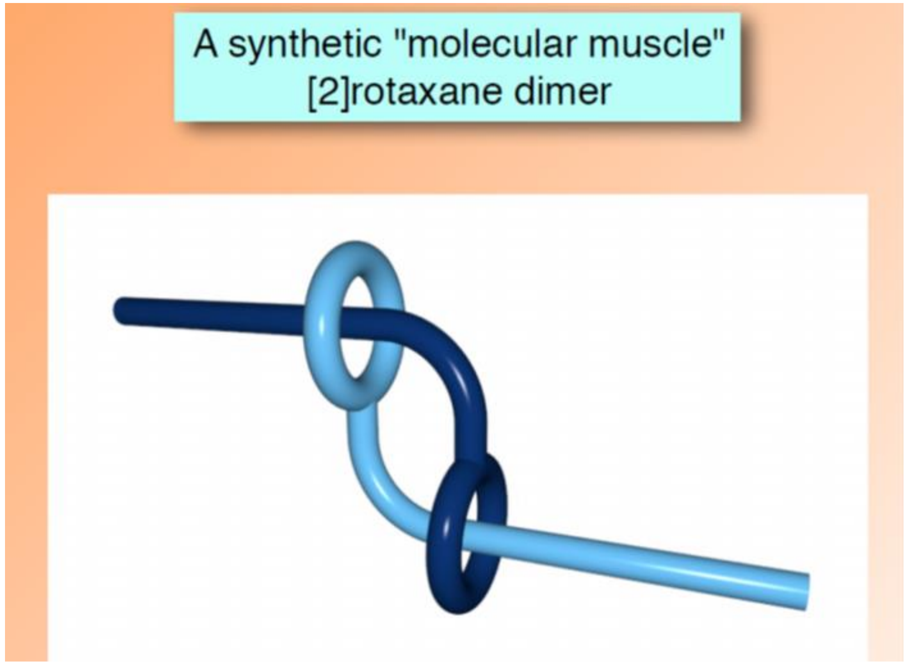


Figure 1. The topology and the shape of a linearly arranged pseudo-rotaxane dimer is adapted to a contraction/stretching motion.

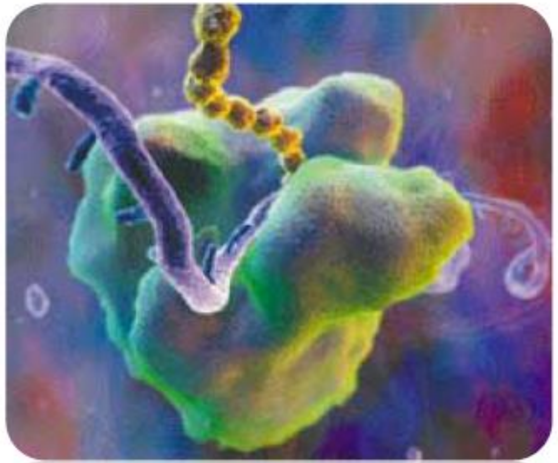
Come sono fatti chimicamente i rotaxani



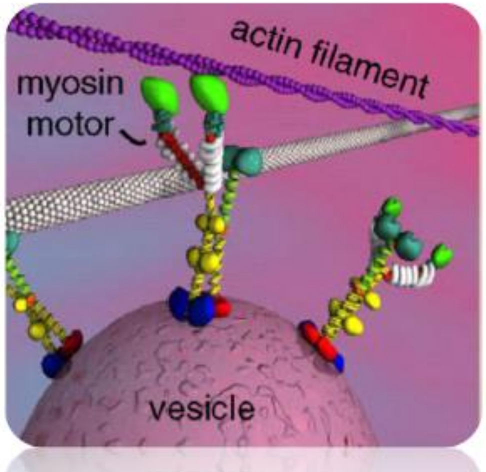

A synthetic "molecular muscle"
[2]rotaxane dimer

Biomolecular Machines

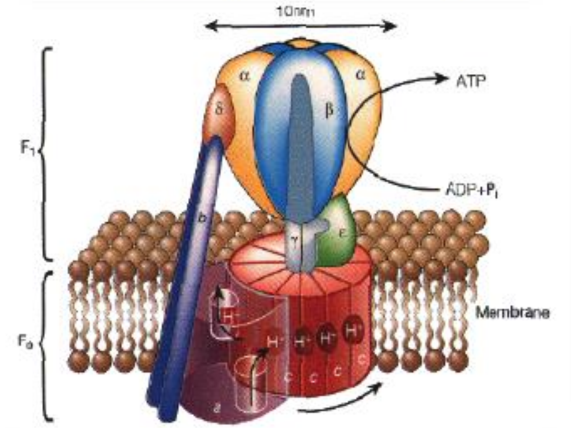
Ribosome
protein synthesis



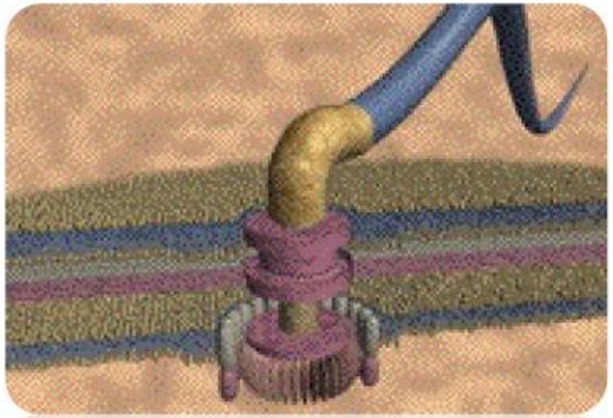
Bio-Nanomotors
transport – muscle function



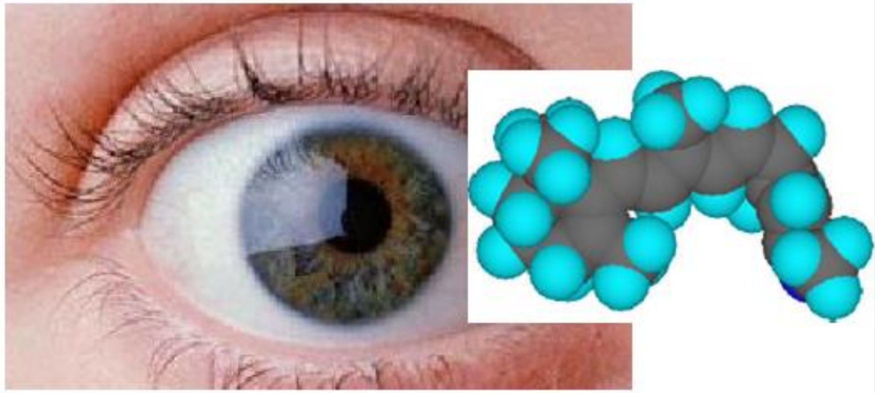
Rotary Motor
transport-catalysis



Bacterial Flagellar Motor
propulsion

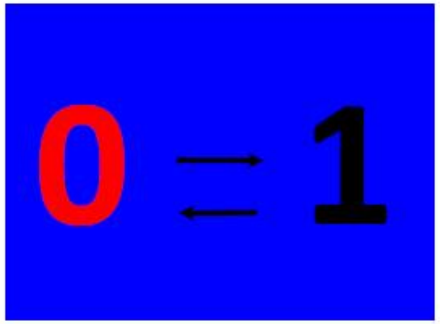


Optical Switching
Information



Molecular Nanoscience

molecular light switch



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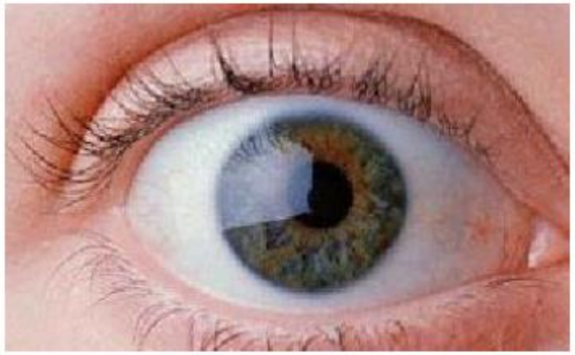
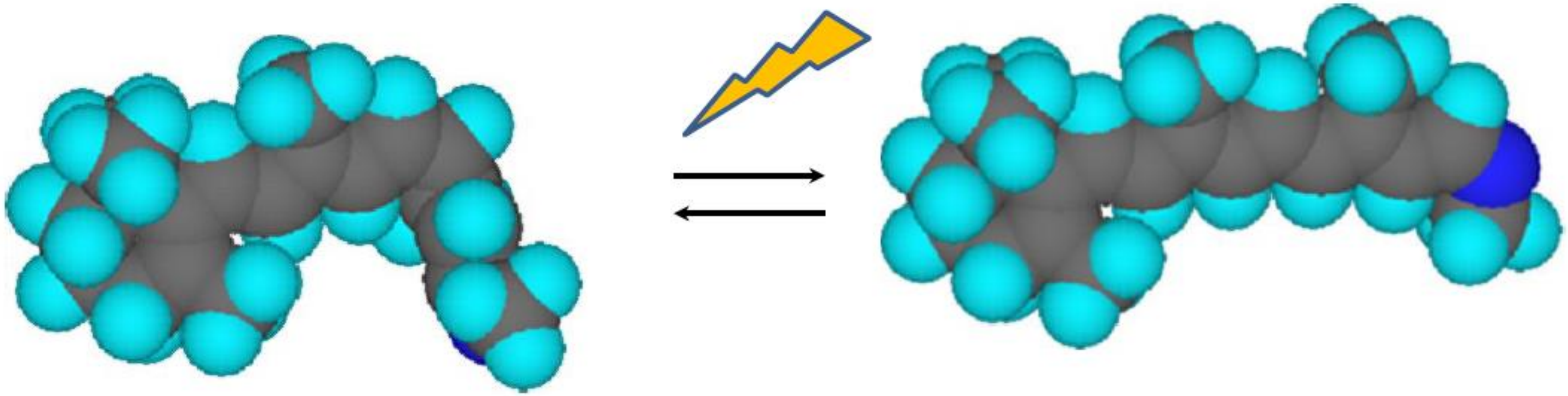
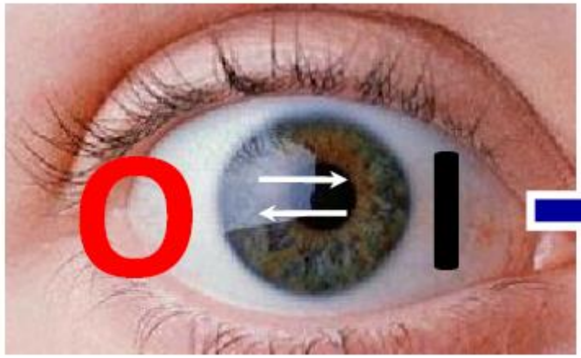
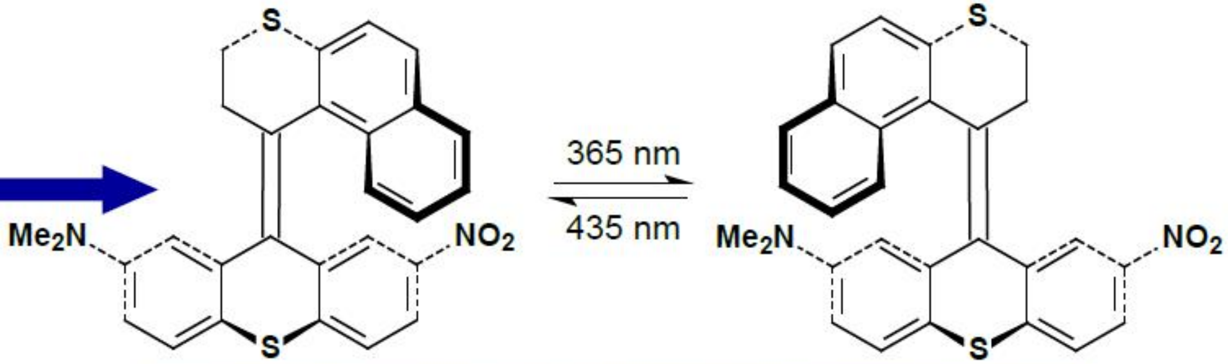




Optical Molecular Switch

Binary System at the Molecular Level



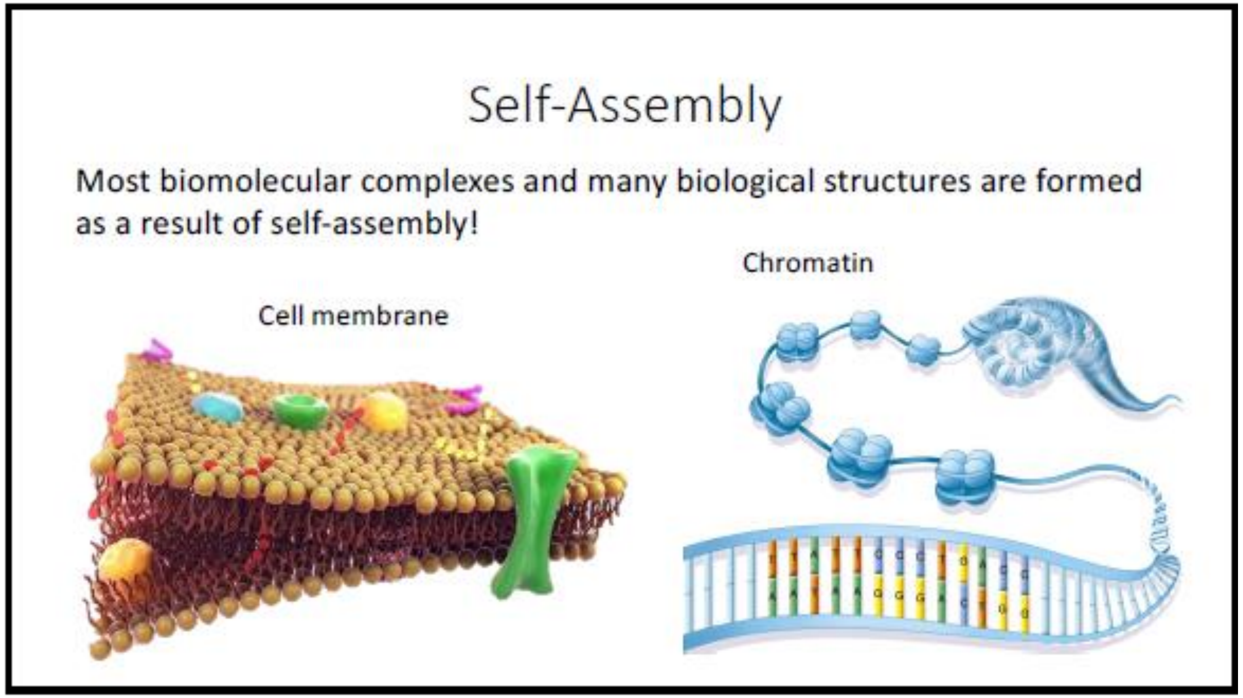


Left (0)　　**Right (1)**

Information Storage

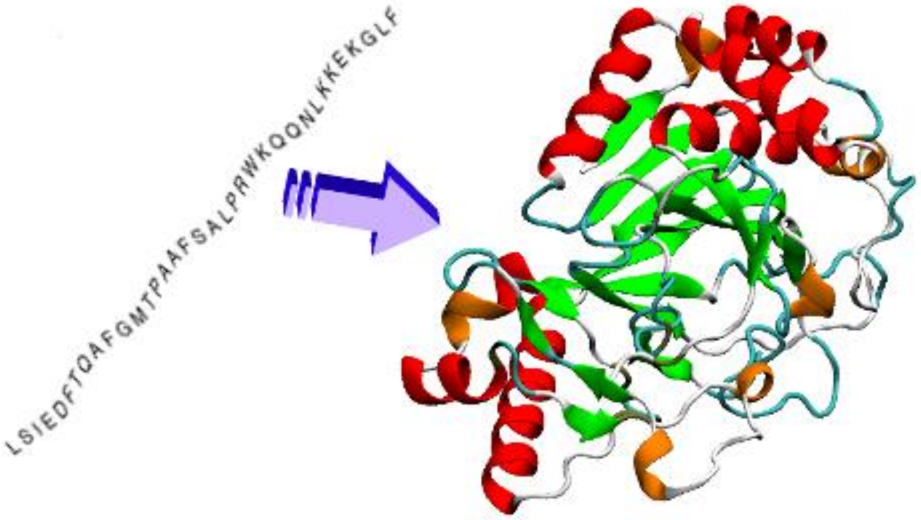
Non-destructive read-out

Self-assembly in natura: virus, proteine, membrane cellulari, DNA nella cromatina



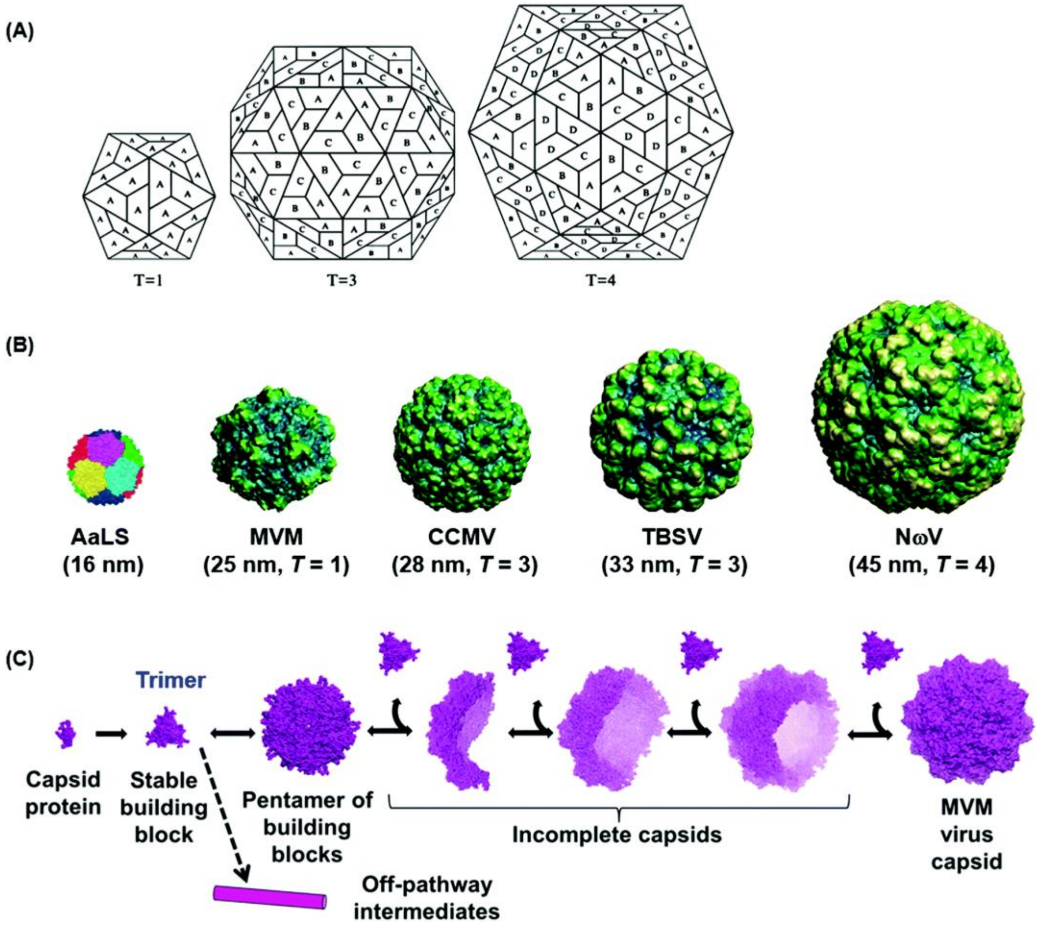
Self-Assembly

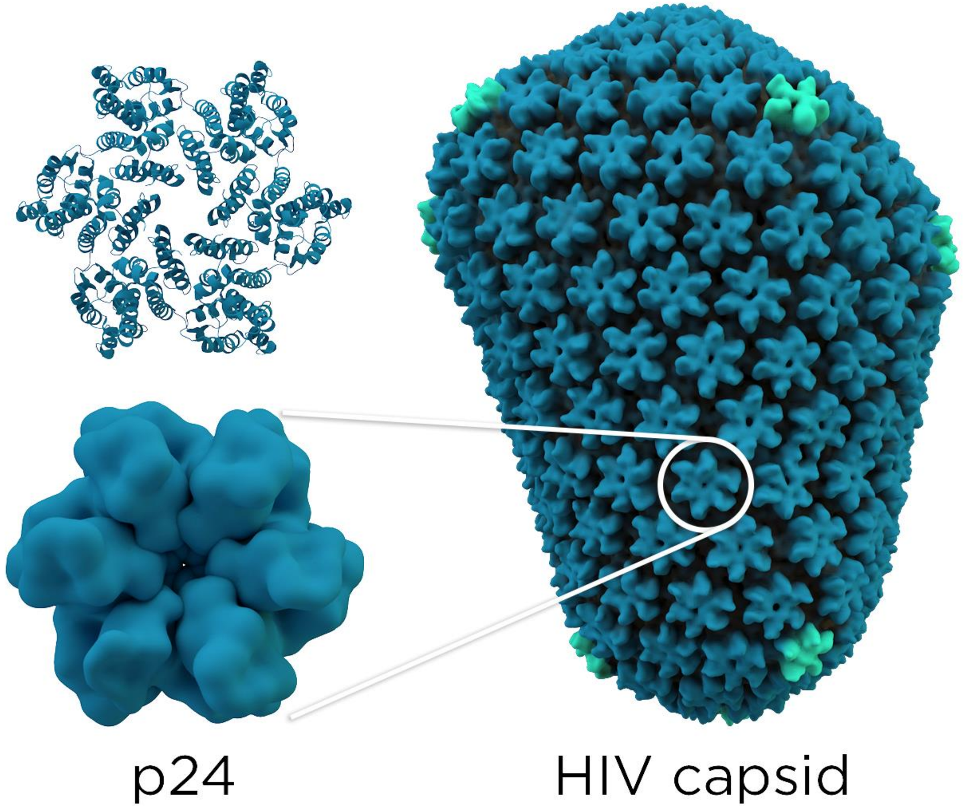
Most biomolecular complexes and many biological structures are formed as a result of self-assembly!



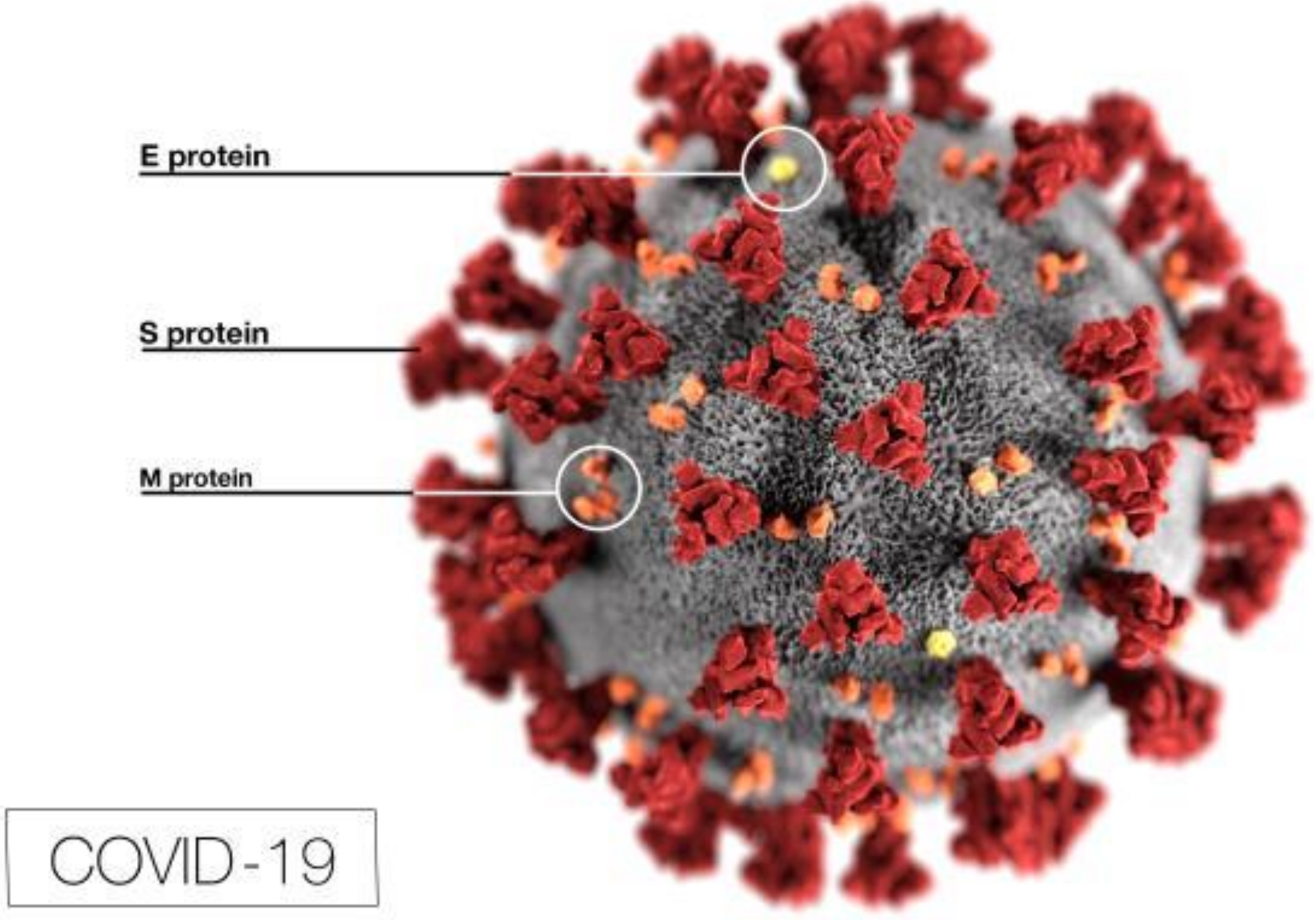
Folding delle proteine

Self-assembly in natura: i capsidi virali





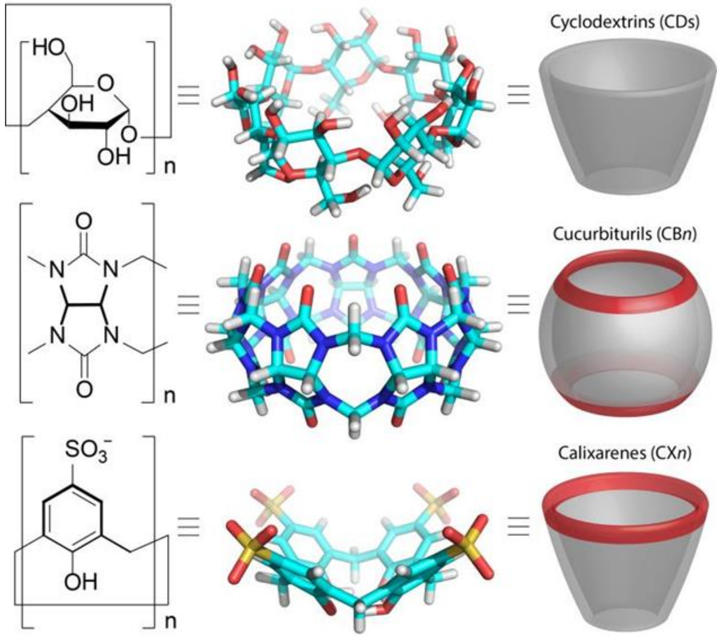
COVID-19 e la chimica supramolecolare



Interazione con
organismo umano
(host/guest)
Self-assembling
structure

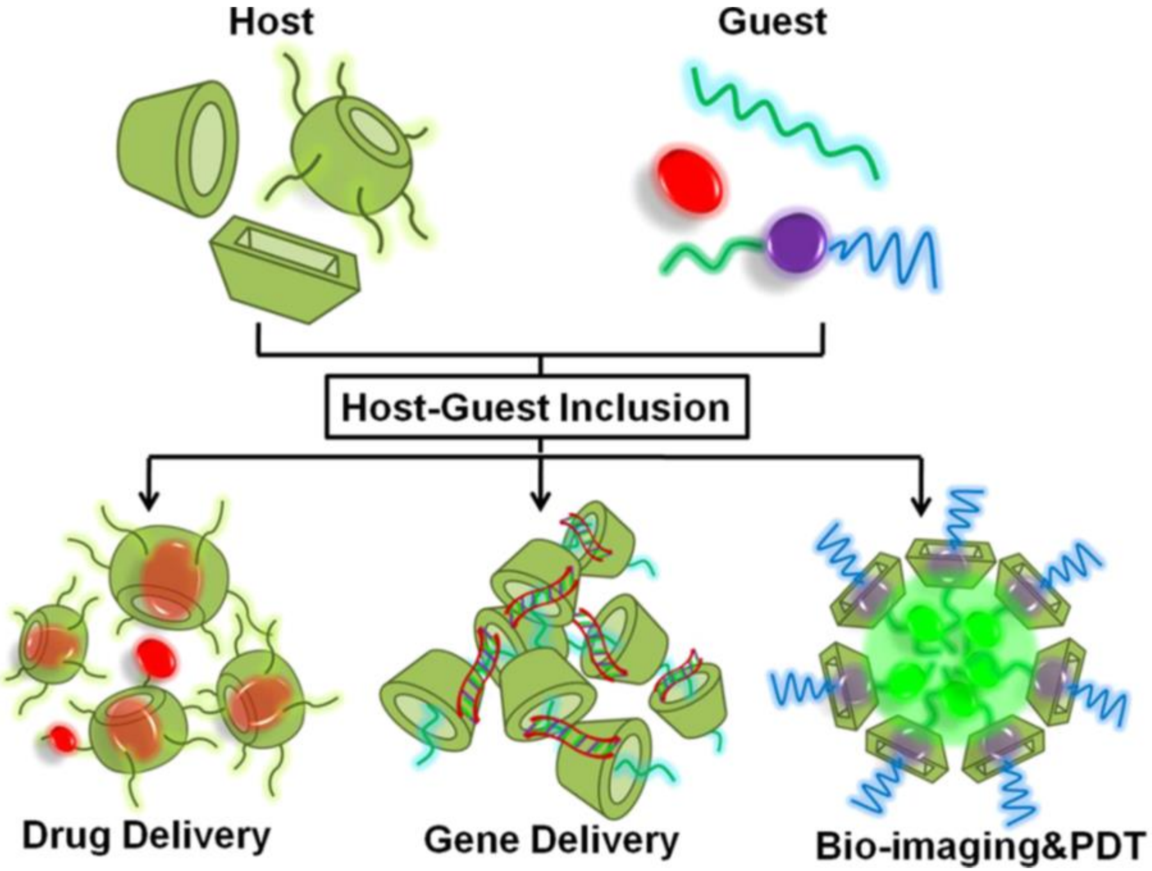
From simple host-guest to host-guest + self-assembly

HOSTS



Scheme 8. Representations of Inclusion Complexes for the Main Classes of Macrocyclic Hosts[a]

[a] Regions of negative charge density are shown as red rims.



SELF-ASSEMBLY

Vantaggi della chimica supramolecolare sulla chimica di sintesi (molecolare)

- Le strutture supramolecolari si assemblano in modo semplice raggiungendo complessità notevole senza sforzo sintetico
- Semplicemente mescolando building blocks in soluzione a temp. Ambiente si ottengono strutture supramolecolari complesse.
- SELF-ASSEMBLY
- Riduzione dei costi, basso impatto ambientale

the supramolecular materials are capable of being **recycled** and **self-repaired** from external mechanical damage.

Esempio di self-assembly per ottenere nanostrutture

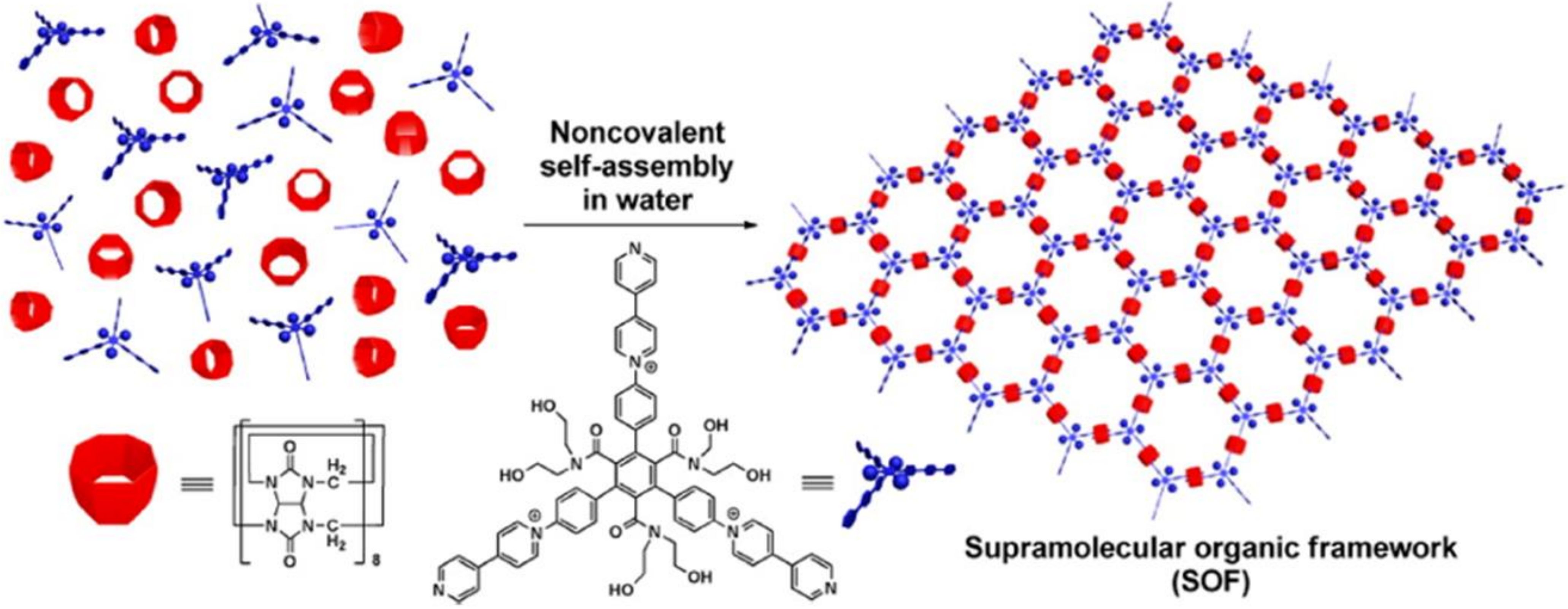


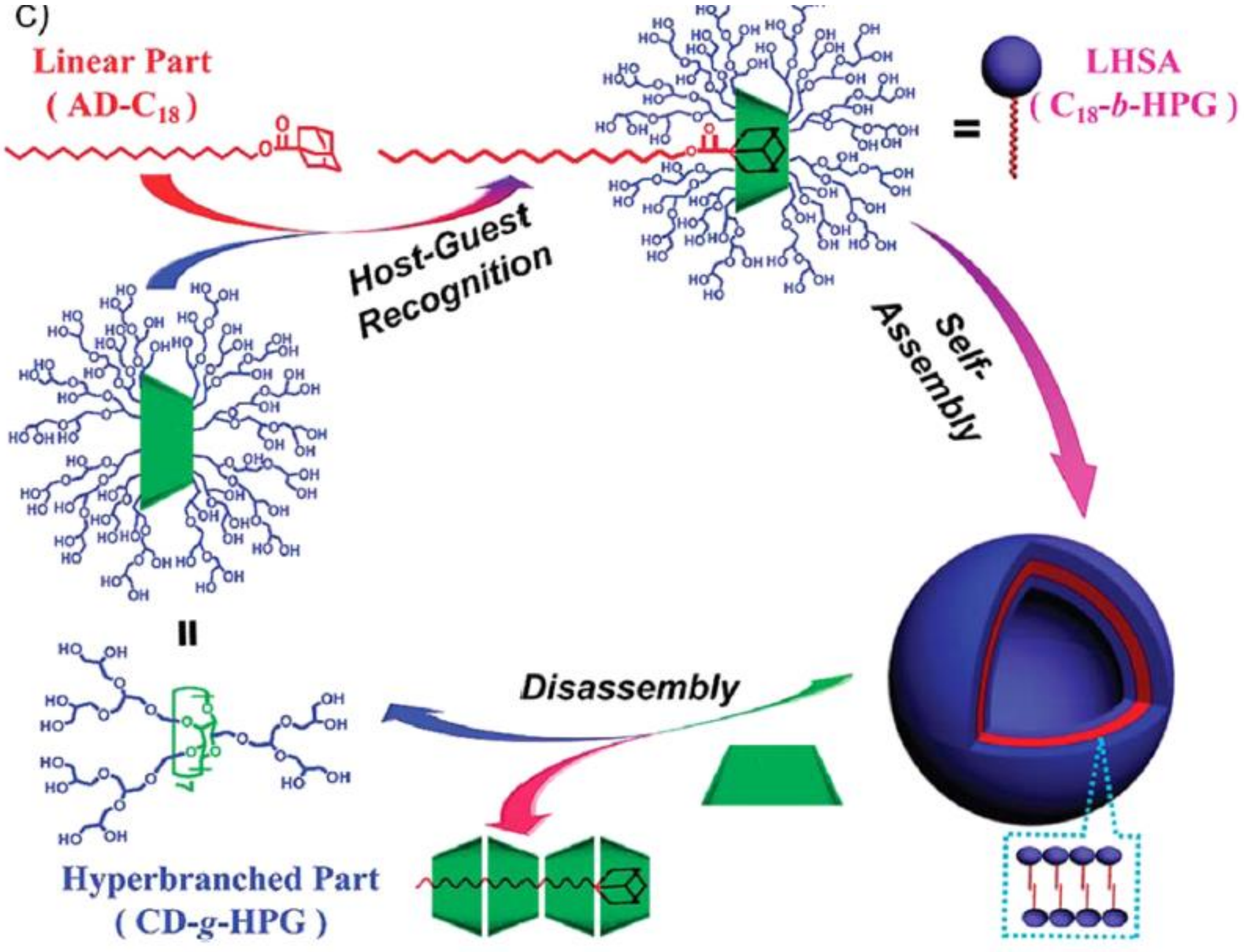
Figure 30. Schematic representation of the self-assembly of monomer D20 and CB[8]. Reproduced with permission from ref 286. Copyright 2014

Bottom-up fabrication of nano-objects and nanomaterials

At last, supramolecular chemistry provides a possibility of manipulating molecules or supramolecular building blocks at a molecular level, allowing the “bottom-up” method to control the sizes and morphologies of the resulting supramolecular materials.

Especially, the fabrication of supramolecular materials with uniform size within nanometer range has become a hot research topic.

Example of bottom-up self-assembly to give a nano-object that can be reversibly disassembled



Preparation, self-assembly, and disassembly of the vesicle by a linear hyperbranched supramolecular amphiphile.

Materiali e molecole che rispondono a stimoli esterni

Furthermore, it has adaptive capability in response to external stimuli that can trigger the structure change of supramolecular materials

Upon external stimuli, the supramolecular materials can rearrange their structures or morphologies toward most stable states driven by the decrease of Gibbs free energy.

Therefore, this adaptive capability can be utilized for the design and fabrication of stimuli-responsive functional materials based on supramolecular chemistry

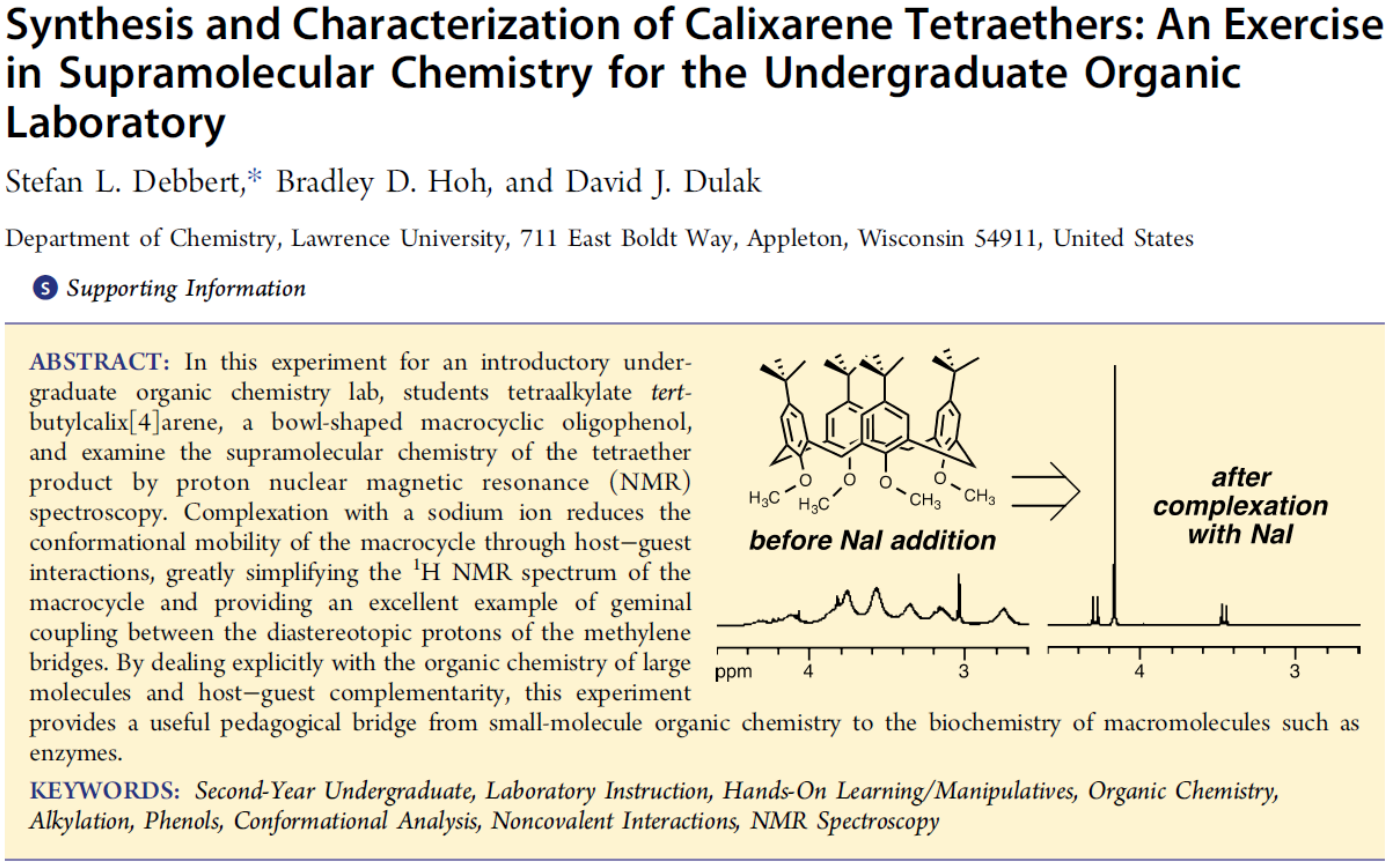
The“modern organic chemistry” is more a covalent or a supramolecuar chemistry?

- Top journals in the sector (High Impact Factors):
- Nature Chemistry (IF 28.129)
- Angewandte Chemie Int. Ed. Engl. (IF 11.99)
- JACS (IF 13.5)
- JOC (IF 4.89)
- Tetrahedron Letters
- Organic Letters
- Synlett

Compito a casa

- Andare a vedere gli articoli più recenti usciti nelle riviste citate ad alto fattore d’impatto:
- Quanti riguardano al chimica covalente (molecolare) e quanti la supramolecolare?
- Portate in classe un articolo che vi ha affascinato in particolare che riguardi la chimica supramolecolare (interazioni tra molecole, self-assembly, nanostrutture sensori, macchine molecolari)

Laboratorio T029
1, 3, 4, 7, 8, 11 Giugno
Carlotta Ciaramelli ed Andrea Luraghi



Synthesis and Characterization of Calixarene Tetraethers: An Exercise in Supramolecular Chemistry for the Undergraduate Organic Laboratory

Stefan L. Debbert,* Bradley D. Hoh, and David J. Dulak

Department of Chemistry, Lawrence University, 711 East Boldt Way, Appleton, Wisconsin 54911, United States

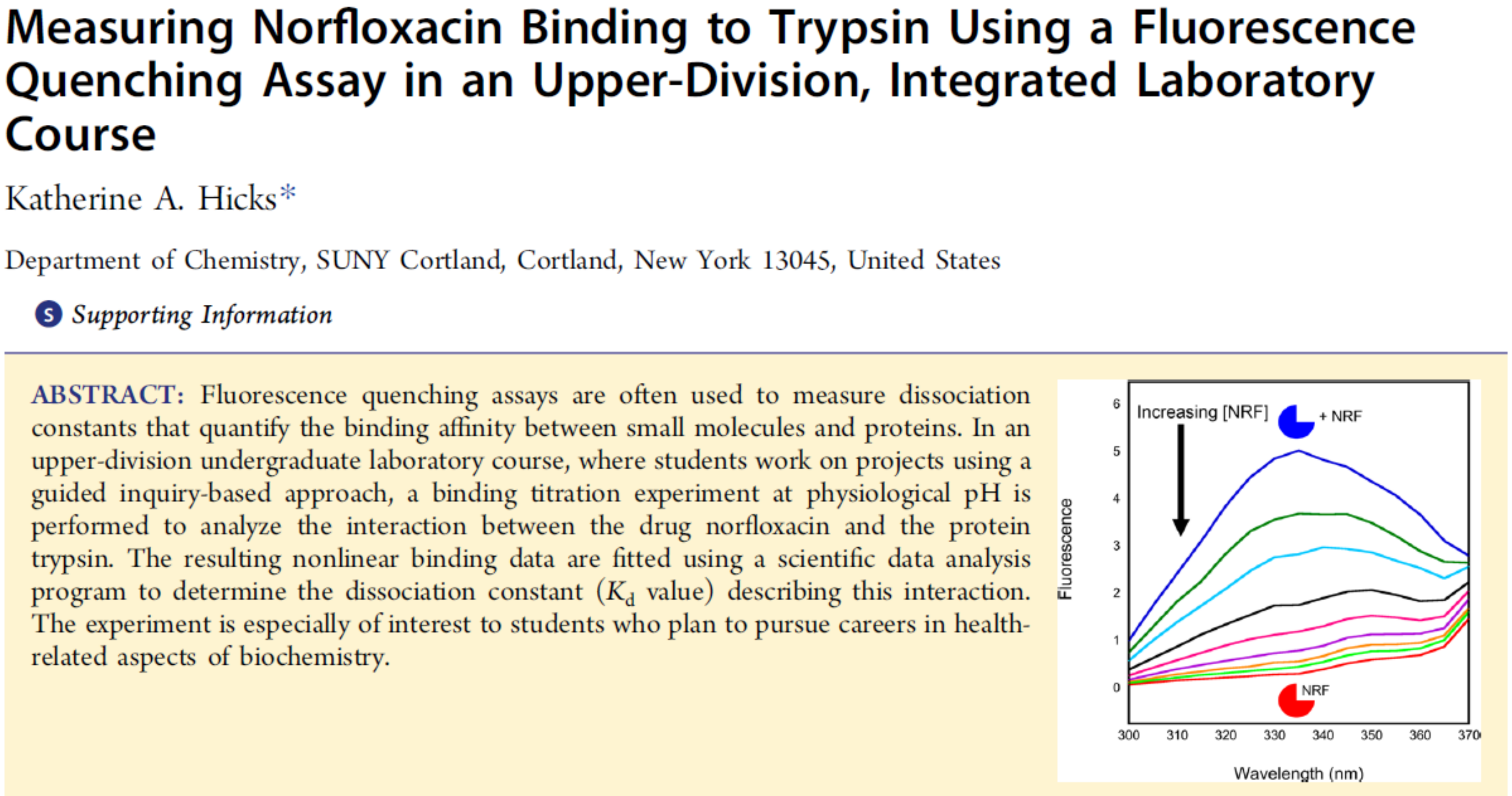
Supporting Information

ABSTRACT: In this experiment for an introductory undergraduate organic chemistry lab, students tetraalkylate *tert*-butylcalix[4]arene, a bowl-shaped macrocyclic oligophenol, and examine the supramolecular chemistry of the tetraether product by proton nuclear magnetic resonance (NMR) spectroscopy. Complexation with a sodium ion reduces the conformational mobility of the macrocycle through host−guest interactions, greatly simplifying the ^{1}H NMR spectrum of the macrocycle and providing an excellent example of geminal coupling between the diastereotopic protons of the methylene bridges. By dealing explicitly with the organic chemistry of large molecules and host−guest complementarity, this experiment provides a useful pedagogical bridge from small-molecule organic chemistry to the biochemistry of macromolecules such as enzymes.

KEYWORDS: *Second-Year Undergraduate, Laboratory Instruction, Hands-On Learning/Manipulatives, Organic Chemistry, Alkylation, Phenols, Conformational Analysis, Noncovalent Interactions, NMR Spectroscopy*

3 e 4 Giugno

1 Giugno



Measuring Norfloxacin Binding to Trypsin Using a Fluorescence Quenching Assay in an Upper-Division, Integrated Laboratory Course

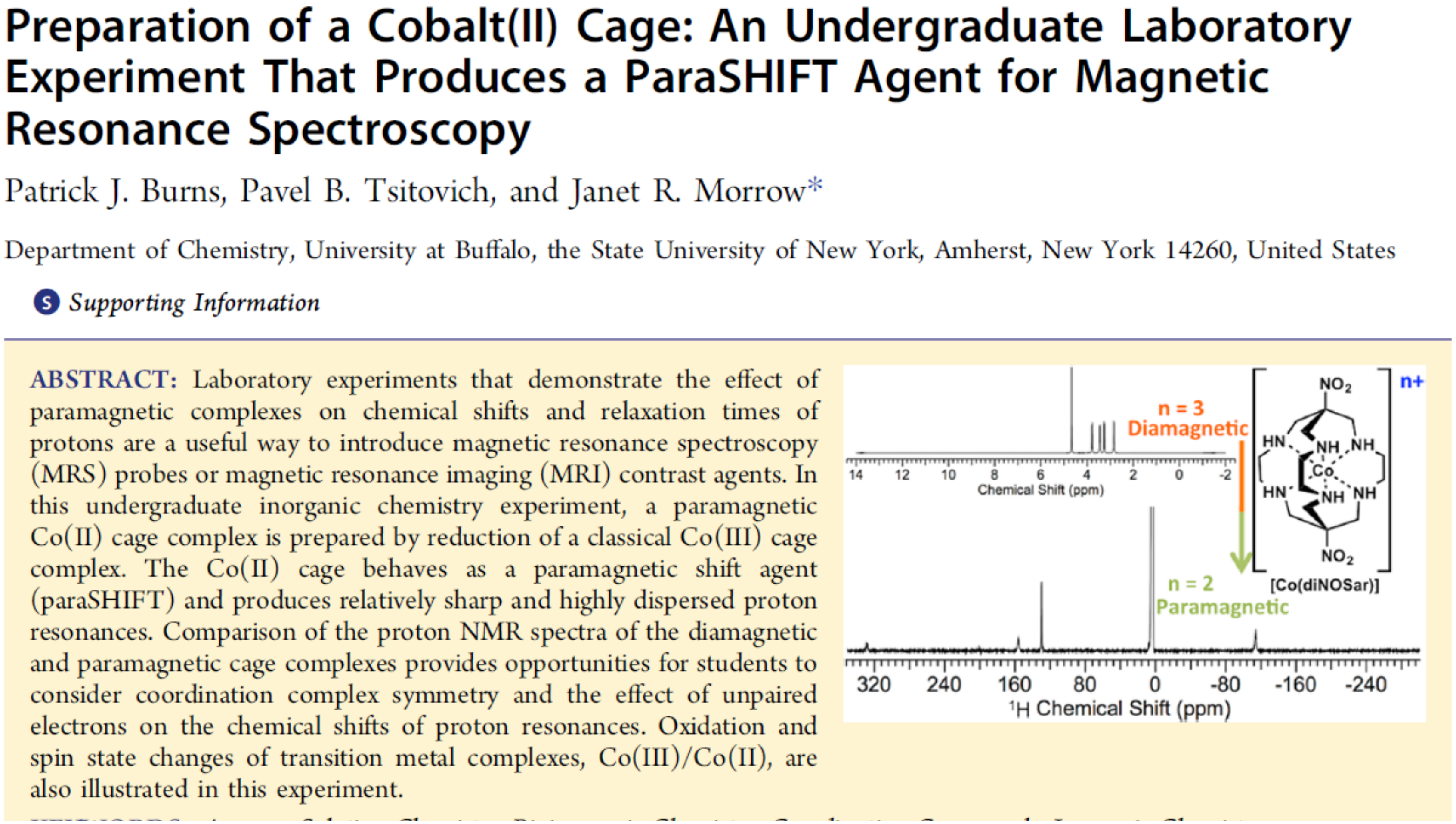
Katherine A. Hicks*

Department of Chemistry, SUNY Cortland, Cortland, New York 13045, United States

Ⓢ *Supporting Information*

ABSTRACT: Fluorescence quenching assays are often used to measure dissociation constants that quantify the binding affinity between small molecules and proteins. In an upper-division undergraduate laboratory course, where students work on projects using a guided inquiry-based approach, a binding titration experiment at physiological pH is performed to analyze the interaction between the drug norfloxacin and the protein trypsin. The resulting nonlinear binding data are fitted using a scientific data analysis program to determine the dissociation constant (K_d value) describing this interaction. The experiment is especially of interest to students who plan to pursue careers in health-related aspects of biochemistry.

7, 8 Giugno



Preparation of a Cobalt(II) Cage: An Undergraduate Laboratory Experiment That Produces a ParaSHIFT Agent for Magnetic Resonance Spectroscopy

Patrick J. Burns, Pavel B. Tsitovich, and Janet R. Morrow*

Department of Chemistry, University at Buffalo, the State University of New York, Amherst, New York 14260, United States

Supporting Information

ABSTRACT: Laboratory experiments that demonstrate the effect of paramagnetic complexes on chemical shifts and relaxation times of protons are a useful way to introduce magnetic resonance spectroscopy (MRS) probes or magnetic resonance imaging (MRI) contrast agents. In this undergraduate inorganic chemistry experiment, a paramagnetic Co(II) cage complex is prepared by reduction of a classical Co(III) cage complex. The Co(II) cage behaves as a paramagnetic shift agent (paraSHIFT) and produces relatively sharp and highly dispersed proton resonances. Comparison of the proton NMR spectra of the diamagnetic and paramagnetic cage complexes provides opportunities for students to consider coordination complex symmetry and the effect of unpaired electrons on the chemical shifts of proton resonances. Oxidation and spin state changes of transition metal complexes, Co(III)/Co(II), are also illustrated in this experiment.