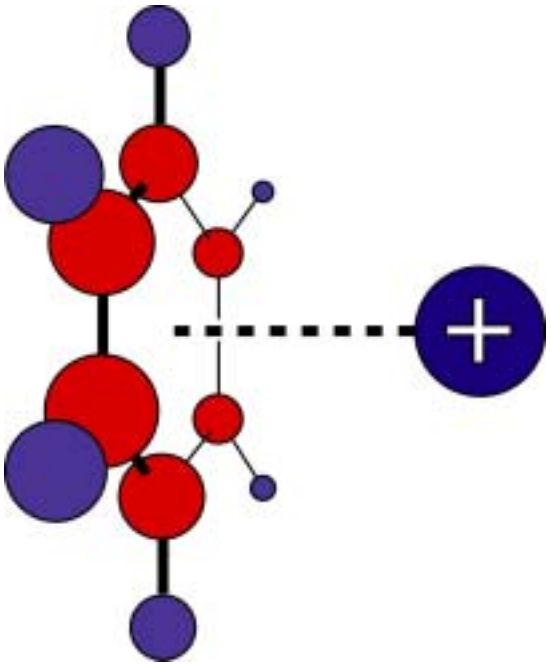
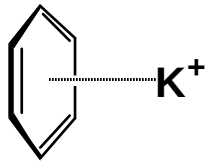
The Cation-π Interaction



Stabilizing Interaction Between a Cation and the Face of a Simple Aromatic

DA Dougherty, DA Stauffer, *Science*, **250**, 1558 (1990)
DA Dougherty, *Science*, **271**, 163 (1996)
JC Ma, DA Dougherty, *Chem. Rev.*, **97**, 1303 (1997)
N Zacharias, DA Dougherty *TiPS*, **23**, *281 (2002)*

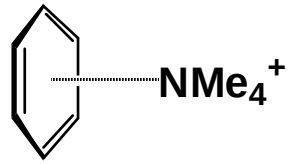
Gas Phase Cation-π Interactions



$-\Delta H_{exptl}$ = 19.2 kcal/mol

H_2O ····· K^+

$-\Delta H_{exptl}$ = 17.9 kcal/mol



$-\Delta H_{exptl}$ = 9.4 kcal/mol

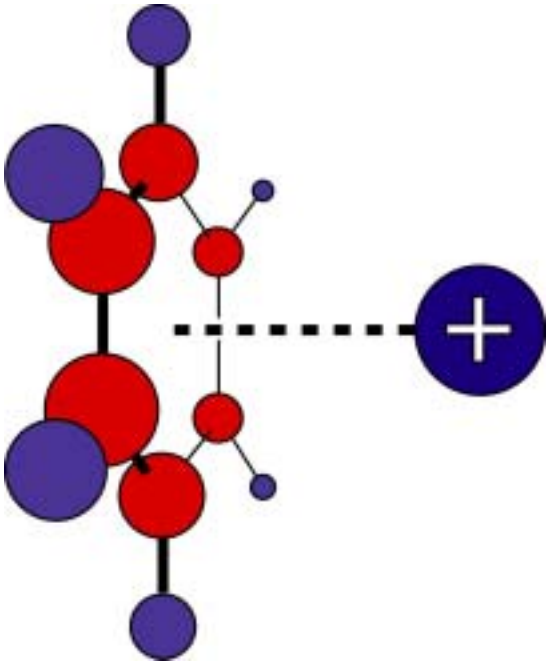
H_2O ····· NMe_4^+

$-\Delta H_{exptl}$ = 9.0 kcal/mol

Kebarle, et al. *J. Chem. Phys.* **1981**, *85*, 1814
Meot-Ner, et al. *J. Am. Chem. Soc.* **1985**, *107*, 469 & 474

Benzene binds cations better than water!

Quite Strong Binding in the Gas Phase



M^+	Binding Energy (kcal/mol)
Li^+	38
Na^+	28
K^+	19
Rb^+	16

A Classical Electrostatic Trend

Taft, et al. *Pure Appl. Chem.* **1990** *62,* 17; Castleman, et al.*Chem. Phys. Lett.* **1990** *168*, 155;
Kebarle, et al. *J. Phys. Chem.* **1981** *85,* 1814; Dougherty, et al. *Science* **1993** *261,* 1708.

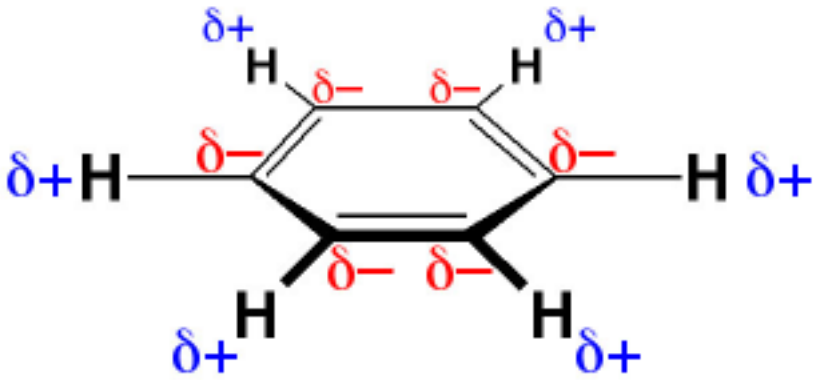
The Electrostatic Model

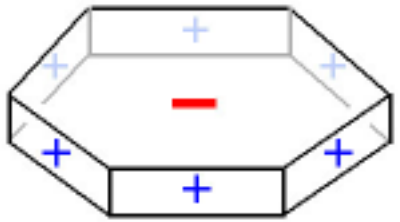
While van der Waals and Dispersion forces and perhaps in some cases donor-acceptor interactions may contribute to the cation-π interaction, they are not the defining characteristic.

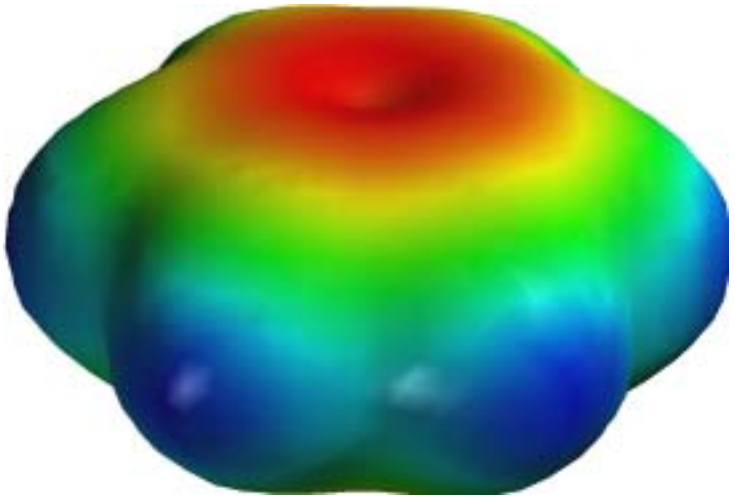
sp^2 carbon is
more electronegative
than hydrogen

The Electrostatic Model

sp^2 carbon is more electronegative than hydrogen

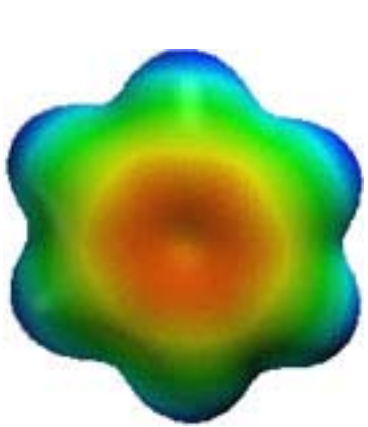




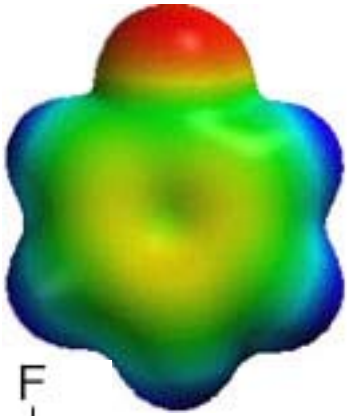


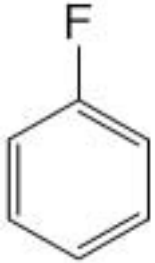
ab initio calculated
electrostatic potential surface;
red = negative; blue = positive

Electrostatics Rationalize Trends in Binding Energies



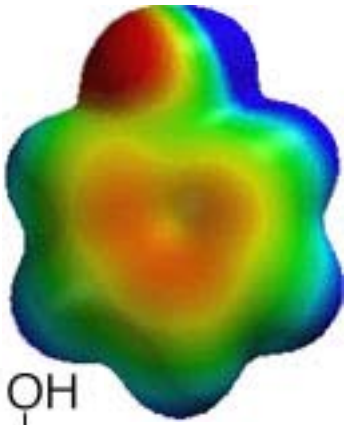
27.1





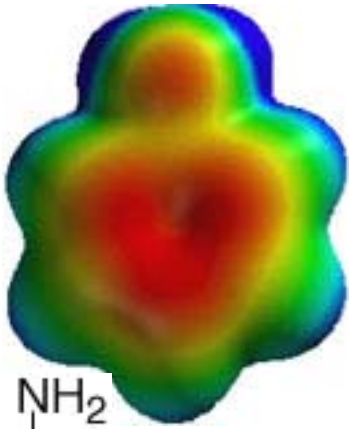
F

22.0



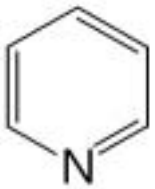
OH

26.9

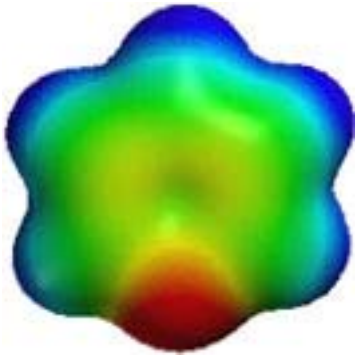


NH_2

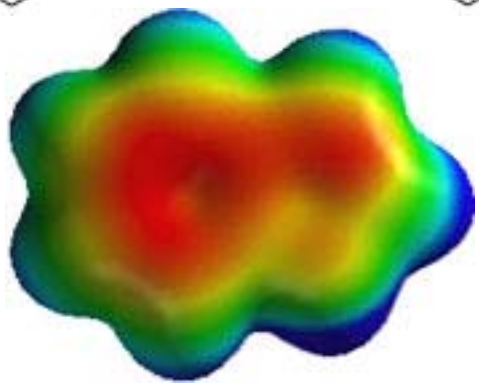
31.8

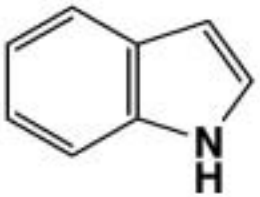


N



20.0

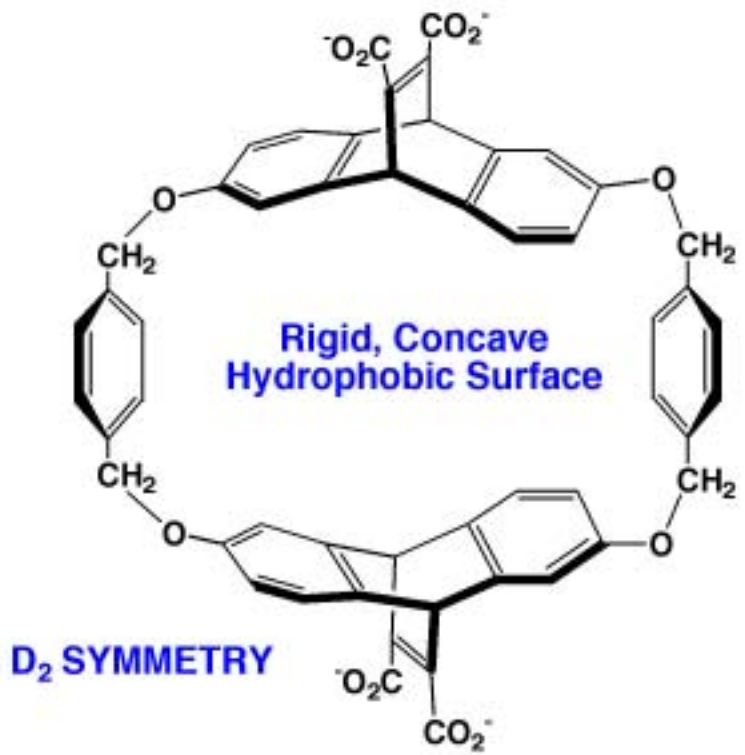




N
H

32.6

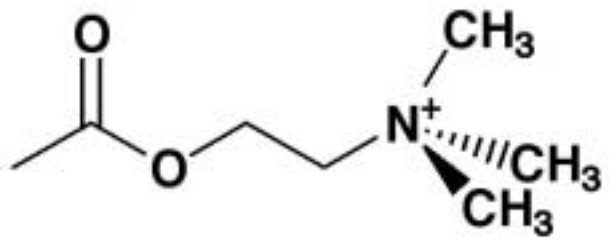
Molecular Recognition in Aqueous Media



Water-Solubilizing Groups External to Binding Site
(controls establish that the charge does not influence binding)

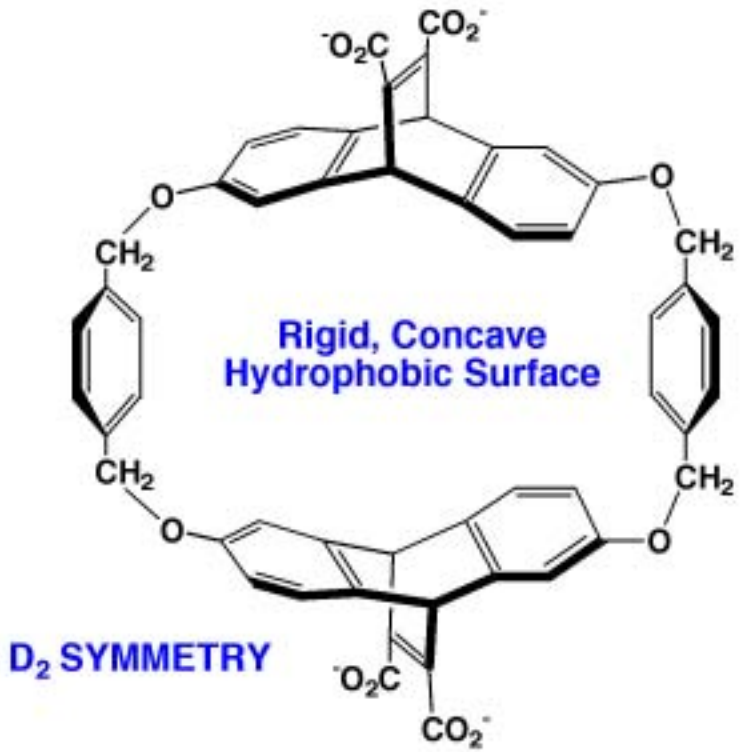
EARLIER STUDIES WITH A WATER-SOLUBLE CYCLOPHANE ESTABLISHED THAT CATION-π INTERACTIONS ARE IMPORTANT IN WATER

Hundreds of binding studies establish the cyclophane as a general receptor for organic cations



including acetylcholine - ACh

Molecular Recognition in Aqueous Media



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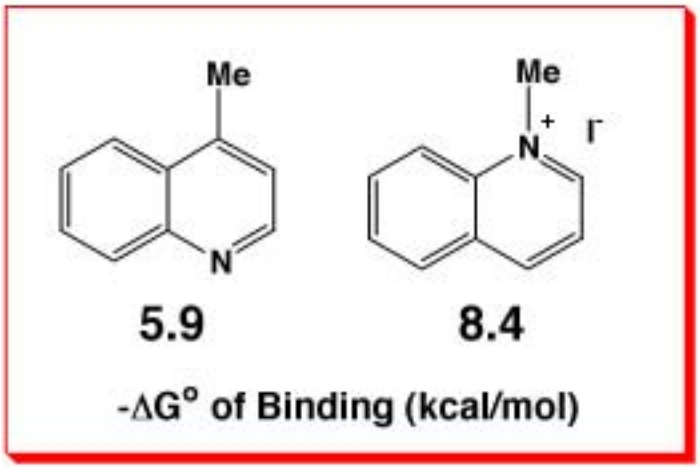
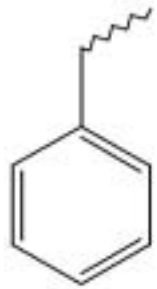


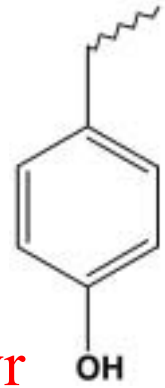
Dougherty Group: 1986 - 1999

How Common Are Cation-π Interactions in Structural Biology ?

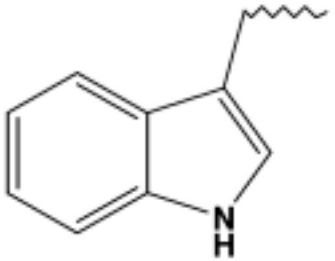
Most statistical analyses of protein structures use geometric criteria. A challenge for the cation-π interaction because of the diverse range of plausible geometries:



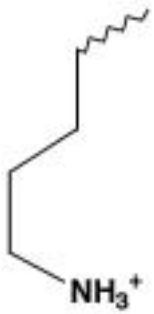
Phe



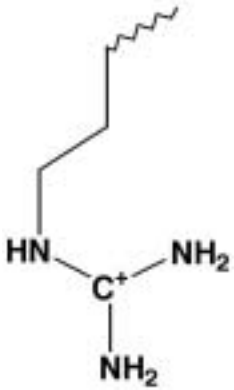
Tyr



Trp



Lys



Arg

An Energy-Based Selection Criterion

•Consider 68 nonhomologous, high-resolution protein crystal structures and look for **interacting pairs** (F,Y,W)•••(K,R) (geometric criterion). 359 interacting pairs found.

•Evaluate all pairs using HF/6-31G** theory

•Develop a force-field model that reproduces the ab initio energy results (~OPLS)

•Apply new energy model to 593 nonhomologous, high-resolution structures

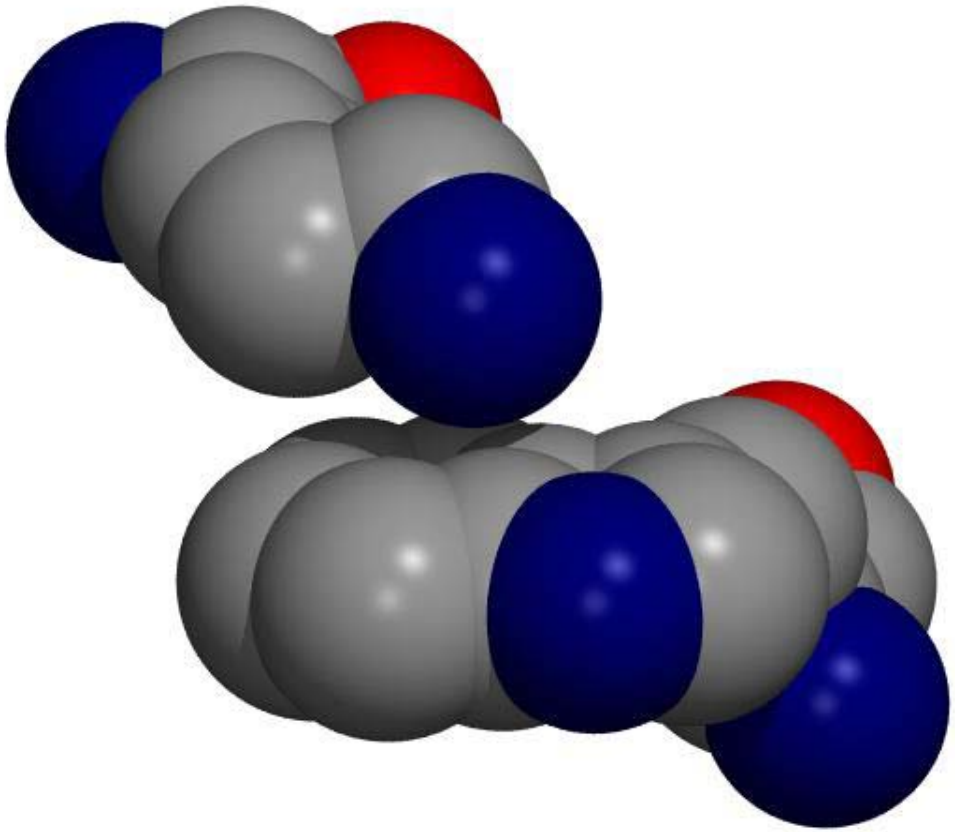
•RESULT: 2994 energetically significant cation-π interactions (14,030 interacting pairs)

Cation-π Interactions in Structural Biology

- One cation-π interaction for every 77 amino acids
- Arginine preferred over lysine
- **Over 25% of all tryptophans involved in a cation-π interaction**

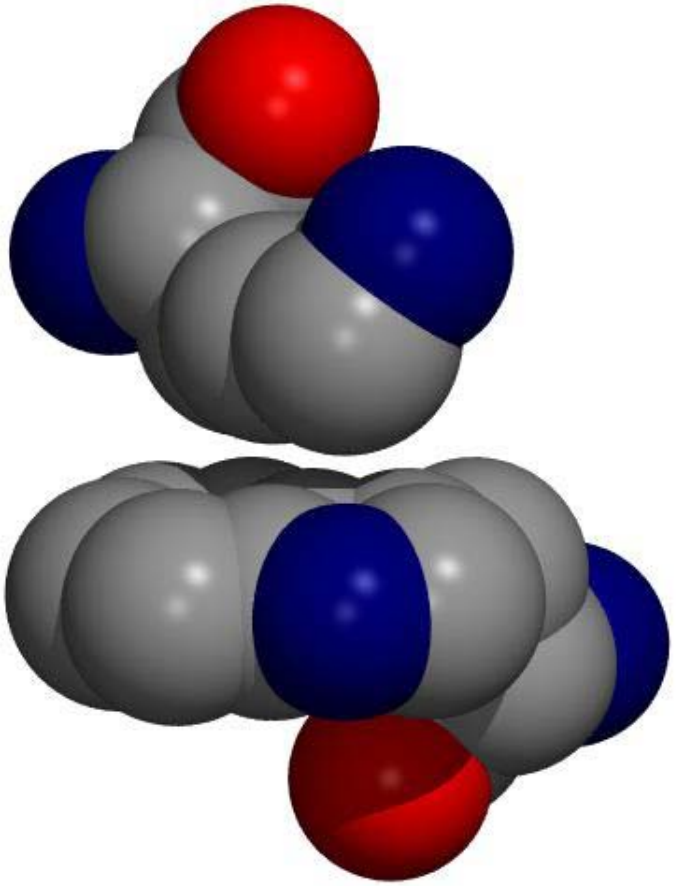
J. P. Gallivan and D. A. Dougherty, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 9459-9464.

Lys 248 – Trp 265 in Aldehyde Oxidoreductase



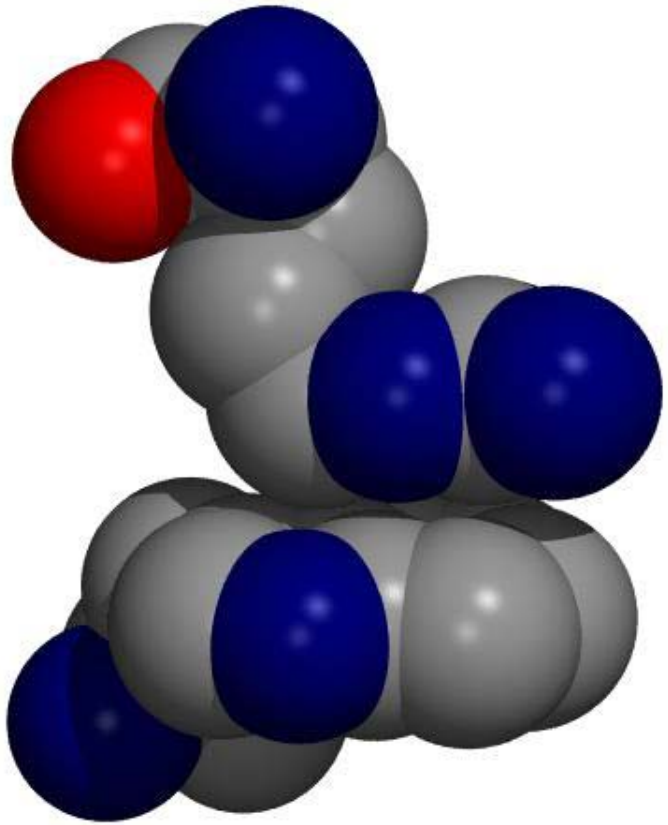
E for this interaction is -8.8 kcal/mol.

Lys 76B and Trp 58B in Transaldolase B.



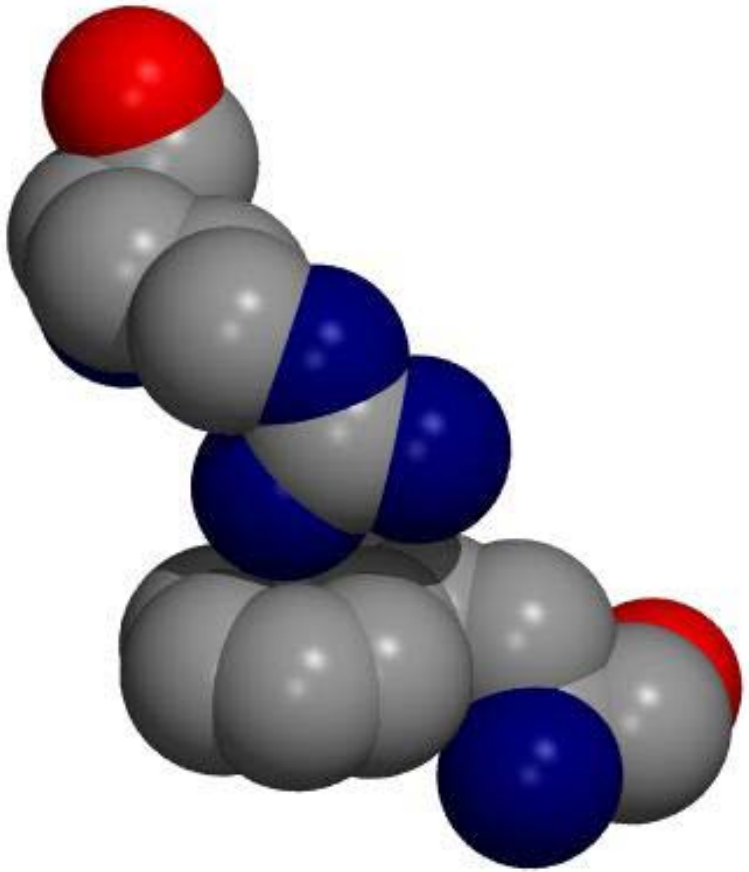
E for this interaction is -4.4 kcal/mol.

Arg 77A – Trp 211A in the oligopeptide binding protein, OPPA .



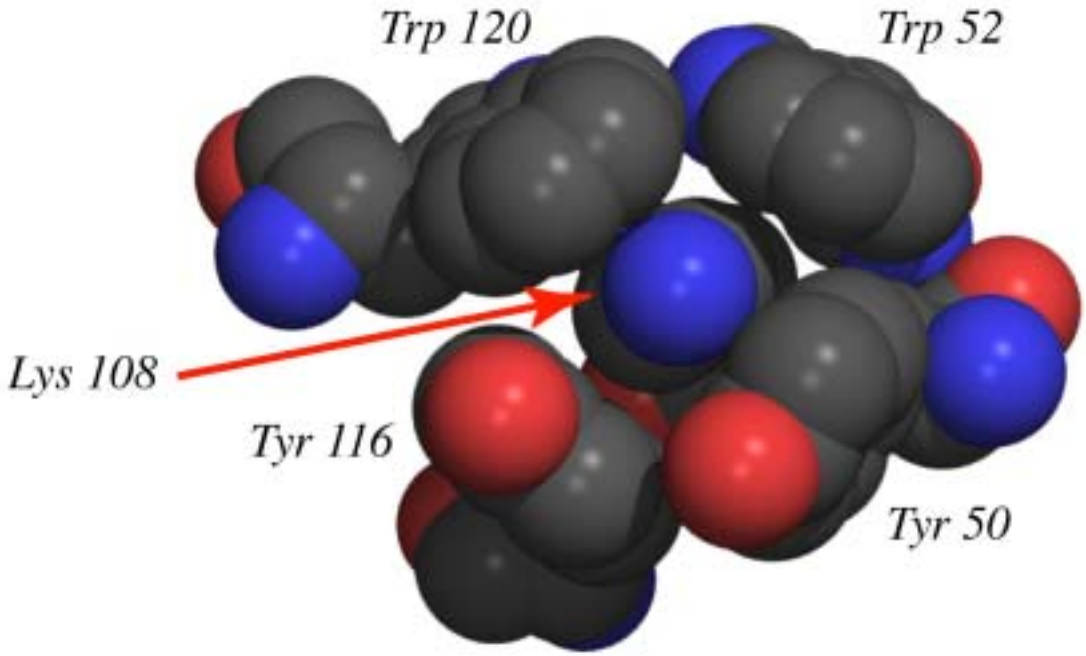
E for this interaction is -8.4 kcal/mol.

Arg 1136 – Trp 1175 in the tyrosine kinase domain of the Insulin Receptor .



E for this interaction is -6.8 kcal/mol.

A Fourfold Cation-π Interaction
Glucoamylase (1gai.pdb)



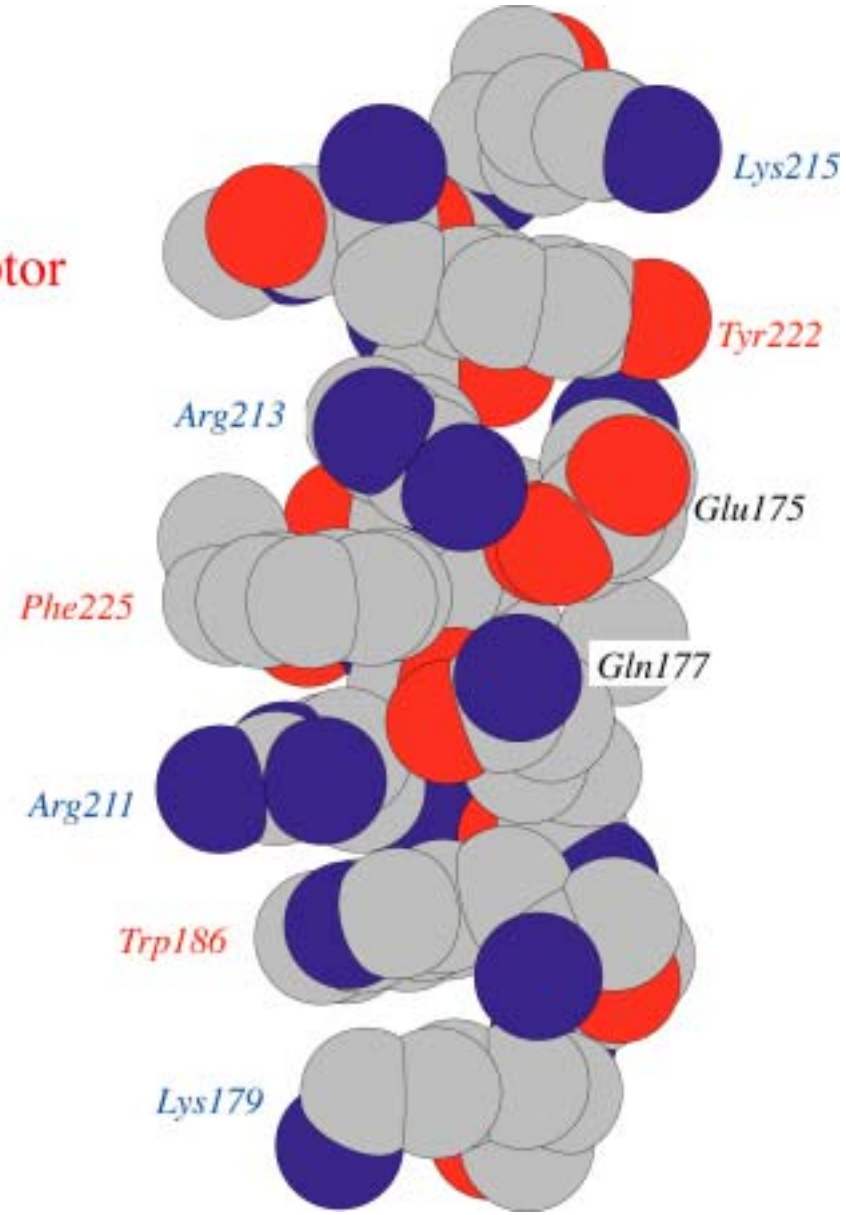
In the gas phase, the sum of these interactions is worth as much as 30 kcal/mol of stabilization

Trp120-Lys108 is one of the strongest interactions in the dataset

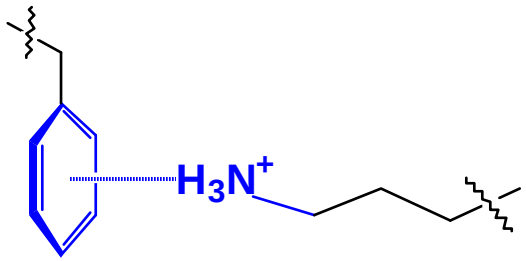
A Spectacular Example: Extended Cation-π Interactions in the Human Growth Hormone Receptor Extracellular Domain.

Coordinates are taken directly from the Brookhaven Protein Data Bank file 3HHR.

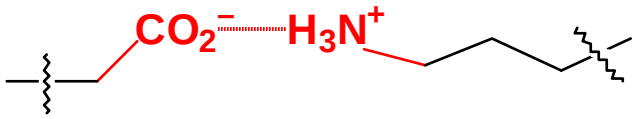
The figure is based on a view first presented by Wilson - Science, ***273,*** *464 (1996)*



The Cation-π Interaction vs. a Salt Bridge



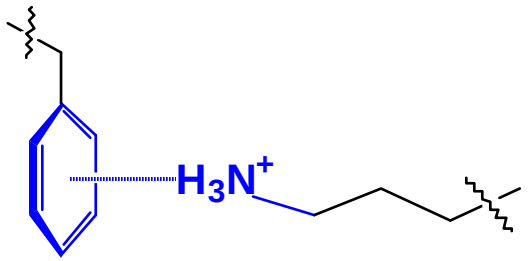
Phe *Lys*



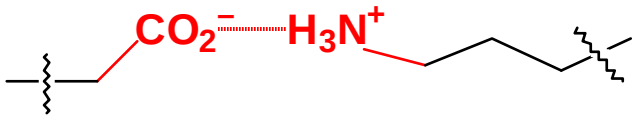
Asp *Lys*

GAS PHASE	19 kcal/mol	120 kcal/mol

The Cation-π Interaction vs. a Salt Bridge



Phe ***Lys***

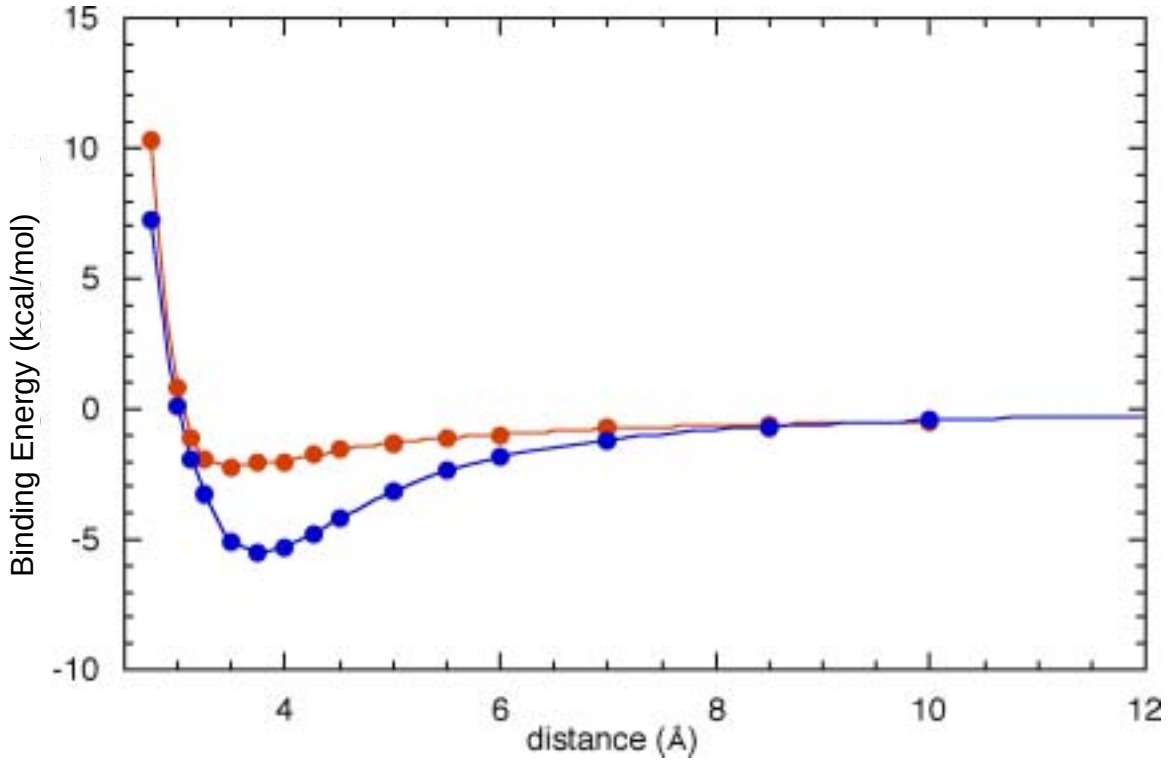


Asp ***Lys***

Aqueous Medium

SM5.42R/HF – 6-31G**

J. P. Gallivan and D. A. Dougherty, *J. Am. Chem. Soc* **2000**, *122 (5)*, 870-874.



Cation-π Contributions to Protein-Ligand/Drug-Receptor Interactions

Cys-loop receptors binding ACh, serotonin, and GABA

G protein-coupled receptors for ACh, dopamine, epinephrine …

Glutamate receptors

Factor XA (coagulation factor; serine protease)

Multidrug resistance protein and related transporters (MDR/P-glycoprotein)

SH2 domains - bind phosphotyrosine

Cationic polyene cyclization of terpene/steroid biosynthesis

mRNA cap recognition (7-Me-G)

S-Adenosylmethionine (SAM, Ado-Met) reactions

Alkylamine dehydrogenases

Antibody hypervariable regions