Course Name: **Supramolecular & Photoinorganic Chemistry**

Paper Number: **101**

Section: **B**

Course Instructor: **Prof. Rajeev Gupta**

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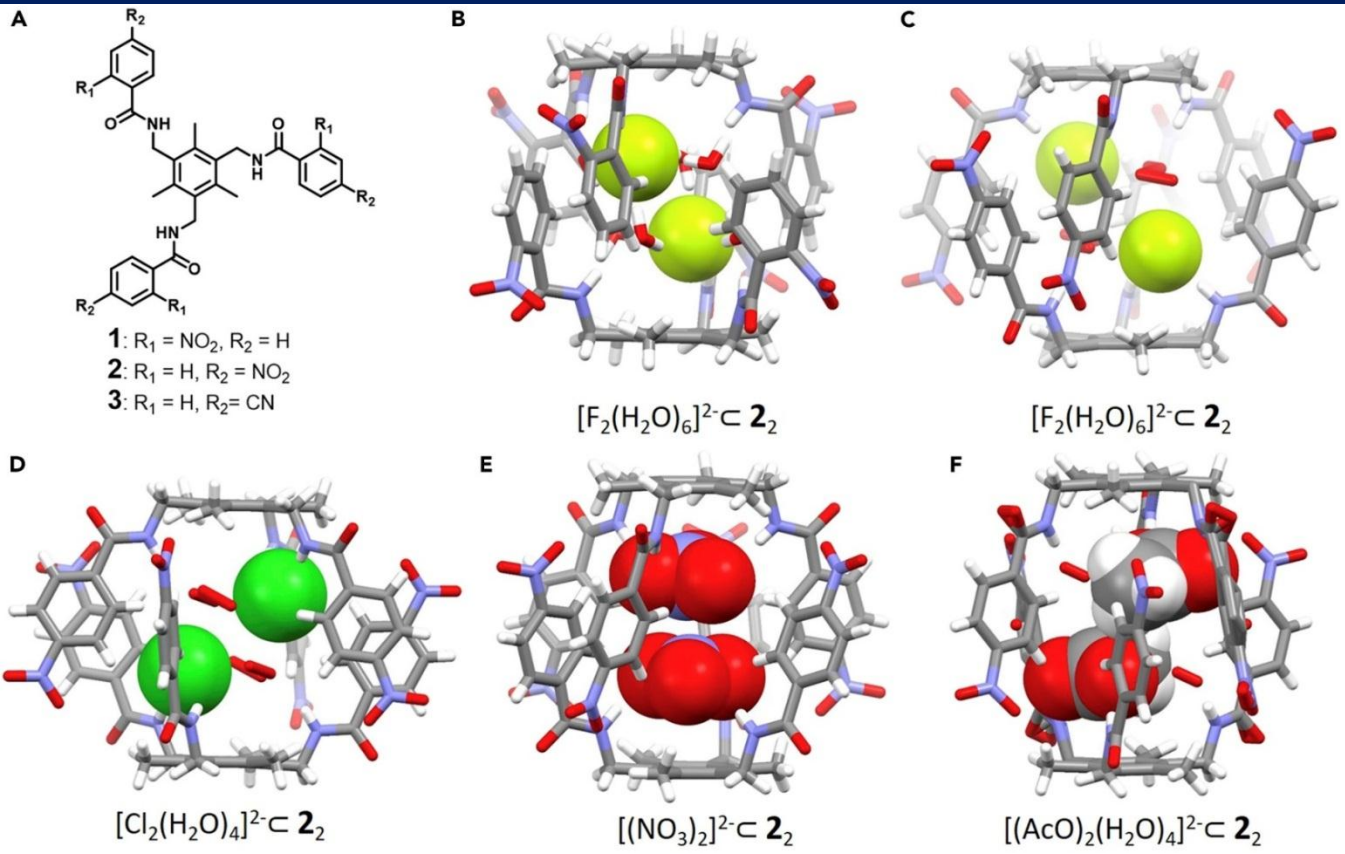
Part – 2

PART II: ANION BINDING



Source / Materials:

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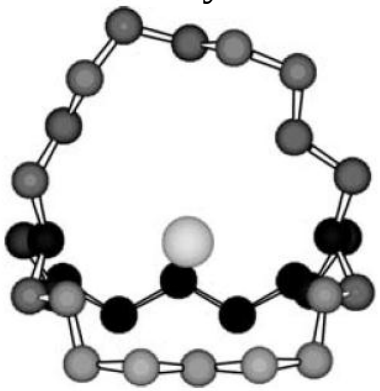
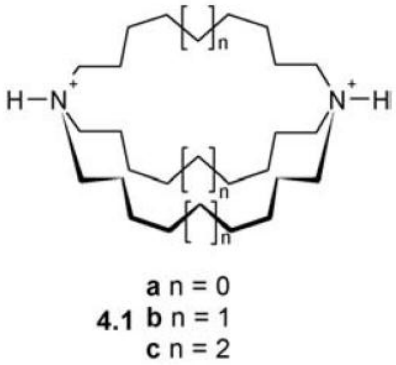
2. Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*, *Second Edition*, John Wiley & Sons, Ltd: West Sussex, U.K., 2009.
3. Gale, P. A. Anion receptor chemistry *Chem. Commun.,* **2011**, *47*, 82–86.
4. Steed, J. W.; Turner, D. R.; Wallace, K. J. Core Concepts in Supramolecular Chemistry and Nanochemistry; John Wiley & Sons: West Sussex, U.K., 2007.
5. Cragg, P. J. *Supramolecular Chemistry: From Biological Inspiration to Biomedical Applications*, Springer: Dordrecht, 2010.
6. Lehn, J. -M. *Supramolecular Chemistry: Concepts & Perspectives;* Wiley-VCH: Weinheim, 1995.

HISTORY OF ANION BINDING

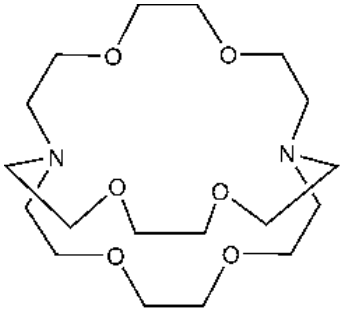
- The field of non-covalent anion coordination chemistry as we know it today may be traced back to Park and Simmons of the du Pont de Nemours Company in 1968, concerning the halide complexation properties of a series of macrobicyclic hosts termed *katapinands*.
- The katapinands (named from the Greek *katapino*, meaning to swallow up or engulf) are able to bind halide ions within their macrobicyclic cavity when protonated at the bridgehead nitrogen atoms which was later confirmed by X-ray crystal structure determination.
- It was the first example of anion binding by a macrocyclic host, and preceded the discovery of the cryptates by several years.
- As a matter of fact, Simmons and Park's paper, submitted in 1967, was the second major contribution to the then unborn field of supramolecular chemistry
- Seven months earlier, Charles Pedersen had submitted his landmark work on the cation-binding behaviour of dibenzo[18]crown-6, which marked the beginning of modern supramolecular chemistry.



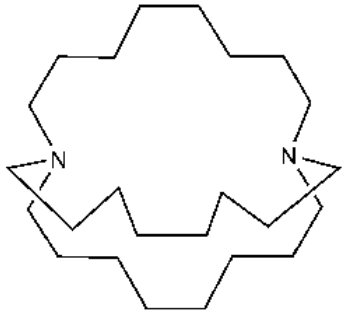


4.1 **a** n = 0
b n = 1
c n = 2

Minimised structure of the chloride complex of 1,11 diazabicyclo[9.9.9]nonacosane; katapinand **4.1b**



Polyether Cryptand
[2.2.2]

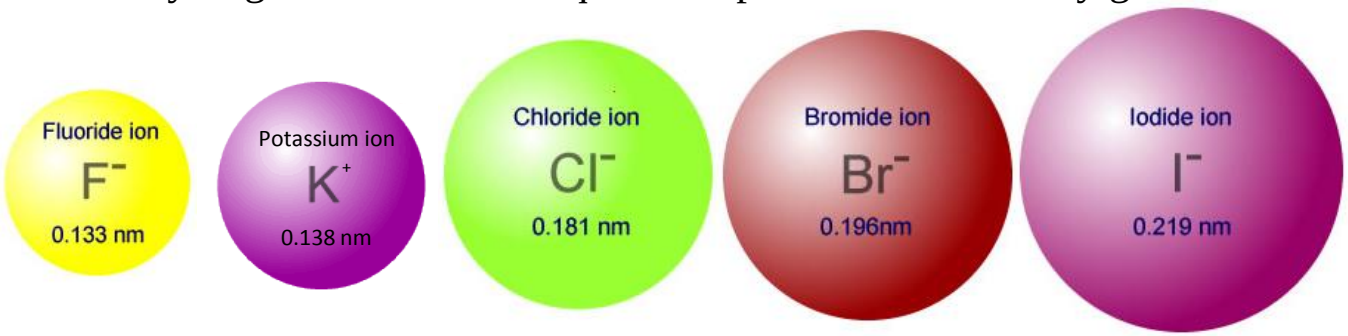


Katapinand
1

Structural difference between cryptand and katapinands

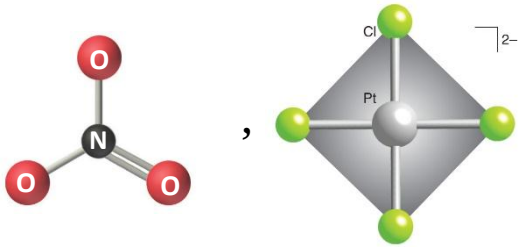
CHALLENGES IN ANION RECEPTOR CHEMISTRY

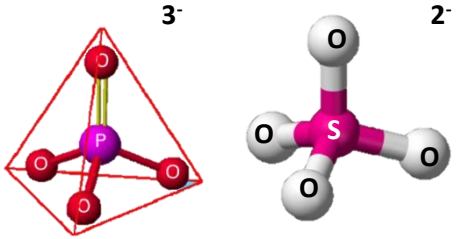
❖ Anions are relatively large and therefore require receptors of considerably greater size than cations.

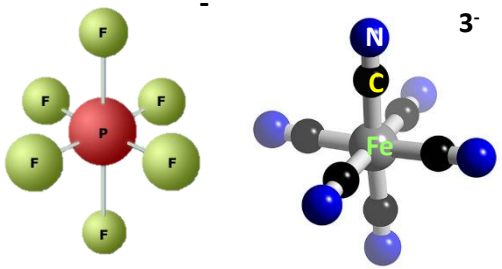


❖ Even simple inorganic anions occur in a range of shapes and geometries.

- Spherical: Halides, Cl^-, Br^-
- Linear: 

- Planar: 

- Tetrahedral: 

- Octahedral: 

❖ In comparison to cations of similar size, anions have high free energies of solvation and hence anion hosts must compete more effectively with the surrounding medium, *e.g.*

- $\Delta G_{hydration}(F^-) = -465$ kJ mol^{-1}, • $\Delta G_{hydration}(CO_3^{2-}) = -1315$ kJ mol^{-1} $\Delta G_{hydration}(PO_4^{3-}) = -2765$ kJ mol^{-1}
- $\Delta G_{hydration}(K^+) = -295$ kJ mol^{-1} • $\Delta G_{hydration}(SO_4^{2-}) = -1080$ kJ mol^{-1}

CHALLENGES IN ANION RECEPTOR CHEMISTRY

- Many anions exist only in a relatively narrow pH window, which can cause problems especially in the case of receptors based upon polyammonium salts where the host may not be fully protonated in the pH region in which the anion is present in the desired form.

- Anions are usually coordinatively saturated and therefore bind only *via* weak forces such as hydrogen bonding and van der Waals interactions, although they can form dative bonds.

- *High Polarisability:* Anions are highly polarisable and so van der Waals interactions will be significant. While non-directional, these are related to the contact surface area of host and anion, and so three dimensional encapsulation of the anion should enhance binding of all anions capable of fitting within the host.

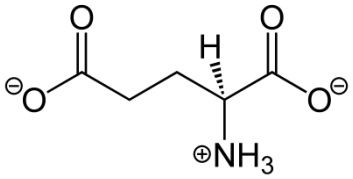
- *Solvation:* Anions generally have high solvation energies and so, the medium in which solution–anion complexation experiments are carried out will strongly influence binding constant measurements. Binding constants for monovalent inorganic anions of about 10^2–10^3 in water represent strong binding, whereas strong binding is achieved much more readily in non-polar solvents, such as chloroform, because of the anions' solvophobic properties.

IMPORTANCE OF ANIONS

- Simple inorganic anions are ubiquitous in the natural world.
- **Chloride** is a major component of the oceans and it is the dominant anion in biological extra-cellular fluid. It is the major extracellular anion, and it is responsible for the maintenance of ionic strength.
- **Nitrate** (from N_2 oxidation) and **sulfate** from burning organo-sulfur compound containing fossil fuels) are key components in acid rain and roadside particulate matter.
- **Sulfate** and **acetate** anions are also quite common biological anions.
- **Hydrogen carbonate and carboxylates** are also key biological anions, while **carbonates**, **phosphates** and **silicates** are the major anions in bio-mineralised materials such as the exoskeletons of radiolarian, and in bone.
- **Phosphates and nitrates** in fertilisers are beneficial to agriculture but also major pollution hazards since such bioavailable sources of phosphorus and nitrogen are often *biolimiting*, *i.e.* rate of microorganism growth is limited by the amount of these elements that are present.
- **Perchlorate** was used extensively as an explosive and rocket propellant.
- Other anthropogenic anions are also major pollutants, *e.g.* the highly soluble and mobile **TcO_4^- and ClO_4^-**

BIOLOGICAL SIGNIFICANCE OF ANION TRANSPORT

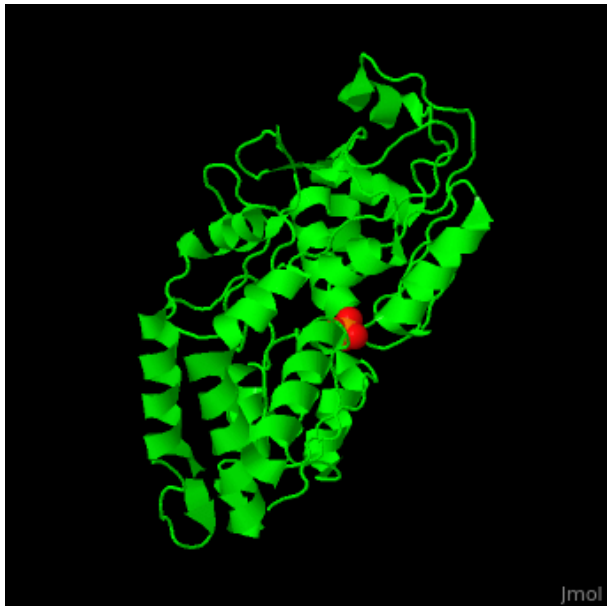
- Anions are crucial in biological systems – perhaps this is why imbalances in their concentration have such serious effects.
- Between 70 and 75% of enzyme substrates and cofactors are anions, very often phosphate residues (as in ATP and ADP) or as inorganic phosphate (H_2PO_4).
- At least 14 mitochondrial anion transport systems have been identified to date including systems involving flux of ADP, ATP, citrate, phosphates, glutamate, fumarate, maleate, oxaloacetate and halides.
- Glutamate in particular plays the central role in mammalian nitrogen flow, serving as both a nitrogen donor and nitrogen acceptor, and is a key ingredient in aminotransferase-catalysed amino acid synthesis.
- In biochemical anion binding, the enzyme or protein host is always part of a functioning biological system, *e.g.* in biocatalysis or anion transport.
- Natural anion binding systems must not only have high affinity for their target anion and low affinity for other species present in the cell or extracellular fluid but must also complex and release their substrates rapidly and at the appropriate time.



Glutamate

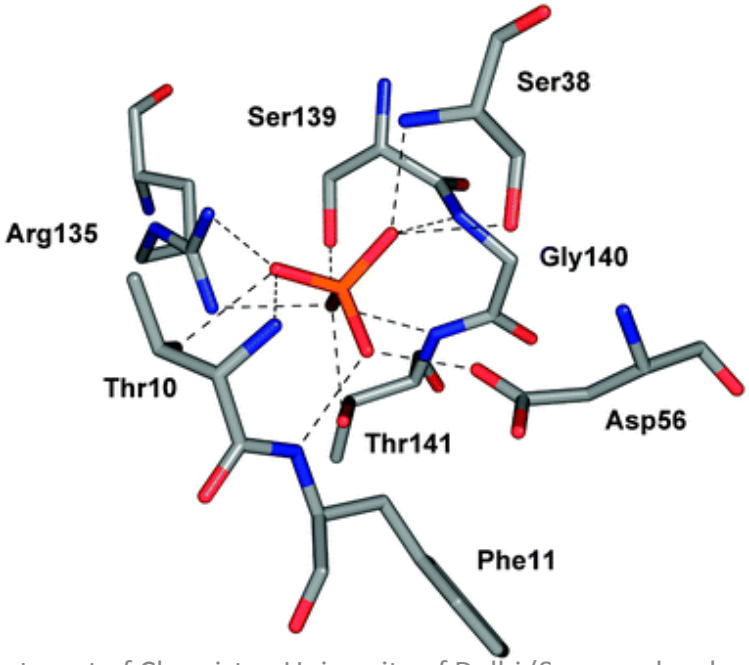
ANION BINDING PROTEINS

- There are two types bacterial periplasmic anion transport proteins termed phosphate binding protein (**PBP**) and sulfate binding protein (**SBP**).
- The function of the proteins is to bind tightly to the anion once it has crossed the bacterial cell membrane by passive diffusion.
- The structures of the two proteins are remarkably similar to one another.
- In each case, the anions are bound within a cleft some 8 Å deep, formed by the intersection of two protein globular domains, folded in a similar way to one another.
- The crucial difference between the two structures, which gives rise to their almost complete selectivity for their respective substrates (selectivity factor of about 10^4), is the arrangement of hydrogen bonding residues at the protein binding site.
- The average hydrogen bonding S=O…H angle of 127.9° is some 9 degrees larger than in the analogous phosphate interaction.
- Also, sulfonyl hydrogen bonding interactions are clustered much more densely about this value than are phosphoryl analogues.
- The former also tend towards a nearly eclipsed geometry in contrast to the phosphoryl preference for gauche interactions.



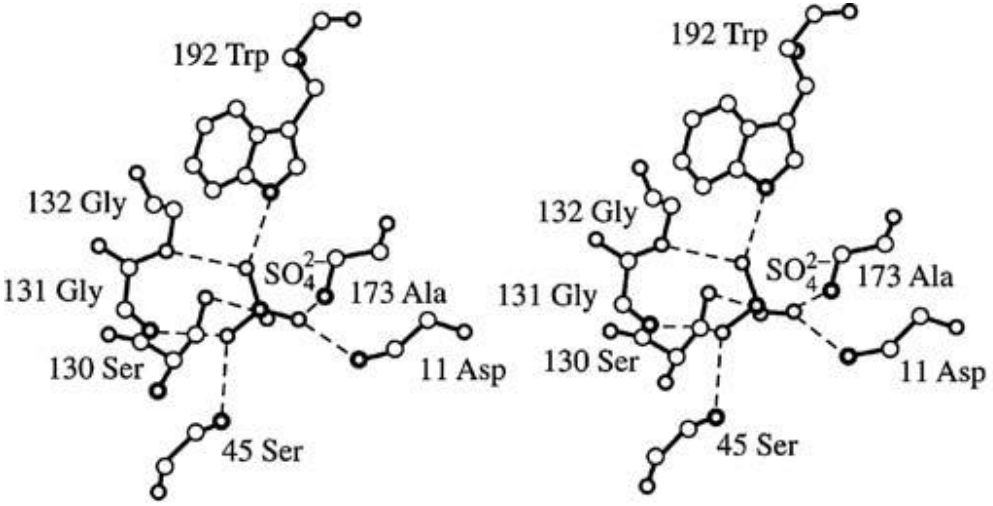
PHOSPHATE BINDING PROTEIN (PBP)

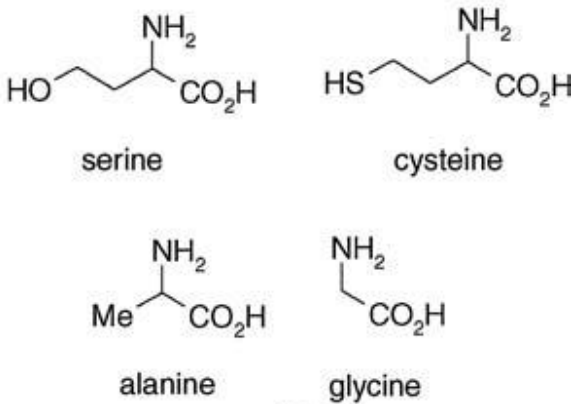
- The protein responds to the fact that both HPO_4^{2-} and $H_2PO_4^-$ are capable of acting as hydrogen bond donors as well as acceptors.
- The crystal structure determinations of this protein all include well-resolved, bound HPO_4^{2-}, which is held in place by a total of 12 hydrogen bonding interactions with N/O … O distances between 2.62 and 2.92Å.
- Seven are from NH groups from the protein main chain or arginine side chain residues, four are from OH groups (two serine and two threonine), and one involves an oxygen atom from a carboxylate anion (Asp56), which acts as a hydrogen bond acceptor.
- It is this H-bonding accepting group that induces “SELECTIVITY”, this group is absent in SBP



SULFATE BINDING PROTEIN (SBP)

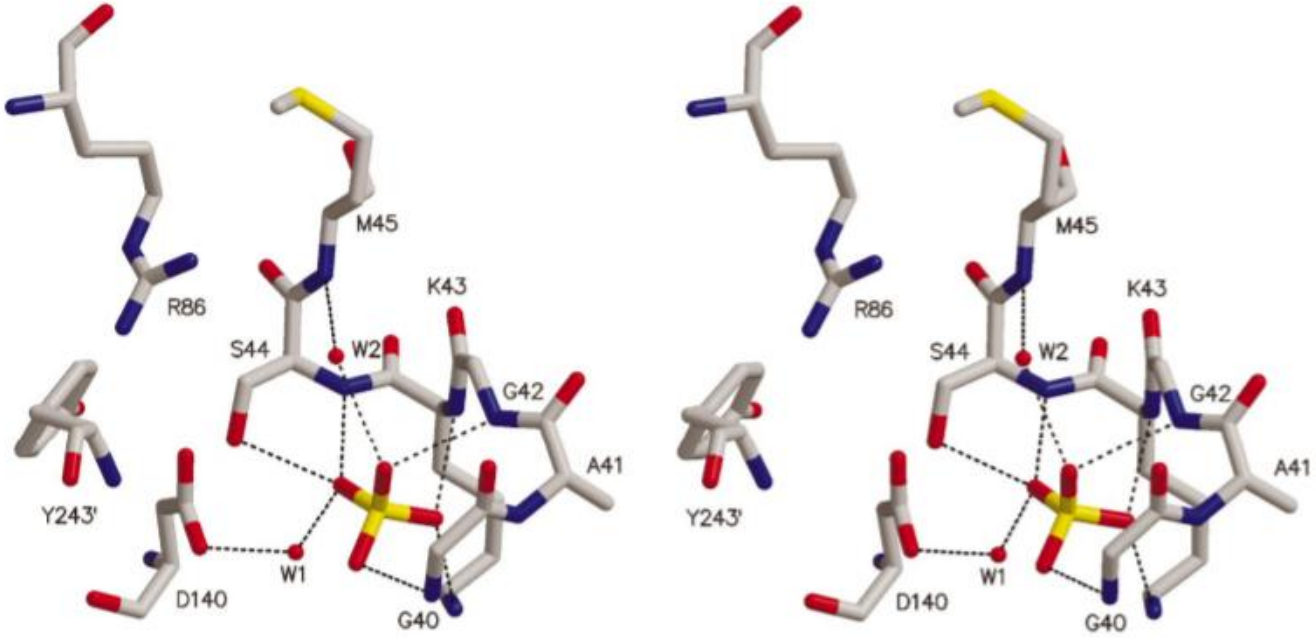
- The sulfate anion in the SBP structure is held in place by a total of seven hydrogen bonds from backbone NH, serine OH and tryptophan NH groups, all of which act as hydrogen bond donors.
- Replacement of the hydrogen bond donor serine130 with cysteine (SH instead of OH), alanine (CH3 substituent) or glycine (no substituent) by site-directed mutagenesis reduces the affinity of the protein for sulfate.
- In the case of cysteine, the reduction in affinity is by a factor of about 3200 as a result of unfavourable steric interactions.
- The other replacements (which result in the loss of one of the seven hydrogen bonds) both reduce affinity by 100 and 15 times, respectively, corresponding to the loss of a hydrogen bond of about 7 kJ mol^{-1}.





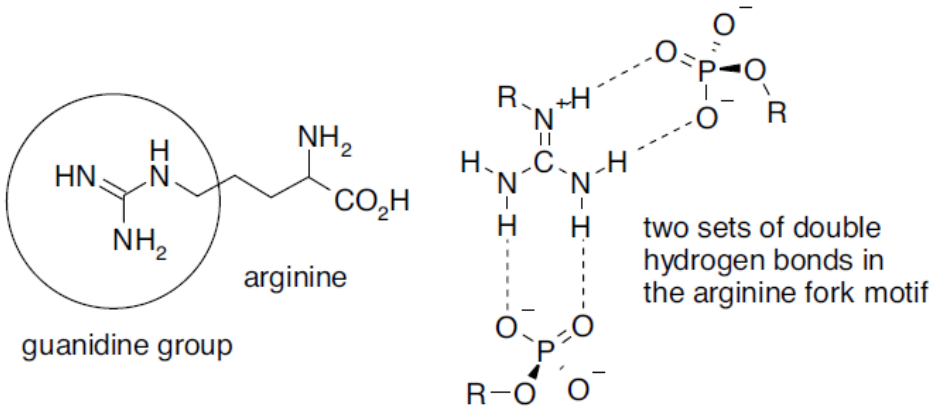
SULFATE BINDING PROTEIN (SBP)

- The crystal structure of the sulfate complex of DNA helicase RepA reveals a total of six hydrogen bonding interactions between anion and protein with a seventh interaction to a water molecule.
- The sulfate anions are occupying the active sites where the product phosphate residues usually bind.
- Sulfate binding induces significant conformational changes in the enzyme suggesting a structural change to an ‘open’ form upon binding and hydrolysis of the nucleotide 5′-triphosphate substrate that could be essential for DNA duplex-unwinding activity.



ARGININE AS AN ANION BINDING SITE

- Of particular importance in anion binding proteins and enzymes is the arginine residue, which contains a guanidine group.
- Guanidinium, the protonated form of guanidine, is an excellent anion binding site because it remains protonated over an extremely wide pH range (pK_a =13.5 for the parent CN_3H_6) and can participate in double hydrogen bonds with carboxylates, phosphate, sulfate *etc.*, as well as a unique interaction with two anions termed the *arginine fork* motif .
- Important arginine-containing biological systems include superoxide dismutase (a Cu, Zn enzyme that catalyses the transformation of superoxide (O_2^-) into hydrogen peroxide and dioxygen), and citrate synthase.
- It has been proposed that arginine-based proteins are able to use the arginine fork motif to recognise particular loops and bulges in RNA and indeed RNA-binding regions in proteins such as the human immuno-deficiency (HIV) virus that protein exhibit arginine-rich regions.



The amino acid arginine and the 'arginine fork' binding mode with phosphate anion residues.

DESIGNING OF ANION BINDING HOSTS

- The most obvious way in which to address the binding properties of anions is to combine electrostatic attraction for a positively charged host with the anions' Lewis basic character, which should enable then to act as hydrogen bond acceptors.

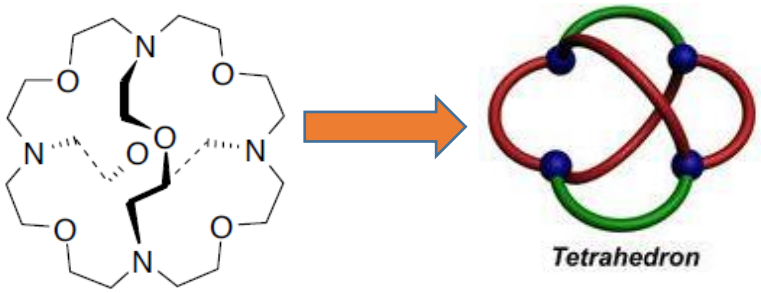
- There exists an enormous variety of cryptands designed for complexation of metal ions by virtue of the Lewis basic nature of their tertiary nitrogen bridgeheads and polyether or secondary amine chains

- A simple change in solution pH should result in the protonation of the host, according to their relative basicities, to give a katapinand-like host for anions with decent binding properties.

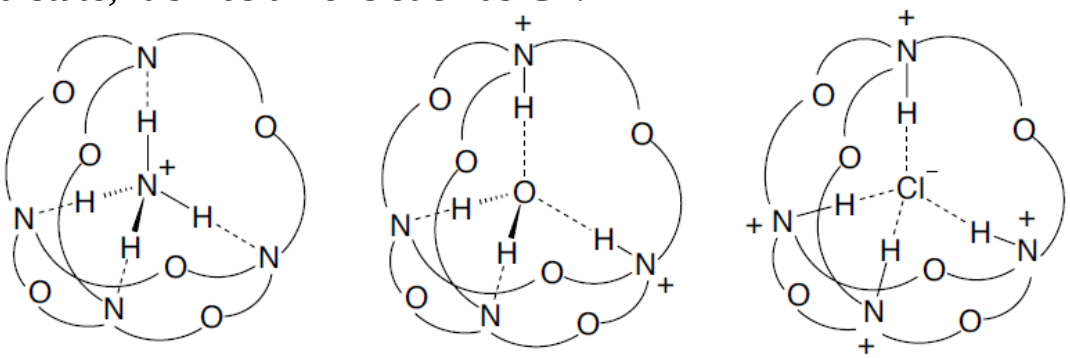
- The only factors of real importance are that the cryptand should be large enough to incorporate the anion and that there are not so many repulsions between the protonated host so that the host is incapable of converging, or is rendered too weakly basic and does not protonate at all.

TETRAHEDRAL RECEPTORS

- The designing of anion binding host is beautifully illustrated by the macrotricyclic cryptand, which may be regarded as arising from four fused triaza[18]crown-6 rings.

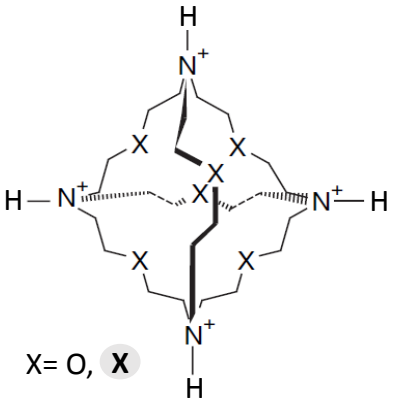


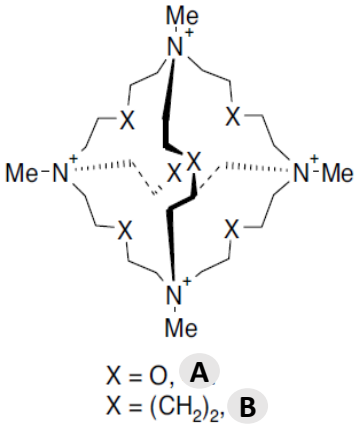
- This Compound has been termed a ‘soccer ball’ molecule because of its nearly perfect spherical shape.
- The presence of the four nitrogen bridgeheads on this molecule make it a highly versatile example of a tetrahedral receptor.
- In addition to its Lewis basic properties, which enable it to bind strongly to cations, in its tetraprotonated form it is also capable of binding anions such as Cl^-, acting via the formation of four hydrogen bonds supported by electrostatic interactions with the ether oxygen atoms.
- Thus, depending on the pH of the medium, the neutral host may bind cations, especially
- ammonium (NH_4^+); in its diprotonated state, it binds neutral molecules, particularly water; and in its tetraprotonated state, it binds anions such as Cl^-.



Prof. Rajeev Gupta, Department of Chemistry, University of Delhi (Supramolecular Chemistry; Paper No. 101 Section-B)

PROTONATION VS METHYLATION: SIZE OF CAVITY

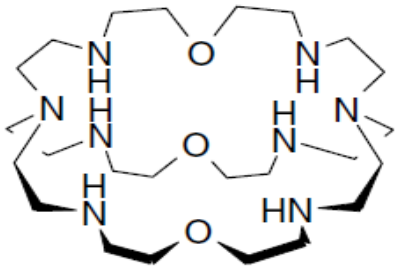




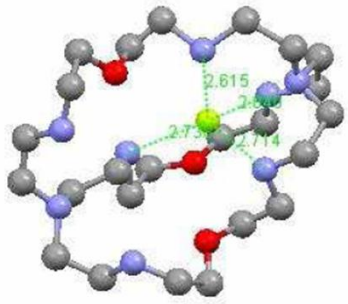
- In the protonated soccer ball (**X**), has an extremely high affinity (log K_{11}>4, methanol/ Water)and selectivity for Cl^- over Br^- by a factor of about 50.
- The X-ray crystal structure shows that the N—H … Cl^- hydrogen bonded distances are 3.09 Å, indicating that host is geometrically complementary to chloride.
- The greater affinity of **X** for Cl^- is due to much more preorganised nature, its greater positive charge and the greater number of binding sites.
- The lower affinity for Br^- is related to the non-optimal match between the longer N—H … Br hydrogen bond distances and the cavity dimensions.
- The addition of the methyl group causes the hosts to adopt an outward conformation otherwise the methyl groups would be forced into close proximity with one another at the centre of the molecule.
- This makes the cavity much larger than in tetraprotonated host and as a result the highest binding constants are observed for bromide and iodide (log K= 2.25 in water).
- The X-ray crystal structure of the iodide complex of **A** and reveals that the iodide anion is situated centrally in the tetrahedral macrotricyclic cage, some 4.54Å from the cationic nitrogen centres.

SHAPE SELECTIVITY

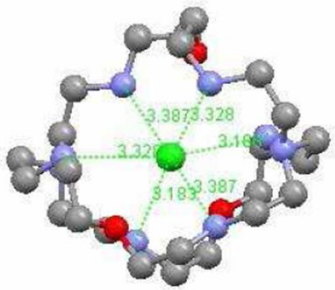
- In the case of the tetrahedral receptors, the halide coordination geometries may be described as tetrahedral.
- Halide coordination numbers range from two to six.
- Factors affecting anion binding selectivity is obtained by the binding characteristics of the cylindrical macrobicycle bis(tren).



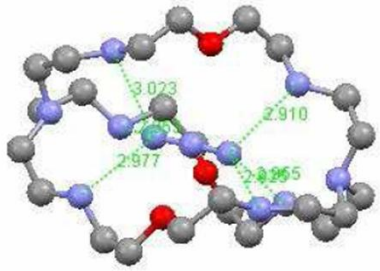
bis(tren)



Fluoride



Chloride



Azide

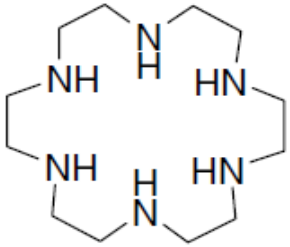
ANION	Log K	N...X (Å)
F^-	4.19	2.72
Cl^-	3.0	3.19–3.39
Br^-	2.6	3.33–3.47
I^-	2.15	-
N_3^-	4.30	2.81–3.02
$P_2O_7^{4-}$	10.30	-

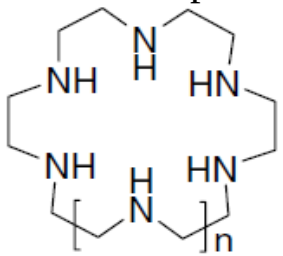
- Surprisingly, the order of halide binding constants follows their hydration energies with the most highly solvated (fluoride) also bound the most strongly. This is even more remarkable as F^- is a very poor fit for the long, cylindrical bis(tren) cavity.
- The larger Cl^- and Br^- ions are situated much more symmetrically in the cavity, interacting with six NH groups.
- The best fit to the cylindrical cavity in terms of shape and topological match is the cylindrical azide anion which is bound the most strongly.
- The binding is composed of a combination of electrostatic contributions, in which anions with a relatively high charge density such as F^- are bound strongly, and a topological (i.e. shape as opposed to size) complementarity favouring azide (which also has a high negative charge density).
- The electrostatic factors become apparent as soon as the affinity for multiply charged species such as $P_2O_7^{4-}$ (log K =10.30), ATP^{4-} and $ADP^{3-}$are examined and the result shows high binding constants.

TWO-DIMENSIONAL HOSTS

† Hexacyclen, [18]aneN$_6$, the aza analogue of [18]crown-6, has been shown by potentiometric titration to be an extremely strong diprotic acid in its hexaprotonated form, meaning that for most practical purposes in all but very acidic solutions, it exists as the tetraprotonated form.

Hexacyclen





n=2-7

† This is a general kind of observation for macrocycles of type II in which the nitrogen atoms are separated by only two carbon atoms.

† Protonation of all of the nitrogen atoms results in severe electrostatic repulsions between the NH_2^+ groups and dramatically lowers p*K*a values compared to acyclic analogues, which almost invariably adopt a linear, all-*anti* conformation when fully protonated to minimise repulsion between the cationic groups.

† In solution, hexacyclen binds NO_3^- in preference to halide anions, but none of these anions is included within the macrocycle.

† Halides adopt a perching geometry with N … Cl^- distance of 3.07–3.28Å, while in tetraprotonted ($2Cl^-$,$2NO_3^-$), the NO_3^- interact with the host indirectly via included water molecules.

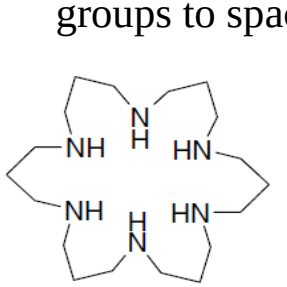
† Crystals of hexaprotonted ($2Cl^-$,$4NO_3^-$), do show direct interaction with the NO_3^- via one hydrogen bond each.

† Clearly the hexacyclen cavity, similar in size to [18]crown-6, but partially filled by the NH protons, is much too small to include anions.

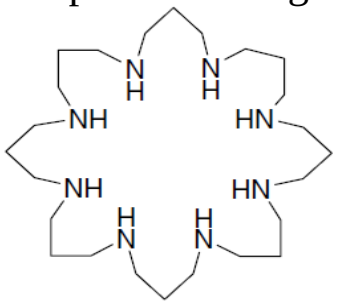
† large-ring species such as H_{10}[30]aneN_{10}^{10+} are able to act as hosts for large inorganic anions such as $[PdCl_4]^{2-}$,whilst $[Fe(CN)_6]^{4-}$ can be accommodated by [27]aneN$_9$ in its various protonated form.

VARIATION OF pK_a WITH SPACER LENGTH

- In order to avoid the problem of increasing difficulty in fully protonating macrocycles like hexacyclen and higher analogues, macrocycles such as **A** and **B** allow protonated nitrogen atoms to separate further by use of propenyl spacers, while **C** and **D**, which are less conformationally flexible, use ether groups to space out positive charge.



A



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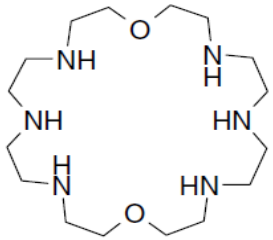
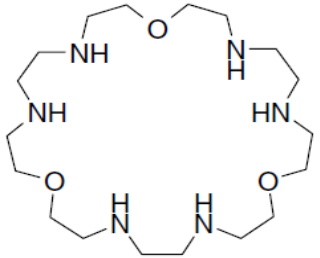
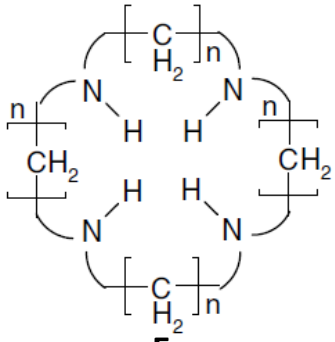


C



D



E

- This strategy proved successful in that the fully protonated species all exhibit pK_a values above 7.
- The dependence of pK_a upon spacer length is exemplified by the series [4n]aneN_4 (n=2–4, **E**), which shows the pK_a variation given in Table.

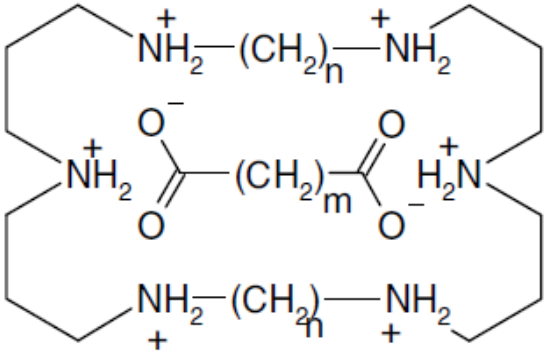
n	pK_3	pK_4
2	1.7	<1
3	6.9	5.4
4	10.6	8.9

- For **A-D**, anion binding behaviour is similar to that hexacyclen type, however, with binding constants increasing with anion charge.
- For anions of the same charge, structural effects were observed in which anions that matched the symmetry of the macrocycles were bound most tightly.
- larger anions tend to complex more strongly with the larger macrocycle.

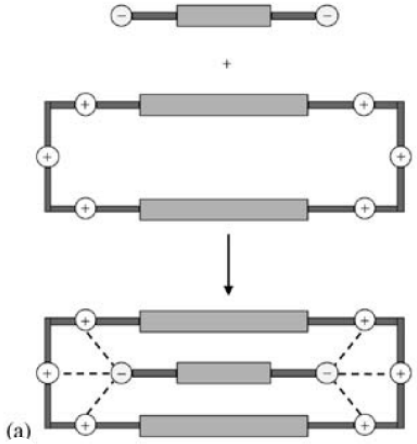
- Interestingly, binding constants for multiply charged anions such as ATP are significantly higher than analogous acyclic reference compounds such as spermine, indicating a significant anion binding macrocyclic effect, analogous to that found for the crown ethers as cation hosts.

SIZE RECOGNITION

- The ability of monocyclic azacrown type hosts to recognise anions on a size and shape fit basis has been investigated further by the preparation of hosts of type **F** that contain two-binding-domains.

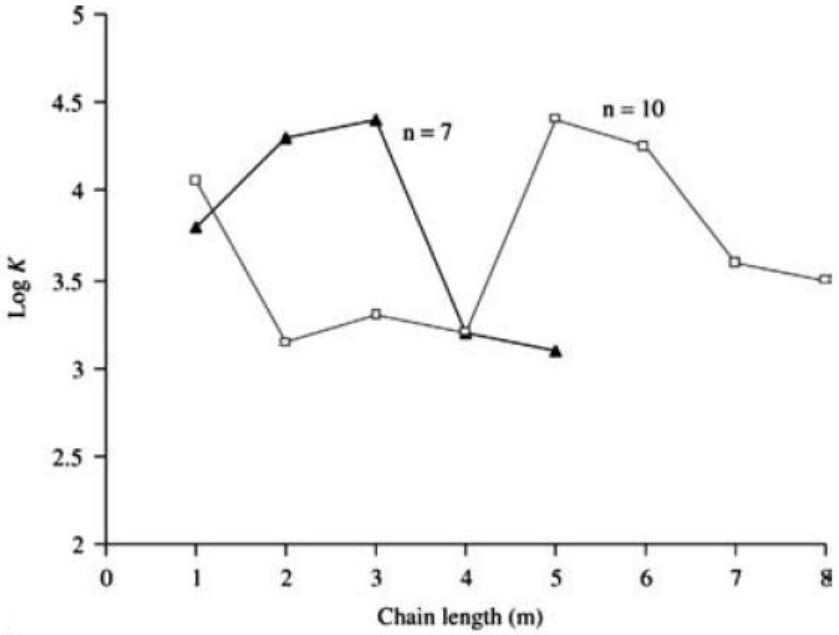


F (n = 7 and 10)
with α,ω-dicarboxylic acid guest



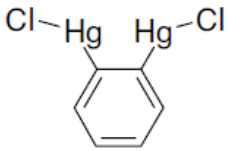
Length-based recognition of α,ω-dicarboxylic acids by monocyclic hosts **F**

- Those dianionic guests that best fit the cavity should be bound the strongest.
- Observed binding constants for compounds **F** with *n* =7 and 10 as a function of guest length, *m*, are shown in Figure.
- Modest peak selectivities are observed, signifying the dimensional matching of the host and guest, despite the relative flexibility of both partners

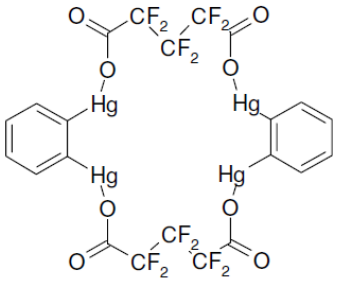


ANTI-CROWNS

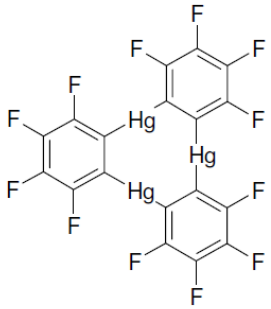
- A crown ether analogue made up from electron acceptor residues, as opposed to Lewis bases in the conventional crown ethers, can be thought of as an 'anti-crown' because of its opposite complexation behaviour—affinity for Lewis basic anions instead of Lewis acids such as alkali metal cations.
- As part of a macrocyclic ring system, anti-crowns should benefit from stabilisation of the complex by the macrocyclic effect and the chelate effect, as well as enhanced pre-organisation. E.g.



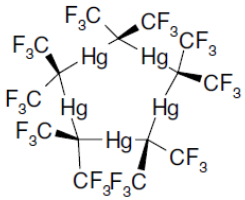
A



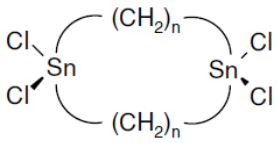
B



C

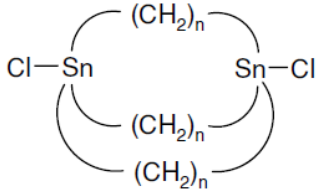


D



n=8,10,12

E



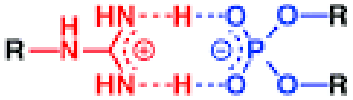
n= 6, 8

F

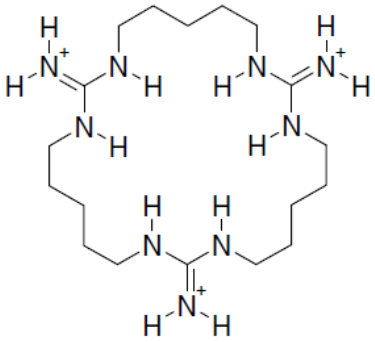
- Starting from an oxo-bridged analogue of the *o*-phenylenedimercurial residue **A**, a tetrametallic anticrown **B** has been prepared.
- The X-ray crystal structure of **B** reveals that the macrocycle binds THF molecules as guests, which are coordinated to the Lewis acid mercury sites.
- Compound **C**, forms a 1:1 polymer with Br^- in the solid state in which the Br^- anions perch above the Hg_3 plane. The Hg—Br distances of 3.07–3.39Å are considerably longer than normal Hg—Br covalent bonds (about 2.54Å).
- The analogous Cl^- complex has a 3:2 stoichiometry suggesting a triple-decker sandwich of type [**C** … Cl … **C** … Cl … **C**]$^{2-}$**.**
- Compound **D** adopts a 1:2 host:guest stoichiometry, in which the two Cl^- anions perch above and below the Hg_5 plane, one anion bridging quadruply and the other interacting with three Hg centres.
- Compound **E** binds Cl^- in acetonitrile; however, the binding constant is only twice that of open-chain analogues and is independent of ring size, suggesting little cooperativity to the binding.
- The macrobicyclic compounds **F** have been characterised by X-ray crystallography as the fluoride (n=6) and chloride (n =8) derivatives.

GUANIDINIUM-BASED RECEPTORS

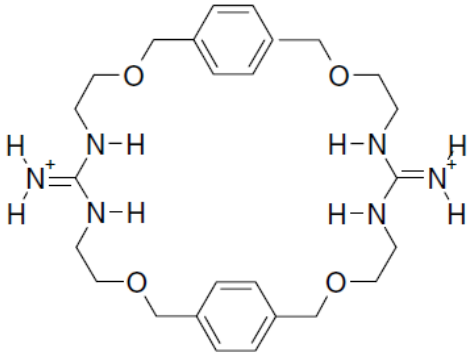
- The guanidinium ion is very popular motif in the design of anion complexation hosts.
- The native guanidinium ion has a p*K*a of 13.5, meaning that it is protonated and therefore positively charged and an effective hydrogen bond donor, over a wide pH range.
- In the solid state, methylguanidinium forms a 1:1 complex with dihydrogen phosphate, indicating clearly its bidentate hydrogen bonding coordination mode.



- To take advantage of this behaviour in a macrocyclic host, macromonocycles **A** and **B** were prepared.



A



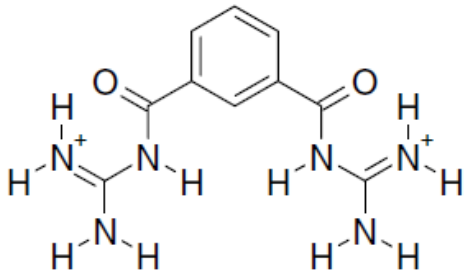
B

- The +3 charge and threefold symmetry of **A** suggests that this host should bind strongly to PO_4^{3-}.
- Because of the low Brønstead acidity of the protonated guanidinium moieties, the host should remain protonated under the highly basic conditions required for the existence of PO_4^{3-}

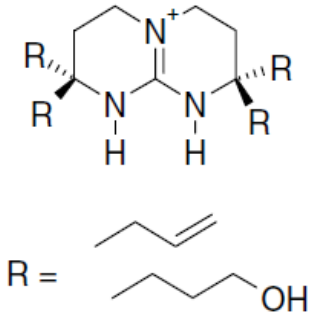
- log *K* values are only 2.4 and 1.7 for **A** and **B**, respectively.
- It was suggested initially that this may arise from the low charge density of the guanidinium moiety, implying weak electrostatic interactions, but this would be surprising given its biological ubiquity.
- It is possible that the macrocycles are both too small to accommodate the large phosphate anion and too inflexible to direct their guanidinium moieties towards an anion in a perching geometry.
- The high degree of solvation of the guanidinium ion in polar solvents is probably also detrimental to strong binding.

GUANIDINIUM-BASED RECEPTORS

- Despite these disappointing results, a great deal of activity has focused on guanidinium-based hosts.
- The majority of recent systems are acyclic, however, analogous to podand hosts for cations.
- These species combine ease of synthesis (no high dilution required) and the fast complexation/decomplexation kinetics observed in biological systems, at the expense of preorganisation.
- Simple bis(guanidinium) compounds, such as **A**, exhibit excellent cooperative binding of phosphodiesters ($R_2O_2PO_2^-$) with association constants in acetonitrile of about 5×10^4 M^{-1}.
- The hosts also act as catalysts for transesterification reactions (exchange of one R group for another in esters -C(O)OR), with rate enhancements of up to 300-fold compared with the uncatalysed reaction.



A



B

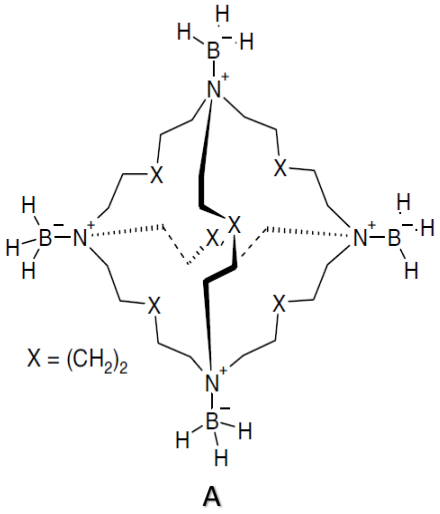
- A breakthrough in guanidinium-based anion hosts came with the synthesis of the bicyclic derivative **B** in 1980.
- The presence of the hydrocarbon backbone reduces dramatically the solvation of the guanidinium moiety and increases its lipophilicity, resulting in complexes with *p*-nitrobenzoate guest, for example, with association constants of the order of 1.4×10^5 M^{-1} in chloroform.

NEUTRAL RECEPTORS

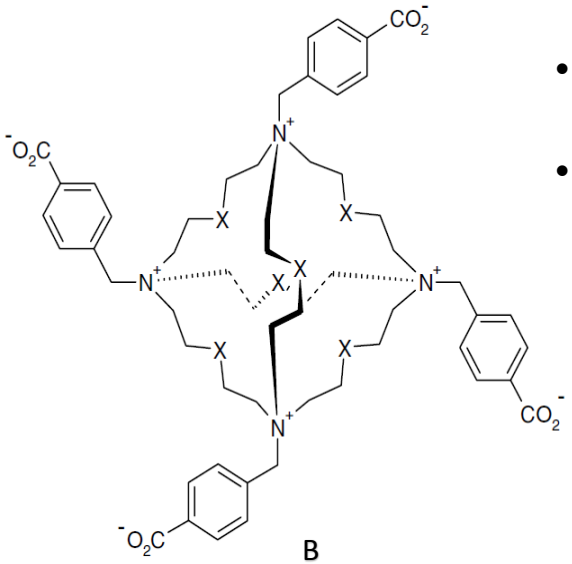
- All of the hosts examined till now possess a formal positive charge, which assists in their anion complexing ability through the formation of non-directional electrostatic interactions.
- Despite the strong binding by charged hosts, there are two potential disadvantages to the use of cations as anion complexing agents:
    - the non-directional nature of electrostatic forces means that all anions are bound with some degree of strength, which can reduce anion selectivity.
    - As well as being non-selective, each cationic host must have a counter anion, incorporated at the time of synthesis, in order to fulfil the requirement of overall electro-neutrality.
    - These counter anions generally interfere with binding of the target anion, and observed binding constants are ratios of the affinity for one anion over the other, rather than representing absolute host guest affinity.
- As a result of both the non-directional electrostatic binding and inter-anion competition, it is more difficult to incorporate selectivity into charged hosts.
- a neutral host does not interact solely with an anion, but in fact must bind both the anion and its counter-cation and so is formally a host for an ion pair.

ZWITTER IONS

- A zwitter ion is a neutral molecule containing both positive and negative charge (*e.g.* the amino acids).
- The majority of biological anion binding proteins and enzymes are zwitter ionic, having positively charged regions in which the anion binding occurs, coupled to negatively charged carboxylates, which impart overall electrical neutrality, facilitating the proteins' membrane solubility.



A



B

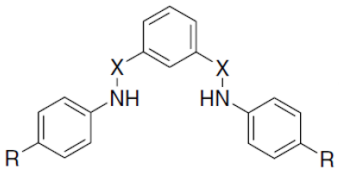
- In preparing neutral host molecules, **A** and **B** were prepared.
- In **A**, overall charge is neutral, but the host still possesses a signifi cant amount of positive charge on the nitrogen atoms as a result of the $^{+}N—B^{-}$ dipolar bonds, which exert directionality, encouraging anions to enter the cavity and hence promote selectivity.

- In **B**, the anionic carboxylate portions of the molecule are prevented from entering the cavity by the rigidity of the aryl spacers.
- As a result, the compound is highly water-soluble, consistent with a lack of intramolecular ion pairing of the charged CO_2^- groups with the quaternary ammonium functionalities, and again binds anions readily.
- Association constants for halides and CN^- in water of (300–600) $\times 10^3$ M^{-1} are observed.

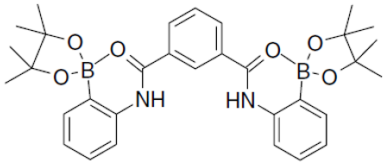
H-BONDING HOSTS

Amide-Based Receptors:

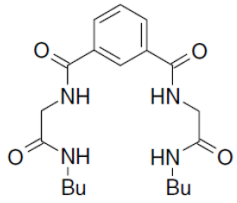
- The secondary amide group, –C(O)NHR, is ubiquitous in protein structures where hydrogen bonding from the amide NH group to the carbonyl oxygen atom is responsible for much of the secondary structure of proteins such as α-helices and β-sheets.
- The electron withdrawing effect of the carbonyl oxygen atom make the amide NH group a strong and directional hydrogen bond donor.



A1 R = H, X = CO
A2 R = n-Bu, X = CO
A3 R = H, X = SO_2

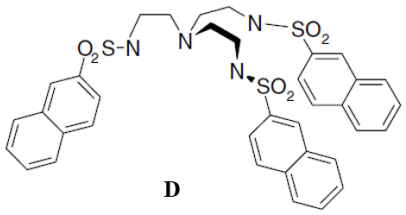


B

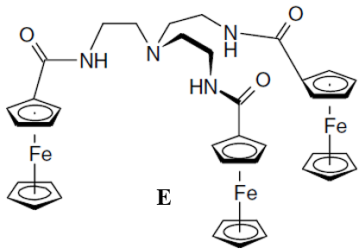


C

- The low solubility of **A1** meant that solution studies in CH_2Cl_2 were carried out on alkylated analogues such as **A2** which **A3** forms both 1:1 and 2:1 complexes with F^- and acetate and is relatively unselective, perhaps reflecting a lowered degree of preorganization.
- In the very highly preorganised boronic acid derivative **B,** boron atom forms an adduct with the lone pairs of the carbonyl oxygen atoms, inhibiting molecular rotation in the host by forming a cyclic framework.



D



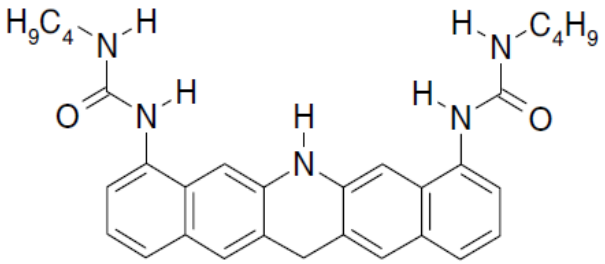
E

- The slight modification in **C** significantly enhances binding, particularly for oxyanions such as dihydrogen phosphate with all four amide NH groups interacting with the polyatomic anions.
- Hosts **D** and **E** are based on the tren motif, which presents three N–H bonds convergently towards a central binding site.
- In the case of **D**, binding is aided by the presence of stacking interactions with the napthyl rings, while in **E**, the three ferrocenyl moieties act as redox sensors to detect anion binding as well as providing stabilisation by the Lewis acidity of the metal and C—H … anion interactions.

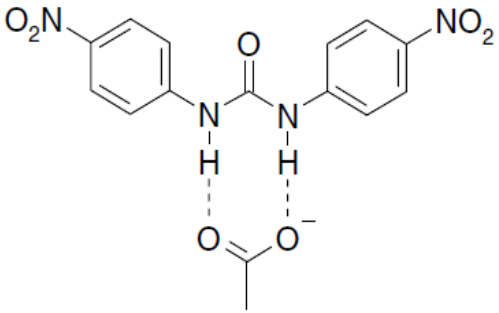
H-BONDING HOSTS

Urea based Receptors:

- The NH groups of urea has strong hydrogen bonding ability as urea molecules self-associate by NH···O=C interactions due to which it results in high anion affinities.
- urea is very readily synthesised by reaction of an isocyanate with an amine and hence provide very versatile anion binding sites.



A

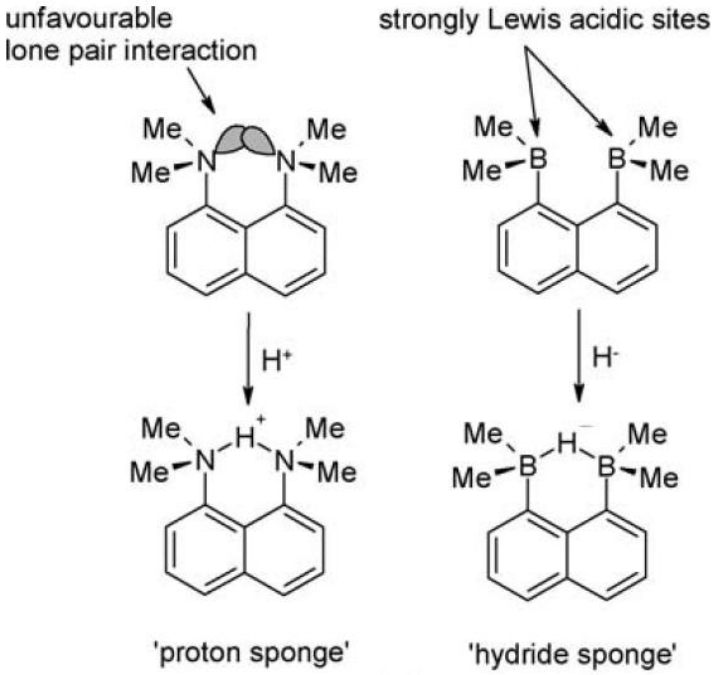


B

- Rigid urea-based molecular ‘cleft’ host (**A**) is able to chelate carboxylate, phosphate, sulfonate and similarly shaped anions.
- Anion affinity depends on the Brønsted basicity and charge of the guest; the greater the better, although the variation is not very large.
- Even the very simple urea derivative **B** interacts strongly with fluoride, acetate and benzoate to give a bright yellow colour in the case of oxoanions (absorption at *ca.* 370 nm), log *K* values 7.38, 6.61 and 6.42, respectively in acetonitrile solution.

HYDRIDE & PROTON SPONGE

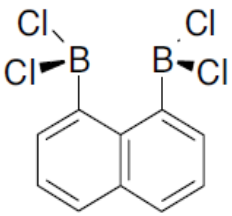
- One of the most obvious ways to bind anions is to incorporate functionality into a host that forms direct (possibly covalent) coordination interaction to the anionic guest.
- Since most anions are Lewis bases then Lewis acid functionality is an appropriate choice.



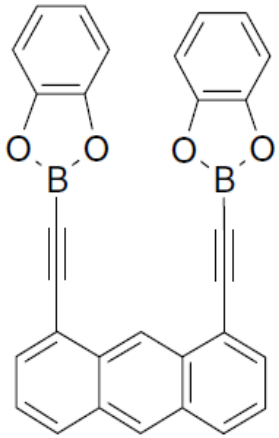
- Proton sponge, 1,8-bis(dimethylamino)naphthalene (**A**) is an extremely effective proton chelating agent.
- The protonation of one of the NMe_2 groups serves to significantly reduce the repulsion between the two nitrogen atoms in the free host, and consequently enhances greatly the basicity of the diamine.
- The $N—H^+—N$ hydrogen-bonded bridge is almost symmetrical.
- If the two amines are replaced by BMe_2, groups a highly electron-deficient anion host, termed 'hydride sponge' **B** is created, which demonstrates a marked ability to abstract hydride from almost all other hydride sources (*e.g.* $HBEt_3^-$).

- The interaction energy between the H-guest and the diboron ligand has been estimated to be at least 71 kJ mol^{-1}
- An X-ray crystal structure of the complex shows that the hydride ligand is coplanar with the boron atoms and napthalene ring, although it is situated asymmetrically between the two boron atoms within the three-centre, two-electron bond with the two B—H distances being 1.49 and 1.20Å in the KH complex .

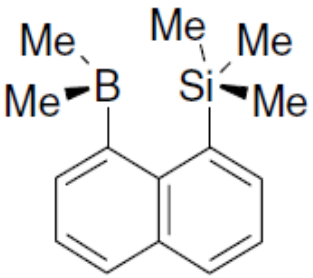
HYDRIDE SPONGE



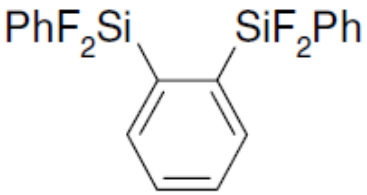
A



B



C



D

- Compound **A** chelates Cl^- in a distinctly out-of-plane fashion because of the large size of Cl^- compared to the B … B separation in the rigid napthelenyl system.
- Compound **B** was designed to offer a much larger chelate 'bite' angle and displays a distinct chelate coordination to the complementary neutral molecule 5-methylpyrimidine.
- Compounds **C** and **D** formally contain tetravalent silicon, which is not electron-deficient.
- It is, however, a strong Lewis acid, and on reaction with F^-, five-coordinate silicon compounds are obtained.
- In the case of **C**, the fluoride anion is localised mainly on the boron atom, although it does display dynamic behaviour involving hopping between boron and silicon.
- Compound **D** as the KF adduct contains two five-coordinate silicon atoms that chelate the F^- anion.