

# **TINKER – *Software Tools for Molecular Design***

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TINKER is a complete package for performing empirical force field molecular mechanics and dynamics calculations. It is intended to serve as a platform for algorithm development and parameterization, while still being efficient enough for most production work. The available potentials include Amber *ff94*, *ff96*, *ff98* and *ff99*, CHARMM19, CHARMM27, DANG, MM2, MM3, OPLS-UA, OPLS-AA, OPLS-AA/L and our AMOEBA polarizable atomic multipole-based potential. Other force fields can be added via new parameter files; ENCAD and UFF are under consideration presently.

Programs are provided to perform many functions including: (1) energy minimization over Cartesian coordinates, torsional angles or rigid bodies via conjugate gradient, variable metric or our truncated Newton method, (2) molecular, stochastic and rigid body dynamics with periodic boundaries and control of temperature and pressure, (3) normal mode vibrational analysis, (4) distance geometry including an efficient random pairwise metrization, (5) building protein and nucleic acid structures from sequence, (6) simulated annealing with various cooling protocols, (7) analysis and breakdown of single point potential energies, (8) verification of analytical derivatives of standard and user defined potentials, (9) location of a transition state between two minima, (10) full energy surface search via our Conformation Scanning method, (11) free energy calculations via free energy perturbation or weighted histogram analysis, (12) fitting of intermolecular potential parameters to structural and thermodynamic data, and (13) global optimization via energy surface smoothing including our own Potential Smoothing and Search (PSS) method.

Analytical Cartesian derivatives through the Hessian and analytical torsional derivatives through the gradient are available. Energy minimization and vibrational analysis can be performed in either Cartesian or torsional spaces. The user can define rigid bodies and compute scaled energies between or within bodies. Atomic multipoles through the quadrupole and induced dipole polarization, as well as simpler electrostatic models, are implemented. Restraint potentials may be included in all types of computations or partial structures can be frozen in space. Both replicative and image boundary conditions are supported for all unit cell types and for truncated octahedra. Nonbonded interactions can be cutoff using smoothing windows via double loop searches or the Method of Lights. Particle mesh Ewald (PME) is available for partial charges, and standard Ewald for polarizable atomic multipoles. The molecular volume and surface area as well as their derivatives are included. Various continuum solvation models, such as GB/SA, are implemented. User-defined potentials can be easily added.

The heart of the TINKER package is a modular set of callable routines which allow the manipulation of coordinates and evaluation of potential energy and derivatives in a straightforward fashion. The author welcomes development by others of new

modules for TINKER and is willing to serve as a resource and distribution center for such development efforts.

A complete Java GUI for TINKER, call Force Field Explorer or FFE, is available as an adjunct to the basic package. FFE is tightly integrated with the TINKER code via a socket mechanism, and can be used to setup, launch and visualize TINKER calculations. The GUI allows for interactive use on a single machine, as well as connection to jobs running on a remote server.

The TINKER package is written in a portable Fortran dialect that makes use of some common extensions to the Fortran77 standard. Program control is via an optional Keyword Parameter file. TINKER coordinate input files are also compatible with Cambridge Scientific Software's CHEMDRAW & CHEM3D programs and with the gOpenMol, MOLDEN and ReView molecule viewers. A modified version of RasMol for TINKER is also available for viewing molecular structures. Auxiliary programs are provided to convert Protein Data Bank files to and from the TINKER formats. Output can also be generated in formats compatible with the Tripos Sybyl, Accelrys InsightII, and Xmakemol programs.

#### Selected References:

1. P. Ren and J. W. Ponder, Polarizable Atomic Multipole Water Model for Molecular Mechanics Simulation, *J. Phys. Chem. B*, **107**, 5933-5947 (2003).
2. R. V. Pappu, R. K. Hart and J. W. Ponder, Analysis and Application of Potential Energy Smoothing for Global Optimization, *J. Phys. Chem. B*, **102**, 9725-9742 (1998).
3. Y. Kong and J. W. Ponder, Reaction Field Methods for Off-Center Multipoles, *J. Chem. Phys.*, **107**, 481-492 (1997).
4. M. J. Dudek and J. W. Ponder, Accurate Modeling of the Intramolecular Electrostatic Energy of Proteins, *J. Comput. Chem.*, **16**, 791-816 (1995).
5. C. E. Kundrot, J. W. Ponder and F. M. Richards, Algorithms for Calculating Excluded Volume and Its Derivatives as a Function of Molecular Conformation and Their Use in Energy Minimization, *J. Comput. Chem.*, **12**, 402-409 (1991).
6. J. W. Ponder and F. M. Richards, An Efficient Newton-like Method for Molecular Mechanics Energy Minimization of Large Molecules, *J. Comput. Chem.*, **8**, 1016-1024 (1987).

Availability:	Executables and Source at <a href="http://dasher.wustl.edu/tinker/">http://dasher.wustl.edu/tinker/</a>
Version:	TINKER 4.2 and Force Field Explorer 4.2 of June 2004
Language:	Fortran77 with common extensions and some C, Complete C translation via f2c available, FFE GUI in Java with Java 3D extensions
Lines of Code:	134,500 in TINKER Package (Fortran77 and some C) 30,000 in Force Field Explorer (Java and some C)