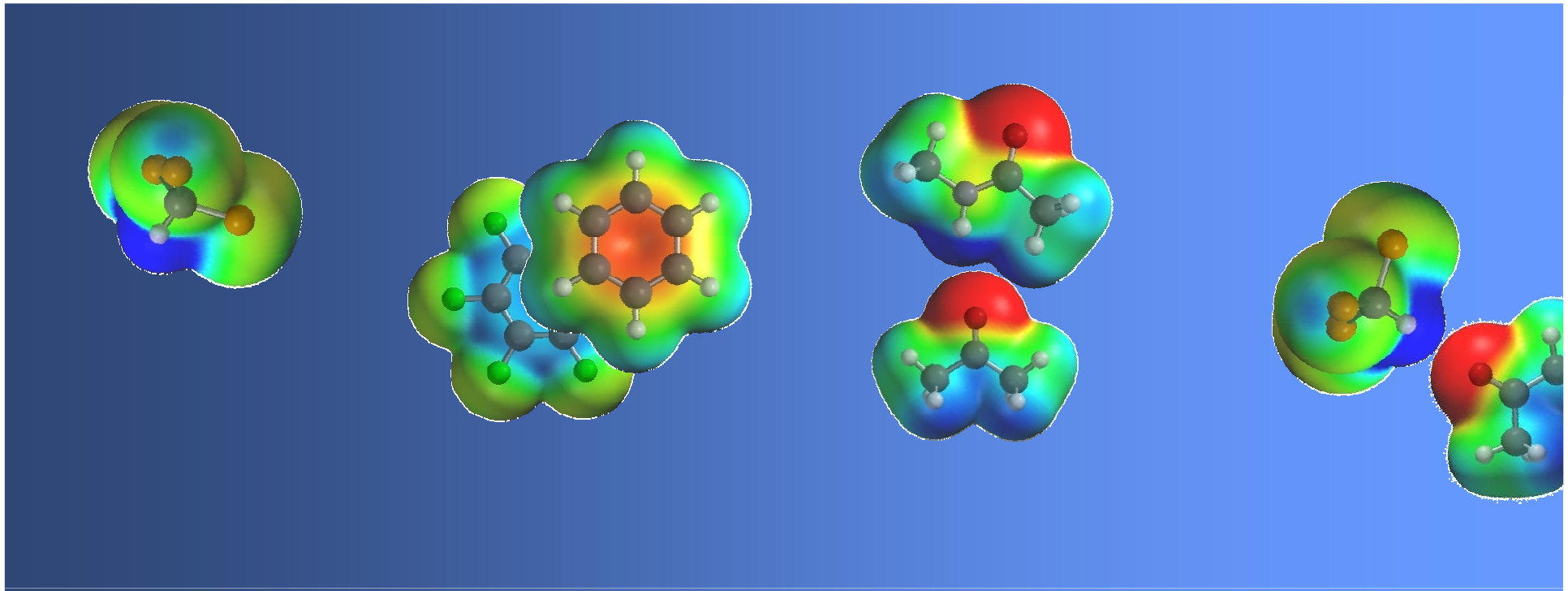


Solvent & geometric effects on non-covalent interactions

Scott L. Cockroft

PhysChem Forum 10, Syngenta, Jealott's Hill, 23rd March '11

QSAR & Physical Organic Chemistry

Quantifiable Physicochemical Properties

- Non-covalent interactions (α, β, MEP)
- Electronic descriptors (σ_m, σ_p, σ^*, F, R)
- Solubility
- Lipophilicity (logP/D, π)
- Ionisable groups (pK_a)
- Shape
- Molecular weight

Administration

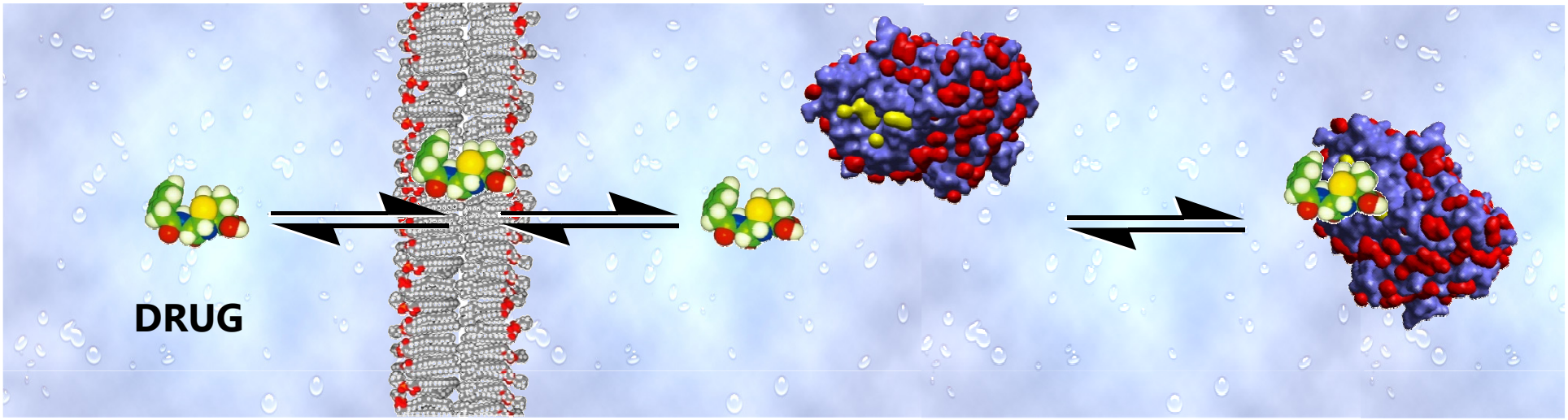
QSAR

Quantifiable Biological Properties

- Interactions with target
- Absorption
- Distribution
- Metabolism
- Excretion
- Toxicology

output: e.g. identify structural features giving good potency, identify outliers, predict new structures with better biological profiles

Why study non-covalent interactions and solvation?



Drug-solvent interactions

Drug-lipid interactions

(octanol?)

+

solvent-solvent interactions

(liberated water)

Drug-solvent interactions

+

Protein-solvent interactions

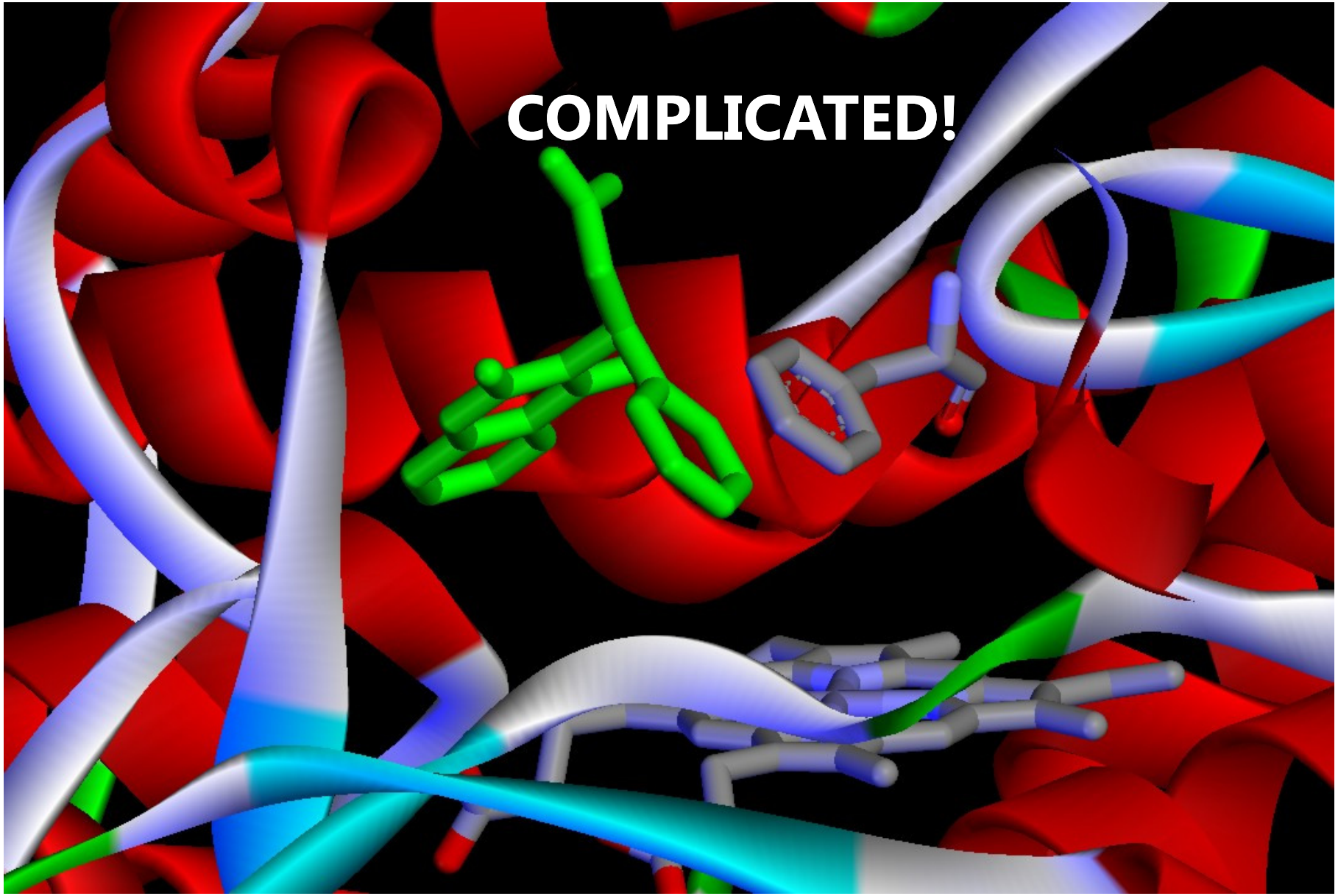
Drug-receptor interactions

+

solvent-solvent interactions

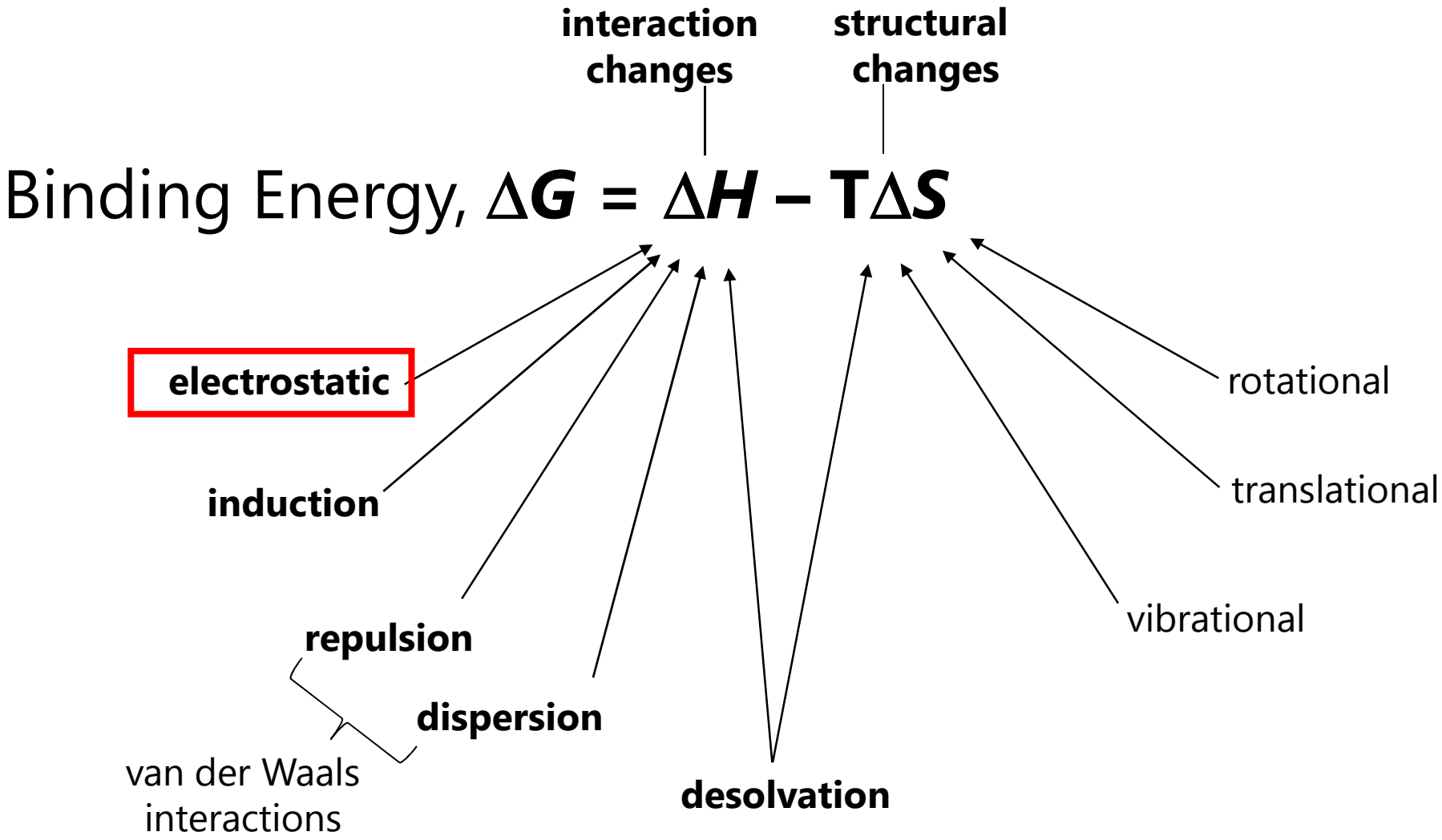
(liberated water)

Non-covalent interactions in biological recognition



P. A. Williams, J. Cosme *et al*, *Nature*, 2003, 424, 464-468

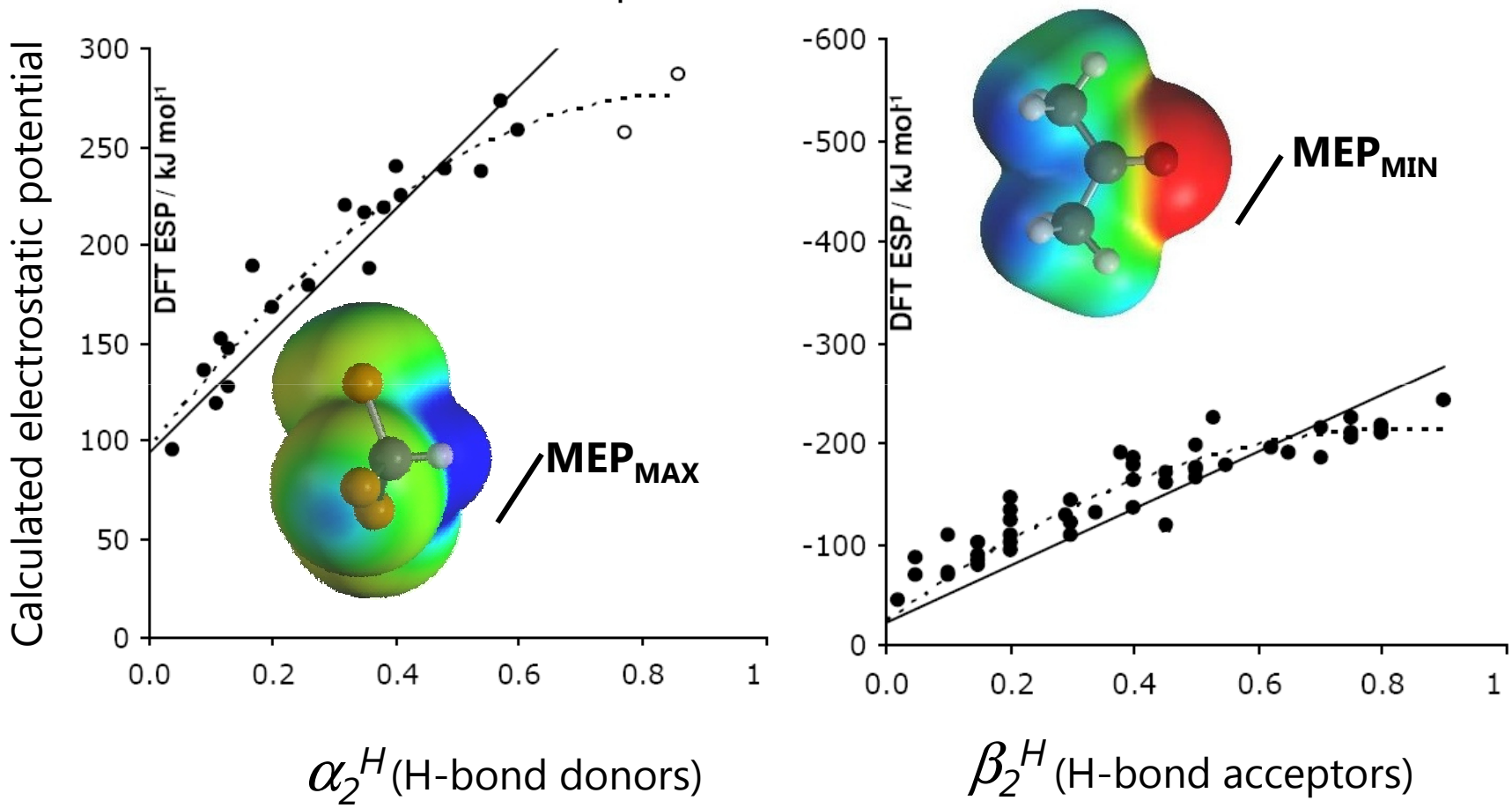
Total binding energy contributions



Energy contributions from the WHOLE system = drug, solvent, receptor

H-bonds: back to basics, experiment vs. theory

H-bond interaction energies are highly correlated with the maxima and minima of calculated molecular electrostatic potential surfaces.

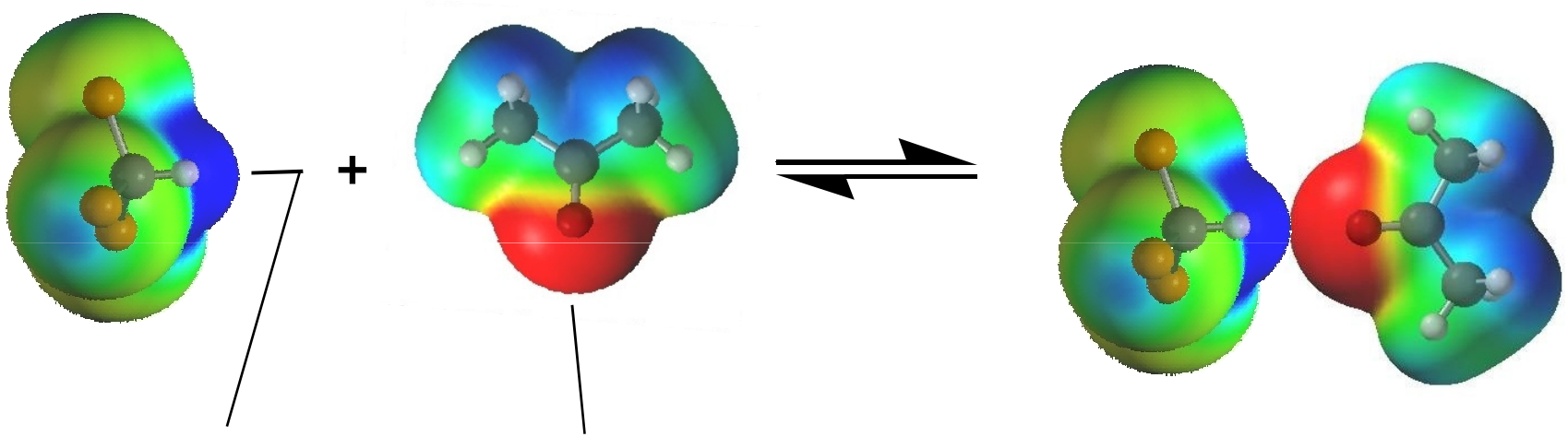


Experimental H-bond parameters measured in CCl_4

M. H. Abraham, J. A. Platts, *J. Org. Chem.* 2001, *66*, 3484-3491
Hunter & Cockroft unpublished results

H-bond scales

Possible to rescale α_2^H and β_2^H H-bond constants such that:



α
= H-bond donor constant

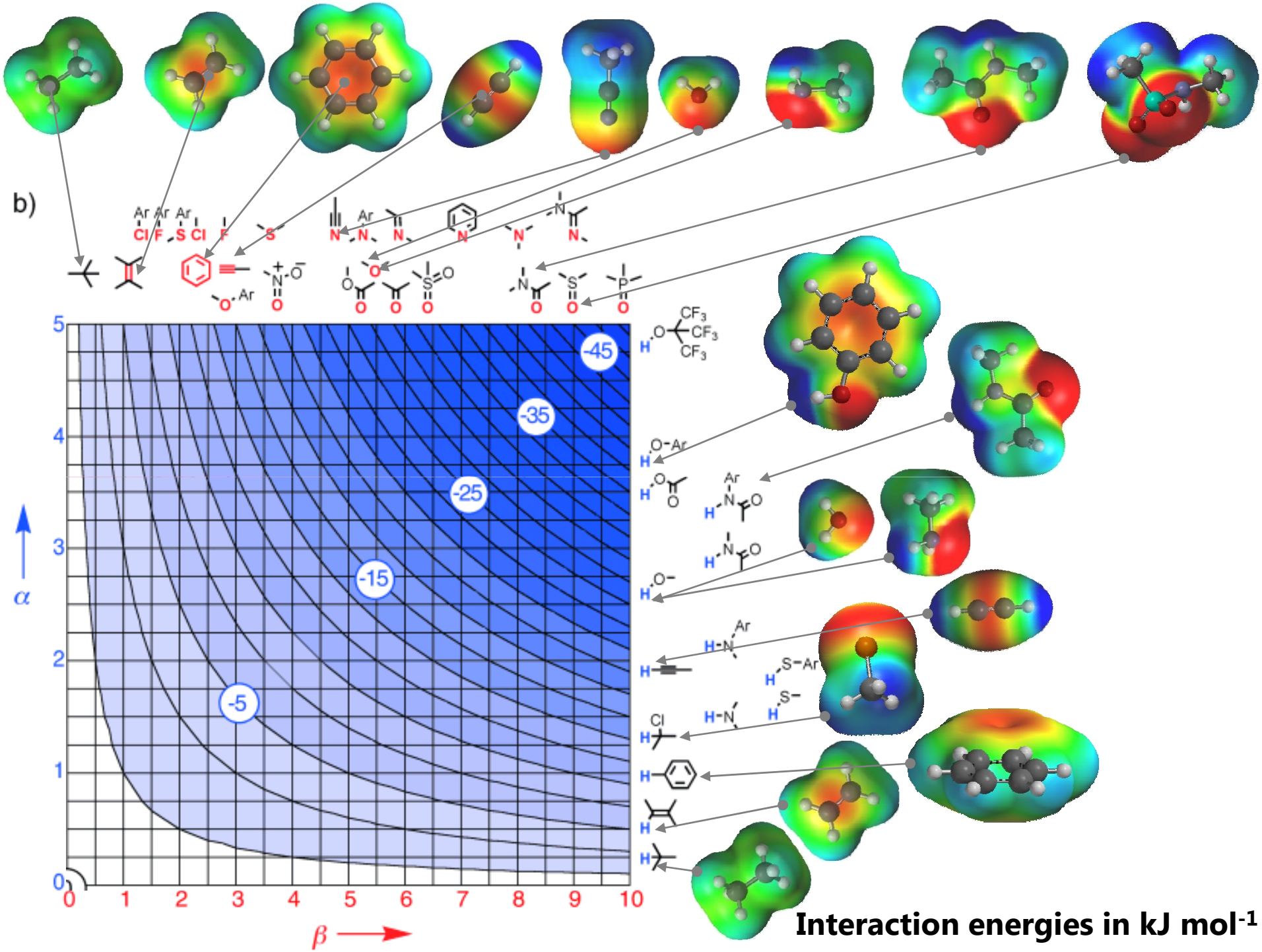
β
= H-bond acceptor constant

H-bond donor-acceptor interaction

$\Delta G = -\alpha\beta$

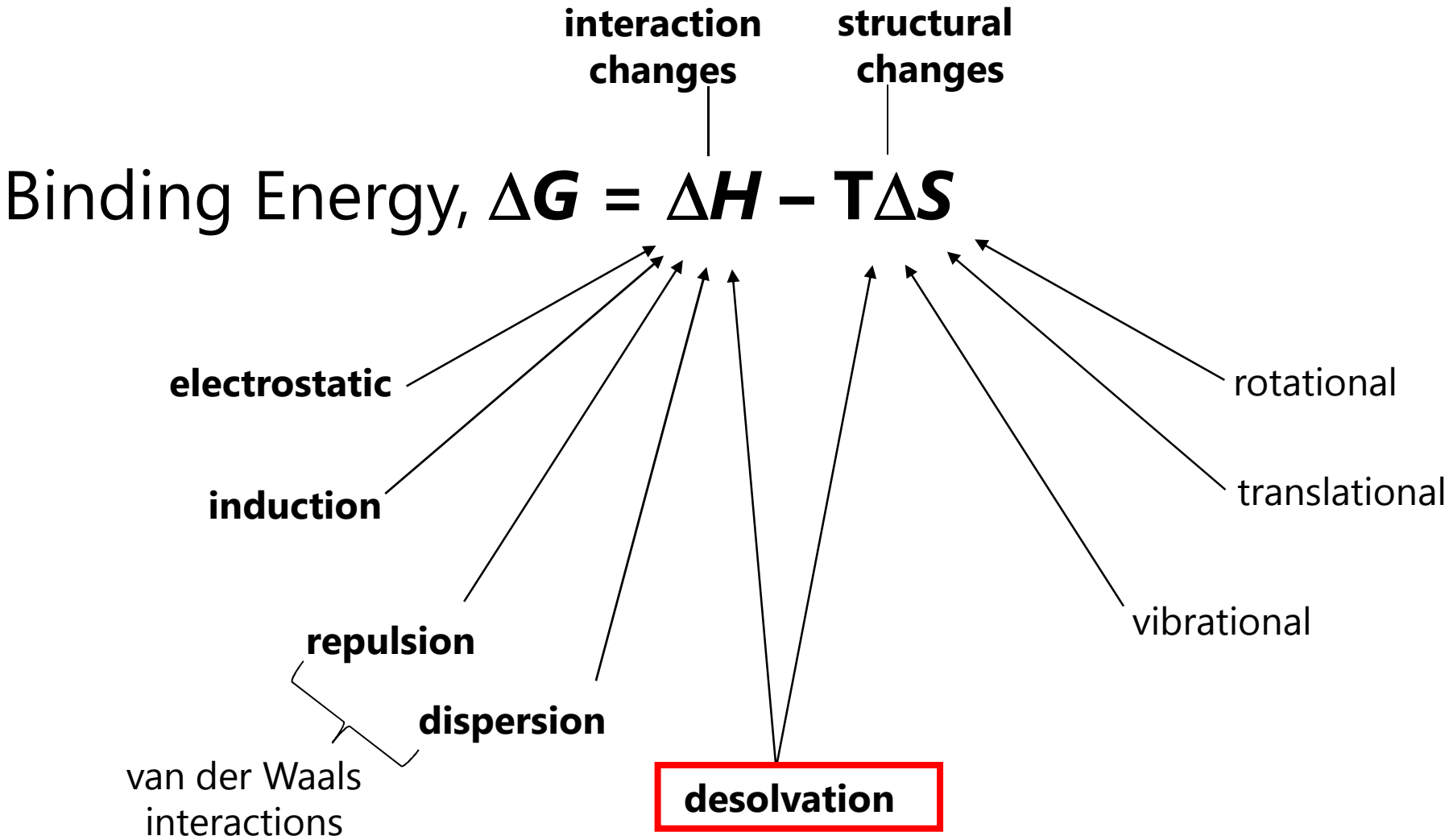
in kJ mol^{-1}

C. A. Hunter, *Angew. Chem. Int. Ed.* 2004, *43*, 5310-5324



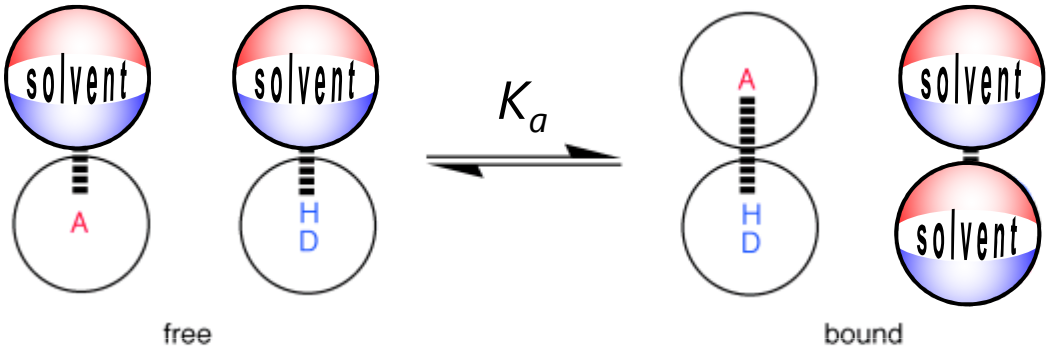
Interaction energies in kJ mol^{-1}

Total binding energy contributions



Energy contributions from the WHOLE system = drug, solvent, receptor

Solvent effects on non-covalent interactions



$\alpha_s\beta$ $\alpha\beta_s$ $\alpha\beta$ $\alpha_s\beta_s$

$$\Delta\Delta G = \alpha_s\beta + \alpha\beta_s - \alpha\beta + - \alpha_s\beta_s + \text{entropic term}$$

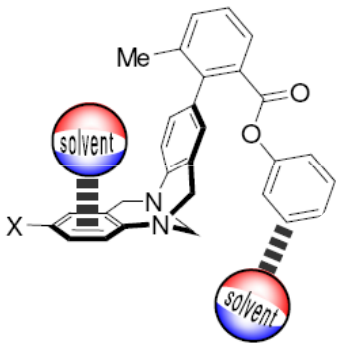
α/β obtained from experimental measurements or calculated electrostatic potentials

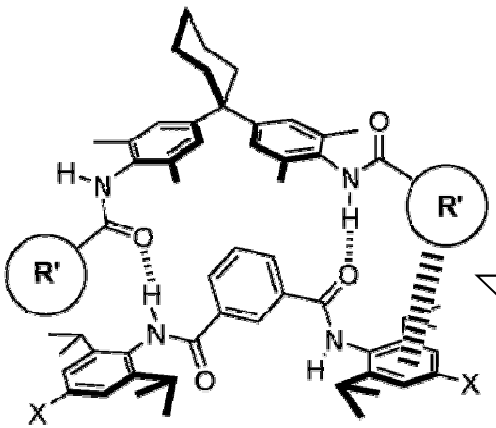
C. A. Hunter, *Angew. Chem. Int. Ed.* 2004, *43*, 5310-5324

Solvent effects on non-covalent interactions

This simple model has been applied in a range of circumstances:

$(CF_3)_3C–OH \bullet\bullet\bullet\bullet O=P(n\text{-}Bu)_3$





COMPLEXITY

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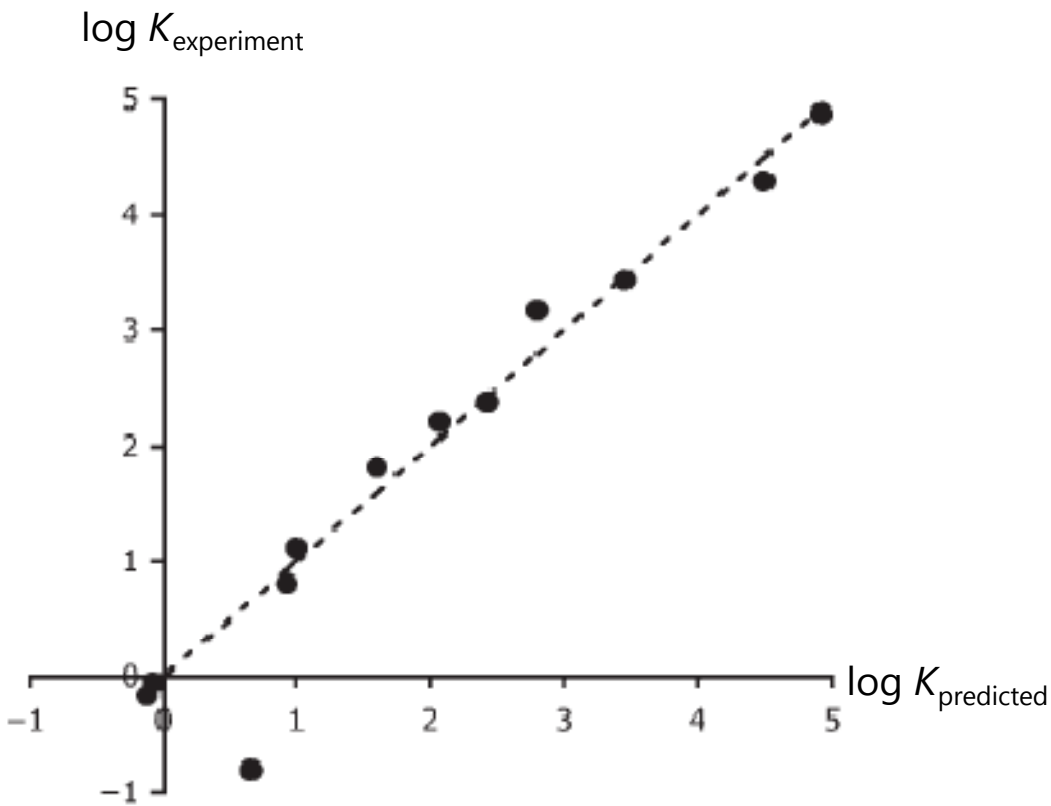
  S. L. Cockroft, C. A. Hunter. *Chem. Commun.* 2006 & 2009

Solvent effects on H-bonding interactions

$(CF_3)_3C–OH \cdots\cdots O=P(n\text{-}Bu)_3$



solvent	Log K expt	Log K pred
n-decanol	−0.8	0.7
DMSO	−0.2	−0.1
NMF	−0.1	−0.1
pyridine	0.8	0.9
pyrrole	1.1	1.0
acetone	1.8	1.6
acetonitrile	2.2	2.1
tetrahydrofuran	2.4	2.4
nitromethane	3.2	2.8
$CHCl_3$	3.4	3.5
benzene	4.3	4.5
CCl_4	4.9	4.9
cyclohexane	>5	6.9

J. L. Cook, C. A. Hunter *et al. Angew. Chem. Int. Ed.* 2007, 46, 3706-3709

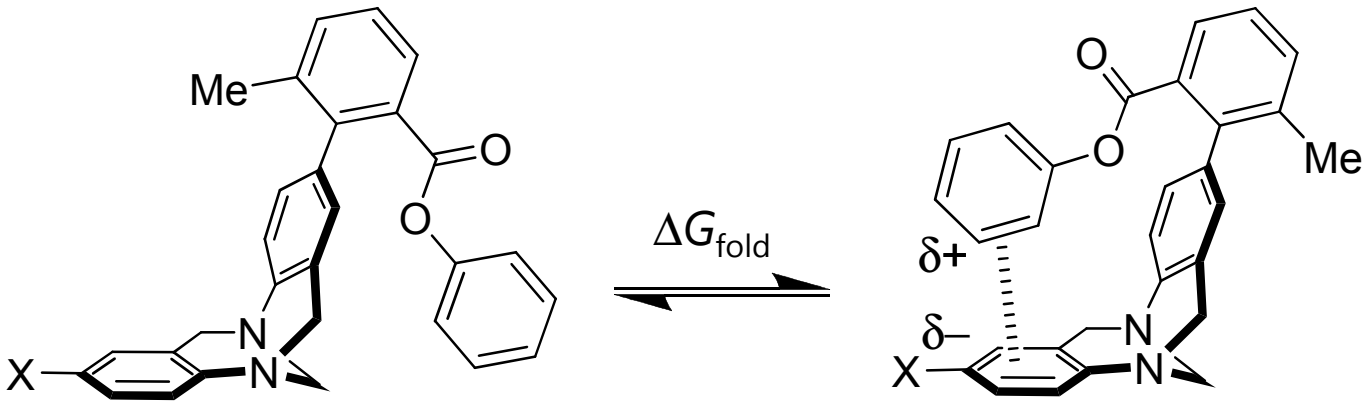
The puzzle of the Wilcox torsion balance

The α/β scale works well for simple H-bond interactions

one step up from a single H-bond, a simple supramolecular system.

Is it really that simple?

X	ΔG_{fold} /kJ mol^{-1}
NO_2	–0.88
CN	–1.26
I	–0.96
Br	–1.09
CH_3	–1.12
OH	–0.96
NH_2	–0.75

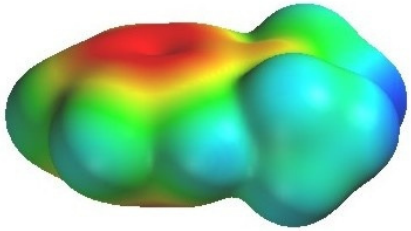


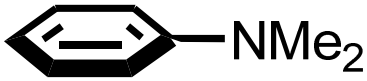
No obvious trend with variation of X-substituents.

>250 literature citations

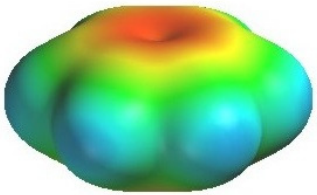
S. Paliwal, S. Geib, C. S. Wilcox, *J. Am. Chem. Soc.* 1994, 116, 4497
E. Kim, S. Paliwal, C. S. Wilcox, *J. Am. Chem. Soc.* 1998, 120, 11192

Aromatic rings as H-bond acceptors

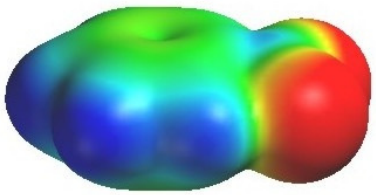




2.5



1.2



0.2

+100 kJ mol^{-1}

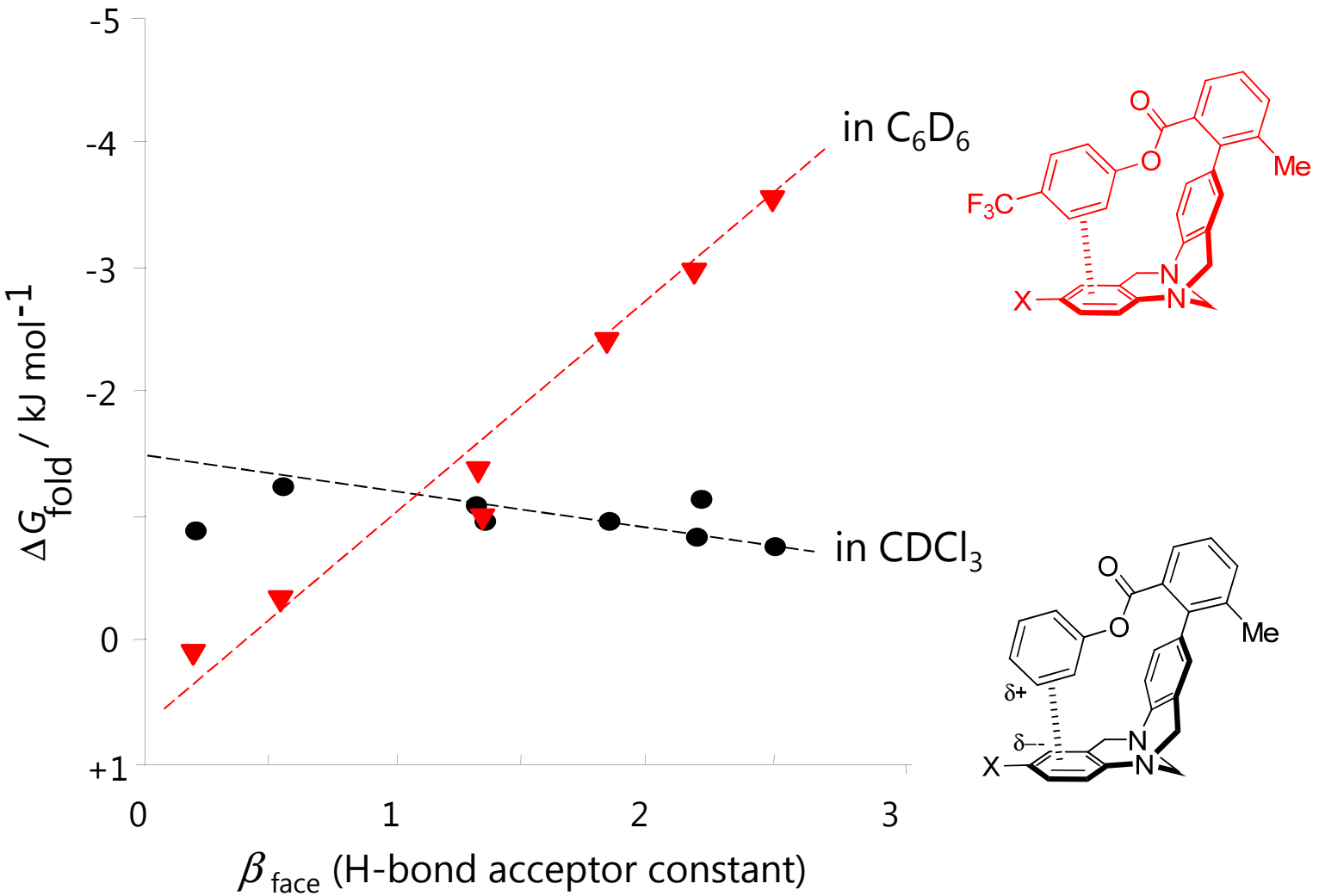
0 kJ mol^{-1}

– 100 kJ mol^{-1}

β_{face}

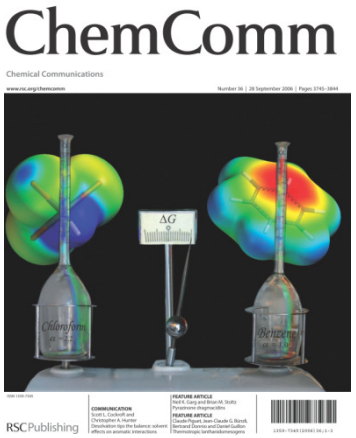
(H-bond acceptor constant)

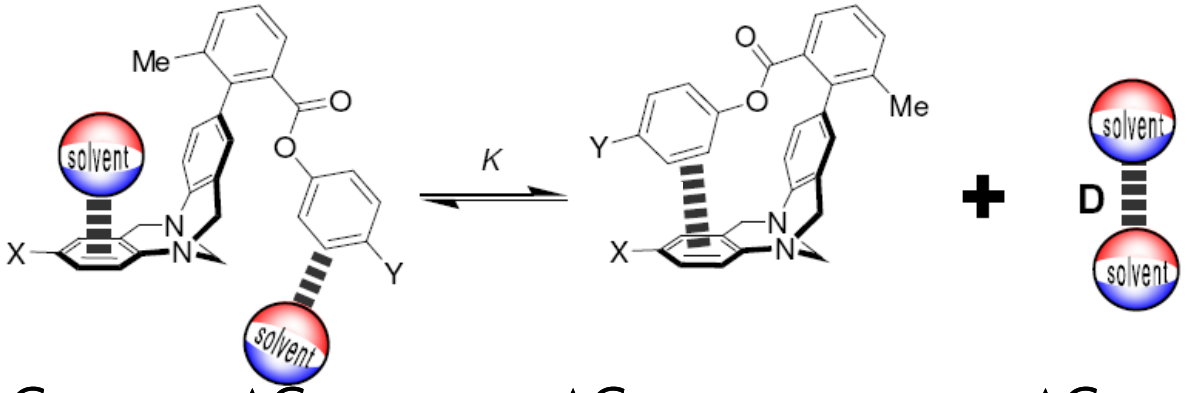
Benzene vs. Chloroform



F. Hof, D. M. Scofield, W. B. Schweizer, F. Diederich, *Angew. Chem. Int. Ed.* 2004, *43*, 5056 –5059

S. L. Cockroft, C. A. Hunter. *Chem. Commun.* 2006, *36*, 3806-3808



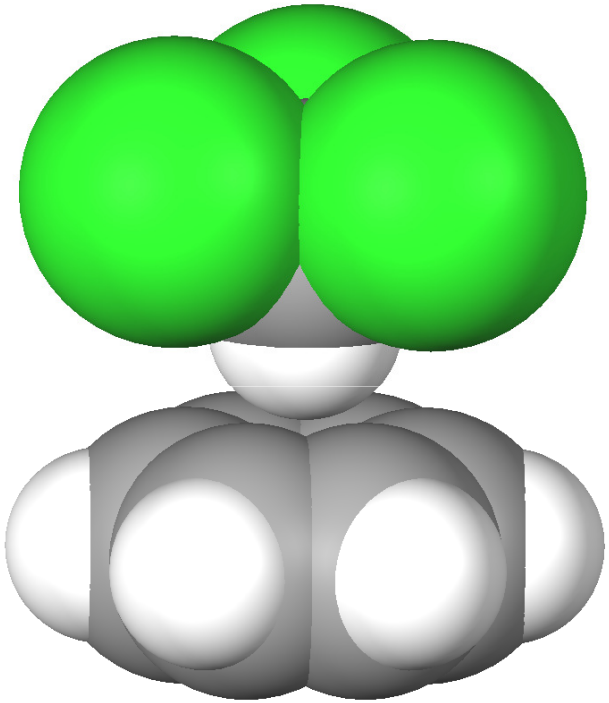


$\Delta G_{\text{sol-face}}$ $\Delta G_{\text{sol-edge}}$ $\Delta G_{\text{edge-face}}$ $\Delta G_{\text{sol-sol}}$

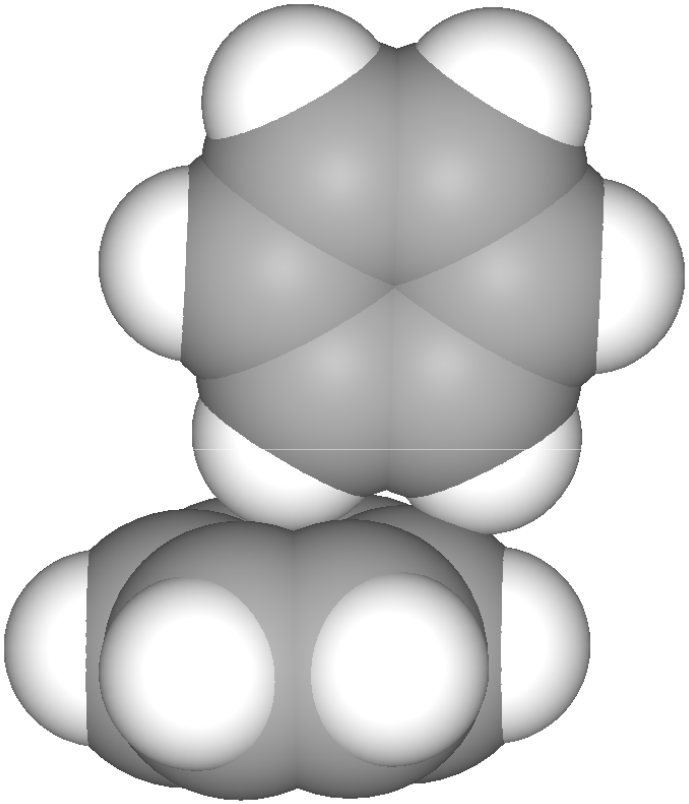
$\alpha_{\text{sol}} \times \beta_{\text{face}}$ constant $\alpha_{\text{edge}} \times \beta_{\text{face}}$ constant

S. L. Cockroft, C. A. Hunter. *Chem. Commun.* 2006, *36*, 3806-3808

Aromatic solvation

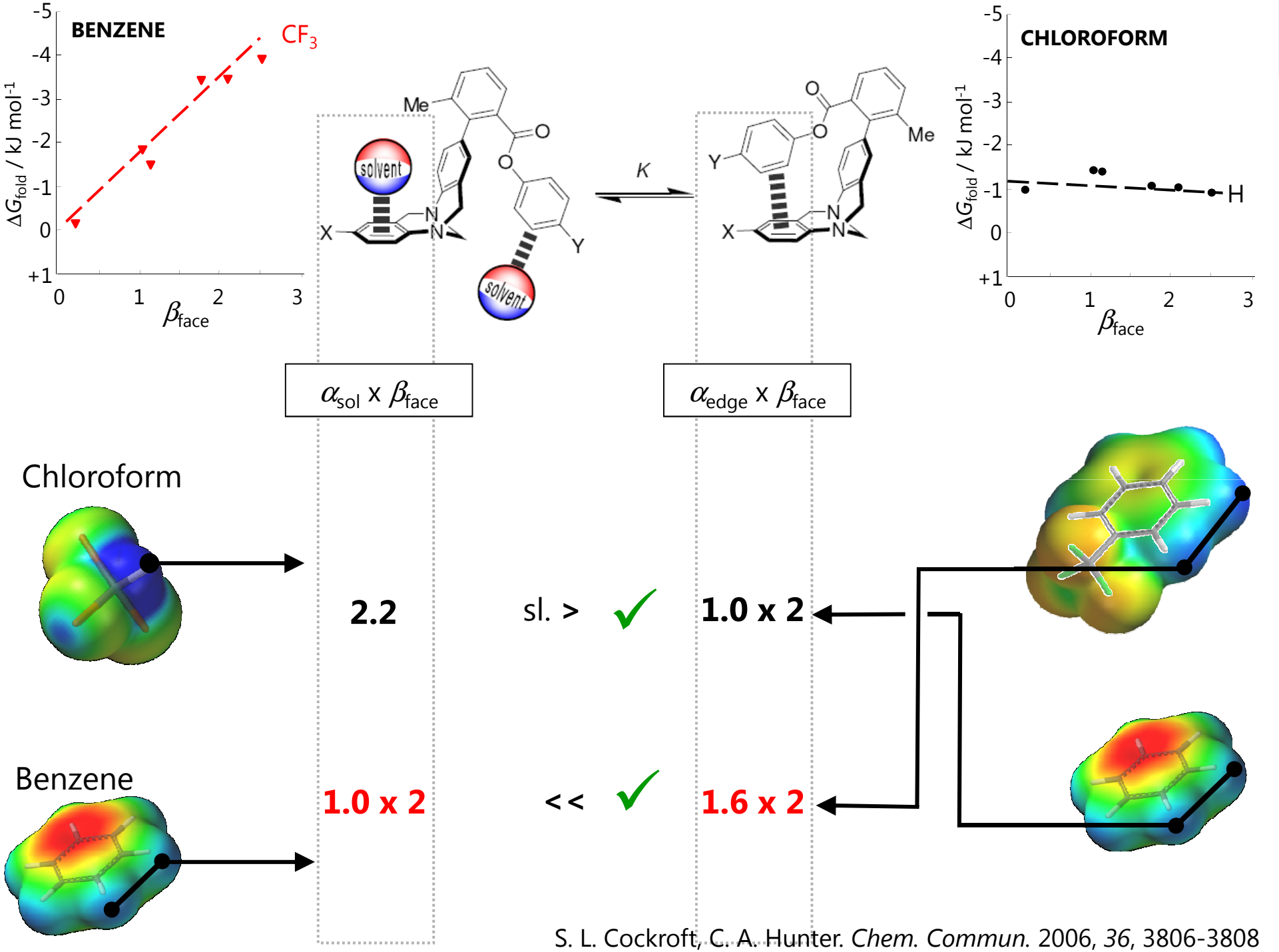


1 x α_{sol}



2 x α_{sol}

S. L. Cockroft, C. A. Hunter. *Chem. Commun.* 2006, *36*, 3806-3808



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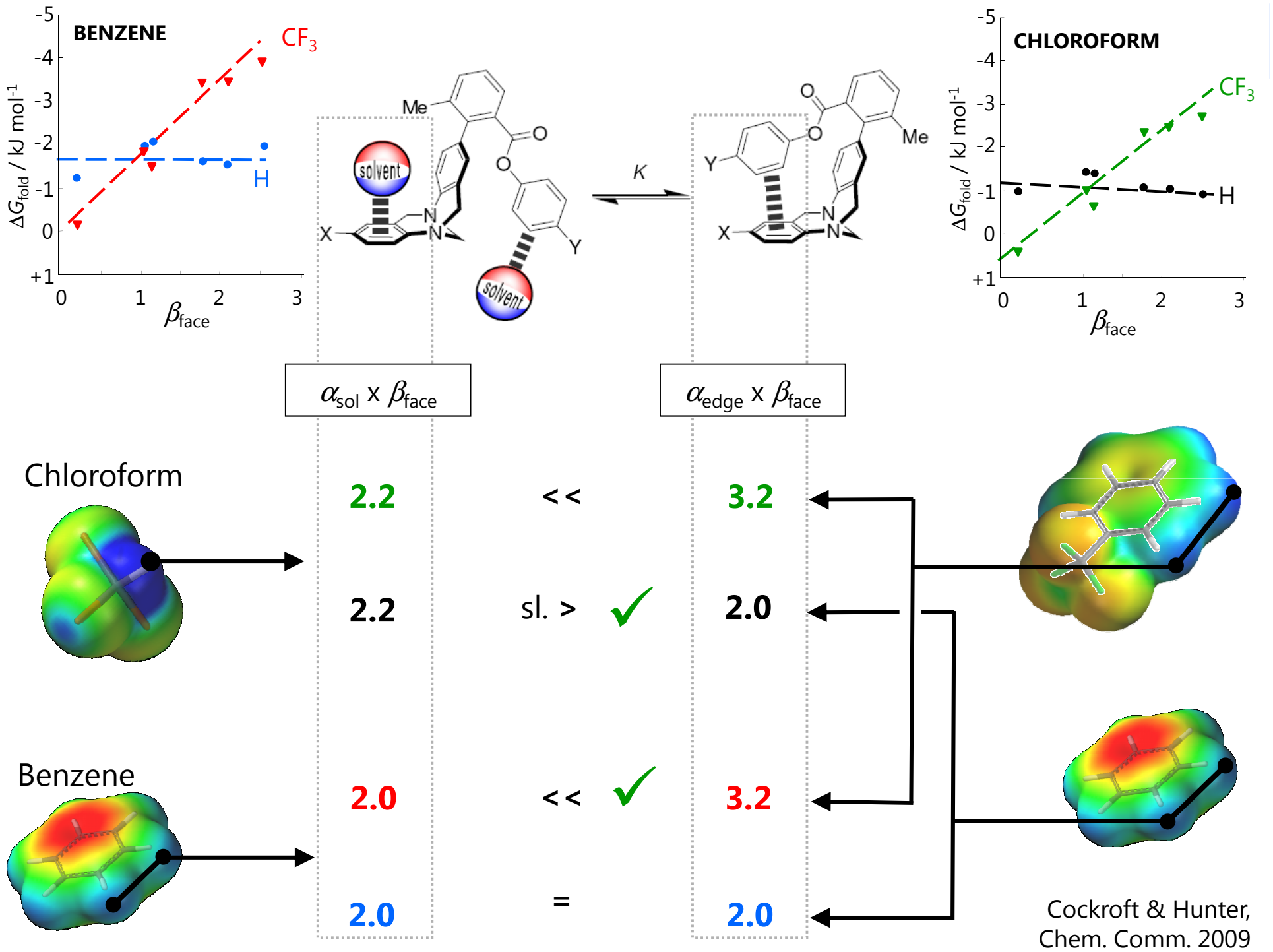
BENZENE
CF3
H
ΔGfold / kJ mol-1
βface
CHLOROFORM
CF3
H
ΔGfold / kJ mol-1
βface
Me
O
O
X
N
N
Y
solvent
solvent
K
Y
O
O
Me
X
N
N
αsol x βface
αedge x βface
Chloroform
2.2
<<
3.2
2.2
sl. >
2.0
Benzene
2.0
<<
3.2
2.0
=
2.0
Cockroft & Hunter,
Chem. Comm. 2009

Solvent effects on non-covalent interactions

This simple model has been applied in a range of circumstances:

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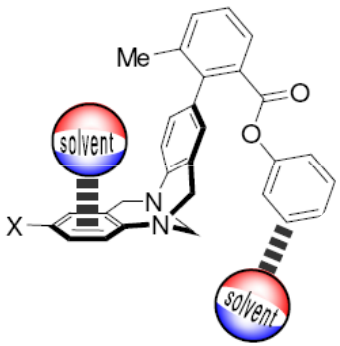

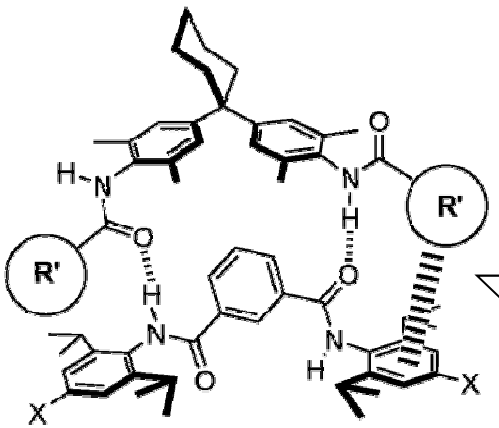

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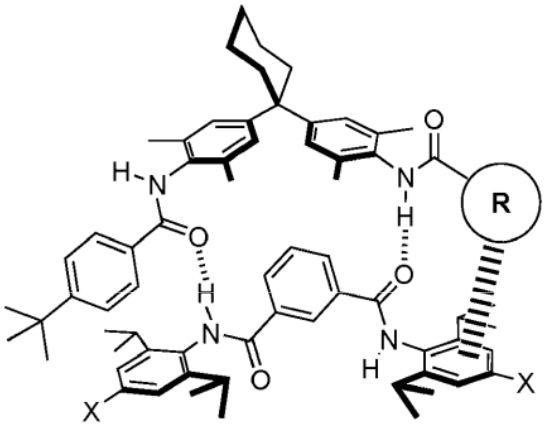
  S. L. Cockroft, C. A. Hunter. *Chem. Commun.* 2006 & 2009

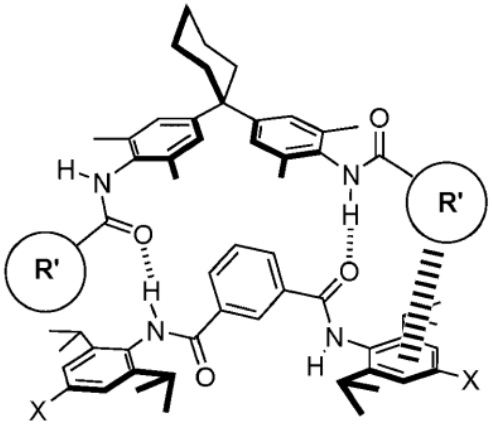
BIOLOGY???

Range of aromatic interactions quantified

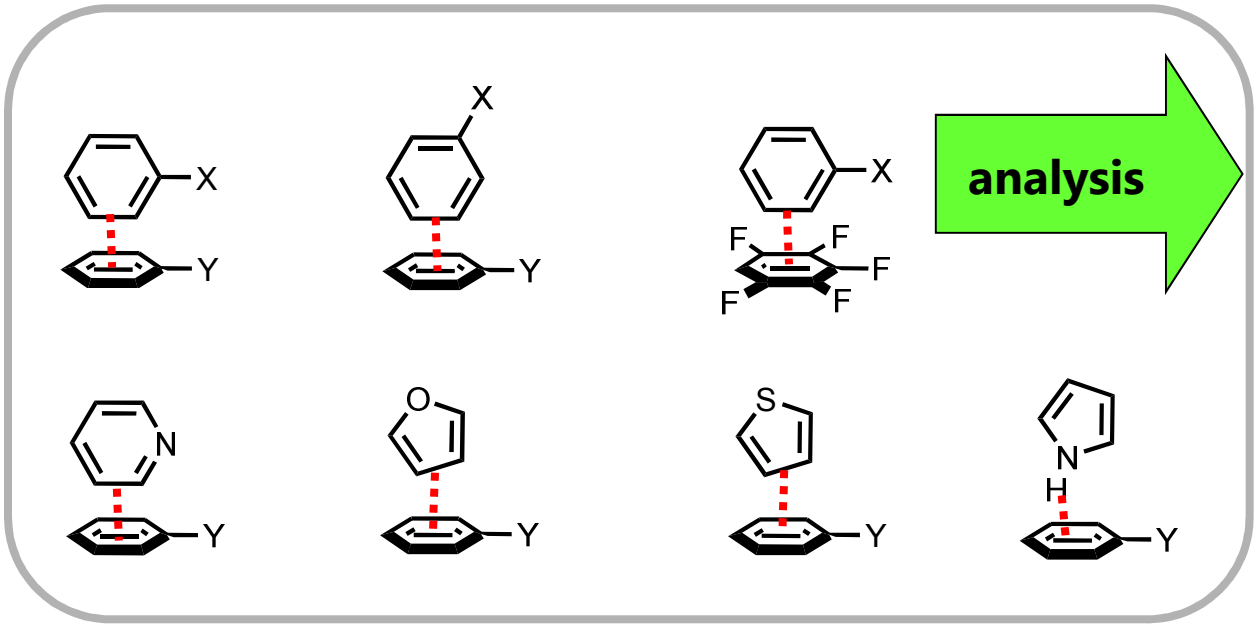
Y = NMe_2, H, NO_2

X = NMe_2, *t*-Bu, H, NO_2, F, I, CF_3



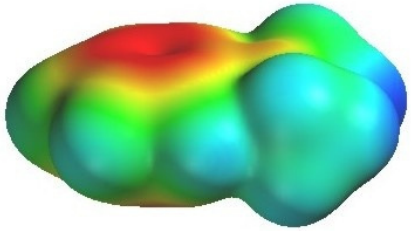


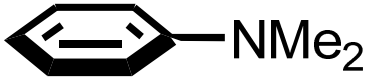
- **27 edge-face interactions (+2 to –7 kJ mol^{-1})**

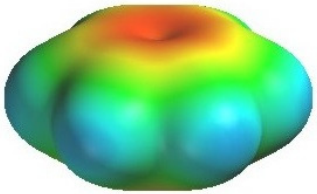


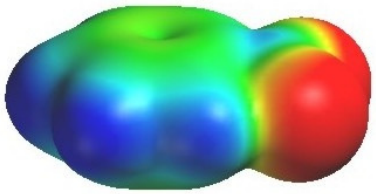
Cockroft & Hunter,
Chem. Comm. 2009

from electrostatic potentials to α_{edge} & β_{face}





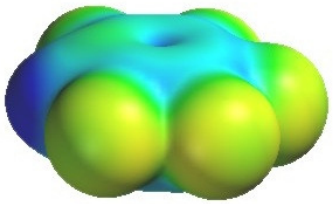


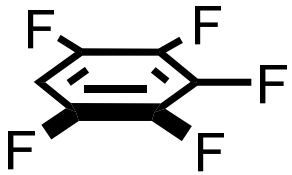


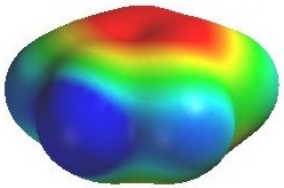
+100 kJ mol^{-1}

0 kJ mol^{-1}

– 100 kJ mol^{-1}



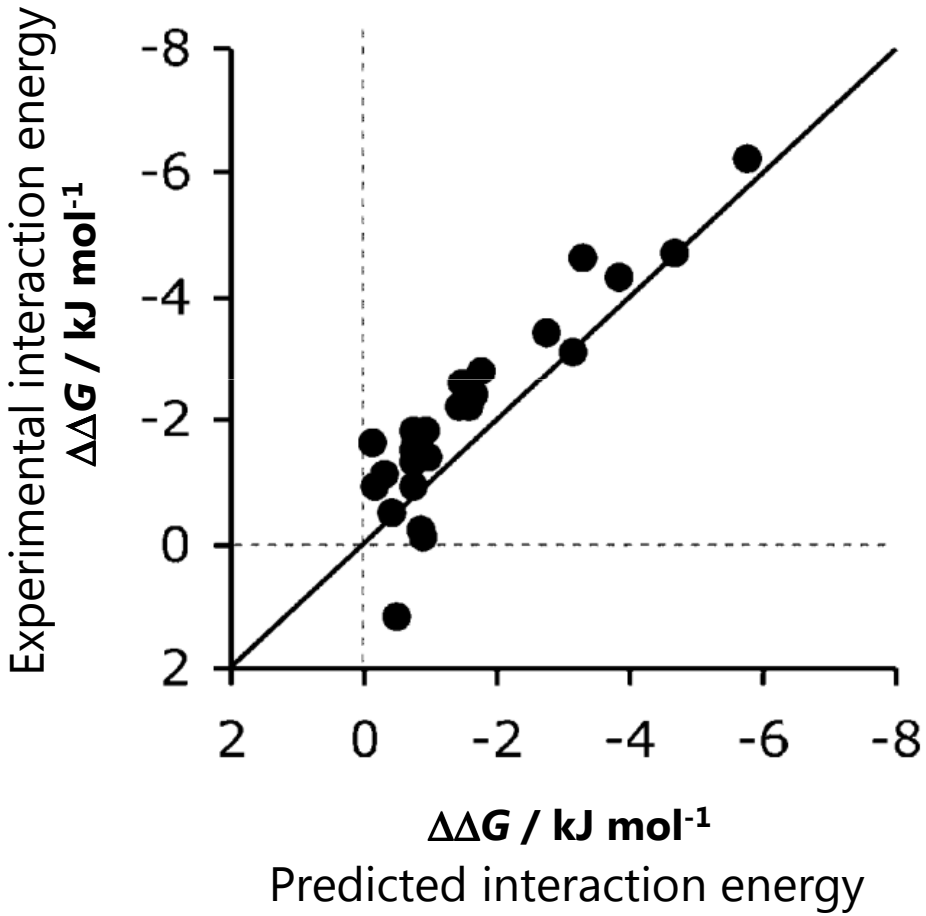


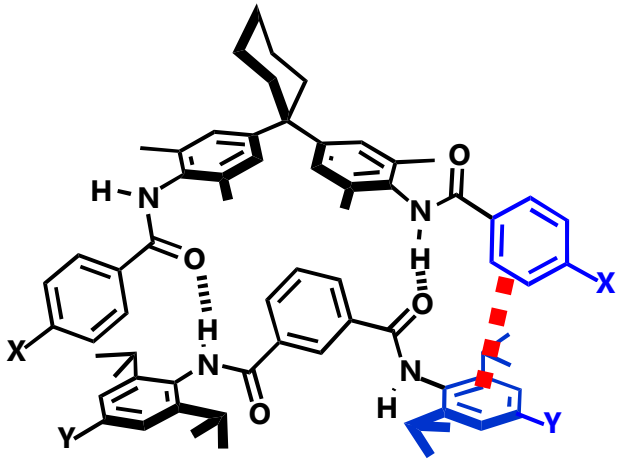


Cockroft & Hunter,
Chem. Comm. 2009

Electrostatic control of aromatic interactions

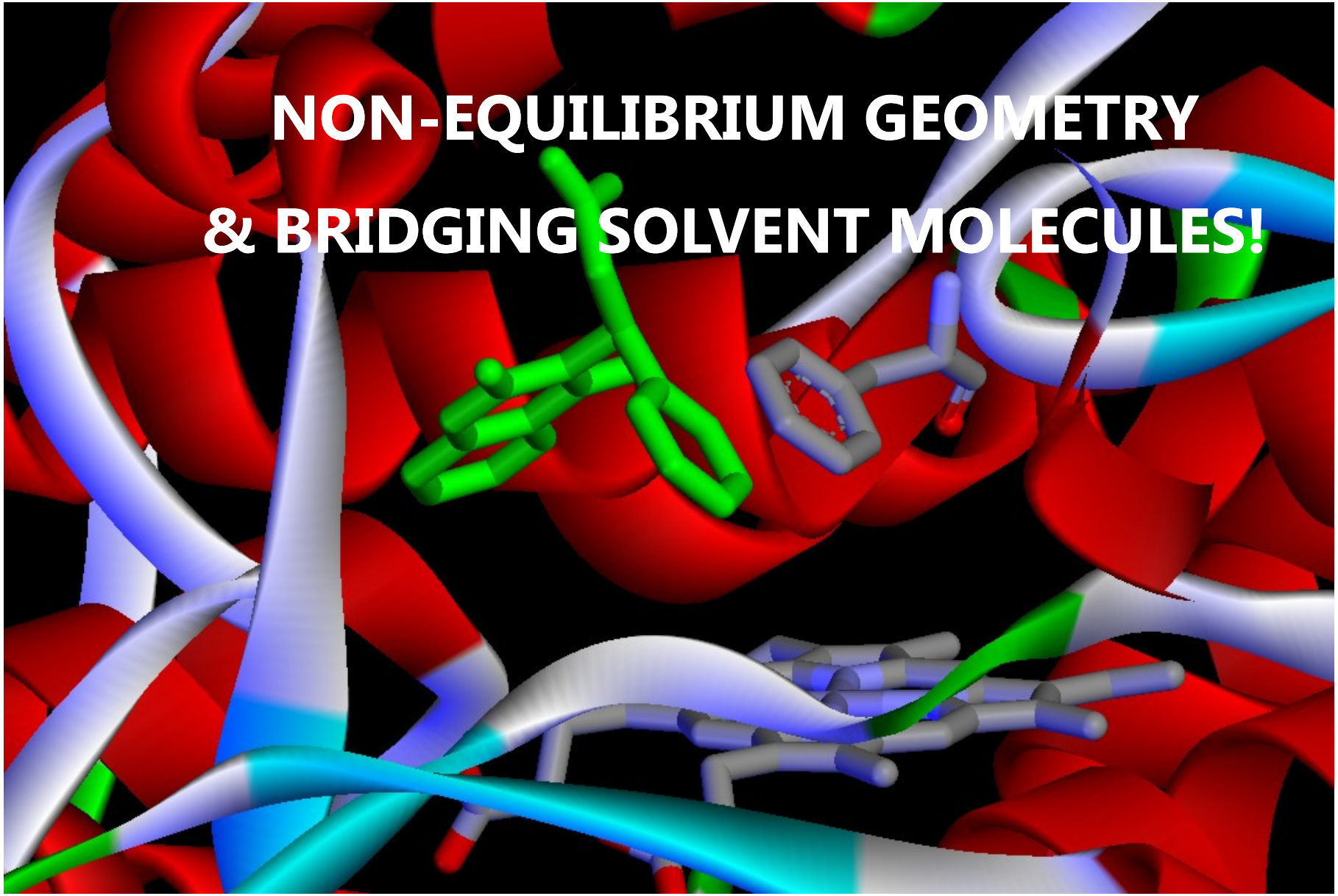
Same model as used to analyse Diederich data!





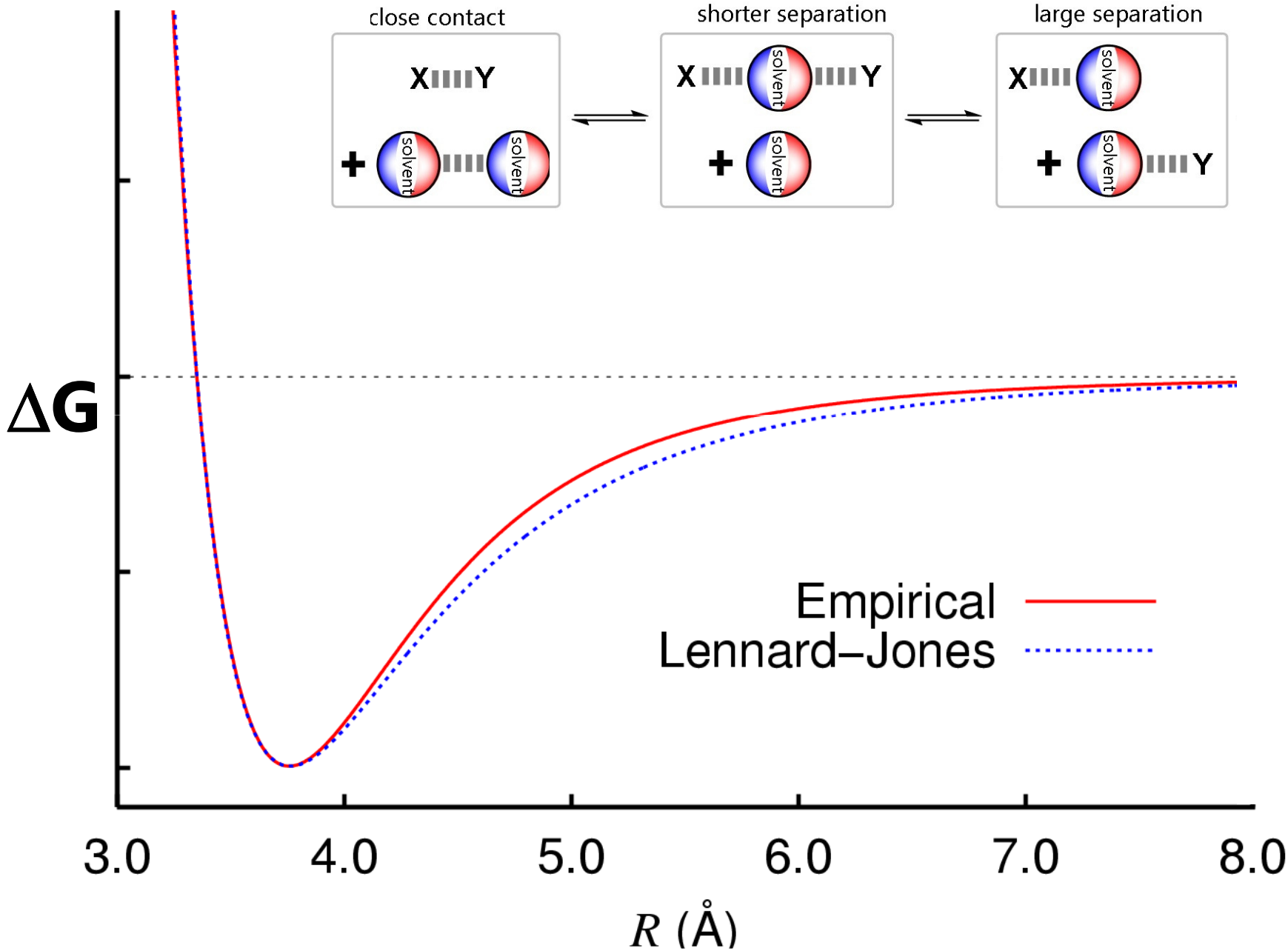
Cockroft & Hunter, Chem. Comm. 2009

Non-covalent interactions: non-equilibrium geometry

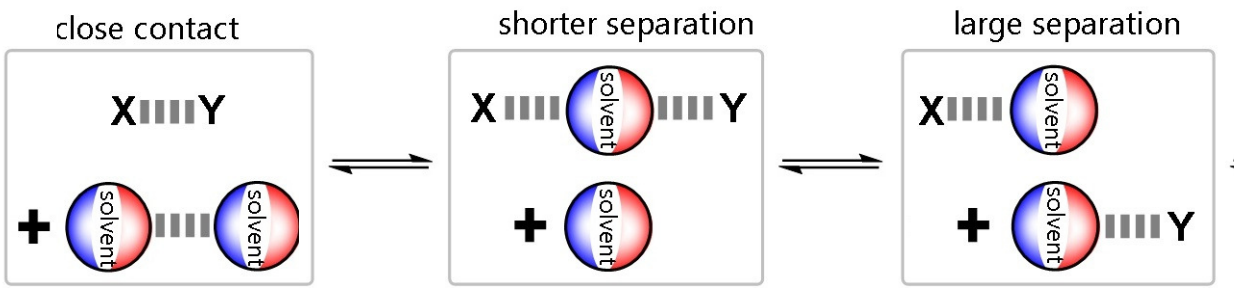


P. A. Williams, J. Cosme *et al*, *Nature*, 2003, 424, 464-468

Separation-interaction profiles



Separation-interaction profiles

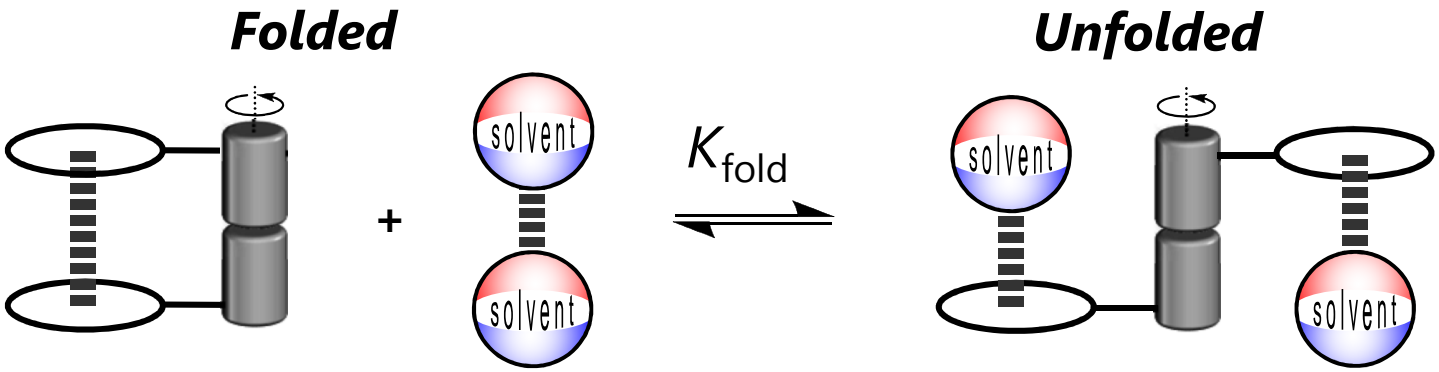


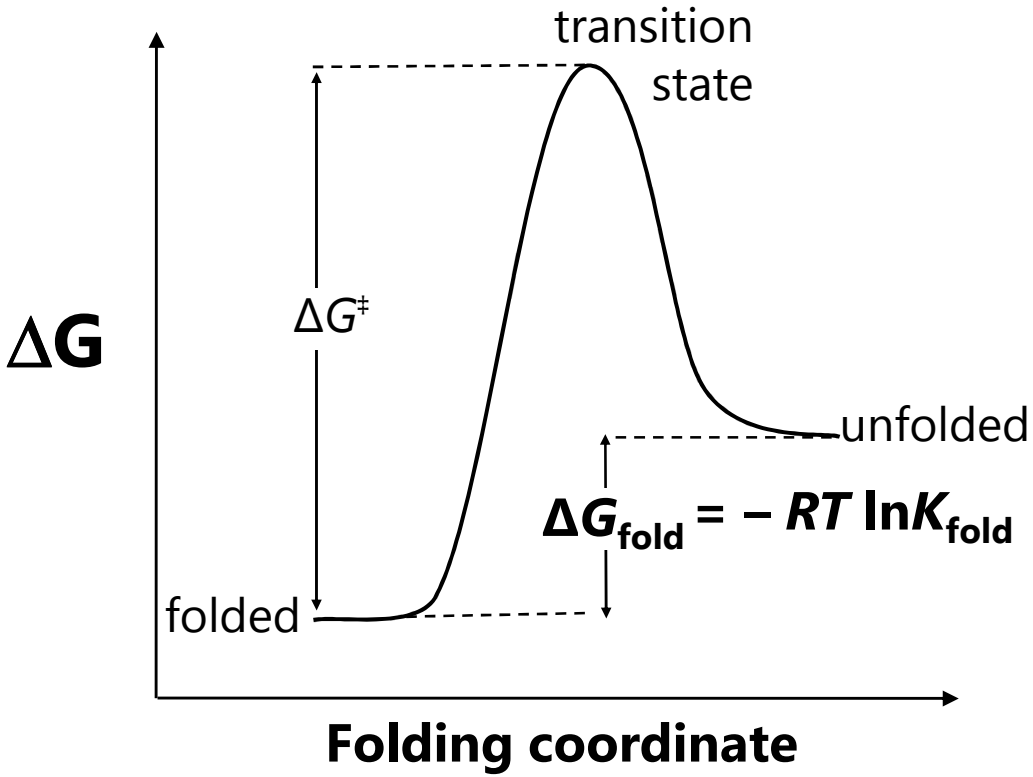
Implications:

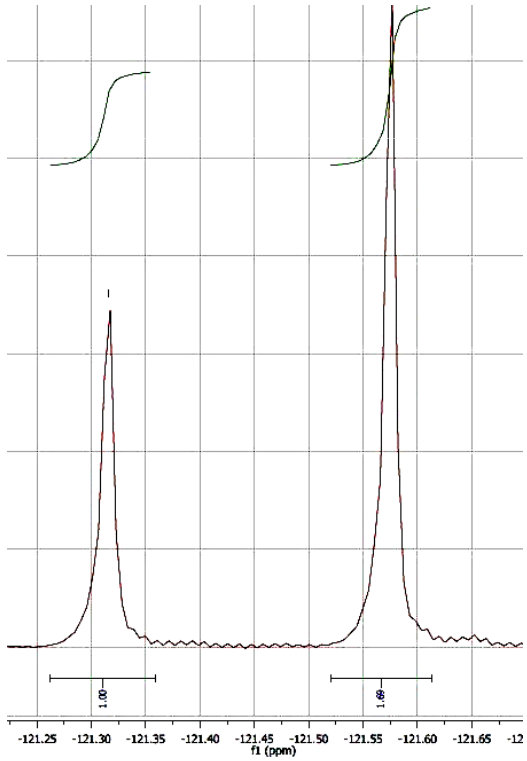
- understand interplay of solvent and geometry & conformation of small molecules
- determine importance of dispersion interactions-what happens when solvent excluded?
- quantify significance of long-range solvent-mediated (bridging) interactions
- predict solubility
- better force-fields for molecular modelling/docking, crystal structure prediction etc…

Many computational docking simulations use solvent fields because adding explicit solvent molecules is computationally expensive, is this a valid approach?

Solvent effects on molecular folding

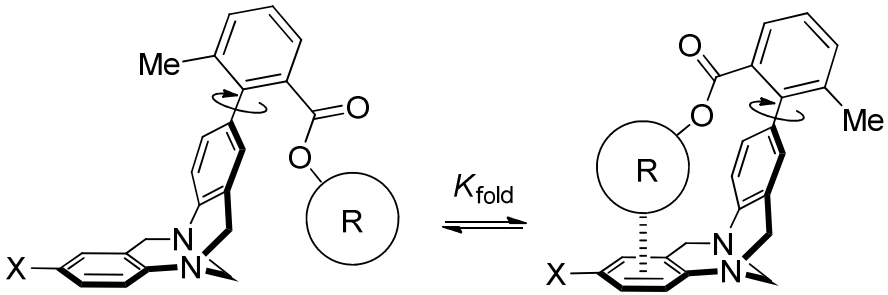




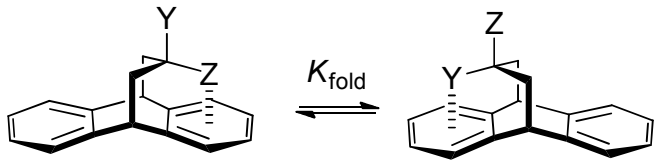


I. K. Mati & S. L. Cockroft. *Chem. Soc. Rev.* 2010

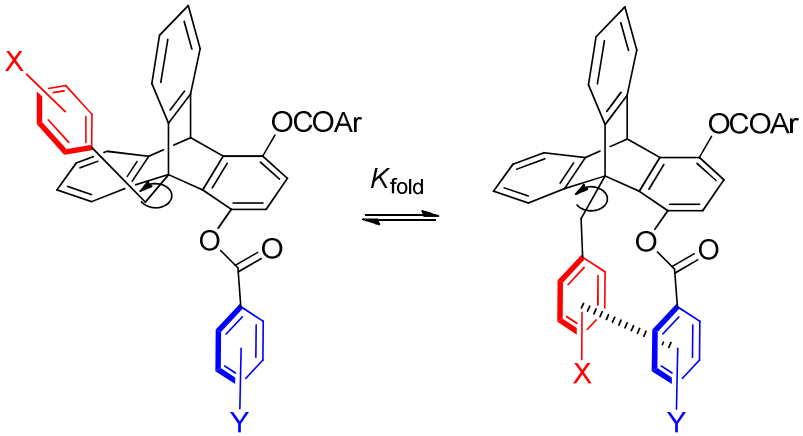
Foldamers for quantifying non-covalent interactions



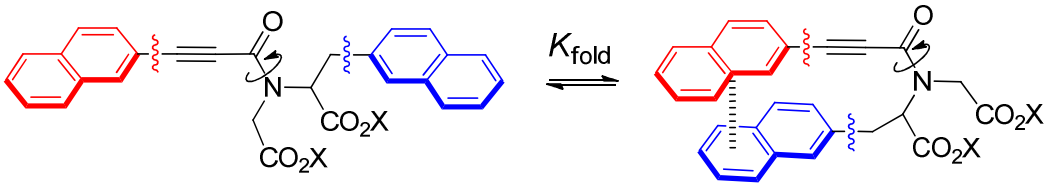
Wilcox, Diederich



Motherwell



Oki, Gung



Gellman

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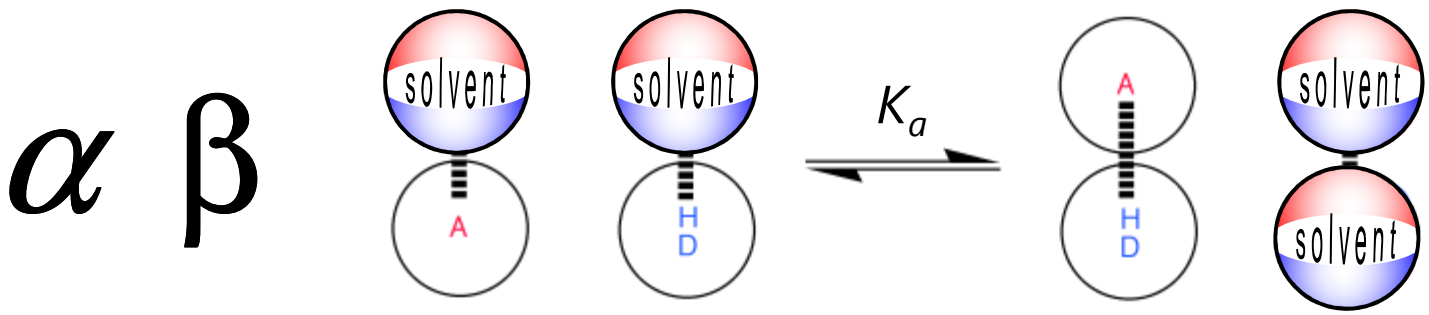
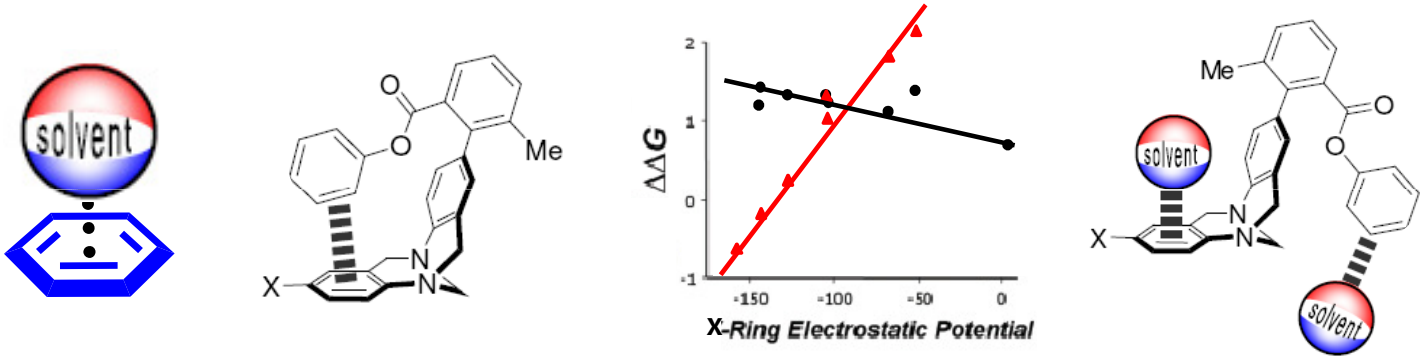
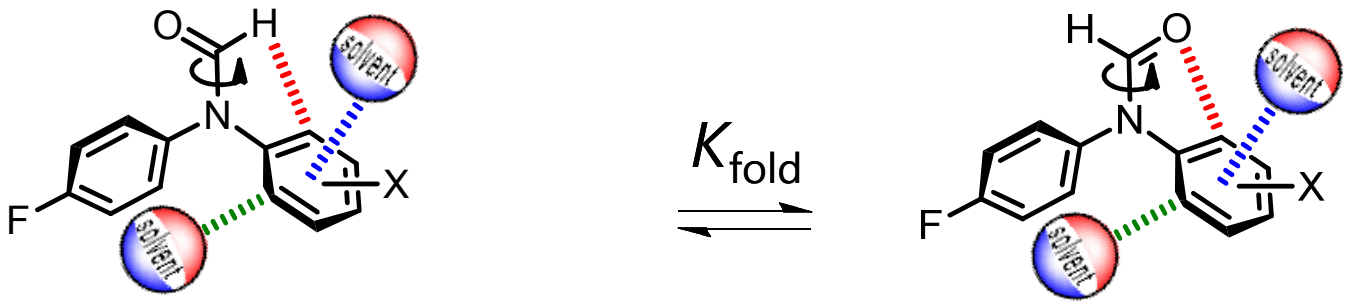
Non-covalent interactions summary

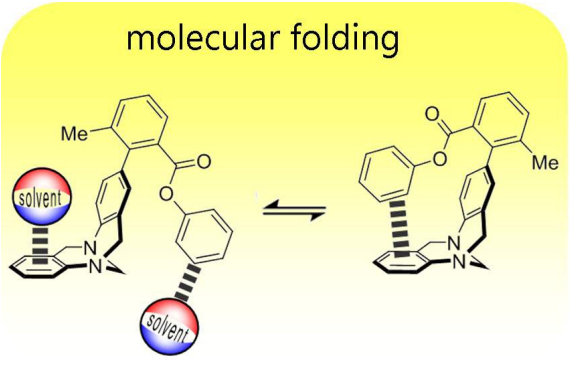


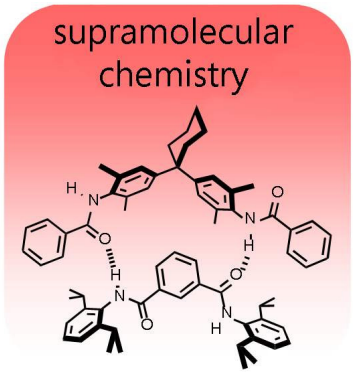


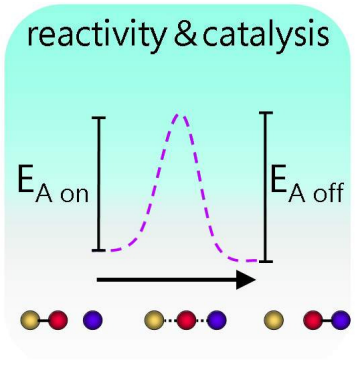


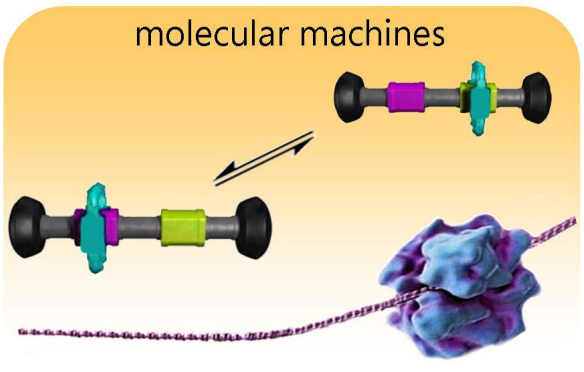
dispersion interactions… non-equilibrium geometries…solvent effects


Scott Cockroft
Martyna Snopek
Ula Wolkowicz
Lixu Yang
Catherine Adam
James Brown
Sophie Spurr
Giulia Iadevia
(Hunter group)
John Brazier
Lina Mati
Mike Stockton
Ma Long
March 2010
Sheep Heid, Edinburgh
(Oldest pub in Scotland)



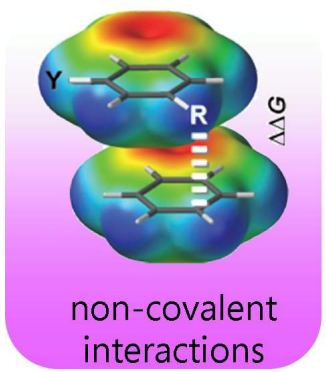


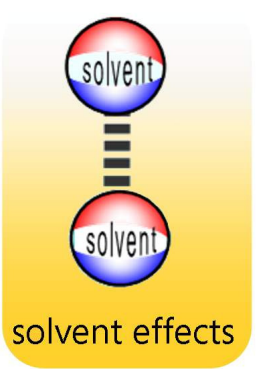


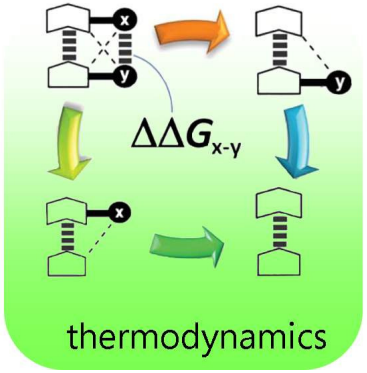


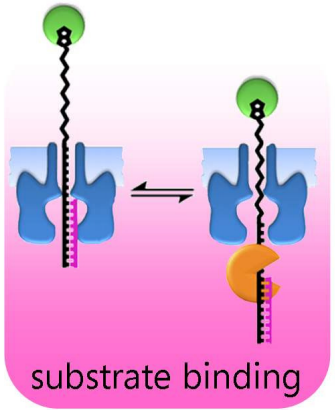
Physical Organic Chemistry

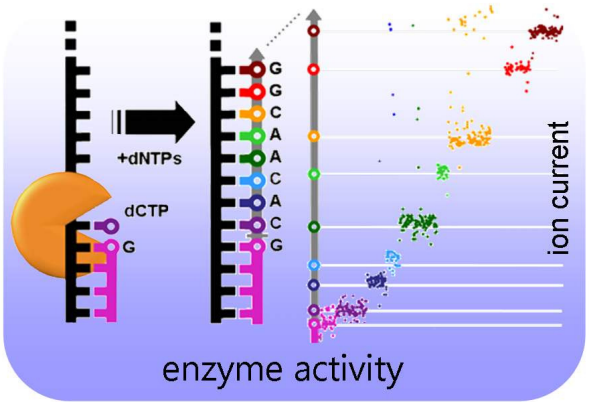
Single Molecule Studies











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