

# SYBYL

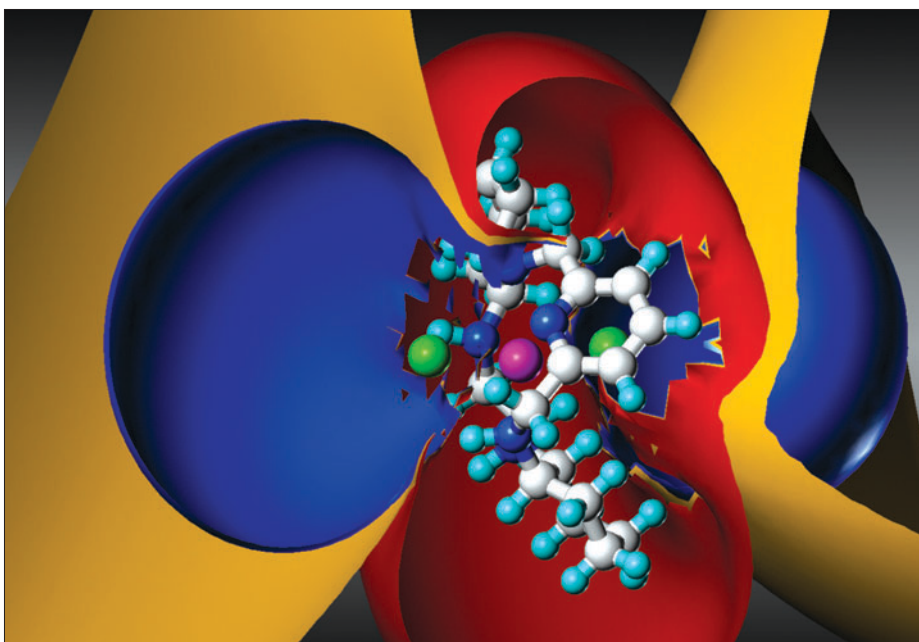
A COMPLETE COMPUTATIONAL CHEMISTRY AND MOLECULAR MODELING ENVIRONMENT



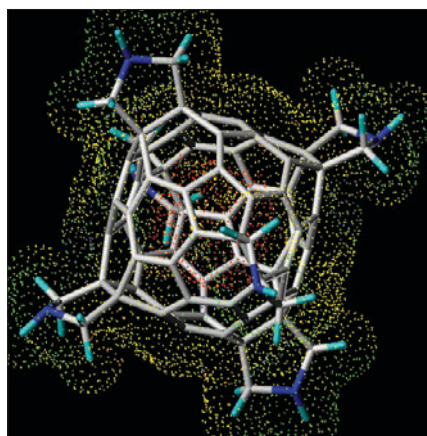
SYBYL<sup>®</sup>, the heart of Tripos' expert molecular modeling environment, provides the fundamental components for understanding molecular structure and properties with a special focus on the creation of new chemical entities. SYBYL provides essential construction, editing, and visualization tools for both large and small molecules. Data organization and analysis rely on the Molecular Spreadsheet<sup>™</sup>, which integrates chemical information with standard data manipulation tools. SYBYL's programming language and open architecture facilitate customized drug design methods.

## Applications

- **Building and Editing** – Visualize and investigate new chemical entities
- **Computation** – Organize and share molecular data via the Molecular Spreadsheet
- **Analysis and Organization** – Unify data from diverse sources
- **Visualization** – Construct and refine molecular models
- **Customization** – Create custom drug discovery methods



An enzyme mimic, this small organomanganese complex duplicates the catalytic activity of super oxide dismutase, a 31KD protein. The complex is rendered in ball-and-stick mode and shown with an isopotential contour.



An electroluminescent fullerene rendered as capped sticks and surrounded by a dot surface color-coded by atomic charge.

## Building and Editing

Molecular structures can be entered from a variety of sources. SYBYL reads many formats, including MOL and SD, Cambridge Structural Database, Protein Data Bank, and SMILES. Direct entry of structures is also possible using SYBYL's sketcher or 3D building tools. Editing of existing structures requires only a simple point-and-click to alter atoms, bonds, isomerization, or stereochemistry. Bond distances, bond angles, and torsions may also be modified. Large and small molecules are modeled in the same window, with no requirement for an elaborate setup process.

## Features

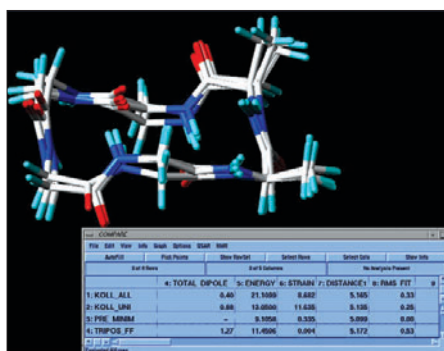
- 3D sketching
- Libraries of common molecules and functional groups
- Interface to the Cambridge Structural Database
- Editing of existing atoms, bonds, geometry, stereochemistry, and conformation
- Support for many file formats

## Computation

Geometry optimization (minimization) is performed via molecular mechanics or quantum mechanical methods to produce high quality models. SYBYL offers a variety of force fields as well as several options for computing or importing atomic charges. Several algorithms are available for generating solvent models.<sup>1</sup> Geometric features such as planes, normals, and centroids can be defined. Distance, angle, and torsion constraints for minimization can be keyed to individual atoms or geometric features. Computational resources and local geometries can be conserved by defining aggregates of rigid atoms. Field fit options drive two or more structures in the direction of shape and electrostatic similarity. Multiple structures can also be compared using several different approaches to molecular superpositioning.

## Features

- Tripos, Amber, MM2 and MMFF94 force fields
- Periodic boundary conditions for energy calculations and minimization



A cyclic hexapeptide optimized using several different force fields. The results are compared by superimposing the optimized structures and by measuring geometric and energetic properties within the Molecular Spreadsheet.

- Constrained minimization
- Multiple charge calculation methods
- Solvent models including the Molecular Silverware™ solvent packing algorithm
- Molecular superpositioning
- Field fitting
- Manual interactive docking
- MOPAC 6
- Interfaces to Gaussian, MOPAC, EHMO and Connolly

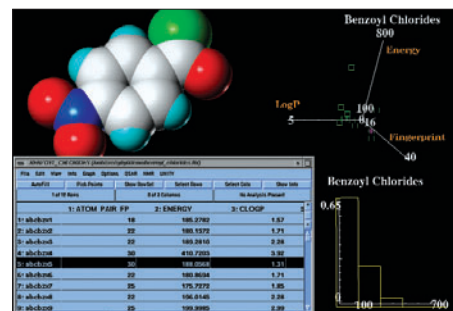
## Analysis and Organization

SYBYL contains built-in tools for analysis of molecular structure, as well as the interactive Molecular Spreadsheet. Geometric features such as distances, angles, and torsions can be measured statically or monitored interactively. Topographical data and other molecular information can be listed and exported. SYBYL calculates single point energies from a variety of force fields. The Molecular Spreadsheet (MSS) organizes the analysis of molecule sets. Rows represent molecules and columns contain related metrics such as molecular weight, topographical data, energies, and biological activity. Over 60 built-in metrics are available in SYBYL, with others provided by additional modules. The MSS supports unlimited numbers of rows and columns, as well as standard spreadsheet functionalities including sorting, filtering, and basic statistics. Scatter plots, histograms, isocontours, and mesh plots provide additional ways to investigate data.

The molecules from the MSS rows can be viewed in 3D or automatically depicted as 2D images. The MSS, data graphs, and molecular displays are dynamically connected—clicking on a cell instantly highlights related graph points and displays the associated molecule. New column types are built from equations, combinations of other columns, or entirely new routines written in the SYBYL Programming Language. Information in the MSS can be exported in several ASCII file formats, as an HTML table, or printed.

## Features

- Analyze sets of molecules
- Measure distances, angles, and torsions
- Interactive monitoring of distances and hydrogen bonds
- Basic spreadsheet functionality
- Dynamic connection among MSS, displayed molecules, and graphs
- Unlimited number of rows and columns



The Molecular Spreadsheet provides data organization, automatic metric generation, and visualization capabilities. Interactivity between graphs, the Spreadsheet, and molecular displays speed the identification of relationships within data. When a graph point is selected, the related row is highlighted and the corresponding structure is displayed.

- Over 60 built-in metrics, including MW, distances, angles, and torsions
- Scatter plots, histograms, isocontour, and mesh plots
- Automatic 2D depictions of molecules
- Print results to files, printers or an HTML table
- Easily define new column types

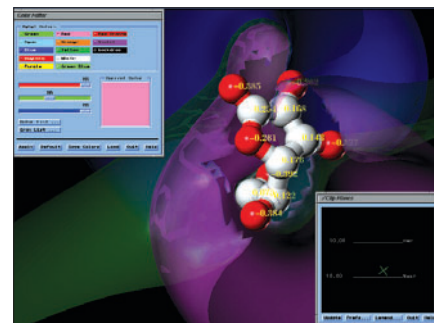
## Visualization

SYBYL offers extensive display options. Molecules can be displayed as lines, sticks, ball-and-stick, or space-filling spheres. These representations can be mixed for additional emphasis or to highlight key portions of a molecule. Colors, labels, depth cueing, shading, stereo view mode, and Z-clipping can be readily changed through the SYBYL toolbar. Volume displays, contours, grids, and dotted surfaces provide the ability to visualize molecular properties. Images on the screen can be scaled, rotated, and translated using the mouse, the virtual dialbox, or the keyboard. Views can be annotated with arrows and text, either in 2D

or with elements that rotate and translate with the molecules. These views can be captured at printer or screen resolution in a variety of formats for inclusion in electronic documents or for hard copy.

### Features

- Line, stick, ball-and-stick, or spacefilling representations, alone or in combination
- Dots, grids, contours, and opaque surfaces
- Full control of colors, labels, and screen annotation
- High quality output in a variety of formats
- Toolbar to manipulate visual options

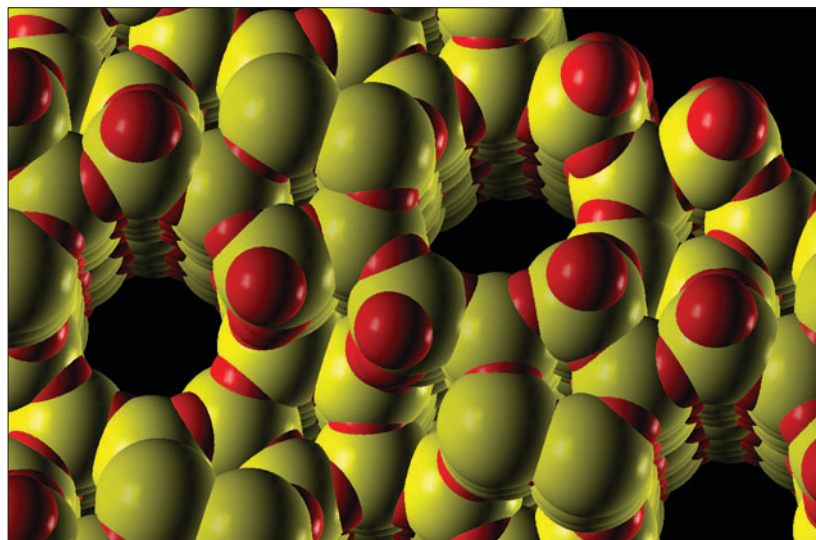


SYBYL allows complete control of graphic displays, including colors, labels, annotations, depth cueing, and z-clipping. Vitamin C is shown above in ball-and-stick mode with a recolored and z-clipped isopotential surface. Point charges are labeled. The toolbar at the far left provides access to tools such as the color editor, which makes it possible to prepare a custom color palette for objects and backdrops.

## Customization

SYBYL enables custom drug design methods via the SYBYL Programming Language (SPL). SPL connects, automates, and integrates existing functionality while providing the ability to create new user interfaces and entirely new computational techniques. Expression generators within SPL return information about atoms, bonds, substructures, molecules, tables, and graphics. SPL programs combine this information with SYBYL commands to create specific research methodologies. SPL accesses UNIX shell scripts so that external software programs can be run and their results combined with SYBYL computations.

Groups of objects such as atoms, bonds, and substructures can be defined as named sets. These sets can be saved, used by SPL routines, or selected interactively. Parameters underlying the SYBYL commands can be modified. Energy terms are scalable and the parameters that comprise force field equations are customizable. These personal preferences can be included in a startup file. Journaling saves both commands and textual information returned by SYBYL for review or playback.



A zeolite rendered as CPK spheres. The knowledge of crystallographic space groups within SYBYL/Base simplifies construction of complex molecules.

### Features

- Create completely new computational methods
- Customize the SYBYL interface
- Directly access hundreds of callable SYBYL commands and functions
- SPL control of graphics and display
- Automate repetitive tasks

## Validation

The force fields in SYBYL have been extensively tested and validated against the literature. The validation of the Tripos force field<sup>2</sup> was based upon crystal structures of small molecules and peptides. SYBYL includes implementations of the Amber united-atom and all-atom force fields,<sup>3,6</sup> as well as MMFF94<sup>7-9</sup> and MM2.<sup>10</sup>

## Complementary Software

SYBYL is the foundation for the Tripos expert molecular modeling environment. The capabilities of SYBYL can be expanded by licensing additional functionality to meet specialized research needs.

### SYBYL Base

SYBYL  
MOLCAD™  
Advanced Computation  
Dynamics  
Savol

### SYBYL Applications

#### Ligand-Based Design

##### ■ Pharmacophore Perception & Molecular Alignment

GASP™  
DISCOtech™  
Tuplets™  
GALAHAD™  
FlexS™

##### ■ SAR & ADME

QSAR with CoMFA®  
Advanced CoMFA®  
Volsurf™  
Almond™  
HQSAR™  
Distill™  
ClogP/CMR  
Molconn-Z™

#### Receptor-Based Design

##### ■ Docking

FlexX™  
FlexX-Pharm™  
FlexE™  
CombiFlexX®  
CScore™

##### ■ de novo Design

EA-Inventor™  
Leapfrog®  
RACHEL™

#### Library Design

##### ■ Library Creation

Legion™  
CombiLibMaker™  
OptDesign®

##### ■ Molecular Diversity

Selector™  
DiverseSolutions®

#### Structural Biology

##### ■ Macromolecular Modeling

Biopolymer  
Protoble™  
SiteID™  
ORCHESTRAR™  
Composer™

##### ■ Bioinformatics

Genefold®  
MatchMaker™  
FUGUE™

#### Cheminformatics

##### ■ Data Mining

UNITY®

##### ■ Structure Representation

Concord®  
Confort™  
MM4™  
StereoPlex®  
ProtoPlex™

#### Supplemental Technologies

AMPAC™  
GSSI  
hint!®  
HiVol™  
HSCF  
MM3™  
ZAP™

## Hardware and Software Requirements

SYBYL requires a license and runs on workstations operating under IRIX® (SGI®) or Linux® (x86).

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