

Lecture XXVII: Applications of Supramolecular Chemistry in Synthesis Chem 6353/12-03-2008

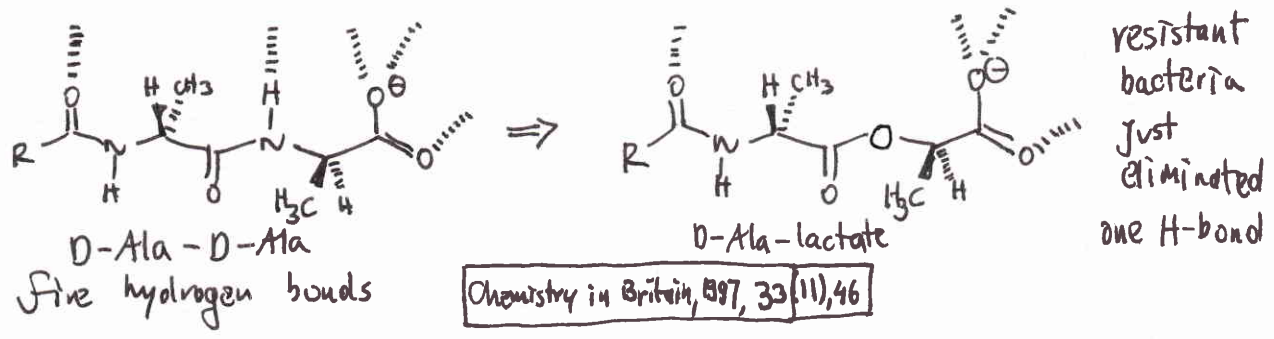
- ① Binding of neutral guests
- ② Mechanically interlocked molecules
- ③ Supramolecular catalysts
- ④ Dynamic covalent chemistry

Today is our final lecture. We will finish on a lighter note, by tying some loose ends and then I will tell you about selected examples of supramolecular chemistry that I worked on.

① Binding of neutral guests

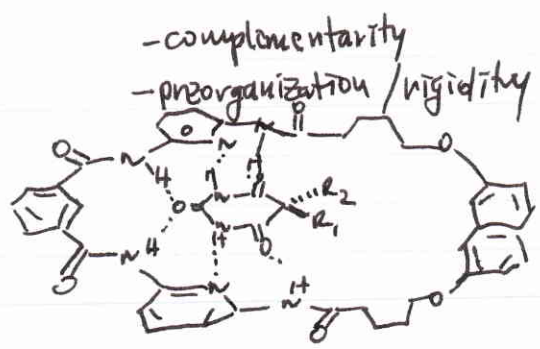
Most organic molecules are neutral. They are more difficult to bind, but are very relevant. Example:

Vancomycin is an antibiotic of last resort, prevents bacterial cell wall synthesis by binding to some cell wall peptides:

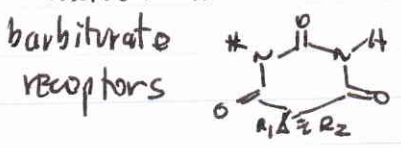


So, how do you go about binding neutral guests:

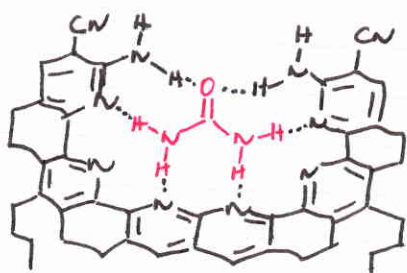
Ⓐ Hydrogen bonds



Andrew Hamilton (Yale)



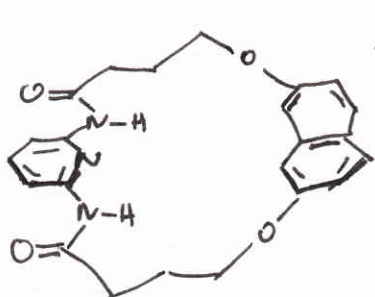
Satisfy all "supramolecular valences":



this complex survives even in hot DMSO highly H-bond competing solvent!!!

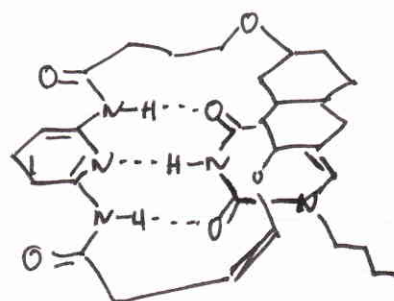
but, keep in mind secondary H-bond interactions!

Hydrogen bonding is often supplemented by other interactions in biology. Synthetic chemists reproduced this in several examples:

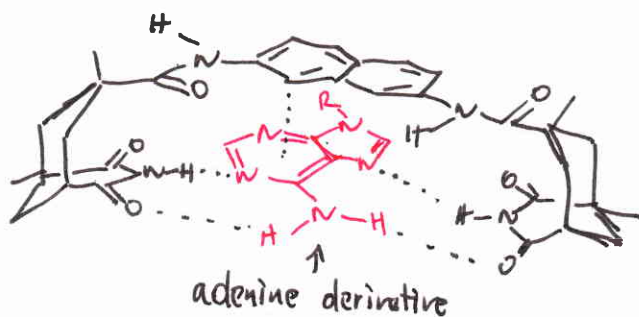


Andy Hamilton (Yale)

thymine derivative



Julius Rebek (Scripps):

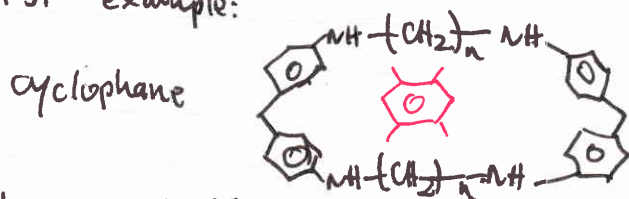


Both of these receptors, as well as many other hydrogen-bonded systems, operate only in noncompetitive solvent (CHCl₃).

Ultimately, one would desire to develop binding in water as the biological medium. Key => exploration of hydrophobic effect.

B Hydrophobic effect

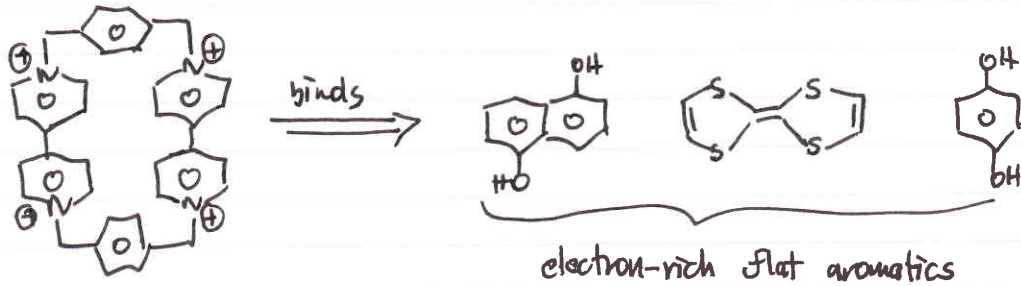
Build a "greasy wall" around the substrate
First example:



Koga et al. JACS, 1980, 102, 2504.

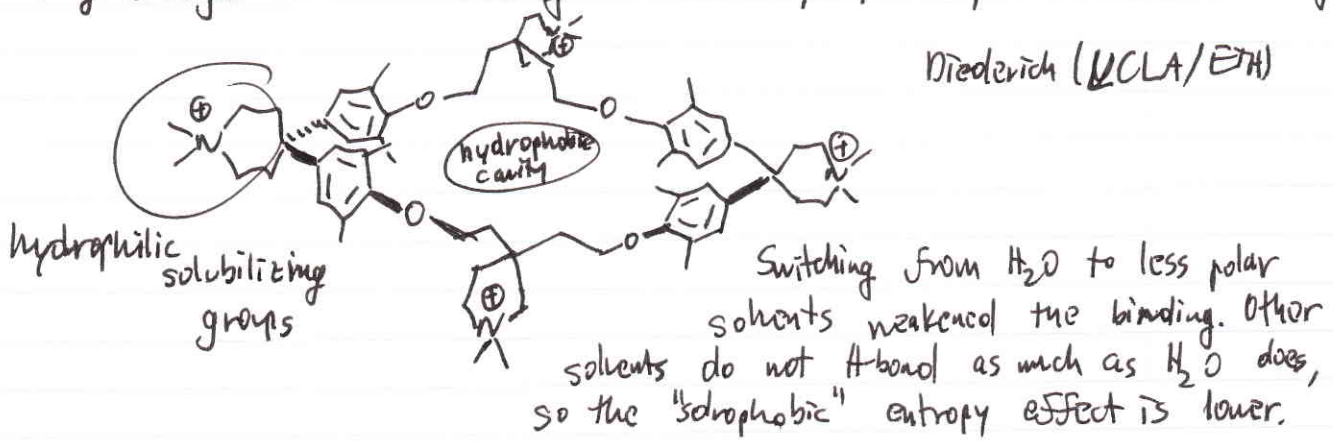
durene (tetramethylbenzene)
inclusion: crystallographically characterized
done @ pH < 2 to ensure water solubility

Other examples of polar cyclophanes:



Stoddart (1989)

Taking charges out of the ring increases hydrophobicity and assists in binding:



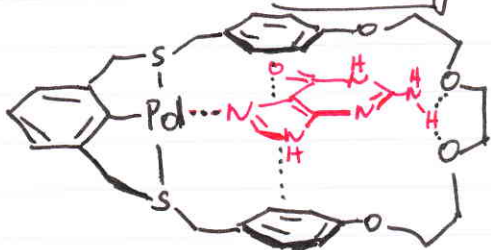
Other molecules used as hydrophobic binders:
 - cyclodextrins, calixarenes, carceranols

© Dative bond formation

Is $Pt \cdots NH_3$ bond covalent or non-covalent?

- one of the "grey areas"

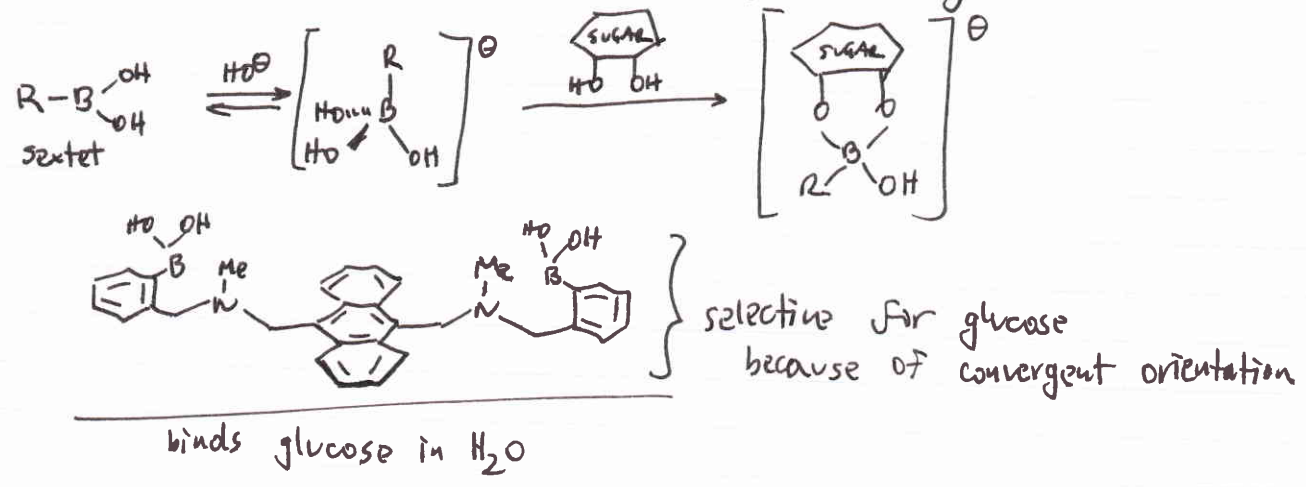
Dative bonds are strong and allow guest binding even in competitive media



Three different kinds of interactions stabilize this assembly

It can extract solid nucleobases into acetone.

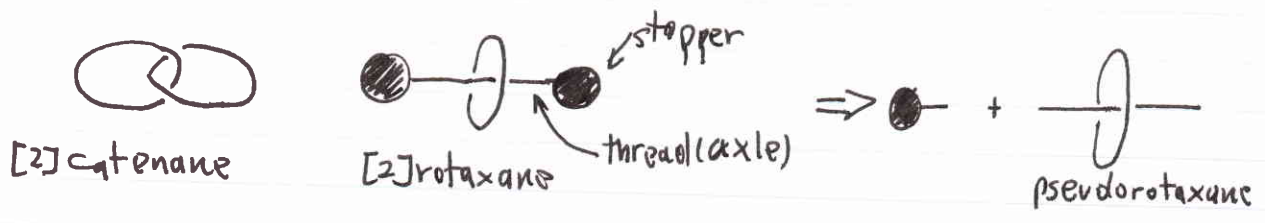
Seiji Iitaka => Boronic acid-based receptors for sugars:



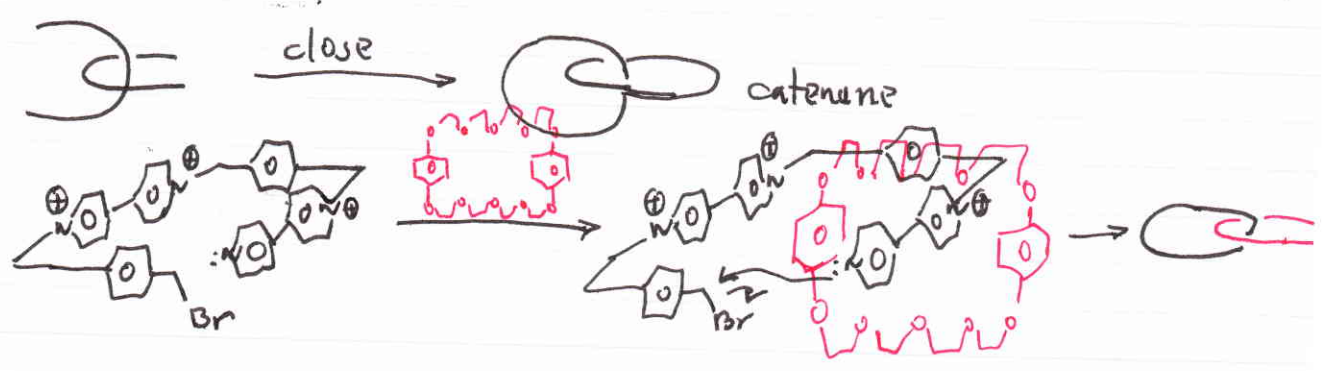
SOME SELECTED APPLICATIONS OF SUPRAMOLECULAR CHEMISTRY

② Mechanically interlocked molecules

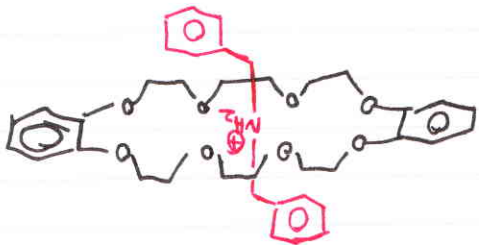
A class of molecules which are not held by covalent, but by mechanical bonds. Still, to break them apart, one needs to cleave a true chemical bond:



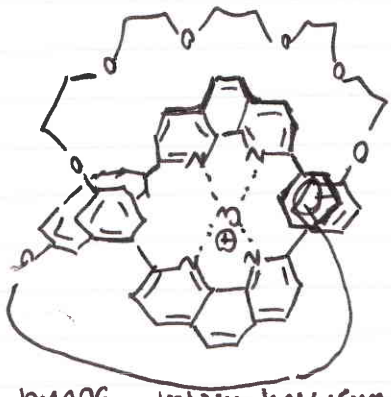
and many other topologies are possible...
Developing a synthesis of these molecules is very difficult without relying on supramolecular chemistry.



Hydrogen-bonded systems:



Transition-metal bond systems:



Jean-Pierre Sauvage

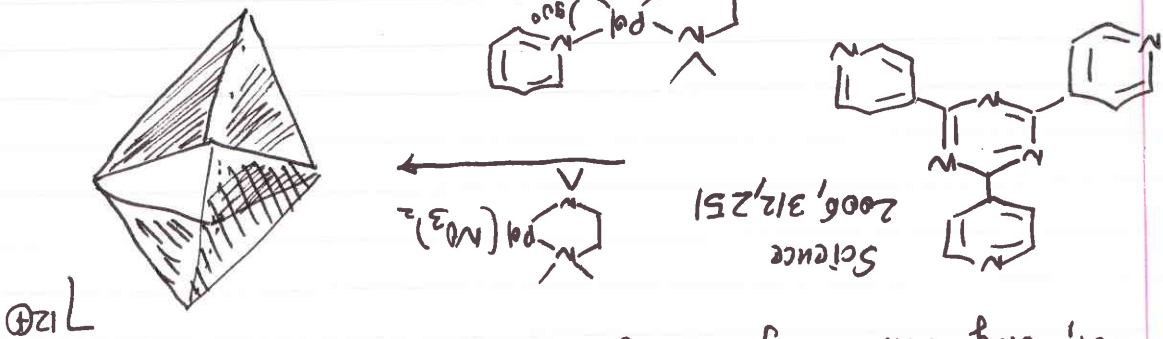
These systems can be used as molecular switches and machines.

③ Supramolecular catalysis

Rarely parallels molecular catalysis in TDN, but can often give unusual selectivities and/or induce reactivity in unusual media:



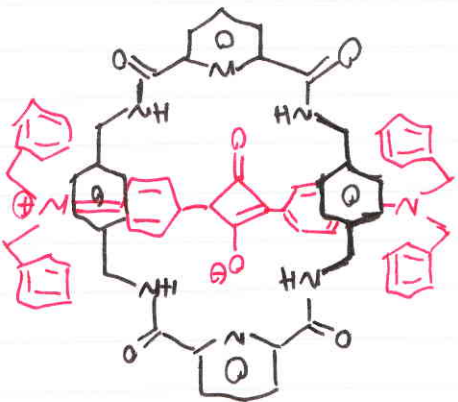
But, using Makoto Fujita's octahedron:



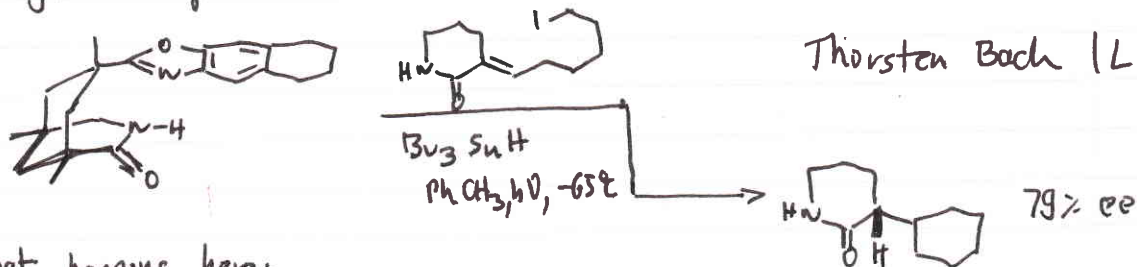
12M₃[⊖]

712[⊕]

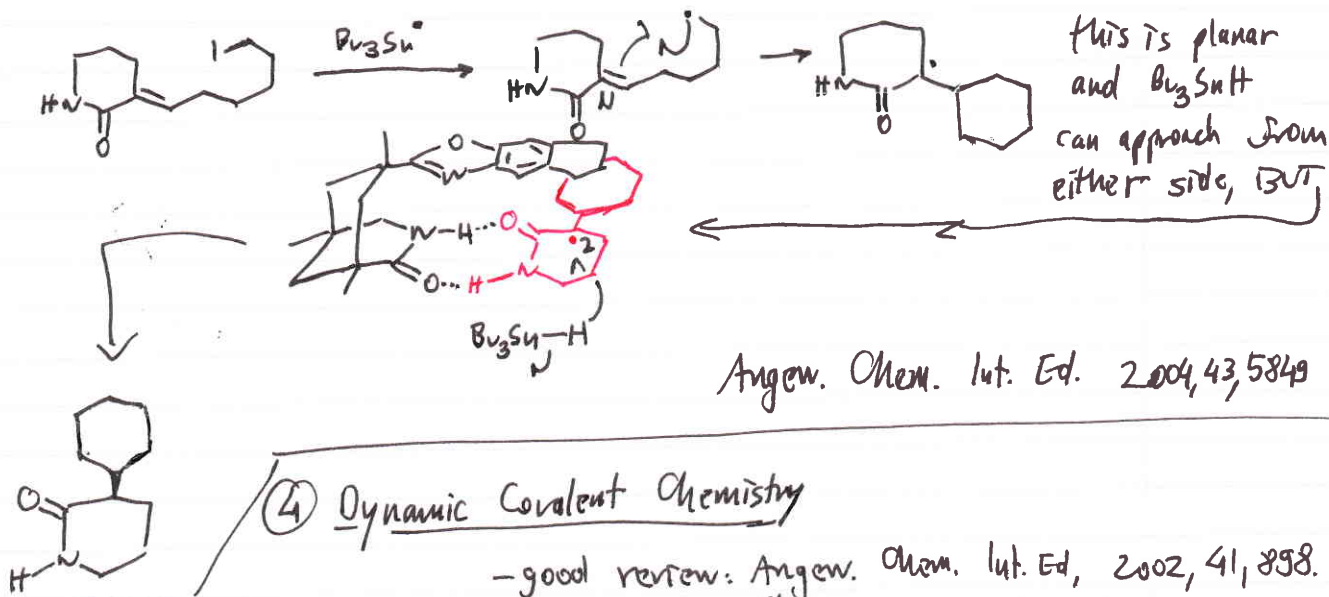
square dye is protected from solvent attack within this rotaxane



Hydrogen-bonding can induce stereoselectivity:

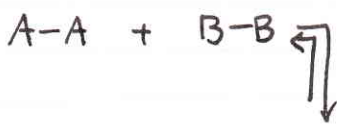


What happens here:



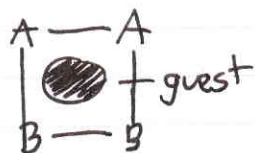
④ Dynamic Covalent Chemistry

- good review: Angew. Chem. Int. Ed. 2002, 41, 898.
Chem. Rev. 2006, 106, 3652



crazy mixture of compounds, comparable in stability (same bonds formed and broken)

But what if you can stabilize one of them?

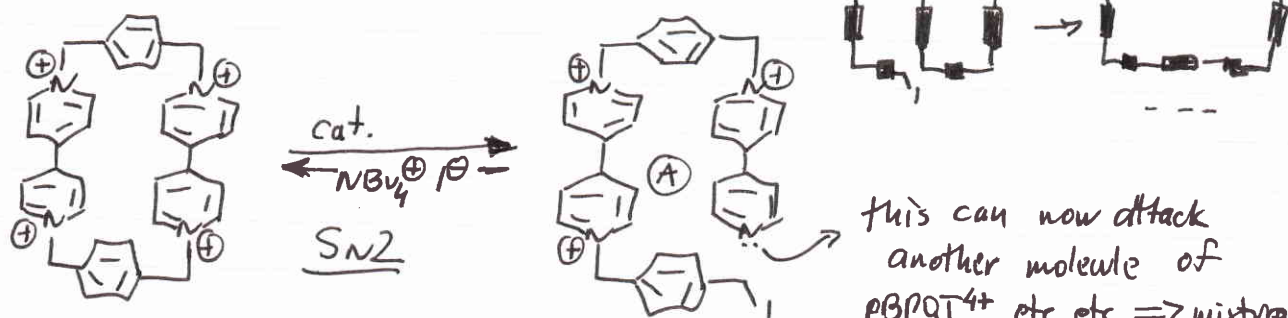


} now this combination is stable; since everything is reversible, eventually all the starting materials funnel into this product

This is Thermodynamically controlled synthesis - unlike most of synthetically useful reactions. If your product is not the thermodynamically most stable species \Rightarrow either give up or stabilize it!

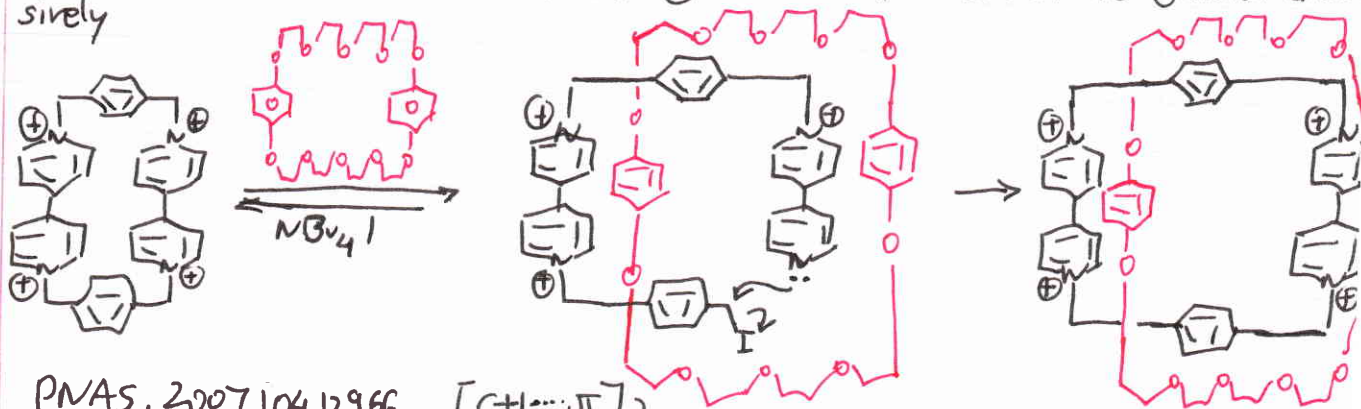
BENEFITS: If your product is stable, you will get ~100% yield, since reversibility assures full recycling of starting materials.

Example from my postdoc work:



All possible products have same bonds, so their stability is roughly the same.

But what if we stabilize compound (A) somehow? It should be formed exclusively



PNAS, 2007, 104, 12966



magic ring experiment

This approach was used to find and design natural receptors, substrates for enzymes, ion extraction agents etc.

Other reactions that are reversible: -imine exchange; -SH \rightarrow -S-S-; acetal exchange, transesterification etc...

This is the end of our course. We talked about:

- SMALL MOLECULES
- REACTIVE INTERMEDIATES
- "NO INTERMEDIATE" REACTIONS (PERICYCLIC)
- ORGANOMETALLICS
- BIG MOLECULES (POLYMERS, ORG. MATERIALS)
- SMALL MOLECULES THAT LIKE TO BE BIG (SUPRAMOLECULAR)

Still, there were a couple of common threads that (I hope) ran through the course:

- mechanisms
- methods for determining mechanisms
- structure ↔ reactivity relationships in the broad sense of the word
 - HOMO-LUMO gap
 - supramolecular affinity

EXAM: 12/17/2008; 5pm @ 201 SEC

Stop by my office any time before that
 problem-solving session on Friday
 will send out a pre-exam email
 PS10 is due 12/10 in my office