

Short Course:

**Solution Structure Determination
In Organic Chemistry and Chemical Biology**

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II. Structure mediated by aromatic-aromatic interactions

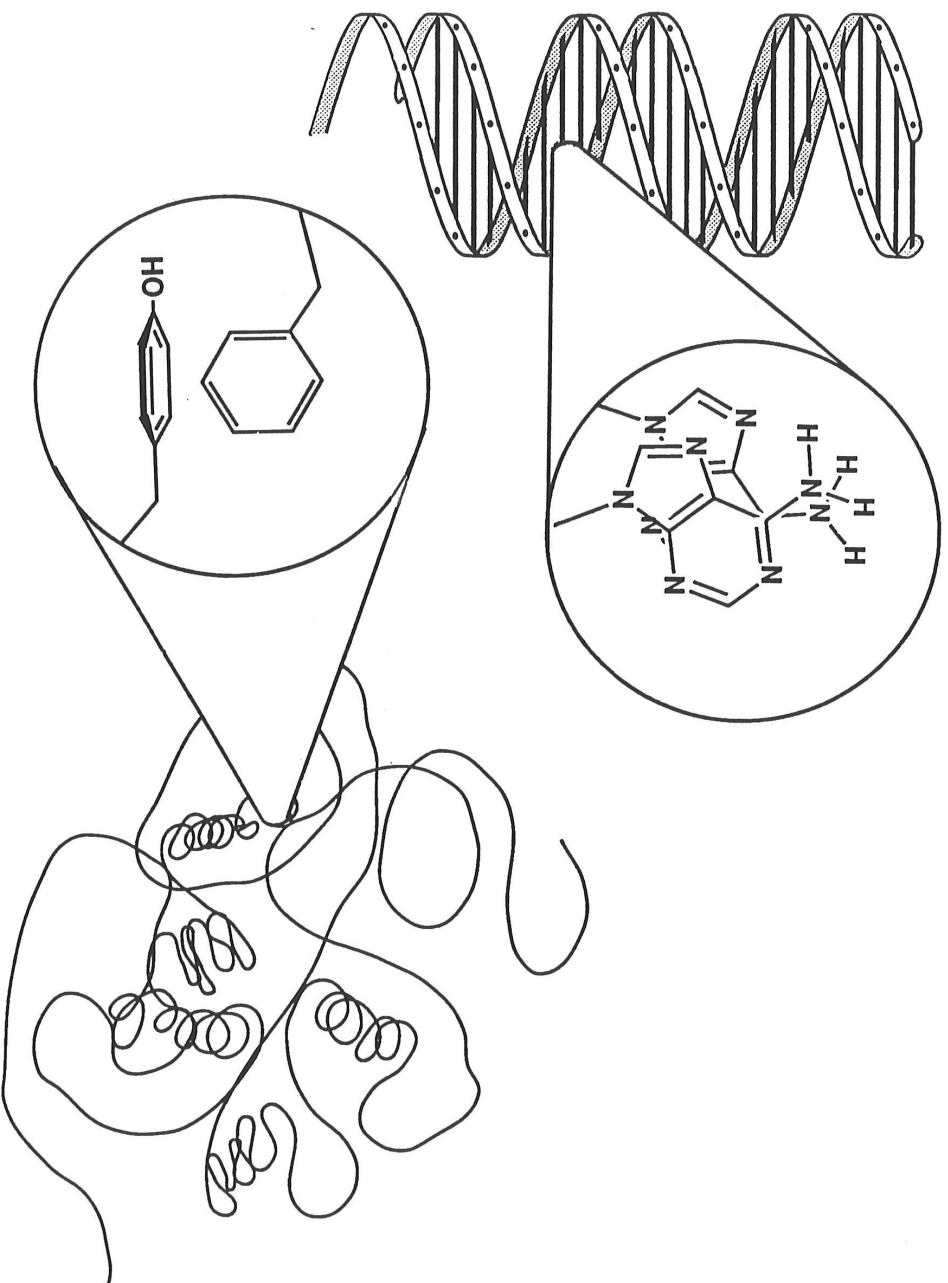
Recall: What is “solution structure”?

When flexible molecules equilibrate among different conformations in solution, then we have an opportunity to address a set of interrelated questions.

1. Why does the molecule adopt particular shapes in solution?
2. What intramolecular forces determine the shape preferences?
3. What shapes are preferred, and by how much (in terms of free energy)?
4. How does the environment (solvent, etc.) affect shape preferences?

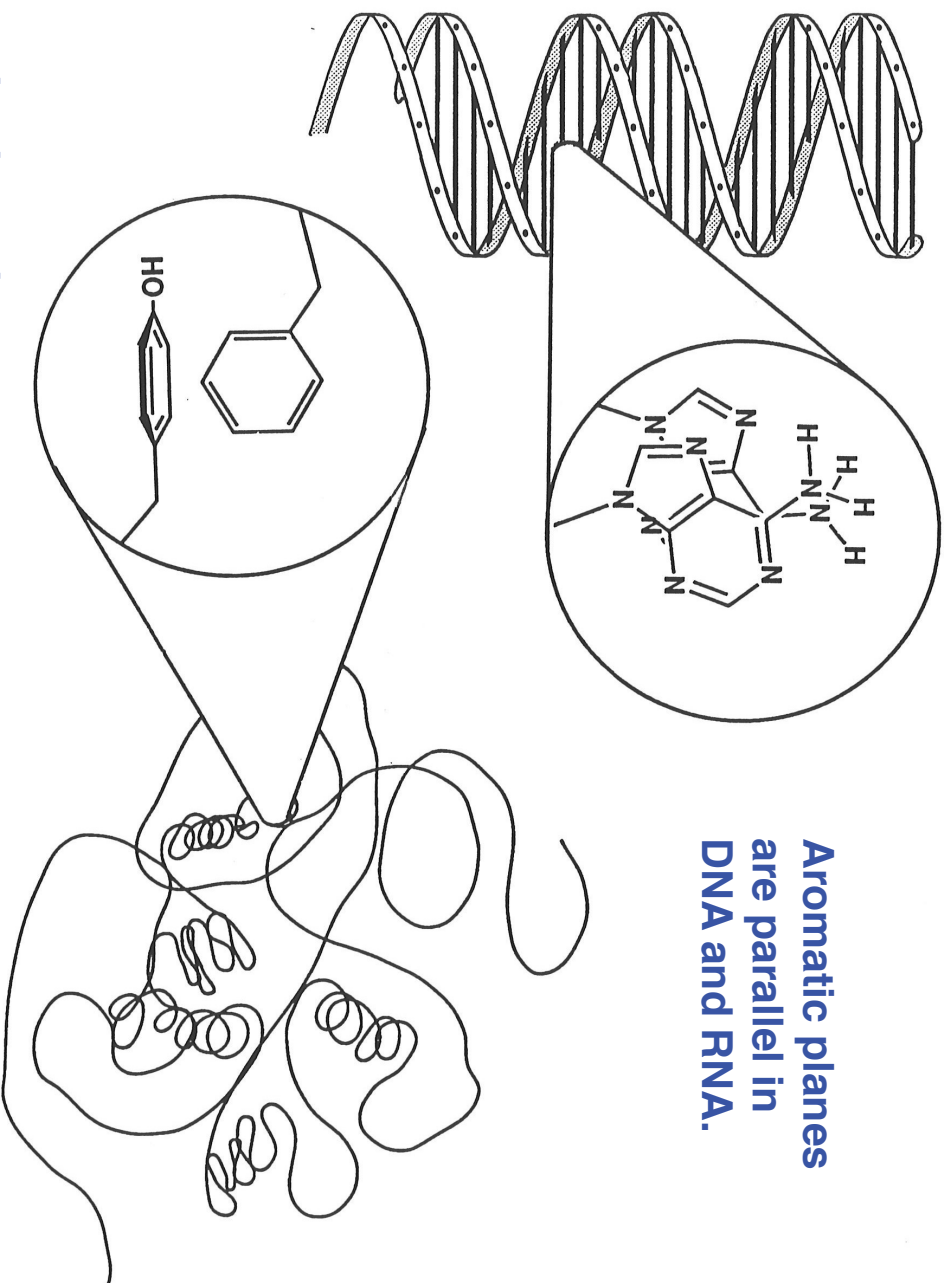
Most of the examples discussed in this short course will involve not only strategies for determining molecular shapes in solution, but also strategies for understanding the origins of those shapes. Often the questions are interwoven.

Aromatic-Aromatic Interactions in Proteins and Nucleic Acids



Aromatic-Aromatic Interactions in Proteins and Nucleic Acids

Geometry Considerations

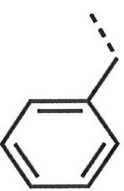


**Aromatic planes
are parallel in
DNA and RNA.**

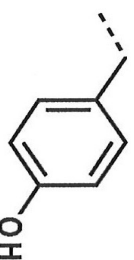
**Aromatic planes have
diverse orientations in
proteins.**

Different Types of Aromatic Groups: Proteins vs. DNA/RNA

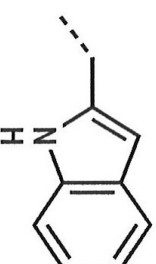
Protein Side Chains



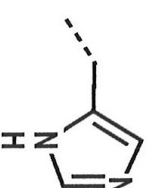
Phe



Tyr

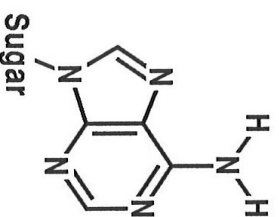


Trp

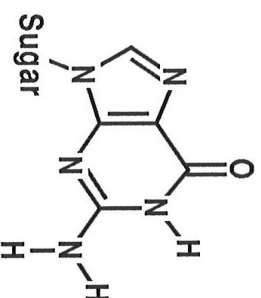


His

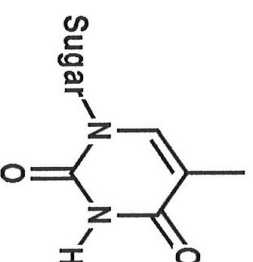
Nucleotide Bases



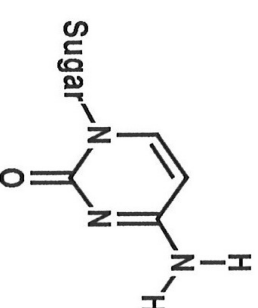
A



G



T (U)



C

Purines

Pyrimidines

Many potential questions to be addressed...

1. What set of non-covalent forces makes base stacking favorable? Is there a contribution from the hydrophobic effect? Polar interactions?
2. What set of non-covalent forces makes interactions between aromatic side chains in proteins favorable? Is this purely a manifestation of the hydrophobic effect? Is there a polar or other sort of component?
3. How strong are geometric preferences for aromatic interactions, such as parallel “stacking” among nucleotide bases? Are there intrinsic geometric preferences for hydrocarbon aromatics? If so, what are they, and how strong are they?
4. How can we address these questions without complications from a complex molecular context (e.g., the interior of a folded protein or of double-stranded DNA)?

Many potential questions to be addressed...

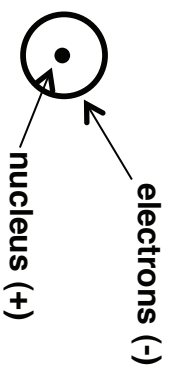
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What are the simplest manifestations of these aromatic-aromatic interactions? Can we use the tools of solution structure determination to devise and conduct useful experiments?

Background: Forces that Can Cause Attraction Between Uncharged Molecules or Subunits in Aqueous Solution

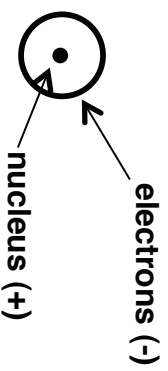
1. Dispersion Interactions
2. Interactions involving fixed dipoles or multipoles
3. Hydrophobic effect

Dispersion: Attraction Involving Transient Induced Dipoles (Over-Simplified View)

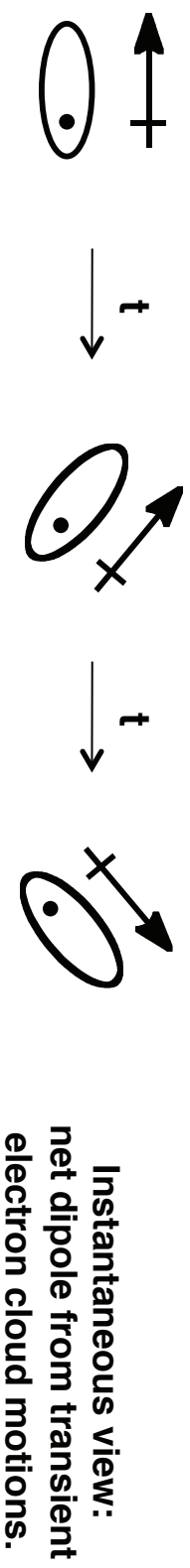


**Filled shell atom or fragment:
time-averaged species has no net dipole.**

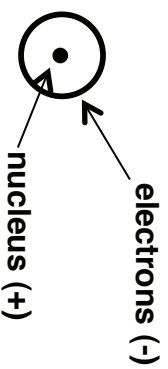
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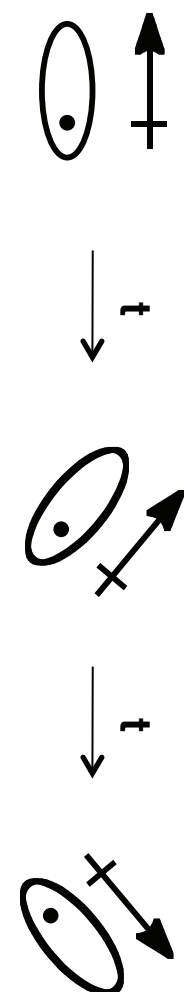
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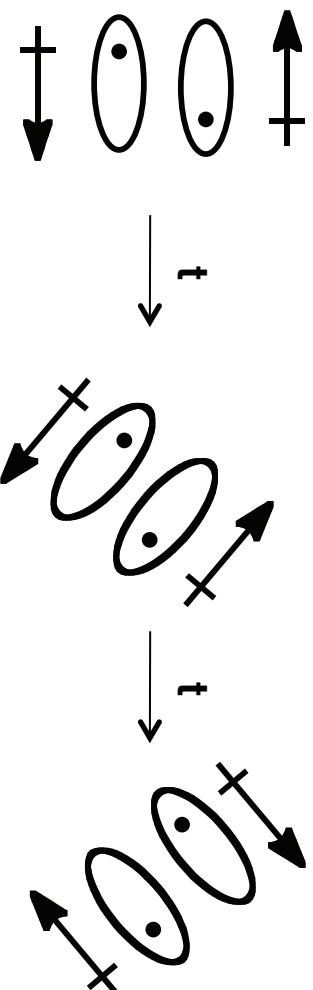
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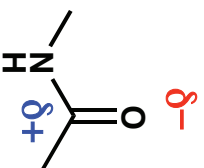
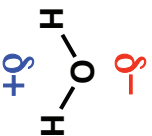


Instantaneous view:
net dipole from transient
electron cloud motions.



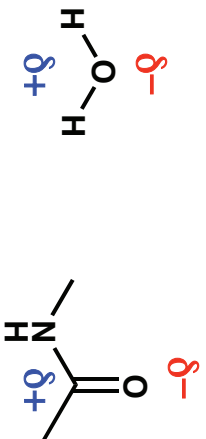
Correlation of transient dipoles:
net attraction of "nonpolar" species
(dispersion)

Dipole/Multipole Interactions

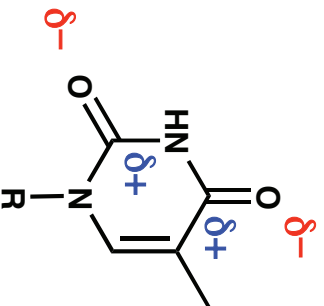


**Simple molecules or functional groups:
Dipoles
(Important in H-bonding?)**

Dipole/Multipole Interactions

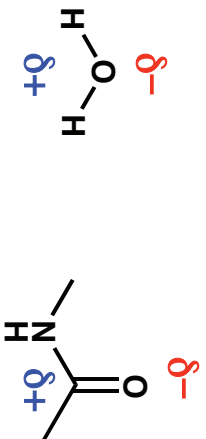


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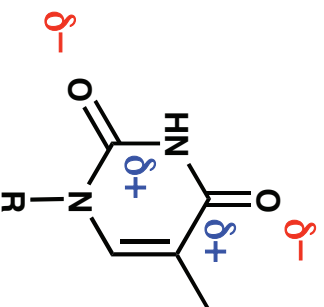


**Complex functional group arrays:
Multipoles**
(Important in base stacking?)

Dipole/Multipole Interactions



Simple molecules or functional groups:
Dipoles
(Important in H-bonding?)



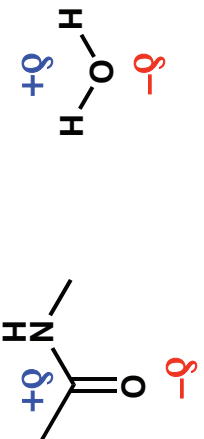
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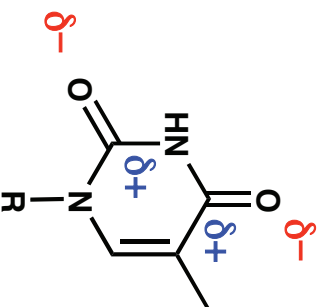
Benzene has no dipole
but a substantial quadrupole.



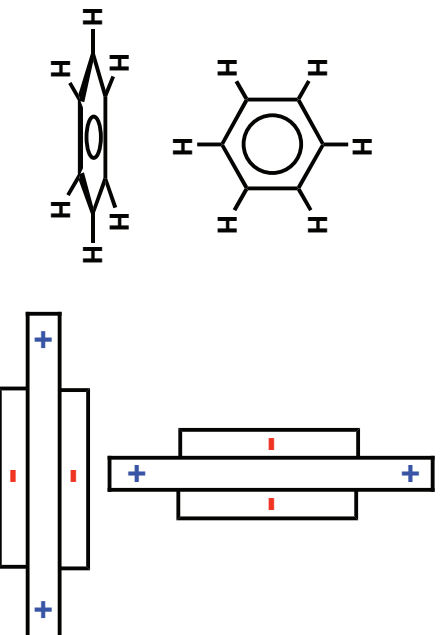
Dipole/Multipole Interactions



Simple molecules or functional groups:
Dipoles
(Important in H-bonding?)



Complex functional group arrays:
Multipoles
(Important in base stacking?)



Benzene has no dipole
but a substantial quadrupole.
(Determines geometry of dimer?)

Hydrophobic Effect: Hydrocarbons Dissolve Poorly in Water

TABLE 1. Solubility, Gibbs energy, enthalpy, entropy and heat capacity increment of transfer of some typical non-polar substances from the pure liquid phase to water at 25°C

Substance and its surface area in Å ²	Solubility in mole fractions x 10 ⁴	ΔG (kJ·mol ⁻¹)	ΔH (kJ·mol ⁻¹)	ΔS (J·K ⁻¹ ·mol ⁻¹)	ΔC _p (J·K ⁻¹ ·mol ⁻¹)
Benzene 240	4.01	19.4	2.08	-58.06	225
Toluene 275	1.01	22.8	1.73	-70.7	263
Ethylbenzene 291	0.258	26.2	2.02	-81.0	318
Cyclohexane 273	0.117	28.2	-0.10	-94.8	360
Pentane 272	0.095	28.7	-2.00	-102.8	400
Hexane 282	0.020	32.5	0	-109.1	440

See refs. 2,3.

Privalov and Gill, *Pure Appl. Chem.* 1989, *61*, 1097.

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Hydrophobic Effect: Aromatic vs. Saturated Hydrocarbons

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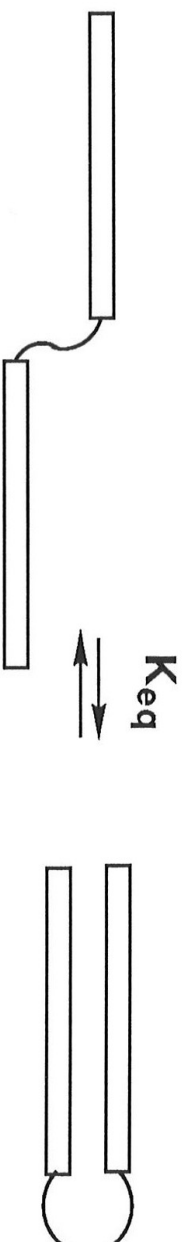
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Is benzene less 'hydrophobic' than cyclohexane?

Privalov and Gill, *Pure Appl. Chem.* 1989, *61*, 1097.

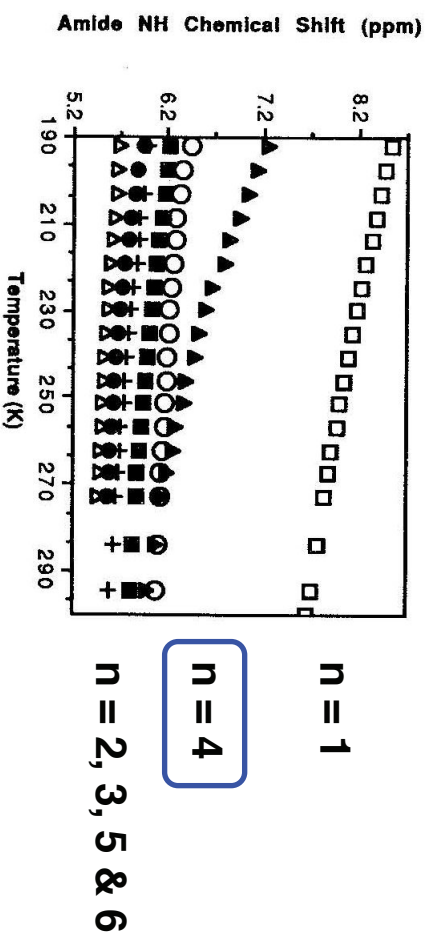
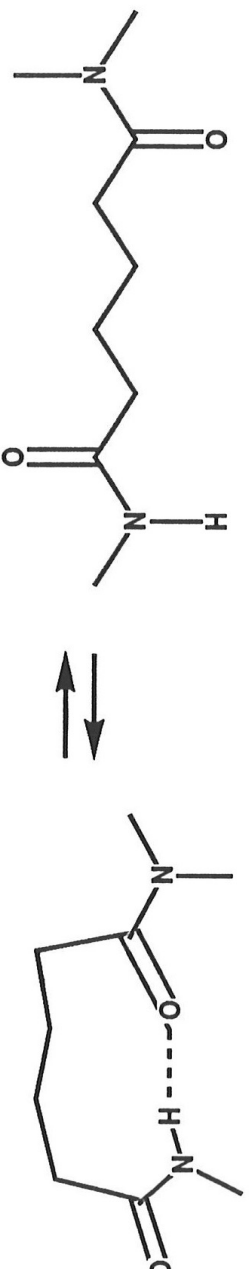
Minimal Model System for Study of Aromatic-Aromatic Interactions?



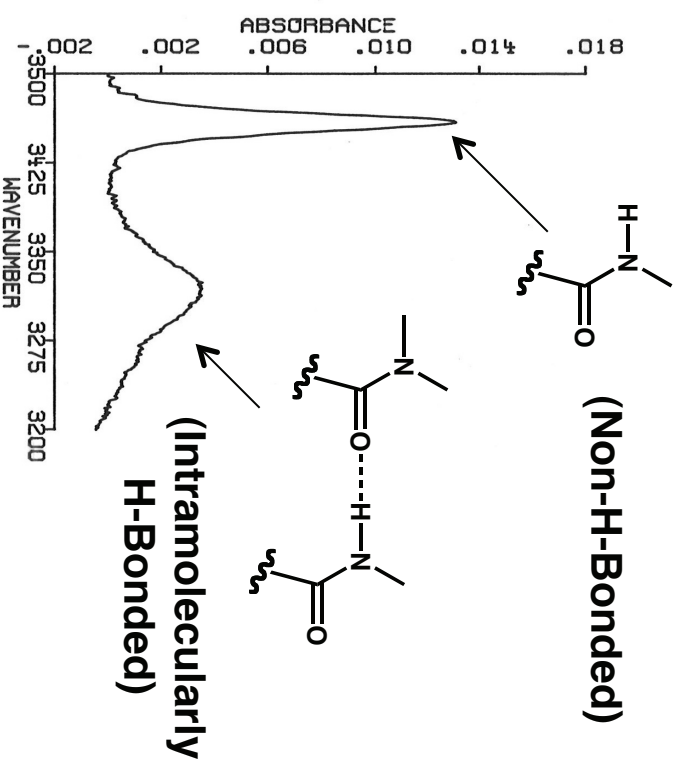
Caveat: If equilibration is rapid on the measurement time scale, determination of K_{eq} will be difficult or impossible

Recall: Minimal Systems for H-Bond-Mediated Folding.

H-Bonds as Driving Force *and* Basis for Detection

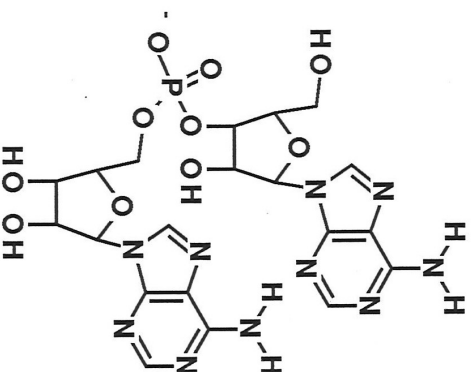
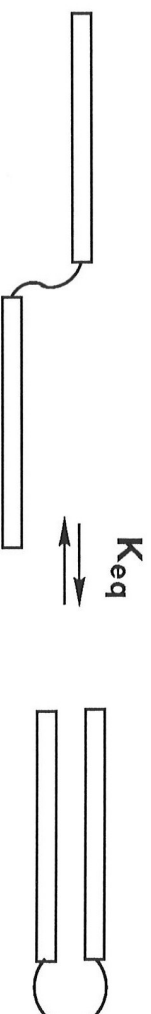


$^1\text{H NMR}$



IR

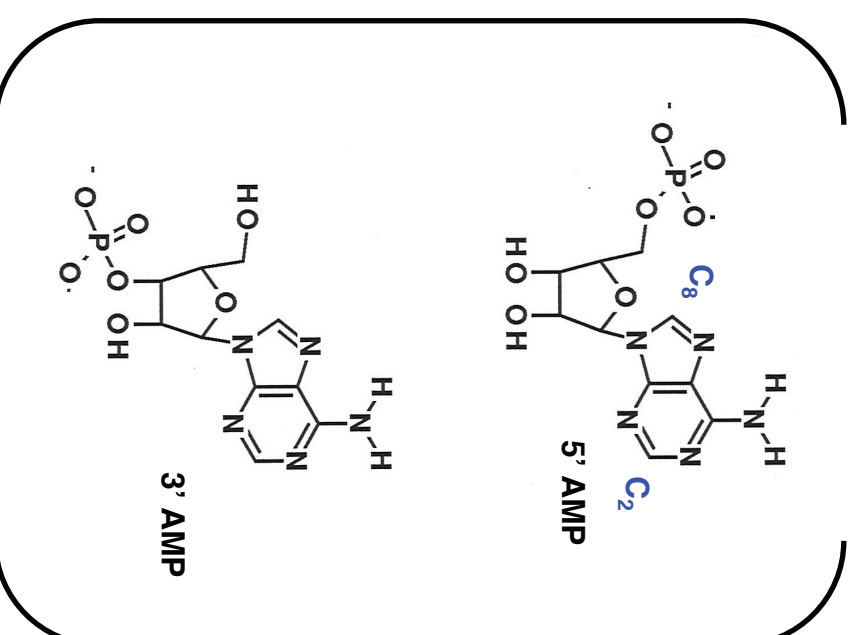
Minimal Systems for Base Stacking: Dinucleotides



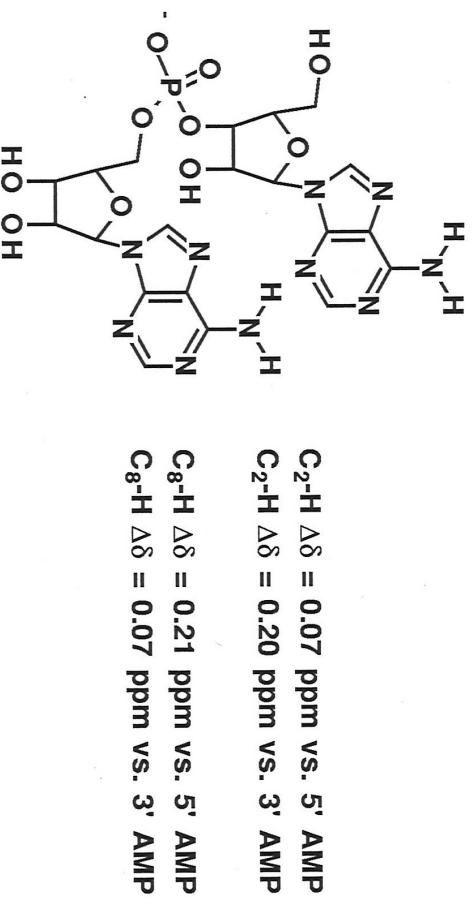
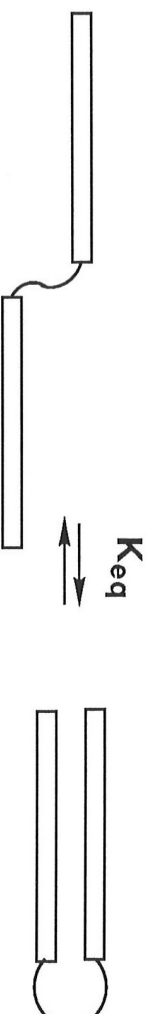
$C_2\text{-H } \Delta\delta = 0.07 \text{ ppm vs. } 5' \text{ AMP}$
 $C_2\text{-H } \Delta\delta = 0.20 \text{ ppm vs. } 3' \text{ AMP}$
 $C_8\text{-H } \Delta\delta = 0.21 \text{ ppm vs. } 5' \text{ AMP}$
 $C_8\text{-H } \Delta\delta = 0.07 \text{ ppm vs. } 3' \text{ AMP}$

Chan and Nelson, *J. Am. Chem. Soc.* 1969, *91*, 168.

Upfield shift of adenine ring δCH arises from shielding caused by the other aromatic ring; this effect is generally useful for detecting aromatic-aromatic interactions.



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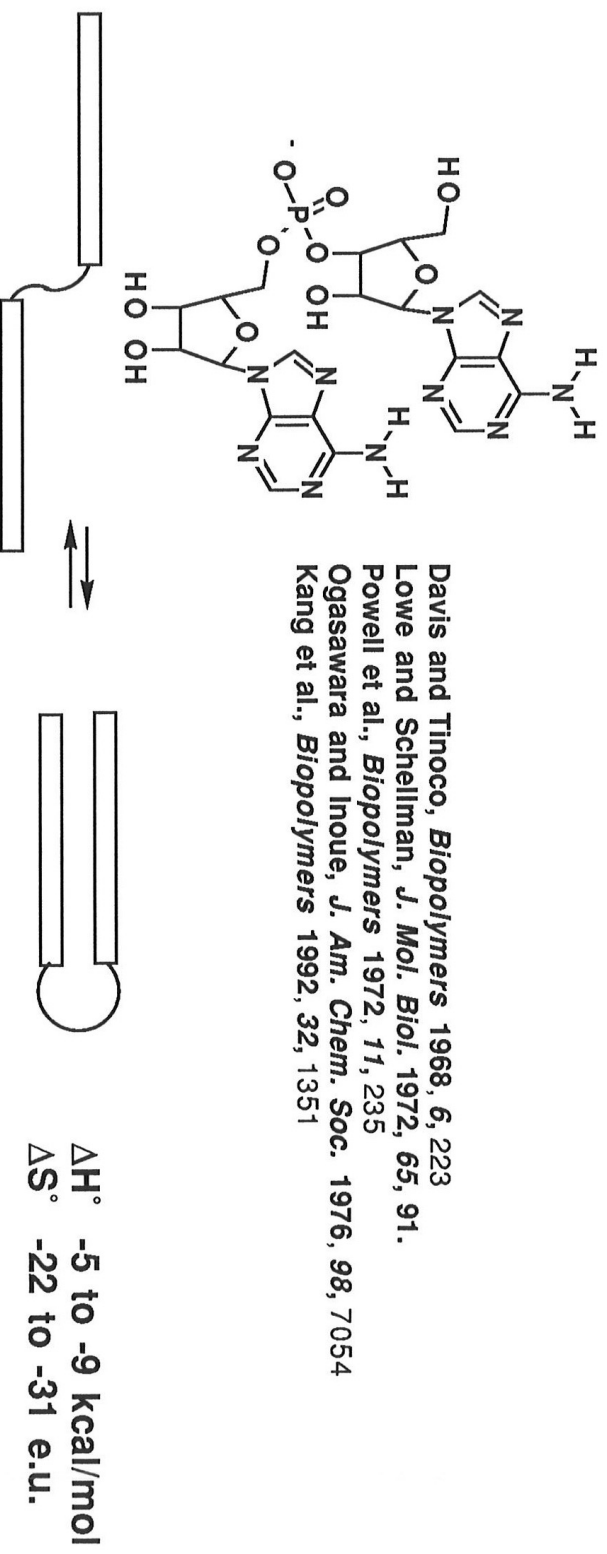
Chan and Nelson, *J. Am. Chem. Soc.* 1969, *91*, 168.

Conformational equilibrium
(unfolded vs. folded) is
rapid on the NMR time scale;
 K_{eq} is challenging to
determine.

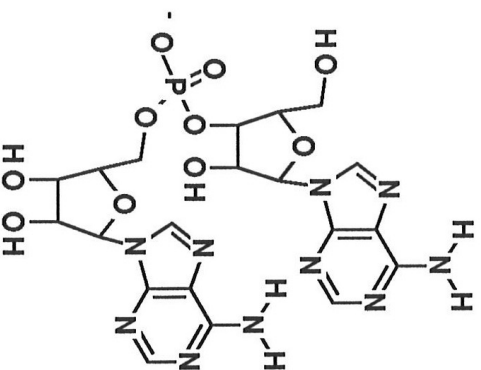
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Thermal Unfolding of ApA Dinucleotide (NMR)

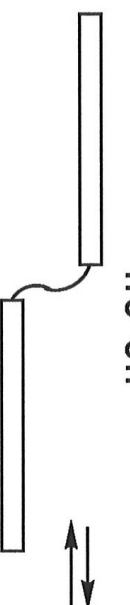
Davis and Tinoco, *Biopolymers* 1968, 6, 223
 Lowe and Schellman, *J. Mol. Biol.* 1972, 65, 91.
 Powell et al., *Biopolymers* 1972, 11, 235
 Ogasawara and Inoue, *J. Am. Chem. Soc.* 1976, 98, 7054
 Kang et al., *Biopolymers* 1992, 32, 1351



Thermal Unfolding of ApA Dinucleotide (NMR)



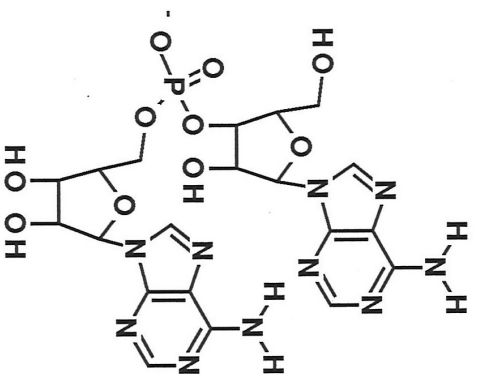
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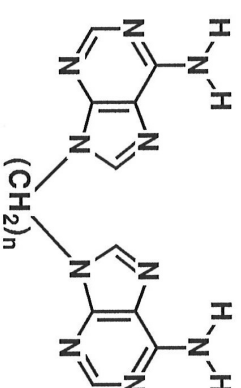
ΔH° -5 to -9 kcal/mol
 ΔS° -22 to -31 e.u.

Base stacking is enthalpically favorable in water; therefore, the hydrophobic effect is not the dominant driving force.

Further Simplification



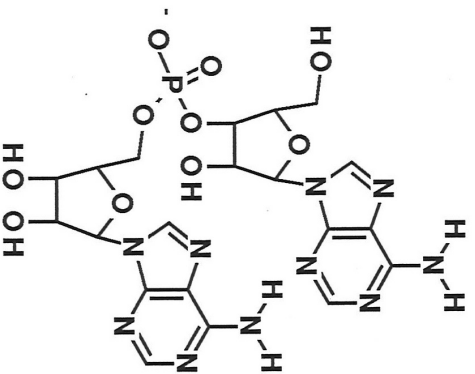
VS.



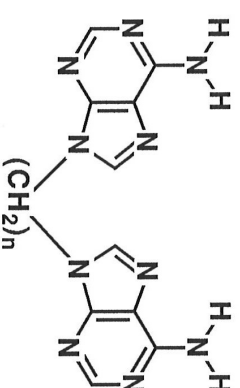
Leonard, *Acc. Chem. Res.* 1979, 12, 423.

Maximum stacking for $n = 3$

Further Simplification



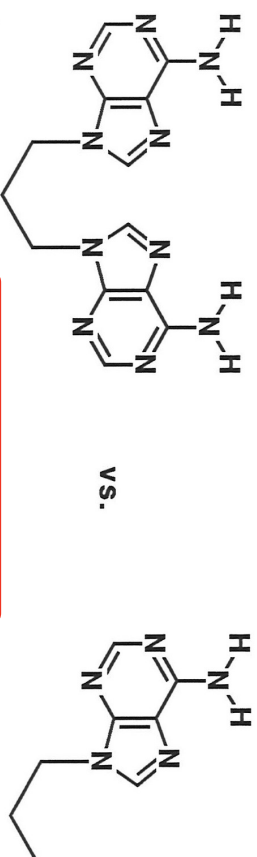
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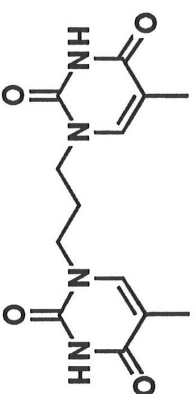
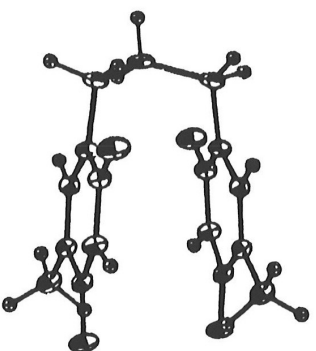
Detect stacking via impact on UV absorbance (stacking causes a decline in extinction coefficient).



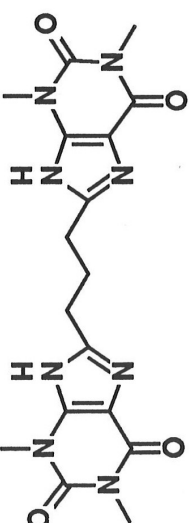
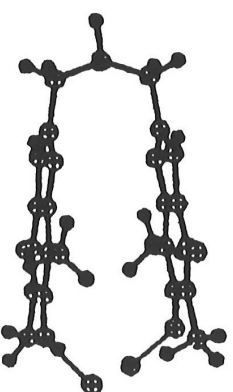
Hypochromism = 15%

Leonard and Ito, *J. Am. Chem. Soc.* 1973, 95, 4010.

Three-Carbon Linker Allows Stacking (Crystal Structures)



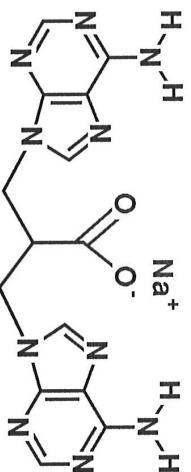
JACS 95:2324 (1973)



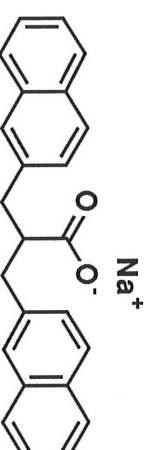
Acta Cryst. B27:952 (1970)

Simple Linkers Allow Direct Comparison of Nucleotide Bases (Heterocycles) with Hydrocarbon Aromatics?

Experimental Evidence For or Against a “Hydrophobic” Component
to Base Stacking?



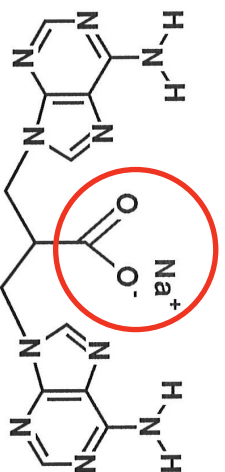
vs.



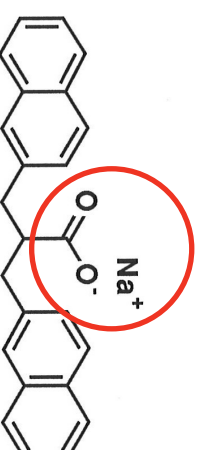
Newcomb, Gellman *J. Am. Chem. Soc.* **116**:4993 (1994)

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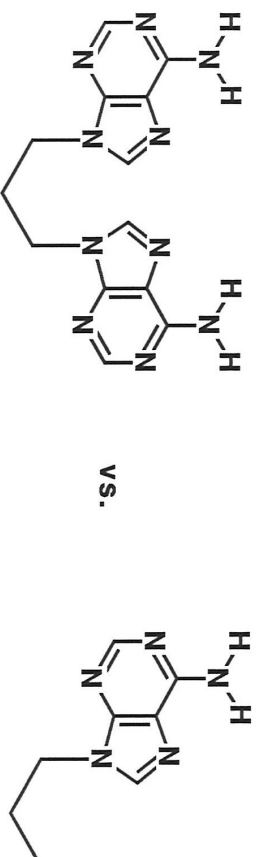


VS.



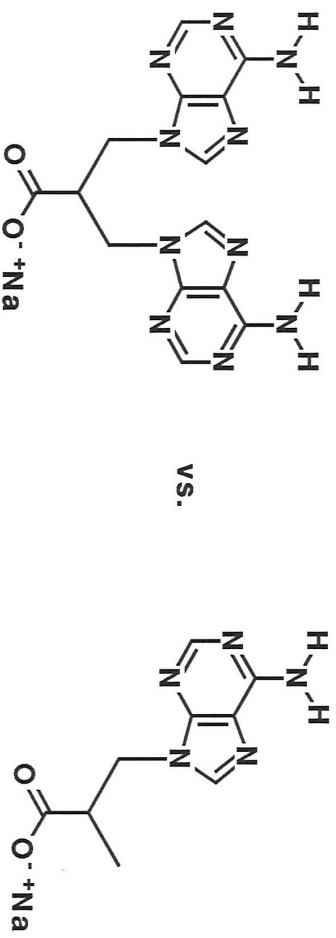
Carboxylate required to provide adequate aqueous solubility for NMR analysis.

Control Study: Impact of Carboxylate?



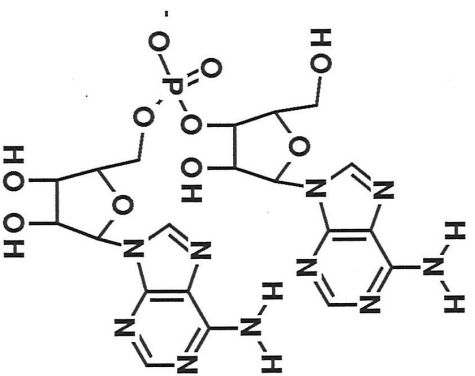
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Leonard and Ito, *J. Am. Chem. Soc.* 1973, 95, 4010.



Hypochromism at 258/260 nm = 9%

Control Study: Impact of Carboxylate?



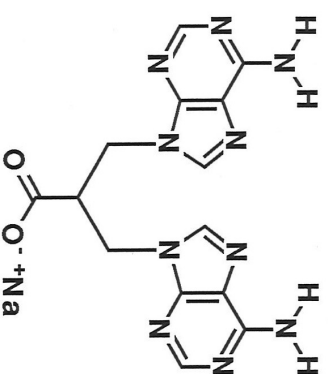
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C₈-H $\Delta\delta$ = 0.21 ppm vs. 5' AMP

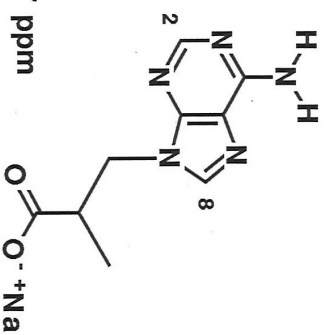
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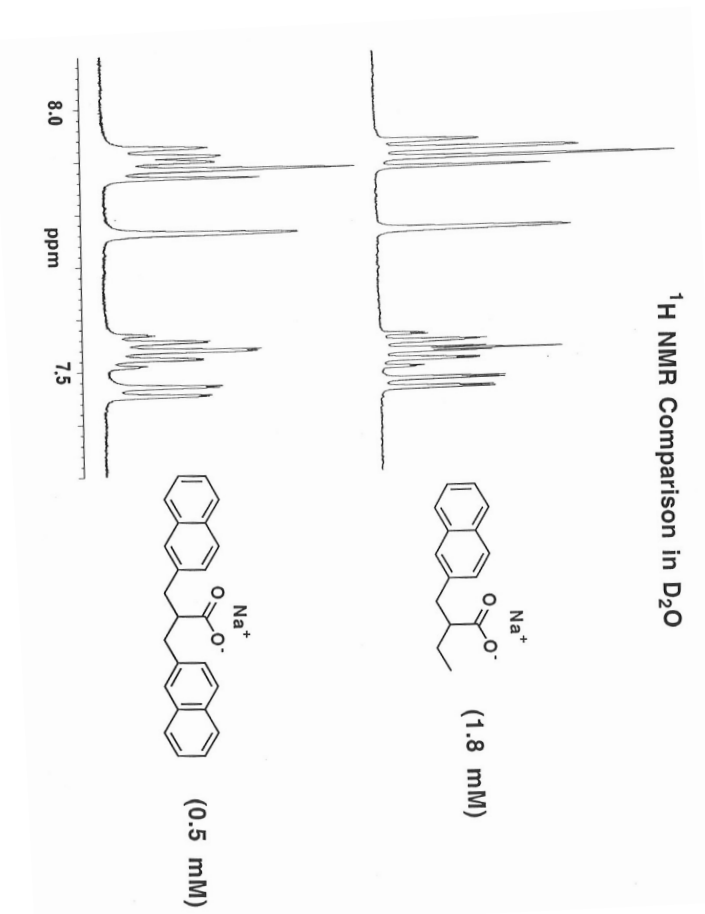


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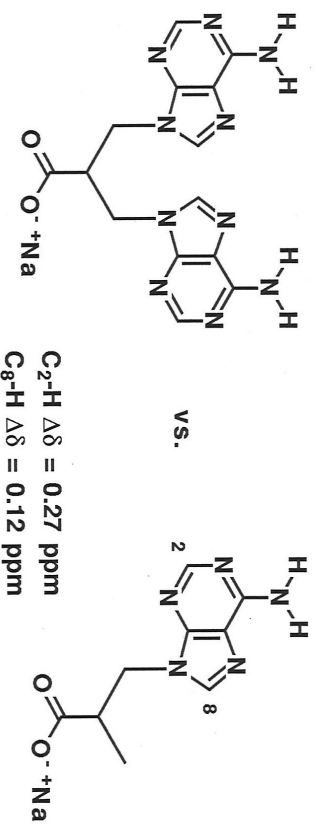
C₂-H $\Delta\delta$ = 0.27 ppm
C₈-H $\Delta\delta$ = 0.12 ppm



Dramatic Difference Between Base (Heterocycle) and Hydrocarbon Aromatic



“No Stacking”

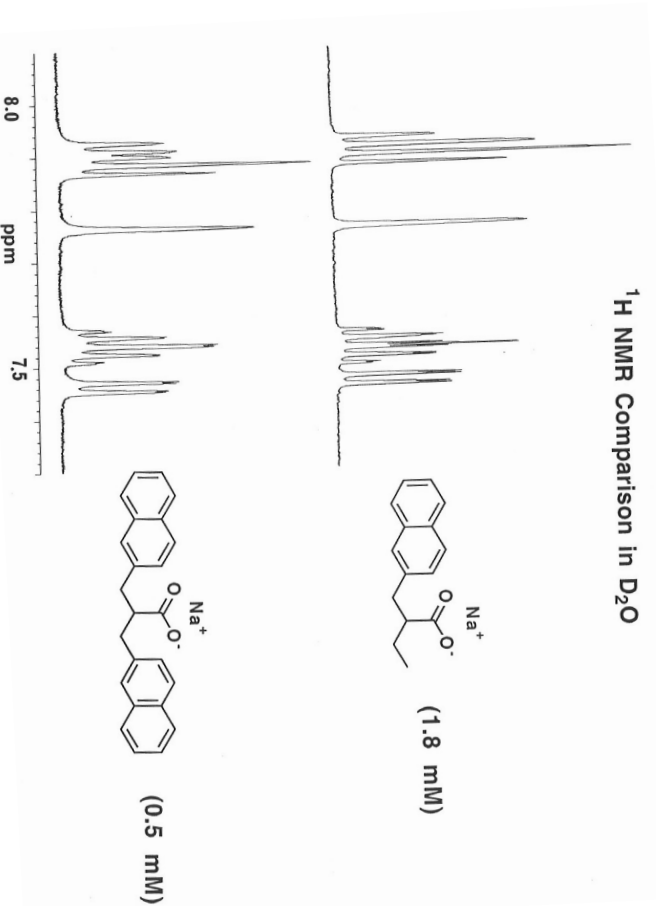


$C_2-H \Delta\delta = 0.27 \text{ ppm}$
 $C_8-H \Delta\delta = 0.12 \text{ ppm}$

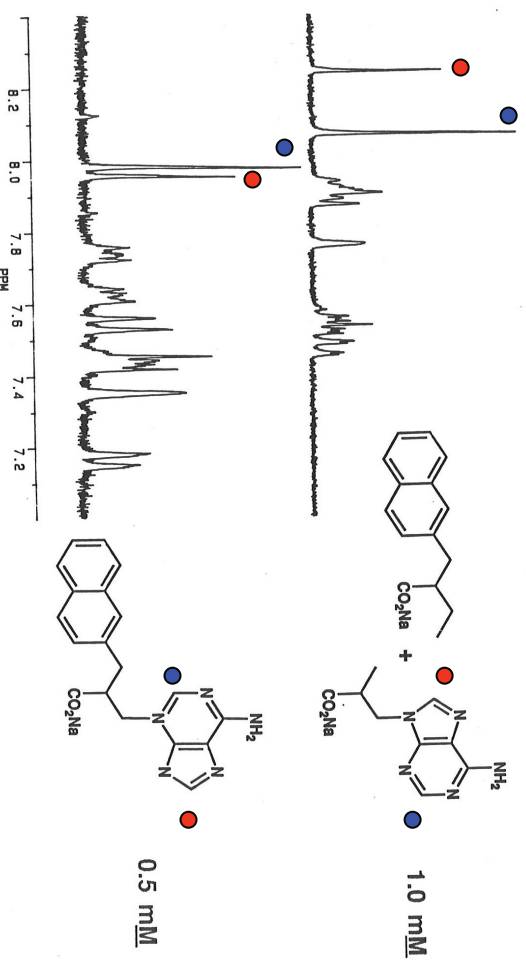
“Stacking”
(How much?)

“Hetero-Stacking”: Heterocycle + Hydrocarbon Aromatic

¹H NMR Comparison in D₂O

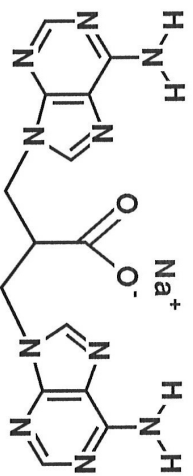


“No Stacking”

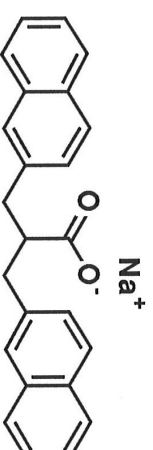


“Stacking”
(How much?)

Tentative Conclusions



vs.



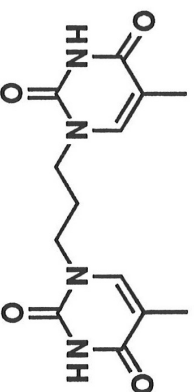
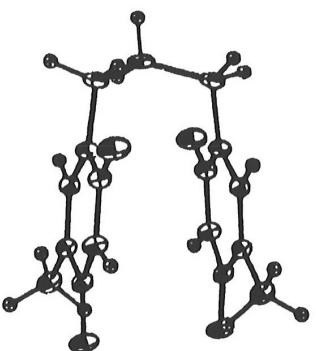
Stacking in aqueous solution

NO stacking in aqueous solution



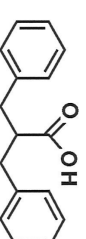
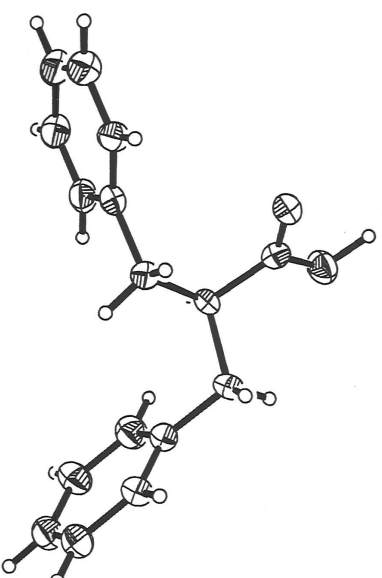
**Stacking interactions involving nucleic acid bases
are not primarily driven by the hydrophobic effect.**

Caveat: Is Three-Carbon Linker Sufficiently Long?
(Contrast between crystal structures)

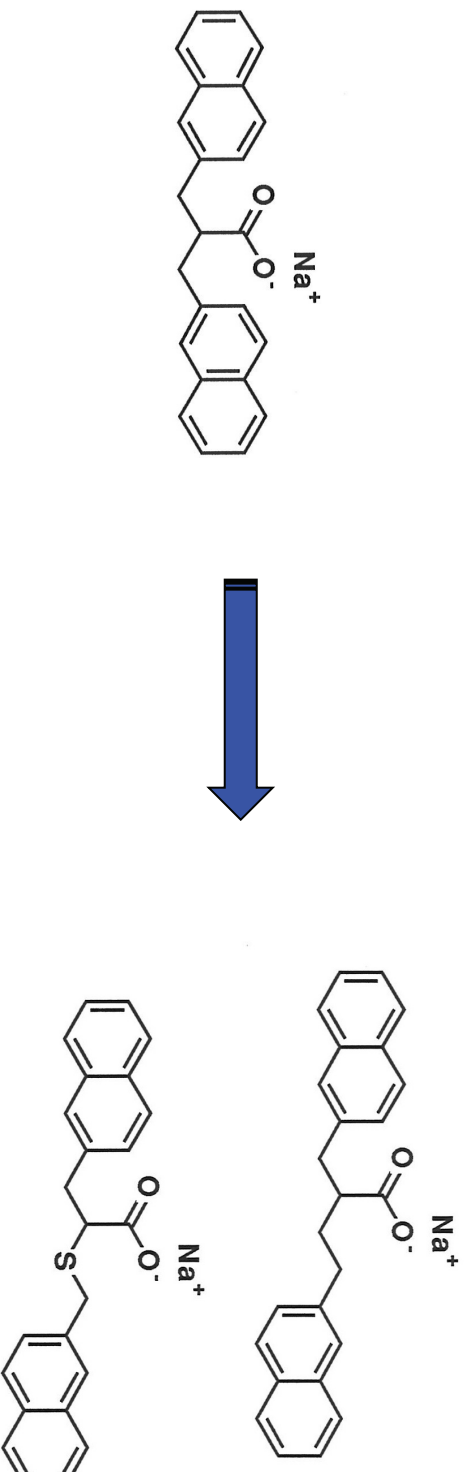


JACS 95:2324 (1973)

VS.

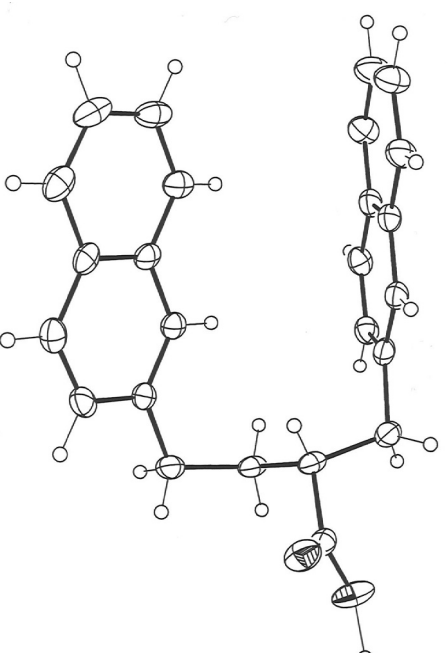
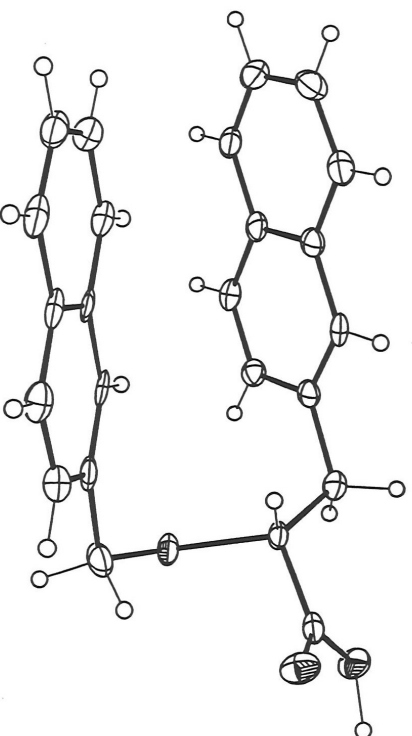
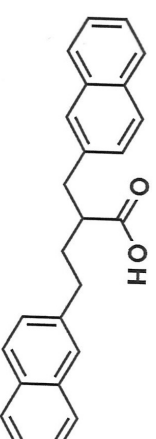
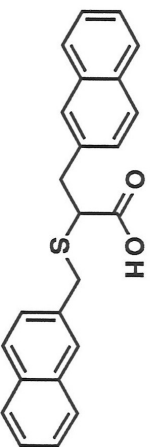


Lengthen Tether



Newcomb, Haque, Gellman *J. Am. Chem. Soc.* 117:6509 (1995)

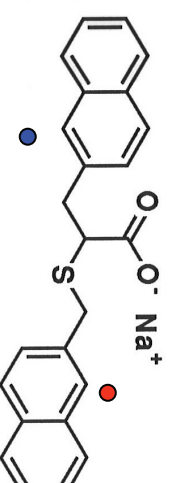
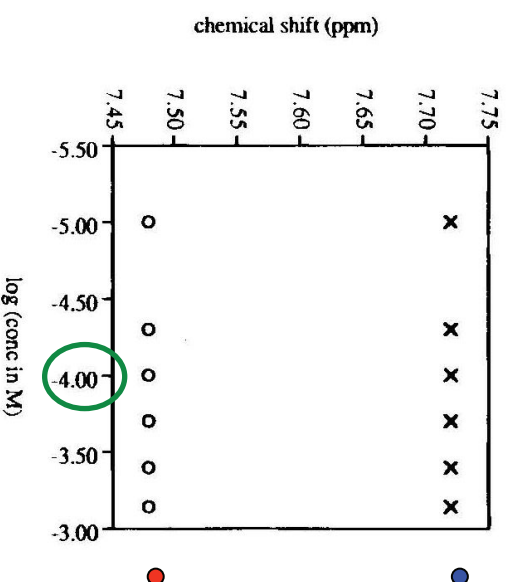
Crystal Structures Show that Naphthyl-Naphthyl Folding is Possible



**Intramolecular Interplanar Angles = 51°
(both structures)**

Folding in Water?

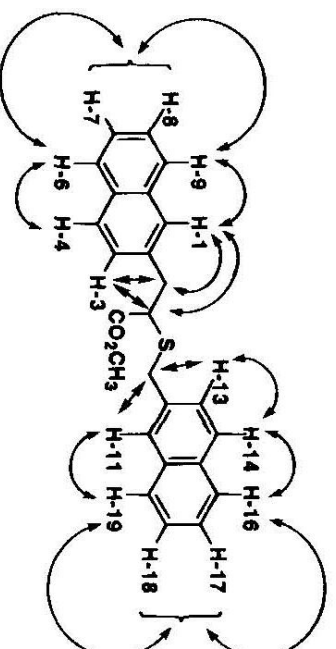
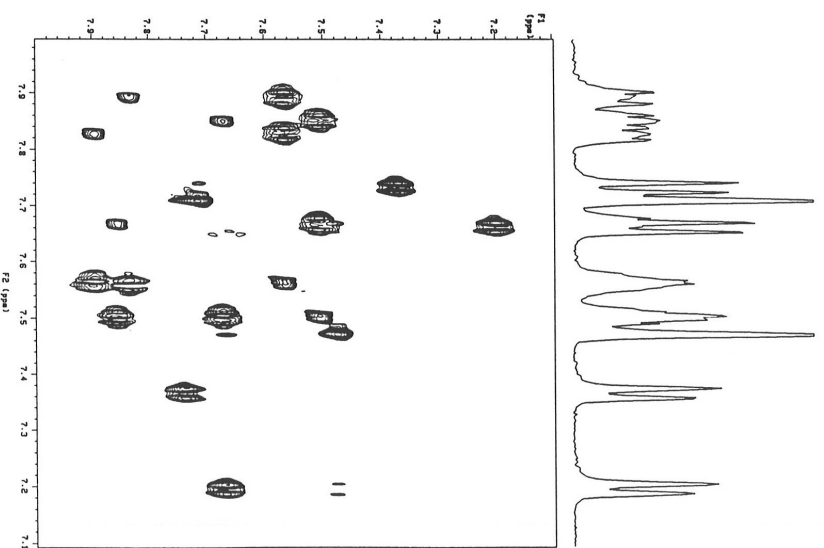
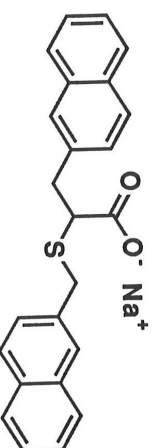
Controls (Avoid Self-Association)



Measurements at 0.1 mM should not be influenced by self-association.

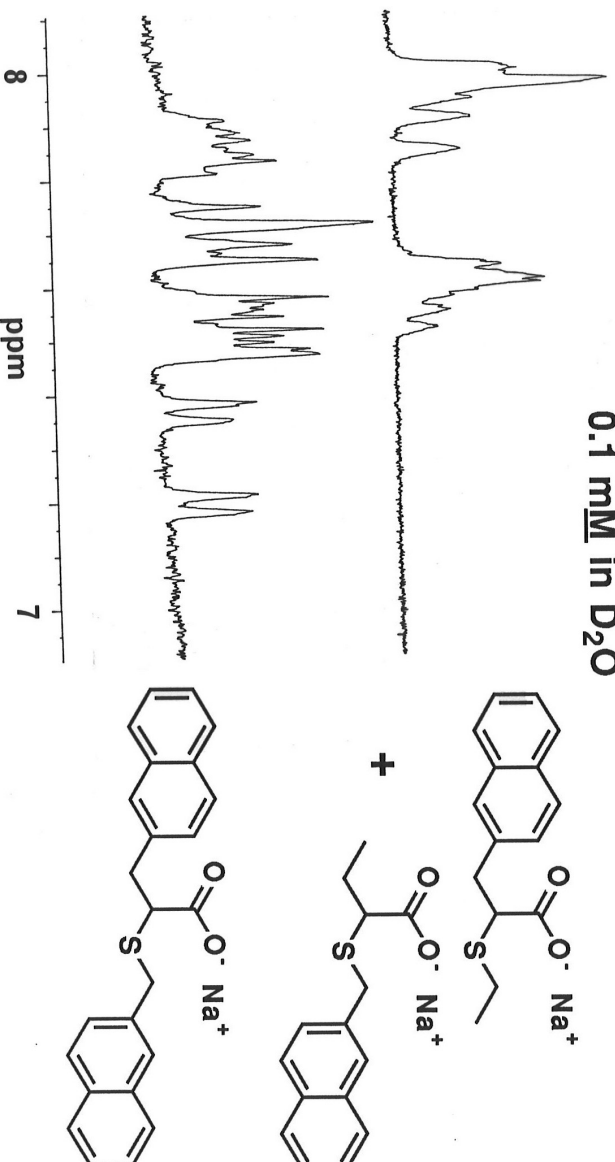
Naphthyl Ring ¹H Resonance Assignments

¹H NMR assignment
via NOE and TOCSY
(0.2 mM in D₂O)



Folding in Water?

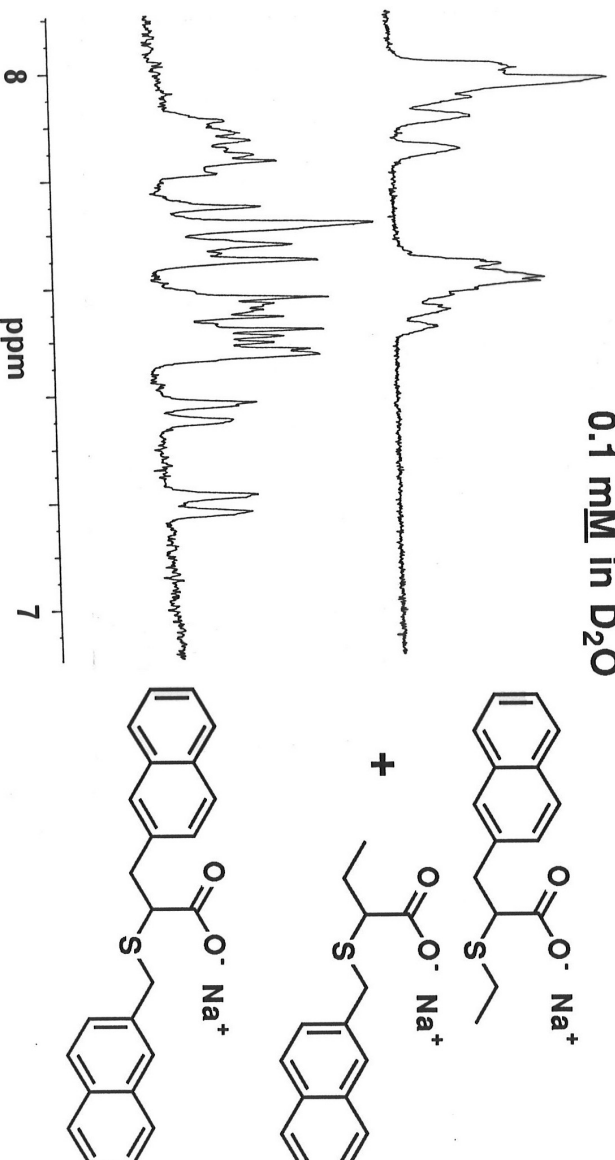
^1H NMR Comparison 0.1 mM in D_2O



**Upfield shifts of aromatic protons in the lower spectrum
show that the naphthyl rings spend time near
one another in the bis-naphthyl compound, on average.**

Folding in Water?

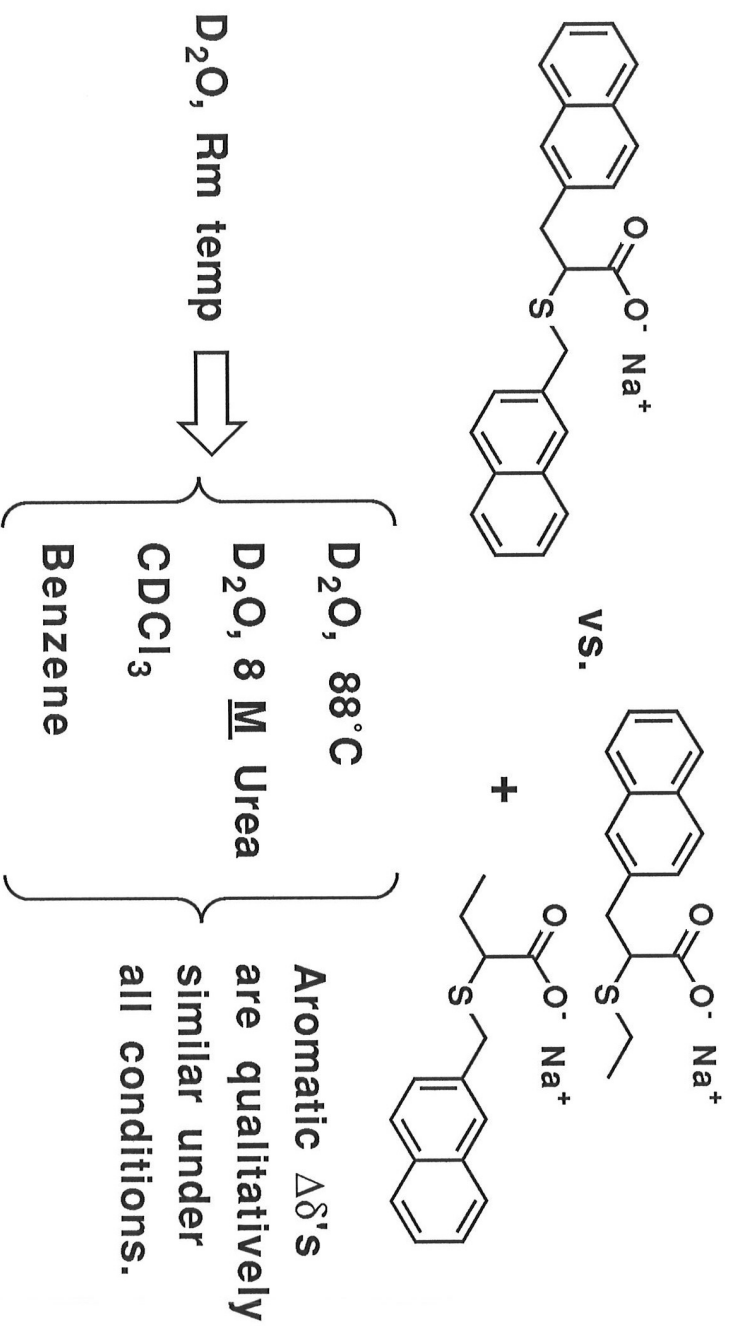
^1H NMR Comparison 0.1 mM in D_2O



Upfield shifts of aromatic protons in the lower spectrum show that the naphthyl rings spend time near one another in the bis-naphthyl compound, on average.

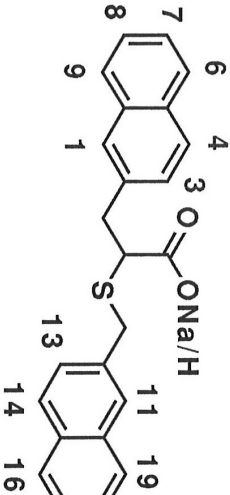
Are the intramolecular naphthyl encounters a manifestation of the “hydrophobic effect”, or simply a result of random conformational fluctuations?

Can We “Denature” the Naphthyl-Naphthyl Cluster?



Can We “Denature” the Naphthyl-Naphthyl Cluster?

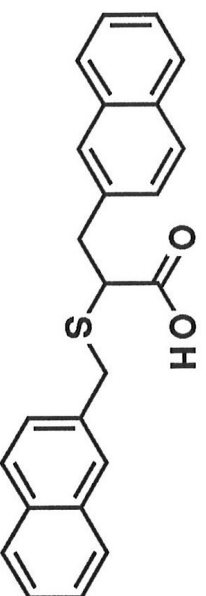
Example: Water vs. Benzene

		vs. Mononaphthyl control compounds	
			
Proton	$\Delta\delta(D_2O)$	$\Delta\delta(C_6D_6)$	$\Delta\Delta\delta$
1	-0.34	-0.27	-0.07
3	-0.30	-0.25	-0.05
4	-0.25	-0.15	-0.10
6	-0.09	-0.04	-0.05
7	-0.05	-0.01	-0.04
8	-0.05	-0.01	-0.04
9	-0.28	-0.14	-0.14
11	-0.15	-0.13	-0.02
13	-0.22	-0.17	-0.05
14	-0.20	-0.15	-0.05
16	-0.04	-0.03	-0.01
17	0.00	0.00	0
18	0.00	0.00	0
19	-0.10	-0.08	-0.02



Small differences between water and benzene suggest small hydrophobic drive for folding (water)?

What Should We Expect for Hydrophobically Driven Folding in This Case?



Crystal structure suggests that 88 Å² of water-accessible nonpolar surface can be buried by folding.

Honig et al., *Biochemistry* 1991, 30, 9686:

ΔG° increment of 46 cal/Å² hydrophobic surface buried in aqueous solution at room temp; therefore,

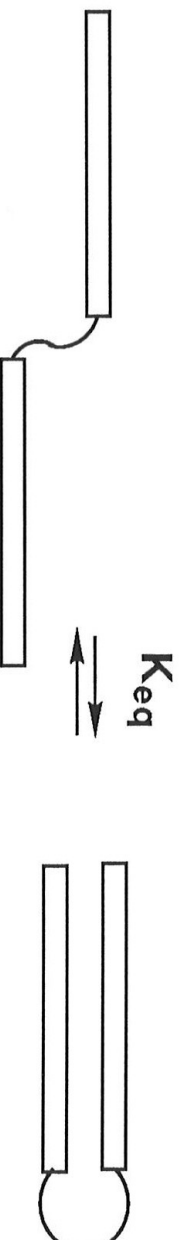
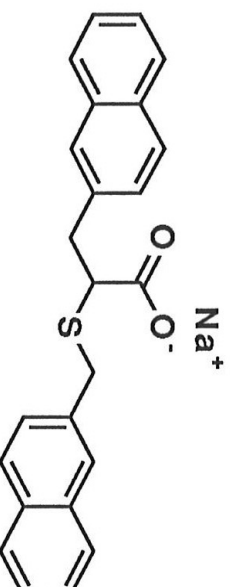
$\Delta G^\circ = -4.0$ kcal/mol for 88 Å²

Tanford et al., *PNAS* 1974, 71, 2925:

ΔG° increment of ≤ 20 cal/Å² hydrophobic surface buried in aqueous solution at room temp; therefore,

$\Delta G^\circ \leq -1.8$ kcal/mol for 88 Å²

The Nature of the Experimental System Limits What We Can Learn:
Inadequate Tools for Determining “Solution Structure”
When the Folding Equilibrium is Rapid



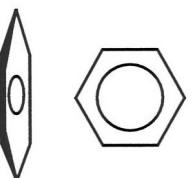
Folding equilibrium is fast on NMR time scale; no way to estimate K_{eq} .

➡ Quantitative comparisons impossible.

Interlude:

Preferred Geometries for Hydrocarbon Aromatic Associations

“Edge to face”



vs.



“Stacked”

Crystalline state: Gavezzotti and Desiraju, *Acta Cryst.* 1989, B44, 427.

Gas Phase: Klempner et al., *J. Chem. Phys.* 1979, 70, 4940.

Protein interiors: Burley and Petsko, *Science* 1985, 229, 23.

Singh and Thornton, *FEBS Lett.* 1985, 191, 1.

Blundell et al., *Science* 1986, 234, 1005.

Organic solvents: Wilcox et al., *J. Am. Chem. Soc.* 1994, 116, 4497.

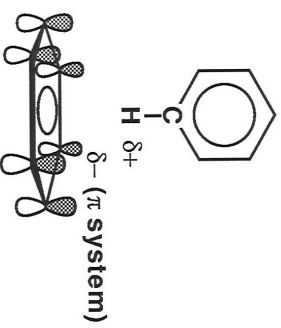
Aqueous Solution (Molecular dynamics):

Jorgensen and Severance, *J. Am. Chem. Soc.* 1990, 112, 4768.

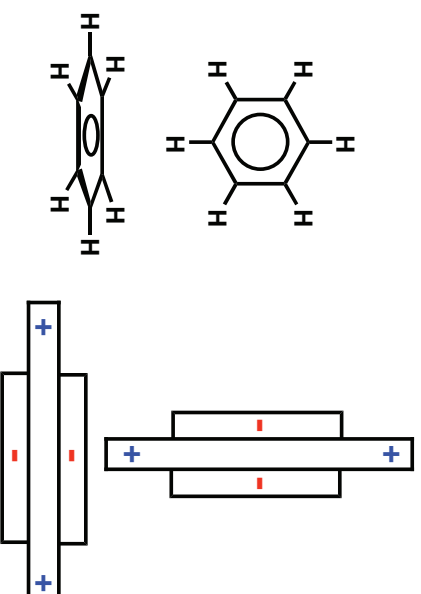
Linse, *J. Am. Chem. Soc.* 1992, 114, 4366; 1993, 115, 8793.

Why Would Edge-to-Face Geometries Be Favorable?

C-H $\cdots$ π

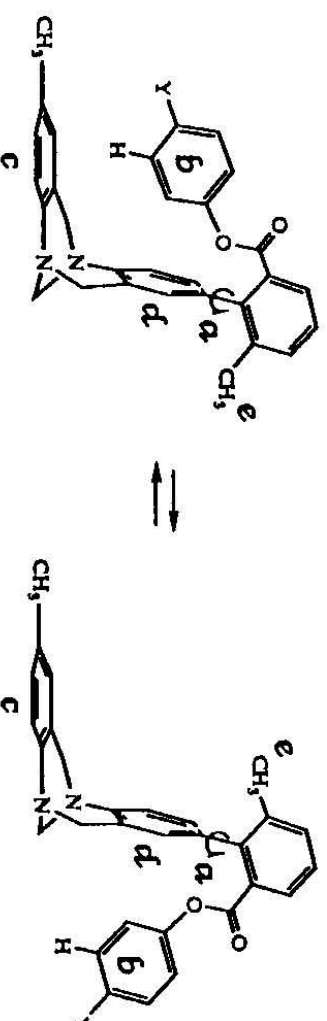


Quadrupole-quadrupole



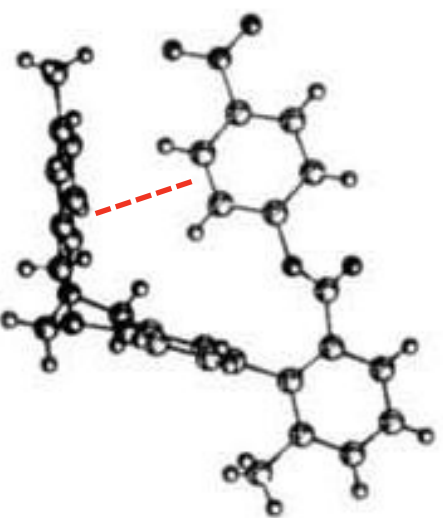
(Would surface area burial be the dominant factor in water?)

A Molecular “Torsion Balance” to Study Edge-to-Face Interactions



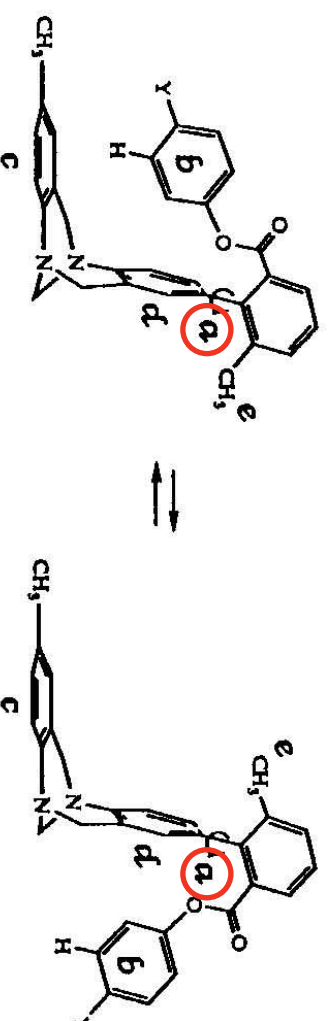
Crystal Structure (Y = NO₂)

Perfect edge-to-face geometry
between rings b and c.



Paliwal, Geib, Wilcox *J. Am. Chem. Soc.* **116**:4497 (1994)

A Molecular “Torsion Balance” to Study Edge-to-Face Interactions



Folded

Unfolded

Bond *a* is a hindered biphenyl connection: rotational characteristics are perfect for population analysis by NMR

Bond rotation $E_a \sim 16$ kcal/mol

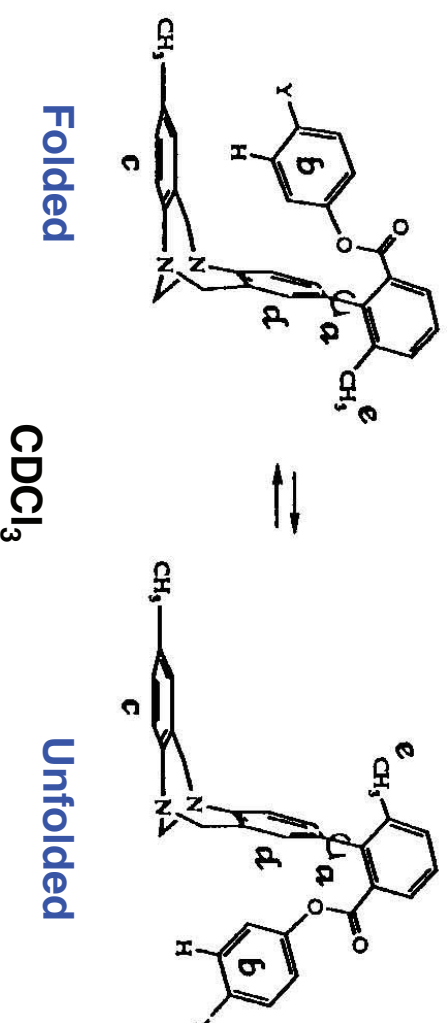
Separate resonances for “Folded” and “Unfolded” at room temp.

Equilibrium reached within minutes.

→ K_{eq} determined directly from NMR integration.

Paliwal, Geib, Wilcox *J. Am. Chem. Soc.* **116**:4497 (1994)

A Molecular “Torsion Balance” to Study Edge-to-Face Interactions



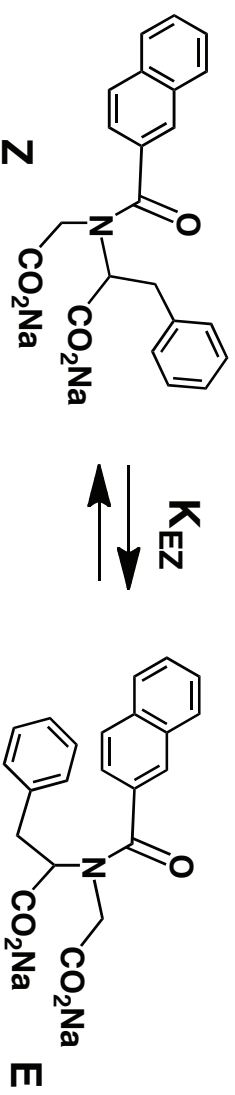
p-Methylphenyl ester ($\text{R} = \text{CH}_3$): Folded favored by 0.37 kcal/mol

Cyclohexyl ester: Folded favored by 0.37 kcal/mol

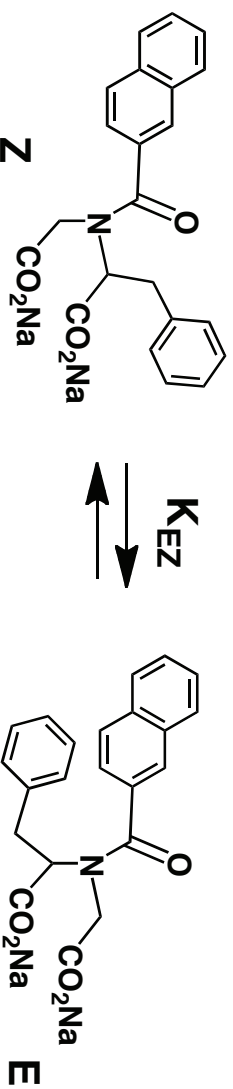
Edge-to-face interactions are weak, and not different from simple dispersion.

Paliwal, Geib, Wilcox *J. Am. Chem. Soc.* **116**:4497 (1994)

Use “Slow Rotation” Strategy for Quantify Aromatic-Aromatic Interactions/Hydrophobic Effects in Water?



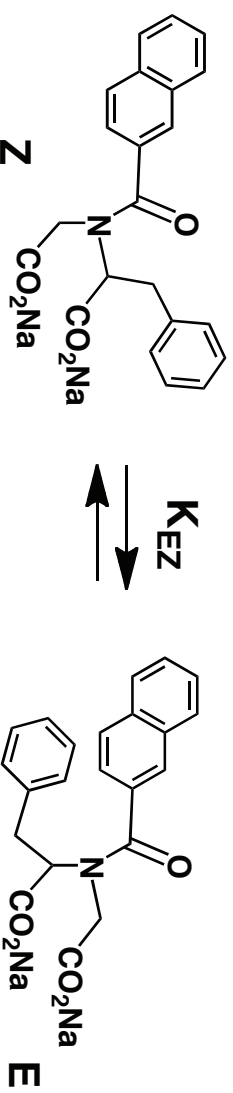
Use “Slow Rotation” Strategy for Quantify Aromatic-Aromatic Interactions/Hydrophobic Effects in Water?



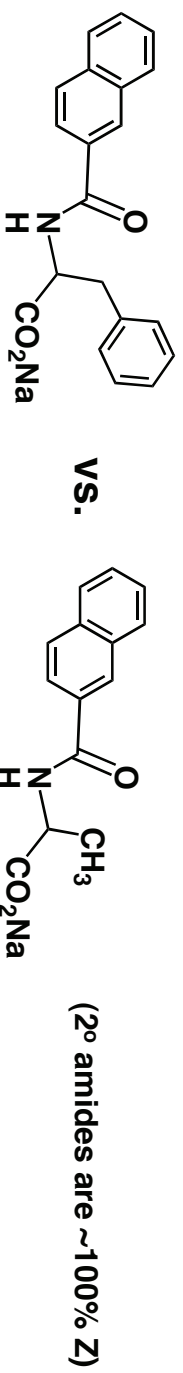
No aromatic-aromatic
Interactions (?)

Aromatic-aromatic
Interactions (?)

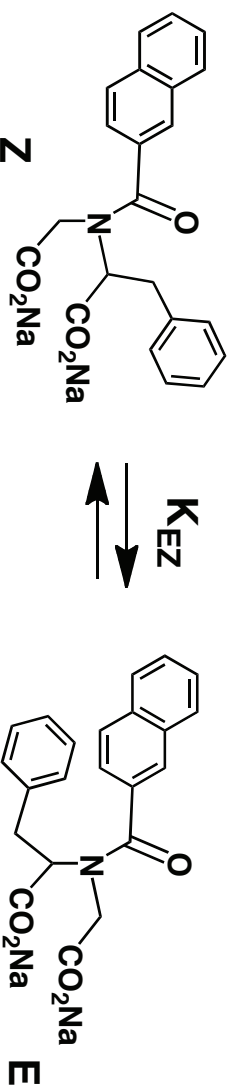
Use “Slow Rotation” Strategy for Quantify Aromatic-Aromatic Interactions/Hydrophobic Effects in Water?



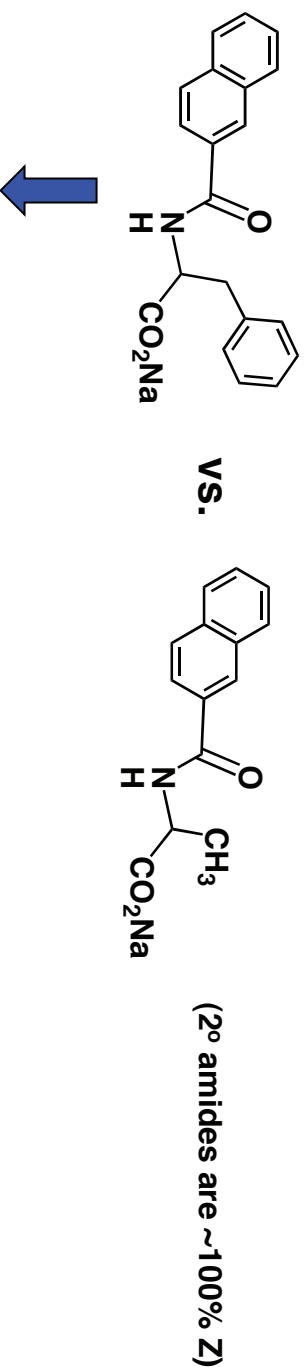
Control for aromatic-aromatic interactions in Z conformers:



Use “Slow Rotation” Strategy for Quantify Aromatic-Aromatic Interactions/Hydrophobic Effects in Water?

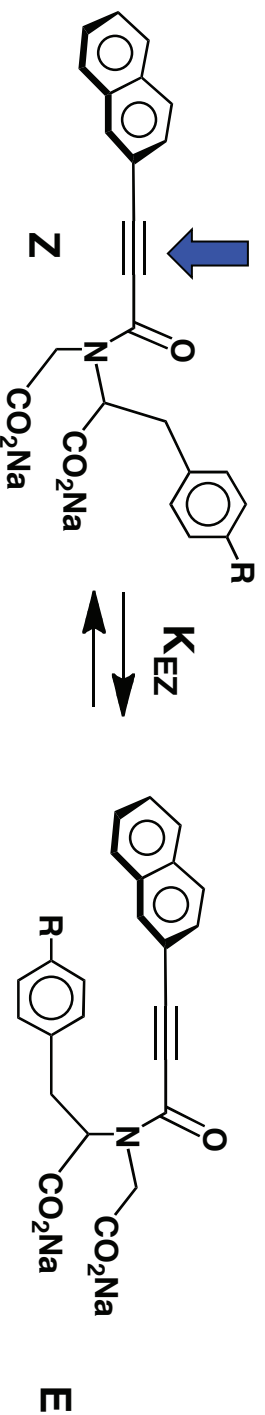


Control for aromatic-aromatic interactions in Z conformers:



Substantial upfield shifts in naphthyl ^1H resonances, relative to “methyl” analogue, imply naphthyl-phenyl proximity in Z conformer.

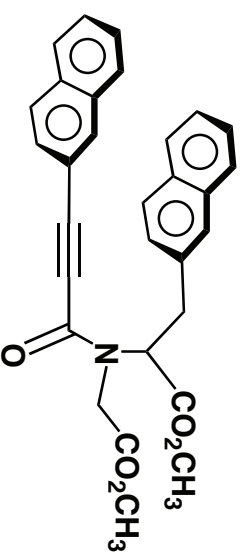
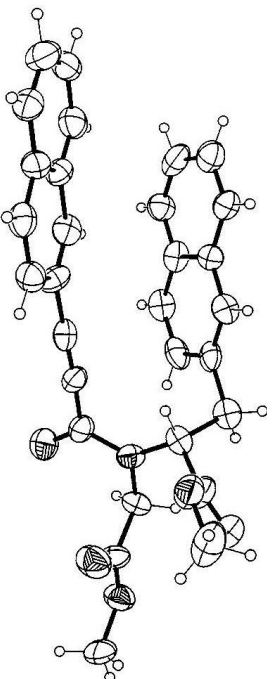
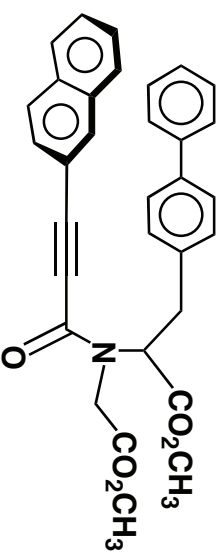
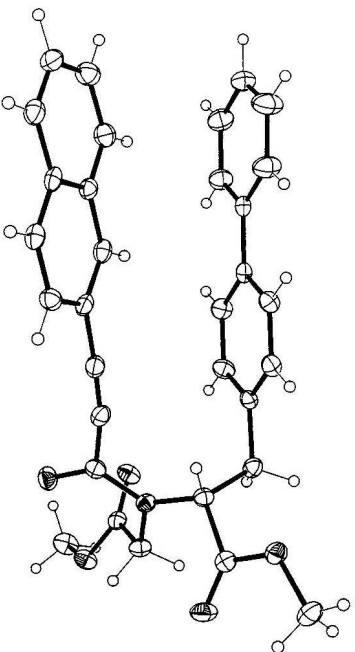
Redesign



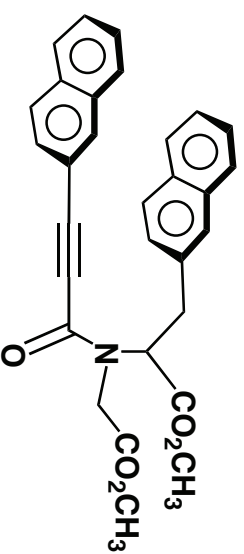
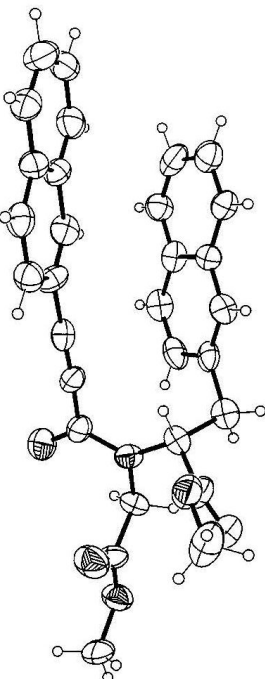
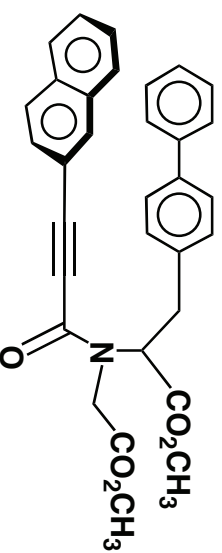
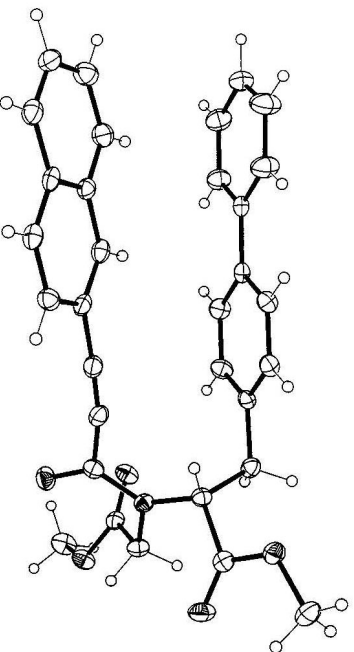
(2° amide control studies suggest that there is still a small extent of aromatic-aromatic interaction in the Z conformer, but simulations suggest minimal hydrophobic surface area burial.)

Gardner, Christianson, Gellman *J. Am. Chem. Soc.* 119:5041 (1997)

Diester Crystal Structures: Aromatic-Aromatic Proximity in E Conformers



Diester Crystal Structures: Aromatic-Aromatic Proximity in E Conformers

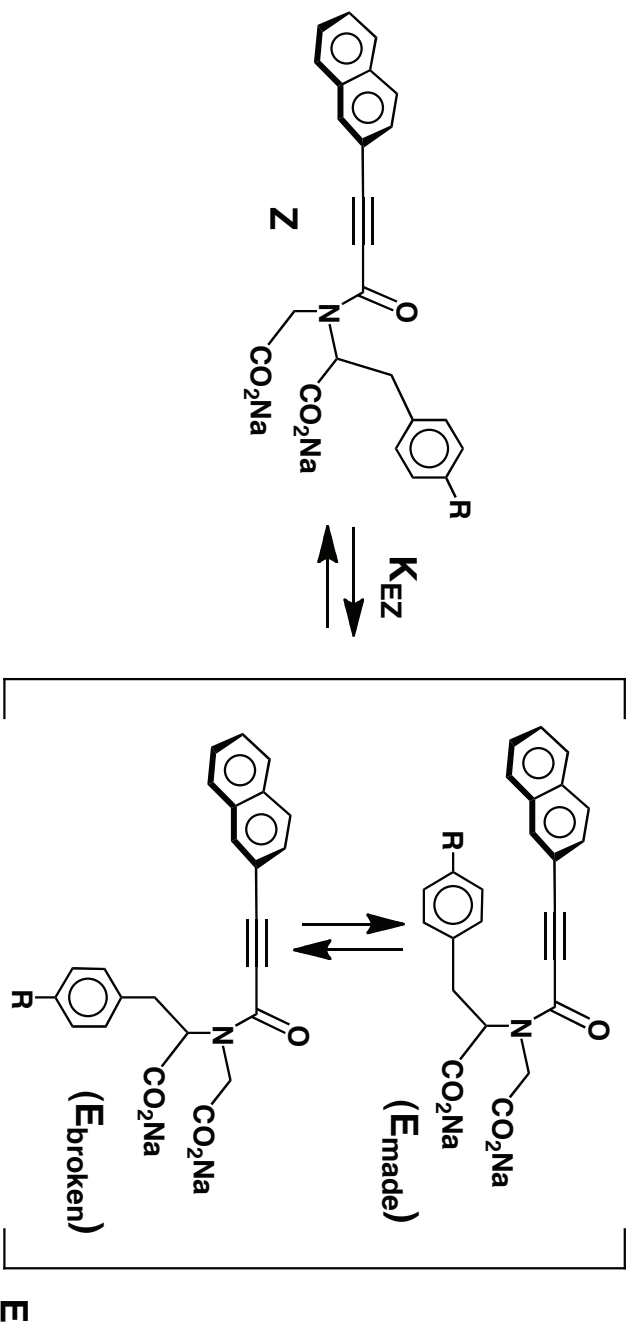


Dissolve in CDCl_3 :

Initially detect one rotamer by ^1H NMR (low temp) $\rightarrow$ E

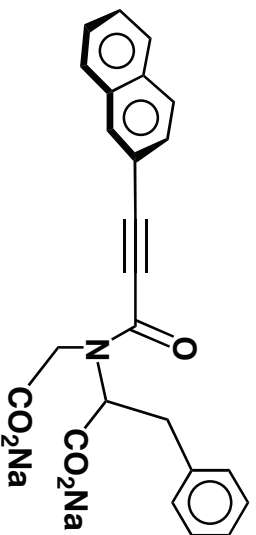
Another rotamer grows in slowly $\rightarrow$ Z

Redesign: Deeper Consideration

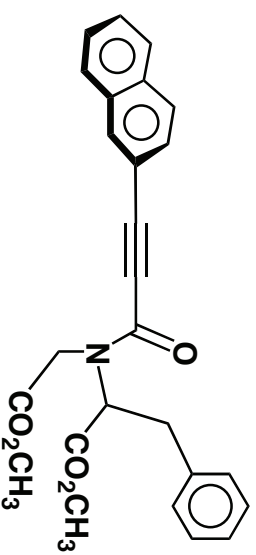


K_{EZ} is not a precise measure of naphthyl – R interactions, but this parameter should still provide useful insight.

Control Measurements



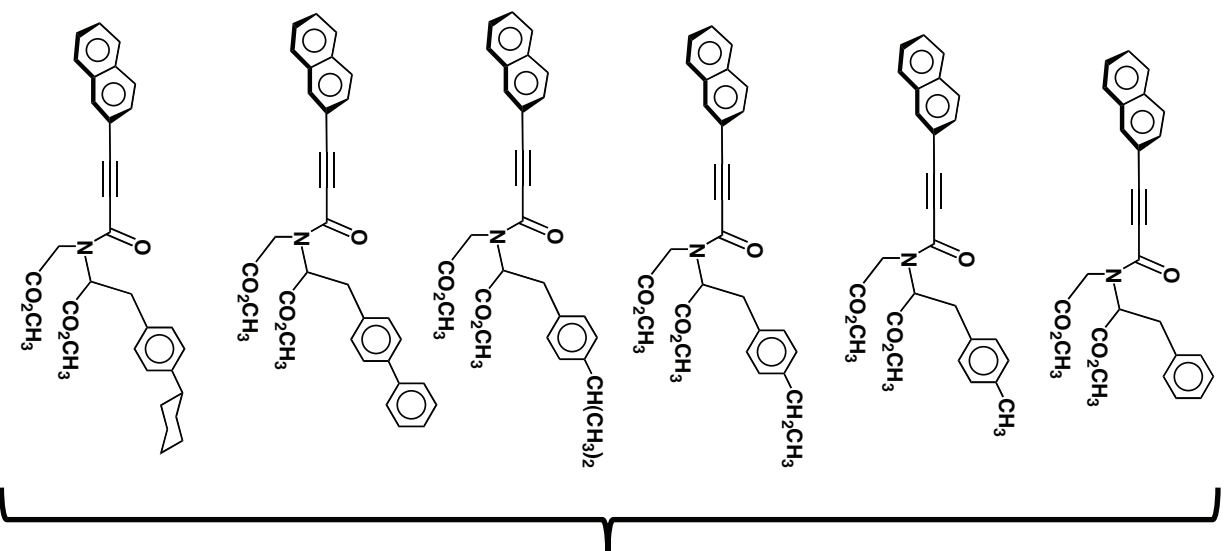
K_{EZ} in D_2O = 1.4



K_{EZ} in CDCl_3 = 1.5

↓ This 3° amide framework has a small intrinsic bias for the E conformer, but this bias does not reflect a hydrophobic effect.

Control Measurements

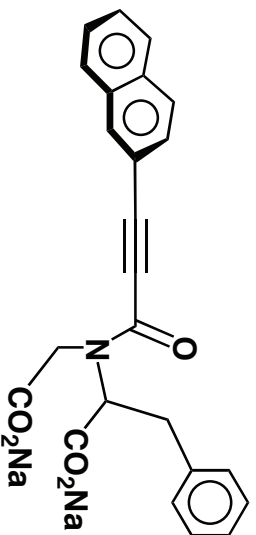


$$K_{\text{EZ}} \text{ in } \text{CDCl}_3 = 1.6 \pm 0.1$$

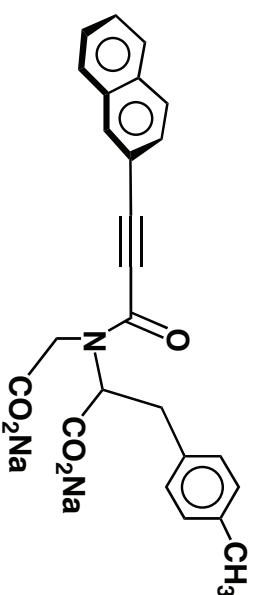


There is no intrinsic attraction
between the phenyl substituent
and the naphthyl group in CDCl_3 .

Probing for Minimum Increments of the Hydrophobic Effect



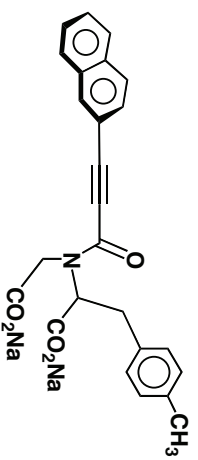
$$K_{\text{EZ}} \text{ in } \text{D}_2\text{O} = 1.4$$



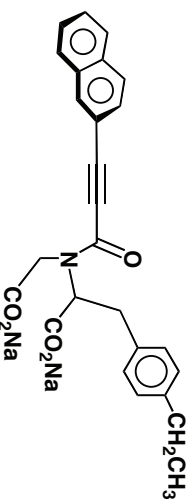
$$K_{\text{EZ}} \text{ in } \text{D}_2\text{O} = 1.8$$

$$\Delta\Delta G = -0.15 \text{ kcal/mol}$$

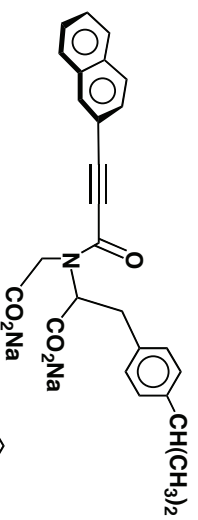
Probing for Minimum Increments of the Hydrophobic Effect



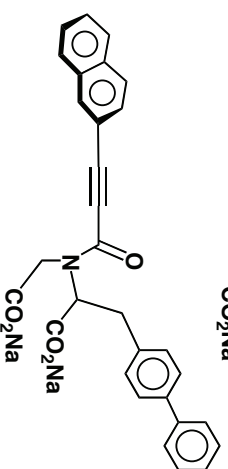
$$\Delta\Delta G = -0.15 \text{ kcal/mol}$$



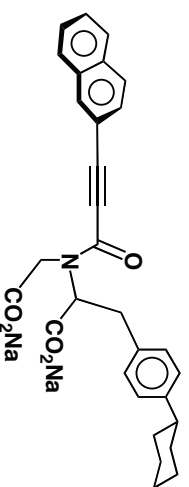
$$\Delta\Delta G = -0.21 \text{ kcal/mol}$$



$$\Delta\Delta G = -0.34 \text{ kcal/mol}$$

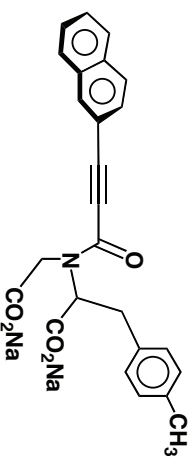


$$\Delta\Delta G = -0.61 \text{ kcal/mol}$$

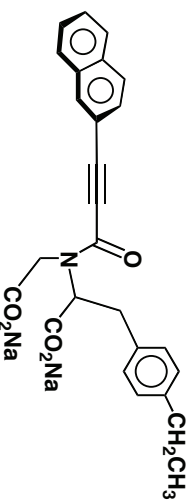


$$\Delta\Delta G = -0.45 \text{ kcal/mol}$$

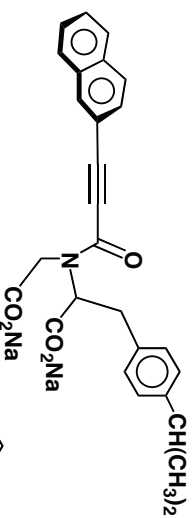
Probing for Minimum Increments of the Hydrophobic Effect



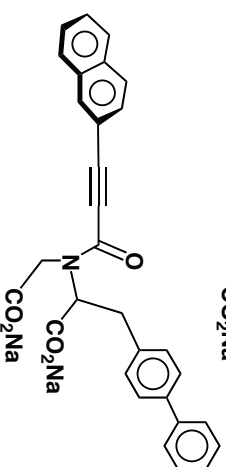
$$\Delta\Delta G = -0.15 \text{ kcal/mol}$$



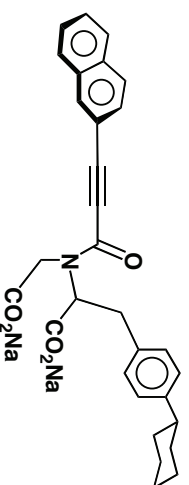
$$\Delta\Delta G = -0.21 \text{ kcal/mol}$$



$$\Delta\Delta G = -0.34 \text{ kcal/mol}$$



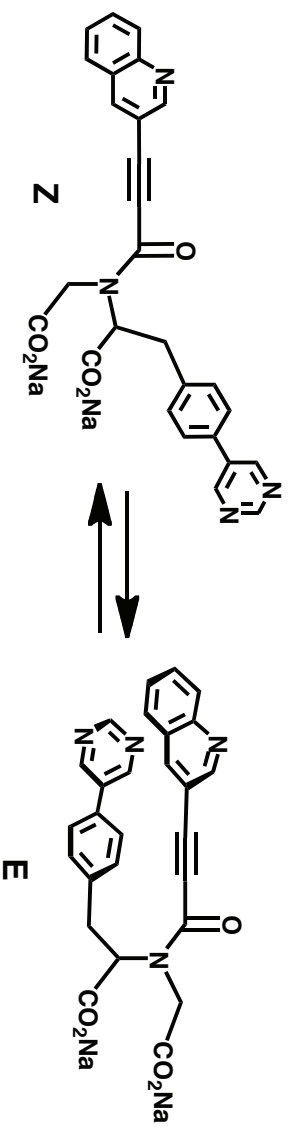
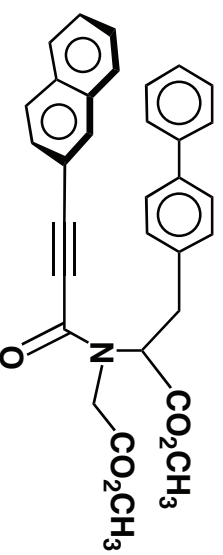
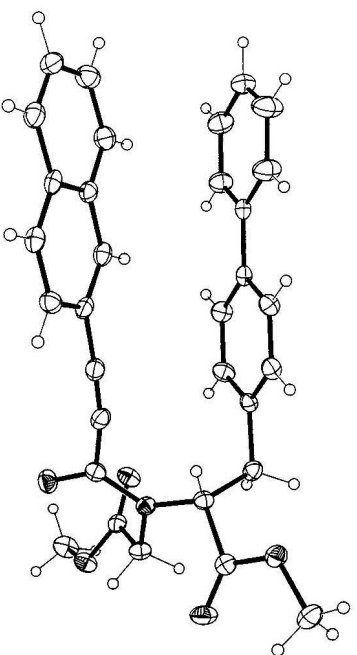
$$\Delta\Delta G = -0.61 \text{ kcal/mol}$$



$$\Delta\Delta G = -0.45 \text{ kcal/mol}$$

Benzene is far more soluble in water than cyclohexane. Thus, perhaps there is a special intrinsic attraction between phenyl groups in water?

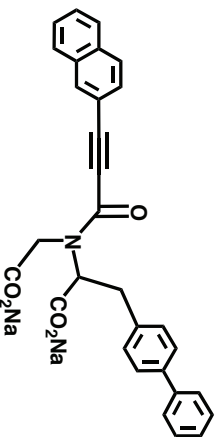
Toward Base Stacking: Heteroaromatic Analogues



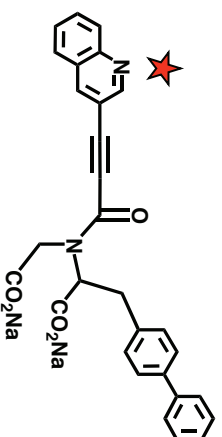
McKay, Haptonstall, Gellman *J. Am. Chem. Soc.* **123**:1244 (2001)

Toward Base Stacking: Heteroaromatic Analogues

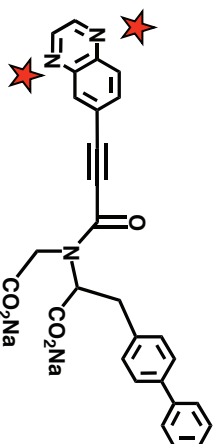
K_{EZ} in D_2O



2.9



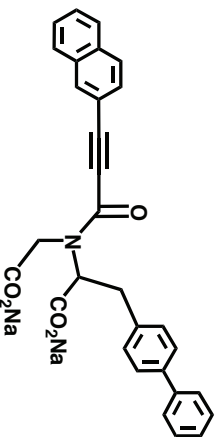
3.8



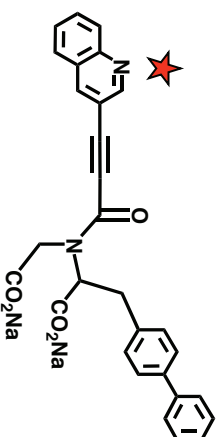
4.3

Toward Base Stacking: Heteroaromatic Analogues

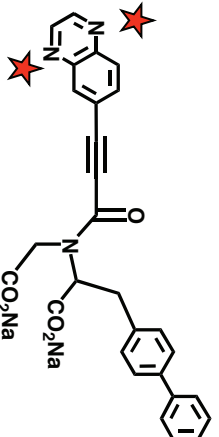
K_{EZ} in D_2O



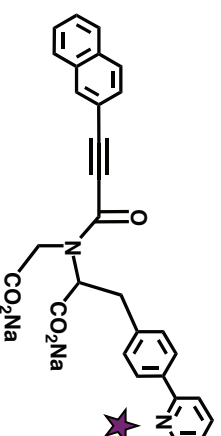
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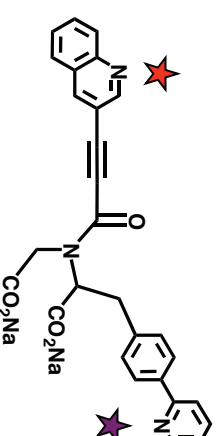
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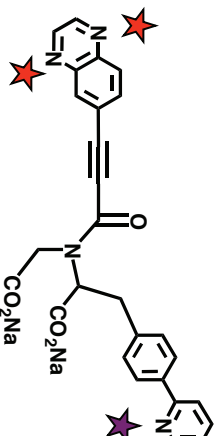
4.3



3.6



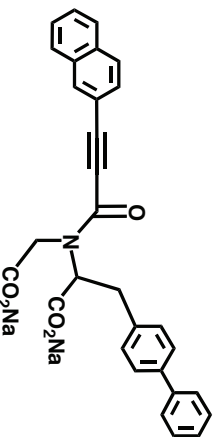
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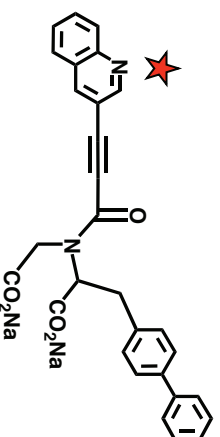
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Toward Base Stacking: Heteroaromatic Analogues

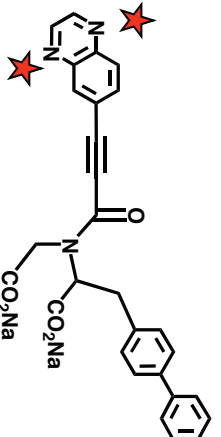
K_{EZ} in D_2O



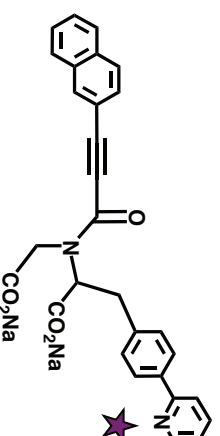
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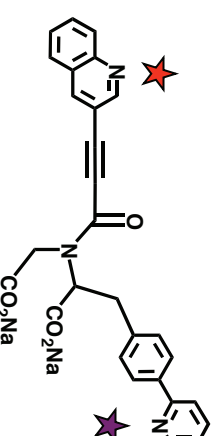
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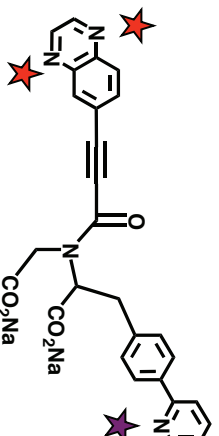
4.3



3.6



5.0



5.6

Heteraromatic rings manifest distinctive attractions in water, but this phenomenon appears not to be a classical hydrophobic effect, because the heteromatic units are more water-soluble with increasing N atoms.

Conclusions

Devising systems that allow incisive quantitative analysis of minimal aromatic–aromatic interactions in solution is challenging.

The origins of aromatic–aromatic interactions remain unclear...

Composite of hydrophobic effects and intrinsic attractions?

Hydrocarbon vs. heteroaromatic causes mechanistic change?

