

*Multipole Models Fit to 6-31G** Electric Potentials*

<u>Molecule</u>	<u>Points</u>	Relative RMS Error		
		<u>M only</u>	<u>M+D</u>	<u>M+D+Q</u>
Methane	455	13.53	1.04	0.39
Water	363	8.44	0.88	0.01
Ammonia	404	9.90	2.31	0.02
Methanol	483	8.35	1.31	0.02
Acetone	614	2.31	0.98	0.02
Acetylene	438	1.34	0.06	0.02
Formamide	492	3.68	0.65	0.03
Me Acetate	559	6.03	0.67	0.02
DiMe Amine	583	16.27	1.48	0.03
NMA	685	3.26	0.30	0.01

Data from D. E. Williams, *J. Comput. Chem.*, **9**, 745-763 (1988)

Polytensor Formulation of Multipole Interactions

Two Atoms A and B
with Atom Centered
Multipole Moments

$$\text{Multipole Energy} = \begin{matrix} t \\ \bullet \end{matrix} \cdot \begin{matrix} 1 & \nabla & \nabla^2 \\ \nabla & \nabla^2 & \nabla^3 \\ \nabla^2 & \nabla^3 & \nabla^4 \end{matrix} \left(\frac{1}{r} \right) \cdot \begin{matrix} t \\ \bullet \end{matrix}$$

Atom A Atom B

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

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

Dipole Polarizability

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

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

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

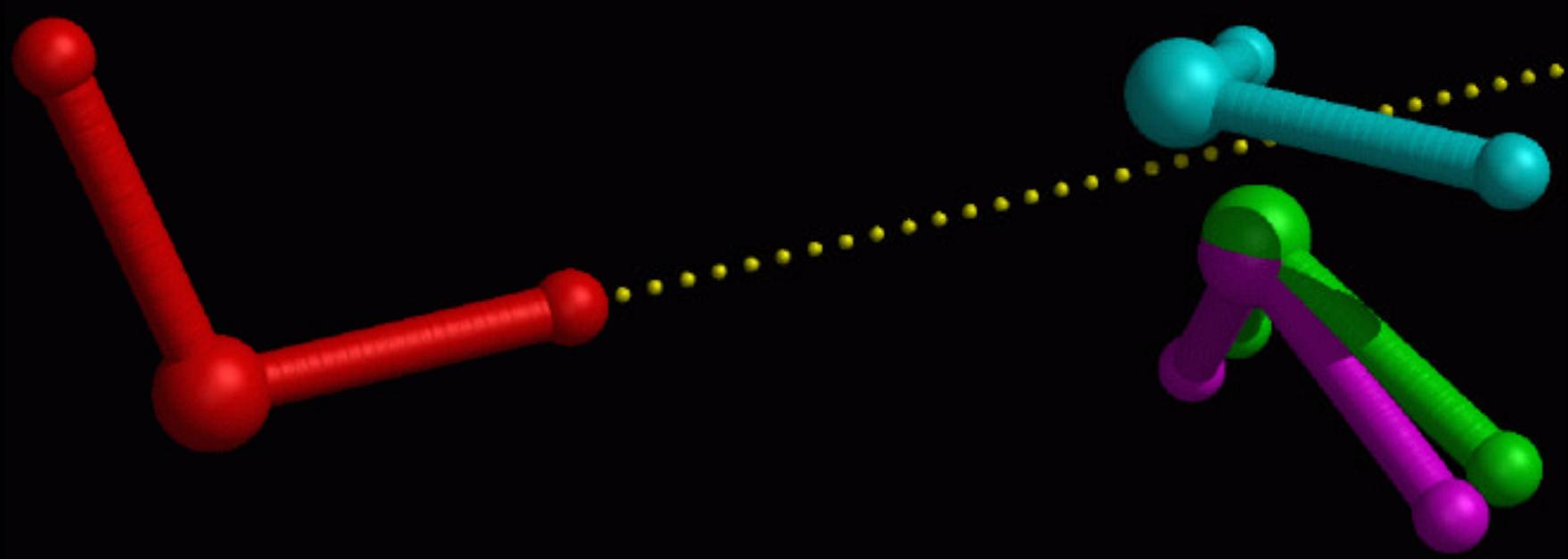
Water Dimer Structure and Energy

	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

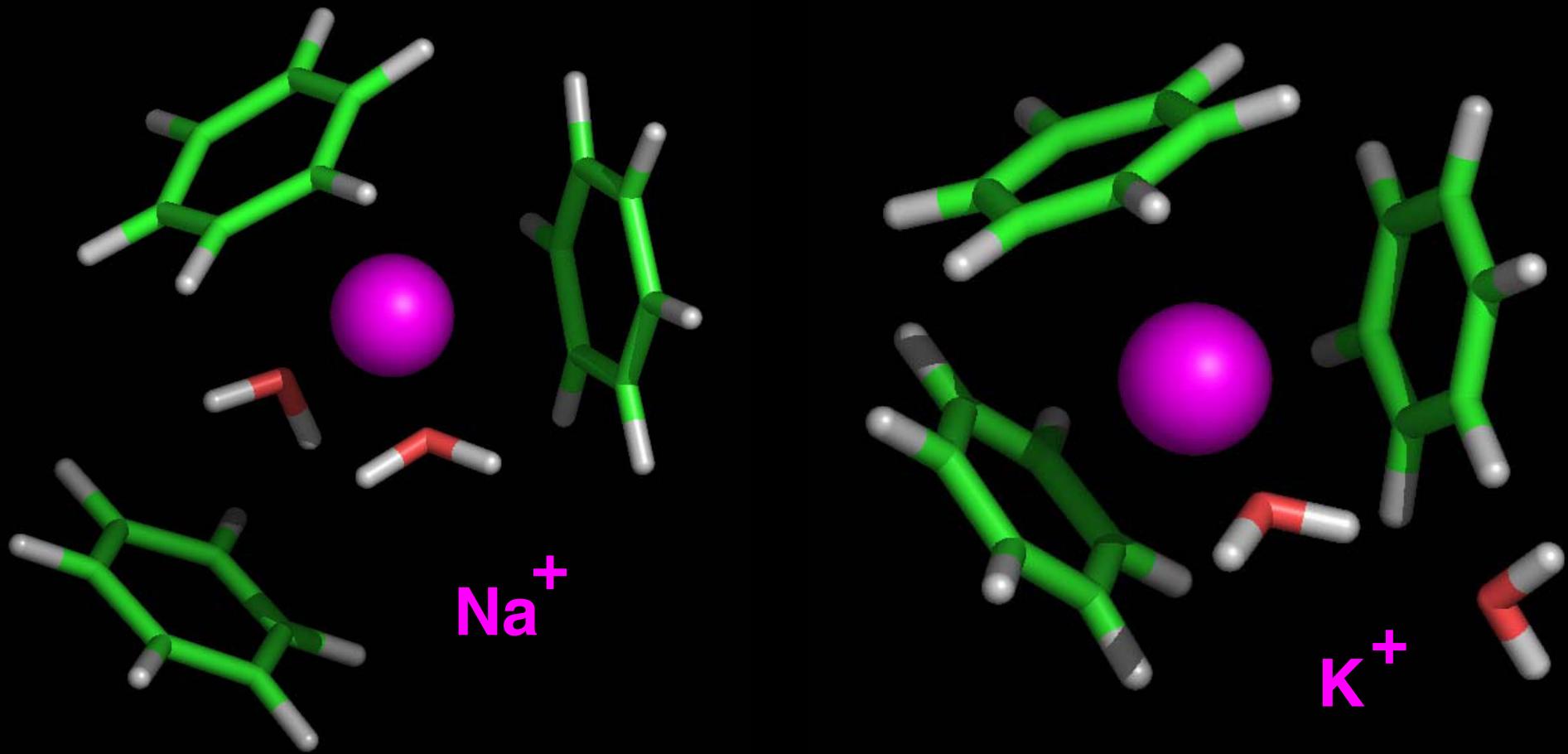


π -Cation Interactions

Catastrophic Failure of the Standard Model

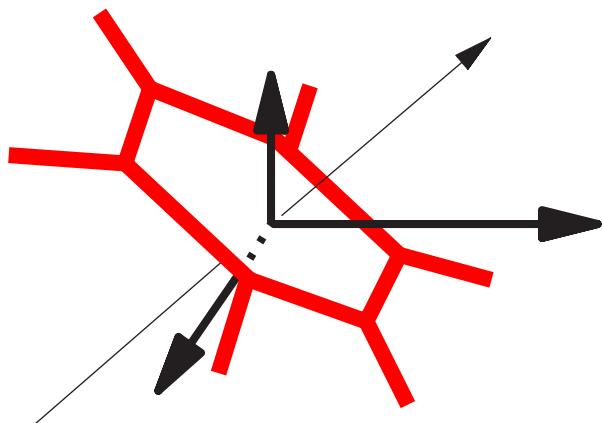
	ΔE_0	K^+ -Centroid	ΔH_{298}
OPLS-AA	-9.32	2.90	
CHARMM27	-11.06	2.81	
Amber <i>ff94</i>	-12.55	2.74	
Amber <i>ff02</i>	-15.87	2.63	
AMOEBA	-19.27	2.81	-18.15
MP2/6-311+G(2d,2p)	-18.4	2.81	
MP2/aVQZ	-19.9	2.79	
CCSD(T)/CBS	-20.6	2.79	-20.1
Expt (HPMS)			-18.3
Expt (CID)			-17.7

Ion Selectivity by Benzene-Water



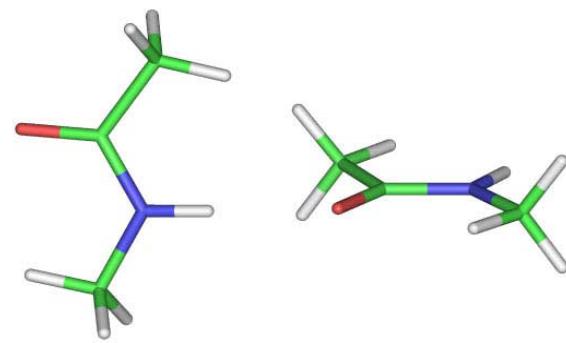
Molecular Dipole Polarizability

$$\mathbf{E} = [0.1, 0.1, 0.1]$$



- 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

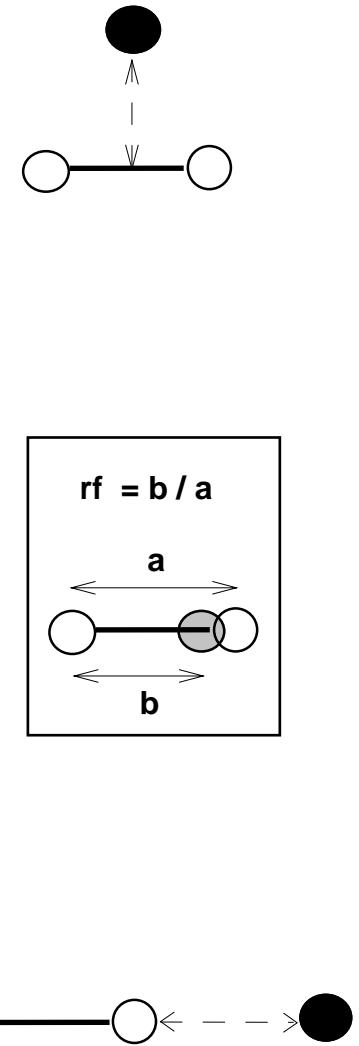
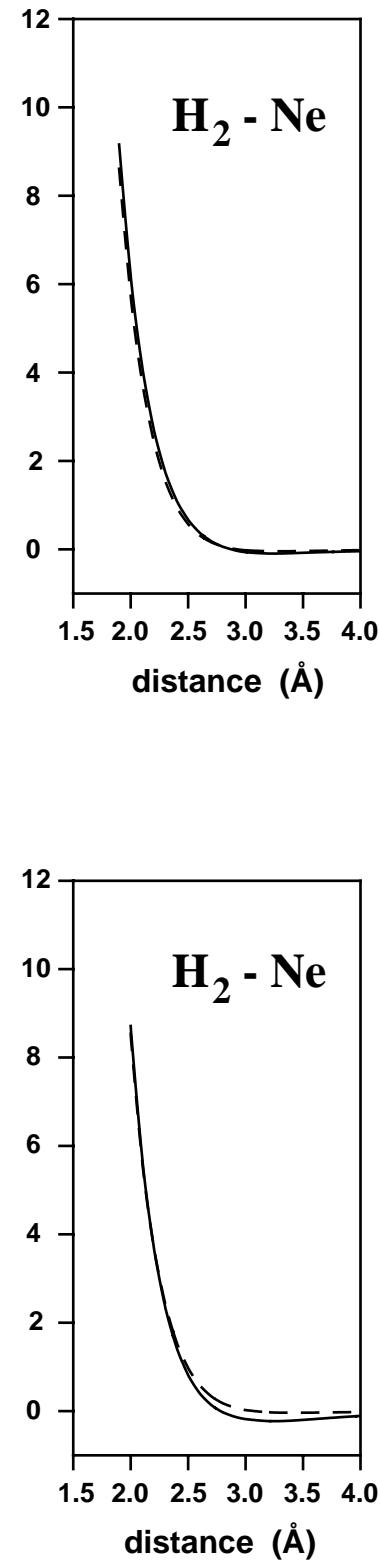
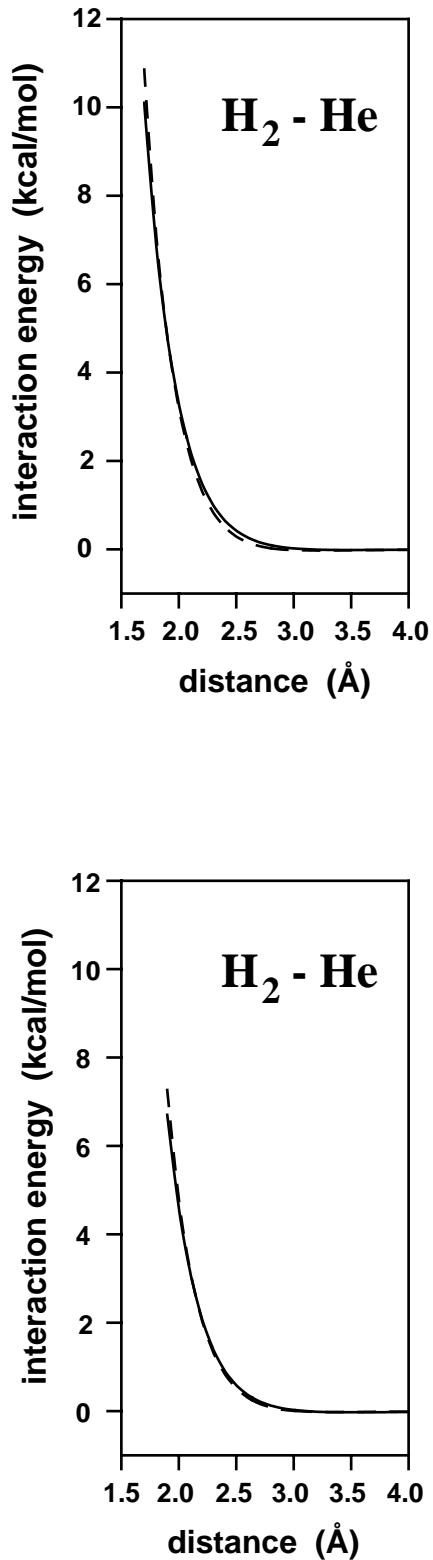


	Dimer DMA/ QM Dipoles	Monomer DMA	Monomer DMA + Polarization
ESP RRMS	6.9 %	16.6 %	6.5 %
Total Dipole	7.88	6.64	7.83
Dx	7.73	6.46	7.69
Dy	0.09	0.01	0.03
Dz	1.51	1.52	1.48

	Dimer DMA/ QM Dipoles	Monomer DMA	Monomer DMA + Polarization
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 Homodiatom Molecules

H₂

3.50 0.010 0.80

N₂

3.72 0.076 1.04

O₂

3.39 0.106 0.99

F₂

3.22 0.109 0.96

Ne

3.15 0.073

Cl₂

3.925 0.340 0.935

Ar

3.82 0.260

Kr

4.09 0.359

Xe

4.37 0.498

T
(K)

P
(atm)

Density (g/cm³)

H_{vap} (kcal/mol)

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>van der Waals</i>	R^0 (Å)	ϵ (kcal/mol)	<i>H Multipoles</i>	(a.u.)
O	3.405	0.110	Q	0.25983
H	2.655	0.0135	d_x	-0.03859
H _{reduction}	91%		d_y	-0.05818
<i>Polarizability</i>	α (Å ³)		Q_{xx}	-0.03673
O	0.837		Q_{yy}	-0.10739
H	0.496		Q_{xz}	-0.00203
			Q_{zz}	0.14412

Water Dimer Equilibrium Properties

	<i>AMOEBA</i>	<i>ab initio</i>	<i>exp</i>
D_e	4.96	4.98 ^a	5.02 ^b
$r_{\text{O-O}}$	2.892	2.907 ^a	2.912 ^b
α	4.18	4.2 ^a	5.5 ^b
θ	57.2	56.9 ^a	55.6 ^b
$\langle \mu_{\text{mol}} \rangle$	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.

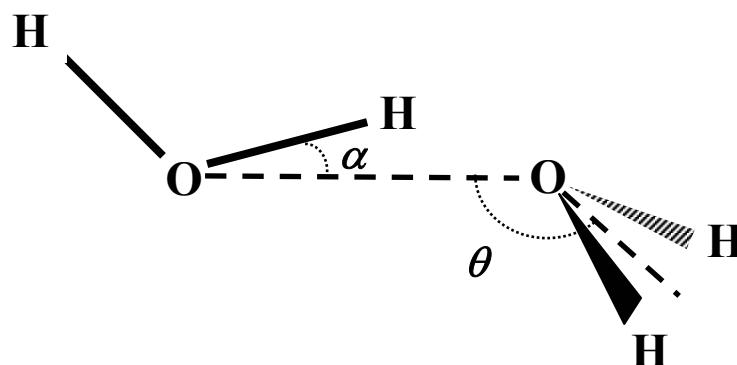
^b Complete basis set estimate from correction of CCSD(T) calculations.

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

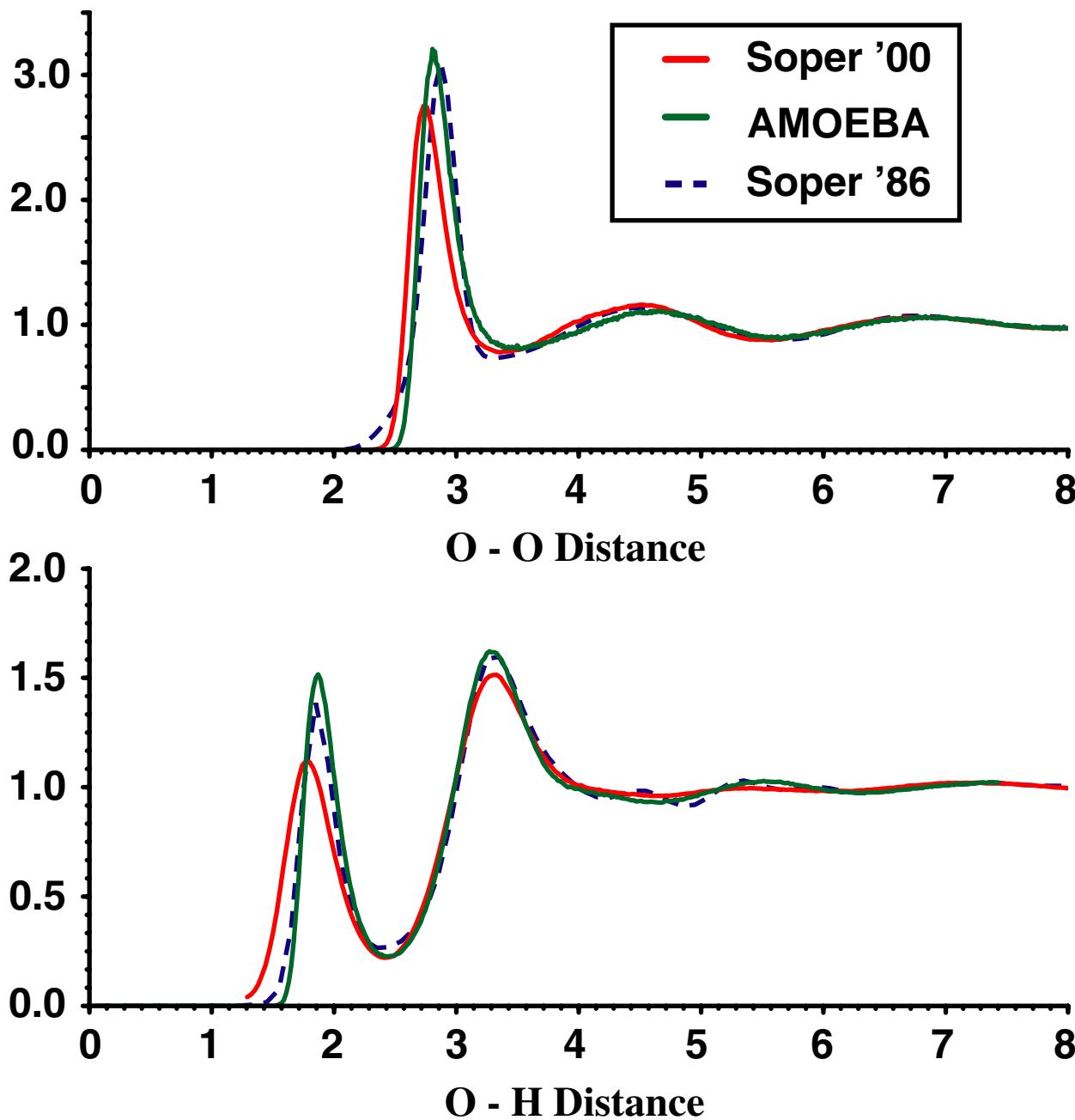
^d From MP2/TZ2P++ calculations.

^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

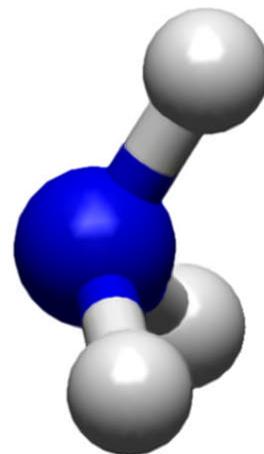
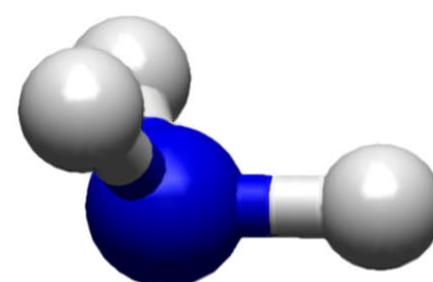


	Expt	AMOEBA
Heat Vaporization (kcal)		
298K	10.51	10.48
Density (g/cc)		
298K	0.997	1.000
323K	0.988	0.992
363K	0.962	0.964
Dielectric Constant		
273K	87.7	86.8
298K	78.3	80.7
323K	69.9	66.5
Diffusion (10^{-5} cm/s 2)		
298K	2.3	2.0
C _p (cal/mol K)		
298K	18.0	20.9 / 27.6
Avg Mol Dipole (Debye)		
	2.6-3.0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

Ammonia

Monomer, Dimer

and Liquid



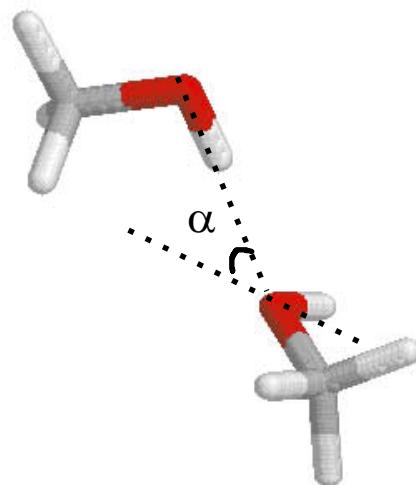
MONOMER	Dipole	Quadrupole
Expt	1.471	-2.42, -2.45
AMOEBA (unscaled)	1.528	-3.093
AMOEBA (60% Q)	1.528	-2.491

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	

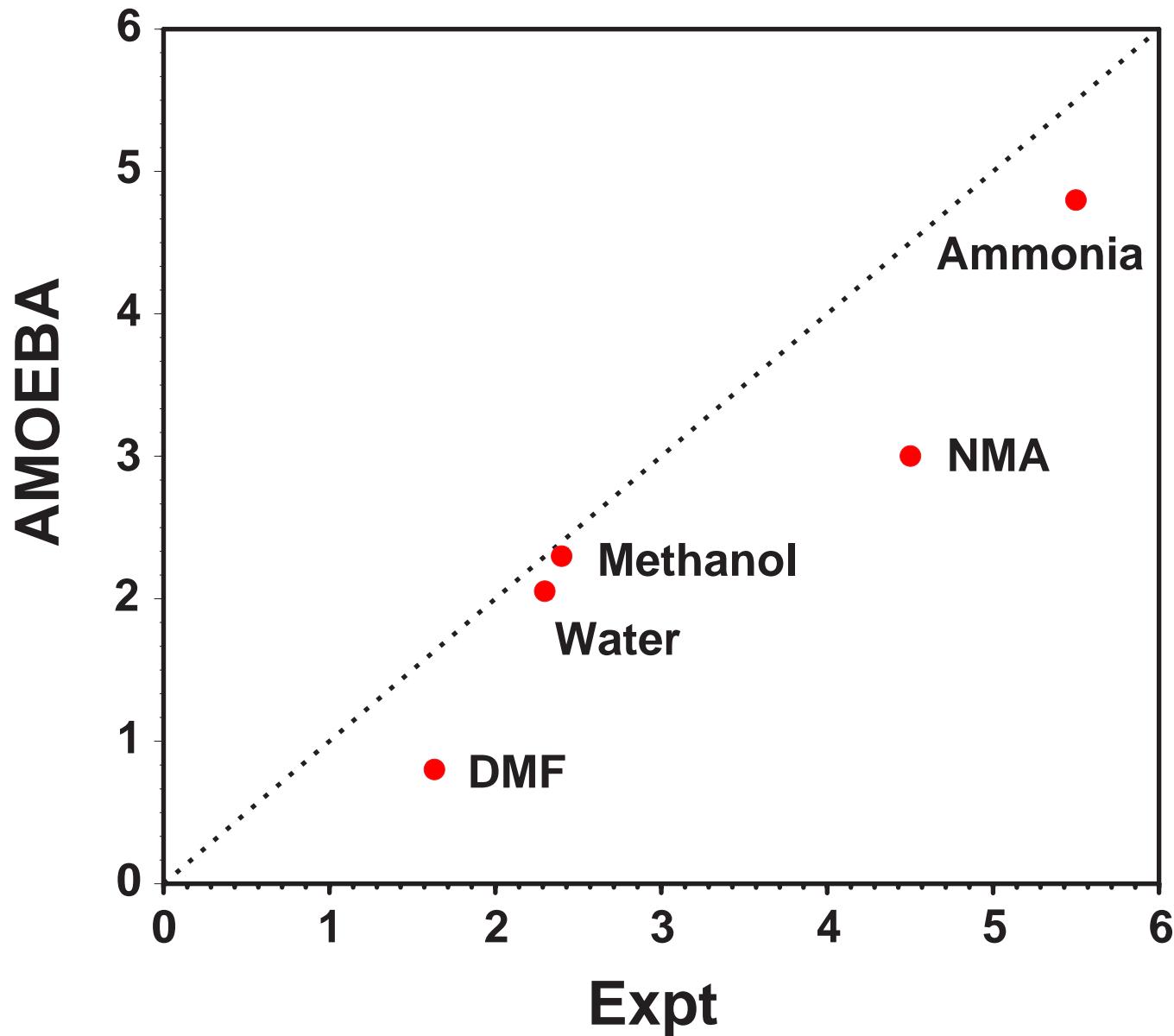
Methanol Dimer



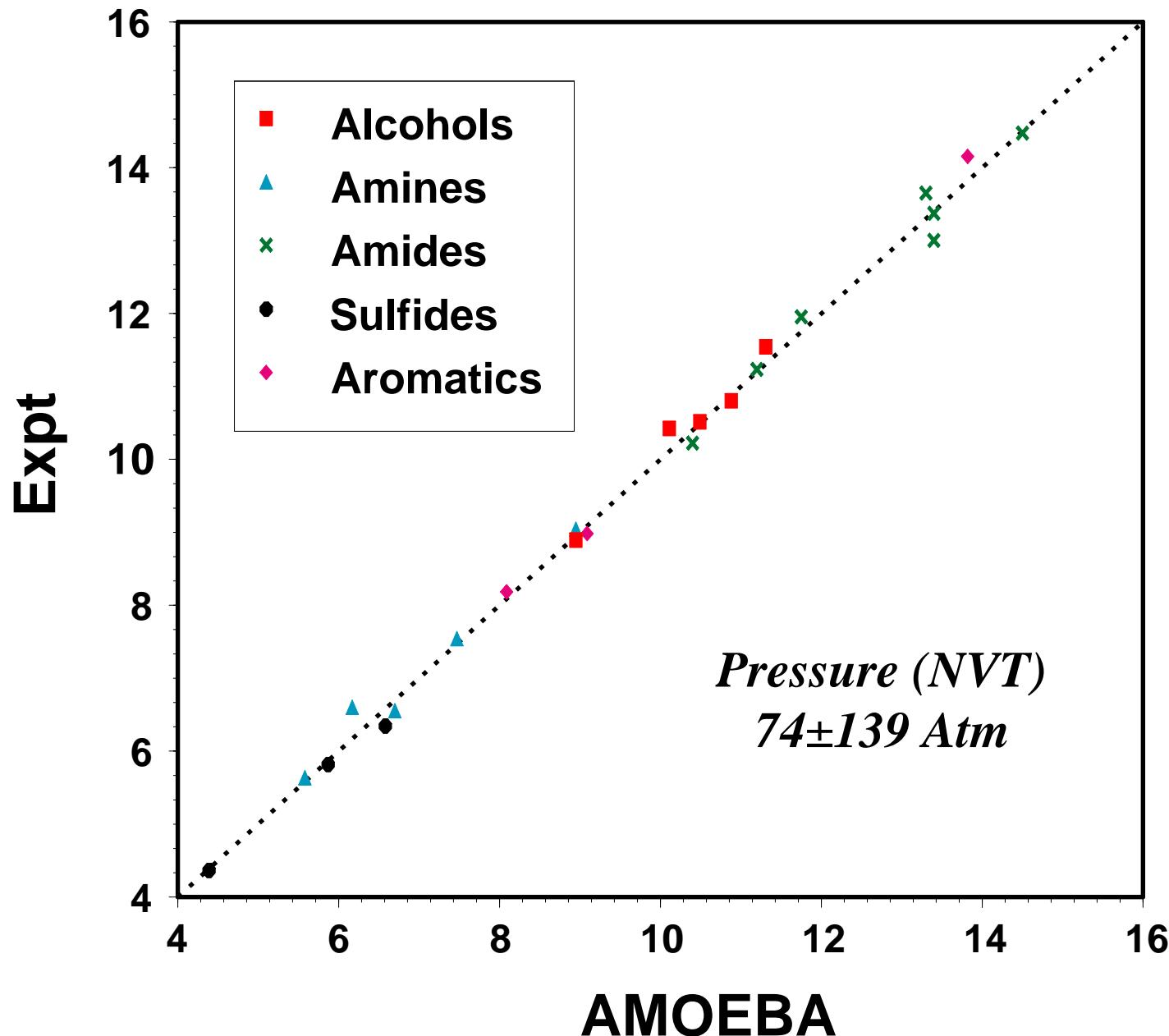
	QM #	AMOEBA	CHARMM
E (kcal/mol)	5.44	5.38	6.99
R _{O..O} (Å)	2.87	2.91	2.80
α (deg)	44	44	23
β (deg)	179	174	178

MP2 Calculations from Mooij, *et al.*, 1999

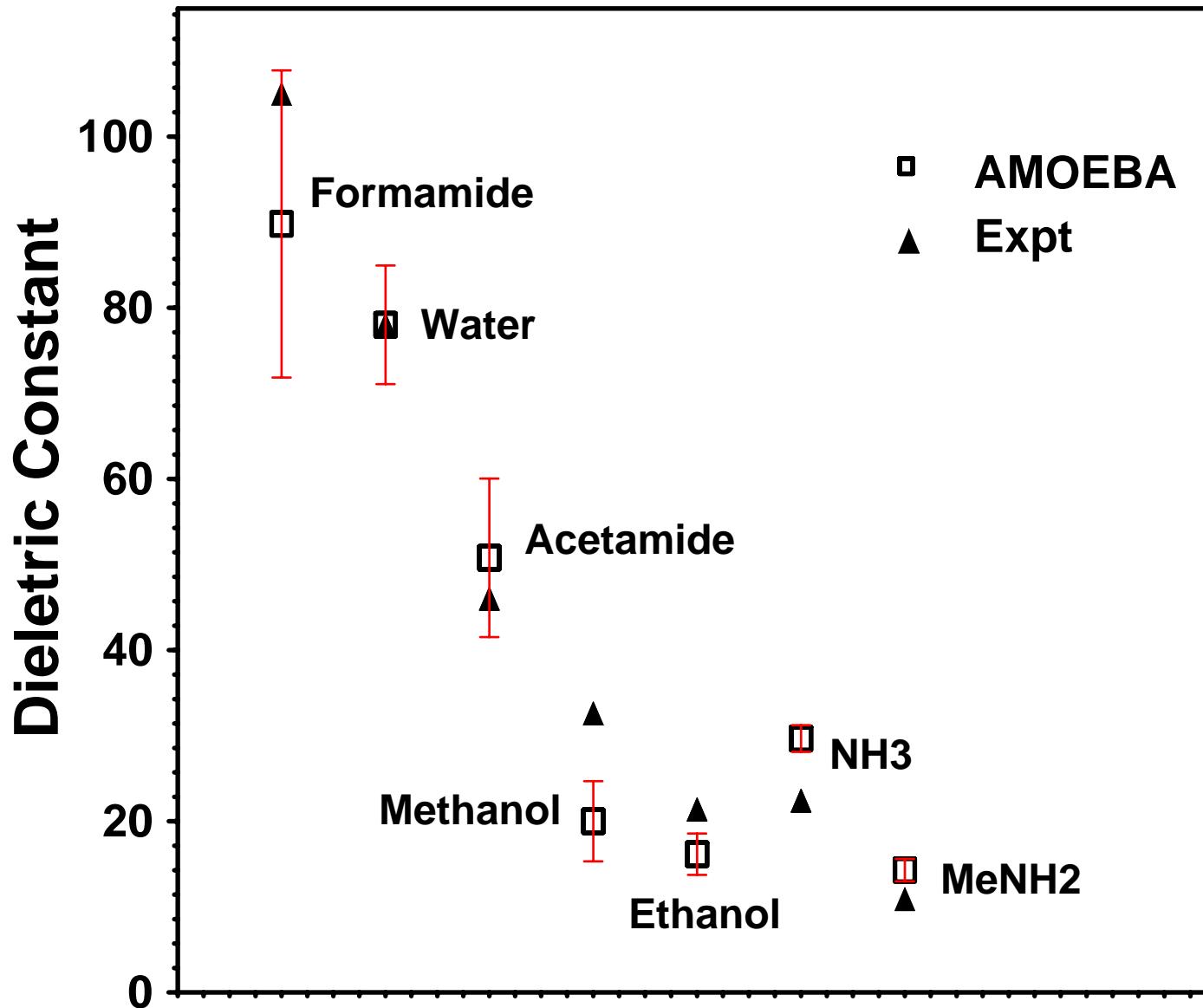
Self-Diffusion Coefficient ($10^{-5} \text{ cm}^2/\text{s}$)



Heat of Vaporization (kcal/mol)



Dielectric Constants: AMOEBA vs. Expt



Formamide Dimer Energy Minima

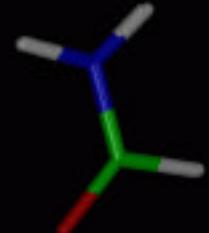


A



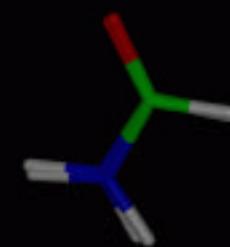
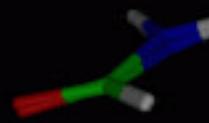
$E = -16.0 \text{ kcal/mol}$
 $rms = 0.02 \text{ \AA}$

B

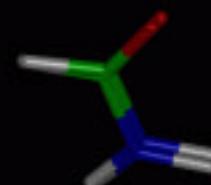


$E = -10.3 \text{ kcal/mol}$
 $rms = 0.04 \text{ \AA}$

C



$E = -9.0 \text{ kcal/mol}$
 $rms = 0.09 \text{ \AA}$



D

$E = -7.5 \text{ kcal/mol}$
 $rms = 0.28 \text{ \AA}$

E



$E = -7.3 \text{ kcal/mol}$
 $rms = 0.03 \text{ \AA}$



F

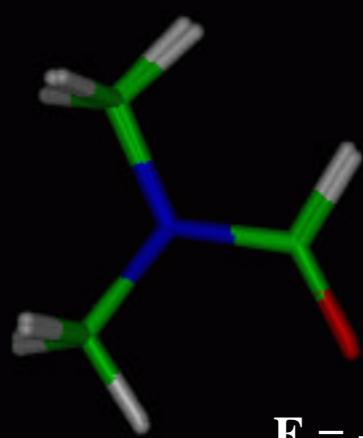


$E = -5.5 \text{ kcal/mol}$
 $rms = 0.05 \text{ \AA}$

Formamide Dimer Association Energies

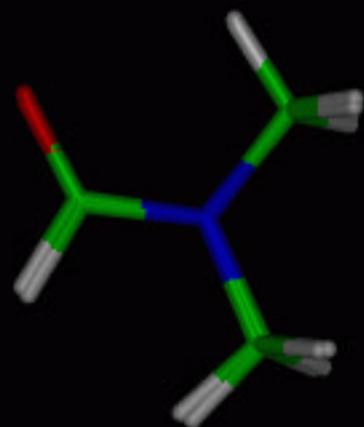
	A cyclic	B side	C nonplan	D nonplan	E side	F head-tail
MP2/6-31G**	-13.4	-8.5	-6.9	-5.8	-6.1	-3.6
B3LYP/6-31G(d)	-13.4	-8.3	-6.7	-6.0	-6.7	-3.2
<i>MP2/aug-cc-pVTZ</i>	-16.1	-10.6	-8.2	-7.2	-6.9	-5.4
AMOEBA	-16.0	-10.3	-9.0	-7.5	-7.3	-5.5
<i>RMS</i>	0.02	0.04	0.09	0.28	0.03	0.05
OPLS-AA	-14.2	-7.8	-8.2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

Comparison of DMF Dimers: AMOEBA vs Dixon/Hay



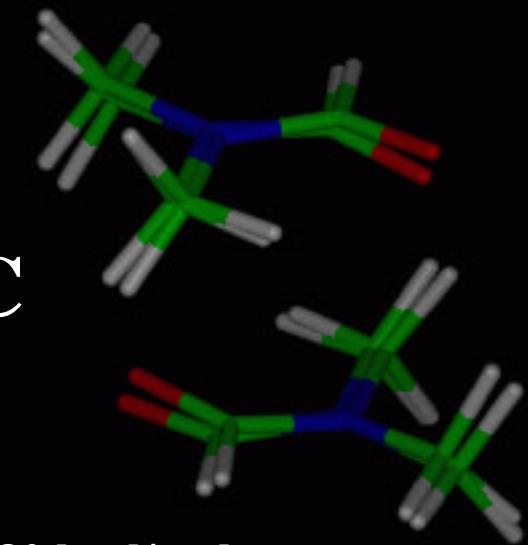
A

$E = -4.97 \text{ kcal/mol}$
 $rms = 0.08\text{\AA}$



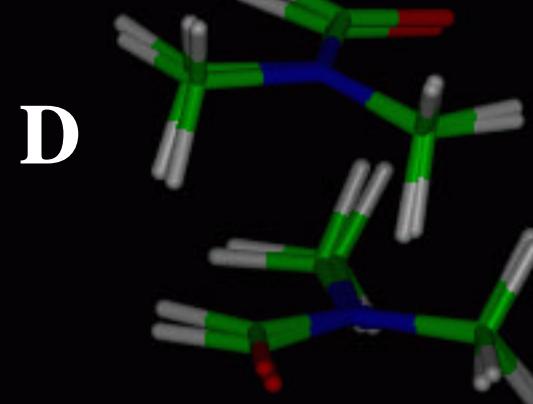
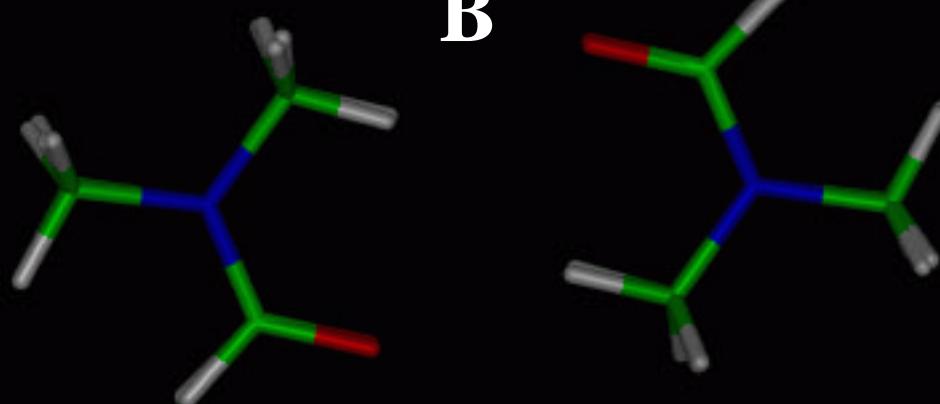
B

$E = -5.37 \text{ kcal/mol}$
 $rms = 0.09\text{\AA}$



C

$E = -7.80 \text{ kcal/mol}$
 $rms = 0.24\text{\AA}$



D

$E = -8.79 \text{ kcal/mol}$
 $rms = 0.15\text{\AA}$

Dimethylformamide Dimer Structure and Energy

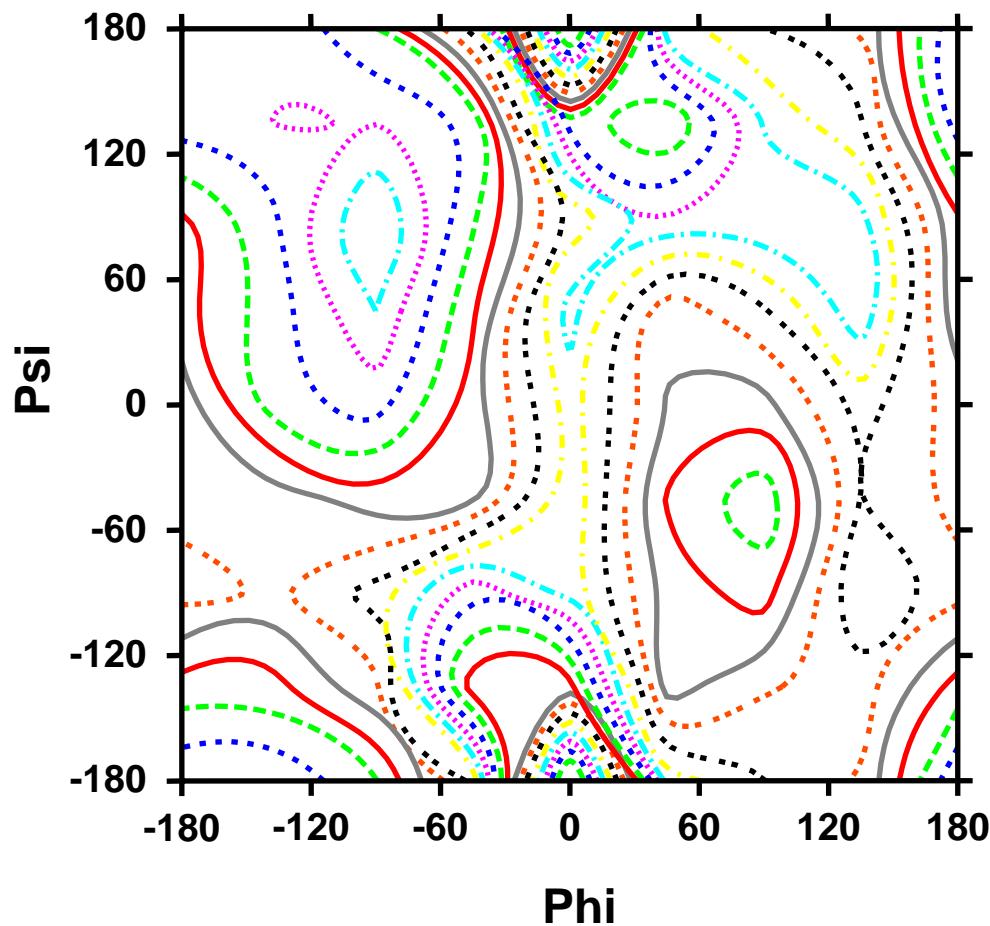
	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>
MP2/DZP+diffuse #	-6.61	-5.51	-10.32	-10.98
BSSE Corrected	-4.07	-3.31	-5.86	-6.36
MP2/aug-cc-pVTZ #	-6.95	-5.82	-11.41	-12.11
BSSE Corrected	-5.35	-4.14	-8.34	-8.90
AMOEBA (single)	-4.94	-5.03	-7.37	-8.60
AMOEBA (opt)	-4.97	-5.37	-7.80	-8.79
<i>RMS</i>	0.08	0.09	0.24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

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

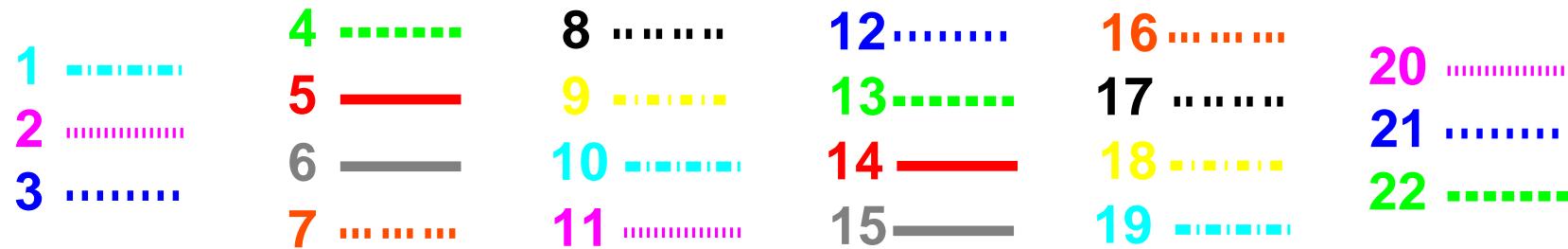
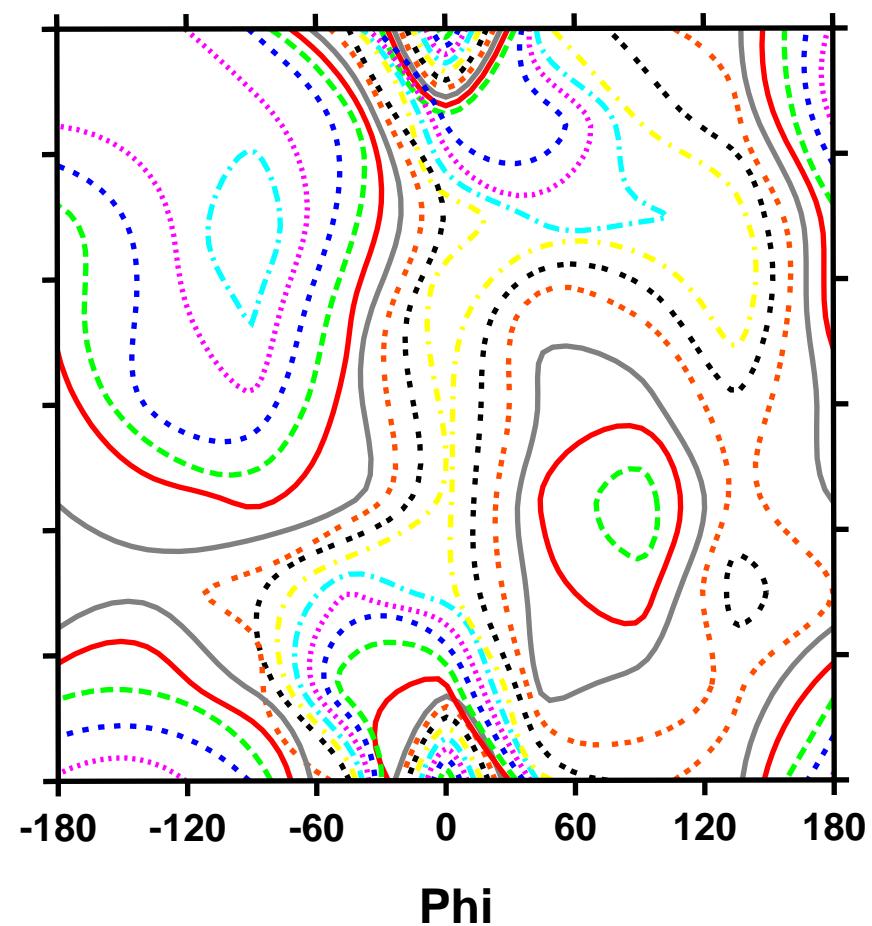
Parameterization for Polypeptides

- 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

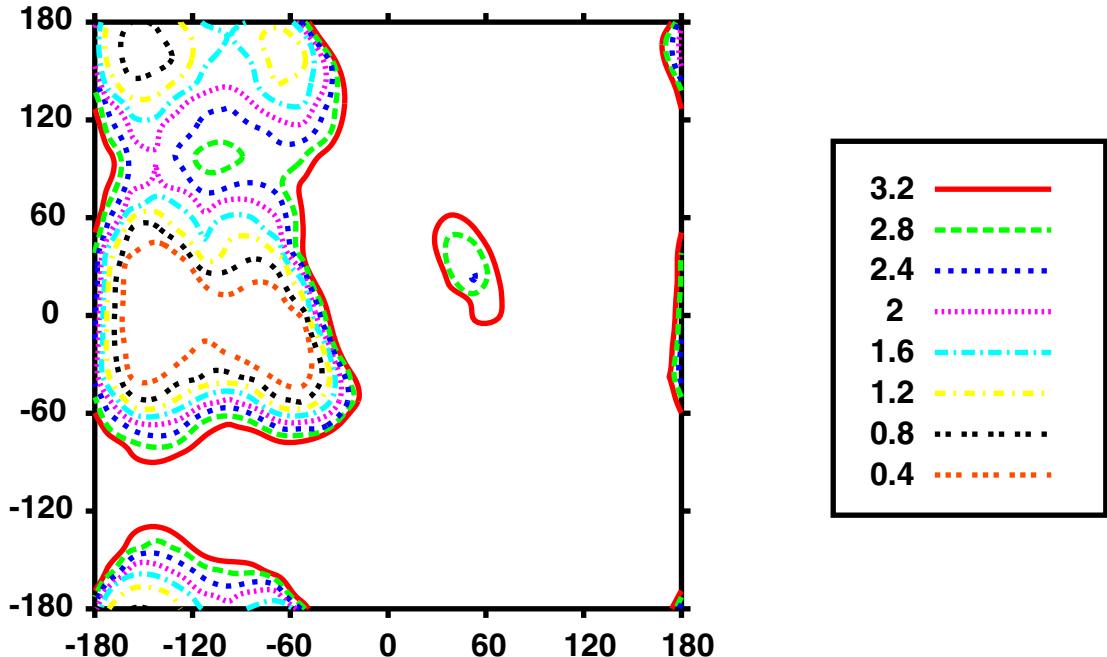
MP2/6-311+G(2d,2p)



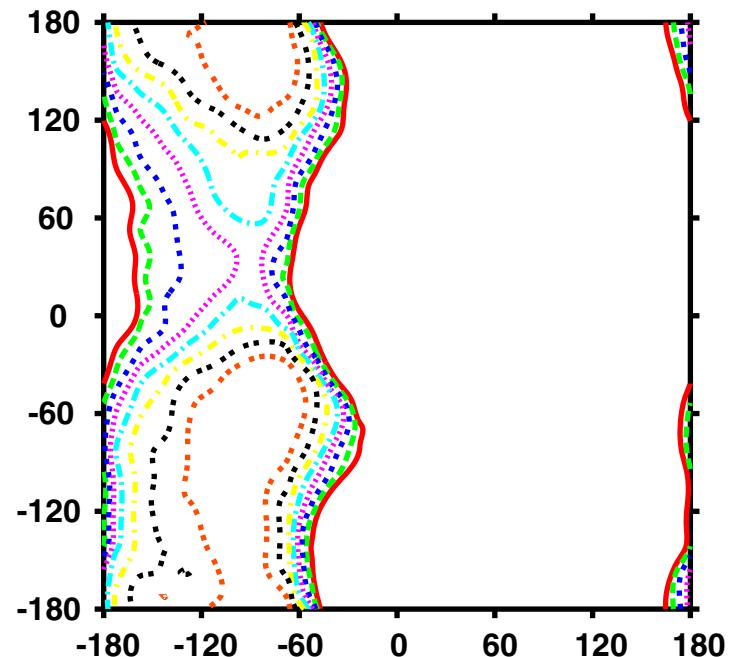
LMP2/cc-pVTZ(-f)



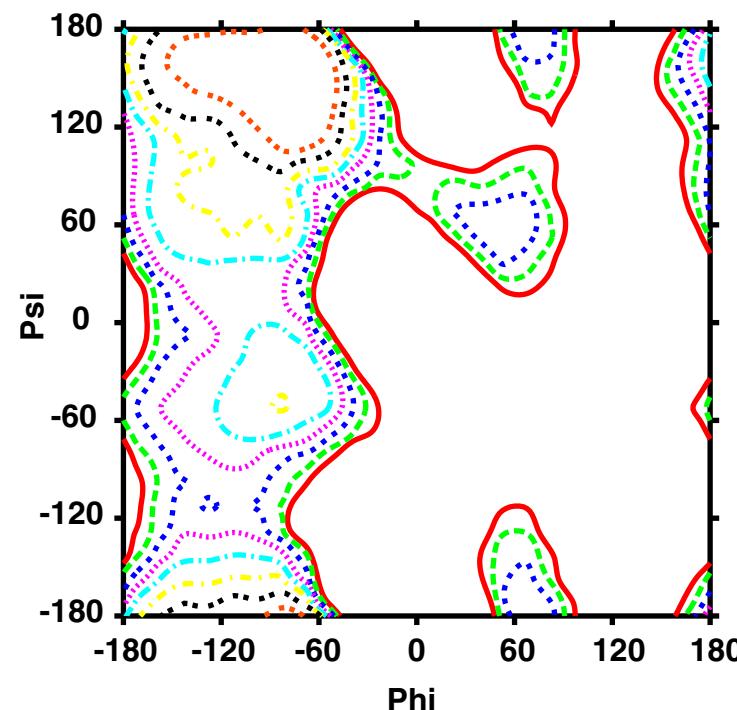
AMBER ff99



CHARMM27



OPLS-AA



*Solvated
Alanine
Dipeptide*

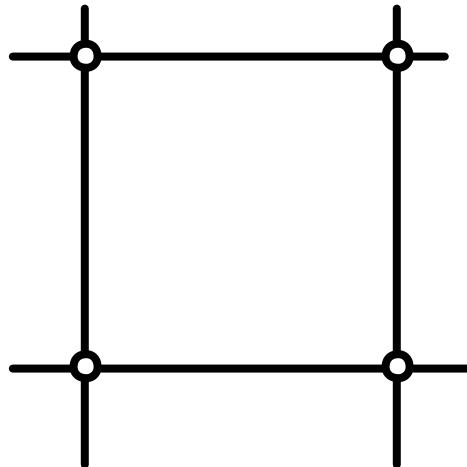
*Free
Energy
Surfaces*

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:

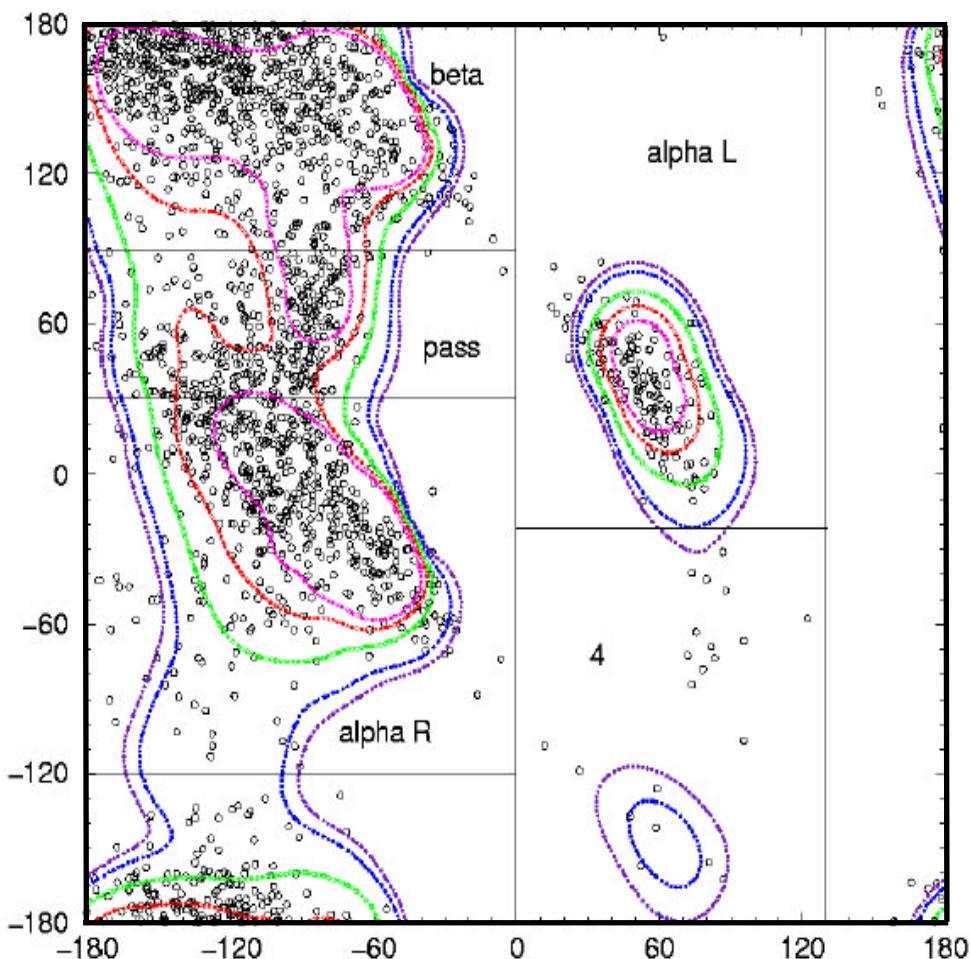
- z
- $\partial z / \partial x$
- $\partial z / \partial y$
- $\partial z^2 / \partial x \partial y$

Output:

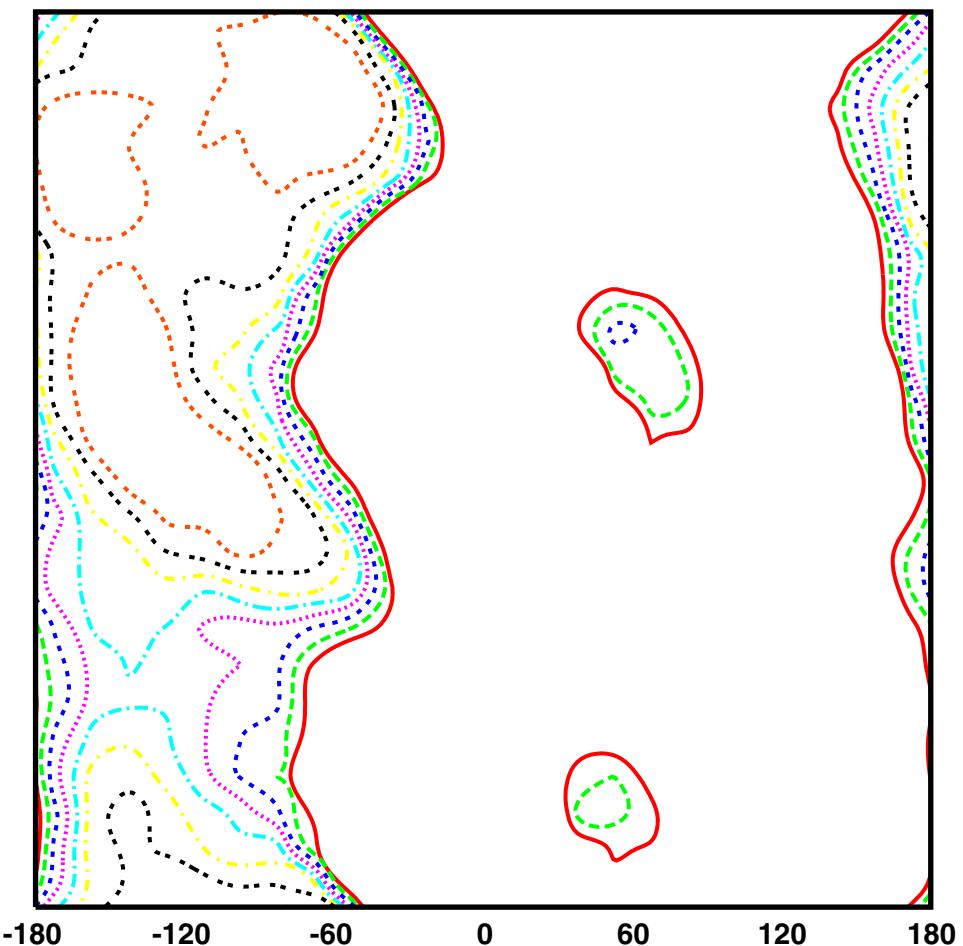
- $z(x_i, y_i)$
- Smooth first derivative
- Continuous second derivatives

Comparison of QM/MM, PDB and AMOEBA Results

QM/MM vs. PDB



AMOEBA
(Fixed Charge Water)



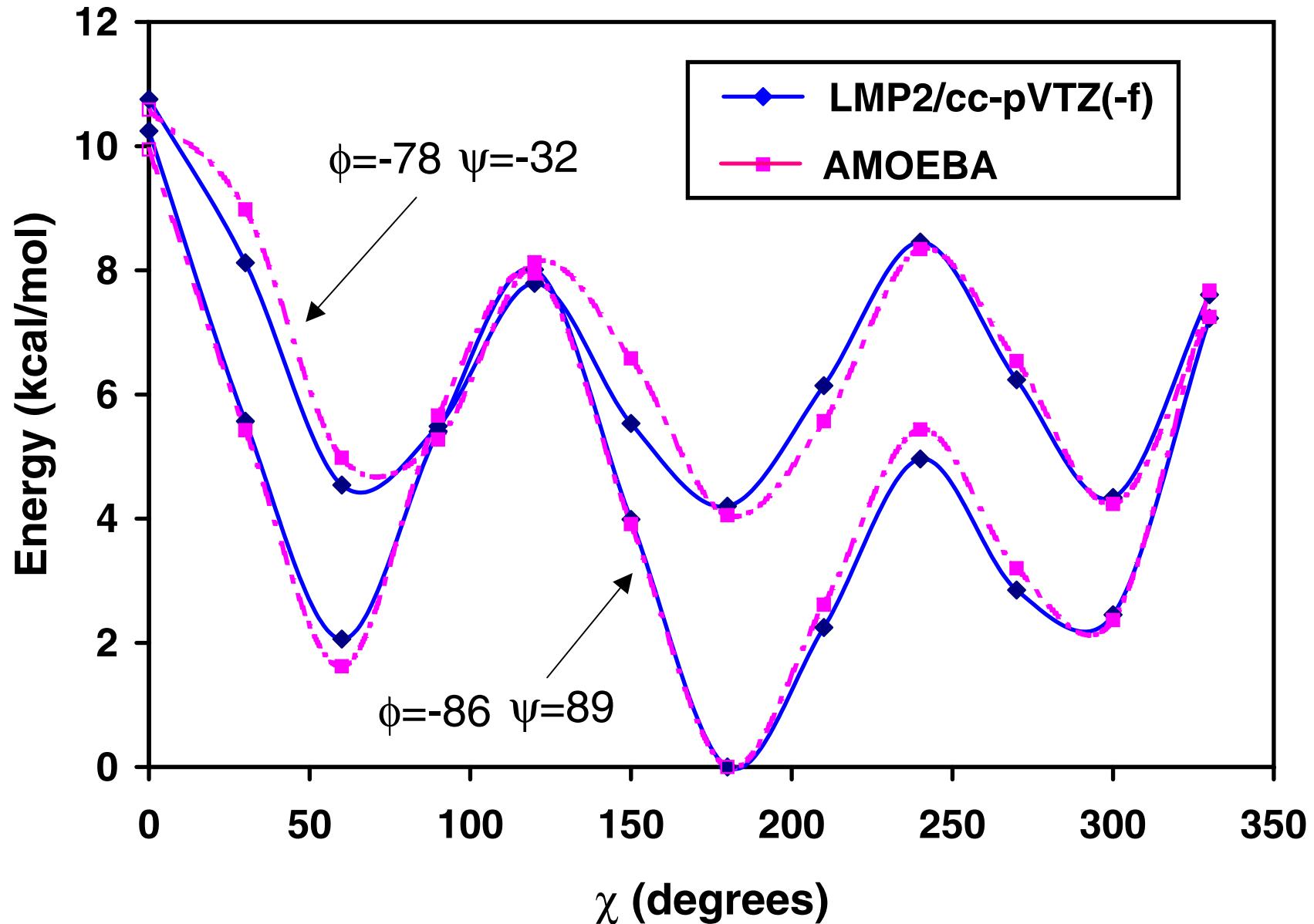
*QM/MM, Jan Hermans, UNC
PDB, Jane Richardson, Duke*

3.6 —
3.2 —
2.8 —
2.4
2 —
1.6
1.2
0.8
0.4 —

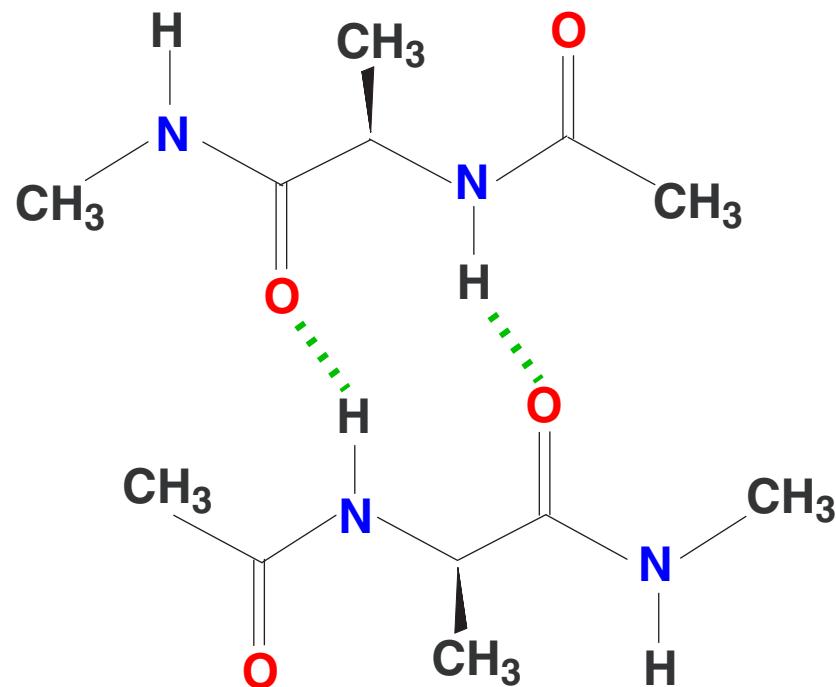
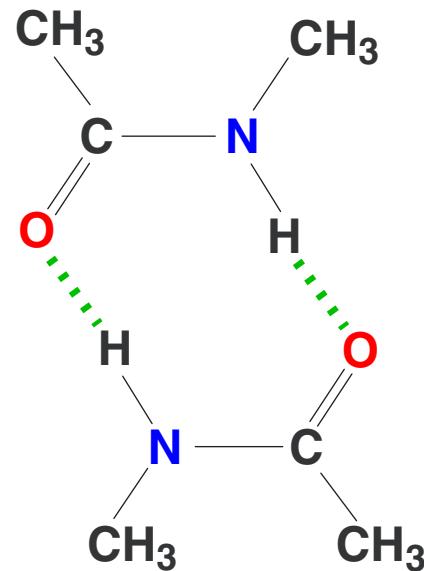
Conformational Populations

	<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)