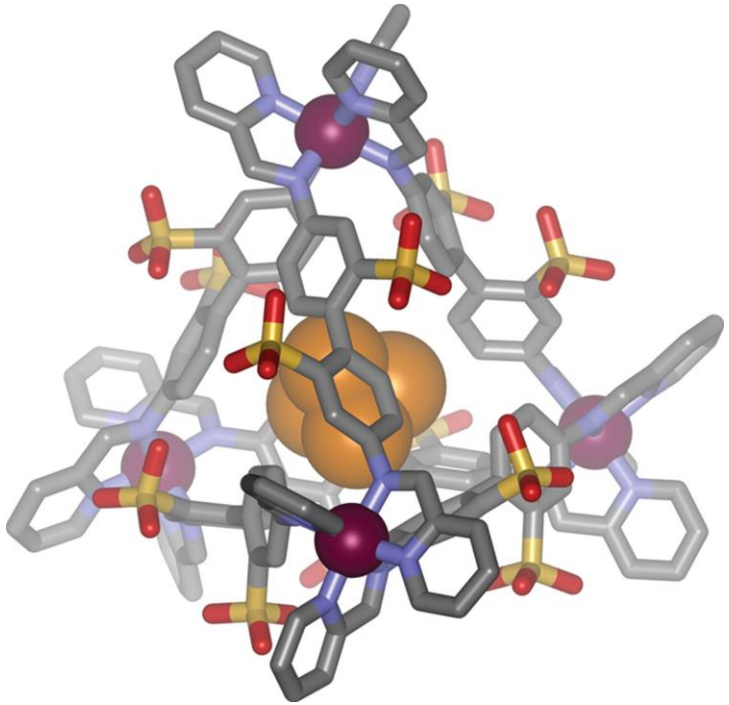
MUNI PHARM

Department of Natural Drugs



Supramolecular Pharmacy

3. Metallo-supramolecular cages

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Supramolecular chemistry

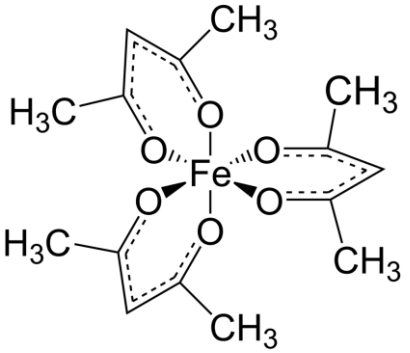
Can be divided into three main branches based on interactions used in assembly process:

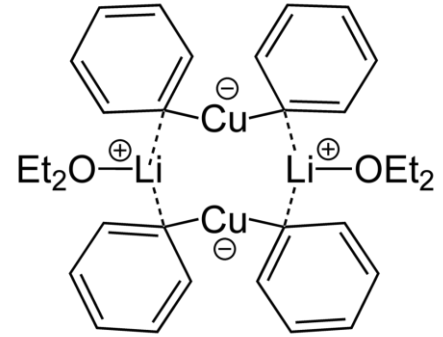
- (i) those that utilize H-bonding motifs in the supramolecular architectures;
- (ii) processes that primarily use other noncovalent interactions such as ion-ion, ion-dipole, π-π stacking, cation-π, van der Waals, and hydrophobic interactions;
- (iii) those that employ strong and directional metal-ligand bonds for the assembly process.

Coordination chemistry

- Organometallic compound x (metal-organic) coordination compound

= chemical compound containing at least one chemical bond between a carbon atom of an organic molecule and a metal x organic ligands bind the metal through a heteroatom such as oxygen or nitrogen





- Studies of supramolecular complexes of metal cations is the coordination chemistry of relatively labile (*i.e.* ligand substitution is relatively rapid under ambient conditions) metal ions and relatively elaborate, usually chelating or multidentate ligands

Coordination complex

- **Ligand** (from the Latin *ligare*, to bind) – ion or a molecule which is bonded to the central atom(s) in a complex compound. Ligands are generally Lewis bases (electron donors; often lone pair donors) capable of independent existence. Ligands can have one or more donor atoms and the number is then referred to as denticity (chloride, 1,2-diaminoethane).

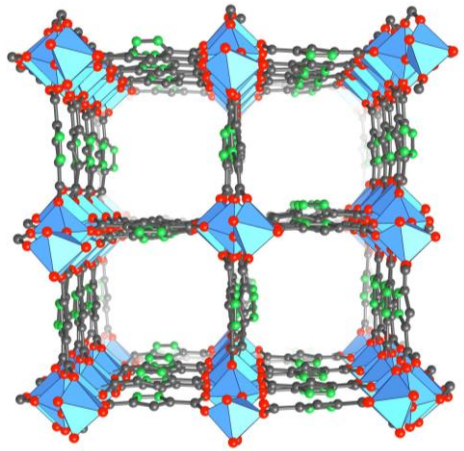
- **Metal** (oxidation state, coordination number, geometry)

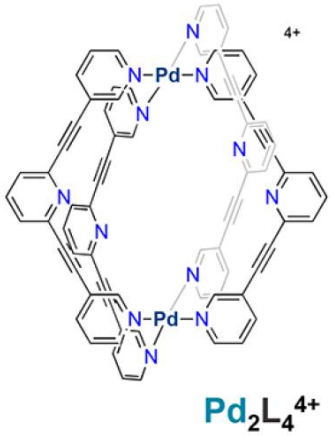
- **Bonding** ranges from ionic ion-dipole type interactions, where ligand‘s lone pair of electrons forms a dative bond to a positively charged metal cation to entirely covalent in which there is significant orbital overlap between metal and ligand valence orbitals.

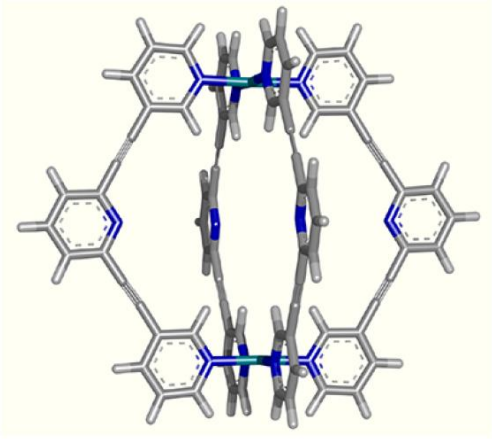
Metallosupramolecular chemistry

- Metal-organic frameworks (MOFs)
  - metal−organic porous coordination polymers consisting of metal ions or clusters and organic linkers that are connected by metal−ligand coordination bonds

- Supramolecular coordination cages (SCCs)
  - Well-defined, discrete 2D or 3D molecular entities with suitable metal centers undergoing coordination-driven self-assembly with ligands containing multiple binding sites

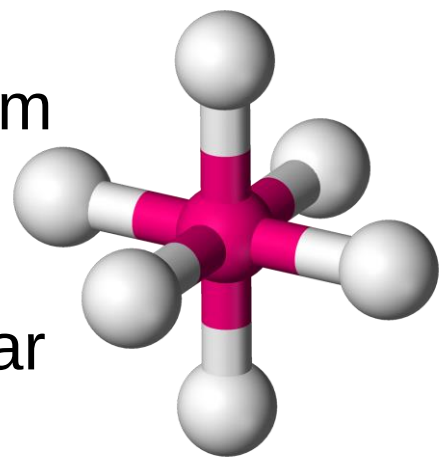


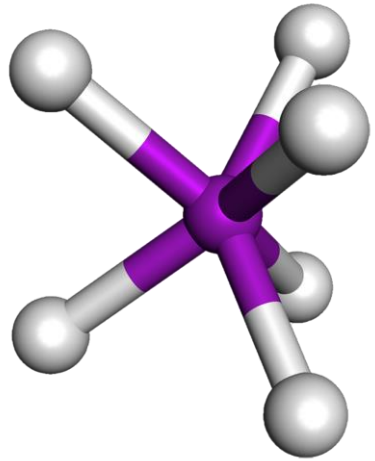




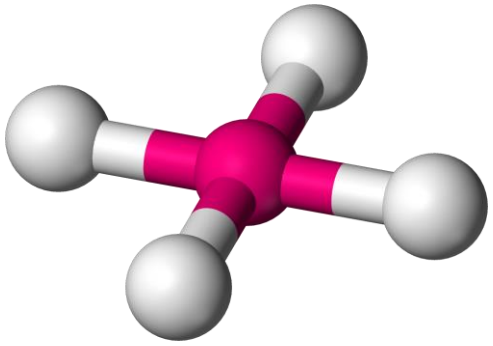
Metal geometry

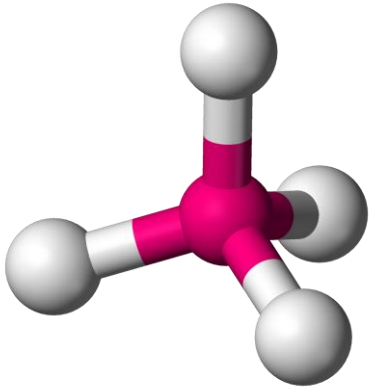
- the coordination number and geometry of the complex is dependent on the number of ligands that can pack around the small metal center (majority 4-6)
- 6 coordinate geometry is octahedron or trigonal prism





- 4 coordinate geometry is tetrahedral or square planar





- metals in lower oxidation states or those with unfilled sub-shells such as the transition metals tend to form more covalent complexes with well-defined coordination geometries and a preference for more polarisable ligands

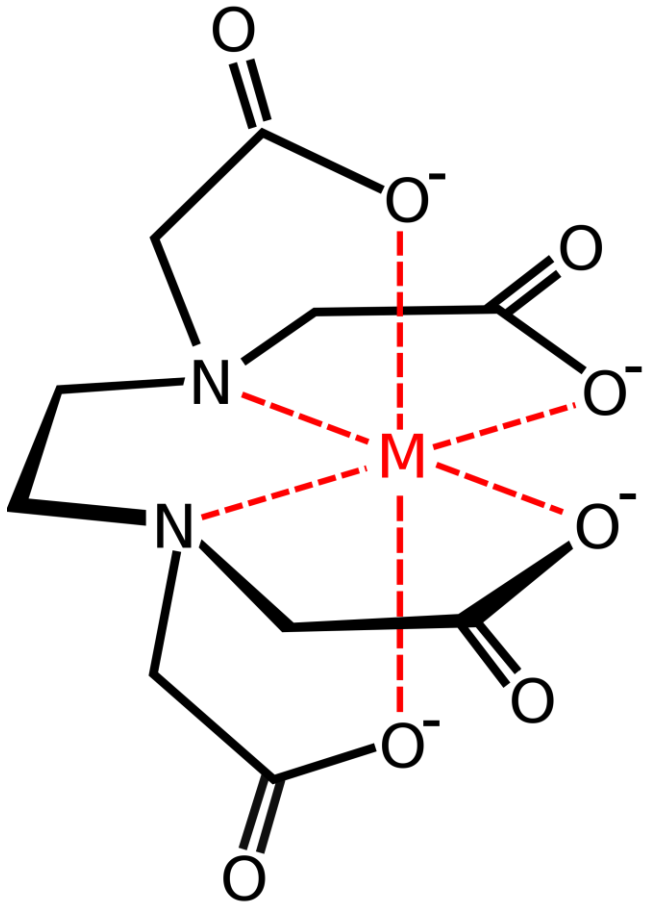
Hard and soft acids and bases (HSAB)

- Using concept of Lewis acids and bases, so that acids are electron acceptors and bases are electron donors

- ***Hard acids***: the acceptor atom is of high positive charge, small size, and does not have easily excited outer electrons, i.e. non-polarisable. E.g.: H^+, Na^+, Ca^{2+}, high oxidation states of the transition metals.
- ***Soft acids***: the acceptor atom is of low positive charge, large size, and has several easily excited outer electrons, i.e. it is polarisable. E.g.: Pt^{2+}, Pd^{2+}, Rh^+, Hg^{2+}, low oxidation states of the transition metals.
- ***Hard bases***: the donor atom is of low polarisability, high electronegativity, hard to reduce, and associated with empty orbitals of high energy and hence inaccessible. E.g.: F^-, ligands with oxygen or to some extent nitrogen donor atoms.
- ***Soft bases***: the donor atom is of high polarisability, low electronegativity, easily oxidised and associated with empty, low-lying orbitals. E.g. : I^-, R_2S, H^-

Hard and soft acids and bases (HSAB)

- Hard to hard and soft to soft

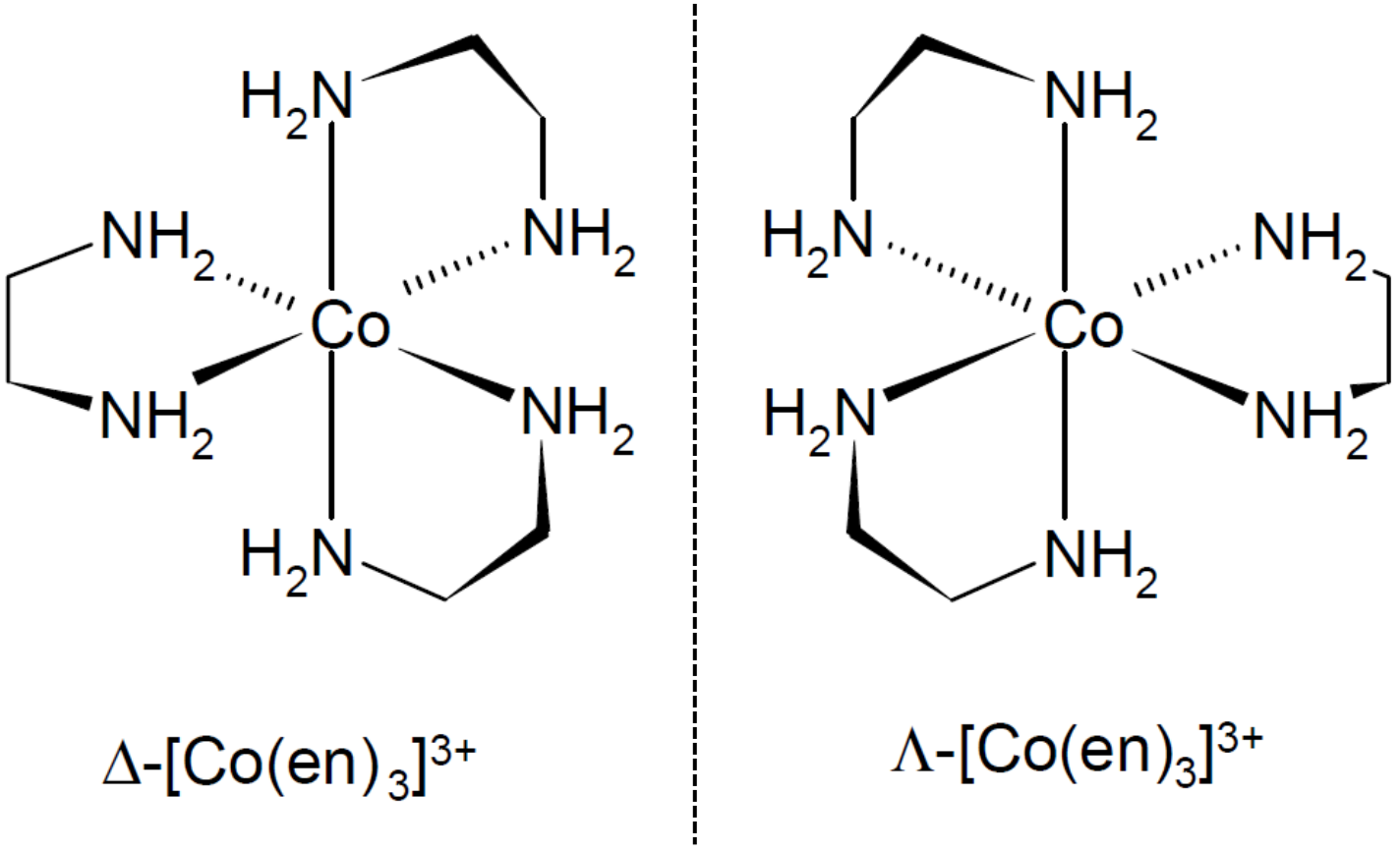


$$LiI + CsF \rightarrow LiF + CsI$$

	Na^+	Ca^{2+}	Lu^{3+}
radius (Å)	0.95	0.99	0.93
log *K* (EDTA)	1.7	10.7	20.0

	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
radius (Å)	0.65	0.99	1.13	1.35
charge/radius	3.07	2.02	1.77	1.48
log *K* ($EDTA^{4-}$)	8.7 (7 coord.)	10.7	8.6	7.8

Chirality of coordination complexes



Δ-$[Co(en)_3]^{3+}$ Λ-$[Co(en)_3]^{3+}$

en = ethylenediamine, $NH_2CH_2CH_2NH_2$

Right-handed twist Left-handed twist

Coordination driven self-assembly

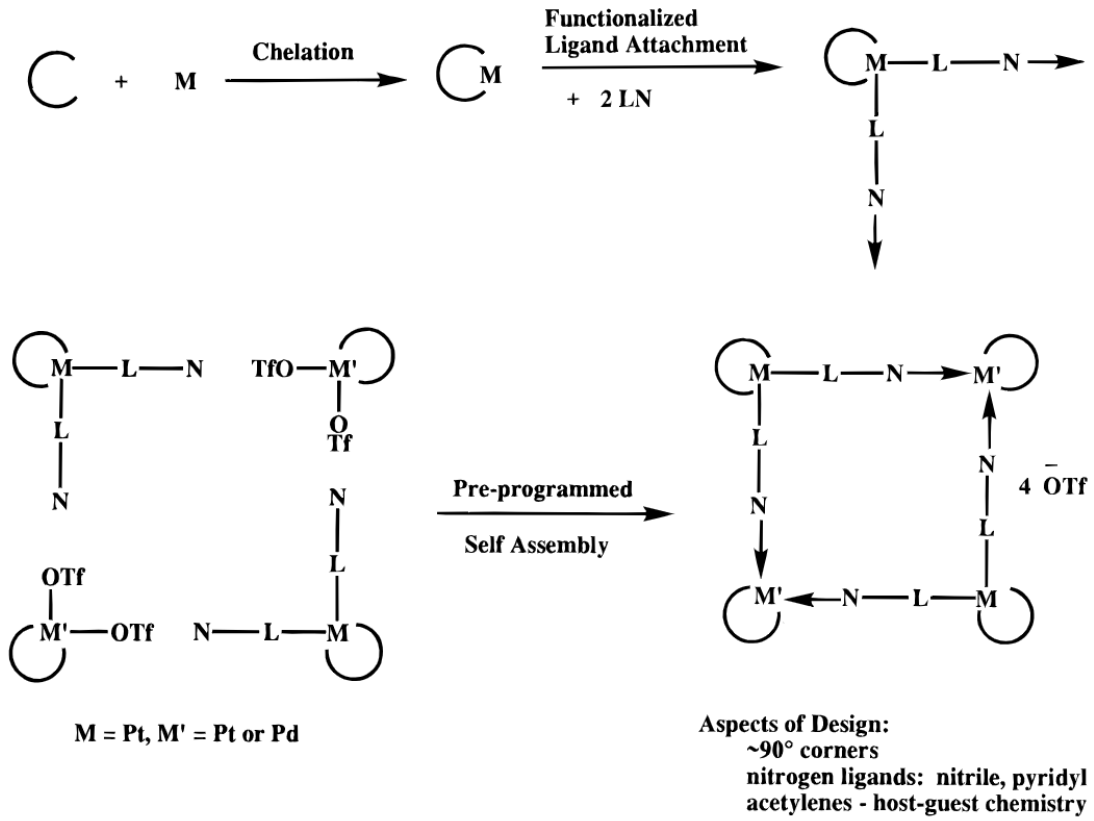
- Preparation: certain amount of ligand and metal in suitable solvent (heating)

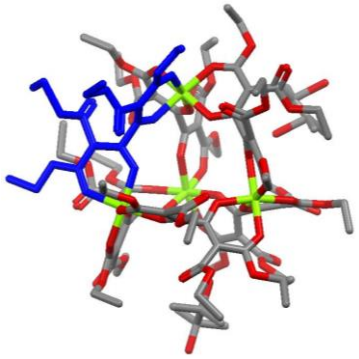
- The kinetic reversibility between complementary building blocks, reaction intermediates, and self-assembled architectures provides a way for the system to self-correct (an “incorrectly” formed bond can dissociate and reassociate “correctly”) leading to a product that is thermodynamically more stable than the starting components and any kinetically formed intermediates

- Transition metals, with their preferred coordination geometries, have served as acceptor units that can logically self-assemble with various rigid or flexible donors into predictable architectures

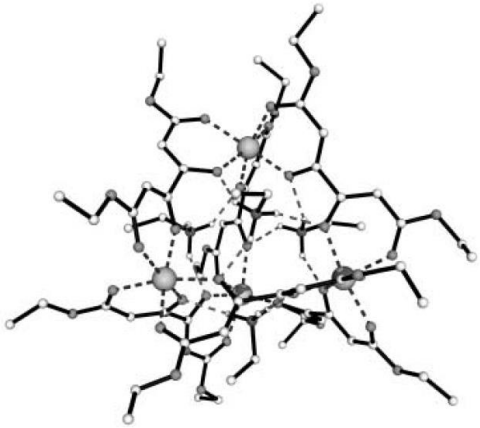
Coordination driven self-assembly

- Rational synthesis of molecular squares in early 90s (Fujita, Stang)
- The era of cage-like structures begun in 2002





Mg_4L_6

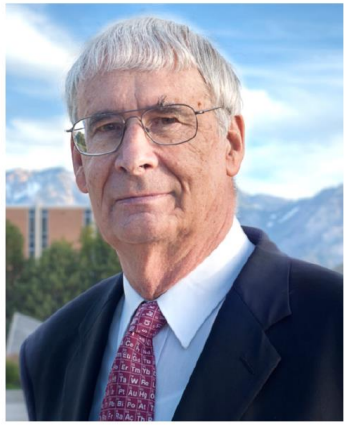


a) Stang et al. *J. Am. Chem. Soc.* **1997**,119, 2524-2533. b) Saalfrank et al. *Chem. Eur. J.* **2002**, 8, No. 12, 2679.

Synthetic and design strategies

- Many design and synthetic strategies have been developed using metal-ligand coordination, *e.g.*, directional bonding, symmetry interaction, molecular paneling

Makoto Fujita



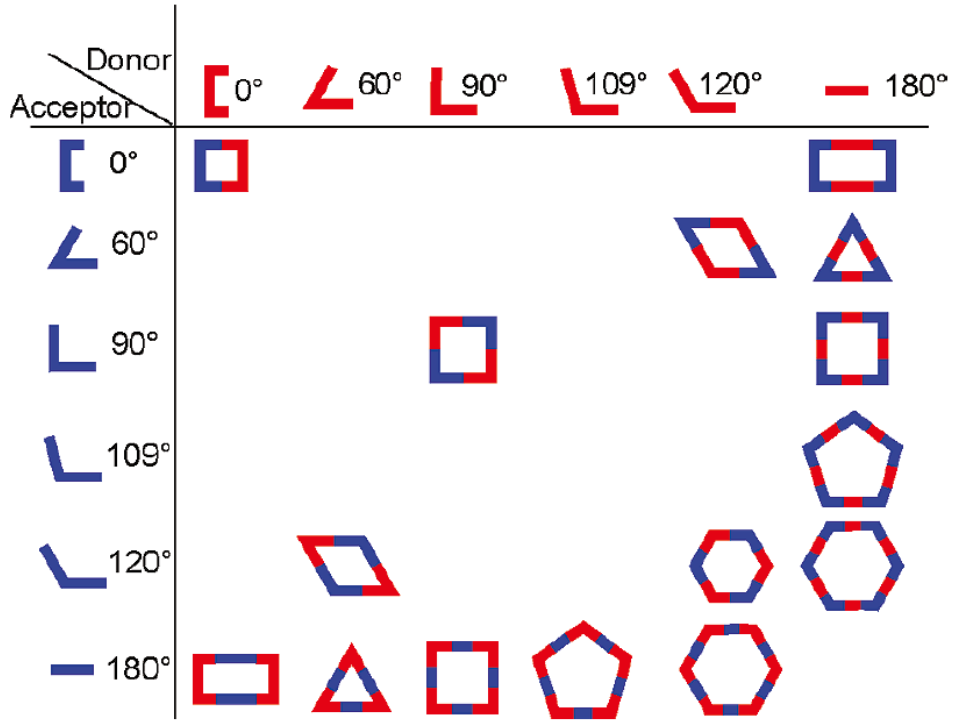
Peter J. Stang

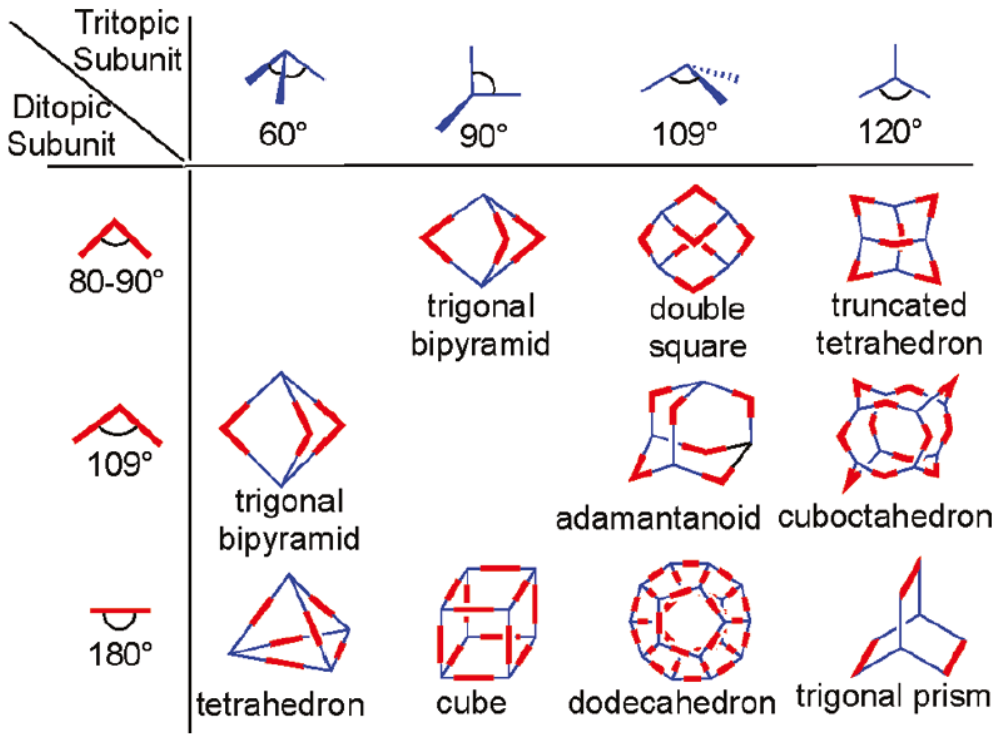
Kenneth N. Raymond

Stang et al. *Chem. Rev.* **2011**, 111, 6810–6918.

Directional bonding strategy

- Directional bonding strategy: complementary precursor units must be structurally rigid with predefined bite angles; and second, the appropriate stoichiometric ratio of the precursors must be used

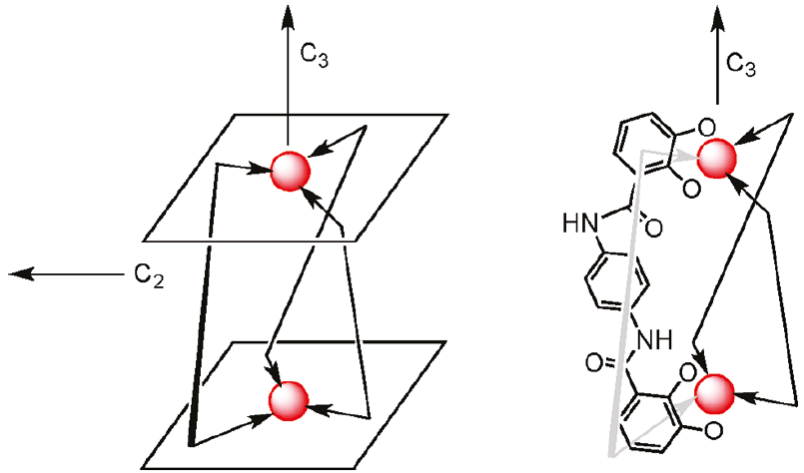


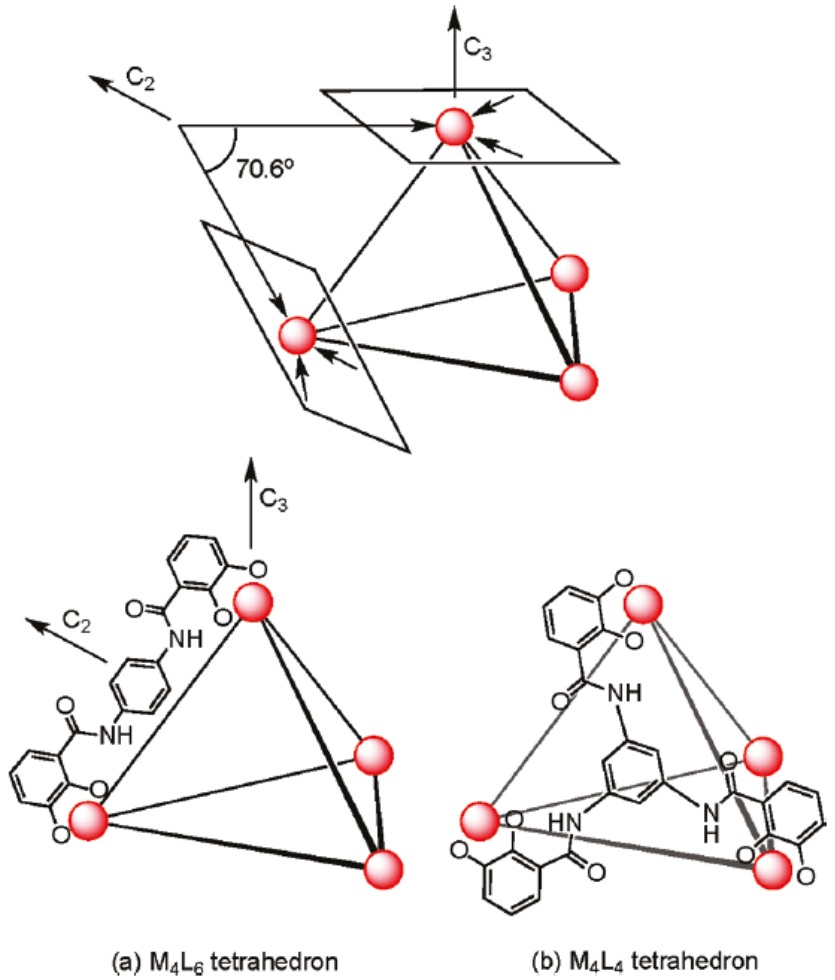


Stang et al. *Chem. Rev.* **2011**, 111, 6810–6918.

Symmetry interaction strategy

- rational synthetic approach for the synthesis of high-symmetry coordination assemblies using metal-ligand bonds (Raymond)
- multibranched chelating ligands with rigid backbones are used in conjunction with transition metals or main group metals



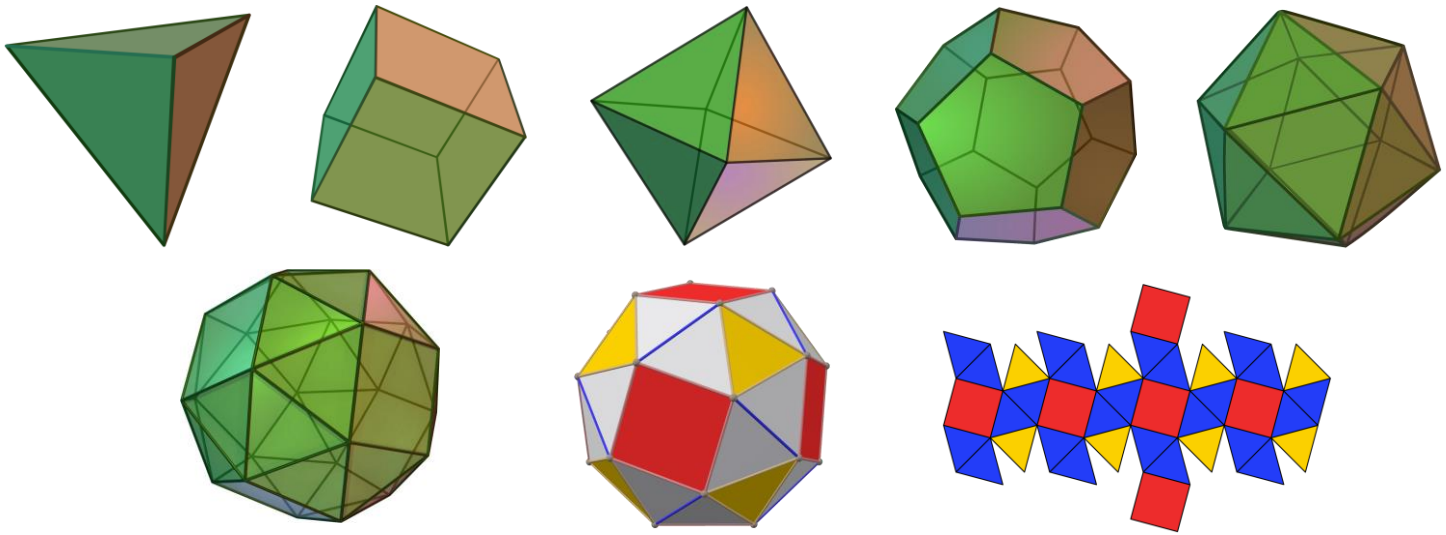


(a) M_4L_6 tetrahedron (b) M_4L_4 tetrahedron

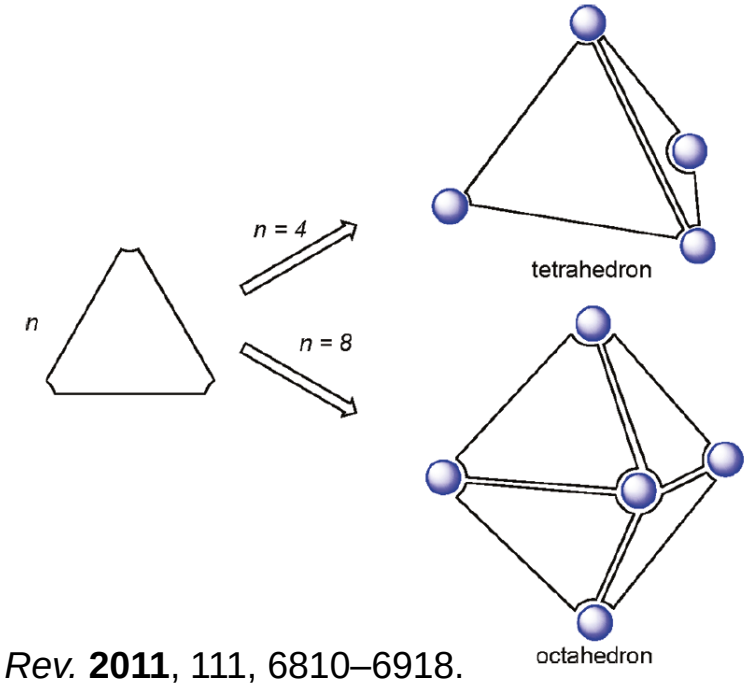
Stang et al. *Chem. Rev.* **2011**, 111, 6810–6918.

Molecular paneling strategy

- pioneered by Fujita and co-workers, formation of various functional and aesthetically elegant 3D architectures that resemble platonic solids (polyhedras are reduced to molecular components)
- e.g., tetrahedron can be designed by stitching together four triangular panels, while an octahedron can be prepared by bringing together eight such triangular panels

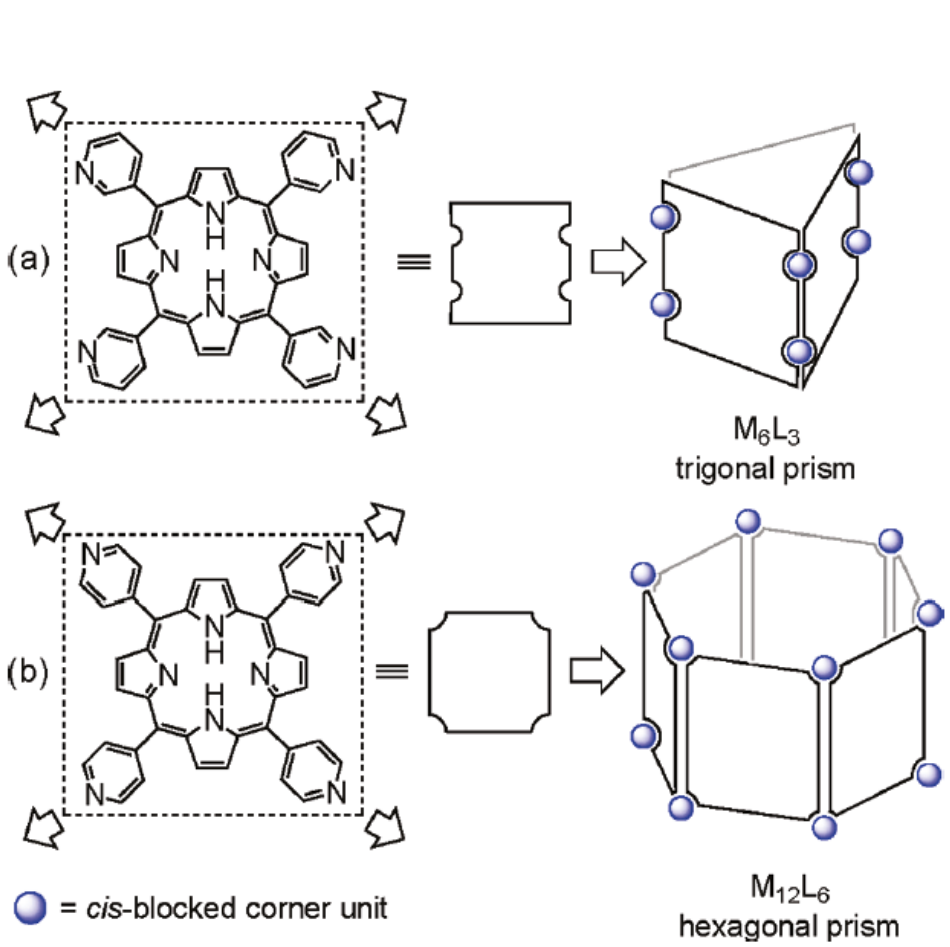


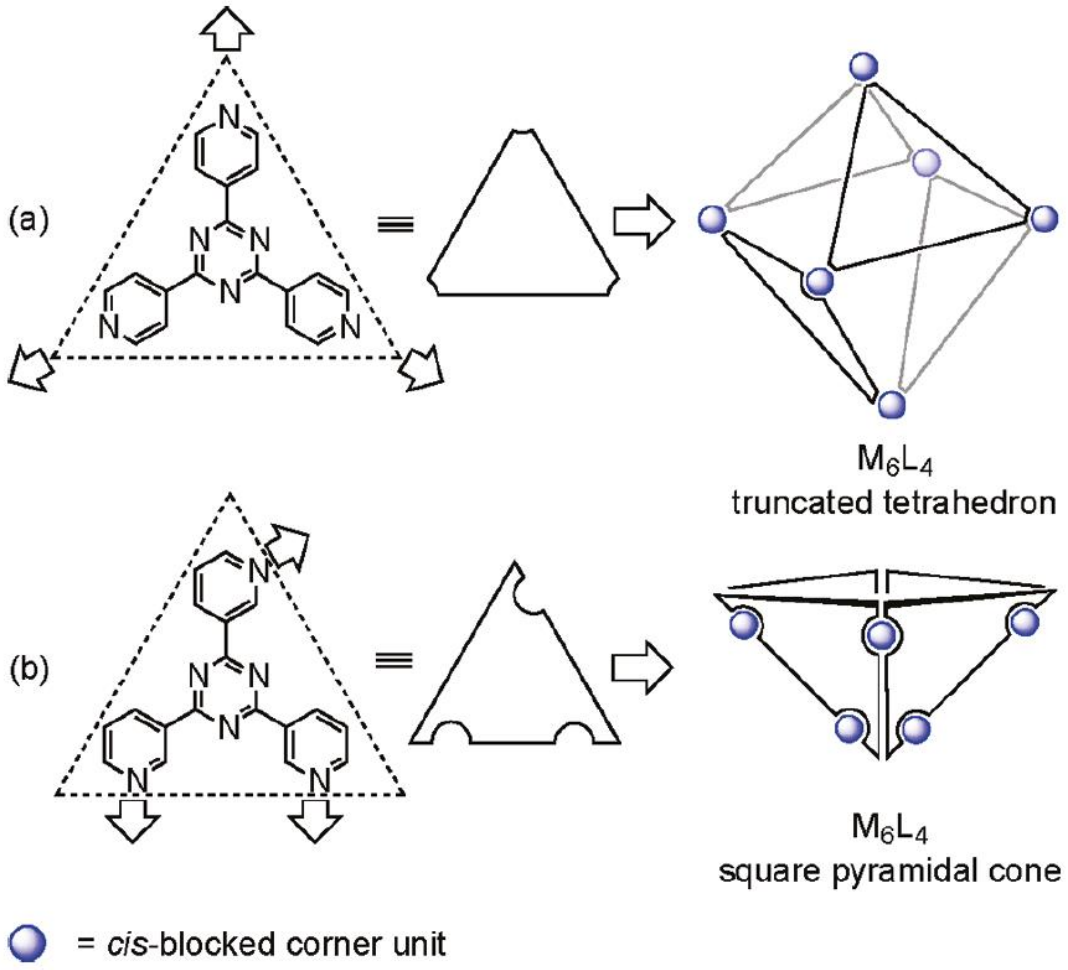
snub cube (snub cuboctahedron)



Stang et al. *Chem. Rev.* **2011**, 111, 6810–6918.

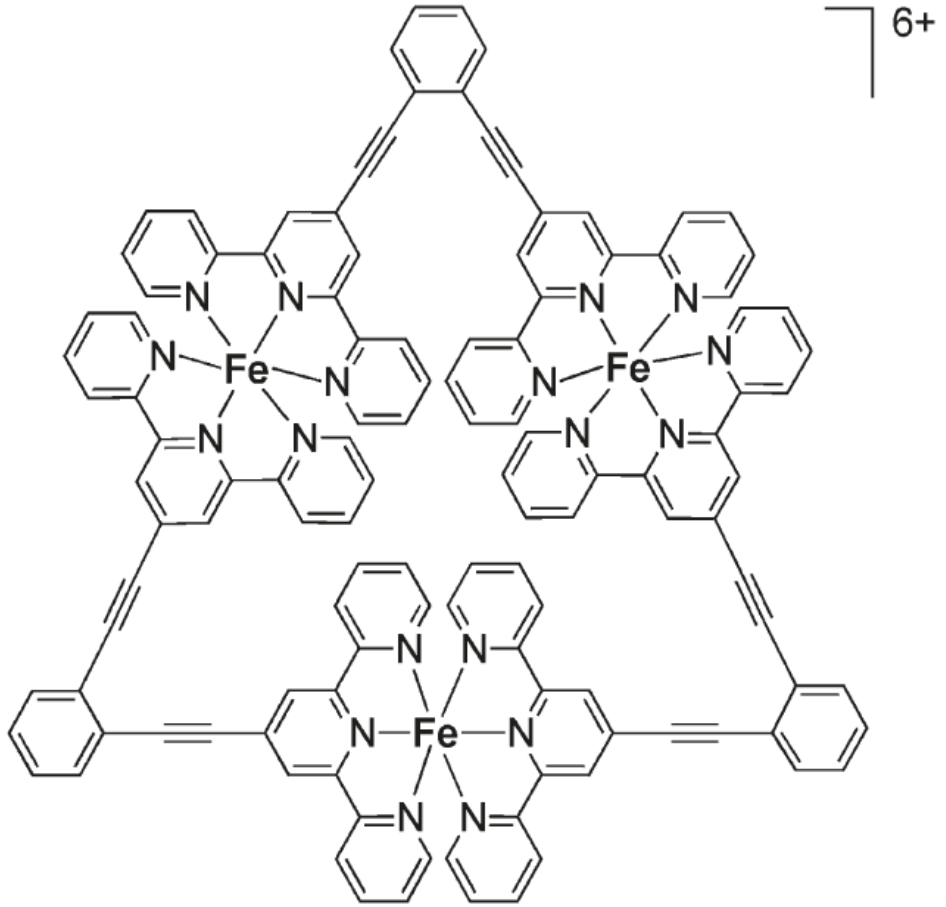
Molecular paneling strategy

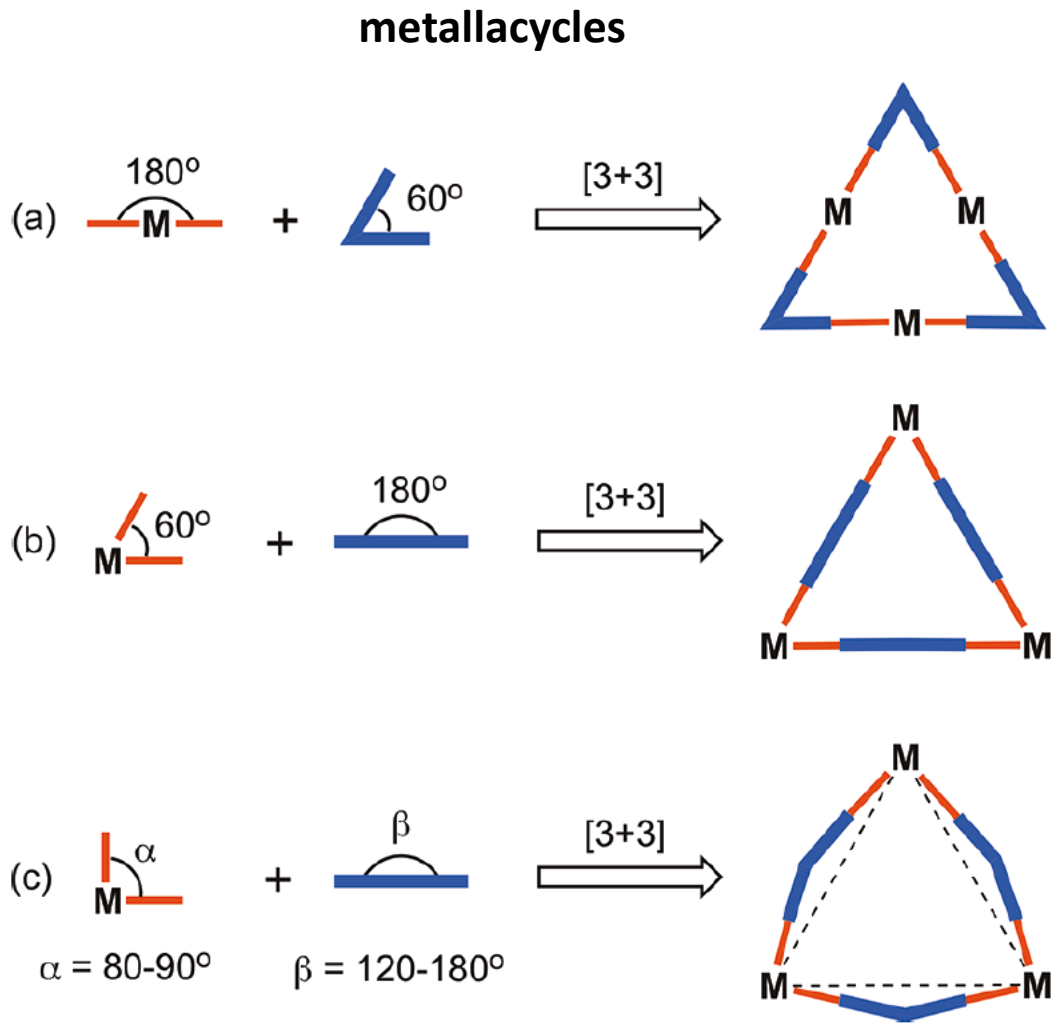




Stang et al. *Chem. Rev.* **2011**, 111, 6810–6918.

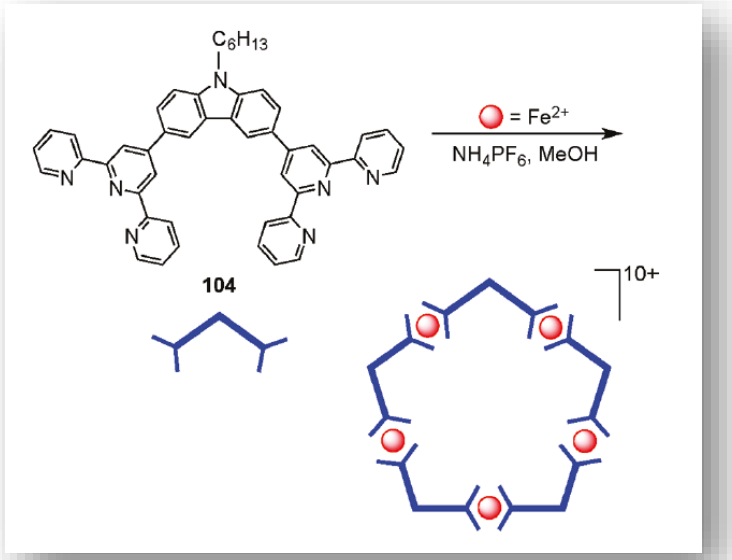
Supramolecular coordination self-assemblies

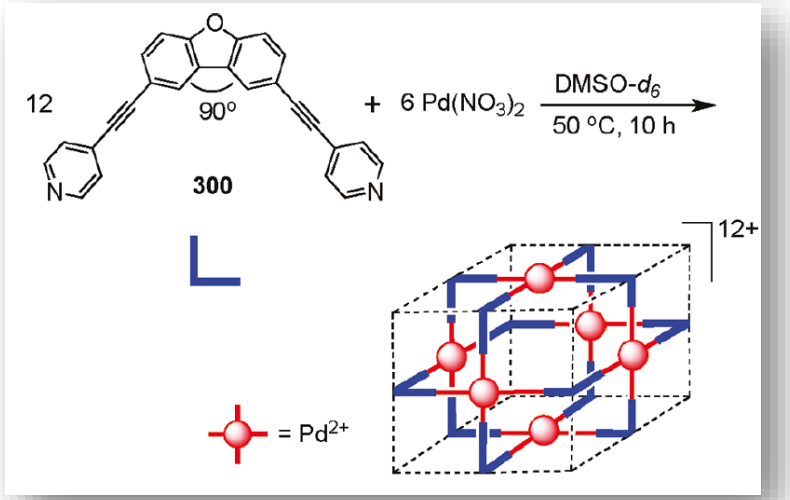


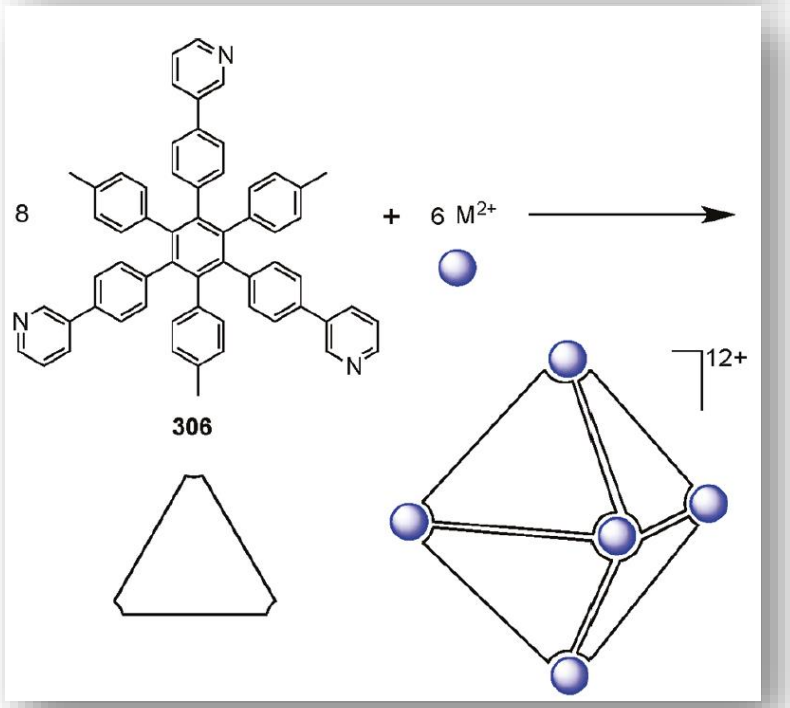


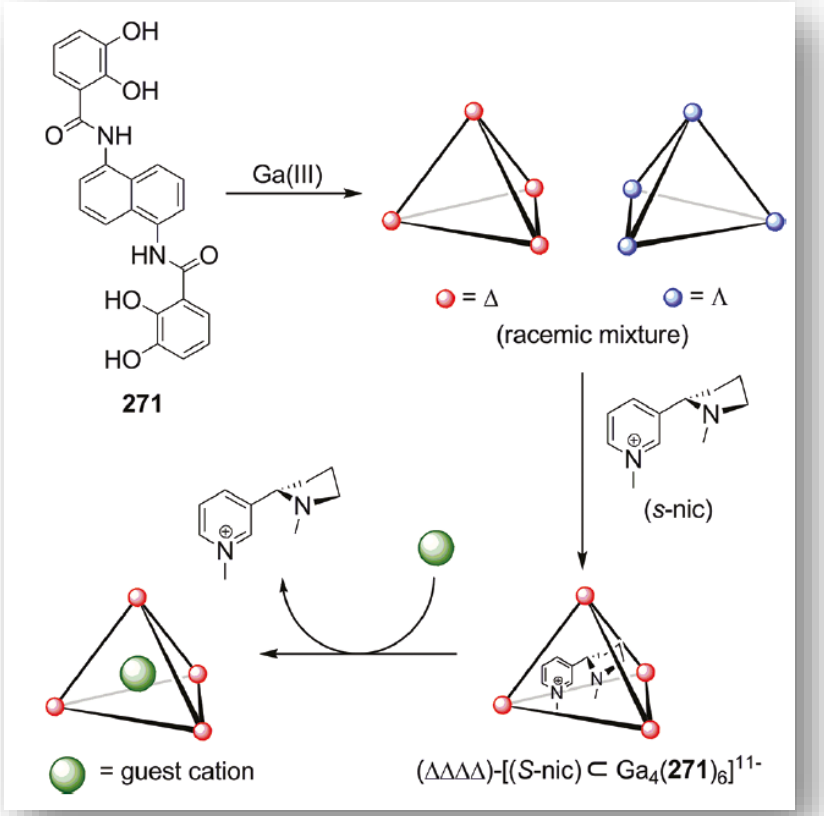
Stang et al. *Chem. Rev.* **2011**, 111, 6810–6918.

Supramolecular coordination self-assemblies



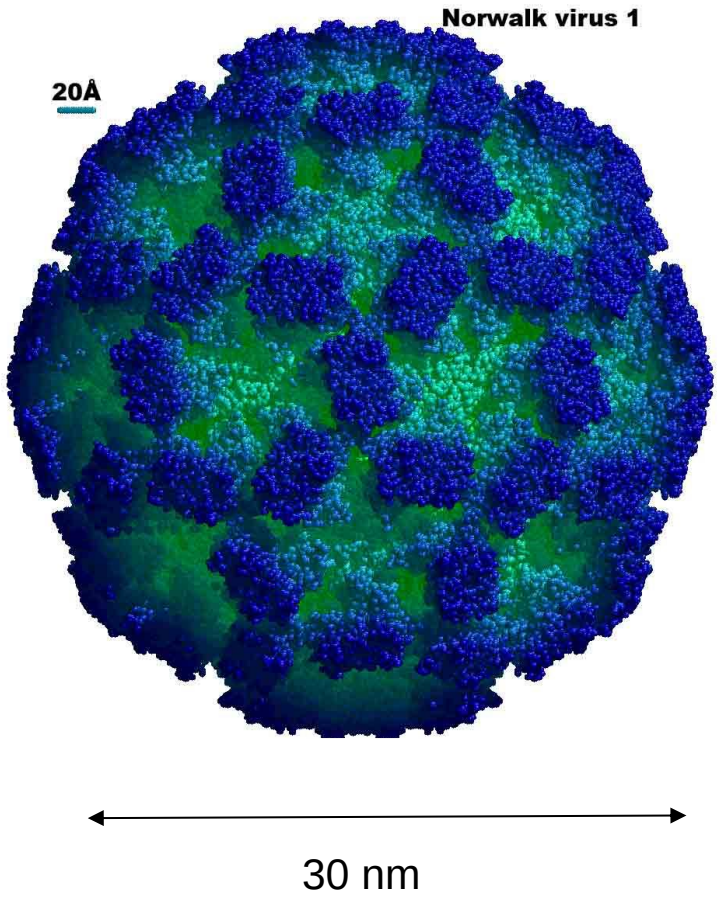




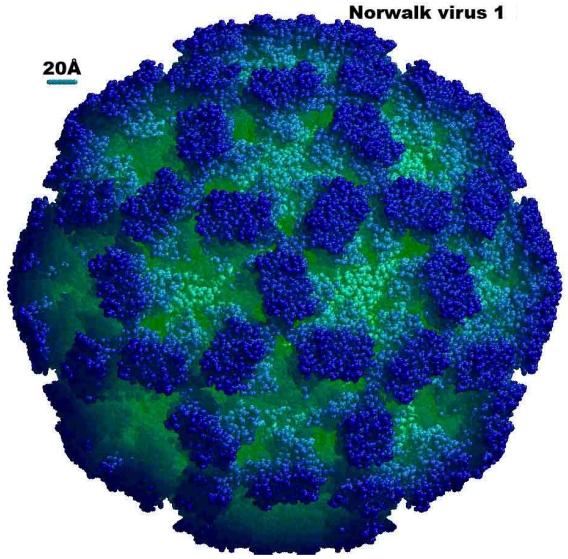


Stang et al. *Chem. Rev.* **2011**, 111, 6810–6918.

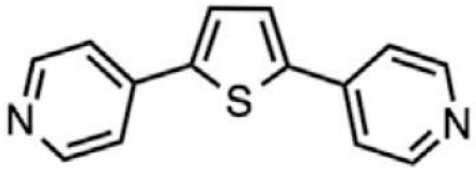
And the greatest supramolecular chemist is: Nature



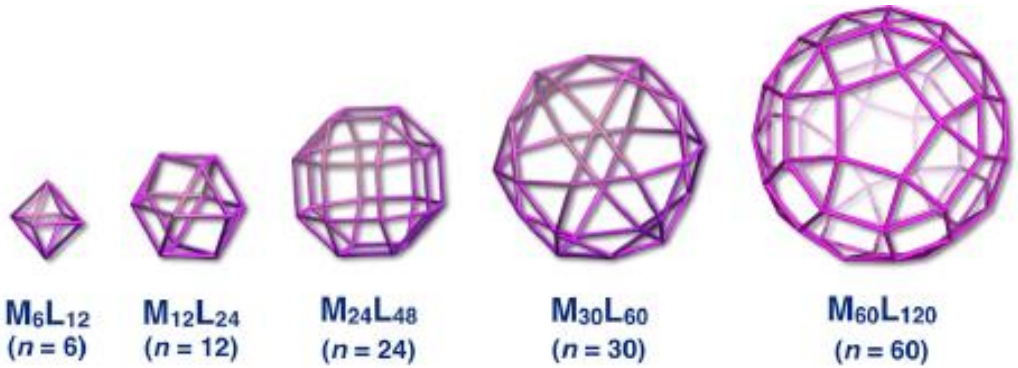
And the greatest supramolecular chemist is: Nature… and Prof. Fujita



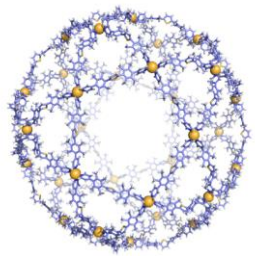
30 nm



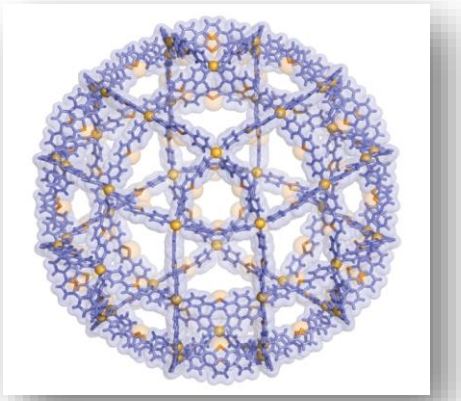
θ = 150°



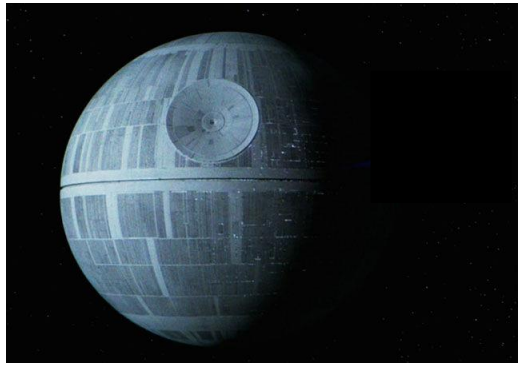
$M_{30}L_{60}$



8.2 nm

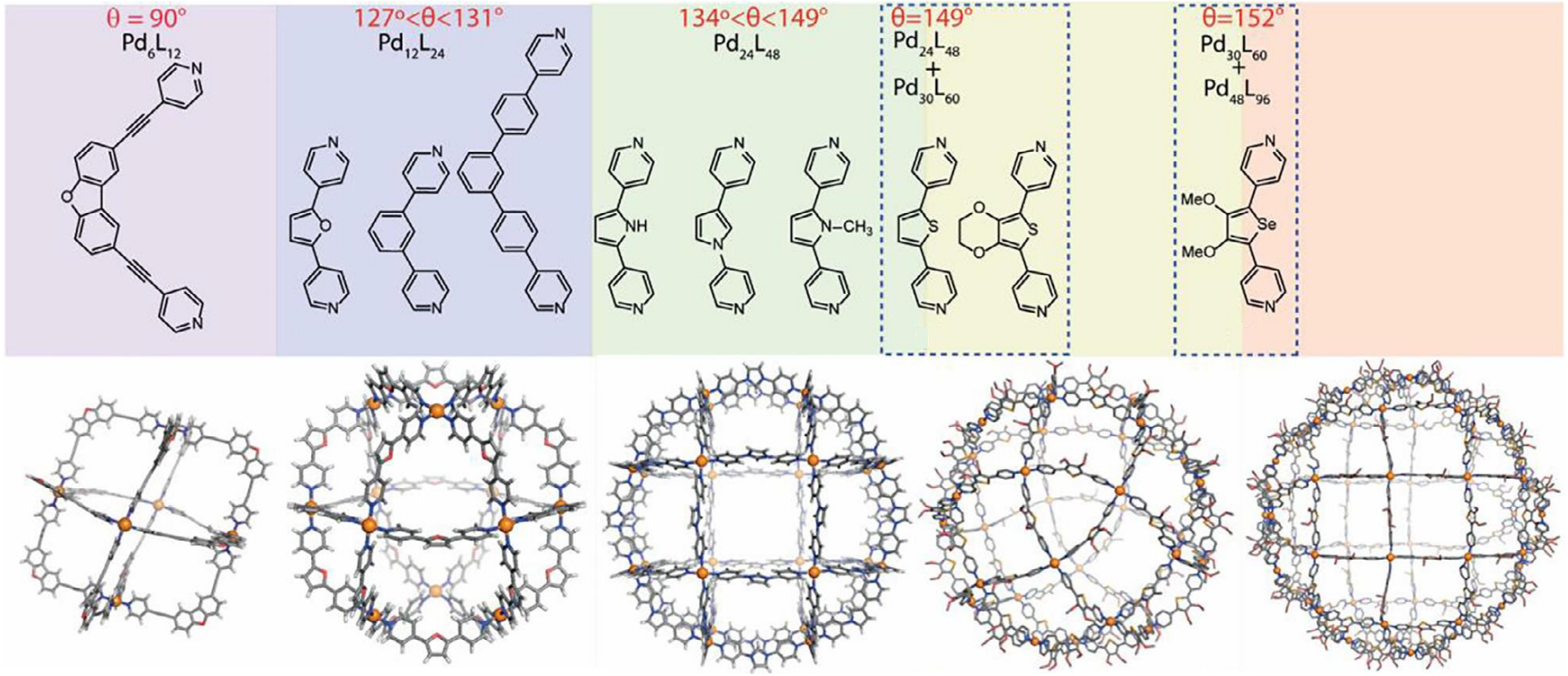


$Pd_{48}L_{96}$



Fujita D., Ueda Y., Sato S., Yokoyama H., Mizuno N., Kumasaka T., **Fujita M.**: *Chem* **2016**, *1*, 91-101.

Ditopic pyridyl ligands and their Pd_nL_{2n} self-assemblies



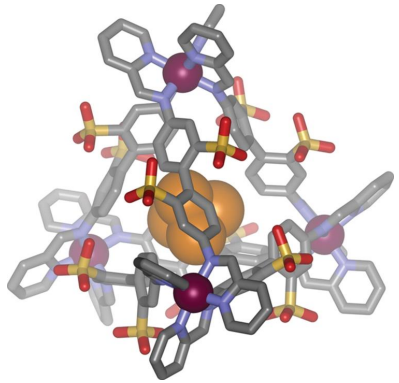
Ligands of increasing bend angle leading to complexes from Pd_6L_{12} up to $Pd_{48}L_{96}$ spheres

S. Saha, I. Regeni, G. H. Clever, *Coord. Chem. Rev.* **2018**, *374*, 1-14.

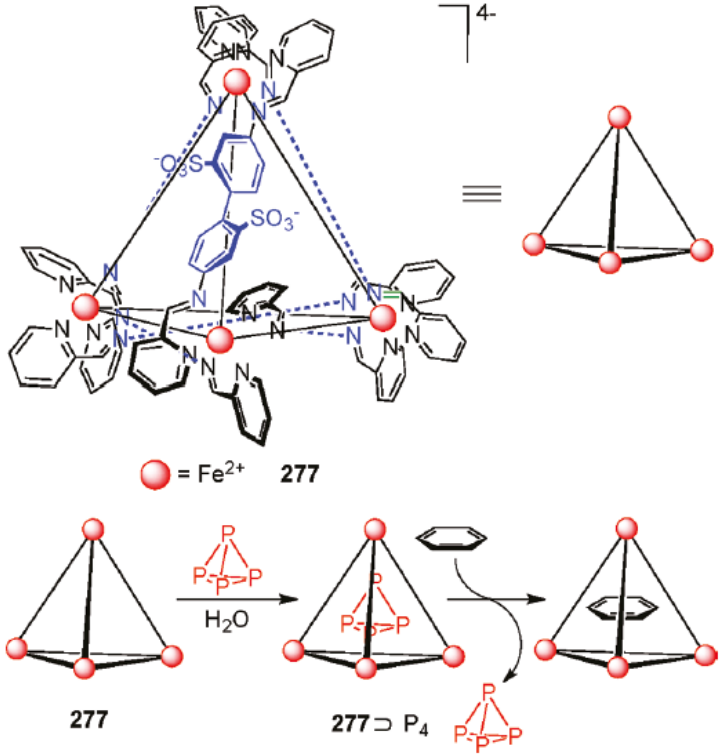
D. Fujita, Y. Ueda, S. Sato, N. Mizuno, T. Kumasaka, M. Fujita, *Nature* **2016**, *540*, 563-566.

Functionalized systems

- By functionalization of 3D supramolecular assemblies we can emulate biological systems leading to their applications in various fields such as host-guest chemistry, cavity directed synthesis, catalysis, photonics, redox activity, magnetic behaviour, self-organization, sensing, and medicine



air-stable P_4

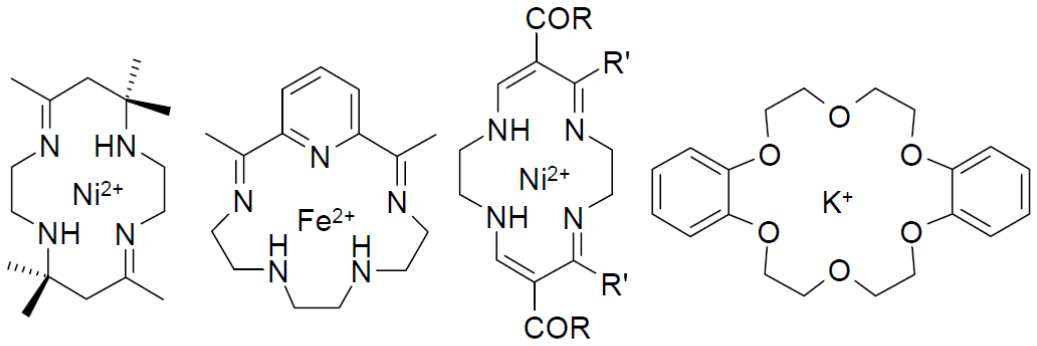


Nitschke et al. *Science* **2009**, *324*, 1697.

Host-Guest Chemistry

- A molecule binding another molecule producing **host-guest complex**

- Ignoring the electronic effects, it can be imagined as hand catching a ball



Curtis 1961 Busch 1964 Jäger 1964 Pedersen 1967

- One of the first cage-like host-guest definition by H.M. Powell 1948 (Oxford)
- **Cavitands** = hosts having permanent intramolecular cavities
- Forces = mostly electrostatic – **complex**; less specific, weaker non-directional interaction, van der Waals, crystal close packing = **cavitate, clathrate**

Cram *et al.:* J. Am. Chem. Soc., 1977, 99, 2564–2571

Determination of strength of host-guest interaction

- Binding constant K = thermodynamic stability of a host-guest complex in a given solvent at a given temperature ($dm^3\ mol^{-1}$, M^{-1}) (also formation, dissociation, association, or stability constant)

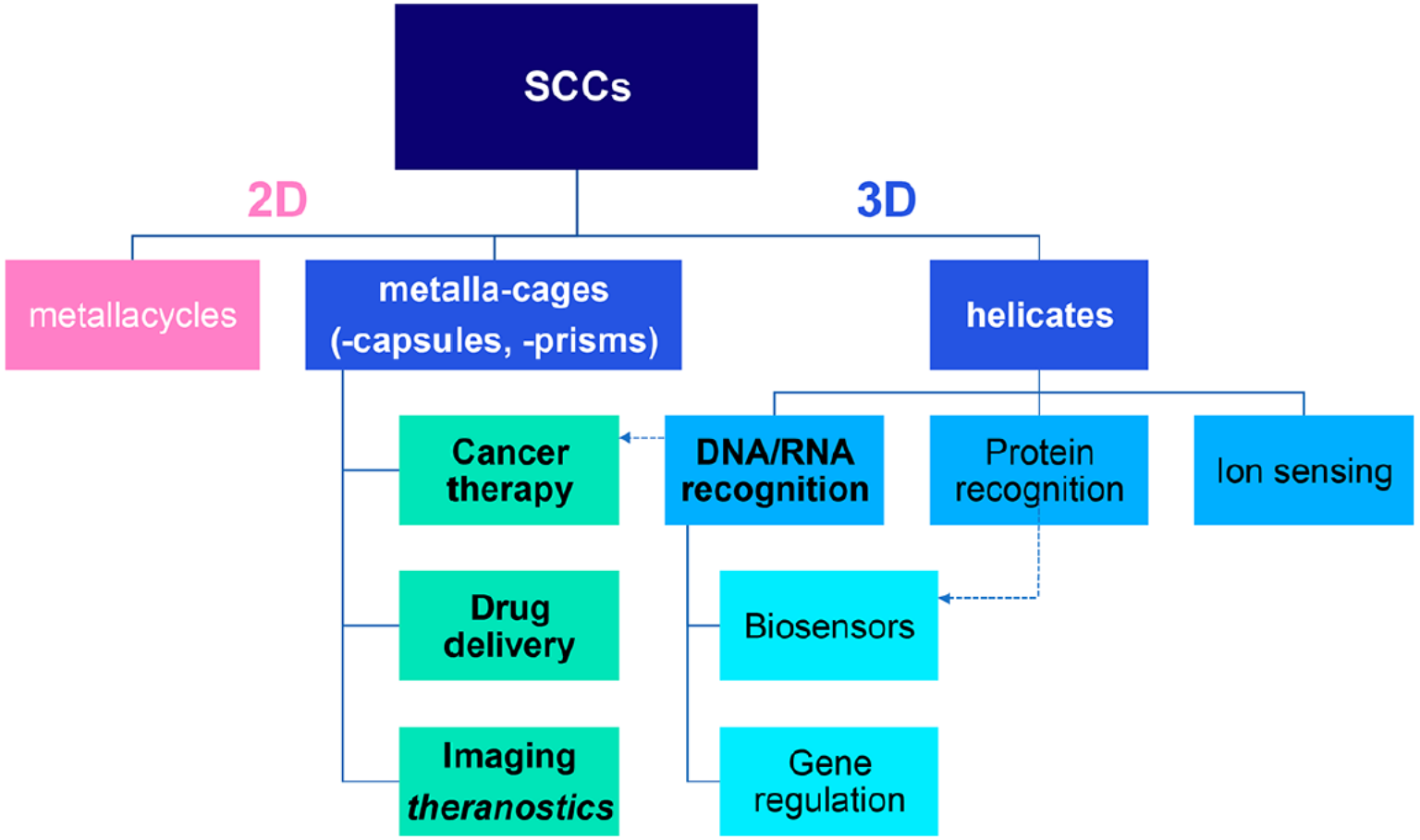
$$H + G \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HG$$

- $K = \frac{[HG]}{[H][G]}$ or $K = \frac{k_1}{k_{\_1}}$ (rate constants)

- Gibbs energy (accociation process)

$$-\Delta G^0 = RT \ln K$$

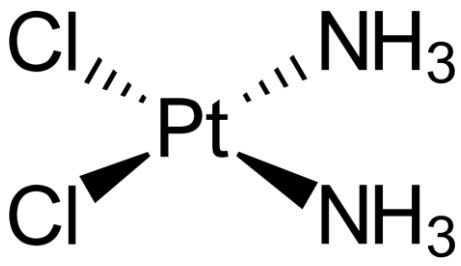
Supramolecular coordination cages (SCCs) and their biomedical applications

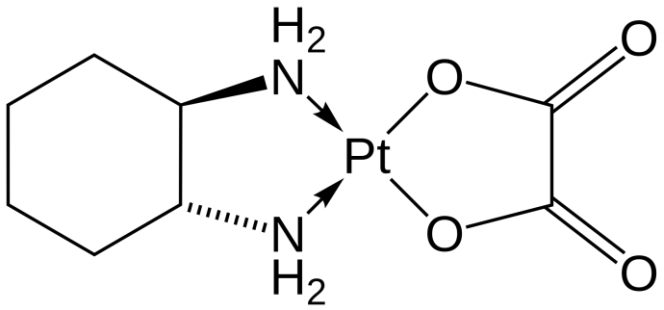


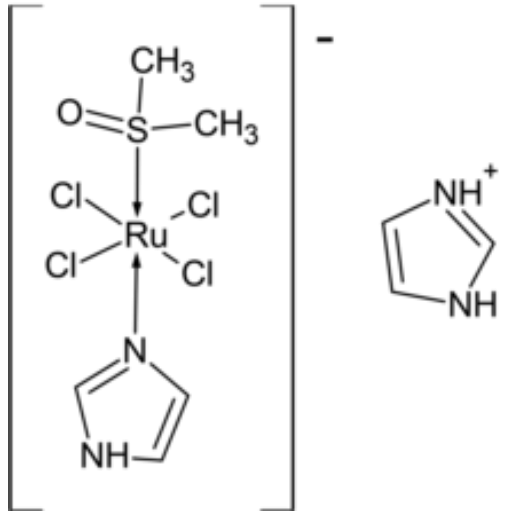
Casini *et al. Inorg. Chem.* **2017**, *56,* 14715−14729.

Biomedical applications

- Inspired by the clinically used or tested metallodrugs derived from Pt(II), Ru(II), or Ru(III)







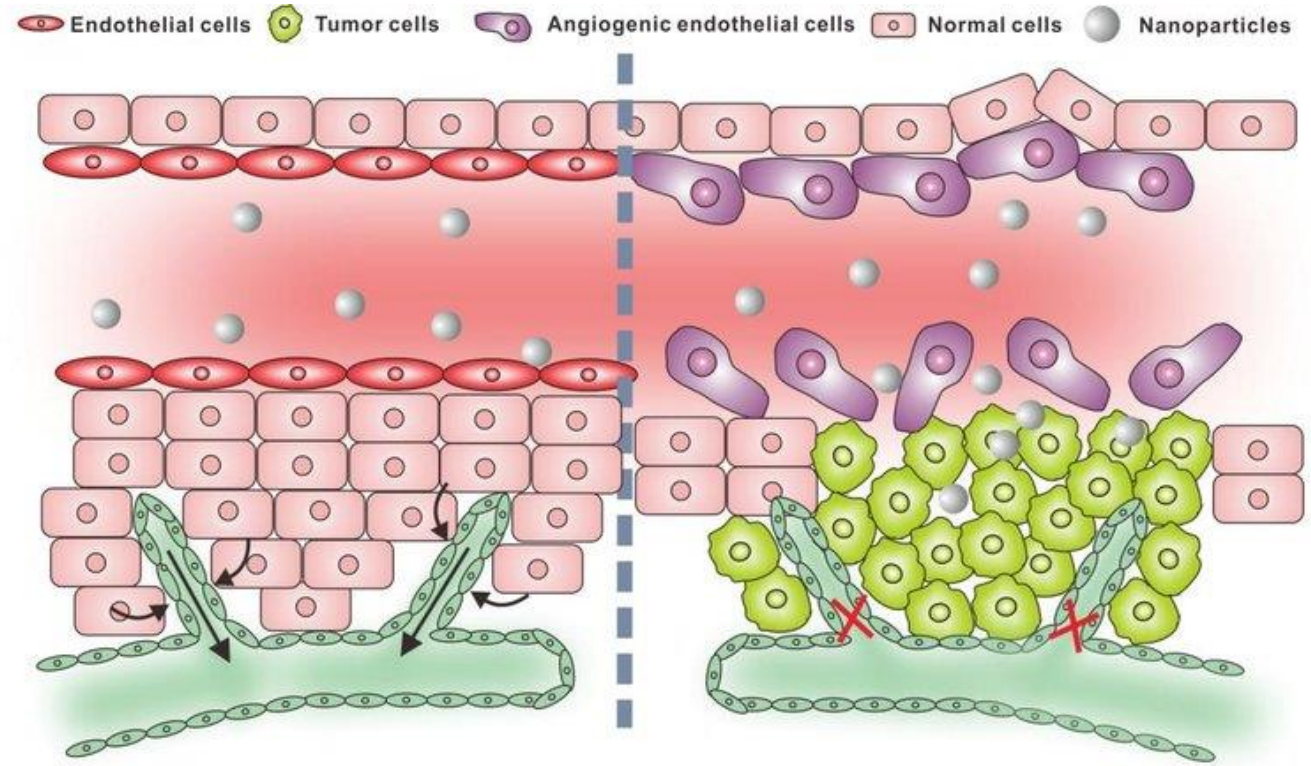
- Pioneered by Therrien, organometallic Ru(II) metallacycles and cages

- Three main areas: metallacycles, metallacages, metallohelicates (and nanoparticles derived)

a) Casini *et al. Inorg. Chem.* **2017**, *56,* 14715−14729. b) Ahmedova (ed. Crowley) *Front. Chem.* **2018**, *6*, 620.

Enhanced permeability and retention (EPR) effect

- high–molecular weight nontargeted drugs and prodrugs accumulate in tissues that offer increased vascular permeability, such as in sites of inflammation or cancer



Xie et al. *Curr. Cancer Drug Target* **2019**, *19*(4), 257.

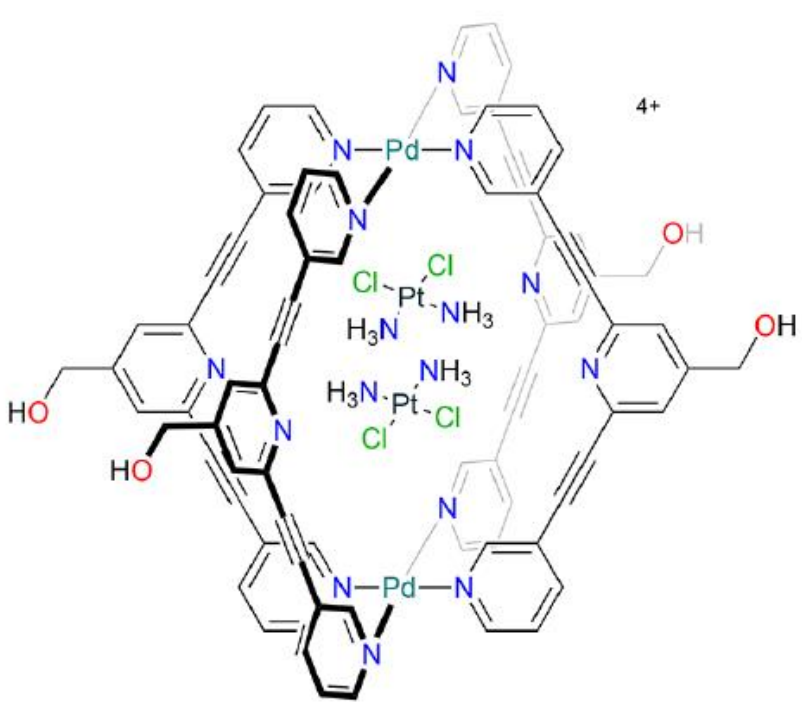
Biomedical applications

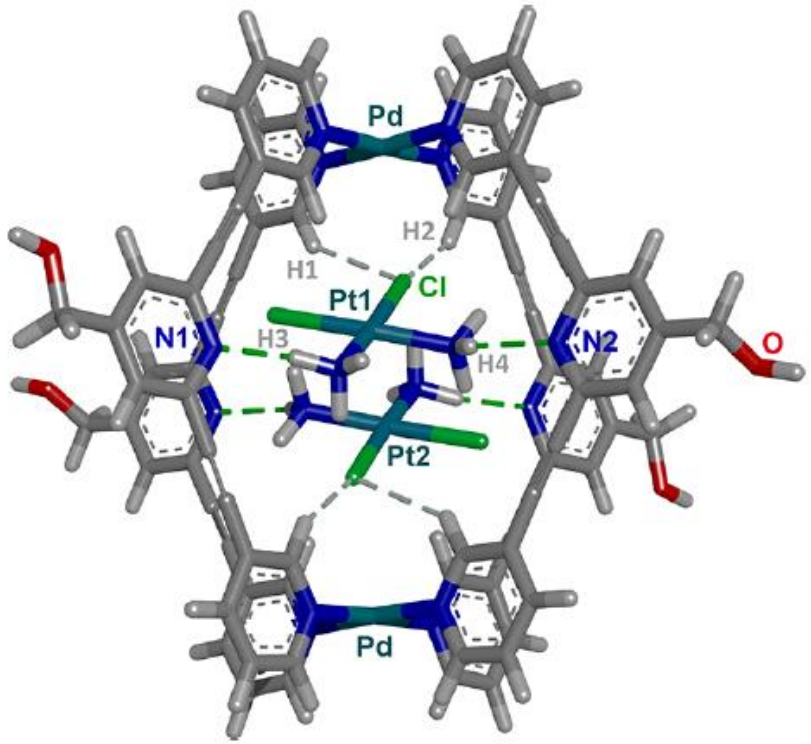
- The Pt(II) metallacycles bind to DNA
- Metallacages can be excellent hosts for bioactive guests or have bifunctional molecular moieties
- Metallahelicates can have specific helicity that is capable of selective interactions with biomolecules with certain conformation, such as DNA fragments
- Allow combination of therapeutic and diagnostic properties – theranostic applications

a) Casini *et al. Inorg. Chem.* **2017**, *56,* 14715−14729. b) Ahmedova (ed. Crowley) *Front. Chem.* **2018**, *6*, 620.

Biomedical applications

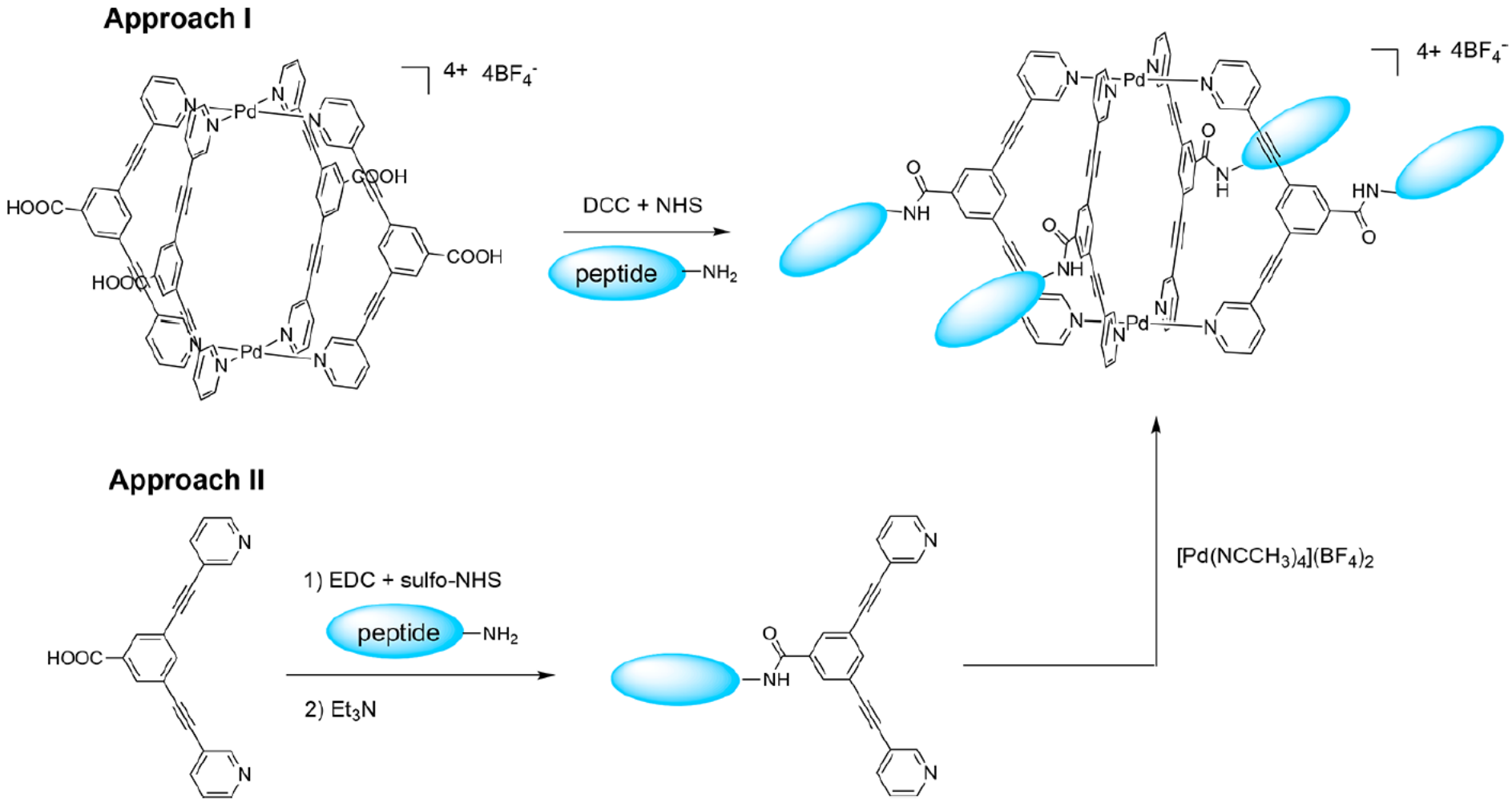
- Classic work by Crowley





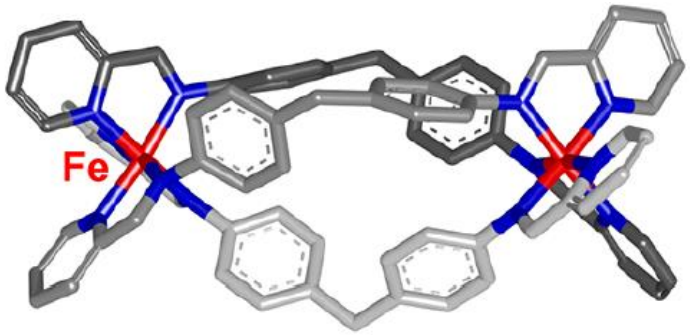
Crowley et al. *Chem. Sci.* **2012**, *3*, 778–784. b) Casini *et al. Inorg. Chem.* **2017**, *56,* 14715−14729.

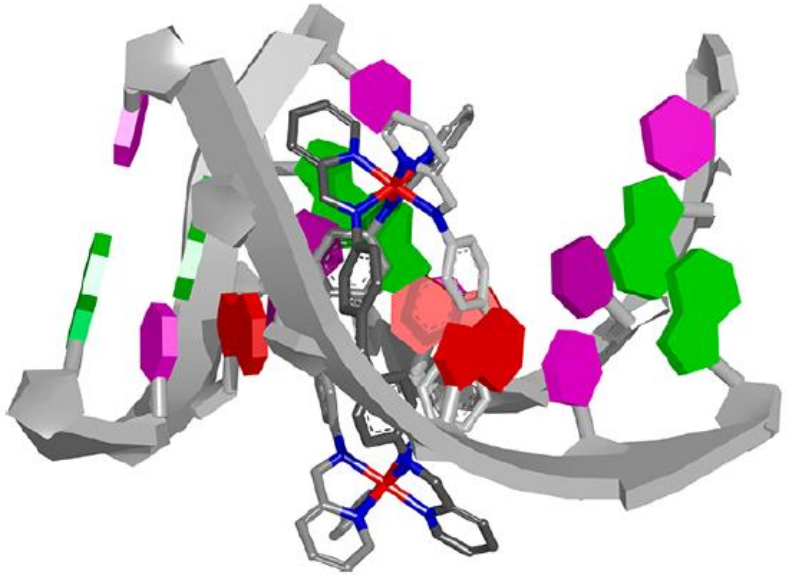
Biomedical applications

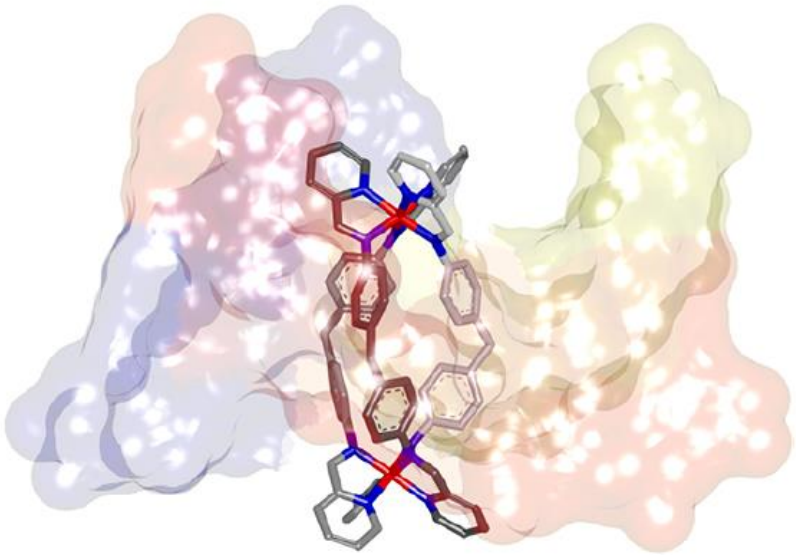


Casini *et al. Inorg. Chem.* **2017**, *56,* 14715−14729.

Biomedical applications

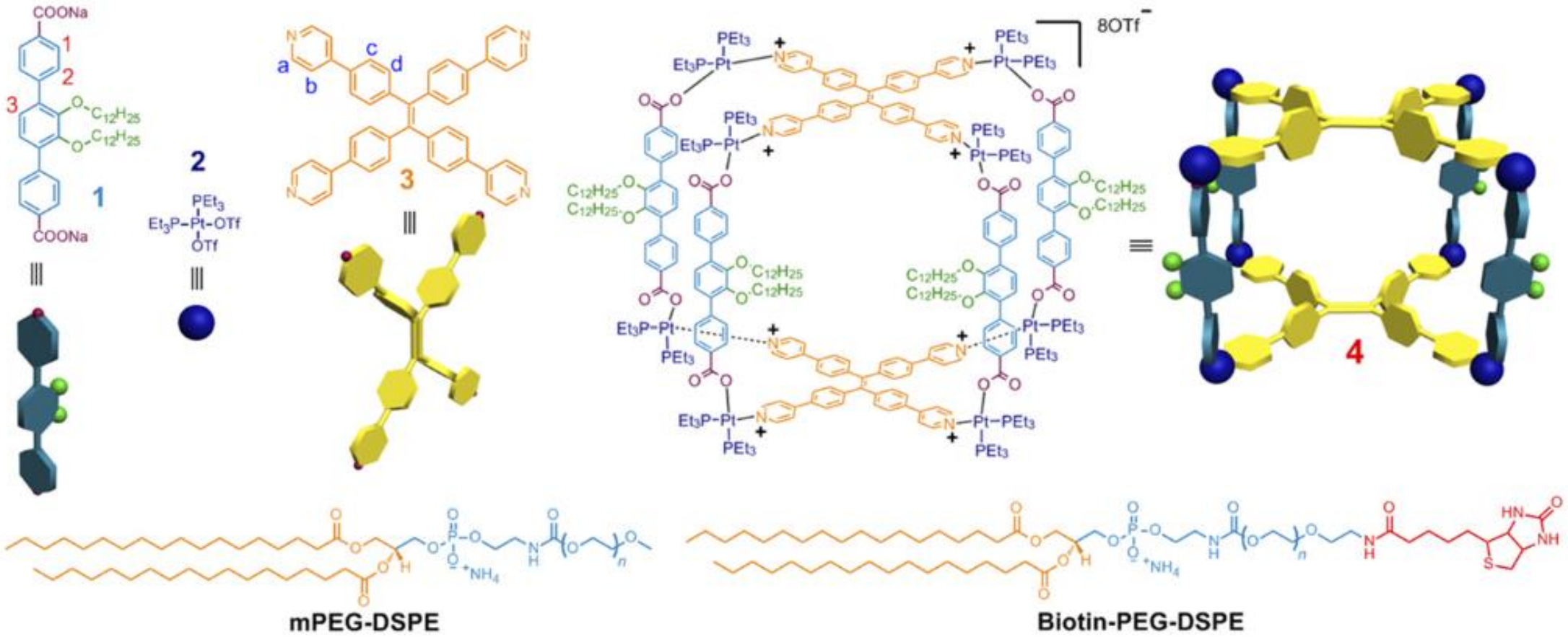






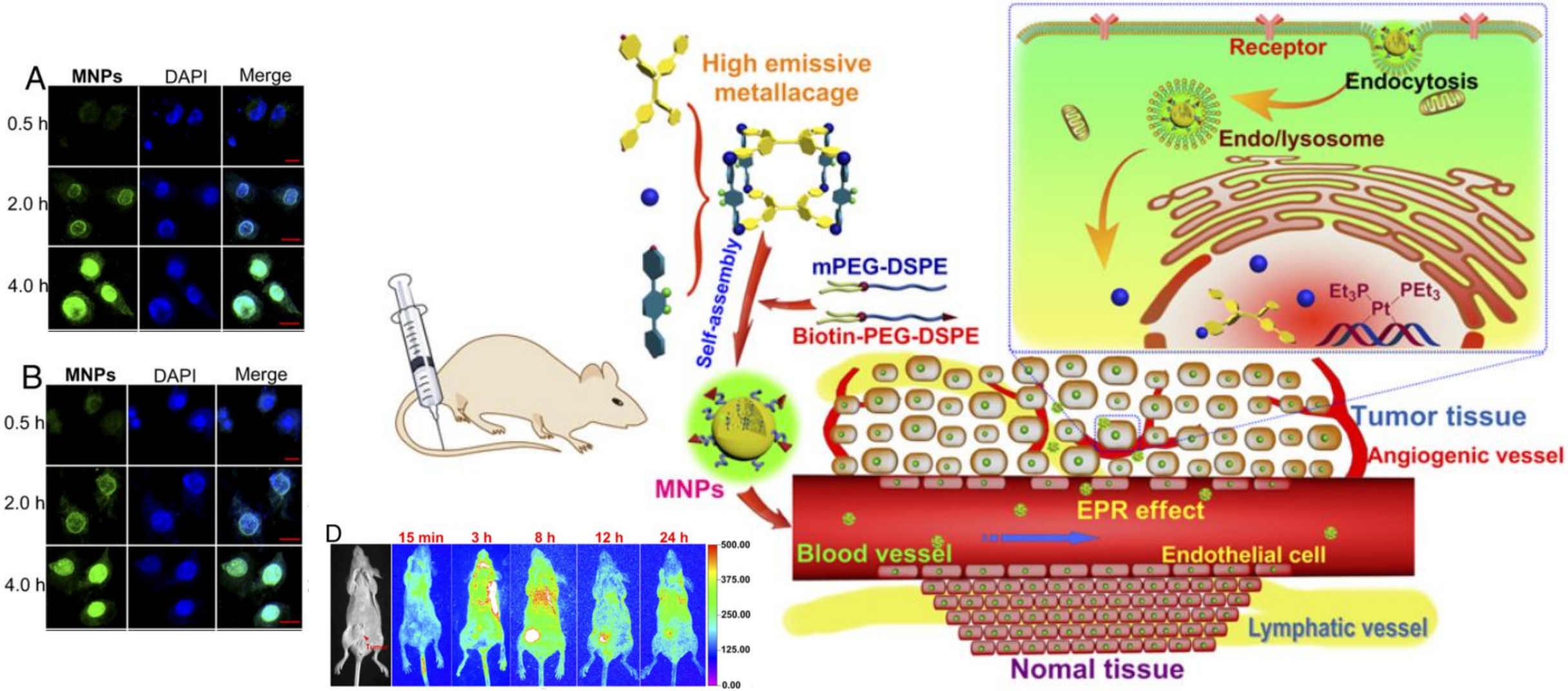
Casini *et al. Inorg. Chem.* **2017**, *56,* 14715−14729.

Biotin-targeted metallocage-loaded emissive nanoparticles



Stang *et al. PNAS* **2016**, *113(48)*, 13720.

Biotin-targeted metallocage-loaded emissive nanoparticles



Stang *et al. PNAS* **2016**, *113(48)*, 13720.

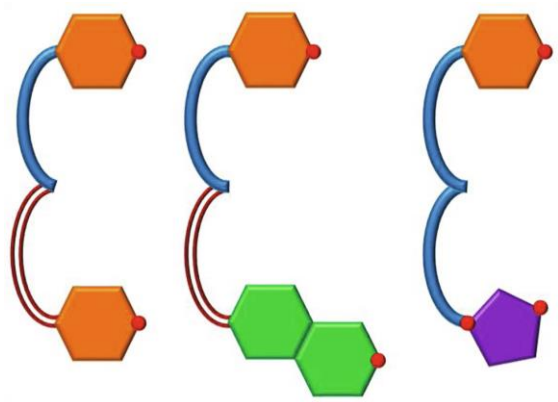
Biomedical applications challenges

- Attaining a selective and spatially controlled release of guest molecules remains a difficult task – stimuli responsive building blocks mechanisms exploiting pH, temperature, redox reactions, polarity, light, or electric field (e.g., in tumor tissues)

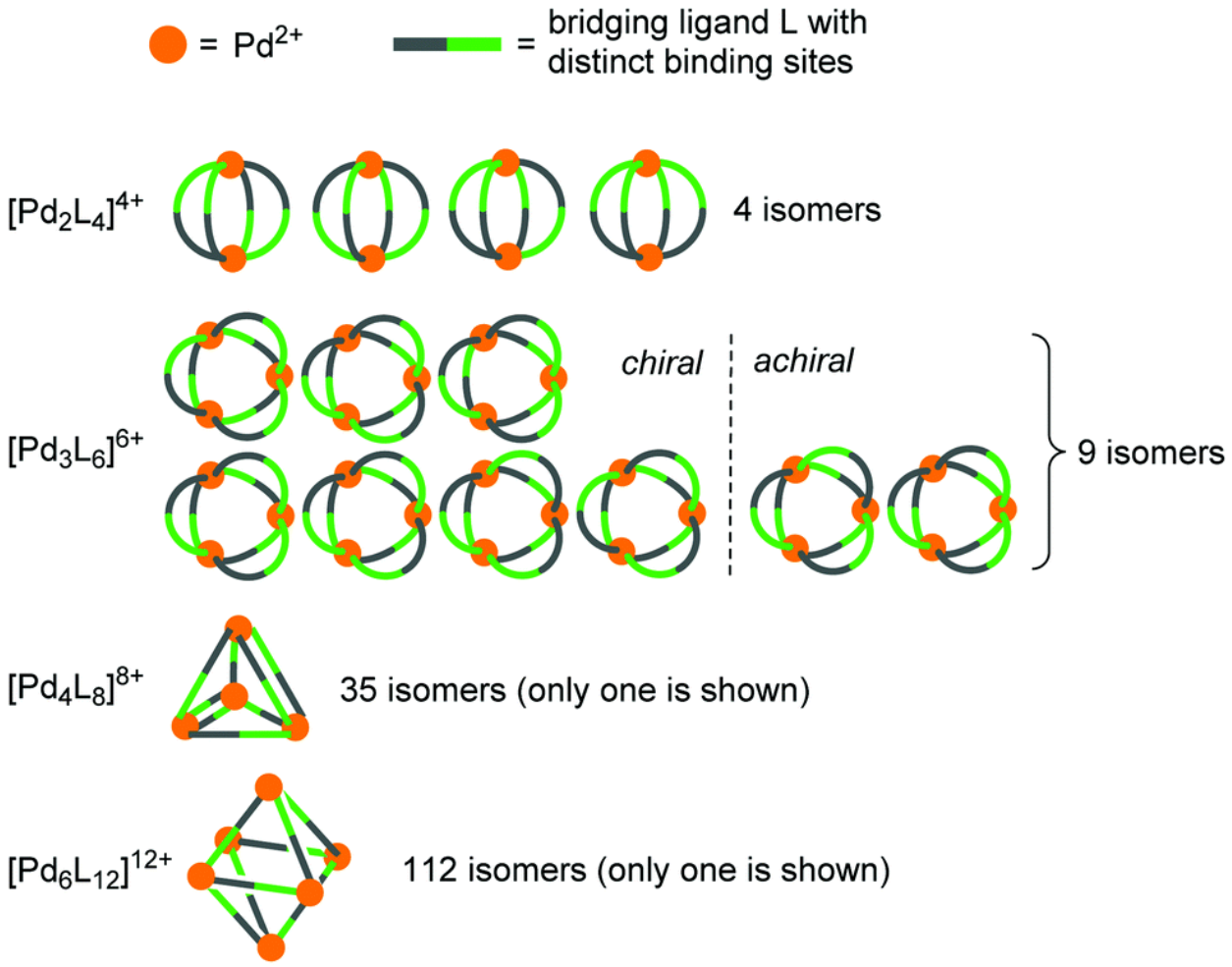
- Possibility of encapsulating different drug molecules in the same supramolecular metallacage

- Possibility of controlling destiny of SCCs in a physiological environment in order to avoid possible side effects (related also to toxicity of naked and encapsulated drug, stability *in vitro*, *in vivo,* solubility, etc.)

Our contribution to the field



Different types of unsymmetric bidentate ligands

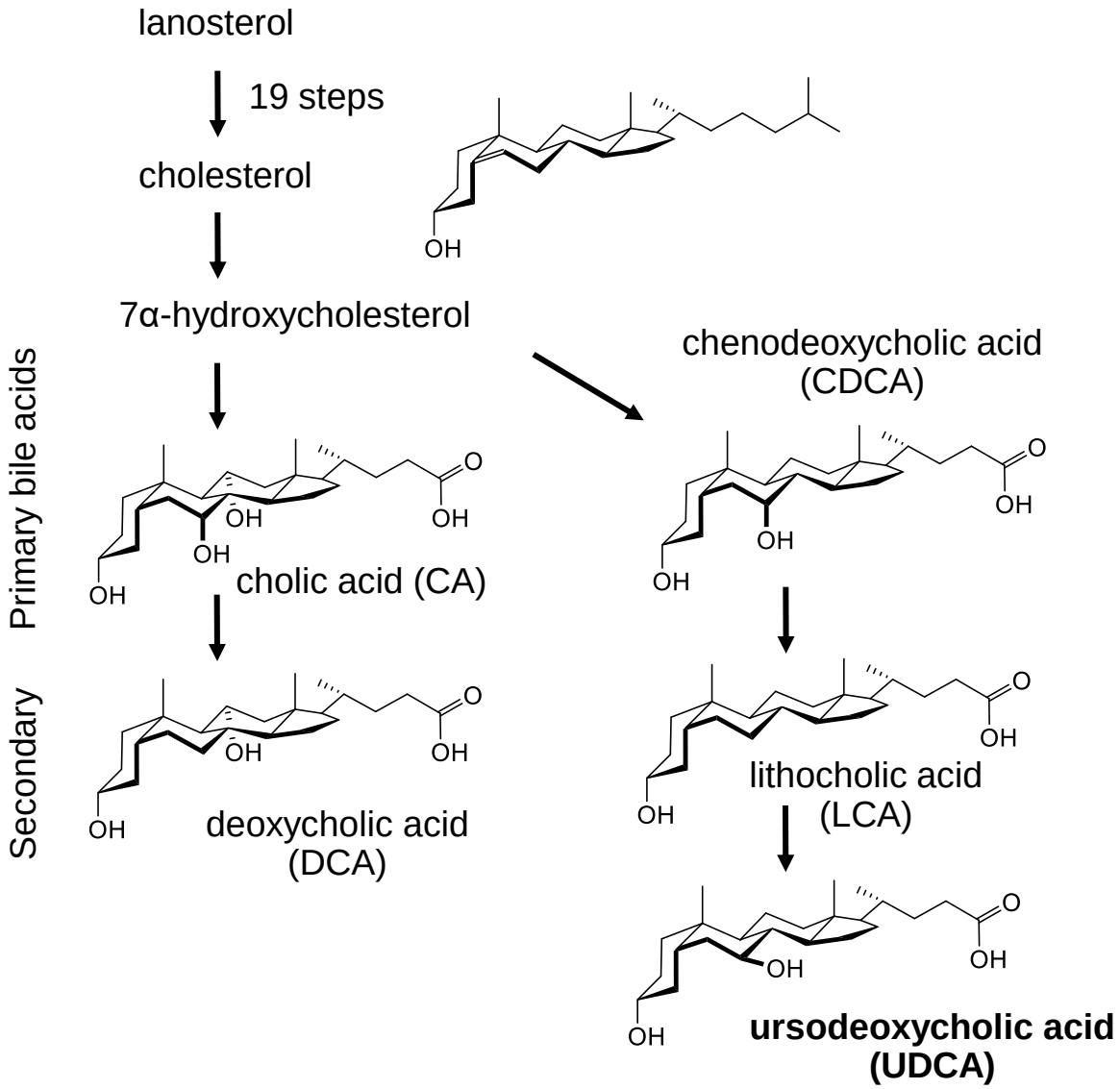


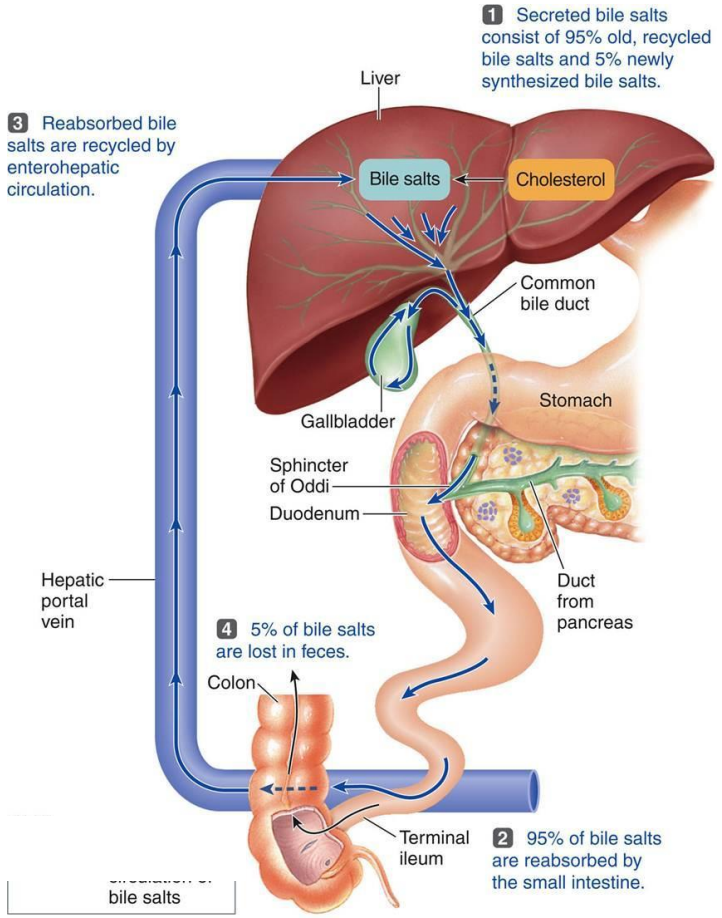
D. Tripathy, N. B. Debata, K. C. Naik, H. S. Sahoo, *Coord. Chem. Rev.* **2022**, *456*, 214396-214423.

R. Li, A. Marcus, F. Fadaei-Tirani, K. Severin, *Chem. Commun.* **2021**, *57*, 10023-10026.

Bile acid as scaffold of unsymmetric chiral ligands

- Enterohepatic circulation, transmembrane transport activity



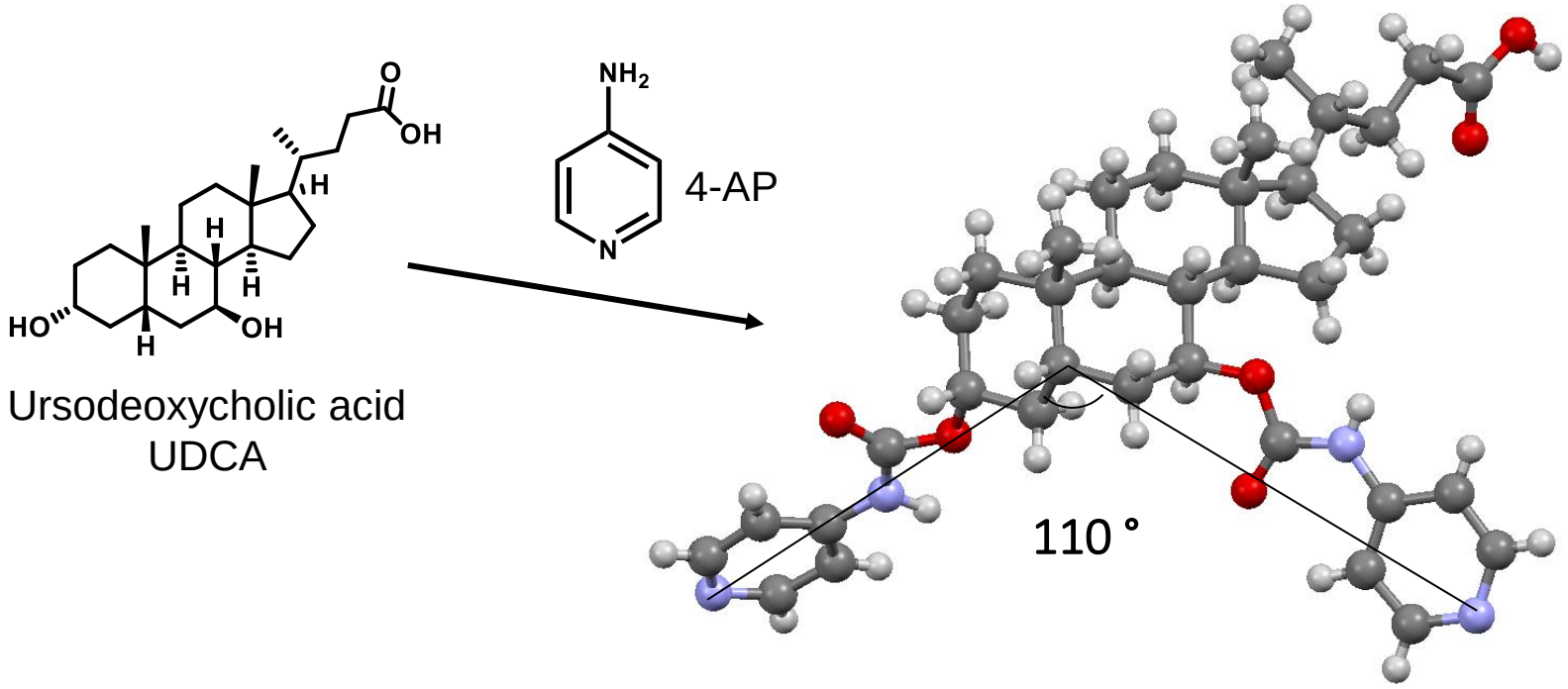


- prodrug design, carriers

Conjugates of 4-AP and bile acids = ligands

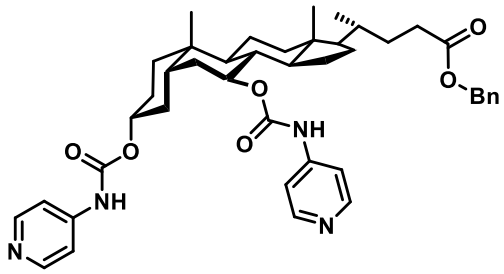
- pyridyl moiety is often used in supramolecular chemistry in design of ligands for metallo-coordination self-assemblies, SYMMETRIC, ACHIRAL

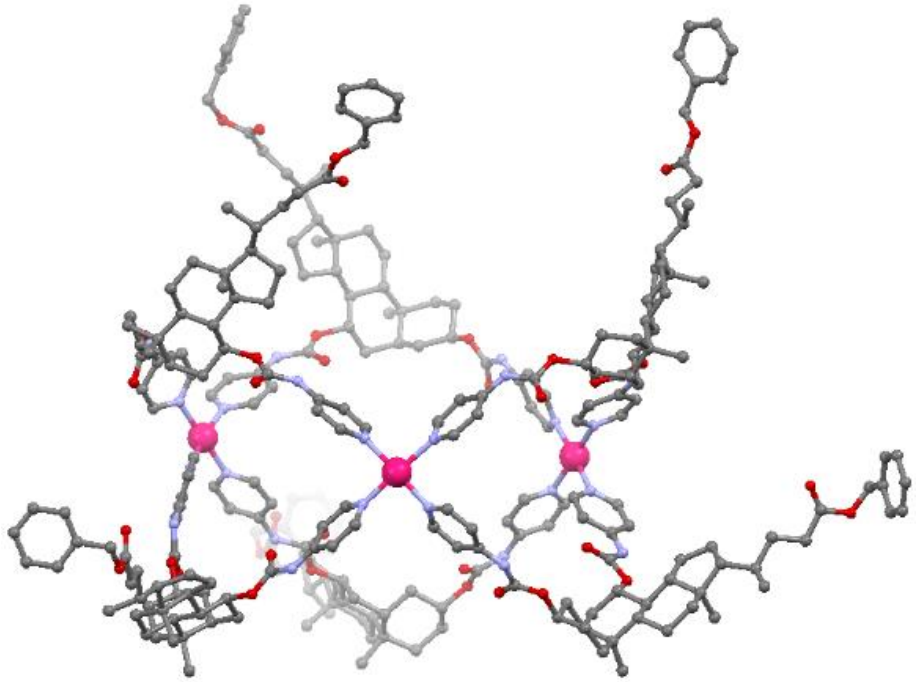
- bile acid ligands are ASYMMETRIC, CHIRAL, AMPHIPHILIC, *e.g.*, UDCA with bend angle 110 °



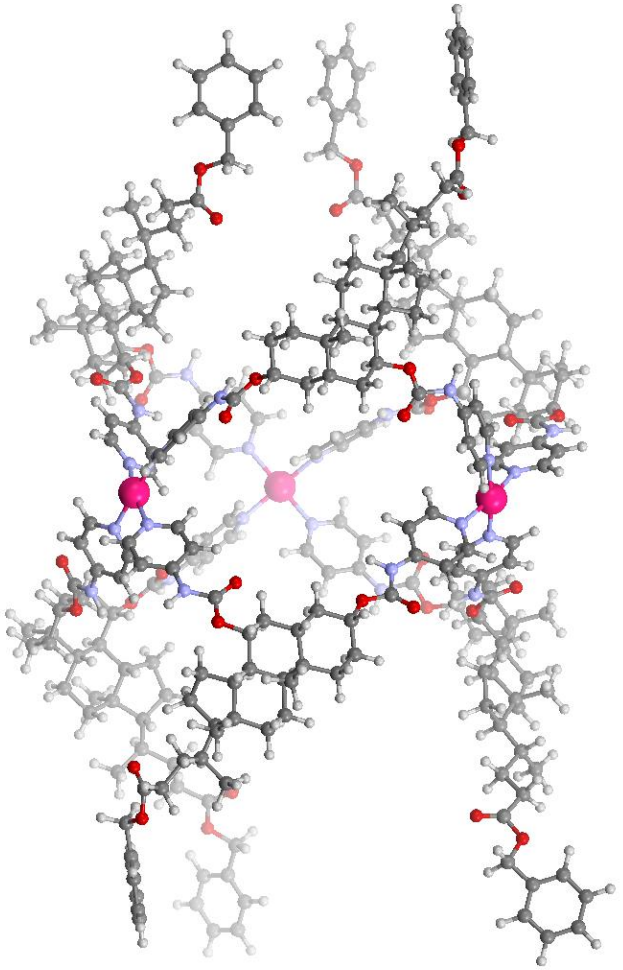
Ursodeoxycholic acid
UDCA

In C_3 symmetry two possible constitutional Pd_3L_6 isomers



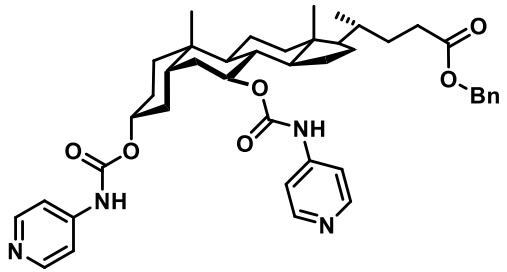


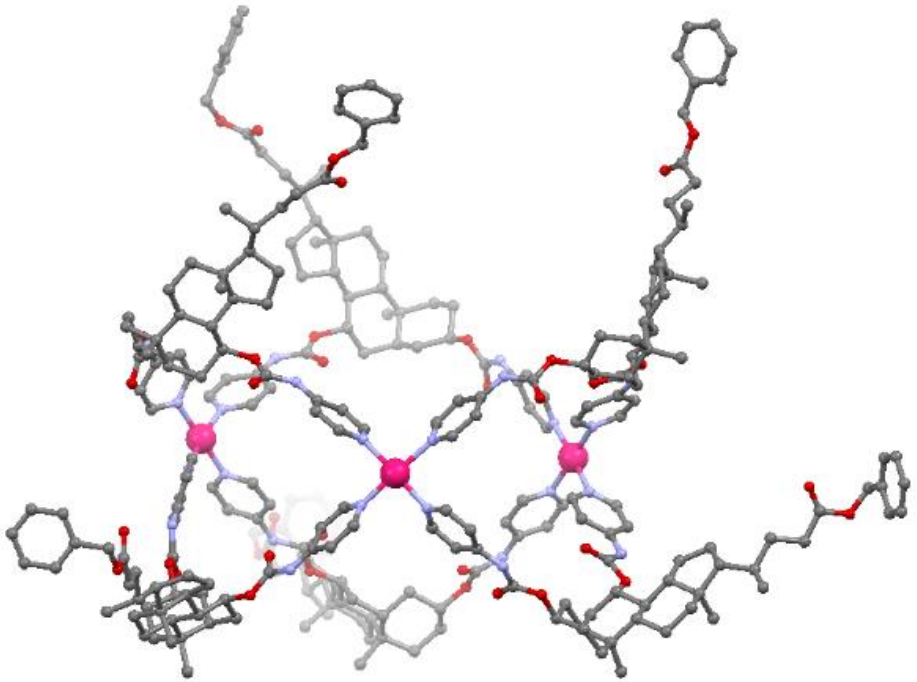
Flower-like structure

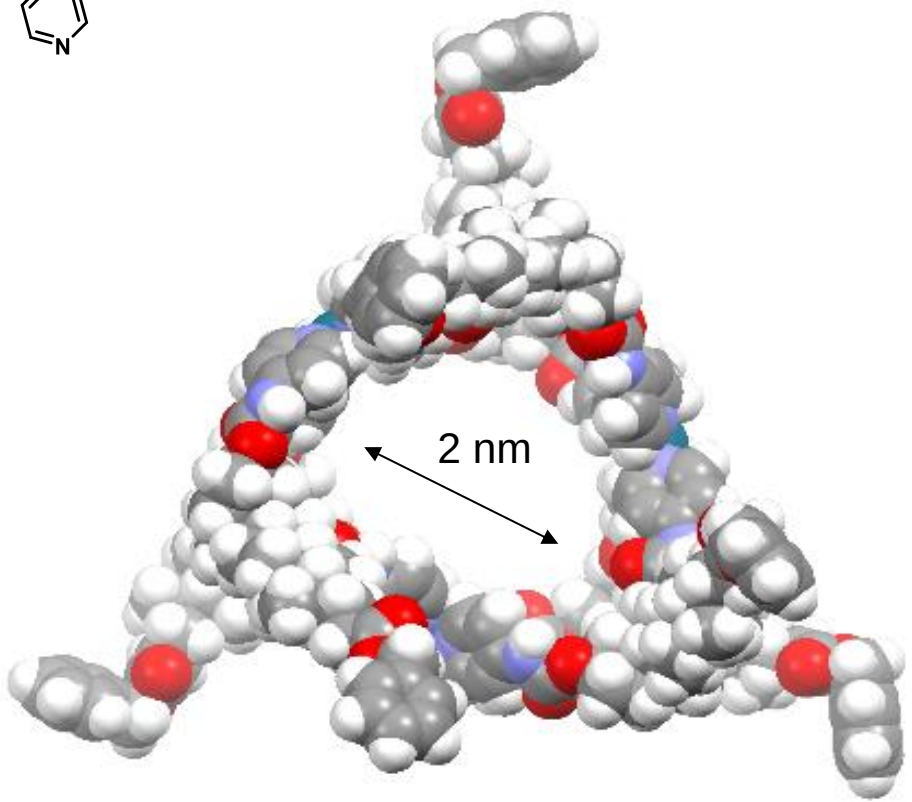


Barrel-like structure

Crown-like Pd_3L_6 isomer is the one

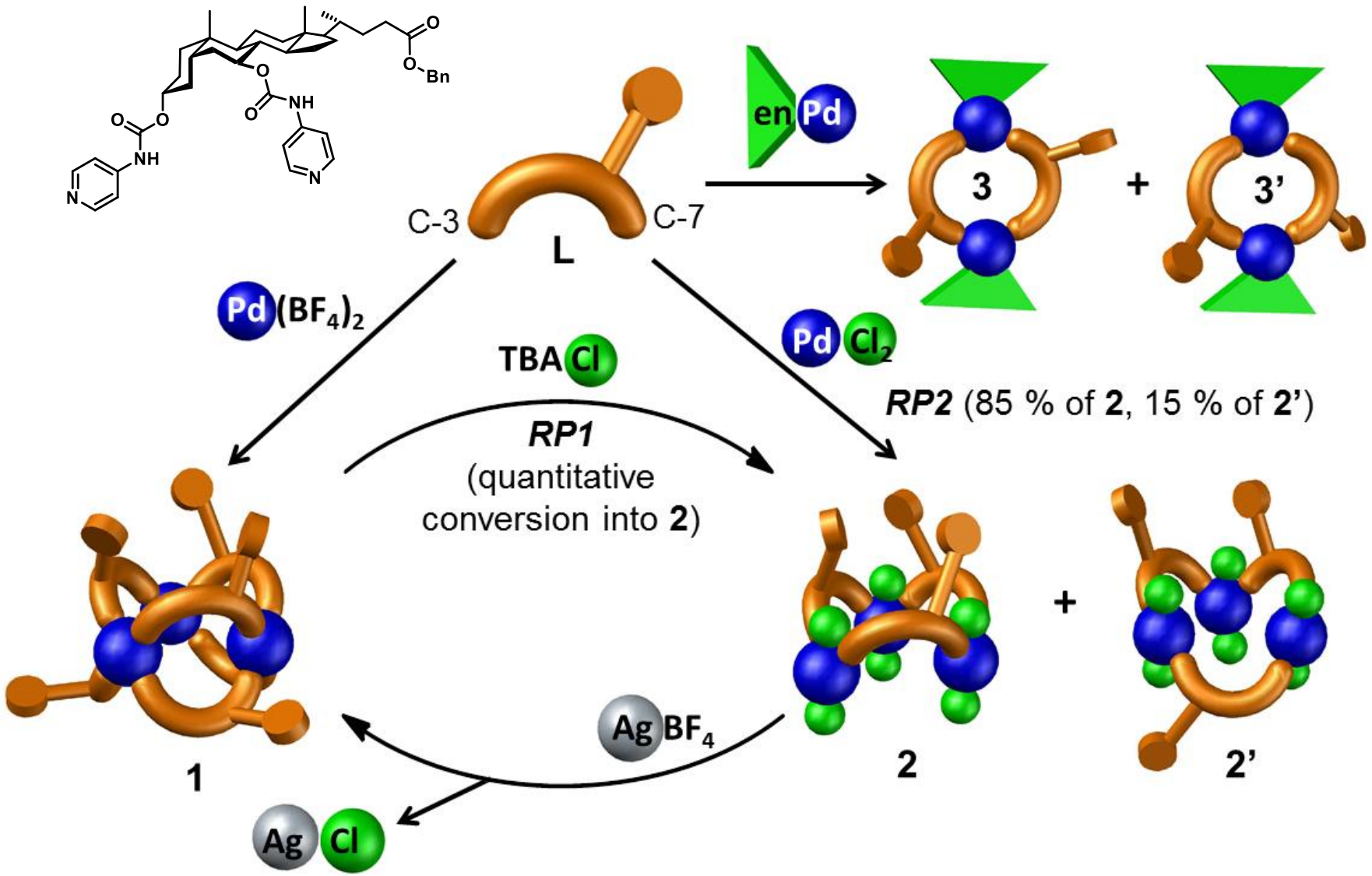






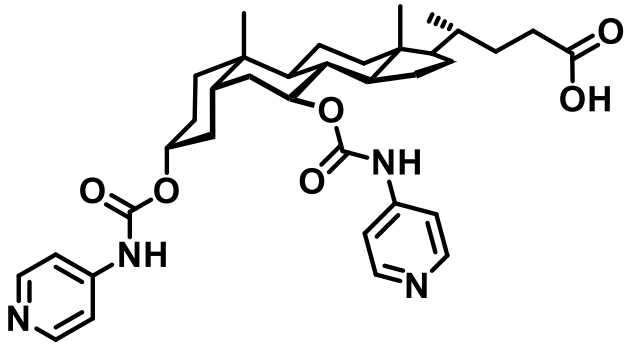
Jurček O., Bonakdarzadeh P., Kalenius E., Linnanto J. M., Ihalainen J. A., Rissanen K.: *Angew. Chem. Int. Ed.* **2015**, *54*, 15462-15467.

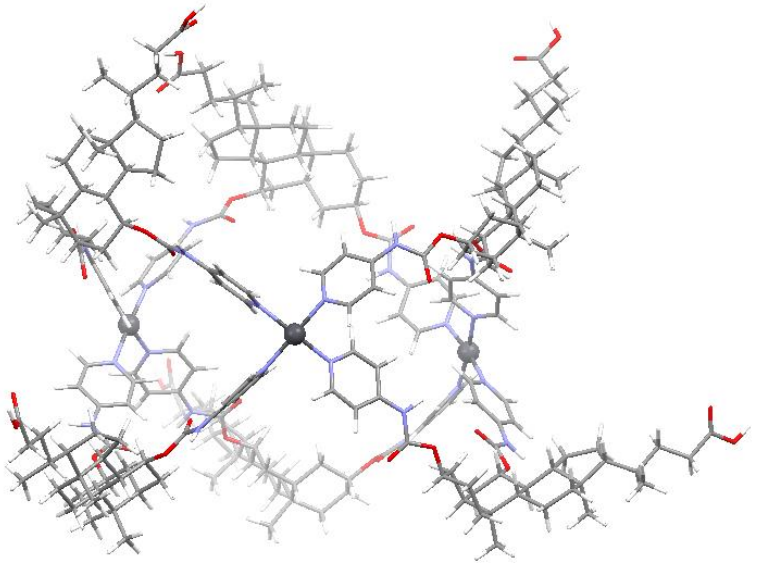
Logical structure-transformation analysis



Tritopic bile acid-based ligand

- water soluble ligand with amphiphilic character
- expectation of easier crystallization
- transmetalation synthetic approach
- stable in aqueous solution
- forms gelly substance with water





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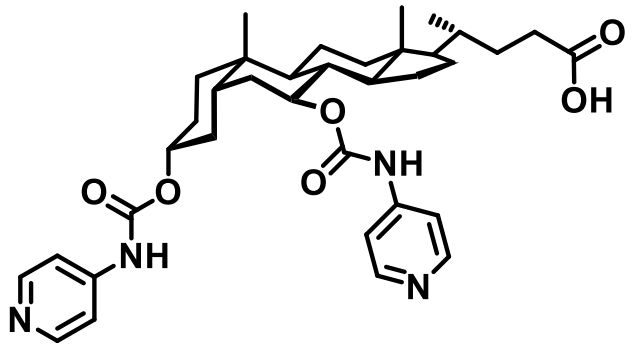
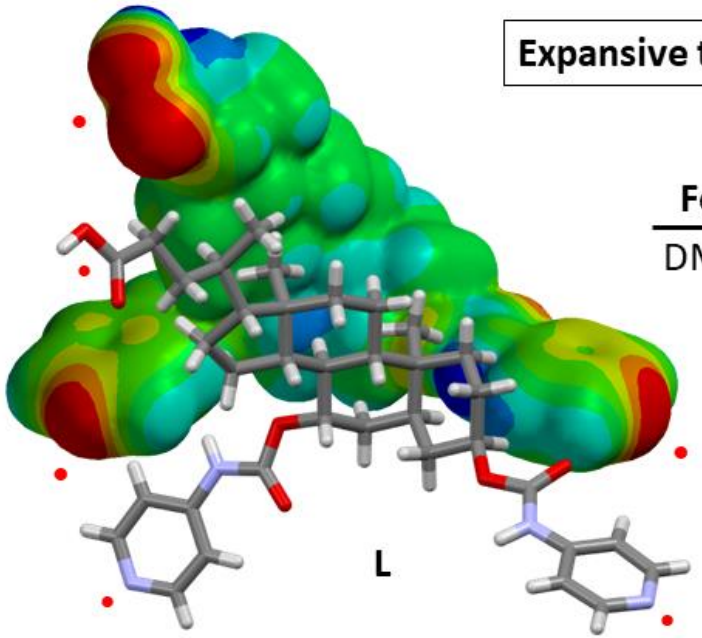
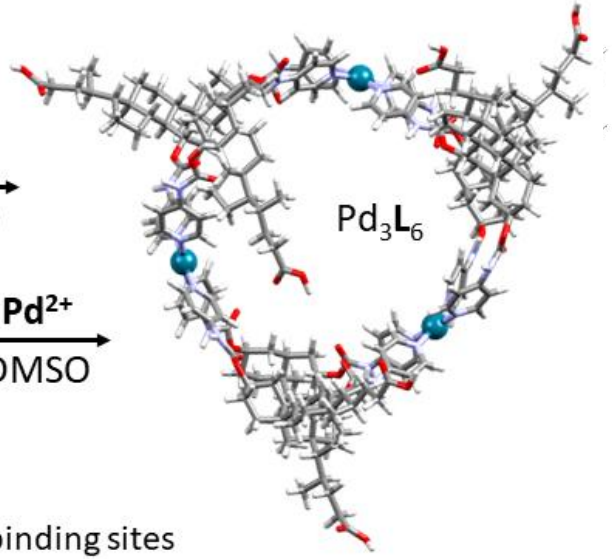




Expansive transmetalation self-assembly

Fe^{3+} / DMSO → Mixture $Fe_{(1-2)}L_{(1-2)}$ → Pd^{2+} / DMSO

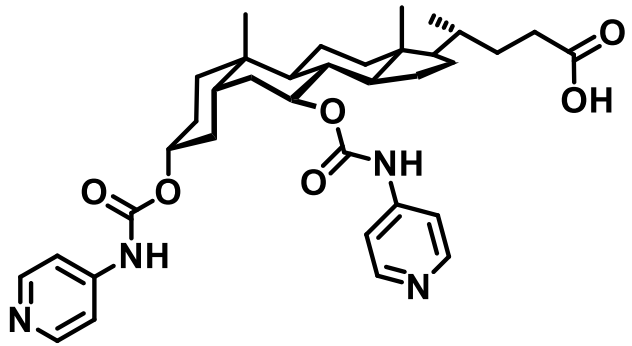
Cu^{2+} / DMSO → Mixture $Cu_{(1-3)}L_{(1-4)}$ → Pd^{2+} / DMSO

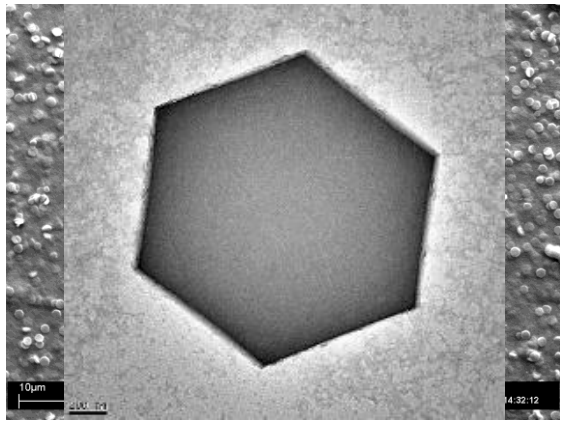


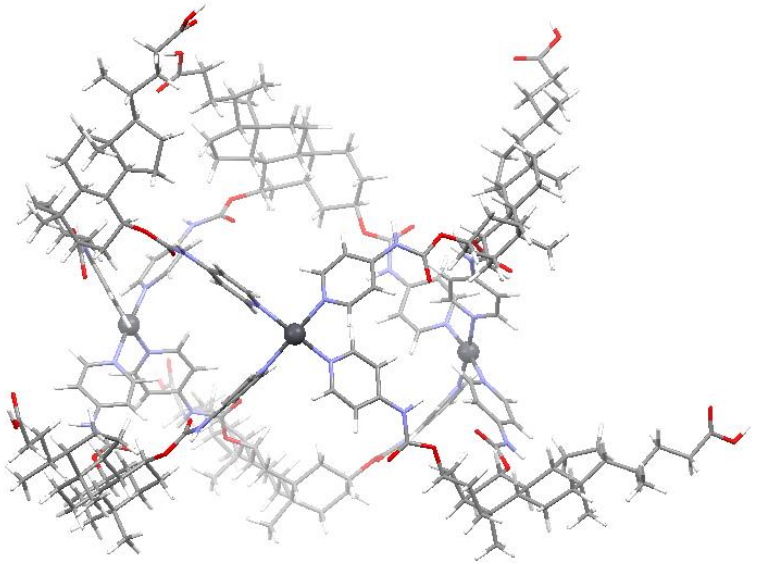
- Metal binding, electron rich, binding sites

Tritopic bile acid-based ligand

- water soluble ligand with amphiphilic character
- expectation of easier crystallization
- transmetalation synthetic approach
- stable in aqueous solution
- forms gelly substance with water

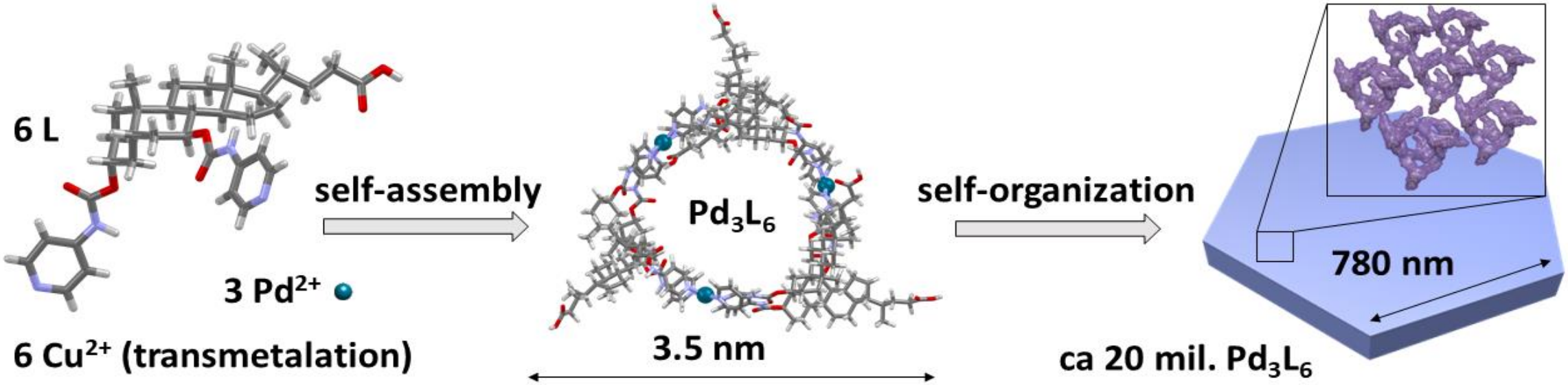






Jurček O., Nonappa, Kalenius E., Jurček P., Linnanto J. M., Puttreddy R., Valkenier H., Houbenov N., Babiak M., Peterek M., Davis A. P., Marek R., Rissanen K.: *Cell Rep. Phys. Sci.* **2021**, *2*, 100303.

Tritopic bile acid-based ligand



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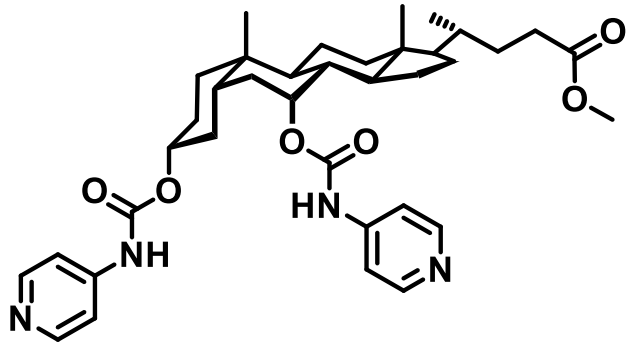
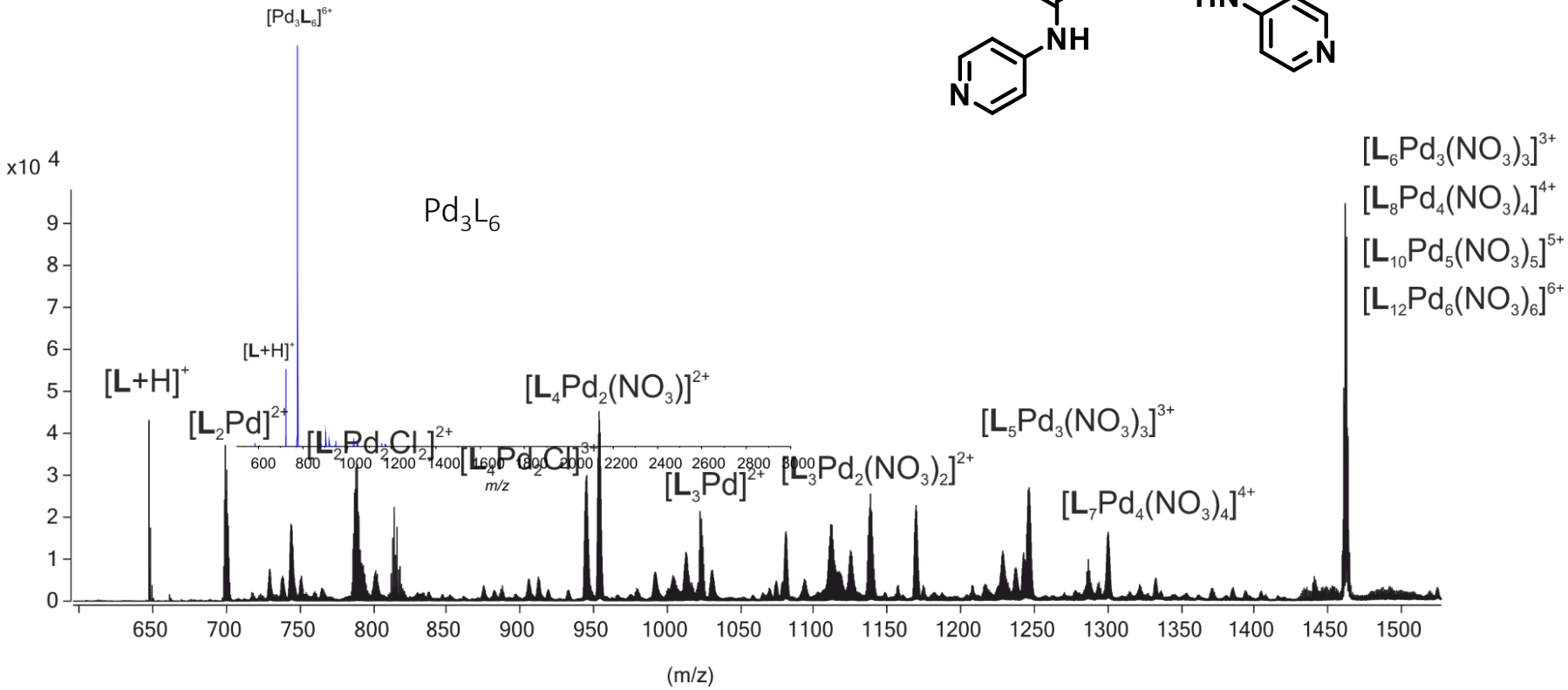
Chenodeoxycholic acid (CDCA) bispyridyl ligand

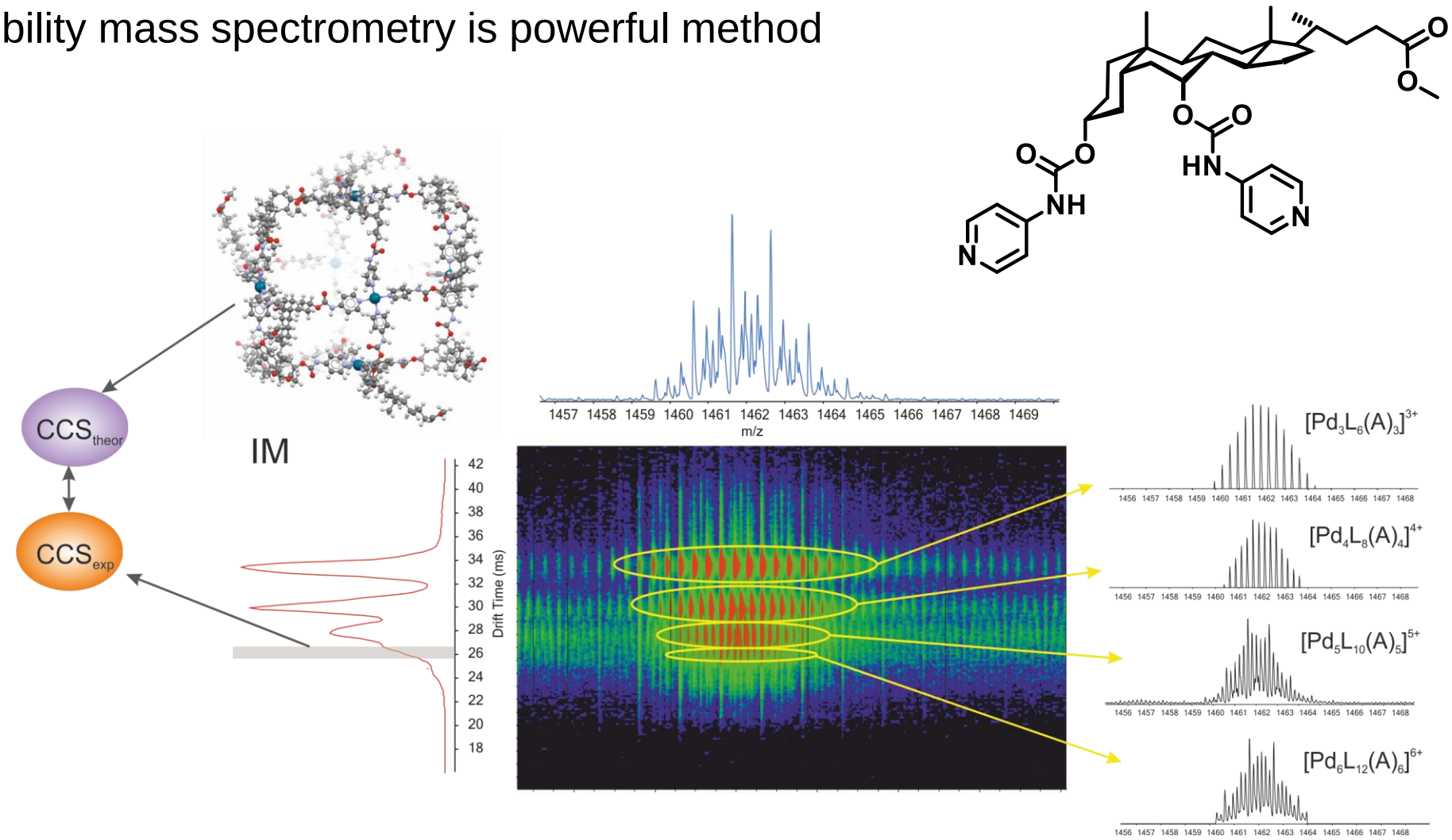
- opposite chirality at C7
- coordination with Pd^{2+} leads to a mixture





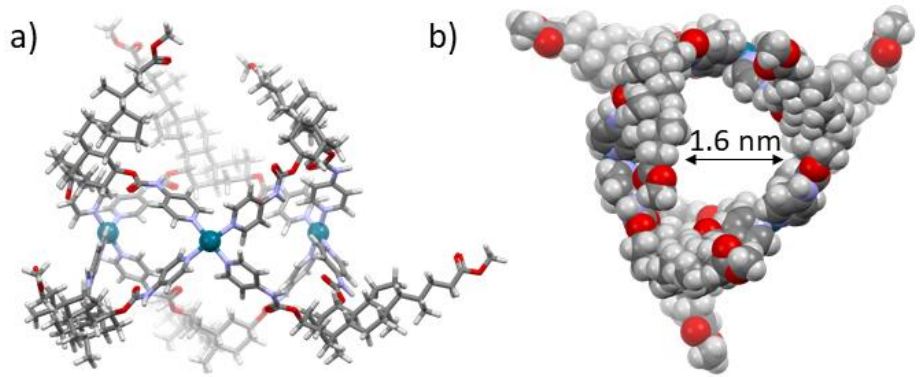
Chenodeoxycholic acid (CDCA) bispyridyl ligand

- opposite chirality at C7
- Ion mobility mass spectrometry is powerful method

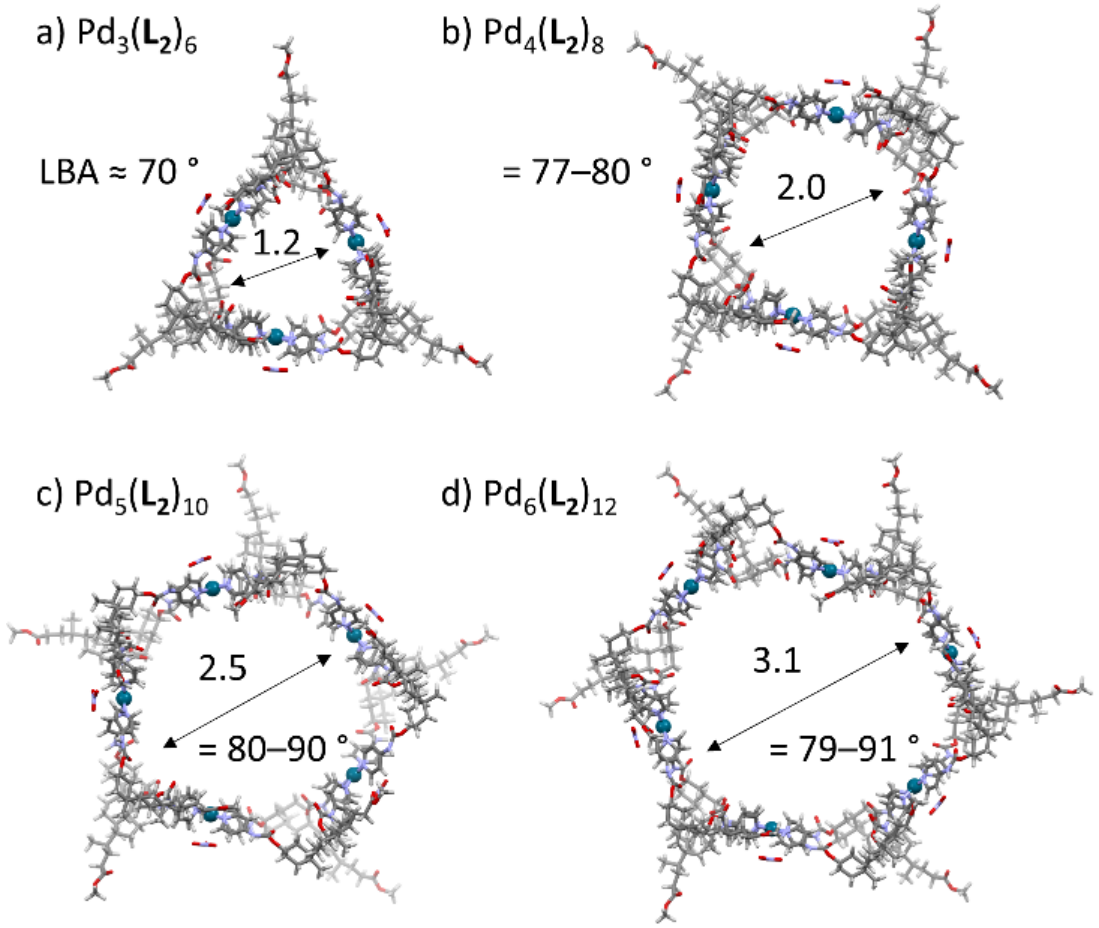


Chenodeoxycholic acid (CDCA) bispyridyl ligand

UDCA

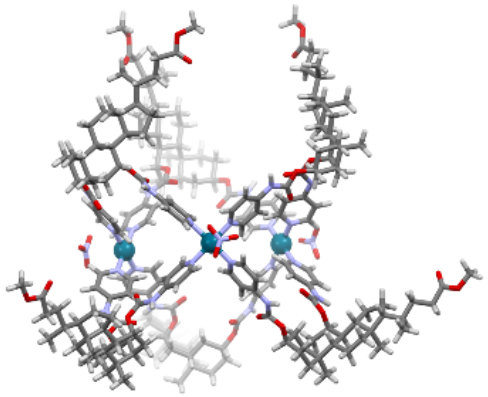


CDCA

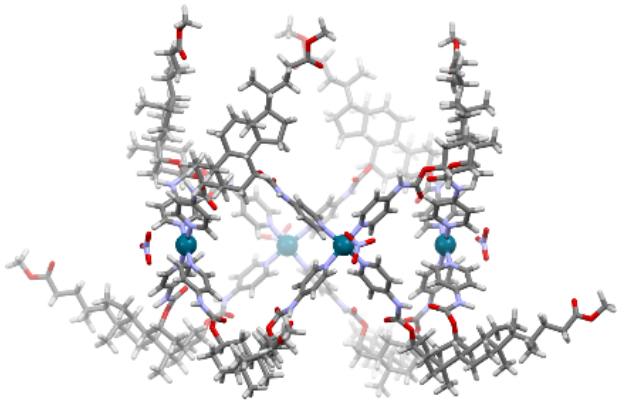


Jurček O., Chattopadhyay S., Kalenius E., Linnanto J. M., Kiesilä A., Jurček P., Radiměřský P., Marek R..: *Angew. Chem. Int. Ed.* **2024**, *63,* e202409134.

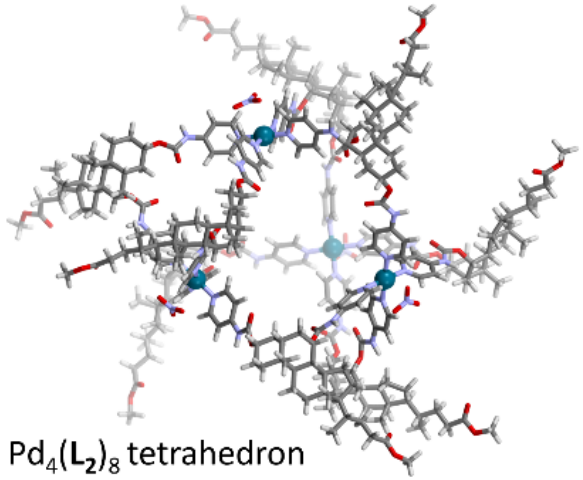
Chenodeoxycholic acid (CDCA) bispyridyl ligand



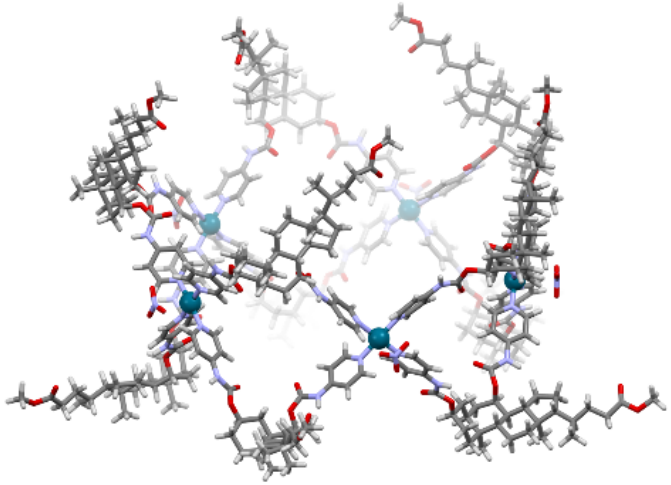
$Pd_3(\mathbf{L_2})_6$ tetracycle



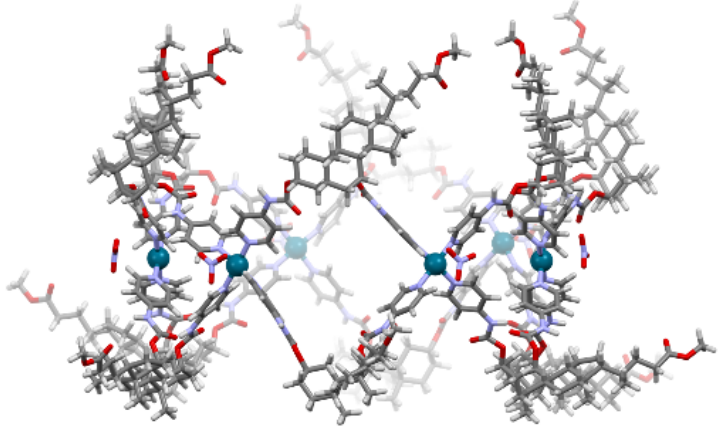
$Pd_4(\mathbf{L_2})_8$ pentacycle



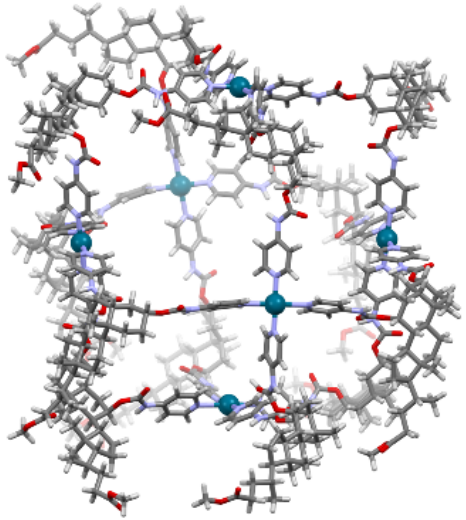
$Pd_4(\mathbf{L_2})_8$ tetrahedron



$Pd_5(\mathbf{L_2})_{10}$ hexacycle



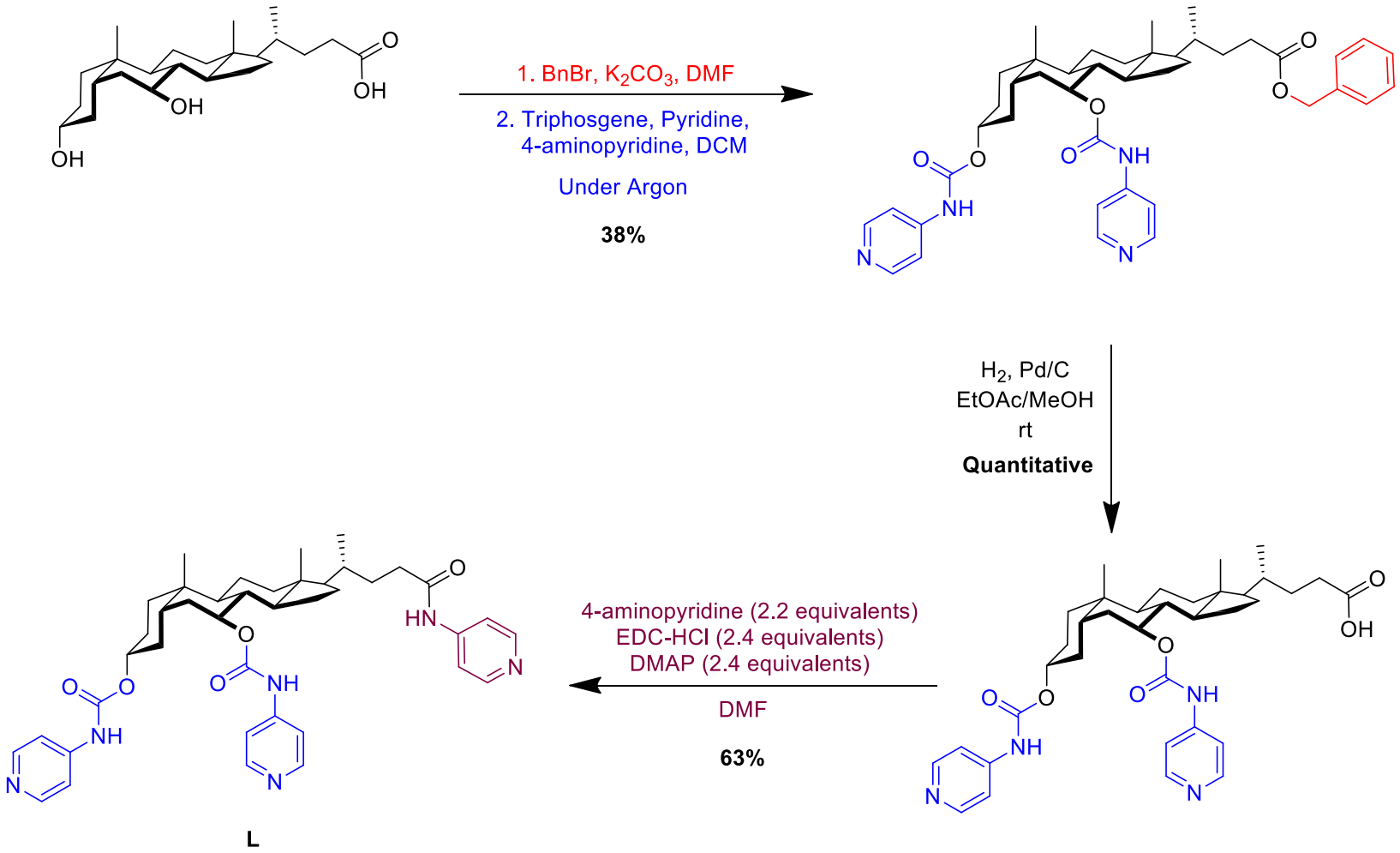
$Pd_6(\mathbf{L_2})_{12}$ heptacycle



$Pd_6(\mathbf{L_2})_{12}$ cuboid

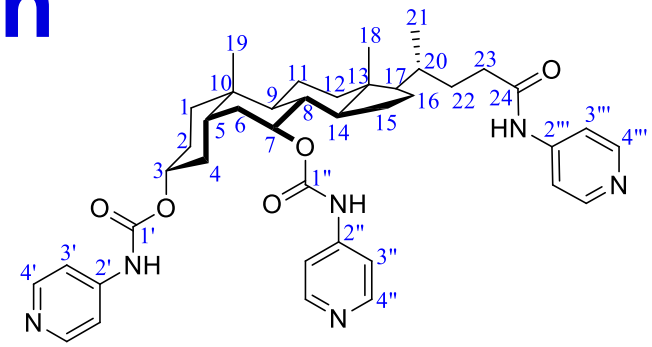
Jurček O., Chattopadhyay S., Kalenius E., Linnanto J. M., Kiesilä A., Jurček P., Radiměřský P., Marek R..: *Angew. Chem. Int. Ed.* **2024**, *63,* e202409134.

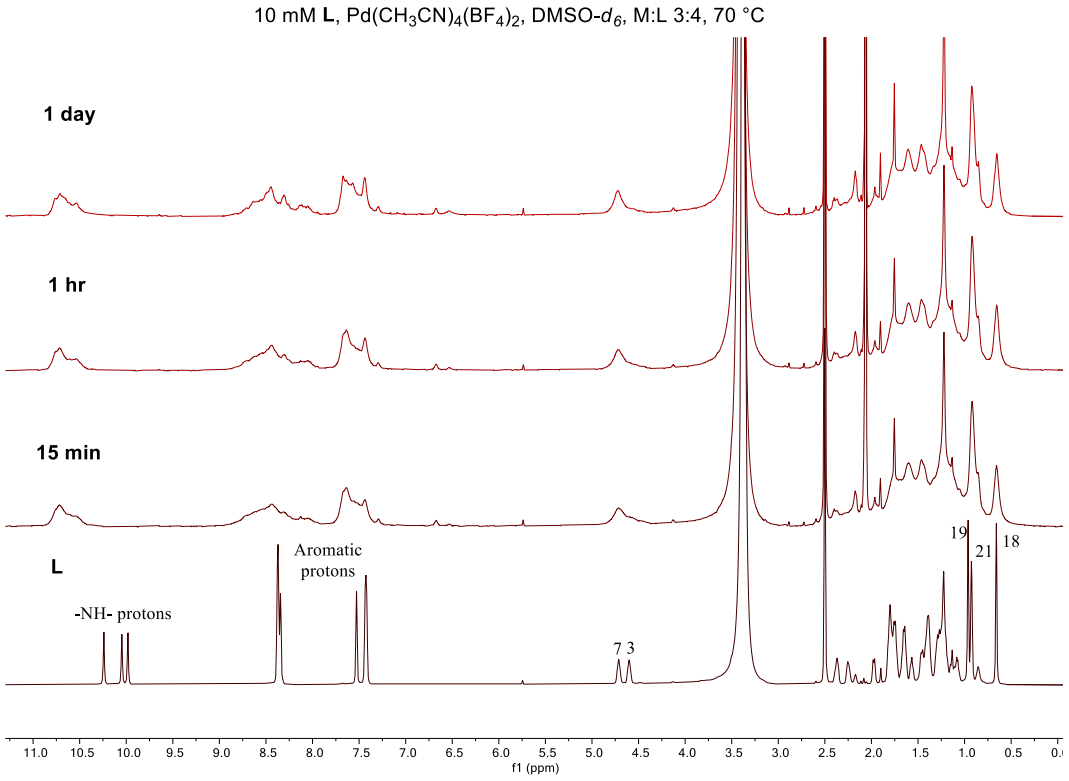
Synthesis of UDCA trispyridyl ligand (tridentate)

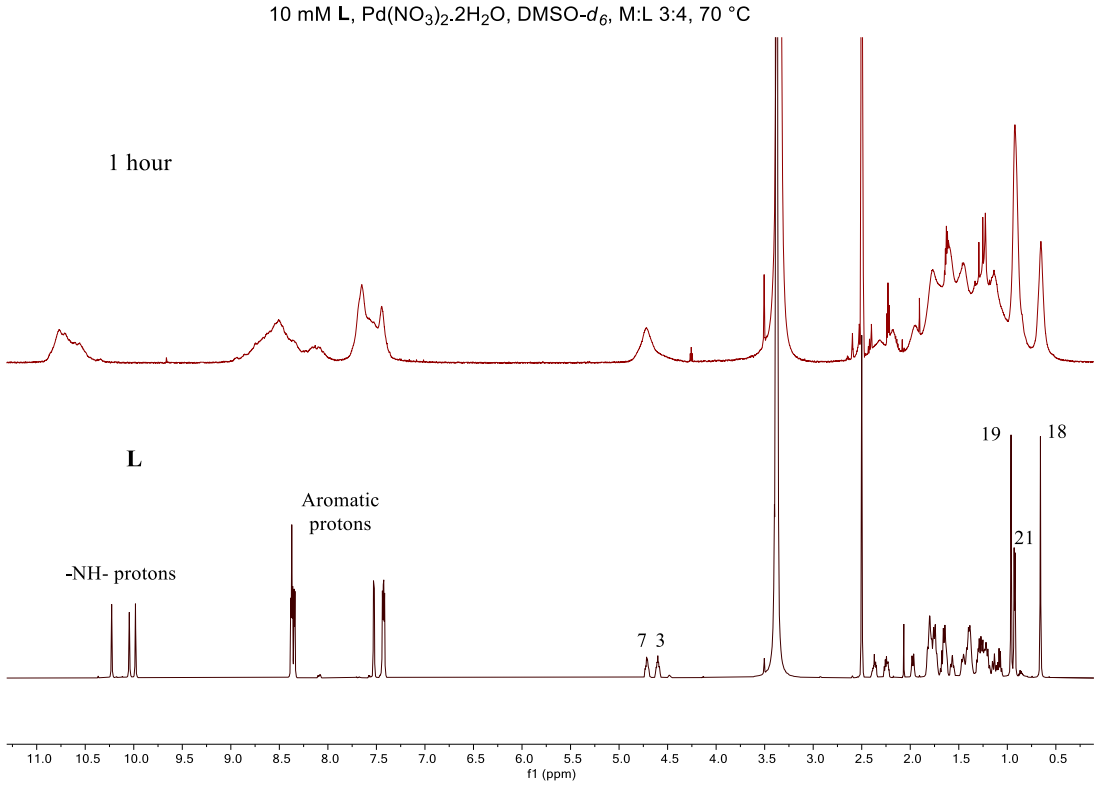


Angew. Chem. Int. Ed. **2015**, *54*, 15462 –15467
Cell Reports Physical Science, **2021**, *2*, 100303-100323

Ligand complexation

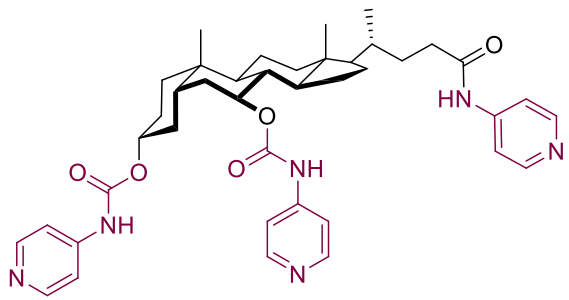






^{1}H NMR spectrum measured in DMSO-d_6 at 700 MHz and 298.2 K

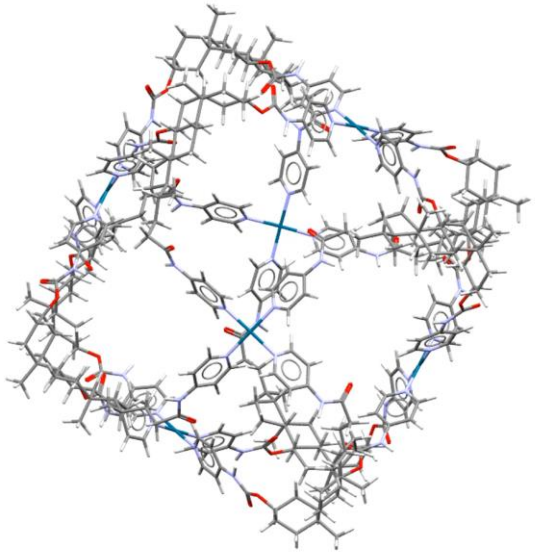
Mass spectrometry



L

$Pd(CH_3CN)_4(BF_4)_2$

10 mM, DMSO-d_6, 70 °C



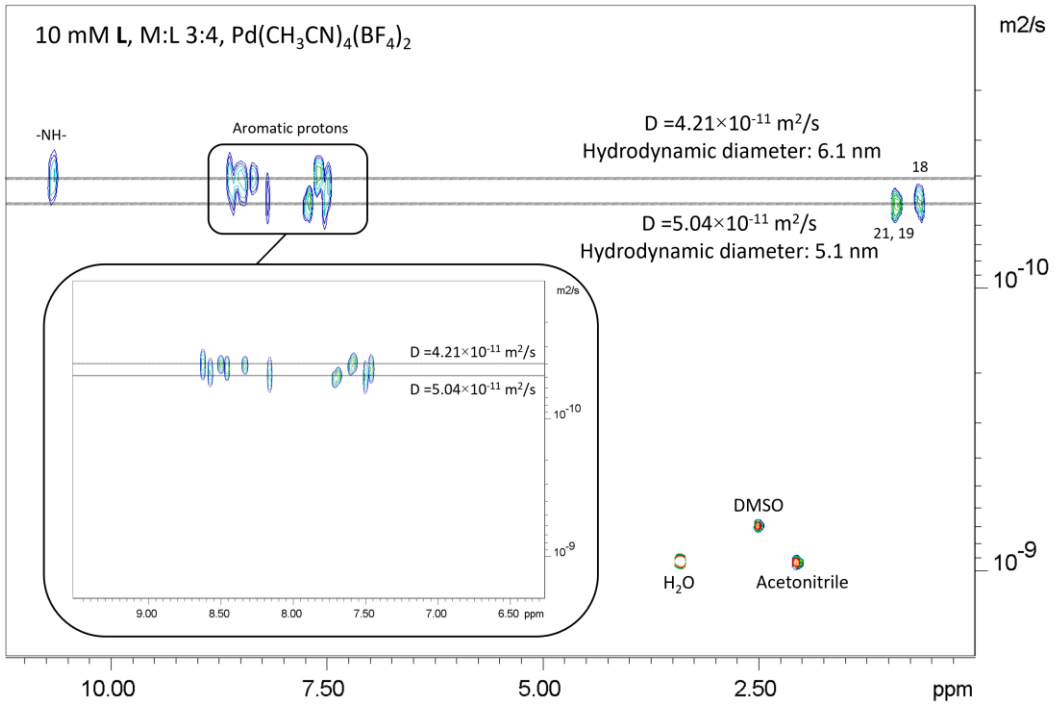
Pd_6L_8

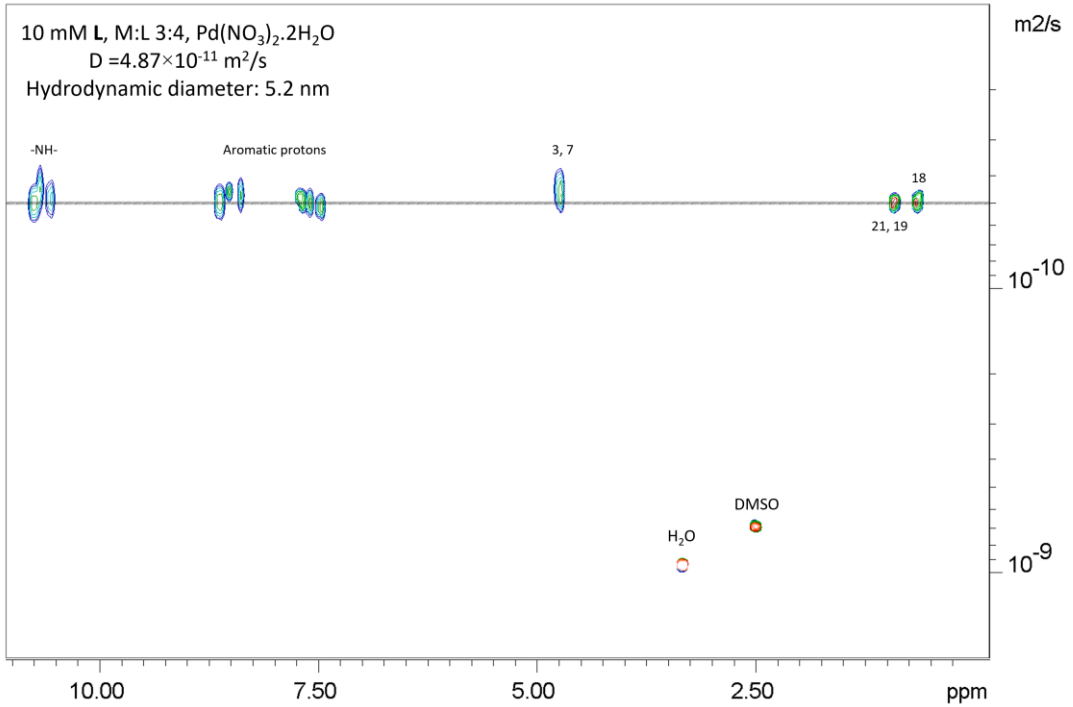
+ $Pd_{12}L_{16}$

Entry	Salt	M:L	Time	Pd_6L_8 (%)[a]	$Pd_{12}L_{16}$ (%)[a]
1	$Pd(CH_3CN)_4(BF_4)_2$	1:2	2 days	36.7	54.9
2	$Pd(CH_3CN)_4(BF_4)_2$	1:2	1 hour	27.8	66.3
3	$Pd(CH_3CN)_4(BF_4)_2$	3:4	1 day	22.8	71.1
4	$Pd(CH_3CN)_4(BF_4)_2$	6:4	1 hour	73.8	22.0
5	$Pd(NO_3)_2.2H_2O$	3:4	1 hour	In process	In process

a. estimated based on the height of the drift peak in IM-MS

^{1}H-DOSY NMR

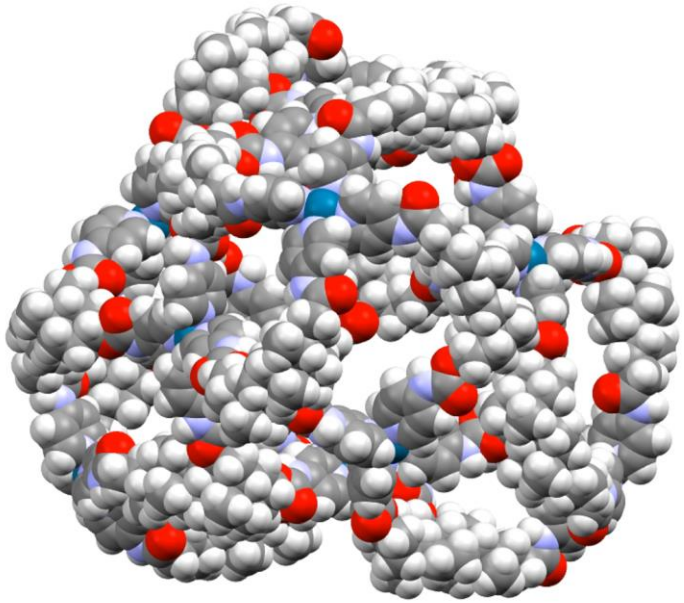




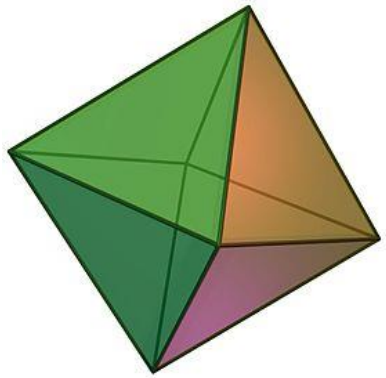
$$D = \frac{k_B T}{6\pi\eta R}$$

SCCs	Salt	Diffusion coefficient	CCS (IM-MS)	Hydrodynamic diameter	Diameter (IM-MS)
$Pd_{12}L_{16}$	$Pd(CH_3CN)_4(BF_4)_2$	4.21×10^{-11} $m^2\,s^{-1}$	2676 Å ($[Pd_{12}L_{16}(BF_4)_6]^{18+}$)	6.1 nm	5.8 nm
Pd_6L_8	$Pd(CH_3CN)_4(BF_4)_2$	5.04×10^{-11} $m^2\,s^{-1}$	1463.8 Å ($[Pd_6L_8(BF_4)]^{11+}$)	5.1 nm	4.3 nm
$Pd_{12}L_{16}$	$Pd(NO_3)_2.2H_2O$	4.87×10^{-11} $m^2\,s^{-1}$	-	5.2 nm	-
L	-	1.57×10^{-10} $m^2\,s^{-1}$	-	1.6 nm	-

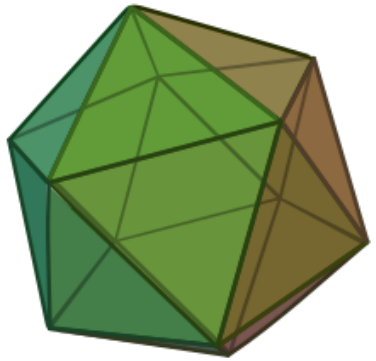
Structural analysis of complexes



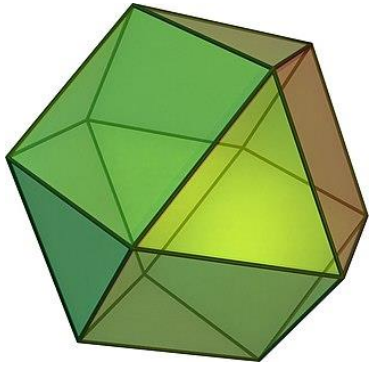
$Pd_{12}L_{16}$



Octahedron



Icosahedron

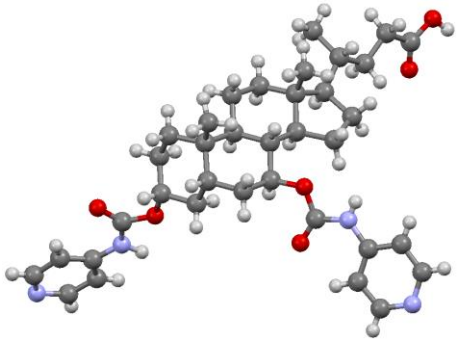


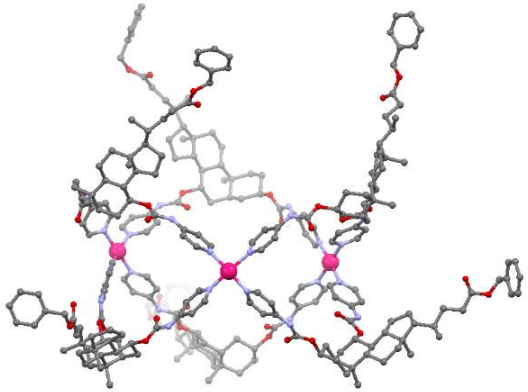
Cuboctahedron

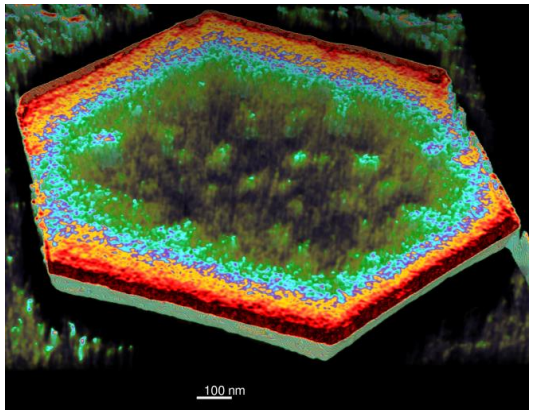
- Studied on HepG2 hepatospheroids showing anticancer activity

Progressions between an octahedron, pseudoicosahedron, and cuboctahedron.

Porous bile acid-based nanoparticles



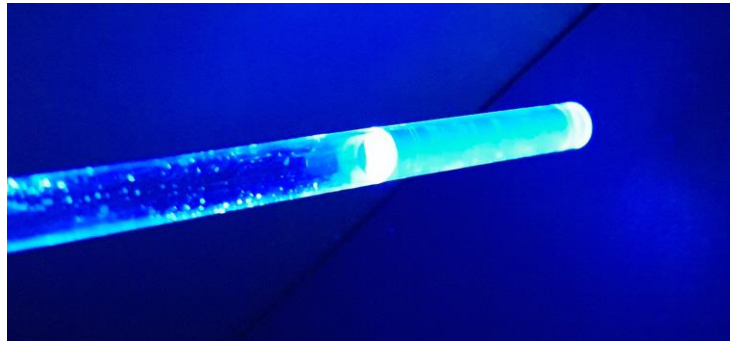


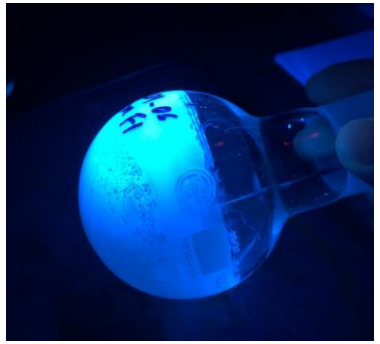


L +

Anion	Co(II)	Ni(II)	Ca (II)	Cr(III)	Mg(II)	Mn(II)	Cu(II)	Zr(IV)	Fe(III)	Zn(II)
NO_3^-	✓	✓	✓	✓	✓	✓	✓	-	✓	✓
AcO^-	✓	✓	✓	✓	✓	✓	✓	-	✓	✓
Cl^-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

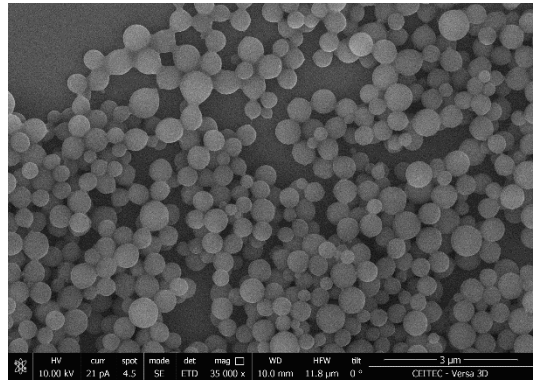
- Variable ratios, temperature, time, concentration, solvent system, synthetic method, modulants



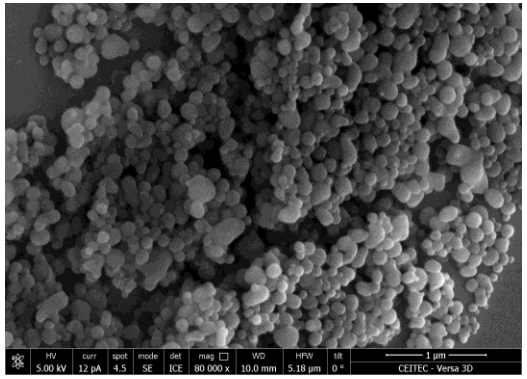


Porous bile acid-based nanoparticles

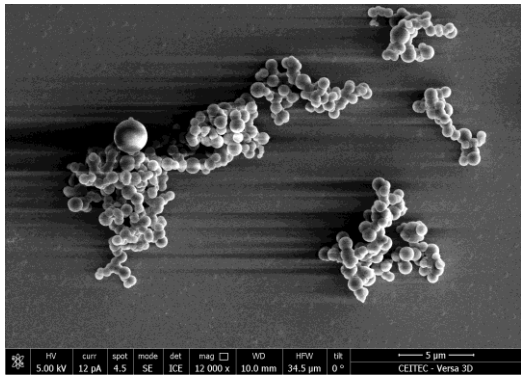
- Size: d = 20-200 nm
- Studies of their drug adsorption
- SAXS, PXRD, gas adsorption, IR, ssNMR, TEM, TG, and DSC, EDX



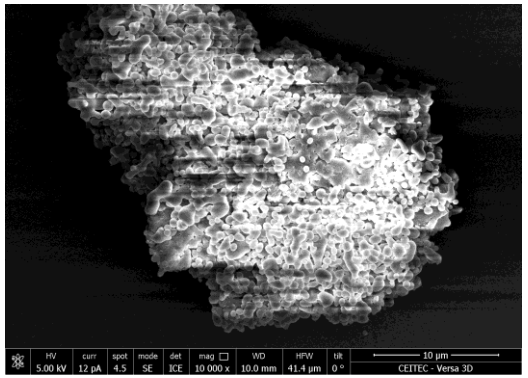
Mn(II)



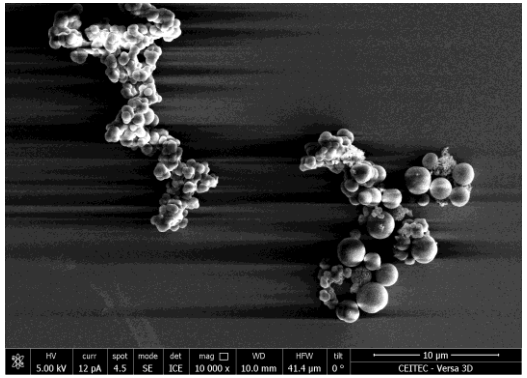
Fe(III)



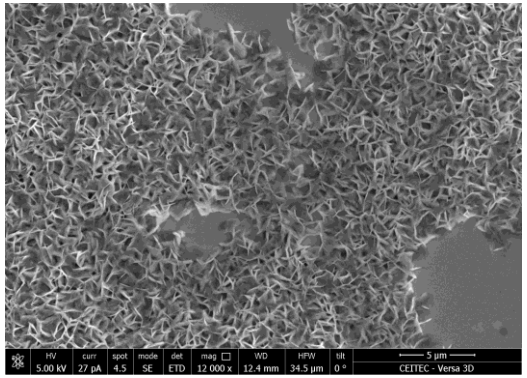
Cr(III)



Zn(II)



Mn(II)



Ca(II)

In the next class…

Artificial anion transporters and covalent cages

Thank you for your attention!