MUNI PHARM

Department of Natural Drugs

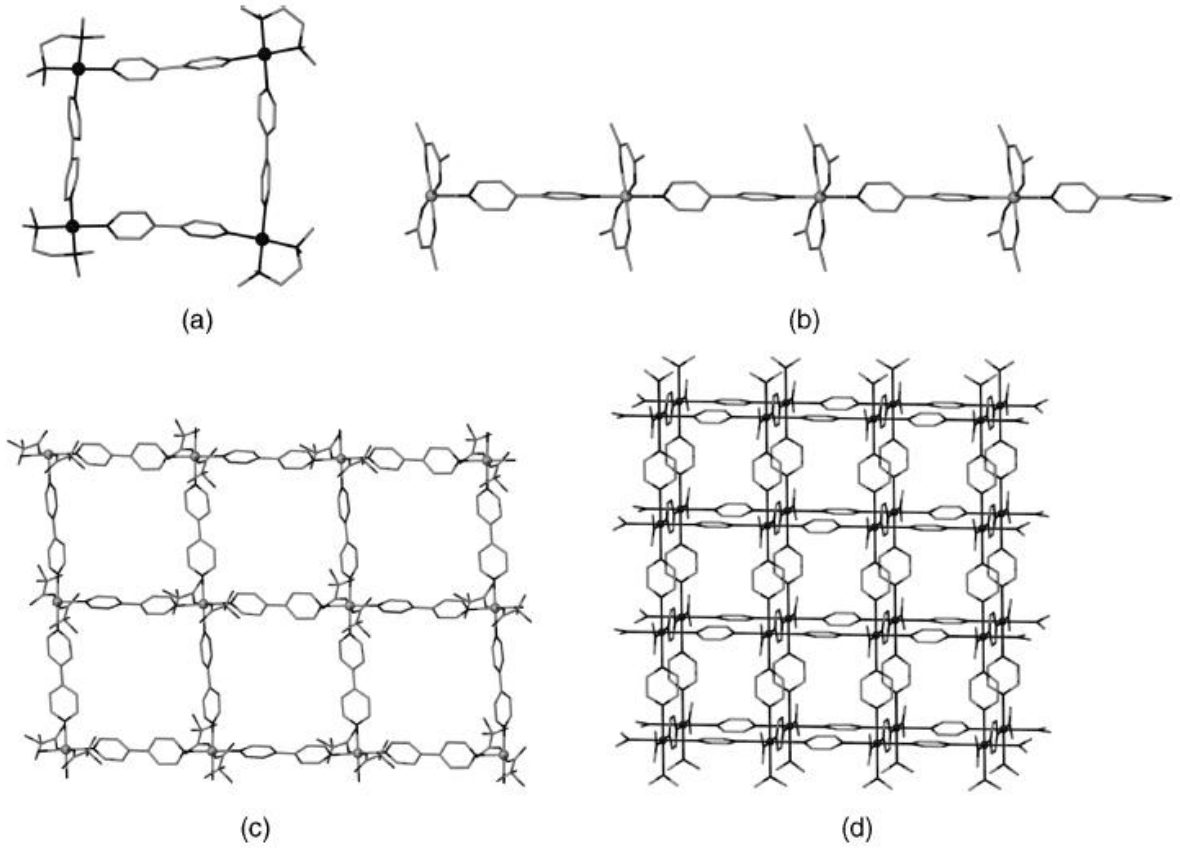
Supramolecular Pharmacy

9. Porous solids, metal-organic frameworks (MOFs)

Ondřej Jurček

Coordination compounds

- 0-D distinct coordination complexes
- Coordination polymers refer to any structure based on metal ions linked into an infinite chain (1D), sheet (2D), or three-dimensional architecture by bridging ligands (usually containing organic carbon)



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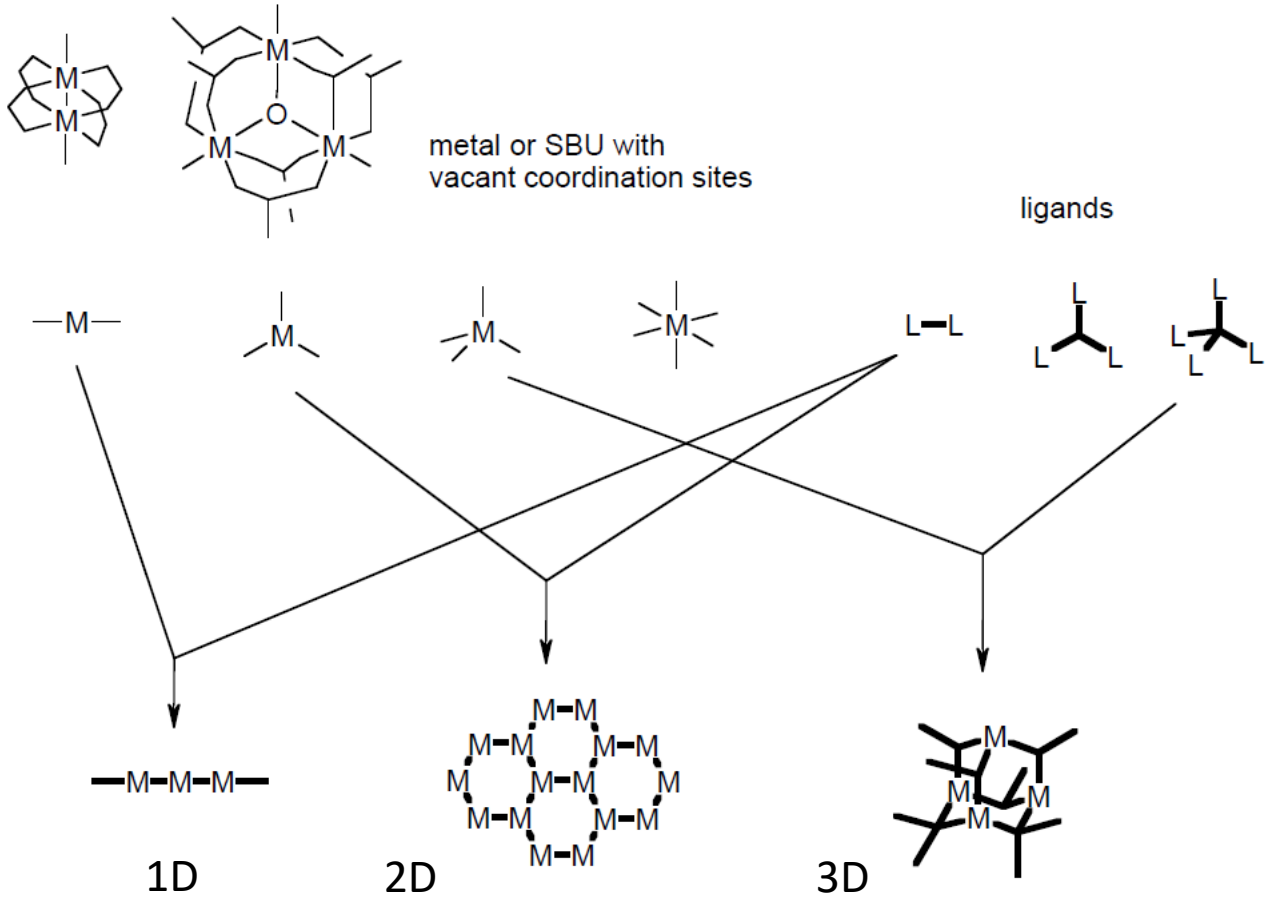
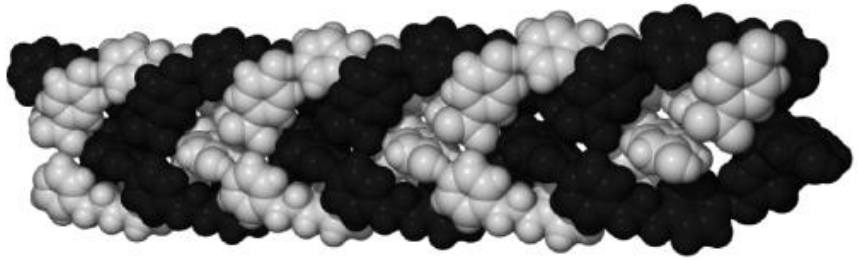
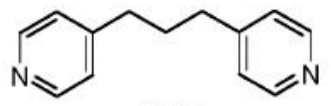


Coordination polymers, metal organic framework (MOF)

- ***Infinite coordination polymers*** (ICP) can be amorphous and crystalline
- 3D infinite crystalline and porous coordination polymers are called ***metal-organic frameworks*** (MOFs), MOF-n – n usually signs chronological order, e.g., MOF-5
- ***Secondary building unit*** (SBU) – geometry of metal coordination cluster fragment unit
- ***Reticular synthesis*** – the synthesis of periodic repeating nets
- ***Isoreticular expansion*** – increasing of the length of the spacer while retaining the same network topology (isoreticular MOF = IRMOF-n)
- ***Decoration*** means replacing a vertex within a net with a series of vertices
- ***Interpenetration*** – mutual intergrowth of two or more networks (no chemical link)
- ***Supramolecular isomerism*** – the existence of more than one type of network superstructure for the same molecular building blocks





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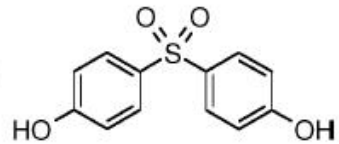
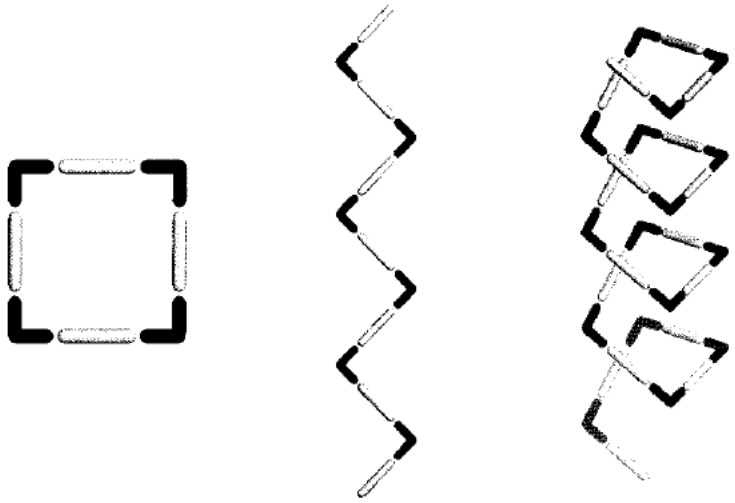
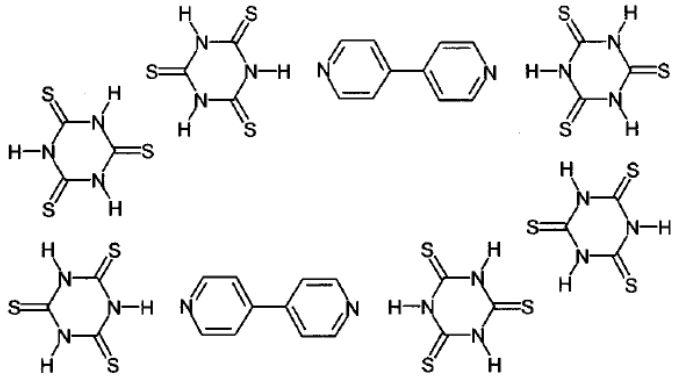


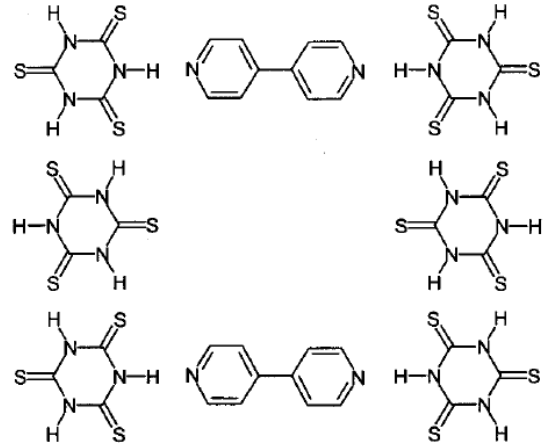
9.13

Supramolecular isomerism (polymorphism)

- Defined by Zaworotko: „existence of more than one type of network superstructure for the same molecular building blocks“
- related to structural isomerism at the molecular level







Porosity

- Len Barbour defined porosity in following terms:

  1) Permeability should be demonstrated (e.g. by gas sorption measurements, spectroscopic evidence of guest exchange or crystallography)
  2) The host framework should remain substantially unaffected by guest uptake and removal

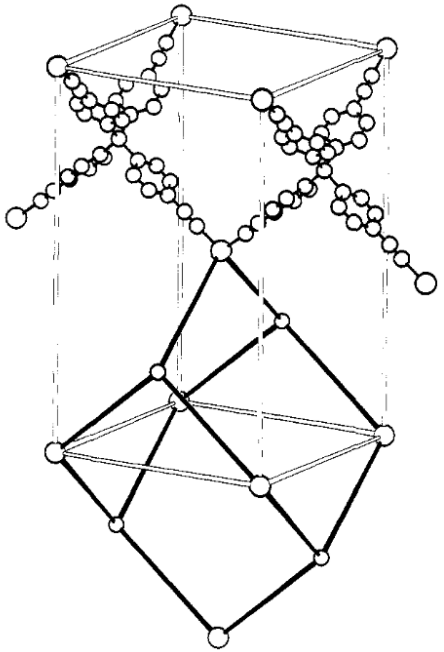
- Porosity by pore size:

  1) Microporous (smaller than 2 nm)
  2) Mesoporous (2-50 nm)
  3) Macroporous (larger than 50 nm)

Barbour, L. J. ‘Crystal porosity and the burden of proof’ *Chem. Commun.* 2006, 1163–1168.

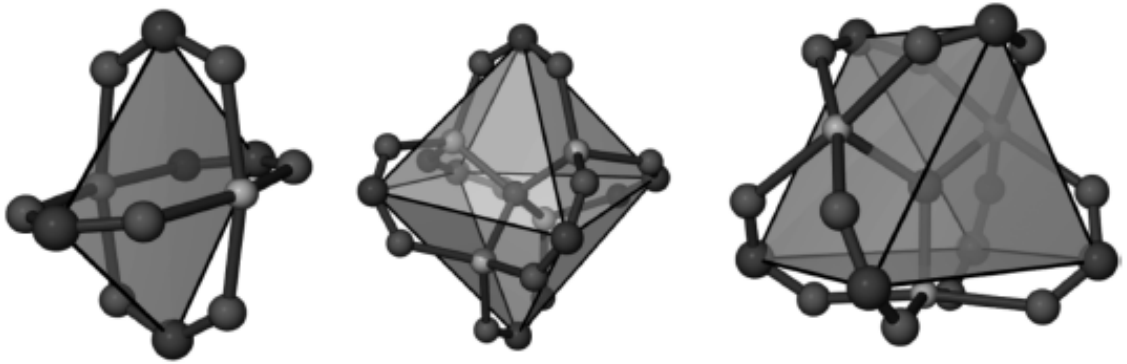
Metal-organic frameworks (MOFs)

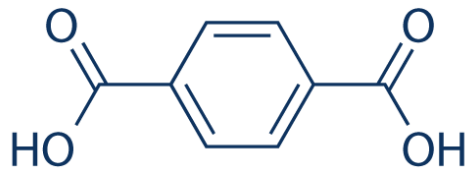
- 1989 synthesis of the first MOF by the group of Richard Robson



$\{Cu[C(C_6H_4 \cdot CN)_4]\}_n^{n+}$

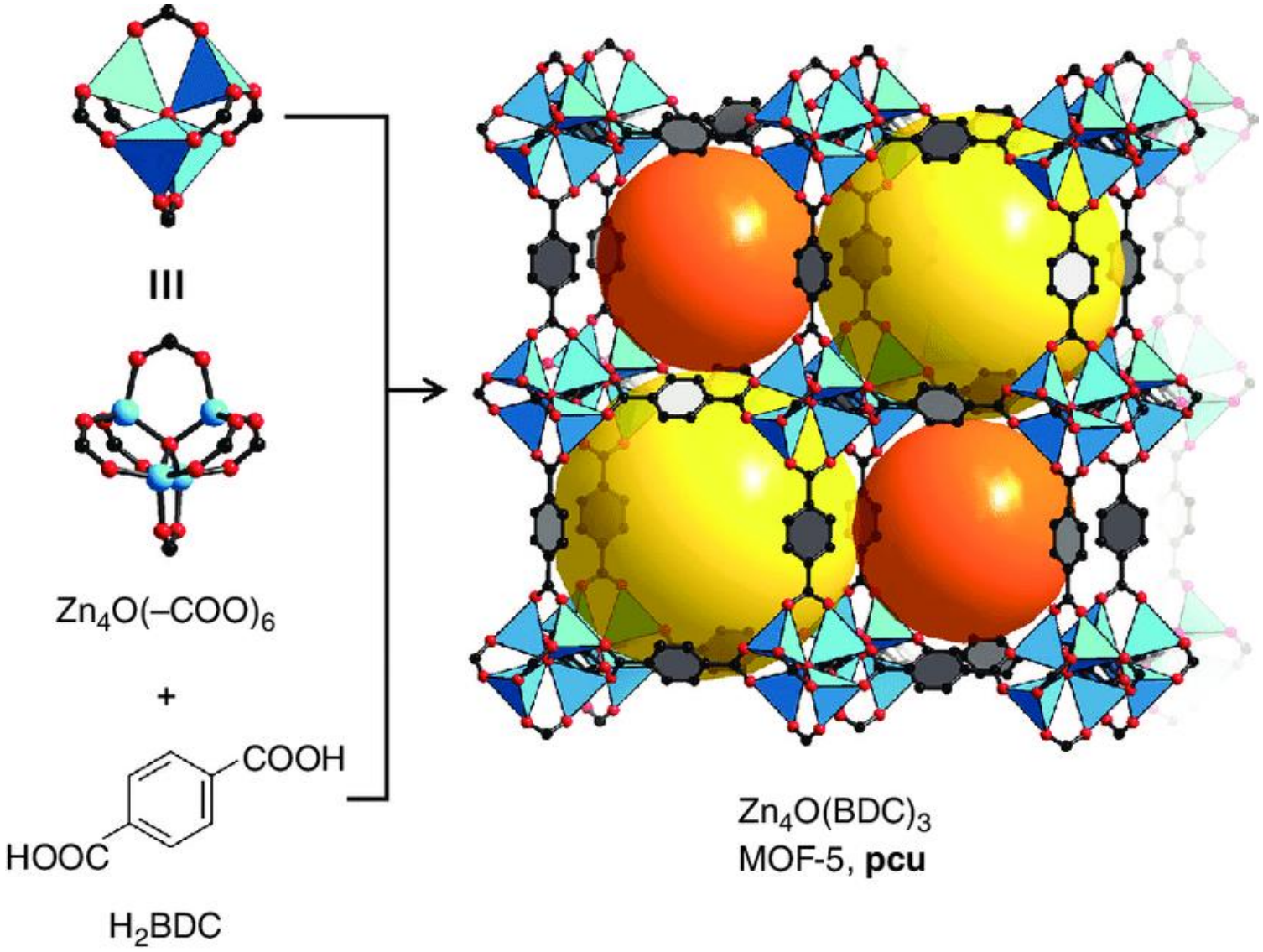
- 1999 discovery of MOF-5 by the group of Yaghi: important, produced commercially
- Octahedral zinc(II) oxo-centered SBU + terephthalic acid





a) Hoskins, B. F.; Robson, R. *J. Am. Chem. Soc.* 1989, 111, 5962; b) Yaghi O. et al. *Nature* 1999, 402, 276-279.

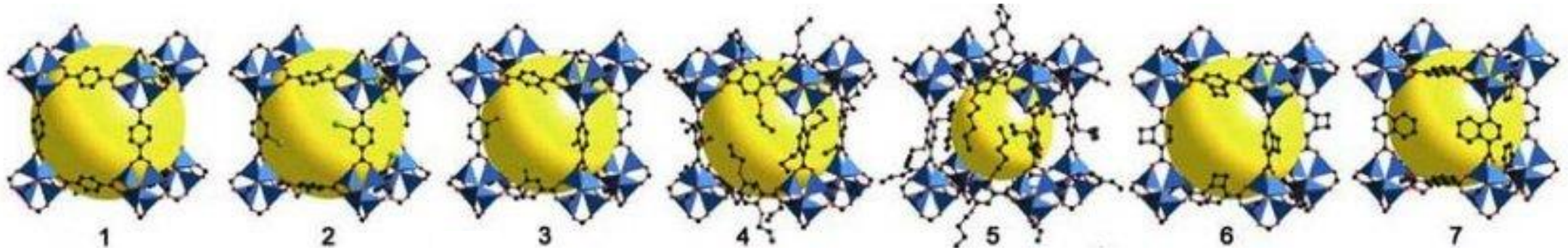
MOF-5



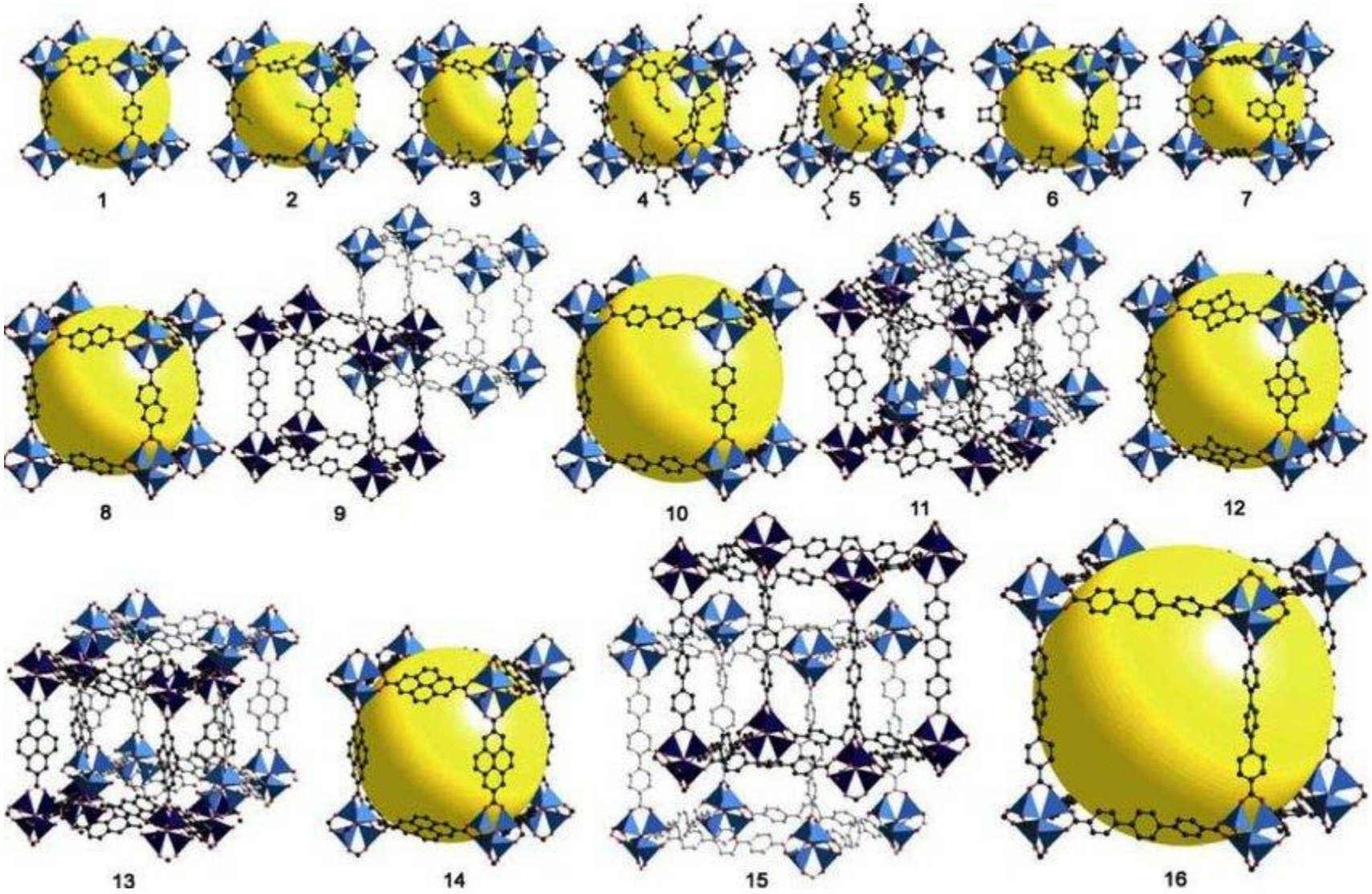
O. Yaghi, ch. 9: Macrocyclic and Supramolecular Chemistry: How Izatt–Christensen Award Winners Shaped the Field

MOF-5

- 1999 synthesis of MOF-5 *quasi*-solvothermally in DEF using terephthalic acid and $Zn(AcO)_2 \cdot 4H_2O$ at 85-105 °C in a closed vessel yields 90 % of solid crystalline phase
- The structure can be further expanded by using larger linear dicarboxylates – *isoreticular synthesis* (IRMOFs)
- Stable true porosity even without adsorbed guests
- Guest adsorption ranges based on the size of the organic linker, e.g., IRMOF-6 adsorbs 240 cm^3/g of methane



IRMOFs of MOF-5



Zeolites

- Are naturally occurring and artificial porous aluminosilicates
- Their anionic framework is balanced by cations
- General structure by IUPAC:

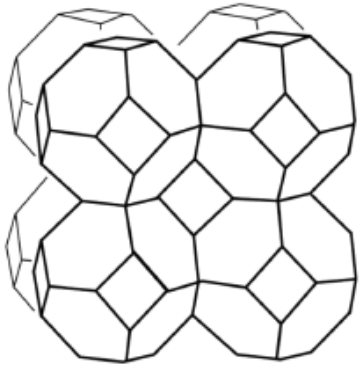
$[A_aB_bC_c]$	$\{(Al_dM_eSi_f)O_g\}$	$(xH_2O,\ yN)$
Cations A, B, C	Framework composition	Occluded guests

- Globally produced in mil. tons
- Catalysis, separation, petrochemical industry (separations, catalytic cracking), ion exchange (water softeners), etc.
- Highly stable, but limited structural variability and possibility for size increase

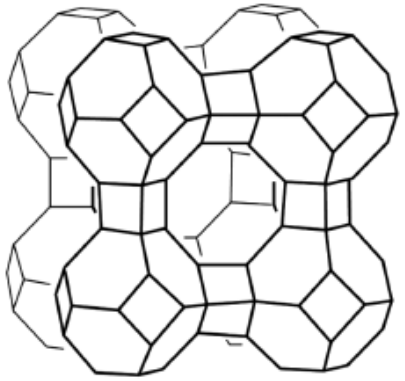
Structure type code	Type of material		Framework composition	Channel system	Pore opening	Cage	Comments
	Name	Formula					
AFI	$AlPO_4$-5	$Al_{12}P_{12}O_{48}$	$AlPO_4$-based High silica	1D	12-rings 7.3 Å	None	
FAU	Faujasite	$M_{29}[Al_{58}Si_{134}O_{384}]\cdot 240H_2O$	Aluminosilicate	3D	12-rings	*fau*	ABC stacking of puckered sodalite cage layers
		(M = Na_2, Ca, Mg)	High silica		7.4 Å	*sod*	
			$AlPO_4$-based			d6R	

Zeolites

Sodalite



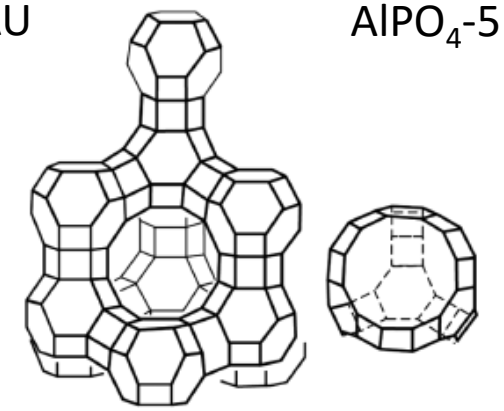
(a)



(b)

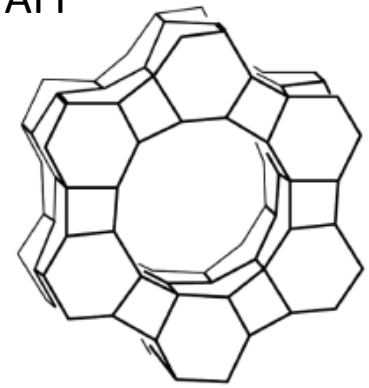
Linde type A

Faujasite - FAU



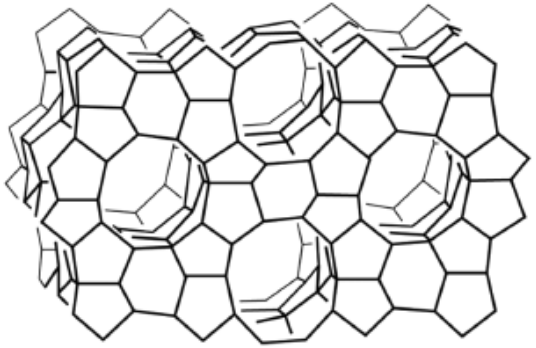
(c)

$AlPO_4$-5 - AFI



(d)

ZSM-5

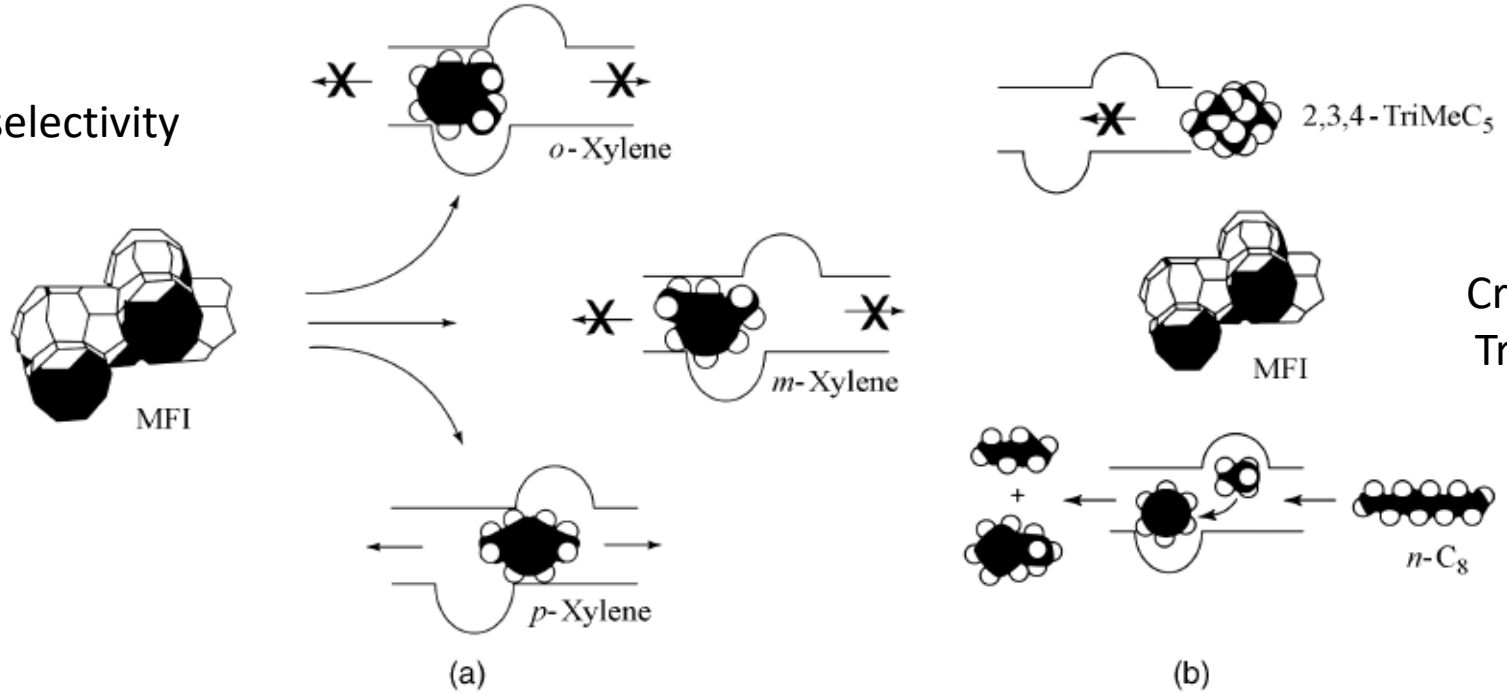


(e)

The vertices represent the positions of AlO_4^- or SiO_4 tetrahedra while straight lines represent Si–O–Si or Si–O–Al linkages.

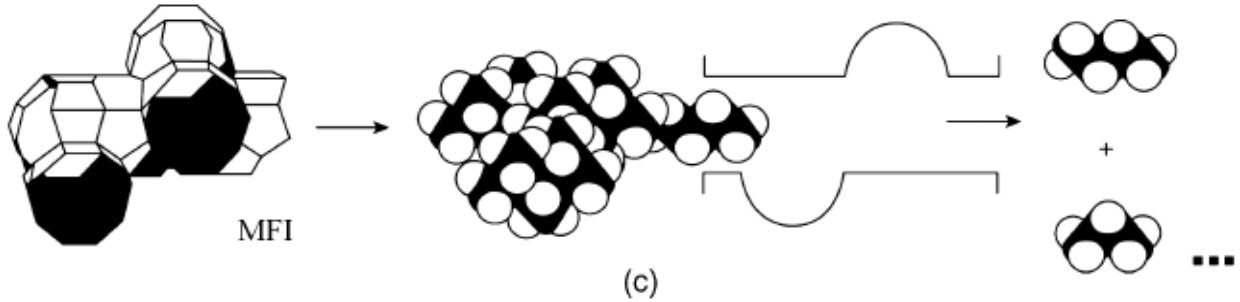
Zeolites

Diffusion selectivity



Cracking and alkylation
Transforming benzene

Separation
and cracking



Processes in MFI type zeolites

MOF properties (compared to zeolites)

- Surface area is larger, it can range between 1 000 – 10 000 m^2/g of material
- Possibility to fine-tune their properties having at hand a large amount of various organic linkers (polycarboxylates, phosphonates, sulfonates, imidazolates, amines, pyridyl, phenolates) and metal nods
- Possibility for surface or internal post-synthetic modifications to further control their physicochemical properties
- MOFs have larger panel of pore size and shape unlike zeolites

MOF synthesis: Control of particle size

- Preparation of homogeneous, monodispersed, and stable nanoparticles is an important issue for biomedical applications
- Particle size represents limitations for some administration routes
- E.g., parenteral route requires stable solutions/suspensions of nanocrystals smaller than 200 nm to freely circulate through capillaries
  - Conventional hydro/solvothermal synthesis
  - Reverse phase microemulsion – CTABr micelles in isooctane/1-hexanol/water mixture (large volumes, hard to isolate)
  - Sonochemical synthesis
  - Microwave assisted hydro/solvothermal synthesis – local superheated nucleation spots

- Avoid toxic solvents, usual are DMF, pyridine, or methanol with LD_{50} values (oral administration in rats) of 2800, 891, and 5628 $mg \cdot kg^{-1}$

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Crystallization synthetic technique

- **Hydrothermal (solvothermal) method**

Analysis of MOFs

- Single crystal X-ray diffraction
- Powder X-ray diffraction
- Differential scanning calorimetry
- Thermogravimetry
- Vibrational spectroscopy (IR, Raman)
- Solid state magic angle spinning NMR
- Neutron diffraction

Host-guest chemistry – how to get a drug inside MOF?

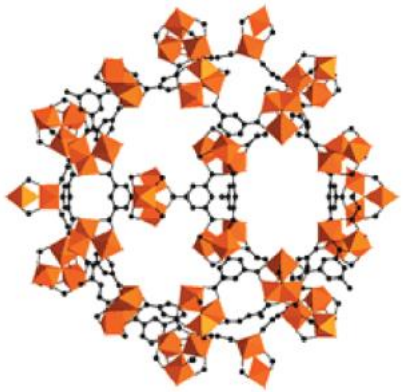
- MOF synthesis
- Filtration
- Structural study
- MOF with sufficient pore size and volume matching with a size of a guest
- MOF activation using vacuum (heating) – removal of volatile components (solvents)
- Re-check of MOF structure (risk of collapsing upon removal of solvents)
- Suspension of crystals added to solution of guest, adsorption (penetration)
- Filtration (washing of the crystals), analysis, quantification of guest uptake
- Stability study, drug release study
- Biological study

Biomedical applications of MOFs

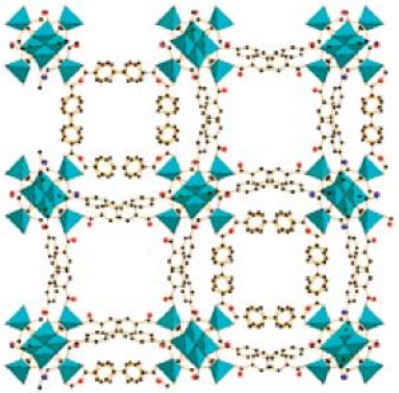
- MOFs for biomedical application require biocompatible composition
- So far, the data are mostly evaluated based on toxicity of components
- Dose, frequency, application route
- Exogeneous and endogenous linkers
- Polycarboxylic or imidazolate linkers are not very toxic (rat oral doses of 1.1, 5.5 and 8.4 g/kg for terephthalic, trimesic, 2,6-napthalenedicarboxylic acid
- Muconate, gallate – low MOF porosity, cyclodextrins – low stability
- MIL-100(Fe) trimesic acid, CPO-27(Mg) 2,5-dihydroxyterephthalate, or BioMOF-1 zinc adeninate-4,4´-biphenyldicarboxylate

metal	LD_{50} (g/kg)	daily dose (mg)
Zr	4.1	0.05
Ti	25	0.8
Cu	0.025	2
Mn	1.5	5
Fe	0.45	15
Fe°	30	
Zn	0.35	15
Mg	8.1	350
Ca	1	1000

[a] Oral LD_{50}(in g/kg) for zirconyl acetate,[19,20] titanium dioxide,[21] copper(II)sulfate,[22] manganese(II) chloride,[23] iron(II) chloride,[24] zinc chloride,[25] magnesium chloride,[26] calcium chloride.[27]



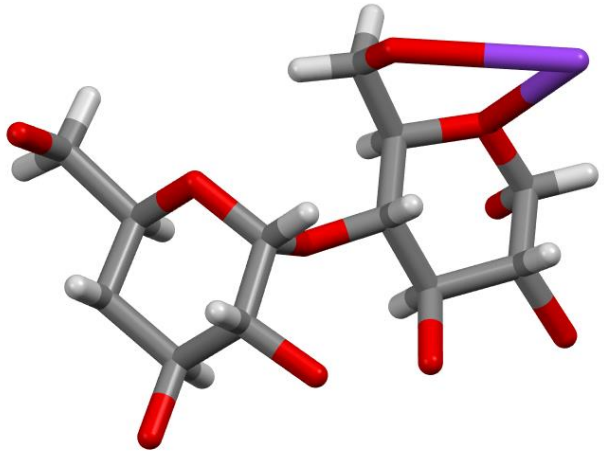
MIL-100



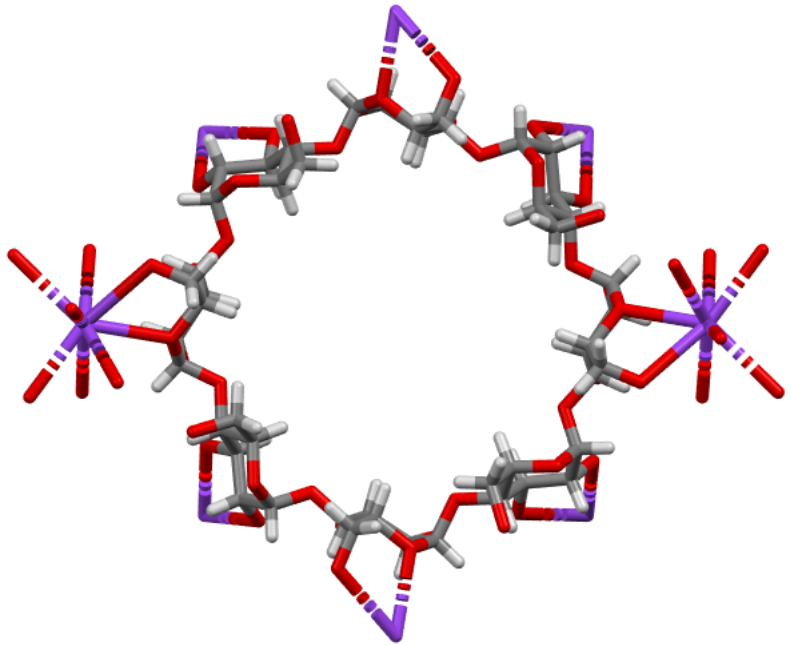
BioMOF-1

P. Horcajada, G. Férey, R. E. Morris, C. Serre et al. *Chem. Rev.* 2012, 112, 1232–1268.

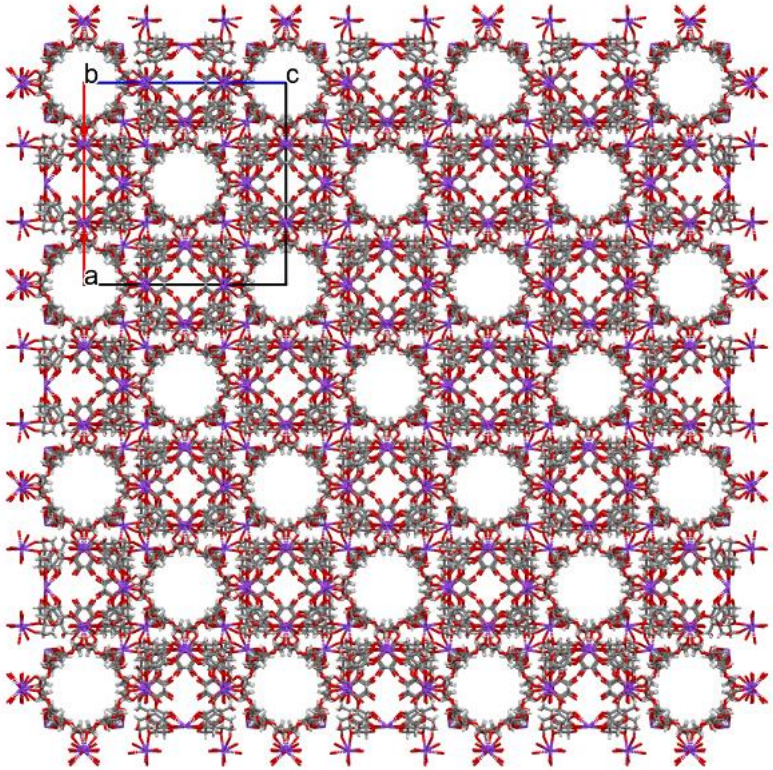
CD-MOF-1



Asymmetric unit



Unit cell



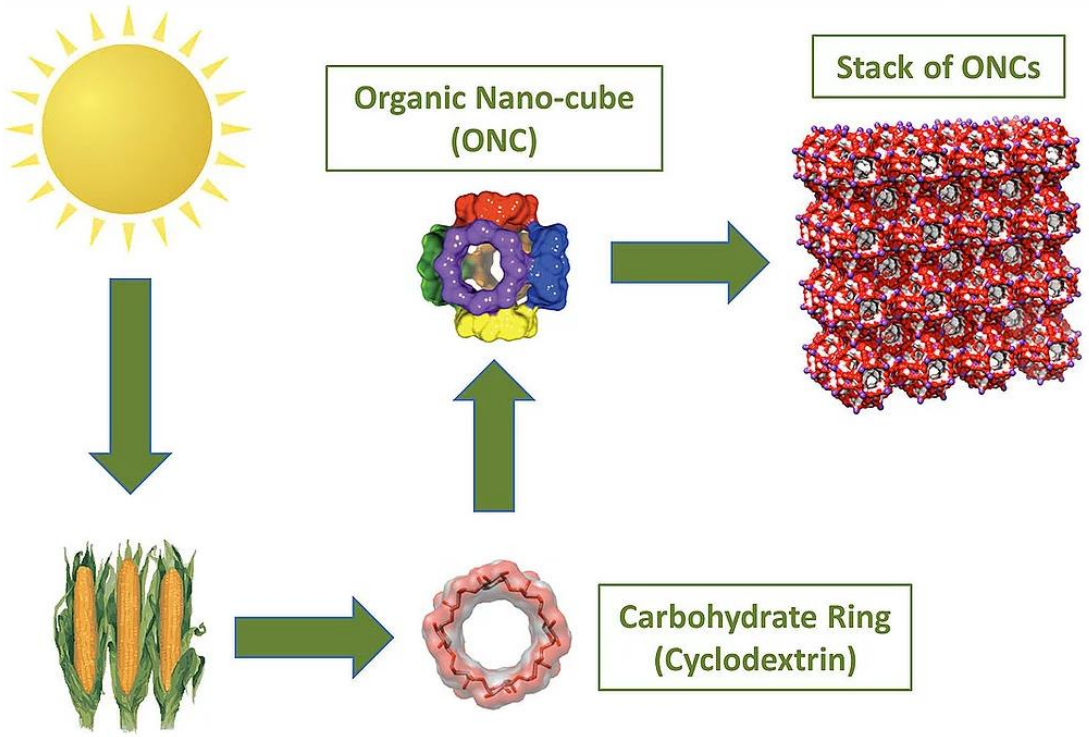
Crystal packing

CD-MOF-1

J. F. Stoddart: *J. Am. Chem. Soc.* **2012**, *134*, 406–417.

Interesting supramolecular applications of CDs – CD-MOF

- γ-CDs for Organic Nano-Cubes (ONCs) developed by (metal-organic frameworks – CD-MOFs

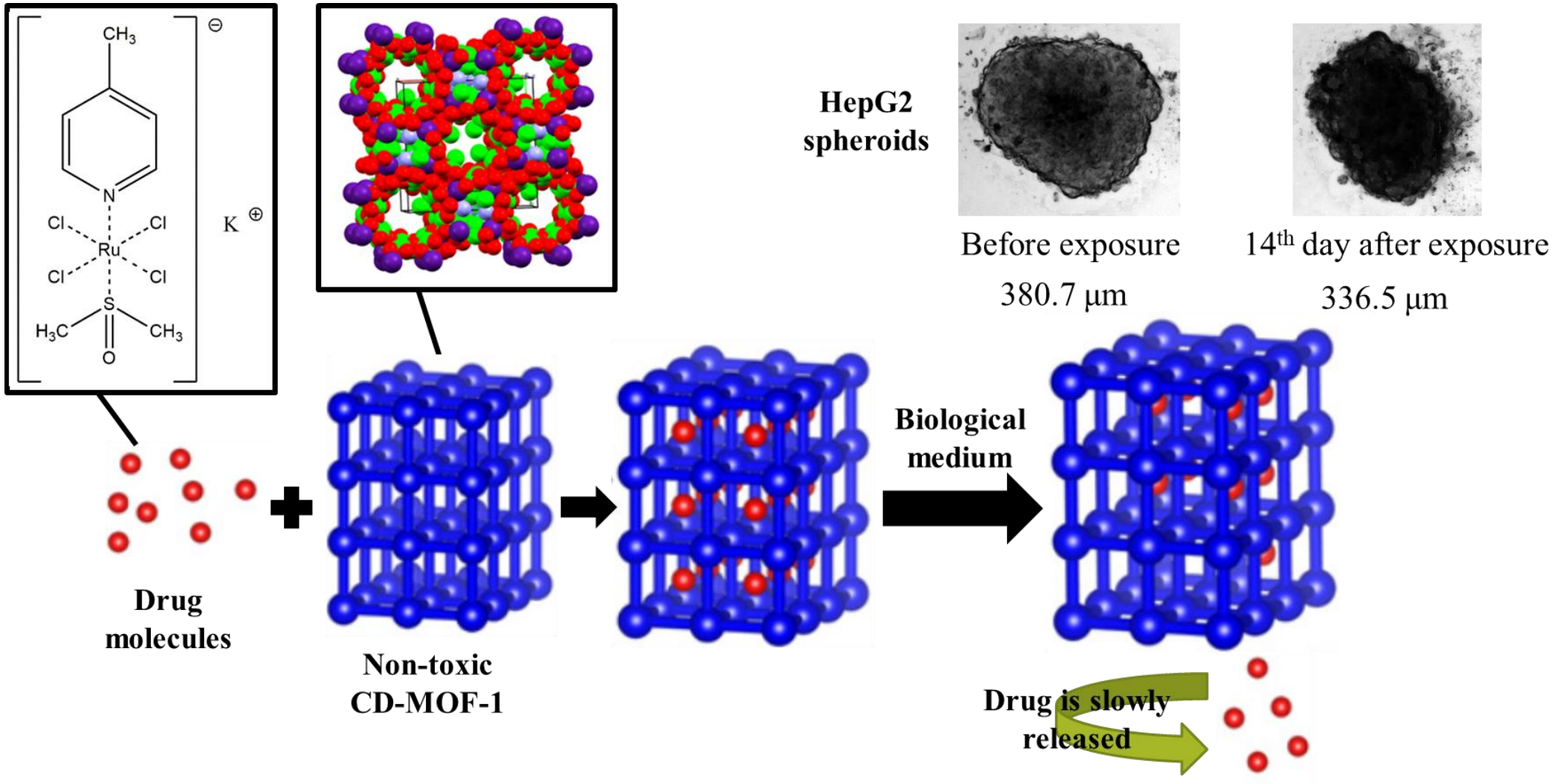


- in cosmetics (NOBLE antiaging skin care), but also chemical and petrochemical industry, home and personal care, food and beverages and pharmaceuticals

a) Stoddart J. F. *et al.*: *J. Am. Chem. Soc.* **2012**, *134*, 406-417. b) Yaghi, O. M.; Stoddart J. F. *et al.*: *Angew. Chem. Int. Ed.* **2010**, *49*, 8630-8634.

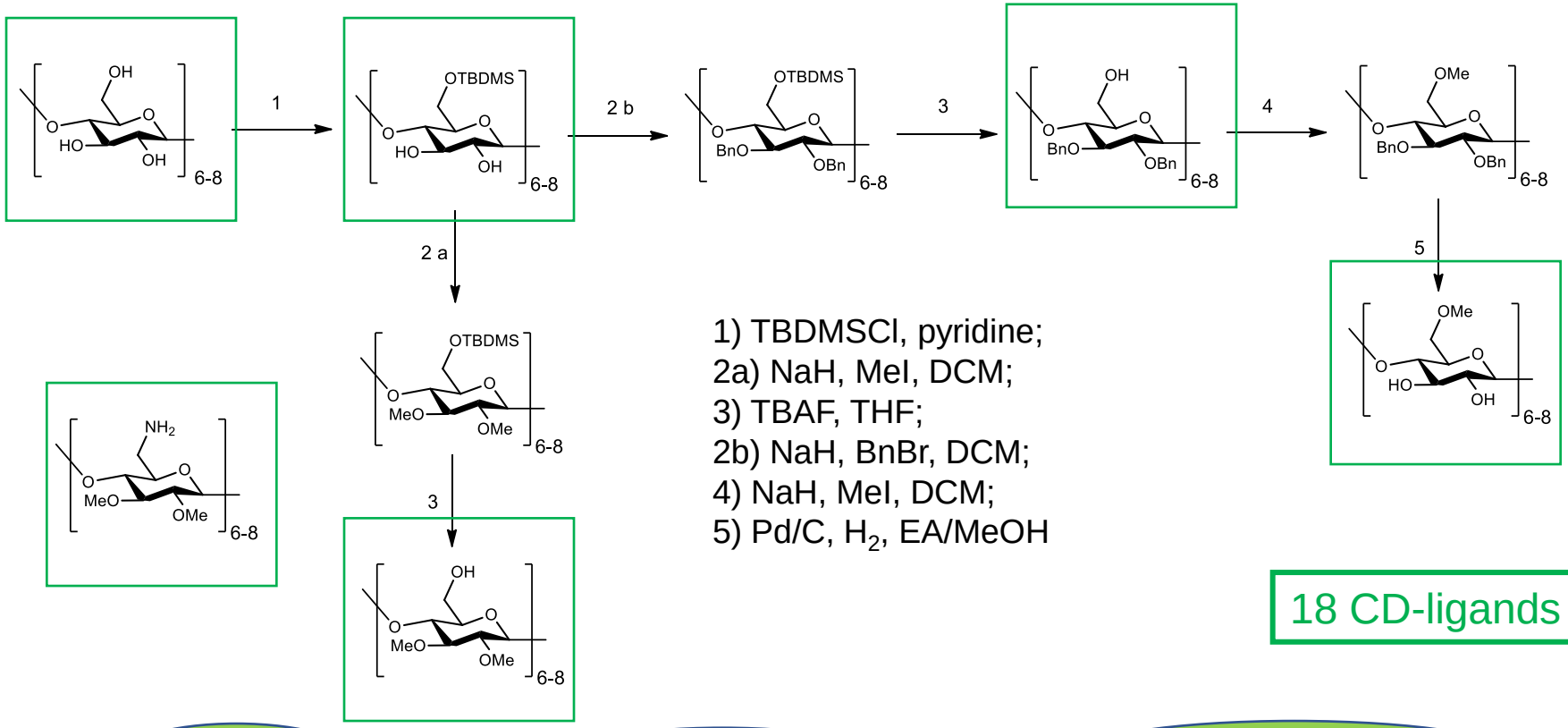
Porous drug carriers: Examples from our lab

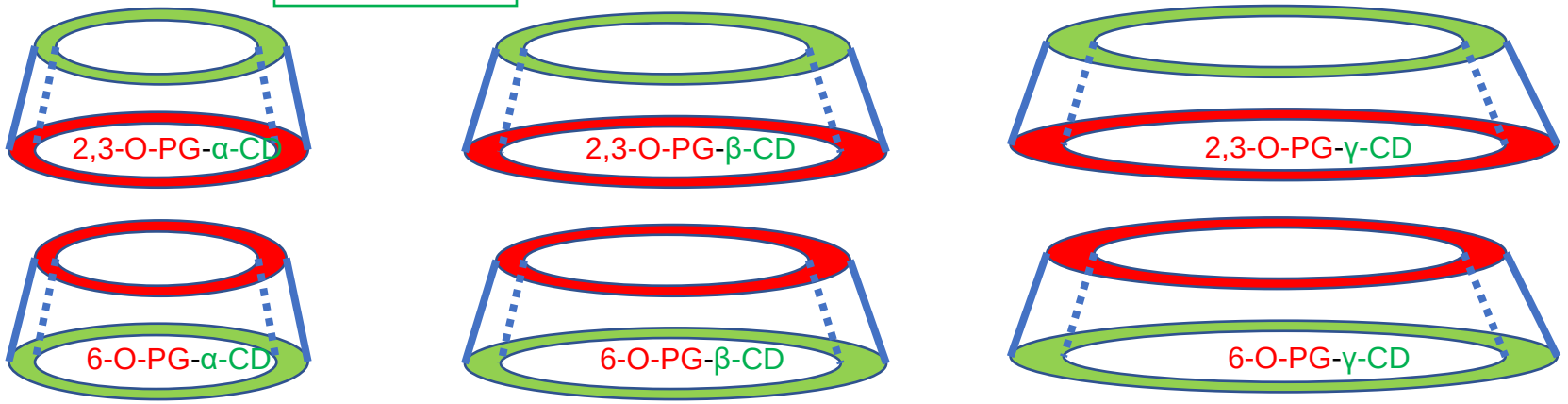
- Anticancer ruthenium(III) complex in CD-MOF-1



Marzabad M. A. et al. under revision in *Cryst. Growth Des.*

Development of novel CD-MOFs using modifed CDs





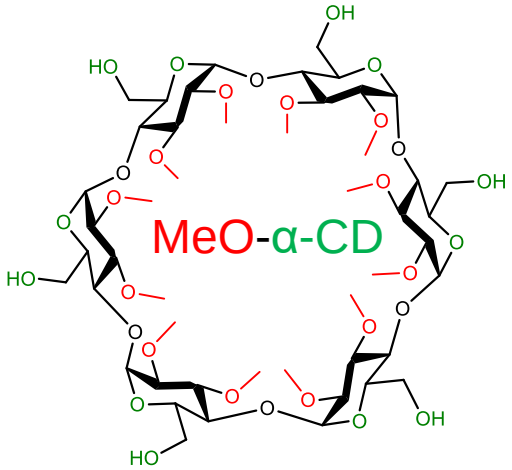
Game of cyclodextrins, metal complexation, crystallization

Methylated cyclodextrin (10 mg) M salt/BS	α	β	γ
RbF/MeOH	evapor. (7,3) X	evapor. (6,3) CRS	evapor. (5,5) X
RbF/MeOH	-	-	EA (5,5) CRS, C
RbF/MeOH	-	ACN (6,3)	ACN (5,5) CRS
RbF/MeOH	H (7,3)	H (6,3)	H (5,5)
RbF/MeOH	E (7,3) CS	E (6,3) C	E (5,5) F
H_2O	evapor. X	evapor. X	evapor. X
RbF/H_2O	evapor. (7,3) X	evapor. (6,3) X	evapor. (5,5) CRS
$ZnBr_2$/MeOH	E (11,8) N, C	E (11,8)	E (10,4)
$ZnBr_2$/MeOH	DIP (11,8) P	-	-
$ZnBr_2$/MeOH	DIP (11,8) P, N, C	-	-
[2] MeOH	E	E	E, C , N, F
[2] RbF/MeOH	E (1 mg, 1 eq.) C , CRS	-	-
[2] RbF/MeOH	E (2,7, 3), N, C	-	-
[2] RbF/MeOH	E (5,5, 6) C	-	-
[2] RbF/EtOH	E (5,5, 6) C , CRS	-	-
[3] RbF/EtOH	-	-	E (5,5) 1 H, CRS, G, C
[4] RbF/EtOH	-	E (6,3)	E (5,5)
[4] RbF/EtOH	-	H (6,3)	H (5,5)
[4] RbF/EtOH	-	ACN (6,3)	ACN (5,5)
[4] RbF/EtOH	-	-	EA (5,5)
[5] KAcO/MeOH	E (5,2)	-	-
[5] KOH/MeOH	E (3,5) N, C	-	-
[5] $Zn(AcO)_2$/MeOH	E (11,5) CRS	-	-
[5] $Zn(NO_3)_2.6H_2O$/MeOH	E (15,7)	E (15,6)	E (13,7)

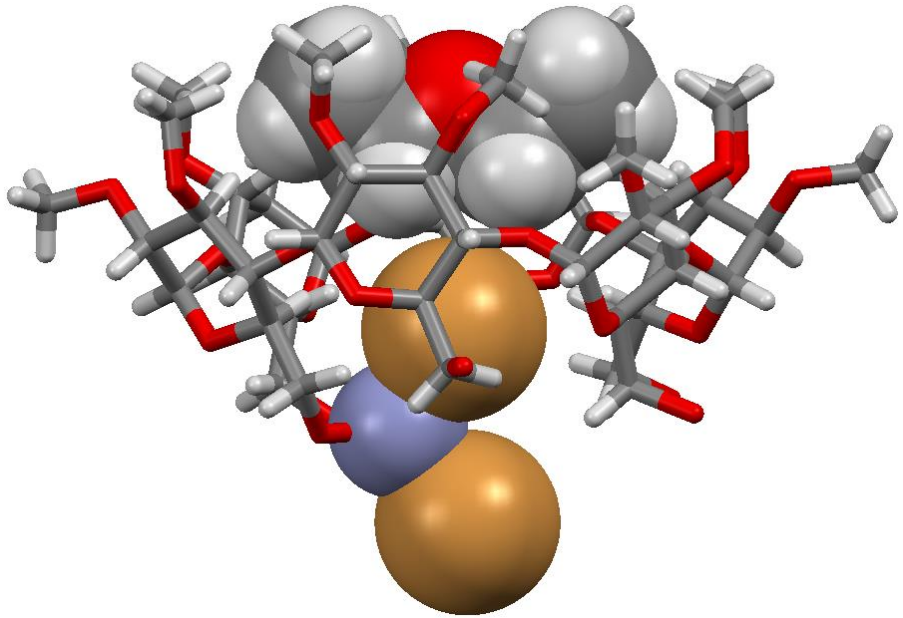
Methylated cyclodextrin (10 mg) M salt/BS	α
$EuCl_3.6H_2O$/ MeOH	E (19,3) + TMAOH (22 µL)
$EuCl_3.6H_2O$/ MeOH	E (19,3)
$ZrCl_4$/MeOH	E (12,3) + TMAOH (22 µL)
$ZrCl_4$/MeOH	E (12,3)
$ZrOCl_2.8H_2O$/MeOH	E (17) C
MoO_2(doaa)/MeOH/H_2O (20)	freezer -20, (34)
$TiCl_4$/MeOH	E (5,8 µL)
$Y(NO_3)_3.5H_2O$/MeOH	E (19,2)
$UO_2(AcO)_2.2H_2O$/MeOH	E (22,3, 6 eq.) + TMAOH (22 µL)
$UO_2(AcO)_2.2H_2O$/MeOH	DIP (22,3, 6 eq.)
LiOH/MeOH/H_2O	evapor. (1,3 mg)

Methylated amino-cyclodextrin M salt/BS	γ
No/MeOH	E, C
No/water	EtOH
$ZrOCl_2.8H_2O$/MeOH	E (17) C
RbF/MeOH	E (5,5) P, G
RbF/water	EtOH (5,5)
$ZnBr_2$/MeOH	E (11,9)
$Zn(NO_3)_2.6H_2O$/MeOH	DIP (15,7)

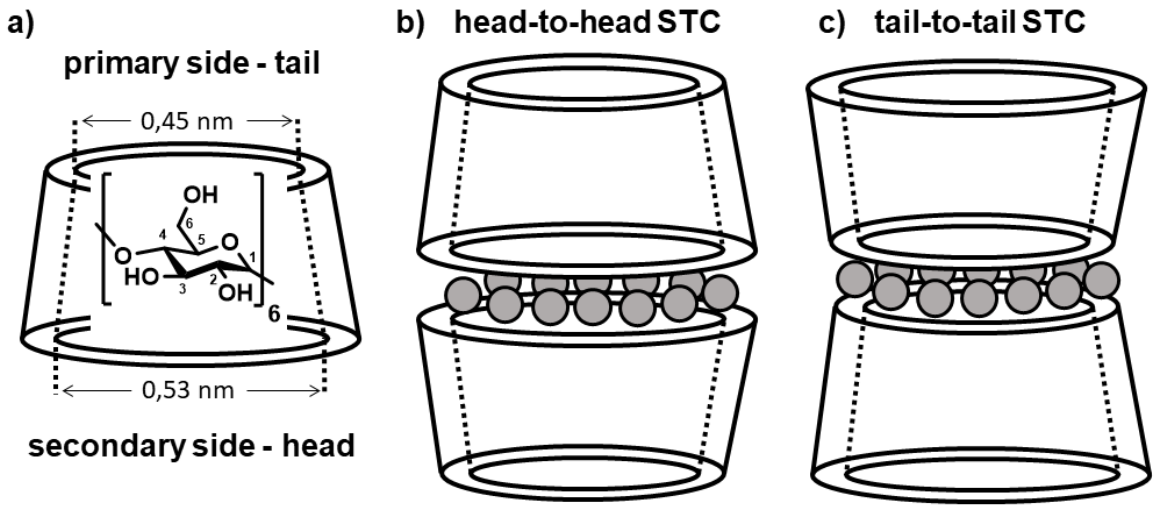
Development of novel CD-MOFs

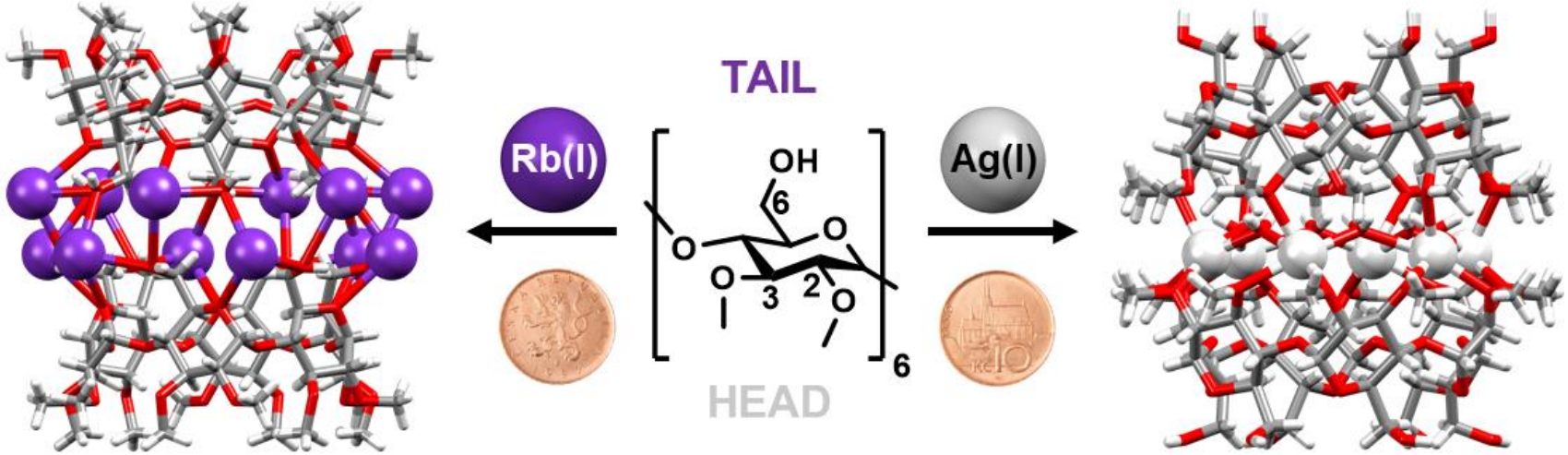


+ $ZnBr_2$

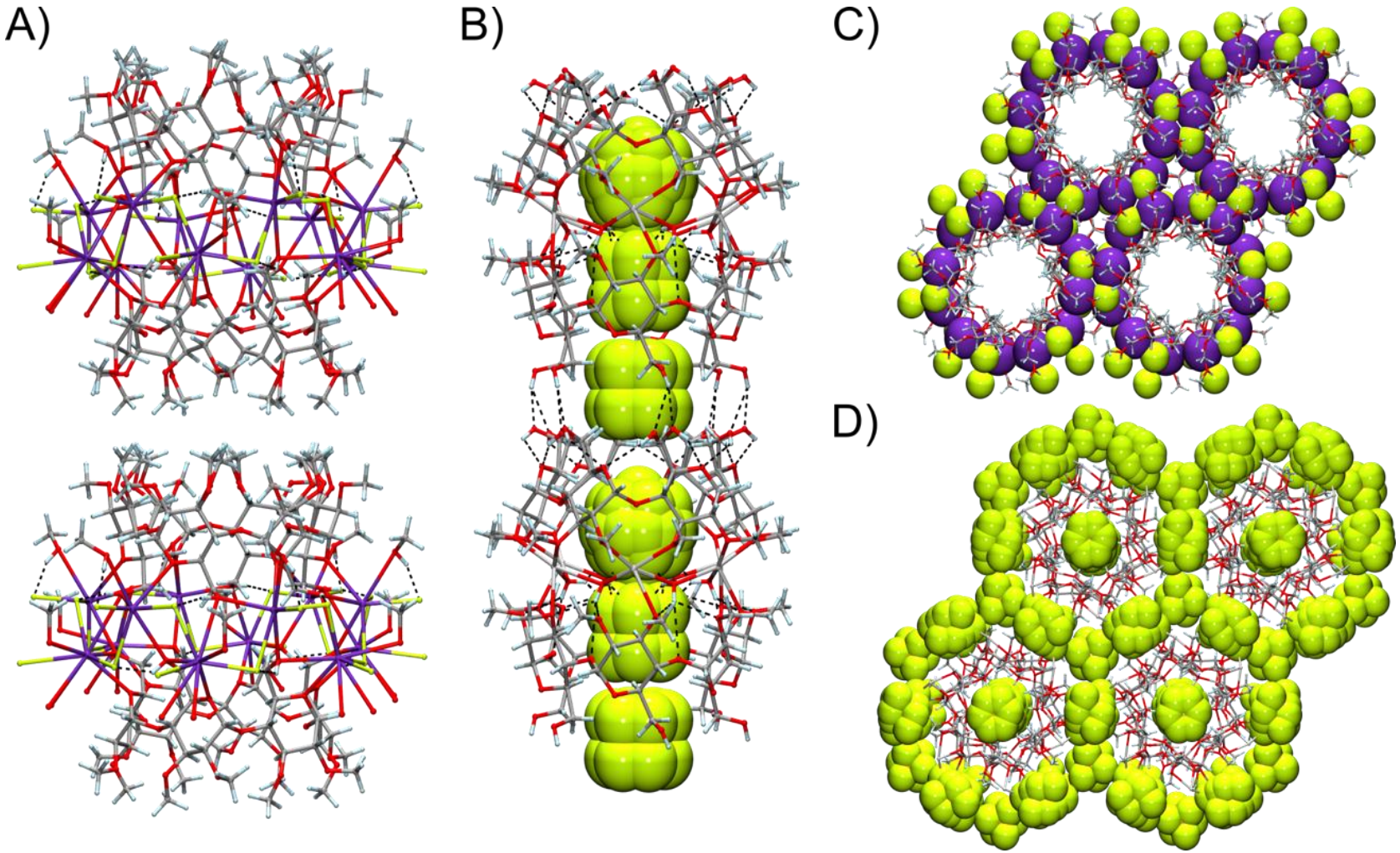


Sandwich-like dimeric structures using Rb(I) and Ag(I)



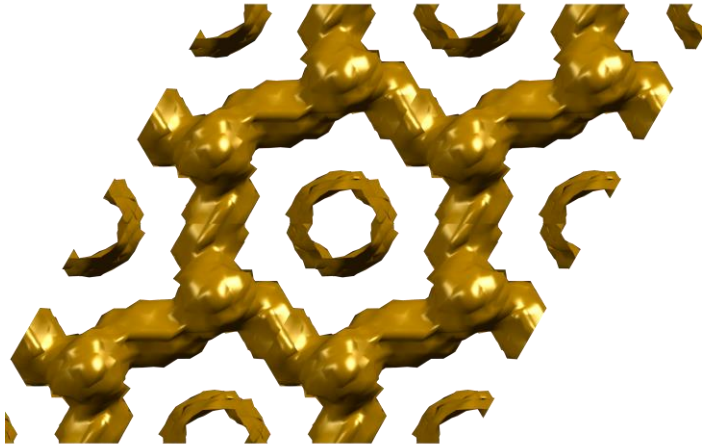


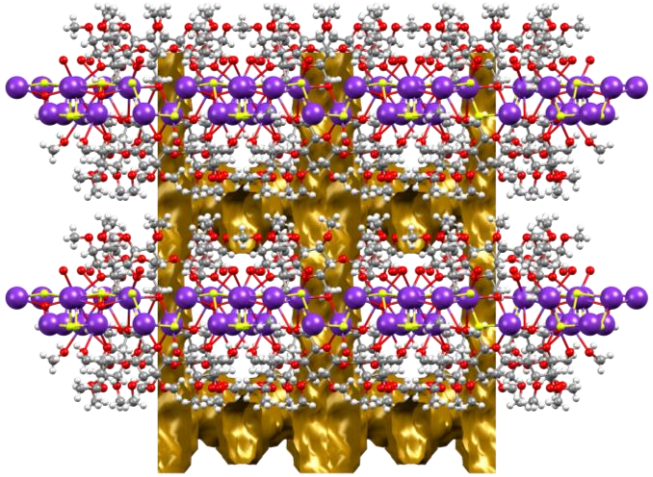
Porous sandwich-type complexes (STCs)

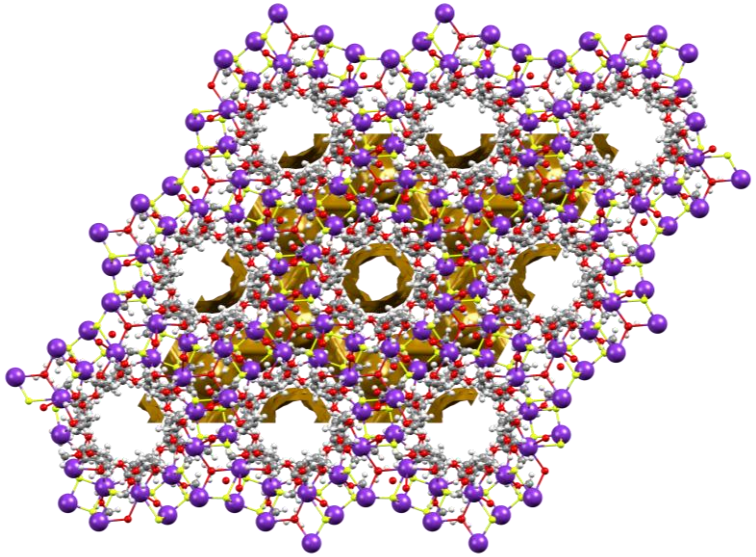


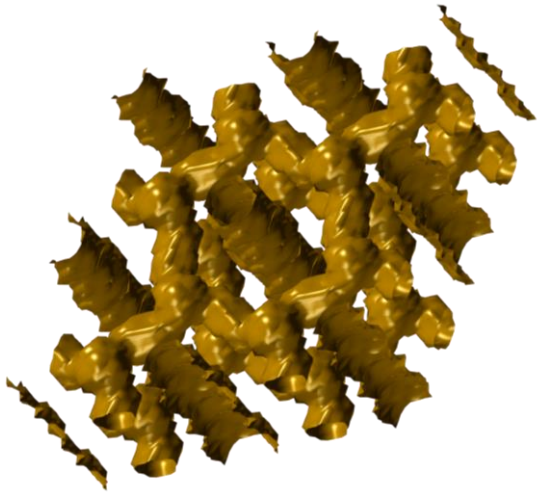
Jurček O. et al. *Cryst. Growth Des*. 2020, 20, 6, 4193–4199.

Porous sandwich-type complexes (STCs)









Jurček O. et al. *Cryst. Growth Des*. 2020, 20, 6, 4193–4199.

Drug delivery

- Drugs faces problems with low stability in biological conditions, poor solubility and/or inadequate ability to bypass natural barriers
- 1970s started development of drug carriers to protect both the organism from toxic side effects and the API from biological degradation increasing drug's efficiency and intracellular penetration
- Moreover, nanotechnologies allow specific targeting of tissues, cells and even subcellular structures
- General issues are low drug loading capacity (<5 wt%), the presence of a burst release, poor biological barrier bypass and/or toxicity
- MOFs offer interesting alternative

	drug loading (wt%)			
drug	BioMOF-1	MIL-100	MIL-101_NH_2	MIL-53
ethoxysuccinato-cisplatin			12.8	
procainamide	22			
busulfan		25.5		14.3
azidothimidine triphosphate		21.2	42.0	0.24
azidothimidine		6.1		
cidofovir		16.1	41.9	
doxorubicin		9.1		
ibuprofen		33		22
caffeine		24.2		23.1
urea		69.2		63.5
benzophenone 4		15.2		5
benzophenone 3		1.5		

P. Horcajada, G. Férey, R. E. Morris, C. Serre et al. *Chem. Rev.* 2012, 112, 1232–1268.

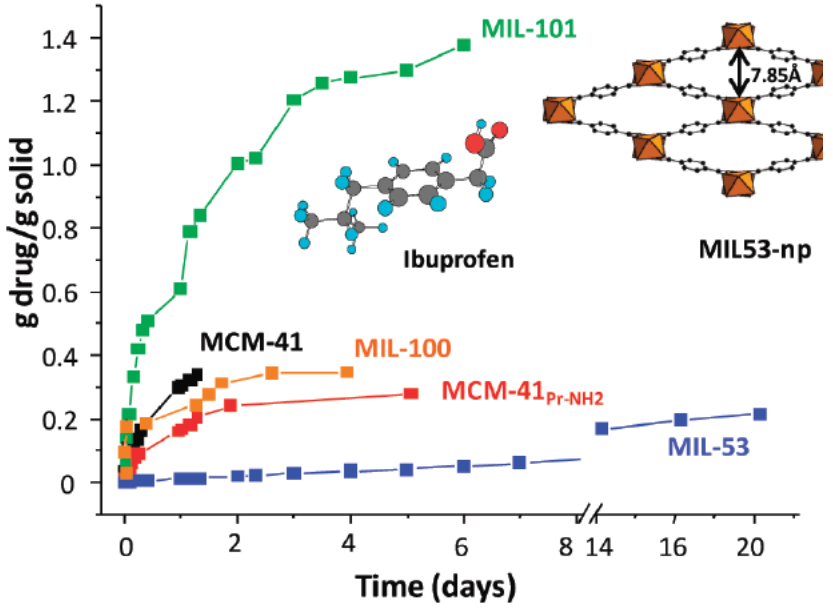
MOF formulations

- Oral administration
  - Requirements for chemically and mechanically stable formulations under the corresponding biological conditions, i.e., acidic stomach or basic intestinal conditions, intestinal motility, enzymes, etc.)
  - Powders, pellets, tablets, or gels are suitable
- Cream/ointment or patch/membrane
  - E.g., wound healing antibacterial dressing based on NO-loaded nickel carboxylate CPO-27(Ni) particles and hydrocolloids (cellulose, polyisobutanol (PIB)) was studied. This composite patch is able to release NO over 10 days.

P. Horcajada, G. Férey, R. E. Morris, C. Serre et al. *Chem. Rev.* 2012, 112, 1232–1268.

Drug delivery

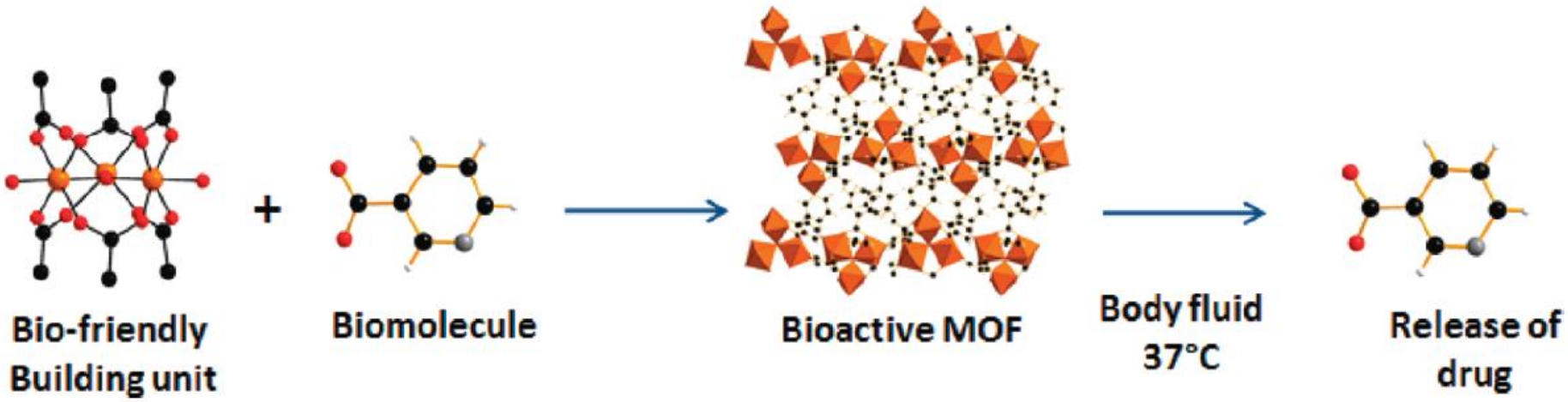
- Anti-inflammatory and analgesic ibuprofen was studied in model mesoporous rigid chromium carboxylates MOFs, MIL-100(Cr), MIL-101(Cr), MIL-53(Fe, Cr) – continuous delivery of drug for 3 weeks
- Cationic antiarrhythmic drug, procainamide (short *in vivo* half-life, administration every 3-4 h), introduced BioMOF-1 (22 %wt loading in 15 days) – release has been achieved in 3 days in phosphate buffer (PBS at pH 7.4)



a) J. An et al. *J. Am. Chem. Soc.* 2009, 131, 8376. b) P. Horcajada, G. Férey, R. E. Morris, C. Serre et al. *Chem. Rev.* 2012, 112, 1232–1268.

Bioactive MOFs

- MOFs are likely to be degraded in bodily fluids releasing exogenous organic linker and potentially toxic metal salts
- Ideally using endogenic ligands or the actual bioactive compounds as a building block
- Vitamin B_3, nicotinic acid, can be used with Fe(II)/Fe(III) for synthesis of BioMOF Bio-MIL-1 (pellagra-curative, vasodilating and antilipemic effect)



P. Horcajada, G. Férey, R. E. Morris, C. Serre et al. *Chem. Rev.* 2012, 112, 1232–1268.

Limitations in MOFs‘ use

- Large scale production is limited
- Avoiding the use of expensive and dangerous reactants
- Introducing low pressure conditions and ideally room temperature synthesis
- There are already some MOFs produced at ton scale by BASF, e.g., HKUST-1 (copper trimesate), MIL-53 (aluminium terephthalate), etc., but mostly for separation or catalytic purposes
- Additional toxicity data for biomedical MOFs are needed

Amorphous infinite coordination particles (ICPs)

- Unlike MOFs, these ICPs exhibit a higher level of structural tailorability, including size- and morphology-dependent properties, and therefore, the promise of a wider scope of utility

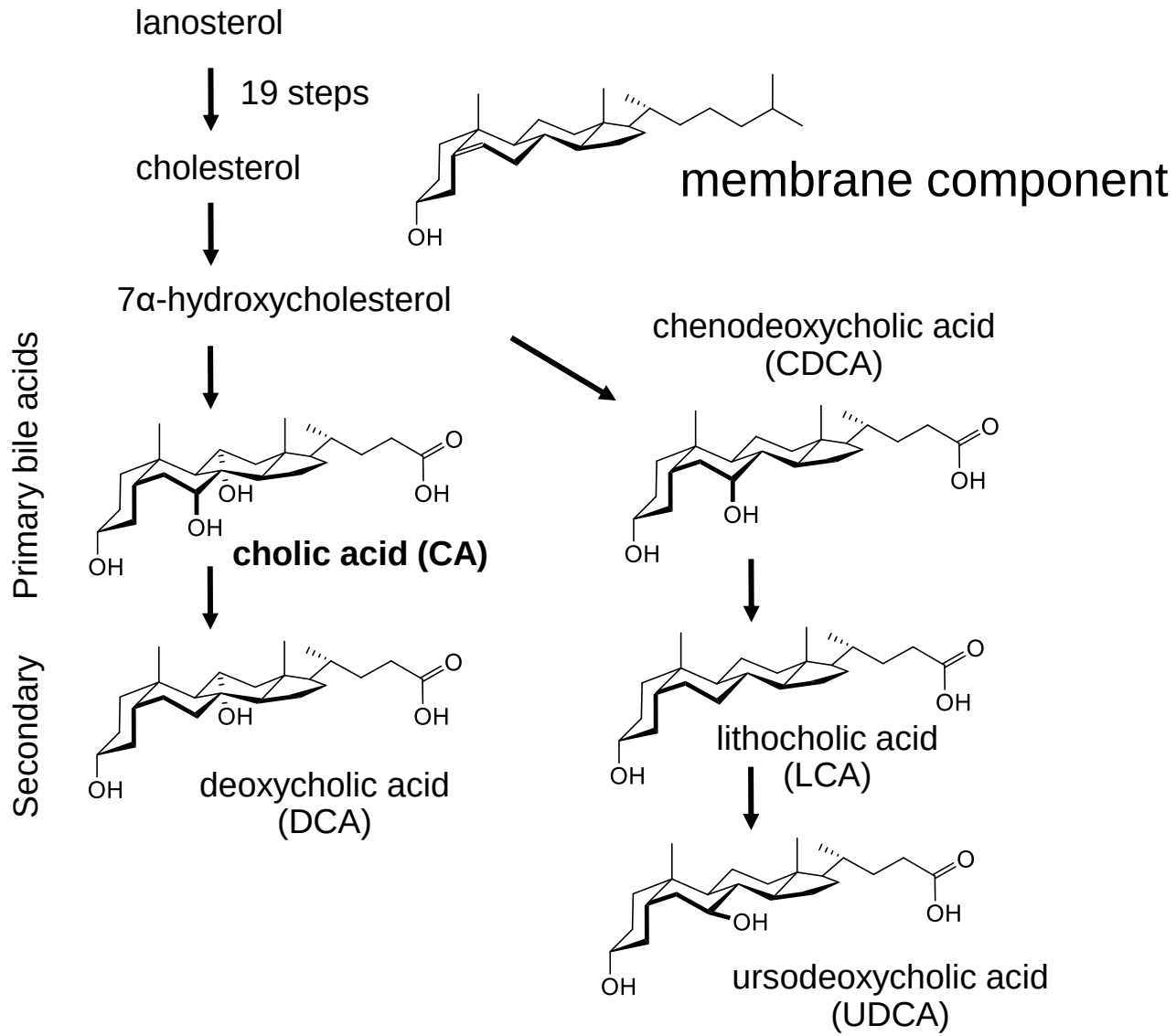
- Various methods of their preparation are available offering a control over their morphology

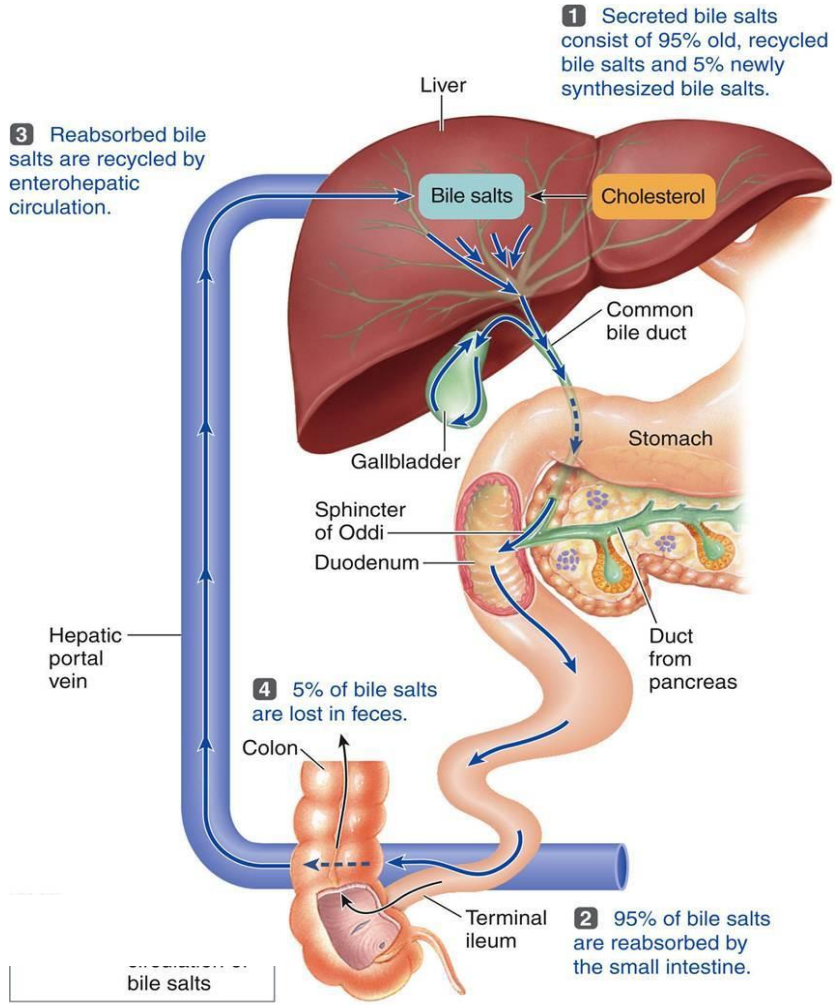
- ICP structures can be depolymerized (sometimes reversibly) much faster and under milder conditions than MOFs, which makes them attractive for a variety of biomedical applications

C. Mirkin et al. *Chem. Soc. Rev.* 2009, 38, 1218–1227.

Bile acids as scaffolds of unsymmetric chiral ligands

- Enterohepatic circulation, transmembrane transport activity

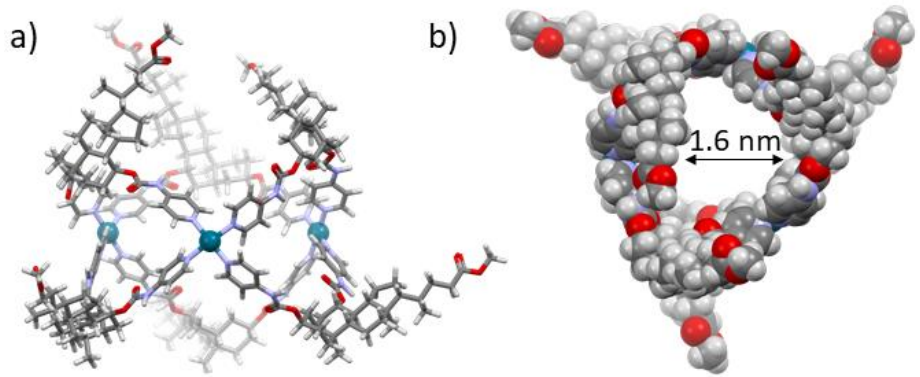




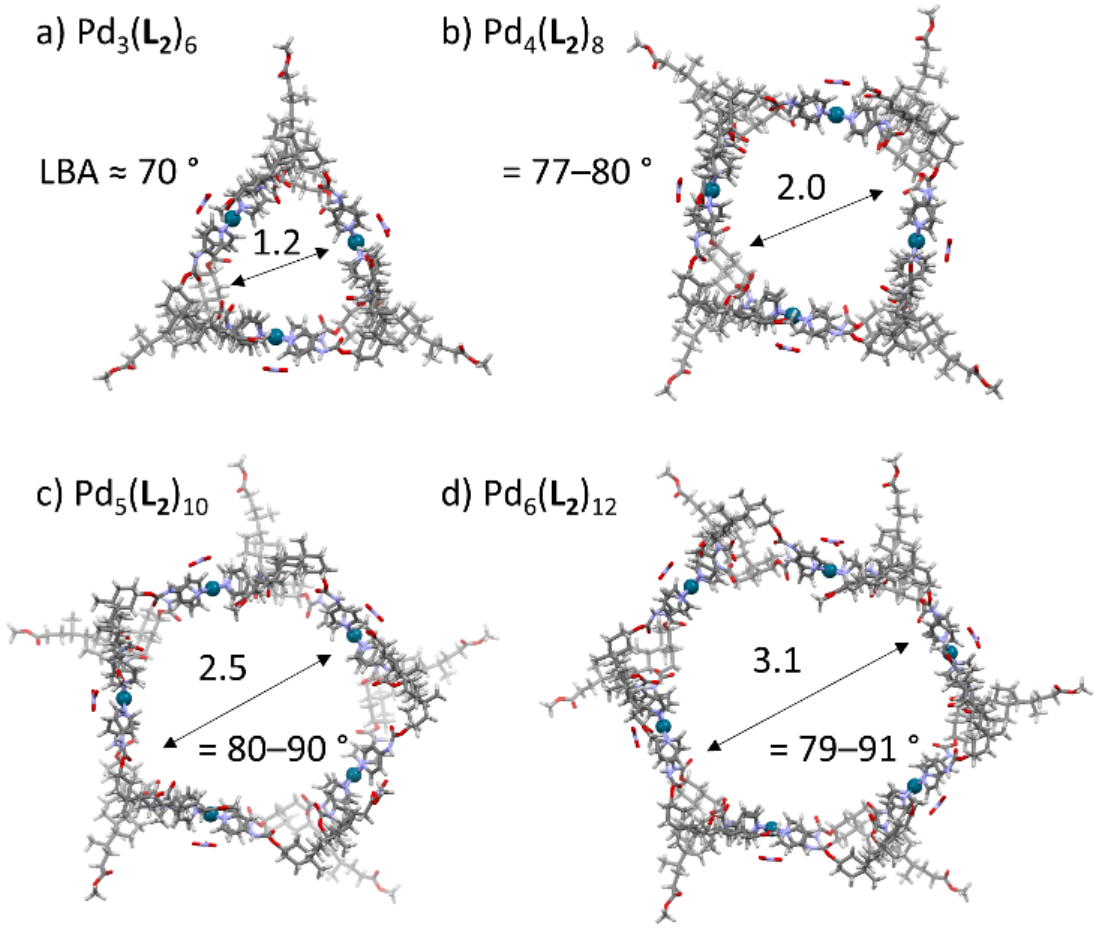
Jurček O. et al. *Molecules* **2022**, *27*(9), 2961.

Distinct metallosupramolecular complexes

UDCA

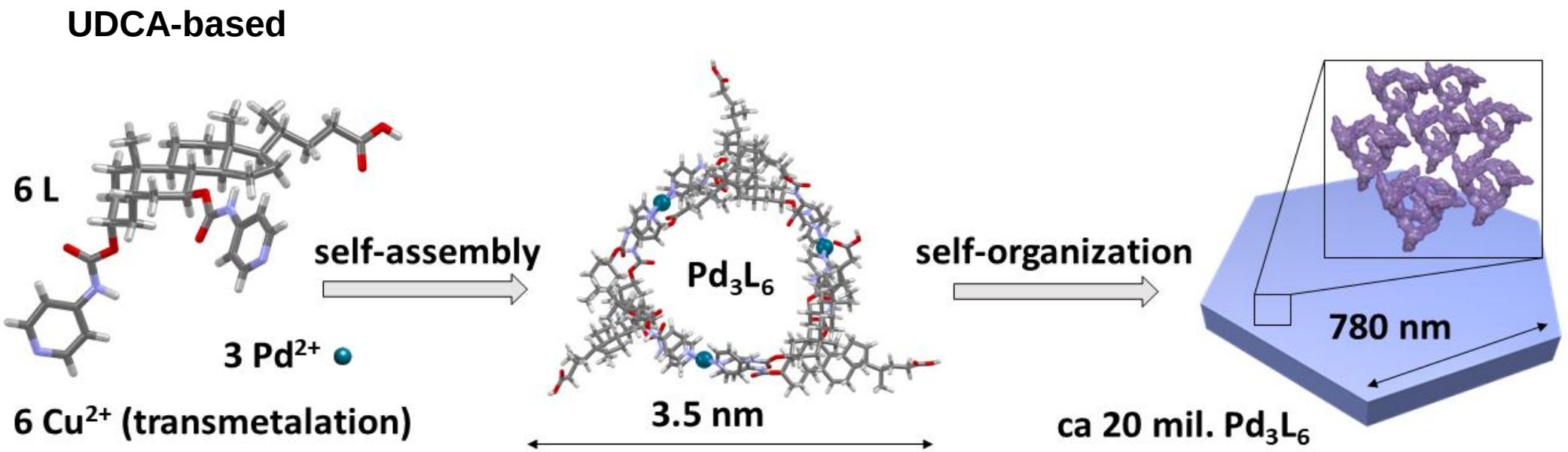


CDCA



Jurček O. et al. *under revision in Angew. Chem. Int. Ed.*

Self-organization of large coordination complexes



Jurček O. et al. *Cell Rep. Phys. Sci.* 2021, *2*, 100303.

In the next class…

Nanoparticles for drug delivery

Thank you for your attention!

With many thanks to Jonathan W. Steed, Jerry L. Atwood for Supramolecular Chemistry, ISBN: 978-1-119-58251-9.