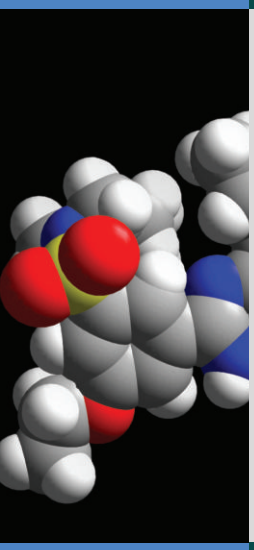


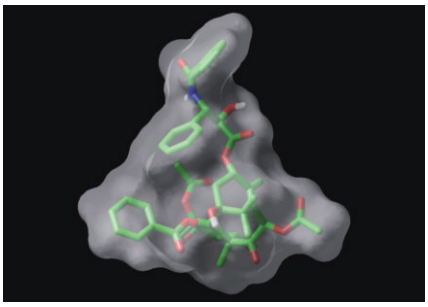
MacroModel

The most trusted name in molecular modeling software

MacroModel combines leading force fields, accurate effective solvation models, and advanced conformational searching methods to provide the most complete molecular modeling package suitable for a wide array of research.

SCHRÖDINGER.

The Advantages of Force Field-based Molecular Modeling

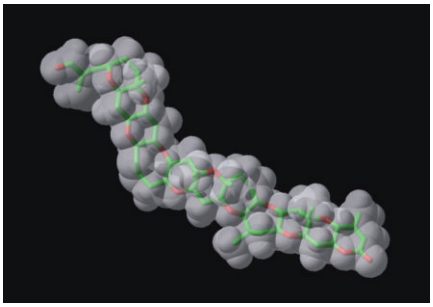


Taxol is an important terpenoid that disrupts the formation of microtubules. The model shown here is the lowest energy conformation found in a Multiple Minimum Monte Carlo conformation search. The search used GB/SA continuum solvent and OPLS-AA. The volume around the molecule represents the molecular surface.

The energy and properties of a chemical system depend on the exact three-dimensional molecular structure. Subtle variations in functional groups can result in dramatic differences in behavior. Force field methods that represent the potential energy of a molecule as simple functions of distances and angles between atoms have proven to be an efficient and effective approach to obtaining accurate relative energies for chemical systems. The efficiency of force field-based calculations allows the exploration of large portions of the conformational space, revealing the detailed relationship between structure and energy.

Force field-based molecular modeling is routinely applied to examine molecular conformations, molecular motion, and intermolecular interactions, such as those in a ligand-receptor complex.

MacroModel: The Gold Standard of Molecular Modeling

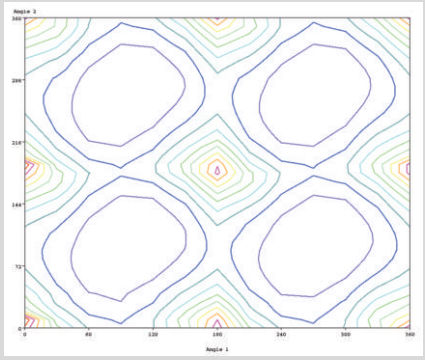


Brevetoxin B, a neurotoxin produced by the "red tide" dinoflagellate Gymnodinium breve. The model shown here is geometry-optimized with the OPLS-AA force field. The atoms and bonds are shown in a tube representation, while the van der Waals surface is shown in translucent white.

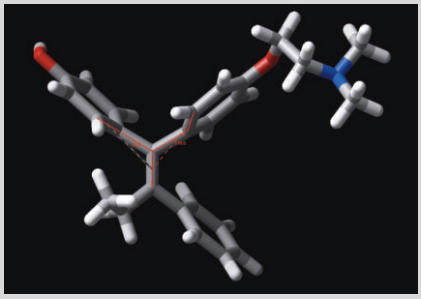
MacroModel, one of the most widely used applications in over a decade, continues to set the industry standard for force field-based molecular modeling:

- **Unmatched accuracy:** MacroModel's combination of high-quality force fields and GB/SA effective solvation model leads to reliably accurate estimations of energies.
- **Advanced simulation:** MacroModel performs molecular dynamics simulations to model systems at finite temperatures using stochastic dynamics and mixed Monte Carlo algorithms. MacroModel computes free energy changes using free energy perturbation method and the MINTA analysis module.
- **Superior conformational analysis:** MacroModel supports a wide range of conformational searching methods, capable of handling systems ranging from small molecules to entire proteins.
- **Easy-to-use interface:** MacroModel supports automated setup of energy minimizations, conformational searches, LogP estimation, and eMBrAcE (protein-ligand relaxation and energetics) analysis for large numbers of molecular systems within a single calculation. The Maestro user interface makes it easy to build and visualize structures, set up calculations, and analyze computational results.
- **Cross-platform support:** MacroModel supports Linux, SGI and IBM/AIX. Calculations may be distributed, with load balancing, across multiple heterogeneous CPUs for maximum throughput.

Performance-Driven Technology



Above is a contour plot of potential energy as a function of two dihedrals in 4-hydroxytamoxifen. The interactions between stilbene substituents are investigated to find the most favorable geometry. The blue and purple contours denote favorable angles, while the red and orange contours denote higher energy conformations.

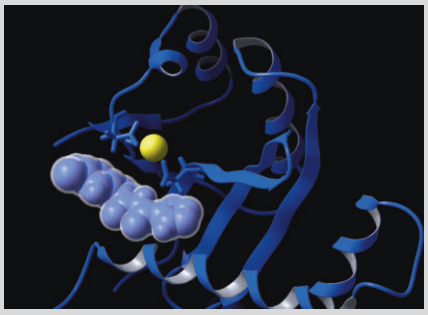


One of the four lowest energy dihedral combinations that exhibits minimal steric clash between substituents. This conformation was identified by using the interactive 2D-plot feature in Maestro as shown above.

MacroModel owes its success to superior technology and a commitment to continuous development:

- **Force field selection:** MacroModel supports all leading force fields, including MM2, MM3, AMBER, AMBER94, MMFF, OPLS, MMFFs and OPLS-AA, to support a wide range of research applications.
- **Solvation model:** The GB/SA effective solvent model, now an industry standard, was first developed in MacroModel. Water, trichloromethane, and octanol may be used as solvent in GB/SA computations.
- **Conformational analyses:** Searches of torsional space may be conducted in a stochastic or systematic manner. In addition, the low-mode (LMOD) method uses low frequency normal modes to construct collective conformational changes. Large-scale low-mode (LLMOD) can be applied to systems as large as entire proteins. Mixed MCMM/LMOD and MCMM/LLMOD calculations are also supported. XCluster is an interactive clustering tool which analyzes the large number of structures generated by a conformational search and rationally groups conformers into a few representatives for further study.
- **Computational efficiency:** MacroModel's substructure utility dramatically reduces the CPU time required to study large systems, such as protein-ligand complexes, by allowing a fully flexible region to be surrounded by multiple shells of atoms that are restrained or frozen. MacroModel's recently implemented bond-dipole cutoff method effectively eliminates mathematical artifacts that could arise from interactions between substructure regions, while significantly reducing memory requirements.
- **Development commitment:** Schrödinger is committed to the continued development of MacroModel. MacroModel has evolved over the years, driven by one of the largest user bases in molecular modeling, to enhance capabilities, improve performance, and to incorporate the latest scientific advances.

Molecular Flexibility



HIV integrase with Magnesium cofactor and inhibitor 5-CITEP. The Magnesium cofactor is shown in yellow and the chelating residues are shown in tube representation. The ligand is shown in 90% CPK (blue) and 100% CPK volume (translucent white). The geometry of the ligand and key residues was predicted with MacroModel.

Understanding receptor and ligand flexibility is frequently a critical part of elucidating important binding interactions. MacroModel is an ideal tool for investigating molecular flexibility.

HIV integrase catalyzes a set of reactions that inserts the viral genome into the host's DNA. This integration is an important area of AIDS research. In a study of HIV integrase, *JACS,* **2001,** *123,* 12708-12709, MacroModel was successfully applied to study the flexible ligand-receptor complex. The study used a large-scale low-mode (LLMOD) search to explore the conformational space of the system. Starting from an intentionally incorrectly-docked complex, the search found structures near the global energy minimum that agreed extremely well with experimental findings.

Evaluation Copies

To request an evaluation copy of MacroModel, please contact info@schrodinger.com. Our staff of support scientists will be happy to assist you in giving MacroModel a thorough trial.

MacroModel

The most trusted name in molecular modeling software

System Requirements:

LINUX
- Pentium or better
- Linux kernel 2.4 (Red Hat 7.3) or later
- 256 MB memory

SGI
- R5000 or better
- IRIX 6.5.2m or later
- 256 MB memory

IBM AIX
- Power series
- AIX 4.3.3 or AIX 5.x
- 256 MB memory

Additional Information:

www.schrodinger.com
info@schrodinger.com

A Coordinated Family of Products

In addition to MacroModel, Schrödinger offers Jaguar, a general-purpose quantum mechanics program; QikProp, a rapid ADME properties prediction program; and Prime, an integrated suite for protein structure predictions. Schrödinger also provides the FirstDiscovery Suite, which consists of three integrated modules:

- **Glide:** High-throughput ligand-receptor docking for fast library screening
- **Liaison:** Ligand-receptor binding free energies for lead optimization
- **QSite:** Mixed QM/MM for reactive chemistry at the enzyme active site

All Schrödinger products are seamlessly integrated through the Maestro graphical interface.

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