MUNI PHARM

Department of Natural Drugs

Supramolecular Pharmacy

2. Host-guest chemistry (cyclodextrins)

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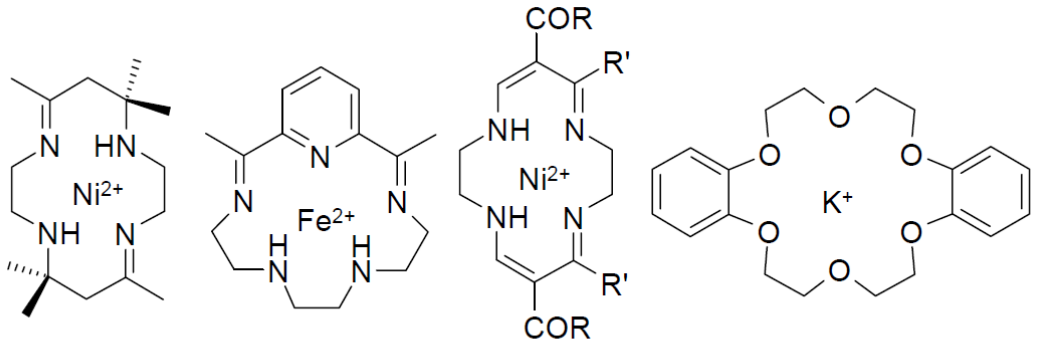
Host-Guest Chemistry

- 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)

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

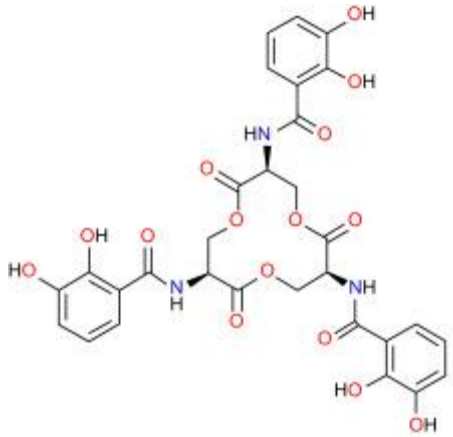
- $K = \frac{[HG]}{[H][G]}$ or $K = \frac{k_1}{k_{\_1}}$ (rate constants)

- Gibbs energy (accociation process)

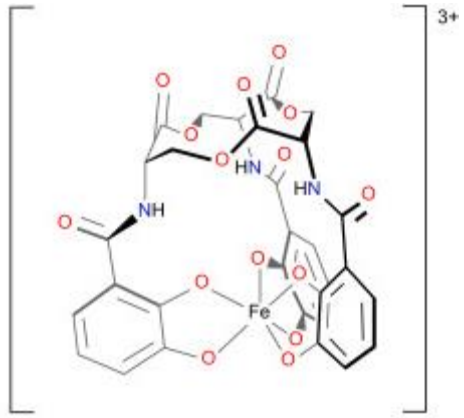
$$-\Delta G^0 = RT \ln K$$

Examples of host-guest complexes

Guest	Host	Solvent	K_{11}/M^{-1}	$\Delta G^{o}/kJ\ mol^{-1}$
Na^+	ClO_4^-	H_2O	3.2	−3
Iodine	Hexamethylbenzene	CCl_4	1.35	−0.8
Tetracyanoethylene	Hexamethylbenzene	CH_2Cl_2	17	−7.1
7,7,8,8-Tetracyanoquinodimethane	Pyrene	CH_2Cl_2	0.94	~0.0
Salicylic acid	Caffeine	H_2O	44	−9.7
Hydrocortisone	Benzoate ion	H_2O	2.9	−2.5
Methyl *trans*-cinnamate	Imidazole	H_2O	1.0	0.0
p-Hydroxybenzoic acid	α-Cyclodextrin	H_2O	1130	−17.6
Caffeine	Caffeine	H_2O	19	−7.1
Phenol	Dimethylformamide	C_6H_6	442	−15.0
K^+	[18]crown-6	H_2O	100	−11.4
K^+	[18]crown-6	Methanol	10^6	−34.2
K^+	[2.2.2]cryptand	Methanol	10^{10}	−57.0
Fe^{3+}	enterobactin	H_2O	10^{52}	−296

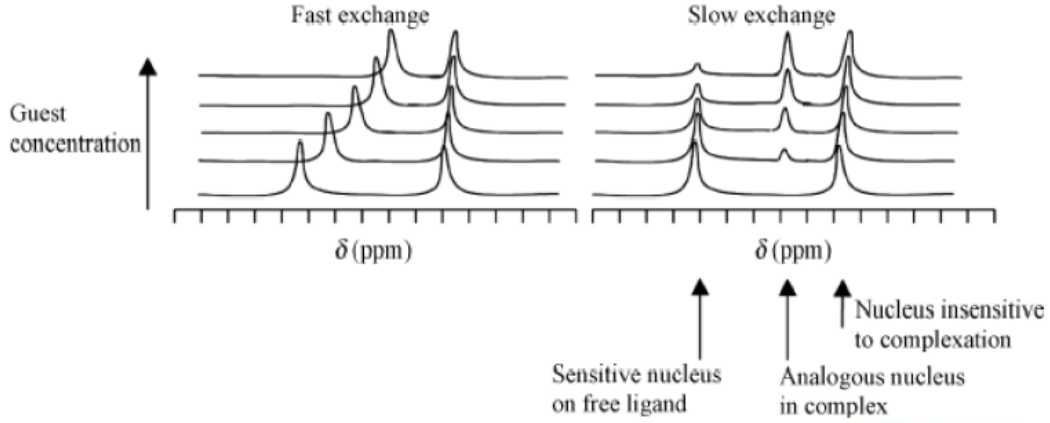


siderophore enterobactin



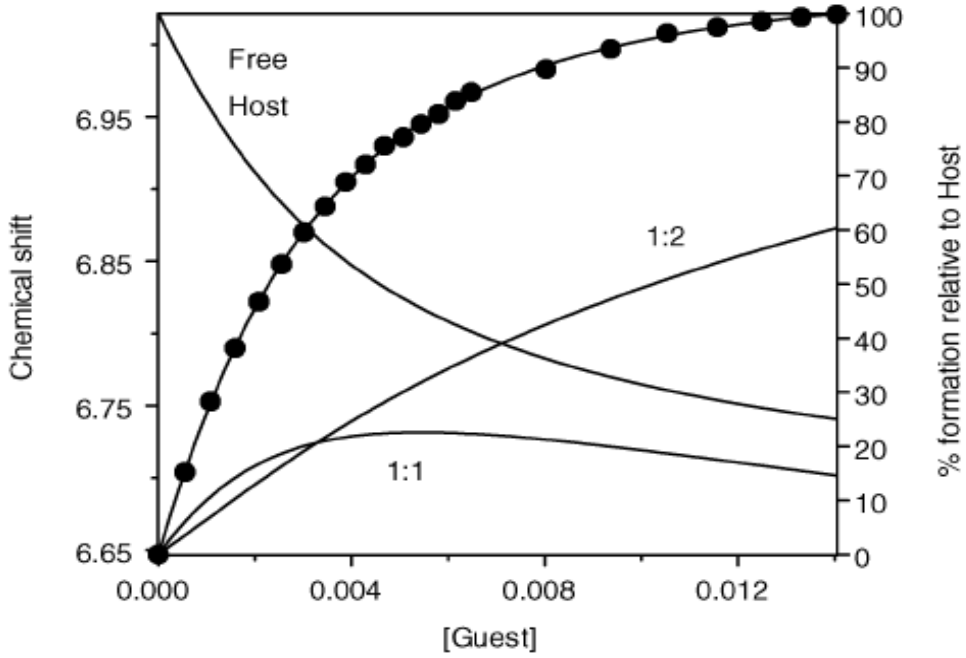
Determination of binding constant

- Any analytical method which can detect concentration of H-G complex in function of changing concentration of host (H) and guest (G)
  - **Potentiometric titration**
    - Charged species, acid-base titration (protonated/deprotonated)
  - **Nuclear magnetic resonance (NMR) spectroscopy**
    - ***Slow*** exchange on the NMR scale – the binding constant can be evaluated based on integration of bound/unbound host or guest
    - ***Fast*** – average between free and bound species



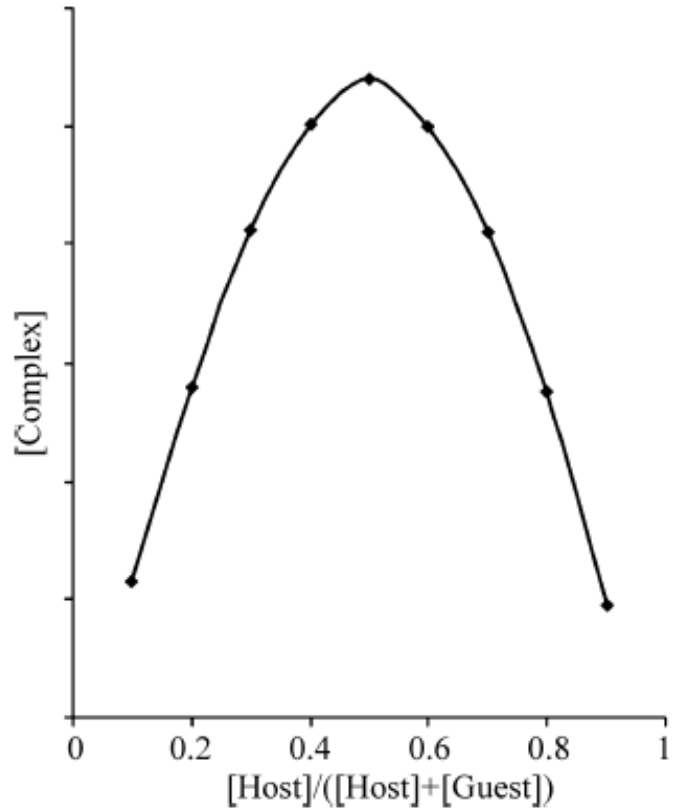
Determination of binding constant

- **Nuclear magnetic resonance (NMR) spectroscopy**
  - *Procedure (NMR titration)*: small aliquots of guest are added to the solution of host with known concentration (or vice versa) in a deuterated solvent and the chemical shifts (Δδ) are monitored as a function of the guest concentration of host:guest ratio
  - the most shifting NMR signals are those which are interacting
  - the shape of the titration curve gives quantitative information about the binding constant (analyzed by least-squares curve fitting program, *e.g*, HypNMR)
  - useful for determination of binding constants in range 10-10^4 M^{-1}



Determination of binding constant

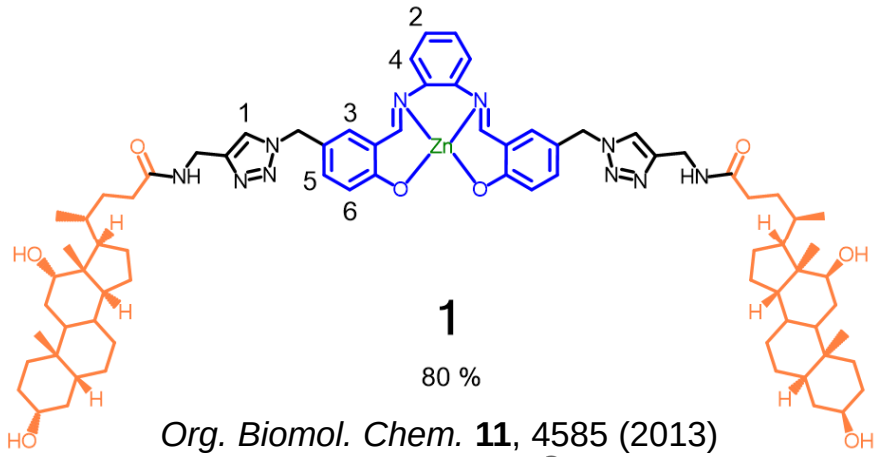
- **Nuclear magnetic resonance (NMR) spectroscopy**
  - *Job plot.* Solutions with varying host:guest ratios while the total concentration of host and guest is constant
  - a peak at 0.5 corresponds to 1:1 ratio, 0.66 to 2:1 stoichiometry, *etc.*
  - the concentration of the complex is related to some observable quantity such as Δδ



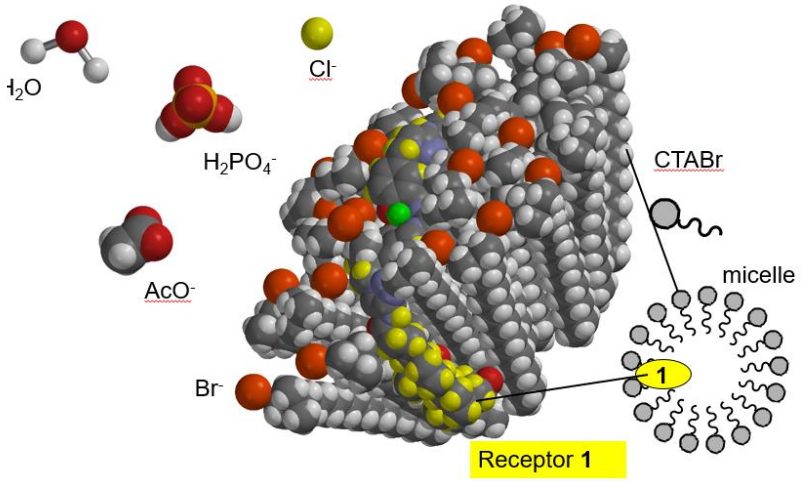
Determination of binding constant

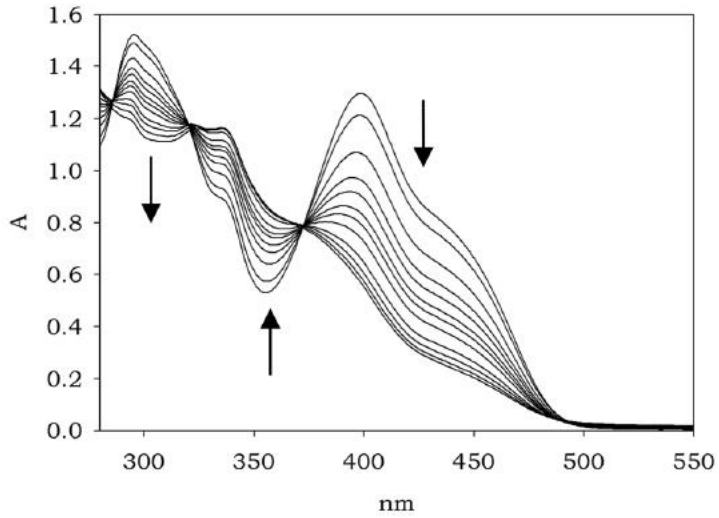
- **Fluorescence titration**
  - based on proportion of fluorescent intensity to concentration of fluorophore (fluorescent species in solution)

- **UV-Vis spectrophotometric titration**
  - monitoring the intensity of an electronic absorption band at a particular wavelength that is characteristic of either the complex or free host or guest (both are more sensitive than NMR)



Org. Biomol. Chem. **11**, 4585 (2013)

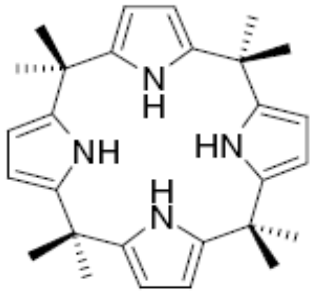


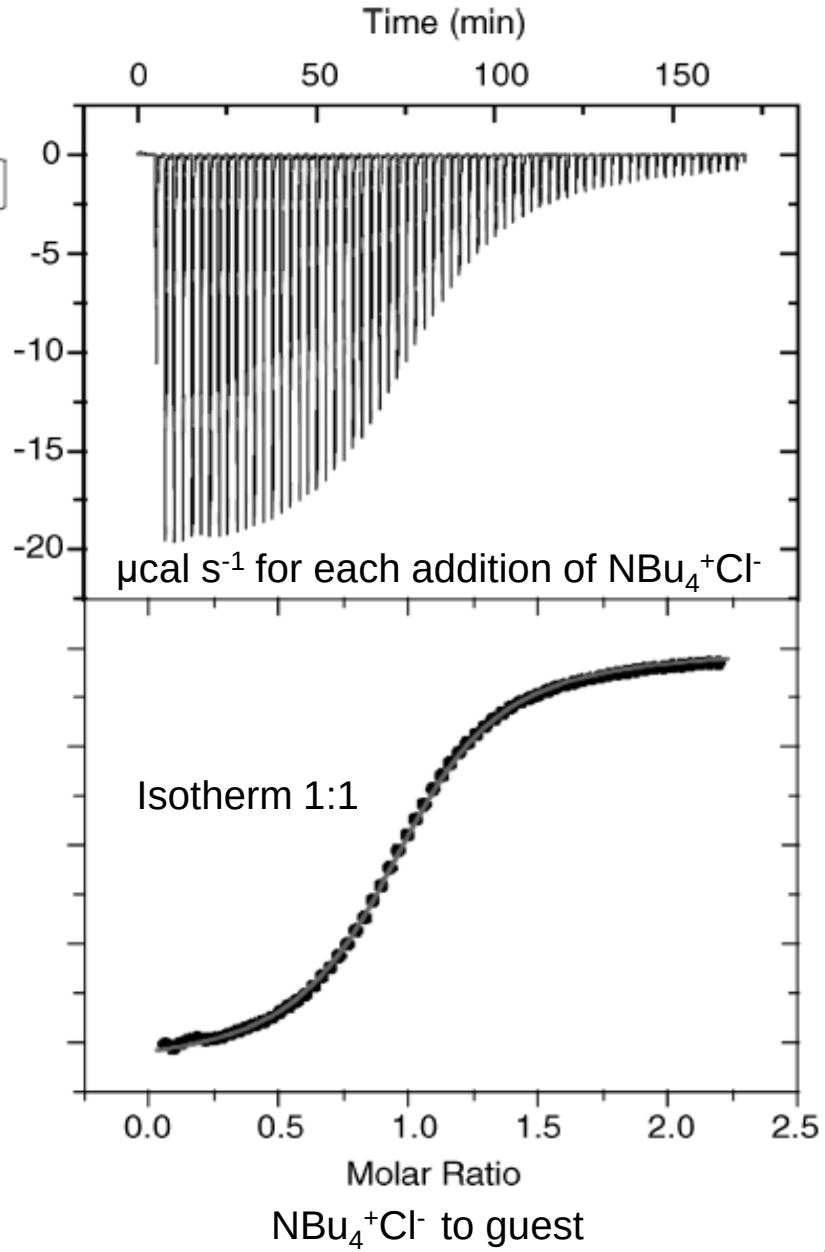


1 : 1 equilibrium and association constant K = 450 ± 30 M^{-1}

Determination of binding constant

- **Calorimetric – Isothermal Titration Calorimetry (ITC)**
  - careful measurement of the heat (enthalpy) evolved from a carefully insulated sample as a function of added guest or host concentration
  - the gradient of the ITC curve can be fitted to determine the binding constant and hence $\Delta G_{complex}$, integration of the total area under the ITC plot gives the complexation enthalpy ($\Delta H_{complex}$), thus we can get all thermodynamic parameters $\Delta G_{complex} = \Delta H_{complex} - T\Delta S_{complex}$
  - binding constants that range from ca. 10^2 – 10^7 M^{-1}





Determination of binding constant

- **Extraction experiment**
  - distribution (partition) coefficient K_d and extraction coefficient K_e between the aqueous and organic phase can be used to explore the selectivity of the host to range of guests in given conditions
  - usually, picrate salts are used as guests and chloroform as an organic phase, host must be insoluble in water
  - concentration ca be determined by UV-vis
  - quick but relatively inaccurate technique, binding energies in the range 25–70 kJ mol^{-1} (i.e., binding constants of ca. 10^4–10^{12}). Binding energies in excess of 70 kJ mol^{-1} are assessed by competition with hosts of known binding energy

$$\text{Selectivity} = \frac{K_{guest1}}{K_{guest2}}$$

$$[M^+ \cdot Pic^-]_{org} + [Host]_{org} = [M^+ \cdot Host \cdot Pic^-]_{org} \quad K_{11} \text{ (binding constant)}$$

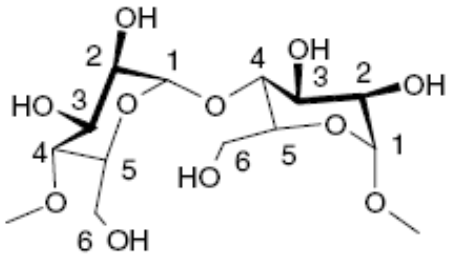
$$[M^+]_{aq} + [Pic^-]_{aq} + [Host]_{org} = [M^+ \cdot Host \cdot Pic^-]_{org} \quad K_e \text{ (extraction constant)}$$

$$[M^+]_{aq} + [Pic^-]_{aq} = [M^+ \cdot Pic^-]_{org} \quad K_d \text{ (distribution coefficient)}$$

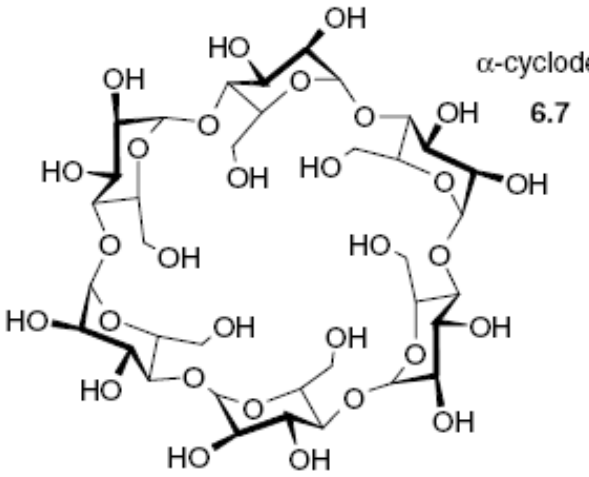
$$K_{11} = K_e / K_d$$

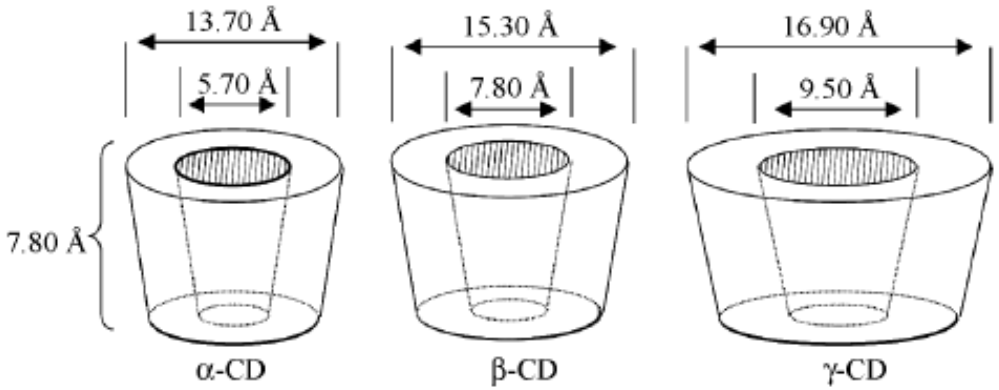
Very popular host in pharmacy: cyclodextrin (CD)

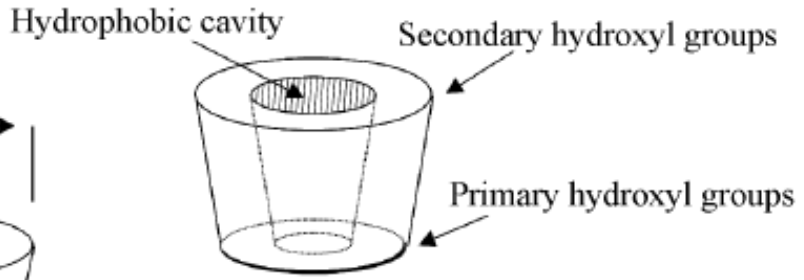
- Macrocyclic hosts built of glucose molecules
- Cyclodextrins are prepared from starch or cellulose (via dextrins): degradation of starch by glucosyltransferase enzyme results in hydrolysis of glycosidic linkages and formation of cyclodextrins, which are isolated by complexation with non-polar guests (e.g., toluene)



- 3 main types of cyclodextrins containing 6, 7, or 8 glucose units: α-, β-, γ-CD
- The most common, the most studied and the cheapest hosts



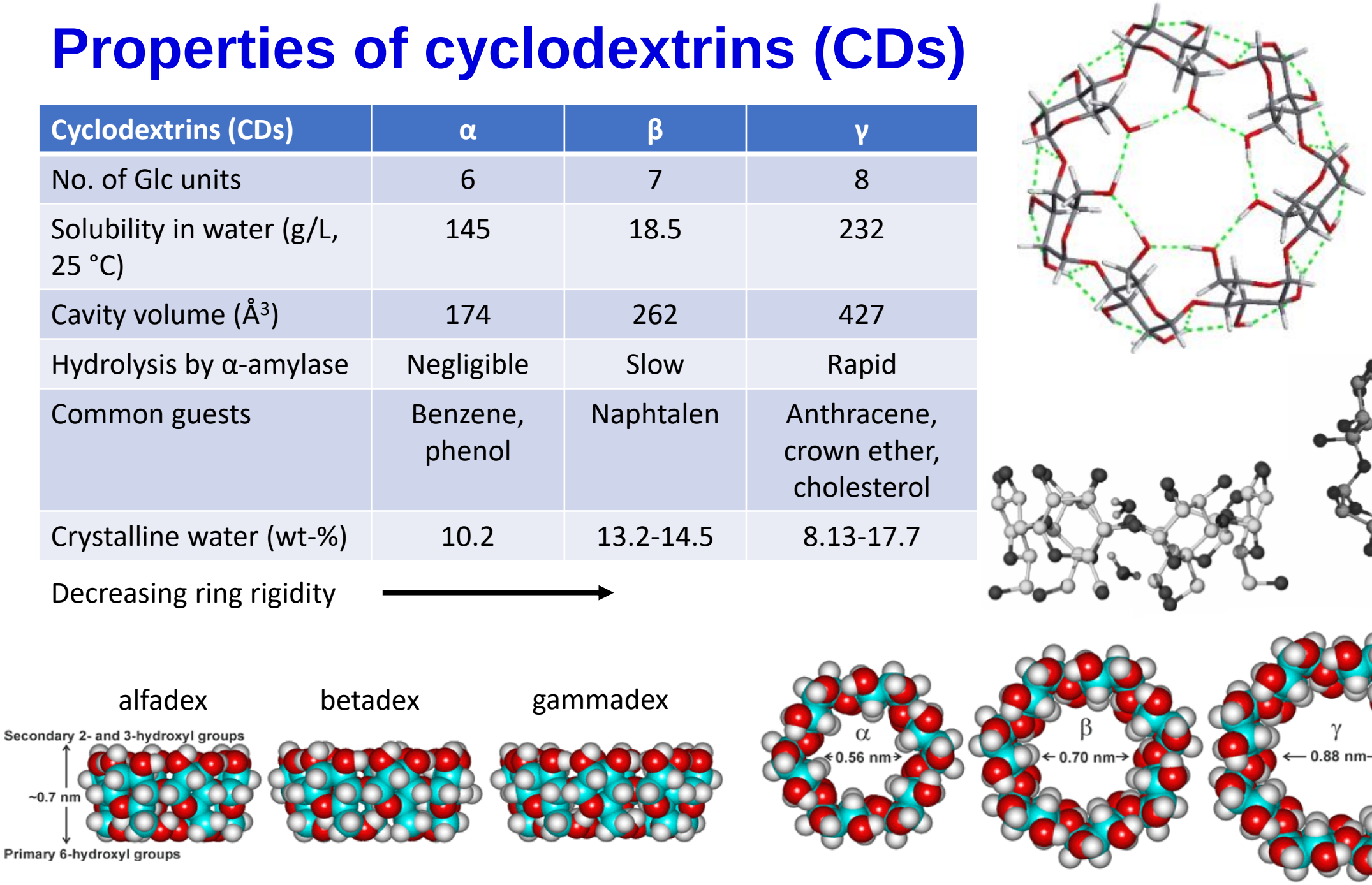




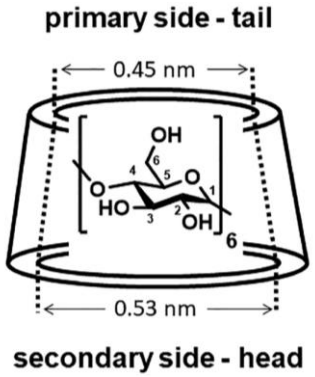
Properties of cyclodextrins (CDs)

Cyclodextrins (CDs)	α	β	γ
No. of Glc units	6	7	8
Solubility in water (g/L, 25 °C)	145	18.5	232
Cavity volume (Å^3)	174	262	427
Hydrolysis by α-amylase	Negligible	Slow	Rapid
Common guests	Benzene, phenol	Naphtalen	Anthracene, crown ether, cholesterol
Crystalline water (wt-%)	10.2	13.2-14.5	8.13-17.7

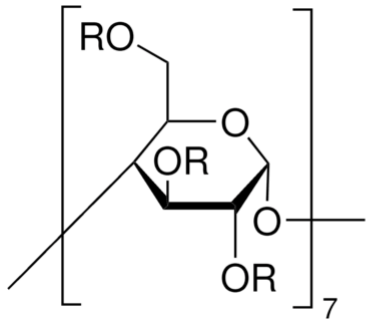
Decreasing ring rigidity ⟶

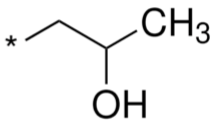


Cyclodextrin rims, cyclodextrin derivatives



- Primary and secondary hydroxyl groups
- Various chemical modifications available
- Synthetic modifications changes properties of CDs (e.g., solubility, bioavailability)
- Hydroxypropyl (HP), sulfobutylether (SBE), randomly methylated (RM)

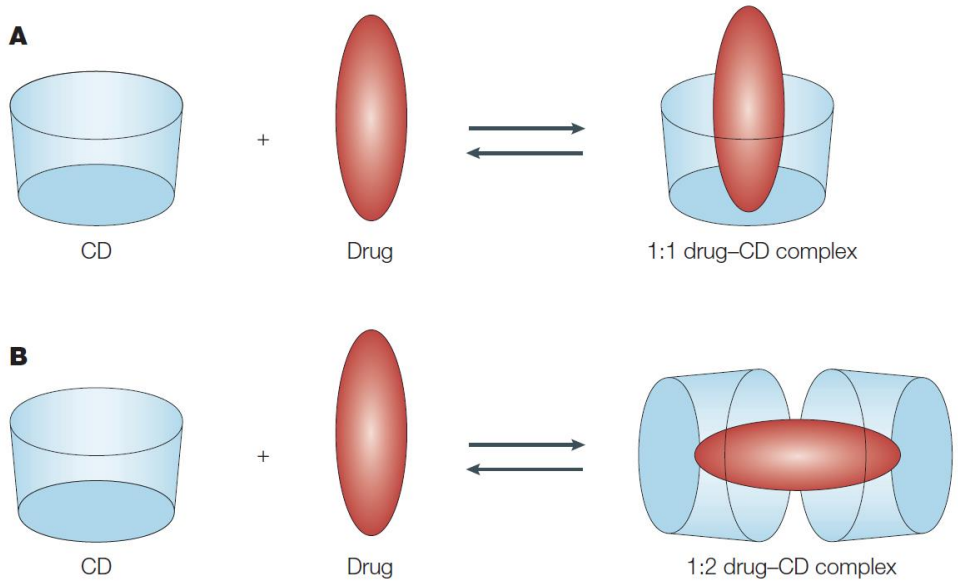


R = H or *  , H or $-CH_2CH_2CH_2CH_2SO_3Na$, H or $-CH_3$

- Disturbs the intra- and intermolecular HB, increases solubility, extension of hydrophobic cavity

Complexation of CDs

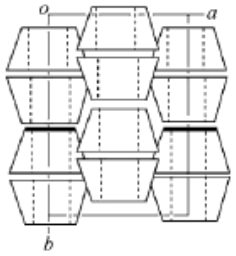
- Larger cyclodextrins have poorer complexation due to flexibility
- Usually the complexes with non-polar compounds in water are formed as 1:1 but also 2:1 inclusion complexes
- The complexation is driven by:
    - Steric fit
    - Release of high energy water
    - Hydrophobic effect
    - VdW interactions and dispersive forces
    - Dipole-dipole interactions
    - Charge transfer interactions
    - Electrostatic interactions
    - H-bonding

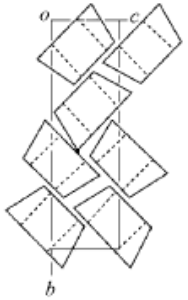


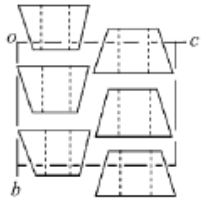
Nature Reviews, VOLUME 3 | DECEMBER 2004 | 1023

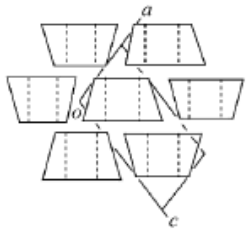
Effect of complexation (guest size) on crystal packing

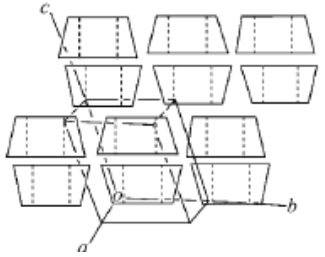
- The complexation in liquid state can be detected by various methods, *e.g.*, nuclear magnetic resonance spectroscopy (NMR), etc.
- In solid state, *e.g.*, by X-ray crystallography: solid state complexes can be divided into channels, cages, layers depending on the guest and the organization of the CD molecules, *i.e.*, cages are observed with small guests (benzen, methanol), channels are observed with larger guests (ferrocene) which do not fit inside the cavity thus lead to extension

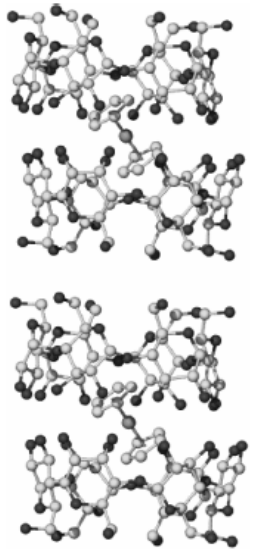












Cyclodextrins as excipients in pharmacy

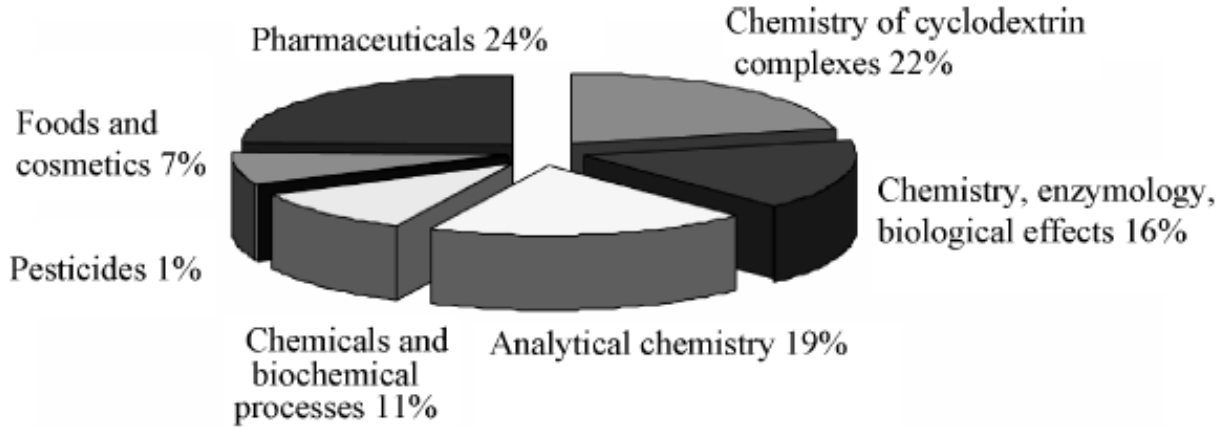
- To increase bioavailability and stability of poorly water-soluble drugs
- Can lower the free concentration of drugs and thus the pharmacokinetics and pharmacodynamics can be changed significantly
- CDs can reduce or prevent gastrointestinal and ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent pre-systemic drug-drug or drug-additive interactions within a formulation, or to convert oil and liquid drugs into microcrystalline or amorphous powders
- There is a number of pills, aqueous parenteral solutions, nasal sprays, eye drop solutions, or even vaccines

	α-CD	β-CD	γ-CD	n.s.
Parent	3	53	4	5
HP		36	4	2
SBE		14		
RM		3		
Sulfolipo		1		
Total	3	111	8	

n.s.: not specified

CD applications

- Non-toxic, high-temperature stable, cheap, slow-release, delivery media and enzyme mimics
- Food industry: odor, color, pigment, and flavor carriers and binders – cholesterol binders, prevents oxidation, photochemical degradation, thermal decomposition, loss by sublimation
- Pharmaceutical industry: prevents premature drug metabolism, modify solubility and biological transportation properties, relieves local irritation and drug-induced damages, masks unpleasant taste
- Separations: as additive to mobile phase or stationary phase



Safety concerns in use of cyclodextrins (2017, EMA)

- European Medicines Agency (EMA) - is an agency of the European Union which is in charge of the evaluation and supervision of pharmaceutical products (9 October 2017 EMA/CHMP/495747/2013 Committee for Human Medicinal Products)

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Cyclodextrins e.g.: Alfadex Betadex (E 459) γ-cyclodextrin Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD) Hydroxypropyl betadex Randomly methylated β-cyclodextrin (RM-β-CD)	All routes of administration	20 mg/kg/day	This medicine contains x mg cyclodextrin(s) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Do not use in children less than 2 years old unless recommended by your doctor.	Cyclodextrins (CDs) are excipients which can influence the properties (such as toxicity or skin penetration) of the active substance and other medicines. Safety aspects of CDs have been considered during the development and safety assessment of the drug product, and are clearly stated in the SmPC. There is insufficient information on the effects of CDs in children < 2 years old. Therefore, a case by case judgement should be made regarding the risk/benefit for the patient. Based on animal studies and human experience, harmful effects of CDs are not to be expected at doses below 20 mg/kg/day.
	Oral	200 mg/kg/day	Cyclodextrins may cause digestive problems such as diarrhoea.	At high doses cyclodextrins can cause reversible diarrhoea and cecal enlargement in animals.
	Parenteral	200 mg/kg/day and use for > 2 weeks	If you have a kidney disease, talk to your doctor before you receive this medicine.	In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of cyclodextrins. In patients with moderate to severe renal dysfunction accumulation of cyclodextrins may occur.

CD-containing drugs

- The first drug was prostaglandin E1 with α-CD (Japan, 1976, vasodilator)
- Development: 24 (2004), 35 (2007), 48 (2013), 129 (2022) approved pharmaceutical ingredients formulated with either parent CDs or their hydroxypropyl, sulfobutyl, randomly methylated or sulfolipo derivatives

	α-CD	β-CD	γ-CD	HP-β-CD	HP-γ-CD	SBE-β-CD	RM-β-CD	Sulfolipo CD	n.s.
Oral	2	46	3	13					1
Nasal							1		
Rectal		3		1					
Vaginal		1							
Dermal/ungual		5	1	2					5
Ocular		1		8	2		2		1
Parenteral	1	1		17	2	14		1	
Total	3	57	4	41	4	14	3	1	7

a) Puskás, I., Szente, L., Szőcs, L., Fenyvesi, É. "Recent List of Cyclodextrin-Containing Drug Products", Periodica Polytechnica Chemical Engineering, 67(1), pp. 11–17, 2023. b) *Journal of Inclusion Phenomena and Macrocyclic Chemistry* (2020) 98:171–186.

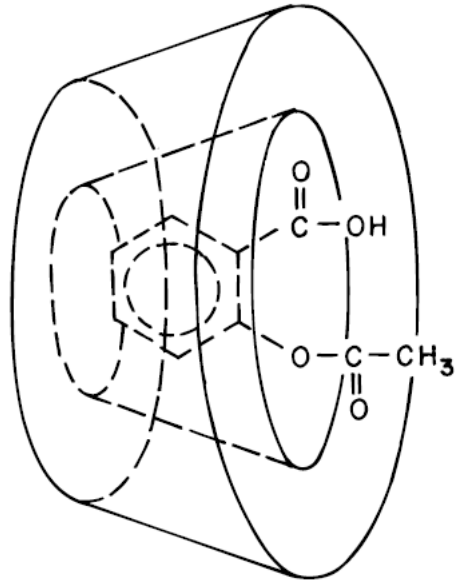
CD-containing drugs

	α-CD	β-CD	γ-CD	HP-β-CD	HP-γ-CD	SBE-β-CD	RM-β-CD	Sulfolipo CD	n.s.
Tablet/Capsule	3	43	1	8					1
Oral solution		5	2	7					
Nasal spray							1		
Suppository		3		1					
Cream, ointment		4	1						4
Vaginal gel		1							
Lacquer				2					
Face mask									1
Deodorant stick		1							
Eye drops		1		8	2		2		1
Infusion/injection	1	1		17	2	14		1	
Total	3	58	4	43	4	14	3	1	7

Puskás, I., Szente, L., Szőcs, L., Fenyvesi, É. "Recent List of Cyclodextrin-Containing Drug Products", Periodica Polytechnica Chemical Engineering, 67(1), pp. 11–17, 2023. https://doi.org/10.3311/PPch.21222

Examples of CD-containing drugs

Bromhexin	β-CD	Bisolvon tablet	Sanofi
Cetirizine	β-CD	Zyrtec, chewing tablet	Losan Pharma, UCB Pharma
		WalZyr OD tablet	Sandoz, Walgreen, Sawai Pharm.
		Revicet dry syrup	Nichi-Iko, Takeda
Cholecalciferol	β-CD	Vitamin D3 tablet	Natures Aid (U.K.)
Garlic Extract	β-CD	various dragees	Various
Menthol/camphor	β-CD	Pain relief gel	ointment MMA Elite,Doctor Hoy‘s
Nicotine	β-CD	Nicorex, Nicorette tablet	Pierre Fabre
		Nicogum,chewing gum	Pfizer
Nitroglycerin	β-CD	Nitropen sublingual tablet	Nippon Kayaku
Acetaminophen	HP-β-CD	Paracetamol infusion, chewable tablet	Uni-Pharma, 7T Pharma



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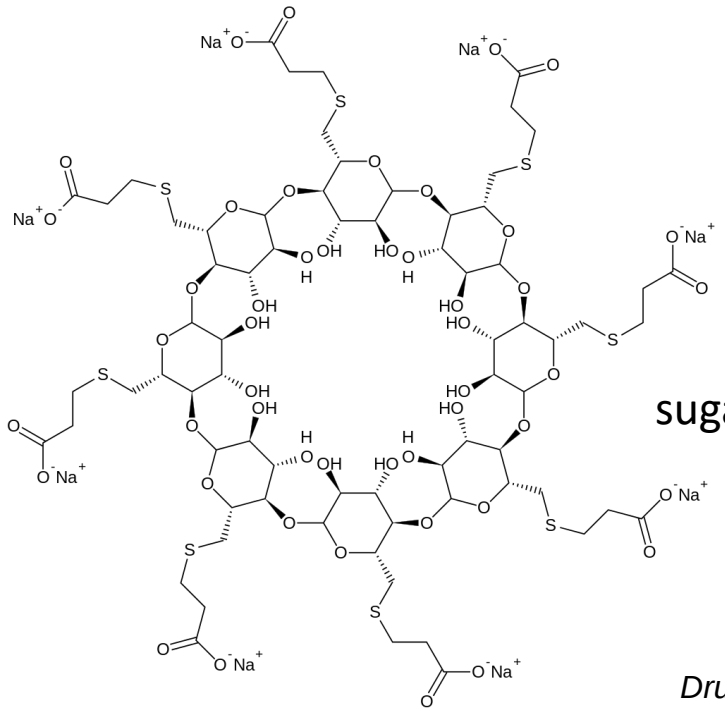
Examples of CD-containing drugs

Ad26.COV2.S	HP-β-CD	Jcovden (previously COVID-19 Vaccine Janssen)	vaccine	J&J
Diclofenac	HP-γ-CD	Voltaren Ophta CD, Voltarol	eye drop	Novartis
Docetaxel	HP-β-CD	Docetaxel Teva Generics	infusion	Teva
Larotrectinib	HP-β-CD	Vitrakvi	capsules, oral solutions	Bayer
Carbamazepine	SBECD	Carnexiv	i.v.	Lundbeck
Remdesivir	SBECD	Veklury	i.v.	Gilead Sciences
Chloramphenicol	RAMEB	Clorocil	eye drop	Oftalder
Estradiol	RAMEB	Aerodiol	nasal spray	Servier
Inactivated porcine circovirus	Sulfolipo-CD	Suvaxin-PCV	vaccine	Pfizer

Puskás, I., Szente, L., Szőcs, L., Fenyvesi, É. "Recent List of Cyclodextrin-Containing Drug Products", Periodica Polytechnica Chemical Engineering, 67(1), pp. 11–17, 2023.

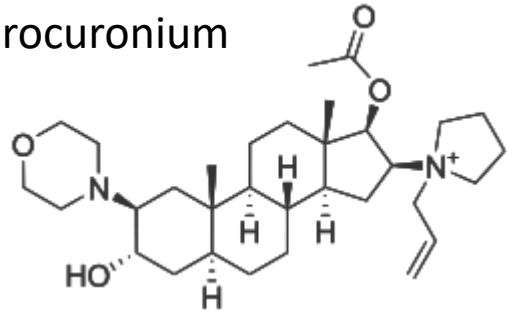
Use of cyclodextrins as drugs

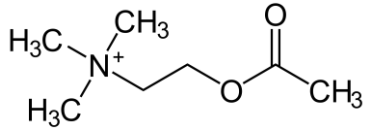
- Sugammadex – used as reversal of neuromuscular blockade induced by rocuronium and vecuronium in general anaesthesia (by competing for the cholinoceptors at the motor end plate, thereby exerting its muscle-relaxing properties, which are used adjunctively to general anesthesia)
- EMA ()



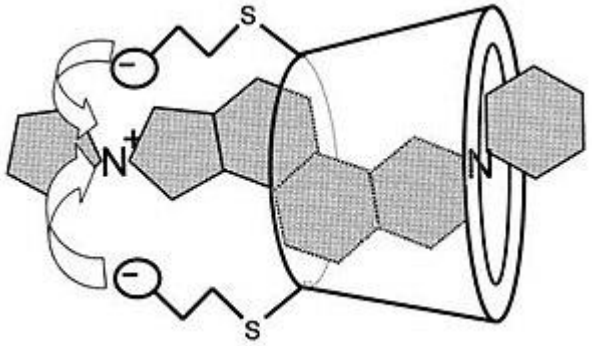
sugammadex

rocuronium



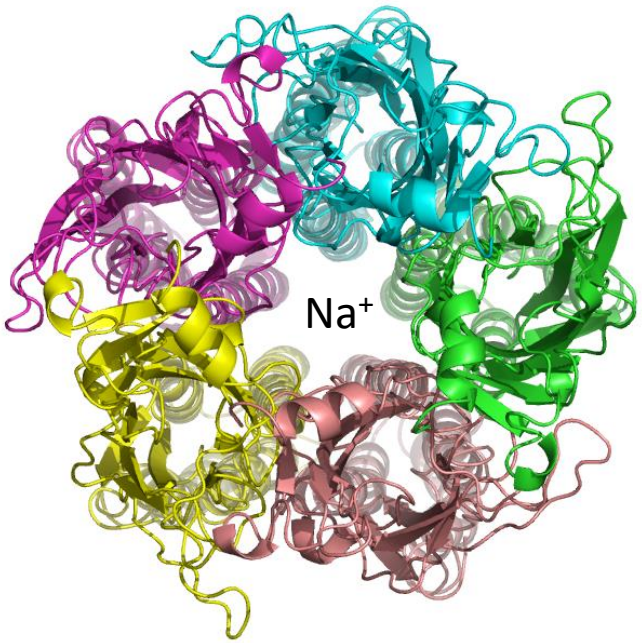


acetylcholin



HG-complex

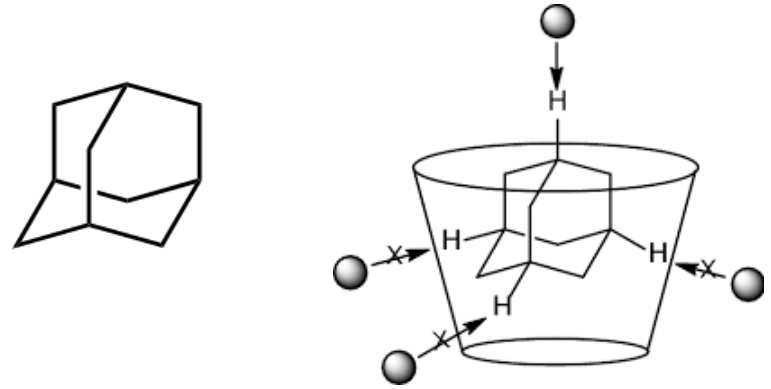
acetylcholin receptor



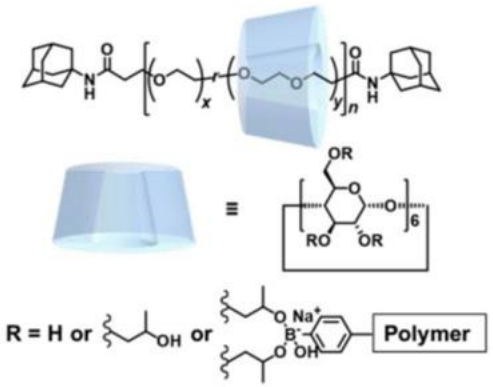
Drugs 2009, 69, 919–942

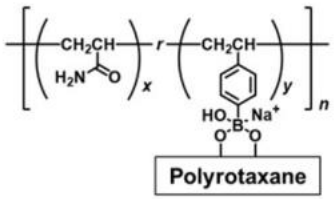
Self-healing soft materials

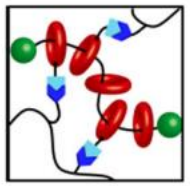
- Using the strong afinity between adamantane and β-CD



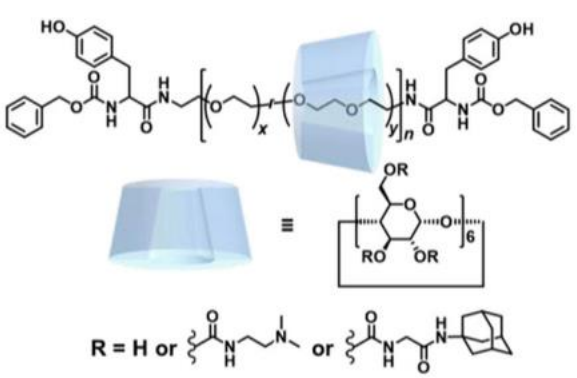
Collect. Czech. Chem. Commun. 1933, 5, 1-5

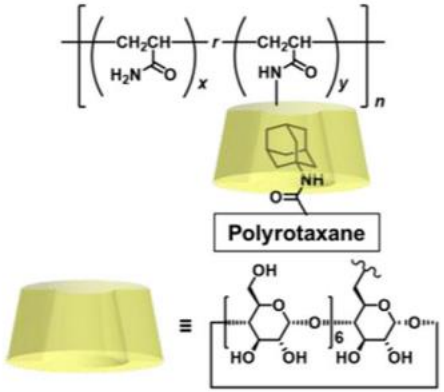




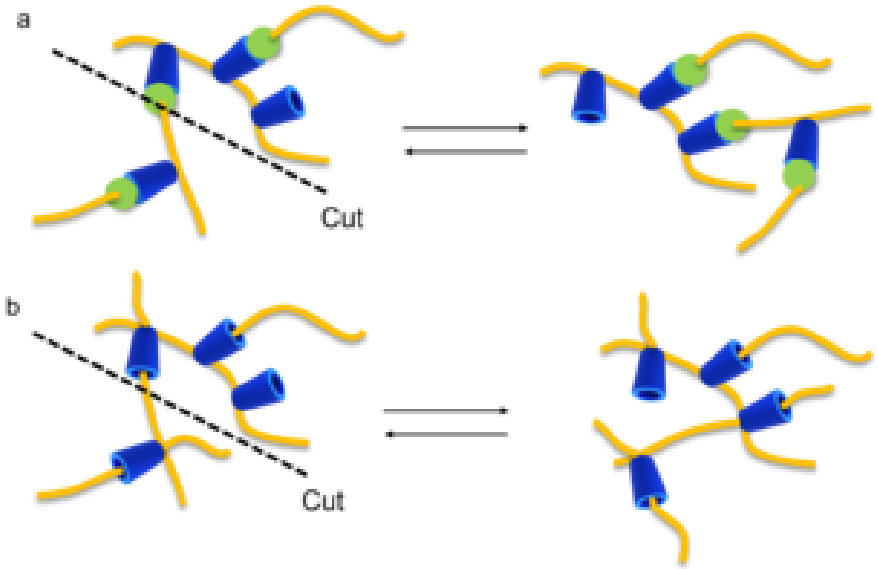


σ/σ_0 ~100% (15 min/r.t.)





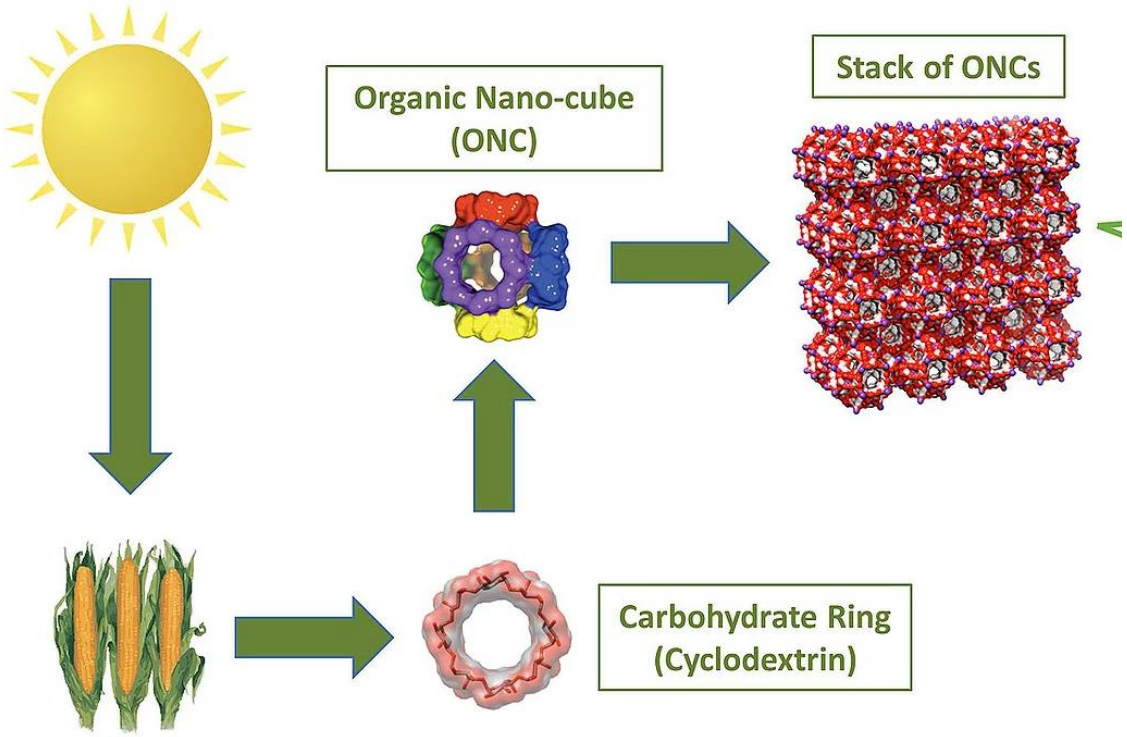
σ/σ_0 ~60% (2 h/r.t.)



Ikura et al. NPG Asia Materials (2022) 14:10

Interesting supramolecular applications of CDs – CD-MOF

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

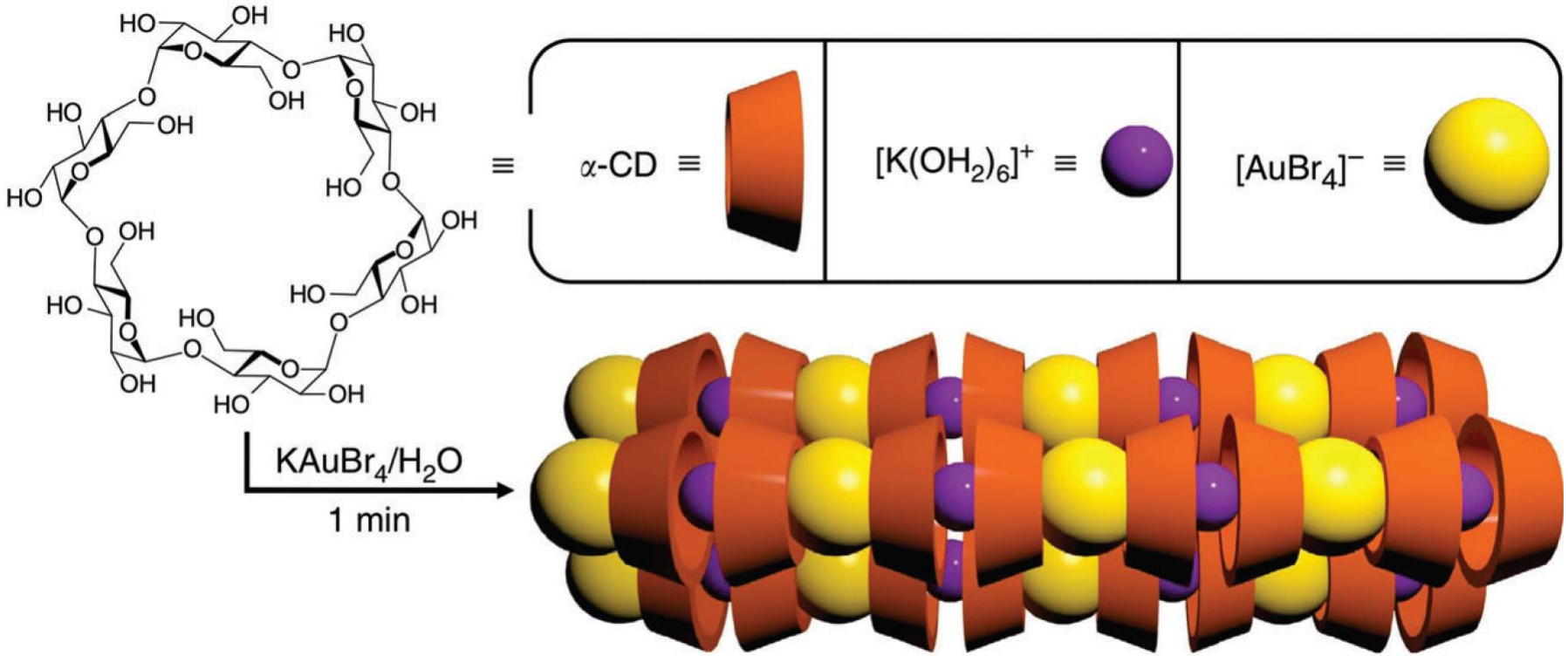


- in cosmetics (NOBLE antiaging skin care), but also chemical and petrochemical industry, home and personal care, food and beverages and pharmaceuticals

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.

Gold extraction

- α-CDs for isolation of gold from crude ores, patented 2014 (avoiding use of mercury)



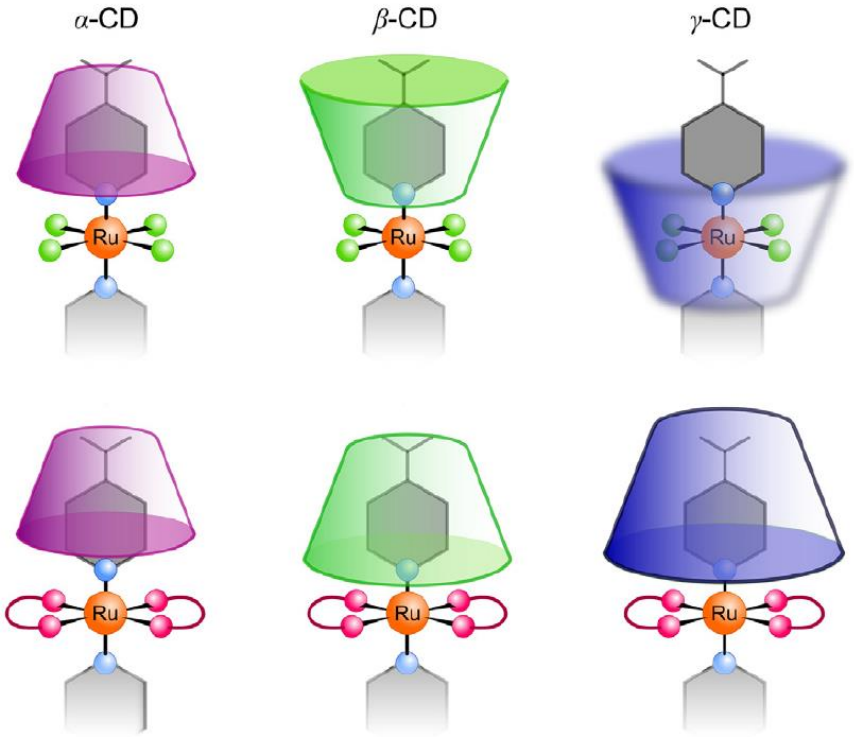
Liu, Z.; Frasconi, M.; Lei, J.; Fahrenbach, A. C.; Botros, Y. Y.; Farha, O. K.; Hupp, J. T.; Mirkin, C. A.; Stoddart, J. F. *Nat. Commun.* **2013**, *4*, Article 1855.

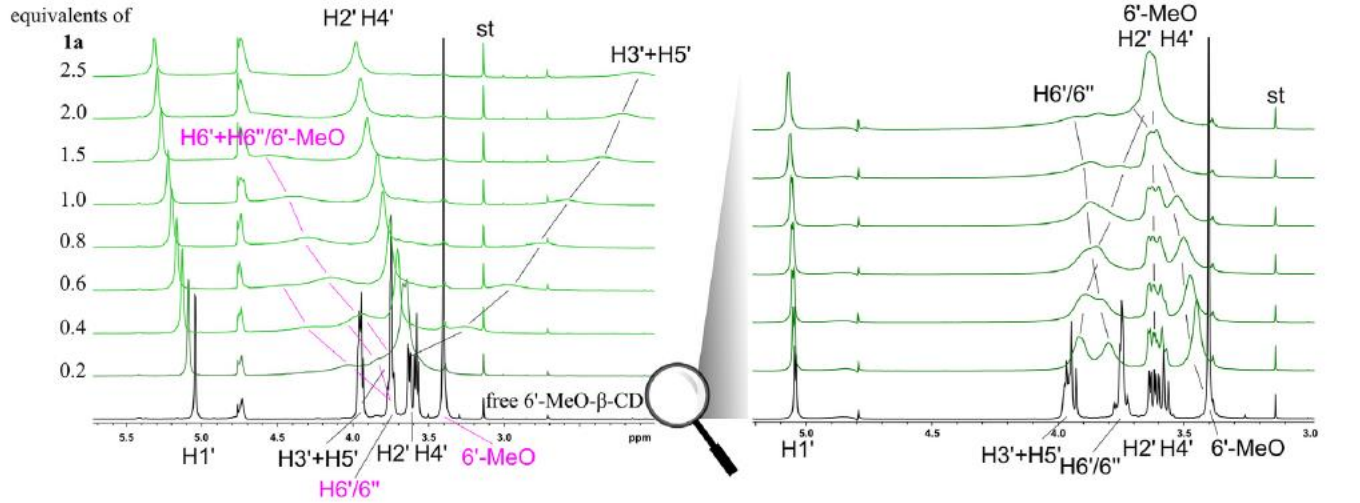
Waste water treatment

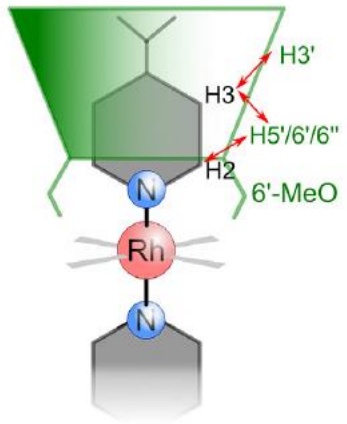
- Using the strong afinity between steroidal compounds and β- (or γ-CD)

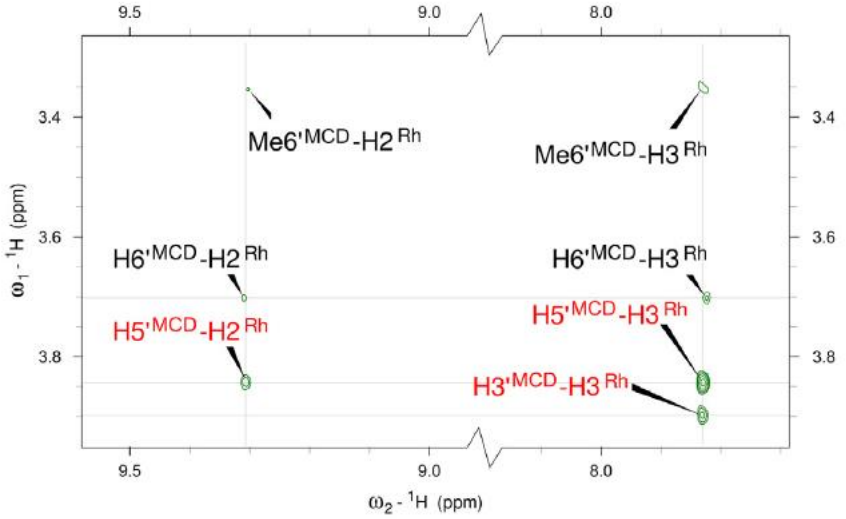
a) Environmental Science and Pollution Research (2022) 29:1585–1604, b) Carbohydrate Polymers (2017) 173: 37-49

Cyclodextrins as carriers of Ru(III)-metallodrugs





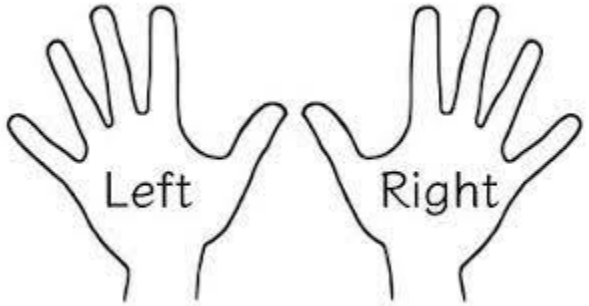


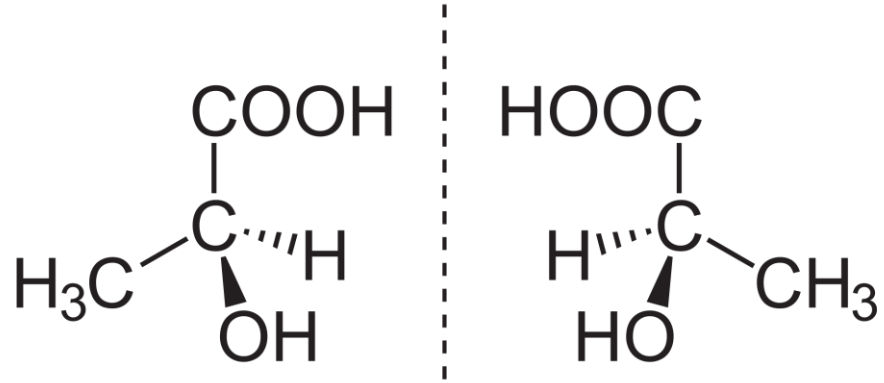


Cell Reports Physical Science 4, 101461, July 19, 2023

Separation of enantiomers

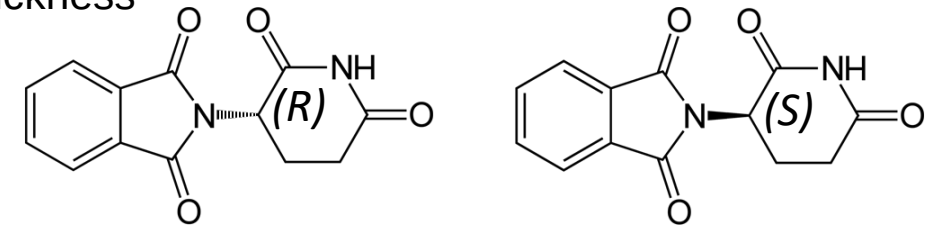
- Enantiomers or optical isomers are stereoisomers which are not superposable – analogous to left and right hand

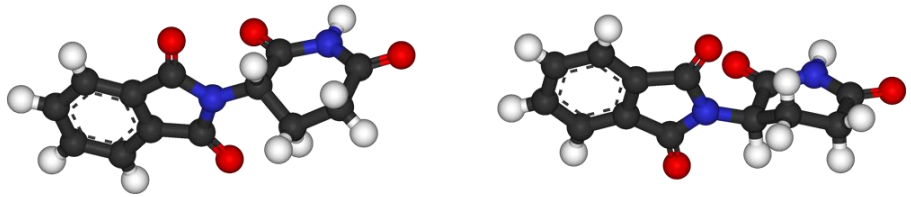




(*S*)-(+)-lactic acid (*R*)-(-)-lactic acid

- Thalidoimide case (Contergan) (1957-1961) – *R*- and *S*-isomers
  - Originally for trouble sleeping, anxiety, morning sickness
  - (*S*)-thalidoimide is terratogenic, (*R*) is not
  - The (*R*) is interconverted into the (*S*) *in vivo*
  - 10000 children affected by serious birth defects (40 % children died in the first year of life)





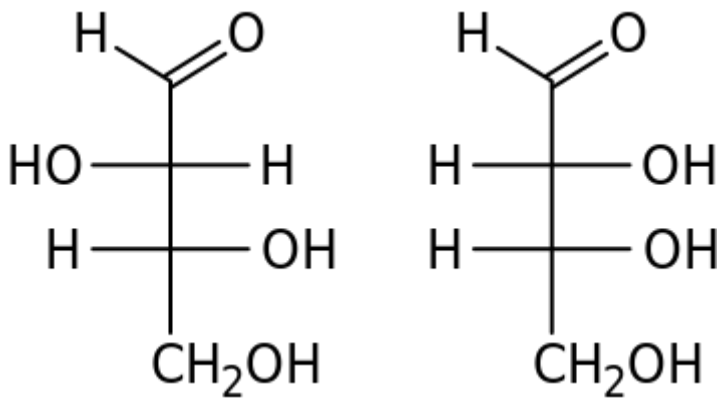
Separation of enantiomers

- Diastereomers like enantiomers share the same molecular formula and are not superposable, however, they are not mirror images

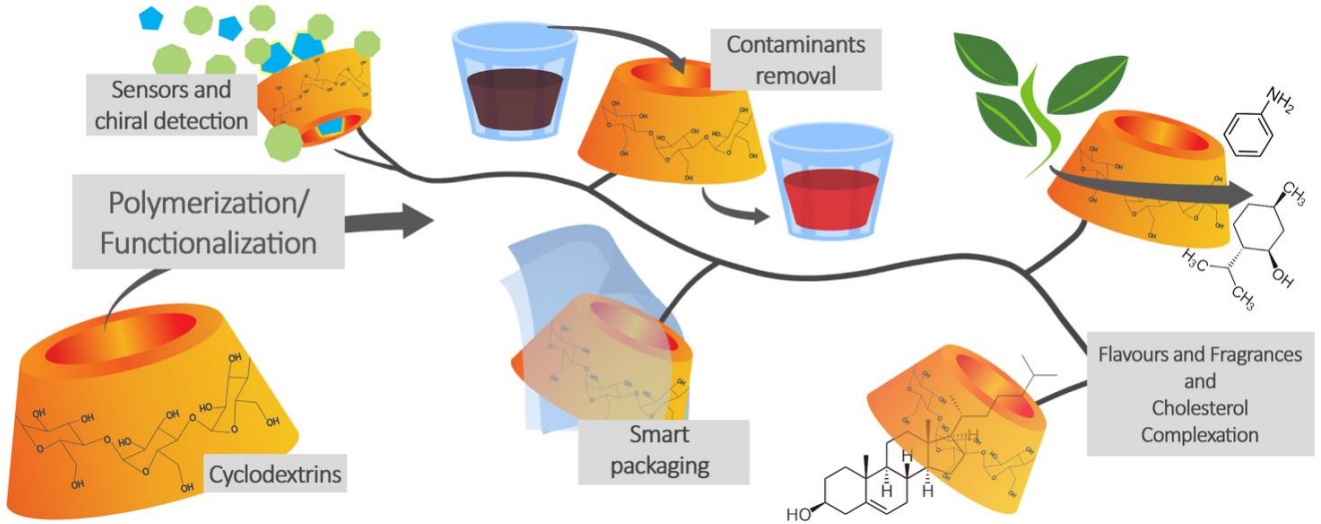
- Enantiomers in achiral environment are not distinguishable, in chiral environment they can behave like diasteromers and can be distinguished and separated

- CDs form chiral environment for chiral resolution or racemic mixtures (enantiomers in 1:1 ratio)

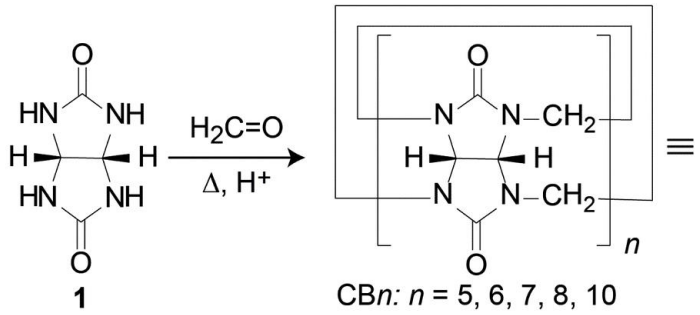
Diastereomers

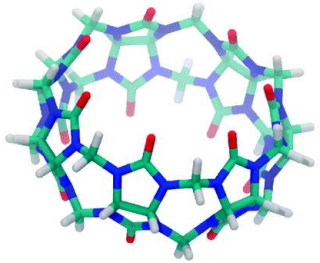


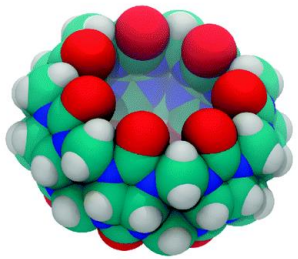
D-Threose D-Erythrose

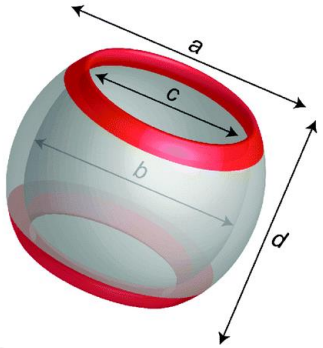


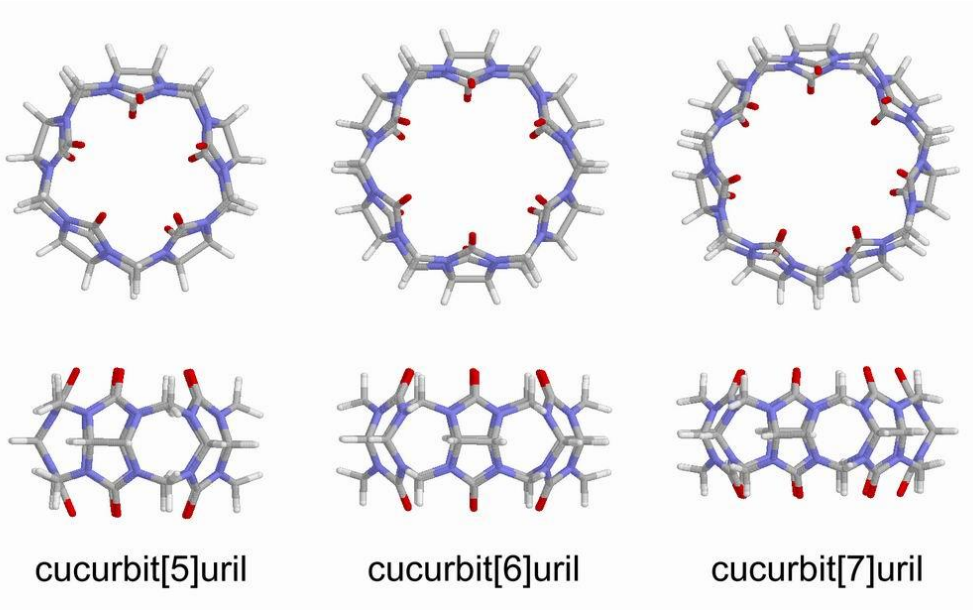
Other macrocycles used in supramolecular chemistry

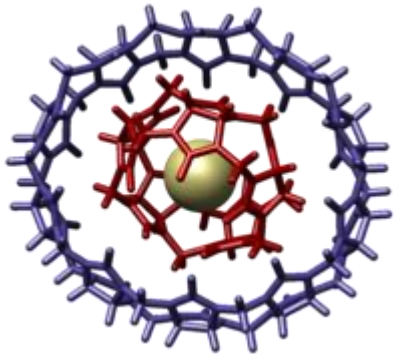


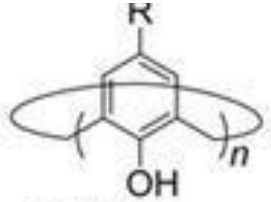


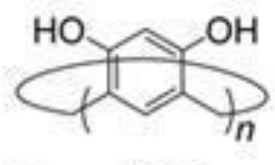


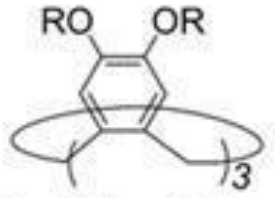


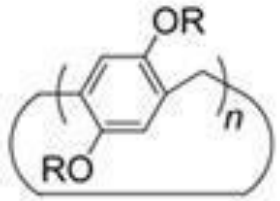


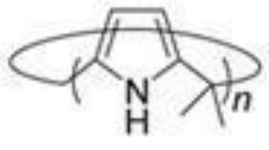












In the next class…

Metallo-supramolecular cages

Thank you for your attention!