Lecture 23: Noncovalent Interactions

Reading: Anslyn & Dougherty, Chapter 3

Annoucements

- Problem Set 6 due now. Answer Key will be posted immediately.
- Final Exam: Mon, 12/12, 7-10pm, 207 BRL
  - Comprehensive

Today: Weak, Noncovalent Interactions

- Although usually weak, multiple noncovalent interactions can add up to BIG influence on reactivity or selectivity.
- Observed in solvent effects, enzymes, small molecule catalysis, etc.

Types of Noncovalent Interactions

- Steric hindrance (repulsive) – not today
- Hydrogen bonds
- π-Interactions
  - Cation–π
  - π-π
- Hydrophobic effect

(Note: This is not an inclusive list.)

Hydrogen Bonds

- Generally between a heteroatom & heteroatom–H:

  X········H–Y

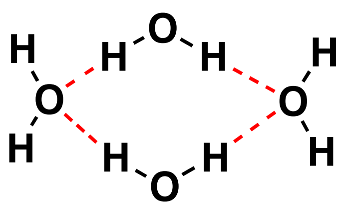
- Complicated
- Short range
- Energy of interaction proportional to $-1/r^2$

Different Strengths of H-bonds

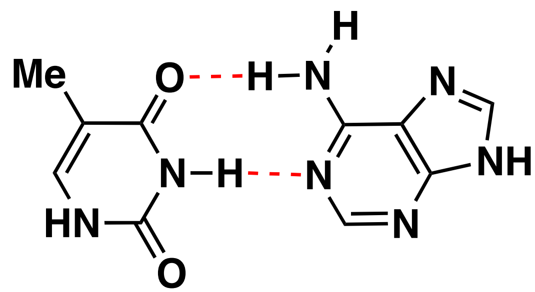
Strength	A–H·····B interaction	Relative bond lengths	Bond angle	Bond energy (kcal/mol)
Strong	Mostly covalent	A–H ≈ H–B	175–180°	14–40
Medium	Mostly electrostatic	A–H < H–B	130–180°	4–15
Weak	Electrostatic	A–H << H–B	90–150°	<4

Jeffrey. *An Introduction to H-Bonding.* Oxford University Press: NY, 1997.

Examples of H-bonds in Nature



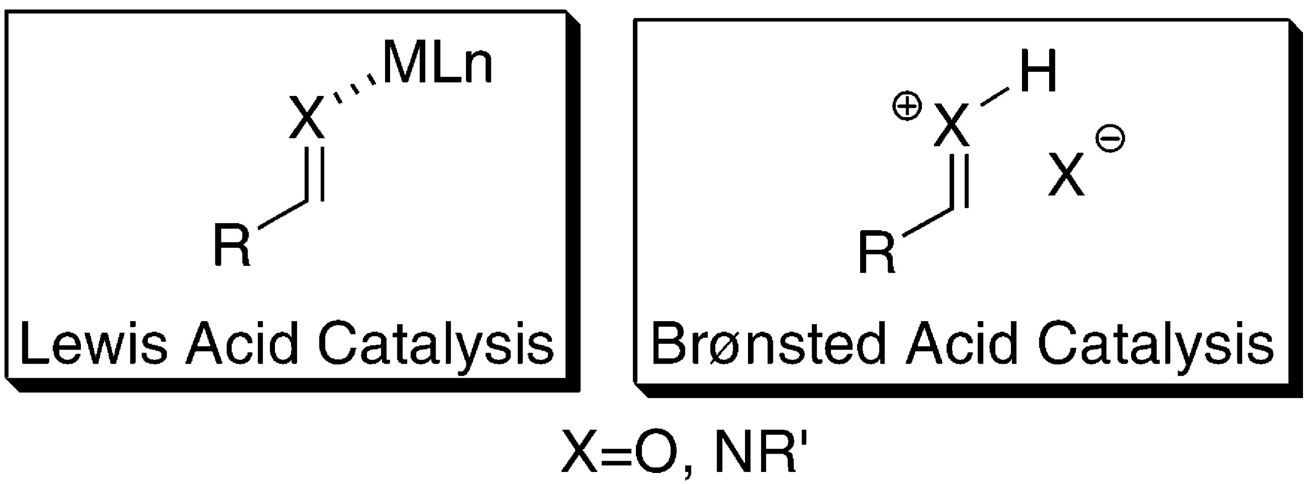
in water



in DNA/RNA
(ex: thymine–adenine)

H-Bonds in Small-Molecule Catalysis

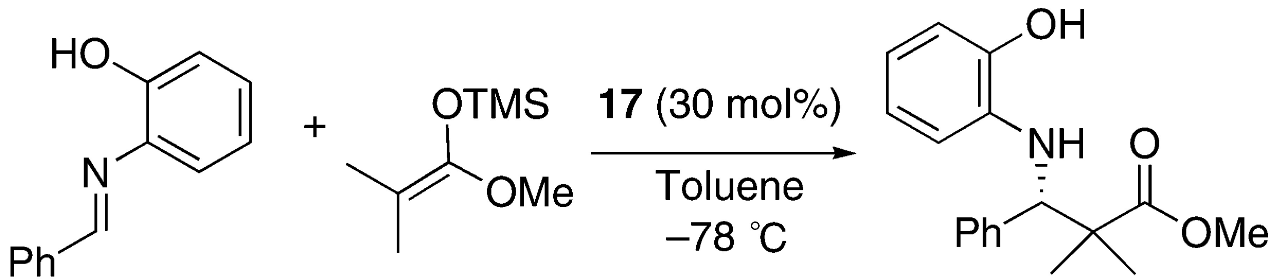
General Review: *Chem. Rev.*, **2007**, 5713



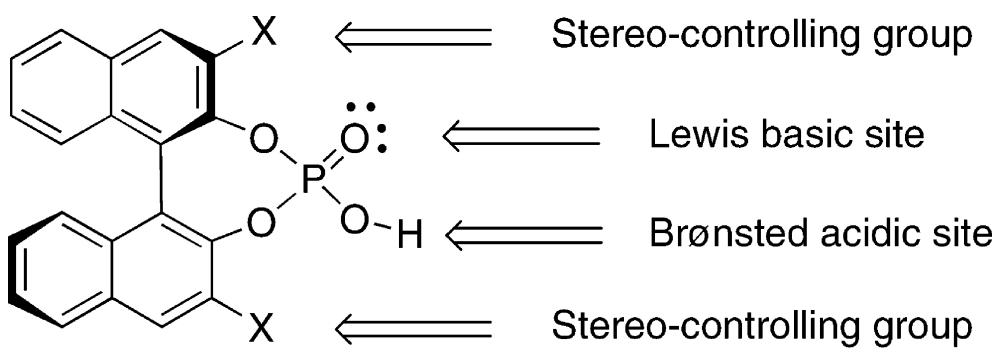
Published in: Takahiko Akiyama; *Chem. Rev.* **2007,** 107, 5744-5758.
DOI: 10.1021/cr068374j

H-Bonds in Small-Molecule Catalysis

General Review: *Chem. Rev.*, **2007**, 5713



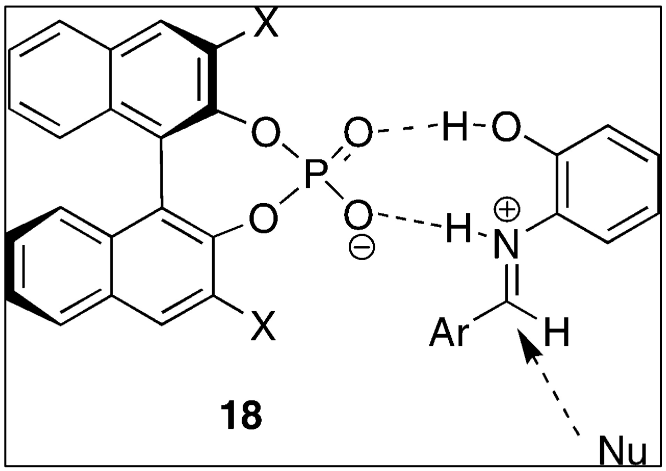
17a: 57%, 0% ee
17b: 100%, 27% ee
17c: 96%, 87% ee



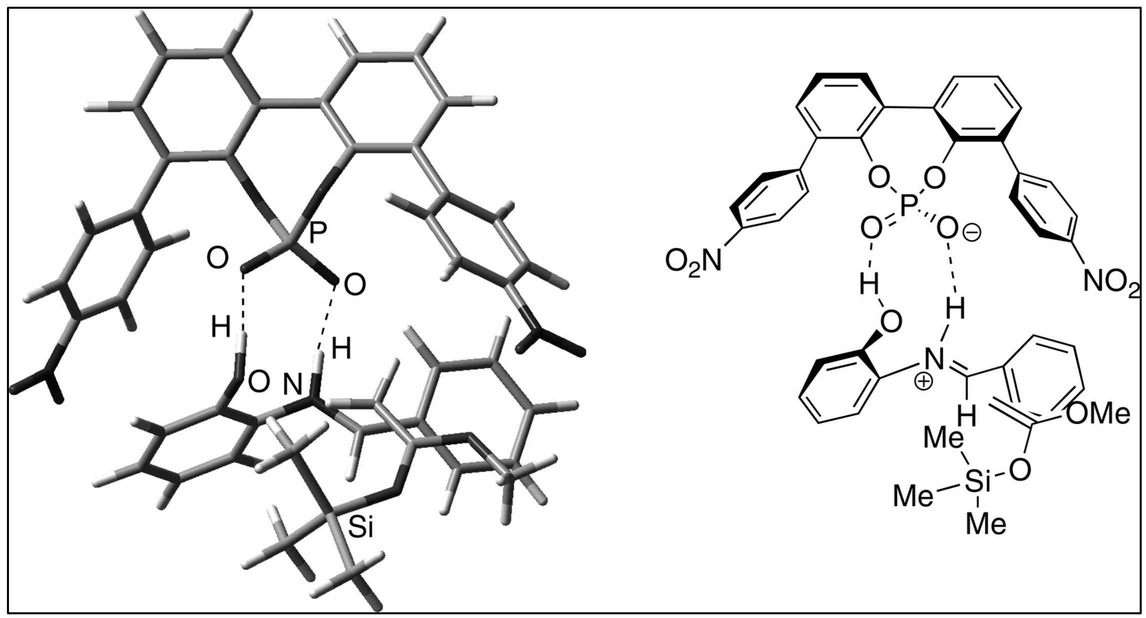
Published in: Takahiko Akiyama; *Chem. Rev.* **2007,** 107, 5744-5758.
DOI: 10.1021/cr068374j

H-Bonds in Small-Molecule Catalysis

General Review: *Chem. Rev.*, **2007**, 5713



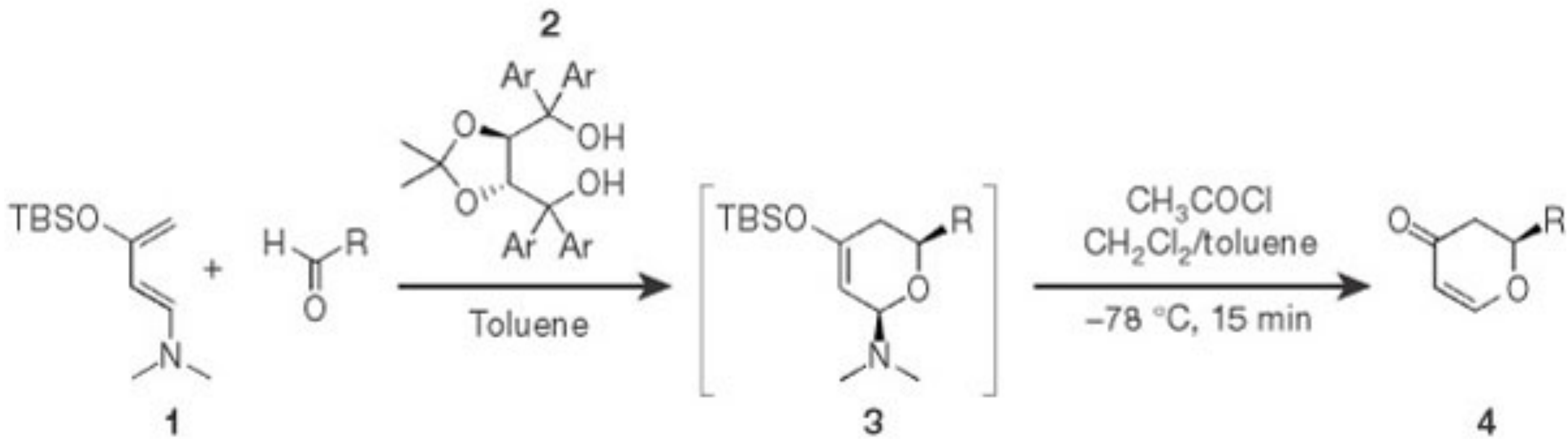
18



Published in: Takahiko Akiyama; *Chem. Rev.* **2007,** 107, 5744-5758.
DOI: 10.1021/cr068374j

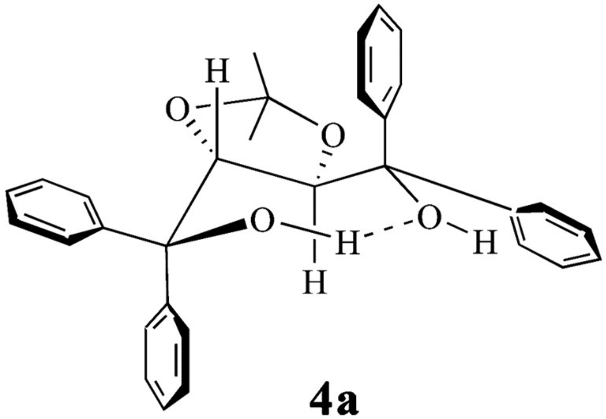
H-Bonds in Small-Molecule Catalysis

General Review: *Chem. Rev.*, **2007**, 5713

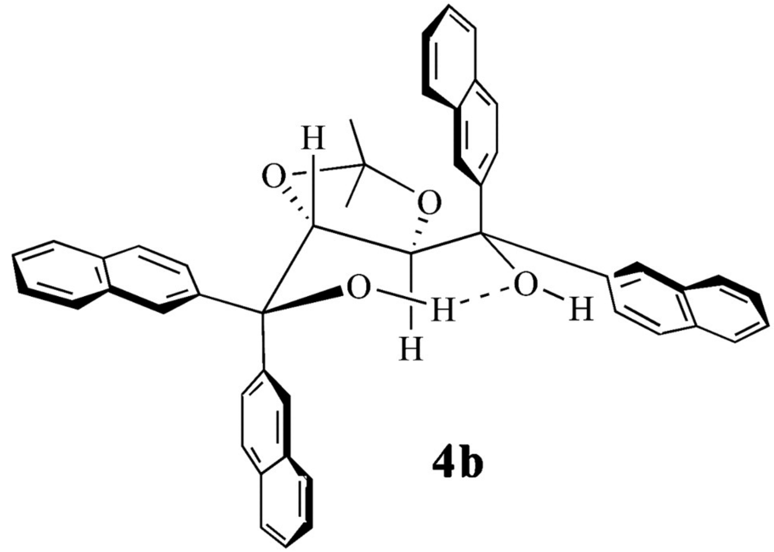


Yong Huang, Aditya K. Unni, Avinash N. Thadani and Viresh H. Rawal
Nature **424**, 146

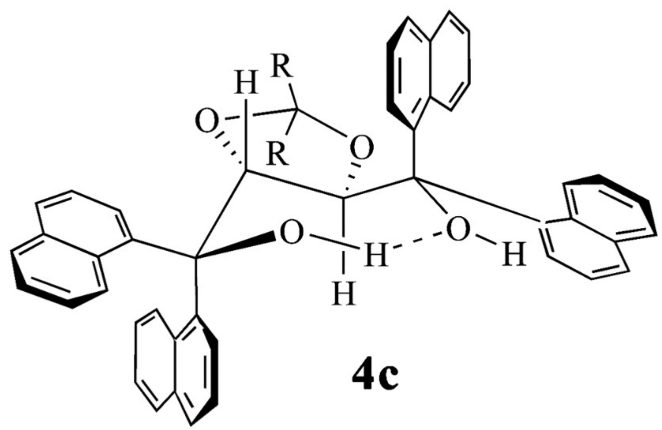
Solid-state structures of TADDOL 4a–c.



4a



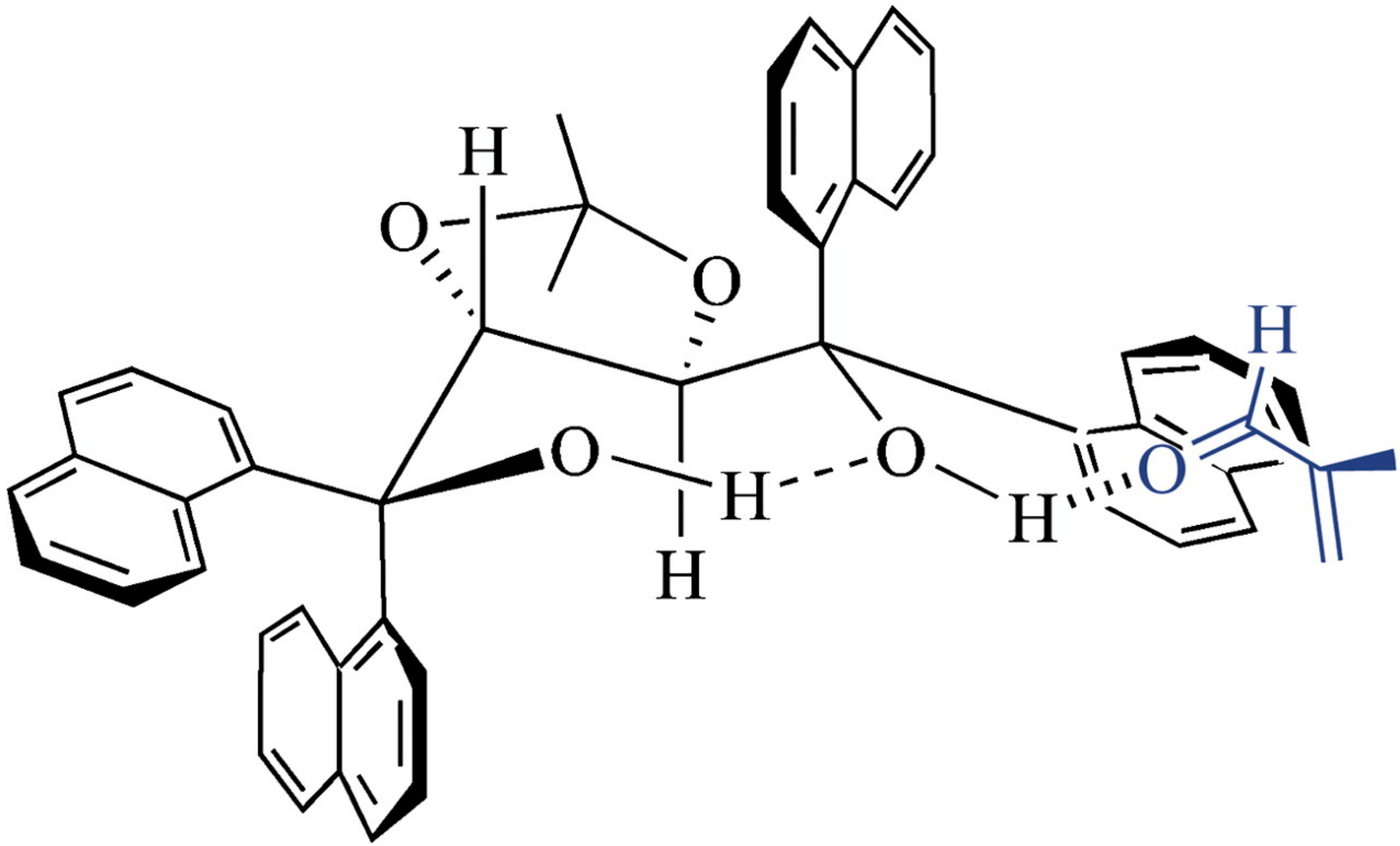
4b



4c

Avinash N. Thadani et al. PNAS 2004;101:5846-5850

A proposed working model for the TADDOL-catalyzed Diels–Alder reactions.



Avinash N. Thadani et al. PNAS 2004;101:5846-5850

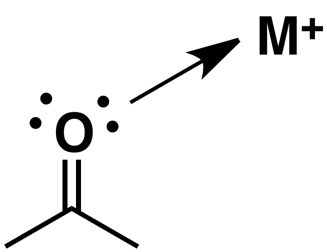
Many Other Types of H-Bonds in Small-Molecule Catalysis

General Review: *Chem. Rev.*, **2007**, 5713

- Dual H-bond donors:
  - Jacobsen *Nature* **2009**, *461*, 968
  - Jacobsen *JACS* **2009**, *131*, 15358
- H-bonding in Lewis acidic catalysts:
  - Corey *JACS* **2002**, *124*, 9992
  - Fadden-Row, Sherburn *ACIE* **2008**, *47*, 7013

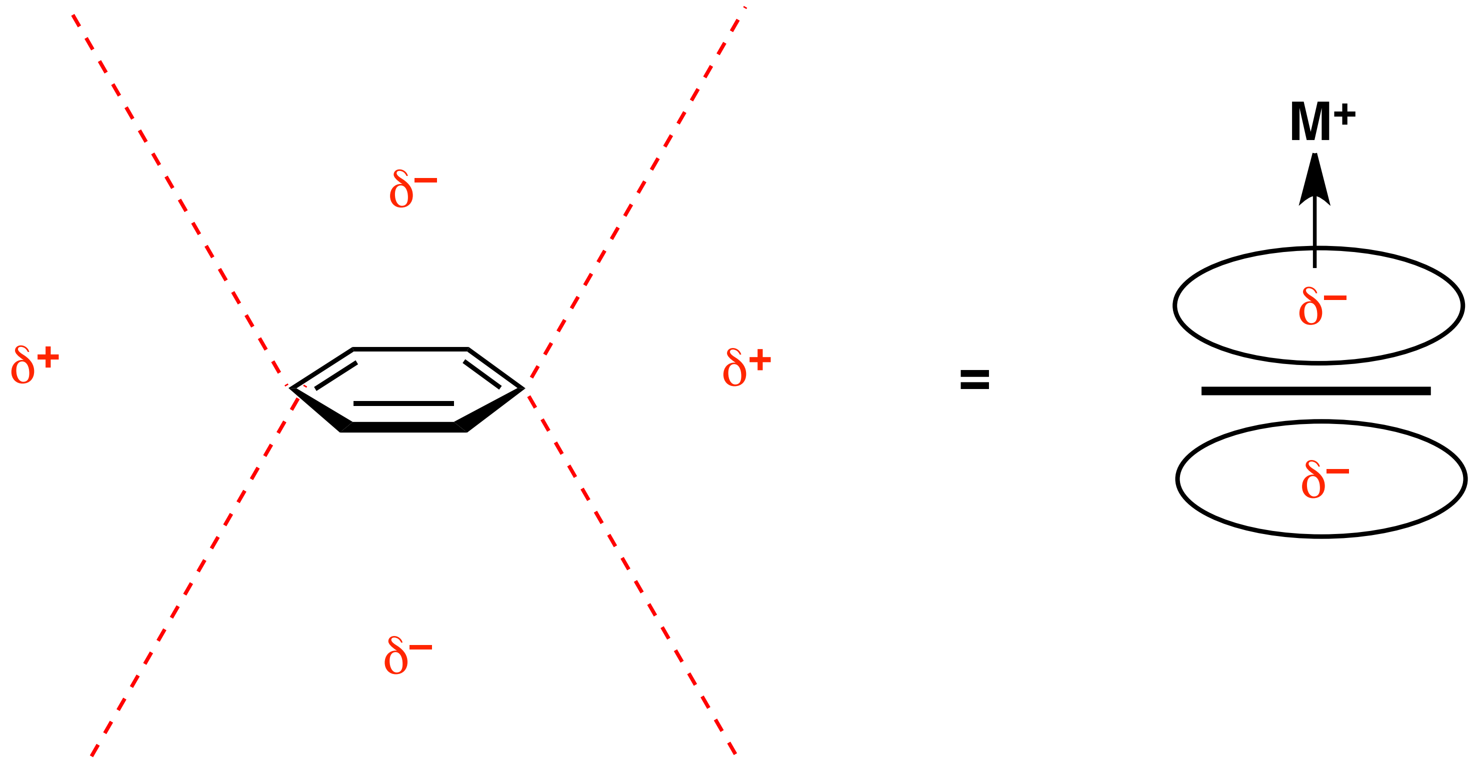
Cation–π Interactions

Recall:



M^+ = H^+, Lewis acid, etc.

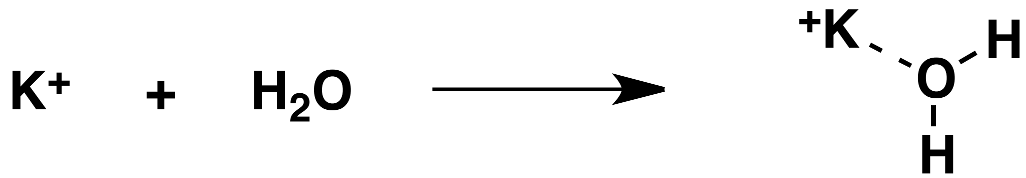
Cation–π Interactions



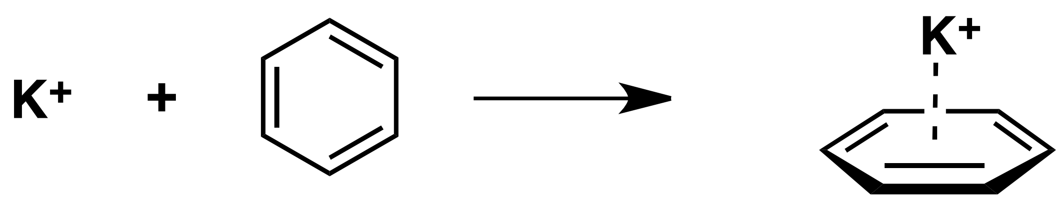
- Linear correlation between strength of cation–π interaction & electrostatic potential of arene.
- Predominantly electrostatic (but not exclusively, also some hydrophobic effects, etc.). EDG's strengthen cation–π interations.

Cation-π Interaction Strengths

Gas Phase Binding Energy (kcal/mol)



18

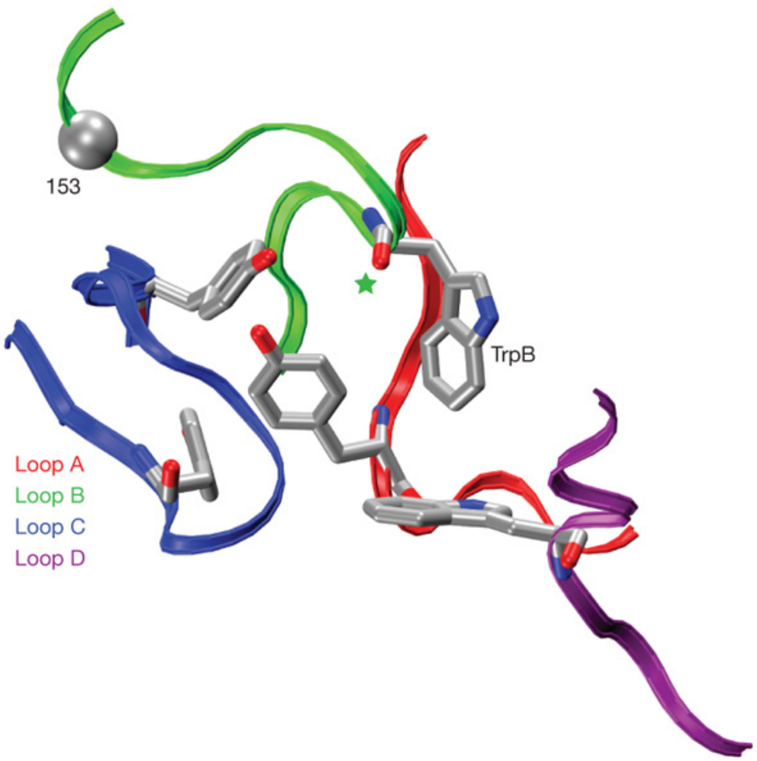


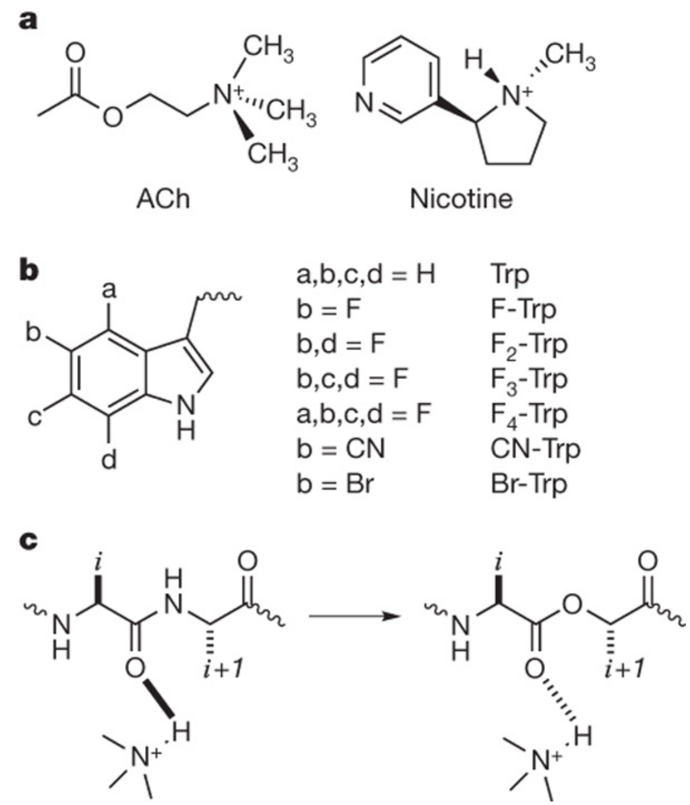
19

Size of cation also matters... Li^+ is bound more tightly than Rb^+ or NMe_4^+.

Phys Org Studies: *JACS* **1996**, 2307. *Chem Rev* **1997**, 1303. *Science* **1996**, 163.

Cation–π in Nature: Acetyl Choline Binding Proteins: Brain vs. Muscle



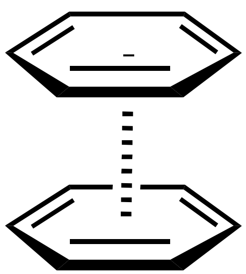


XN Xiu *et al.* *Nature* **000**, 1-4 (2009) doi:10.1038/nature07768

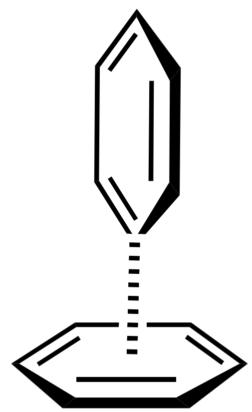
π–π Interactions

- Due to electrostatic & dispersion & other forces

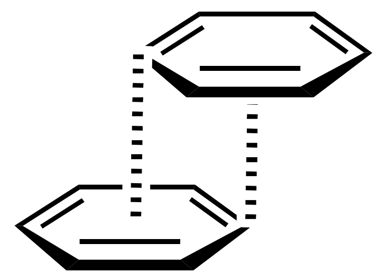
stacked or sandwich



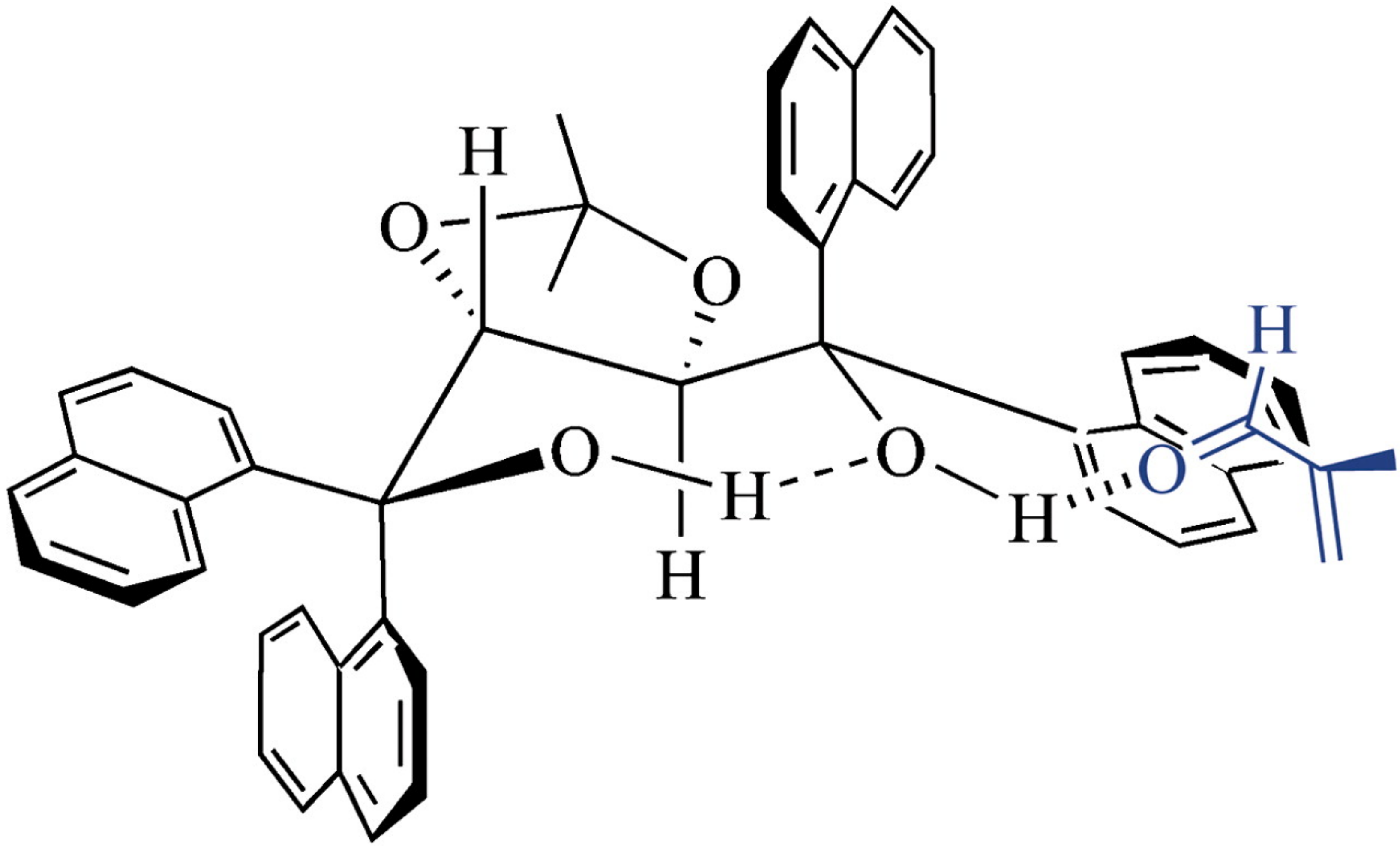
T-shape or edge-face



slip-stack



A proposed working model for the TADDOL-catalyzed Diels–Alder reactions.

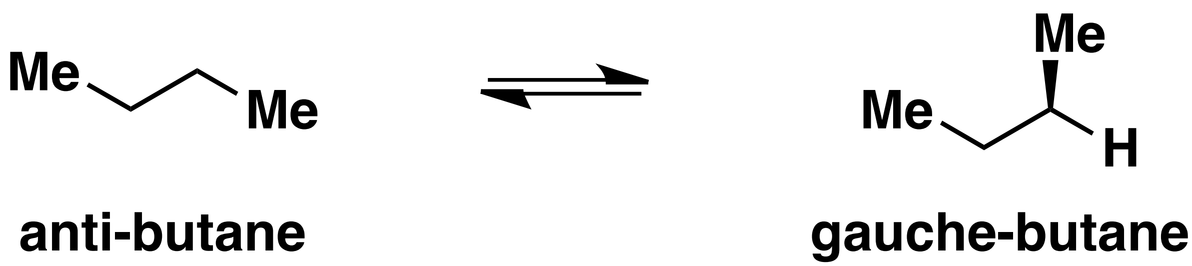


Avinash N. Thadani et al. PNAS 2004;101:5846-5850

Hydrophobic Effect

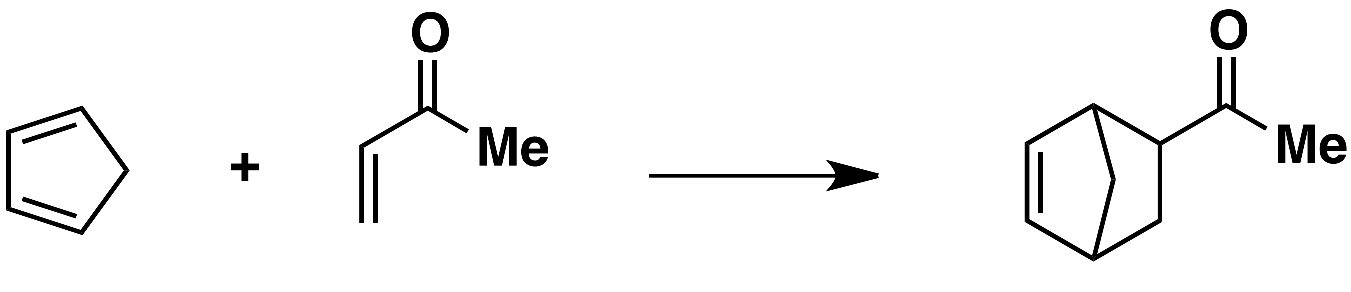
- "Observation that hydrocarbons & related 'organic' compounds are insoluble in water."
- Aggregation of organics in H_2O
- *Not* electrostatic
- Not well understood in quantitative sense
- Related to surface area of organics
- Important in protein structure, binding substrates to enzymes, micelles, bilayers, and organic chemistry!

Hydrophobic Effect: Surface Area Importance



Medium	Anti : Gauche
Gas phase or liquid butane	70 : 30
H_2O	55 : 45

Hydrophobic Effect: Effect on Reactivity



(mixture of endo & exo isomers)

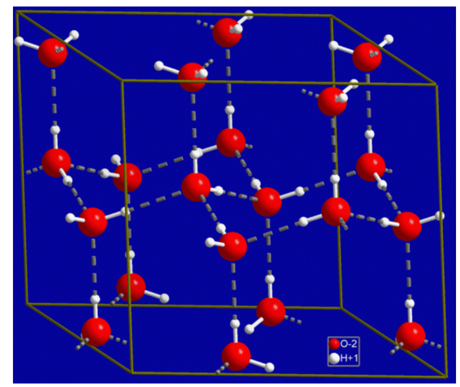
Solvent	K_{rel}
Isooctane	1
MeOH	12
H_2O	730

Origin of the Hydrophobic Effect

First consider H_2O...

At room temperature: liquid

· high cohesive energy/surface tension, but dynamic (more disordered, higher entropy)



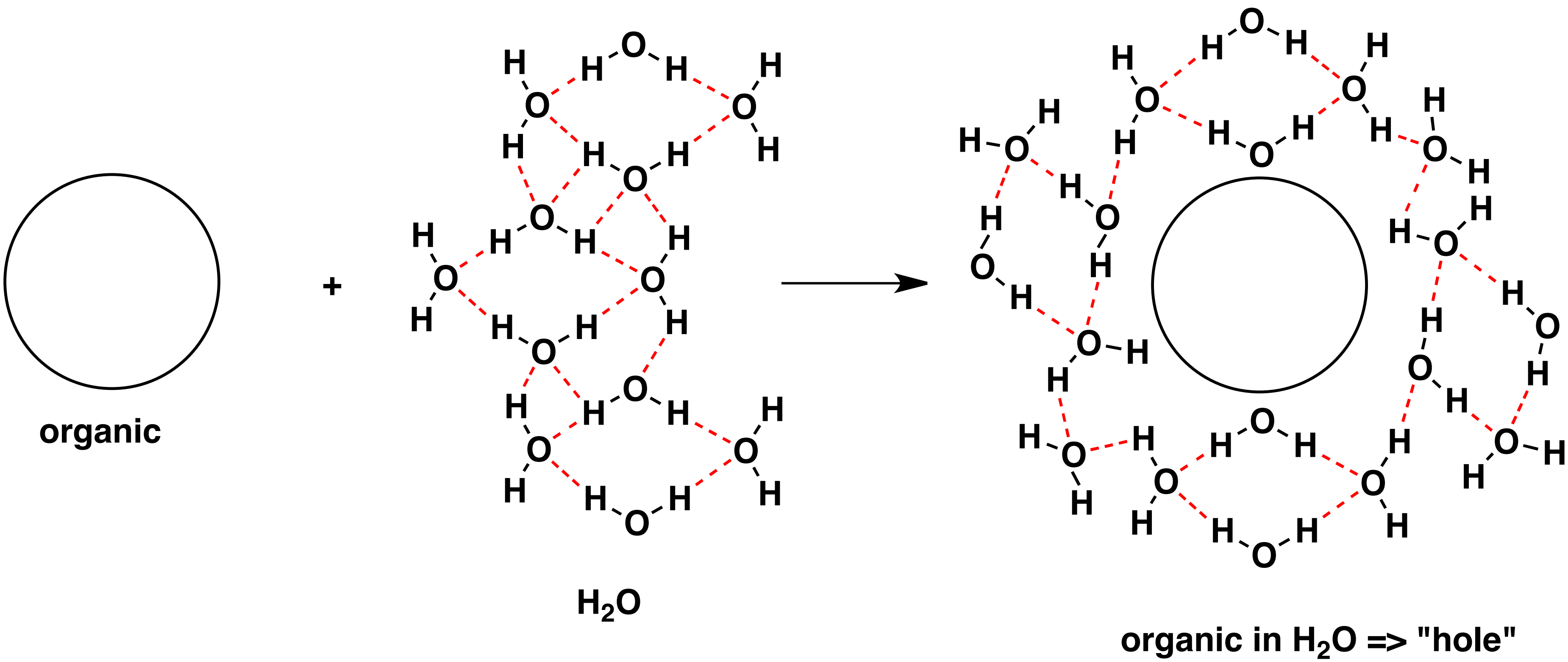
At 0 °C: solid (ice)

· 4 H-bonds for each H_2O molecule

· enthalpically favorable (lots of good H-bonding)

· entropically costly (very ordered)

Origin of the Hydrophobic Effect



- Around “hole”, H-bonds are lost.
- To compensate, remaining H-bonds get stronger –> Enthalpically neutral!
- But, results in “ice-like” structure around hole –> Entropy decreases (costly).
- Because 2 “holes” have more surface area than 1 “hole”, aggregation of organics in water is less entropically costly.

Thanks for a great semester!!