

MacroModel 9.9

Quick Start Guide

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Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

Font	Example	Use
Sans serif	Project Table	Names of GUI features, such as panels, menus, menu items, buttons, and labels
Monospace	<code>\$SCHRODINGER/maestro</code>	File names, directory names, commands, environment variables, command input and output
Italic	<i>filename</i>	Text that the user must replace with a value
Sans serif uppercase	CTRL+H	Keyboard keys

Links to other locations in the current document or to other PDF documents are colored like this: [Document Conventions](#).

In descriptions of command syntax, the following UNIX conventions are used: braces { } enclose a choice of required items, square brackets [] enclose optional items, and the bar symbol | separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

File name, path, and environment variable syntax is generally given with the UNIX conventions. To obtain the Windows conventions, replace the forward slash / with the backslash \ in path or directory names, and replace the \$ at the beginning of an environment variable with a % at each end. For example, `$SCHRODINGER/maestro` becomes `%SCHRODINGER%\maestro`.

Keyboard references are given in the Windows convention by default, with Mac equivalents in parentheses, for example CTRL+H (⌘H). Where Mac equivalents are not given, COMMAND should be read in place of CTRL. The convention CTRL-H is not used.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

Getting Started

1.1 About MacroModel

MacroModel 9.9 is a general purpose, force-field-based molecular modeling program with applicability to a wide range of chemical systems. MacroModel provides multiple advanced methods to aid in the understanding of chemical structure, energetics, and dynamics. A large selection of force fields is included, along with the latest technical advances introduced into the OPLS force fields. Numerous minimization methods are available, enabling geometry optimizations for a broad selection of structural classes. A wide range of methods is available for conformational searching, which allows efficient sampling of the potential energy surface for low-energy structures, including entire proteins. Solvation effects can be accounted for using the efficient continuum solvation model in MacroModel. Additional advanced features include molecular dynamics simulations, free-energy perturbation simulations, and pure- and mixed-ensemble sampling methods.

1.2 About this Manual

This manual contains exercises designed to help you learn the basic tasks for preparing and initiating MacroModel calculations from Maestro. Once you have worked through these exercises, you will have an understanding of the basic MacroModel features. The exercises are divided into groups:

- [Chapter 2](#) contains exercises on a number of basic operations in Maestro.
- [Chapter 3](#) contains exercises on the calculation and minimization of the energy.
- [Chapter 4](#) contains exercises on conformational searching.
- [Chapter 5](#) contains exercises on various other MacroModel capabilities.

The exercises contain only the information required for basic understanding and to complete the task at hand. For more information about a particular MacroModel feature, see the *MacroModel User Manual*. To learn more about the command line MacroModel and MacroModel operation codes, see the *MacroModel Reference Manual*.

Maestro comes with automatic context-sensitive help (Auto-Help), Balloon Help (tool tips), an online help facility, and a set of manuals. For information on using Maestro, see the Maestro online help or the *Maestro User Manual*.

To perform the exercises, you must have access to an installed version of Maestro 9.3 and MacroModel 9.9. For installation instructions, see the *Installation Guide*.

The MacroModel installation contains the structure files used in the following exercises. The installation also contains sample input files, which you can use to run exercises without having to complete all of the preceding exercises.

1.3 Preparing for the Exercises

To run the exercises, you need a working directory in which to store the input and output, and you need to copy the input files from the installation into your working directory. This is done automatically in the Tutorials panel, as described below. To copy the input files manually, just unzip the `macromodel` zip file from the `tutorials` directory of your installation into your working directory.

On Linux, you should first set the `SCHRODINGER` environment variable to the Schrödinger software installation directory, if it is not already set:

```
cshtcsh:      setenv SCHRODINGER installation-path
sh/bash/ksh: export SCHRODINGER=installation-path
```

If Maestro is not running, start it as follows:

- **Linux:** Enter the following command:

```
$SCHRODINGER/maestro -profile Maestro &
```

- **Windows:** Double-click the Maestro icon on the desktop.

You can also use Start → All Programs → Schrodinger-2012 → Maestro.

- **Mac:** Click the Maestro icon on the dock.

If it is not on the dock, drag it there from the `SchrodingerSuite2012` folder in your Applications folder, or start Maestro from that folder.

Now that Maestro is running, you can start the setup.

1. Choose Help → Tutorials.

The Tutorials panel opens.

2. Ensure that the Show tutorials by option menu is set to Product, and the option menu below is labeled Product and set to All.
3. Select MacroModel Quick Start Guide in the table.

4. Enter the directory that you want to use for the tutorial in the Copy to text box, or click Browse and navigate to the directory.

If the directory does not exist, it will be created for you, on confirmation. The default is your current working directory.

5. Click Copy.

The tutorial files are copied to the specified directory, and a progress dialog box is displayed briefly.

If you used the default directory, the files are now in your current working directory, and you can skip the next two steps. Otherwise, you should set the working directory to the place that your tutorial files were copied to.

6. Choose Project → Change Directory.
7. Navigate to the directory you specified for the tutorial files, and click OK.

You can close the Tutorials panel now, and proceed with the exercises.

Using Maestro

The exercises in this section present a quick tour of some aspects of the Maestro interface, including the following:

- Importing a structure file
- Deleting portions of a Workspace structure
- Using the Find feature to locate particular structural elements
- Displaying, undisplaying, and labeling atoms and molecules
- Generating and displaying surfaces
- Defining atom sets for use when selecting atoms

You can find additional information about Maestro in the *Maestro User Manual*.

Most of the exercises in this chapter use the structure in `1err.pdb`, which you copied to your working directory.

2.1 Importing a Structure

To display an existing structure in the Workspace, you must import the structure into the current project. Follow the instructions below to import the `1err` protein-ligand complex into a named project. (You can work in a scratch project, but using a named project enables you to organize the results of your calculations.)

1. Click the Save As button on the Project toolbar.



2. In the File name text box, enter `1err.prj`, then click Save.
3. Click the Import button on the Project toolbar.



The Import panel opens (see [Figure 2.1](#)). It should display the common structure files in your working directory (Maestro, PDB, SD, MOL2).

You can also open the Import panel by choosing Project → Import Structures in the main window or by choosing Table → Import → Structures in the Project Table panel.

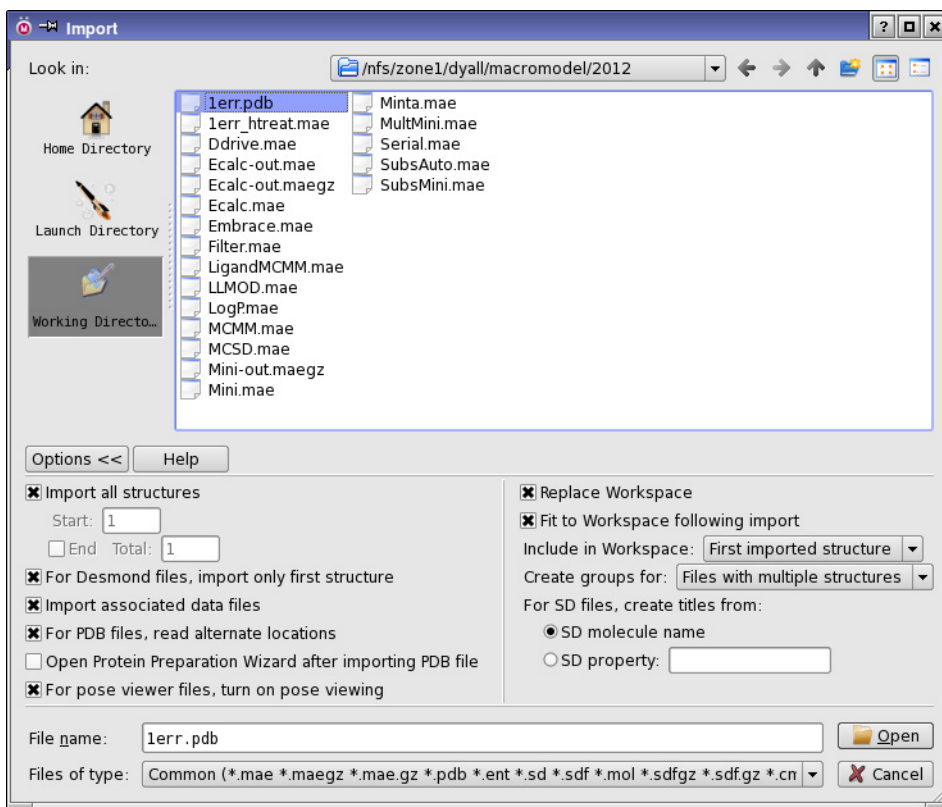


Figure 2.1. The Import panel.

4. Select `1err.pdb` from the list of files.
5. Click Open.

The Import panel closes, and a warning dialog box appears, but it isn't critical for this exercise. Click OK.

When Maestro imports a PDB file, problematic parts of imported structures, such as non-standard functional groups, are colored orange, red, green, or blue. For this exercise, it is not necessary to correct the protein structure. However, when you begin to work on other proteins, you may want to investigate and manually adjust marked portions. See [Section 3.1.6](#) of the *Maestro User Manual* for more information.

2.2 Identifying, Labeling, and Deleting Structure Elements

This exercise demonstrates how to use Maestro's display tools to inspect the protein-ligand complex and delete parts of the structure that are not needed for a calculation.

The protein-ligand complex imported in the last exercise was obtained from the Protein Data Bank repository. The structure contains crystallographic water molecules, which need to be removed. Also, the structure is dimeric, and for most purposes only the monomer is required.

To label the water molecules with the PDB name:

1. In the Workspace, right-click on an atom in one of the outlying water molecules to spot-center on the atom.
2. Zoom in on the water molecules by scrolling with the mouse wheel or by dragging with the middle and right mouse buttons, until you have a good view of the water molecules.
3. Choose Composition from the Pick to Label button menu on the Labels toolbar.



The Atom Labels panel opens (see [Figure 2.2](#)).

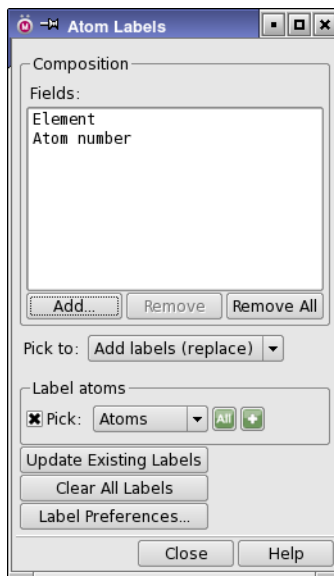


Figure 2.2. The Atom Labels panel.

4. Click Remove All to remove the current properties from the Fields list.
5. Click Add, select Residue name in the Atom Properties tab, and click OK.
6. Choose Molecules from the Pick option menu in the Label atoms section.
7. In the Workspace, select one of the outlying water molecules of the structure to display its label: HOH.
8. Close the Atom Labels panel.

To delete unwanted atoms:

1. Choose Waters from the Delete button menu on the Edit toolbar.



All the water molecules are deleted.

2. Click the Fit button on the Workspace toolbar.



The entire protein is now visible.

3. Pause the pointer over various atoms in the protein until you find one that is in chain B.

Information on an atom is displayed in the status area at the bottom of the main window when the pointer pauses over the atom, beginning with the chain name.

4. Choose Chains from the Delete button menu, and click on an atom in chain B.



The entire chain, including the ligand, is deleted, leaving chain A.



Figure 2.3. The Find Toolbar.

2.3 Using the Find Toolbar to Identify Molecules

The imported structure contains three discrete molecules. Find and visualize the three separate molecules with the Find toolbar:

1. If the Find toolbar is not displayed, choose Edit → Find, or press CTRL+F. (See [Figure 2.3](#)).
2. From the Find option menu, choose Specified atoms.
3. Enter mol.num 1 in the text box and press ENTER.
4. The view zooms to molecule number 1, and the atoms in the molecule are selected.
5. Change the number in the text box to 2 and press ENTER, to find molecule 2. Repeat for molecules 3 and 4. Molecule 4 is the ligand.
6. When you have finished finding the molecules, clear all the options in the lower left of the panel and close the Find panel.

2.4 Displaying and Undisplaying Atoms

By undisplaying atoms that do not contribute to active site functionality, you can more easily examine the active site. Atoms can be displayed and undisplayed in the Workspace using the toolbar, the Display/Undisplay Atoms panel, or by entering an `undisplayatom` command with an appropriate Atom Specification Language (ASL) expression in the command input area. Below are instructions for using the toolbar. For information on the other methods, see [Section 7.5](#) of the *Maestro User Manual*.

1. Choose Select from the Display Only button menu on the Display Atoms toolbar.



The Atom Selection dialog box opens (see [Figure 2.4](#)).

2. In the Molecule tab, choose Molecule Number from the list on the left and enter 4 in the Molecule Number text box.

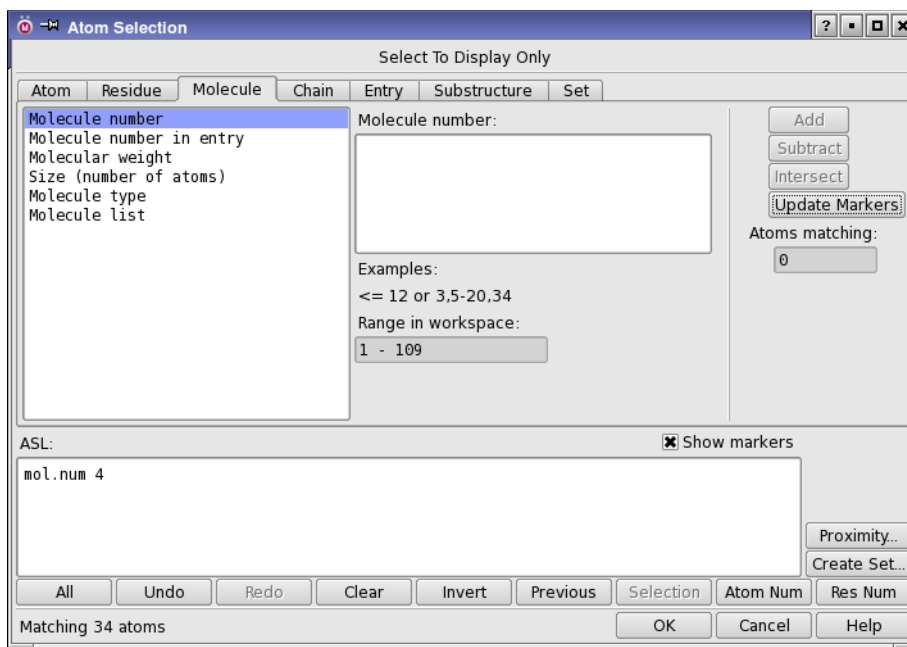


Figure 2.4. The Atom Selection dialog box, Molecule tab.

3. Click Add, then click OK.

The ligand, molecule number 4, is displayed and the remaining atoms are undisplayed.

4. Choose Protein Backbone from the Also Display button menu. Repeat for Protein Side Chains and for Waters.



You have now redisplayed the entire protein. However, the crystallographic water molecules have not been redisplayed because they were deleted, not undisplayed, in the exercise in [Section 2.2 on page 7](#).

You can also display residues that have atoms within a specified distance of the currently displayed atoms. This is useful for displaying the part of a protein that is close to a ligand.

1. Choose Molecules from the Display Sel button menu.



2. Click on an atom in the ligand to display only the ligand.

3. Choose +6 Å from the Within button menu.



For more complicated atom selections, you can use the Display/Undisplay Atoms panel (choose Workspace → Display/Undisplay Atoms).

4. Redisplay all atoms by choosing All from the Also display button menu.

2.5 Applying and Removing Atom Labels

You can apply labels to any atoms in the Workspace. You can also specify the label content, label placement, and label appearance. In the exercise in [Section 2.2 on page 7](#), you labeled atoms with their PDB residue names. This exercise demonstrates how to apply and remove various types of atom labels.

To apply atom labels:

1. Choose Composition from the Pick to Label button menu.



The Atom Labels panel opens.

2. Click Remove All to remove the current properties from the Fields list.
3. Click Add, select Atom number, Atom type (MacroModel), and Formal charge in the Atom Properties tab, and click OK.
4. In the Label atoms section, choose Molecules from the Pick menu.
5. In the Workspace, click on an atom in the ligand to label its atoms.

To remove atom labels:

1. From the Pick to option menu, choose Clear labels.

The Label atoms section is renamed Clear labels, to reflect the new action.

2. Click the Atom Selection button and choose Select.



The Atom Selection dialog box opens.

3. In the Atom tab, select Element from the list on the left, then select O from the Element list in the center.
4. Click Add, then click OK to remove the labels for all oxygen atoms.
5. In the Atom Labels panel, click Clear All Labels to remove all atom labels.
6. Close the Atom Labels panel.

2.6 Adjusting Bond Orders, Atom Types, and Formal Charges

Most PDB structures derived from X-ray crystallography data do not have hydrogen atoms, formal charges, or bond orders. When the structure is imported into Maestro, the conversion utility uses templates for assigning multiple bonds in standard residues, but cannot do so for ligands. Thus you need to explicitly add multiple bonds and formal charges to the ligands if necessary. In this exercise you will learn how to perform these structural corrections manually, however the Protein Preparation Wizard (see the *Protein Preparation Guide*) is designed to automate many of these routine tasks. The tools for these tasks are found in the Build panel or on the Build toolbar. The 1err ligand Raloxifene needs multiple bonds assigned, and the piperidine nitrogen adjusted to be a four-coordinate, positively charged ammonium group. In this exercise you will convert single bonds to double bonds and adjust the formal charges. In the next exercise, the hydrogen atoms will be added.

1. Choose Molecules from the Display Sel button menu and select an atom in the ligand.



You can choose Molecule Number from the Color Scheme button menu on the Representation toolbar, to help distinguish the ligand.

2. If the molecule is not displayed in wire representation, choose Molecule from the Wire button menu on the Representation toolbar and pick an atom in the ligand.



3. Choose Element from the Color Scheme button menu.



4. Click the Build button on the Manager toolbar, or choose Window → Toolbars → Build.

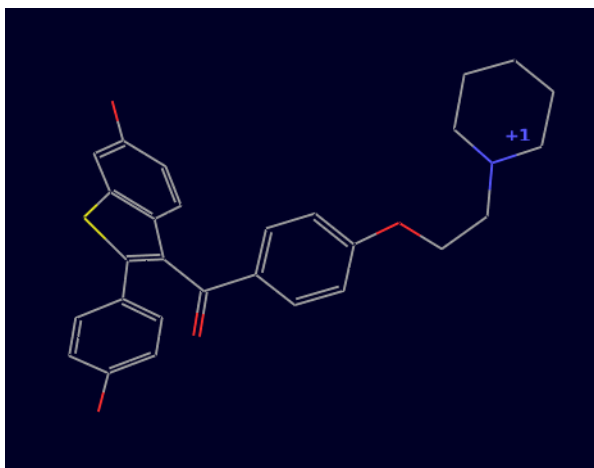


Figure 2.5. The raloxifene molecule after fixing bond orders and formal charge.

5. Click the + Bond Order button on the Build toolbar.



6. Click on the aryl C–C bonds that need to be converted to double bonds.

There are two phenyl rings and a fused ring.

7. Click on the carbonyl C–O bond.
8. Click the + Formal Chg button on the Build toolbar.



9. Click on the nitrogen atom of the piperidine in the Workspace.

The formal charge of the nitrogen atom is now +1, and the atom type is automatically adjusted. To check the formal charge, choose Formal Charge from the Label All button menu. Choose Delete Labels from the Label All button menu to remove the label.

Maestro also provides a tool for automatic assignment of bond orders. To use it, choose Tools → Assign Bond Orders. Automatic assignments should always be checked, because the rules that are used for the assignments cannot cover every possibility.

2.7 Adding Hydrogens to a United Atom Structure

Modern force fields use all-atom structures, and Maestro contains a facility to rationally add the appropriate number of hydrogens to carbon atoms with approximately the correct geometry. This exercise demonstrates how to use the tools in the Add Hydrogens - Advanced panel to add hydrogens to the structure in the Workspace.

1. Choose Edit → Add Hydrogens → Advanced.
2. Choose All-atom with No-Lp from the Treatments option menu (see [Figure 2.6](#)).
3. Under Modify hydrogen treatment, click All to add a full complement of hydrogens to the original structure.
4. Close the Add Hydrogens - Advanced panel.

You can also add hydrogen atoms with the Add H toolbar button. This button applies the current hydrogen treatment to the selected atoms.



Now save the modified structure as a new entry in the project:

1. Click the Create Entry button on the Workspace toolbar.



2. Enter `terr_htreat` in the Entry name text box and click Create to update the Project Table with the new entry.

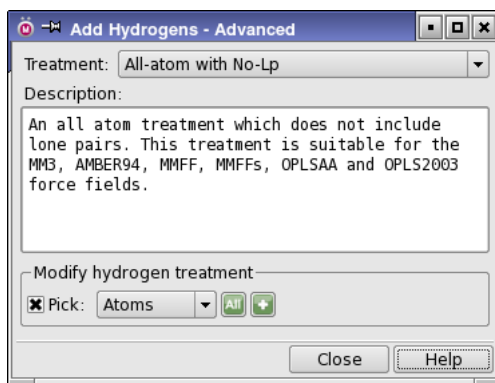


Figure 2.6. The Add Hydrogens - Advanced panel.

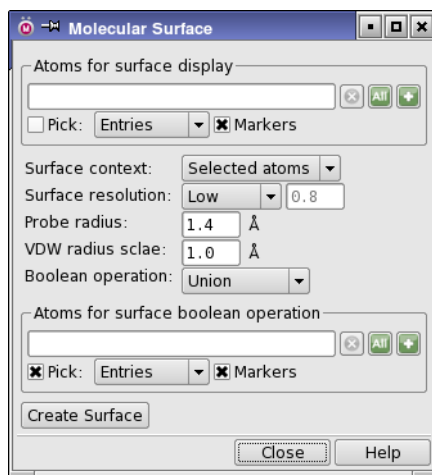


Figure 2.7. The Molecular Surface panel.

2.8 Creating and Viewing Surfaces

Examining the surface of a molecule frequently leads to valuable insights. Maestro can create several surface types. Surfaces can be rendered in different styles, color schemes, and transparency. Maestro surfaces are associated with project entries.

This set of exercises uses the `1err.prj` project from the previous section. If you are starting the tutorial at this point, follow the instructions in [Section 2.1](#), [Section 2.2](#), [Section 2.6](#), and [Section 2.7](#) to set up the project for these exercises.

2.8.1 Creating a Molecular Surface of a Complex

Maestro can create molecular surfaces that represent solvent-accessible regions of an entry. The molecular surface is a Connolly surface where a probe, typically with a radius of 1.4 Å, is rolled over the molecule. The surface is defined by the contact of the probe's outer radius and the molecule's van der Waals radius.

To generate a molecular surface for all atoms in the entry:

1. Open the Project Table panel (Table button on the Project toolbar).



2. Click the In column for the `1err` entry to include it in the Workspace.

3. Choose Workspace → Surface → Molecular Surface in the main window.

The Molecular Surface panel opens (see Figure 2.7).

4. Under Atoms for surface display, choose Entries from the Pick menu.
5. Choose Entry from the Surface Context option menu.

The *surface context* describes the atoms for which the surface is created. The *surface display* describes the atoms for which the resulting surface is displayed. You can change the atoms for which the surface is displayed after surface generation by using the Limit feature, which you will do in the next exercise.

6. In the Workspace, select any atom in the entry.
7. Click Create Surface.

When the surface generation is complete, the surface is displayed in the Workspace. If you have the preference set for it, the Manage Surfaces panel opens (see Figure 2.8).

You can experiment with the surfaces by doing any of the following:

- Generate the same surface with High image quality.
This calculation takes longer to generate, but the resulting surface has superior quality. Also, the resulting high quality surface may be slower to rotate depending on your workstation resources.
- In the Manage Surfaces panel, click Display Options and experiment with different styles and color schemes.

The Partial Charge color scheme uses white until a calculation is performed. The structure was imported from a PDB record, which has no information about the fractional atomic charges. Therefore, these must be calculated before Maestro can render the partial charge values on the surface. To use the partial charges from the OPLS_2005 force field, you can choose Assign Partial Charges from the Tools menu.

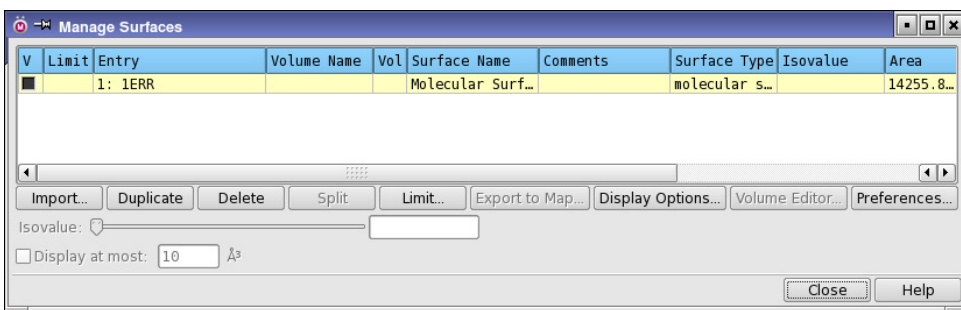


Figure 2.8. The Manage Surfaces panel.

2.8.2 Limits to a Surface

Frequently the entire surface of an entry is not required. Instead of creating another surface with a smaller subset of atoms, you can display a portion of a generated surface using the Limit panel. This exercise demonstrates how to limit the surface generated in the previous exercise from the entire entry to a smaller section of the entry.

1. In the table, click the V field of the first row to display the surface.
2. Click Limit (in the lower portion of the Manage Surfaces panel) to open the Limit panel.
3. Enter mol.num 1 in the ASL text box.
4. Click Apply to see the changes.

The surface is limited to the part that is generated for molecule number 1.

5. Click the Atom Selection button and choose Select to open the Atom Selection dialog box.



6. In the Molecule tab, choose Molecule Number from the list and enter 2 in the Molecule Number text box.
7. Click Add, then click OK.
8. In the Limit panel, click OK.

The surface is extended to include molecule number 2.

9. In the Manage Surfaces panel, deselect the Limit box for the first row to remove the surface limit and redisplay the entire surface.

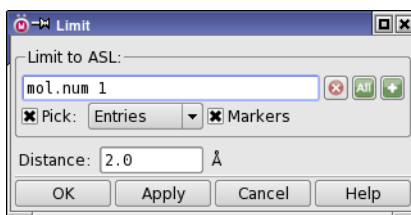


Figure 2.9. The Limit panel.

2.8.3 Generating a Surface for One Molecule in a Complex

An entry can be composed of multiple molecules, such as a co-crystallized receptor-ligand complex. Maestro is capable of generating a surface using a subset of atoms in the entry. In this example, you will use the `1err` entry to create a surface of just the atoms near the binding site, ignoring the ligand.

1. Choose Workspace → Surface → Molecular Surface in the main window.
2. Under Atoms for surface display, click the Clear button to clear the ASL text box.



3. Click the Atom Selection button and choose Select to open the Atom Selection dialog box.



4. In the Molecule tab, select Molecule Number from the list on the left and enter 4 in the Molecule Number text box.
5. Click Add.
6. Click Proximity.

The Proximity dialog box opens (see [Figure 2.10](#)).

7. Under Proximity, select Within and Angstroms, and enter 5.0 in the text box.
8. Under Fill, select Residues and select Exclude source.
9. Click OK in the Proximity dialog box and in the Atom Selection dialog box.
10. In the Molecular Surface panel, under Surface context, select Molecule.
11. Click Create Surface.

The resulting surface clearly defines the topology of the binding site.

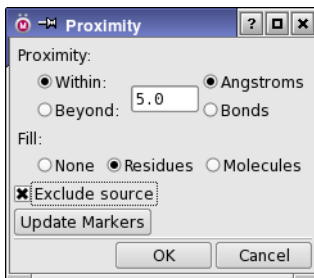


Figure 2.10. The Proximity dialog box.

12. Close the Molecular Surface panel.

In the Manage Surfaces panel, you can click Display Options and color the surface by partial charge or residue charge to visualize the electrostatics topology. You can also change the style or transparency to see the atoms under the surface. When you are finished, close the Display Options panel and the Manage Surfaces panel.

13. Choose Workspace → Surface → Undisplay All.

2.8.4 Creating a Map of the Binding Site

Maestro can be used to create “maps” of receptors. The map shows hydrophobic and hydrophilic regions, and is a tremendous asset when manually docking or adjusting ligands in a receptor. For this exercise, use the structure that was given the hydrogen treatment and map the region near the ligand. The atoms in the ligand do not need to be mapped, so they are excluded from the structure to map, but the ligand makes a logical center to place the bounding box.

1. Open the Project Table panel (Table button, Project → Show Table, or press CTRL+T).



2. Click the In box of the `1err_htreat` entry to display it in the Workspace.
3. Choose Workspace → Surface → Hydrophobic/philic.

The Hydrophobic/philic Surfaces panel opens.

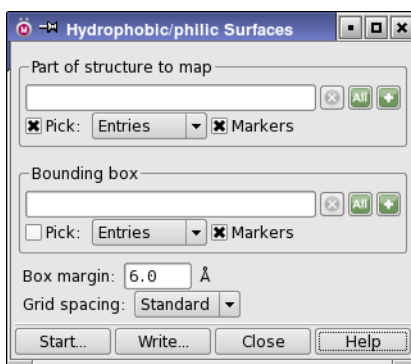


Figure 2.11. The Hydrophobic/philic Surfaces panel.

4. In the Part of structure to map section, click the Atom Selection button, then click Select.



The Atom Selection dialog box opens.

5. In the Molecule tab, choose Molecule Number from the list on the left and enter 3 in the Molecule Number text box.
6. Click Add.
7. Click Proximity to open the Proximity dialog box.
8. Under Proximity, select Within and Angstroms, and enter 5.0 in the text box.
9. Under Fill, select Residues and select Exclude source.
10. Click OK in the Proximity dialog box and in the Atom Selection dialog box.
11. In the Hydrophobic/philic Surfaces panel, under Bounding box, choose Molecules from the Pick menu and select an atom in the ligand.
12. Enter 6.0 in the Box margin text box and choose Standard from the Grid Spacing option menu.
13. Click Start to open the Start Job dialog box.

The Start dialog box opens. You can keep the default settings.

14. Click Start to start the job.
15. Enter `sitemap1SHD` in the Name text box.
16. Click Start to launch the job.

When the job finishes, the surface is displayed in the Workspace and the Manage Surfaces panel opens.

17. In the Manage Surfaces panel, experiment with the transparency and the isovalue. For example, select the `philic` surface in the table and enter `-15.0` in the Isovvalue text box at the bottom of the panel. Enter `-0.3` for the `phobic` isovalue.
18. When you have finished, close the Manage Surfaces panel and the Hydrophobic/philic Surfaces panel.

2.9 Creating and Manipulating Atom Sets

Defining subsets of atoms can be useful for many analysis and visualization tasks as well as for preparing MacroModel calculations. The Sets panel allows you to create and manipulate sets using the full range of atom selection tools. Once created, sets can be used in the Atom Selection dialog box or from relevant Pick menus. Sets are saved within a Maestro project. To use defined sets in another project, you can write them to a file using the Write button, then read them into the new project using the Read button.

These exercises use the all-atom protein-ligand complex in `1err.mae`:

1. Choose New from the Project menu and name the project `1errsets`.
2. Import the structure from `1err_htreat.mae`.

2.9.1 Defining an Atom Set by Selecting Atoms

With the contents of `1err_htreat.mae` displayed in the Workspace, make a set that includes all atoms in the ligand:

Set 1: Ligand

1. Choose Tools → Sets.

The Sets panel opens.

2. Click New (in the lower portion of the panel).

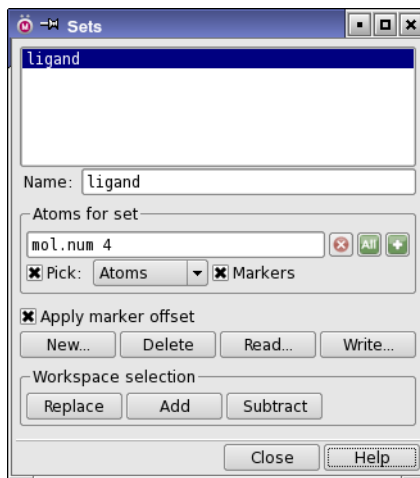


Figure 2.12. The Sets panel.

3. Enter `ligand` in the Set name text box, and click OK.

A new set is created, named `ligand`.

4. In the Sets panel, under Atoms for set, select Markers (see [Figure 2.12](#)).
5. Choose Molecules from the Pick menu.
6. In the Workspace, select an atom in the ligand to define the `ligand` set.

If you need to identify the ligand, color the atoms by molecule number, or use the Find Atoms panel described on [page 9](#). If you do use Find Atoms, deselect Mark found atoms once you have selected the desired atom.

Maestro highlights the atoms in the `ligand` set in green. Highlights are displayed as lines and dots, or as boxes, depending on the molecular representation of the atoms and bonds.

2.9.2 Defining an Atom Set with the Atom Selection Dialog Box

This exercise uses the Atom Selection dialog box to define more complex sets of atoms.

Set 2: Glycine residues

Create a set that contains all glycine residues in the structure:

1. Create a new set named `glycine`.
2. In the Sets panel, select Markers.
3. Under Atoms for set, click the Atom Selection button, then click Select.



The Atom Selection dialog box opens.

4. In the Residue tab, select Residue Type from the list on the left, then select GLY from the Residue Type list in the center.
5. Click Add, then click OK.

You can switch between sets by selecting a set from the list at the top of the Sets panel.

Set 3: All residues with atoms within 5 Å of the ligand

Create a set containing the ligand and all atoms in complete residues within 5.0 Å of the ligand:

1. Create a new set named `lig+5A`.

2. Under Atoms for set, click the Atom Selection button and choose Select.



The Atom Selection dialog box opens.

3. In the Set tab, select User-defined from the list on the left, then select `ligand` from the User-defined list in the center, and click Add.
4. Click the Proximity button.
5. Under Proximity, select Within and Angstroms, and enter 5.0 in the text box.
6. Under Fill, select Residues.
7. Click OK in the Proximity dialog box and in the Atom Selection dialog box.

The `lig+5A` set is defined.

Set 4: Alpha carbons

Create a set of all the alpha-carbon atoms in the structure (atoms with a PDB atom type C-alpha):

1. Create a new set named `alphaC`.
2. Under Atoms for set, click the Atom Selection button and choose Select.



The Atom Selection dialog box opens.

3. In the Atom tab, select PDB type from the list on the left, then select `CA` from the PDB type list in the center.
4. Click Add, then click OK to define the `alphaC` set.

2.9.3 Defining Atom Sets With Boolean Operations

New sets can be created from existing sets using Boolean operations. If you do not already have the Sets panel displayed, open it from the Tools menu.

Set 5: NOT the ligand and NOT within 5 Å

Create a new set that contains all atoms that are neither in the ligand molecule nor within 5 Å of the ligand:

1. Create a new set named `frozen`.
2. Under Atoms for set, click the Atom Selection button and choose Select.



The Atom Selection dialog box opens.

3. In the Sets tab, select User-defined from the list on the left, then select `lig+5A` from the User-defined list in the center.
4. Click Subtract.
5. Click OK to define the `frozen` set.

This set could be used to specify those atoms to be fixed or frozen in a MacroModel calculation.

Set 6: The ligand and all the glycine residues

Create a set containing the atoms in the ligand and in the glycine residues:

1. Create a new set named `lig_or_gly`.
2. Under Atoms for set, click the Atom Selection button and choose Select.



The Atom Selection dialog box opens.

3. In the Sets tab, select User-defined from the list on the left, then select `ligand` from the User-defined list in the center.
4. Click Add.
5. In the Residue tab, select Residue Type from the list on the left, then select `GLY` from the Residue Type list in the center.
6. Click Add, then OK to define the `lig_or_gly` set.

Set 7: All glycine residues in the lig+5A set

Create a set containing only atoms in the glycine residues within the `lig+5A` set:

1. Create a new set named `lig_and_gly`.
2. Under Atoms for set, click the Atom Selection button and choose Select.



The Atom Selection dialog box opens.

3. In the Sets tab, select User-defined from the list on the left, then select `glycine` from the User-defined list in the center.
4. Click Add.
5. In the Sets tab, select User-defined from the list on the left, then select `lig+5A` from the User-defined list in the center.
6. Click Intersect, then OK to define the `lig_and_gly` set.

2.10 Filtering Structures: Sorting and the Plot Facility

It is often useful to identify subsets of a group of structures based on properties such as energy or dihedral angle, which can be stored as properties in the Project Table. Energetic properties are generated from the results of calculations and incorporated automatically into the Project Table. In addition, geometric properties can be created from the Measurements panel and applied to selected entries in the Project Table by selecting Create property for selected entries when making the measurement selection.

Once the properties have been incorporated into the Project Table, there are two independent methods to filter the structures based on a range of the properties. The first method is to use the Sort facility to sort the structures in the Project Table by property value in increasing or decreasing order. The second method is to use the Plot facility and graphically select the structures based on the property values.

2.10.1 Generating Data

This exercise demonstrates how to create properties from measurements for a set of conformers. The properties are automatically added to the Project Table.

1. Import the structures in `Filter.mae`, using the directions in [Section 2.1 on page 5](#).

The structures are imported as a new entry group, and are selected.

2. Include one of the entries in the Workspace (click the In column).
3. Choose Tools → Measurements to open the Measurements panel.

4. Select Create property for selected entries (see [Figure 2.13](#)).
5. Choose Atoms or Bonds from the Pick menu and select the four atoms or the three bonds that define the torsion of interest.

When the torsion is defined, Maestro calculates the dihedral angle for each selected entry and transfers the data to the Project Table as a new property.

6. Close the Measurements panel.

2.10.2 Filtering by Sorting

This exercise demonstrates how to sort the structures based on the dihedral angle generated in the previous section.

1. In the Project Table, select the entries to be sorted.

You can use shift-click and control-click to select a range of items. Select the entries for which you created properties in the previous section (these should already be selected).

2. Right-click on the column heading of the Dihedral property that you created, and choose Sort → Selected Rows.

The entries in the Project Table are reordered based on the sort criteria.

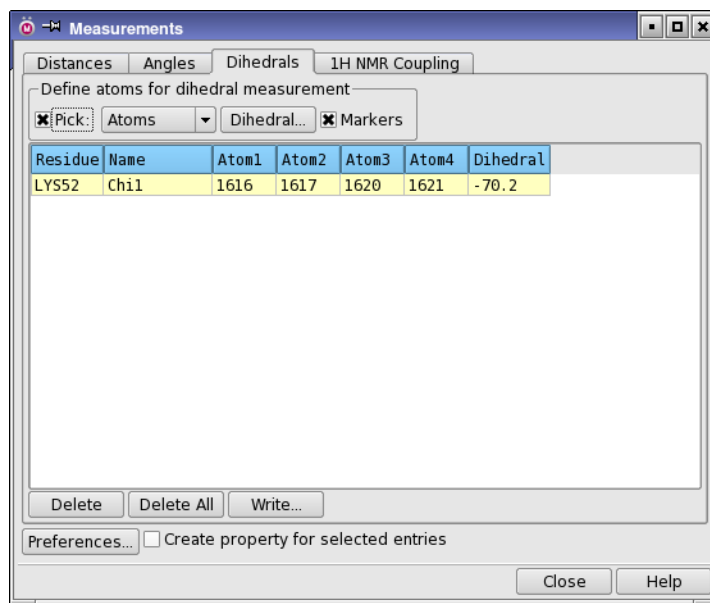


Figure 2.13. The Measurements panel showing the Dihedrals tab.

You can then select a subset of entries with the desired range of properties. These structures can be written to disk or investigated further.

2.10.3 Filtering Using the Plot Facility

This exercise demonstrates how to plot the dihedral angle generated in the previous section and select the desired entries from the plot.

1. In the Project Table, select the structures to be filtered.
2. Click the Plot button on the toolbar.



3. The Manage Plots panel opens.
4. Click New Scatter Plot.

A Scatter Plot panel opens. A new scatter plot is created, with the name Scatter-1 (see [Figure 2.14](#)). You can rename it by selecting it and clicking Rename in the Manage Plots panel.

5. Choose Entry ID from the X-axis option menu.
6. Choose the recently defined dihedral angle from the Y-axis option menu.

Once you have selected properties for the axes, the points are plotted in the default style.

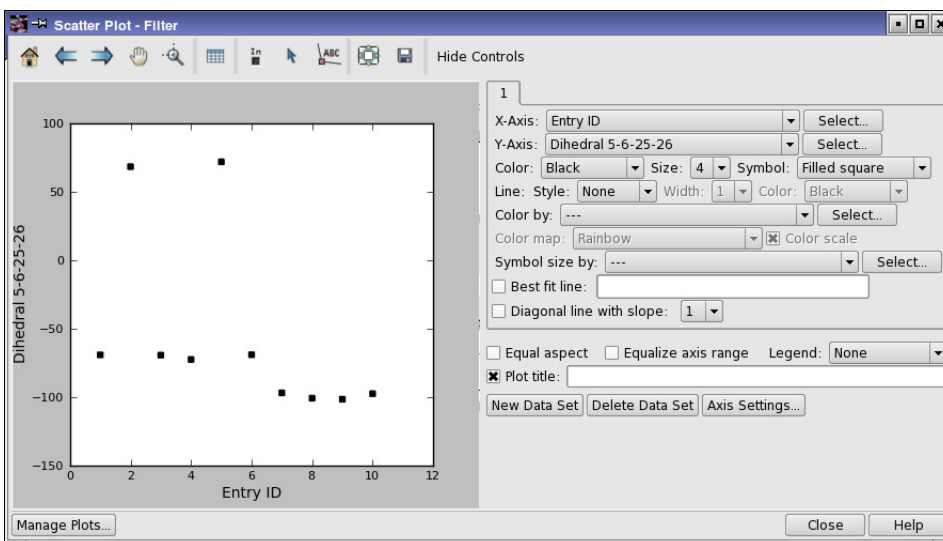


Figure 2.14. The Scatter Plot panel.

7. Choose your preferred plot and drawing styles.
8. In the Scatter Plot panel, click Rename.
9. Change the name to Filter, and click OK.
10. Click the Pick to select entries button on the Scatter Plot toolbar.



Circles are placed around the plot symbols, showing which entries are selected.

11. Click or drag to select a set of points corresponding to a range of dihedral angle values.

The corresponding entries are selected in the Project Table, and the plot symbols for are circled only for the selected entries.

Similarly, you can include entries in the Workspace with the Pick to include entries button.



Energy Calculation and Minimization

3.1 Current Energy Calculations

Many types of energetic calculations are available using MacroModel. This section introduces the MacroModel energetic panels and basic energetic parameters. These exercises calculate the current molecular mechanics energy of a structure in gas phase, then in solution phase.

Before starting the calculations, import the substituted thymine structure from `Ecalc.mae`, which you copied to your working directory in [Section 1.3 on page 2](#). If you have not copied these files, do so now. See [Section 2.1 on page 5](#) for instructions on importing structures.

3.1.1 Calculating the Gas-phase Potential Energy

1. Choose Applications → MacroModel → Current Energy.
2. Choose Workspace (included entries) from the Use structures from option menu.
3. In the Potential tab, choose MMFFs from the Force Field option menu and choose None from the Solvent option menu.
4. In the ECalc tab, choose Complete from the Energy Listing option menu.
5. Click Start.

The Start dialog box opens (see [Figure 3.1](#)).

6. Choose Replace existing entries from the Incorporate option menu.
7. Enter `Ecalc` in the Name text box.

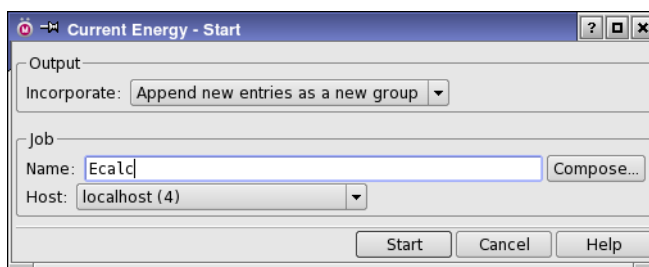


Figure 3.1. The Start dialog box.

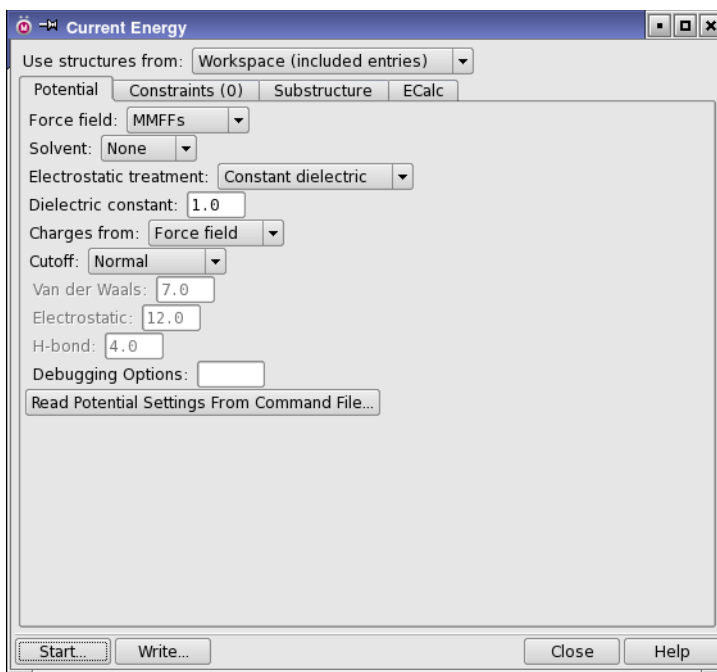


Figure 3.2. The Current Energy panel showing the Potential tab.

8. Click Start to launch the job.

The energetic settings you selected instruct the Maestro job control facility to use the contents of the Workspace as input to perform a current energy calculation and to replace the entry that is in the Workspace with the structural results of the calculation. The settings also instruct Maestro to use the MMFFs force field, not to use a solution model (since this is a gas phase calculation), and to generate a complete listing of the molecular mechanics energy terms.

The job finishes quickly, and the results are incorporated into the project. Since you selected Replace existing entries, no new entries are added to the Project Table. Job files for this calculation are placed in your working directory or the directory you chose for output files. The detailed energy listing is written to a separate file, `Ecalc-out.mmo`.

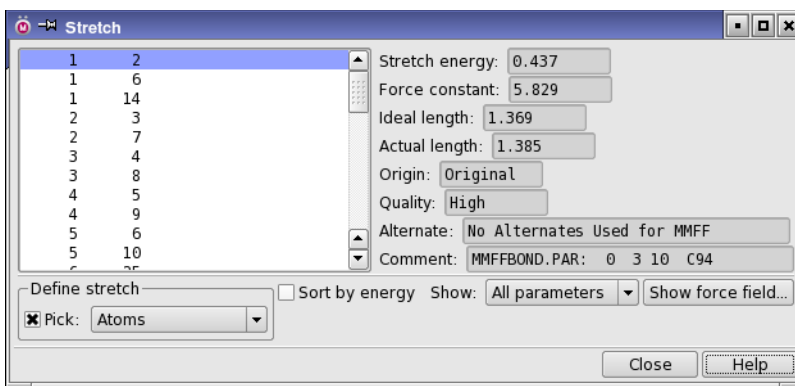


Figure 3.3. The Stretch panel.

3.1.2 Investigating Force Field Interactions

1. Choose Tools → Force Field Viewer.
2. Click Browse, select Ecalc-out.mmo from the Files list, and click Open.
3. Click Stretch to open the Stretch panel (see Figure 3.3).
4. Click on a numbered pair in the list on the left to select a stretching interaction and display it in the Workspace with a magnifying glass icon.
5. To sort the stretching interactions, select Sort by Energy in the lower center portion of the panel.

The list of stretching interactions is re-sorted so that the stretch with the lowest energy (that is, the least strained atom pair) is at the top of the list.

6. To investigate a particular stretching interaction, choose Bond from the Define Stretch pick menu and click on the desired bond in the Workspace.
7. To view stretching interactions by parameter quality, select the desired quality level from the Show option menu. View relevant force field parameters by clicking Show force field. This feature has limited utility for the BMFF force fields (MMFF and OPLS_2001).

The other panels opened from the Force Field Viewer panel are similar to the Stretch panel. You can experiment with bond angle, electrostatic, and other parameters.

8. When you have finished, close the Stretch panel and the Force Field Viewer.
9. Click the Clear Workspace button on the toolbar.

3.1.3 Calculating the Solution-phase Current Energy

1. Include the `Ecalc` entry in the Workspace.
2. Choose MacroModel → Current Energy from the Applications menu.
3. Choose Workspace (included entry) from the Use structures from option menu.
4. In the Potential tab, choose MMFFs from the Force Field option menu, and choose Water from the Solvent option menu.
5. Enter 1.0 in the Dielectric constant text box.

For all calculations using the GB/SA solvation model, the constant dielectric treatment is automatically used for the electrostatic part of the calculation. We recommend using a low molecular dielectric constant (for example, 1.0).

6. Click the `ECalc` tab and choose None from the Energy Listing option menu.
7. Click Start to open the Start dialog box.
8. Under Incorporate, select Append new entries as a new group.
9. In the Name text box, type `EcalcSolv`.
10. Click Start to launch the job.

Because you selected the Append new entries option, when the job finishes, a new entry is added to the Project Table with the total potential energy as a property. You can use the output in the Monitor panel or in the output `Ecalc.log` and `EcalcSolv.log` files to examine the details of the energies for the gas-phase and solution-phase calculations.

3.2 Energy Minimization

MacroModel energy minimizations are set up from the Minimization and Multiple Minimization panels within Maestro. Minimization calculations can be performed on single structures and multi-structure collections. In addition, for single structure calculations, the MacroModel substructure facility can be used to select fixed and frozen atoms for the minimization of a subset of atoms within a large structure.

For the next two exercises, you can either use the structure from [Section 3.1.3](#) or import `Mini.mae` from your working directory. The entry title is `Ecalc`. See [Section 2.1 on page 5](#) for instructions on importing structures.

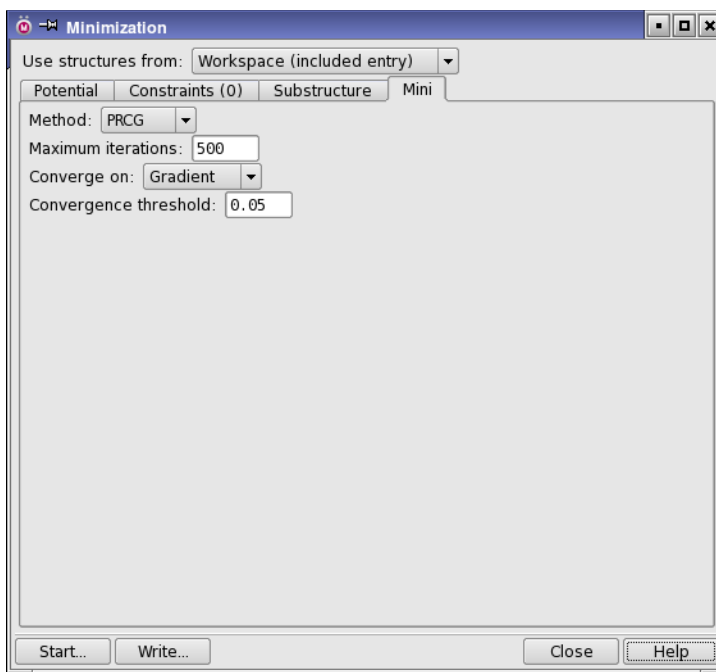


Figure 3.4. The Minimization panel showing the Mini tab.

3.2.1 Energy Minimization of a Single Structure

1. Choose Applications → MacroModel → Minimization.
2. Choose Workspace (included entry) from the Use structures from option menu.
3. Click Start to open the Start dialog box.
4. Under Incorporate, select Append new entries individually.
5. In the Name text box, type Mini.
6. Click Start to launch the job.

An intermediate structure is displayed in the Workspace with the atoms colored according to the energy gradient of the minimization at the time of monitoring. After job completion, the final minimized structure is incorporated into the project as a new entry. If you wish to change the default minimization setting, click the Mini tab.

3.2.2 Comparing Structural Results by Superposition

One useful way of comparing structural results is to superimpose them. Maestro provides tools for superimposing molecules based on a selection of atoms. For a pair of molecules, you can select the corresponding atoms manually, and Maestro superimposes them by minimizing the RMSD of the selected atom distances. You can also select atoms in one structure using the Atom Selection dialog box or ASL and use this set as the basis of superposition. The atom specification is applied to each entry included in the Workspace. This is useful for groups of conformers, but may have unintended results for non-conformers. Superposition is discussed in detail in [Section 10.3](#) of the *Maestro User Manual*. The following exercise demonstrates superposition for two conformers.

1. Click the Clear button on the Workspace toolbar.



2. Open the Project Table panel (Table button on the Project toolbar, choose Project → Show Table, or type CTRL+T).



3. Click the In column for the unminimized job input structure.
4. Control-click the In column for the minimized output structure.

The two structures are superimposed in the Workspace, but do not necessarily have the best alignment.

5. Choose Tools → Superposition.

The Superposition panel opens.

6. Click the ASL tab.

7. In the Superimpose by ASL text box, enter the expression `not atom.element H` and press RETURN. (see [Figure 3.5](#)).

The minimized structure is superimposed on the input structure, using only the non-hydrogen (heavy) atoms.

8. Close the Superposition panel.

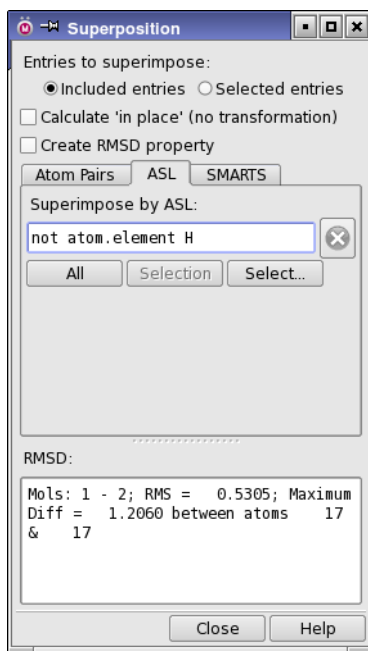


Figure 3.5. The Superposition panel.

3.2.3 Energy Minimization of Multiple Structures

A collection of structures, either conformers or non-conformers, can be minimized in one computation using the Multiple Minimization panel.

1. Click the Import button on the Project toolbar.



The Import panel opens.

2. If the options are not displayed, click Options.
3. Ensure that Import all structures is selected.
4. Select `MultMini.mae` from the list of files, and click Open.

This file contains 10 small molecular structures, which are imported as a new group named `MultMini`.

5. Open the Project Table panel.

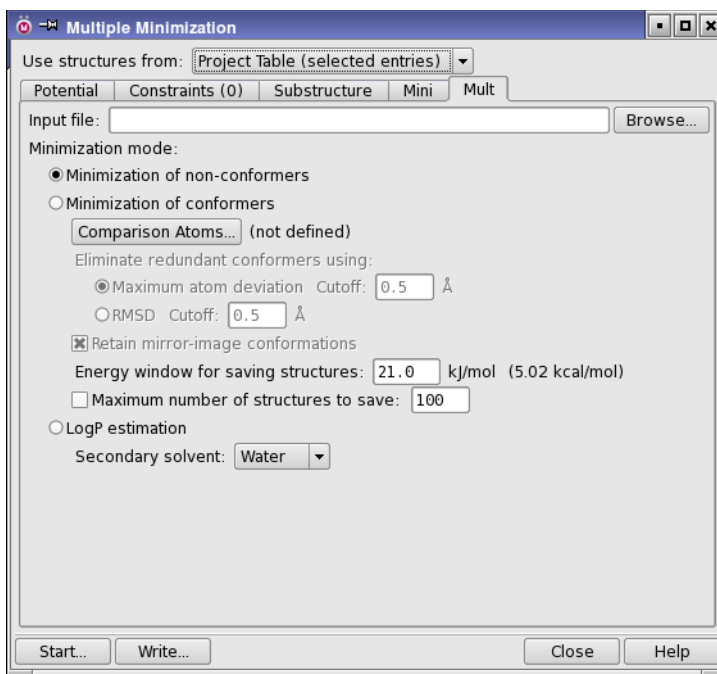


Figure 3.6. The Multiple Minimization panel showing the Mult tab.

6. Ensure that all 10 structures are selected in the Project Table.
7. Choose Applications → MacroModel → Multiple Minimization in the main window.
8. Choose Project Table (selected entries) from the Use structures from option menu (see Figure 3.6).
9. Click Start to open the Start dialog box.
10. Under Incorporate, select Replace existing entries.
11. In the Name text box, type MultMini.
12. Click Start to launch the job.

This job uses the selected entries as the input structure file and replaces the input entries in the Project Table with the resulting energy minimized structures at the conclusion of the job.

For multi-conformer computations, you can eliminate duplicate minima and reduce the output by using the tools in the Mult tab of the Multiple Minimization panel to define an energetic window and identify comparison atoms.

3.2.4 Energy Minimization of a Substructure

The time required to minimize large structures can be drastically reduced by focusing on a particularly important section of the structure and restraining, freezing, or ignoring the rest. This exercise uses the protein-ligand complex from [Section 2.1](#) to perform a substructure minimization. The ligand and all residues within 5.0 Å of the ligand are freely minimized. The atoms between 5.0 Å and 10.0 Å from the ligand are restrained, while the atoms between 10.0 Å and 15.0 Å from the ligand are frozen. The remaining atoms are ignored. For more information on the Substructure facility, see [Section 4.3.3](#) of the *MacroModel User Manual*.

1. Click the Clear Workspace button on the toolbar.



2. Import the structure in `SubsMini.mae` from your working directory.

The ligand in this complex is molecule number 4.

First, you will create an atom set for use in the definition of the substructures:

1. Choose Tools → Sets.

The Sets panel opens.

2. Click New (in the lower portion of the panel).
3. Enter `lig+5A` in the Set name text box, and click OK.

A new set is created, named `lig+5A`.

4. In the Sets panel, under Atoms for set, select Markers.
5. Choose Molecules from the Pick menu.
6. In the Workspace, select an atom in the ligand.

If you need to identify the ligand, color the atoms by molecule number, or use the Find Atoms panel described in [Section 2.3 on page 9](#). If you do use Find Atoms, deselect Mark found atoms once you have selected the desired atom.

7. In the Sets panel, under Atoms for set, click the Atom Selection button and choose Select.



The Atom Selection dialog box opens.

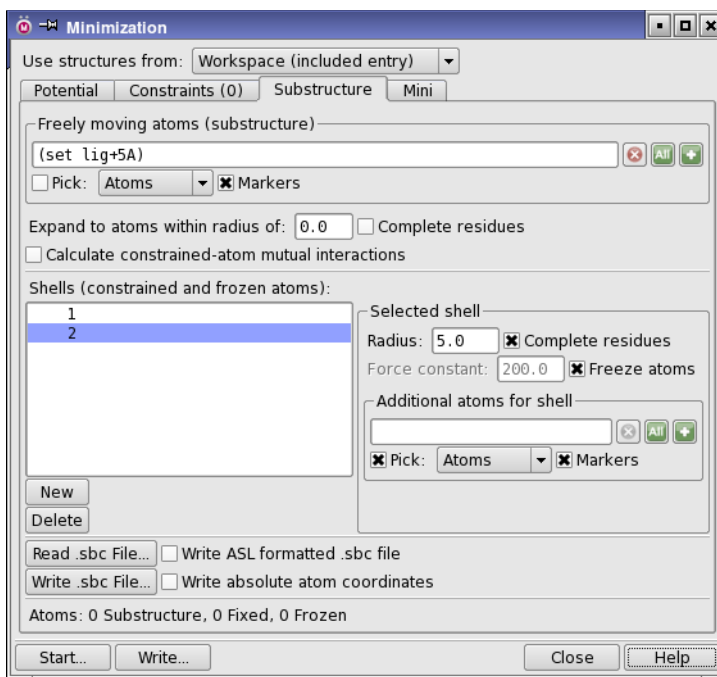


Figure 3.7. The Minimization panel showing the Substructure tab.

8. In the Molecule tab, click the Proximity button.

The Proximity dialog box opens.

9. Under Proximity, select Within and Angstroms, and enter 5.0 in the text box.

10. Under Fill, select Residues.

11. Click OK in the Proximity dialog box and in the Atom Selection dialog box.

The `lig+5A` set is now defined, and you can proceed to set up the job:

12. Choose MacroModel → Minimization from the Applications menu.

13. Choose Workspace (included entry) from the Use structures from option menu.

14. In the Potential tab, choose OPLS_2001 from the Force field option menu.

15. In the Mini tab, enter 5000 in the Maximum iterations text box.

16. In the Substructure tab (see Figure 3.7), under Freely moving atoms (substructure), click the Atom Selections button and choose Select.

The Atom Selection dialog box opens.

17. In the **Set** tab, select **User-defined** from the list on the left, then select **lig+5A** from the **User-defined** list in the center.
18. Click **Add**, then click **OK**.
19. Select **Markers** to highlight the atoms in the substructure.

This is the section of the structure that is minimized without restraints.

Next, you will define a shell of restrained atoms and another shell of frozen atoms.

20. Click **New** in the middle part of the **Substructure** tab below **Shells** (constrained and frozen atoms).
21. Under **Selected shell**, select **Complete residues**.
22. Enter **5.0** in the **Radius** text box.

The restrained atoms are highlighted in orange in the **Workspace**.

23. Click **New** again.
24. Under **Selected shell**, select **Complete residues and Freeze Atoms**.
25. Enter **5.0** in the **Radius** text box.

The frozen atoms are labeled in red in the **Workspace**.

26. Click **Start**.
The **Start** dialog box opens.
27. Choose **Append new entries individually** from the **Incorporate** option menu.
28. Enter **SubsMini** in the **Name** text box.
29. Click **Start** to launch the job.

This job may take several minutes to finish.

Conformational Searches

The goal of conformational searching is to locate the low-energy configurations of a molecular structure. MacroModel includes a number of conformational searching algorithms as well as mixed methods. This exercise first explores three standard conformational searches, then explores searches with the ligand/protein system prepared earlier. The final search is a large-scale low-mode search with another protein.

4.1 MCMM Search

The first conformational search is a Monte Carlo Multiple Minimum (MCMM), which generates trial conformations by randomly adjusting rotatable bonds.

1. Import `MCMM.mae` from your working directory.
2. Choose Applications → MacroModel → Conformational Search in the main window.
3. Choose Workspace (included entries) from the Use structures from option menu (see [Figure 4.1 on page 42](#)).
4. In the Substructure tab, clear any previously defined substructures and shells.
5. In the CSearch tab, choose Torsional sampling (MCMM) from the Method option menu.
6. Deselect Multi-ligand and Perform automatic setup during calculation.
7. Click the Perform Automatic Setup button.

The parameters of the calculation should be displayed as markers on the structure. If they are not, click the Display All Markers button in the Search Variables section. Many of the variables define conformational comparisons, which govern how the generated structures are compared and duplicates eliminated. They can be individually examined from the parameter panels, which you open by clicking the respective parameter buttons in the center of the tab. The defaults are sufficient for this exercise.

8. Enter 200 in the Maximum number of steps text box.
9. Click Start to open the Start dialog box.
10. Choose Append new entries as a new group from the Incorporate option menu.
11. Enter MCMM in the Name text box.

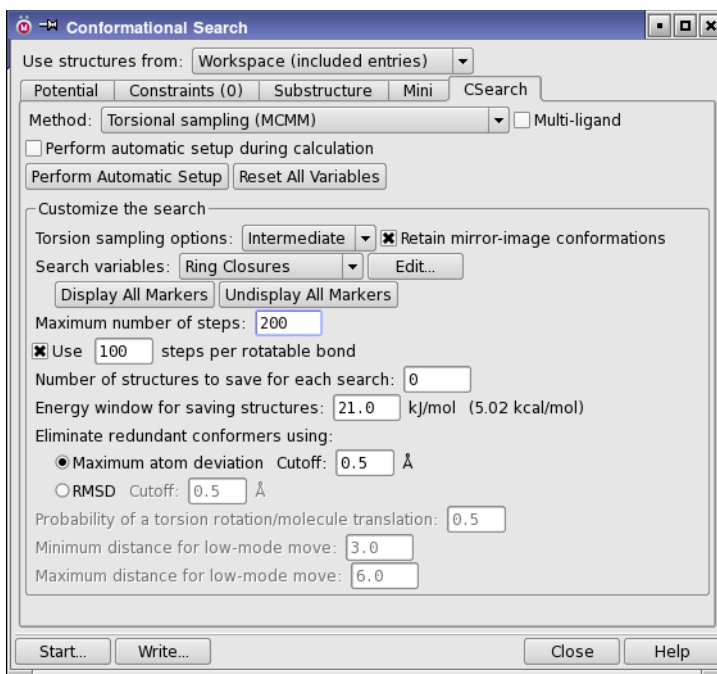


Figure 4.1. The Conformational Search panel showing the CSearch tab.

12. Click Start to launch the job.

This calculation takes a couple of minutes to finish. The Workspace is updated with the current low-energy structure during the calculation.

The output structure file, `MCMM-out.mae`, contains all structures found within the specified energetic window. The output log file, `MCMM.log`, includes a convenient listing of the molecular mechanics potential energy of all the output structures.

4.2 Serial MCMM Conformational Search

Serial MCMM conformational searches perform an MCMM conformation search on each input structure, with MCMM parameters that are set up automatically (by means of an AUTO opcode in the command file).

1. Import `Serial.mae` from your working directory.
2. In the Project Table, select the three imported entries.
3. Choose Applications → MacroModel → Conformational Search.

4. Choose Project Table (selected entries) from the Use structures from option menu.
5. In the CSearch tab, choose Torsional sampling (MCMM) from the Method option menu.
6. Select Multi-ligand.

Perform automatic setup during calculation (at the top of the panel) is automatically selected and dimmed because it is mandatory for this type of calculation.

7. Enter 100 in the Number of steps text box.
8. Click Start to open the Start dialog box.
9. Choose Append new entries as a new group from the Incorporate option menu.
10. Enter SerialMCMM in the Name text box.
11. Click Start to launch the job.

The output structures are incorporated into the Project Table when the conformational search is finished as a group named SerialMCMM.

The `serial_split` utility can be used to divide the results of a serial search into individual output files for the individual input structures. See [Section 18.7](#) of the *MacroModel User Manual* for more information.

4.3 Serial Low-Mode Search

Low-mode searching explores the low-frequency eigenvectors of the system to generate new conformations. A low-mode calculation does not require the designation of ring structures and variable torsion angles.

1. Import `Serial.mae` from your working directory.
2. In the Project Table, select the three imported entries.
3. Choose Applications → MacroModel → Conformational Search from the main window.
4. Choose Project Table (selected entries) from the Use structures from option menu.
5. In the CSearch tab, choose Low-mode sampling from the Method option menu and select Multi-ligand.
6. Enter 100 in the Number of steps text box.
7. Click Start to open the Start dialog box.
8. Choose Do not incorporate from the Incorporate option menu.
9. Enter SerialLLMOD in the Name text box.

10. Click Start to launch the job.

The output structure file, `SerialLMOD-out.mae`, contains a collection of minimized configurations for each input structure.

4.4 Ligand Conformational Search with a Frozen Receptor

In [Section 3.2.4](#), a protein-ligand complex was minimized using the OPLS_2001 force field. There are multiple approaches to performing a subsequent conformational search on the complex. Two methods are demonstrated in the following two sections.

This first exercise demonstrates how to perform a substructure conformational search on the protein/ligand complex, keeping the protein frozen. The MCMM method is used for the ligand.

To set up the job:

1. Import the minimized structure `LigandMCMM.mae` from your working directory.
2. Display the structure in the Workspace.
3. Choose Applications → MacroModel → Conformational Search.
4. Choose Workspace (included entries) from the Use structures from option menu.
5. In the Potential tab, choose OPLS_2005 from the Force field option menu and choose None from the Solvent option menu.
6. In the CSearch tab, choose Torsional sampling (MCMM) from the Method option menu.
7. Deselect Multi-ligand.
8. For a shorter computation, enter 200 in the Maximum number of steps text box.

To set conformational search parameters manually for the ligand:

Note that this setup would not be adequate for a complete search of conformational space.

1. Choose Ligands from the Display only toolbar button to display only the ligand molecule.



2. Click the Fit button on the Workspace toolbar.



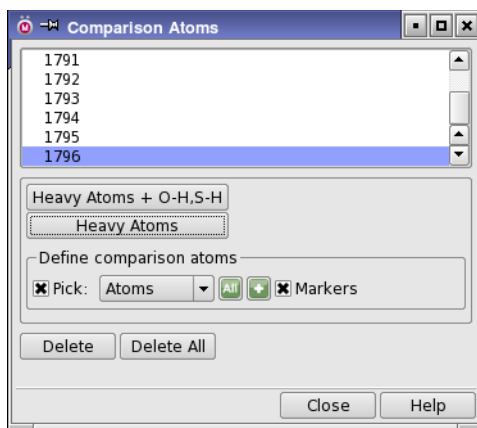


Figure 4.2. The Comparison Atoms panel.

3. In the CSearch tab of the Conformational Search panel, deselect Perform automatic setup during calculation.
4. Click Reset All Variables.
5. From the Search variables option menu, choose Comparison Atoms, then click Edit, to open the Comparison Atoms panel (see [Figure 4.2](#)).

The procedure below selects the non-hydrogen atoms of the ligand. You can also do this by clicking Heavy Atoms, which is defined as all non-hydrogen atoms.

6. Under Define comparison atoms, click the Atom selection button and choose Select, to open the Atom Selection dialog box.
7. In the Molecule tab, select Molecule Number from the list and type 4 in the Molecule Number text box (or click on the molecule in the Workspace), then click Add.
8. In the Atom tab, select Element from the list on the left, then select H from the Element list, and click Subtract to remove the hydrogen atoms from the selection set.
9. Click OK, then close the Comparison Atoms panel.
10. In the CSearch tab, from the Search variables option menu choose Torsion Rotations, then click Edit, to open the Torsion Rotations panel (see [Figure 4.3](#)).

Torsion rotations specify the torsions that are randomly rotated during the search. All non-trivial C-C and N-C bonds (except amide torsions) could be selected. It is only necessary to choose the second and third atoms of the torsion.

11. Choose Atoms from the Pick menu and select a few torsions from the structure in the Workspace, (e.g., 1770/1771, 1779/1780, 1789/1790).

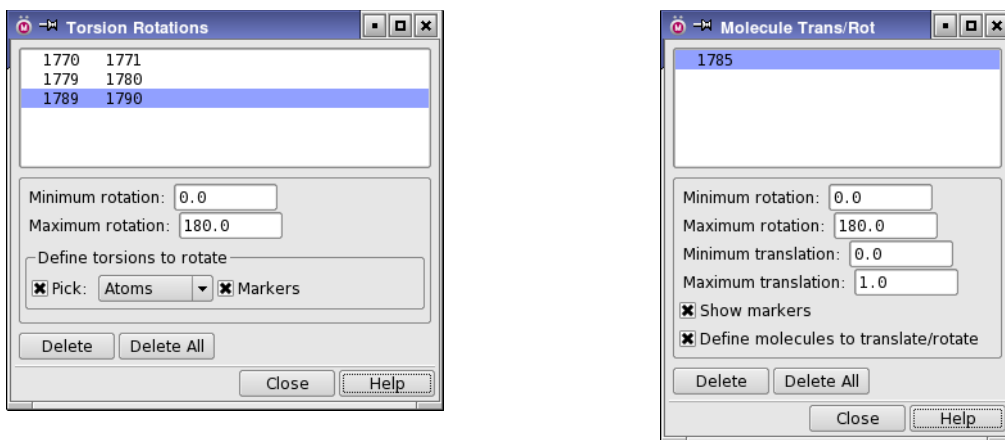


Figure 4.3. The Torsion Rotations panel (left) and the Molecule Trans/Rot panel (right).

12. Close the Torsion Rotations panel.
13. In the CSearch tab, from the Search variables option menu choose Molecule Trans/Rot, then click Edit, to open the Molecule Trans/Rot panel (see [Figure 4.3](#)).

The Molecule Trans/Rotation feature identifies molecules that are to be rotated and translated relative to each other. Only the ligand needs to be specified in this example.

14. In the Workspace, select any atom in the ligand. Use the default minimum and maximum values.
15. Close the Molecule Trans/Rot panel.

To freeze the protein and start the job:

This section uses the Substructure facility to freeze the receptor atoms that are within 6 Å of the ligand. MacroModel automatically ignores any remaining atoms in the computation.

1. Display all atoms by double-clicking the Display Sel button on the Display Atoms toolbar.



2. In the Substructure tab of the CSearch panel, clear any previously defined substructures and shells.
3. In the Freely moving atoms (substructure) section, enter the following in the ASL text box:

```
mol.n 4
```

4. Click **New** in the Shells (constrained and frozen atoms) section.
5. Select **Complete residues** and enter **6.0** in the Radius text box.
6. Select **Freeze atoms**.

Maestro colors the frozen atoms orange; the remainder are ignored in the computation.

7. Click **Start**.
8. In the **Start** dialog box, choose **Append new entries as a new group** from the **Incorporate** option menu.
9. Enter **LigandMCMM** in the Name text box.
10. Click **Start** to launch the job.

This computation will take one to three hours, depending on your computer. When the calculation is complete, the output structures are incorporated as a group named **LigandMCMM**.

11. Use the **ePlayer** to view the different low-energy orientations.

For more information on the **ePlayer**, see [Section 9.7](#) of the *Maestro User Manual*.

4.5 Substructure Conformational Search with Automatic Setup

The last exercise demonstrated a computation in which the ligand was manually assigned Monte Carlo conformational search parameters while the entire receptor was held frozen. This exercise demonstrates a modified conformational search that enables increased receptor flexibility, using **Perform Automatic Setup** to define the **MCMM** search variables.

The steps below prepare a substructure conformational search calculation in which the receptor is divided into freely moving, fixed, and frozen regions. Computations using substructures use less resources than full receptor simulations. **Automatic Setup** recognizes substructures and assigns the **MCMM** conformational search parameters only to functional groups in the substructure, and not to those in the restrained or frozen part of the structure.

To set up the job:

1. Import the structure in **SubsAuto.mae** from your working directory.
2. Display the structure in the **Workspace**.
3. Choose **Applications** → **MacroModel** → **Conformational Search** from the main window.

4. Choose Workspace (included entries) from the Use structures from option menu.
5. In the Potential tab, choose OPLS_2001 from the Force field option menu and choose None from the Solvent option menu.
6. In the Mini tab, enter 5000 in the Maximum iterations text box.

To set up the substructure and shells that define moving, fixed, and frozen atoms:

In this example, the freely-moving portion includes the ligand, as well as all residues within 3 Å of the ligand.

1. Click the Substructure tab.
2. In the Freely moving atoms (substructure) section, choose Molecules from the Pick menu and click on an atom in the ligand in the Workspace.
3. Enter 3.0 in the Expand to atoms within radius of text box and select Complete residues.

You could achieve the same result by using the Atom Selection dialog box to select molecule number 4 and the atoms within 3 Å, or by entering the following expression in the ASL text box:

```
fillres within 3 (mol.num 4)
```

4. Under the Shells list, click New.
5. In the Selected shell section, select Complete residues and enter 2.0 in the Radius text box.

This is the shell of fixed atoms, with harmonic constraints of 200 kJ/mol Å² applied.

6. Click New.
7. In the Selected shell section, select Complete residues and Freeze atoms and enter 2.0 in the Radius text box.

This is the shell of frozen atoms.

The moving, fixed, and frozen regions have now been defined and are indicated in the Workspace as white, orange, and purple regions.

To set up the search method and search variables:

In this example, you will use the automatic setup features to define the MCMM conformational search variables. You can set up variables either for the entire moving region (the substructure) or only for the ligand molecule. Atoms in the fixed or frozen atom regions do not have conformational search variables assigned to them when using Perform Automatic Setup.

8. In the CSearch tab, choose Torsional sampling (MCMM) from the Method menu.
9. Ensure that Multi-ligand is not selected.
10. Do one of the following:
 - Select Perform Automatic Setup during calculation to assign MCMM parameters for the freely-moving substructure region automatically during the calculation.
 - Deselect Perform Automatic Setup during calculation, click Reset All Variables, then click Perform Automatic Setup to assign MCMM parameters to the entire freely-moving region.
 - Enter the following command in the command input area of the main window to assign MCMM parameters to the ligand only:

```
autosetup mol.n 4
```
11. For a shorter computation, change the value in the Number of steps text box to 200.

To enter the job information and start the job:

1. Click Start.
2. In the Start dialog box, choose Append new entries as a new group from the Incorporate option menu.
3. Enter SubsAuto in the Name text box.
4. Click Start to launch the job.

The sample files included in the distribution have conformational search variables defined only for the ligand.

4.6 Large-Scale Low-Mode Conformational Search

The large-scale low-mode (LLMOD) conformational searching routine is a unique method for generating candidate conformations of very large structures, including full proteins. Combinations of low-frequency vibrational modes are used to produce candidate structures. These modes represent simultaneous, concerted conformational changes in the structure.

Specialized applications of LLMOD include protein loop optimization, homology model refinement, and fully flexible docking for induced-fit modeling. In addition, LLMOD-generated conformations can be used for subsequent rigid docking studies.

For this exercise, you will use the crambin structure 1crn, which is contained in the file LLMOD.mae in your working directory. This is a 14-amino acid sequence. Large proteins can take multiple hours to complete the LLMOD conformational search. Solvation should gener-

ally be used for LLMOD searches, but it is not used in this exercise in order to speed the computation.

The example structure has been minimized with OPLS_2001 without solvation. Any structure used in an LLMOD conformational search must be initially minimized to a low gradient with the same force field and solvation treatment that will be used in the conformational search.

1. Import the protein in `LLMOD.mae` from your working directory.
2. Choose Applications → MacroModel → Conformational Search from the main window.
3. Choose Workspace (included entries) from the Use structures from option menu.
4. In the Potential tab, choose OPLS_2001 from the Force field option menu.
5. In the Constraints tab, clear any previously set constraints by clicking Reset All in both the Constrain section and the Freeze section.
6. In the Substructure tab, clear any previously defined substructures and shells.
7. In the CSearch tab, select Large scale low-mode sampling from the Method option menu.
8. Enter 100 in the Maximum number of steps text box.
9. In the Mini tab, enter 1.00 in the Convergence threshold text box.
10. Click Start to open the Start dialog box.
11. Choose Append new entries as a new group from the Incorporate option menu.
12. Enter LLMOD in the Name text box.

After the job finishes, Maestro incorporates the structures into the Project Table. Depending on the size of the structure, the computation may take some time to complete.

Other Calculations

MacroModel has a range of other capabilities than those already encountered. This chapter provides exercises to illustrate some of these capabilities:

- Embrace—ligand binding to a receptor
- Molecular dynamics
- Energy profiles as a function of dihedral angles
- Free energy calculations using MINTA
- Partition coefficients between two solvents
- Cluster analysis of structures

5.1 Ligand Binding using Embrace

Embrace is an automated routine that uses a collection of individual ligands, each pre-positioned with respect to a given receptor. Embrace automatically performs energetic calculations on each complex formed from the receptor and the individual ligands. Embrace can work in two modes—interaction mode and energy difference mode. In the first, the receptor and the ligand are individually treated as separate sets, and only the energy components between sets are evaluated and recorded. The Embrace energy difference mode reports the minimized energy of both the individual ligand and receptor subtracted from the minimized energy of the complex. It is also possible to perform Embrace calculations using conformational searches.

Embrace calculations can be accelerated by using substructures with constraints applied to atom positions. The substructure need only include elements of the protein, not any ligands. This exercise demonstrates how to import a receptor and a group of ligands, and import a substructure and run the calculations with constraints.

1. Import `Embrace.mae` from your working directory.

If you are not sure how to import a structure, use the directions in [Section 2.1 on page 5](#).

This file contains a single protein and four pre-positioned ligands. Only the first structure, the receptor, is displayed in the Workspace.

2. In the Project Table, select all of the entries.

The structural input to an Embrace calculation must contain the receptor first, followed by the pre-positioned ligands. In Maestro, the receptor must be the first selected entry.

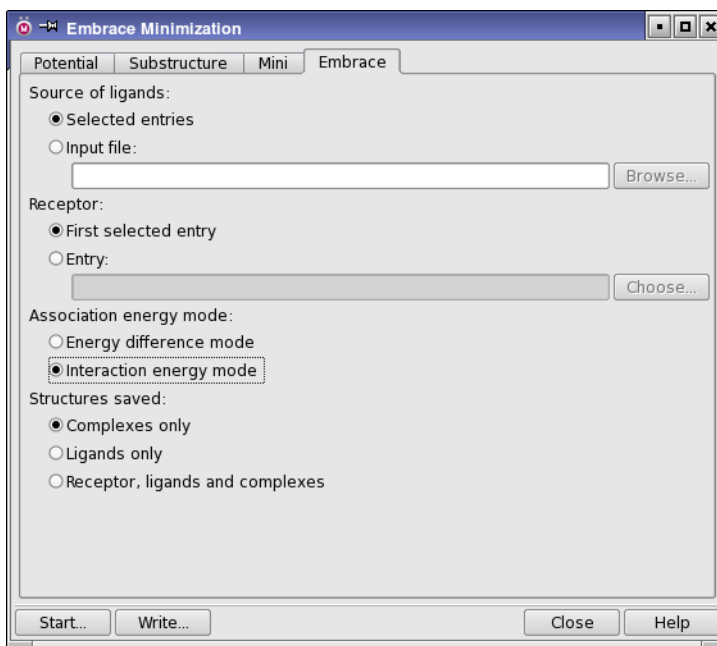


Figure 5.1. The Embrace Minimization panel showing the Embrace tab.

3. Choose Applications → MacroModel → Embrace Minimization from the main window.
4. In the Potential tab, choose OPLS_2001 from the Force field option menu and choose None from the Solvent option menu.
5. In the Mini tab, enter 1000 in the Maximum Iterations text box.
6. Click the Embrace tab (see [Figure 5.1](#)).
7. Under Source of ligands, select Selected entries.
8. Under Receptor, select First selected entry.
9. Under Association energy mode, select Interaction energy mode.
10. Under Structures saved, select Complexes only.
11. In the Substructure tab, click Read .sbc file.
12. Select Embrace.sbc from your working directory.

The atoms in the structure are highlighted: white markers for the substructure, orange markers for shell 1, and purple markers for shell 2.
13. Click Start to open the Start dialog box.

14. Choose **Append** new entries from the **Incorporate** option menu.
15. Enter `Embrace` in the **Name** text box.
16. Click **Start** to launch the job.

This calculation may take 10 minutes. When the calculation is complete, the results are placed in a table at the end of the `Embrace.log` file and are incorporated into the **Project Table**.

5.2 Molecular Dynamics

Molecular dynamics calculations simulate molecular movement over time using Newton's equations of motion. In this exercise, you will run an MC/SD dynamics calculation.

In the MC/SD simulation, an initial minimization is performed to ensure that the structure is at a minimum on the potential energy surface. Geometric structural parameters can be monitored over the course of the dynamics simulation, and structures can be sampled during the simulation at constant intervals. Since MC/SD uses Monte Carlo methods, it is also necessary to define the Monte Carlo parameters.

1. Import the structure in `MCSD.mae` from your working directory.

This structure has been minimized to a low gradient with MMFFs in the gas phase.

2. Choose **Applications** → **MacroModel** → **MC/SD** from the main window.
3. Choose **Workspace** (included entry) from the **Use structures** from option menu.
4. In the **Potential** tab, choose **MMFFs** from the **Force field** option menu and choose **None** from the **Solvent** option menu.
5. In the **Constraints** tab, clear any previously set constraints by clicking the **Reset All** button in both the **Constrain** section and the **Freeze** section.
6. In the **Substructure** tab, click the **Clear** button in both the **Atoms** for substructure section and in the **Shells** section, to clear any previously defined substructures and shells.
7. In the **Shells** section, click **Delete Shells** until all shells are deleted.
8. In the **Mini** tab, enter `5000` in the **Maximum iterations** text box and enter `0.002` in the **Convergence threshold** text box.

These parameters are required for the initial minimization.

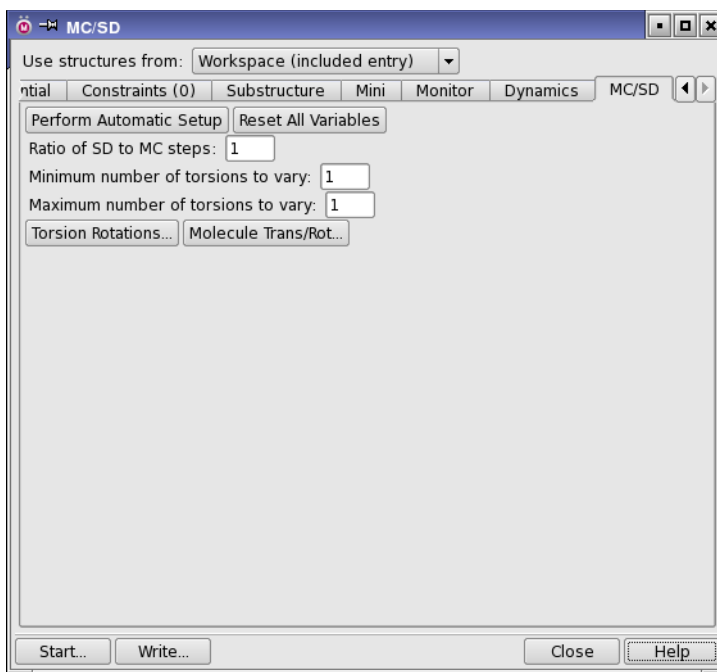


Figure 5.2. The MC/SD panel showing the MC/SD tab.

9. In the Monitor tab, enter 10 in the Number of structures to sample text box.

You can use the buttons in this tab if you want to conduct additional structural monitoring.

10. In the Dynamics tab, choose Stochastic dynamics from the Method option menu, and choose Nothing from the SHAKE option menu.

SHAKE is not recommended for MC/SD simulations.

11. In the MCSD tab, click Perform Automatic Setup (see [Figure 5.2](#)).

To view the selected torsions, click Torsion Rotations in the middle of the panel.

12. Click Start to open the Start dialog box.

13. Choose Append new entries as a new group from the Incorporate option menu.

14. Enter MCSD in the Name text box.

15. Click Start to launch the job.

The ten sampled structures are incorporated into the Project Table at the completion of the computation. After incorporation, you can view the sample trajectory using Maestro's ePlayer. The incorporated structures should already be selected in the Project Table. Click the Play forward button on the ePlayer toolbar to view the trajectory in the Workspace.



For more information on the ePlayer, see [Section 9.7](#) of the *Maestro User Manual*.

5.3 Creating Energy Profiles from Coordinate Scans

A contour diagram describing the molecular mechanics potential energy of a structure, relative to the value of either one or two coordinates (distances, angles, or dihedrals), can be generated with MacroModel. These exercises demonstrate how to produce a contour diagram describing the variation in energy of a molecule with respect to rotation of two dihedral angles.

5.3.1 Performing a Coordinate Scan Calculation

1. Import the structure in `Ddrive.mae` from your working directory.
2. Choose Applications → MacroModel → Coordinate Scan from the main window.
The Coordinate Scan panel opens.
3. Choose Workspace (included entry) from the Use structures from option menu.
4. In the Potential tab, choose MMFFs from the Force Field menu and choose None from the Solvent option menu.
5. In the Substructure tab, click the Clear button to clear any substructure.



6. Click Delete enough times to clear all shells.
7. From the Label atoms button menu on the main toolbar, choose Atom Number.
All atoms in the workspace are labeled with their corresponding atom number.
8. In the Scan tab of the Coordinate Scan panel, under Define coordinate to scan, choose Dihedral from the Coordinate type option menu.
9. Choose Atoms from the Pick menu (see [Figure 5.3](#)).

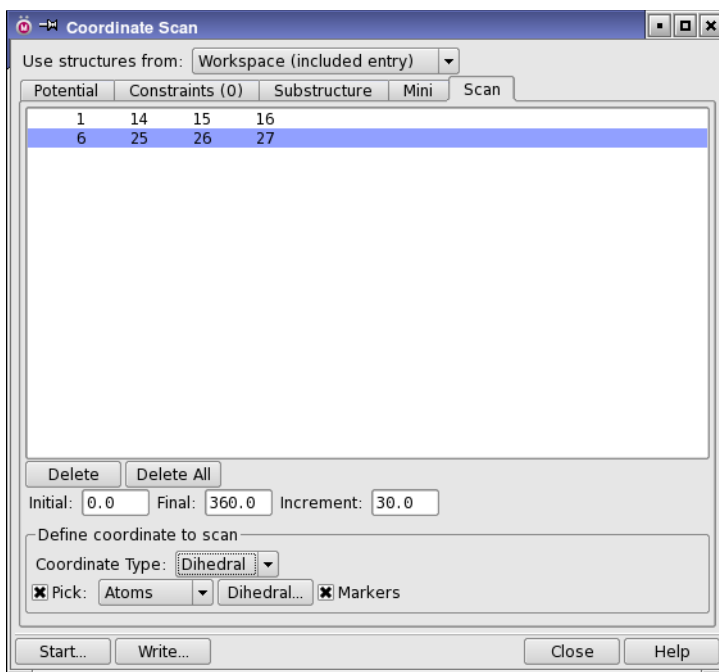


Figure 5.3. The Coordinate Scan panel showing the Scan tab.

10. In the order listed, pick the atoms in the Workspace that define the two angles: 1, 14, 15, 16, and 6, 25, 26, 27. (Use the middle mouse button to rotate the structure, if necessary.)
11. Click Start to open the Start dialog box.
12. Choose Do not incorporate from the Incorporate option menu.
13. Enter Ddrive in the Name text box.
14. Click Start to launch the job.

Two files are produced:

- Ddrive-out.grd contains the energetic results of the calculation
- Ddrive-out.mae contains the structural output.

5.3.2 Analyzing the Results of the Coordinate Scan

You can create a contour diagram of Ddrive-out.grd in the Plot of Two-Coordinate Scan panel (see Figure 5.4):

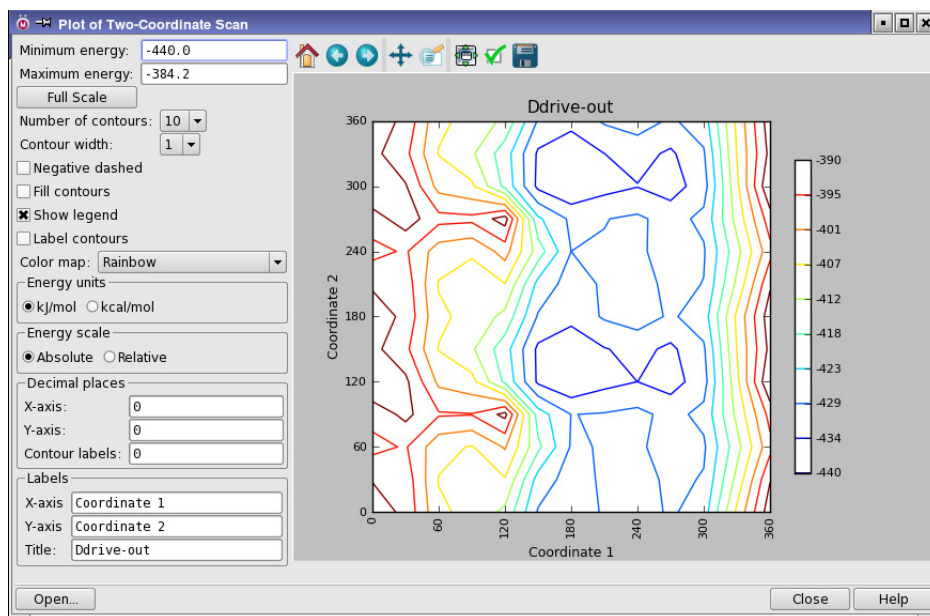


Figure 5.4. The Plot of Two-Coordinate Scan panel.

1. Choose Tools → Plot Coordinate Scan → Two Coordinates.
2. Click Open and select Ddrive-out .grd from your working directory.
3. Click Open.

The plot is displayed in the plotting area.

4. When you have finished examining the plot, close the Plot of Two-Coordinate Scan panel and choose Project → Close.

5.4 MINTA Prediction of Free Energy

MINTA is a powerful tool for estimating free energies from individual conformations or collections of conformations. Many common methods for estimating the free energy of a conformation do so based on a single point in conformation space (i.e., the exact coordinates provided). A key feature of MINTA is that an integration is performed over the normal modes for each conformation in order to accurately estimate the free energy of the local potential minimum as a whole. As with other free energy methods, performing multiple MINTA calculations and taking the appropriate differences among them can yield estimates of binding free energies. Note that while MINTA and MacroModel are tightly coupled, additional licensing is needed to run MINTA.

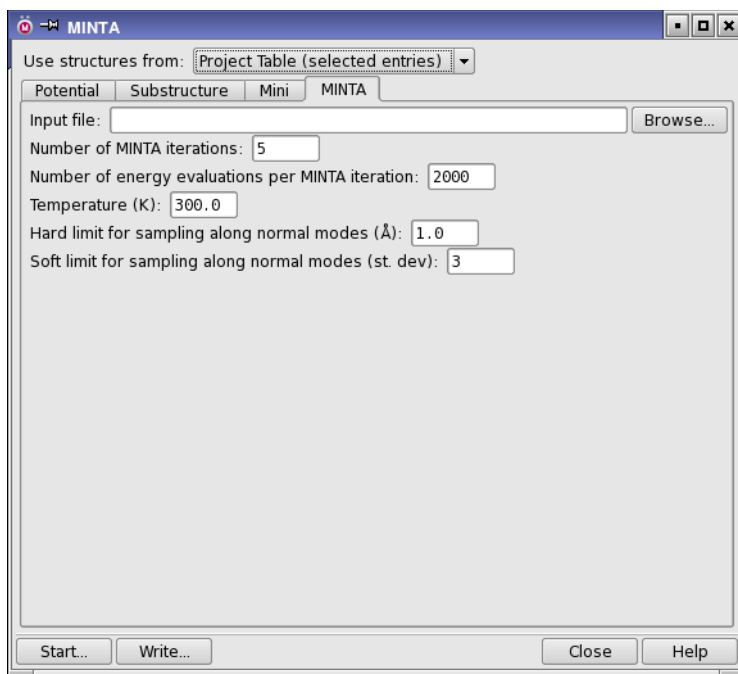


Figure 5.5. The MINTA panel showing the MINTA tab.

This exercise uses MINTA to estimate the free energy of the substituted thymine structure based on the results of the conformational search in [Section 4.1 on page 41](#).

The MCMC computation contained multiple structures in the output file. The entire set of conformers can be used as input to MINTA, or, to shorten the computation, a subset of the lowest energy structures can be used.

1. Import the structures in `Minta.mae` from your working directory.
2. Select all entries in the Project Table, or just a subset of the lowest energy structures.
3. Choose Applications → MacroModel → MINTA from the main window.
4. Choose Project Table (selected entries) from the Use structures from option menu (see [Figure 5.5 on page 58](#)).
5. In the Potential tab, choose the same force field that you used to perform the conformational search. (The `Minta.mae` file was generated using MMFFs.)
6. Click Start to open the Start dialog box.
7. Choose Append new entries as a new group from the Incorporate option menu.

8. Enter `Minta` in the Name text box.
9. Click **Start** to launch the job.

The MINTA free energy and other information is written at the end of the `.log` file and is included as a set of properties in the Project Table.

5.5 Partition Coefficient Between Two Solvents

MacroModel can estimate the logarithm of the partition coefficient of a solute between two solvents. The GB/SA parameterized solvents available are water, octanol, and chloroform. Multiple solutes can be used as input by selecting entries in the Project Table. The input structures are minimized in each solvent, and the resulting difference in solvation energies is used for the logP calculation.

The octanol-water partition coefficient, $\log P(o/w)$, is often used as a measure of molecular hydrophobicity and other environmental parameters. In this exercise, you will run a $\log P(o/w)$ calculation from Maestro.

1. Import the structure in `LogP.mae` from your working directory.
2. Choose **Applications** → **MacroModel** → **Multiple Minimization** from the main window.
3. Choose **Workspace** (included entries) from the **Use structures from** option menu.
4. In the **Potential** tab, choose **MMFFs** from the **Force field** option menu and select **Octanol** from the **Solvent** option menu.
5. In the **Mini** tab, enter `5000` in the **Maximum iterations** text box and enter `0.02` in the **Convergence threshold** text box.
6. In the **Mult** tab, select **LogP estimation** and choose **Water** from the **Secondary solvent** option menu (see [Figure 5.6](#)).
7. Click **Start** to open the **Start** dialog box.
8. Choose **Append new entries as a new group** from the **Incorporate** option menu.
9. Enter `logP` in the Name text box.
10. Click **Start** to launch the job.

The $\log P(o/w)$ value is written to the log file and is added to the output structure file as a property, which you can view in the Project Table.

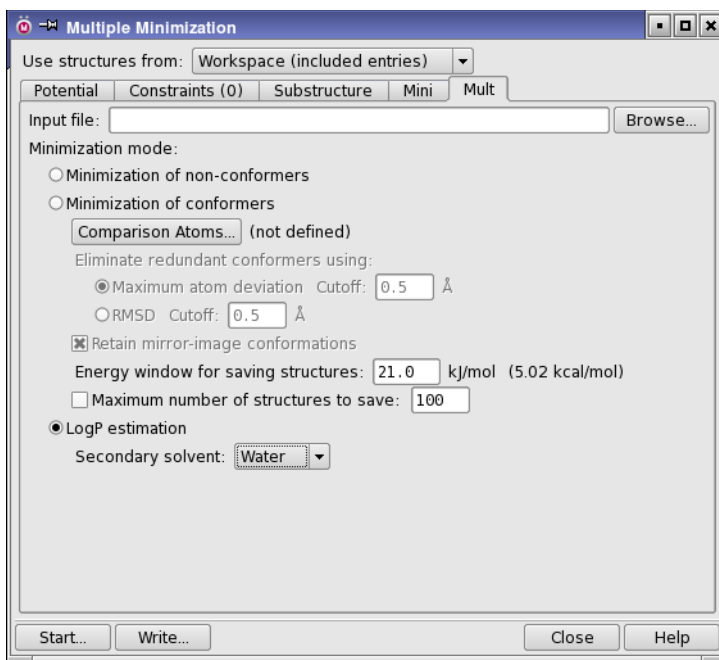


Figure 5.6. The Multiple Minimization panel showing LogP selected in the Mult tab.

Getting Help

Information about Schrödinger software is available in two main places:

- The `docs` folder (directory) of your software installation, which contains HTML and PDF documentation. Index pages are available in this folder.
- The Schrödinger web site, <http://www.schrodinger.com/>, particularly the Support Center, <http://www.schrodinger.com/supportcenter>, and the Knowledge Base, <http://www.schrodinger.com/kb>.

Finding Information in Maestro

Maestro provides access to nearly all the information available on Schrödinger software.

To get information:

- Pause the pointer over a GUI feature (button, menu item, menu, ...). In the main window, information is displayed in the Auto-Help text box, which is located at the foot of the main window, or in a tooltip. In other panels, information is displayed in a tooltip.

If the tooltip does not appear within a second, check that **Show tooltips** is selected under **General** → **Appearance** in the Preferences panel, which you can open with CTRL+, (⌘,). Not all features have tooltips.

- Click the **Help** button in a panel or press F1 for information about a panel or the tab that is displayed in a panel. The help topic is displayed in your browser.
- Choose **Help** → **Online Help** or press CTRL+H (⌘H) to open the default help topic in your browser.
- When help is displayed in your browser, use the navigation links or search the help in the side bar.
- Choose **Help** → **Manuals Index**, to open a PDF file that has links to all the PDF documents. Click a link to open the document.
- Choose **Help** → **Search Manuals** to search the manuals. The search tab in Adobe Reader opens, and you can search across all the PDF documents. You must have Adobe Reader installed to use this feature.

For information on:

- Problems and solutions: choose Help → Knowledge Base or Help → Known Issues → *product*.
- Software updates: choose Maestro → Check for Updates.
- New software features: choose Help → New Features.
- Scripts available for download: choose Scripts → Update.
- Python scripting: choose Help → Python Module Overview.
- Utility programs: choose Help → About Utilities.
- Keyboard shortcuts: choose Help → Keyboard Shortcuts.
- Installation and licensing: see the *Installation Guide*.
- Running and managing jobs: see the *Job Control Guide*.
- Using Maestro: see the *Maestro User Manual*.
- Maestro commands: see the *Maestro Command Reference Manual*.

Contacting Technical Support

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

E-mail: help@schrodinger.com

USPS: Schrödinger, 101 SW Main Street, Suite 1300, Portland, OR 97204

Phone: (503) 299-1150

Fax: (503) 299-4532

WWW: <http://www.schrodinger.com>

FTP: <ftp://ftp.schrodinger.com>

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information:

- All relevant user input and machine output
- MacroModel purchaser (company, research institution, or individual)
- Primary MacroModel user
- Installation, licensing, and machine information as described below.

Gathering Information for Technical Support

This section describes how to gather the required machine, licensing, and installation information, and any other job-related or failure-related information, to send to technical support.

For general enquiries or problems:

1. Open the Diagnostics panel.
 - **Maestro:** Help → Diagnostics
 - **Windows:** Start → All Programs → Schrodinger-2012 → Diagnostics
 - **Mac:** Applications → Schrodinger2012 → Diagnostics
 - **Command line:** `$SCHRODINGER/diagnostics`
2. When the diagnostics have run, click Technical Support.

A dialog box opens, with instructions. You can highlight and copy the name of the file.
3. Attach the file specified in the dialog box to your e-mail message.

If your job failed:

1. Open the Monitor panel in Maestro.

Use Applications → Monitor Jobs or Tasks → Monitor Jobs.
2. Select the failed job in the table, and click Postmortem.

The Postmortem panel opens.
3. If your data is not sensitive and you can send it, select Include structures and deselect Automatically obfuscate path names.
4. Click Create.

An archive file is created in your working directory, and an information dialog box with the name of the file opens. You can highlight and copy the name of the file.
5. Attach the file specified in the dialog box to your e-mail message.
6. Copy and paste any log messages from the window used to start Maestro (or the job) into the email message, or attach them as a file.
 - **Windows:** Right-click in the window and choose Select All, then press ENTER to copy the text.
 - **Mac:** Start the Console application (Applications → Utilities), filter on the application that you used to start the job (Maestro, BioLuminate, Elements), copy the text.

If Maestro failed:

1. Open the Diagnostics panel.
 - **Windows:** Start → All Programs → Schrodinger-2012 → Diagnostics
 - **Mac:** Applications → Schrodinger2012 → Diagnostics
 - **Linux/command line:** \$SCHRODINGER/diagnostics
2. When the diagnostics have run, click Technical Support.

A dialog box opens, with instructions. You can highlight and copy the name of the file.
3. Attach the file specified in the dialog box to your e-mail message.
4. Attach the file `maestro_error.txt` to your e-mail message.

This file should be in the following location:

- **Windows:** %LOCALAPPDATA%\Schrodinger\appcrash
(Choose Start → Run and paste this location into the Open text box.)
 - **Mac:** Documents/Schrodinger
 - **Linux:** Maestro's working directory specified in the dialog box (the location is given in the terminal window).
5. On Windows, also attach the file `maestro.EXE.dmp`, which is in the same location as `maestro_error.txt`.

120 West 45th Street
17th Floor
New York, NY 10036

155 Gibbs St
Suite 430
Rockville, MD 20850-0353

Quatro House
Frimley Road
Camberley GU16 7ER
United Kingdom

101 SW Main Street
Suite 1300
Portland, OR 97204

Dynamostraße 13
D-68165 Mannheim
Germany

8F Pacific Century Place
1-11-1 Marunouchi
Chiyoda-ku, Tokyo 100-6208
Japan

245 First Street
Riverview II, 18th Floor
Cambridge, MA 02142

Zeppelinstraße 73
D-81669 München
Germany

No. 102, 4th Block
3rd Main Road, 3rd Stage
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