

Aromatic Interactions

1. Cation π

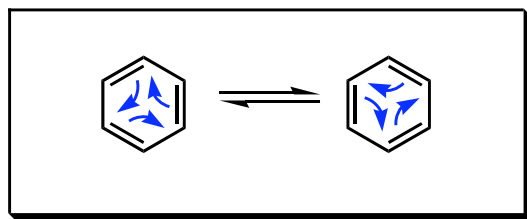
2. π - π

3. X-H π

Rob Knowles
MacMillan Group Meeting
February 9th, 2005

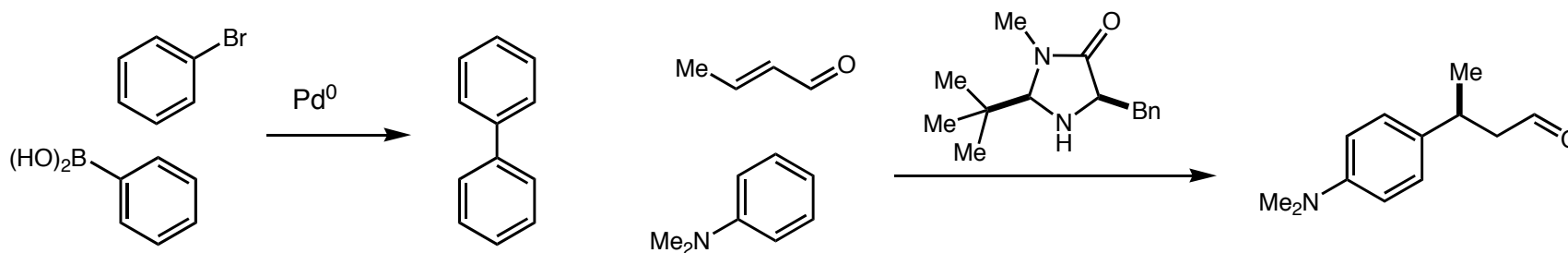
Perspective on Aromatic Chemistry

- Kekule puts forth a proposal for the nature of bonding in benzene in 1865



"I turned my chair to the fire [after having worked on the problem for some time] and dozed. Again the atoms were gamboling before my eyes.... all twining and twisting in snakelike motion. But look! What was that? One of the snakes had seized hold of its own tail, and the form whirled mockingly before my eyes. As if by a flash of lightning I awoke... Let us learn to dream, gentlemen." - Kekule

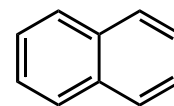
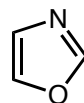
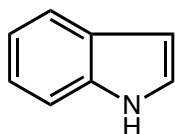
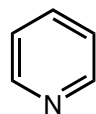
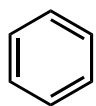
- In the late 19th century aromatic chemistry helps launch the development of modern organic chemistry and its associated industries



- Aromatic chemistry is still being actively researched and developed

Quick Review of Aromatic Chemistry

- Aromatic molecules are highly unsaturated and are remarkably stable



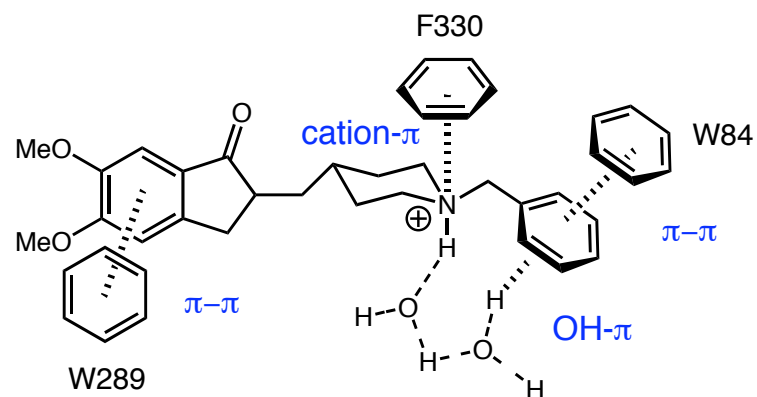
Rules for determining the aromaticity of a molecule

1. The molecule must have a cyclical, planar arrangement of p orbitals
2. There must be $(4n+2)$ electrons in the π system

- Aromatics typically undergo substitution reactions rather than the addition processes typical of olefins
- Resonance energy for benzene is 36 kcal/mol – it very much wants to retain its uninterrupted π cloud
- The unique electronic structure of aromatics gives rise to their interesting physical properties, not least of all the class of intermolecular forces known as the aromatic interactions

Aromatic Interactions

- Aromatic interactions are intermolecular forces involving π electron rich molecules that have long been known, but have long been ignored by organic chemists
- They are difficult to study, but aromatic interactions offer great potential in drug design, structural biology, conformational analysis and asymmetric catalysis



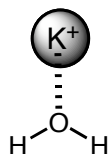
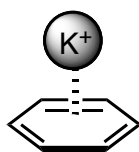
Binding of Eisai's anti-Alzheimer drug Aricept to active site of acetylcholinesterase from *Torpedo californica*

- Though related, the various aromatic interactions vary drastically in their strength, physical nature, and specificity. Thus it useful to consider them individually

The Cation π Interaction

- The cation π interaction arises from the electrostatic interaction of a cation with the face a π system
- First evidence of interaction in the gas phase came out of work by Kebarle in 1981

In a systematic study of ion solvation by various solvents, Kebarle happened upon the puzzling fact that benzene stabilizes K^+ ions better in the gas phase than water does!



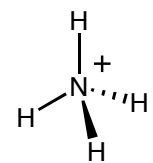
	ΔG (kcal/mol)
K^+ -Water	-18
K^+ -Benzene	-19

- Kebarle correctly postulated the interacting geometry was a result of the ion interacting with the quadrupole moment of benzene....more on this to come
- At the end of the paper describing this work Kebarle urges computational groups to model these systems in an attempt to reveal the nature of the interaction

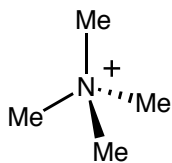
Cation π - Not Just for Metals Anymore!

■ In the mid 1980's research begins in earnest

■ Studies by Meot-Ner demonstrate the more complex organic cations are also good π binders in the gas phase



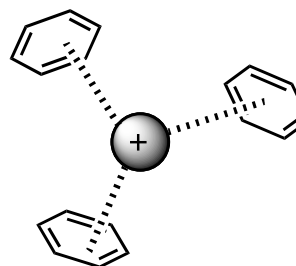
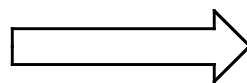
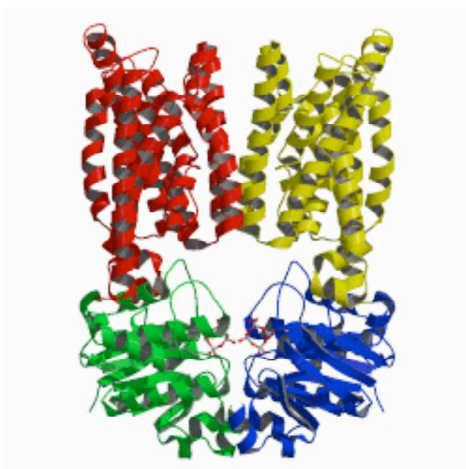
ammonium



tetramethylammonium (TMA)

	<u>ΔG (kcal/mol)</u>
NH₄⁺-Benzene	-19.3
NMe₄⁺-Benzene	-9.4

■ In a survey of 33 high resolution protein crystals structures, a significant tendency is noted for cations to be in close proximity to aromatic rings.



Meot-Ner, *JACS*, **1985**, 107, 474

Burley, *Science*, **1985**, 229, 23

A General Model for Cation π Interactions Emerges

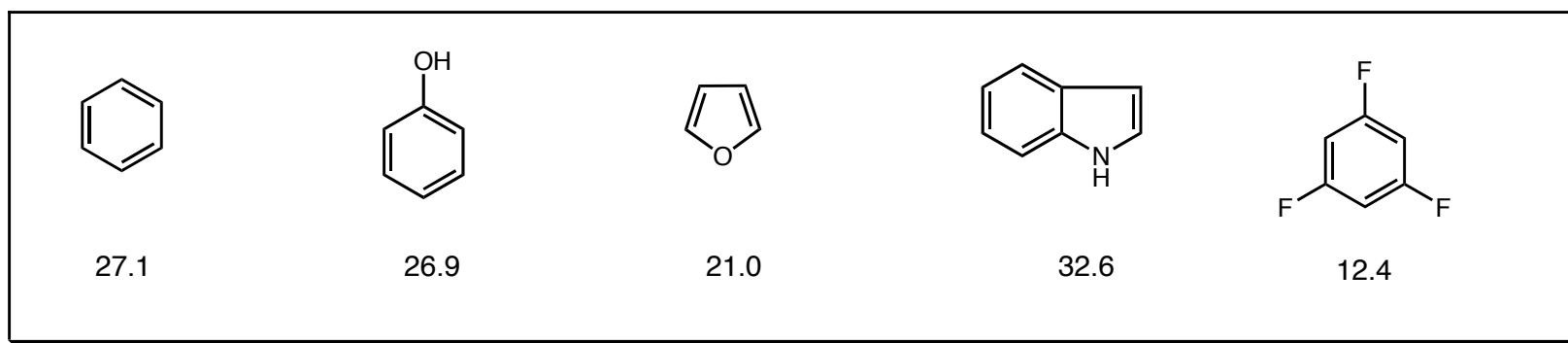
- Experimental and theoretical treatment of alkali cation-benzene complexes reveals a trend

	ΔG (kcal/mol)	
	<u>Experimental</u>	<u>Computational</u>
Li ⁺	-38.3	-43.8
Na ⁺	-28.0	-29.5
K ⁺	-19.2	-19.2
Rb ⁺	-	-15.8

1. The trend follows the classical electrostatic series i.e. the trend would be the same if benzene was replaced by chloride

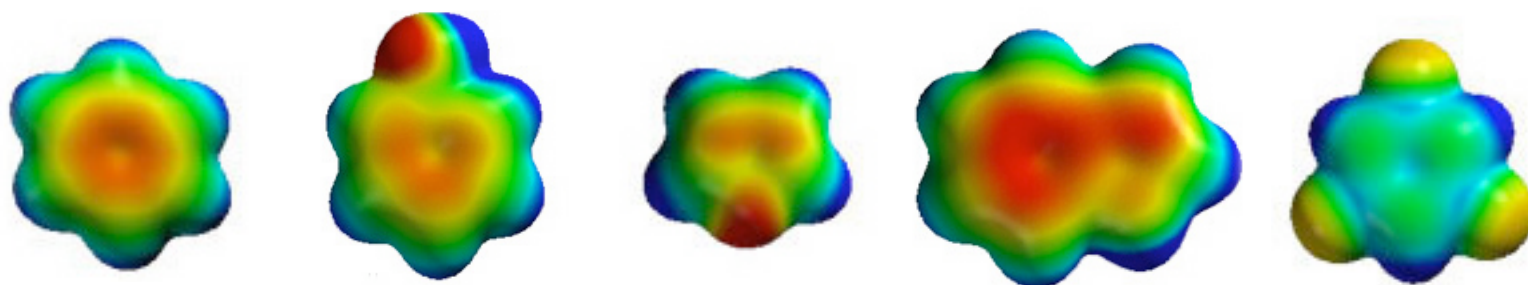
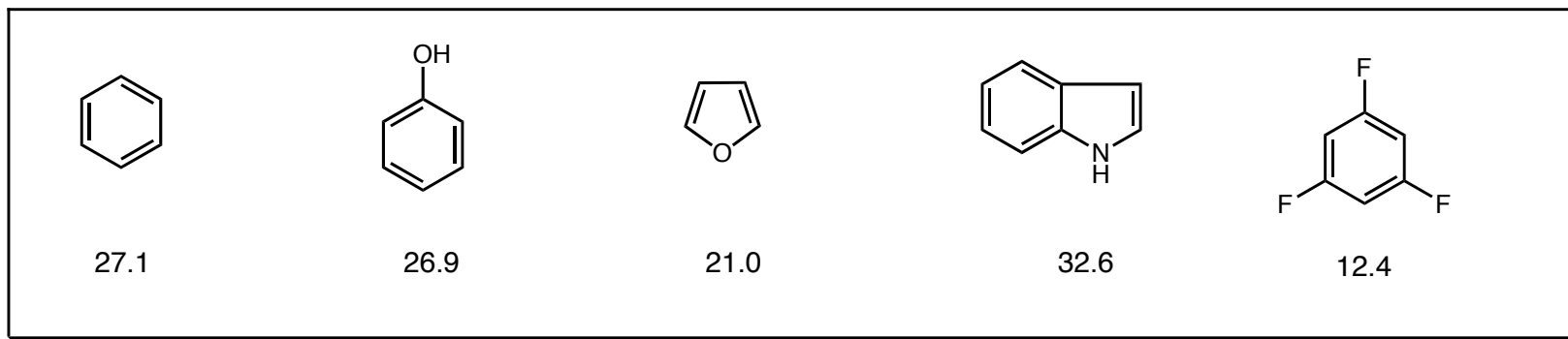
2. Quarternary amine binding shows that charge transfer does not play a big role i.e. FMO effects are not primarily involved

- Comparison of aromatics is informative (theoretical values for gas phase binding of Na⁺ in kcal/mol)



- Rationale can be drawn by observing electrostatic potentials of the aromatics...

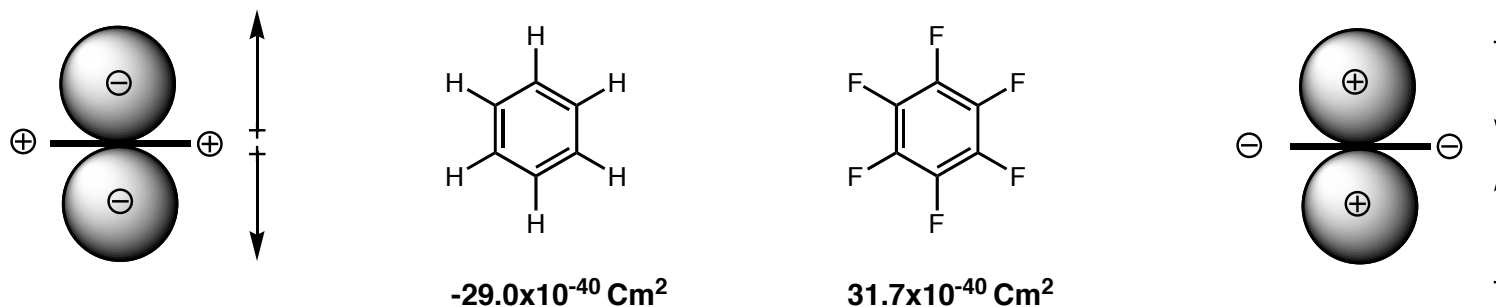
Electrostatic Surfaces



- The more negative the electrostatic charge over the center of the ring, the better cation π binder
- The physical basis for these energy surfaces stems from the molecular quadropole moment of each aromatic ring
- So...what is a quadropole moment?

Quadropole Moment

- The electrostatic interaction arises from the cation interacting with arene quadropole moment



- Quadropole moment comes from two dipoles aligned such that there is no net dipole moment . It is topologically analogous to the d_{z^2} orbital



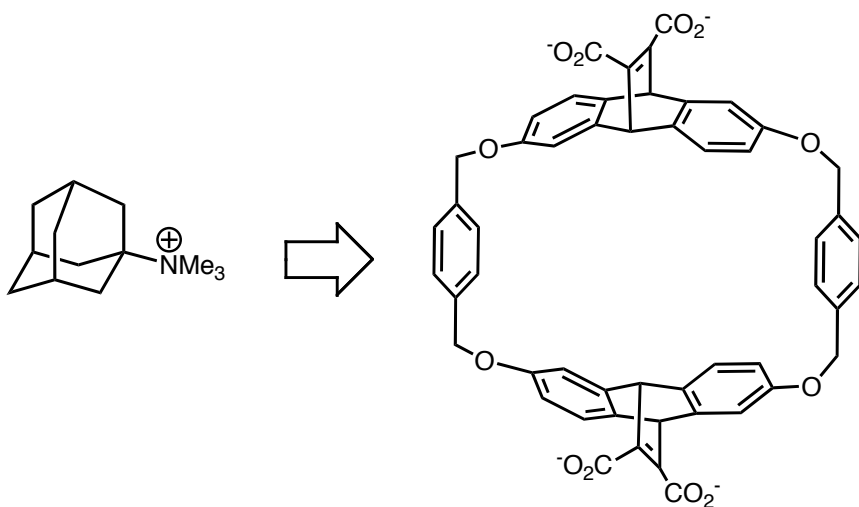
Theoretically, the ion-dipole interaction should not be any stronger than an ion-quadrupole interaction

Remember that sp^2 carbons are more electronegative than a proton. This gives rise to six dipoles that form the molecular quadrupole of benzene

- A caveat: Quadropole moments provide a way to visualize the electrostatic interaction and to predict the geometries of the complexes. However, strictly speaking they are not sufficient to estimate meaningful quantitative interaction strengths.

Dougherty Enters the Fray

■ In the mid 1980's supramolecular chemistry and selective binding was a hot topic. In fact, in 1987 Cram, Lehn, and Pedersen shared the Nobel Prize for their work in the field



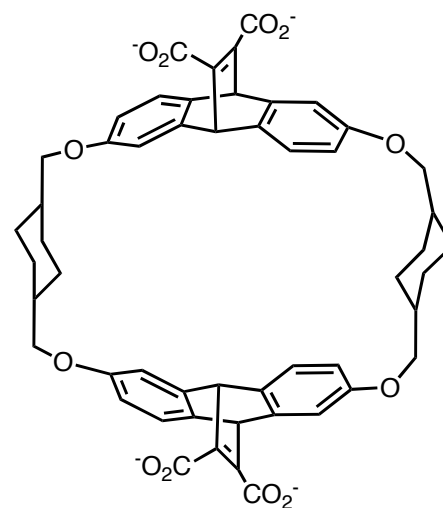
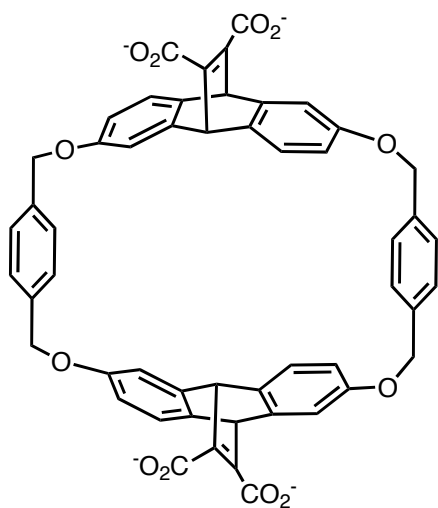
■ Most of the work upto 1986 had been based on binding flat aromatics, but Dougherty wanted to use his very hydrophobic cyclophanes to bind aliphatic molecules

■ The trimethyl ammonium end of the guest molecule was chosen to make the guest water soluble. However, it was found that alkylammonium end, not the adamantyl, that binds into the hydrophobic pocket of the host, even in aqueous solution.

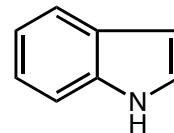
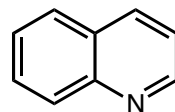
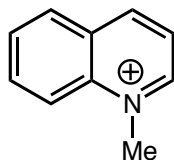
■ This went against all the contemporary dogma of host-guest chemistry, but Dougherty was able to see that something more interesting was at work.

A Breakthrough of Sorts

■ The host molecules are systematically varied and it is found that the phenyl cyclophane binds aromatics much better than does its cyclohexyl analogue.



■ Moreover, the phenyl host is found to bind cationic guests much more strongly than neutral or electron rich substrates

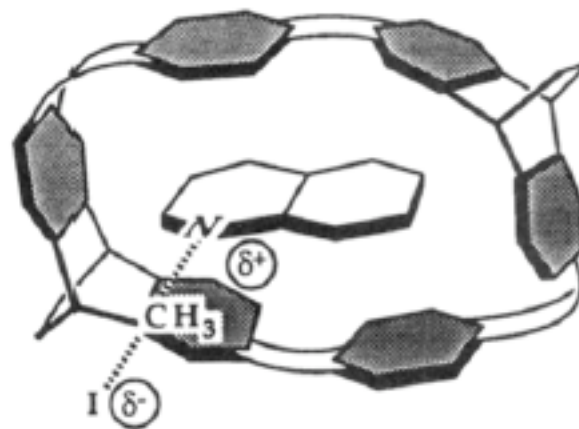
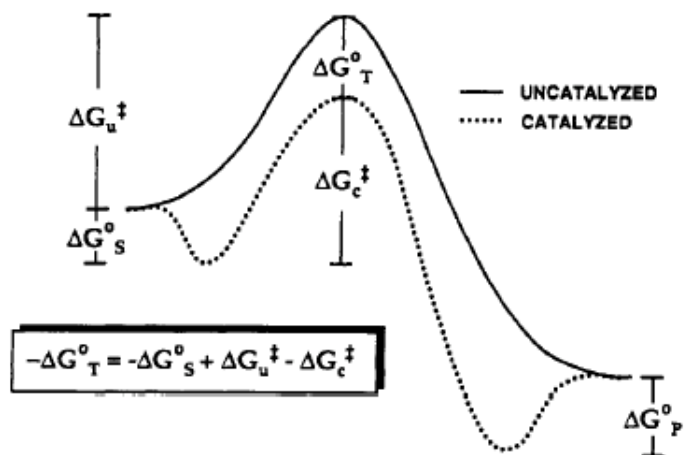


phenyl	400,000	10,000	1,400
cyclohexyl	27,000	22,000	1,600

Dougherty, *JACS*, **1988**, *110*, 1983

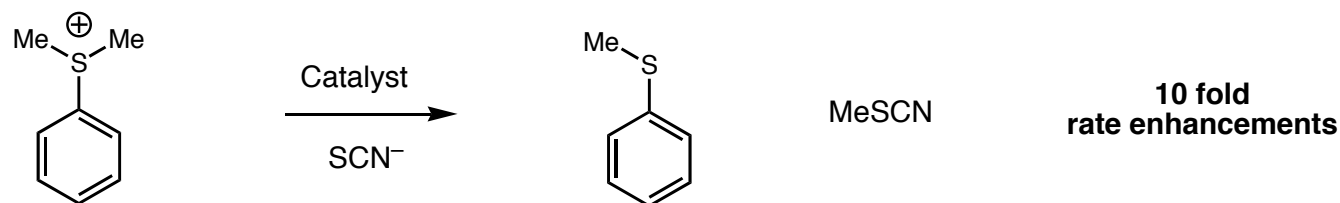
Cyclophanes Catalyze Alkylation

- Rate accelerations of upto 8,000% are observed in the alkylation of quinolines (Menschutkin Reaction)



- Dougherty calculates that catalysis lies in the fact that the host cyclophane binds more tightly to the transition state than to the substrate or the product. This is attributed to both cation π and polarizability effects.

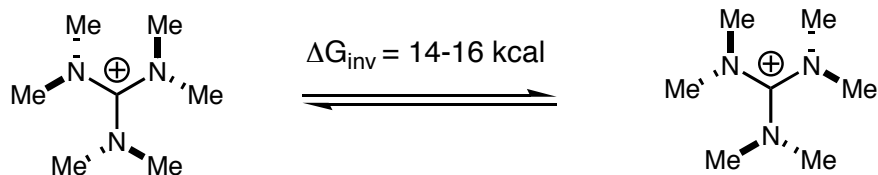
- Thus by the same logic, the same cyclophane catalyst can also accelerate the rate of the reverse reaction



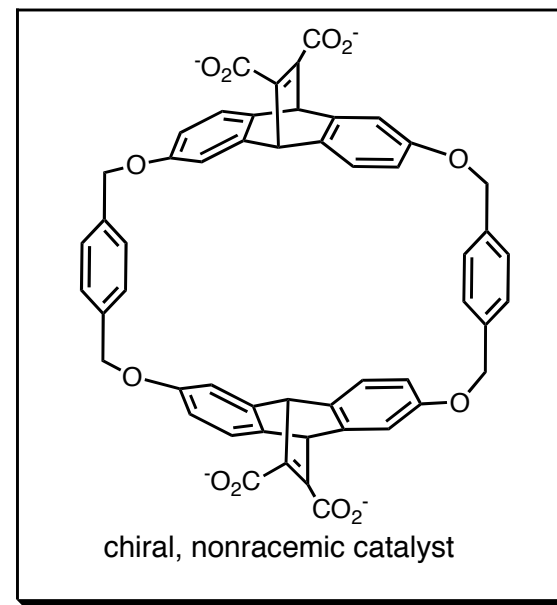
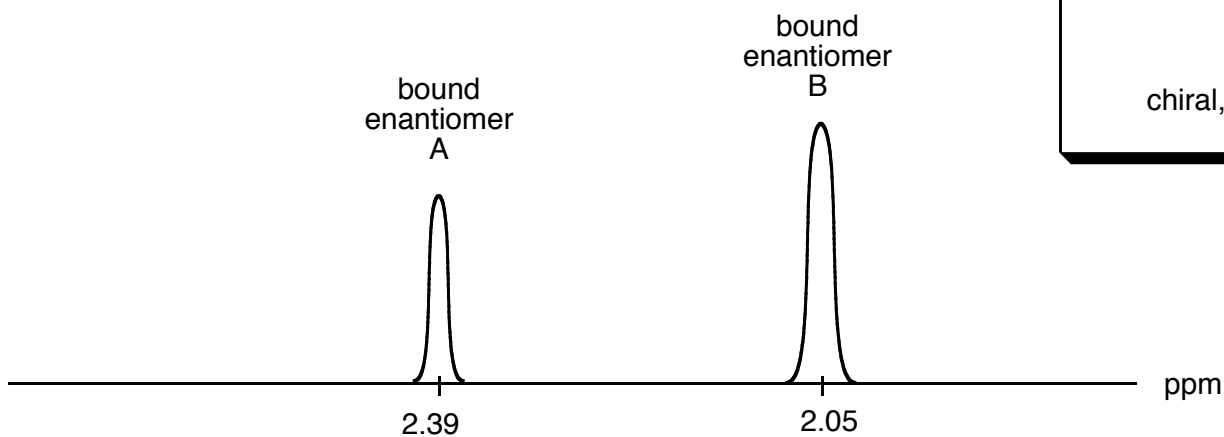
Dougherty, *JACS*, 1992, 114, 10314

Enantioselective Recognition in Cation Binding Hosts

- Hexamethylguanidiniums are D_3 symmetric, like a propeller



- Inversion is facile at room temperature, but is slow on NMR timescale



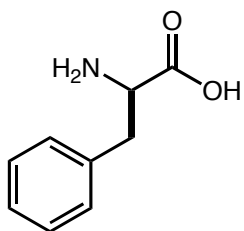
- Selective complexation of one enantiomer is weakly favored by approximately 0.5 kcal/mol, but shows evidence that selective binding is possible.

Dougherty, *JACS*, **1993**, *115*, 9907

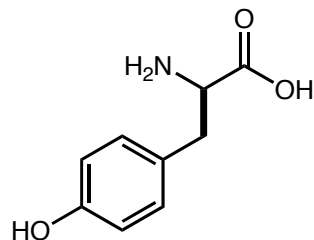
Dougherty, *JACS*, **1992**, *114*, 10314

Putting the Pieces Together

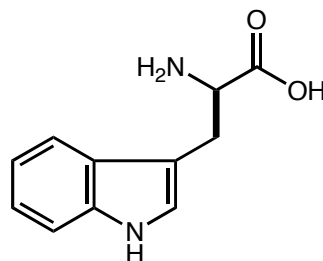
■ From the cyclophane work we learned that cation π effects can pluck cations out of water in hydrophobic pockets, enable novel forms of catalysis, and permit enantioselective active site binding



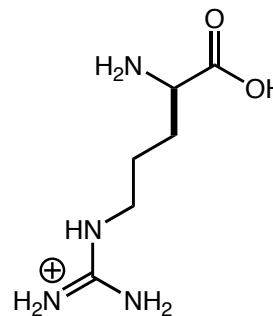
phenylalanine



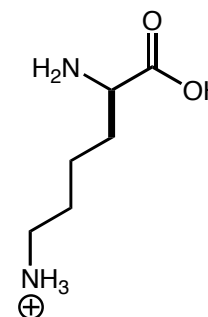
tyrosine



tryptophan



arginine



lysine

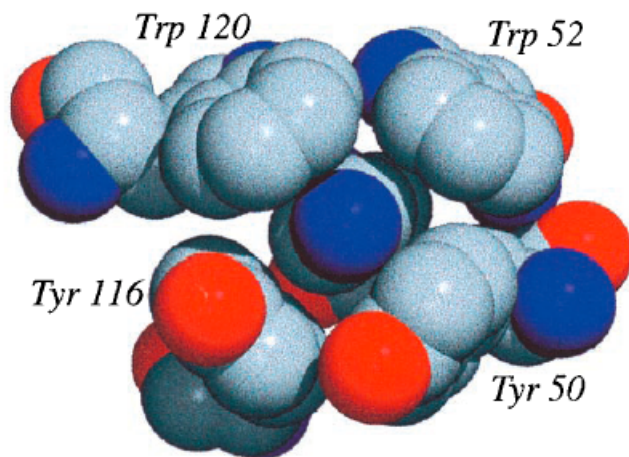
■ It was becoming clear that this force might likely be a powerful organizational force in protein structure

■ Dougherty realizes that these residues have a highly complimentary and unique functional ability, to be hydrophobic and neutral polar groups.

■ This intermolecular force can even be strong and specific in pure water, where more typical strong noncovalent forces seem to fail (i.e. ion pairs and hydrogen bonds)

Cation π Interactions in Proteins

- Survey of protein database shows that cation- π stabilization is a major facet of protein structure and enzyme catalysis



Fragment of protein glucoamylase. The total stabilization energy is roughly -22 kcal/mol.

- A comprehensive survey that one out of every 77 residues is involved in an energetically meaningful cation π interaction
- As a general rule arginine binds more often than does lysine
- Similarly tryptophan participates more commonly than phenylalanine or tyrosine do.
- As a result of this work cation π effects are now considered as important as hydrogen bonding, ion pairing, and hydrophobic effects in determining protein structures

Cation π Interactions in Water

- In the early 1990's cation π binding is postulated to be operative in highly selective K^+ channels. These channels exhibit selectivities for K^+ over Na^+ that are greater than 1000:1.
- Dougherty investigates the cation π energies for the alkali metals in aqueous solution computationally and finds that the trend is very different than it was in the gas phase.

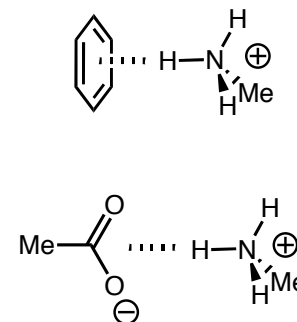
Gas Phase	$Li^+ > Na^+ > K^+ > Rb^+$
Aqueous	$K^+ > Rb^+ \gg Na^+, Li^+$

- The explanation comes from the fact that Li^+ ions bind most strongly to π systems, but they are also the most strongly solvated in aqueous solution. The desolvation energy required for them to bind to the benzene ring is just too high
- K^+ ions are less strongly solvated by water but are still good π binders. As a result of balancing these forces, it was shown that K^+ is the best alkali metal binder in aqueous solution

Computational Studies Show Surprising Results

- High level theoretical comparison of cation π binding with salt bridges in a range of solvents

<u>Interaction Energy (kcal/mol)</u>			
	<u>Benzene</u>	<u>Acetate</u>	<u>Dielectric</u>
Gas	-12.5	-125.5	1.0
CCl₄	-7.8	-53.4	2.2
EtOH	-5.6	-5.2	24.9
CH₃CN	-5.6	-3.8	37.5
H₂O	-5.5	-2.2	78.0



- Cation π is strong and specific even across a range of solvents, whereas most other intermolecular forces are sharply attenuated in polar media.
- Ions must desolvate to bind one another. They also neutralize each other to some extent, and thus decrease their long range solvation. For cation π , benzene is already desolvated in water to a large extent, and no charge cancellation occurs so the cation can still reap the benefits of long range solvation
- Dougherty claims that most cation π interactions in proteins are located at the surface, where salt effects would be the weakest. This points again to the importance of cation π events in protein structure

Counterion Effects

■ In tight ion pairs the anion will effect the ability of the cation to participate in cation π binding. Until 1999 the effect of counterion had never been comprehensively studied

<u>Binding Energy (kcal/mol)</u>			
	<u>Tetramethylammonium</u>		<u>Acetylcholine</u>
picrate	-8.35	iodide	-5.99
triflate	-7.68	bromide	-3.88
TFA	-6.05	chloride	-3.21
chloride	-4.64	picrate	-6.33
acetate	-2.70	2,4 DNN	-4.64

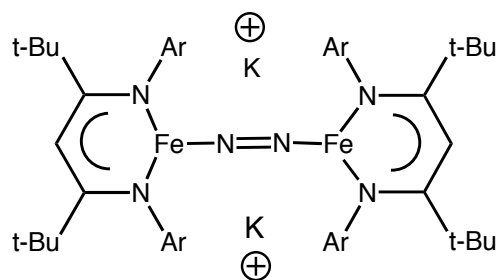
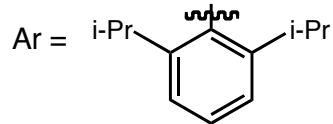
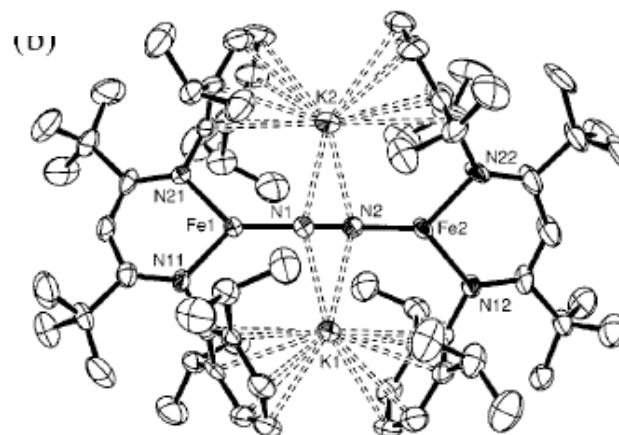
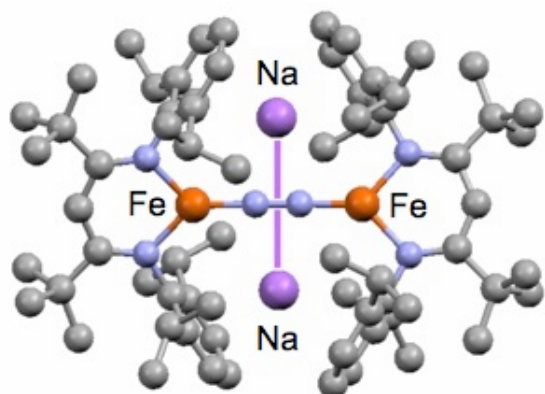
■ The measurements were made by examining the binding strengths of the salts above to cyclophane hosts. Most early cation π work was done in borate buffers where the anion was overwhelmed by borate and counterion effects were washed out.

■ Computational studies show that strongly associated counterions can diminish the strength of the interaction by upto 80%

■ Correlation shown that least soluble salts are the most strongly bound, other features of this are still being worked out

Cation π in Nitrogen Fixation?

- Pat Holland notices potassium ions in his dinitrogen structure seem to stabilize the complex

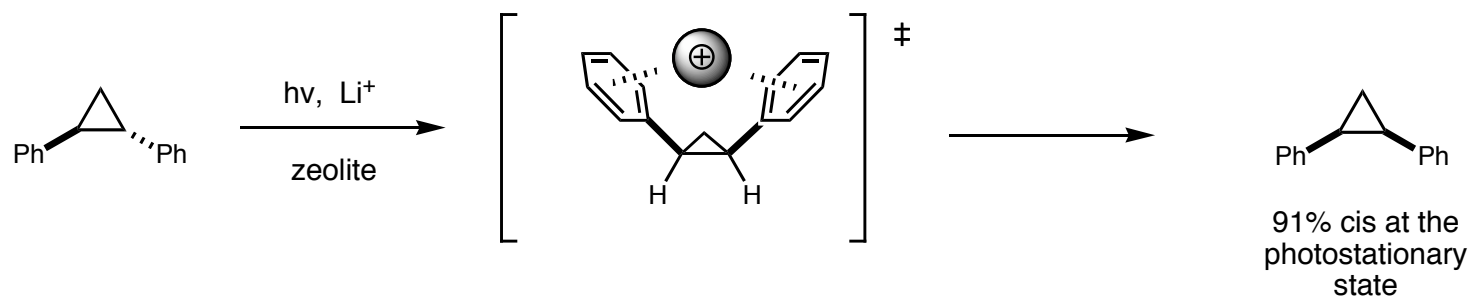


Bimetallic
catalysis is often
found in
biological systems

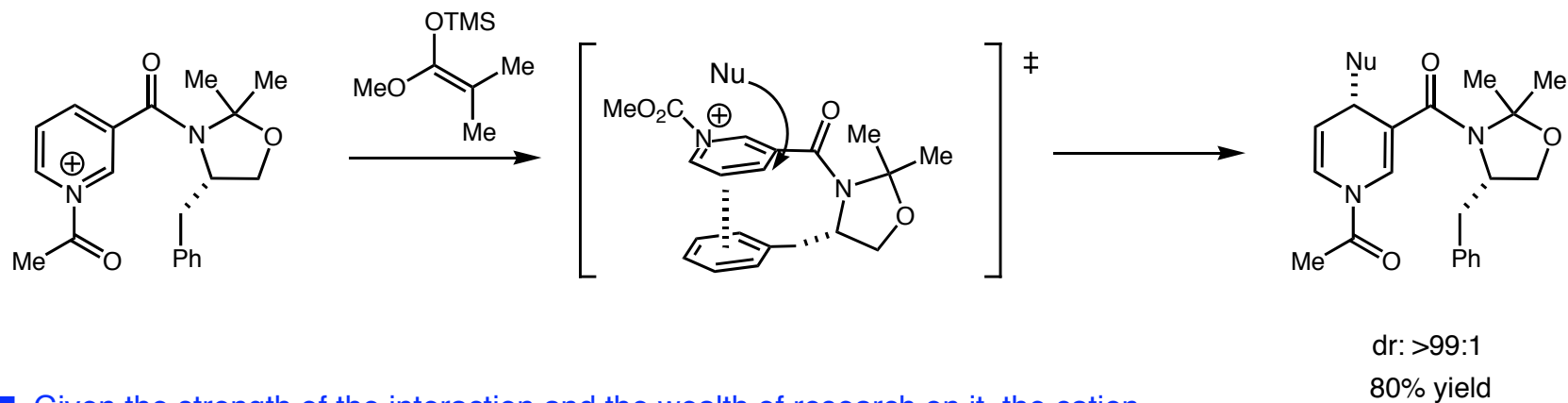
- Holland postulates that potassium may be important. Haber-Bosch process requires addition of potassium powder that is known to promote N_2 binding

Cation π in Stereoselective Synthesis

- Diphenyl cyclopropanes can be photoisomerized in the presence of alkali metal ions



- Yamada uses cation π effects to direct nucleophilic additions to pyridinium ions



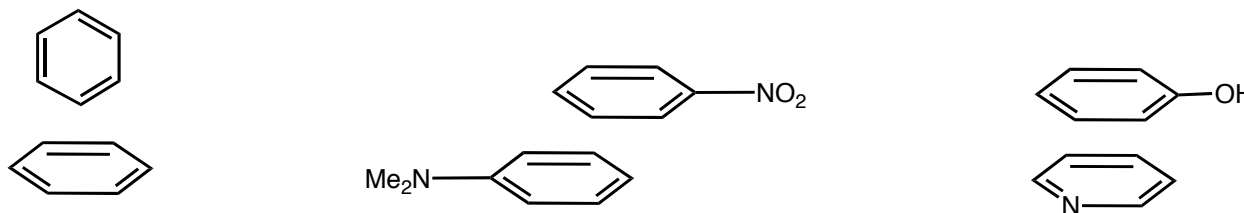
- Given the strength of the interaction and the wealth of research on it, the cation π interaction has been woefully underutilized in synthesis

Rammamurthy, *JACS*, **2000**, *122*, 4825

Yamada, *JACS*, **2002**, *124*, 8184

π - π Interactions

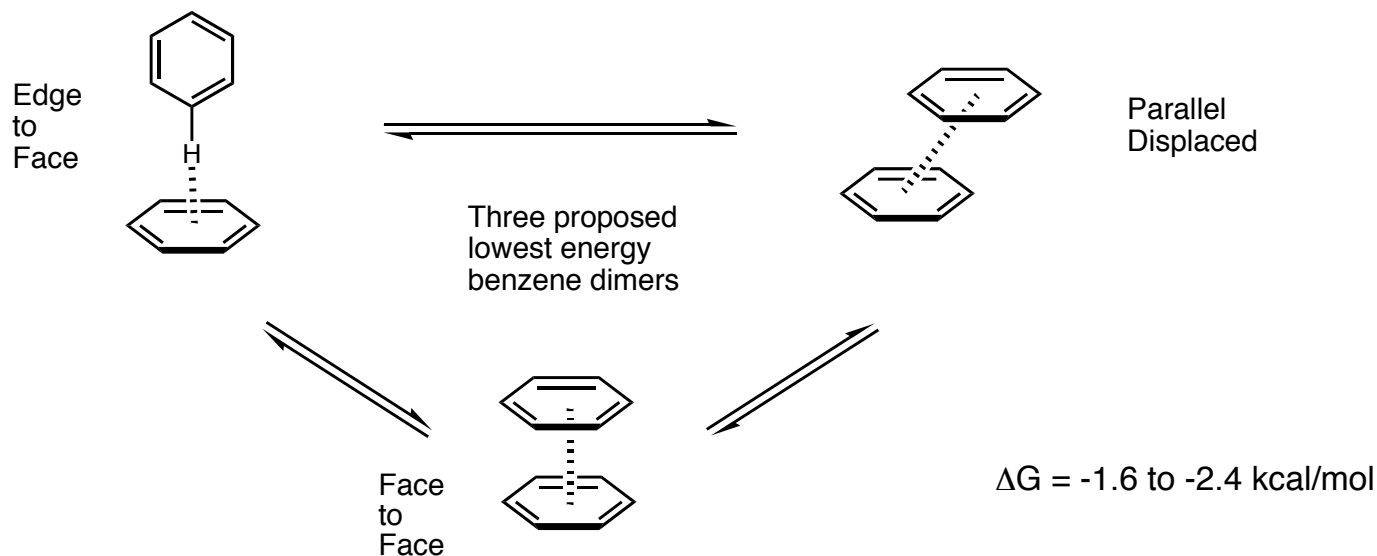
- This class of interaction involves direct attraction between arene rings



- This was long considered to be a charge transfer phenomenon, but this was later disproved
- The main energetic contribution to these interactions are VDW dispersion and electrostatics but there is considerable debate about which is dominant
- These interactions have been implicated in DNA stabilization, drug intercalation, protein structure and widely in supramolecular chemistry
- Caveat: These interactions are still being actively debated in the literature. All results must be taken and applied with caution

Benzene Dimer: An Unending Source of Controversy

- The lowest energy conformation is continually debated in the literature

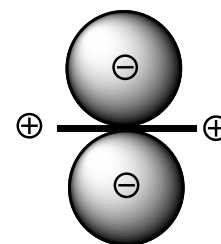


- Barriers to interconversion between the three are all very low, and it is likely that they exist in a dynamic equilibrium. All three are energetically attractive
- Experimental evidence points to the edge to face interaction as being the true ground state
- Theoretical predictions are all over the map. The simplest model of the interaction proves to be exceedingly difficult to study theoretically

A Model for $\pi - \pi$ Interactions

- This went largely unstudied until about 1990, when Hunter and Sanders began to investigate
- They proposed an electrostatic model to account for the energetics and geometries of the complexes

1. The σ and π systems are considered separately
2. Aromatic molecules attract one another when π system on one arene interacts more strongly with the σ system of the other than the $\pi-\pi$ repulsion destabilizes the complex



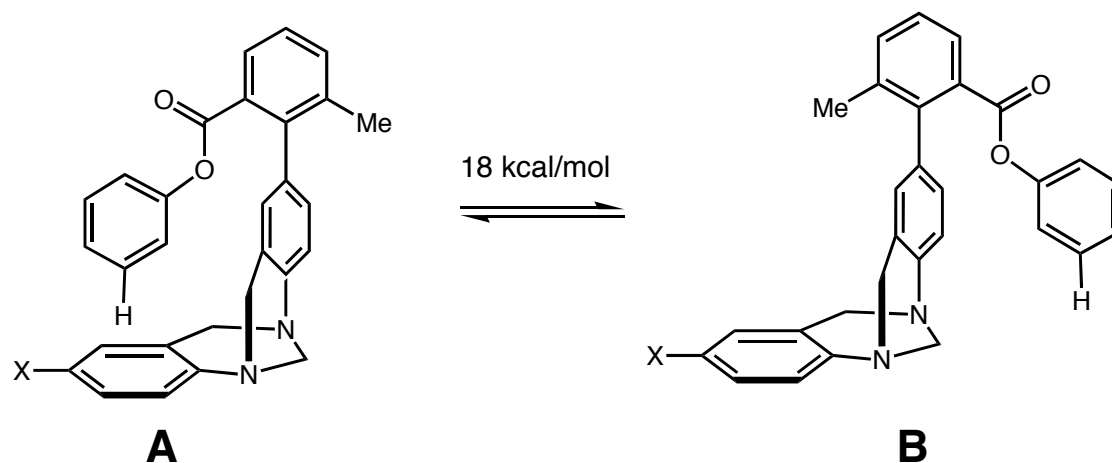
- Application of this model gives a set of empirical rules to rationalize $\pi-\pi$ complexes

1. $\pi - \pi$ repulsion terms disfavor the face to face interaction
2. $\pi - \sigma$ attraction terms dominate the edge to face interaction
3. $\pi - \sigma$ attraction terms dominate the offset interaction

- Substituent effects become very important in ordering the balance between attractive and repulsive forces

Torsional Balances Lead Everyone Astray

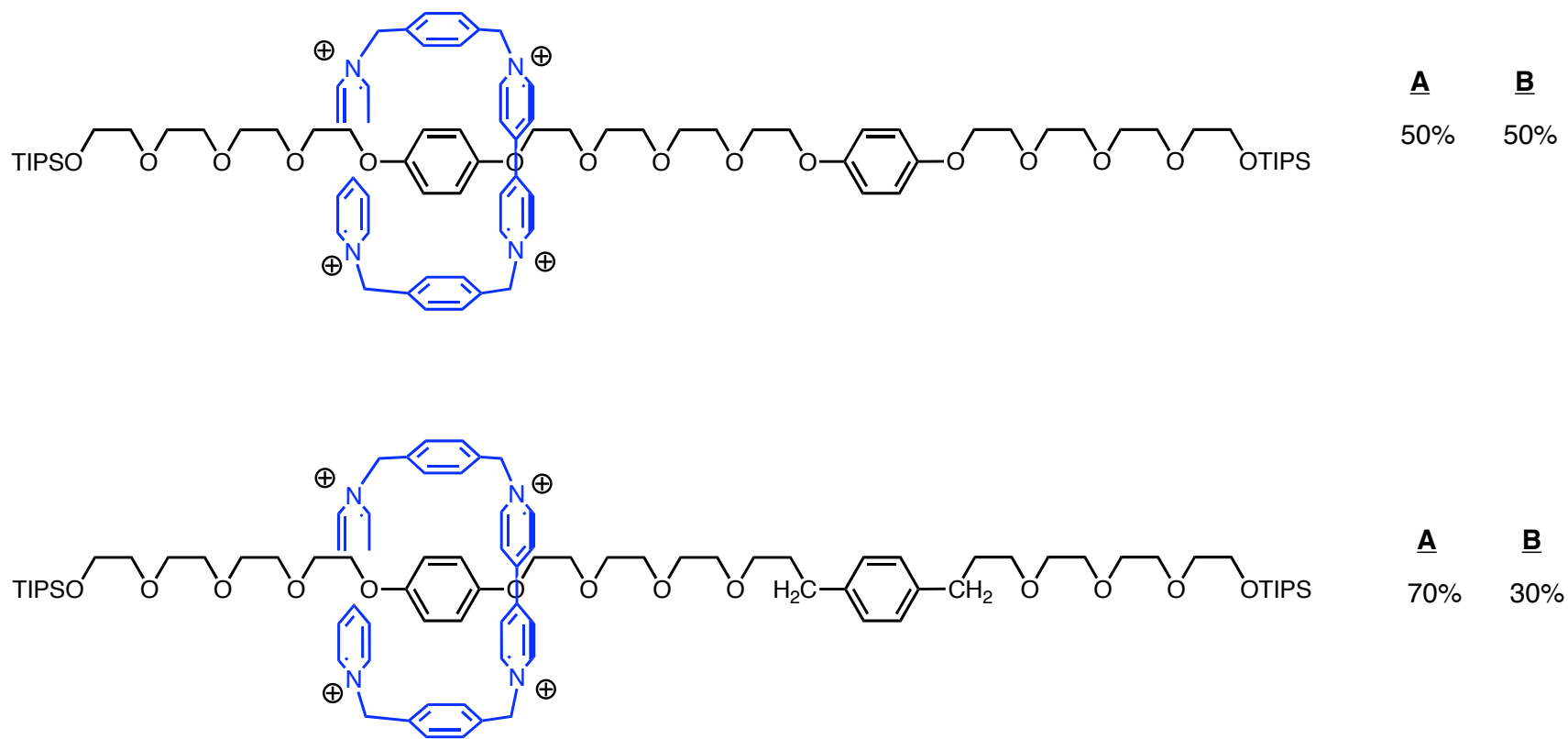
- Wilcox proposes an NMR study to determine equilibrium constants that should help quantify energetics of edge to face interaction



- A small attractive interaction was found to stabilize A by about 0.24-0.65 cal/mol for a range of X, with strongly electron donating substituents being best
- In a subsequent investigation, the isopropyl and tertbutyl esters were found to give similarly sized interaction energies, which calls the importance of the edge to face interaction into question.
- This is further proof that a clear understanding of these interactions is currently elusive

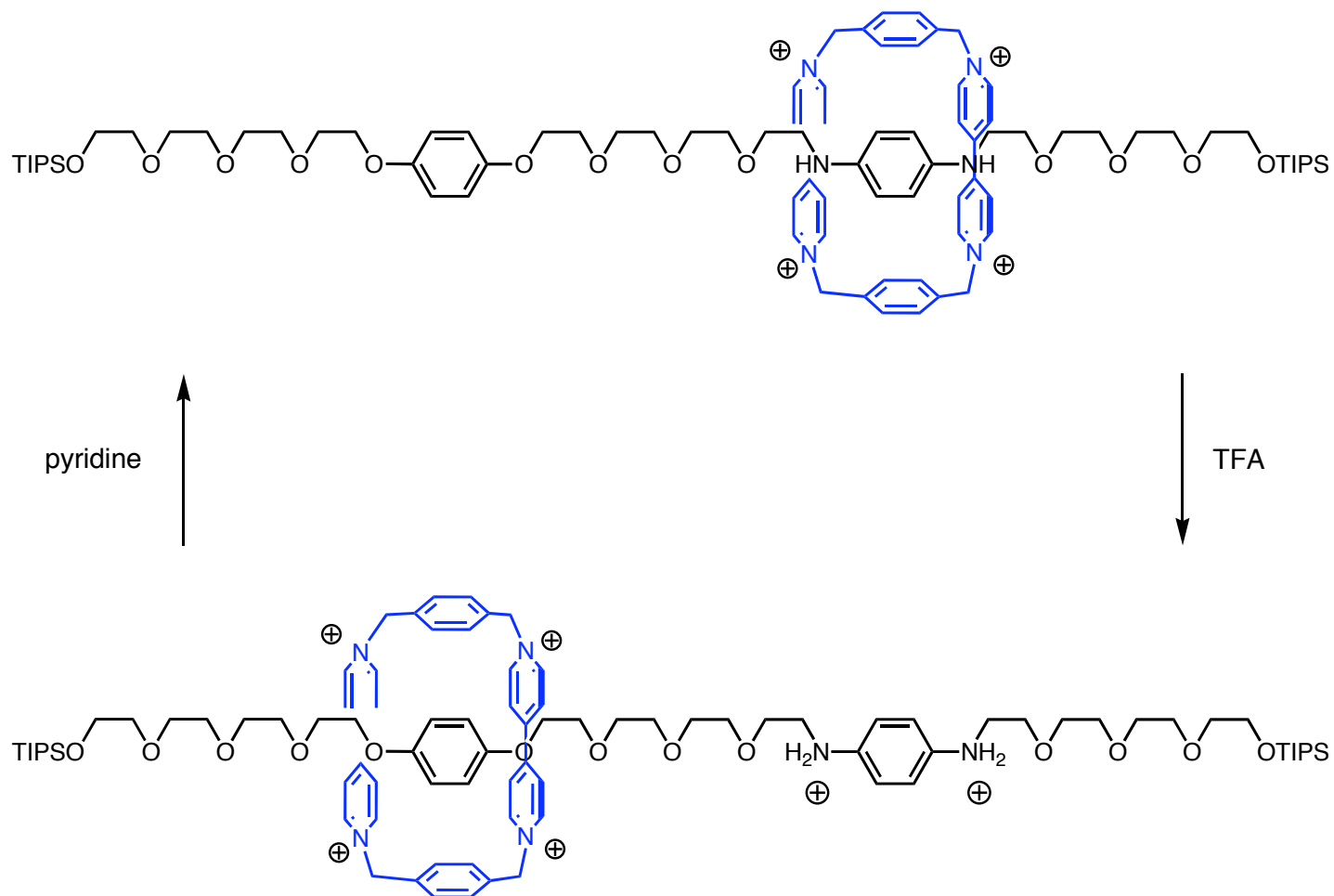
Applications of Aromatic Stacking in Organic Chemistry

- Stoddart employs π stacking in his molecular switches



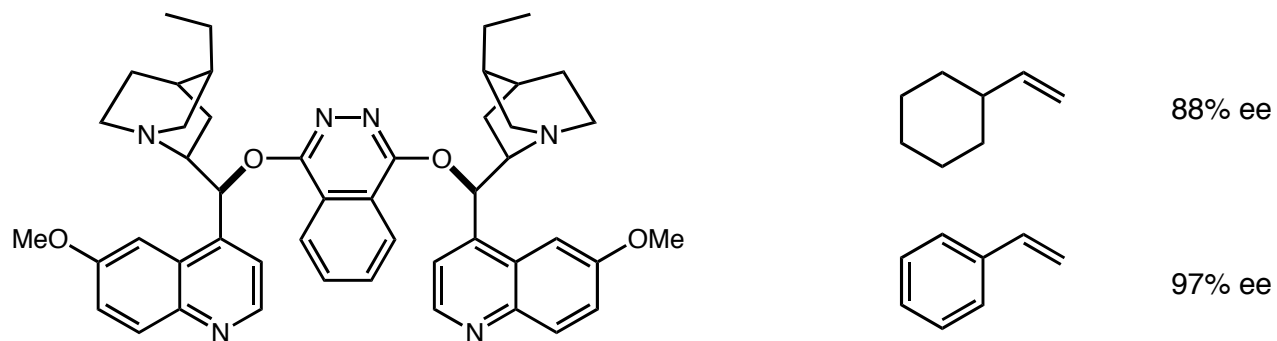
Stoddart Strikes Again

- Stoddart makes a molecular shuttle



Aromatic Stacking in Asymmetric Dihydroxylation

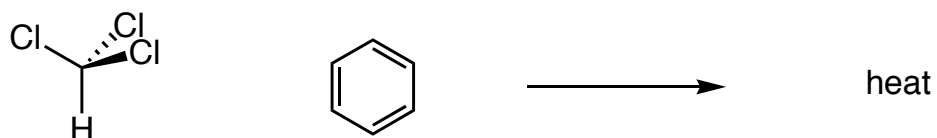
- Sharpless contends that some π stacking may be involved in dihydroxylation with phthalazine ligands



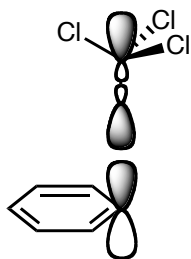
- In general aromatic substrates have significantly higher binding constants to the metal ligand complex
- He also notes that aromatic substrates give very high ee's with this ligand set compared to alkyl substrates

The CH- π Interaction

- First postulated by Tamres in 1952 who noted that dissolving benzene in chloroform was exothermic



- This result was followed up by extensive NMR and IR studies showing that these interactions are qualitatively similar to hydrogen bonds
- Unlike the cation π , the strength of the CH- π interaction arises mainly from charge transfer (frontier orbitals)



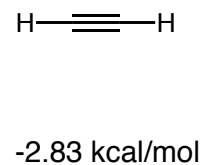
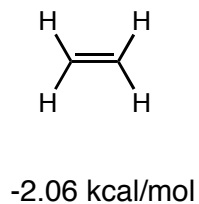
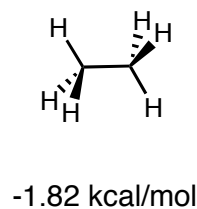
$\pi-\sigma^*$

This gives rise to interaction geometries where the CH bond lies directly in line with a p orbital on the ring.

- Nishio reports that roughly 29% of all known organic crystal structures in the Cambridge database containing a phenyl ring and an alkane region show evidence of a CH- π interaction

The Weakest Hydrogen Bond

- The strength of the interaction is related directly to the acidity of the C-H bond

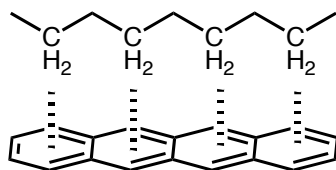


Arenes are referred to as being weak, soft bases

- Exceptionally short CH- π bond lengths are known

Bond Length (\AA)	
CH- π	2.24
H - F	2.25
H - Cl	2.34

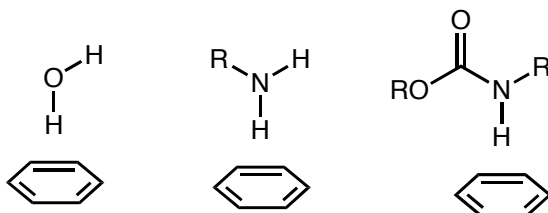
- Though these bonds are individually quite weak, their effects can be additive and in macromolecular systems their influence can be pronounced



$$4 \times -1.82 = -7.28 \text{ kcal/mol}$$

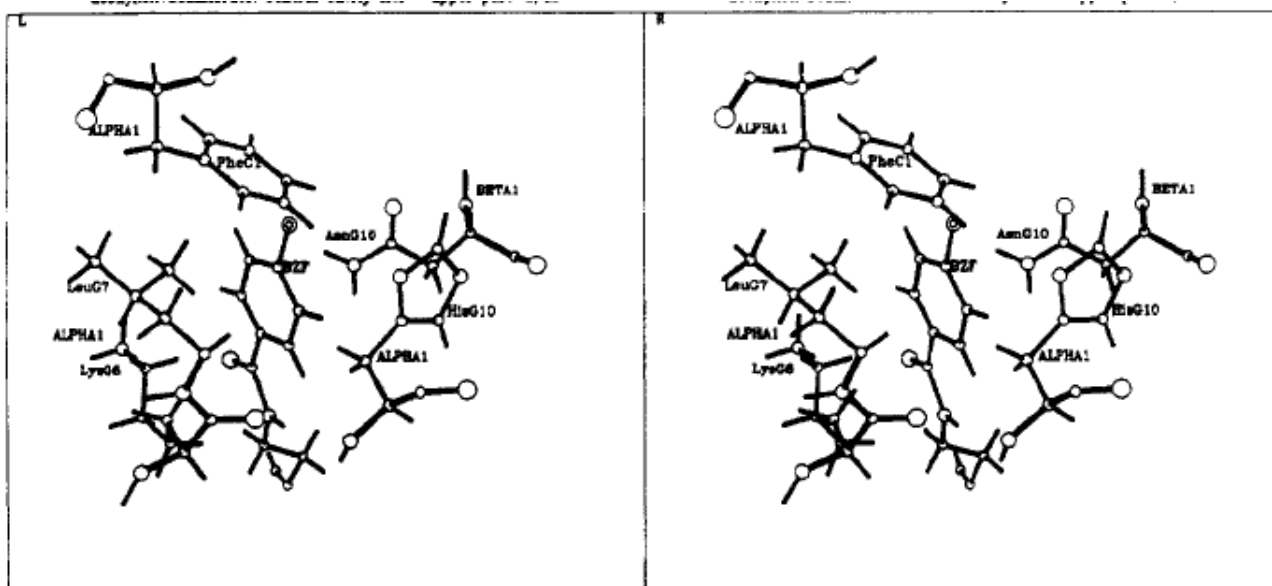
OH and NH Bonding to Aromatics

- Alcohols, amides and amines all bind to aromatic rings



Benzene-water complex is energetically favored by about -2.0 kcal/mol

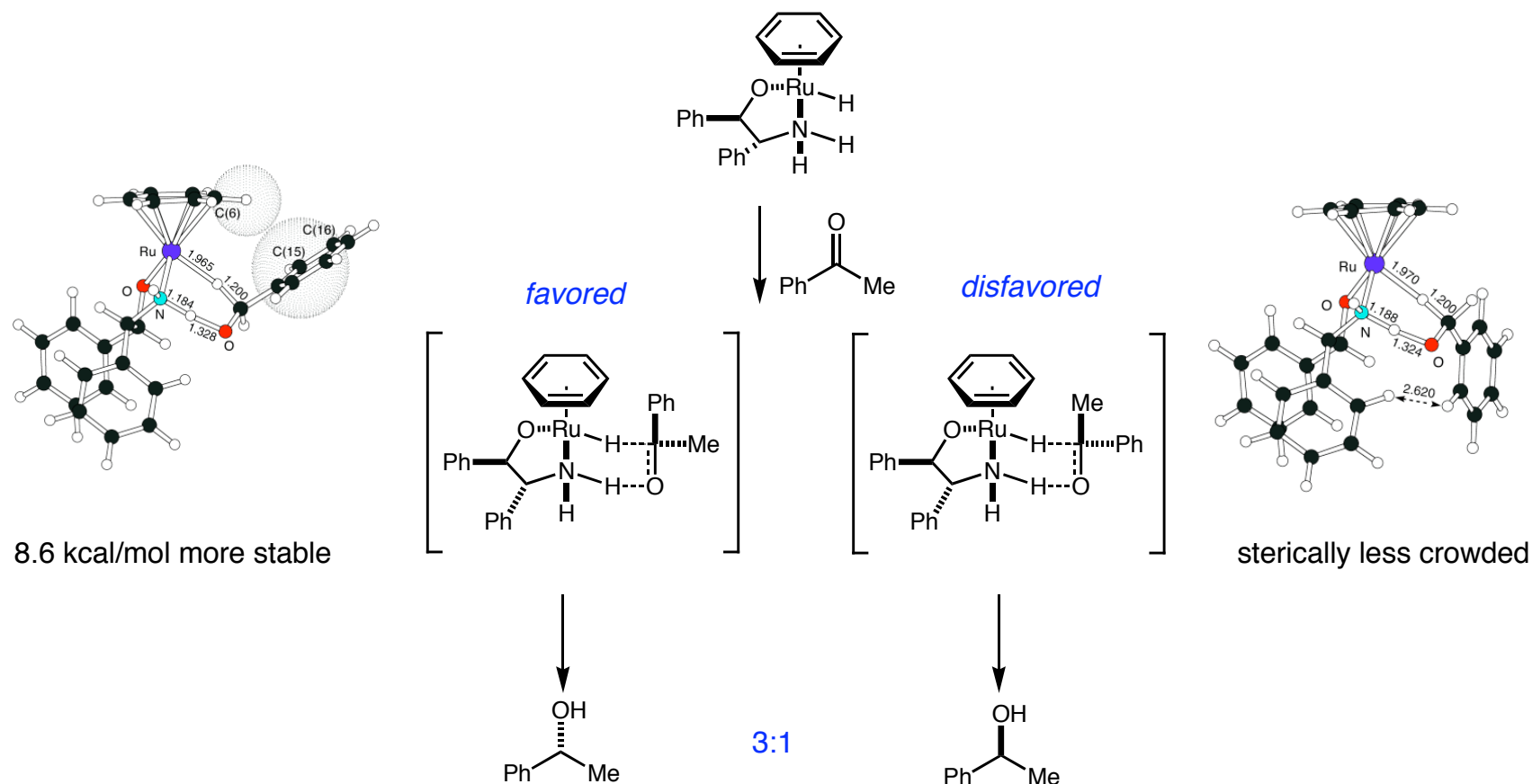
- The potential surface of the benzene-H bond is flat over the entire surface of the ring, making it conceptually similar to a very large flat weak base.
- These interactions are once again implicated in drug binding, with lots of crystallographic evidence



Perutz reports asparagine amide protons pointing directly at a phenyl ring in a "hydrogen bond"

Origins of Enantioselectivity in Asymmetric Transfer Hydrogenation

- CH- π attractive interaction between C(sp²)H of benzene ligand and π system stabilizes T.S.



- π donation of benzene to Ru enhances positive charge on C(sp²)H

- Explains lower ee's in substrates with EWG's on aryl ring

Conclusions

- Cation π interactions are found in all sorts of chemistry, and the nature of the interaction and its energetics are very well understood
- Nature makes extensive use of aromatic interactions
- Given all that is known about these interactions, they are severely underutilized in rational asymmetric catalysis
- The π - π and CH π interactions are still being actively investigated and worked out. More meaningful models ought to appear soon, but as of yet these processes are poorly understood

