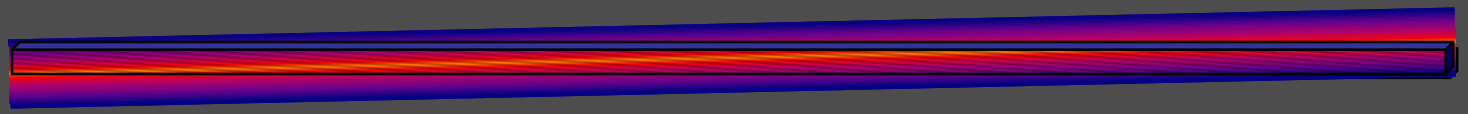
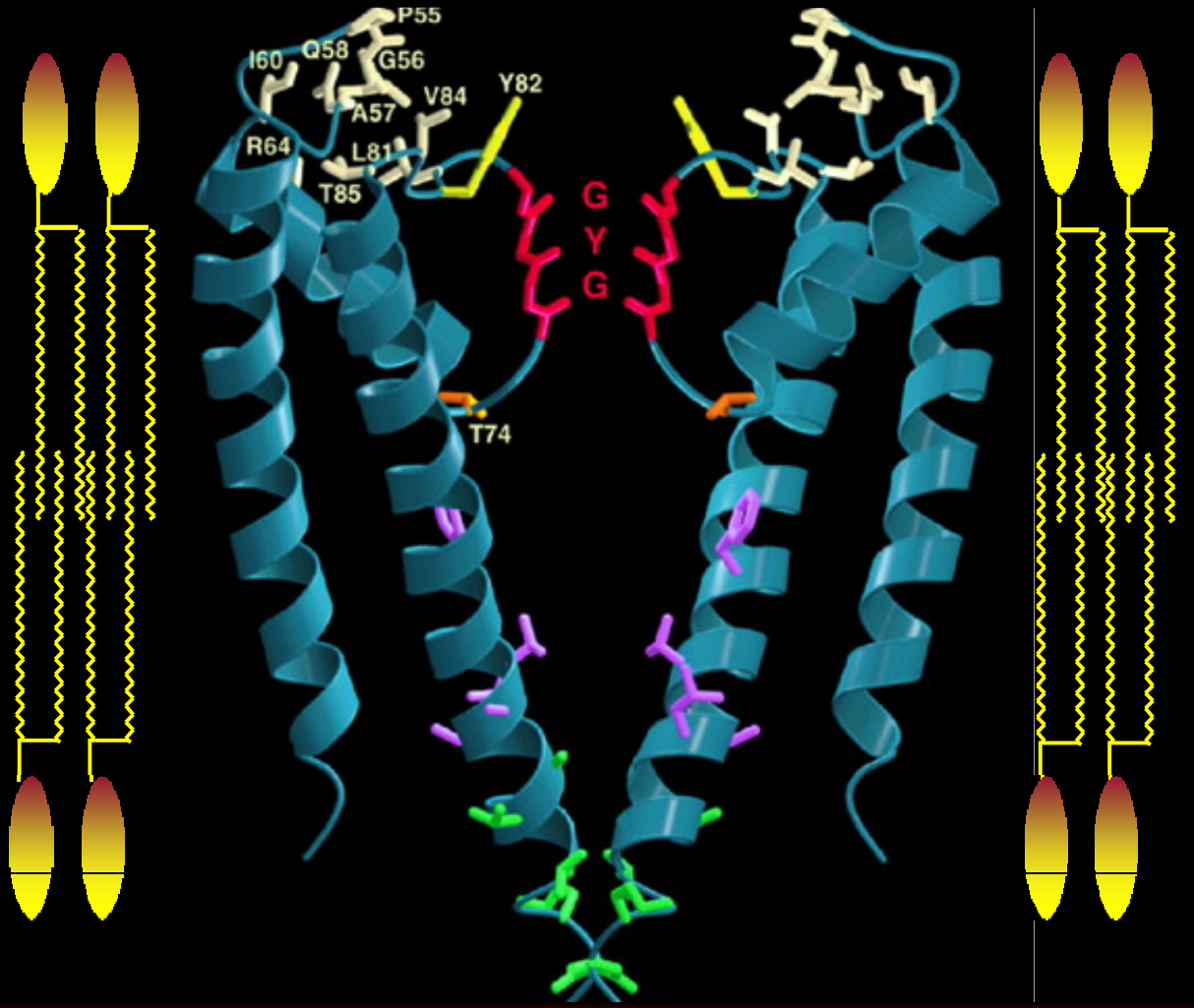
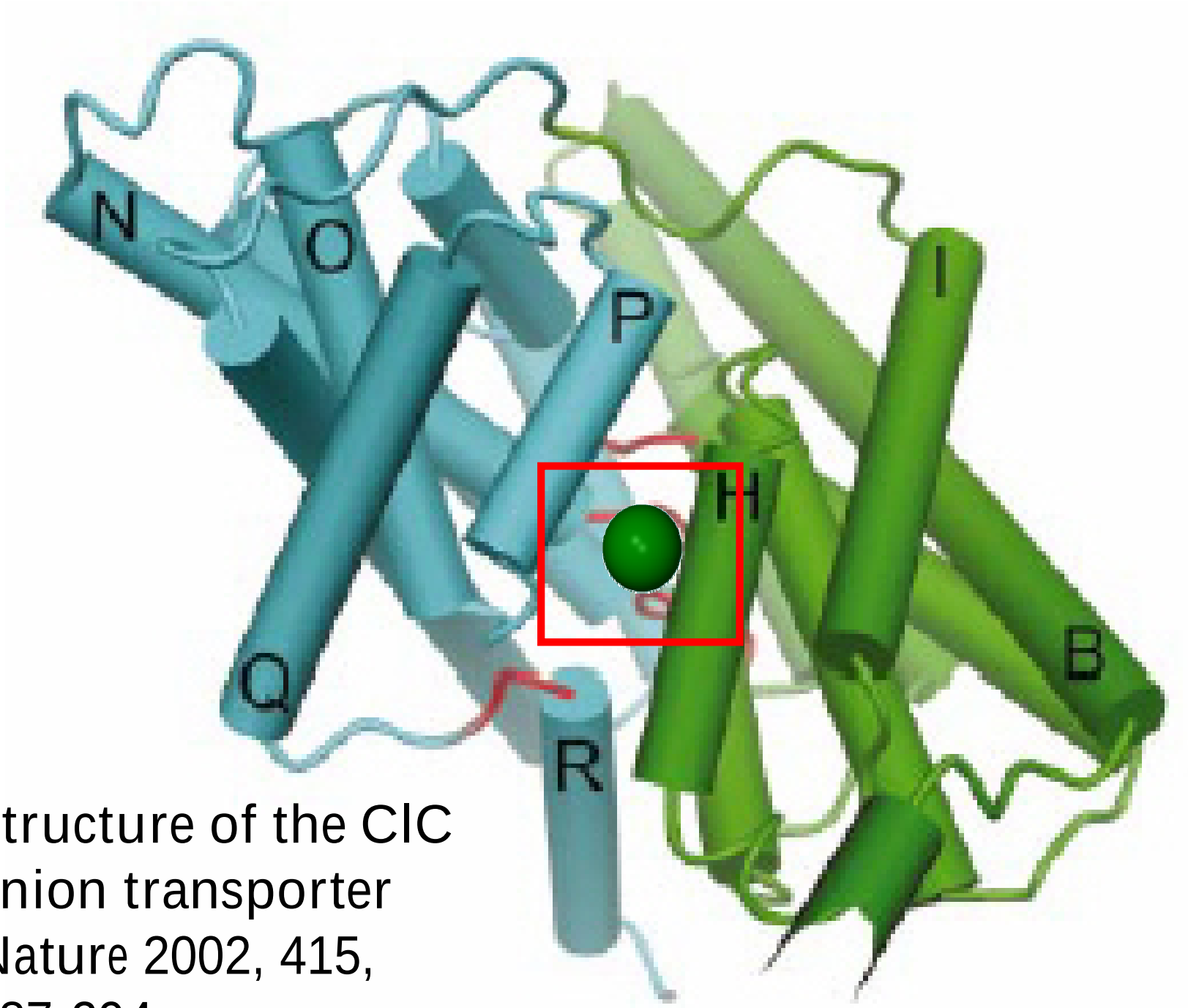
Chemistry Relevant to Biology
Gokel Lab Univ. of Missouri-St. Louis



- Development of synthetic organic model systems
- Synthetic receptors to study cation-pi interactions
- Synthetic ion-conducting channels
- Artificial / synthetic membranes
- Development of drug candidates, especially antibiotics

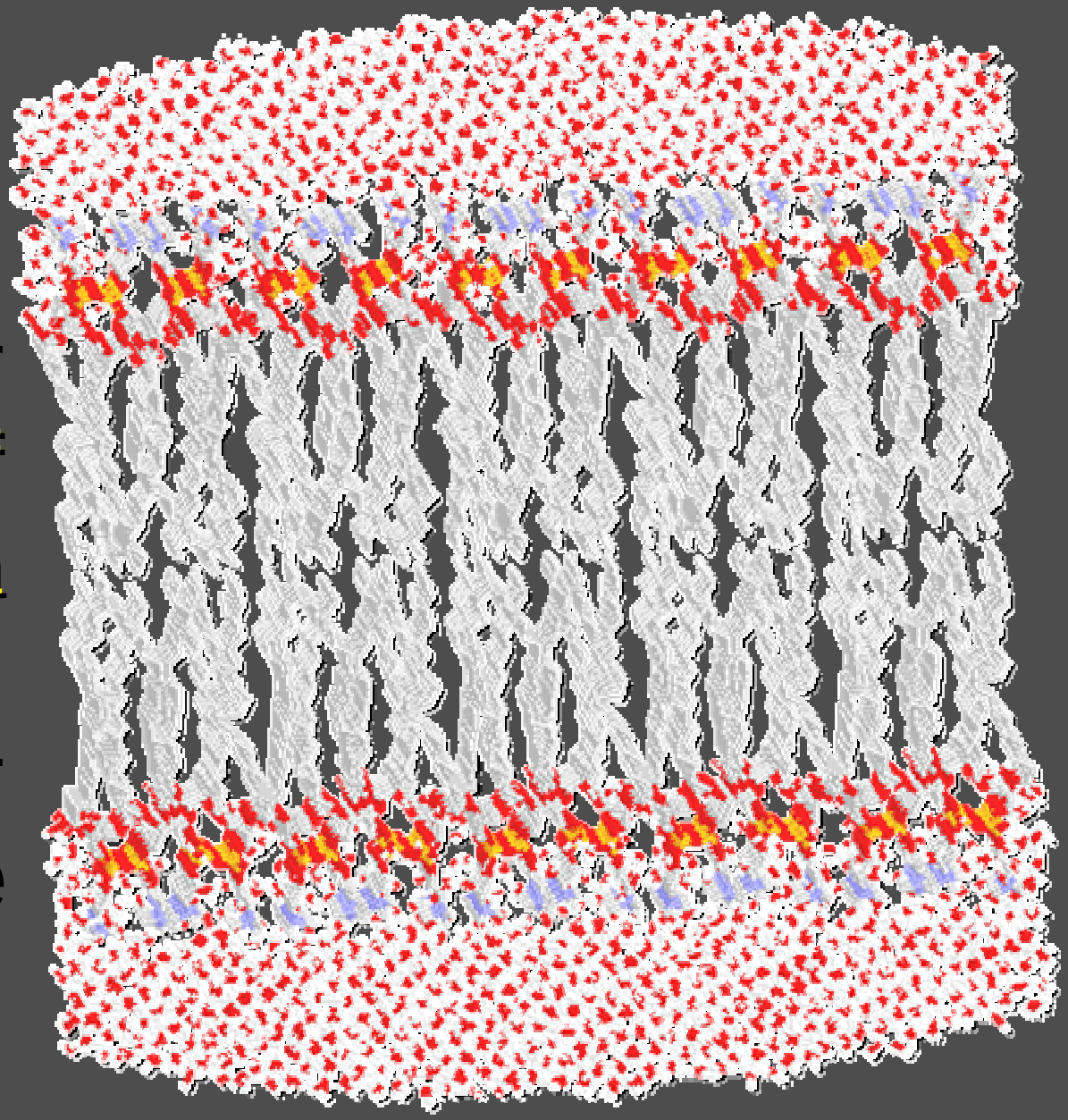


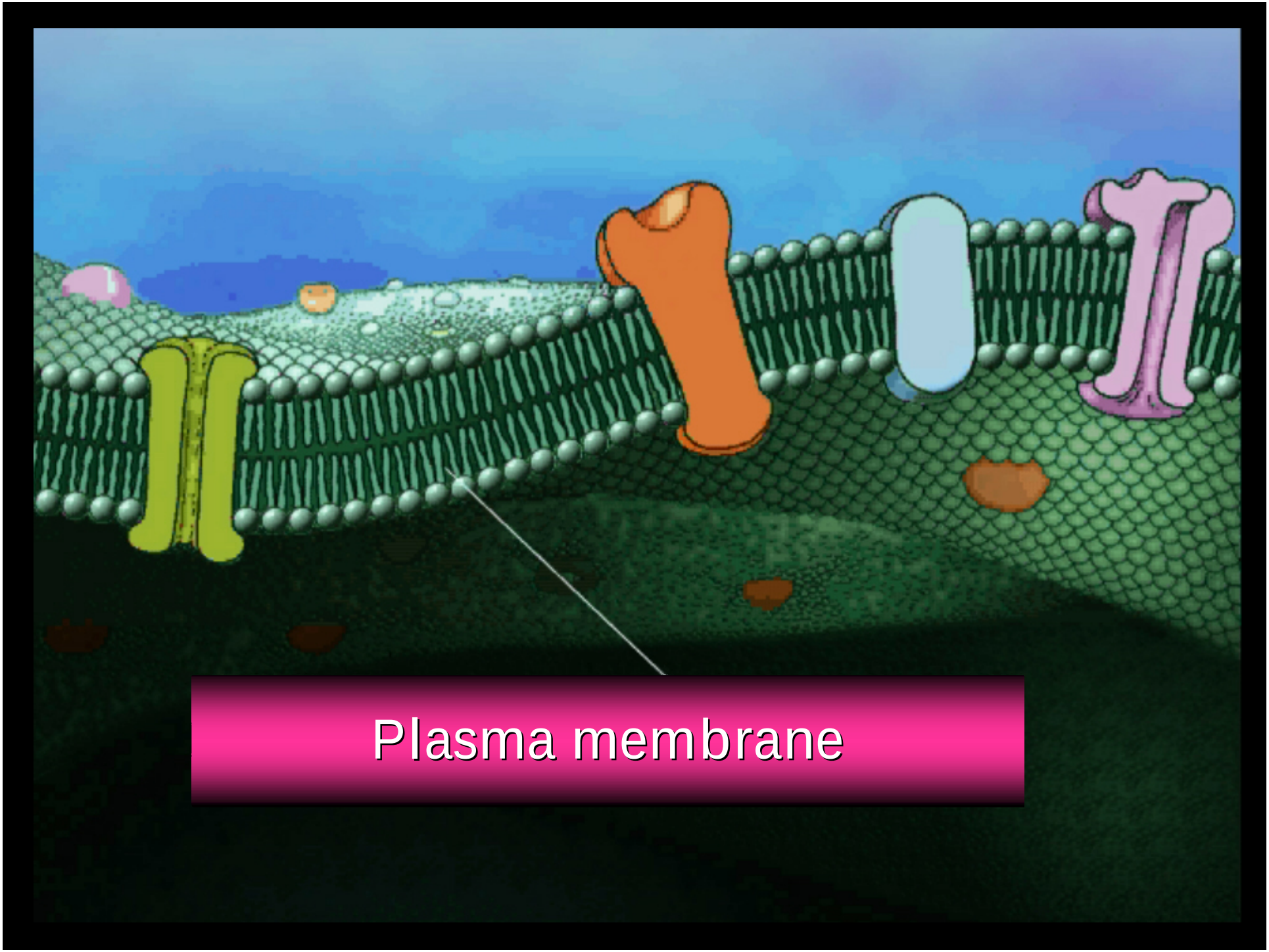
Structure of the KcsA channel of Streptomyces lividans, the first ion channel structure Science 1998, 280, 69-77.



Structure of the ClC anion transporter
Nature 2002, 415, 287-294.

Calculated structure for a segment of a phospholipid bilayer membrane

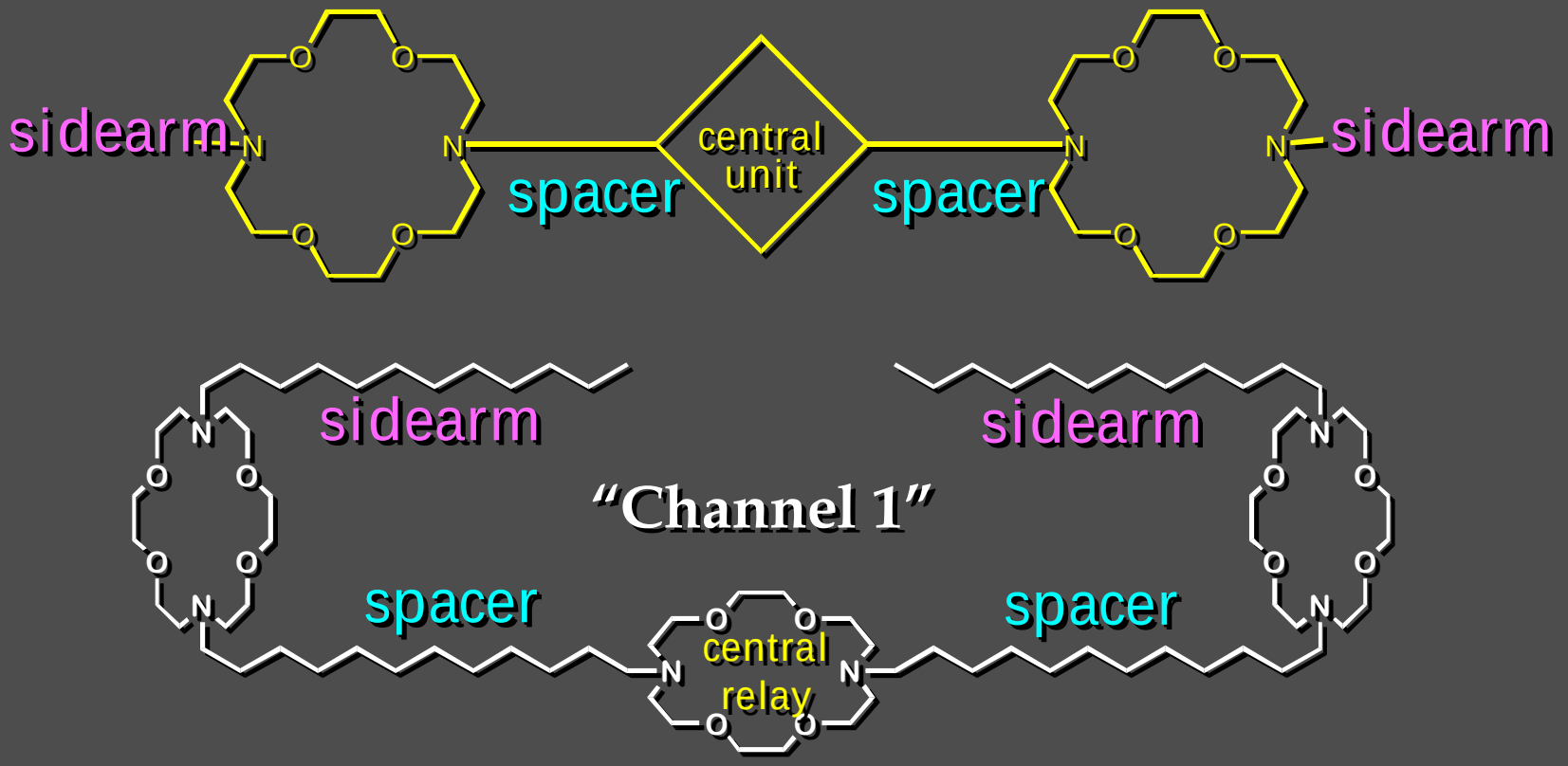



Plasma membrane

Ions in a typical mammalian cell

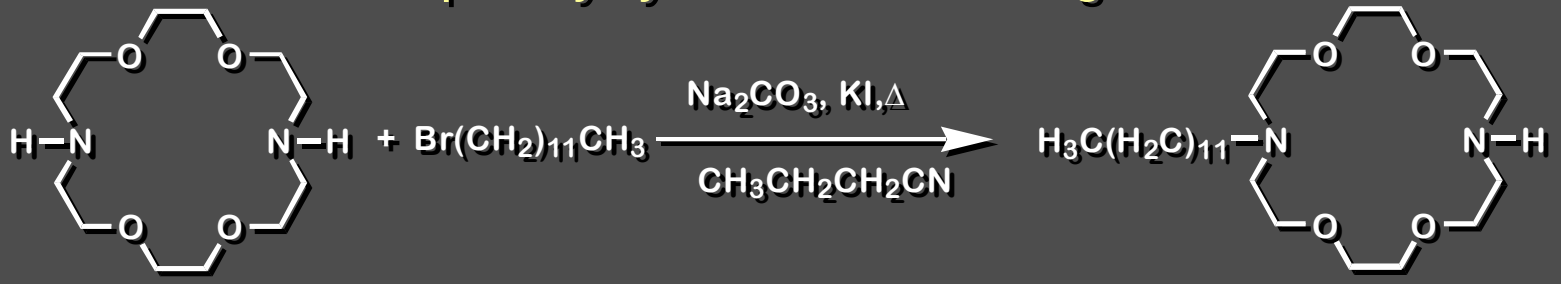
Substance	Extracellular Fluid		Intracellular Fluid	
Na^+	140	mmol/L	10	mmol/L
K^+	4	mmol/L	140	mmol/L
Ca^{2+} (free)	2.5	mmol/L	0.1	μmol/L
Mg^{2+}	1.5	mmol/L	30	mmol/L
Cl^-	100	mmol/L	4	mmol/L
HCO_3^-	27	mmol/L	10	mmol/L
PO_4^{3-}	2	mmol/L	60	mmol/L
Glucose	5.5	mmol/L	0–1	mmol/L
Protein	2	g/dL	16	g/dL

Design schematic for hydraphile channels

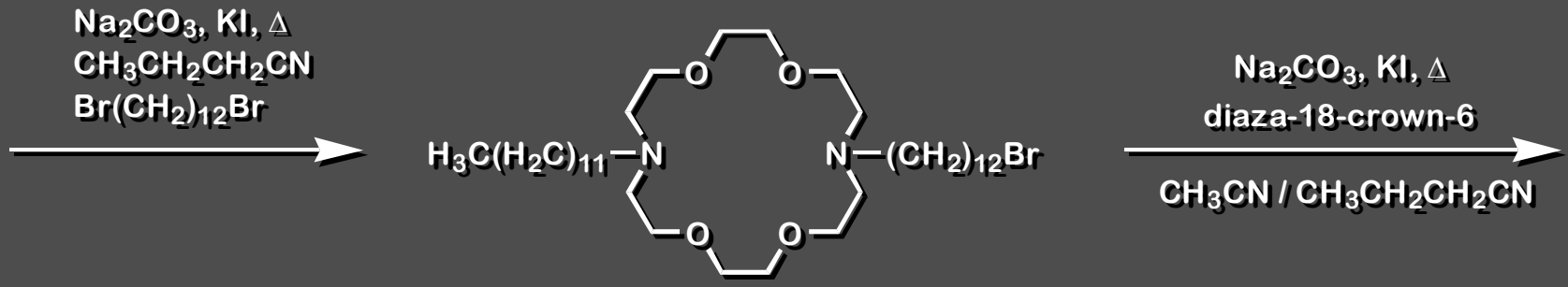


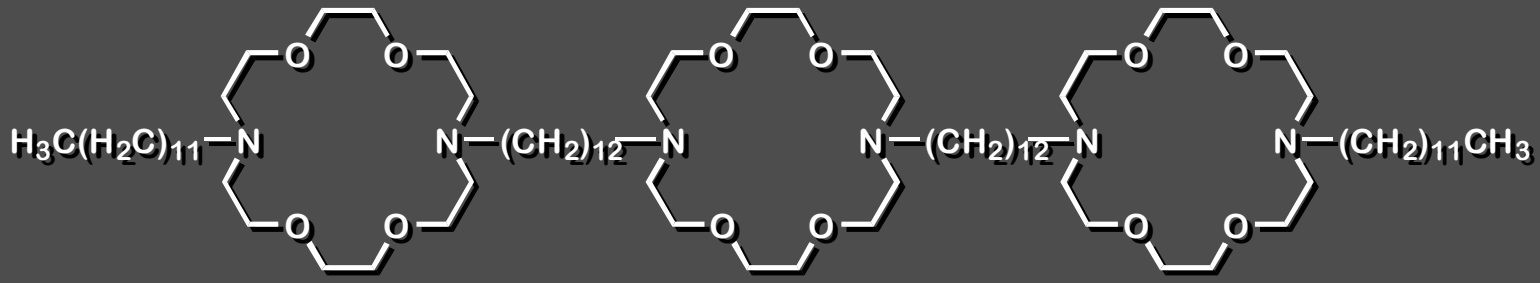
For the tris(macrocycle) channels, the "central unit" was a third macrocycle.

There are two challenges. The first is to design a molecule that performs a biological function. The second is make it. The scheme below shows how a very, but not completely symmetrical compound was prepared from a completely symmetrical starting material.

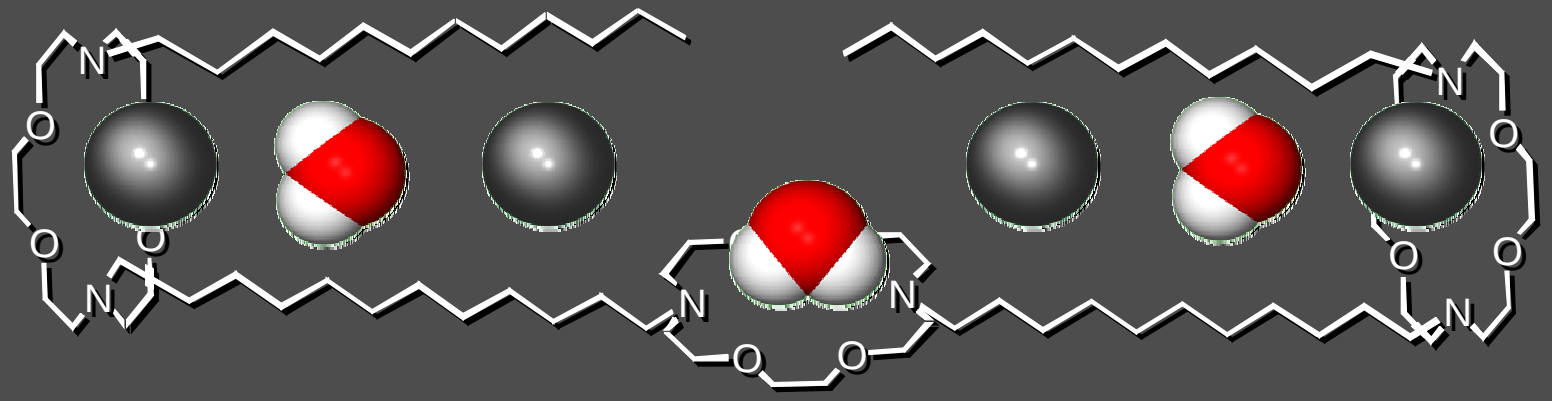


+ dialkylated crown

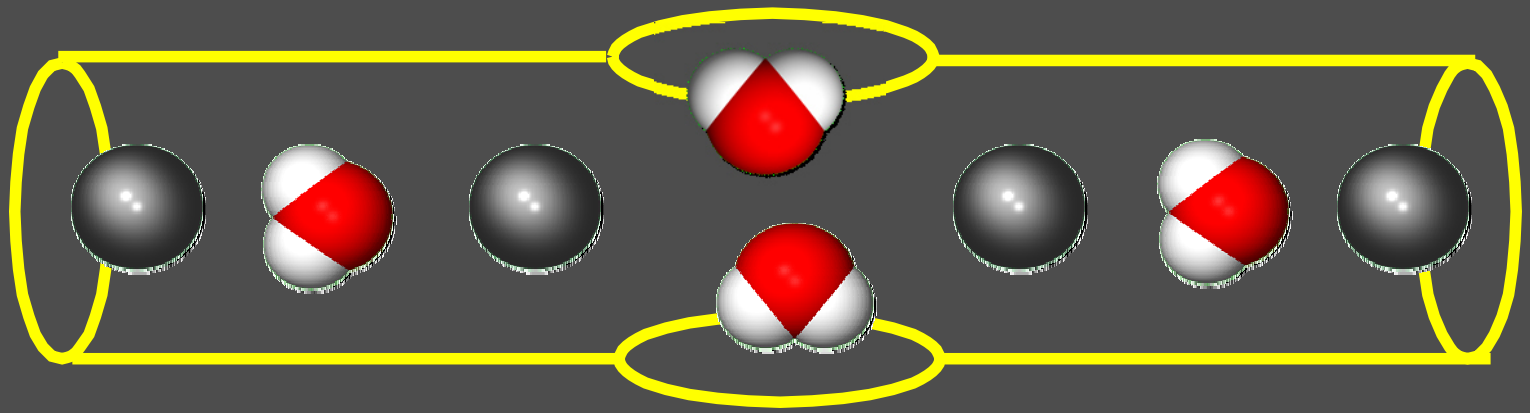




The active conformation is deduced from several experiments.

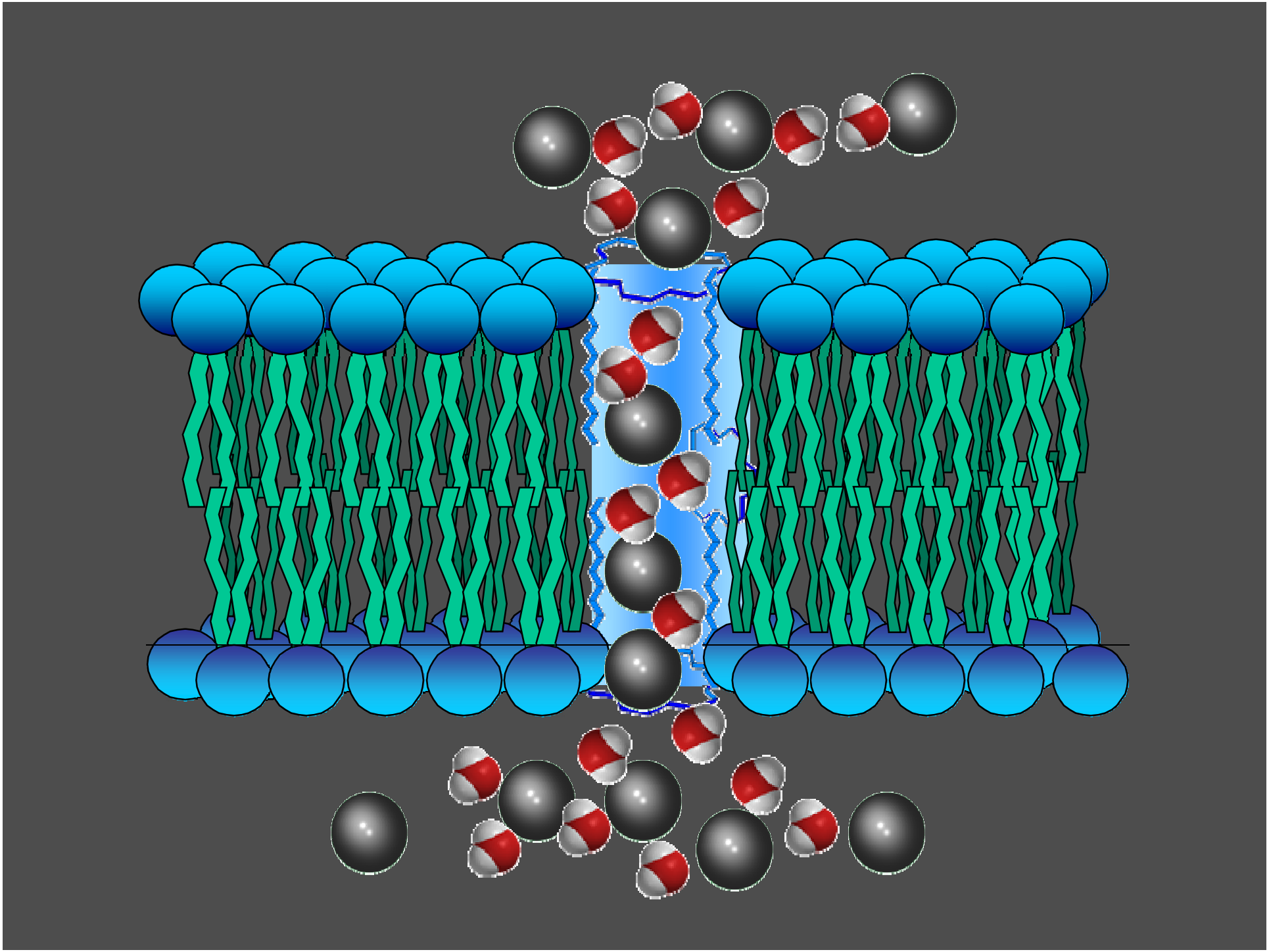


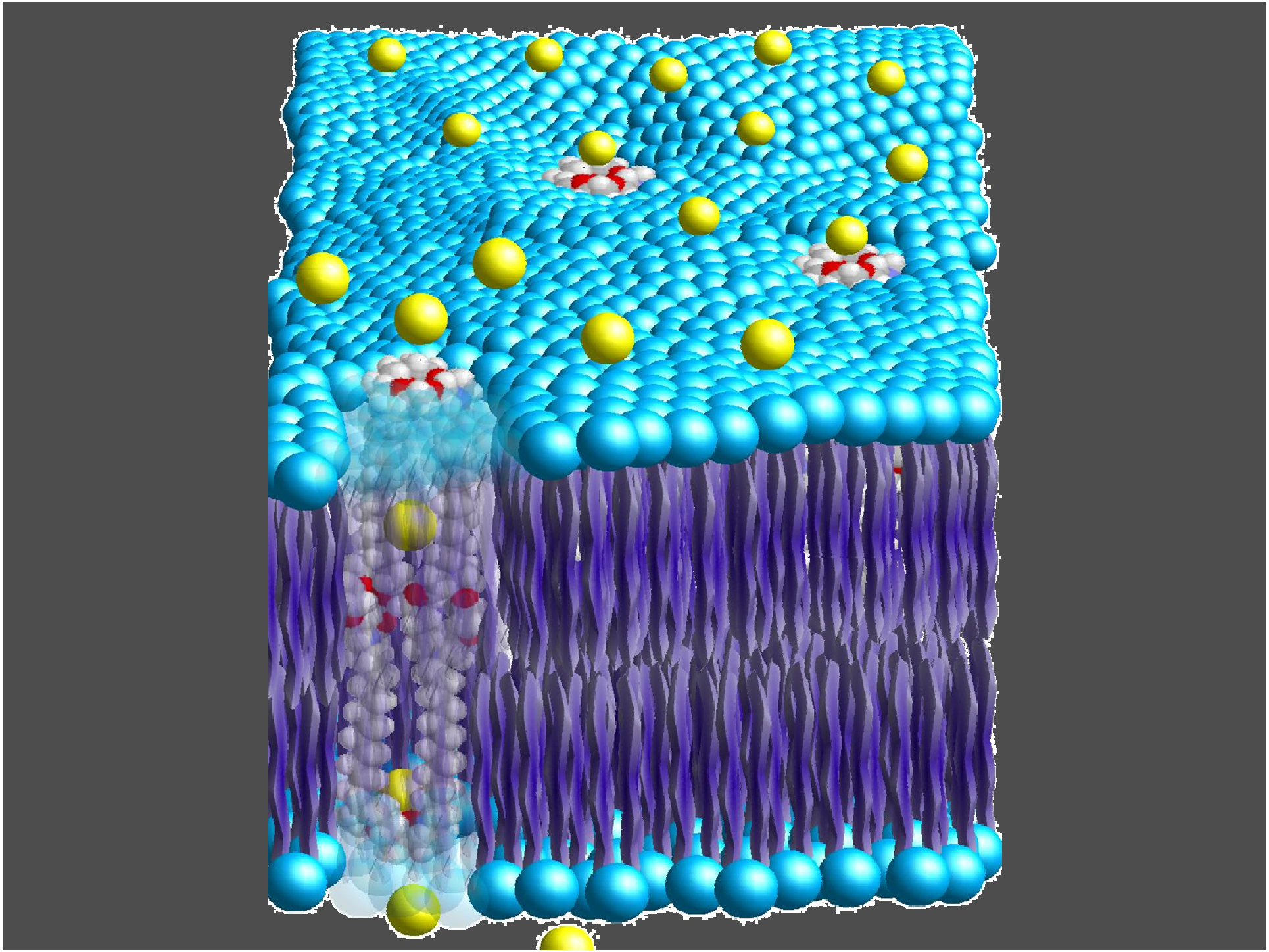
Our most active compound so far is "the tunnel," drawn schematically.

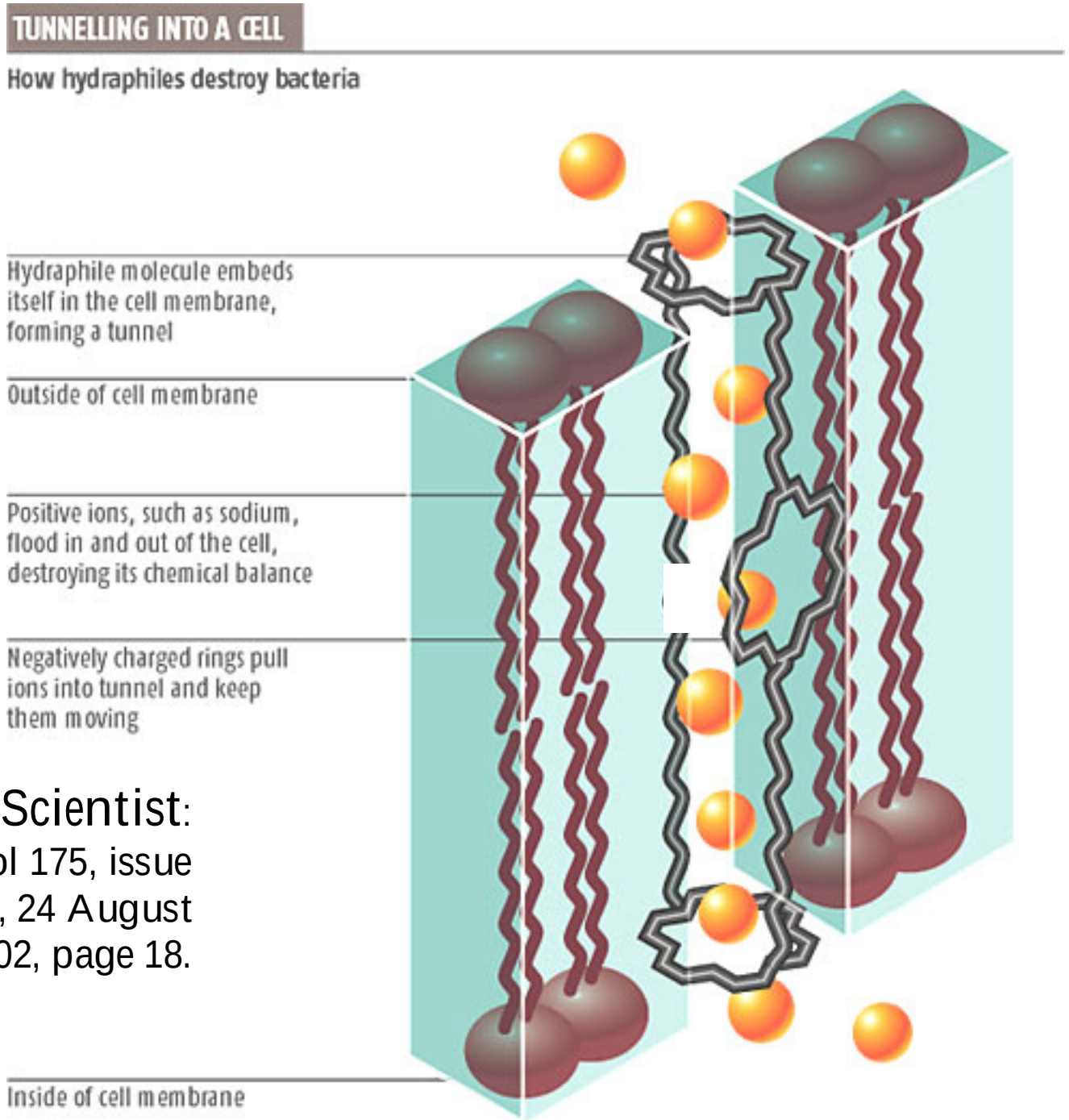


The American Heritage Dictonary defines "hydra" as "any of several small freshwater polyps of the genus Hydra and related genera, having a naked cylindrical body and an oral opening surrounded by tentacles." This definition is strongly suggestive of our structures. We thus call this family of membrane active ion conductors "hydraphiles." They insert in the phospholipid bilayer and mediate ion release. They also show the classic open-close behavior of protein ion channels.

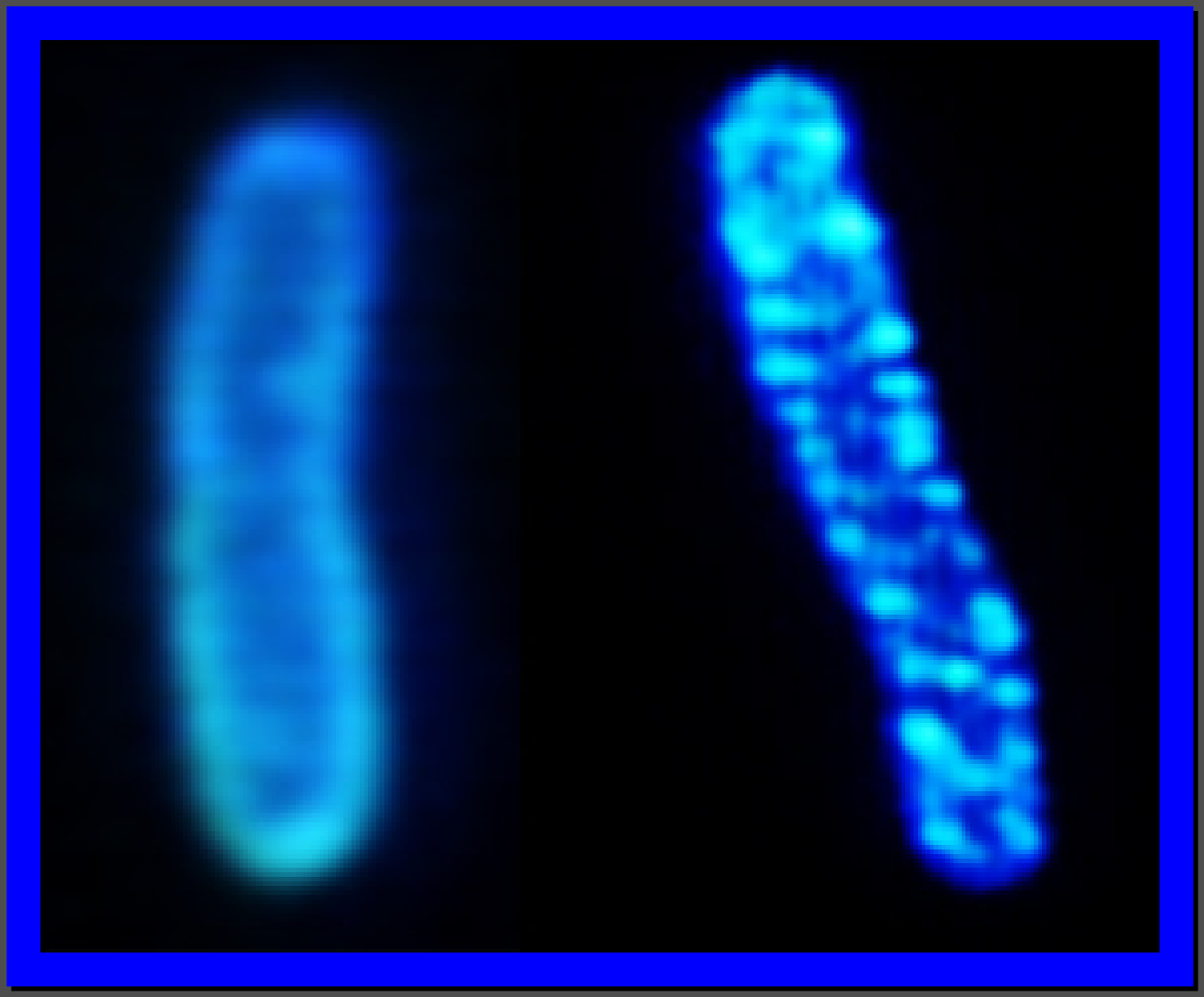
Extensive evidence suggests that these synthetic ion channels function as illustrated in the three following cartoon representations.



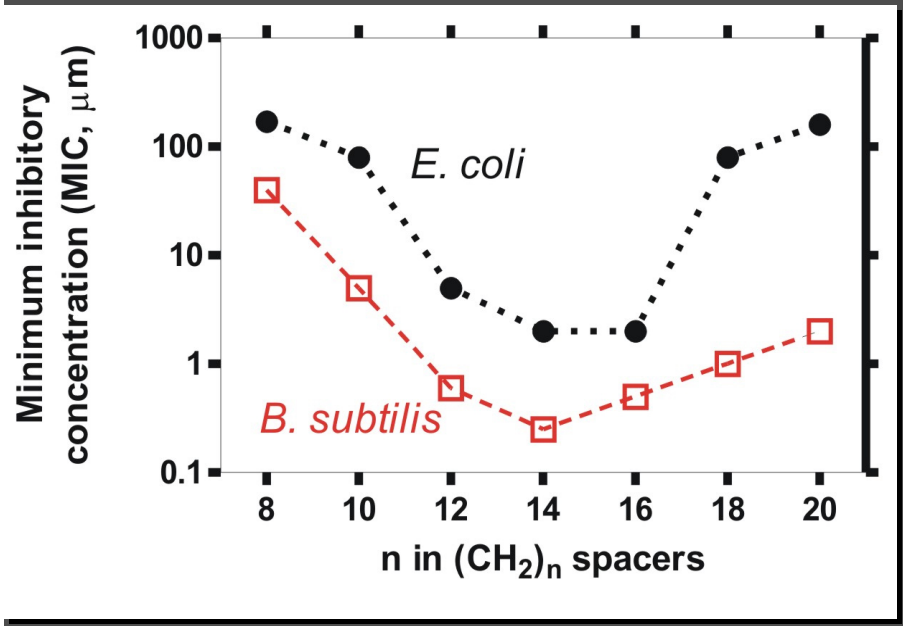


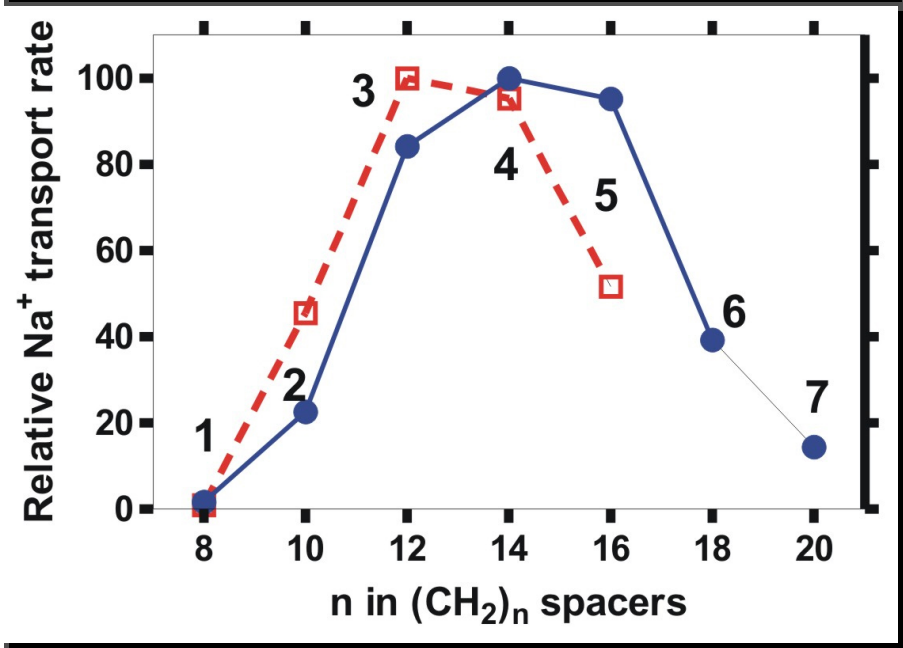


New Scientist: vol 175, issue 2357, 24 August 2002, page 18.

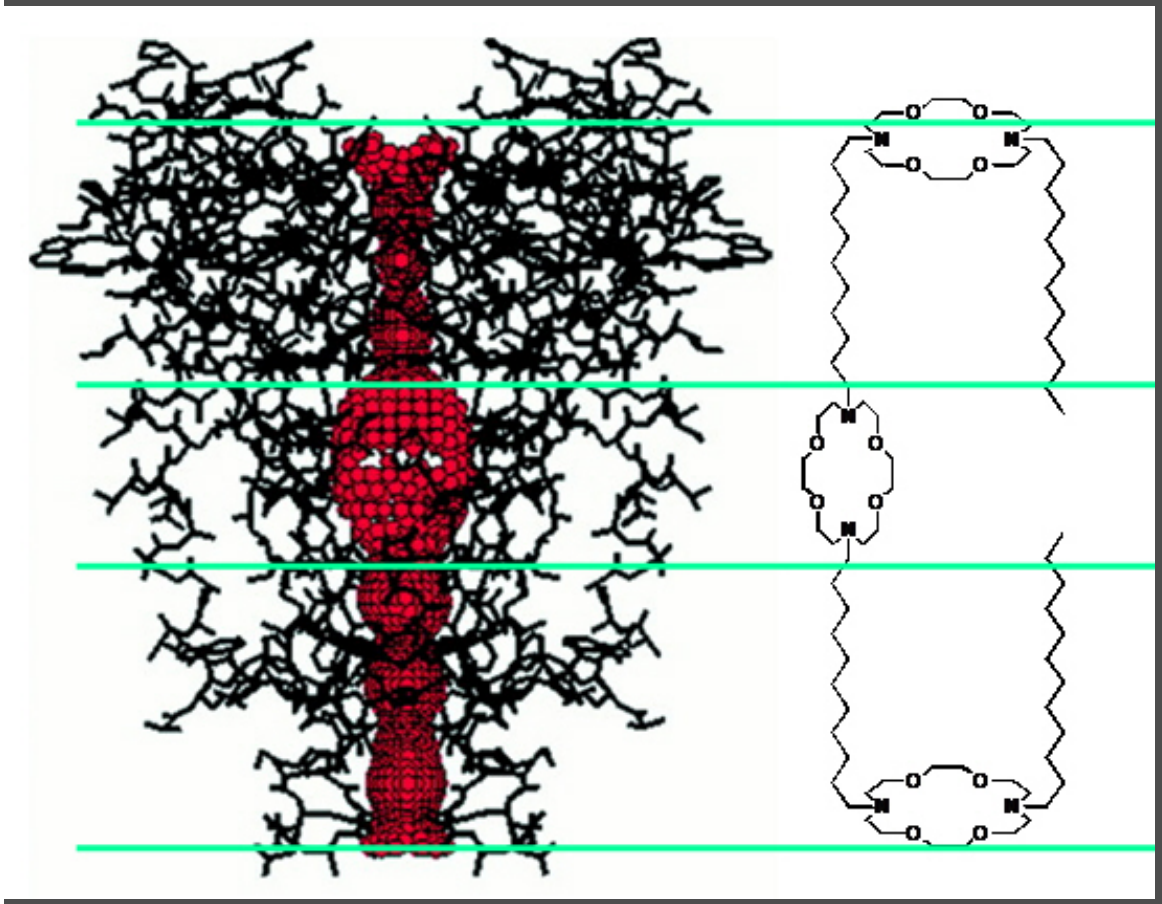


Photomicroscopy shows that a fluorescent hydraphile molecule inserts into the boundary membrane of the bacterium E. coli. The image at the left was acquired as soon after addition of the hydraphile as Possible. The right hand structure was obtained some minutes later. In either case, the hydraphile inserts in to the membrane as ans where expected.



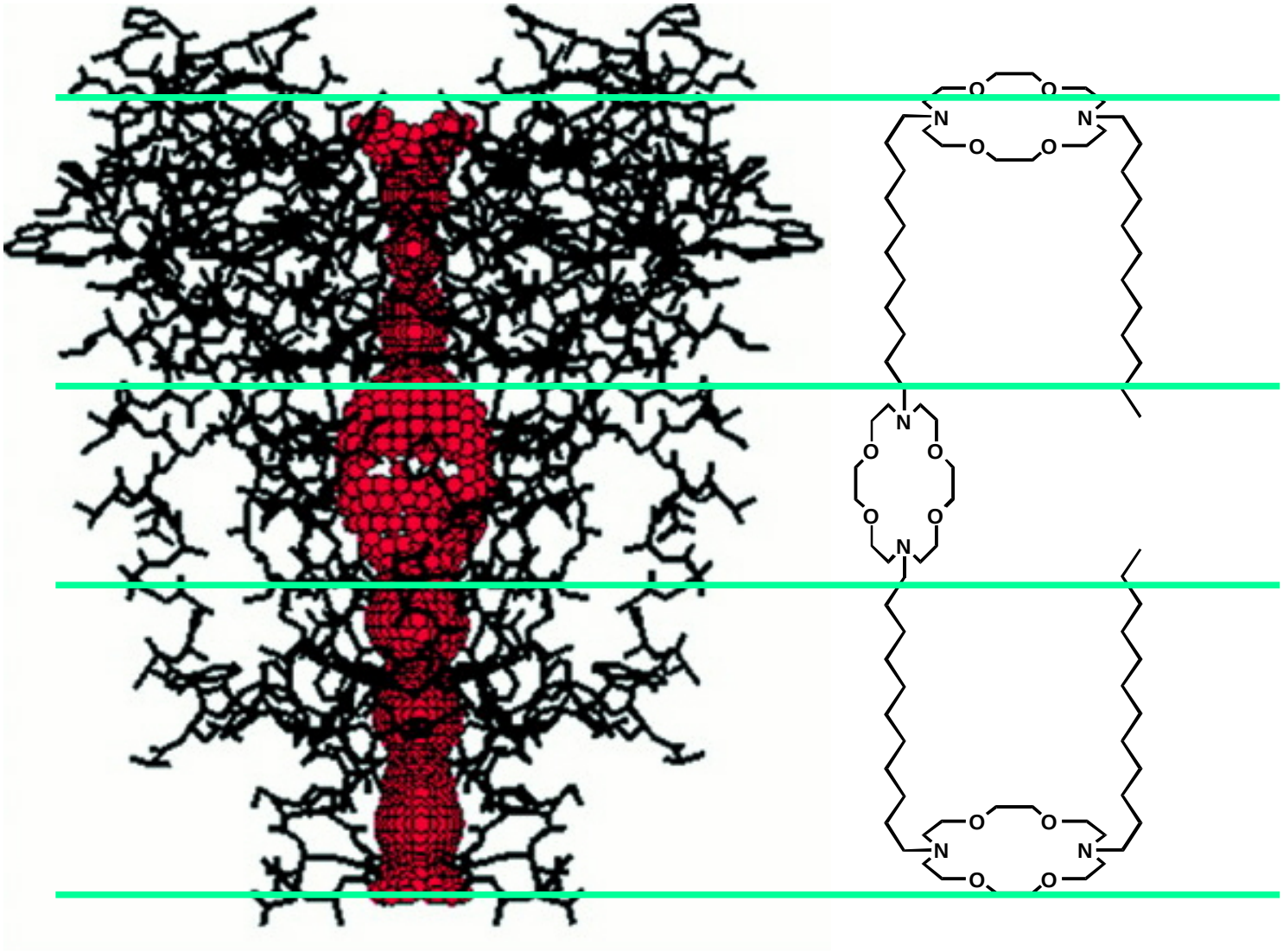


The figures at the left show the behavior of hydraphile channels. The lower panel shows that the channels transport sodium cation very effectively when the spacer chains are in the 12-16 carbon range. Activity is lost if the channels are either too long or too short. Likewise, the ability to kill bacteria by inserting in the bacterial membrane and disrupting osmotic balance parallels this length and efficacy dependence. Ref: Leevy, Weber, & Gokel Chem. Commun. 2005, 89-91.



The center macrocycle was incorporated into the design to lower the energy of transport across the 30-35 Å nonpolar insulator regime of the bilayer. When the first structure of a cation channel appeared, a similar structure was apparent.

We called this medial macrocycle the “central relay.” It was referred to in the protein structure as the “water and ion filled capsule.” Its function is the same as that of the central relay. It is interesting to note that the tubes or tunnels on either side of it are essentially hydrophobic.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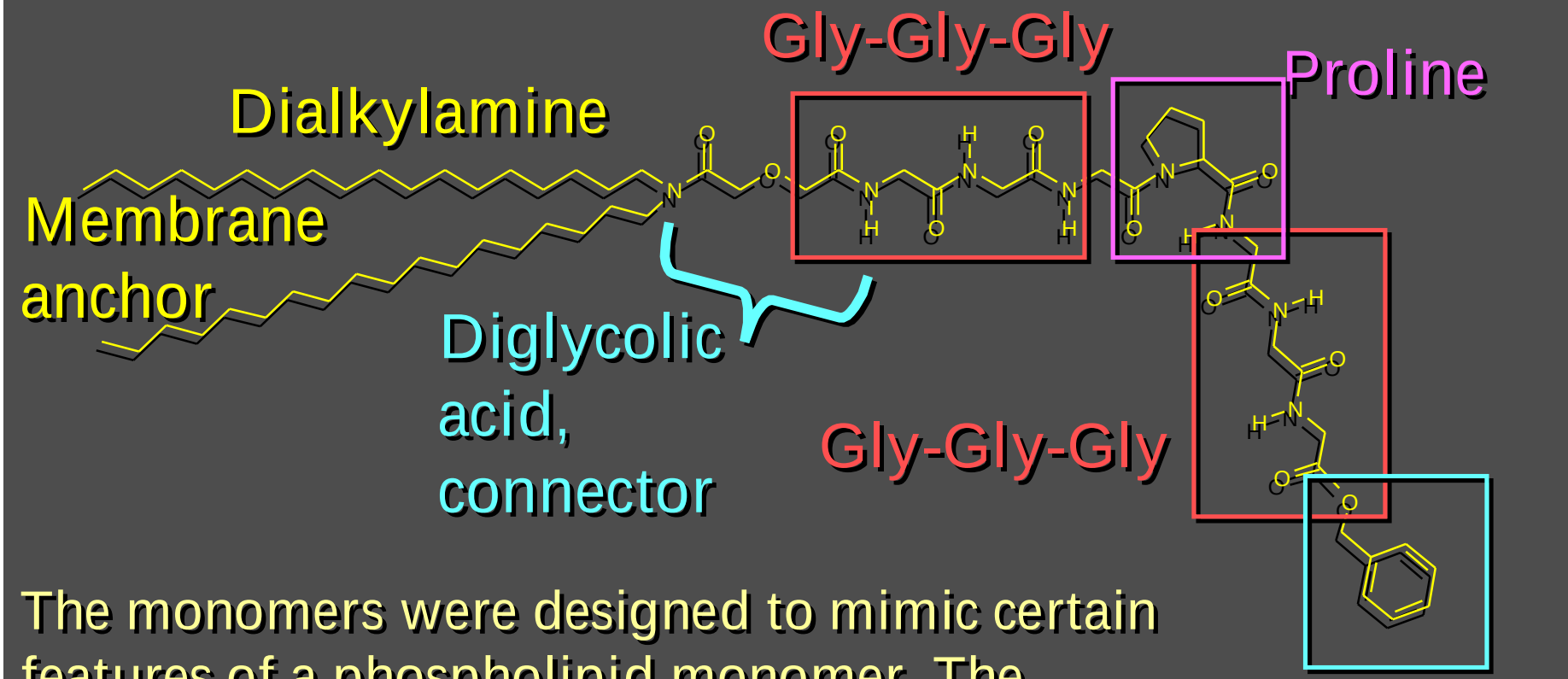
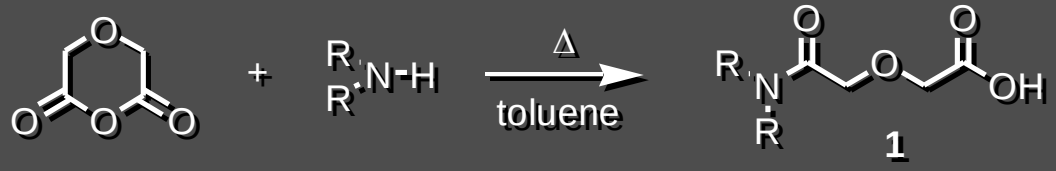
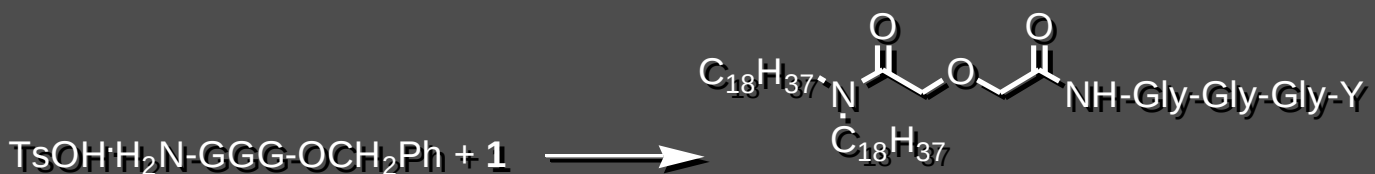
Synthetic Anion Transporters (SATs)



The monomers were designed to mimic certain features of a phospholipid monomer. The hydrocarbon chains mimic the twin fatty acid chains. The diglycoyl unit approximates the glyceryl regime. The peptide sequence was inspired by the putative conductance pore of the ClC family of protein chloride transporters.



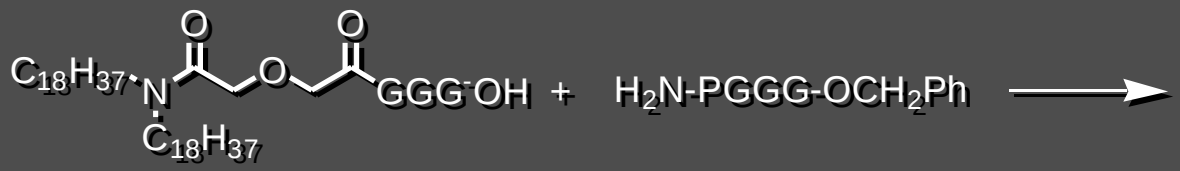
1



Y = CH_2Ph
3, Y = OH

Z-PGGG-OCH_2Ph

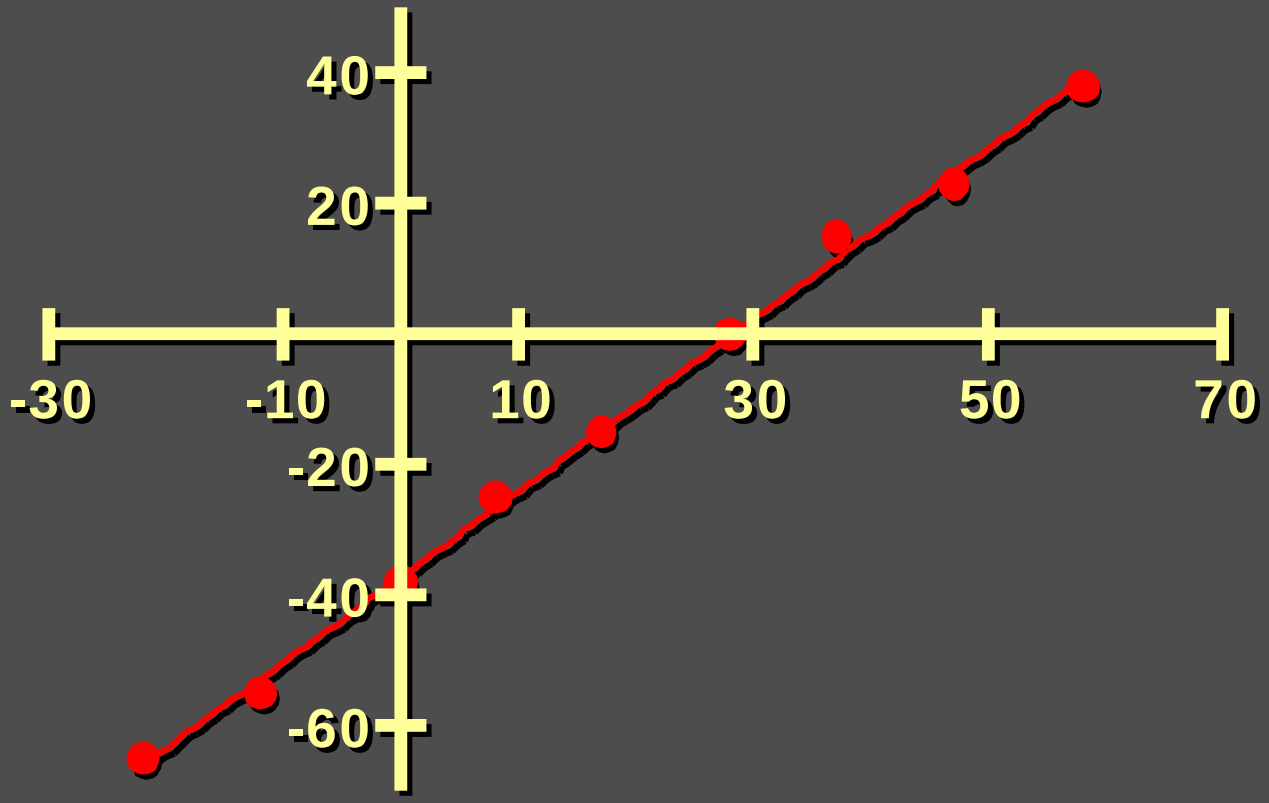
Z = Boc
4, Z = H_2N



2

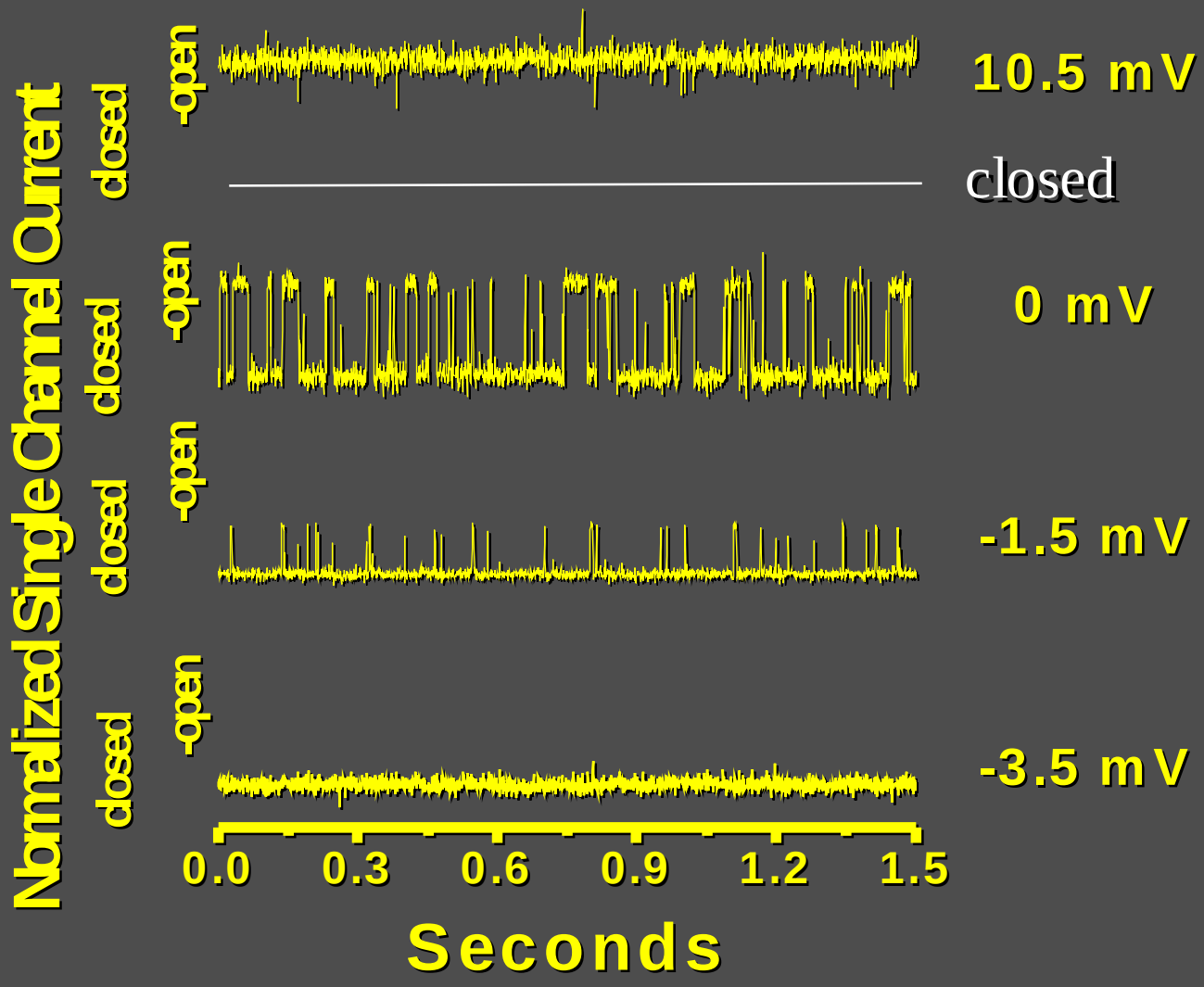
Design and synthetic access are once again issues. In this case, both traditional synthetic methods and peptide chemistry were required to prepare the family of synthetic anion transports or SATs.

Current-Voltage (I-V) Plot for SCMTR-18



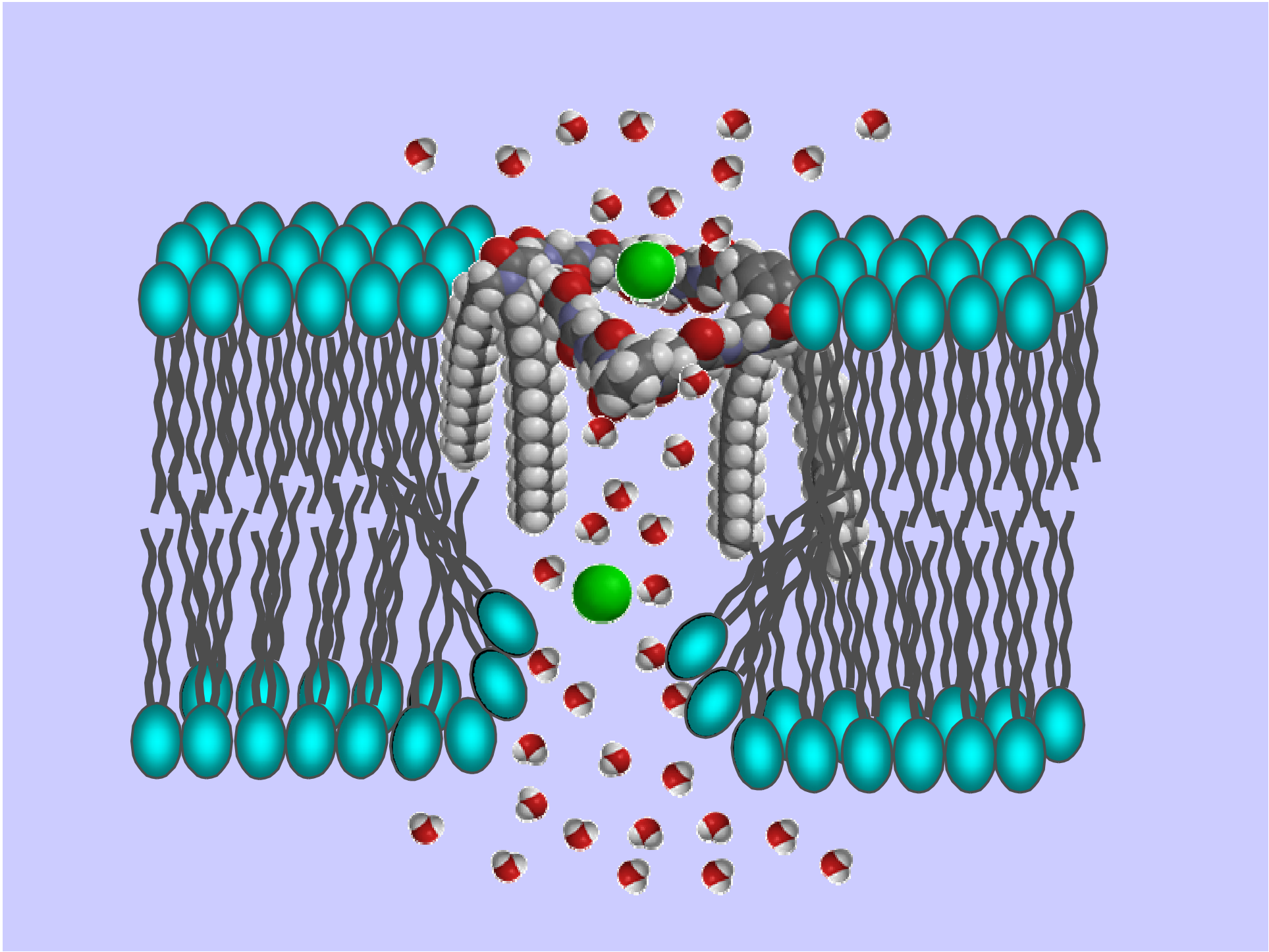
The I-V plot had a slope of 1.3±0.01 nS and a reversal potential (E_{rev}) of 28±0.45 mV, indicating a >10-fold selectivity for Cl^-/K^+.

SCMTR-18_2 shows voltage dependent gating



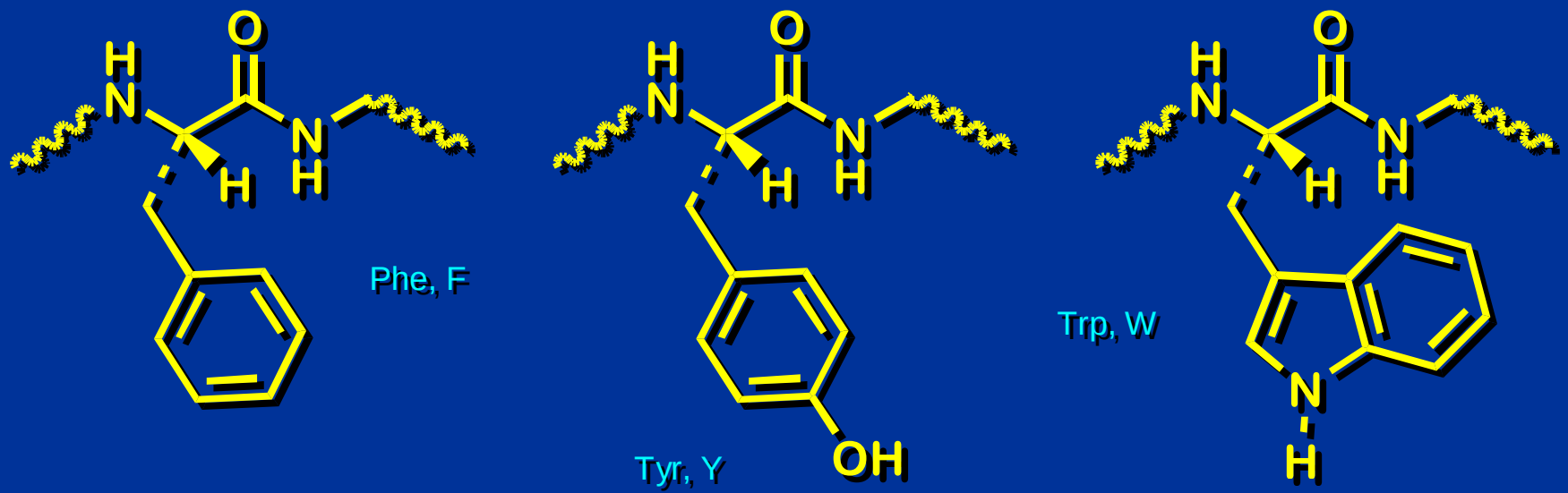
Established Features of SATs

- Hill plots suggest function as a dimer
- Dextran block of carboxyfluorescein (CF) release suggests 7-8 Å opening
- Molecular models suggest a 7-8 Å opening
- GGGPGGG > GGGLGGG
- GGGProGGG > GGGPipGGG

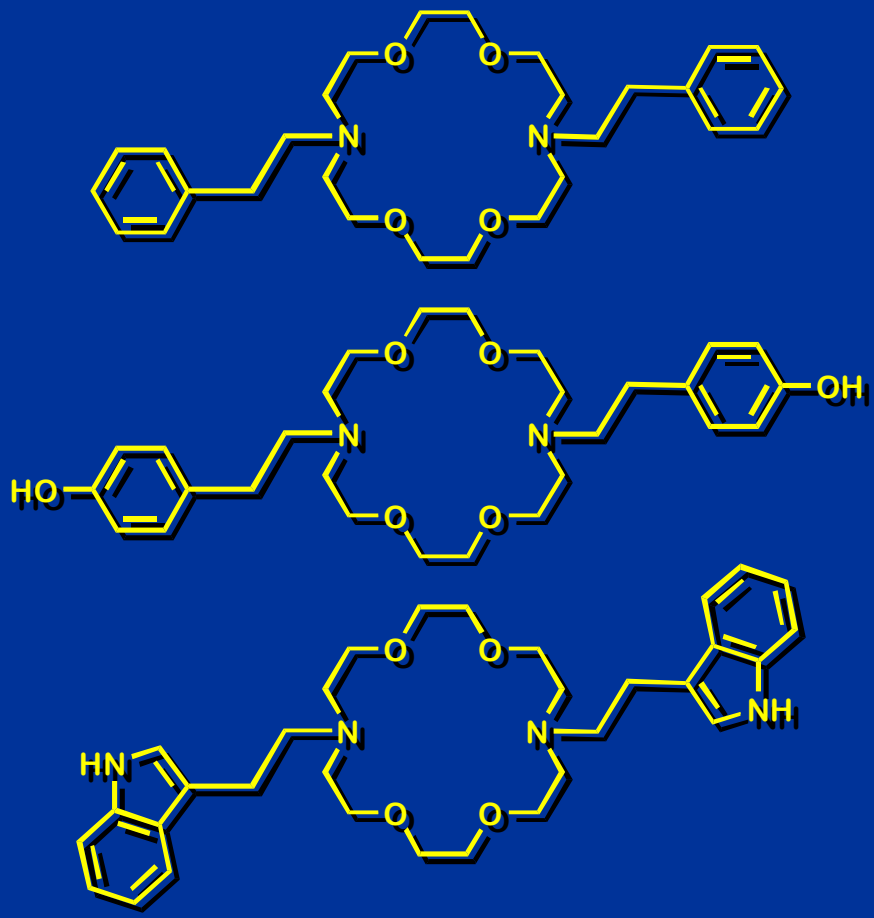


Cation-pi Interactions

Many supramolecular interactions are known ad well characterized. These include hydrogen bonding, ion-dipole and dipole-dipole interactions, and hydrophobic contacts. Until recently, the cation-pi interaction was less well defined.

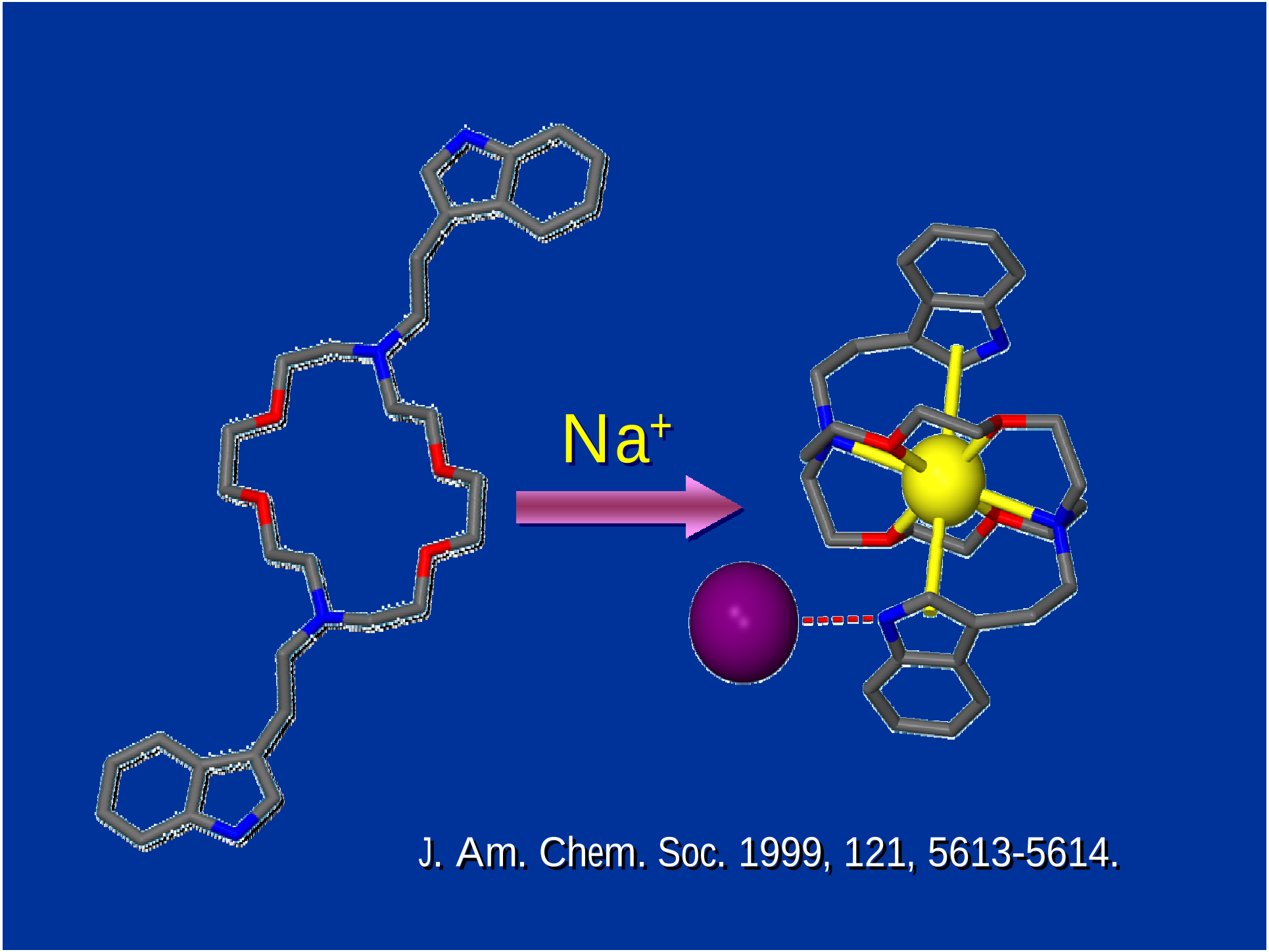


The cation-pi interactions of interest to biology involve phenyl, phenol, and indole as neutral donors, the metal cations Na^+ and K^+, and the organic cations ammonium and guanidinium.



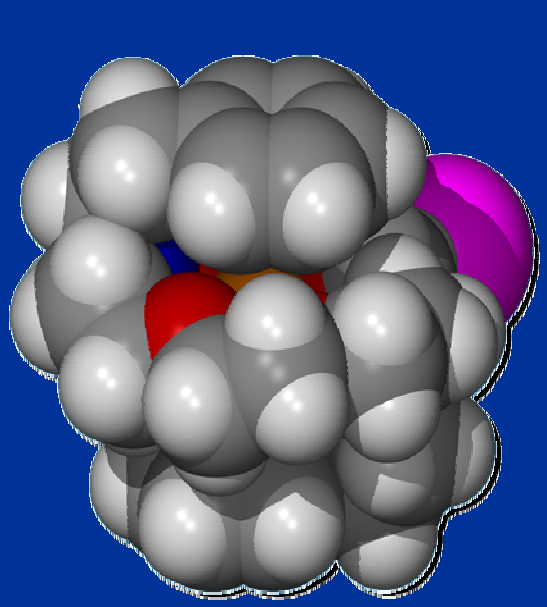
The three receptor molecules shown at the left incorporate benzene, phenol, or indole in the side arms. These are the three electron rich aromatic residues present in the 20 common amino acids. Imidazole, an aromatic residue present on histidine, is electron poor.

These receptors were designed in the expectation that a sodium or potassium cations would be bound in the macroring's center and that the side arm aromatic residues would participate as secondary, apical, cation-pi donors.

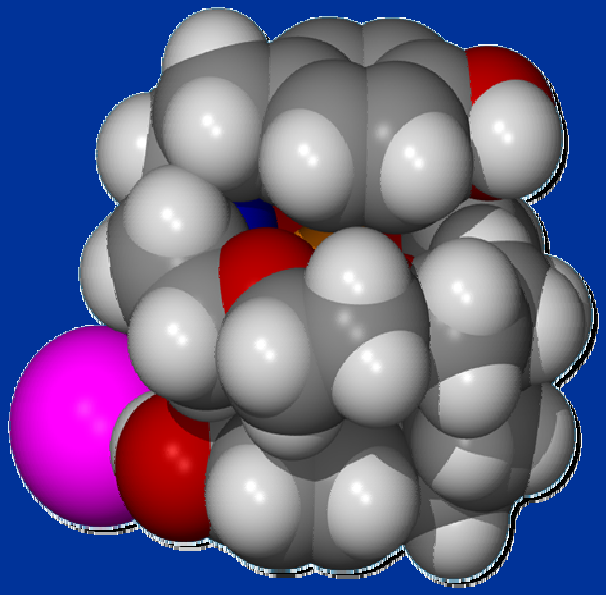


J. Am. Chem. Soc. 1999, 121, 5613-5614.

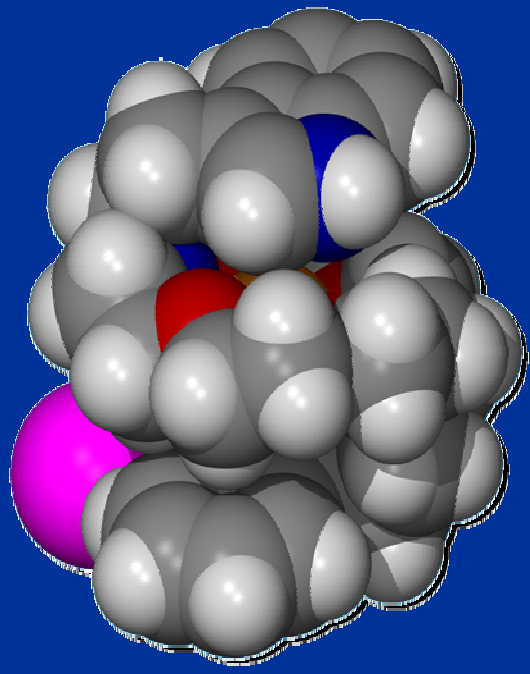
Comparison of KI complexes



Phe, F



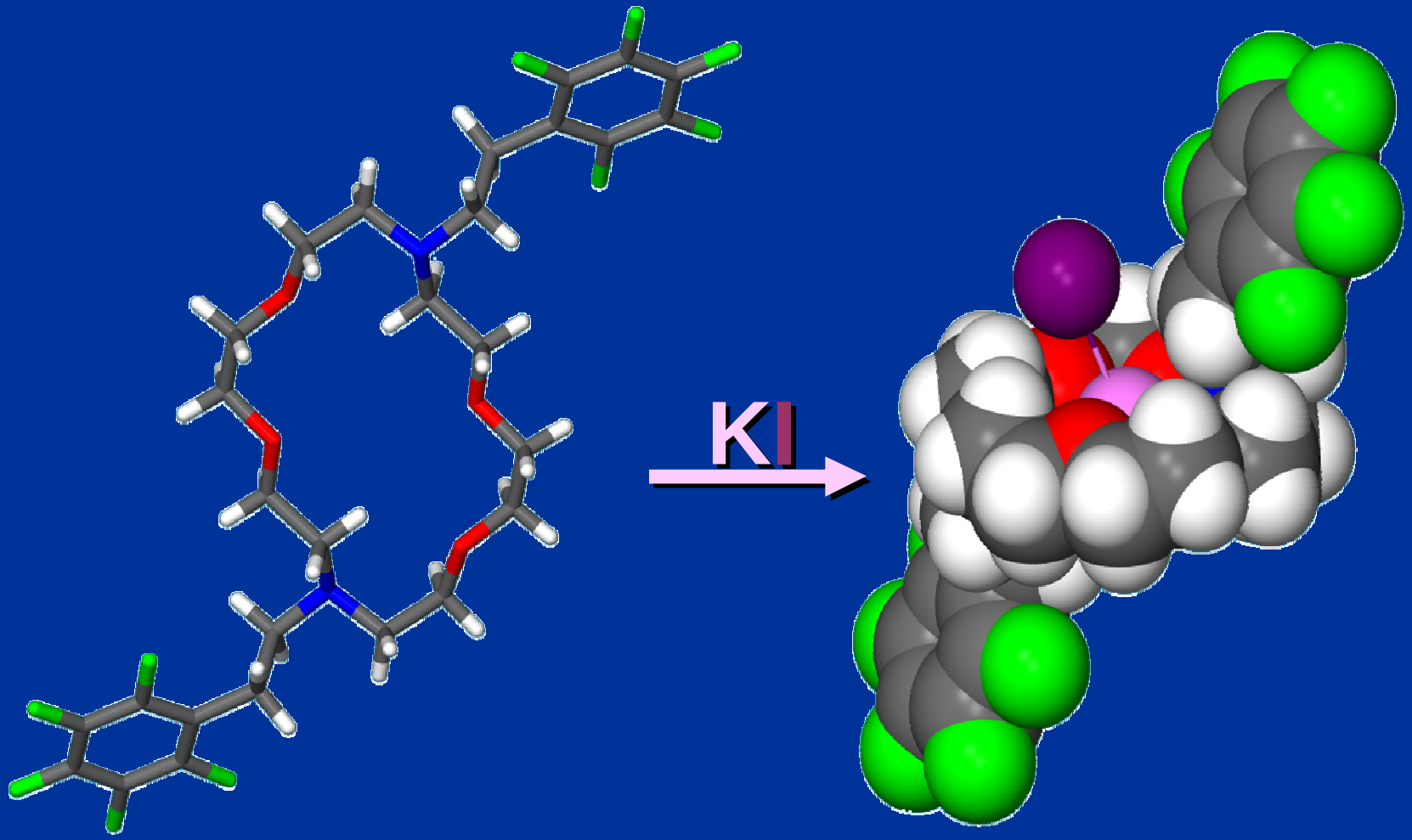
Tyr, Y



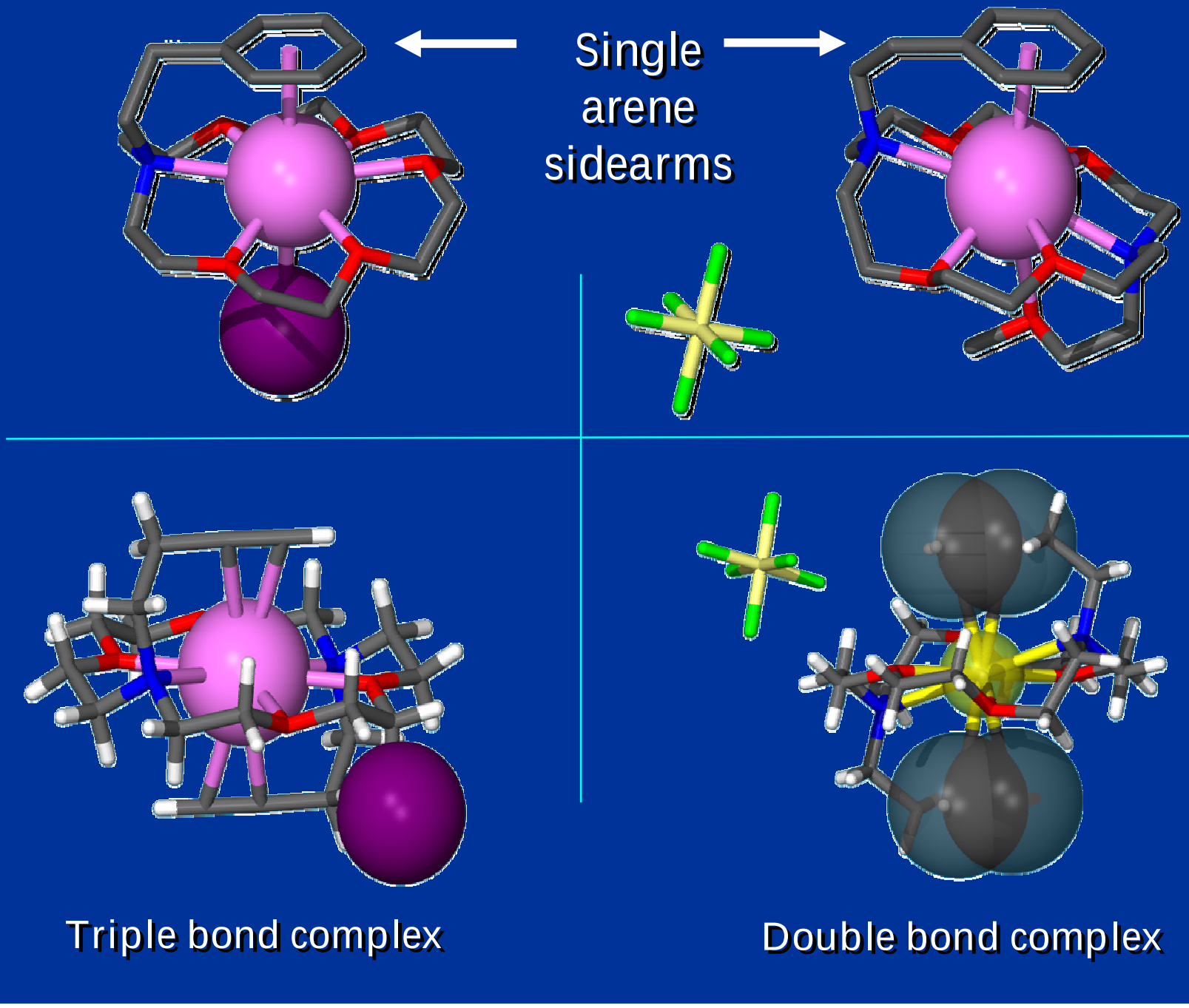
Trp, W

JACS 2001, 123, 3092; Acc. Chem. Res. 2002, 35, 878; PNAS 2002, 99, 5121

When the side chain arene is not a good donor, cation-pi interactions are not observed. In the molecule shown, pentafluorophenyl is a Lewis acid rather than Lewis base.



Proc. Natl. Acad. Sci. USA, 2000, 97, 6271


Single
arene
sidearms
Triple bond complex
Double bond complex

Generalizations

- Synthetic cation and anion channel models are functional in the phospholipid bilayer for ion transport.
- Many properties of complex, modern protein channels are observed in these non-protein model systems.
- The charge relay at the cation channel's center parallels the recent discovery of such a structure in Nature.

Generalizations

- Cation-pi interactions do not explain ion selectivity in protein channels but may have a strong influence in the nonpolar interior of membranes.
- Open-chained peptides can effectively bind chloride-ion pairs.
- "Chloride" complexation is cation dependent.