Computational Material Science
Part I

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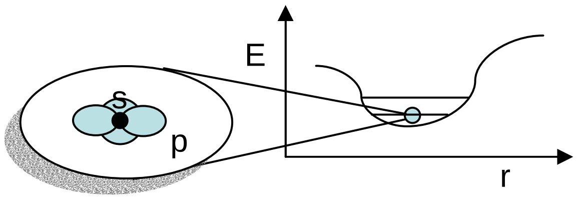
Chemical systems

Bond forming/breaking?
Force field parameter missing?
Smaller than 150 atoms?
Charges of interest?
Orbital information needed?
Excited state?

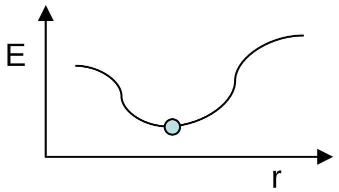
Many structures of similar energies?
Movement of surrounding molecules important?
Need QM or MM for potential energy surface?

QM



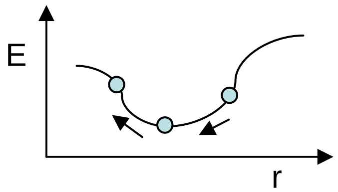
$H\Psi = E\Psi$

MM



$E = \frac{1}{2} kx^2 + \ldots$

MD/MC



$\langle E \rangle$

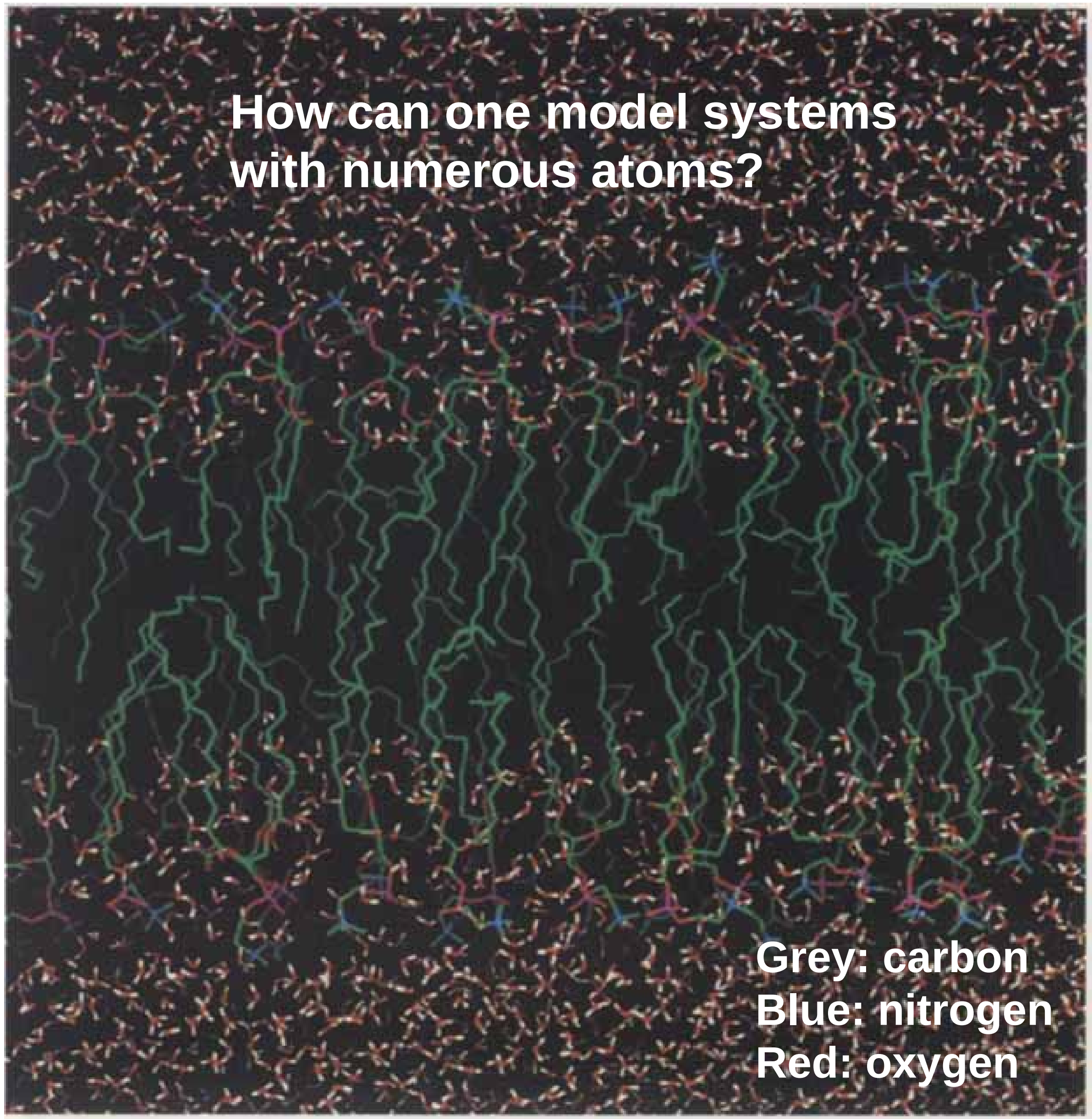
More examples about when molecular dynamic of Monte Carlo simulations are needed

- Adsorption energy of a substance in a porous materials (average of a large number of molecules on different adsorption sites).
- Simulation of lipids, proteins, DNA…
- Study of water molecules in nanotubes

Computational Methodologies

- New tools in research (still under intensive development)
- Reliability changes when different methods used (choose the appropriate method for the property you care)
- Often use the “important” part to carry out the simulation

How can one model systems with numerous atoms?



Grey: carbon
Blue: nitrogen
Red: oxygen

Fig 6.21 Snapshot from a molecular dynamics simulation of a solvated lipid bilayer [Robinson *et al.* 1994]. The disorder of the alkyl chains can be clearly seen.

Molecular Mechanics (MM)

- Born-Oppenheimer approximation: motion of electrons can be decoupled from that of nuclei.
- No electron considered in MM
- Empirical fit to PE surface
- Force field: equations and parameters that define the energy surface
- Fundamental assumptions
  - E(total) can be divided into parts
  - Parameters are transferable between similar chemical systems

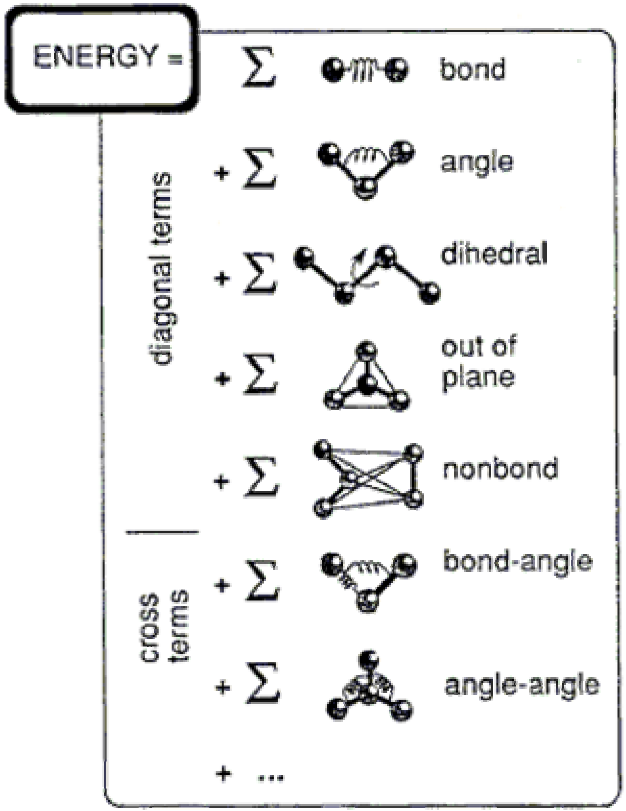


Figure 1 Schematic of molecular force field expression. Diagonal terms refer to interactions that can be expressed as a function of a single internal coordinate, whereas cross terms introduce coupled interactions involving two or more coordinates.

Molecular Mechanics (MM)

- Transferability: the same set of parameters can be used to model a series of related molecules. (Do not have to define new parameters for each molecules.) E.g., alcohols share the same parameters; acids share the same parameters, alkanes share the same parameters
- Functional forms are often a compromise between accuracy and efficient computation; analytic derivatives preferred.
- Two force fields can use the same functions, but different parameters; two force fields may have different functions and parameters, but similar results.
- Avoid mixing parameters, unless tested.

Force Field

Bond stretch

Less often used b/c less amenable to efficient computation

Morse function

$$E_l = \sum D_e[1 - \exp\{-\alpha(l - l_o)\}]^2$$

D_e: dissociation energy
α: force constant
l_o: reference bond length

Simplified approximation

$$E_l = \sum k_l(l - l_o)^2$$

$$E_l = \sum k_l(l - l_o)^2 + k_l'(l - l_o)^3$$

k_l: force constant
l_o: reference bond length

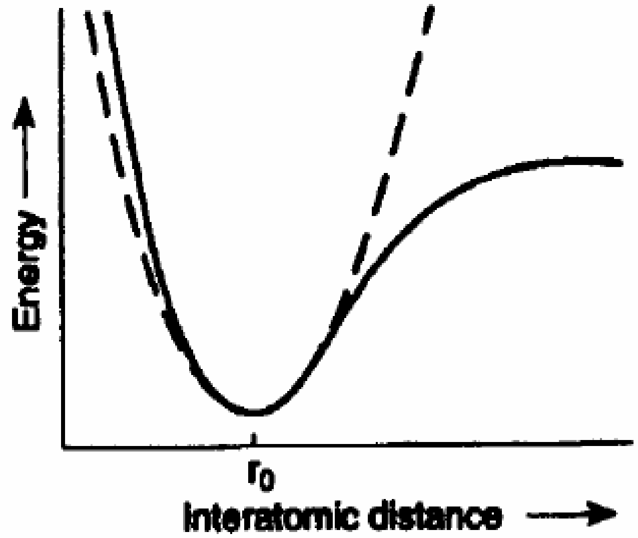


Fig. 3.2 Curves showing the variation of bond stretch energy with distance: — Morse potential; -- harmonic potential.

- **Simplified forms does not describe bond dissociation**

- **The cubic function deviates significantly from the true PES at long bond lengths, so atoms may fly apart when bad initial geometry is given.** Introduce a quartic term may eliminate the inversion problem…

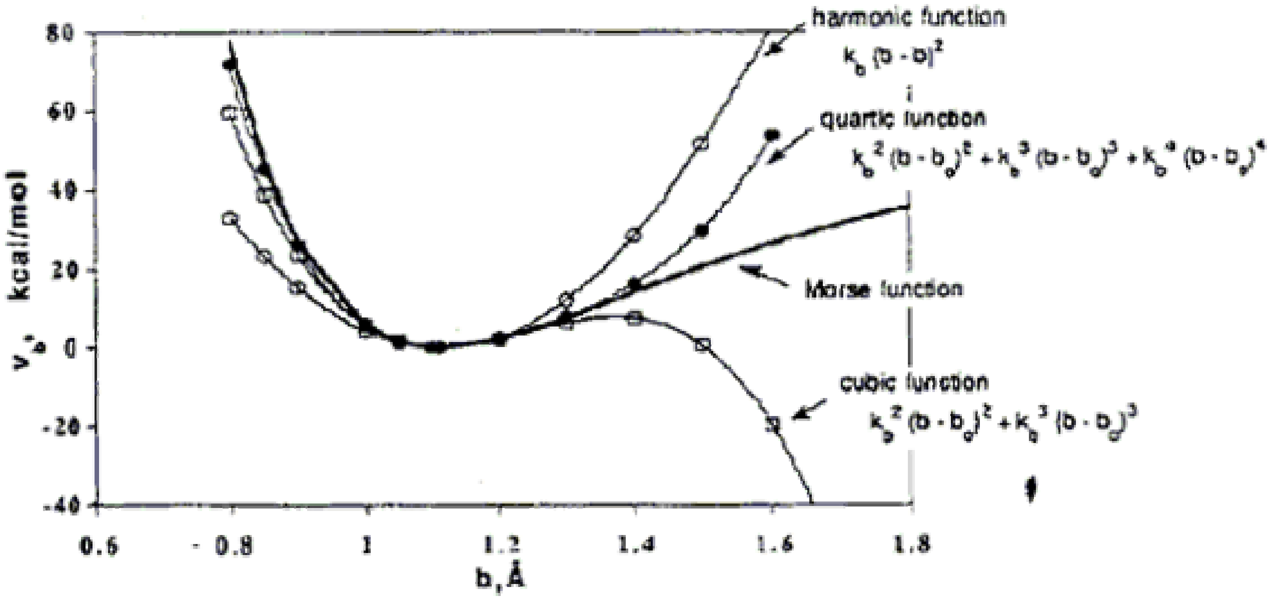
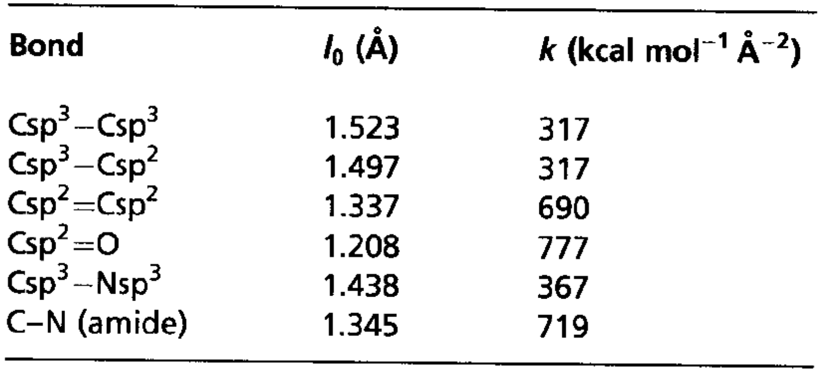


Figure 3 Schematic of a Morse function and the related harmonic, cubic, and quartic potentials (Eqs. [3] and [4]). When the bond length is increased beyond the point of the minimum, the harmonic potential rises too steeply. The cubic term corrects for the anharmonicity locally, but at longer distances turns and goes catastrophically to negative infinity. The quartic potential remains a good approximation over a relatively large range and is always attractive at large distances.



Bond	l_0 (Å)	k (kcal mol^{-1} Å^{-2})
Csp^3-Csp^3	1.523	317
Csp^3-Csp^2	1.497	317
$Csp^2=Csp^2$	1.337	690
$Csp^2=O$	1.208	777
Csp^3-Nsp^3	1.438	367
C–N (amide)	1.345	719

Table 4.1 Force constants and reference bond lengths for selected bonds [Allinger 1977].

- Notice force constants are different for single and double bonds
- 0.2 Å from the reference value raise the energy by 12 kcal mol^{-1} with a 300 kcal mol^{-1} Å^{-2} force constant
- $\boldsymbol{l_o}$ is sometimes called “equilibrium” bond length or “natural” bond length. Note that there are other functions in the force field, so the calculated bond length may not be the same as $\boldsymbol{l_o}$
- When comparing experimental and calculated bond lengths, kept in mind the following:
  - ! Bond lengths from different exptl. techniques give different results
  - ! Temp. also affects the exptl. bond length values (room temp libration in X-ray structure cause errors as large as 0.015 Å)
  - ! The calculated bond length corresponds to a hypothetical motionless state; **MM2** was parameterized to fit the values obtained by electron diffraction, which give the mean distances between atoms averaged over the vibrational motion at room temperature

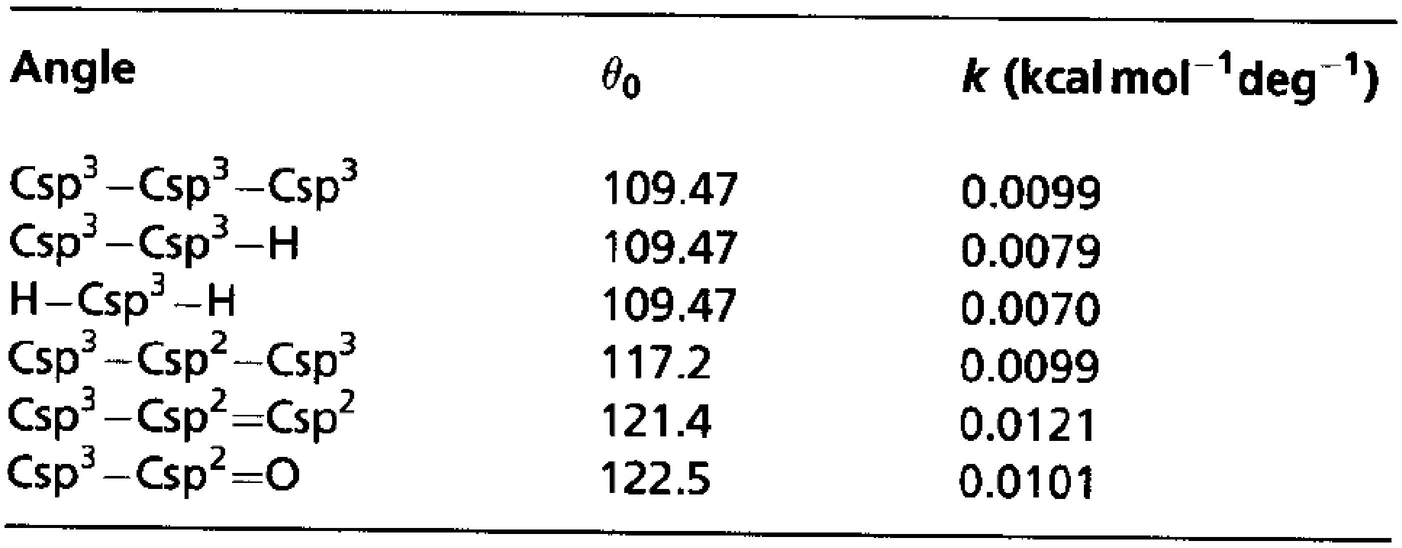
Bond angles

$$E_\theta = \sum k_\theta(\theta - \theta_o)^2$$ + higher order terms

k_θ: force constant
θ_o:equilibrium bond angle

For highly strained systems, different sets of parameters have to be used

e.g.



Angle	θ_0	k (kcal mol^{-1}deg^{-1})
$Csp^3-Csp^3-Csp^3$	109.47	0.0099
Csp^3-Csp^3-H	109.47	0.0079
$H-Csp^3-H$	109.47	0.0070
$Csp^3-Csp^2-Csp^3$	117.2	0.0099
$Csp^3-Csp^2{=}Csp^2$	121.4	0.0121
$Csp^3-Csp^2{=}O$	122.5	0.0101

Table 4.2 Force constants and reference angles for selected angles [Allinger 1977].

- Notice the force constants are much smaller than the bond length force constants

Dihedral angles (Torsional angles)

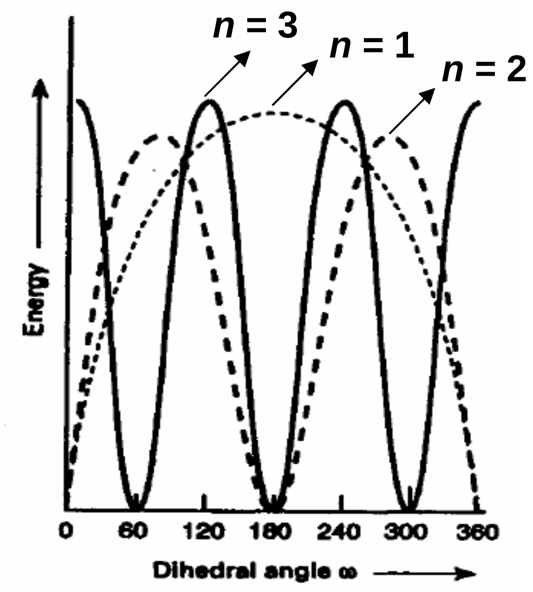


Fig. 3.3 Variation of energy with dihedral angle for one-(···), two-(--) and threefold (—) barriers.

$$E_\omega = \sum V_n (1 + s \cos n\omega)$$

V_n: related to rotational barrier height

n: periodicity of rotation

n = 2 is important for sp^2 species

e.g. ethene $H_2C{=}CH_2$

n = 3 is important for sp^3 species

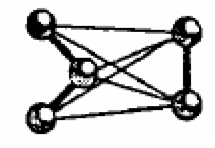
e.g. ethane $H_3C\text{-}CH_3$

s: 1 or -1

ω: dihedral angle

Note: the overall rotational barrier height also has contributions from non-bonded interations.

Non-bonded interactions



distance dependent interactions calculated for all atoms with a 1,4 or greater separation

- **van der Waals interactions**

Long-range attractive force

dispersive force (London force): instantaneous dipole, which arises during fluctuations in the electron clouds, induce a dipole in neighboring atoms, giving rise to an attractive inductive effect

Short-range repulsive force

repulsion between two incompletely shielded nuclei

Lennard-Jones potential

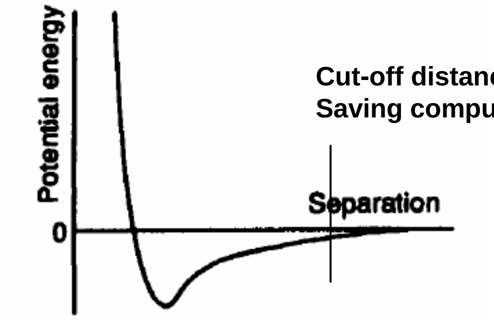
$$E_{vdw} = \sum \varepsilon[(r_m / r)^{12} - 2(r_m / r)^6]$$

ε: well depth

r_m: minimum energy interaction distance

Buckingham potential

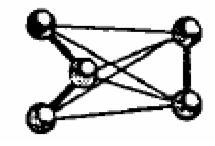
$$E_{vdw} = A\exp(-Br) - Cr^{-6}$$



Cut-off distance for Saving computing time

Fig. 3.4 A typical van der Waals curve.

Non-bonded interactions



distance dependent interactions calculated for all atoms with a 1,4 or greater separation

- **Electrostatic interactions**

Coulomb's law

$$E_{el} = \sum q_i q_j / D r_{ij}$$

***q*: atomic charge**

***D*: dielectric constant of environment; = 1 for gas phase calculation sometimes as a function of distance to damp the long distance interactions**

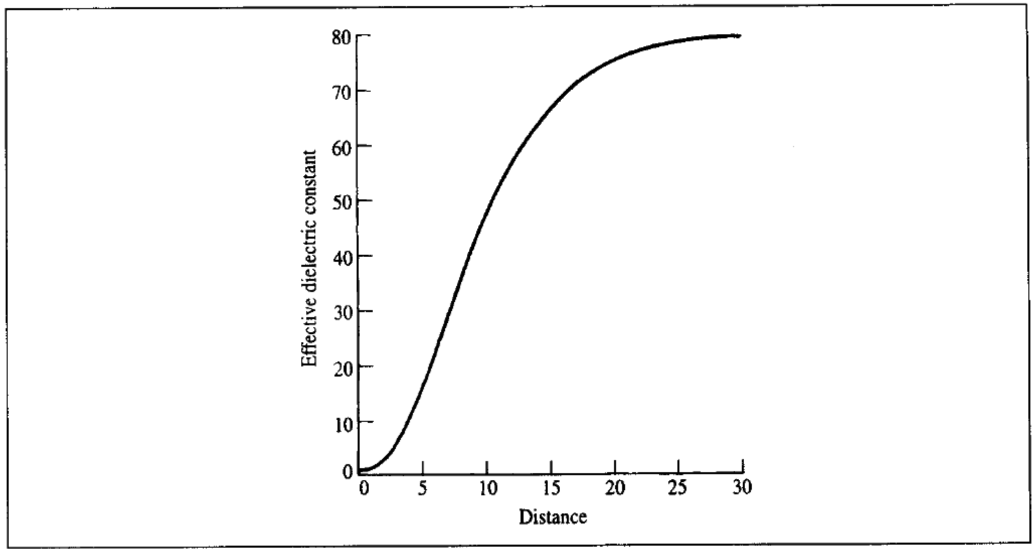


Fig. 4.30: A sigmoidal dielectric model smoothly varies the effective permittivity from 80 to 1 as shown.

- The dilemma of dielectric constant

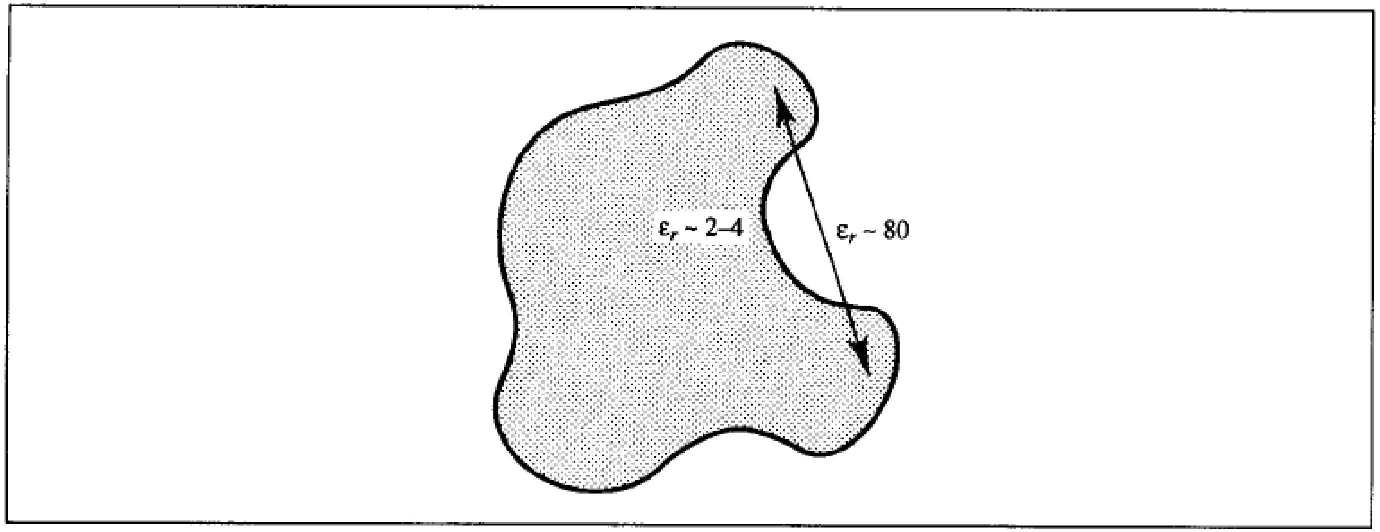
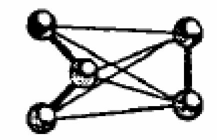


Fig. 4.31: A line joining two points may pass through regions of different permittivity.

Should the dielectric constant of solute to be used, or that of the solvent?



Effective pair potential!

- Polarization effect and many-body effect not considered explicitly; may be included implicitly through parameterization

  E.g.: dipole of gas phase water: 1.85 D

  in most water model: close to liquid water 2.6 D

- no good for metals and semiconductors

➢Reduced Representation: United atom approach

Hydrogen next to carbon are not considered explicitly

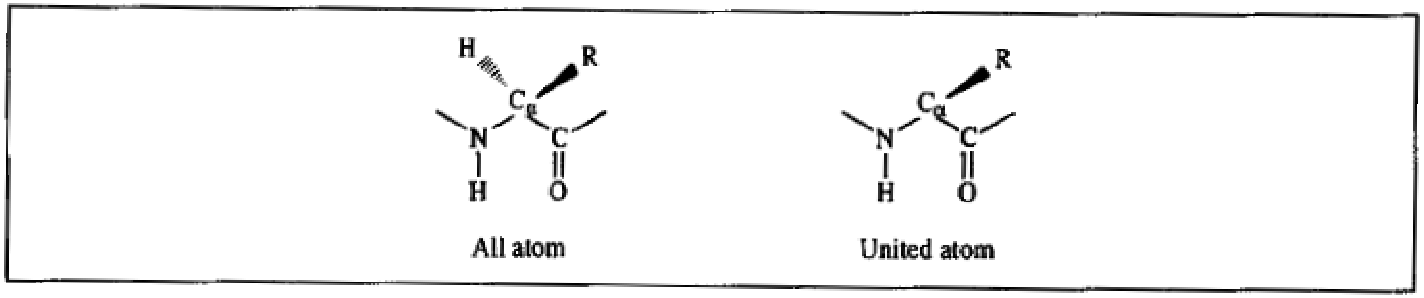


Fig. 4.42: Representations of the naturally occurring amino acids.

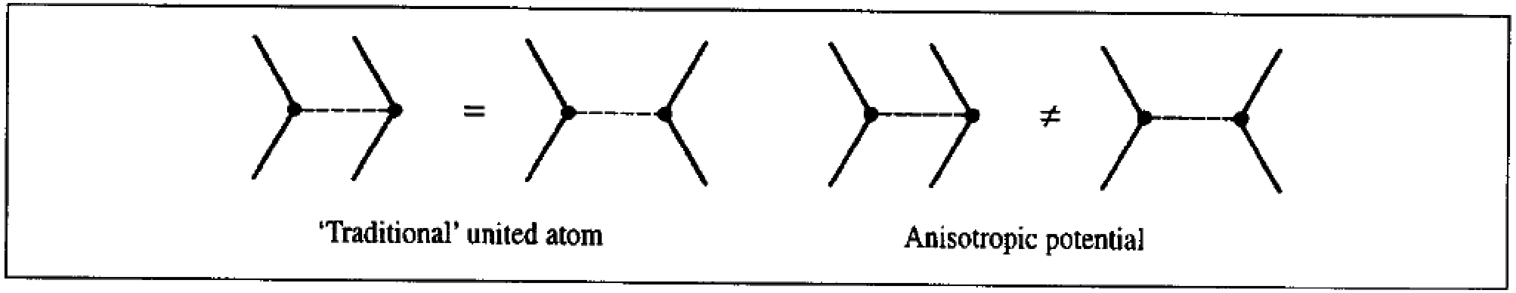


Fig. 4.43: The interaction energy between the two arrangements shown is equal in a 'traditional' united atom force field but different in the Toxvaerd anisotropic model. (Figure adapted from Toxvaerd S 1990. Molecular Dynamics Calculations of the Equation of State of Alkanes. The Journal of Chemical Physics 93:4290–4295.)

In the anisotropic model, the interaction site is at the geometrical center of the CH_2 and CH_3 group.

Other terms

not in all force fields

- **Stretch-bend**

$$E_{l\theta} = \sum\sum k_{l\theta}(l - l_o)(\theta - \theta_o)$$

- **Bend-bend**

$$E_{\theta\theta'} = \sum\sum k_{\theta\theta'}(\theta - \theta_o)(\theta' - \theta'_o)$$

- **Torsion-bend**

$$E_{\theta\theta'\omega} = \sum k_{\theta\theta'\omega}(\theta - \theta_o)(\theta' - \theta'_o)\cos\omega$$

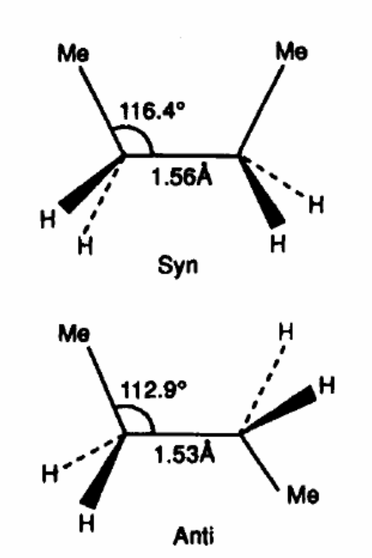
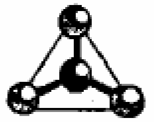


Fig. 3.5 Molecular geometries for *syn* and *anti* butane structures.

- **Out-of-plane bending**

$$E_{\text{opl}} = \sum k_\chi \chi^2$$

χ: **height above the plane**



- **Hydrogen bonding** **O-H•••O** **(Often not needed; replaced by electrostatic interactions)**

$$E_{\text{hb}} = \sum (C_{ij} / r_{ij}^{12}) - (E_{ij} / r_{ij}^{10})$$

vdw Surface/Molecular Surface/ Solvent-Accessible Surface

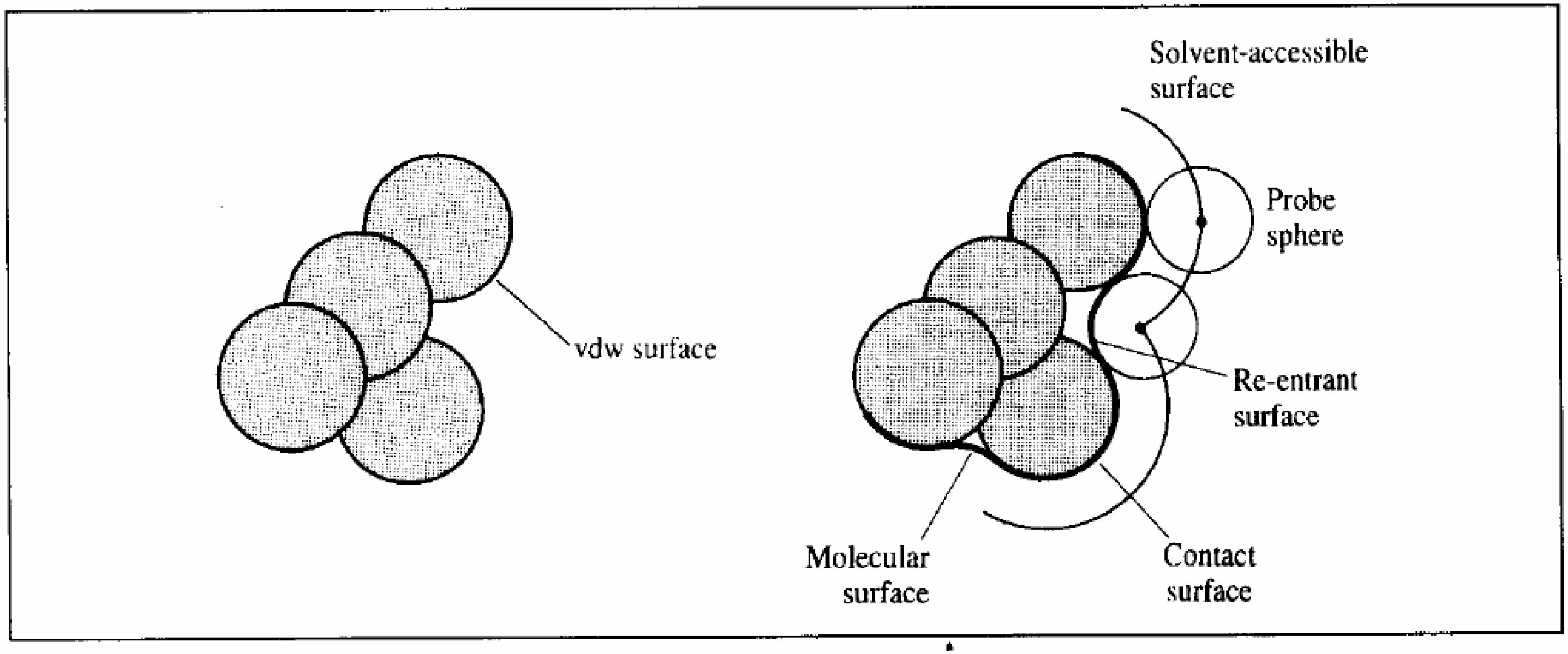
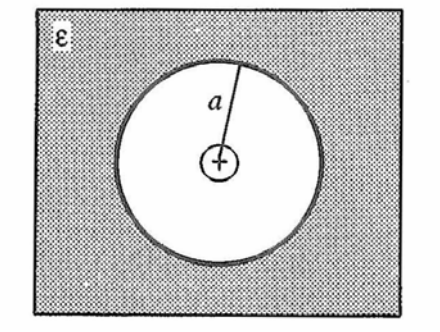


Fig. 1.6: The van der Waals (vdw) surface of a molecule corresponds to the outward-facing surfaces of the van der Waals spheres of the atoms. The molecular surface is generated by rolling a spherical probe (usually of radius 1.4 Å to represent a water molecule) on the van der Waals surface. The molecular surface is constructed from contact and re-entrant surface elements. The centre of the probe traces out the accessible surface.

Solvation free energy based the Born model

-Solvation: from vacuo to solvent

-Born model of electrostatic component of solvation free energy of an ion



vacuo **solvent**

$$\Delta G_{\mathrm{elec}} = -\frac{q^2}{2a}\left(1-\frac{1}{\varepsilon}\right)$$

***a*: radius of solvent cavity**
ε: dielectric constant

-Electrostatic component of solvation free energy of a group of atoms

$$\Delta G_{\mathrm{elec}} = -\left(1-\frac{1}{\varepsilon}\right)\sum_{i=1}^{N}\sum_{j=i+1}^{N}\frac{q_i q_j}{r_{ij}} - \frac{1}{2}\left(1-\frac{1}{\varepsilon}\right)\sum_{i=1}^{N}\frac{q_i^2}{a_i}$$

- Solvation free energy based on generalized Born equation: the GB/SA method

$$\Delta G_{sol} = \Delta G_{cav} + \Delta G_{vdW} + \Delta G_{elec}$$

$$\Delta G_{cav} + \Delta G_{vdW} = \sum \sigma_k SA_k$$

SA_k : solvent-accessible surface area
σ_k : empirical atomic solvation papmeter

$$\Delta G_{elec} = -\frac{1}{2}\left(1-\frac{1}{\varepsilon}\right)\sum_i \sum_j \frac{q_i q_j}{f_{GB}}$$

q **: atomic charge**
f_{GB}: function of *r* (interatomic distances) and *a* (or α; Born radii)

J. Am. Chem. Soc. **1990**, *112*, 6127; Leach 9.9.2

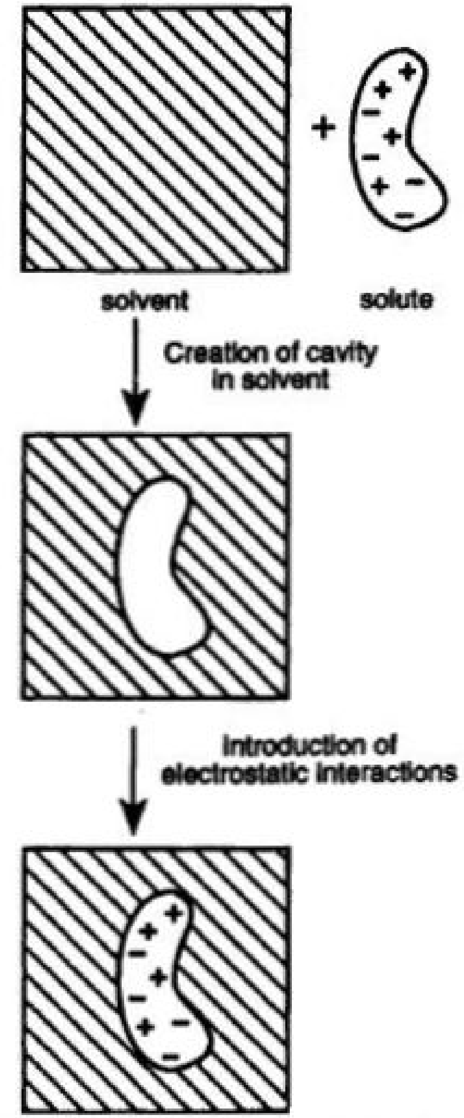


Fig. 4.1 Energy components for the solvation of a charged molecule.

Calculated vs. Experimental

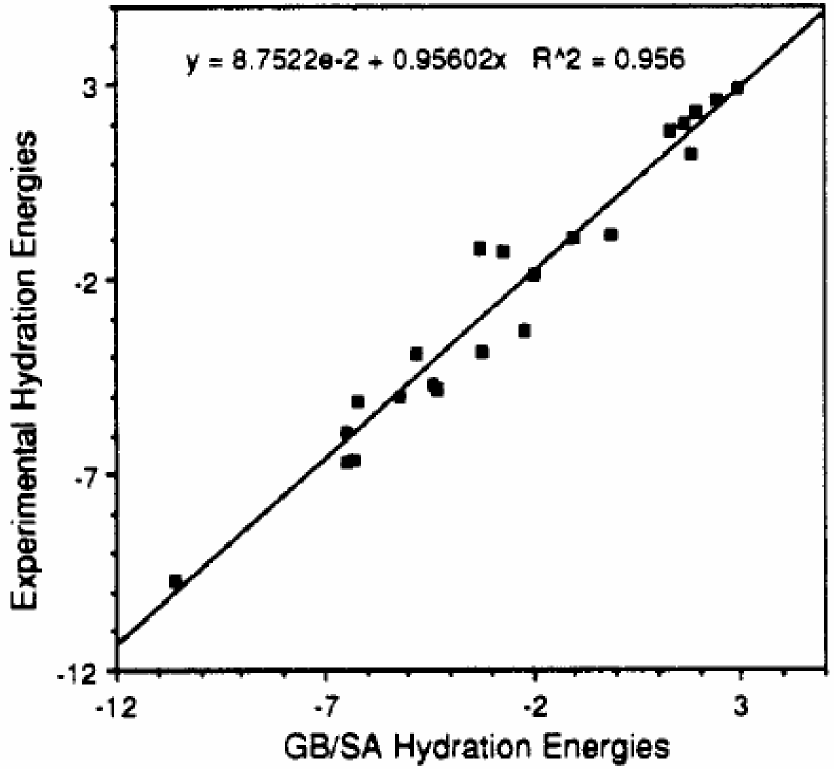


Figure 1. Comparison of experimental free energies of solvation in water (kcal/mol) for neutral small molecules with GB/SA energies calculated by using eqs 2 and 5.

Parameterization

- Need experimental (or ab initio) properties
  - Gas phase structure
  - Vibrational frequency
  - Torsional barriers
  - Crystal lattice constants
  - Sublimation energies
  - Hydrogen-bonding energies and geometries
  - Liquid properties (density, heats of vaporization, radial distribution functions)
  - Free energy of solvation

Advantages and Disadvantages of Molecular Mechanics

- Get structure, dipole moment, energy, frequency, heat of formation, etc…, with little computational efforts
- If compounds belong to an unparameterized class, not reliable
- Electron-related events cannot be modeled. (electronic transition, bond breaking/forming, electron transport)

Docking with force field interaction potential

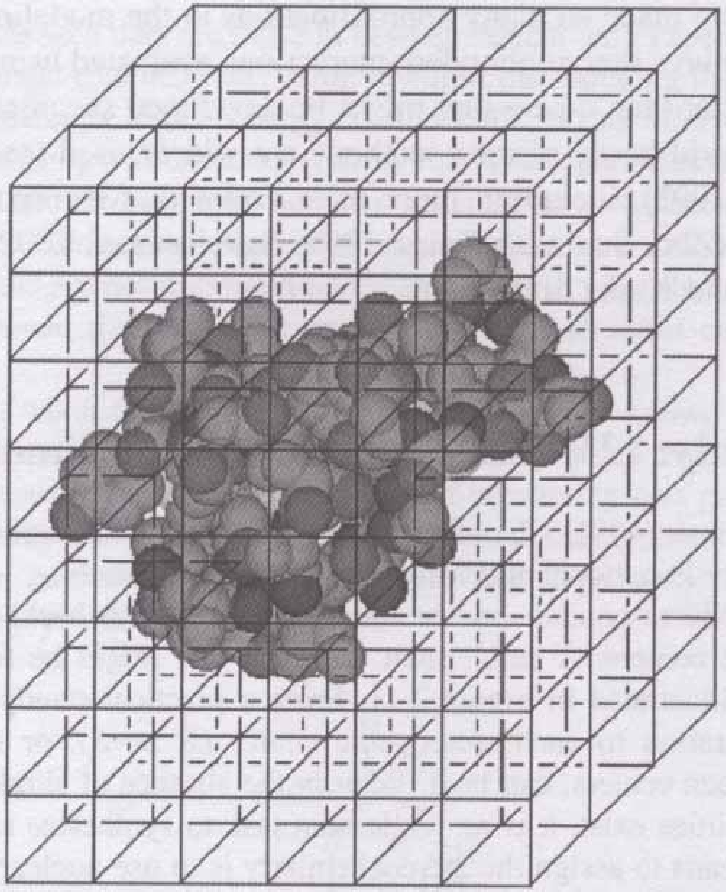


Figure 2.10 Docking grid constructed around a target protein. Each gridpoint can be assigned a force field interaction potential for use in evaluating binding affinities. Note that this grid is very coarse to improve viewing clarity; an actual grid might be considerably finer.

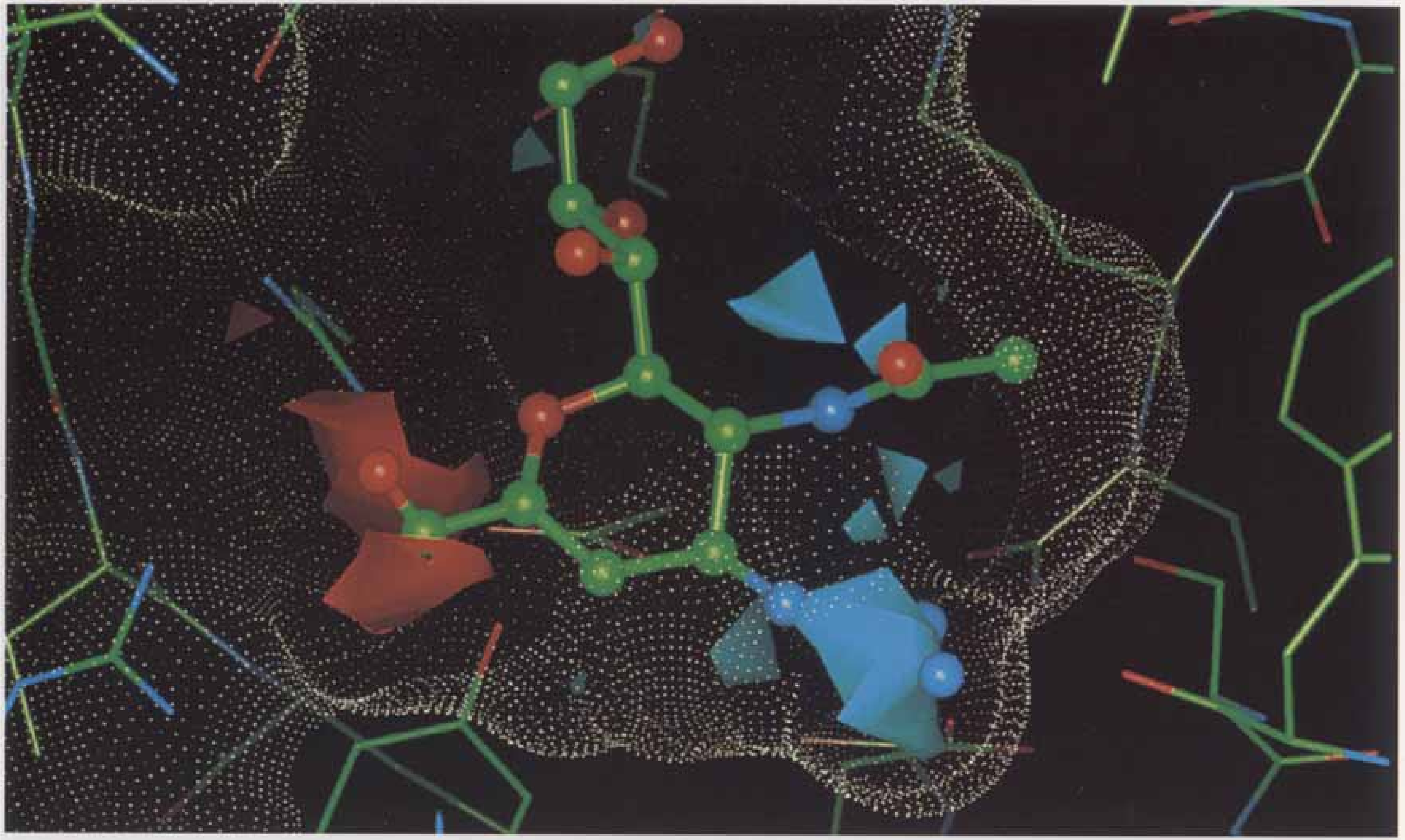


Fig 10.21 The result of a GRID calculation using carboxylate and amidine probes in the binding site of neuraminidase. The regions of minimum energy are contoured (carboxylate red; amidine blue). Also shown is the inhibitor 4-guanidino-Neu5Ac2en which contains two such functional groups [von Itzstein *et al.* 1993].

MM performance on bond length

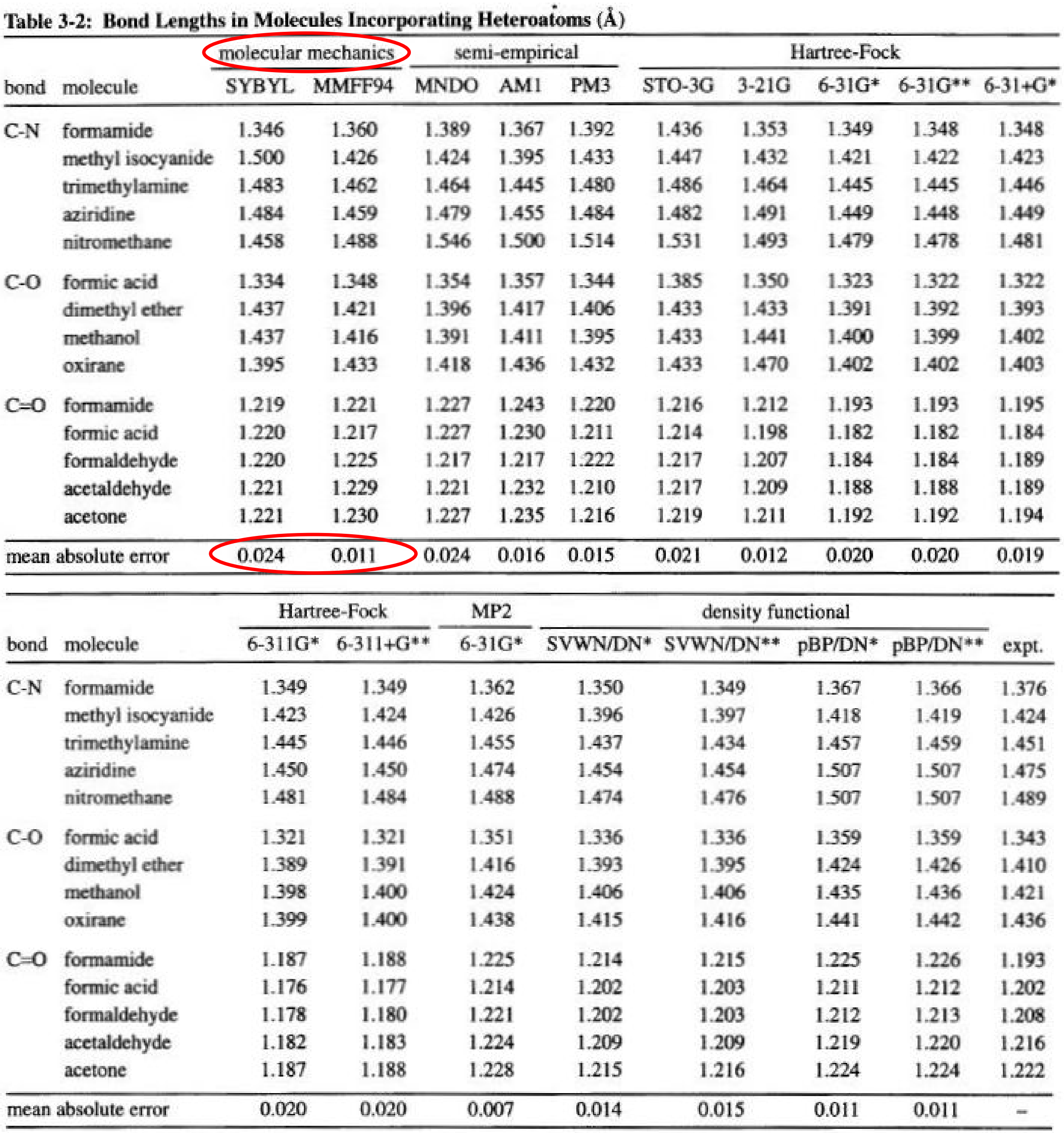


Table 3-2: Bond Lengths in Molecules Incorporating Heteroatoms (Å)

		molecular mechanics		semi-empirical			Hartree-Fock				
bond	molecule	SYBYL	MMFF94	MNDO	AM1	PM3	STO-3G	3-21G	6-31G*	6-31G**	6-31+G*
C-N	formamide	1.346	1.360	1.389	1.367	1.392	1.436	1.353	1.349	1.348	1.348
	methyl isocyanide	1.500	1.426	1.424	1.395	1.433	1.447	1.432	1.421	1.422	1.423
	trimethylamine	1.483	1.462	1.464	1.445	1.480	1.486	1.464	1.445	1.445	1.446
	aziridine	1.484	1.459	1.479	1.455	1.484	1.482	1.491	1.449	1.448	1.449
	nitromethane	1.458	1.488	1.546	1.500	1.514	1.531	1.493	1.479	1.478	1.481
C-O	formic acid	1.334	1.348	1.354	1.357	1.344	1.385	1.350	1.323	1.322	1.322
	dimethyl ether	1.437	1.421	1.396	1.417	1.406	1.433	1.433	1.391	1.392	1.393
	methanol	1.437	1.416	1.391	1.411	1.395	1.433	1.441	1.400	1.399	1.402
	oxirane	1.395	1.433	1.418	1.436	1.432	1.433	1.470	1.402	1.402	1.403
C=O	formamide	1.219	1.221	1.227	1.243	1.220	1.216	1.212	1.193	1.193	1.195
	formic acid	1.220	1.217	1.227	1.230	1.211	1.214	1.198	1.182	1.182	1.184
	formaldehyde	1.220	1.225	1.217	1.217	1.222	1.217	1.207	1.184	1.184	1.189
	acetaldehyde	1.221	1.229	1.221	1.232	1.210	1.217	1.209	1.188	1.188	1.189
	acetone	1.221	1.230	1.227	1.235	1.216	1.219	1.211	1.192	1.192	1.194
mean absolute error		0.024	0.011	0.024	0.016	0.015	0.021	0.012	0.020	0.020	0.019

		Hartree-Fock		MP2	density functional				
bond	molecule	6-311G*	6-311+G**	6-31G*	SVWN/DN*	SVWN/DN**	pBP/DN*	pBP/DN**	expt.
C-N	formamide	1.349	1.349	1.362	1.350	1.349	1.367	1.366	1.376
	methyl isocyanide	1.423	1.424	1.426	1.396	1.397	1.418	1.419	1.424
	trimethylamine	1.445	1.446	1.455	1.437	1.434	1.457	1.459	1.451
	aziridine	1.450	1.450	1.474	1.454	1.454	1.507	1.507	1.475
	nitromethane	1.481	1.484	1.488	1.474	1.476	1.507	1.507	1.489
C-O	formic acid	1.321	1.321	1.351	1.336	1.336	1.359	1.359	1.343
	dimethyl ether	1.389	1.391	1.416	1.393	1.395	1.424	1.426	1.410
	methanol	1.398	1.400	1.424	1.406	1.406	1.435	1.436	1.421
	oxirane	1.399	1.400	1.438	1.415	1.416	1.441	1.442	1.436
C=O	formamide	1.187	1.188	1.225	1.214	1.215	1.225	1.226	1.193
	formic acid	1.176	1.177	1.214	1.202	1.203	1.211	1.212	1.202
	formaldehyde	1.178	1.180	1.221	1.202	1.203	1.212	1.213	1.208
	acetaldehyde	1.182	1.183	1.224	1.209	1.209	1.219	1.220	1.216
	acetone	1.187	1.188	1.228	1.215	1.216	1.224	1.224	1.222
mean absolute error		0.020	0.020	0.007	0.014	0.015	0.011	0.011	–

MM performance on conformer energy

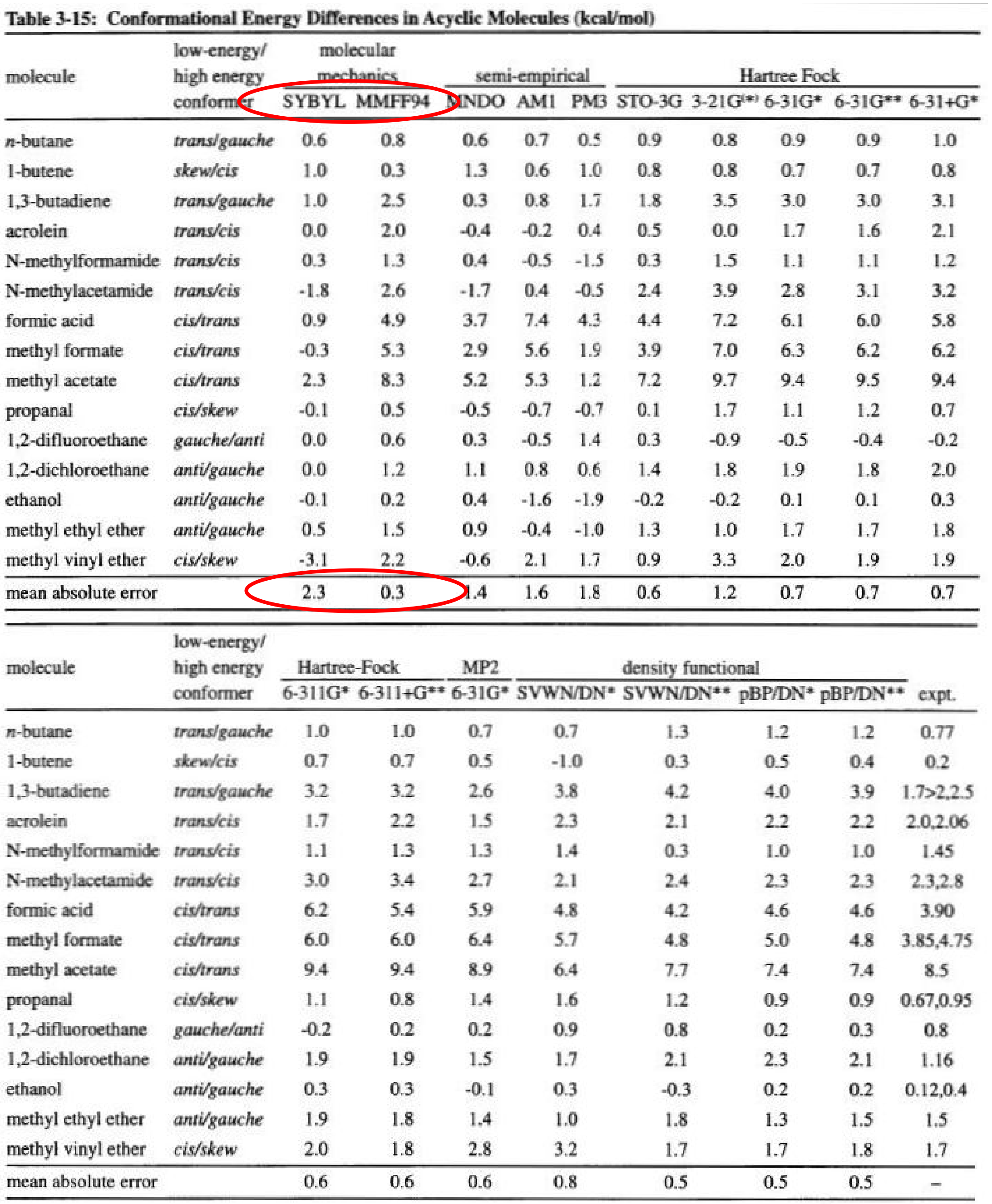


Table 3-15: Conformational Energy Differences in Acyclic Molecules (kcal/mol)

molecule	low-energy/ high energy conformer	molecular mechanics		semi-empirical			Hartree Fock				
		SYBYL	MMFF94	MNDO	AM1	PM3	STO-3G	3-21G$^{(*)}$	6-31G*	6-31G**	6-31+G*
n-butane	*trans/gauche*	0.6	0.8	0.6	0.7	0.5	0.9	0.8	0.9	0.9	1.0
1-butene	*skew/cis*	1.0	0.3	1.3	0.6	1.0	0.8	0.8	0.7	0.7	0.8
1,3-butadiene	*trans/gauche*	1.0	2.5	0.3	0.8	1.7	1.8	3.5	3.0	3.0	3.1
acrolein	*trans/cis*	0.0	2.0	-0.4	-0.2	0.4	0.5	0.0	1.7	1.6	2.1
N-methylformamide	*trans/cis*	0.3	1.3	0.4	-0.5	-1.5	0.3	1.5	1.1	1.1	1.2
N-methylacetamide	*trans/cis*	-1.8	2.6	-1.7	0.4	-0.5	2.4	3.9	2.8	3.1	3.2
formic acid	*cis/trans*	0.9	4.9	3.7	7.4	4.3	4.4	7.2	6.1	6.0	5.8
methyl formate	*cis/trans*	-0.3	5.3	2.9	5.6	1.9	3.9	7.0	6.3	6.2	6.2
methyl acetate	*cis/trans*	2.3	8.3	5.2	5.3	1.2	7.2	9.7	9.4	9.5	9.4
propanal	*cis/skew*	-0.1	0.5	-0.5	-0.7	-0.7	0.1	1.7	1.1	1.2	0.7
1,2-difluoroethane	*gauche/anti*	0.0	0.6	0.3	-0.5	1.4	0.3	-0.9	-0.5	-0.4	-0.2
1,2-dichloroethane	*anti/gauche*	0.0	1.2	1.1	0.8	0.6	1.4	1.8	1.9	1.8	2.0
ethanol	*anti/gauche*	-0.1	0.2	0.4	-1.6	-1.9	-0.2	-0.2	0.1	0.1	0.3
methyl ethyl ether	*anti/gauche*	0.5	1.5	0.9	-0.4	-1.0	1.3	1.0	1.7	1.7	1.8
methyl vinyl ether	*cis/skew*	-3.1	2.2	-0.6	2.1	1.7	0.9	3.3	2.0	1.9	1.9
mean absolute error		2.3	0.3	1.4	1.6	1.8	0.6	1.2	0.7	0.7	0.7

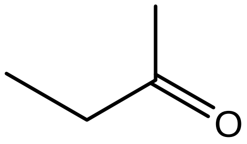
molecule	low-energy/ high energy conformer	Hartree-Fock		MP2	density functional				
		6-311G*	6-311+G**	6-31G*	SVWN/DN*	SVWN/DN**	pBP/DN*	pBP/DN**	expt.
n-butane	*trans/gauche*	1.0	1.0	0.7	0.7	1.3	1.2	1.2	0.77
1-butene	*skew/cis*	0.7	0.7	0.5	-1.0	0.3	0.5	0.4	0.2
1,3-butadiene	*trans/gauche*	3.2	3.2	2.6	3.8	4.2	4.0	3.9	1.7>2,2.5
acrolein	*trans/cis*	1.7	2.2	1.5	2.3	2.1	2.2	2.2	2.0,2.06
N-methylformamide	*trans/cis*	1.1	1.3	1.3	1.4	0.3	1.0	1.0	1.45
N-methylacetamide	*trans/cis*	3.0	3.4	2.7	2.1	2.4	2.3	2.3	2.3,2.8
formic acid	*cis/trans*	6.2	5.4	5.9	4.8	4.2	4.6	4.6	3.90
methyl formate	*cis/trans*	6.0	6.0	6.4	5.7	4.8	5.0	4.8	3.85,4.75
methyl acetate	*cis/trans*	9.4	9.4	8.9	6.4	7.7	7.4	7.4	8.5
propanal	*cis/skew*	1.1	0.8	1.4	1.6	1.2	0.9	0.9	0.67,0.95
1,2-difluoroethane	*gauche/anti*	-0.2	0.2	0.2	0.9	0.8	0.2	0.3	0.8
1,2-dichloroethane	*anti/gauche*	1.9	1.9	1.5	1.7	2.1	2.3	2.1	1.16
ethanol	*anti/gauche*	0.3	0.3	-0.1	0.3	-0.3	0.2	0.2	0.12,0.4
methyl ethyl ether	*anti/gauche*	1.9	1.8	1.4	1.0	1.8	1.3	1.5	1.5
methyl vinyl ether	*cis/skew*	2.0	1.8	2.8	3.2	1.7	1.7	1.8	1.7
mean absolute error		0.6	0.6	0.6	0.8	0.5	0.5	0.5	–

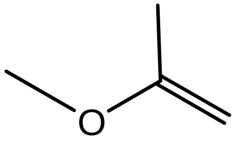
Cautions

- Do not mix parameters from different FF
- Do not compare steric energies of compounds involving different combinations of functions

  e.g. steric energies from different FF

  e.g. steric energies of different molecules





- Do not overemphasize the contribution from each term for intramolecular terms

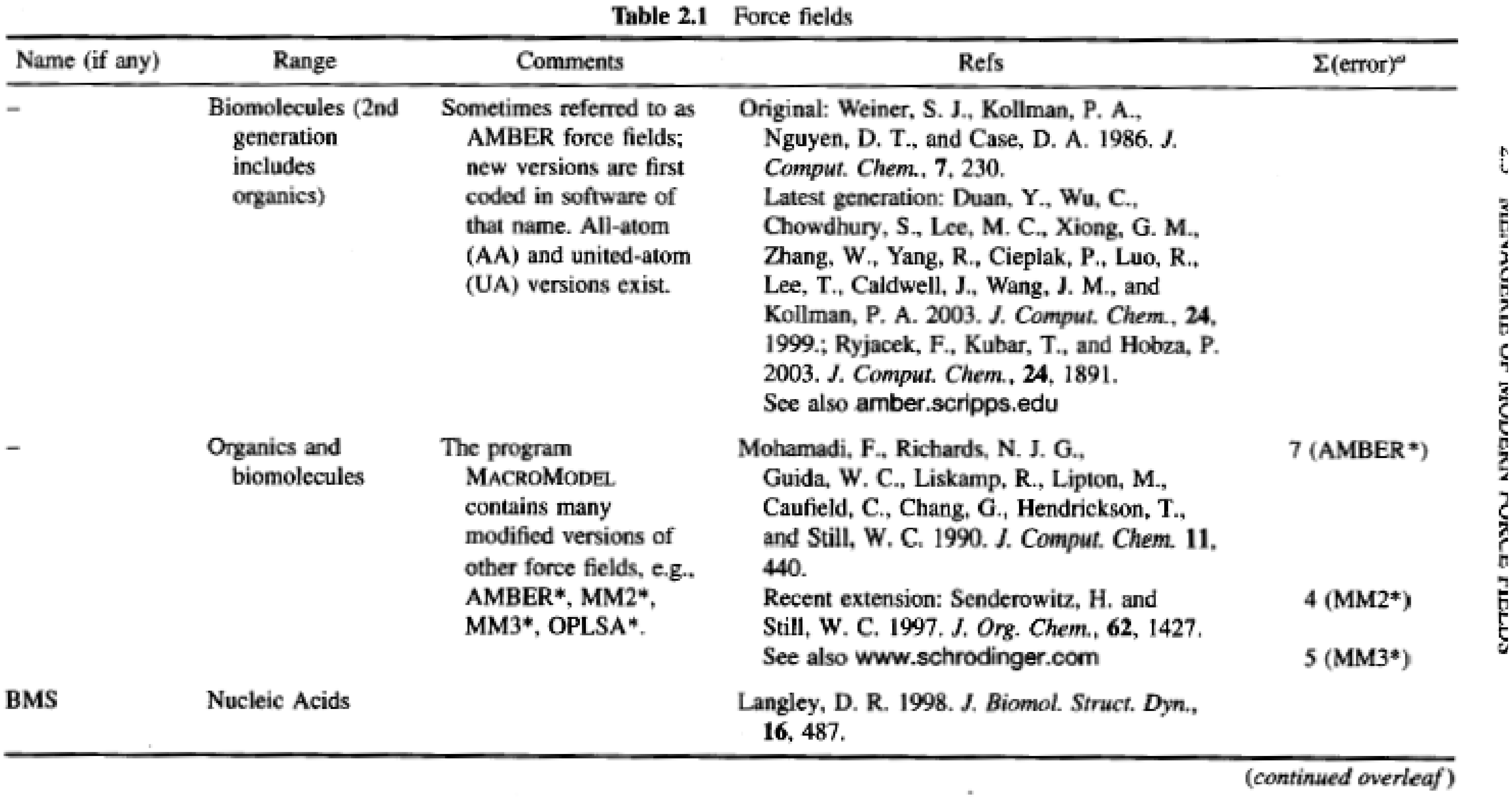


Table 2.1 Force fields

Name (if any)	Range	Comments	Refs	Σ(error)[a]
–	Biomolecules (2nd generation includes organics)	Sometimes referred to as AMBER force fields; new versions are first coded in software of that name. All-atom (AA) and united-atom (UA) versions exist.	Original: Weiner, S. J., Kollman, P. A., Nguyen, D. T., and Case, D. A. 1986. *J. Comput. Chem.*, **7**, 230. Latest generation: Duan, Y., Wu, C., Chowdhury, S., Lee, M. C., Xiong, G. M., Zhang, W., Yang, R., Cieplak, P., Luo, R., Lee, T., Caldwell, J., Wang, J. M., and Kollman, P. A. 2003. *J. Comput. Chem.*, **24**, 1999.; Ryjacek, F., Kubar, T., and Hobza, P. 2003. *J. Comput. Chem.*, **24**, 1891. See also amber.scripps.edu	
–	Organics and biomolecules	The program MACROMODEL contains many modified versions of other force fields, e.g., AMBER*, MM2*, MM3*, OPLSA*.	Mohamadi, F., Richards, N. J. G., Guida, W. C., Liskamp, R., Lipton, M., Caufield, C., Chang, G., Hendrickson, T., and Still, W. C. 1990. *J. Comput. Chem.* **11**, 440. Recent extension: Senderowitz, H. and Still, W. C. 1997. *J. Org. Chem.*, **62**, 1427. See also www.schrodinger.com	7 (AMBER*) 4 (MM2*) 5 (MM3*)
BMS	Nucleic Acids		Langley, D. R. 1998. *J. Biomol. Struct. Dyn.*, **16**, 487.	

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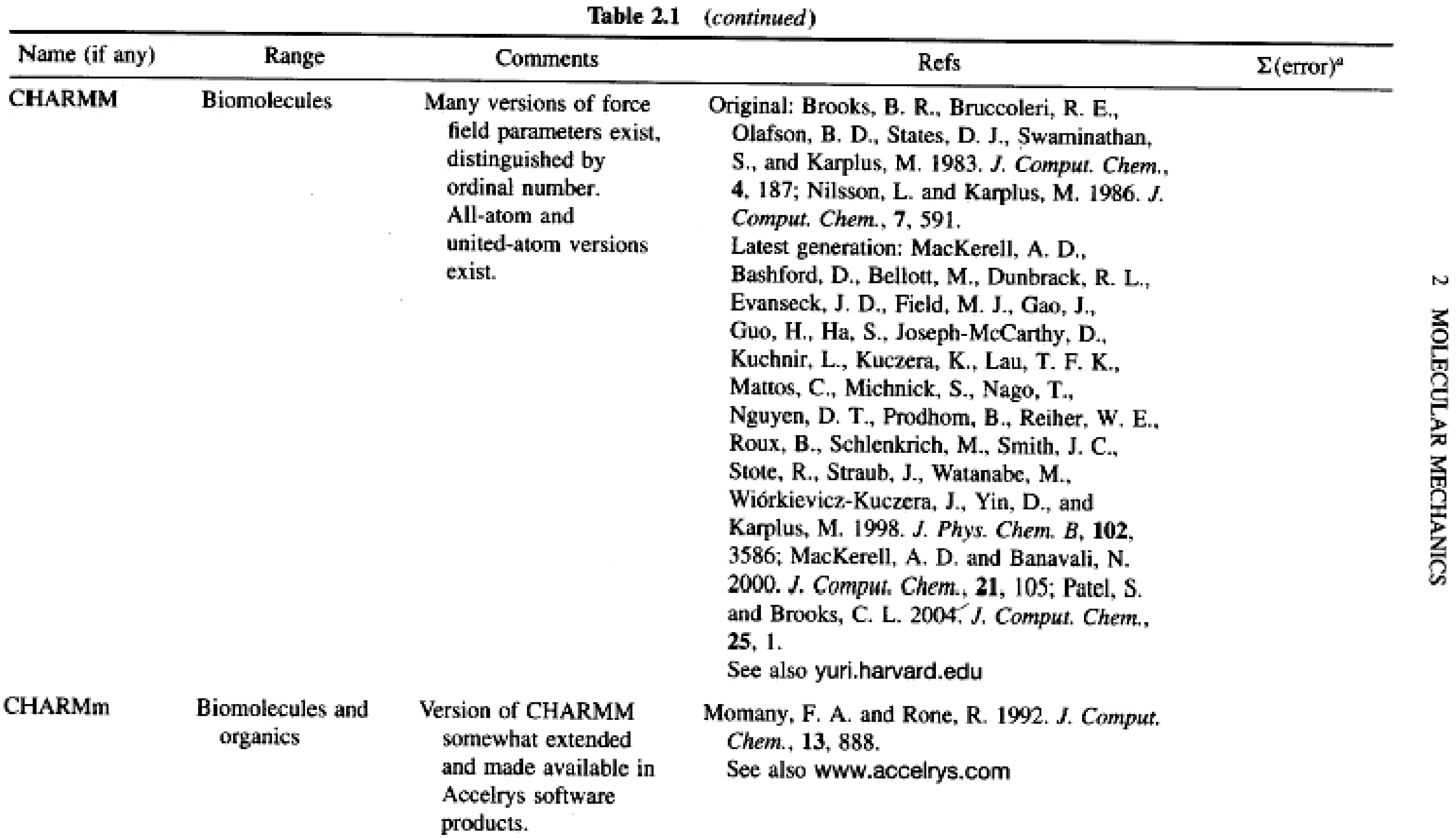
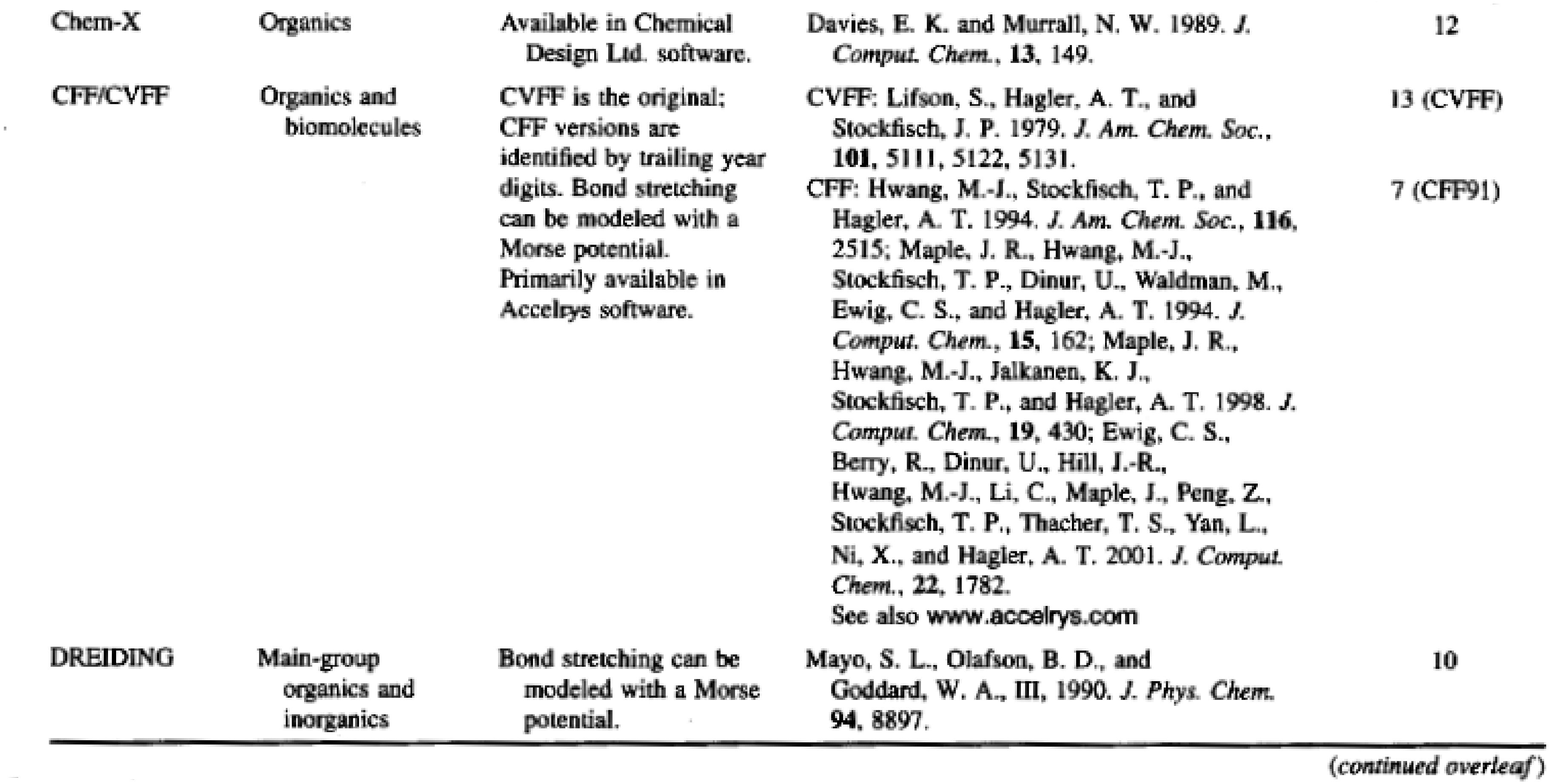


Table 2.1 *(continued)*

Name (if any)	Range	Comments	Refs	Σ(error)[a]
CHARMM	Biomolecules	Many versions of force field parameters exist, distinguished by ordinal number. All-atom and united-atom versions exist.	Original: Brooks, B. R., Bruccoleri, R. E., Olafson, B. D., States, D. J., Swaminathan, S., and Karplus, M. 1983. *J. Comput. Chem.*, **4**, 187; Nilsson, L. and Karplus, M. 1986. *J. Comput. Chem.*, **7**, 591. Latest generation: MacKerell, A. D., Bashford, D., Bellott, M., Dunbrack, R. L., Evanseck, J. D., Field, M. J., Gao, J., Guo, H., Ha, S., Joseph-McCarthy, D., Kuchnir, L., Kuczera, K., Lau, T. F. K., Mattos, C., Michnick, S., Nago, T., Nguyen, D. T., Prodhom, B., Reiher, W. E., Roux, B., Schlenkrich, M., Smith, J. C., Stote, R., Straub, J., Watanabe, M., Wiórkievicz-Kuczera, J., Yin, D., and Karplus, M. 1998. *J. Phys. Chem. B*, **102**, 3586; MacKerell, A. D. and Banavali, N. 2000. *J. Comput. Chem.*, **21**, 105; Patel, S. and Brooks, C. L. 2004. *J. Comput. Chem.*, **25**, 1. See also yuri.harvard.edu	
CHARMm	Biomolecules and organics	Version of CHARMM somewhat extended and made available in Accelrys software products.	Momany, F. A. and Rone, R. 1992. *J. Comput. Chem.*, **13**, 888. See also www.accelrys.com	



Chem-X	Organics	Available in Chemical Design Ltd. software.	Davies, E. K. and Murrall, N. W. 1989. *J. Comput. Chem.*, **13**, 149.	12
CFF/CVFF	Organics and biomolecules	CVFF is the original; CFF versions are identified by trailing year digits. Bond stretching can be modeled with a Morse potential. Primarily available in Accelrys software.	CVFF: Lifson, S., Hagler, A. T., and Stockfisch, J. P. 1979. *J. Am. Chem. Soc.*, **101**, 5111, 5122, 5131. CFF: Hwang, M.-J., Stockfisch, T. P., and Hagler, A. T. 1994. *J. Am. Chem. Soc.*, **116**, 2515; Maple, J. R., Hwang, M.-J., Stockfisch, T. P., Dinur, U., Waldman, M., Ewig, C. S., and Hagler, A. T. 1994. *J. Comput. Chem.*, **15**, 162; Maple, J. R., Hwang, M.-J., Jalkanen, K. J., Stockfisch, T. P., and Hagler, A. T. 1998. *J. Comput. Chem.*, **19**, 430; Ewig, C. S., Berry, R., Dinur, U., Hill, J.-R., Hwang, M.-J., Li, C., Maple, J., Peng, Z., Stockfisch, T. P., Thacher, T. S., Yan, L., Ni, X., and Hagler, A. T. 2001. *J. Comput. Chem.*, **22**, 1782. See also www.accelrys.com	13 (CVFF) 7 (CFF91)
DREIDING	Main-group organics and inorganics	Bond stretching can be modeled with a Morse potential.	Mayo, S. L., Olafson, B. D., and Goddard, W. A., III, 1990. *J. Phys. Chem.* **94**, 8897.	10

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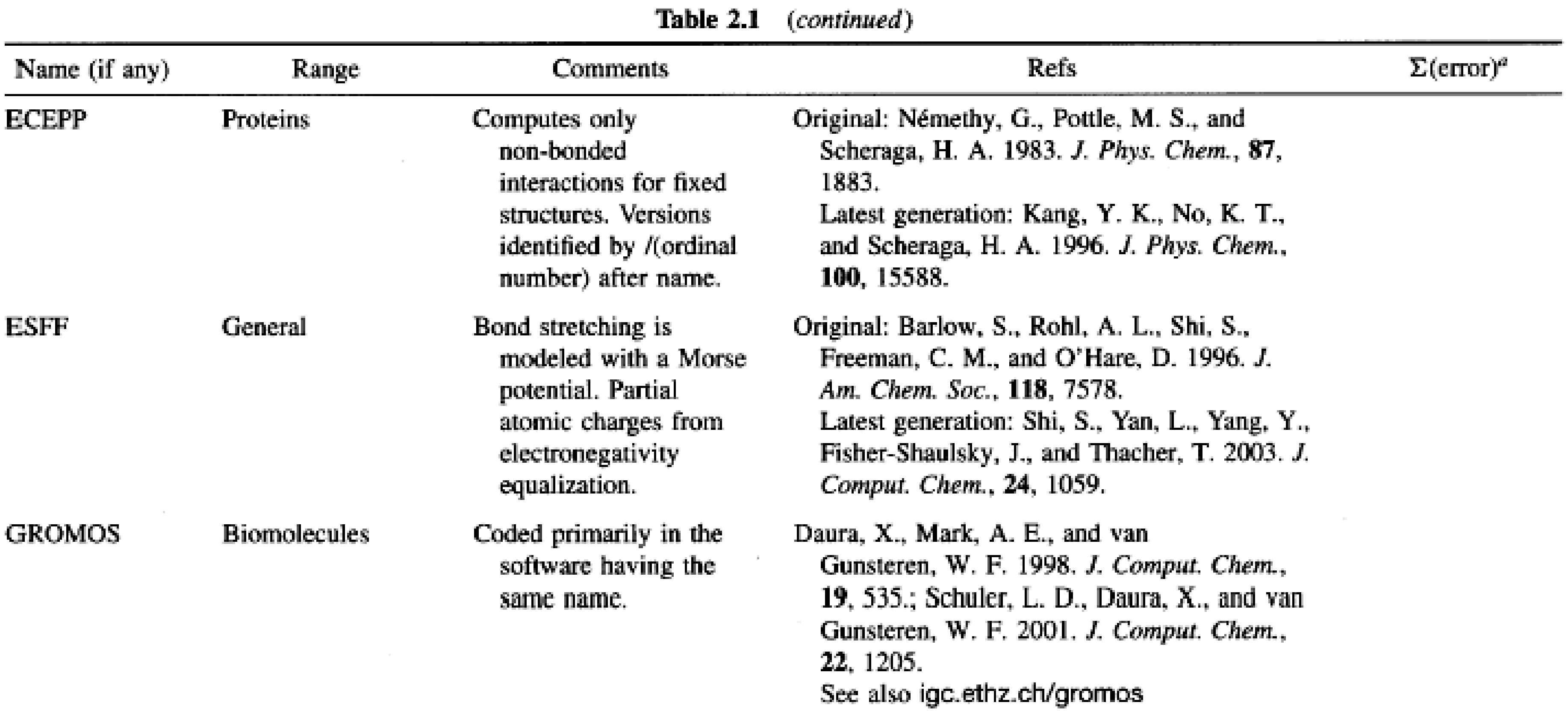
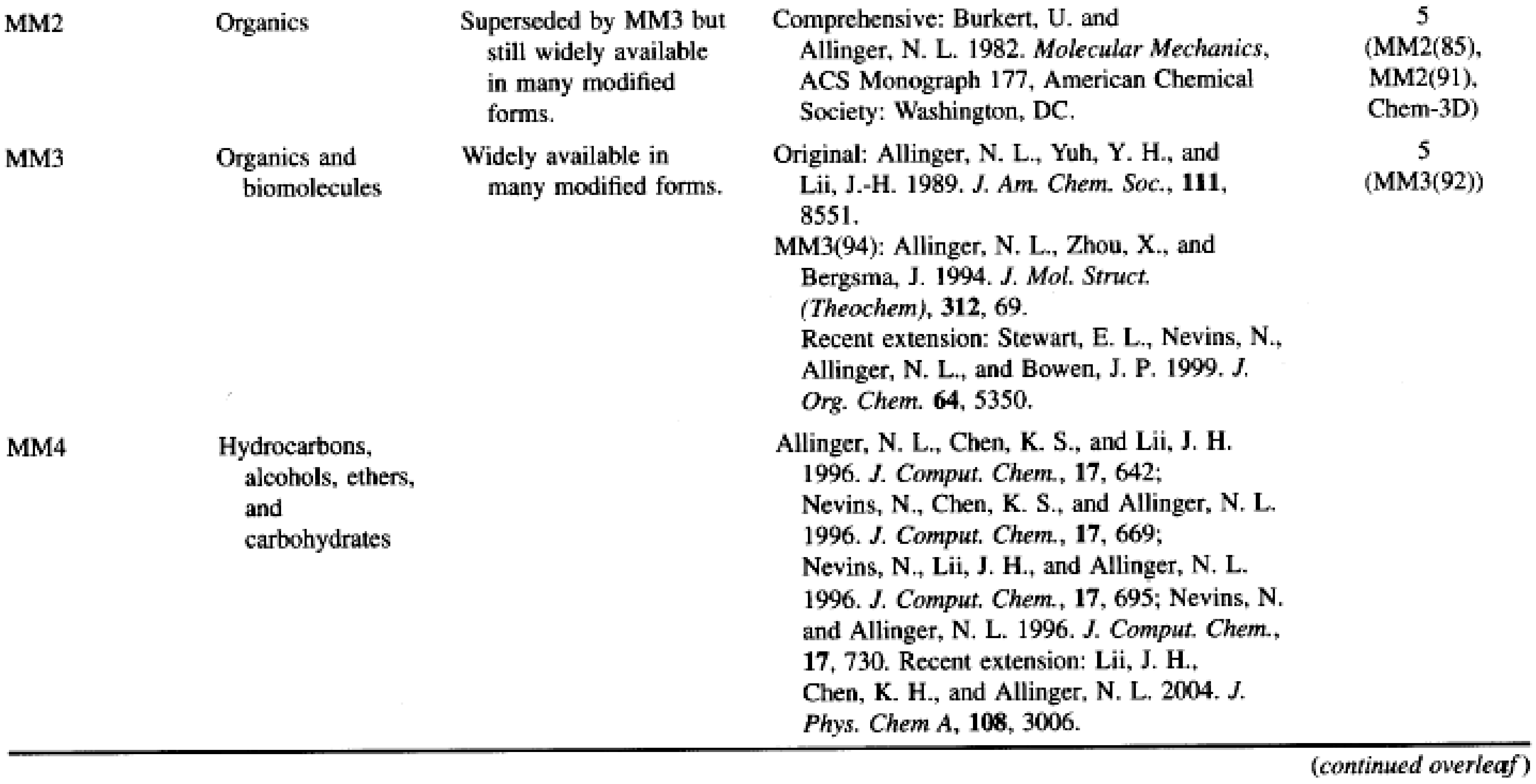


Table 2.1 *(continued)*

Name (if any)	Range	Comments	Refs	Σ(error)^a
ECEPP	Proteins	Computes only non-bonded interactions for fixed structures. Versions identified by /(ordinal number) after name.	Original: Némethy, G., Pottle, M. S., and Scheraga, H. A. 1983. *J. Phys. Chem.*, **87**, 1883. Latest generation: Kang, Y. K., No, K. T., and Scheraga, H. A. 1996. *J. Phys. Chem.*, **100**, 15588.	
ESFF	General	Bond stretching is modeled with a Morse potential. Partial atomic charges from electronegativity equalization.	Original: Barlow, S., Rohl, A. L., Shi, S., Freeman, C. M., and O'Hare, D. 1996. *J. Am. Chem. Soc.*, **118**, 7578. Latest generation: Shi, S., Yan, L., Yang, Y., Fisher-Shaulsky, J., and Thacher, T. 2003. *J. Comput. Chem.*, **24**, 1059.	
GROMOS	Biomolecules	Coded primarily in the software having the same name.	Daura, X., Mark, A. E., and van Gunsteren, W. F. 1998. *J. Comput. Chem.*, **19**, 535.; Schuler, L. D., Daura, X., and van Gunsteren, W. F. 2001. *J. Comput. Chem.*, **22**, 1205. See also igc.ethz.ch/gromos	



MM2	Organics	Superseded by MM3 but still widely available in many modified forms.	Comprehensive: Burkert, U. and Allinger, N. L. 1982. *Molecular Mechanics*, ACS Monograph 177, American Chemical Society: Washington, DC.	5 (MM2(85), MM2(91), Chem-3D)
MM3	Organics and biomolecules	Widely available in many modified forms.	Original: Allinger, N. L., Yuh, Y. H., and Lii, J.-H. 1989. *J. Am. Chem. Soc.*, **111**, 8551. MM3(94): Allinger, N. L., Zhou, X., and Bergsma, J. 1994. *J. Mol. Struct. (Theochem)*, **312**, 69. Recent extension: Stewart, E. L., Nevins, N., Allinger, N. L., and Bowen, J. P. 1999. *J. Org. Chem.* **64**, 5350.	5 (MM3(92))
MM4	Hydrocarbons, alcohols, ethers, and carbohydrates		Allinger, N. L., Chen, K. S., and Lii, J. H. 1996. *J. Comput. Chem.*, **17**, 642; Nevins, N., Chen, K. S., and Allinger, N. L. 1996. *J. Comput. Chem.*, **17**, 669; Nevins, N., Lii, J. H., and Allinger, N. L. 1996. *J. Comput. Chem.*, **17**, 695; Nevins, N. and Allinger, N. L. 1996. *J. Comput. Chem.*, **17**, 730. Recent extension: Lii, J. H., Chen, K. H., and Allinger, N. L. 2004. *J. Phys. Chem A*, **108**, 3006.	

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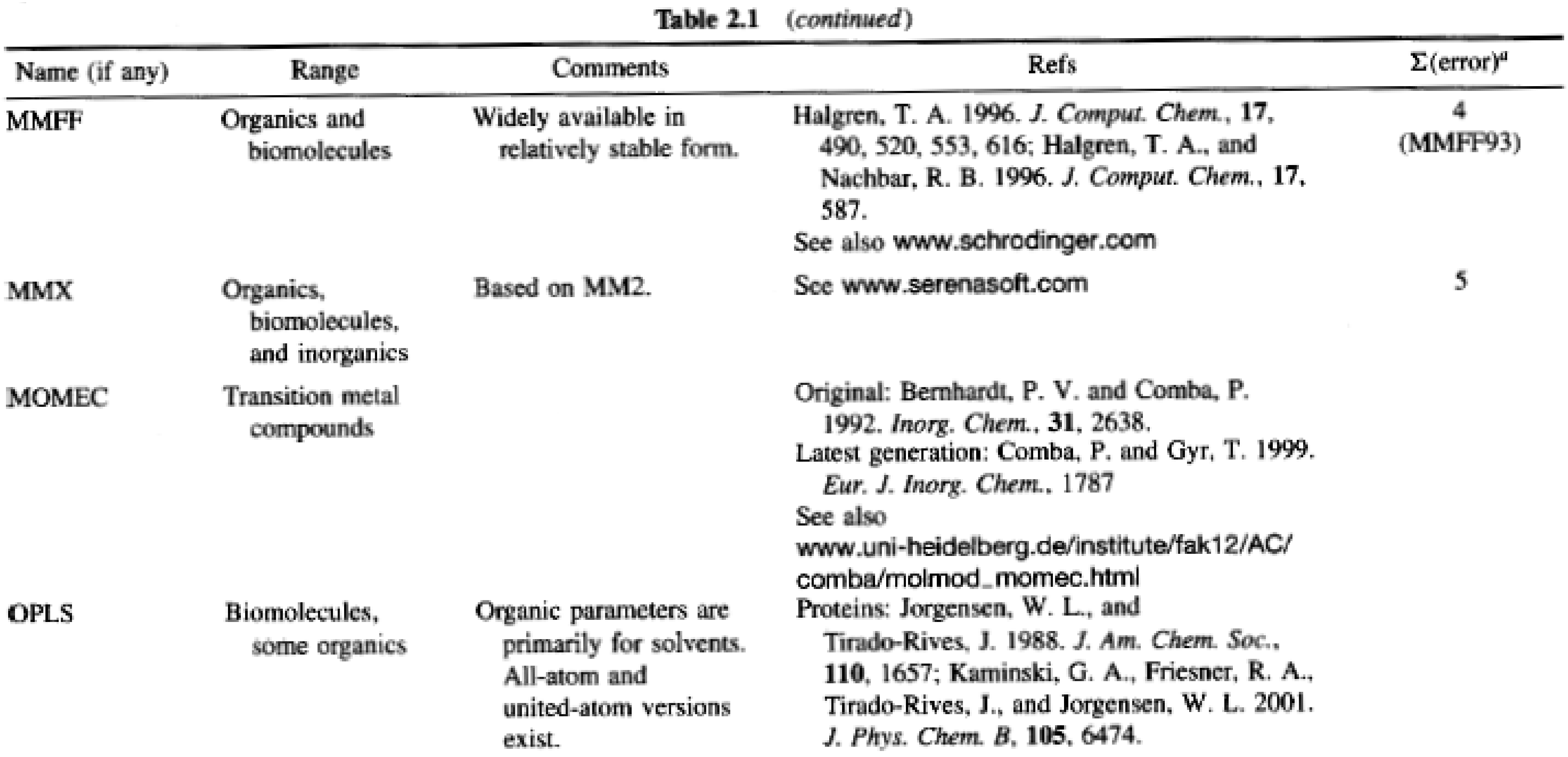
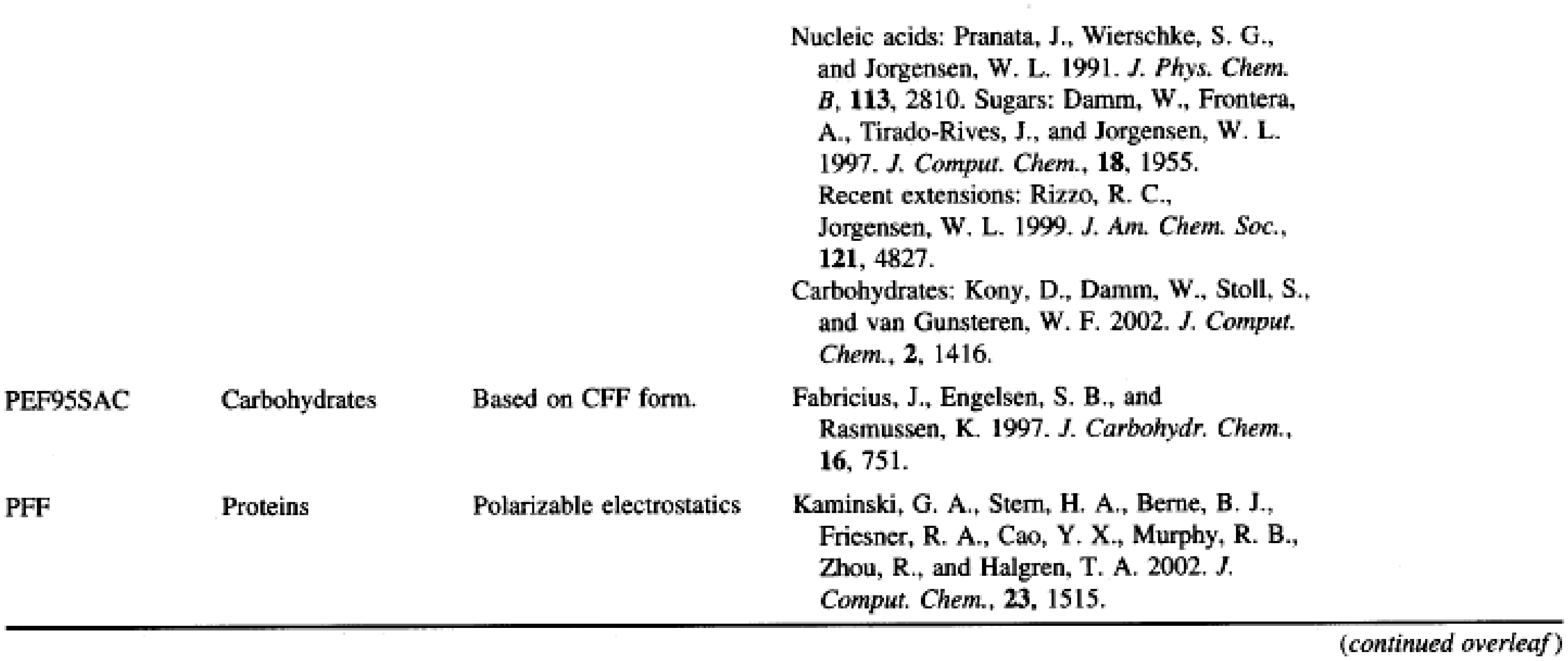


Table 2.1 *(continued)*

Name (if any)	Range	Comments	Refs	Σ(error)[a]
MMFF	Organics and biomolecules	Widely available in relatively stable form.	Halgren, T. A. 1996. *J. Comput. Chem.*, **17**, 490, 520, 553, 616; Halgren, T. A., and Nachbar, R. B. 1996. *J. Comput. Chem.*, **17**, 587. See also www.schrodinger.com	4 (MMFF93)
MMX	Organics, biomolecules, and inorganics	Based on MM2.	See www.serenasoft.com	5
MOMEC	Transition metal compounds		Original: Bernhardt, P. V. and Comba, P. 1992. *Inorg. Chem.*, **31**, 2638. Latest generation: Comba, P. and Gyr, T. 1999. *Eur. J. Inorg. Chem.*, 1787 See also www.uni-heidelberg.de/institute/fak12/AC/comba/molmod_momec.html	
OPLS	Biomolecules, some organics	Organic parameters are primarily for solvents. All-atom and united-atom versions exist.	Proteins: Jorgensen, W. L., and Tirado-Rives, J. 1988. *J. Am. Chem. Soc.*, **110**, 1657; Kaminski, G. A., Friesner, R. A., Tirado-Rives, J., and Jorgensen, W. L. 2001. *J. Phys. Chem. B*, **105**, 6474.	



			Nucleic acids: Pranata, J., Wierschke, S. G., and Jorgensen, W. L. 1991. *J. Phys. Chem. B*, **113**, 2810. Sugars: Damm, W., Frontera, A., Tirado-Rives, J., and Jorgensen, W. L. 1997. *J. Comput. Chem.*, **18**, 1955. Recent extensions: Rizzo, R. C., Jorgensen, W. L. 1999. *J. Am. Chem. Soc.*, **121**, 4827. Carbohydrates: Kony, D., Damm, W., Stoll, S., and van Gunsteren, W. F. 2002. *J. Comput. Chem.*, **2**, 1416.
PEF95SAC	Carbohydrates	Based on CFF form.	Fabricius, J., Engelsen, S. B., and Rasmussen, K. 1997. *J. Carbohydr. Chem.*, **16**, 751.
PFF	Proteins	Polarizable electrostatics	Kaminski, G. A., Stern, H. A., Berne, B. J., Friesner, R. A., Cao, Y. X., Murphy, R. B., Zhou, R., and Halgren, T. A. 2002. *J. Comput. Chem.*, **23**, 1515.

(*continued overleaf*)

Other treatments

not in all force fields

- π systems: MO calculations on the π systems => bond order => scale parameters (e.g. bond stretching) => minimization

- Heat of formation (ΔH_f): steric energy (Etotal) + group/bond increment (e.g. a methyl group contributes -10.05 kcal/mol and a methylene group contributes -5.13 kcal/mol)

- Strain energy: $\Delta H_f - \Delta H_f$ (strain free reference) strain-free reference: one that consists of the same numers of each different type of group