

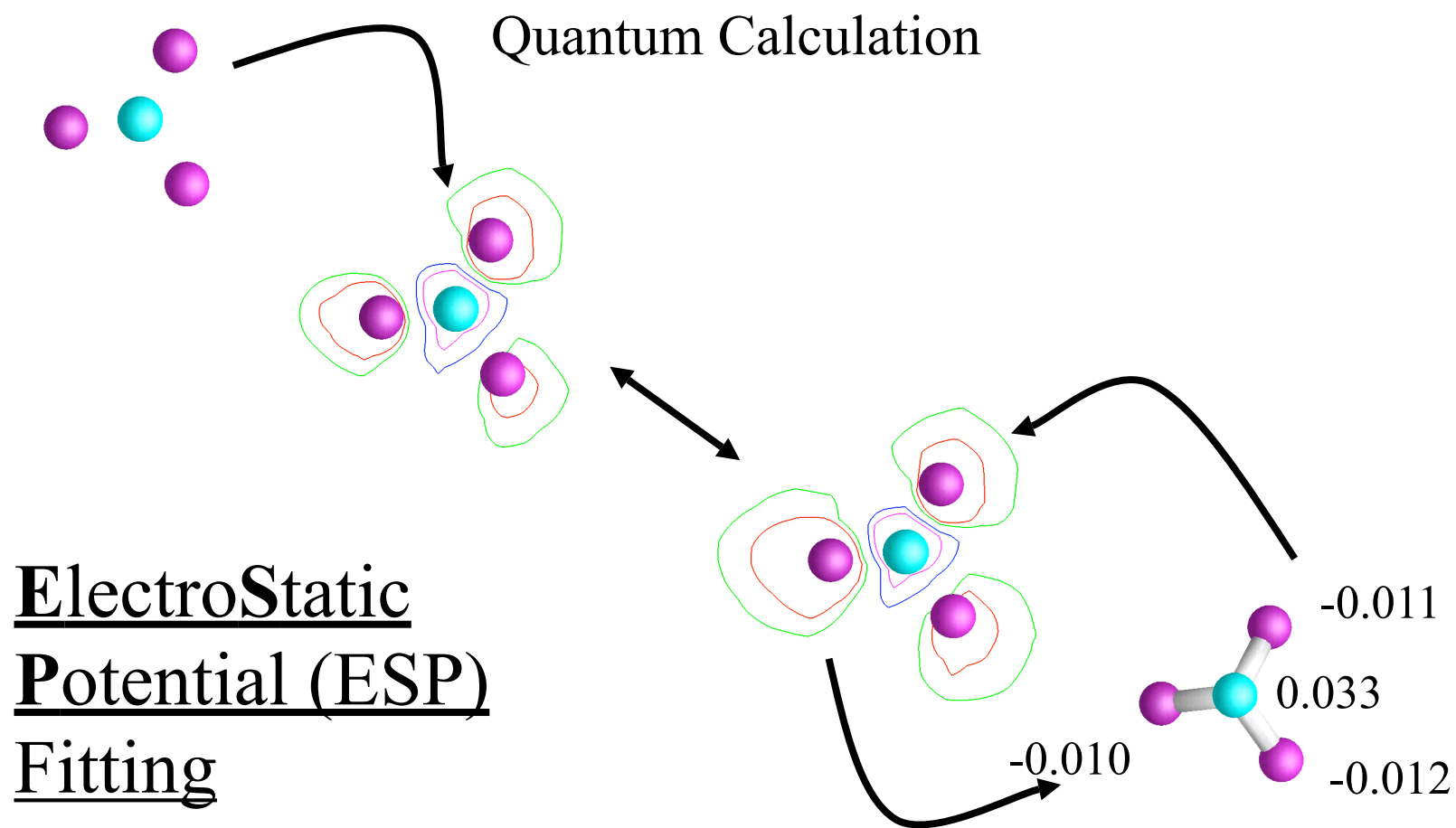
# Dielectric Theory and Solvation

What happens if we choose to believe?

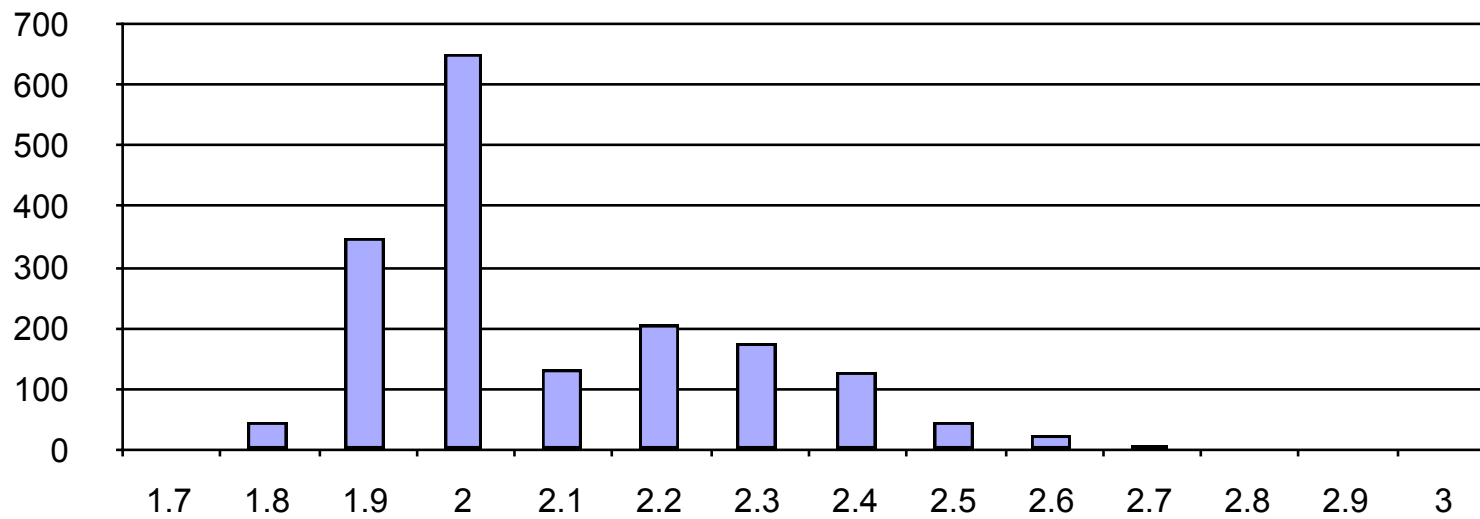
# Puzzles

- Why do 'better' charges give worse results?
- Hydrophobicity strength (air-water, water-hexane)
- Why is Surface Tension  $\gg$  Hydrophobicity
- Macroscopic surface tensions (vac-water, water-oil)
- Cyclic alkanes: why so soluble
- Why do fluorocarbons repel water so?
- Slopes from MD simulations
- Super-hydrophobic surfaces/ hydrophobic gaps

# What are little charges made of ?

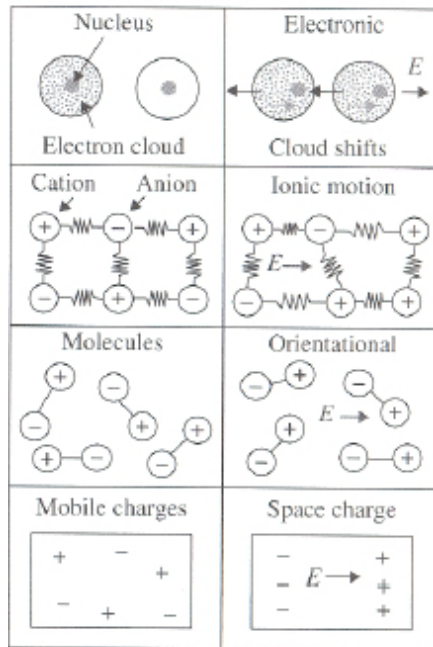


# One Small Problem...

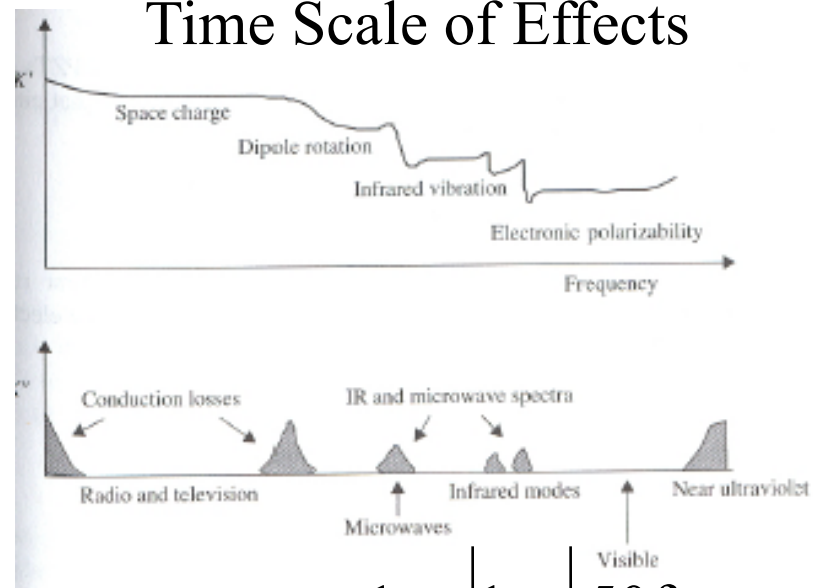


# What is a “Dielectric”?

## Source--Effect



## Time Scale of Effects

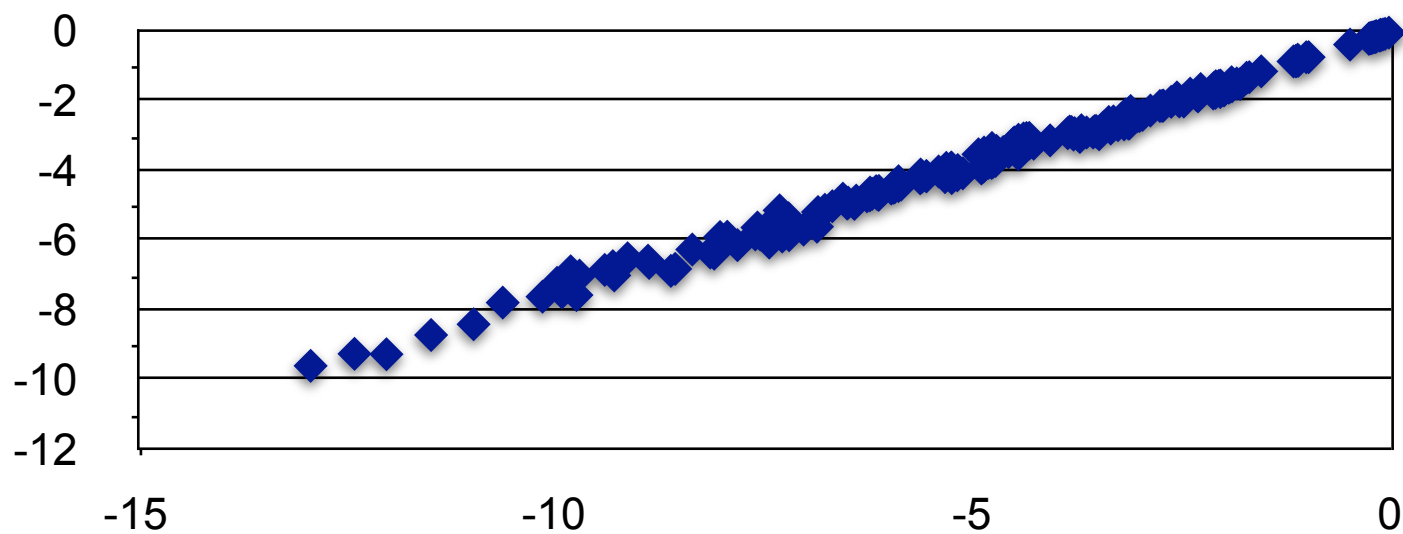


1ns | 1ps | 50fs

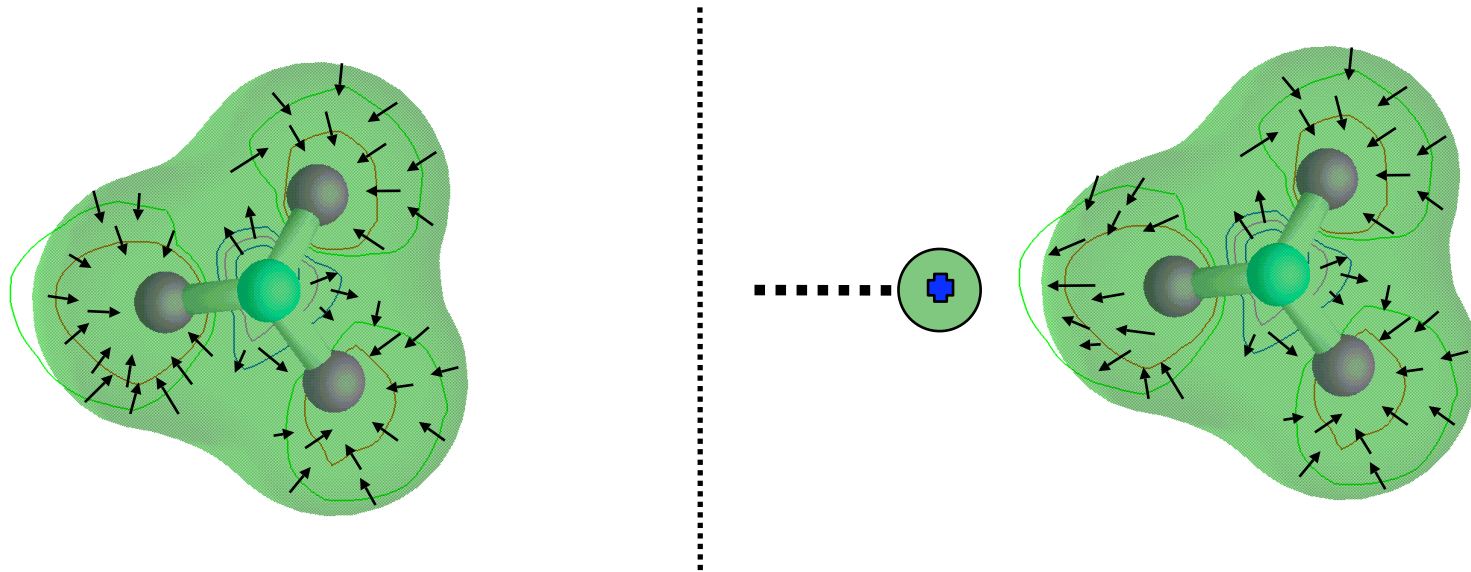
Water Reorients

Dielectric Relaxation

Does the internal dielectric really matter  
for neutral molecules?



# What does an interior dielectric mean?



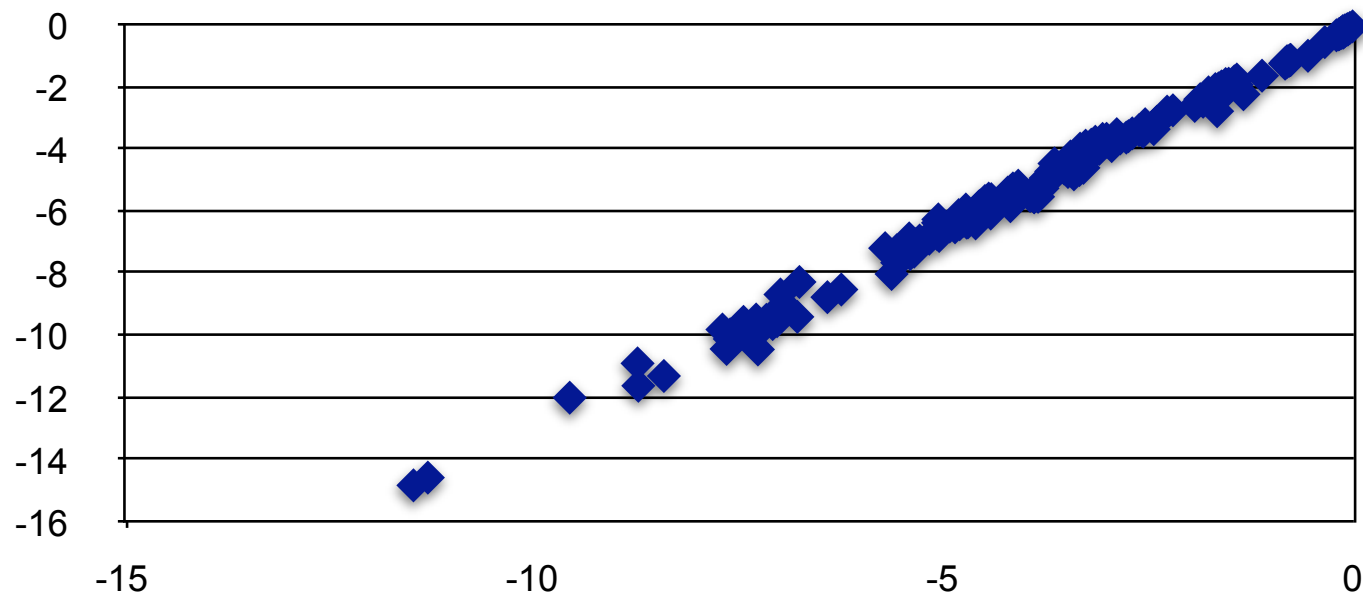
# The heart of the matter: spheres and ions

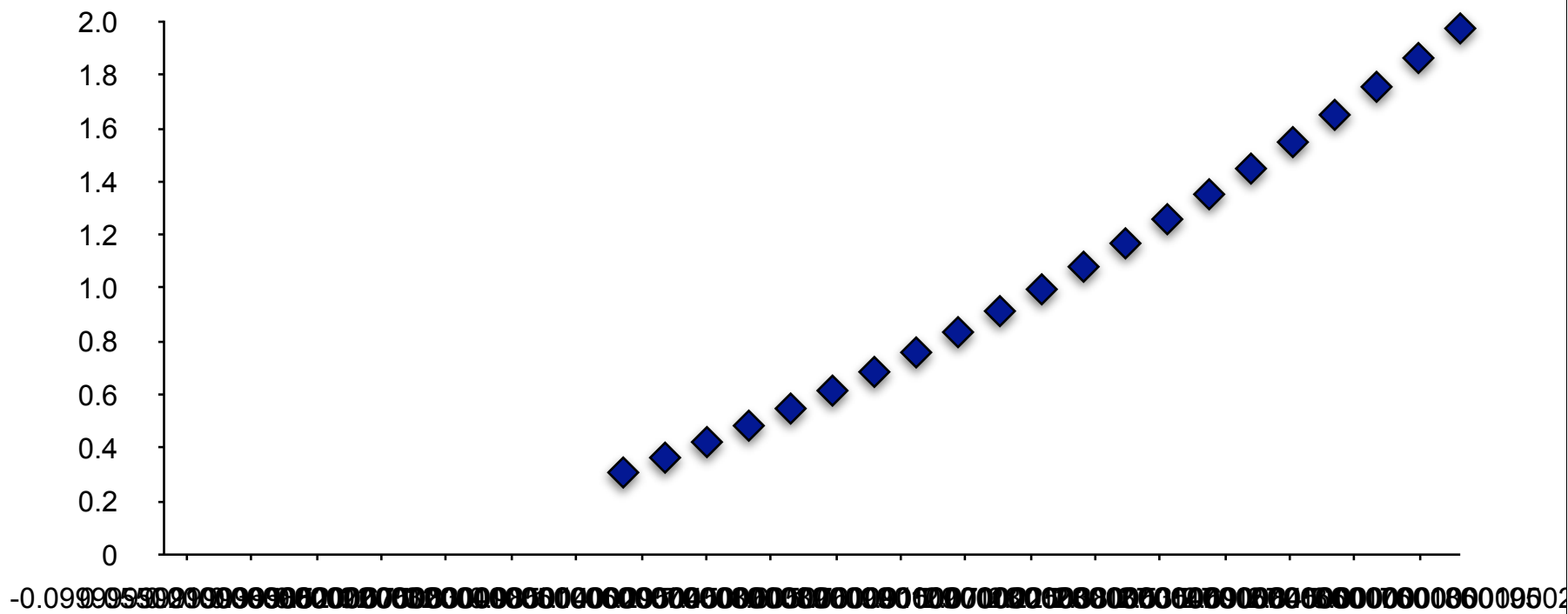
- exterior\_potential= $F(\epsilon_{\text{out}})$
- solvation= $G(\epsilon_{\text{out}}, r)$
- $F=G$  with respect to  $\epsilon_{\text{in}}$

# The heart of the matter: spheres and dipoles

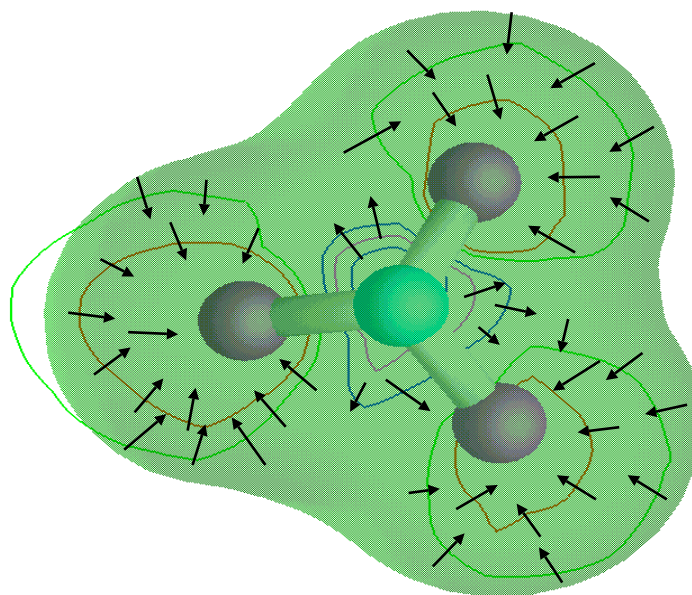
- Exterior\_potential= $F(\epsilon_{in}, \epsilon_{out})$
- Solvation= $G(\epsilon_{in}, \epsilon_{out}, r)$
- $F \neq G$  with respect to  $\epsilon_{in}$
- $F(r^* \delta) = G, \delta(\epsilon_{in})$
- $\delta(2.0) = 1.15$

Small molecules *really* are  
like dipoles in a sphere!





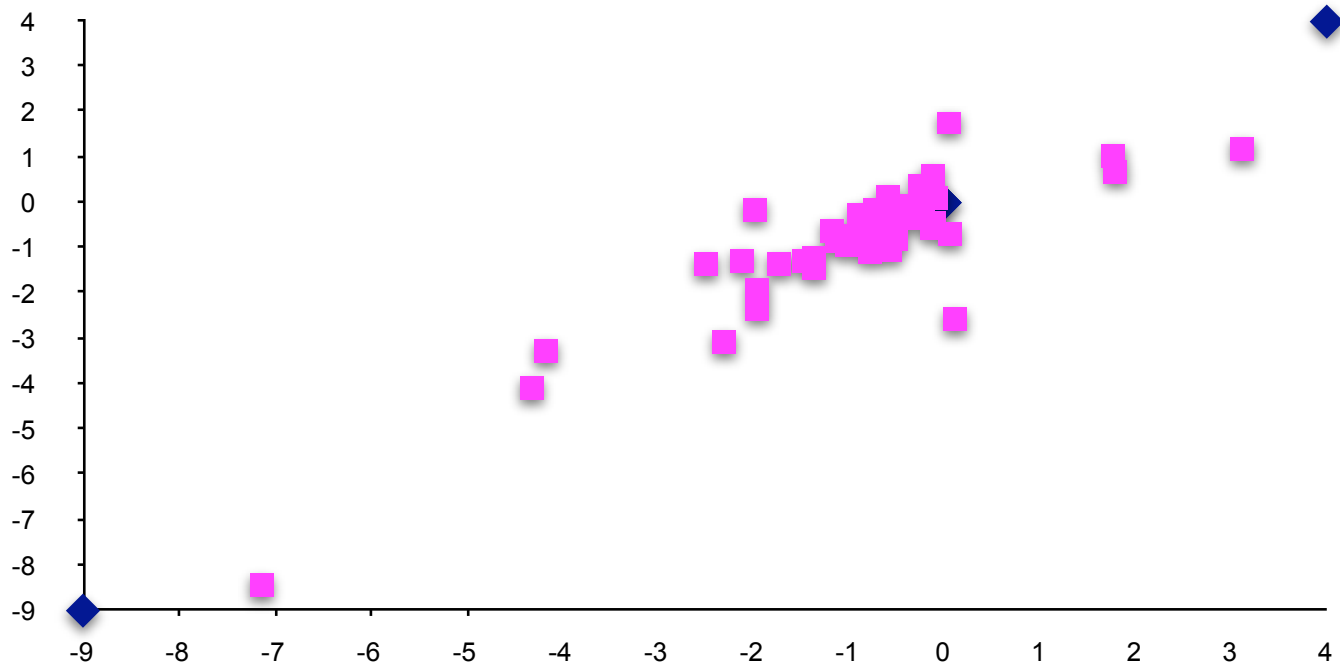
Huh?



Potentials ( $q$ )

Solvation ( $q^2$ )





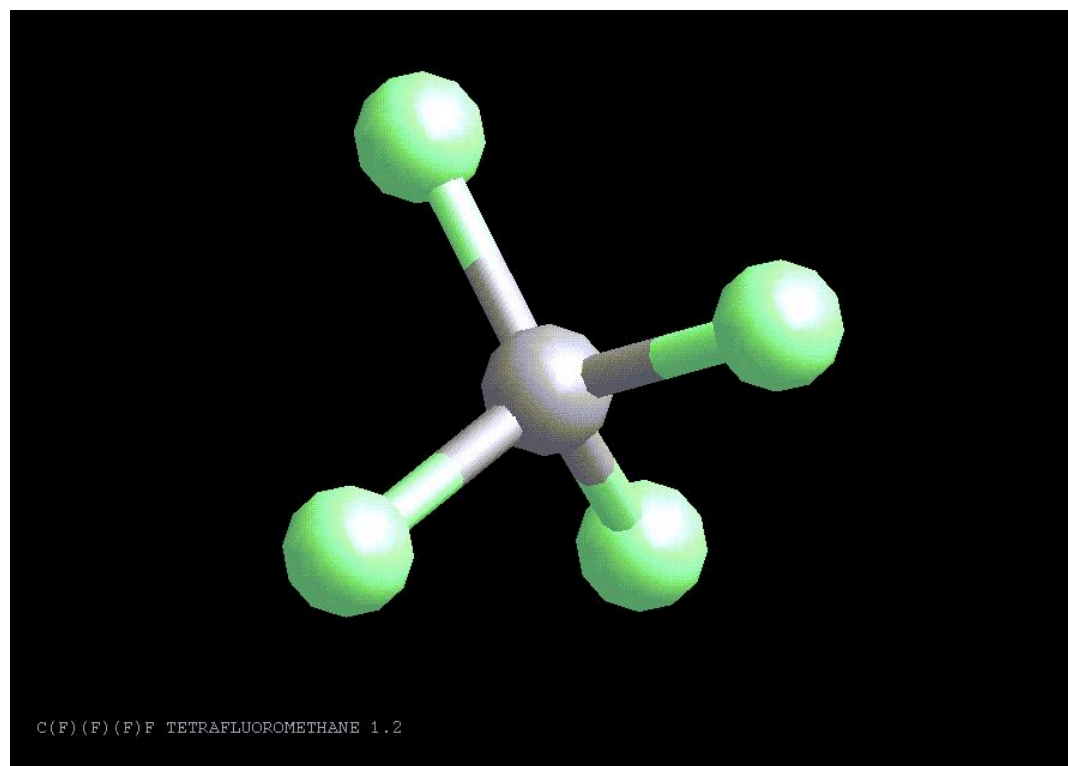
# Bad molecules with no hope of solvation

## Carbon Tetrafluoride

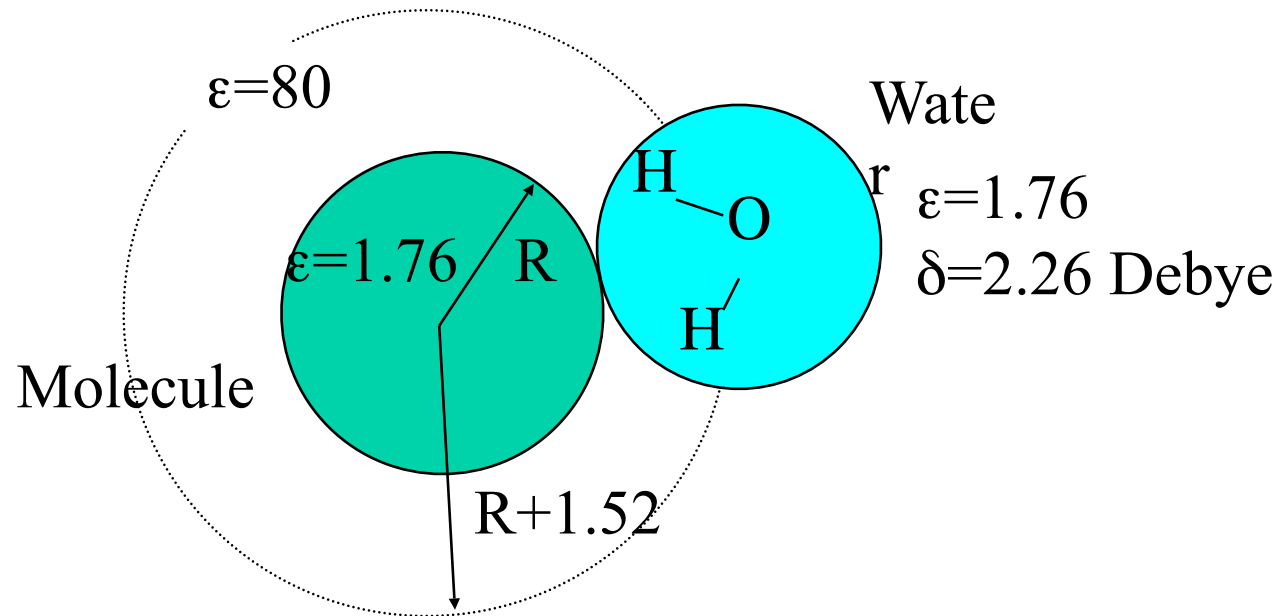
Solvation: +3.1 kcals

Area:  $180 \text{ \AA}^2 \sim +1.4 \text{ kcals}$

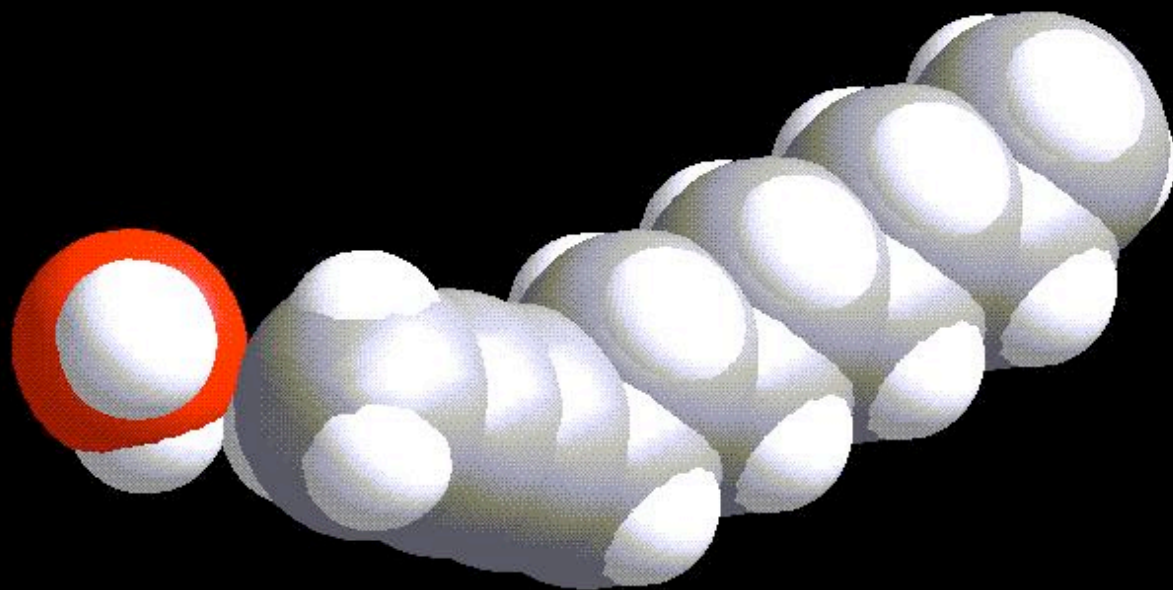
Electrostatics  $\sim -1.5 \text{ kcals}$



# A Dielectric Theory of Hydrophobicity



1. Sample all orientations of water
2. Sample all contact positions around molecule  
~50,000 ZAP calculations



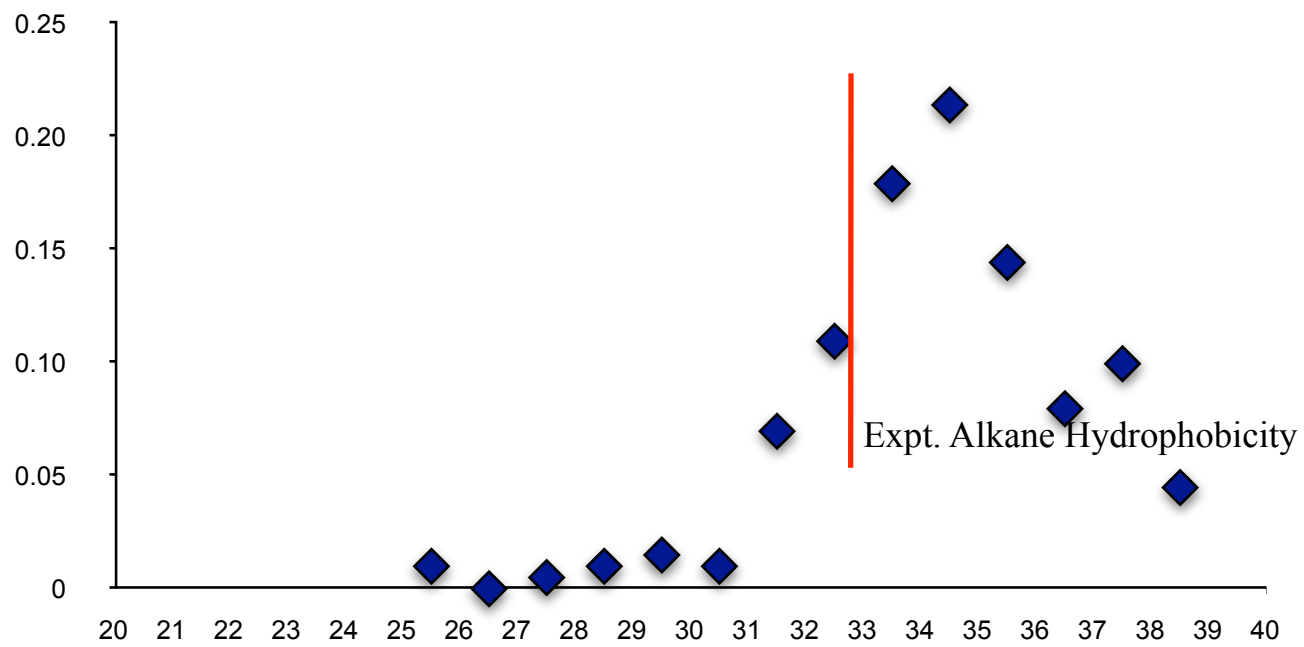
complex.pdb

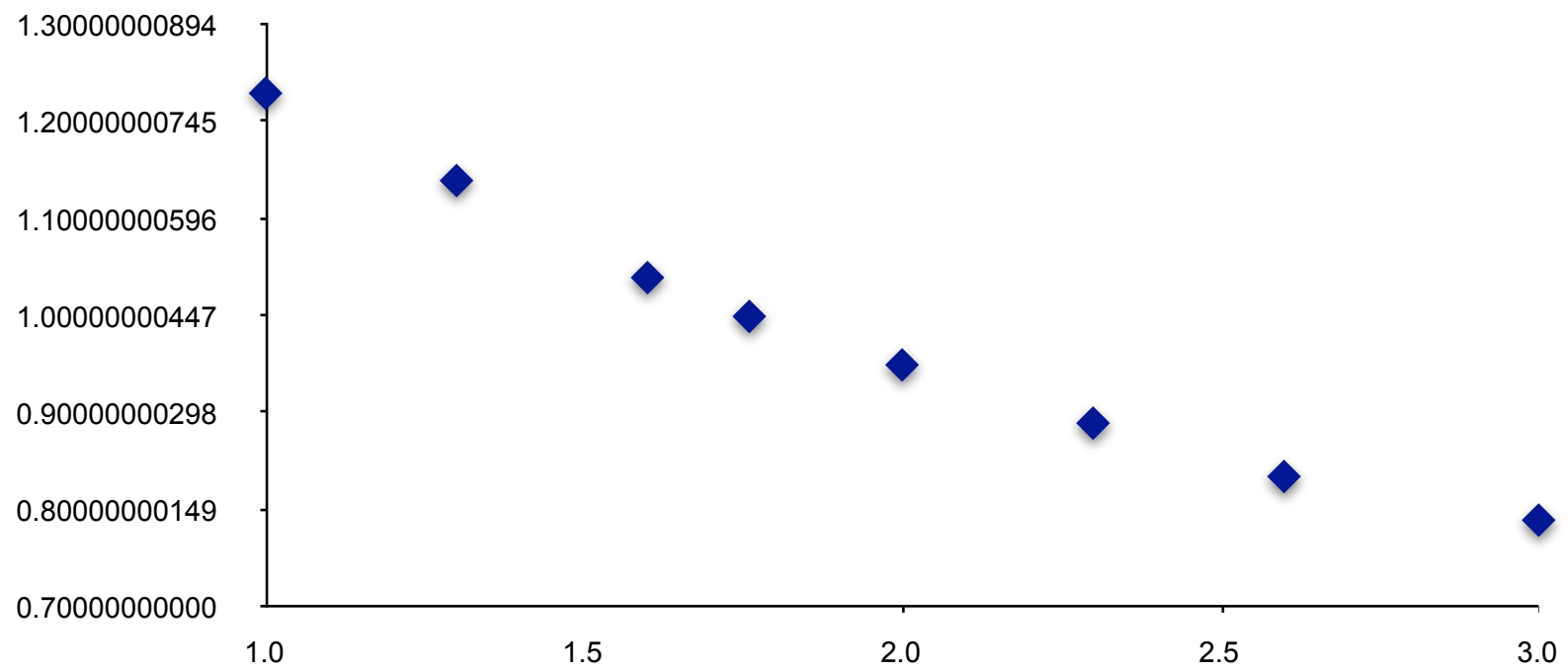
# From ZAP to Hydrophobicity

- Local  $\Delta G$  at each (accessible) surface point
- Multiply by  $\langle \# \text{ of superficial waters} \rangle$  ( $\sim 1$  per  $11 \text{ \AA}^2$ )
- Adjust for the internal dielectric of the molecule

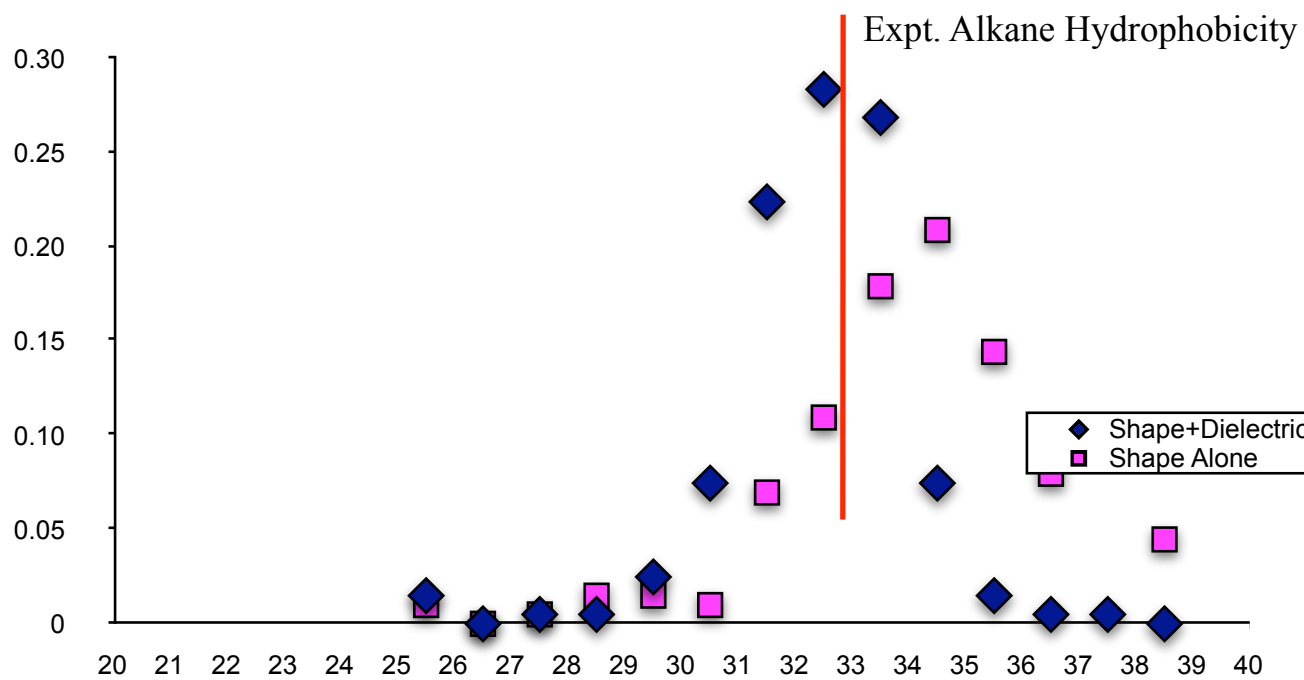
# What are we trying to predict?

- From Ethane to Decane ~ 880 cal/CH<sub>2</sub>
- Accessible area increase ~ 27 Å<sup>2</sup>
- “Hydrophobicity” = 880/27 = **32.6 cal/ Å<sup>2</sup>**

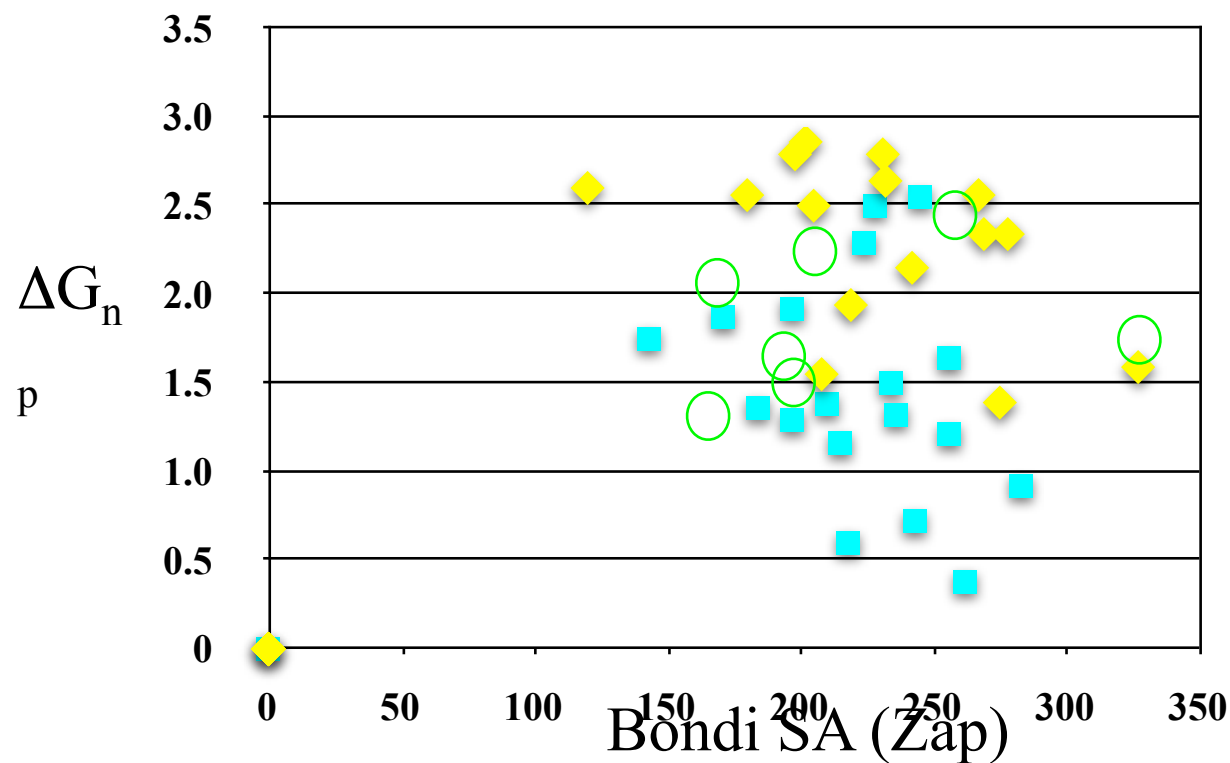








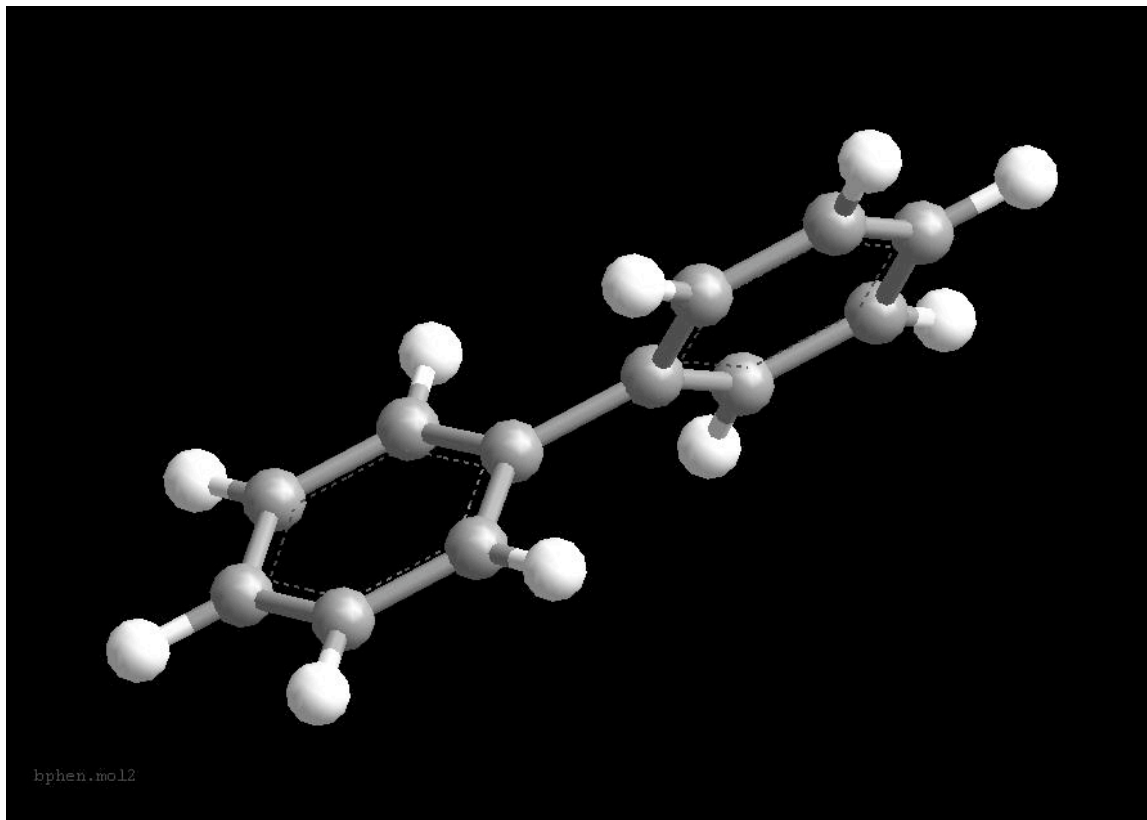
# $\Delta G_{np}$ : “Converged MD” vs SA



Mobley et al. *JCP*  
asap 2007

- No correlation with Surface Area
- With N and O functionality, “Converged MD”  $\Delta G_{np}$  decreases by  $\sim 0.7$  kcal/mol (N, O vdW parameters?)

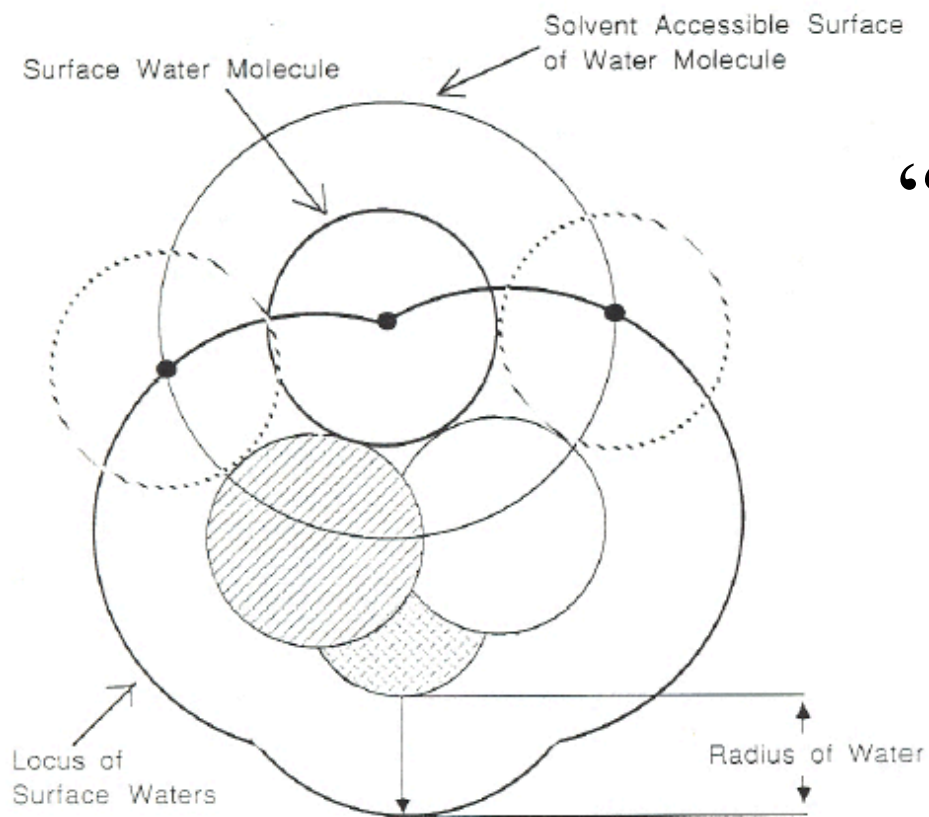
# Why Chris is an awkward bastard



2,2'-dichlorobiphenyl:	-2.76 kcals
AM1BCC+10 cal/ Å <sup>2</sup> :	-3.81 kcals
QM + Dielectric Theory:	-2.56 kcals

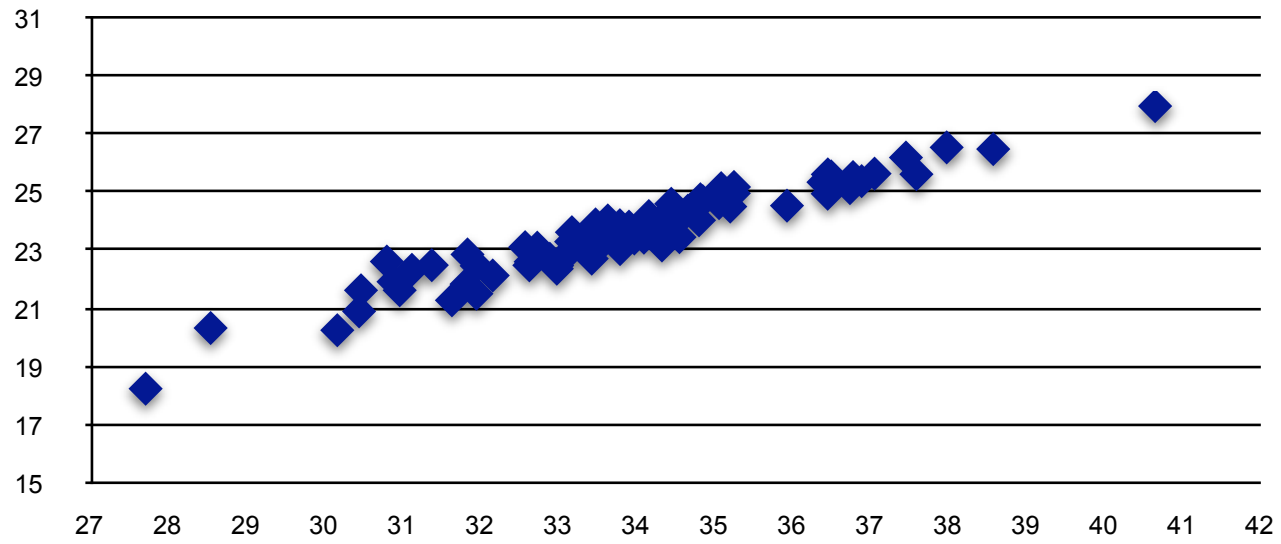
# Happy now, Chris?

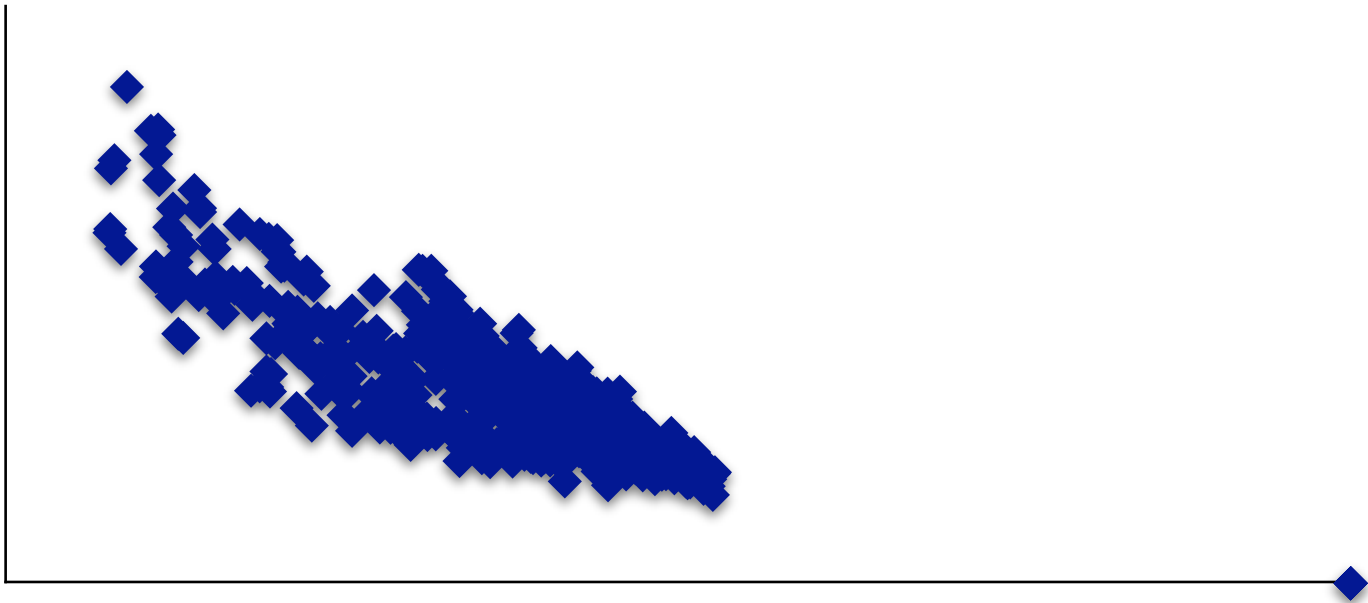
• Molecule	SA cal <sub>s</sub> / Å <sup>2</sup>	Me (kcal)	Dave
• Toluene	9.0	2.2	2.2
• Phenol	8.1	1.9	1.5
• Aniline	6.8	1.6	1.3
• Benzene	8.4	1.7	1.9
• Naph.	8.3	2.5	2.4
• Biphen.	10.2	3.3	1.6

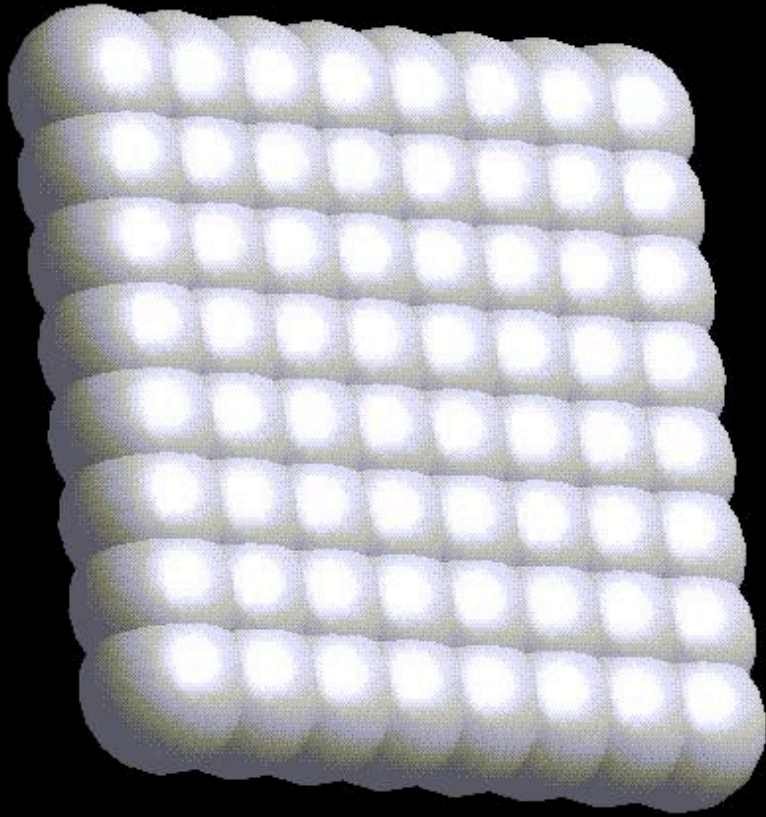


“Curvature”

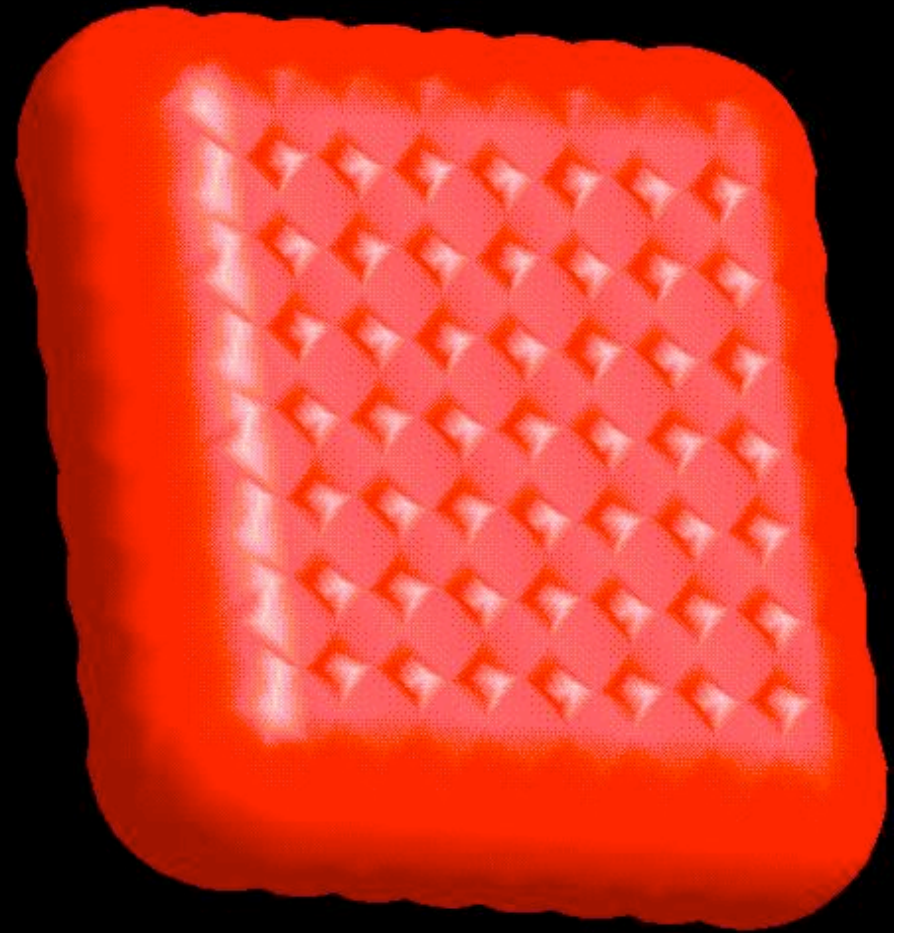
Nicholls, Sharp & Honig, Proteins, Vol.11:281-296 (1991)







array1.pdb



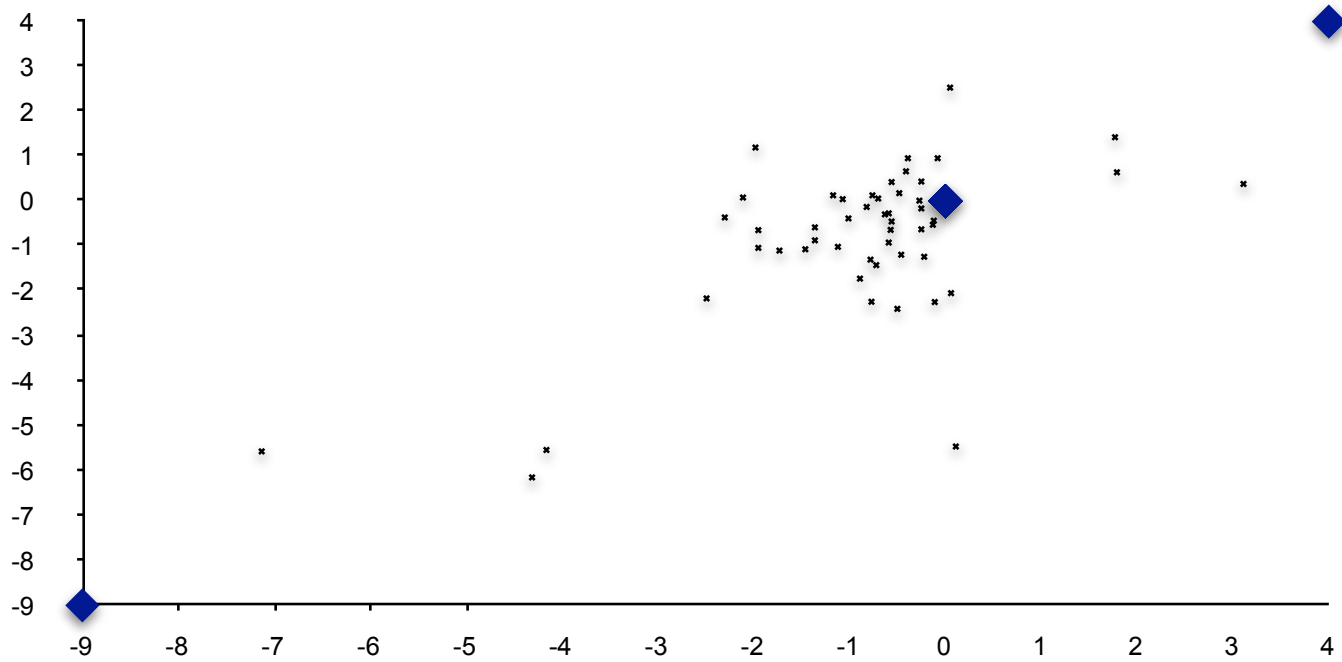
array.srf

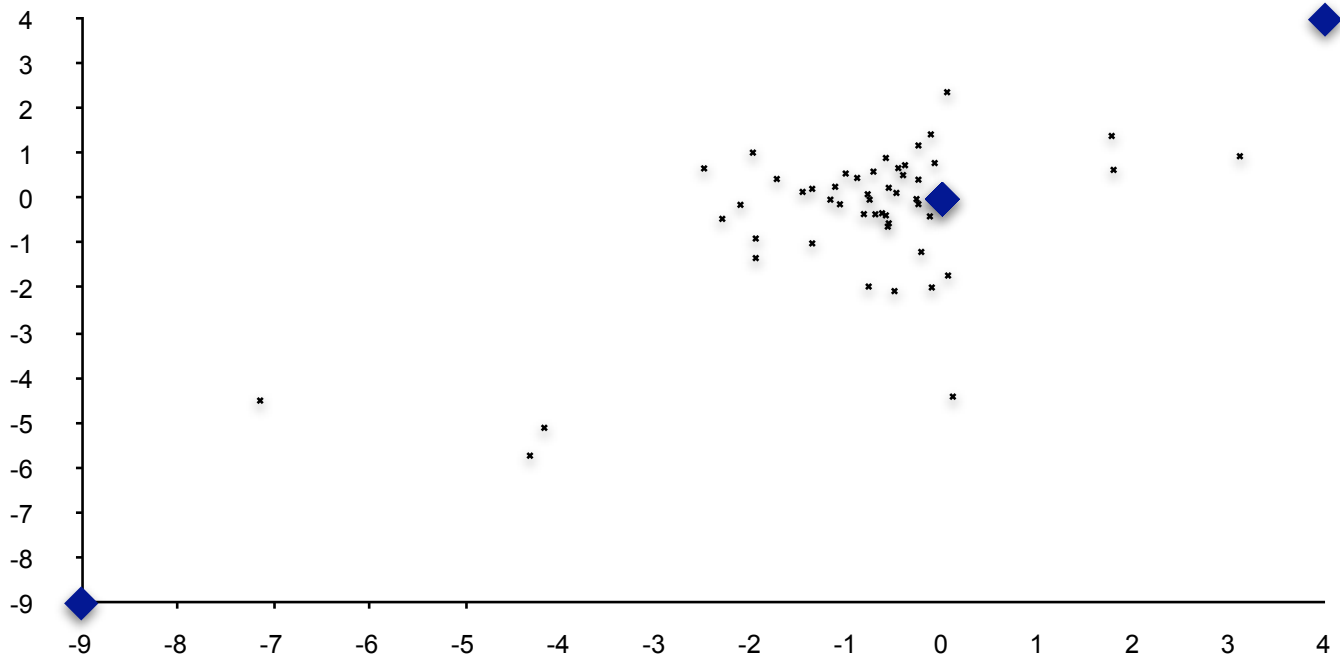
# Prediction of Alkane/Water Surface Tension

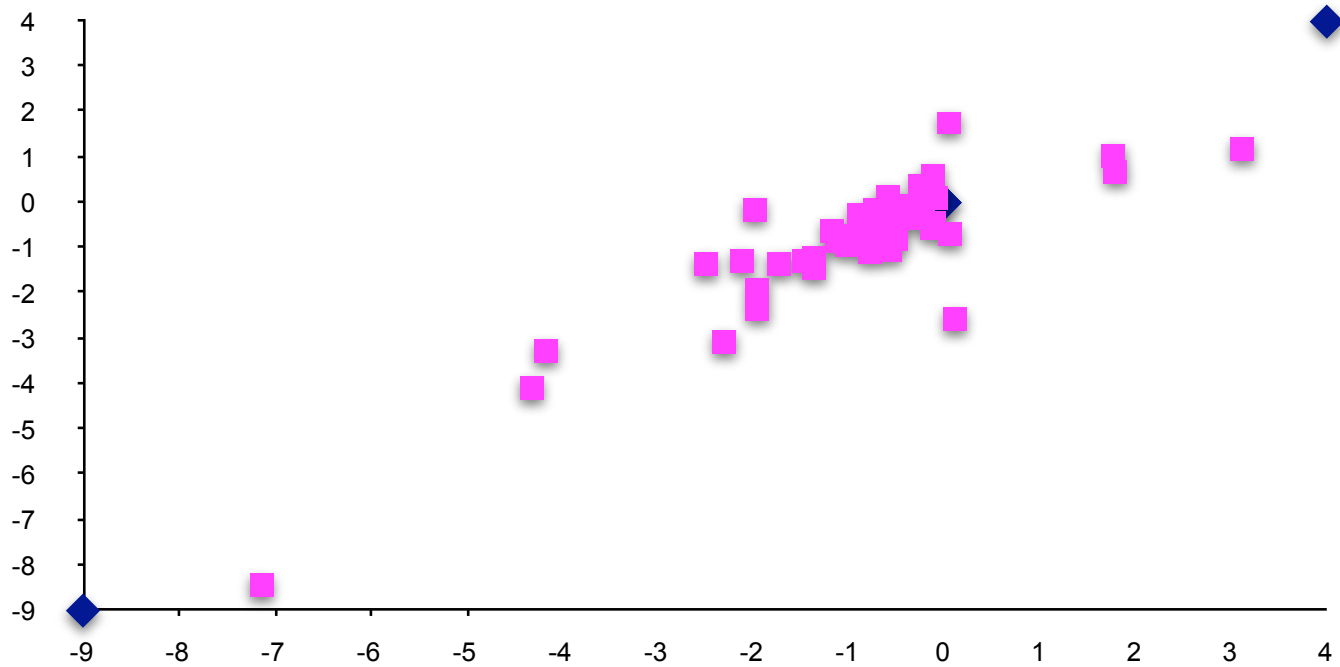
- Flat part of Array  $\sim 63 \text{ cal/A}^{**2}$
- N-S-H 'fudge' factor of 10% "roughness"
- Final value  $\sim 69 \text{ cal/A}^{**2}$
- Experimental Oil-Water  $\sim 72 \text{ cal/A}^{**2}$

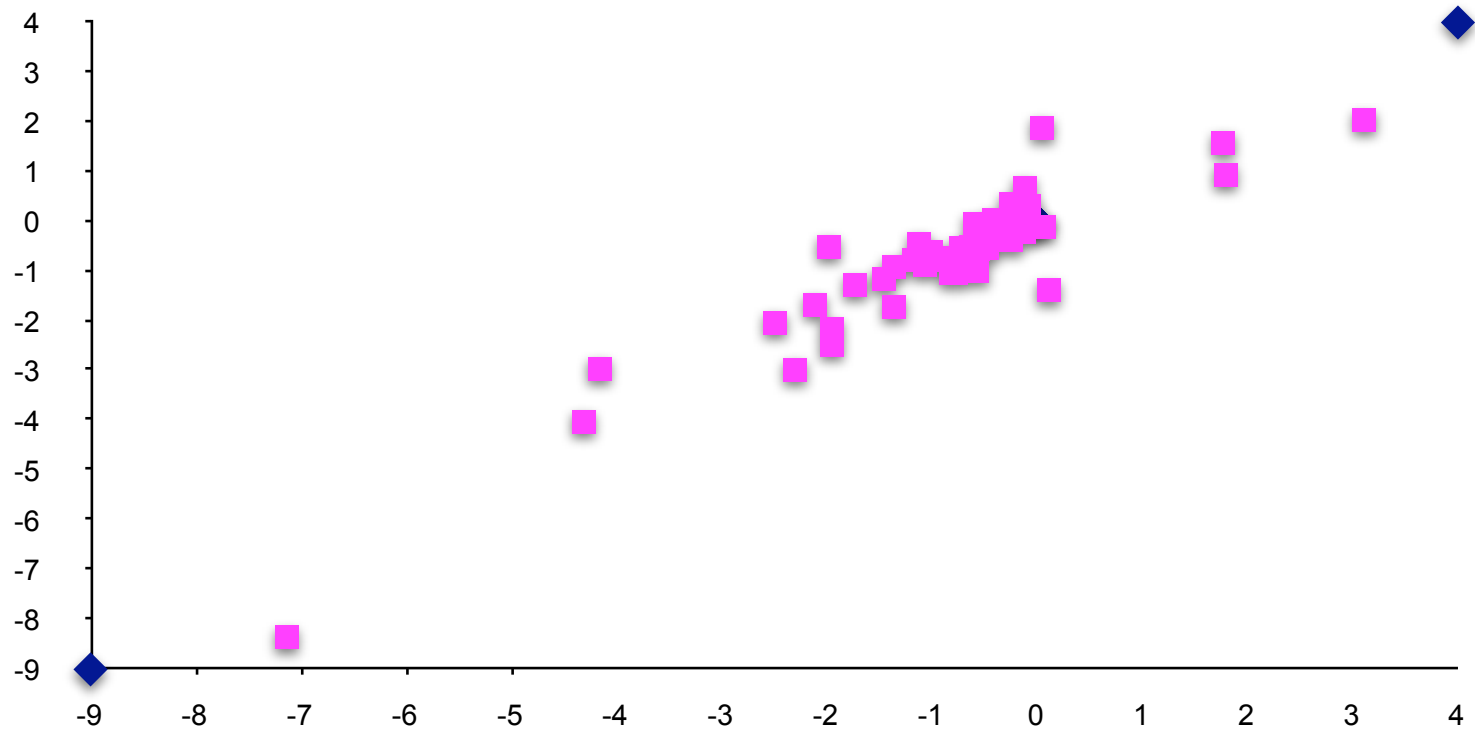
## Prediction of Air-Water Surface Tension/ Or Air-Water Hydrophobicity

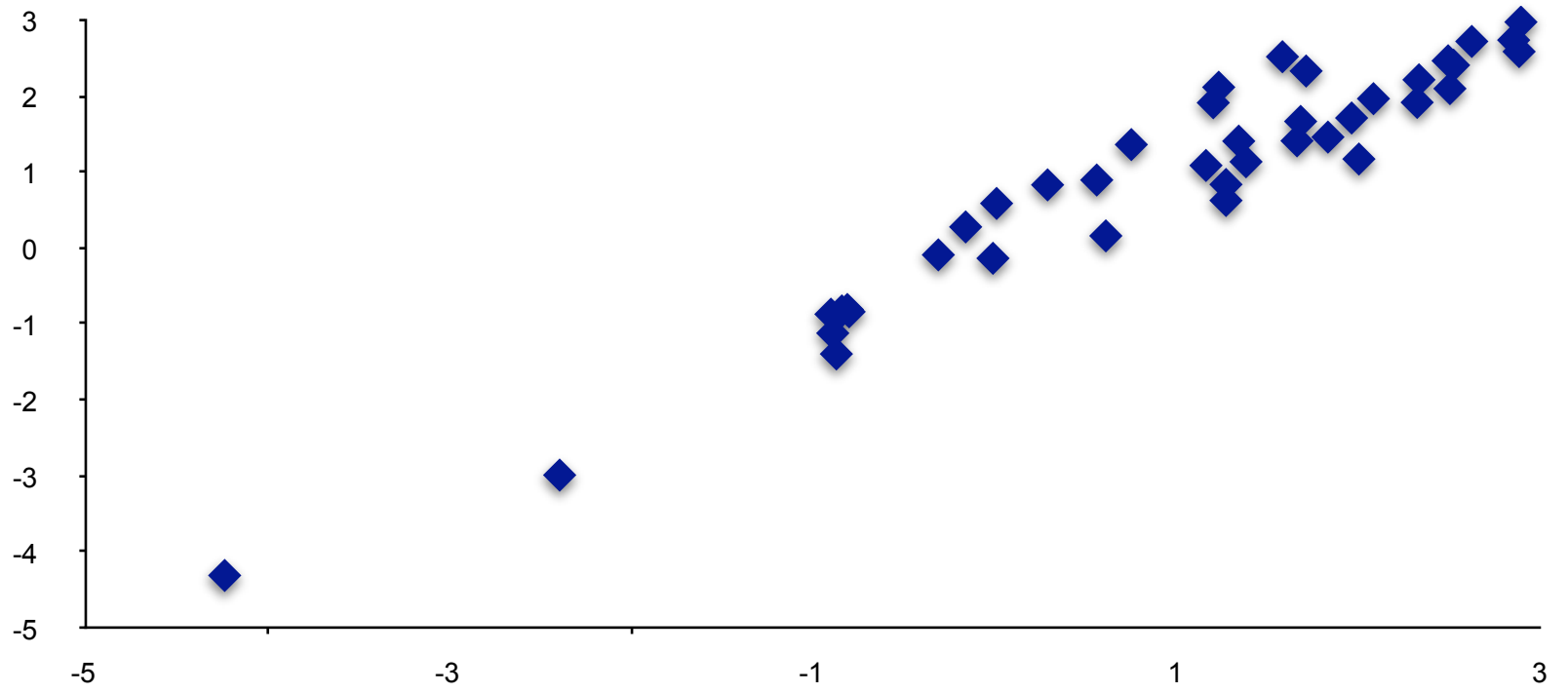
- Water-Vacuum Cavity =  
 $1.31 * \text{Water-Hexane} = 82 \text{ cal}/\text{A}^{**2}$
- Water-Vacuum Surface Tension =  
 $104 \text{ cal}/\text{A}^{**2}$
- Difference = water-oil vdw =  $22 \text{ cal}/\text{A}^{**2}$
- Therefore water-vacuum hydrophobic =  
 $32 - 22 \sim 10 \text{ cal}/\text{A}^{**2}$

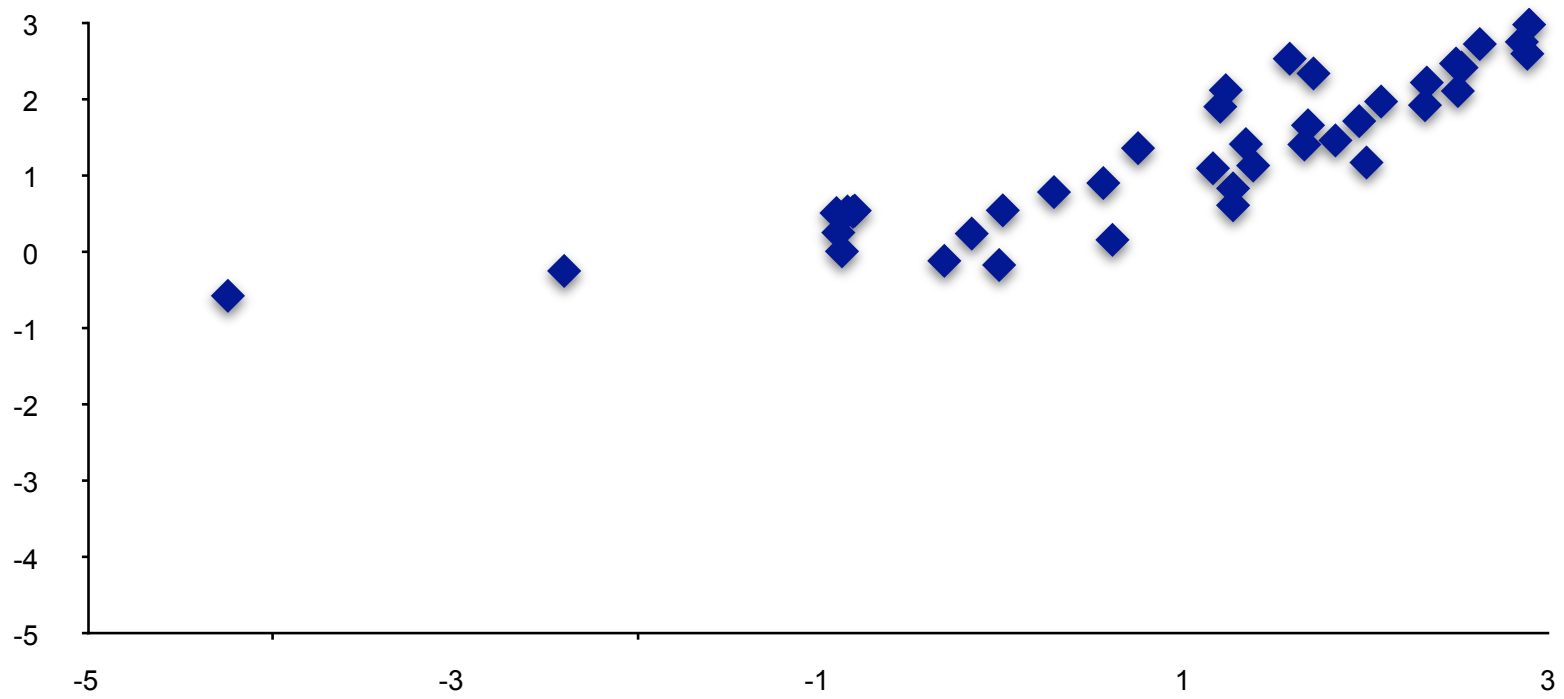


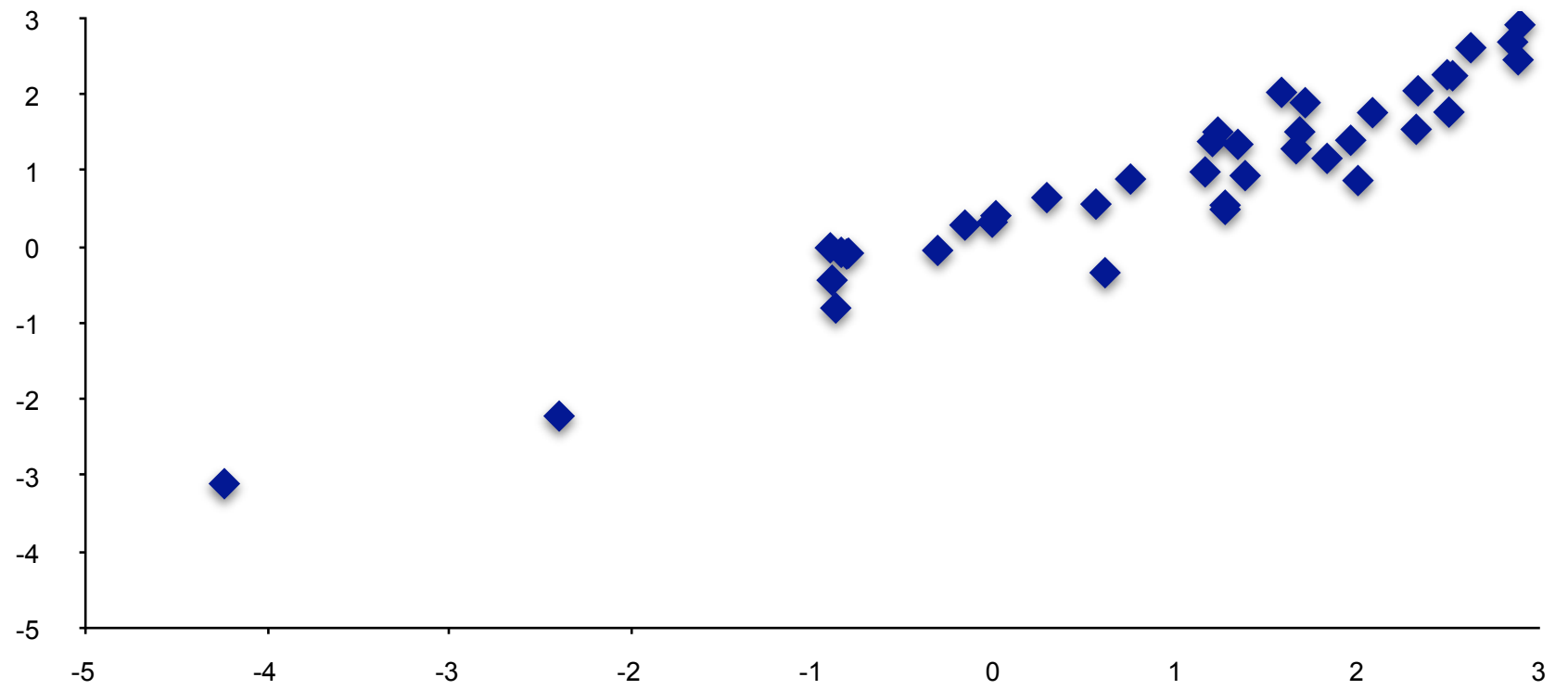


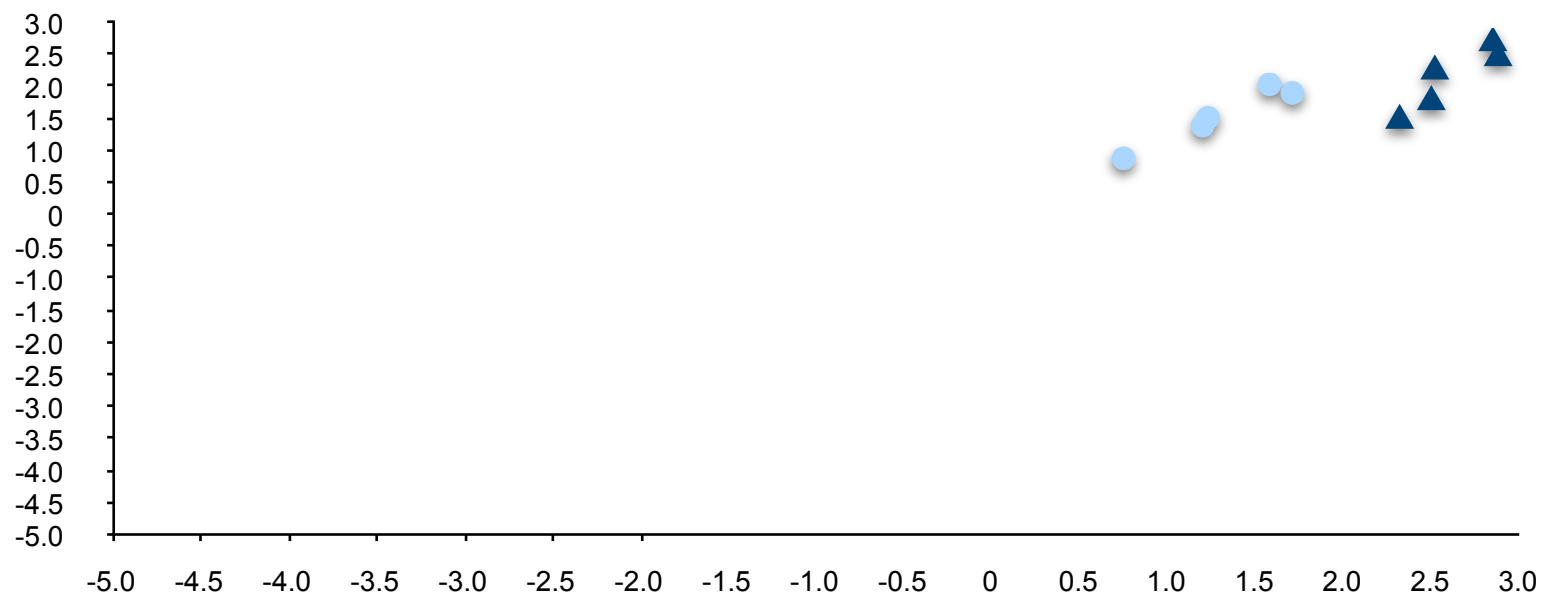


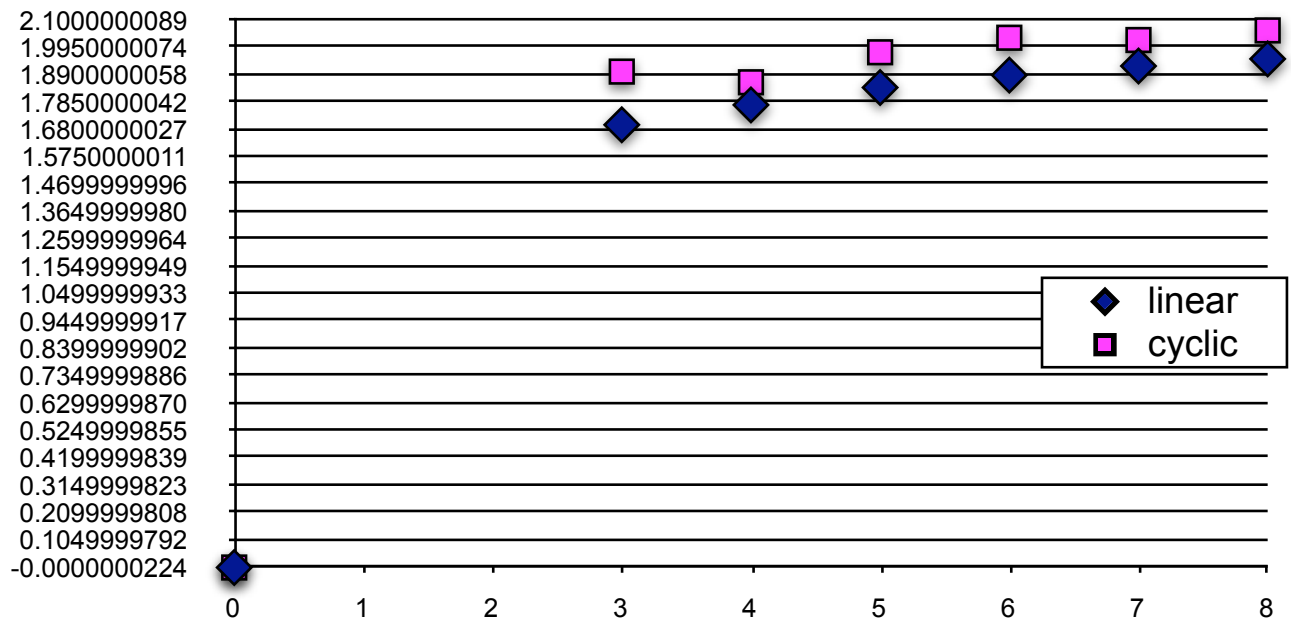


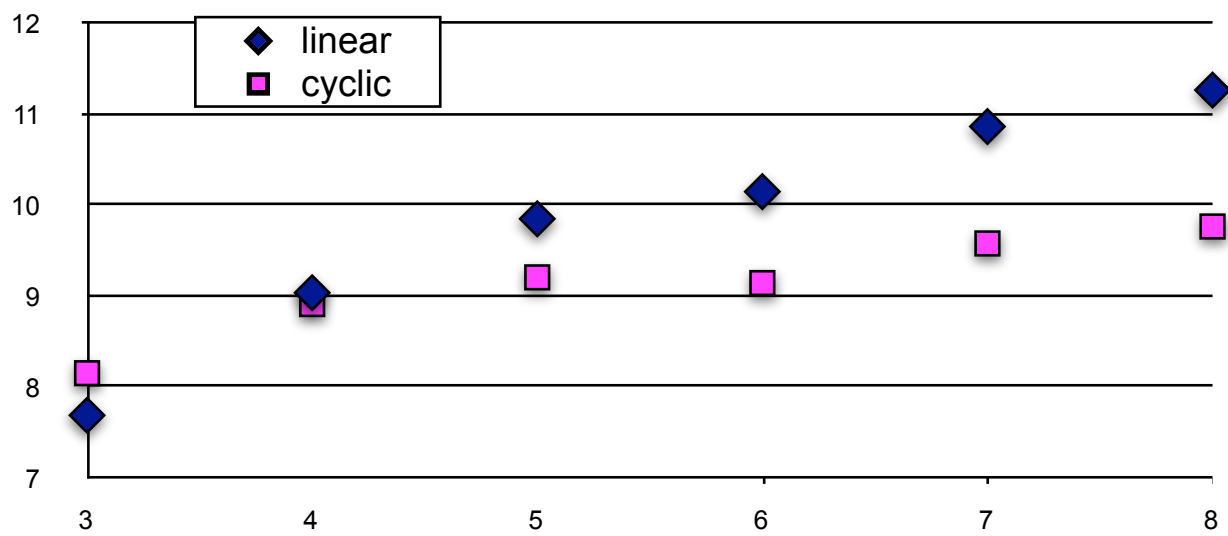


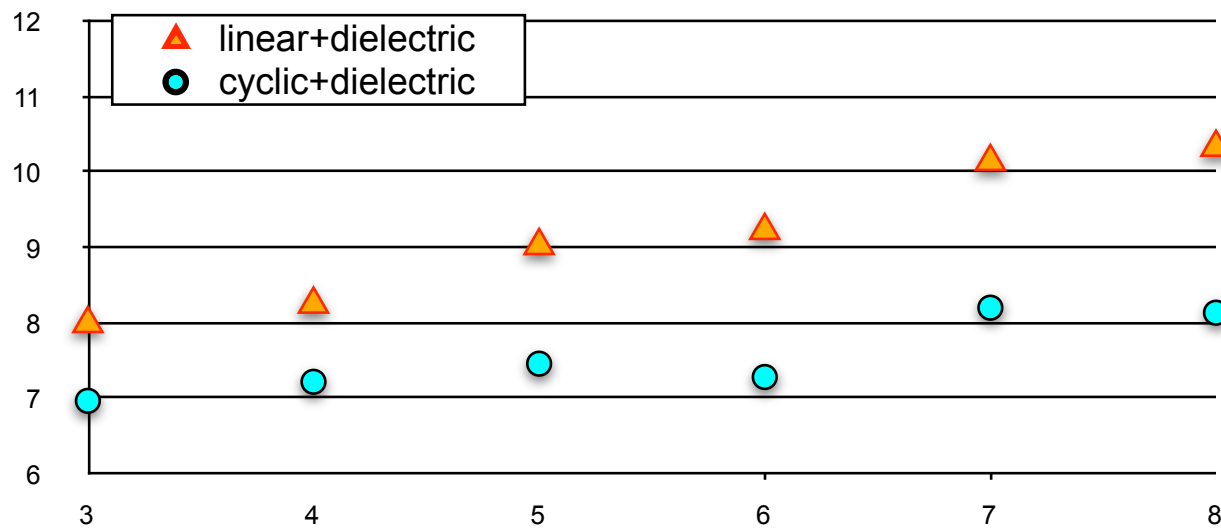


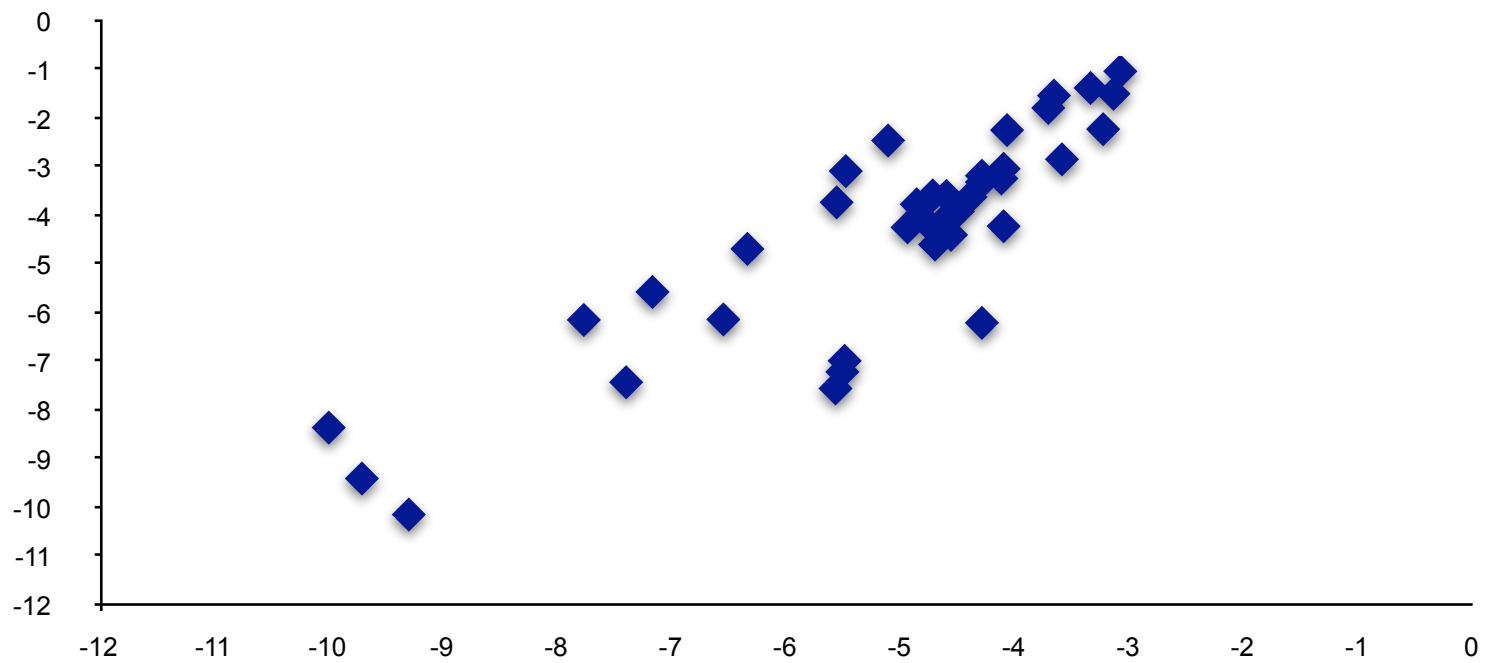


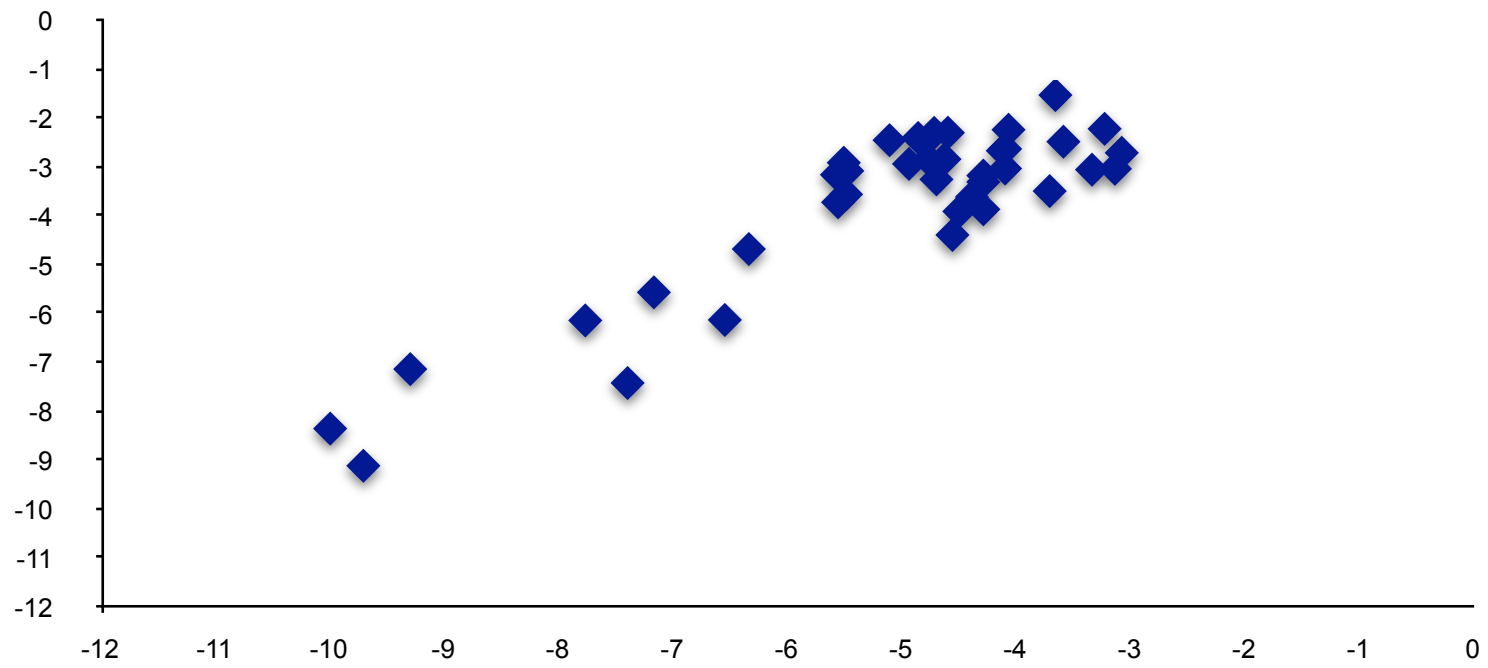


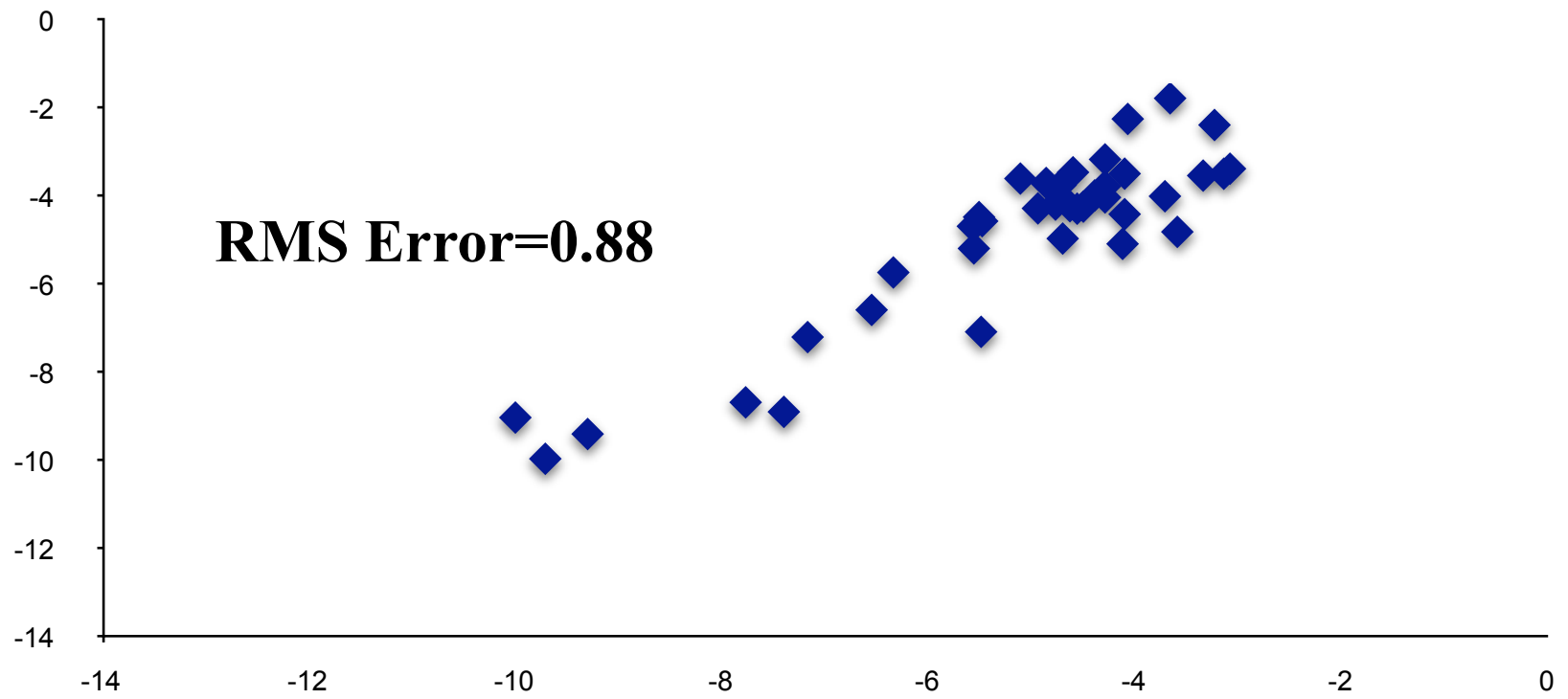


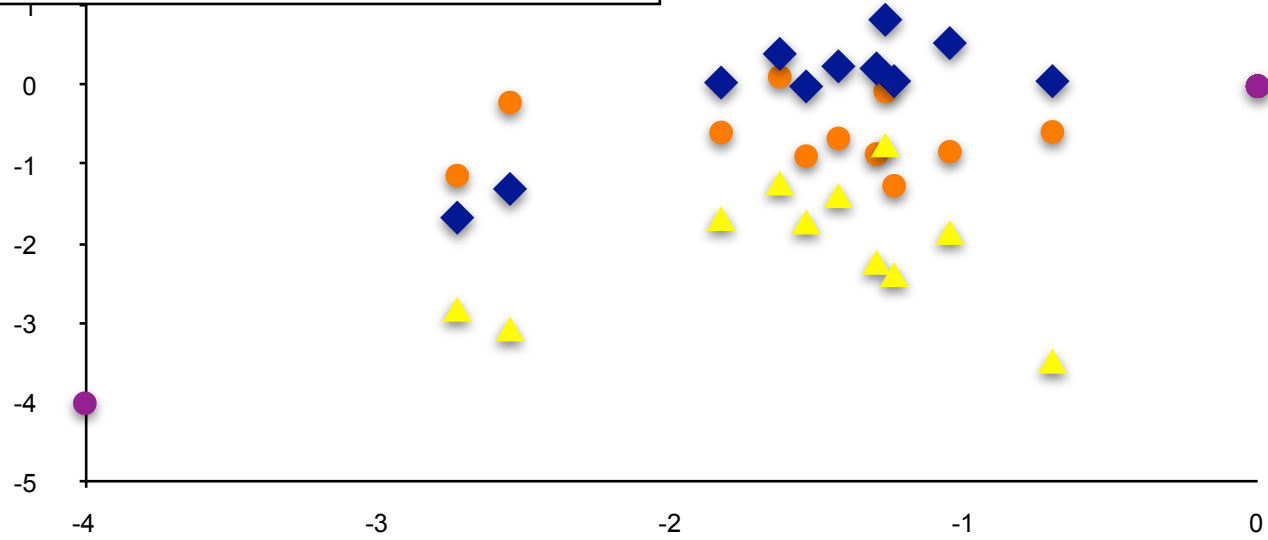
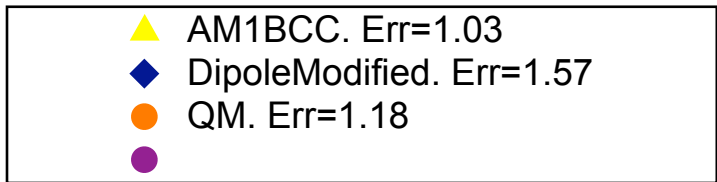


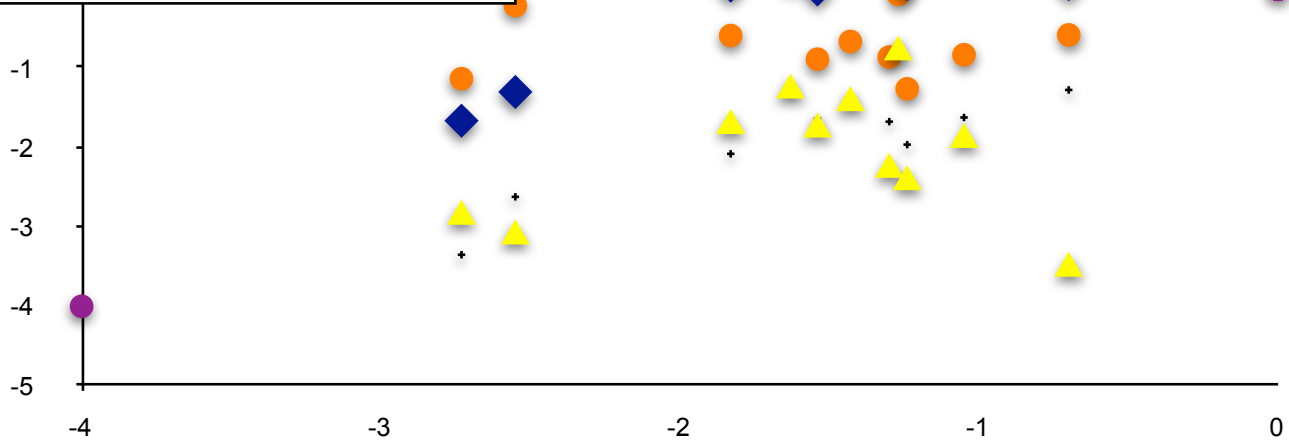
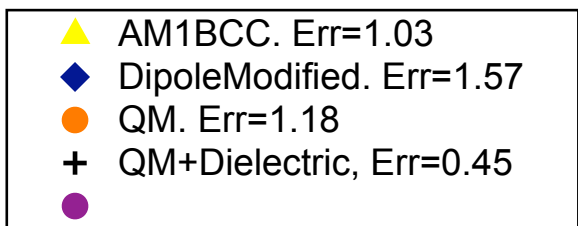


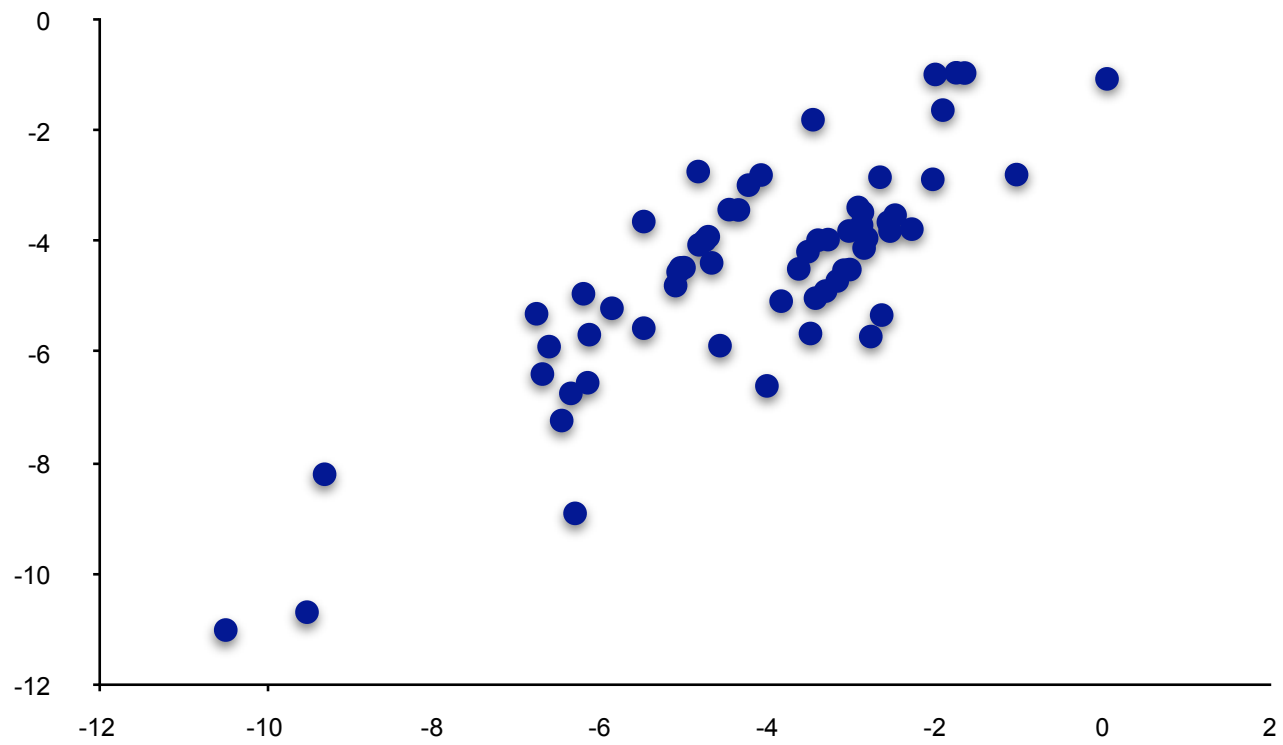


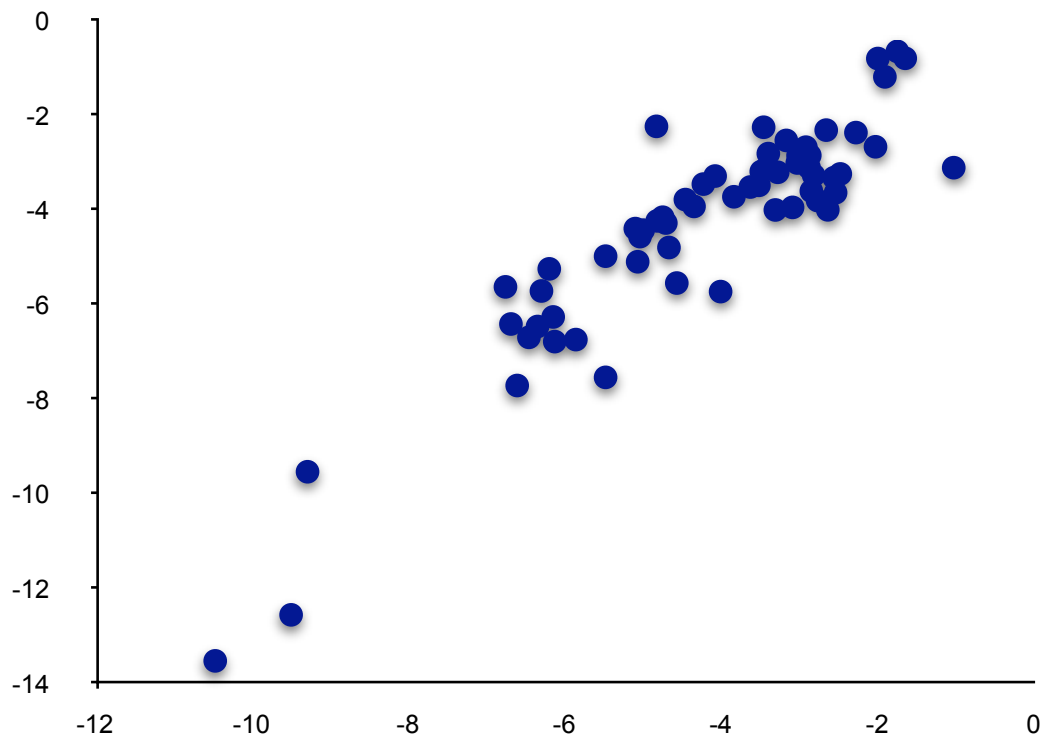






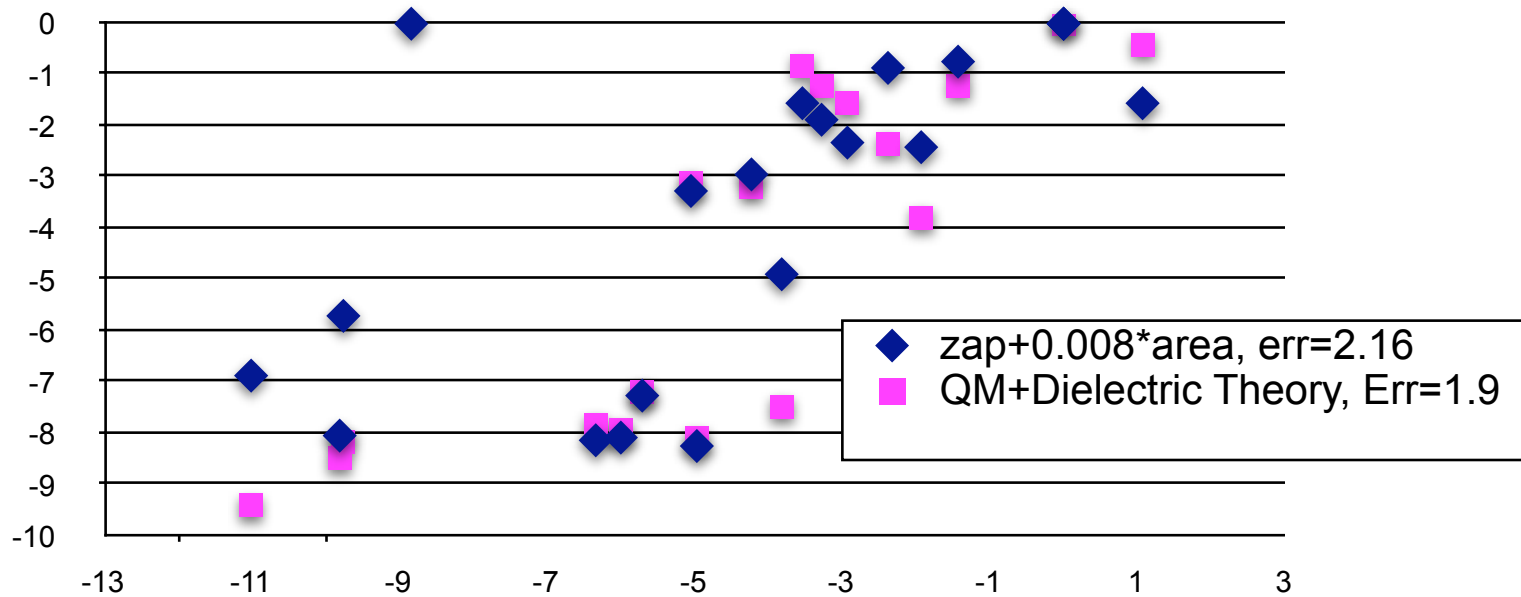






# Summary

class	#	AM1BCC + 10 cal/ A**2	cc_pVTZ AM1BCC +8cals/ A**2	+Dielectric Solvation +8cals/A**2	+Dielectric Solvation+ Hydrophobi c
alkanes	40	0.42	0.59	0.53	0.45
Oxys	61	1.24	0.95	1.12	0.99
N/Nitro	38	1.40	1.23	0.9	0.88
Thiols	11	1.03	0.81	0.35	0.45
Halides	50	1.30	1.40	0.76	0.59
Total	200	1.16	1.08	0.86	0.76



# Prospective Predictions?

- Salt effects on hydrophobicity
- Entropy/ Enthalpy prediction
- Temperature dependence
- Super-hydrophobicity



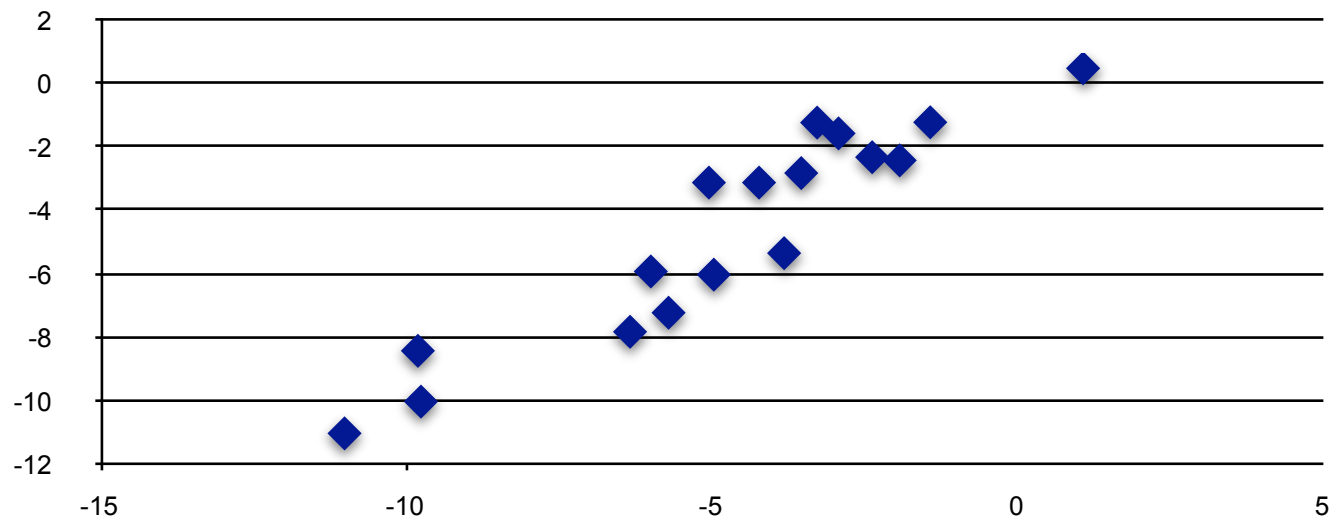
# Conclusions: Do I really believe?

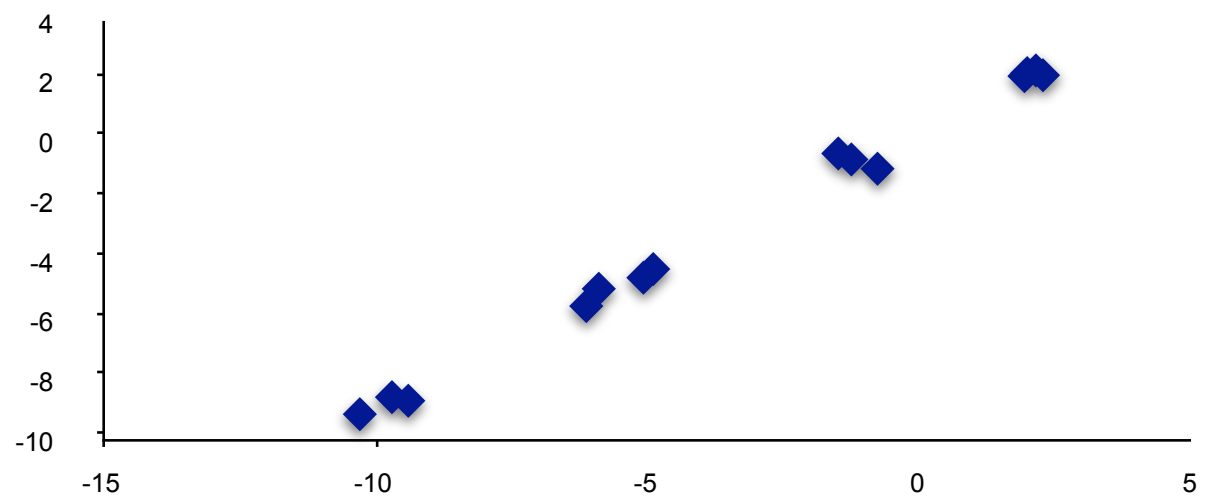
(“The first principle is that you must not fool yourself

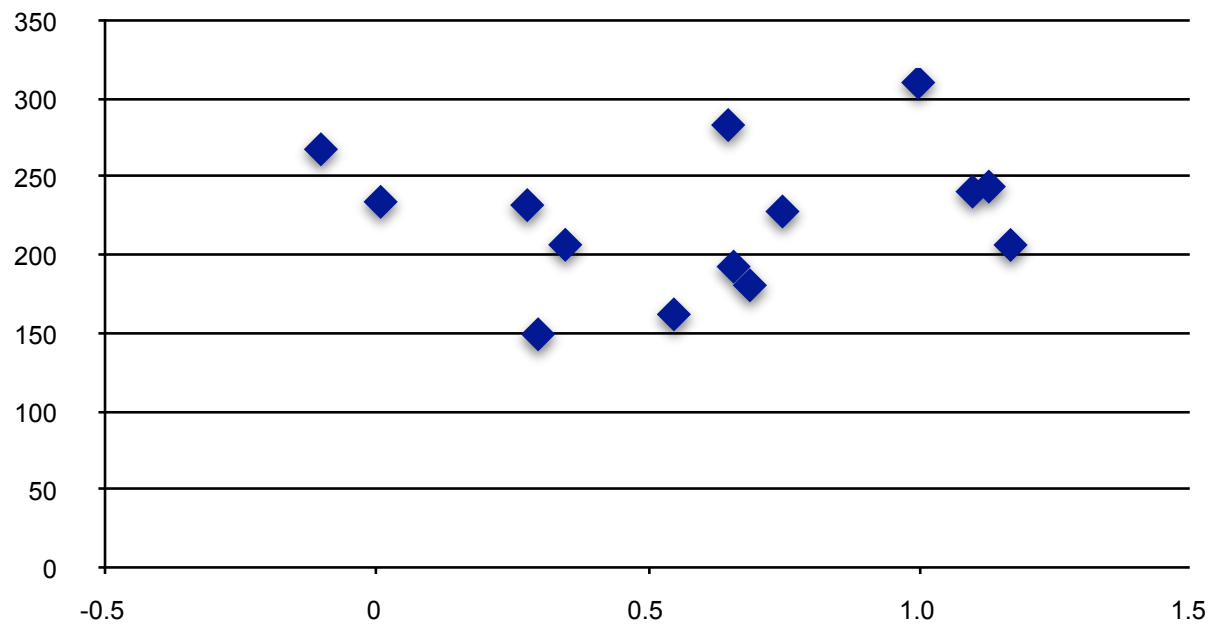
- It’s awfully sweet (NH<sub>3</sub>, SH<sub>2</sub>, Hydrazine, Pyridine, Biphenyl)
- Errors, e.g. benzene derivatives, make sense

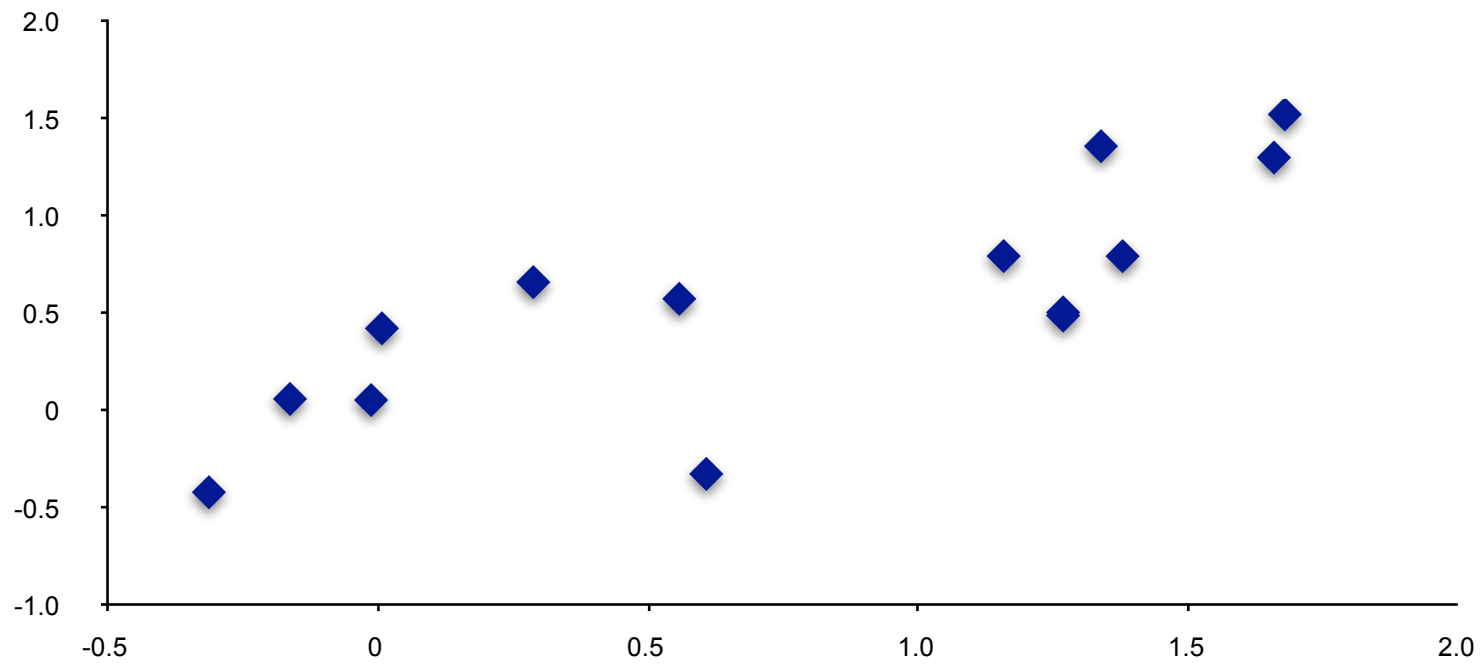
But:

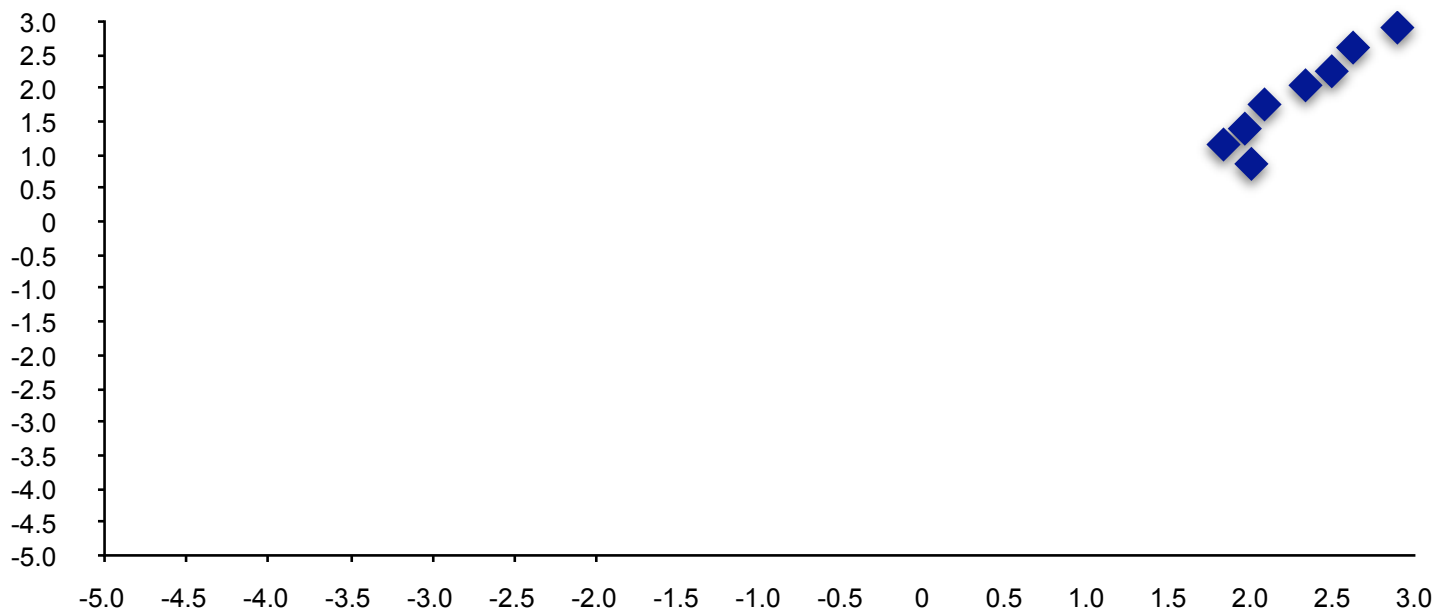
- No VdW
- Density corrections
- Different dielectric models
- Integrating over a volume
- Local dielectrics & much, much work to do
- Secondary, tertiary amines, ethers by HQ-Quantum



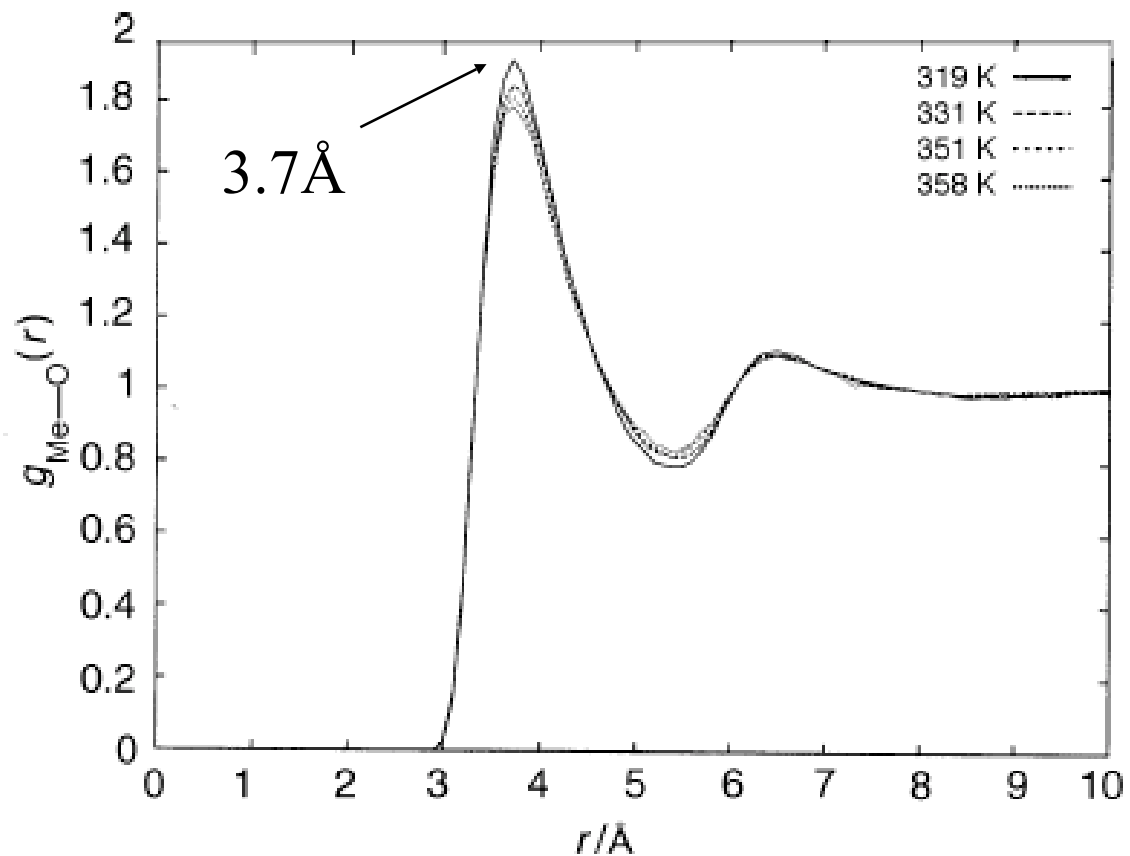






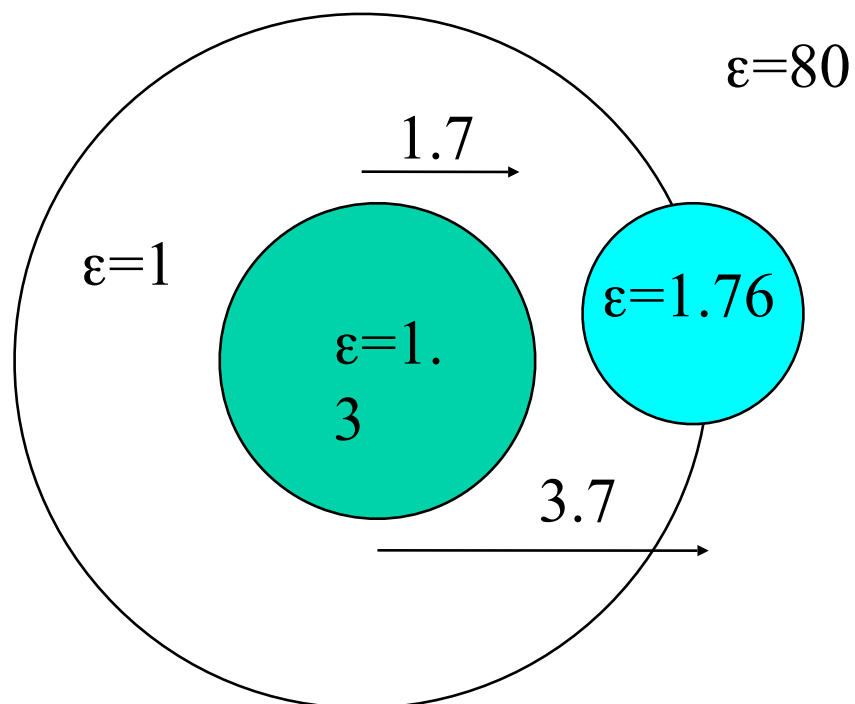


## Radial distribution function of water around methane



“The aggregation of methane in aqueous solution”  
R. L. Mancera, A. D. Buckingham and N. T. Skipper  
J. Chem. Soc., Faraday T rans., 1997, V ol. 93

# Methane 'cavity'



Cavity Area ~ 185 Å<sup>2</sup>

Cavity Dispersion ~ 10 cal/Å<sup>2</sup>

Predicted Solvation ~ 1.85 kcal, Expt = 2.0 kcal