

4 ANION-BINDING HOSTS

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INTRODUCTION, COMPARISON TO CATION-BINDING HOSTS

- There are some intrinsic properties which make anions difficult guests
→ development of hosts that bind anions has been relatively slow
- The most prominent property of anions distinguishing them from any other guest species is their negative charge
- They are relatively large
- Even simple inorganic anions occur in a variety of different shapes and geometries
- High free energies of solvation compared to cations of similar size → must compete more effectively with the surrounding medium
- Many anions exist only in a relatively narrow pH-area
- Anions are usually saturated coordinatively → bind only via weak forces

References: J.W. Steed, J.L. Atwood, Supramolecular chemistry, p.198-200, Wiley, (2000)
F.P. Schmidchen, M. Berger, Chem.Rev., 97, 1609, (1997).

BIOLOGICAL ANION RECEPTORS

- 70-75 % of enzyme substrates and cofactors are anionic (often phosphate residues or inorganic phosphate)
- The major [extracellular](#) anion is Cl⁻
- In biochemical systems the hosts affinity towards a particular guest must be high and towards every other species very low
→ The anion binding proteins tend to be rigidly preorganised macrocyclic or macrobicyclic systems

ARGININE AS AN ANION BINDING SITE

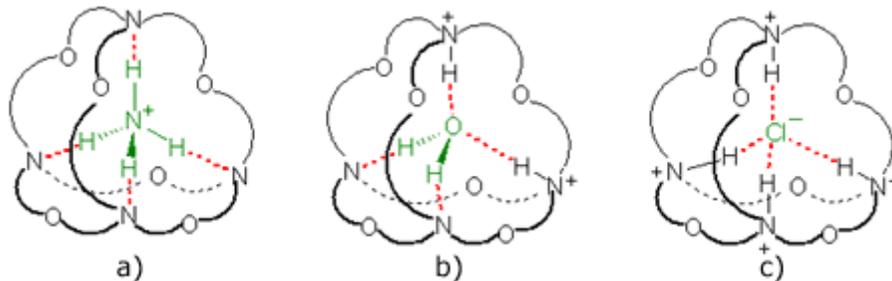
- [Arginine residue](#) contains a guanidine group, which is excellent anion binding site
- E.g. carboxypeptidase A uses arginine residue to bind its anionic substrate

References: J.W. Steed, J.L. Atwood, Supramolecular chemistry, p.200-204, Wiley, (2000).

FROM CATION BINDING HOST TO ANION BINDING HOST BY A SIMPLE CHANGE IN PH

- [Tetrahedral receptors](#)
- Preparing positively charged hosts is probably the most obvious way to achieve anion binding

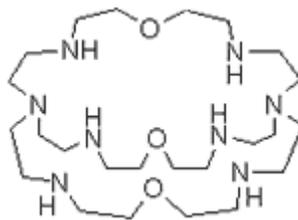
- E.g. cryptands have tertiary nitrogen bridges
 - with a change in the pH the nitrogens can be protonated
 - the host gets charged positively
- This feature can be used when designing hosts which complex different kind of guests depending on the conditions
- Limiting factors are the size of the cryptand cavity (should be large enough to include the anion) and that there shouldn't be too much repulsion between the protonated nitrogens
- The geometry of the coordination of the guests in this kind of host-guest systems can be described as tetrahedral
 - tetrahedral recognition
- A good example is a "soccer ball" cryptand which can bind either NH_4^+ -cation, neutral water molecule or Cl^- -anion depending on the pH of the [medium](#)



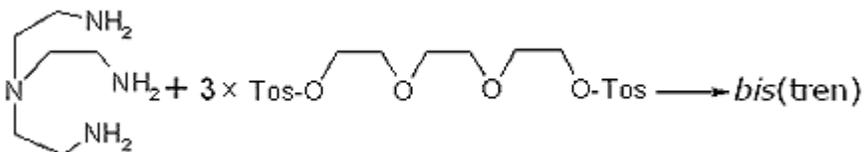
- a) The host is neutral and binds ammonium
- b) The host is diprotonated and binds water
- c) The host is tetraprotonated and binds Cl^- -anion

SELECTIVITY BY THE SHAPE

- An alternative concept for selectivity and stability improvement was aimed at the rigidification of binding sites



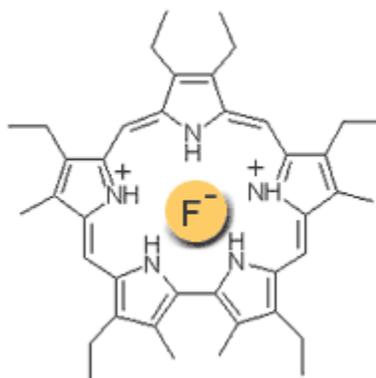
- Lehn et al. have prepared bicyclic cryptates
- Syntheses of bis(tren)



- Linkage can be done as desired
→ the size and the selectivity of the molecule can be altered
- These require acidic medium to form penta- or hexaprotonated species
- The guest is fixed by an oriented set of hydrogen bonds
- The cavities of these molecules are ellipsoidal-shaped and an azide anion that has optimal complementarity to the host (binding is almost symmetrical) can form an extremely stable complex with it
- Also halide anions form complexes with these cryptands but only F^- -anion seems to bind relatively strongly
- This is a consequence of the reduced shape/topological match between the [spherical](#) halide-anions and the ellipsoidal-shaped host cavity (= distances between the anion and the nitrogen are longer than the optimum)
- The linkage in this kind of molecules can be done as desired
→ the size and the selectivity of the molecule can be changed
- The protonation also cuts the size of the cavity
→ only small anion fits
→ control

TWO DIMENSIONAL (FLAT) HOSTS

- Monocyclic hosts
- Recognition of the anion is usually planar
- [Porphyrins](#) are nitrogen macrocycles, cyclic pyrrole structures
- The cavity of porphyrinmacrocycles is just suitable in size to bind F^- → fluoride is bound in the middle of the plane with 5 H-bonds
- In the picture there is a diprotonated sapphyrin molecule which can bind F^- -anion 103 times stronger than Cl^- - or Br^- -anions



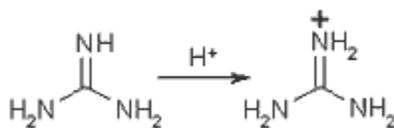
Diprotonated sapphyrin F^- -complex

References: J.W. Steed, J.L. Atwood, Supramolecular chemistry, p.206-220, Wiley, (2000).
Schmidchen, M. Berger, Chem.Rev., 97, 1609, (1997).

GUANIDIUM-BASED RECEPTORS

- Guanidium group as present in the side chain of arginine is ubiquitous in enzymes that bind anionic substrates as indicated earlier
- Two parallel hydrogen bonds in addition to the electrostatic attraction are feature which make the interaction with oxoanions strong

- Guanidine is also highly basic
→ it protonates in a wide pH range
→ makes it attractive in artificial receptors
- First guanidium-based macrocycles were introduced by Lehn et al. in 1978
- These were, however, relatively weak in binding PO_4^{3-} -anions



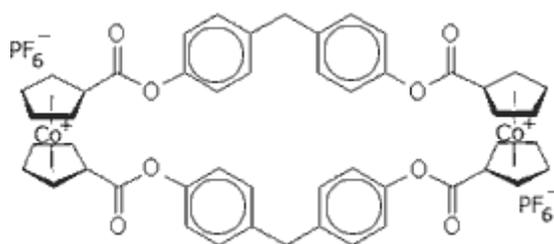
Guanidine

- Binding of phosphates and carboxylates are influenced by a macrocyclic and chelate effect
- Guest selectivity is primarily dependent on the charge density of the anions
- These macrocycles may also be too small and too inflexible to accommodate the large PO_4^{3-} -anion
- Also the high degree of solvation of guanidium ion in polar solvents may hamper binding
- Majority of recent receptors based on guanidium are acyclic (analogous to podands)
- In 1980 Schmidtchen reported about first bicyclic systems in which the guanidium group can be [embedded](#) in a bicyclic framework to improve the binding characteristics
- Further manipulation of substituents could then introduce other binding sites to increase specificity of guest binding

References: J.W. Steed, J.L. Atwood, *Supramolecular chemistry*, p.220-223, Wiley, (2000).

ORGANOMETALLIC RECEPTORS

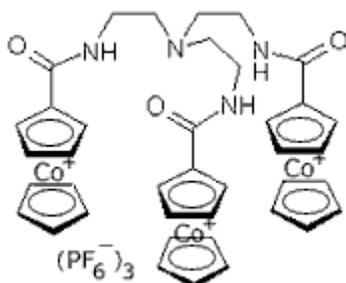
- Paul Beer et al. have prepared novel transition-metal organometallic and coordination systems for anion recognition
- First such a receptor, bis-cobaltocenium macrocycle, was synthesized in 1989
- It is dicationically charged with two Co(III) centres
- It can bind a bromide anion
- Complexation is based purely on electrostatic interaction between the host and the guest



1) Bis-cobaltocenium macrocyclic receptor
(Beer, *Acc. Chem. Res.*, 1998, 31, 71-80)

- Next step was adding secondary amide functionalized "arms" to the cobaltocenium moiety
→ neutral hydrogen bond donor groups capable of coordinating anions was obtained
- This produced variety of acyclic mono-, bis-, and tripodal amide linked cobaltocenium receptors
- Cobaltocenium moiety have since been added to e.g. calix[4]arene [upper rim](#) to produce π -metalated calixarene anion receptors

- By modifying the [lower rim](#) functionalities of calixarenes alteration in anion selectivity is achieved
- There is also a wide range of other kind of organometallic receptors for anions, such as ferrocene based anion receptors and transition-metal bipyridyl based anion receptors



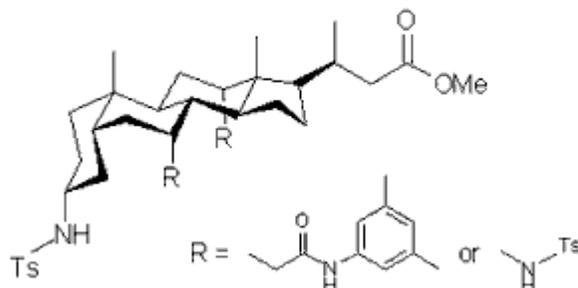
2) Tripodal amide-linked cobaltocenium receptor

References: J.W. Steed, J.L. Atwood, *Supramolecular chemistry*, p.224-230, Wiley, (2000).
P.D. Beer, *Acc. Chem. Res.*, 31, 71, (1998).

NEUTRAL RECEPTORS

- In the nature, the transport of sulfate or phosphate anions through cell membranes is regulated by neutral anion binding proteins
- There are also a variety of synthetic neutral receptors which bind anions
- Bile acid based receptors are subject of research also in the Laboratory of Organic Chemistry in JYU.

Bile acid based neutral anion-receptor

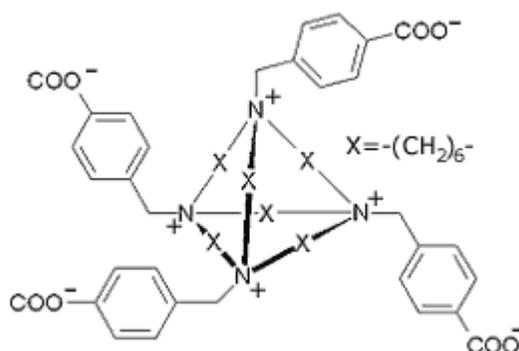


- Neutral receptors have advantages compared to cationic hosts
 - The binding of anions is more selective, because there is no nondirectional electrostatic forces
 - They do not need counter ions, which may complicate the syntheses of cationic hosts as well as analysis of the host-guest affinity
- Those can be divided into two classes according to their interactions with the guest:
- Hosts which have hydrogen bonding or ion-dipole interactions with guests
- Hosts which coordinate their guests at Lewis acid centers of neutral organometallic ligand

References: J.W. Steed, J.L. Atwood, *Supramolecular chemistry*, p.230-235, Wiley, (2000).
M.M.G. Antonisse, D.N. Reinhoudt, *Chem. Commun.*, p.443, (1998).

ZWITTERIONS

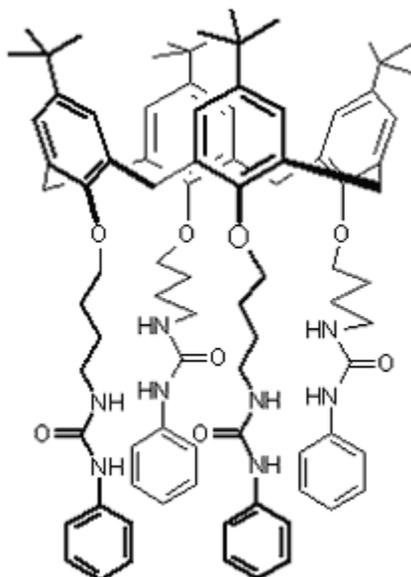
- Receptors which contain both negative and positive charges (thus being neutral) are called [zwitterions](#)
- Biological anion binding proteins and enzymes are mainly zwitterions
- Receptor in the picture forms stronger complexes with Cl^- , Br^- and I^- than comparable receptor without the negative benzoic acid side chains



An example of a zwitterion

HYDROGEN BONDING HOSTS

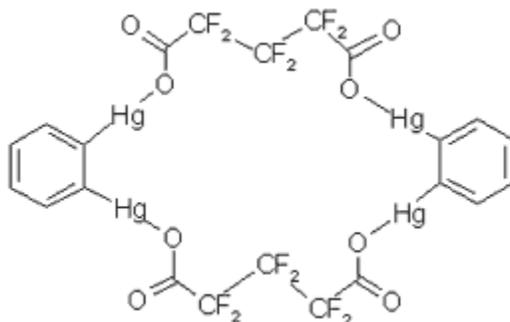
- Hydrogen bonding is strong and directional
- E.g. a hydrogen bond donating substituents at either the upper rim or the lower rim of calixarene yields selective receptor molecules
- Calix[4]arenes functionalized at the lower rims with urea substituents are selective towards halide anions



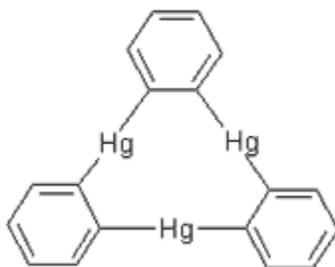
- There is also a variety of other neutral hosts that are more selective because of the hydrogen bonding

ANTICROWNS AND LEWIS ACIDIC HOSTS

- Anticrown = crown ether analogue made up from electron acceptor residues (instead of Lewis bases), "crown ether for anions"
- Their complexation behavior is opposite to that of "normal" crown ethers



Example of an anticrown. Note that the structure resembles very much the structure of dibenzo-18C6

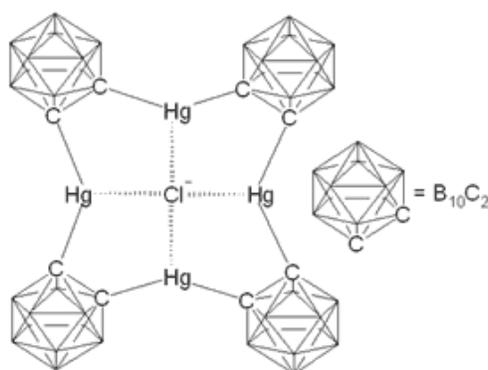


- This planar crown can form sandwich polymer with Br^- -anion
- Br^- -anions are bound between the planes by coordination to Hg's

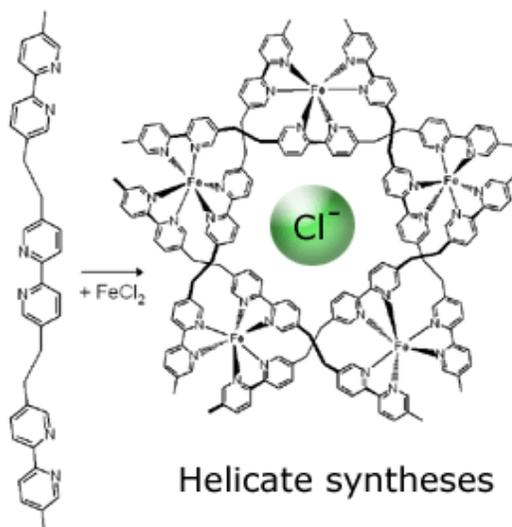
References: J.W. Steed, J.L. Atwood, Supramolecular chemistry, p.239-243, Wiley, (2000).
J.D. Wuest, Acc. Chem. Res., 32, 81, (1999).

NEW TOPICS IN RESEARCH OF ANION-RECOGNITION

- Anion templation and anion directed self-assembly
- Reports of templating influence of anions are nowadays becoming widespread
- One example of template effect caused by an anion during the syntheses of mercuracarborane consisting of four carborane units has been reported



- Cl^- ion is bound in the plane of the macrocycle acting as a template around which the receptor forms
- When Cl^- ion is not used or it is replaced with iodine, the yield from the syntheses decreases (this is because the iodine is too big to fit into the cavity and thus cannot act as
- One example of anion directed self-assembly has been discovered by Lehn et al.:
 - The pentametallic circular helicate only forms in the presence of Cl^- ions
 - Helicate (in picture) can be produced by mixing the tris(bipyridine) ligand with an equimolar amount of FeCl_2
 - The Cl^- ion bounds in the center of the helicate thus coordinating its assembly



ION-PAIR RECOGNITION (DITOPIC HOSTS)

- Simultaneous complexation of cationic and anionic guest species by receptors with multiple binding sites
- This is a new, but emerging topical field in coordination chemistry
- These heteroditopic ligands can be designed to exhibit novel co-operative and allosteric behaviour:
- The binding of one charged guest can influence the subsequent coordination of the pairing ion. This can be due electrostatic and conformational effects
- Potential applications:
 - as selective extraction and transportation reagents for ion-pair species of environmental importans
 - In Zwitterion recognition

Following are some questions on the topics you just read about. Please, take some time to think back what you've just learned about anion binding hosts and try to answer these questions. Notice that there may be more than one correct answer for the questions.

- Development of anion binding hosts has been slower than the development of hosts for cations. What could be reasons for that?
- How can a change on pH be used when designing anion binding hosts and how does it effect the properties of the host? What kind of applications could there be for pH-adjustable systems?
- There are both positively charged and neutral hosts for anions. Compare these two from the perspective of binding properties, selectivity and preparation.