

Why is Quantum Mechanics not more useful?

Can QM get us to heaven*?

Tom Darden
OpenEye

*heaven: a place where chemical accuracy is found



Outline

- Old School QM
- DFT
- Examples of problems with current QM
- How is QM used in pharma today
- How costly is it--can it be made faster?

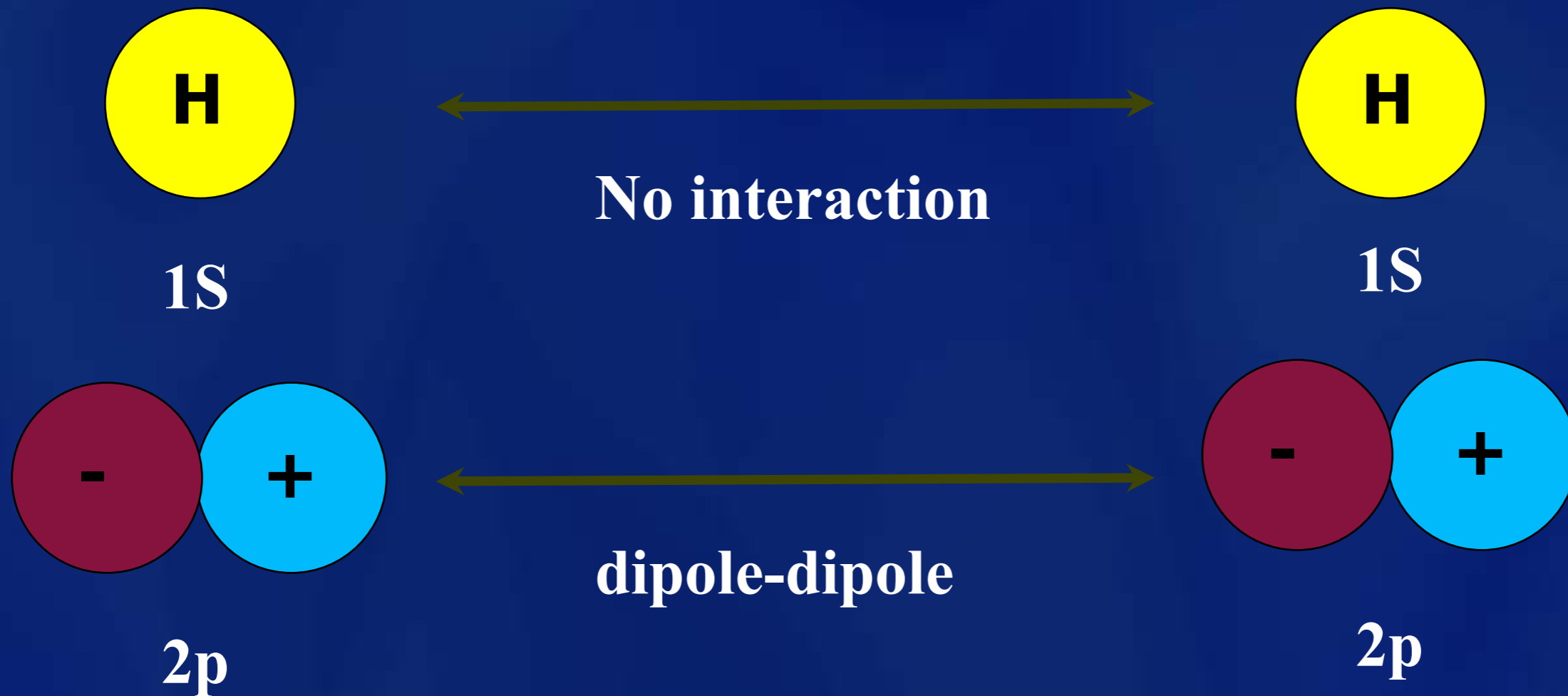


How to get dispersion?

Can't get accurate nonbonded interactions
without accurate dispersion

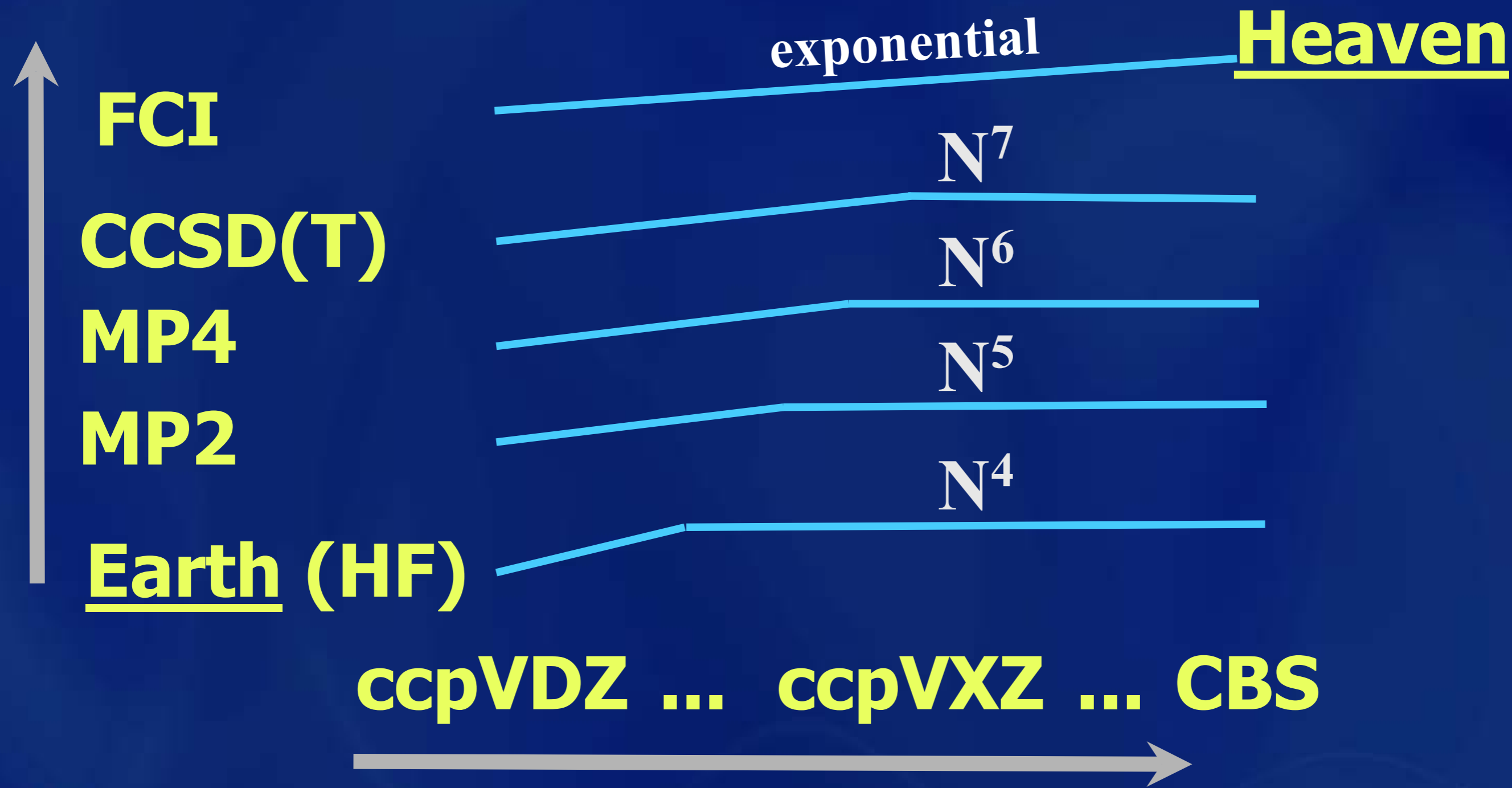


Use some unoccupied orbitals



Problem: # Relevant Combinations of occupied, unoccupied orbitals is really large for big systems

How to get to Heaven (the hard way)



A shortcut: To get to heaven, just need to find XC functional

According to W. Kohn, (Nobel-Prize for this) the electronic energy $E[\rho]$ can be expressed

$$\begin{aligned} E[\rho] = & \text{(electronic) Kinetic energy}[\rho]** \\ & + \text{(elec-elec) Coulombic energy}[\rho] \\ & + \text{(nuc-elec) Coulombic energy}[\rho] \\ & + \text{Exchange-Correlation}[\rho] \end{aligned}$$

** Actually you use orbitals here



How to get XC[ρ], thus -> heaven

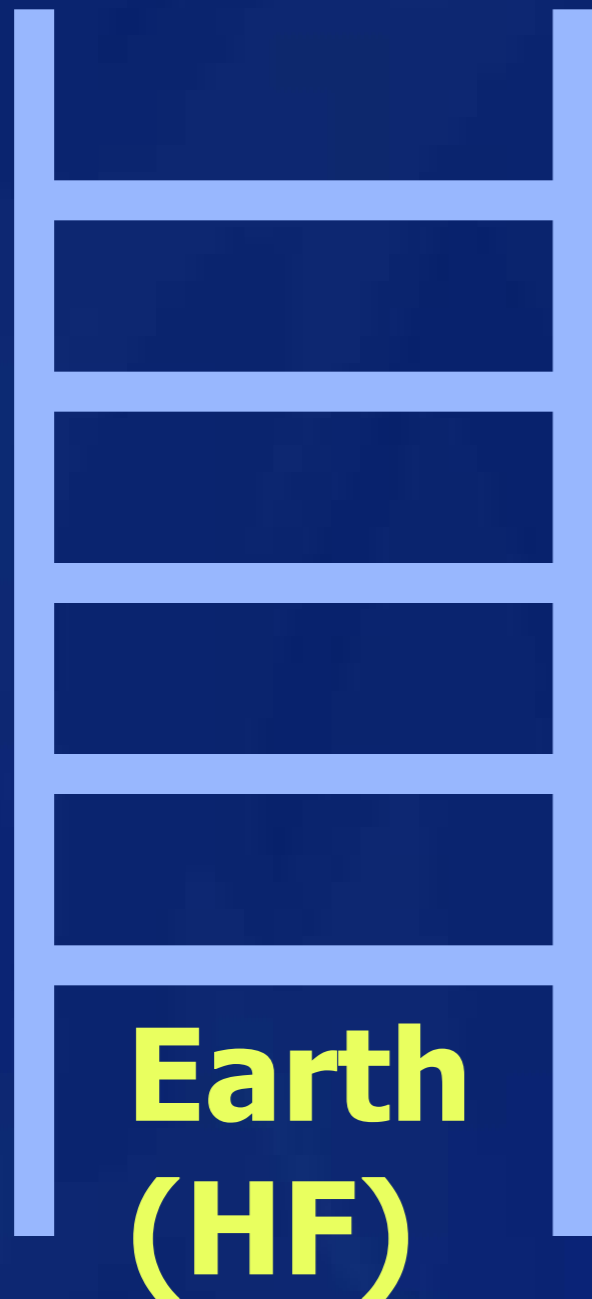
Strategy A: Use Physics: Get values of parameters from physics based constraints

LDA or LSD XC based rigorously on physics of uniform electron gas: no(!!!) fitting to data

J. Perdew, K Burke: extend this approach to GGA XC[$\rho, \nabla\rho$], meta GGA (KE density)--no fitting to data!

To Get to Heaven(XC), add more physics (Jacobs ladder approach)

Heaven



fully nonlocal --future

hybrid meta GGA

meta GGA

GGA

LDA

**Earth
(HF)**



To Get to Heaven, why not cheat?

Motivation: "Genome-wide structure-based drug design"

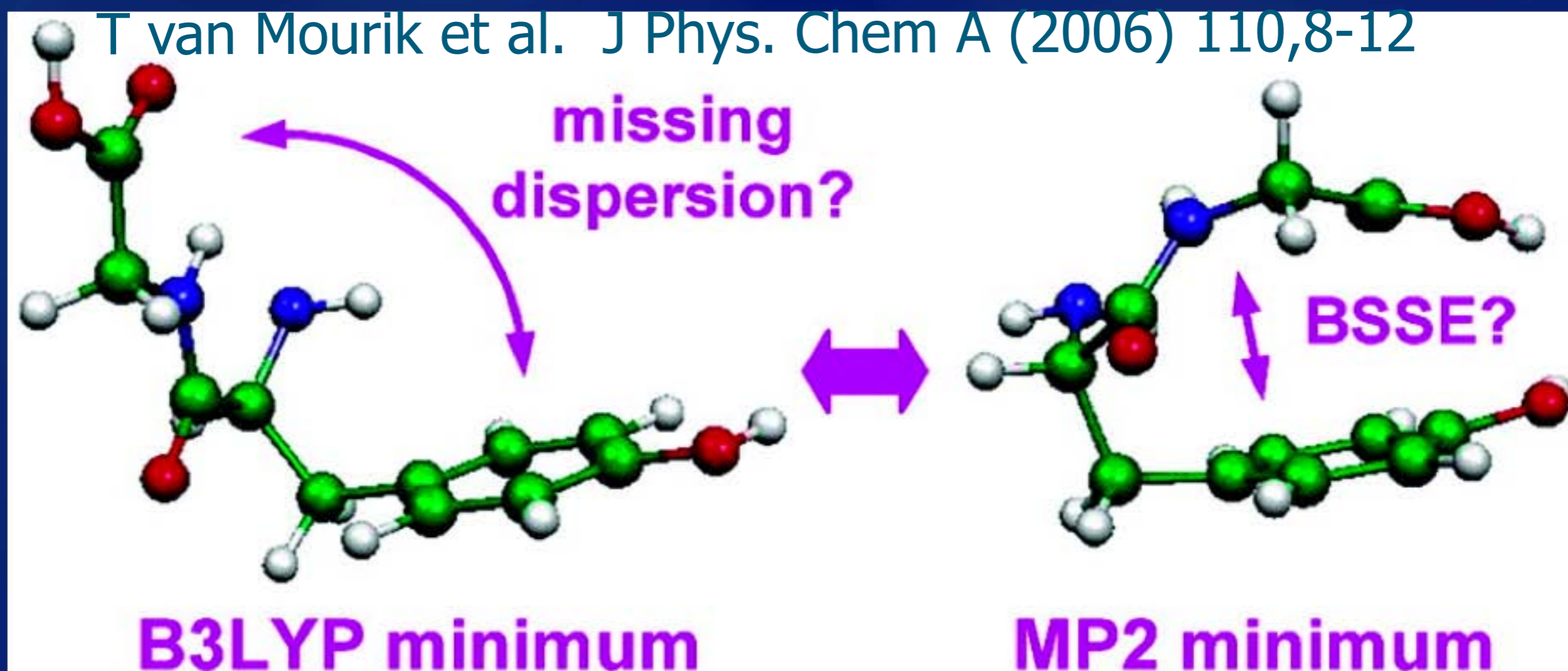
"Combining $F^X(s)$ with the LYP correlation functional leads to **XLYP**, where the mixing parameters were determined through a **least-squares fitting** to the total energies of 10 atoms {H,...,Ne}; the IPs for 16 atoms {Li,...,Ar}; the EAs for 10 atoms {H,...,Cl}; and the atomization energies for 38 molecules {H₂,...,CS₂}".

"In particular, we include He₂ and Ne₂ as representative van der Waals systems."

However, Hartree-Fock or DFT (LDA,GGA, Hybrid GGA) should(!!!) give **incorrect** atomization energies for helium or neon dimers. (Note XLYP, X3LYP fail e.g. at DNA stacking)



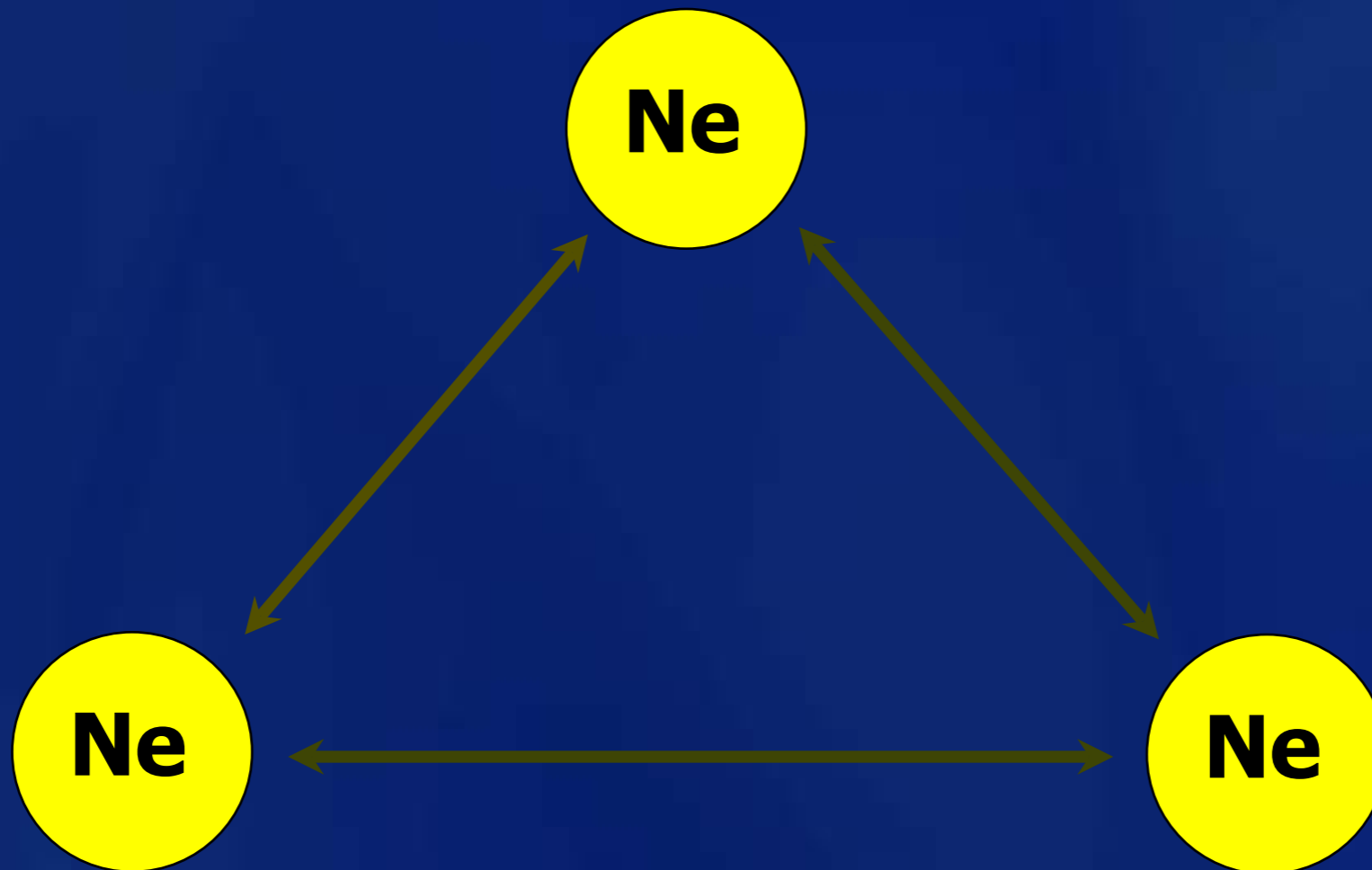
Problems with QM for Tyr-Gly conformational analysis

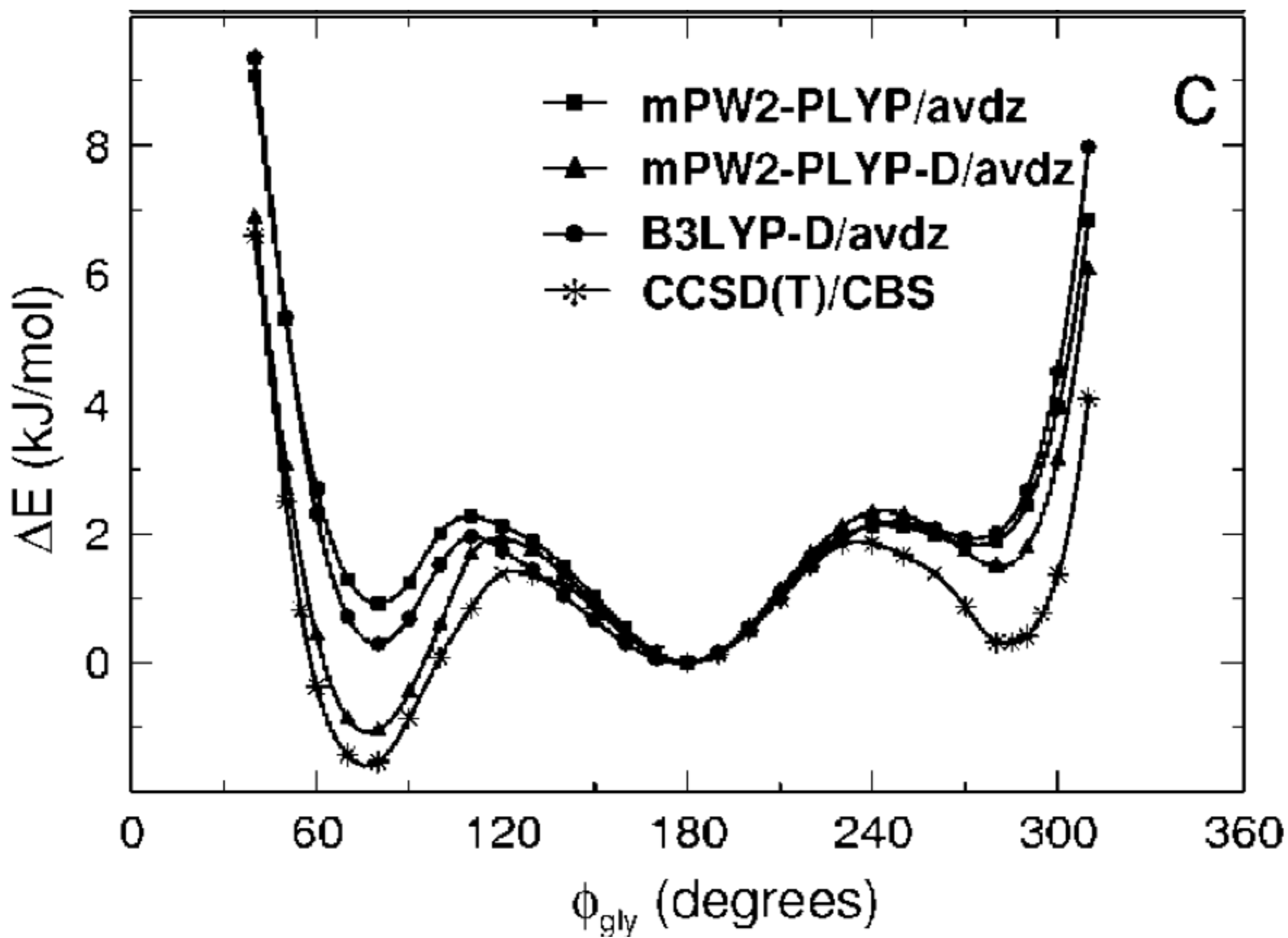


Solution for DFT: add empirical dispersion
Solution for MP2 BSSE: Local MP2

Does empirical dispersion fix DFT?

Tkatchenko, von Lilienfeld; Phys Rev B 78, 045116





JCTC 4,1610 (2008)

B3LYP: How to get to heaven (or at least get past the reviewers)

from "Obituary: Density Functional Theory (1927-1993)"

Aust J Chem 2001, 54, 661-662 , Peter MW Gill

... it (B3LYP) has since attained cult status and has a huge following, particularly among organic chemists. It has recently applied to become a religion.



Summary so far:

- For (typical) cases where HF is not too far away from heaven, MP2 and other perturbative approaches are reliable but need large basis sets, and are otherwise too expensive
- DFT is competitive with MP2 at much lower costs, except for dispersive interactions. Adding empirical FF dispersion term is likely the best fix for now.



What role does QM play in drug discovery/development?

Out of 17 respondents:

<i>conformational scan --strain energy</i>	17
pKa's	9
tautomers	7
charge assignment	7
FF parametrization	2
reaction energies	5
transition states	2
<i>interaction energies</i>	5
<i>polymorph prediction</i>	1
qualitative features	9



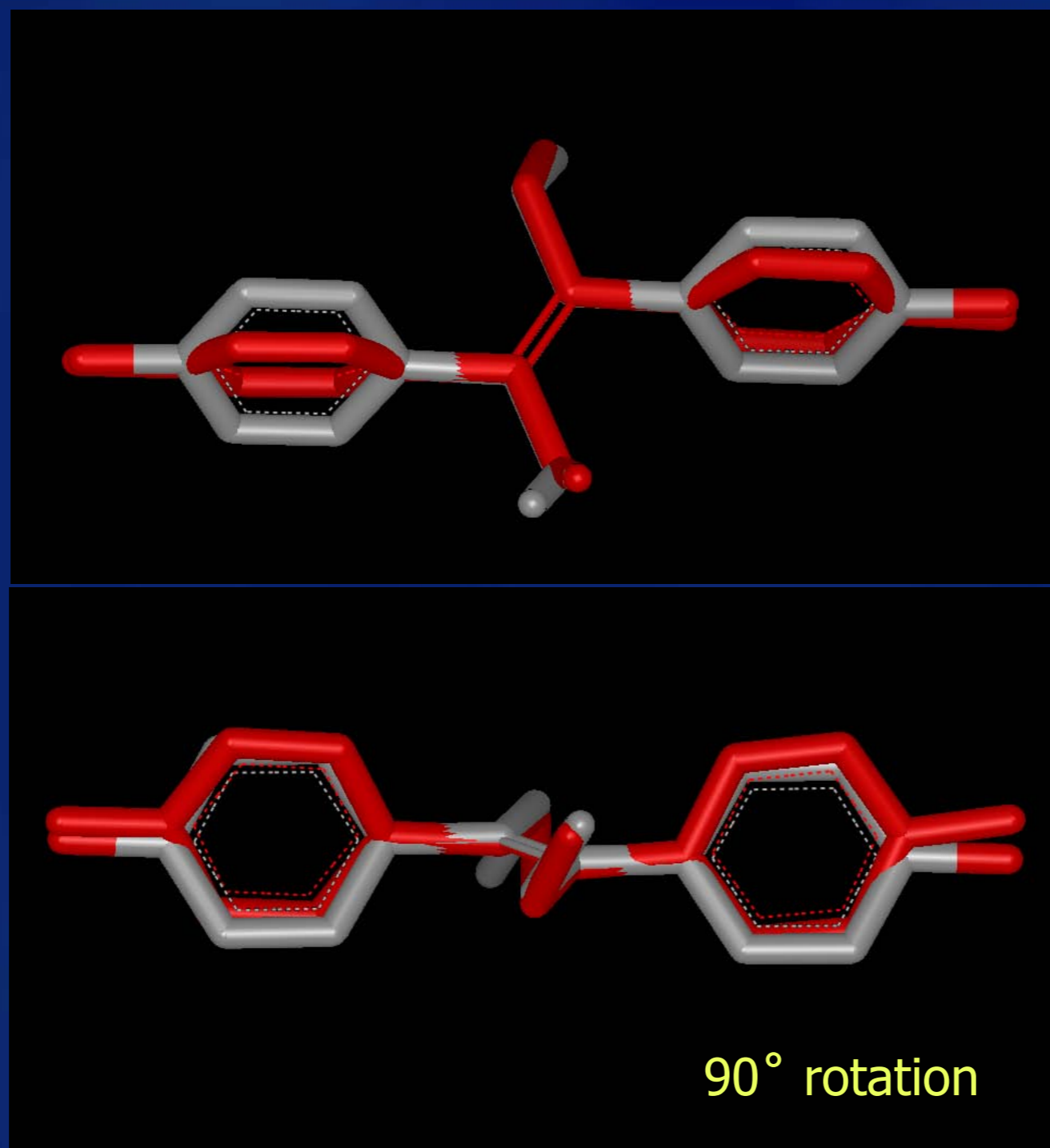
My first modeling project

Conformational analysis of DES

JACS: (1986) T. Darden,..,AT Maynard,..



DES: CSD vs ERa-bound form



Decided to redo calculations-- B3LYP 6-31g* (Santa Fe 2009)

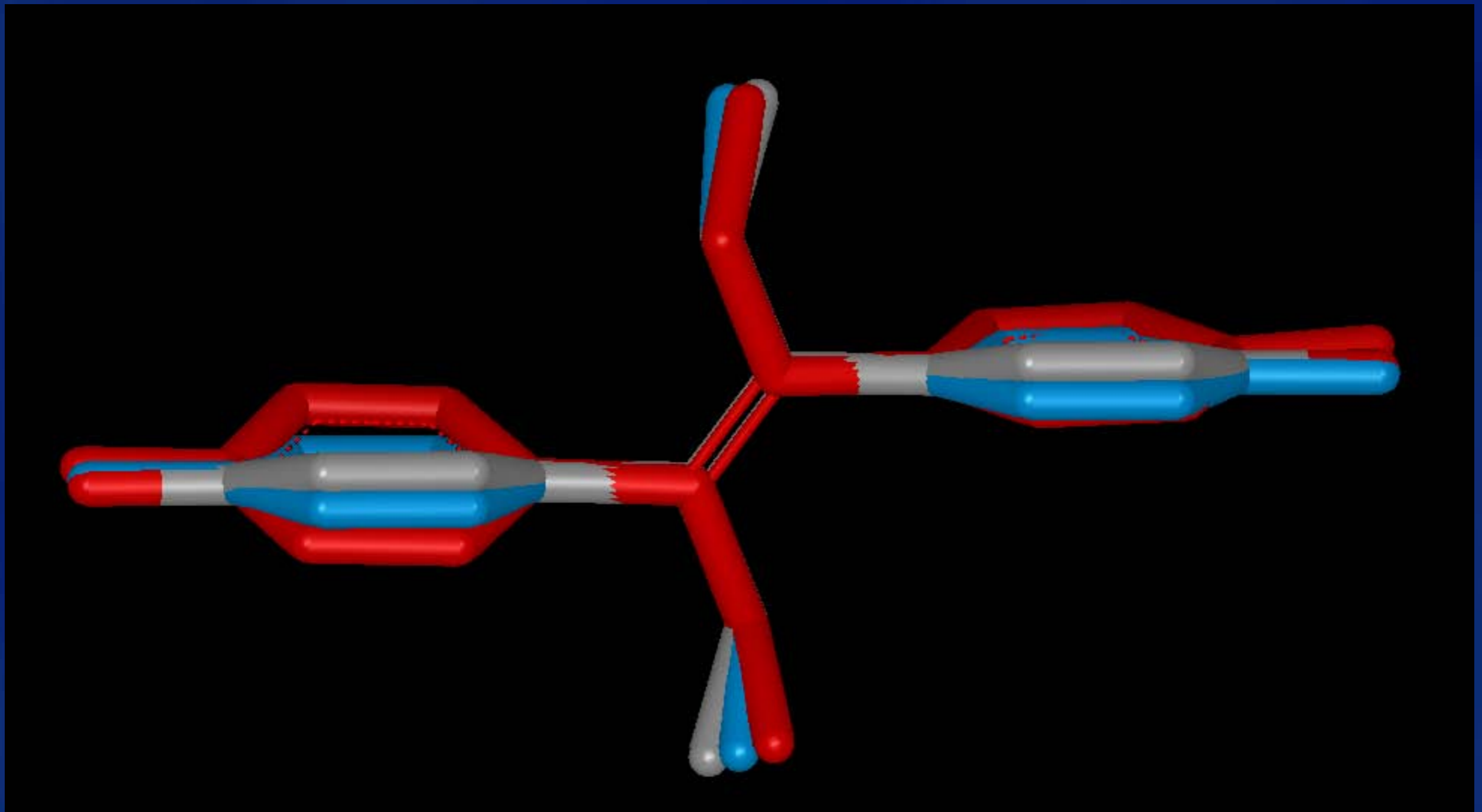
keeping in mind that

“Every calculation based on experience elsewhere, fails in New Mexico”

Lew Wallace, Territorial Governor
1878-81 and author of Ben Hur



DES: CSD (~6,7 kcal), **ERa** (~3.5, 0.6 kcal),
rel to B3LYP 631-g* gas phase min.



Quantitative structure–activity relationship of phenoxyphenyl-methanamine compounds with 5HT_{2A}, SERT, and hERG activities

Scot Mente *, Randall Gallaschun, Anne Schmidt, Lorrie Lebel, Michelle Vanase-Frawley, Anton Fliri

Pfizer Global Research and Development, Groton Laboratories, 1 Eastern Point Road, Groton, CT 06355, USA

Bioorganic & Medicinal Chemistry Letters 18 (2008) 6088–6092

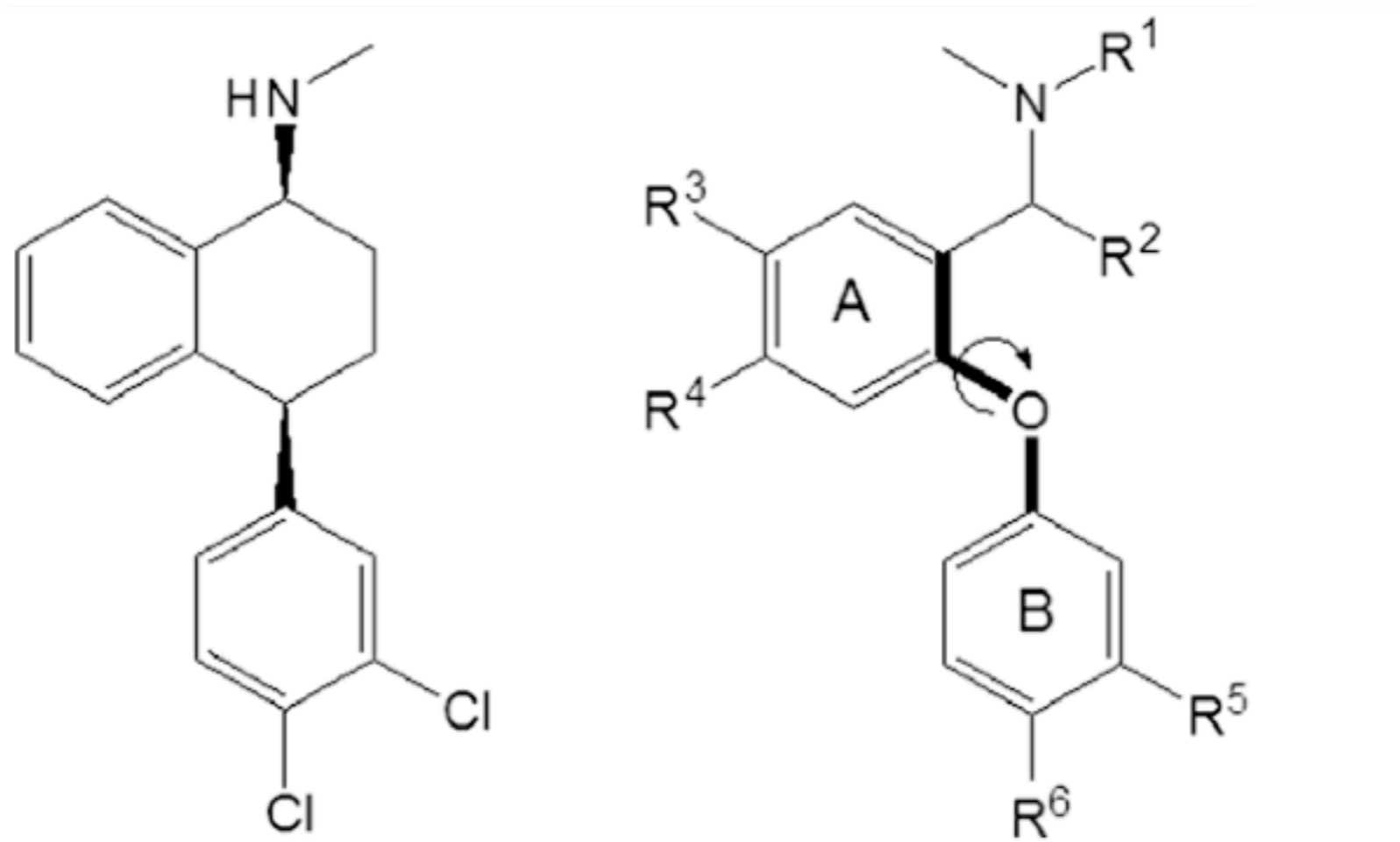
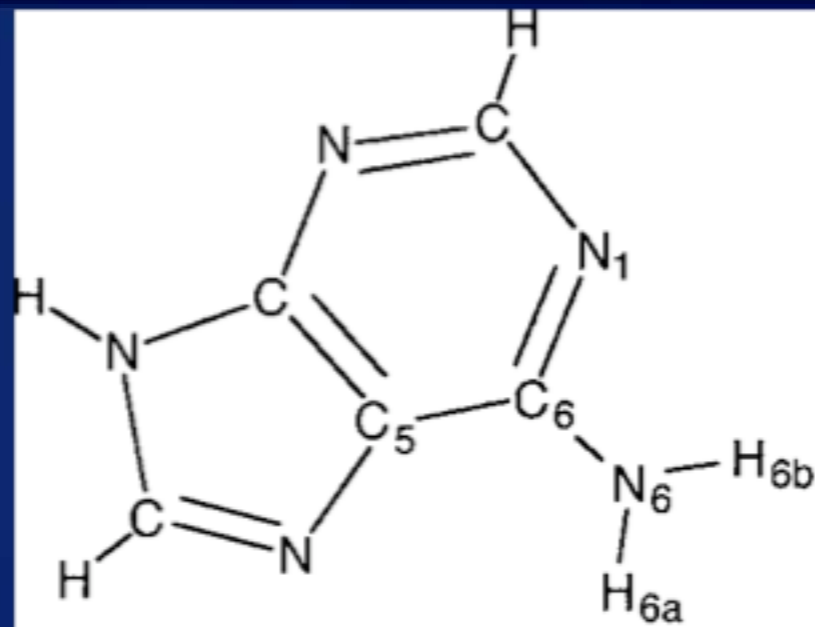
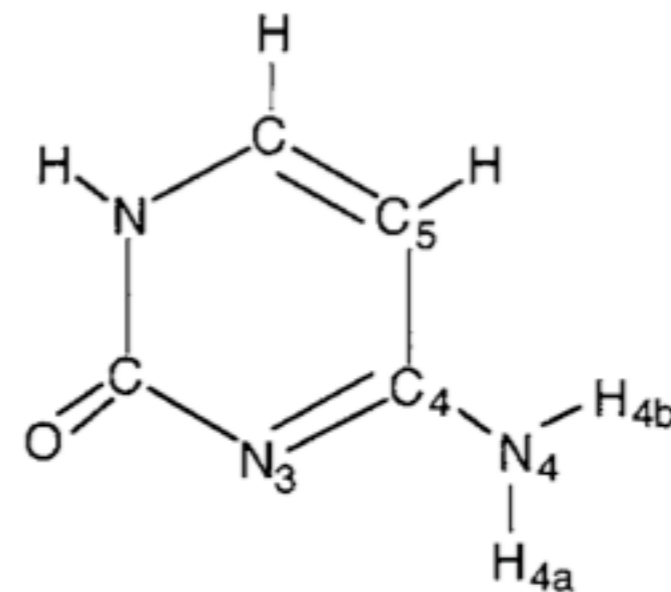


Figure 1. Sertraline (left) and the flexible PPMA scaffold (right).

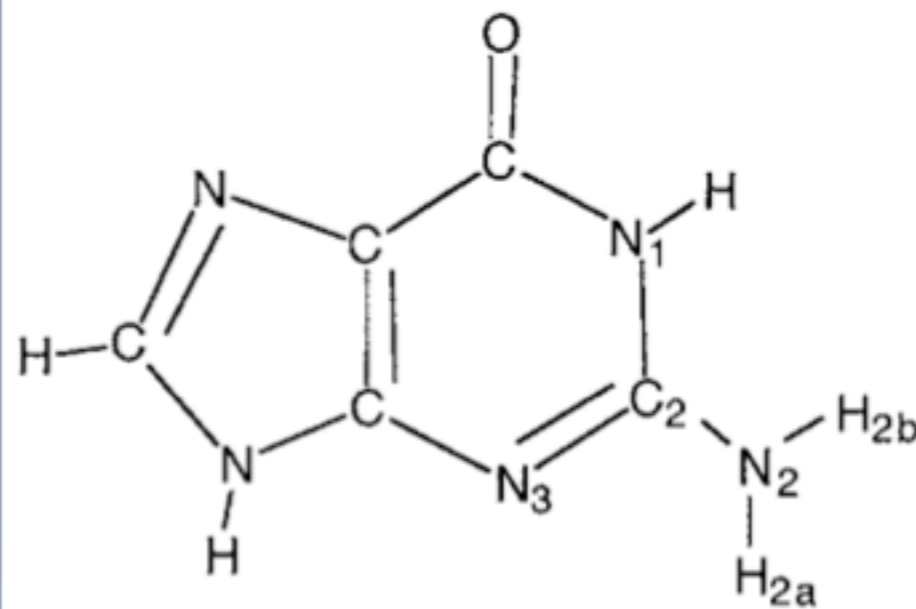
Are the nucleotides planar?



Adenine



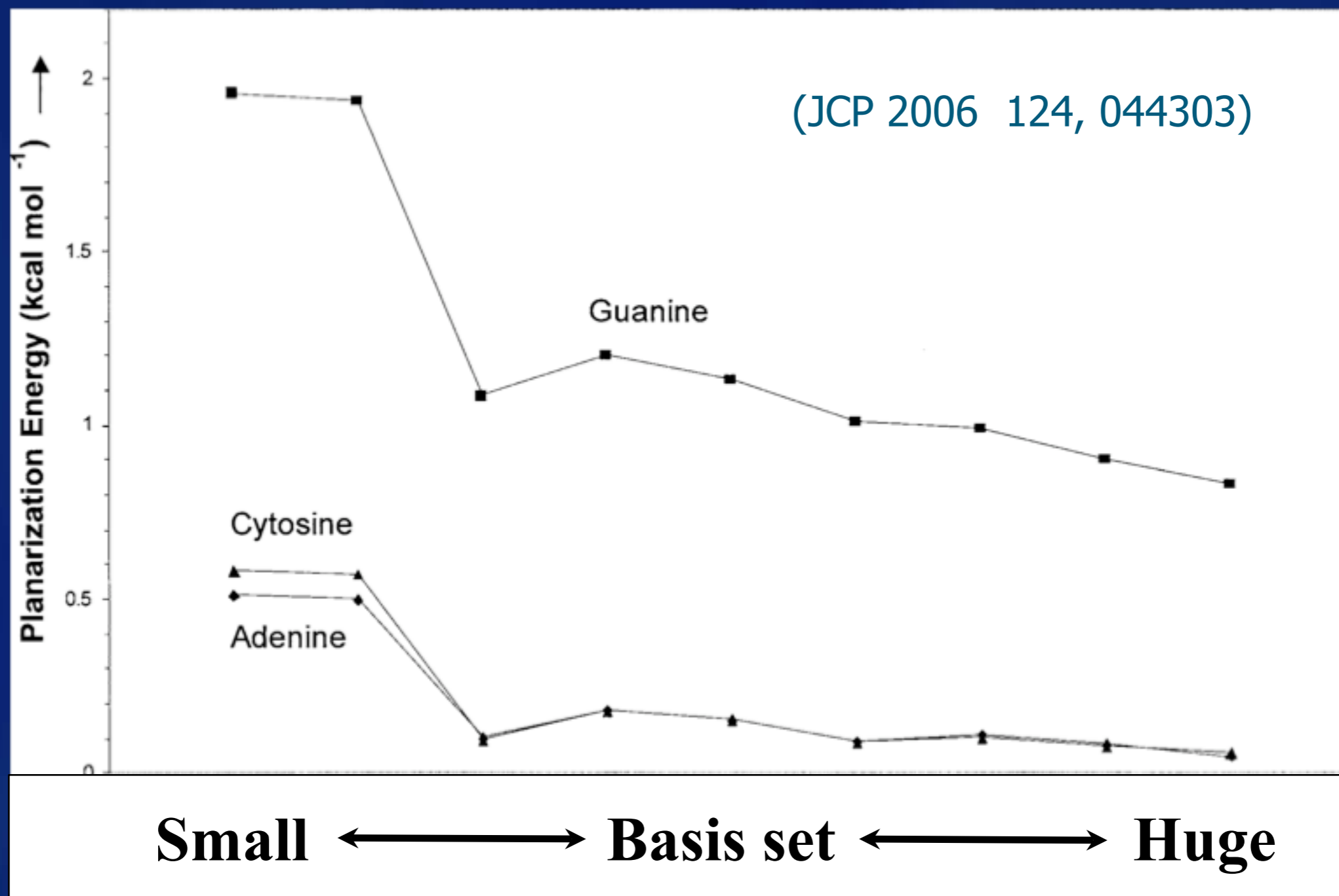
Cytosine



Guanine

Nucleotide planarization barriers

MP2 barriers vs Basis Set

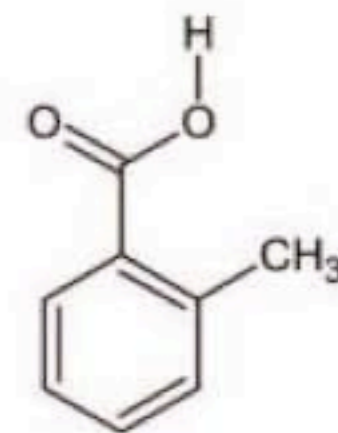
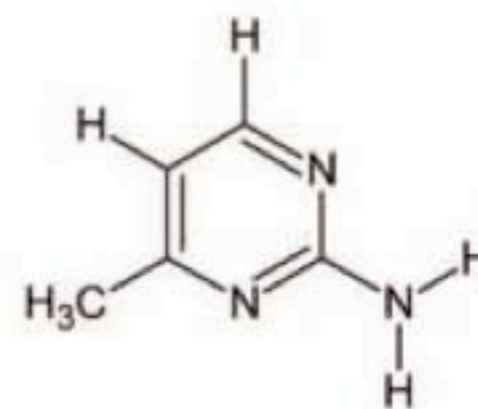
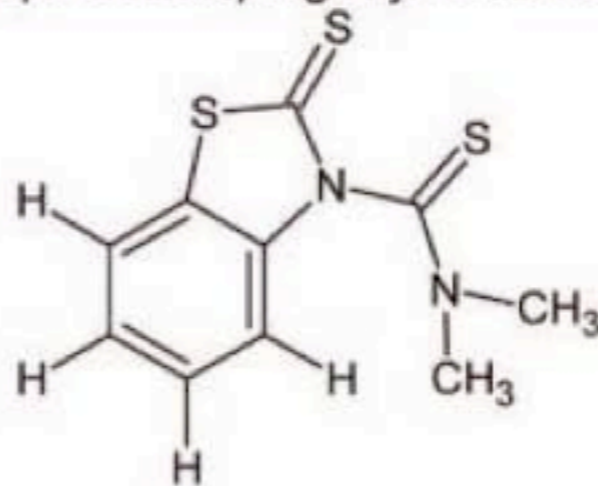
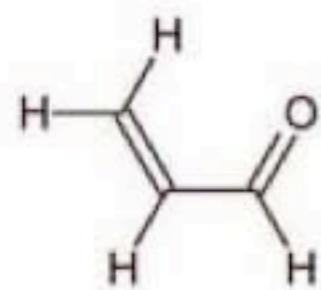


QM in Polymorph prediction

Acc. Chem. Res. (2009) 42, 117 SL Price

latest CSD Blind Test of polymorph prediction

Molecular diagrams sent to groups developing crystal structure prediction methods



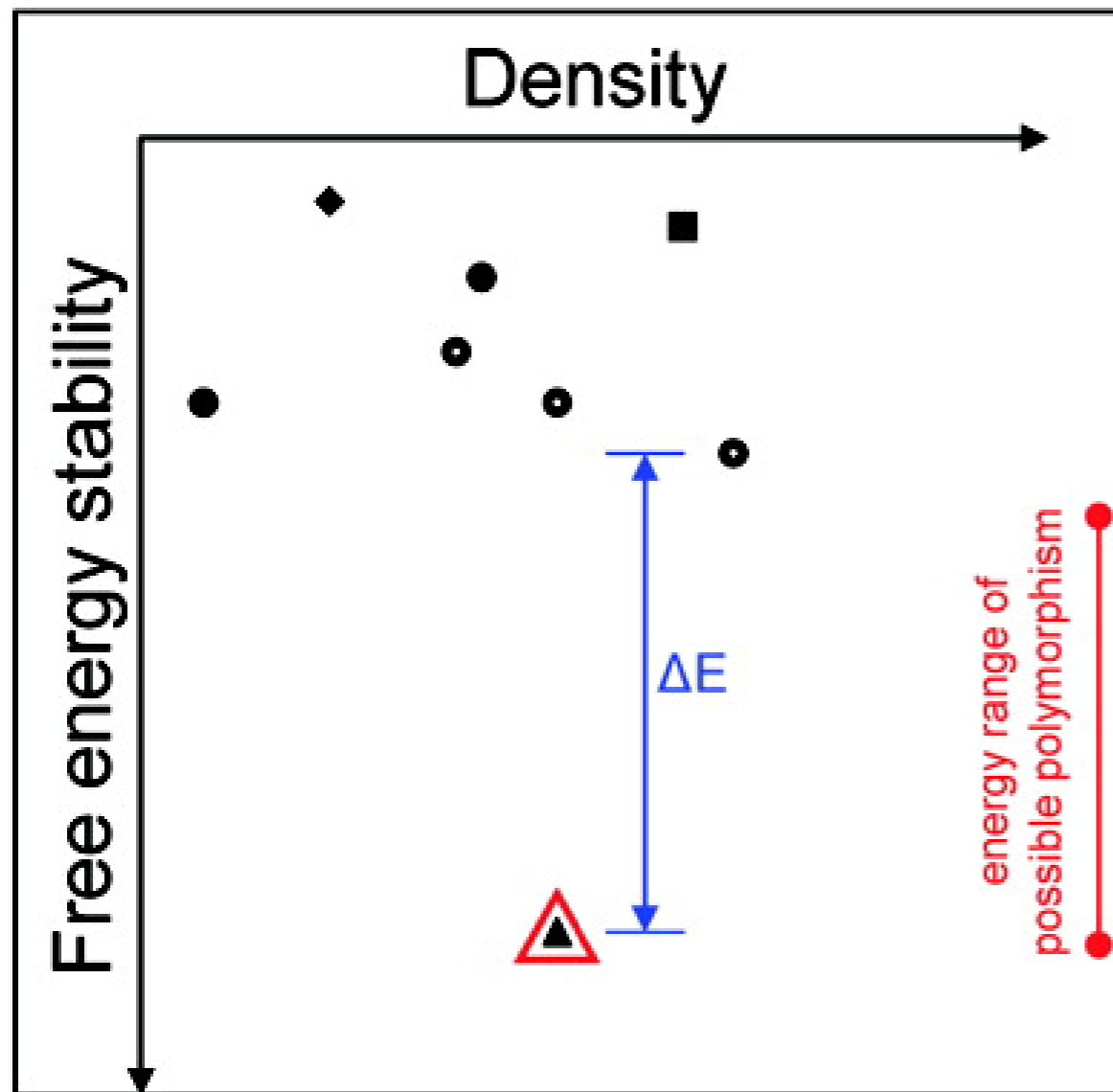
Groups invited to submit 3 "predictions" of the unpublished structures

Best results: plane-wave DFT plus empirical dispersion (4 out of 4)

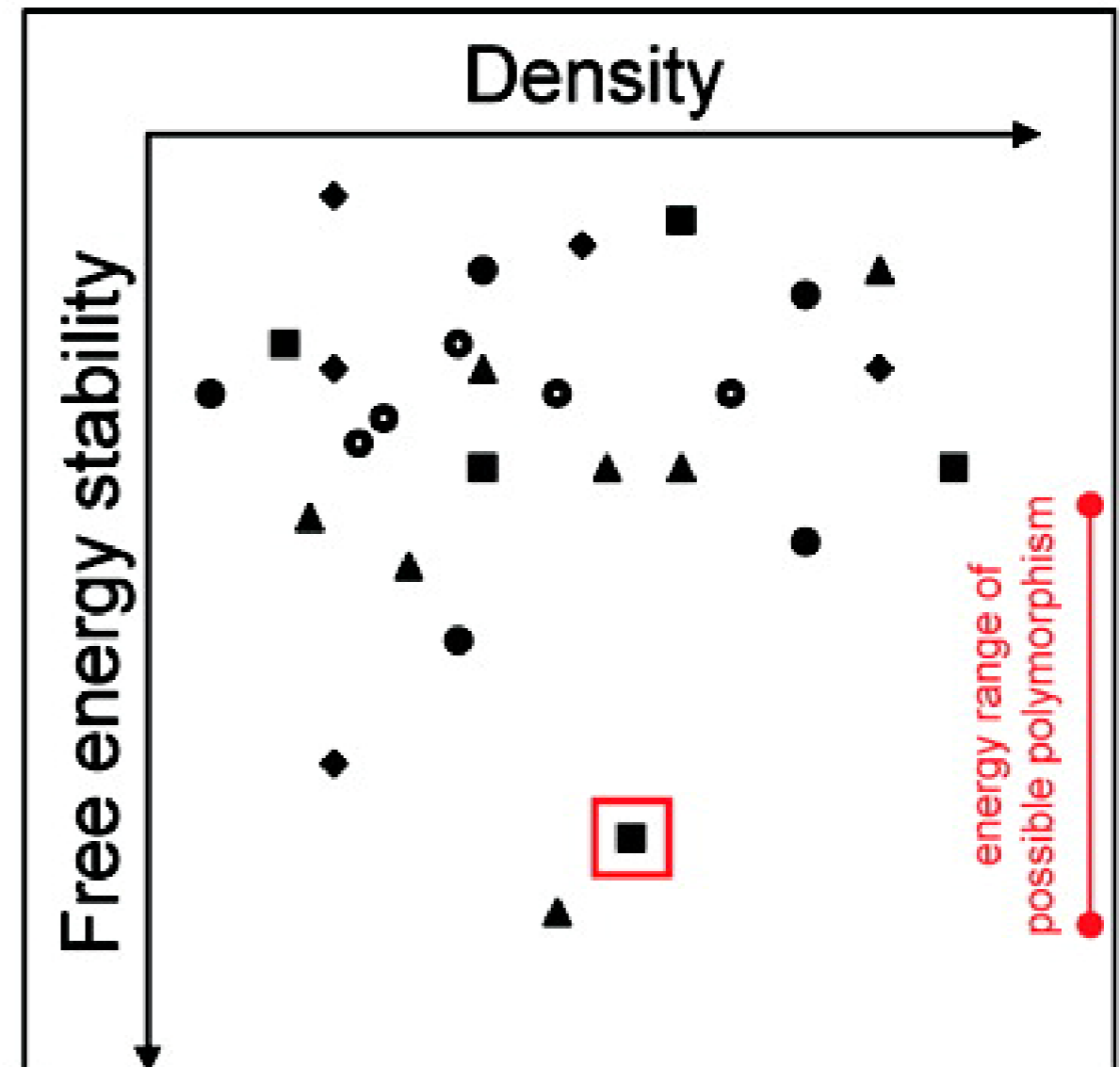


Using polymorphism calculations to complement screening

Monomorphic



Predictive

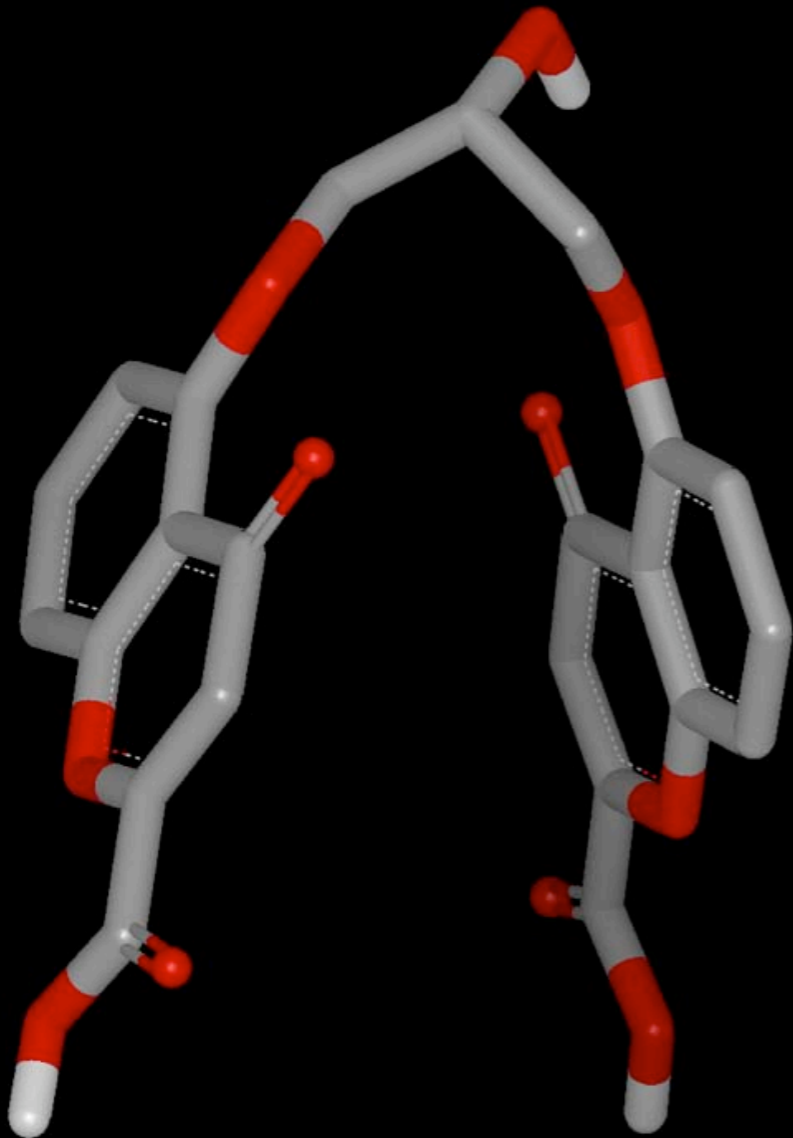


Computational Cost of QM

- How expensive is DFT for Drug size molecules?
- What are the prospects to make it faster?



Timings for 1 step in DFT SCF (usually need ~ 10 steps to converge)



Cromolyn:

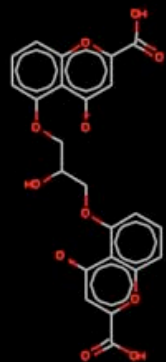
34 heavy atoms, 16 Hydrogens
242 electrons

6-31G* 542 ao functions
 236 shells

cc-pVDZ 590 ao functions,
 252 shells

cc-pVTZ 1430 ao functions
 436 shells

no point group symmetry,
compact structure, lots of overlap



Timings (in secs) for 1 step in SCF

	1e	Q	HF	XC	Diag	Tot
BLYP 631-G*	1	56	0	75	1	87
BLYP cc-pVDZ	2	75	0	104	1	119
BLYP cc-pVTZ	6	321	0	302	34	494
B3LYP 631-G*	1	56	157	75	1	290
B3LYP cc-pVDZ	2	74	336	101	1	516
B3LYP cc-pVTZ	5	327	3194	328	40	3914
	N	N ²	N ⁴	N	N ³	

Prospects for future speedups

- NWCHEM not known for single cpu speed
- 1 electron integrals are inexpensive
- Matrix diagonalization is inherently order N^3
 - no reliable remedy for this as yet, but expense is not bad for drug-like molecules
 - some parallelism possible
- Many methods available to speed up Coulomb
 - good prospects here-- GPUs?
- So the biggest hurdle now is HF exchange
 - density fitting, GPUs?



Conclusions

- QM not a panacea
 - think of as another tool. More reliable than FF however can fail badly, and much more expensive than empirical methods
- DFT appears to be good at local geometry, charge distribution. Larger molecules a challenge--missing dispersion not there in current XC functionals
 - fitting XC parameters gains accuracy for molecules similar to training set, but physics approach of using constraints is the way forward
 - Computational cost still high for larger drug molecules, but prospects are good for the future

