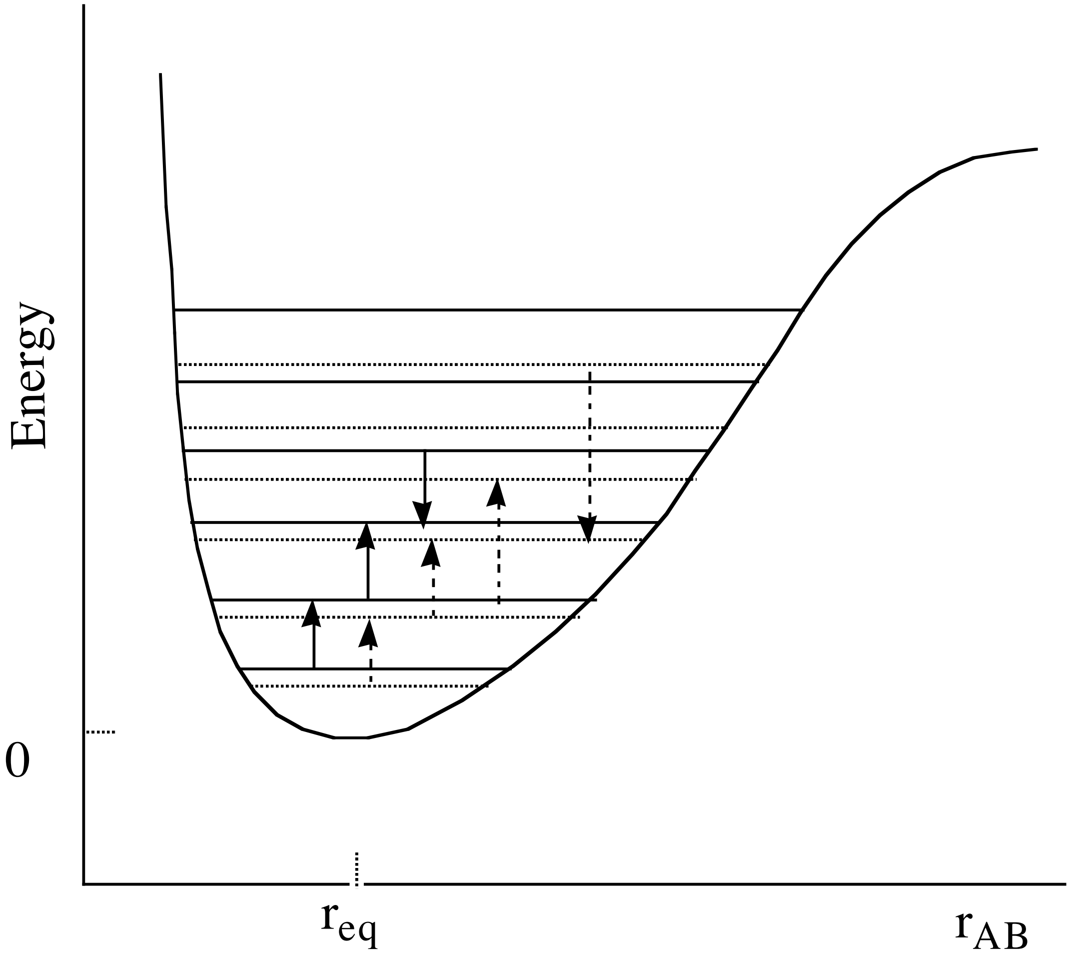
Molecular Mechanics

History and Fundamental Assumptions

First PESs were constructed by molecular spectroscopists. The simplest case – a heterodiatomic molecule – only one degree of freedom, bond length. Vibrational spectroscopy measures the energy separations between different vibrational levels, which are quantized.
Allowed transitions: $\nu = 0 \rightarrow \nu = 1$ or $\nu = n \rightarrow \nu = n \pm 1$
More sensitive experimental apparati: $\nu = n \rightarrow \nu = m$
Spacing also depends on isotope substitutions.



Spacing between different vibrational levels depend on PES.
Spectroscopic data → experimental derivation of PES.

A useful potential energy function should have analytical form. It should be continuously differentiable. Assuming the dissociation energy for the bond to be positive, we define the minimum of the function to have a potential energy of zero (r_{eq}).

Taylor expansion:

$$U(r) = U(r_{eq}) + \left.\frac{dU}{dr}\right|_{r=r_{eq}} (r - r_{eq}) + \frac{1}{2!}\left.\frac{d^2U}{dr^2}\right|_{r=r_{eq}} (r - r_{eq})^2$$

$$+ \frac{1}{3!}\left.\frac{d^3U}{dr^3}\right|_{r=r_{eq}} (r - r_{eq})^3 + \ldots$$

The first two terms are zero: the first by definition and the second because the gradient should be zero at equilibrium structure.

The simplest possible expression:

$$U(r_{AB}) = \frac{1}{2} k_{AB} (r_{AB} - r_{AB,eq})^2$$

This equation is similar to Hooke's law for a spring, *k* – 'force constant' for the spring. Force constants and equilibrium lengths might vary even for the same pair A and B depending on different molecular surrounding (molecular framework).

Experimental spectroscopic data – thousands of molecules have similar bonds (C-C single bonds, for example) – 't**ransferability**' of bond lengths. Thermochemistry results: to a reasonable approximation, molecular enthalpies can be determined as a sum of bond enthalpies. Assuming transferability, if two different molecules were to be composed of identical bonds (isomers), the sum of the differences in the 'strain' of those bonds (which would arise from different bond lengths in the two molecules – we define strain as the positive deviation from the zero of energy) would allow to predict the difference in enthalpies – organic conformational analysis.

Why classical mechanical bond would deviate from its equilibrium bond length? – other energies of interaction must be also considered: repulsive van der Waals interactions between nearby groups may force some bonds connecting them to lengthen. The same is applied to bond angles; they also have transferable force constants and optimal values. Energetically unfavorable non-bonding, non-angle-bending interactions – ‘steric effects’. Minimization of overall steric energy – prediction of optimal structures.

Potential energy functions

Bond Stretching

Force fields use truncated Taylor expansions:

$$U(r_{AB}) = \frac{1}{2}\left[k_{AB} + k_{AB}^{(3)}\left(r_{AB} - r_{AB,eq}\right)\right]\left(r_{AB} - r_{AB,eq}\right)^2$$

$k_{AB}^{(3)}$ - cubic force constant, ‘anharmonic’ force constant. Should be negative to reduce the overly high stretching energy predicted if we use only one term in the Taylor expansion. Drawback – goes to negative infinity with increasing bond length. Then, we may add the next, quartic term:

$$U(r_{AB}) = \frac{1}{2}\left[k_{AB} + k_{AB}^{(3)}\left(r_{AB} - r_{AB,eq}\right) + k_{AB}^{(4)}\left(r_{AB} - r_{AB,eq}\right)^2\right]\left(r_{AB} - r_{AB,eq}\right)^2$$

This expression is used in the MM3 general organic force field. Many force fields are designed to be used in reduced regions of chemical space – quadratic bond stretching potentials.

Why Morse potential is not generally applied?

$$U(r_{AB}) = D_{AB}\left[1 - e^{-\alpha_{AB}\left(r_{AB} - r_{AB,eq}\right)}\right]^2$$

Describes the potential energy curve well but is computationally much less efficient.

Most force fields are designed to study the energetics of molecules whose various degrees of freedom are reasonably close to their equilibrium values, within about 10 kcal/mol. In such a range, the deviation between the Morse function and a quartic function is usually negligible.

We can approximate the exponential in the Morse function as its infinite series expansion truncated at the cubic term:

$$U\left(r_{AB}\right) = D_{AB}\left\{1 - \begin{bmatrix} 1 - \alpha_{AB}\left(r_{AB} - r_{AB,eq}\right) + \frac{1}{2}\alpha_{AB}^{2}\left(r_{AB} - r_{AB,eq}\right)^{2} \\ -\frac{1}{6}\alpha_{AB}^{3}\left(r_{AB} - r_{AB,eq}\right)^{3} \end{bmatrix}\right\}^{2}$$

$$U\left(r_{AB}\right) = D_{AB}\left[\alpha_{AB}^{2} - \alpha_{AB}^{3}\left(r_{AB} - r_{AB,eq}\right) + \frac{7}{12}\alpha_{AB}^{4}\left(r_{AB} - r_{AB,eq}\right)^{2}\right](r_{AB} - r_{AB,e}$$

Then, $k_{AB} = 2\alpha_{AB}^{2}D_{AB}$

The simplest parameters to determine from experiment – k_{AB} and D_{AB}. Then, α_{AB} can be determined and after that the cubic and quartic force constants can be also determined. Direct measurements of cubic and quartic force constants require more spectral data than are available for many kinds of bonds – the derivation from the Morse function facilitates parametrization.

Valence bond angles

For small displacements from equilibrium, vibrational spectroscopy reveals that energy variations associated with bond angle deformation are as well modeled by polynomial expansions as are variations associated with bond stretching.

$$U\left(\theta_{ABC}\right) = \frac{1}{2}\left[k_{ABC} + k_{ABC}^{(3)}\left(\theta_{ABC} - \theta_{ABC,eq}\right) + k_{ABC}^{(4)}\left(\theta_{ABC} - \theta_{ABC,eq}\right)^{2} + \ldots\right]$$

$$\left(\theta_{ABC} - \theta_{ABC,eq}\right)^{2}$$

θ_{ABC} - the valence angle between bonds AB and BC

Whether the equation is truncated at the quadratic term or whether more terms are included depends on the balance between computational simplicity and generality of a given force field. MM3 – up to sextic term for some ABC combinations; biomolecular forcefield of Cornell et al. – up to quartic term.

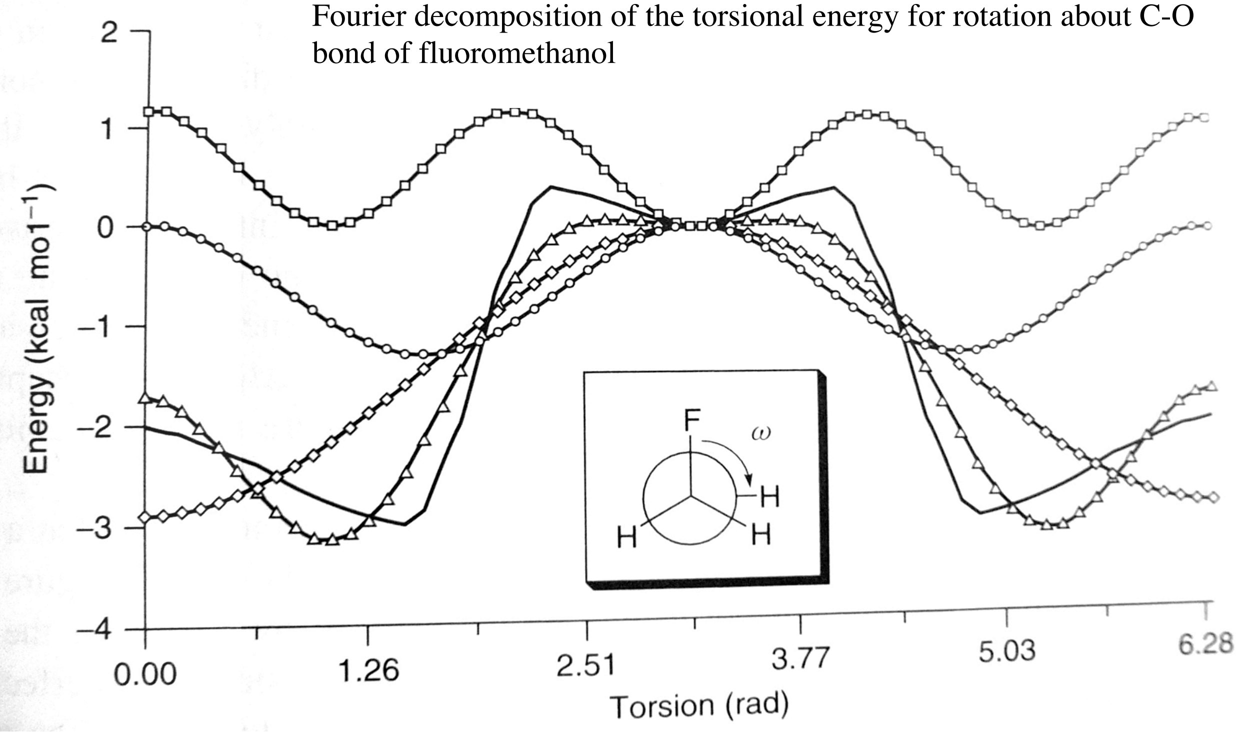
Flaws of such description – inappropriate for linear bond angles ($\theta = \pi$); also when it is possible to have multiple equilibrium values: inorganic systems like trigonal bipyramidal PCl_5; for 'out-of-plane' bending.

Torsions

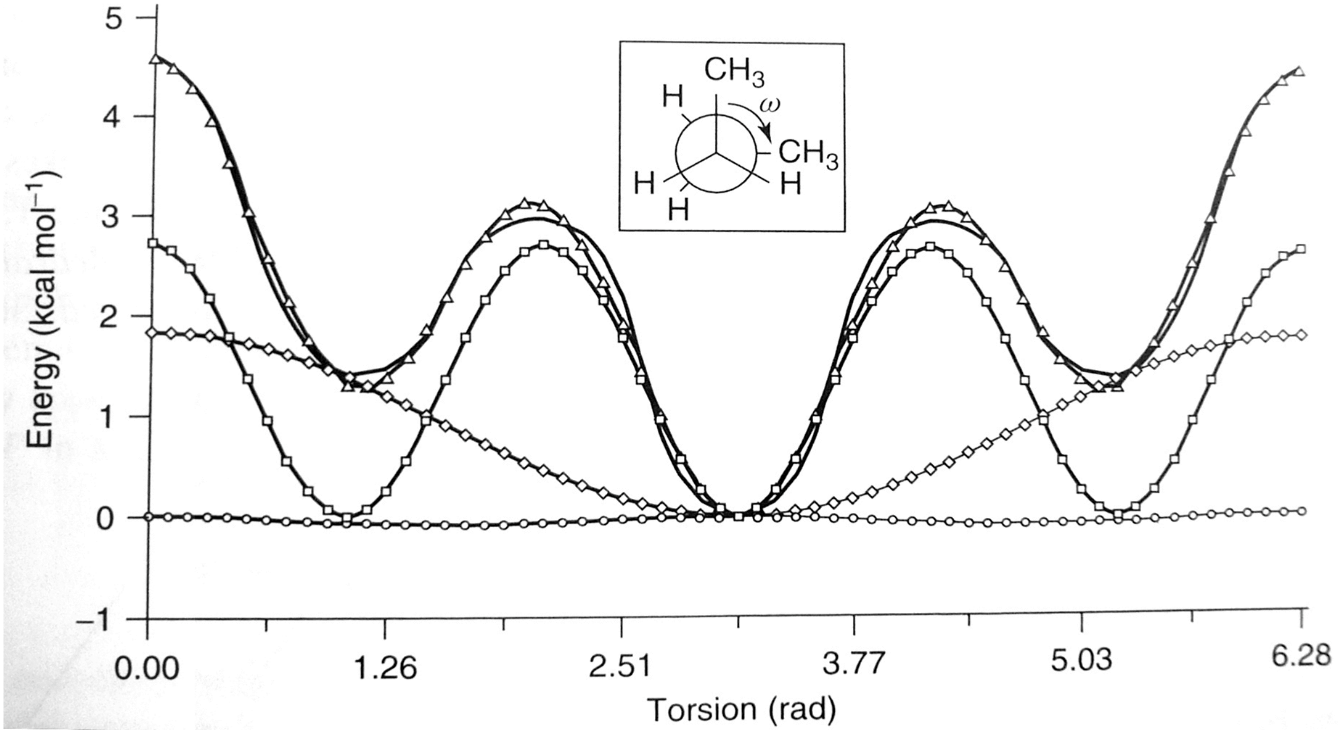
Torsion is periodic – the torsional potential energy should be periodic. It makes sense to model the potential energy function as an expansion of periodic functions (spherical harmonics) – Fourier series. In a general form, typical force fields use

$$U(\omega_{ABCD}) = \frac{1}{2} \sum_{\{j\}_{ABCD}} V_{j,ABCD}\left[1 + (-1)^{j+1} \cos\left(j\omega_{ABCD} + \psi_{j,ABCD}\right)\right]$$

V_j – amplitudes; ψ_j – phase angles used for fine tuning of the fit. If $\psi = 0$, the maximal value is achieved at $\omega = \pi$.



Fourier decomposition of the torsional energy for rotation about C-O bond of fluoromethanol



Fourier decomposition of the torsional energy for rotation about the C-C bond of *n*-butane

How to handle the valence angle bending term in a system where multiple equilibrium angles are present?

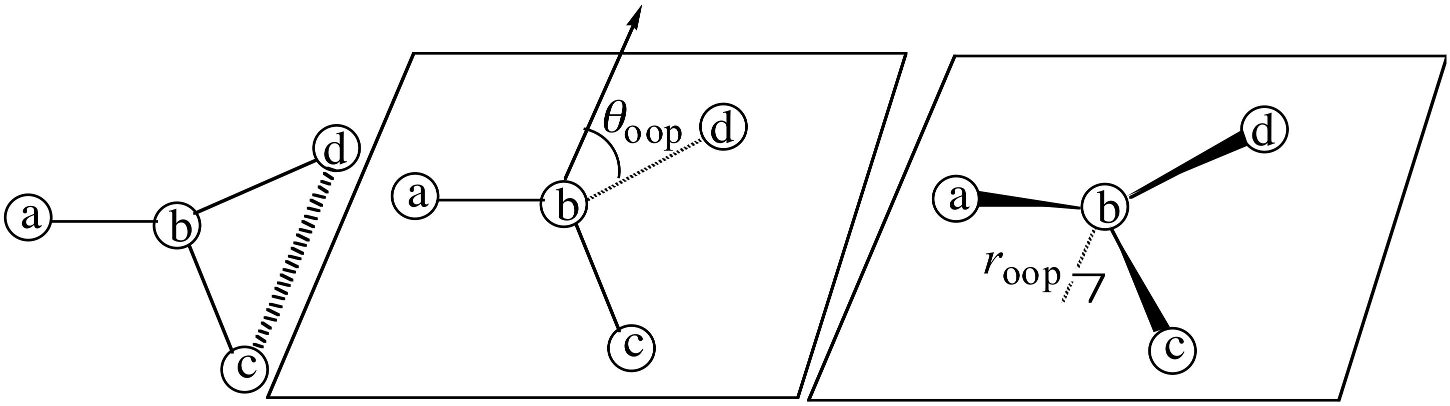
This is analogous to the torsional energy – use Fourier transfer (spherical harmonics). Inorganic SHAPES force field:

$$U\left(\theta_{ABC}\right) = \sum_{\{j\}_{ABC}} k_{j,ABC}^{Fourier}\left[1 + \cos\left(j\theta_{ABC} + \psi\right)\right] \qquad k_{j,ABC}^{Fourier} = 2k_{ABC}^{harmonic} / j^2$$

This expression can be also used in regions of bond angle inversions ($\theta = \pi$).

Alternatively, in metal coordination force fields designed to handle multiple ligand-metal-ligand angles the angle term can be simply removed altogether. It is replaced by a repulsive non-bonded term specific to 1,3-interactions (Urey-Bradley term). A given number of ligands attached to a central atom will tend to organize themselves so as to maximize the separation between any two.

Special situation for angle bending: four-atom systems where a central atom is bonded to three otherwise unconnected atoms – H_2CO, formaldehyde. In this case, a fourth atom is more naturally defined by a bond length to the central atom and its two bond angles to the other two atoms. On the other hand, it can also be defined by a length to the central atom, an angle to the third atom, and a dihedral atom to the fourth atom even though atoms three and four are not connected. Such torsion angles are called 'improper torsions'.



In formaldehyde (a planar molecule), an improper torsion OCHH has a value of 180° (π). Many force fields treat improper torsion like any other torsion. Alternatives – deviation from planarity by the angle θ_{oop} (out-of-plane angle) or the elevation r_{oop} of the central atom above/below the plane defined by the three other atoms. θ_{oop} are r_{oop} are in a sense similar to angle bending and bond stretching and are treated by force field in the manner of Taylor expansion.

Steric interactions between eclipsing atoms groups are also important! If one tries to build a space-filling model of a sterically congested molecule, one can see that atomic balls push against one another creating strain. In cases where dipole-dipole and hypeconjugative interactions are small about a rotating bond, there may not be a need to parametrize torsional function at all.

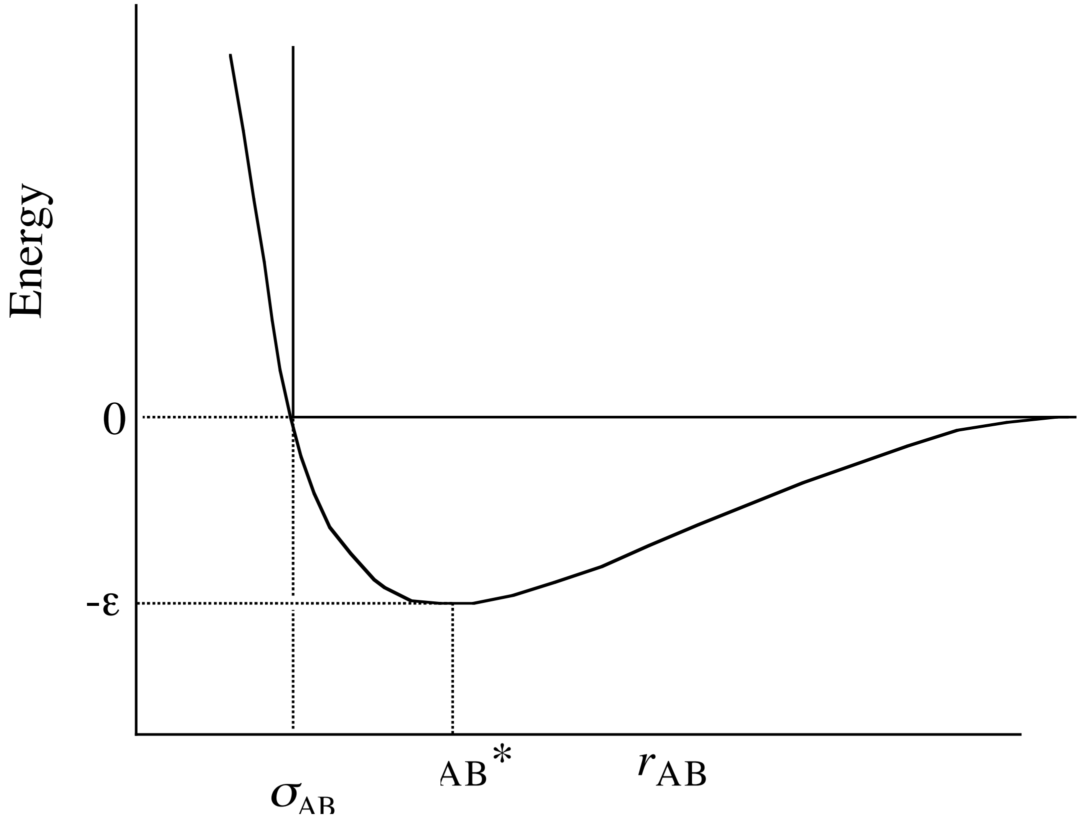
Instead, one could represent atoms as balls with a characteristic radius and develop a functional form for the energetics of ball-ball interactions. This also provides and intuitive model for more distant ‘non-bonded’ interactions.

Van der Waals Interactions

Consider two noble gas atoms. Infinite separation – no interaction between them – the zero of potential energy. There is no electric multipole moments – no attractive force between the atoms as they approach one another.

$$F_q = -\frac{\partial U}{\partial q}$$

There is no force – the slope of the energy curve with respect to the bond length coordinate is zero – the potential energy remains zero as the atoms approach one another. We assign to the atom hard-sphere radii r_{vdW}. When the bond length reaches twice the radius, the two cannot approach one another more closely – the potential energy becomes infinite for $r < r_{\mathrm{vdW}}$.



In the quantum world, electrons (electronic wave functions) are correlated – two atoms simultaneously develop electrical moments oriented to be mutually attractive. This interaction is called 'dispersion', 'London' force, or the 'attractive van der Waals' force. In the absence of a permanent charge, the strongest interaction is dipole-dipole (induced dipole-induced dipole) – inverse sixth power dependence on the distance between two atoms. *He_2 is bound by few cm^{-1}, has one bound vibrational state with a vibrationally averaged bond length of 55 Å!*

As the two atoms continue to approach one another, their electron densities begin to interpenetrate – Pauli repulsion – the energy rises rapidly with decreasing bond length.

Lennard-Jones potential:

$$U(r_{AB}) = \frac{a_{AB}}{r_{AB}^{12}} - \frac{b_{AB}}{r_{AB}^{6}}$$

More typically, it is written as

$$U(r_{AB}) = 4\varepsilon_{AB}\left[\left(\frac{\sigma_{AB}}{r_{AB}}\right)^{12} - \left(\frac{\sigma_{AB}}{r_{AB}}\right)^{6}\right]$$

σ - the interatomic separation at which repulsive and attractive forces exactly balance, $U = 0$.

We find 'equilibrium' value $r_{AB}*$ by differentiating U:

$$\frac{dU(r_{AB})}{dr_{AB}} = \frac{4\varepsilon_{AB}}{r_{AB}}\left[-12\left(\frac{\sigma_{AB}}{r_{AB}}\right)^{12} + 6\left(\frac{\sigma_{AB}}{r_{AB}}\right)^{6}\right] = 0$$

$$r_{AB}^{*} = 2^{1/6}\sigma_{AB}$$

$U = -\varepsilon_{AB}$ – the Lennard-Jones well depth

More general force field for small and medium-size molecules – combination of the Lennard-Jones potential, the Morse potential, and the 'Hill' potential:

$$U(r_{AB}) = \varepsilon_{AB}\left[\frac{6}{\beta_{AB}-6}\exp\left(\beta_{AB}\frac{1-r_{AB}}{r_{AB}^{*}}\right)-\frac{\beta_{AB}}{\beta_{AB}-6}\left(\frac{r_{AB}^{*}}{r_{AB}}\right)^{6}\right]$$

Some force fields reduce the van der Waals interaction energy computed for 1,4-related (torsionally-related) atoms by a constant scale factor.

Electrostatic Interactions

Two molecules A and B interact at a reasonably large distance:

$$U_{\mathrm{AB}} = \mathbf{M}^{(\mathrm{A})}\mathbf{V}^{(\mathrm{B})}$$

$\mathbf{M}^{(\mathrm{A})}$ – an ordered vector of the multiple moments of A: charge (zeroth moment), x, y, and z components of the dipole moment, nine components of the quadruple moment, etc.

$\mathbf{V}^{(\mathrm{B})}$ – a similarly ordered row vector of the electrical potentials deriving from the multiple moments of B.

Both expansions are about single centers – the centers of mass of the molecules. At long distances, one can truncate the moments expansions at reasonably low orders and obtain useful interaction energies.

For a large collection of individual molecules:

$$U = \sum_{A}\sum_{B>A} M^{(A)}V^{(B)}$$

This is not convenient for intramolecular electrostatic interactions. Another drawback – this approach is difficult to parameterize and it is computationally intensive.

More convenient – to describe electrostatic interactions in terms of atoms (van der Waals balls). The simplest way – to assign each van der Waals atom a partial charge. Then,

$$U_{AB} = \frac{q_A q_B}{\varepsilon_{AB} r_{AB}}$$

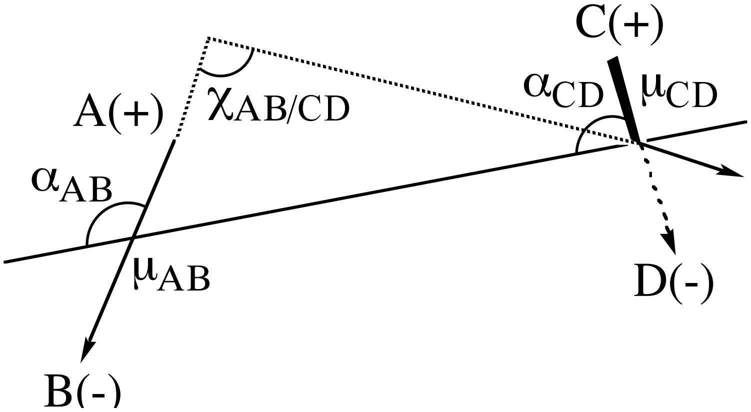
1) The simplest case – the charges are permanent – all atoms of a given type are defined to carry that charge at all situations.

2) The charge is determined from the electronegativity of the atom in question and on the electronegativities of those atoms to which it is connected. Atomic negativity – a parameter, some functional form is chosen in which this parameter serves as a variable. Used in a force field with a reduced number of atom ‘types’ – flexible in recognition of different chemical environments.

3) If the force field is designed to study a particular molecule – the partial charges are chosen to accurately reproduce some experimental or computed electrostatic observable of the molecule.

Instead of the atom, one can define charge polarization for the chemical bond (dipole moment of the bond):

$$U_{AB/CD} = \frac{\mu_{AB}\mu_{CD}}{\varepsilon_{AB/CD} r^3_{AB/CD}} \left(\cos\chi_{AB/CD} - 3\cos\alpha_{AB}\alpha_{CD}\right)$$



ε - dielectric constant (used as a parameter)

$$\varepsilon = \begin{array}{ll} \infty & \text{if A and B are 1,2- or 1,3-related} \\ 3.0 & \text{if A and B are 1,4-related} \\ 1.5 & \text{otherwise} \end{array}$$

Electrostatic interactions between bonded atoms or between atoms sharing a common bonded atom are not evaluated, interactions between torsionally related atoms are evaluated, but are reduced in magnitude by a factor of 2 relative to all other interactions.

Bonds between heteroatoms and hydrogens – the most polar bonds in non-ionic systems – the source of hydrogen bonding. Most force fields – implicit account of hydrogen bonding in th non-bonded terms (van der Waals + electrostatic). Sometimes – an additional non-bonded interaction term (10-12 potential):

$$U(r_{XH}) = \frac{a'_{XH}}{r_{XH}^{12}} - \frac{b'_{XH}}{r_{XH}^{10}}$$

X – heteroatom to which H is not bound. The term is analogous to a Lennard-Jones potential, but has a much more rapid decay of the attractive region with increasing bond length – forces a hydrogen bond to deviate only very slightly from its equilibrium value.

Actual molecules have their electric moments perturbed under the influence of electric field (polarizable). To extant force field to include polarizability – each atom is assigned a polarizability tensor. In the presence of the permanent electric field of the molecule (from atomic charges), a dipole moment is induced at each atom. After that – the total electric field is the sum of the permanent electric field and that created by induced dipoles. Self-consistence procedure: initial charges and polarizabilities – induced dipoles – new charges – until self-consistency is achieved through an iterative procedure.

Computing the electrostatic interaction energy for polarizable force field – an order of magnitude more costly than it is for a static force field. The benefits are usually small.

Cross Terms

Bonds, angles, are not isolated molecular coordinates, they couple with one another. For example, as a bond angle is compressed, the bond lengths to the central atom will lengthen to decrease the non-bonding interaction between the terminal atoms.

Multi-dimensional Taylor expansion:

$$U(q) = U(q_{eq}) + \sum_{i=1}^{3N-6} (q_i - q_{i,eq}) \left.\frac{\partial U}{\partial q_i}\right|_{q=q_{eq}}$$

$$+\frac{1}{2!}\sum_{i=1}^{3N-6}\sum_{j=1}^{3N-6}(q_i - q_{i,eq})(q_j - q_{j,eq}) \left.\frac{\partial^2 U}{\partial q_i \partial q_j}\right|_{q=q_{eq}}$$

$$+\frac{1}{6!}\sum_{i=1}^{3N-6}\sum_{j=1}^{3N-6}\sum_{k=1}^{3N-6}(q_i - q_{i,eq})(q_j - q_{j,eq})(q_k - q_{k,eq}) \left.\frac{\partial^3 U}{\partial q_i \partial q_j \partial q_k}\right|_{q=q_{eq}}$$

For example, one may include the bond length/bond angles coupling terms:

$$U(r_{AB},\theta_{ABC}) = \frac{1}{2} k_{AB,ABC}(r_{AB} - r_{AB,eq})(\theta_{ABC} - \theta_{ABC,eq})$$

Stretch-bend coupling – most useful in highly strained systems and for the computation of vibrational frequencies. Stretch-torsion coupling – useful in systems where eclipsing interactions lead to high degree of strain:

$$U(r_{AB},\omega_{ABCD}) = \frac{1}{2} k_{BC,ABCD}(r_{BC} - r_{BC,eq})(\omega_{ABCD} - \omega_{ABCD,eq})$$

Other useful coupling terms: stretch-stretch, bend-bend. In force field that aim for spectroscopic accuracy – higher order terms.

Parametrization Strategies

A force field – a collection of functional forms and associated constants. The energy of a given molecule can be evaluated by computing the energy associated with every defined type of interactions occurring in the molecule.

We have to pay attention to the individual parameters appearing in the functional forms (force constant, equilibrium coordinate values, phase angles, coupling constants, etc.) – we have to parametrize the force field based upon experimentally (spectroscopically) measurable quantities.

Step 1 – collect appropriate experimental data.

Step 2 – define a 'penalty function' – a function that provides a measure of how much deviation there is between the predicted and experimental values:

$$Z = \left[\sum_{i}^{Observables} \sum_{j}^{Occurences} \frac{\left(calc_{i,j} - \exp t_{i,j} \right)^2}{w_i^2} \right]^{1/2}$$

Step 3 – minimize the penalty function.

Atomic 'types' cannot be defined by atomic number alone. Bonds involving two C atoms fall into at least four classes (single, aromatic, double, and triple). Different atomic hybridizations give rise to different angle bending equilibrium values and torsional angles. If one wants to include metals, different oxidation states give rise to differences in structural and energetic properties.

In order to improve accuracy, a given force field may have a very large number of atom types even for a relatively modest number of nuclei.

Organic force field: MM3 – 153 atom types, MMFF – 99 atom types. Biomolecular force fields: OPLS and AMBER – 41 atom types, universal force field (UFF) – 126 atom types.

How to decrease the scope of the parametrization problem? Make certain parameters that depend on more than one atom themselves functions of single-atom-specific parameters:

$$\sigma_{AB} = \sigma_A + \sigma_B \qquad\qquad \varepsilon_{AB} = (\varepsilon_A \varepsilon_B)^{1/2}$$

Truly general force fields (DREIDING, UFF, and VALBOND) attempt to reduce almost all parameters to being derivable from a fairly small set of atomic parameters.

Another approach – make certain constants depend on bond order or bond hybridization. VALBOND – angle and bending energies at metal atoms are computed from orbital properties of the metal-ligand bonds. MM2, MM3 – stretching force constants, equilibrium bond lengths, and two-fold torsional terms depend on computed π bond orders between atoms.

Yet another way – 'united-atom' (UA) model. Instead of defining only atoms as fundamental units, one also defines certain functional groups (methyl, methylene, aryl CH, etc.). The group has its own single set of non-bonded and other parameters.

Even with reduced number of parameters, a large number of parameters still needs to be found (9000 parameters in the MMFF94 force field). Experimental data may be too sparse and insufficient – supplement them with the highest quality *ab initio* calculations. One can attempt to make force-field energy derivatives correspond to those computed *ab initio*.

Sometimes, we have to accept that there will be some molecules with connectivities outside the range of chemical space to which the force field can be applied.

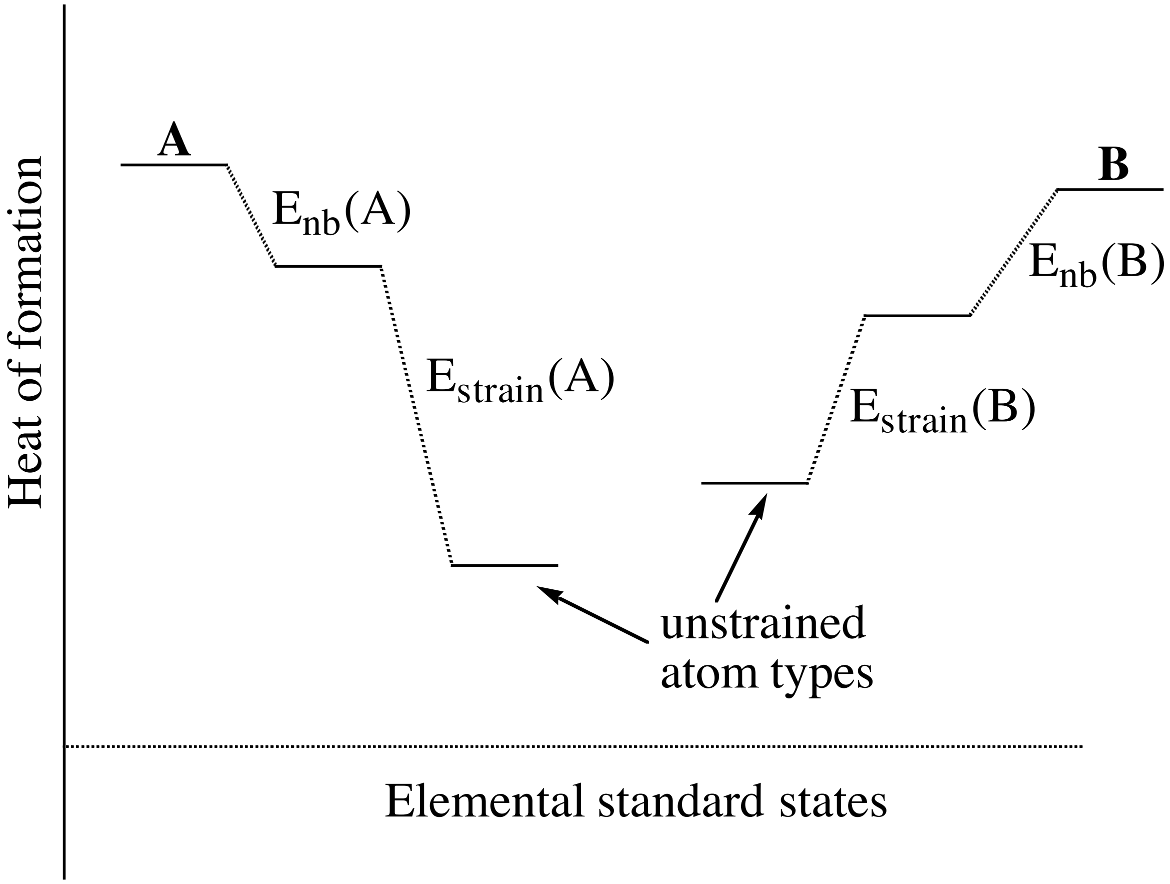
Some atom types for N and C in MM2 (CHEM3D)

C Alkane	C	1.431	Tetrahedral
C Alkene	C	1.462	Trigonal planar
C Alkyne	C	1.462	Linear
C Carbocation	C	1.462	Trigonal planar
C Carbonyl	C	1.462	Trigonal planar
C Carboxylate	C	1.462	Trigonal planar
C Cumulene	C	1.462	Linear
C Cyclopentadienyl	C	1.462	Trigonal planar
C Cyclopropane	C	1.431	Tetrahedral
C Cyclopropene	C	1.462	Trigonal planar
C Epoxy	C	1.431	Tetrahedral
C Isonitrile	C	1.462	1 Ligand
C Metal CO	C	1.462	Linear
C Thiocarbonyl	C	1.462	Trigonal planar
N Amide	N	1.392	Amide Trigonal planar
N Amine	N	1.392	Amine Trigonal pyramidal
N Ammonium	N	1.392	H Ammonium Tetrahedral
N Azide Center	N	1.392	Linear
N Azide End	N	1.392	1 Ligand
N Azo	N	1.392	Amine Bent
N Enamine	N	1.392	Amine Trigonal planar
N Guanidine	N	1.392	Guanidine Trigonal planar
N Imine	N	1.392	Bent
N Immonium	N	1.392	Ammonium Trigonal planar
N Isonitrile	N	1.392	Linear
N Nitrile	N	1.392	1 Ligand
N Nitro	N	1.392	Trigonal planar
N Pyridine	N	1.392	Bent
N Pyridinium	N	1.392	Ammonium Trigonal planar
N Pyrrole	N	1.392	Amine Trigonal planar

Force-field Energies and Thermodynamics

On measure of the accuracy of a force field – its ability to predict heats of formation.

A typical force field provides the following data: 1) a strain energy – the energetic consequence of the deviation of the internal molecular coordinates from their equilibrium value; 2) a force-field energy – the sum of the strain energy and the non-bonded interaction energies (van der Waals and electrostatic); 3) a heat of formation – the sum of the force-field energy and the reference heats of formation for the constituent atom types.



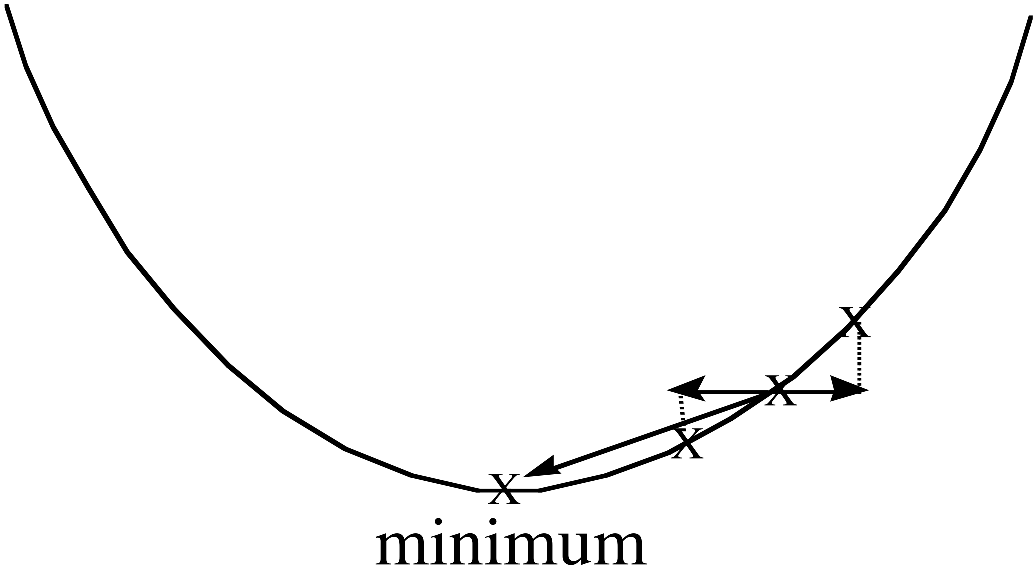
If reference heat of formation for some atom types is not known, energetic comparisons are limited to conformers or other isomers that can be formed without any change in atom types.

Geometry optimization

While the energy of an arbitrary structure can be interesting, real molecules vibrate thermally about their equilibrium structures – finding minimum energy structures is key to describing equilibrium constants, comparing to experiment, etc.

Optimization algorithms

One-dimensional case:



Multidimensional case: find minimum along the first internal molecular coordinate, then the second, and so forth. Repeat this process iteratively until the coordinates of the 'minimum' do not change any more within chemical accuracy. This approach works well if the internal coordinates are not strongly coupled.

More practical approach – move in the direction of the greatest downward slope with respect to all coordinates – the opposite of the gradient vector **g**.

$$g(q)=\begin{bmatrix}\dfrac{\partial U}{\partial q_1}\\ \dfrac{\partial U}{\partial q_2}\\ \dfrac{\partial U}{\partial q_3}\\ \vdots\\ \dfrac{\partial U}{\partial q_n}\end{bmatrix}$$

The gradient can be calculated using numerical differentiation (‘forward difference’ – two points on the potential energy surface (PES) are required or ‘central difference’ – three points on PES are required) or using analytical differentiation, if the analytical, functional form of the derivatives is known. Force field – analytical gradients are available. Example – compute the partial derivative with respect to the *x* coordinate of atom A. We need to evaluate the changes in energy for the various terms contributing to the full force-field energy as a function of moving atom A in *x* direction. Bond stretching terms: only the energy of those bonds that involve atom A will be affected by A’s movement. Use the chain rule:

$$\frac{\partial U}{\partial x_A}=\sum_{i-bonded-to-A}\frac{\partial U}{\partial r_{Ai}}\frac{\partial r_{Ai}}{\partial x_A}$$

$$U(r_{Ai})=\frac{1}{2}\left[k_{Ai}+k_{Ai}^{(3)}\left(r_{Ai}-r_{Ai,eq}\right)+k_{Ai}^{(4)}\left(r_{Ai}-r_{Ai,eq}\right)^2\right]\left(r_{Ai}-r_{Ai,eq}\right)^2$$

$$\frac{\partial U}{\partial r_{Ai}}=\frac{1}{2}\left[2k_{Ai}+3k_{Ai}^{(3)}\left(r_{Ai}-r_{Ai,eq}\right)+4k_{Ai}^{(4)}\left(r_{Ai}-r_{Ai,eq}\right)^2\right]\left(r_{Ai}-r_{Ai,eq}\right)$$

$$r_{Ai}=\sqrt{\left(x_A-x_i\right)^2+\left(y_A-y_i\right)^2+\left(z_A-z_i\right)^2}$$

$$\frac{\partial r_{Ai}}{\partial x_A}=\frac{x_A-x_i}{\sqrt{\left(x_A-x_i\right)^2+\left(y_A-y_i\right)^2+\left(z_A-z_i\right)^2}}$$

We can move in –**g** direction and eventually find a minimum. However, the gradient gives us only the *direction* toward minimum, but not the *step size* to reach it. Therefore, geometry optimization using *only* gradient can be painstakingly slow.

A more robust method – the Newton-Raphson procedure.

$$U(q) = U(q_{eq}) + \sum_{i=1}^{3N-6} (q_i - q_{i,eq}) \left.\frac{\partial U}{\partial q_i}\right|_{q=q_{eq}}$$

$$+\frac{1}{2!}\sum_{i=1}^{3N-6}\sum_{j=1}^{3N-6}(q_i - q_{i,eq})(q_j - q_{j,eq})\left.\frac{\partial^2 U}{\partial q_i \partial q_j}\right|_{q=q_{eq}}$$

$$U\left(q^{(k+1)}\right) = U\left(q^{(k)}\right) + \left(q^{(k+1)} - q^{(k)}\right)g^{(k)} + \frac{1}{2}\left(q^{(k+1)} - q^{(k)}\right)^T H^{(k)}\bigl(q^{(k+1)} - q^{(k)}$$

$\mathbf{q}^{(k)}$ – the reference point; $\mathbf{g}^{(k)}$ – the gradient for the reference point;

$\mathbf{H}^{(k)}$ – the Hessian matrix: $$H_{ij}^{(k)} = \left.\frac{\partial^2 U}{\partial q_i \partial q_j}\right|_{q=q^{(k)}}$$

Imagine our reference point is $\mathbf{q}^{(k)}$ and $\mathbf{q}^{(k+1)}$ is a minimum. Then, by differentiation of the above equation term by term with respect to the *i*th coordinate of $\mathbf{q}^{(k+1)}$ and from the fact that $\mathbf{g}^{(k+1)}$ should be zero, we can obtain:

$$\mathbf{q}^{(k+1)} = \mathbf{q}^{(k)} - (\mathbf{H}^{(k)})^{-1}\,\mathbf{g}^{(k)}$$

Thus, gradient gives us the direction toward a minimum and Hessian provides the step size. Hessian can be evaluated analytically or numerically, using gradients calculated for previous points during the geometry optimization process. The procedure leads to the nearest stationary point (zero gradient) but not necessarily to a minimum. Check the Hessian matrix – all coordinate second derivatives (diagonal elements) should be positive at the minimum.

If the Hessian matrix has one negative diagonal element – a transition state (TS) is found. ***To verify the nature of a located stationary point, it is necessary to compute an accurate Hessian matrix and inspect it eigenvalues.*** With force fields, it is often cheaper and equally effective simply to 'kick' the structure – by hand one moves one or a few atoms to reasonably distorted locations and then reoptimizes to verify that the original structure is again found as the lowest energy structure nearby.

TS (first-order saddle point) structures are very important – a large number of more sophisticated methods exist to locate them. One approach – specify two minima that the TS structure should connect – intermediate structures are evaluated to locate the relevant transition state. Another method – specify one particular coordinate with respect to which the energy is to be maximized while minimizing it with respect to all other coordinates. All TS structure location methods work best when the chemist can provide a reasonably good initial guess for the structure and also are sensitive to the availability of a good Hessian matrix.

Most optimizers are rather good at getting you the nearest *local* minimum, but we may be interested in finding the *global* minimum (the minimum having the lowest energy of all minima). This is a problem of applied math and no one solution is optimal – most methods involve a systematic or random sampling of alternative configurations.

Available Force Fields

1) AMBER – biomolecules and organic – all-atom (AA) and united-atom (UA) versions are available – error – 7 kcal/mol.

2) MACROMODEL – organics and biomolecules – the program MACROMODEL contains many modified versions of other force fields, e.g., AMBER*, MM2*, MM3*, OPLSA* - errors – 4 (MM2*), 5 (MM3*).

3) CHARMM – biomolecules – many versions of force field parameters exist, distinguished by ordinal number – all-atom and united atom versions exist.
4) CHARMm – biomolecules and organics – version of CHARMM extended and made available in Accelrys software.
5) Chem-X – organics – available in Chemical Design Ltd. software – error – 12 kcal/mol.
6) 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 – errors – 13 kcal/mol (CVFF), 7 (CFF91).
7) COSMIC – organics and biomolecules.
8) DREIDING –main-group organics and inorganics – bond stretching can be modeled with a Morse potential – error – 10 kcal/mol.
9) ECEPP – proteins – computes only non-bonded interactions for fixed structures.
10) ESFF – general – bond stretching is modeled with a Morse potential.
11) GROMOS – biomolecules – GROMOS software code.
12) MM2 – organics – suppressed by MM3 but still widely available in many modified forms, available in CHEM3D – error – 5 kcal/mol.
13) MM3 – organics and biomolecules – widely available in many modified forms – error – 5 kcal/mol.
14) MM4 – hydrocarbons.
15) MMFF – organics and biomolecules – error 4 kcal/mol (MMFF93).
16) MMX – organics, biomolecules and inorganics – based on MM2 – error – 5 kcal/mol.

17) MOMEC – transition metal compounds.
18) OPLS – biomolecules, some organics – organic parameters are primarily for solvents. All-atom and united-atom versions exist.
19) PEF95SAC – carbohydrates – based on CFF.
20) SHAPES – transition metal compounds.
21) SYBYL/Tripos – organics and proteins – available in Tripos and some other software – error – 8-12 kcal/mol.
22) UFF – general – bond stretching can be modeled with a Morse potential – error – 21 kcal/mol.
23) VALBOND – transition metal compounds – atomic-orbital dependent energy expressions.

HyperChem – MM+, a general purpose force field, and three specialized biomolecule force fields: Amber, BIO+, CHARMM, and OPLS.
SPARTAN – SYBYL, MMFF94.
GAUSSIAN – AMBER, DREIDING, UFF, MMFF94

Validation

How do I pick the best force field for my problem?
How will I know whether I can trust the results?

One should pick the force field that has previously been shown to be the most effective for the most closely related problem one can find. Periodically in the literature, papers appear comparing a wide variety of force fields for some well-defined problem, and the results can be quite useful in guiding the choices. In general, the best performances are exhibited by the MM2 and MM3 force fields and other force fields that are build upon them. MMFF93 had similar accuracy. The most general force fields do rather badly – UFF fares quite poorly in every category except hydrocarbons.

In looking for an optimal force field there is no guarantee that any system sufficiently similar to the one someone is interested in has ever been studied – then it is hard to make a confident assessment of force-field utility. Assuming some experimental data are available, it is best to survey several force fields and to compare their reliability. When experimental data are not available, look for well-converged quantum mechanical calculations for a few examples (assuming the computational cost is not prohibitive). QM values would then take place of experimental data. Absent any of these alternatives, any force field calculations will simply carry with them a high degree of uncertainty and the results should be used with caution.

Inorganic chemists unfortunately have reached this point – they can receive relatively little guidance from force-field calculations for their problems. The current state of the art does not provide any single force field that is both robust and accurate over a large range of inorganic molecules (particularly metal coordination compounds). Parameter transferability tends to be low; the number of atom types potentially requiring parametrization for a single metal atom, together with the associated very large number of geometric and non-bonded constants, tends to significantly exceed available data. Instead, individual problems tend to be best solved with highly tailored force fields (when those are available) or by combining QM and MM methods. Using available highly generalized force fields increases the risk of significant errors – the focus primarily should be on structural perturbations over a related series of compounds rather than absolute structures or energetics.