

① LECTURE 21 : Pericyclic Rxns

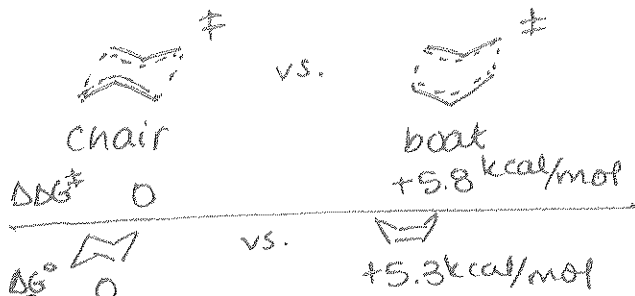
PS 9 due Thurs, 11/19

Seminar: Jennifer Cochran  
(CBI) (Engineered protein  
therapeutics)  
12:30 pm, Wed, 206 BRL

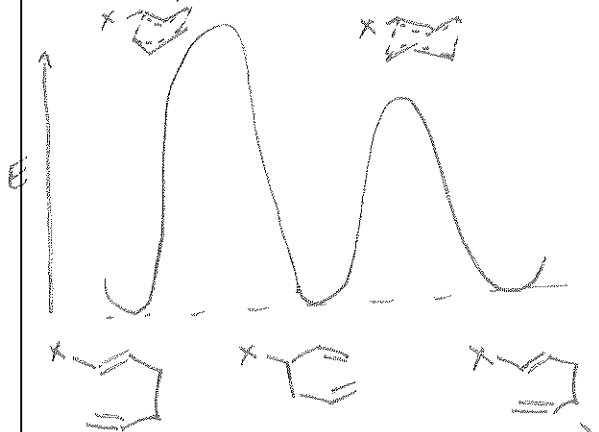
② CORE REARRANGEMENT



Possible TS:

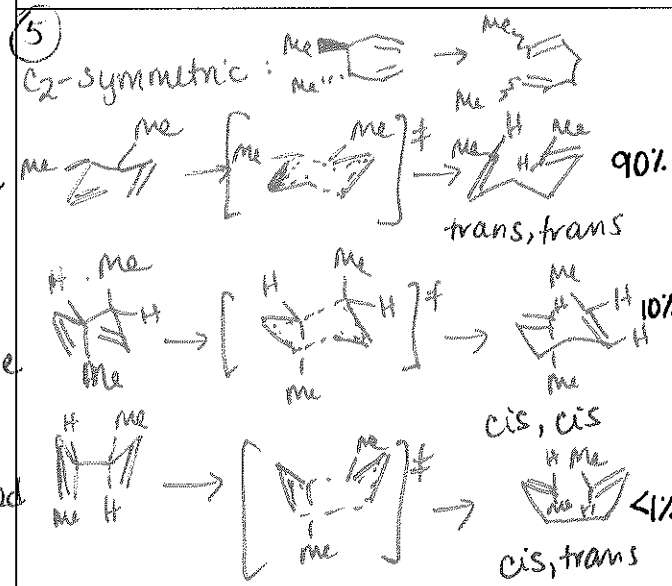
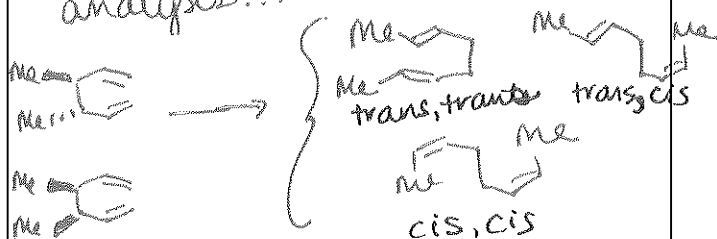


③ Well-defined chair & boat TS. Conformations.

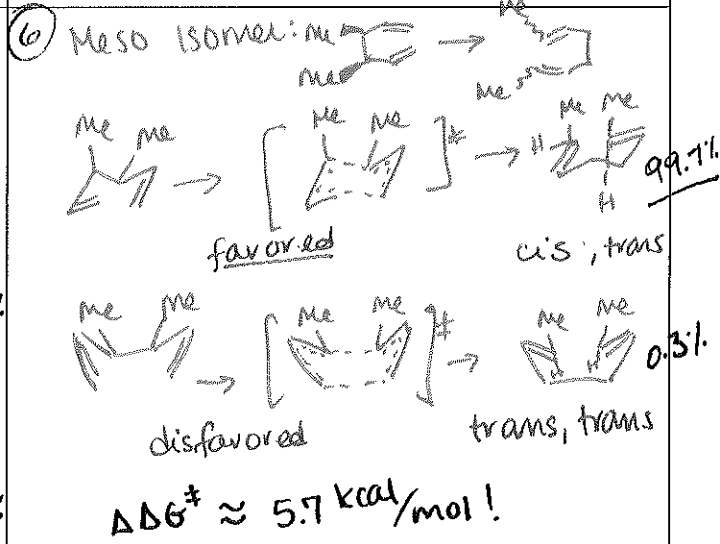


(Thermo-neutral w/o substituents.)

④ Doering & Roth Tetrahedron 1962, 18, 67. Geometry of TS from product analysis...



Note: 2 chair forms!

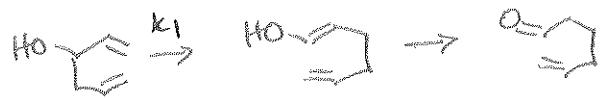


⑦ If thermoneutral, how can we favor desired ptt (high yields)?

1) Ring strain as driving force:



⑧ 2) Tautomerization of Ptt  
→ Oxy-Cope



Anionic oxy-Cope:

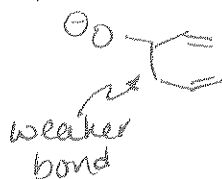


$\frac{k_2}{k_1} = 10^{10} \text{ to } 10^{17}!!!$

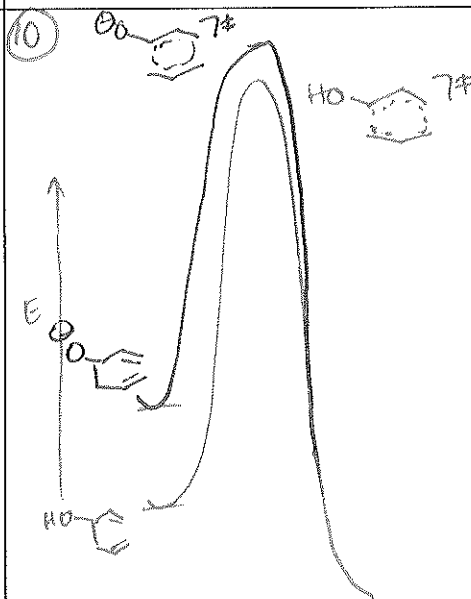
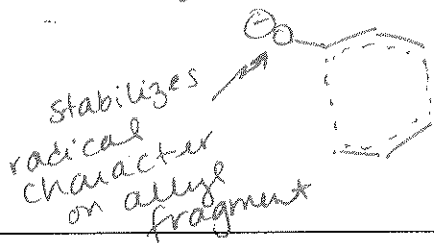
(JACS ~~1975~~ 1975, 97, 4765)

⑨ why? (Evans JACS 1975, 97, 4765)

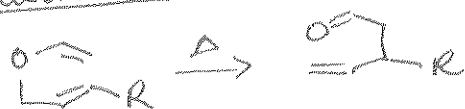
Ground state destabilized:



TS stabilized (asynchronous)



⑪ Claisen Rearr

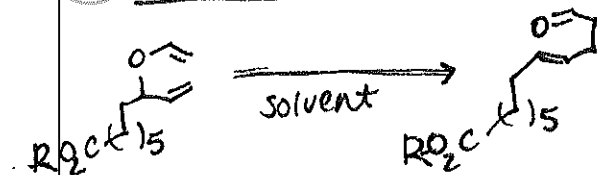


$\Delta H \sim -20 \text{ kcal/mol}$



(other famous variants of [3,3], too).

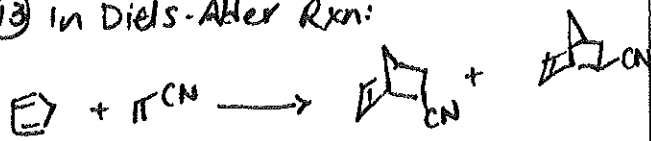
⑫ Hydrophobic Effects:



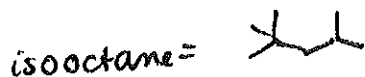
Solvent	R=Me k <sub>rel</sub>	R=Na k <sub>rel</sub>
	1.0	—
MeOH	8.6	9.4
H <sub>2</sub> O	—	214

Gajewski. Acc Chem Res 1997, 30, 219.

⑬ In Diels-Alder Rxn:



solvent	k <sub>rel</sub>
isooctane	1
MeOH	2
H <sub>2</sub> O	30



(Breslow. Acc Chem Res 1991, 24, 159.)

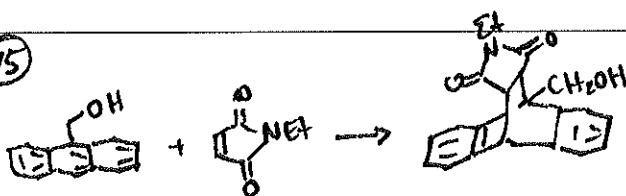
⑭



solvent	k <sub>rel</sub>
isooctane	1
MeOH	12
H <sub>2</sub> O	730

why? - Solvent polarity?  
- H-bonding?

⑮



solvent	k <sub>rel</sub>
isooctane	2
MeOH	1
H <sub>2</sub> O	65

H-bonding helps diene bind dienophile (MeOH messes this up.)

WHY??

⑯

### Hydrophobic Effect

Def: "Tendency of nonpolar species to aggregate in water solution so as to decrease the hydrocarbon-water interfacial area"

Enthalpic or entropic principle force in protein structure, binding substrates to enzymes, micelles, bilayers & ORGANIC CHEMISTRY.

⑰

Hydrophobic Effect = example of weak interaction.

So far, we have focused on things we understand pretty well...  
Covalent bonds (strong interactions)  
Steric repulsion  
Stereoelectronic effects w/in molecules.

Now:

WEAK, NONCOVALENT INTERACTIONS

(A & D, Ch. 3)

⑱



$$\Delta H \approx 5 \text{ kcal/mol}$$

$$\Delta S \approx 6 \text{ kcal/mol (@ rt)}$$

$\Delta G$  is uphill, so difficult to measure.

But can add up to big influence on reactivity.

ex: Diels-Alder hydrophobic effect.

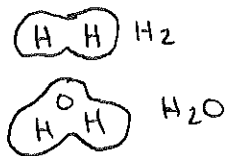
Solvent effects

Enzymes

Small molecule catalysis?

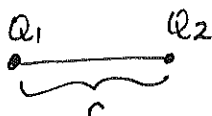
19) Types of Interactions

Covalent or Metallic



Interaction energy  
Short-range, complicated

Charge-charge (electrostatic)

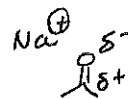


$$\frac{Q_1 Q_2}{4\pi\epsilon_0 r^2}$$

(Coulomb energy)

20)

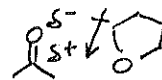
Charge-dipole



Depends on nature of dipole & nature of interaction

Fixed vs. freely rotating dipole w.r.t. charge.

Dipole-Dipole



Fixed vs. freely rotating

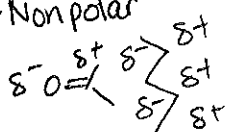
21)

Charge-Nonpolar



↑ induced dipole  
Nonpolar molecule polarizes.

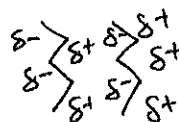
Dipole-Non polar



← induced dipole very weak

22)

Nonpolar-Nonpolar



London dispersion energy

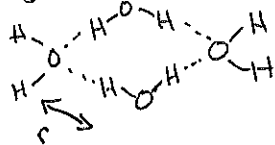
**WEAKEST**

But, this is why hexane is a liquid @ rt, not a gas.

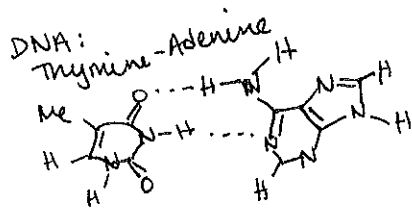
Remember: we're usually w/ org. molecules in org. solvents → may be important.

23)

Hydrogen bond



Complicated short-range energy  $\propto \frac{1}{r^2}$



Cytosine-Guanine

These are all strong H-bonds.

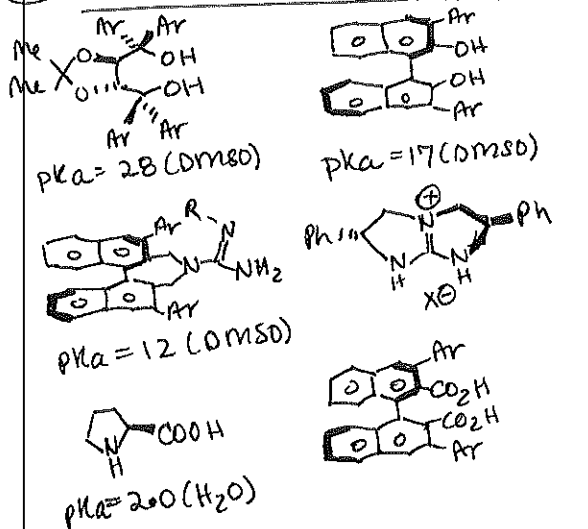
24)

Different Types of H-bonds:

	Strong	Moderate	Weak
A-H...B interaction	mostly covalent	mostly electrostatic	electrostatic
Bond lengths	A-H ≈ H-B	A-H < H-B	A-H << H-B
Bond Angles A-H...B	175-180°	130-180°	90-150°
Bond energy (kcal/mol)	14-40	4-15	< 4

From Jeffrey. An Introduction to Hydrogen Bonding. Oxford University Press, NY, 1997.

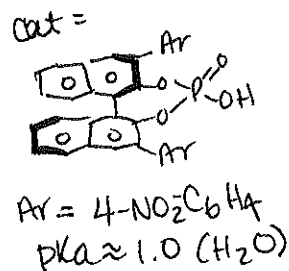
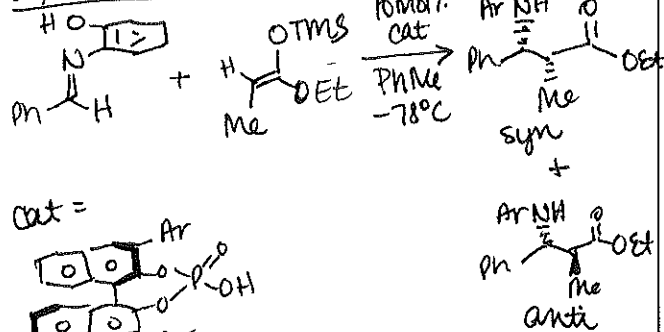
25 H-bond donor catalysts (chiral)



Doyle & Jacobsen, Chem Rev. 2007, 107, 5713.

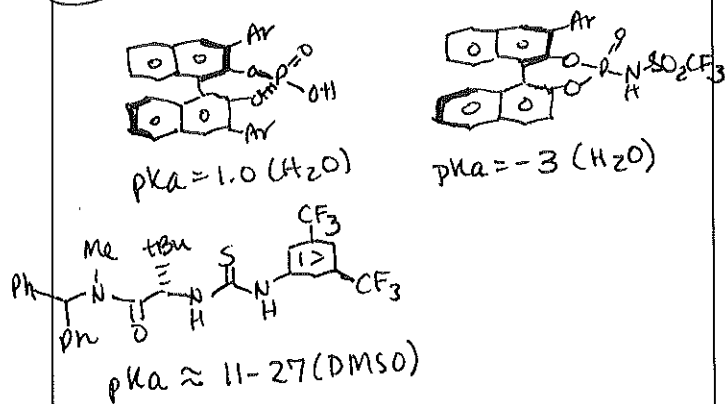
27 How do these work? What do they do?

Brønsted Acids:



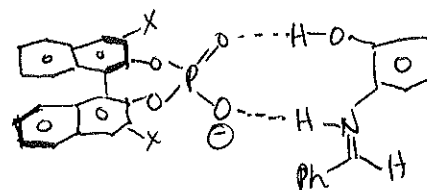
100% yr  
87:13 syn:anti  
96% ee

26



28

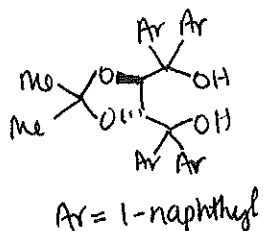
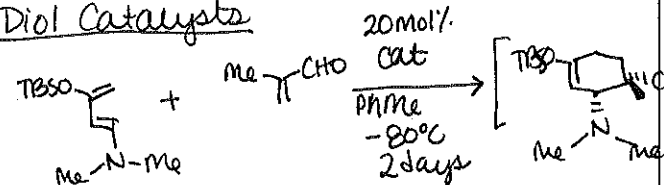
Proposed:



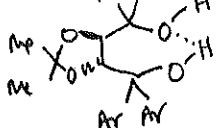
Strong Acid + Pretty Strong Base (Substrate)  
Entropic cost paid w/ 1<sup>st</sup> H-bond.

akiyama, Chem Rev 2007, 107(12), 5744.

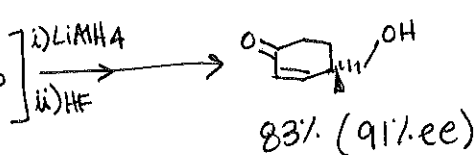
29 Diol Catalysts



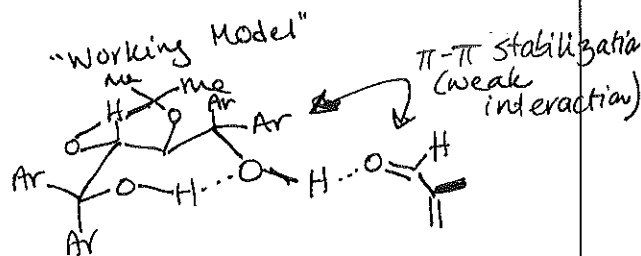
Not so acidic?  
Intramolecular H-bond:  
Increased acidity



30



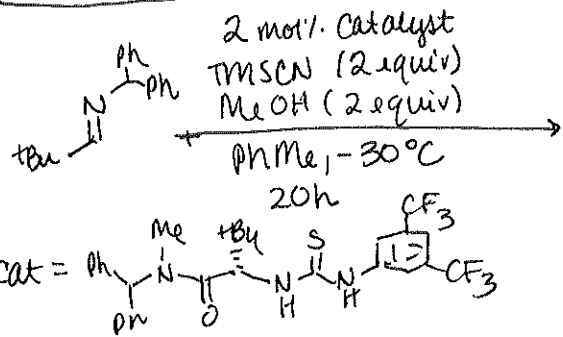
"Working Model"



Rawal et al. PNAS 2004, 101, 5846.

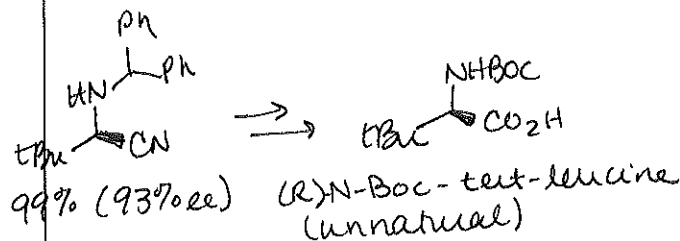
31

Dual H-bond Donors

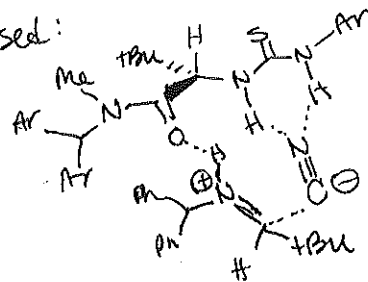


Jacobsen Nature 2009, 461, 968.  
Detailed mech study: Jacobsen  
JACS 2009, 131, 15358.

32



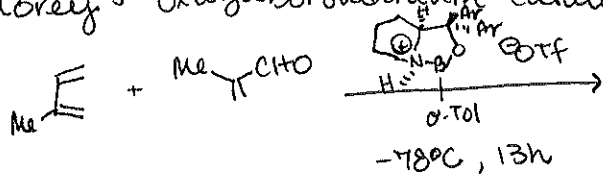
Proposed:



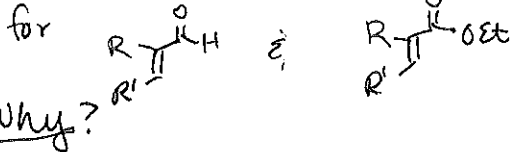
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Weaker H-bonding

Corey's oxazaborolidinium catalyst

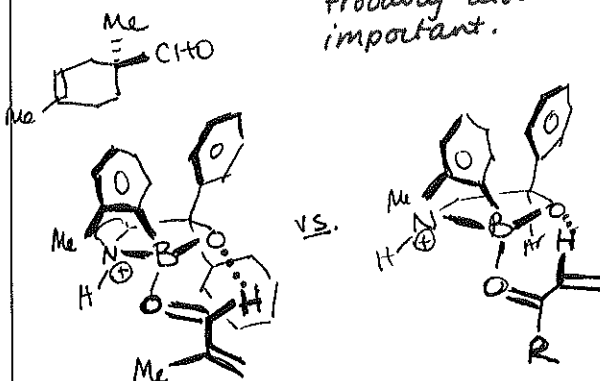


Opposite major enantiomer



34

Note:  $\pi$ -stacking probably also important.



Formyl H-bond (stronger)

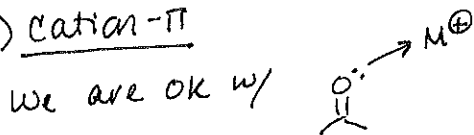
Weaker H-bond

Corey JACS 2002, 124, 9992.  
see also: Padden-Row, Sherburn. AClE 2008, 47, 701

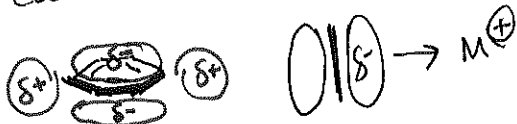
35

$\pi$ -based interactions

1) Cation- $\pi$



Cation- $\pi$ :

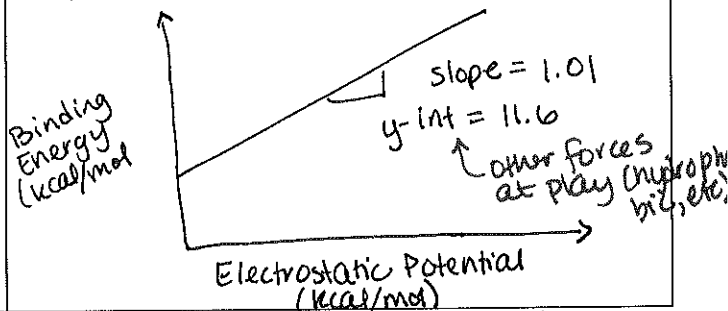
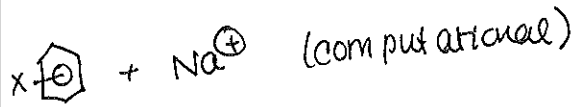


analogous to carbonyl  $\rightarrow M^+$

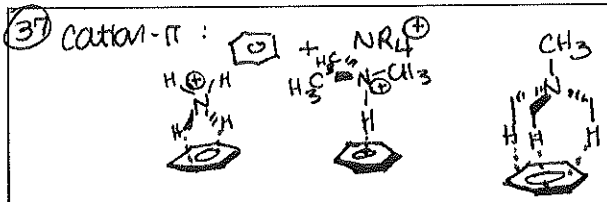
36

Extensive Studies by Dougherty:

Simple Arenes: JACS 1996, 118, 2307  
Other  $\rightarrow$  Chem Rev 1997, 97, 1303  
Science 1996, 271, 163.



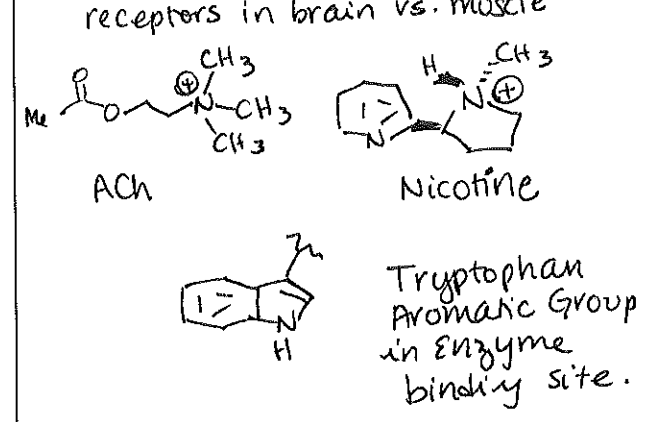
PREDOMINANTLY AN ELECTROSTATIC INTERACTION.  $\rightarrow$  EDG on Arene = More  $\pi$ -donation.



$\Delta G_{\text{bind}}^{\text{ly}}$ (gas phase)	-12.4	-7.6	-3.5
$\Delta G_{\text{bind}}^{\text{ly}}$ (AF/b-31G*)	-8.60	-2.26	+0.04
$\Delta G_{\text{bind}}^{\text{ly}}$ (MP2/6-31G*)	-11.56	-7.62	-3.47
(kcal/mol)			

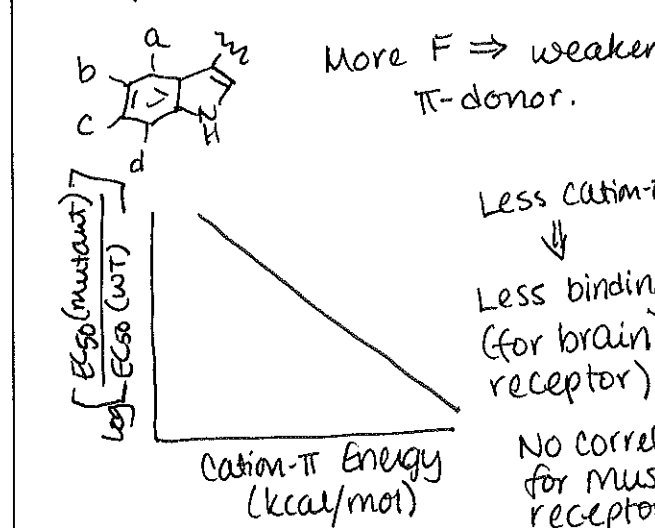
Lee Chem Phys Lett 1995, 232, 67.

38) more complicated examples:

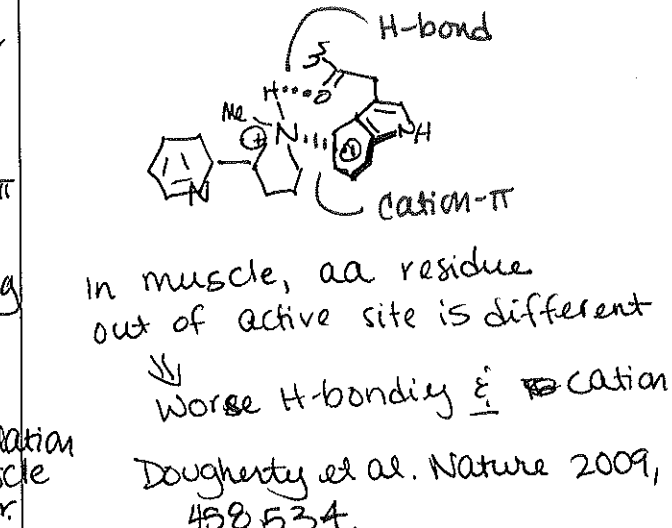


Hypothesis: Cation- $\pi$  is responsible for nicotine (or ACh) binding.

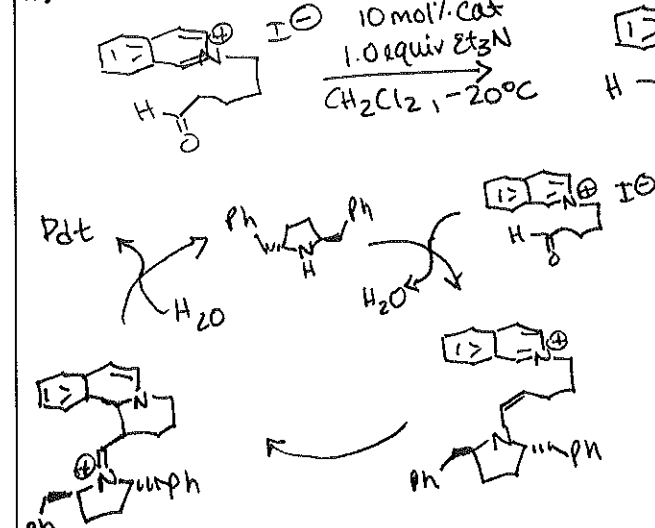
39) The Experiment: Fluorinated Trp.



40) 2<sup>nd</sup> interaction: H-bond



41) 2) In small-molecule catalysis



42) Best catalyst:

