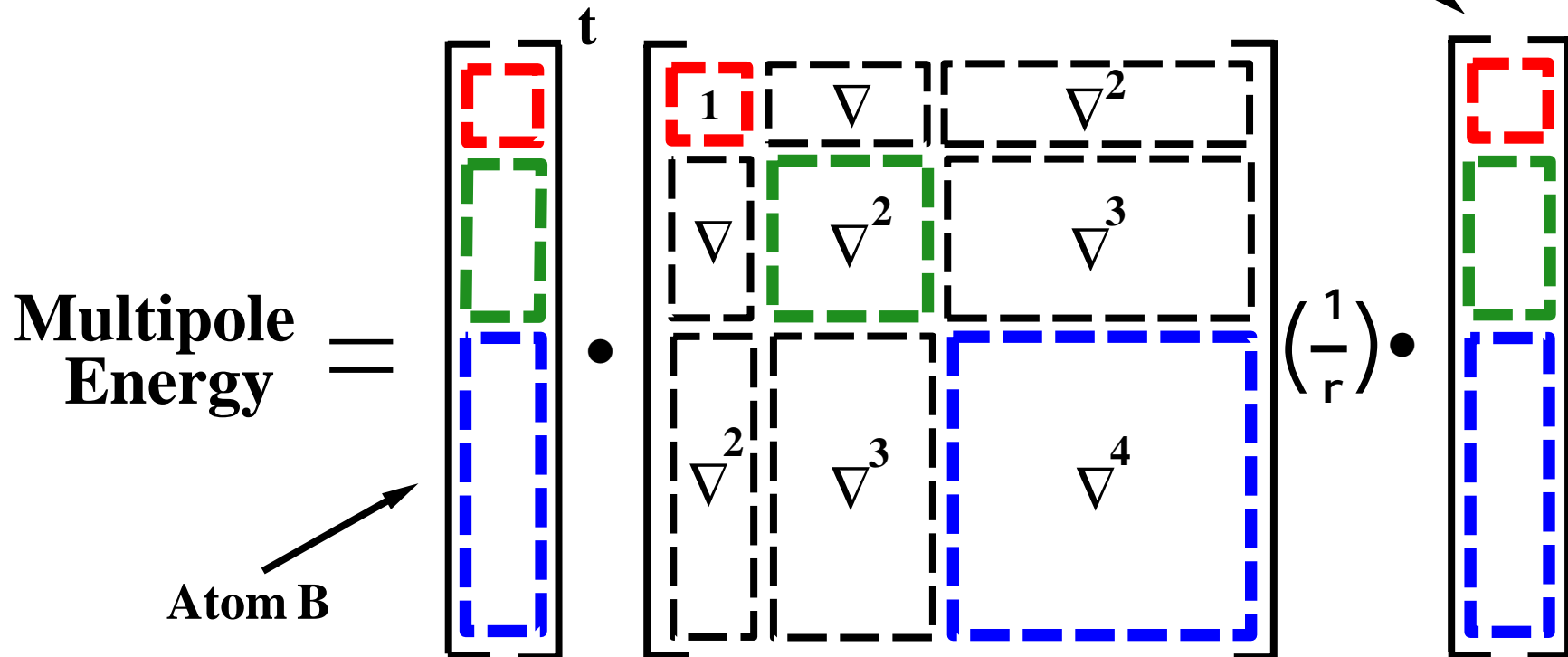
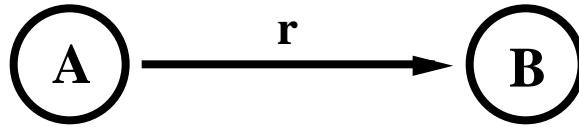


Polytensor Formulation of Multipole Interactions

Two Atoms A and B
with Atom Centered
Multipole Moments



- Monopole (1 Component)
- Dipole (3 Components)
- Quadrupole (9 Components)

$$\nabla^{(n)} = \frac{\partial^i}{\partial x^i} \frac{\partial^j}{\partial y^j} \frac{\partial^k}{\partial z^k}, \quad i+j+k=n$$

Dipole Polarizability

All matter is polarized in direct proportion to the strength of an external field, where the proportionality constant is α , the polarizability:

$$\mu_{\text{induced}} = \alpha \mathbf{E} \quad (\text{i.e., } \mu \text{ is linear, provided } \mathbf{E} \text{ is not too big!})$$

Imagine a one-electron (e) atom with a radius of R placed in an electric field E . The electron's orbit will be shifted away from the nucleus by a distance d . Then the induced dipole is given by:

$$\mu_{\text{induced}} = \alpha E = de$$

At the equilibrium value of d , the external force on the electron due to the field must exactly counterbalance the internal force of displacement between the nucleus and the electron. These forces are:

$$F_{\text{ext}} = eE, \text{ and } F_{\text{int}} = \frac{e^2}{4\pi\epsilon_0 R^2} \sin\theta \approx \frac{e^2 d}{4\pi\epsilon_0 R^3} = \frac{e}{4\pi\epsilon_0 R^3} \mu_{\text{induced}}$$

Since F_{ext} is equal to F_{int} , we obtain for the polarizability: $\alpha = 4\pi \epsilon_0 R^3$. Thus, neglecting the permittivity term, the polarizability should be roughly equal to the volume of the atom or molecule. For water, the experimental value of $\alpha = 1.48 \text{ \AA}^3$ suggests a radius of 1.14 \AA , about 20% less than the standard water radius of 1.4 \AA used in surface area calculations.

The Importance of Polarization

- ***Inter-*molecular polarization is necessary to describe gas-phase and condensed-phase properties within a single model**
- ***Intra-*molecular polarization is needed to treat the conformational dependence of electrostatics**

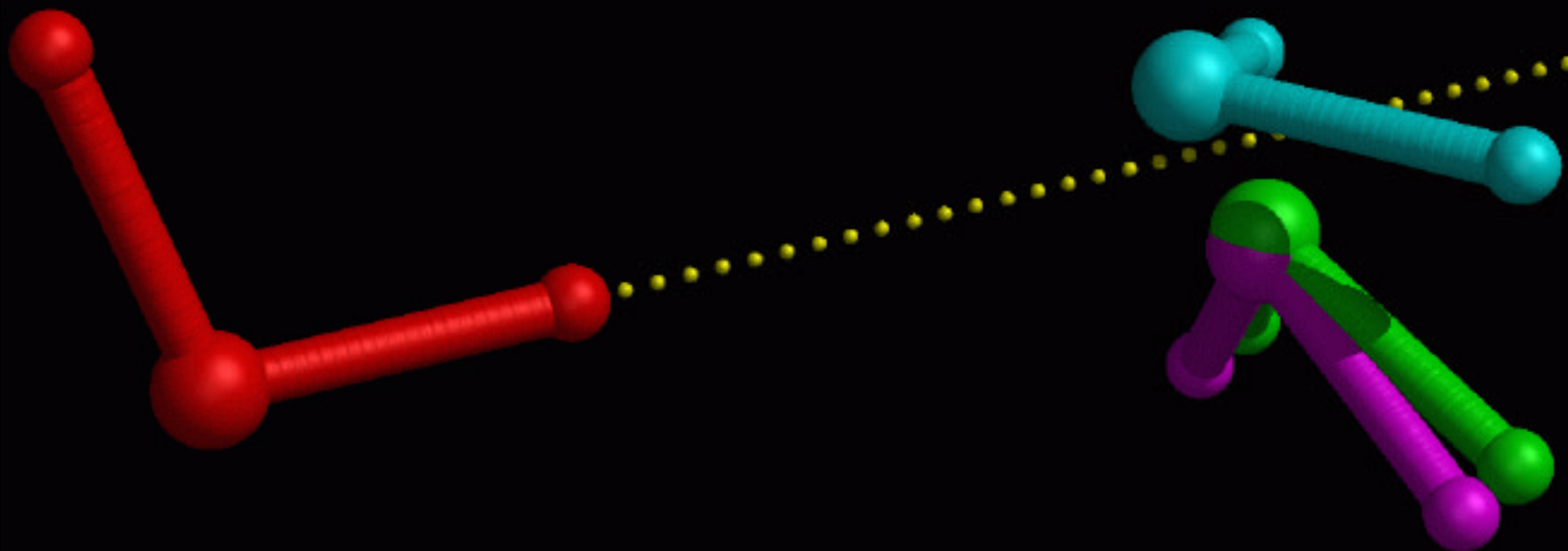
Water Dimer Structure and Energy

	Expt	QM	AMOEBA
O-O Distance (Ång)	2.98	2.907	2.892
O-O Bisector Angle (°)	57 ± 10	56.9	57.1
Dimerization Energy	5.4 ± 0.7	4.98	4.95

● MP2/CBS

● TIP3P

● AMOEBA

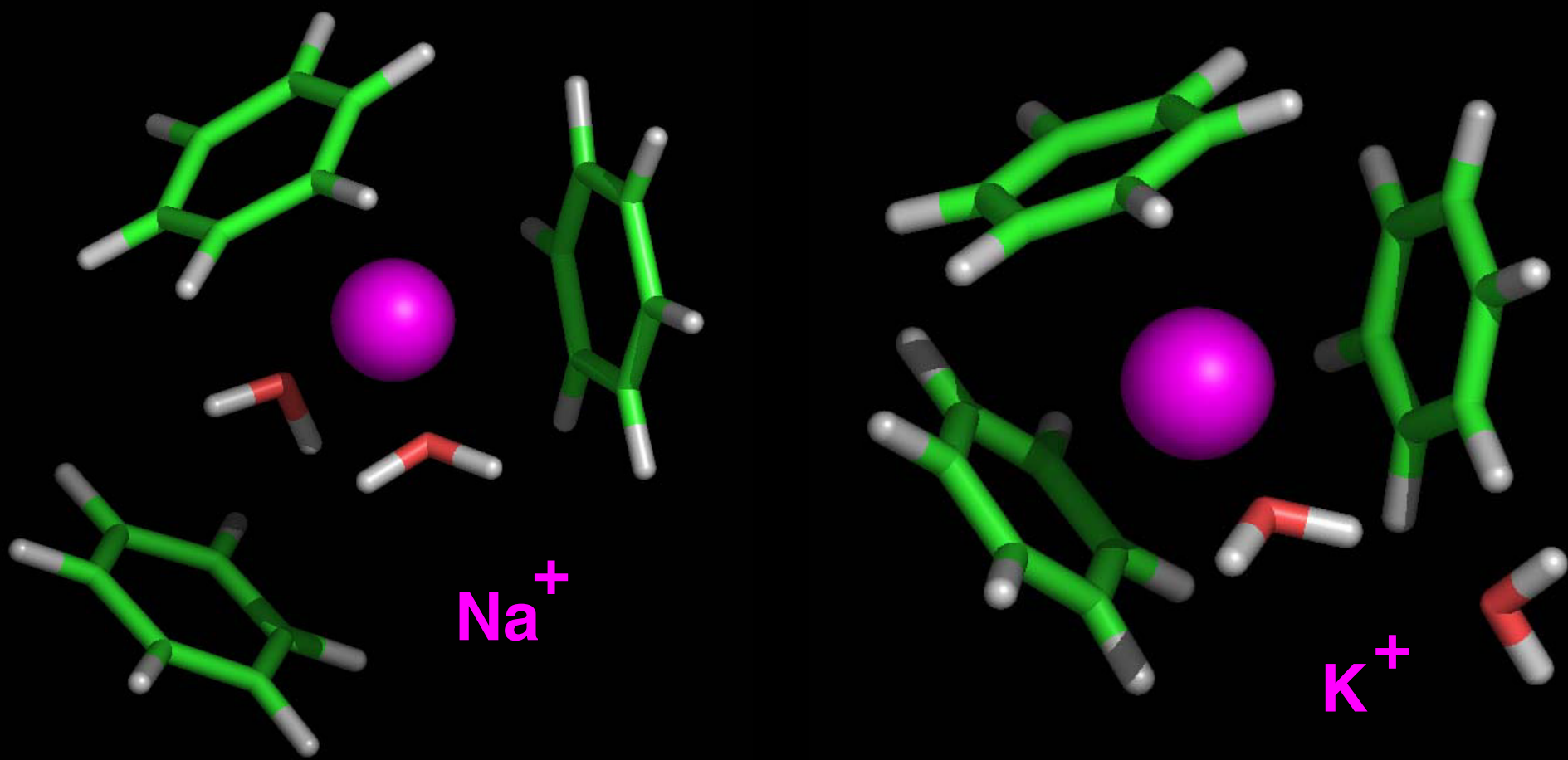


π -Cation Interactions

Catastrophic Failure of the Standard Model

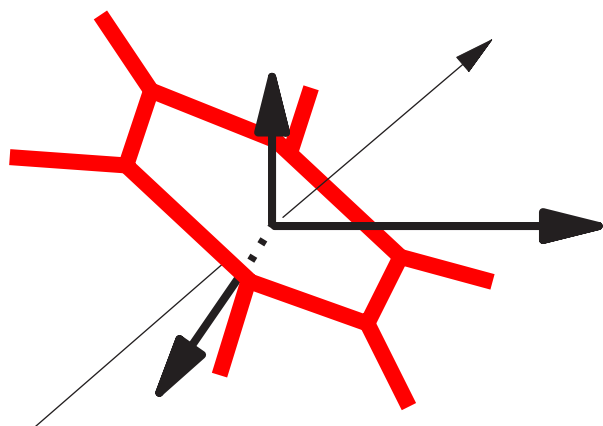
	ΔE_0	K ⁺ -Centroid	ΔH_{298}
OPLS-AA	-9.32	2.90	
CHARMM27	-11.06	2.81	
Amber <i>ff94</i>	-12.55	2.74	
Amber <i>ff02</i>	-15.87	2.63	
AMOEBA	-19.27	2.81	-18.15
MP2/6-311+G(2d,2p)	-18.4	2.81	
MP2/aVQZ	-19.9	2.79	
CCSD(T)/CBS	-20.6	2.79	-20.1
Expt (HPMS)			-18.3
Expt (CID)			-17.7

Ion Selectivity by Benzene-Water



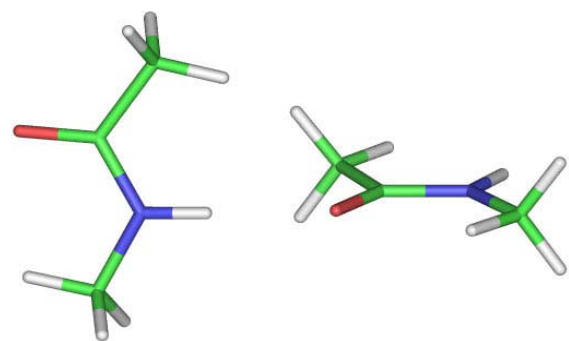
Molecular Dipole Polarizability

$$E = [0.1, 0.1, 0.1]$$



- Based on Thole's modified dipole interaction model
- *Isotropic* atomic dipole polarizabilities are sufficient to reproduce experimental molecular polarizability tensors
- Induced dipoles further *interactively* induce each other within the molecule
- The field and interaction involved in induction are modified (*damped*) at short range

Intermolecular Polarization for NMA



ESP RRMS

6.9%

16.6%

6.5%

Total Dipole

7.88

6.64

7.83

Dx

7.73

6.46

7.69

Dy

0.09

0.01

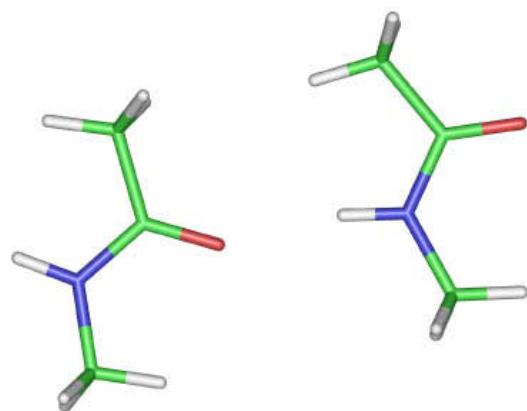
0.03

Dz

1.51

1.52

1.48



ESP RRMS

6.4%

15.9%

5.6%

Total Dipole

8.85

7.49

8.85

Dx

-8.82

-7.44

-8.81

Dy

0.76

0.75

0.82

Dz

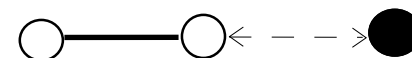
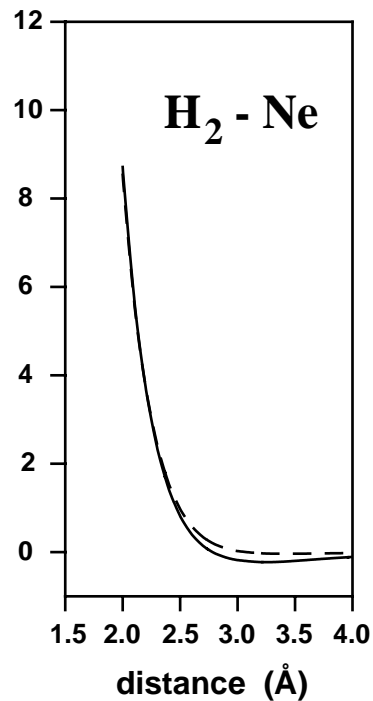
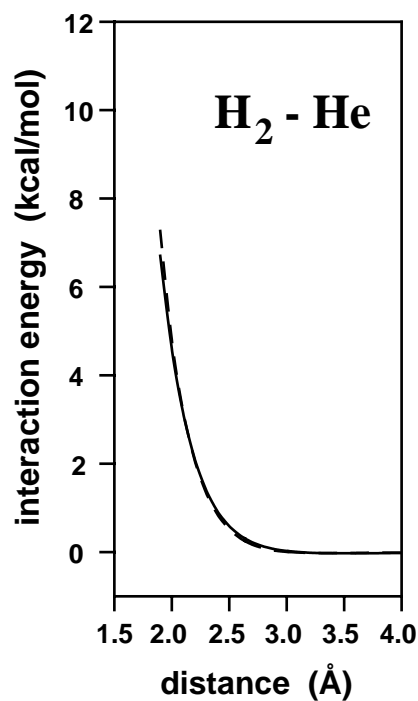
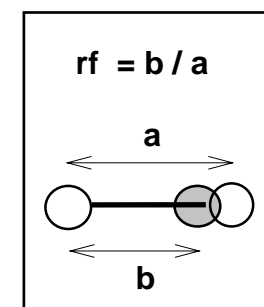
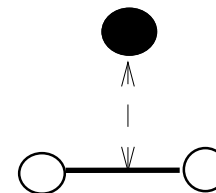
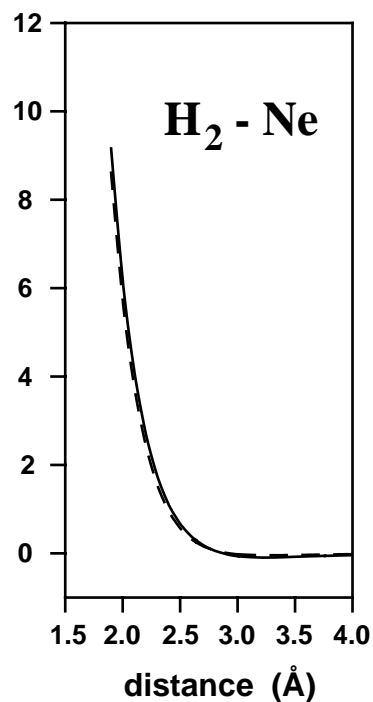
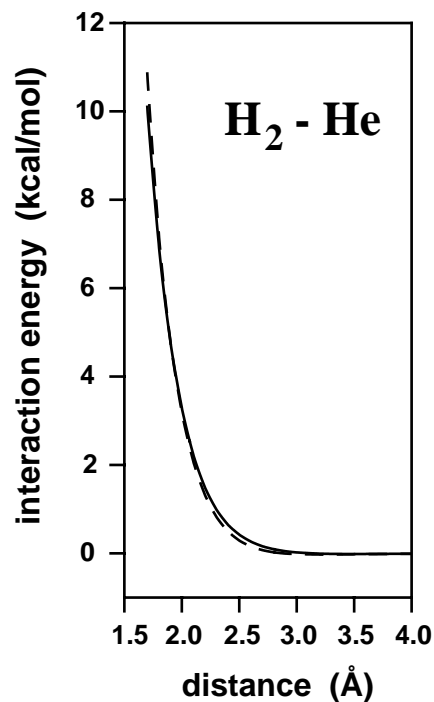
0.02

0.00

0.00

All calculations performed at MP2/6-311G++(2d,2p)

Probing vdW Anisotropy



Small Molecule Database for Parametrization

Neon

Argon

Krypton

Graphite

Dinitrogen

Dioxygen

Difluorine

Methane

Ethane

Propane

Butane

Isobutane

Pentane

Cyclohexane

Benzene

Toluene/Xylenes

Phenol/Cresols

Ammonia

Water

Hydrogen Fluoride

Hydrogen Sulfide

Hydrogen Chloride

Methanol

Ethanol

Isopropanol

Methyl Amine

Ethyl Amine

n-Propyl Amine

Dimethyl Amine

Trimethyl Amine

Formic Acid

Acetic Acid

Carboxylates

Ureas

Methyl Sulfide

Ethyl Sulfide

Dimethyl Sulfide

Dimethyl Disulfide

Formamide

Acetamide

N-Methyl Formamide

Dimethyl Formamide

N-Methyl Acetamide

Dimethyl Acetamide

Imidazoles

Guanidine

Indoles

Tryptamine

+ various strained hydrocarbons, ions and monofunctionals

Noble Gases and Homodiatomic Molecules

H₂	3.50	0.010	0.80											
				N₂		O₂		F₂	Ne					
				3.72	0.076	1.04	3.39	0.106	0.99	3.22	0.109	0.96	3.15	0.073
										Cl₂		Ar		
										3.925	0.340	0.935	3.82	0.260
													Kr	
													4.09	0.359
													Xe	
													4.37	0.498

	T (K)	P (atm)	Density (g/cm ³)			Hvap (kcal/mol)		
			expt	calc	%error	expt	calc	%error
Ne	27.1	-4	1.200	1.203	0.3	0.420	0.421	0.2
Ar	87.5	-34	1.390	1.394	0.3	1.554	1.554	0.0
Kr	120.3	8	2.400	2.405	0.2	2.161	2.163	0.1
Xe	166.1	6	3.100	3.100	0.0	3.018	3.018	0.0
H₂	20.3	-3	0.070	0.069	-1.4	0.218	0.216	-0.9
N₂	77.3	-52	0.804	0.830	3.2	1.332	1.346	1.0
O₂	90.2	-5	1.142	1.145	0.3	1.628	1.617	-0.6
F₂	85.0	-23	1.512	1.511	-0.1	1.554	1.565	0.7
Cl₂	243.2	7	1.552	1.564	0.8	4.857	4.851	0.1

AMOEBA Parameters for Water

<i>O-H Bond</i>	b_0 (Å)	K_b (kcal/Å ² /mol)	<i>O Multipoles</i>	(a.u.)
	0.9572	529.6	Q	-0.51966
<i>H-O-H Angle</i>	θ_0 (deg)	K_θ (kcal/deg ² /mol)	d_z	0.14279
	108.50	34.05	Q_{xx}	0.37928
<i>Urey-Bradley</i>	l_0 (Å)	K_l (kcal/Å ² /mol)	Q_{yy}	-0.41809
	1.5537	38.25	Q_{zz}	0.03881
			<i>H Multipoles</i>	(a.u.)
<i>van der Waals</i>	R^0 (Å)	ϵ (kcal/mol)	Q	0.25983
O	3.405	0.110	d_x	-0.03859
H	2.655	0.0135	d_y	-0.05818
$H_{\text{reduction}}$	91%		Q_{xx}	-0.03673
<i>Polarizability</i>	α (Å ³)		Q_{yy}	-0.10739
O	0.837		Q_{xz}	-0.00203
H	0.496		Q_{zz}	0.14412

Water Dimer Equilibrium Properties

	AMOEBA	<i>ab initio</i>		<i>exp</i>
D_e	4.96	4.98 ^a	5.02 ^b	5.44 ± 0.7 ^c
$r_{\text{O-O}}$	2.892	2.907 ^a	2.912 ^b	2.976 ^f
α	4.18	4.2 ^a	5.5 ^b	-1 ± 10 ^f
θ	57.2	56.9 ^a	55.6 ^b	57 ± 10 ^f
$\langle \mu_{\text{mol}} \rangle$	2.02	2.1 ^c		
μ_{tot}	2.54	2.76 ^d		2.643 ^f

^a Based on calculations at CCSD(T)/TZ2P(f,d)+dif corrected for BSSE.

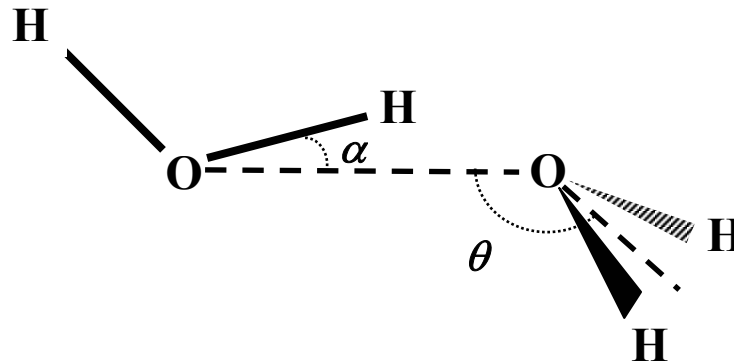
^b Complete basis set estimate from correction of CCSD(T) calculations.

^c Derived from DMA calculation directly on water dimer minimum.

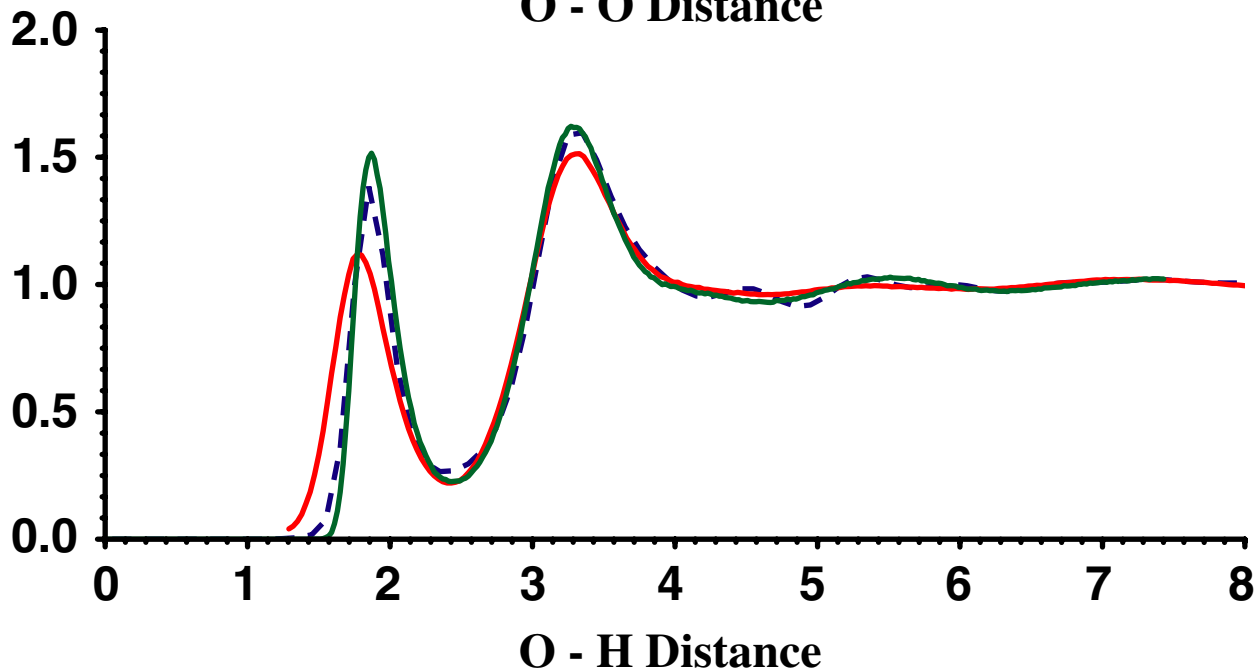
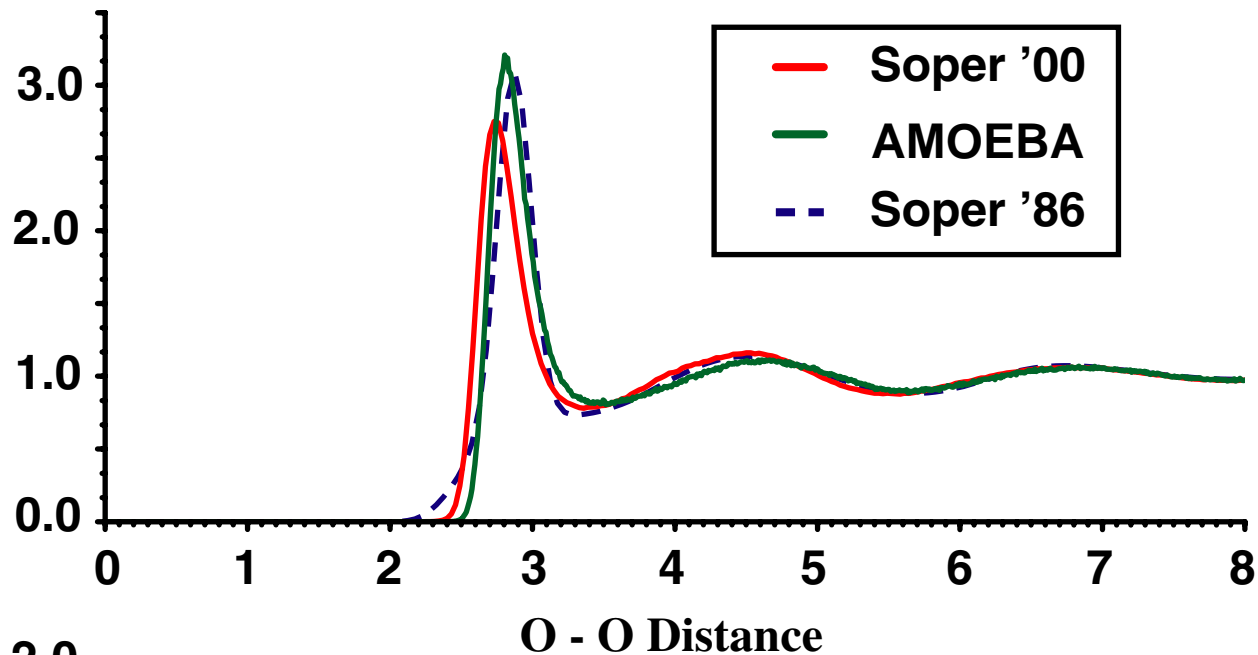
^d From MP2/TZ2P++ calculations.

^e Estimate after vibrational correction of experimental ΔH at 373 K.

^f Microwave spectra from molecular beam resonance experiments at 20 K.

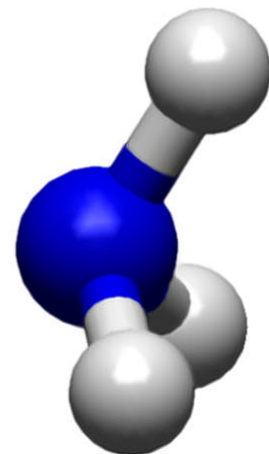
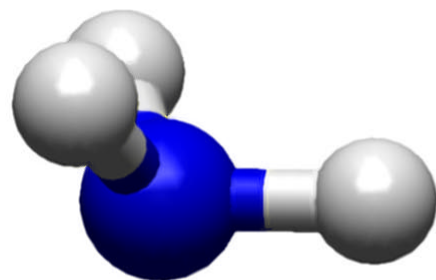


Liquid Water Properties



	Expt	AMOEBA
Heat Vaporization (kcal)		
298K	10.51	10.48
Density (g/cc)		
298K	0.997	1.000
323K	0.988	0.992
363K	0.962	0.964
Dielectric Constant		
273K	87.7	86.8
298K	78.3	80.7
323K	69.9	66.5
Diffusion (10^{-5} cm/s ²)		
298K	2.3	2.0
C _p (cal/mol K)		
298K	18.0	20.9 / 27.6
Avg Mol Dipole (Debye)	2.6-3.0	2.78
E _{pol} / (E _{pol} +E _{perm})		30%

Ammonia Monomer, Dimer and Liquid



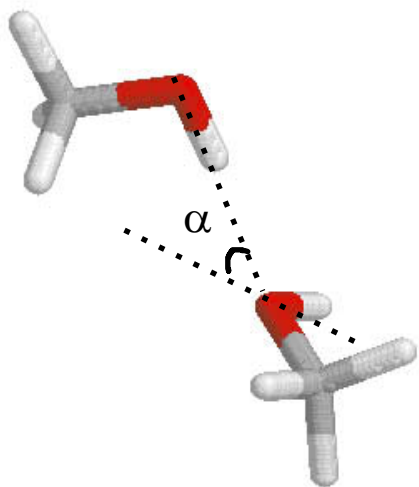
MONOMER	Dipole	Quadrupole
Expt	1.471	-2.42, -2.45
AMOEBA (unscaled)	1.528	-3.093
AMOEBA (60% Q)	1.528	-2.491

DIMER	Energy	N..H	N..N	<HN..H
<i>ab Initio</i> *	3.09	2.226	3.224	135
AMOEBA	3.19	2.248	3.265	120

* aug-cc-pVQZ energy at 6-31+G* minimum

LIQUID	H _{vap}	Pressure	Dx10 ⁵	T(K)
Expt	5.58	1	5.8	240
AMOEBA	5.54	99	5.0	240

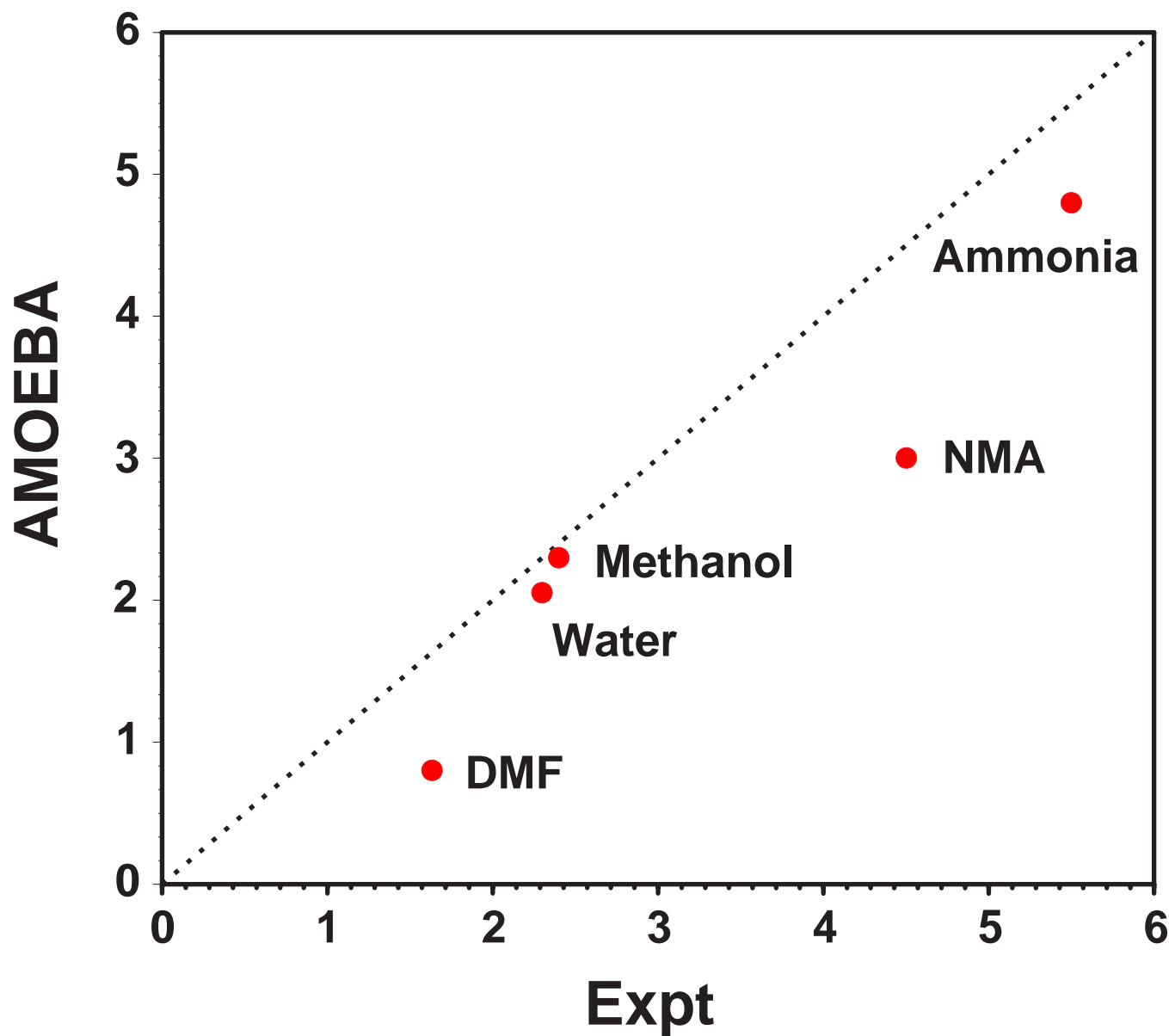
Methanol Dimer



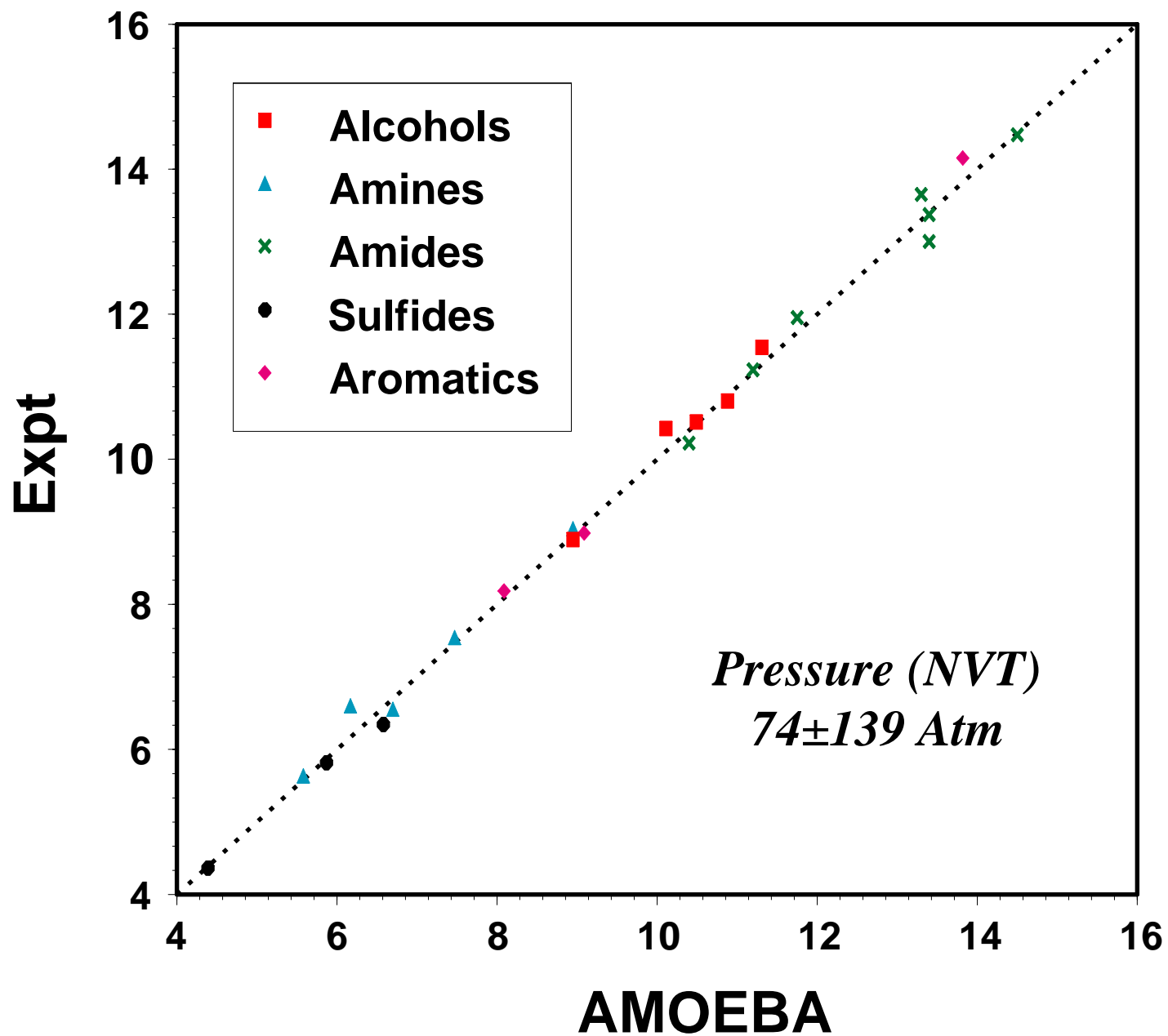
	QM [#]	AMOEBA	CHARMM
E (kcal/mol)	5.44	5.38	6.99
R _{O...O} (Å)	2.87	2.91	2.80
α (deg)	44	44	23
β (deg)	179	174	178

[#] MP2 Calculations from Mooij, *et al.*, 1999

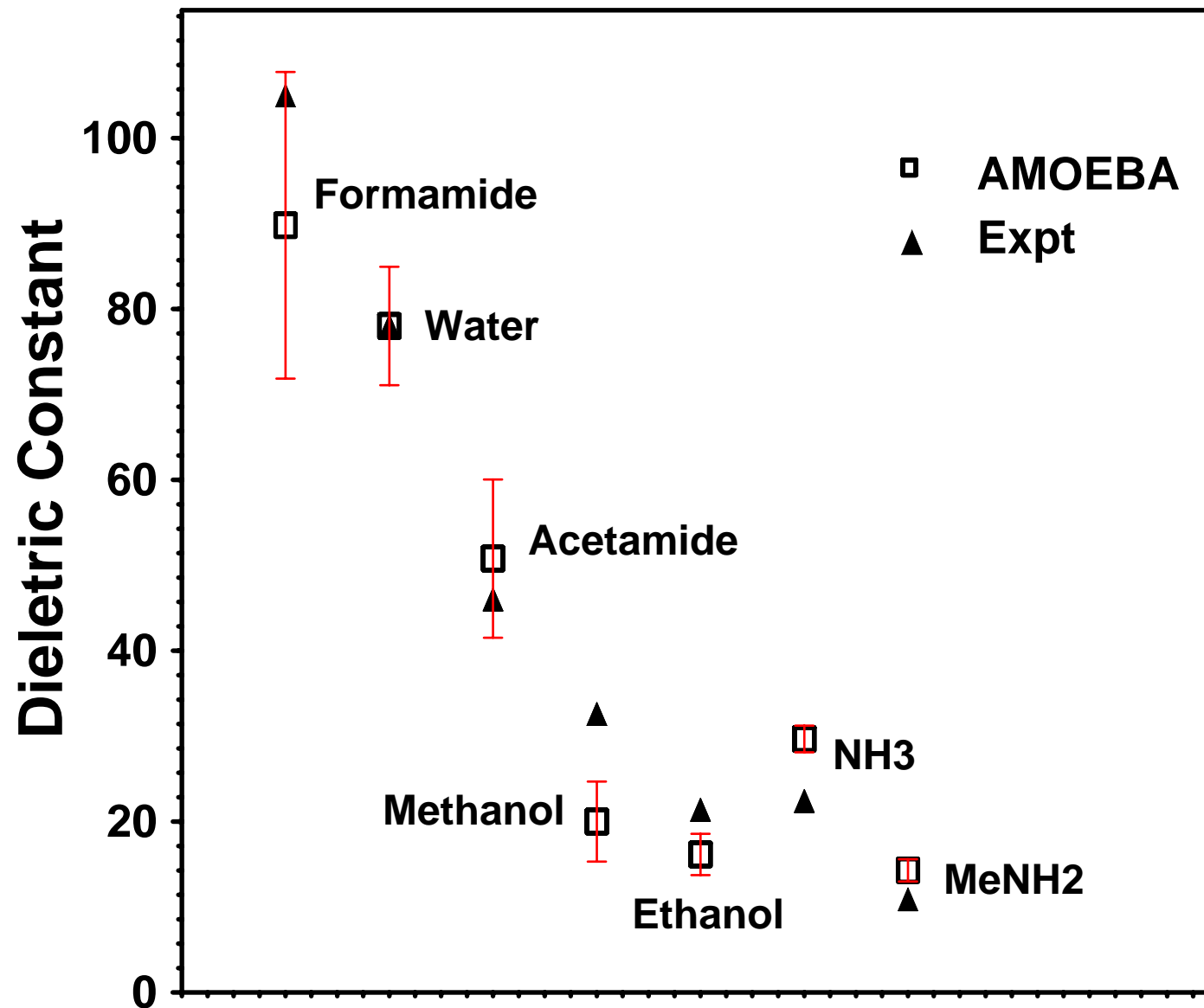
Self-Diffusion Coefficient ($10^{-5} \text{ cm}^2/\text{s}$)



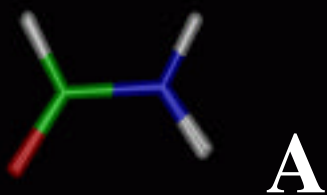
Heat of Vaporization (kcal/mol)



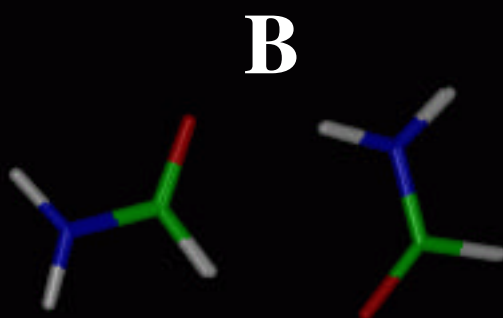
Dielectric Constants: AMOEBA vs. Expt



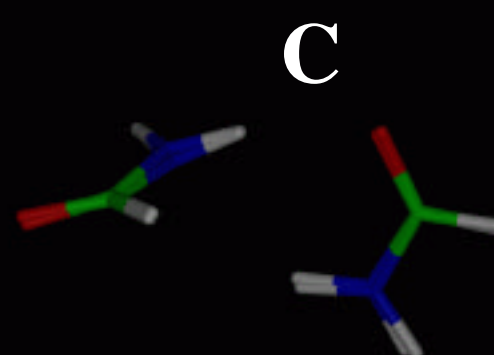
Formamide Dimer Energy Minima



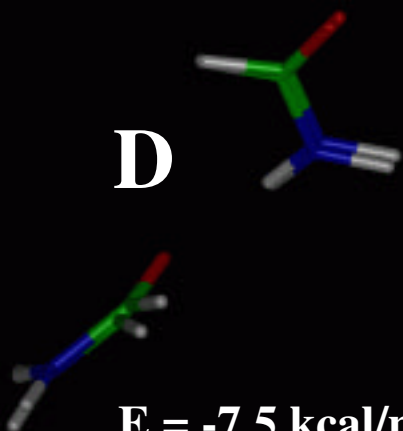
$E = -16.0$ kcal/mol
 $rms = 0.02$ Å



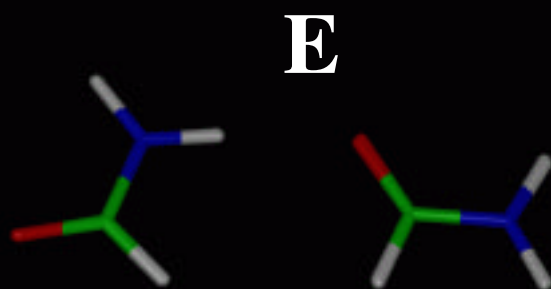
$E = -10.3$ kcal/mol
 $rms = 0.04$ Å



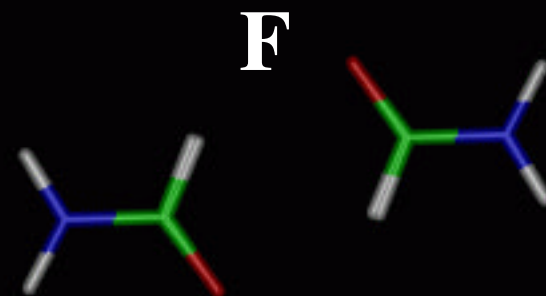
$E = -9.0$ kcal/mol
 $rms = 0.09$ Å



$E = -7.5$ kcal/mol
 $rms = 0.28$ Å



$E = -7.3$ kcal/mol
 $rms = 0.03$ Å

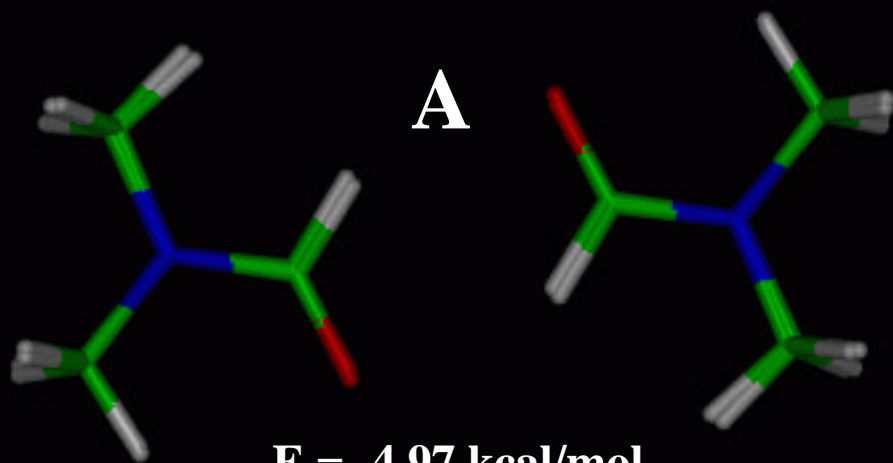


$E = -5.5$ kcal/mol
 $rms = 0.05$ Å

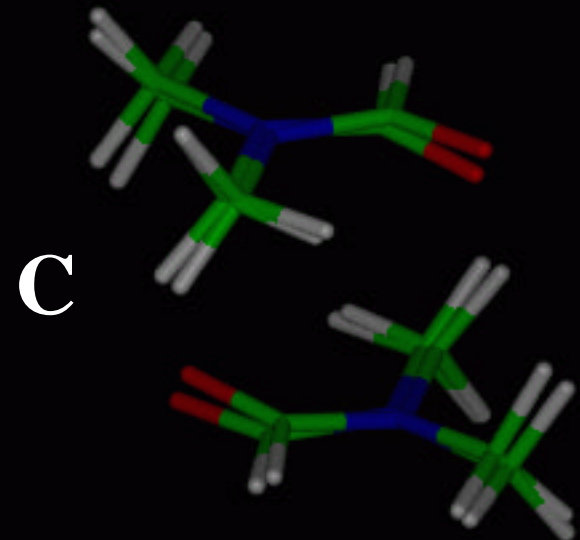
Formamide Dimer Association Energies

	A cyclic	B side	C nonplan	D nonplan	E side	F head-tail
MP2/6-31G**	-13.4	-8.5	-6.9	-5.8	-6.1	-3.6
B3LYP/6-31G(d)	-13.4	-8.3	-6.7	-6.0	-6.7	-3.2
<i>MP2/aug-cc-pVTZ</i>	<i>-16.1</i>	<i>-10.6</i>	<i>-8.2</i>	<i>-7.2</i>	<i>-6.9</i>	<i>-5.4</i>
AMOEBA	-16.0	-10.3	-9.0	-7.5	-7.3	-5.5
<i>RMS</i>	<i>0.02</i>	<i>0.04</i>	<i>0.09</i>	<i>0.28</i>	<i>0.03</i>	<i>0.05</i>
OPLS-AA	-14.2	-7.8	-8.2	-8.2	-8.0	-2.7
<i>RMS</i>	<i>0.06</i>	<i>0.24</i>	<i>0.82</i>	<i>1.03</i>	<i>0.63</i>	<i>0.16</i>
AMBER	-16.8	-9.5	-9.6	-9.0	-8.9	-3.8
<i>RMS</i>	<i>0.06</i>	<i>0.09</i>	<i>0.22</i>	<i>1.03</i>	<i>0.67</i>	<i>0.12</i>
CHARMM	-13.0	-8.2	-8.0	-7.7	-7.6	-4.3
<i>RMS</i>	<i>0.05</i>	<i>0.13</i>	<i>0.21</i>	<i>1.06</i>	<i>0.74</i>	<i>0.10</i>
MM3	-12.0	-6.5	-6.8	-6.8	-6.4	-1.5
<i>RMS</i>	<i>0.06</i>	<i>0.24</i>	<i>0.38</i>	<i>1.37</i>	<i>0.24</i>	<i>0.25</i>

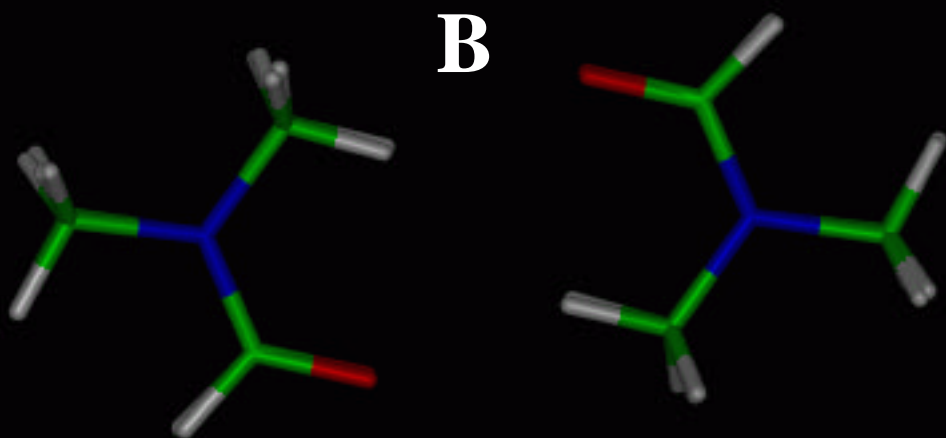
Comparison of DMF Dimers: AMOEBA vs Dixon/Hay



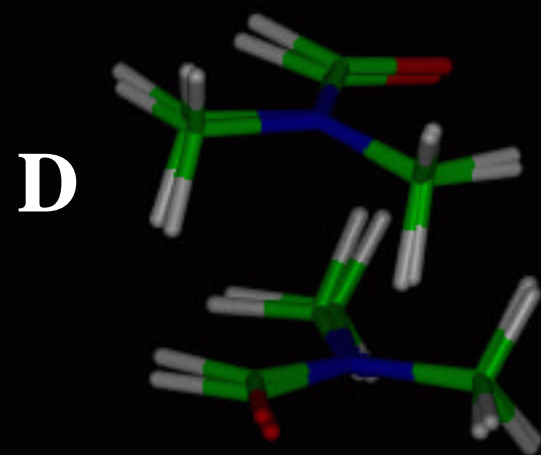
E = -4.97 kcal/mol
rms = 0.08Å



E = -7.80 kcal/mol
rms = 0.24Å



E = -5.37 kcal/mol
rms = 0.09Å



E = -8.79 kcal/mol
rms = 0.15Å

Dimethylformamide Dimer Structure and Energy

	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>
MP2/DZP+diffuse #	-6.61	-5.51	-10.32	-10.98
BSSE Corrected	-4.07	-3.31	-5.86	-6.36
MP2/aug-cc-pVTZ #	-6.95	-5.82	-11.41	-12.11
BSSE Corrected	-5.35	-4.14	-8.34	-8.90
AMOEBA (single)	-4.94	-5.03	-7.37	-8.60
AMOEBA (opt)	-4.97	-5.37	-7.80	-8.79
<i>RMS</i>	<i>0.08</i>	<i>0.09</i>	<i>0.24</i>	<i>0.15</i>
OPLS-AA (single)	-1.68	-0.60	-3.41	-2.48
OPLS-AA (opt)	-3.45	-3.54	-5.42	-5.18
<i>RMS</i>	<i>0.25</i>	<i>0.64</i>	<i>0.41</i>	<i>0.69</i>

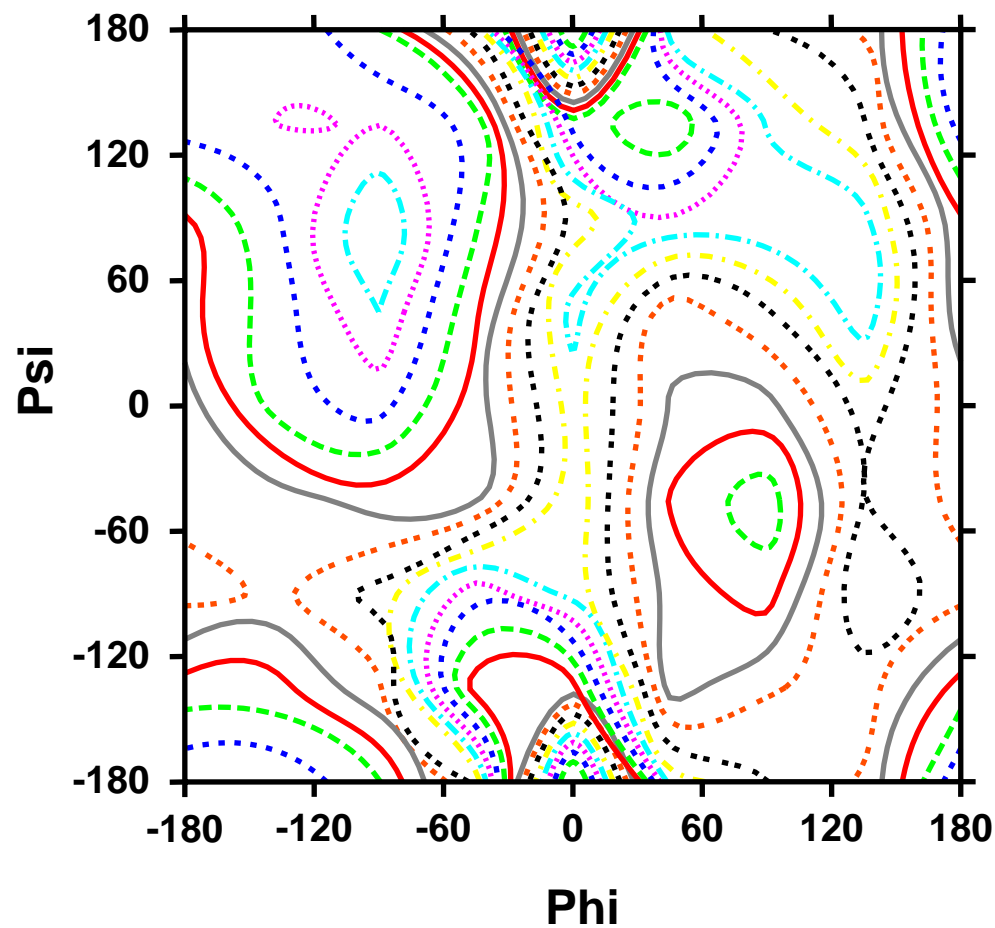
QM Results from Vargas, *et al.*, *JACS*, 122, 4750-4755 (2000)

Parameterization for Polypeptides

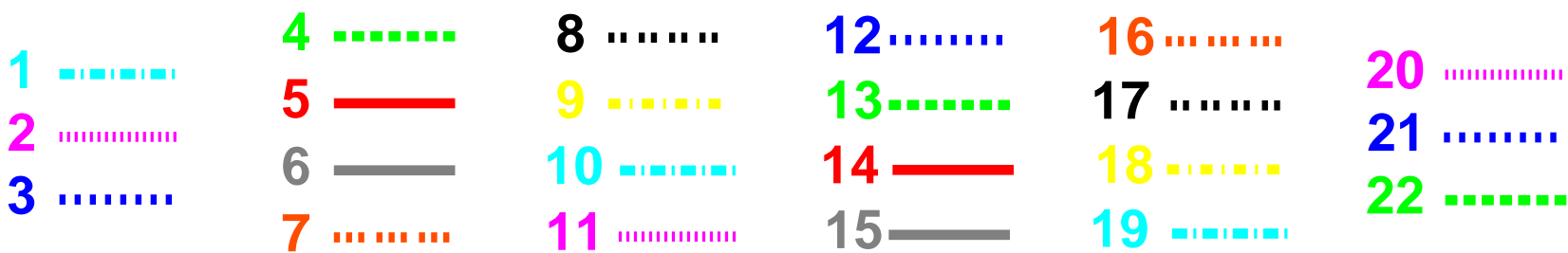
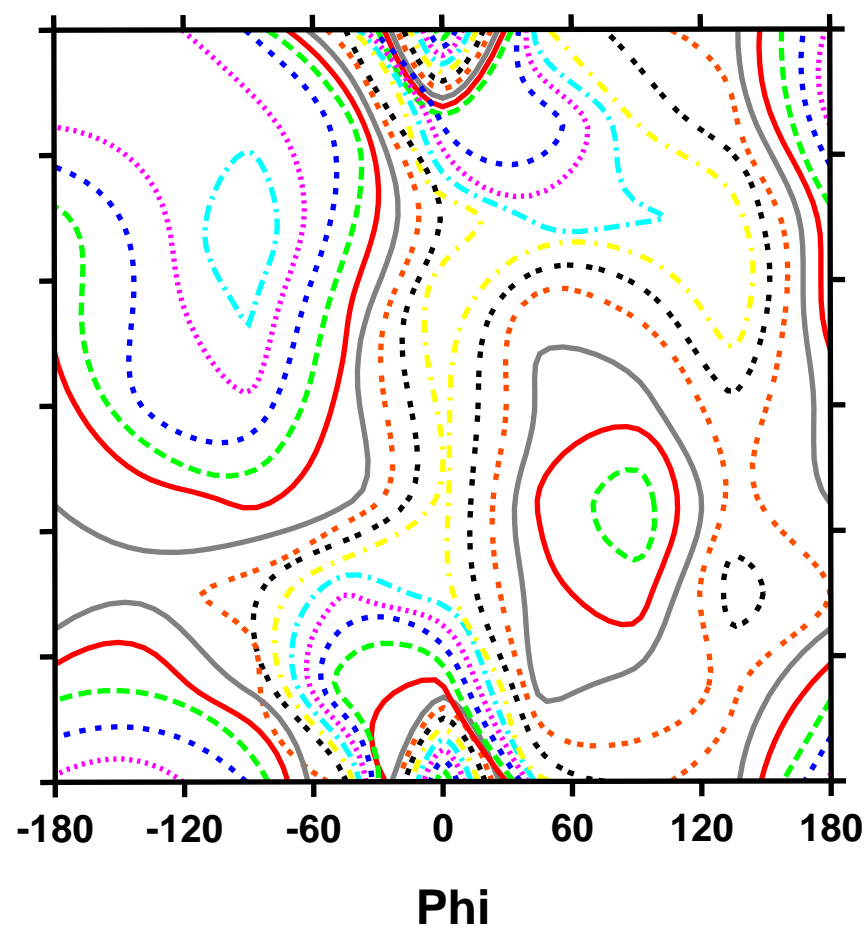
- **vdW parameters and atomic polarizabilities transferred from small molecules**
- **Atomic multipole parameters**
 - > from small molecule fragments (?)
 - > from capped amino acids (?)

Conformational dependence via intramolecular polarization
- **Torsional parameters obtained by fitting to conformational energy surfaces**

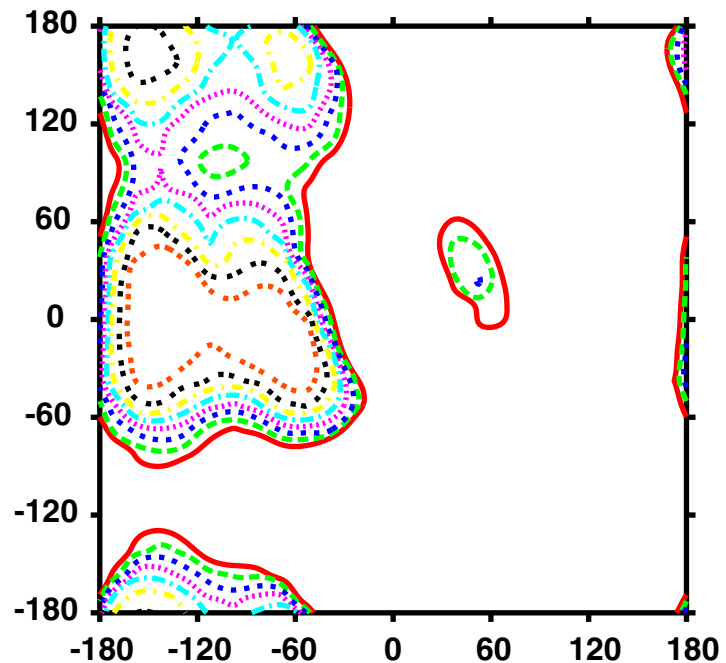
MP2/6-311+G(2d,2p)



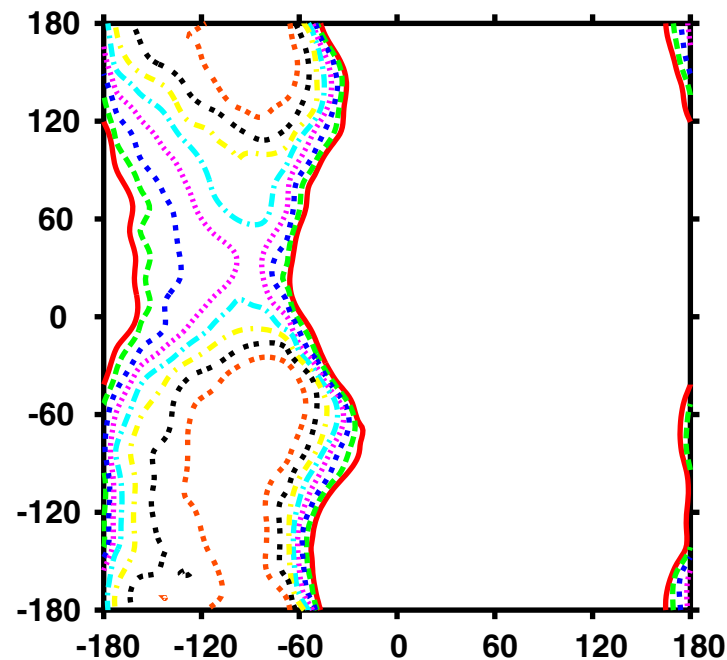
LMP2/cc-pVTZ(-f)



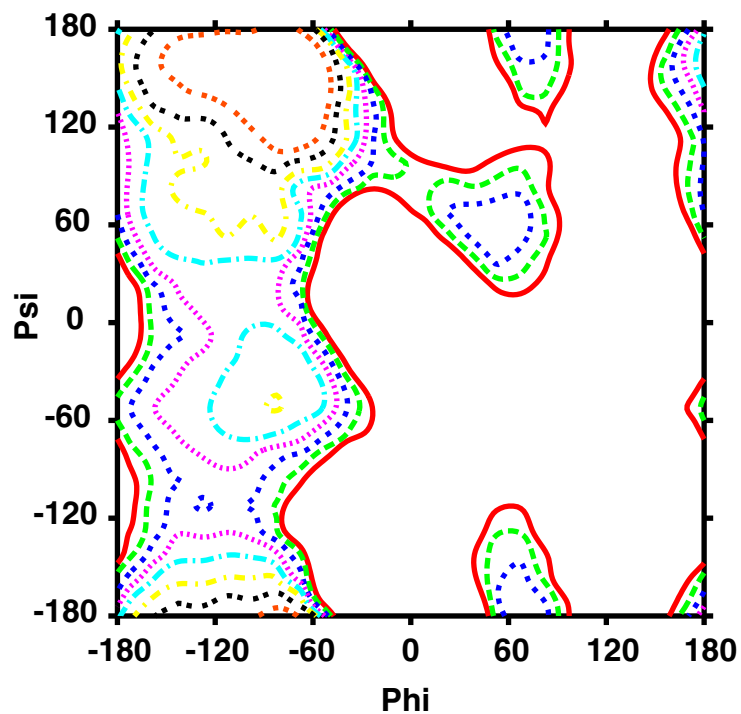
AMBER ff99



CHARMM27



OPLS-AA



*Solvated
Alanine
Dipeptide*

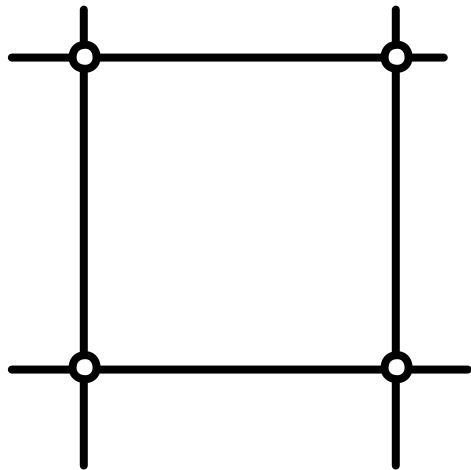
*Free
Energy
Surfaces*

Torsional Energy Functional Forms

- *Fourier series*

$$E_{\text{tors}} = k_1 [1 + \cos(\phi)] + k_2 [1 - \cos(2\phi)] + k_3 [1 + \cos(3\phi)] + \dots$$

- *Bicubic spline*



Input:

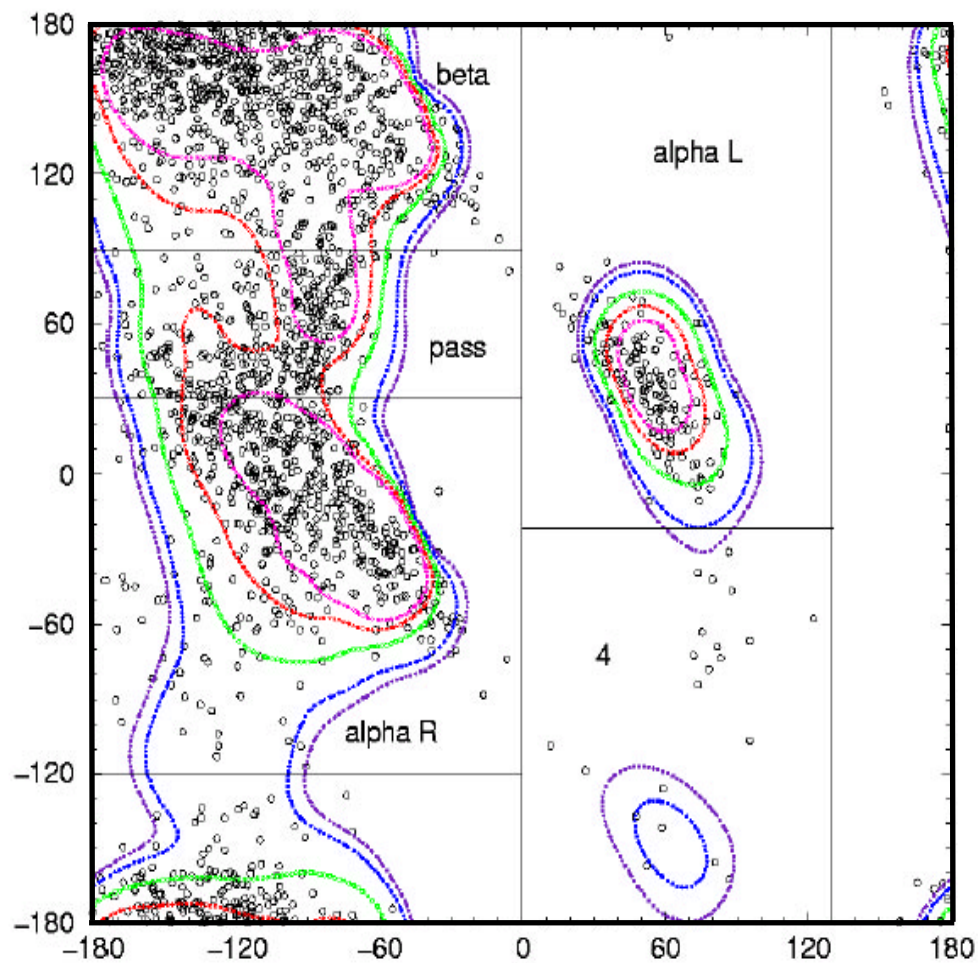
- z
- $\partial z / \partial x$
- $\partial z / \partial y$
- $\partial^2 z / \partial x \partial y$

Output:

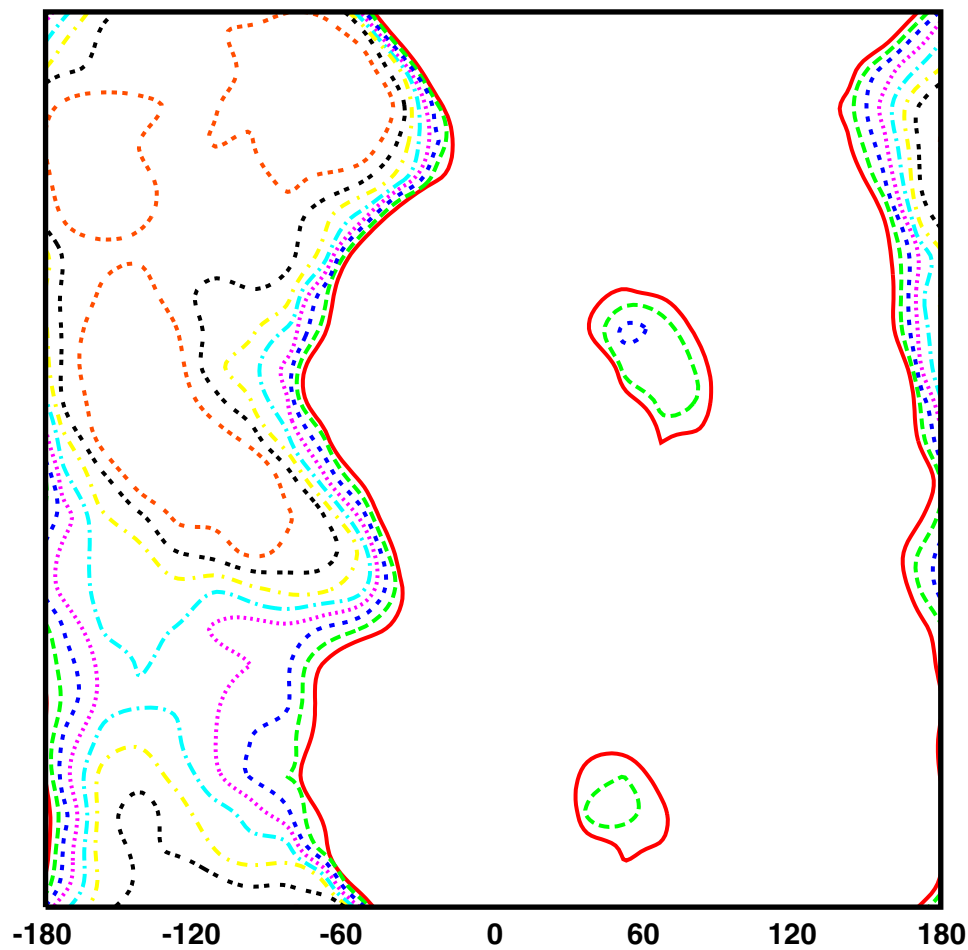
- $z(x_i, y_i)$
- Smooth first derivative
- Continuous second derivatives

Comparison of QM/MM, PDB and AMOEBA Results

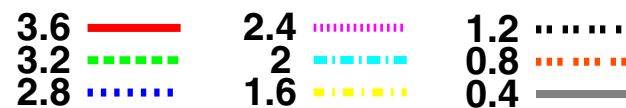
QM/MM vs. PDB



AMOEBA (Fixed Charge Water)



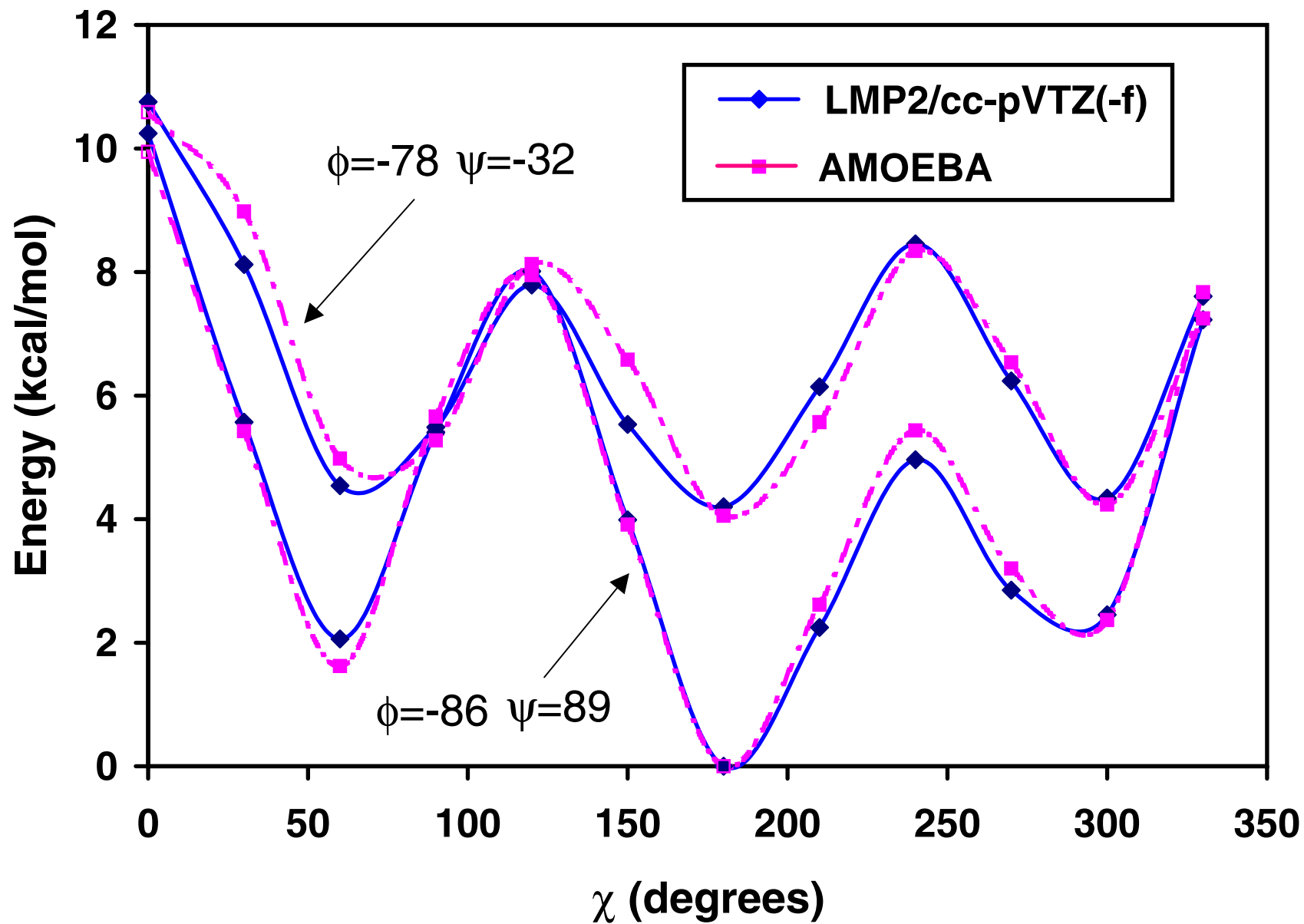
QM/MM, Jan Hermans, UNC
PDB, Jane Richardson, Duke



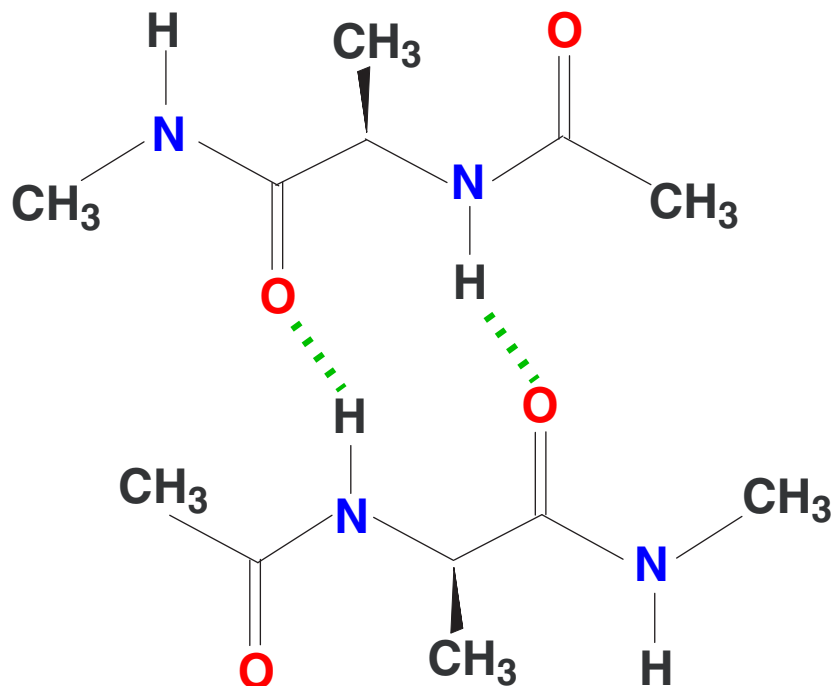
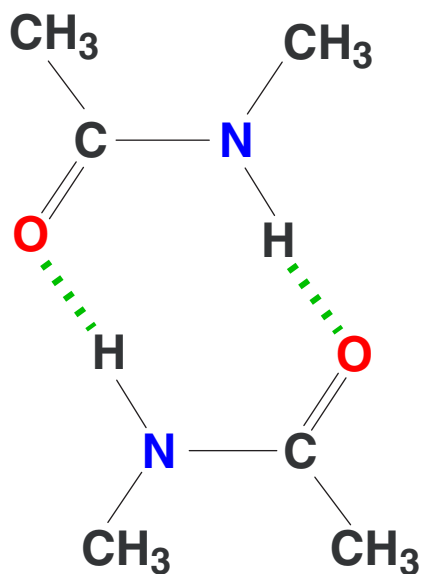
Conformational Populations

	<i>Alpha</i>	<i>Pass</i>	<i>Beta</i>	<i>Other</i>
Amber ff94	68	5	26	1
Amber ff99	77	10	13	1
CHARMM27	46	2	52	0
OPLS-AA	13	9	75	3
OPLS-AA/L	23	8	65	4
SCCDFTB (Amber)	27	16	48	9
SCCDFTB (CHARMM)	33	14	48	4
SCCDFTB (CEDAR)	27	12	61	0
AMOEBA (Polar Water)	29	16	54	1
AMOEBA (Fixed Water)	32	13	54	1

Valine Sidechain Energetics



cis-N-Methylacetamide vs β -Sheet Model



	<i>cis</i> -NMA	β -Sheet	ΔE
MP2/(CEP)4-31G+(2d)	-20.5	-17.5	+3.0
BP/DZVP (BSSE)	-16.2	-8.4	+7.8
SIBFA	-18.7	-17.1	+1.6
TINKER	-17.3	-11.5	+5.8
AMBER94	-11.3	-14.8	-3.5
CHARMM27	-11.6	-16.9	-5.3
OPLS-AA	-11.5	-16.9	-5.4

QM and SIBFA data from Gresh, *et al.*, JACS, 121, 7885-7894 (1999)