Brief Overview on Anion Binding Organic Ligands

MacMillan Group Meeting
Dec. 3rd 2008

-Primary Reviews-

Supramolecular Chemistry of Anions, Bianchi, A.; Bowman-James, K.; Garcia-Espana. E. Eds. Wiley-VCH, **1997**

Schmidtchen, F. P.; Berger, M. *Chem. Rev*. **1997**, *97*, 1609.

Berr, P. D.; Gale, P. A. *Angew. Chem. Int. Ed*. **2001**, *40*, 486.

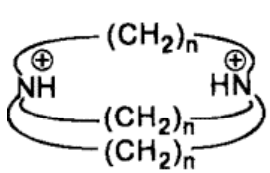
Schmidtchen, F. P. *Topic in Current Chemistry* **2005**, *255*, 1.

Anion Binding Organic Ligands: Outline

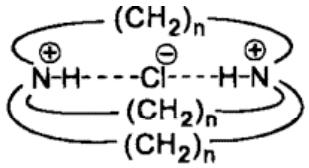
- Introduction
- Challenges / issues
- Binding forces
- Understanding the results
- Conclusion

Mode of Anion Recognition Chemistry: Origins

- First isolated example of anion encapsulation by organic ligand



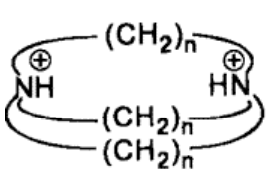
n = 9, 10



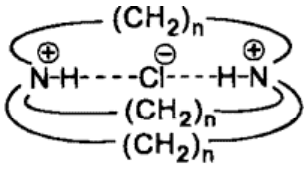
Park, C.H.; Simmons, H. E. *J. Am. Chem. Soc.* **1968**, *90*, 2431.

Mode of Anion Recognition Chemistry: Origins

- First isolated example of anion encapsulation by organic ligand

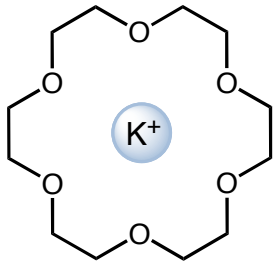


n = 9, 10



Park, C.H.; Simmons, H. E. *J. Am. Chem. Soc.* **1968**, *90*, 2431.

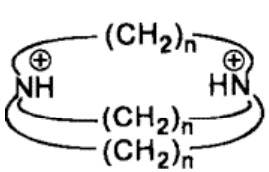
- First systematic study of cation encapsulation by organic ligand



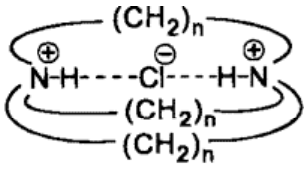
Pedersen, C. J. *J. Am. Chem. Soc.*, **1967**, *89*, 7017

Mode of Anion Recognition Chemistry: Origins

- First isolated example of anion encapsulation by organic ligand

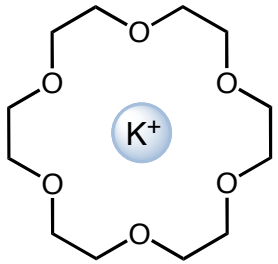


n = 9, 10



Park, C.H.; Simmons, H. E. *J. Am. Chem. Soc.* **1968**, *90*, 2431.

- First systematic study of cation encapsulation by organic ligand



Pedersen, C. J. *J. Am. Chem. Soc.*, **1967**, *89*, 7017

Anion Recognition Chemistry: Introduction

- Ubiquitous in biology as binding motif:
  >70% of substrates and cofactors involved in biological processes carry a net negative charge

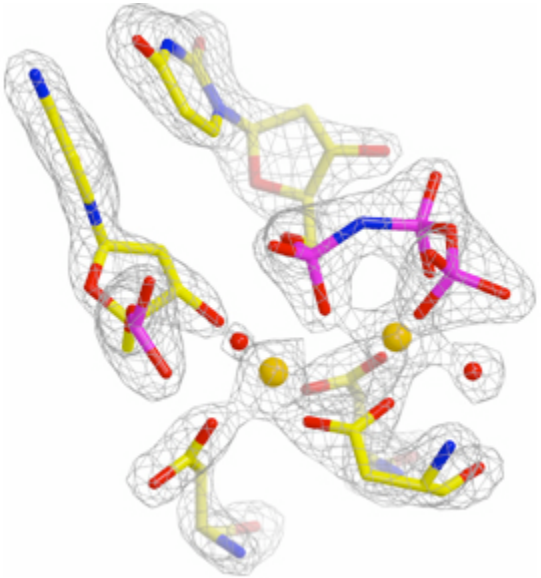
Anion Recognition Chemistry: Introduction

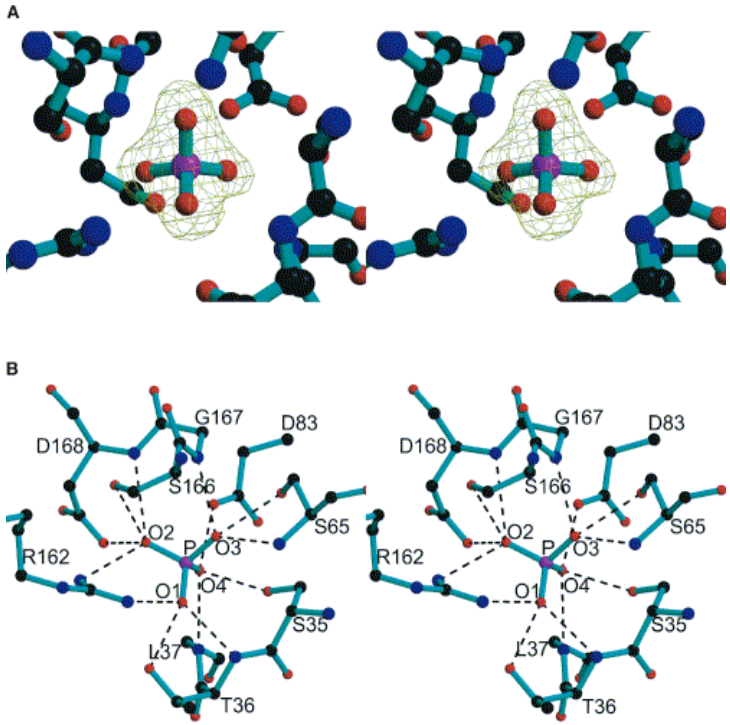
- Ubiquitous in biology as binding motif:
  >70% of substrates and cofactors involved in biological processes carry a net negative charge

- Heavily involved in catalysis:
  Carboxypeptidase, RNAse, ATP synthases, DNA polymerase, Citrate synthase

Anion Recognition Chemistry: Introduction

- Heavily involved in catalysis:
  Carboxypeptidase, RNAse, ATP synthases, DNA polymerase, Citrate synthase





- Mg++ mediated phosphate binding to activate for catalysis

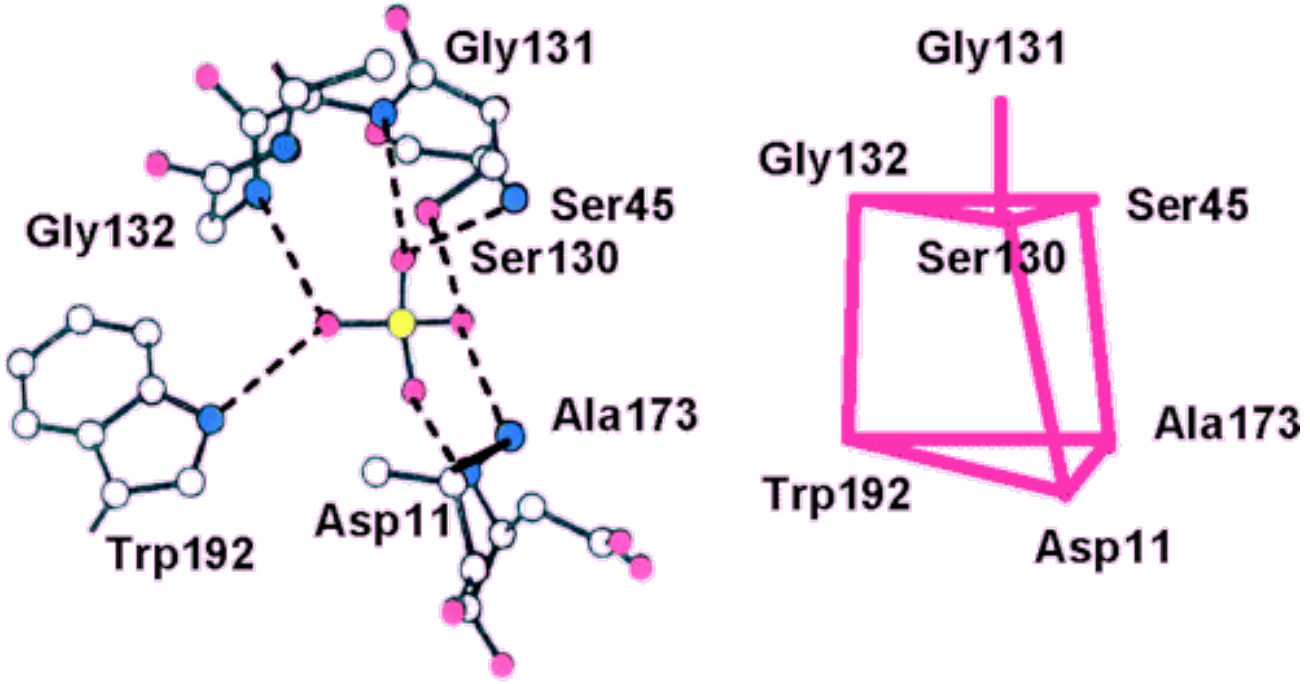
Batra et al. *Structure* **2006**, *14*, 1.

- Phosphate anion binding based on hydrogen bonding

Quiocho et al. *Structure* **2003**, *11*, 765.

Anion Recognition Chemistry: Introduction

- Heavily involved in catalysis:
  Carboxypeptidase, RNAse, ATP synthases, DNA polymerase, Citrate synthase



He, J. H.; Quiocho, F. A. *Science* **1991**, *251*, 1479.

- Even "non-basic" sulfate ions can be engaged in anion recognition for enzymatic catalysis

Anion Recognition Chemistry: Introduction

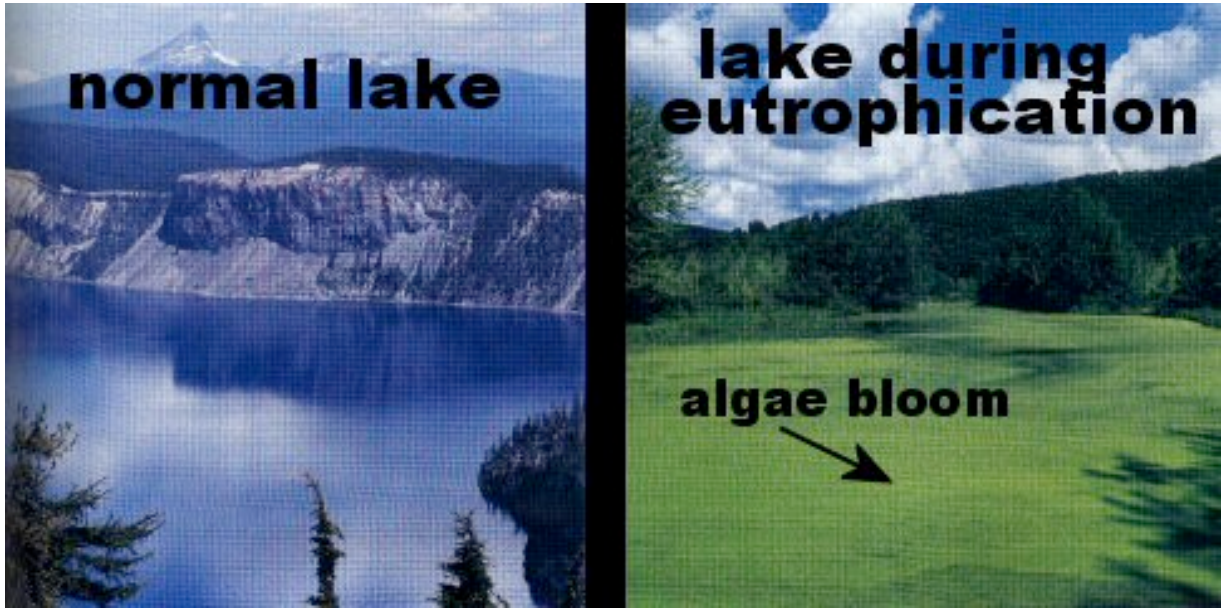
- Ubiquitous in biology as binding motif:
  >70% of substrates and cofactors involved in biological processes carry a net negative charge

- Heavily involved in catalysis:
  Carboxypeptidase, RNAse, ATP synthases, DNA polymerase, Citrate synthase

- Defense against eutrophication of aqueous source:
  phosphate removal from aqueous solution

Anion Recognition Chemistry: Introduction

- Defense against eutrophication of aqueous source:
  phosphate removal from aqueous solution



Anion Recognition Chemistry: Introduction

- Ubiquitous in biology as binding motif:
  >70% of substrates and cofactors involved in biological processes carry a net negative charge

- Heavily involved in catalysis:
  Carboxypeptidase, RNAse, ATP synthases, DNA polymerase, Citrate synthase

- Defense against eutrophication of aqueous source:
  phosphate removal from aqueous solution

- radioactivity:
  removal of pertechnatate from aqueous solution

Challenges in Anion Recognition Chemistry: Negative Charge

- Ion Pairing: universal phenomenon
  require very high dilution ($< 10^{-4}$ M) to avoid detection even in water

Challenges in Anion Recognition Chemistry: Negative Charge

- Ion Pairing: universal phenomenon
  require very high dilution ($< 10^{-4}$ M) to avoid detection even in water

- Larger than isolecetronic cations: Smaller charge to radius ratio

Challenges in Anion Recognition Chemistry: Impact of Size

- Larger than isolecetronic cations

Cation	*r* [Å]	Anion	*r* [Å]
Na^+	1.16	F-	1.19
K^+	1.52	Cl-	1.67
Rb^+	1.66	Br-	1.82
Cs^+	1.81	I-	2.06

Challenges in Anion Recognition Chemistry: Impact of Size

- Larger than isolecetronic cations

Cation	*r* [Å]	Anion	*r* [Å]
Na^+	1.16	F-	1.19
K^+	1.52	Cl-	1.67
Rb^+	1.66	Br-	1.82
Cs^+	1.81	I-	2.06

- Lower charge to radius ratio: charge density is smaller

Challenges in Anion Recognition Chemistry: Negative Charge

- Ion Pairing: universal phenomenon
  require very high dilution ($< 10^{-4}$ M) to avoid detection even in water

- Larger than isolecetronic cations: Smaller charge to radius ratio

- Electrostatic interaction less effective

Challenges in Anion Recognition Chemistry: Negative Charge

- Ion Pairing: universal phenomenon
  require very high dilution ($< 10^{-4}$ M) to avoid detection even in water

- Larger than isolecetronic cations: Smaller charge to radius ratio

- Electrostatic interaction less effective

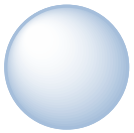
- pH window is narrower / important issue in aquoeus environment

Challenges in Anion Recognition Chemistry: Shape

- do not have uniform shapes like the cations

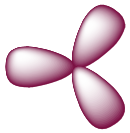
Challenges in Anion Recognition Chemistry: Shape

- do not have uniform shapes like the cations

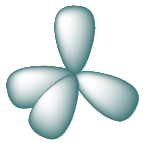


Spherical: F-, Cl-, Br-, I-

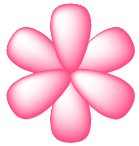
Linear: N_3-, CN-, SCN, OH-



Trigonal planar: CO_3^{2-}, NO_3^-



Tetrahedral: PO_4^{3-}, VO_4^{3-}, SO_4^{2-}, MoO_4^{2-}, SeO_4^{2-}, MnO_4^-, ClO_4^-, ReO_4^-, TcO_4^-



Octahedral: $[Fe(CN)_6]^{4-}$, $[Co(CN)_6]^{3-}$, $[Pd(Cl)_6]^{4-}$

Challenges in Anion Recognition Chemistry: Shape

- do not have uniform shapes like the cations
- can be utilized for selectivity
- customazation of ligand designing is required
- synthesis requires sophistication

Challenges in Anion Recognition Chemistry: Shape

- do not have uniform shapes like the cations
- can be utilized for selectivity
- customazation of ligand designing is required
- synthesis requires sophistication

Challenges in Anion Recognition Chemistry: Shape

- do not have uniform shapes like the cations
- can be utilized for selectivity
- customazation of ligand designing is required
- synthesis requires sophistication

Challenges in Anion Recognition Chemistry: Solvation and Dielectric constant

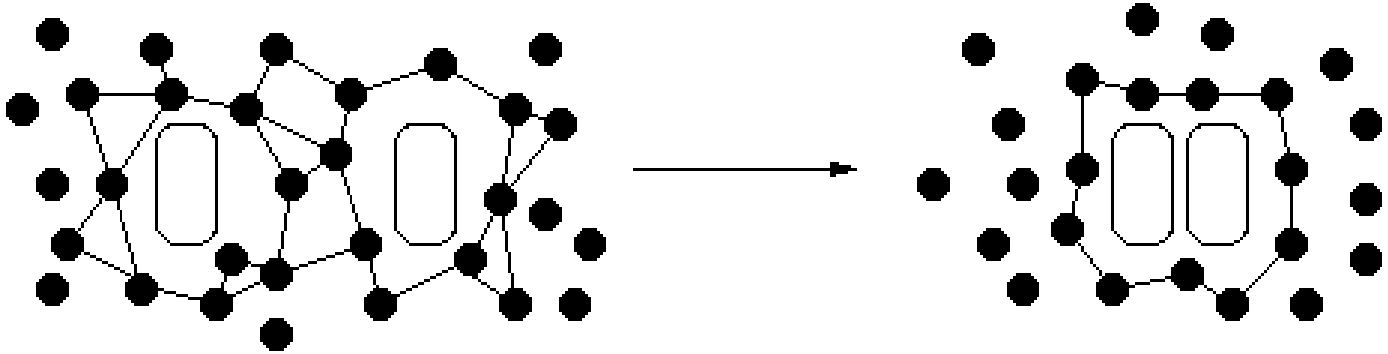
$$\Delta G = \Delta H - T\Delta S$$

- binding is *entropy* driven process in water for organic molecules: result of solvation

Challenges in Anion Recognition Chemistry: Solvation and Dielectric constant

$$\Delta G = \Delta H - T\Delta S$$

- binding is *entropy* driven process in water for organic molecules: result of solvation



- upon association of organic molecules, overall water molecules engaged in organization decreases due to decreased surface area of the organic molecule
  - overall increase in entropy

Challenges in Anion Recognition Chemistry: Solvation and Dielectric constant

$$\Delta G = \Delta H - T\Delta S$$

- binding is *entropy* driven process in water for organic molecules: result of solvation
- dielectric constant of a typical binding pocket of an catalytic enzyme = 2~4

dielectric constant value
of common organic solvents

dioxane = 2.3

toluene = 2.4

MTBE = 2.6

Ethyl Ether = 4.3

Acetic Acid = 6.2

THF = 7.5

DCM = 9.1

Luecke, H.; Quicho, F. A. *Nature* **1990**, *347*, 402

Gilson, M. K.; Honig, B. H. *Biopolymers* **1986**, *25*, 2097.

Challenges in Anion Recognition Chemistry: Solvation and Dielectric constant

$$\Delta G = \Delta H - T\Delta S$$

- binding is *entropy* driven process in water for organic molecules: result of solvation
- organization of solvent molecules: entropy
- stabilization of charge separation: enthalpy

Challenges in Anion Recognition Chemistry: Solvation and Dielectric constant

$$\Delta G = \Delta H - T\Delta S$$

- binding is *entropy* driven process in water for organic molecules: solvation
- organization of solvent molecules: entropy
- stabilization of charge separation: enthalpy

⇨ Depending on the solvent,
direction of enthalpy and the entropy might go against each other

Challenges in Anion Recognition Chemistry: Solvation and Dielectric constant

- binding is entropic driven process in water. organic solvents?
- organization of solvent molecules: entropy
- stabilization of charge separation: enthalpy
- " average interionic geometry" :
  effective interatomic distance is shorter than the hard-sphere model prediction

Challenges in Anion Recognition Chemistry: Solvation and Dielectric constant

- binding is entropic driven process in water. organic solvents?
- organization of solvent molecules: entropy
- stabilization of charge separation: enthalpy
- " average interionic geometry" :
  effective interatomic distance is shorter than the hard-sphere model prediction
- loss of free energy of solvation upon complexation is larger for smaller anions- point charge

Challenges in Anion Recognition Chemistry: Hydrophobicity

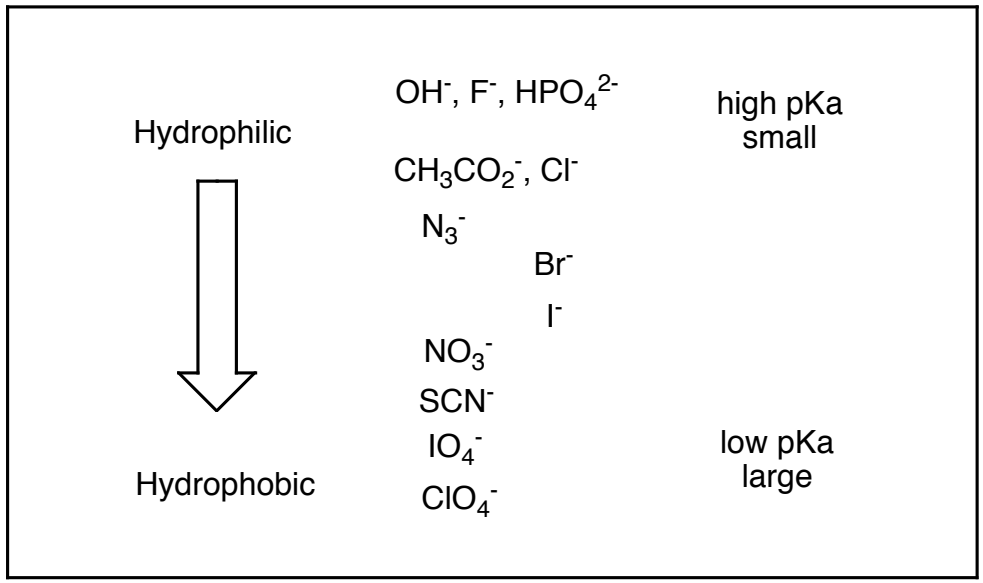
- charges do not necessarily reflect its chemical behavior

Challenges in Anion Recognition Chemistry: Hydrophobicity

- charges do not necessarily reflect its chemical behavior
- Hydrogen bonding ability

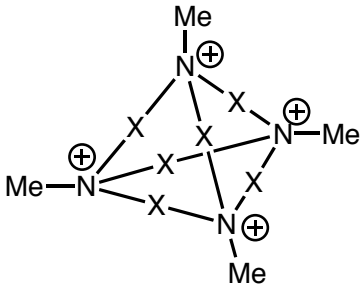
Challenges in Anion Recognition Chemistry: Hydrophobicity

- charges do not necessarily reflect its chemical behavior
- Hydrogen bonding ability
- "Hofmeister series" *Arch. Exp. Pathol. Pharmacol.* **1888**, *24*, 247.

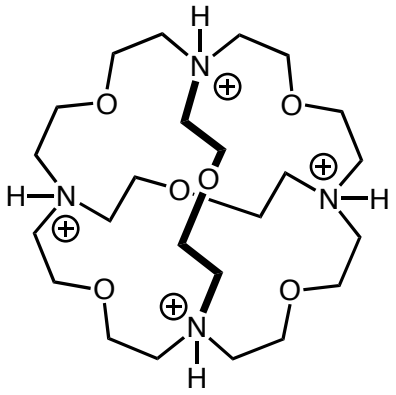


Anion Recognition Chemistry: Binding Forces

- Ion Pairing

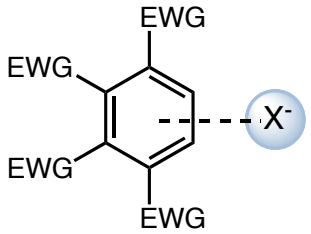


- Ion pariring + H-Bonding



- Hydrogen Bonding

- Anion-π interaction



Mode of Anion Recognition Chemistry: Hydrogen Bonding

- Neutral Directional Electrostatic Interaction

Mode of Anion Recognition Chemistry: Hydrogen Bonding

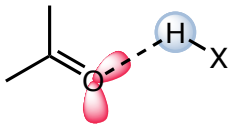
- Neutral Directional Electrostatic Interaction

- Directionality vs. Strength:
  Directionality is more important for weaker (long distance) hydrogen bonding

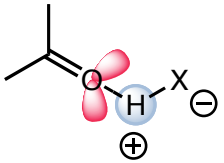
Mode of Anion Recognition Chemistry: Hydrogen Bonding

- Neutral Directional Electrostatic Interaction

- Directionality vs. Strength:
  Directionality is more important for weaker (long distance) hydrogen bonding



encroachment of donor



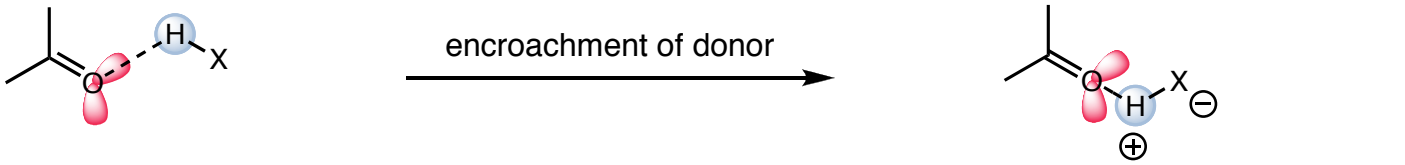
At long distance (> 3.5 Å),
Electrostatic Interaction is maximized
when donor and acceptor is aligned

At short distance (> 2.5 Å),
charge polarization is increased
to compensate for directionality

Mode of Anion Recognition Chemistry: Hydrogen Bonding

- Neutral Directional Electrostatic Interaction

- Directionality vs. Strength:
  Directionality is more important for weaker (long distance) hydrogen bonding



At long distance (> 3.5 Å),
Electrostatic Interaction is maximized
when donor and acceptor is aligned

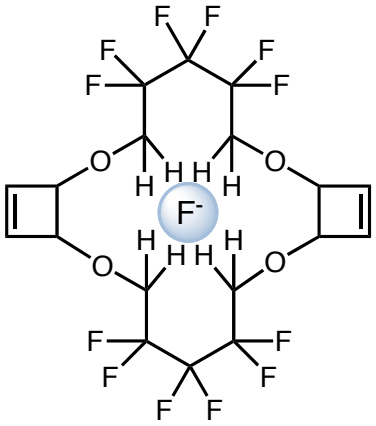
At short distance (> 2.5 Å),
charge polarization is increased
to compensate for directionality

- There exists a controversy whether very strong hydrogen bonds are involved in anion binding :no energy barrier for proton transfer for distance shorter than 2.5 Å

Jeffrey, G. A.; Takagi, S. *Acc. Chem. Res*. **1978**, 264

Mode of Anion Recognition Chemistry: Ion-Dipole Binding

- Neutral Directional Electrostatic Interaction
- Directionality vs. Strength

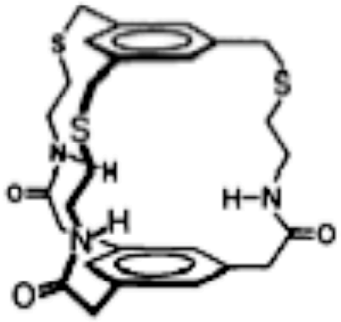


- No binding detected for the open chain analog

Farnham, W. B.; Roe, D. C.; Dixon, D. A.; Calabrese, J. C.; Harlow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 7707.

Mode of Anion Recognition Chemistry: Hydrogen Bonding

- First reported example of an amide-based anion binder

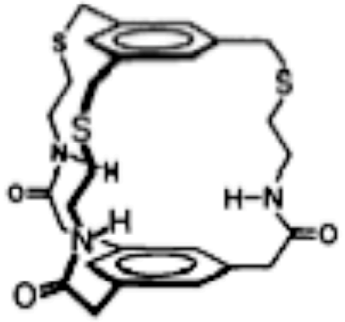


- NMR Data indicates encapsulation of F- in the cavity

Pascal. R. A.; Spergel, J.; Engsbersen, D. V. *Tetrahedron Lett*. **1986**, *27*, 4099

Mode of Anion Recognition Chemistry: Hydrogen Bonding

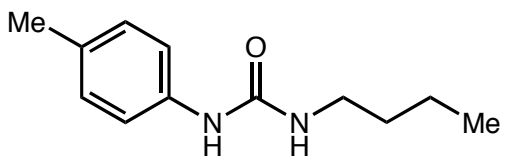
- First reported example of an amide-based anion binder



- NMR Data indicates encapsulation of F- in the cavity

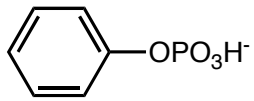
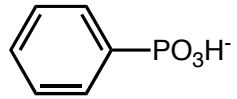
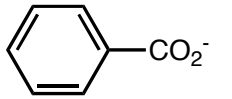
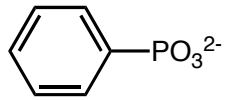
Pascal. R. A.; Spergel, J.; Engsbersen, D. V. *Tetrahedron Lett.* **1986**, *27*, 4099

- Urea/ thio-urea: good H-bond donors

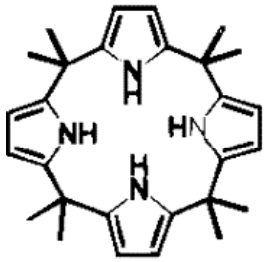


displays stronger binding with basic guests

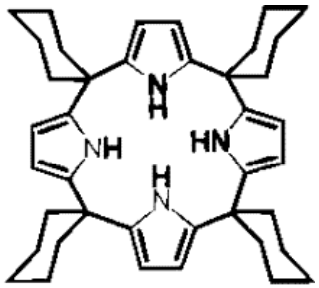
Kelly,T. R.; Kim, M. H.
J. Am. Chem. Soc. **1994**, *116*, 7072

	pK_b	K [M^{-1}]
	13	30
	12	140
	10	150
	7	2500

Mode of Anion Recognition Chemistry: Hydrogen Bonding

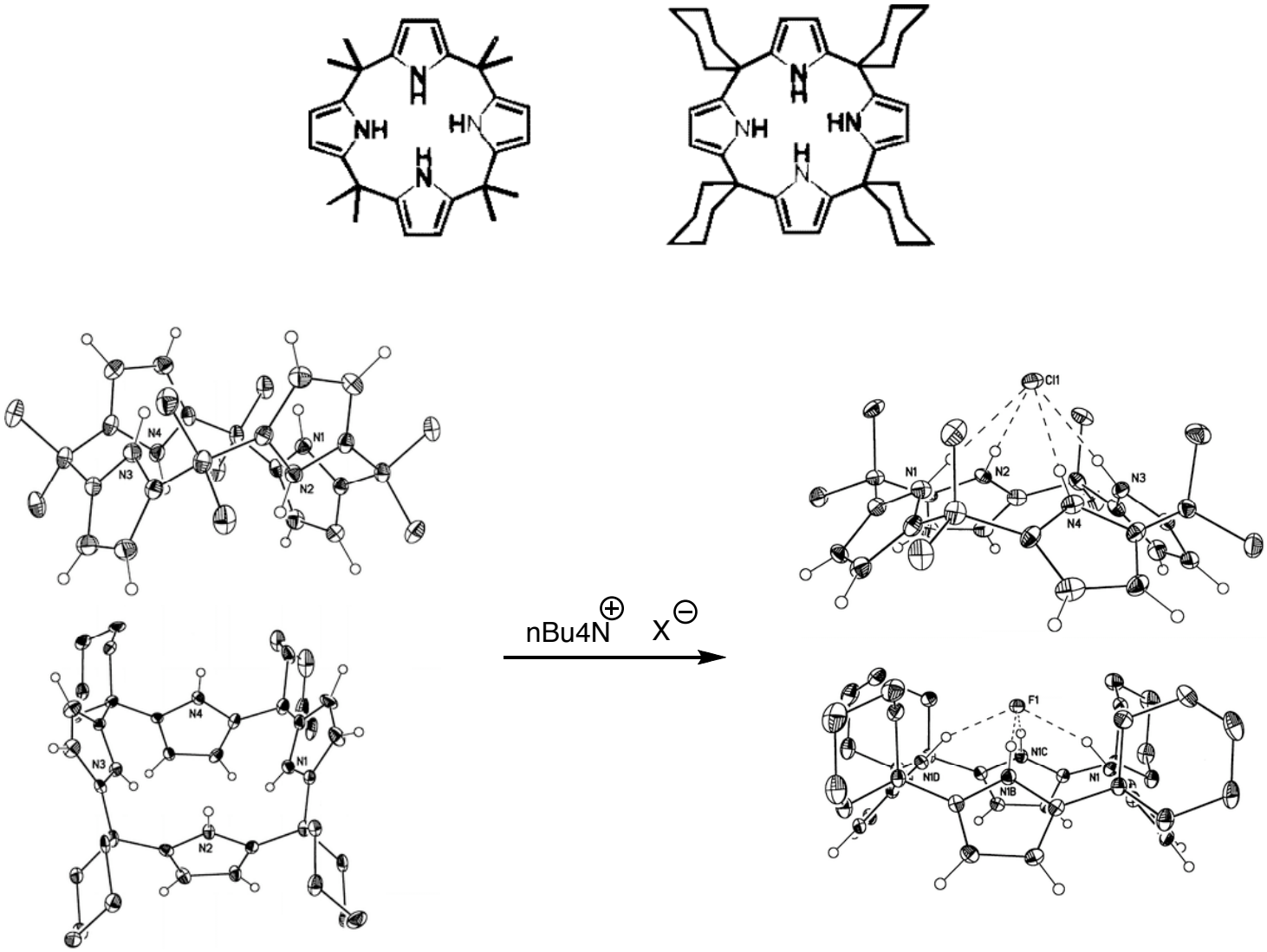


1



2

Mode of Anion Recognition Chemistry: Hydrogen Bonding

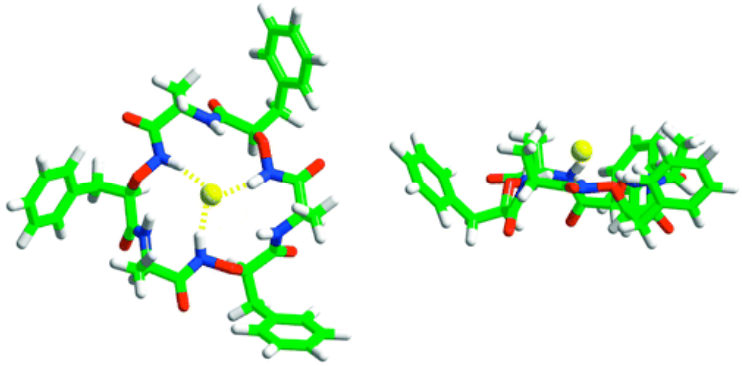


Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140.

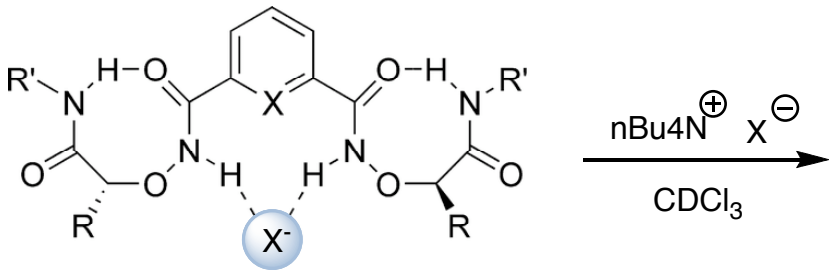
Mode of Anion Recognition Chemistry: Hydrogen Bonding

■ α-aminoxy acid: novel peptidomimetic building block

A



B



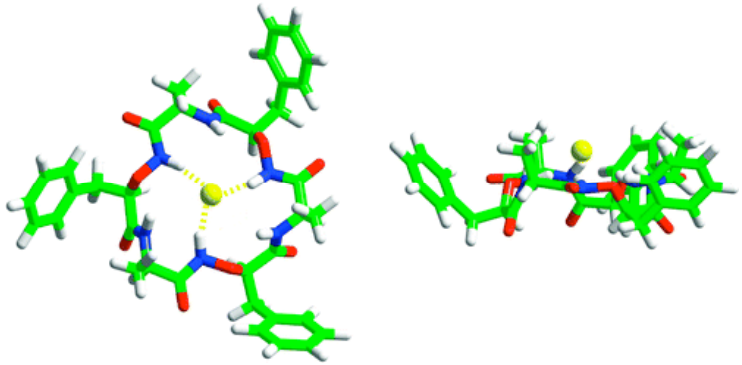
	A	B
Cl-	15000	>150000
Br-	910	18000
I-	51	1500
NO3-	440	1100
H2PO4-		1400

Li, X.; Shen, B.; Yao, X.-Q.; Yang, D. *J. Am. Chem. Soc.* **2007**, *129*, 7264

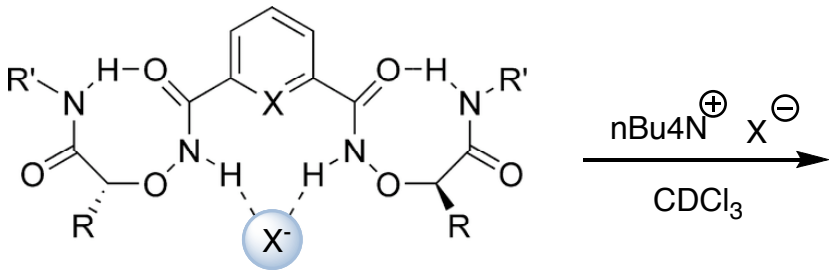
Mode of Anion Recognition Chemistry: Hydrogen Bonding

■ α-aminoxy acid: novel peptidomimetic building block

A



B



	A	B
Cl-	15000	>150000
Br-	910	18000
I-	51	1500
NO3-	440	1100
H2PO4-		1400

■ Acyclic motif is better binder than the cyclic variant:
Acidity of the hydrogen used for H-bonding
-disclaimer: not endorsed by the authors

Li, X.; Shen, B.; Yao, X.-Q.; Yang, D. *J. Am. Chem. Soc.* **2007**, *129*, 7264

Mode of Anion Recognition Chemistry: Hydrogen Bonding

- Neutral Directional Electrostatic Interaction
- Directionality vs. Strength
- dielectric constant of the solvent- charge separation

Mode of Anion Recognition Chemistry: Hydrogen Bonding

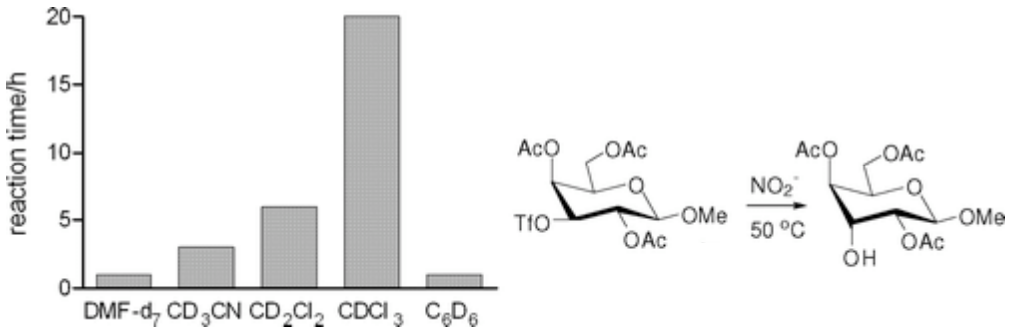
- Neutral Directional Electrostatic Interaction
- Directionality vs. Strength
- dielectric constant of the solvent- charge separation
- geometry of different lone pair electrons

Mode of Anion Recognition Chemistry: Hydrogen Bonding

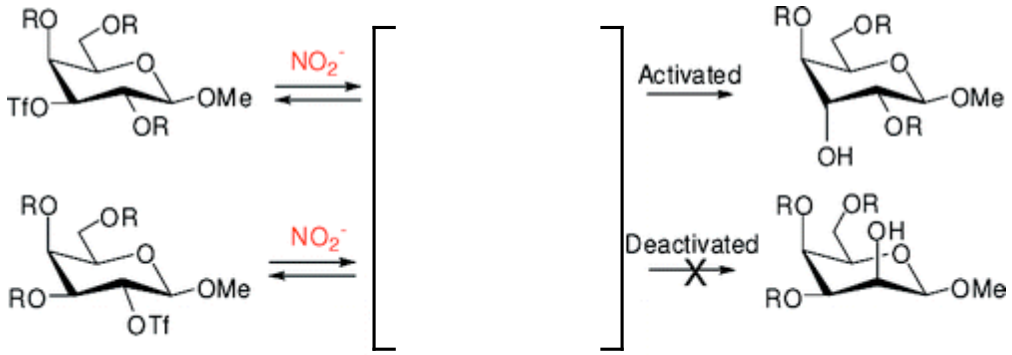
- Neutral Directional Electrostatic Interaction
- Directionality vs. Strength
- dielectric constant of the solvent- charge separation
- geometry of different lone pair electrons
- essentially a number's game

Mode of Anion Recognition Chemistry: Hydrogen Bonding

- Follows typical S_N2 profile until using very non-polar solvent

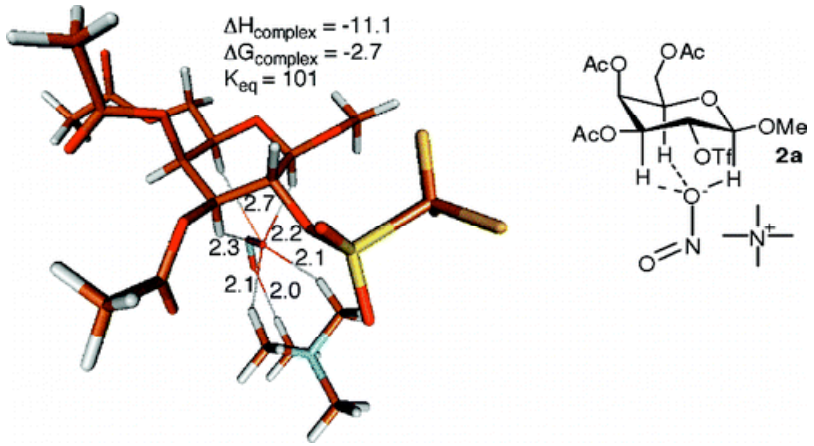


- Stereochemistry of the triflate and the anomeric position is very important

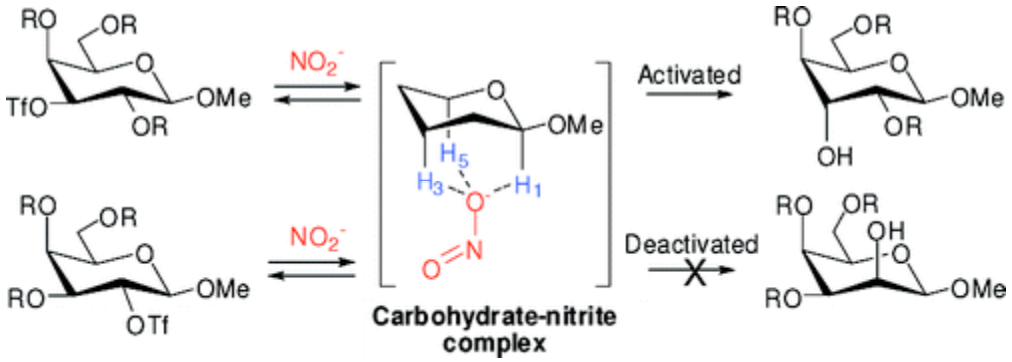


Mode of Anion Recognition Chemistry: Hydrogen Bonding

- DFT and NMR Titration indicate nitrite binding event: "Three point landing surface"



- Stereochemistry of the triflate and the anomeric position is very important



Dong, H.;Rahm, M.; Tore Brinck, T.; Olof Ramström, O. *J. Am. Chem. Soc.*, **2008**, *130*, 15270

*Mode of Anion Recognition Chemistry: Charge * H-bond*

- Additive effect: electrostatic interaction supplemented by
  positioning of the charge in space for a cumulative effect

Modes of Anion Recognition Chemistry: Electrostatic Interaction of Charged Species

- Non-directonal: tunablity? Coulomb's law

Modes of Anion Recognition Chemistry: Electrostatic Interaction of Charged Species

- Non-directonal: tunablity? Coulomb's law
- Solvation ?

Modes of Anion Recognition Chemistry: Electrostatic Interaction of Charged Species

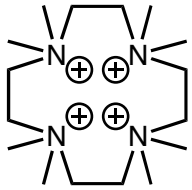
- Non-directonal: tunablity? Coulomb's law
- Solvation ?
- Can be combined with hydrogen bonding: pH issue

Modes of Anion Recognition Chemistry: Electrostatic Interaction of Charged Species

- Non-directonal: tunablity? Coulomb's law
- Solvation ?
- Can be combined with hydrogen bonding: pH issue
- Require strategic placement of cationic species within the same manifold: counterion

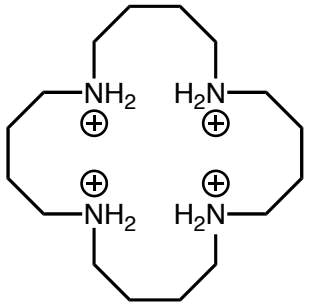
*Mode of Anion Recognition Chemistry: Charge * H-bond*

- Example: binding of tetracationic species in water



does not bind to $Co(CN)_6^{3-}$

Vs.



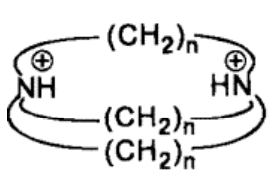
Binds effectively to $Co(CN)_6^{3-}$

- charge density itself does not induce anion binding
- Size is not the main issue
- favorable entropy in both case

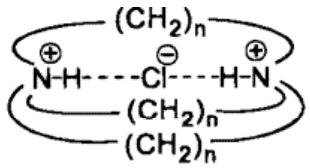
⇨ Directional hydrogen bonding in the salt bridge formation is the main enthalpy driving force

*Mode of Anion Recognition Chemistry: Charge * H-bond*

- First isolated example of anion encapsulation by organic ligand



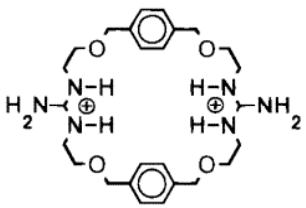
n = 9, 10

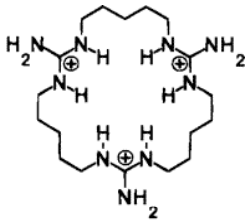


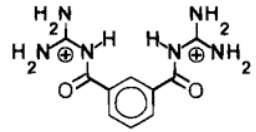
Park, C.H.; Simmons, H. E. *J. Am. Chem. Soc.* **1968**, *90*, 2431.

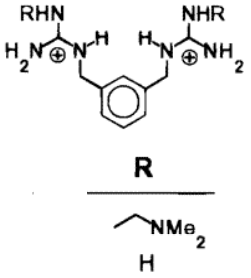
*Mode of Anion Recognition Chemistry: Charge * H-bond*

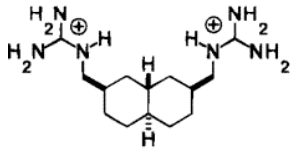
- Protonated Nitrogen species: Extensively used in anion binding hosts

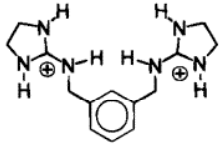








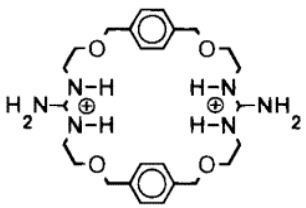


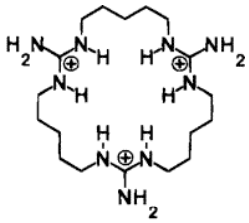


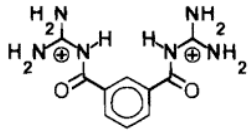
Dietrich, B.; Fyles, D. L.; Fyles, T. M.; Lehn, J. M.
Helv. Chim. Acta **1979**, *62*, 2763.

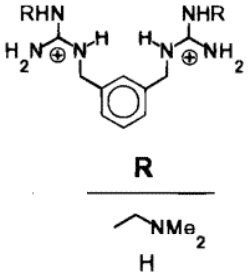
*Mode of Anion Recognition Chemistry: Charge * H-bond*

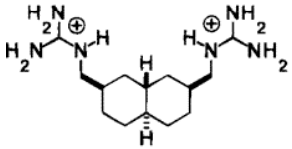
- Protonated Nitrogen species: Extensively used in anion binding hosts

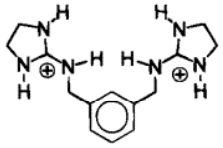


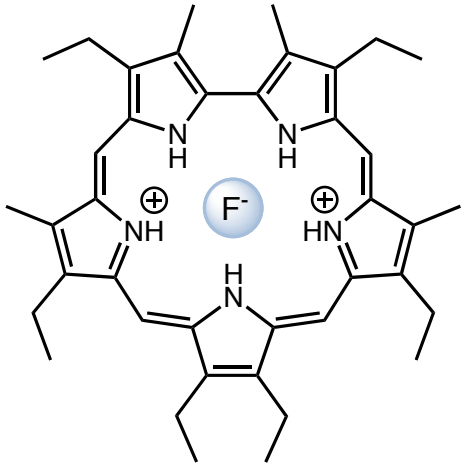












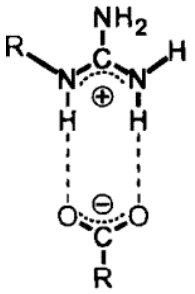
$K_{assn} = 1 * 10^5\ M^{-1}$ in MeOH

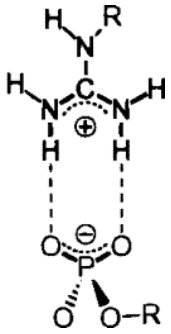
Dietrich, B.; Fyles, D. L.; Fyles, T. M.; Lehn, J. M. *Helv. Chim. Acta* **1979**, *62*, 2763.

Shinoya, M.; Furuta, H.; Lynch, V.; Harriman, A.; Sessler, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 5714.

*Mode of Anion Recognition Chemistry: Charge * H-bond*

- Guaniudinium moiety: Unique directionally charged H-bond donor

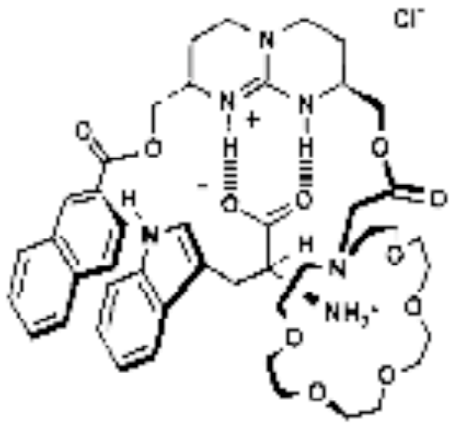




- 2-point binding possible: used extensively in nature-arginine

*Mode of Anion Recognition Chemistry: Charge * H-bond*

- Guaniudinium moiety: Asymmetric recognition



- Guanidinium is responsible for 50% of binding
- aza-crown is 33% and π-π interaction accounts for 17%
- L-isomer can be recognized in 80% ee

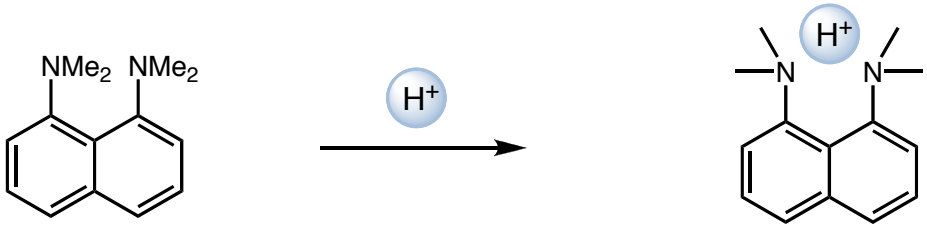
Galán, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; De Mendoza, J. *J. Am. Chem. Soc.* **1992**, *114*, 1511.

Mode of Anion Recognition Chemistry: Lewis Acid-Base Interaction

- Neutral Directional Electrostatic Interaction
- Directionality vs. Strength
- Can utilize the interplay of different type of molecular properties: stereoelectronics, orbtial symmetry, HSAB concept, Back bonding
- Solvation even more important: solvents tend to be Lewis base
- essentially a number's game

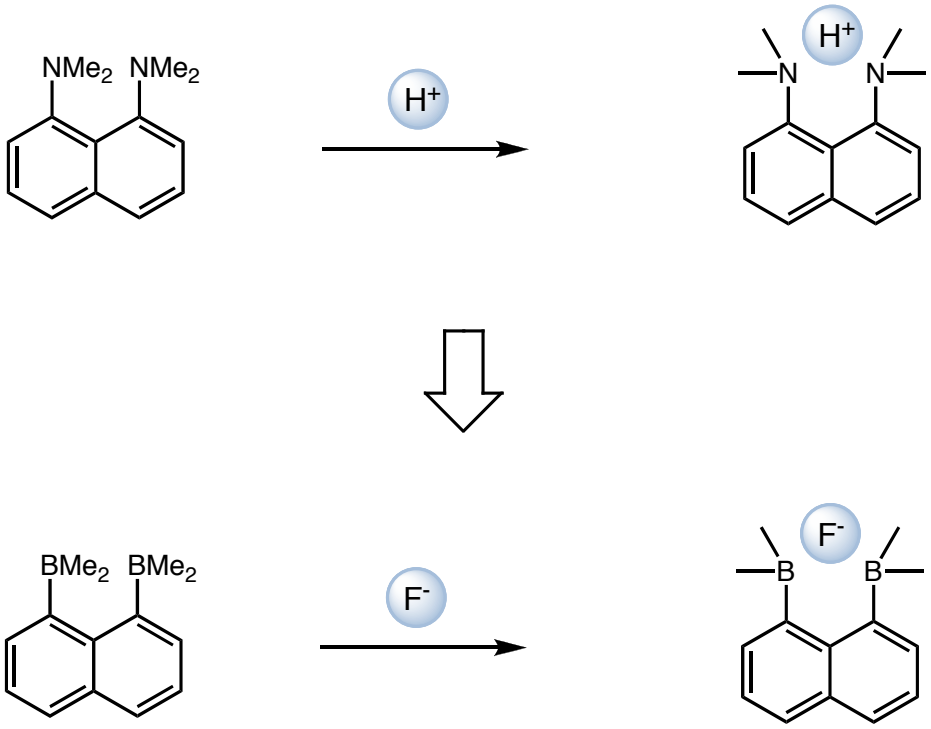
Mode of Anion Recognition Chemistry: Lewis acid Hosts

- *Anti*-Proton Sponge



Mode of Anion Recognition Chemistry: Lewis acid Hosts

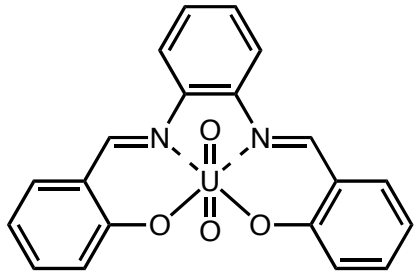
- *Anti*-Proton Sponge



Katz, H. E. *J. Am. Chem. Soc.* **1986**, *108*, 7460.

Mode of Anion Recognition Chemistry: Lewis acid Hosts

- *Salen* Complexes: Lewis acid with tunable ligands



K_{assoc}, M^{-1}

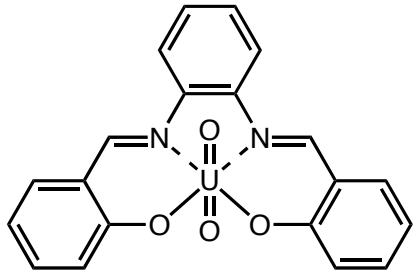
Cl^- = 400
$H_2PO_4^-$ = 14000
HSO_4^- = 50

at r.t.

Rudkevich, D. M.; Stauthamer, W. R. P.; Verboom, W.; Engbersen, J. F. J. Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 9671.

Mode of Anion Recognition Chemistry: Lewis acid Hosts

- *Salen* Complexes: Lewis acid with tunable ligands



- selectivity increases with raising temperature: look at the numbers.

K_{assoc}, M^{-1}	ΔH	ΔS
Cl^- = 400	9.9 Kcal/ mol	84 eu
$H_2PO_4^-$ = 14000	7.1 Kcal/ mol	99 eu
HSO_4^- = 50		

at r.t.

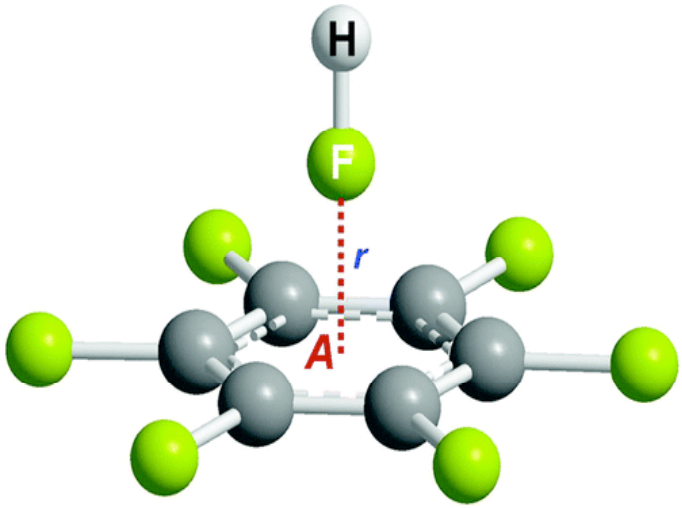
- entropy overrides 3 Kcal/ mol

Rudkevich, D. M.; Stauthamer, W. R. P.; Verboom, W.; Engbersen, J. F. J. Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 9671.

Rudkevich, D. M.; Verboom, W.; Brzozka, Z.; Paly, M. J.; Stauthamer, W. R. P.; van Hummel, G. J. ; Franken, S.; Harkema, S.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 4341.

Mode of Anion Recognition Chemistry: anion-π interaction

■ Electrostatic Interaction: Remember cation-π interaction?



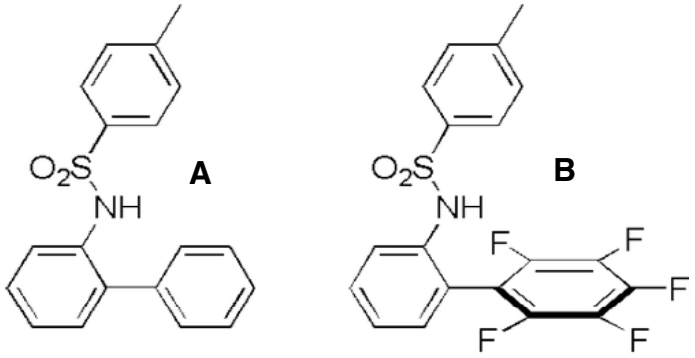
r = 3.127 Å

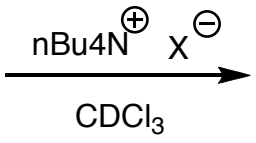
E = - 1.23 Kcal/mol : equivalent to typical H-bonding in enzyme pockets

Alkorta, I.; Rozas, I.; Elguero, J. *J. Org. Chem.*, **1997**, *62*, 4687

Mode of Anion Recognition Chemistry: anion-π interaction

- How much role does can it really play?





	A	B
Cl-	<1	30
Br-	<1	20
I-	<1	34

- It's pretty important

Berryman, O. B.; Hof, F.; Hynes, M. J.; Johnson, D. W. *Chem. Commun.* **2006**, 506

Anion Recognition Chemistry: anion-π interaction in biology

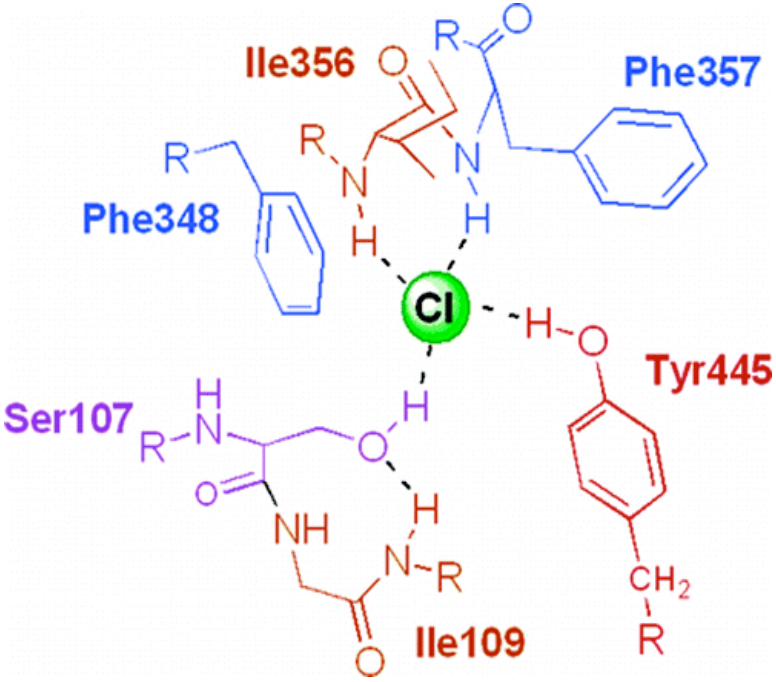
- Chloride ion channels are essential for living forms.
- Of the 6 amino acid present at the binding site, 3 are contain aromatic group.

"...It is noteworthy that in the Cl^- channel the ion does not make direct contact with a full positive charge from lysine or arginine residues… We suggest that a full positive charge would create a deep energy well and cause a Cl^- ion to bind too tightly..."

Dutzler, R.; Campbell, E. B.; Cadene, M.; Chait, B.T.; MacKinnon, R. *Nature*, **2002**, *415*, 287

Anion Recognition Chemistry: anion-π interaction in biology

- Chloride ion channels are essential for living forms.
- Of the 6 amino acid present at the binding site, 3 are contain aromatic group.

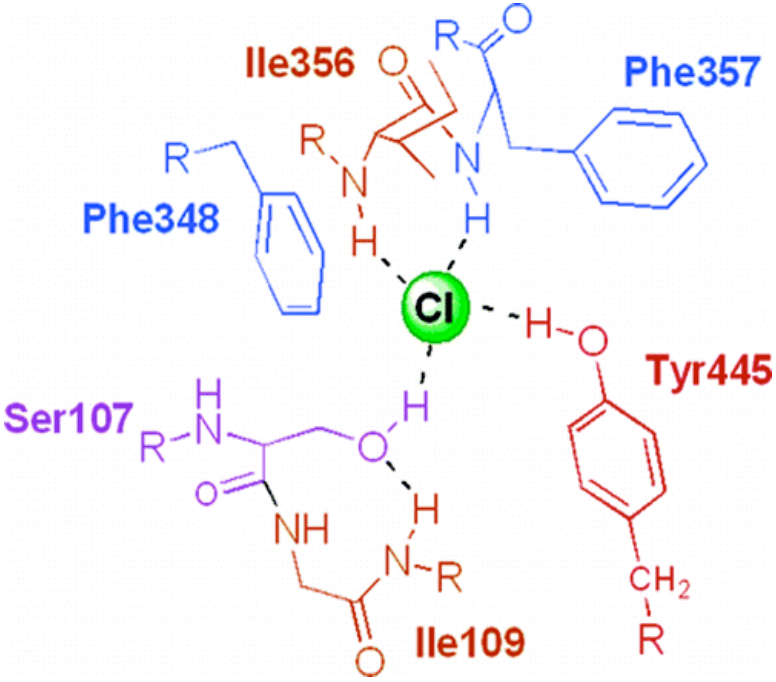


"...It is noteworthy that in the Cl^- channel the ion does not make direct contact with a full positive charge from lysine or arginine residues… We suggest that a full positive charge would create a deep energy well and cause a Cl^- ion to bind too tightly..."

Dutzler, R.; Campbell, E. B.; Cadene, M.; Chait, B.T.; MacKinnon, R. *Nature*, **2002**, *415*, 287

Anion Recognition Chemistry: anion-π interaction in biology

- Chloride ion channels are essential for living forms.
- Of the 6 amino acid present at the binding site, 3 are contain aromatic group.



"...It is noteworthy that in the Cl^- channel the ion does not make direct contact with a full positive charge from lysine or arginine residues… We suggest that a full positive charge would create a deep energy well and cause a Cl^- ion to bind too tightly..."

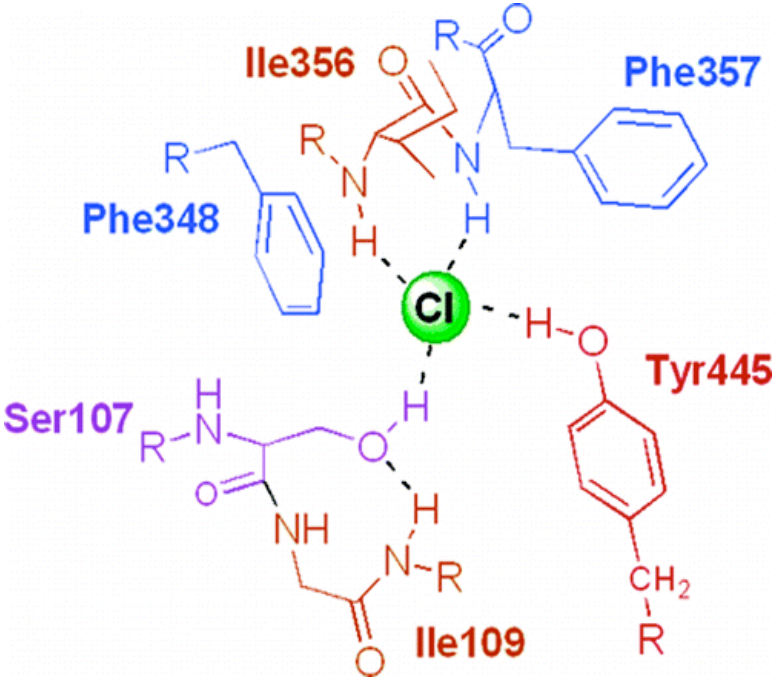
Dutzler, R.; Campbell, E. B.; Cadene, M.; Chait, B.T.; MacKinnon, R. *Nature*, **2002**, *415*, 287

"...Therefore, the phenyl rings(especially, Phe348) may play a role in the chloride recognition."

Gamez, P.; Mooibroek, T. J.; Teat, S. J. Reedijk, J. *Acc, Chem. Res.*, **2007**, *40*, 435.

Anion Recognition Chemistry: anion-π interaction in biology

- Chloride ion channels are essential for living forms.
- Of the 6 amino acid present at the binding site, 3 are contain aromatic group.



"...It is noteworthy that in the Cl^- channel the ion does not make direct contact with a full positive charge from lysine or arginine residues… We suggest that a full positive charge would create a deep energy well and cause a Cl^- ion to bind too tightly..."

Dutzler, R.; Campbell, E. B.; Cadene, M.; Chait, B.T.; MacKinnon, R. *Nature*, **2002**, *415*, 287

"...Therefore, the phenyl rings(especially, Phe348) may play a role in the chloride recognition."

Gamez, P.; Mooibroek, T. J.; Teat, S. J. Reedijk, J. *Acc, Chem. Res.*, **2007**, *40*, 435.

- It is suggested that anion-π interaction might be utilized as extensively as cation-π interaction in biology

Anion Recognition Chemistry: Renewed Look

- One of the fundamental reaction motifs in biological catalysis
- Confined to the area of supramolecular chemistry for sensing purposes
- More or less overlooked by synthetic chemists
- Has great potential to be exploited as a general activation mode
- Still needs deeper understanding of fundamental issues involved especially the kinetic aspect