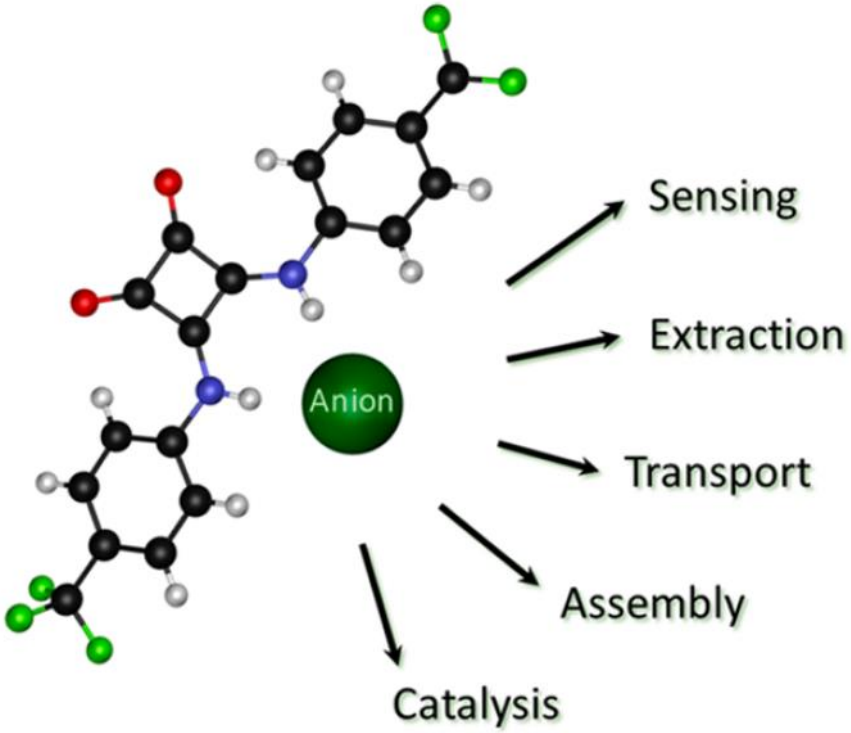
Anion Receptors

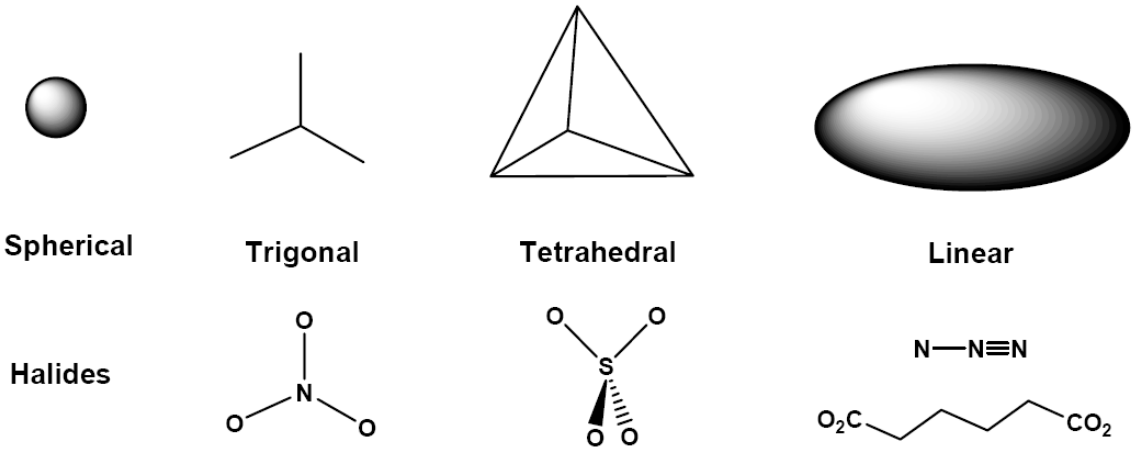


‘Applications of Supramolecular Anion Recognition’
P. Gale et al., *Chem Rev.* **2015**, *115*, 8038.

Anion Recognition – General Considerations

- Due to their negative charge, anions are **larger** than cations within the same periodic row, and in multiple atom anions this effect is magnified considerably. For example, one of the smallest anions, F^-, is comparable in ionic radius to K^+ (1.33 Å versus 1.38 Å).

- Most anions do consist of multiple atoms, and so there are **many shapes** in addition to size issues.



The geometry of the receptor should mach the geometry of the anion.

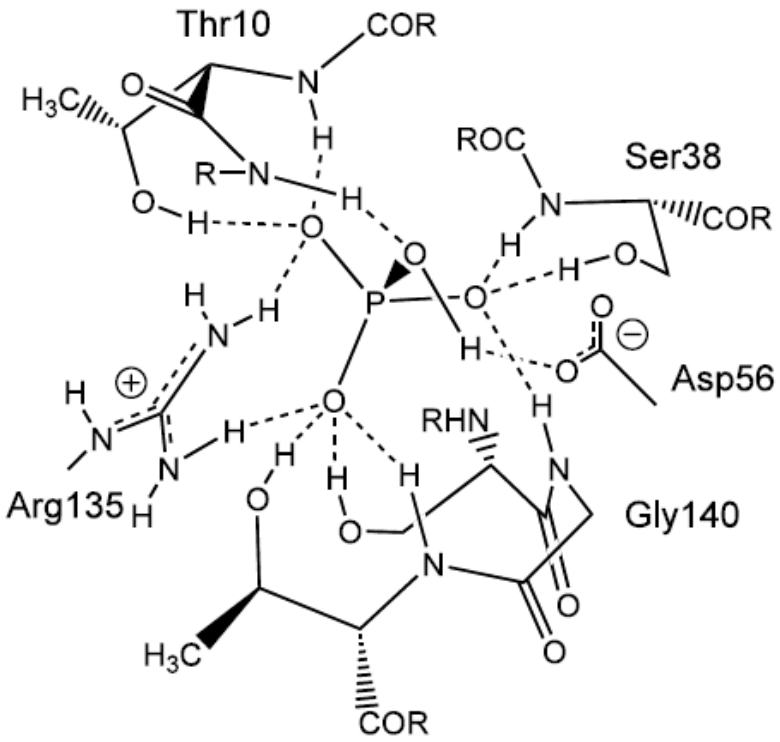
Anion Recognition – General Considerations

- 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. $\Delta G_{hydration}(F^-) = -465$ k*J*mol^{-1}, $\Delta G_{hydration}(K^+) = -295$ k*J*mol^{-1}.

- Anions can also form acids, for example, especially the the oxo acids, and thus the form of the anion can be very **pH dependent**.

Ion	Radius (Å)	$\Delta G_{hydration}$ (kJmol^{-1})
F^-	1.33	- 465
Cl^-	1.81	- 340
Br^-	1.95	- 315
I^-	2.16	- 275
ClO_4^-	2.50	- 430
NO_3^-	1.79	- 300
CO_3^{2-}	1.78	- 1315
SO_4^{2-}	2.30	- 1080
PO_4^{3-}	2.38	- 2765
$H_2PO_4^-$	2.00	- 465
$PdCl_6^{2-}$	3.19	- 695
Na^-	2.2	n/a
Cs^-	3.5	n/a
Li^+	0.69	- 475
Na^+	1.02	- 365
K^+	1.38	- 295
Cs^+	1.70	- 250
Ca^{2+}	1.00	- 505
Zn^{2+}	0.75	- 1955

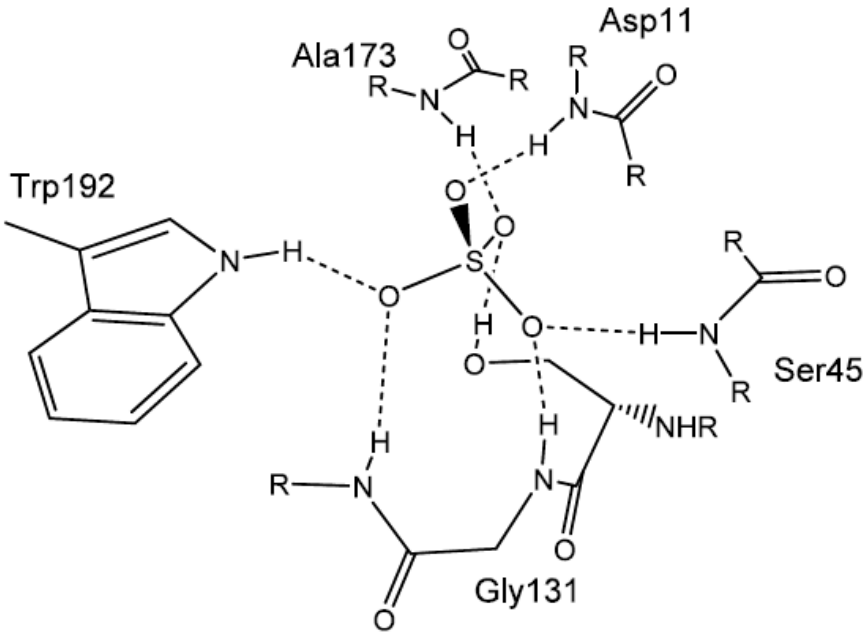
Nature's Way: a Phosphate Binding Protein



- Phosphate binding protein from *E. coli.*
- The anion is bound by **12 hydrogen bonds** in a deep cleft in the protein and is completely desolvated.
- K_a = 1 x 10^6 M^{-1}. **No binding of sulfate** because it can not bind to Asp56.

F. A. Quiocho et al., *Nature* **1990**, *347*, 402.

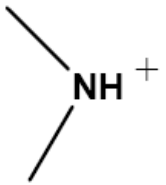
Nature's Way: a Sulfate Binding Protein



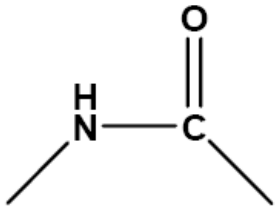
- Sulfate binding protein from *S. typhimurium.*
- The anion is bound by **7 hydrogen bonds** in a deep cleft in the protein and is completely desolvated.
- K_a = 8 x 10^6 M^{-1} for sulfate and 17 M^{-1} for phosphate (lack of hydrogen bond acceptor sites!)

F. A. Quiocho et al., *Nature* **1985**, *314*, 257.

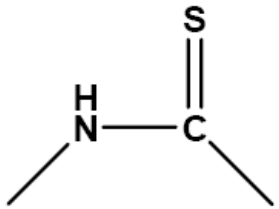
Recognition Elements: H Bonding



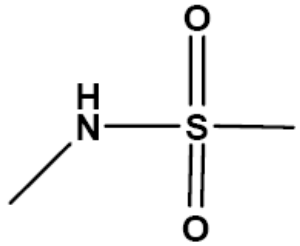
Ammoniums



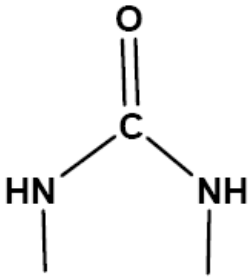
Amides



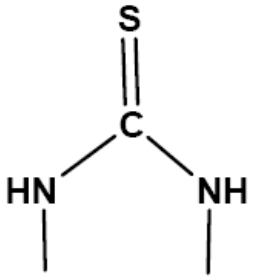
Thioamides



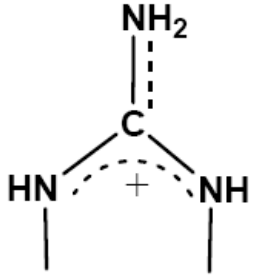
Sulfonamides



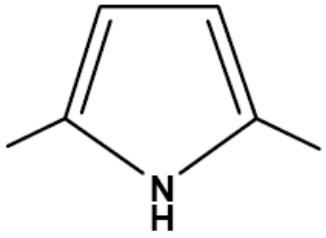
Ureas



Thioureas

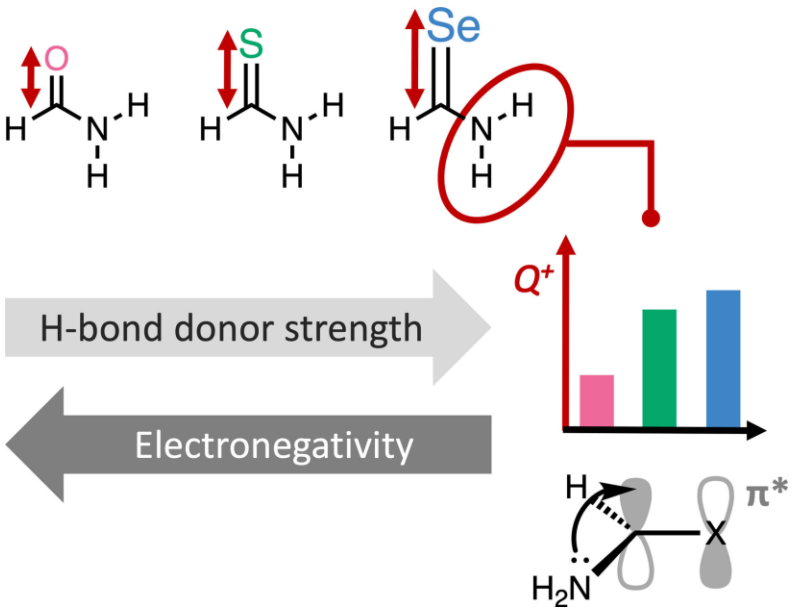


Guanidiniums



Pyrroles

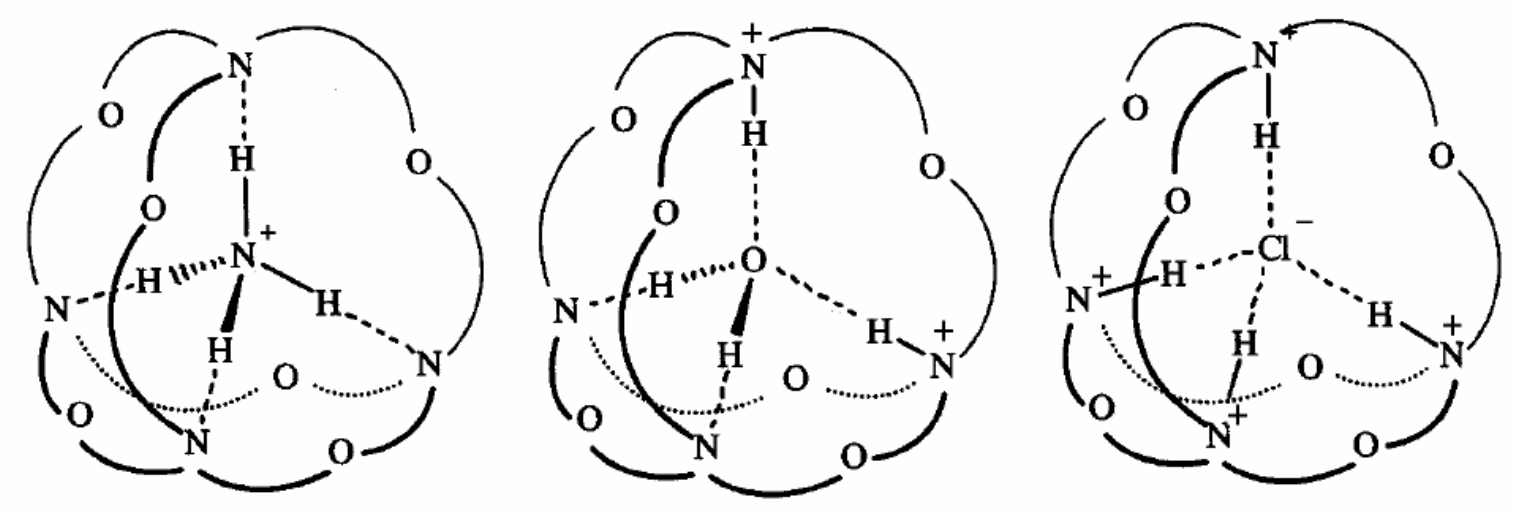
Carboxamides *vs.* Thioamides *vs.* Selenoamides



Thioamides and selenoamides are better hydrogen-bond donors than carboxamides because their amino groups are more positively charged. Quantum chemical analyses explain that counterintuitive phenomenon: Weaker π interaction for S and Se → lower *C=S and π*C=Se levels compared to π*C=O. These energetically lower-lying orbitals can accept more electron density from the nitrogen lone pair of the NH_2 group.

C. Nieuwland, C. Fonseca Guerra, *Chem. Eur. J.* **2022**, *28*, e202200755.

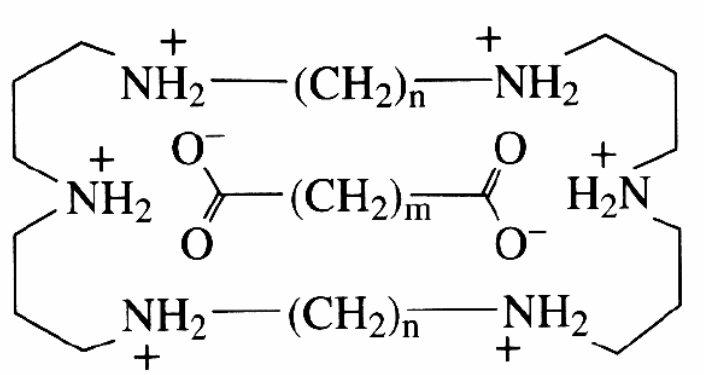
From Cation Receptors to Anion Receptors
A Simple Change in pH

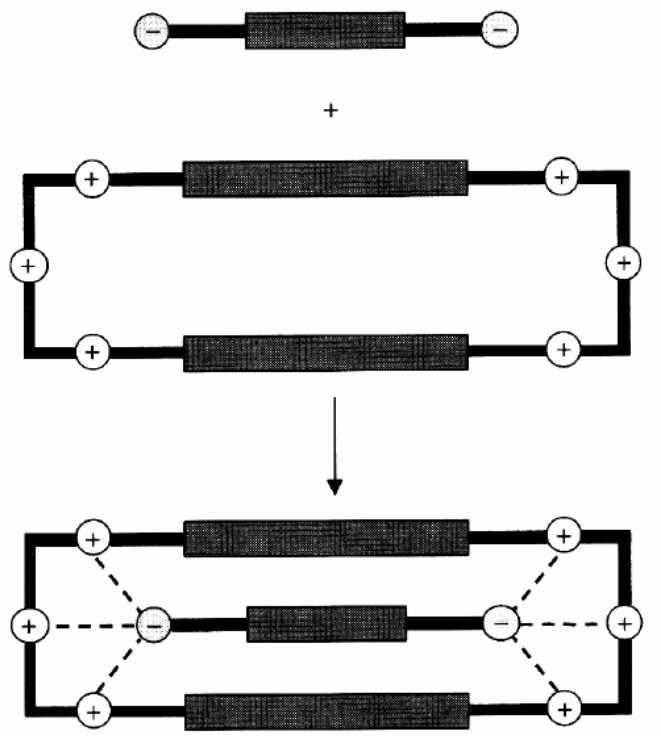


Charge: **1+** **2+** **3+**

Tetrahedral recognition: a cryptand as a receptor for ammonium ion, water or chloride, depending on the pH of the medium.

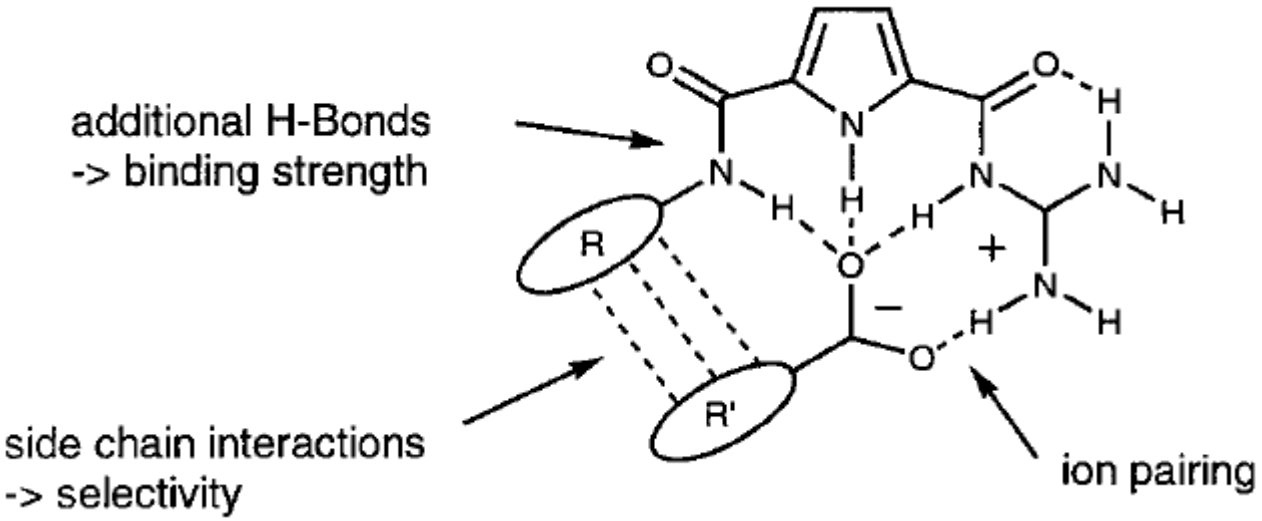
Two Domain Binding Receptors





Host-dependent selectivity for dicarboxylic acids.

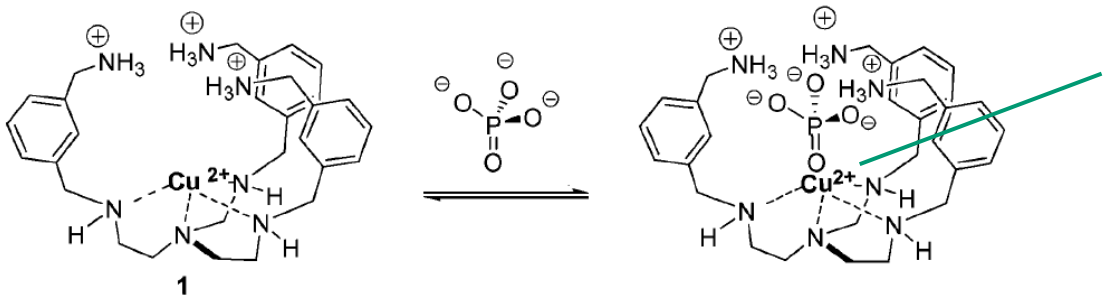
Hydrogen-Bond Receptors for Carboxylic Acids



The 2-(Guanidiniocarbonyl)pyrrole receptors can be used to bind carboxyles in water (K ~ 10^2 – 10^3 M^{-1})

C. Schmuck, *Chem. Eur J.* **2000**, *6*, 709.

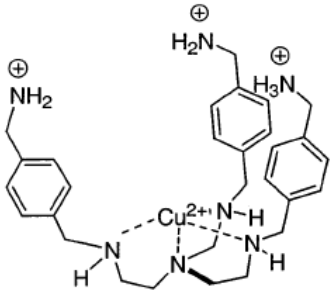
Transition Metal Containing Receptors

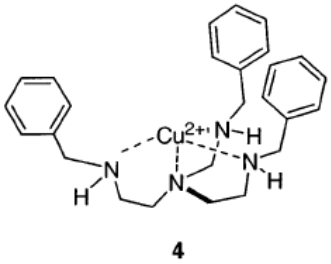


Binding affinity dominated by Cu^{2+}-phosphate interaction

receptor	anion[a]	stoichiometry anion:**1**	binding constants[b] (M^{-1})
1	HPO_4^{2-}	1:1	2.5×10^4 ($\pm 6 \times 10^2$)
1	$HAsO_4^{2-}$	1:1	2.5×10^4 ($\pm 6 \times 10^2$)
1	ReO_4^-	1:1	2.0×10^3 ($\pm 7 \times 10^2$)
1	AcO^-	1:1	<900
1	NO_3^-	1:1	<20
1	HCO_3^-	2:1	n.d.[c]
1	Cl^-	2:1	n.d.
1	SO_4^{-2}	n.d.	n.d.
3	HPO_4^{2-}	1:1	8.0×10^3 ($\pm 7 \times 10^2$)
3	$HAsO_4^{2-}$	1:1	9.0×10^3 ($\pm 7 \times 10^2$)
4	HPO_4^{2-}	1:1	9.0×10^2 ($\pm 3 \times 10^2$)

[a] All counterions to the anions are sodium. [b] K_a values were determined from a curve fit analysis to UV/vis data collected as aliquots of analyte solution were added to an aqueous solution of **1** at pH 7.4 at 25 °C. [c] n.d. = not able to determine.

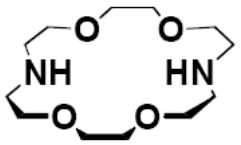




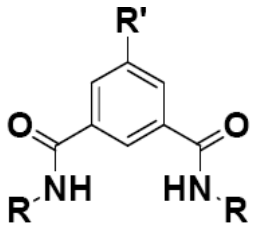
Control Complexes

E. V. Anslyn et al.
J. Am. Chem. Soc. **2003**, *125*, 4026.

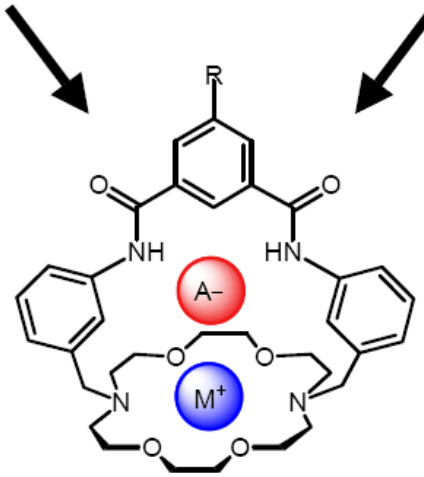
Receptors for Ion Pairs

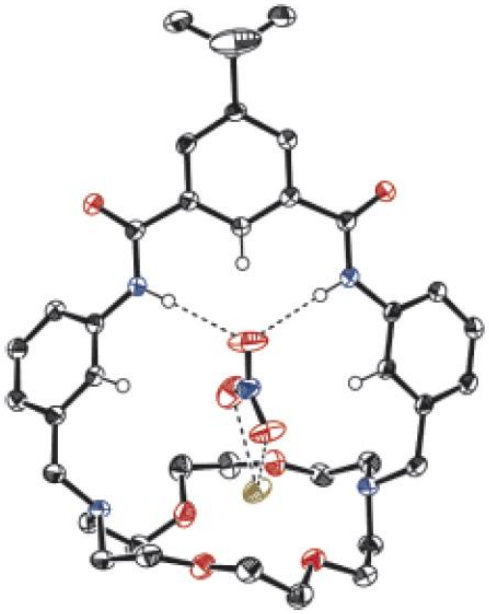


Cation Binding Pocket



Anion Binding Pocket





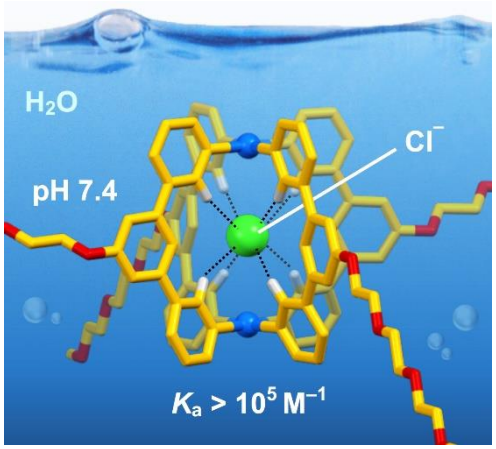
KNO_3 complex

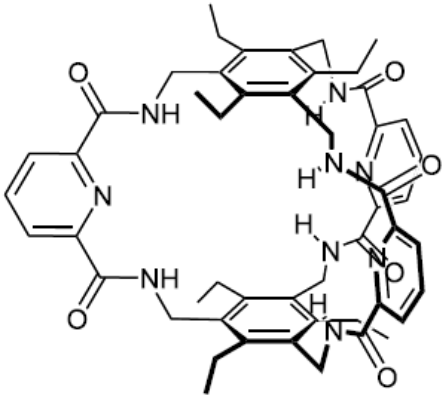
B. D. Smith et al., *J. Am. Chem. Soc.* **2005**, *127*, 2922.

Review: 'Recent Advancements in Ion-Pair Receptors'
R. Ali et al., *Chem Asian J.* **2023**, *18*, e202201080.

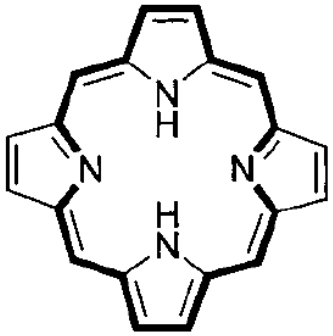
Selected Examples

Anion	Receptor
Fluoride	Sapphyrin
Chloride	Coordination Cage
Iodide	Cyclopeptide
Phosphate	Thiourea Cleft Molecule
Nitrate	Bicyclic Cyclophane

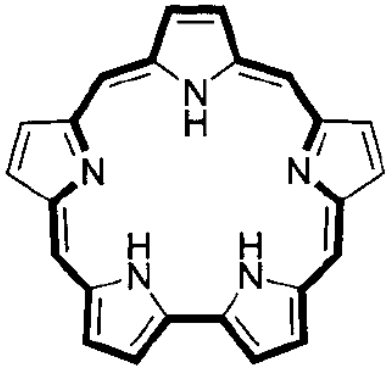




Fluoride Receptors – Sapphyrins



Porphyrin
4 pyrroles
4 bridging carbons
18 π-electron
aromatic core



Sapphyrin
5 pyrroles
4 bridging carbons
22 π-electron
aromatic core

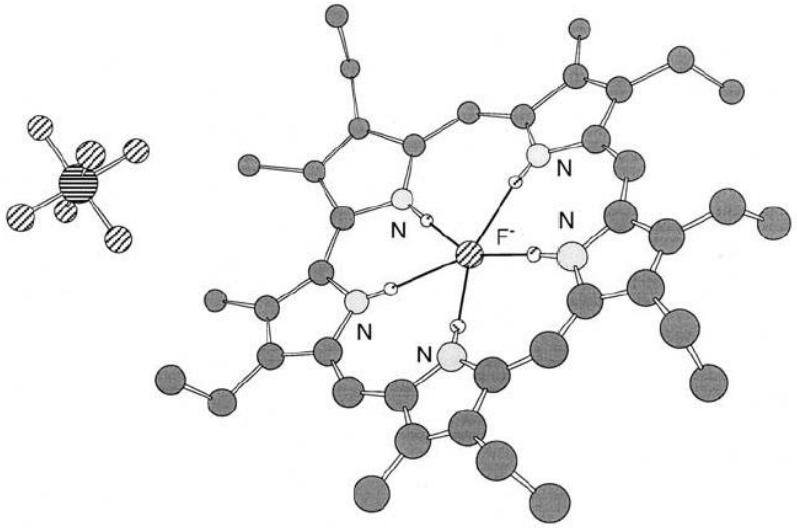
(only the core structure is shown)

- Discovered by accident in the early 1960s by R. Woodward.
- Was the first expanded porphyrin to be reported.
- More acidic than prophyrins.

‘Sapphyrins: versatile Anion Binding Agents’
J. L. Sessler et al, *Acc. Chem. Res.* **2001**, *34*, 989.

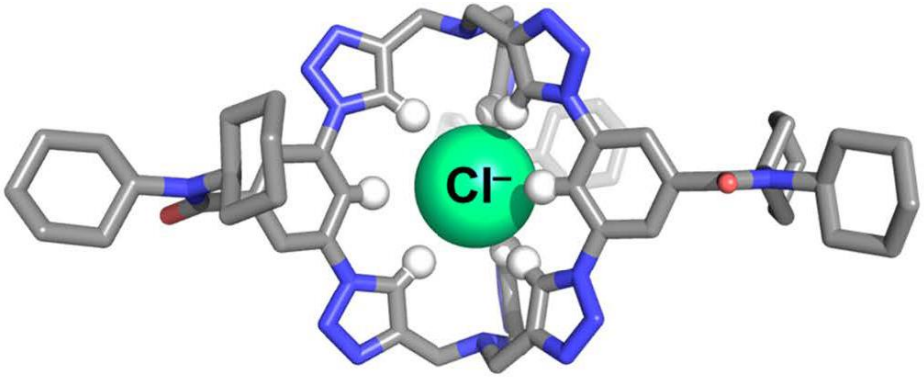
Fluoride Receptors – Sapphyrins

- 1990: a crystallographic analysis of a compound thought to be the bis HPF_6 adduct turned out be a F^- complex (see picture).
- Highly affinity and selective for F^-; Cl^- is too large and sits slightly above the plane.
- Is able to bind F^- in protic solvents such as MeOH (see table).



anion	$K\ (M^{-1})$
F^-	2.8×10^5
Cl^-	100
Br^-	<100

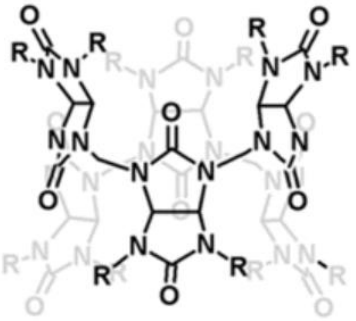
Chloride Receptors – Organic Solvent



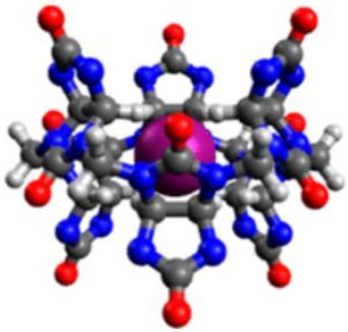
"Atto-molar affinity (10^{17} M^{-1}) was determined using liquid-liquid extractions of chloride from water into nonpolar dichloromethane solvents."

'Chloride capture using a C–H hydrogen bonding cage'
A. H. Flood et al, *Science* **2019**, *365*, 159.

Chloride Receptors – Water

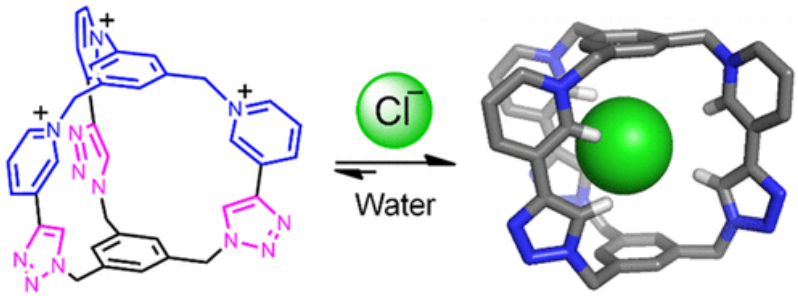


bambusuril



$K_a(Cl^-) = 1.2 \times 10^3\ M^{-1}$

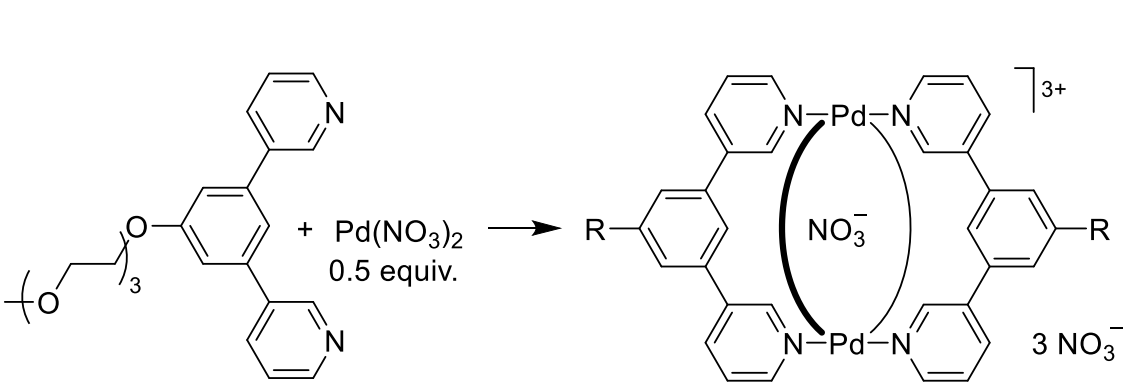
V. Sindelar et al., *J. Org. Chem.* **2018**, *83*, 1903.

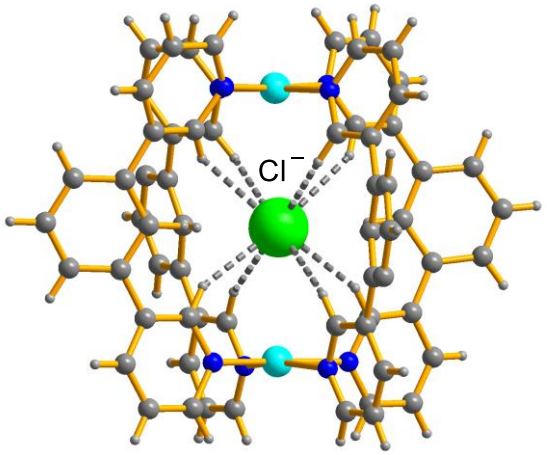


$K_a(Cl^-) = 26\ M^{-1}$

H. Li et al., *Org. Lett.* **2020**, *22*, 4878.

Chloride Receptors – A Coordination Cage

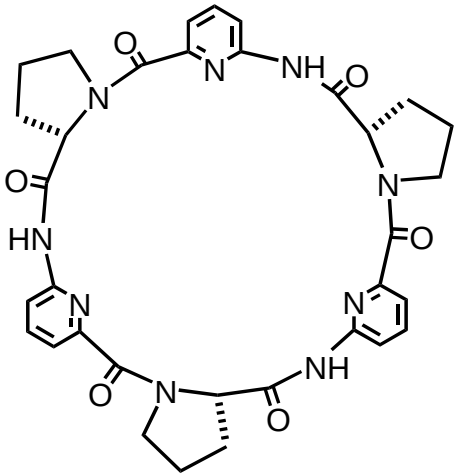


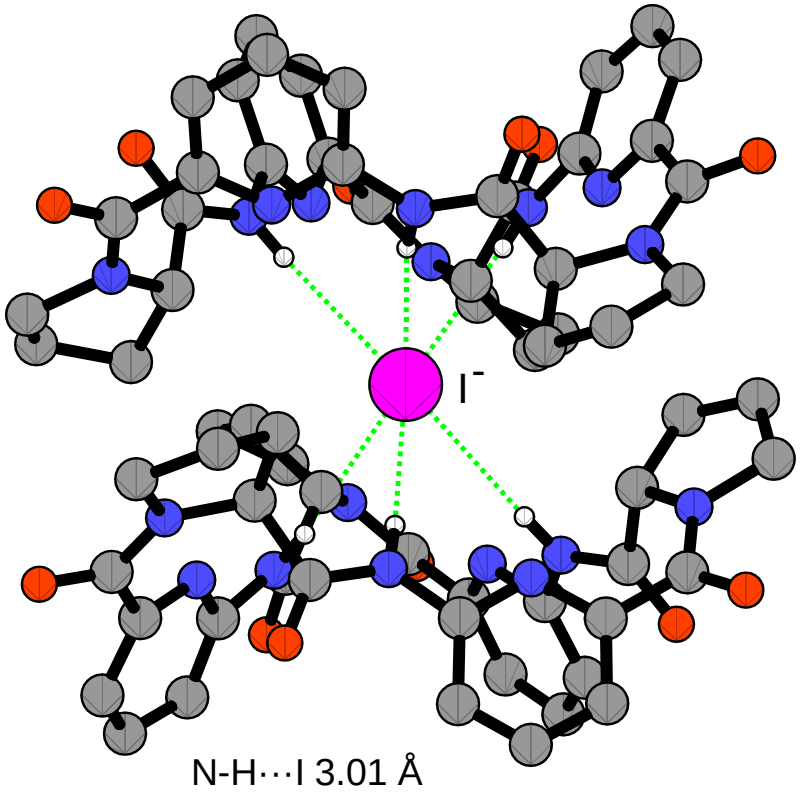


K_a = 1.8 x 10^5 M^{-1}

‘Synthetic Receptors with Micromolar Affinity for Chloride in Water’
K. Severin et al., *Angew. Chem. Int. Ed*. **2023**, *62*, e202218072.

Iodide Receptors – A Cyclopeptide

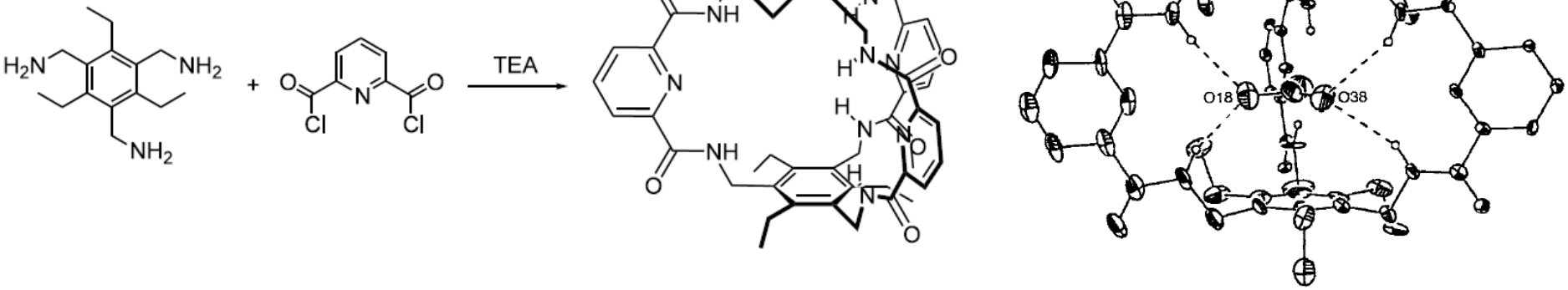




- Highly preorganized
- Binds iodide in 80 % H_2O !
- K_a = 150 M^{-1} (DMSO)
- Complexation is entropy driven (release of water molecules).

S. Kubik et al., *Angew. Chem. Int. Ed. Engl.* **2001**,*40*, 2648.

Nitrate Receptors – A Bicyclic Cyclophane

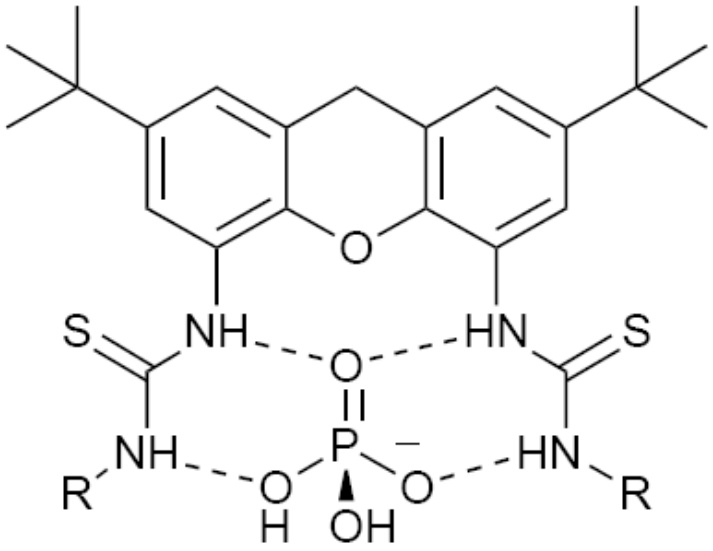


- Six amide hydrogens converge into the center of the molecule. The amide groups act as **neutral H-bond donors** to the anion π-electron system (not the oxygen lone pairs!).

- K_a = 300 M^{-1} for $(NBu_4)NO_3$ in 25% CD_2Cl_2/CD_3CN. Despite its relatively low basicity, nitrate showed enhanced binding due to the **size and shape complementarity** to the macrocycle.

E. V. Anslyn et al., *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2340.

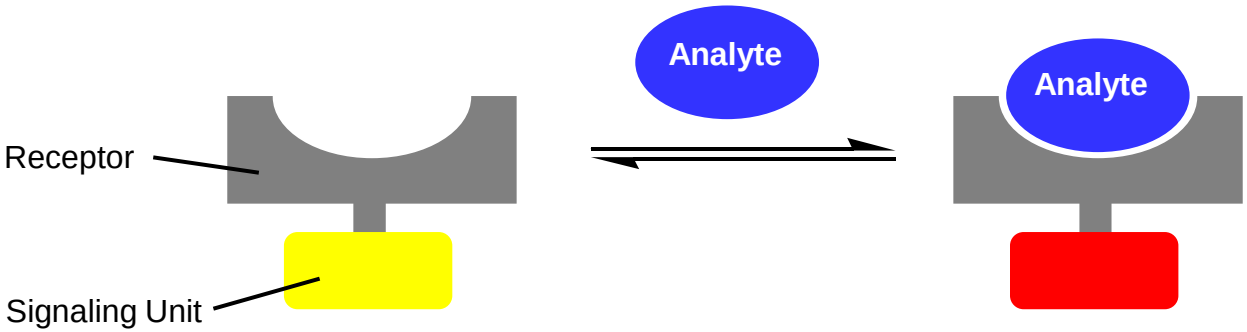
Phosphate Receptors – A Thiourea Cleft Molecule



- Urea and **thiourea are particularly good H-bond donors** and are excellent receptors for Y-shaped anions.
- The ayclic thiourea cleft molecule containing a xanthene spacer binds anions very strongly with stability constants up to 195 000 M^{-1} for $H_2PO_4^-$ ions in DMSO. This is a consequence of the **high degree of preorganization**.
- The selectivity for $H_2PO_4^-$ can be attributed to the complementary hydrogen-bonding array present in the cleft that can form **four hydrogen bonds** to each $H_2PO_4^-$ ion.

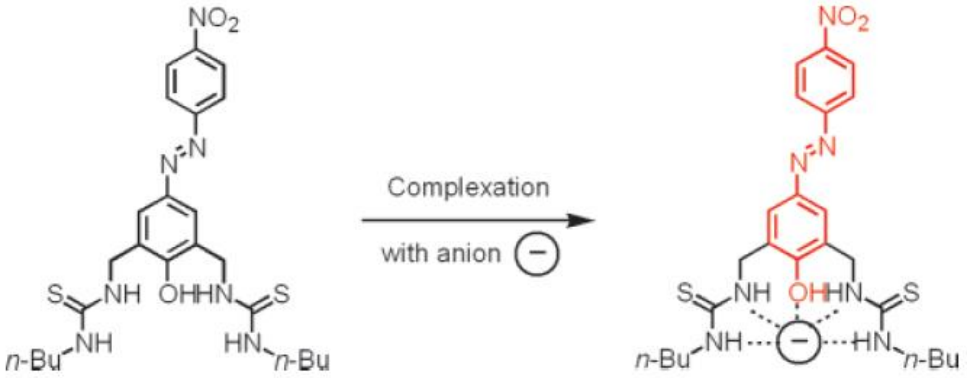
Y. Umezawa et al., *Tetrahedron* **1997**, *53*, 1647.

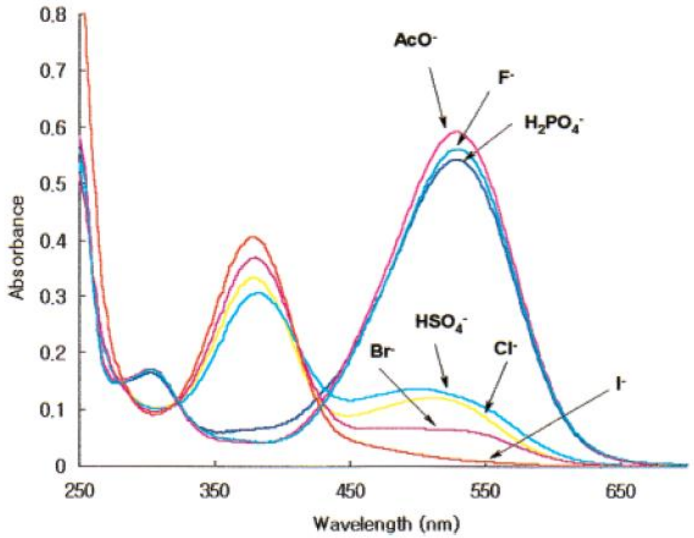
Chemosensors
The 'Classical' Approach



The complexation of the analyte to the receptor leads to a change of the optical or electrochemical properties of the signaling unit. The signaling unit can be attached to the receptor via some type of spacer (as shown) or can be an integral part of the receptor itself.

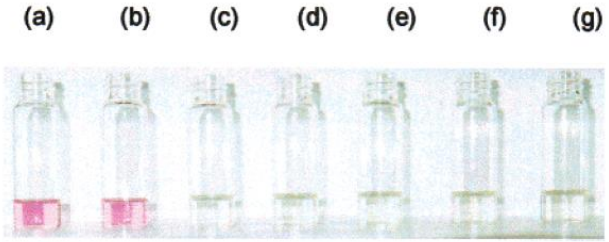
A Chromogenic Sensor





anion	$H_2PO_4^-$	AcO^- [b]	HSO_4^- [c]	Cl^- [c]	Br^- [c]	I^- [c]
K_a	2.6×10^4	1.9×10^4	4800	3000	2000	500

$CDCl_3$ at 20 °C

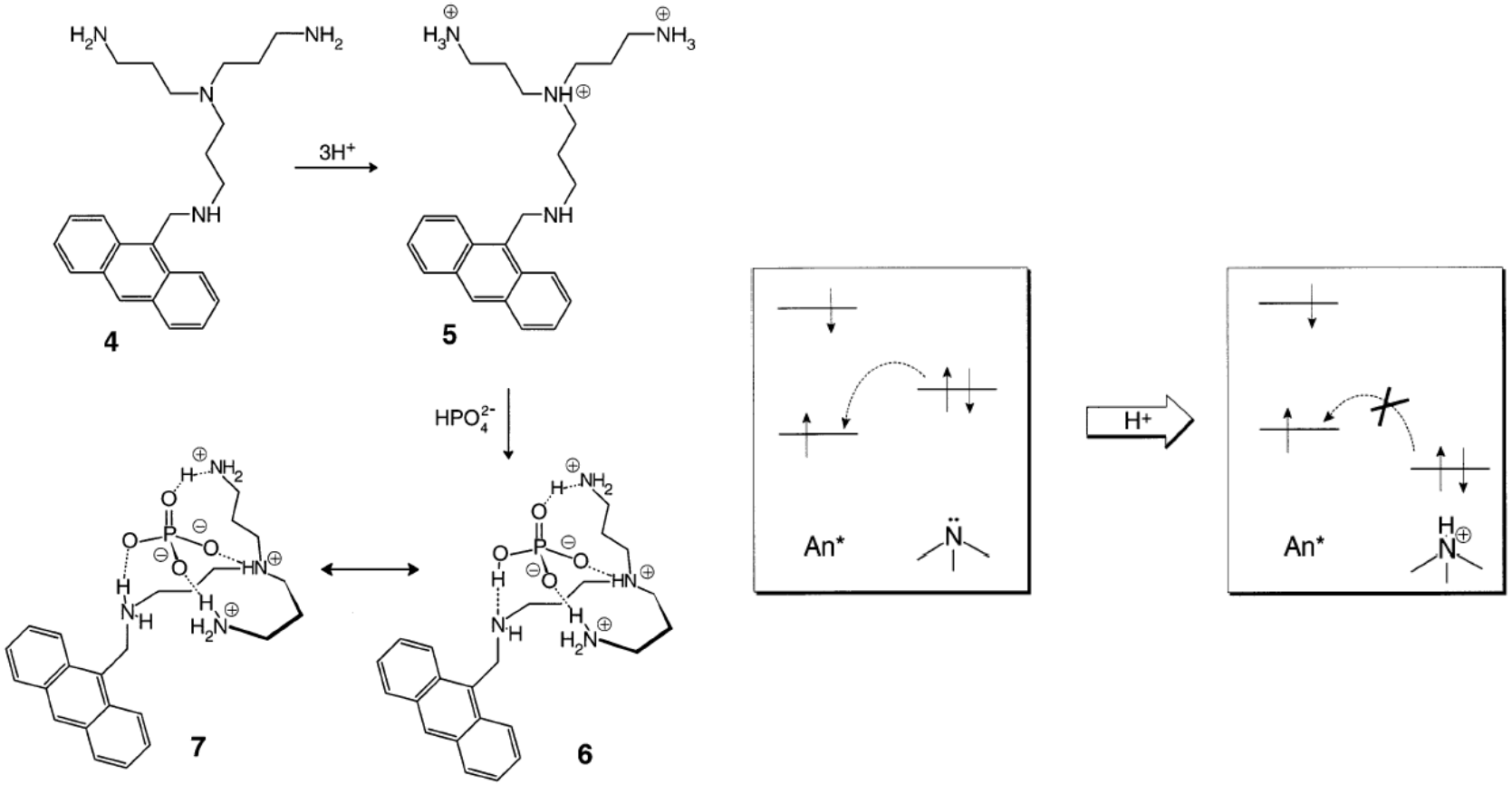


(a) $H_2PO_4^-$, (b) AcO^-

'An Azophenole-Based Chromogenic Anion Sensor'

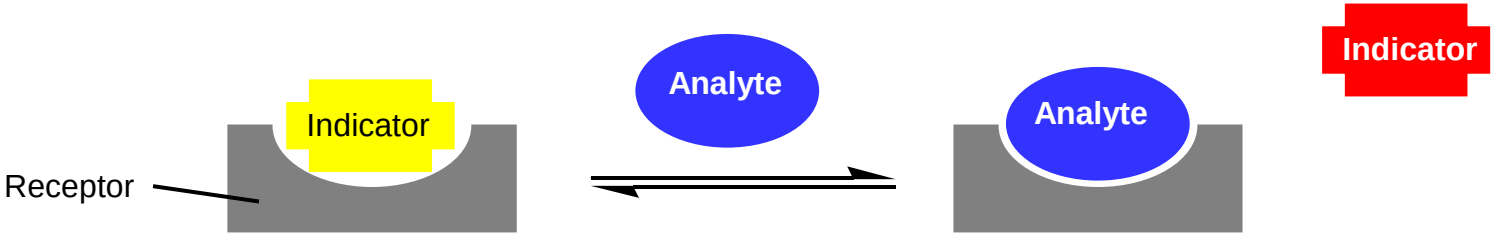
J.-I. Hong et al., *Org. Lett.* **2001**, *3*, 5.

A Fluorescence PET Sensor for Phosphate



Receptor **5** is poorly fluorescent, as an electron transfer process from the anthrylamine nitrogen atom quenches light emission. Following anion binding, the anthrylamine group is engaged in either hydrogen binding (**6**) or ammonium formation (**7**). In any case the eT process is suspended and recognition signaled through fluorescence revival.

Chemosensors
The Indicator Displacement Approach

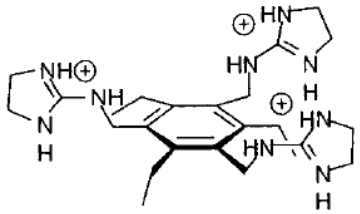


The complexation of the analyte to the receptor leads to a displacement of an indicator which then changes its optical properties.

‘Teaching Old Indicators New Tricks’

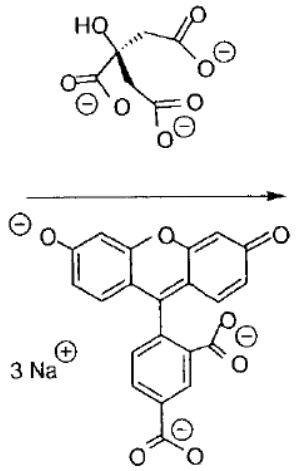
E. V. Anslyn et al., *Acc. Chem. Res.* **2001**, *34*, 963.

An Indicator Displacement Assay for Citrate

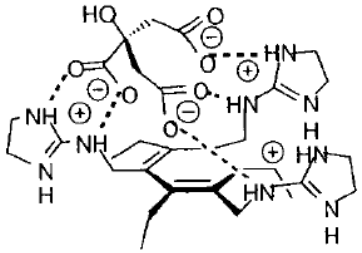


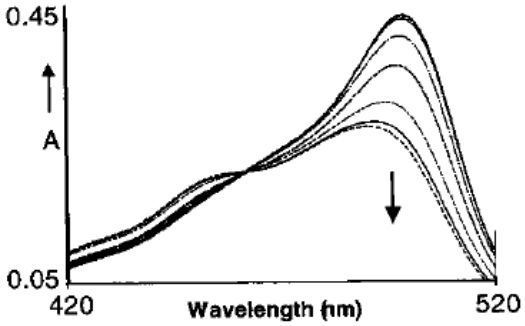
Preorganized receptor

Citrate

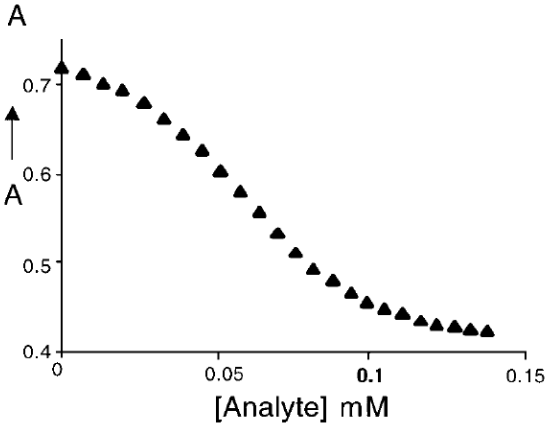


5-Carboxyfluorescein (Indicator)





UV-Vis Titration

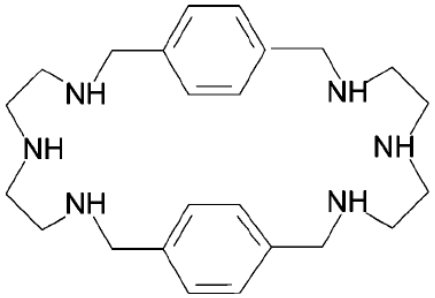


Calibration Curve

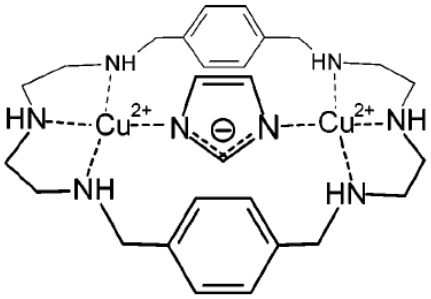
Was used to determine the citrate concentration in beverages such as Coca Cola and Gatorade

Angew. Chem. Int. Ed. **1998**, *37*, 649

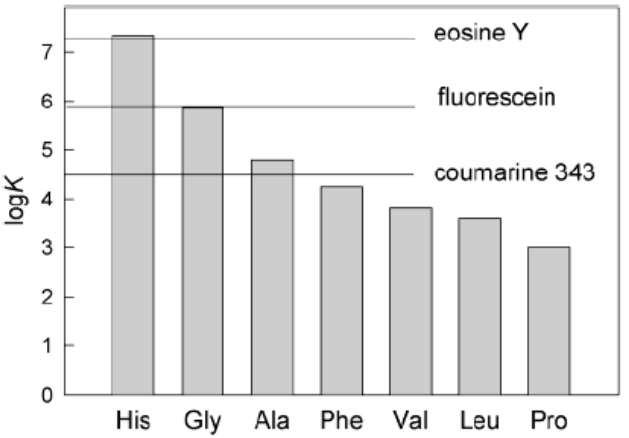
An Indicator Displacement Assay for Histidine



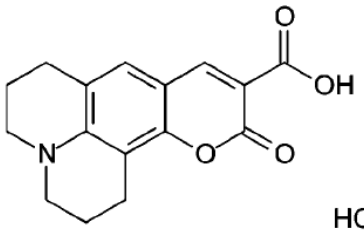
Macrocyclic receptor



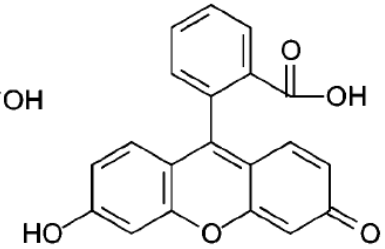
Cu(II) complex with high affinity for imidazole



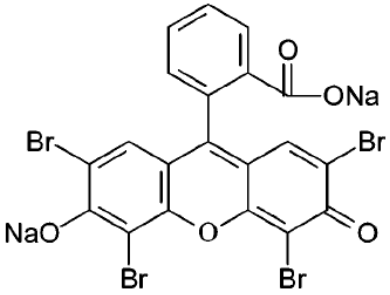
Equilibrium constants for the interaction of the receptor-Cu complex with selected natural amino acids (bars) and indicators (horizontal solid lines). The position of the horizontal line with respect to the bars determines the selectivity of the assay.



Coumarine 343



Fluorescein



Eosine Y

L. Fabbrizzi et al, *J. Am. Chem. Soc.*. **2003**, *125*, 20.