QSite 6.7

User Manual

Schrödinger Press

May 2015

Contents

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	`$SCHRODINGER/maestro`	File names, directory names, commands, environment variables, command input and output
Italic	*filename*	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].

Introduction

1.1 About QSite

QSite is a mixed mode Quantum Mechanics/Molecular Mechanics (QM/MM) program used to study geometries and energies of structures not parameterized for use with molecular mechanics, such as those that contain metals or represent transition states. QSite is uniquely equipped to perform QM/MM calculations because it combines the superior speed and power of Jaguar with the recognized accuracy of the OPLS force field. Jaguar is used for the quantum mechanical part of the calculations, and Impact provides the molecular mechanics simulation.

The Jaguar component can be run in parallel if multiple processors are available, either from the command line or from the GUI.

QSite is run primarily from the Maestro graphical user interface. A tutorial in using QSite from Maestro appears in Chapter 2. QSite can also be run from the command line, as described in Chapter 5. Utilities and scripts are also run from the command line.

Maestro is Schrödinger's powerful, unified, multi-platform graphical user interface (GUI). It is designed to simplify modeling tasks, such as molecule building and data analysis, and also to facilitate the setup and submission of jobs to Schrödinger's computational programs. The main Maestro features include a project-based data management facility, a scripting language for automating large or repetitive tasks, a wide range of useful display options, a comprehensive molecular builder, and surfacing and entry plotting facilities. For detailed information about the Maestro interface, see the Maestro online help or the *Maestro User Manual*.

Protein Preparation for use in QSite can be performed for most protein and protein-ligand complex PDB structures using the Protein Preparation Wizard panel in Maestro.

1.2 Running Schrödinger Software

Schrödinger applications can be run from a graphical interface or from the command line. The software writes input and output files to a directory (folder) which is termed the *working directory*. If you run applications from the command line, the directory from which you run the application is the working directory for the job.

Linux:

To run any Schrödinger program on a Linux platform, or start a Schrödinger job on a remote host from a Linux platform, you must first set the `SCHRODINGER` environment variable to the installation directory for your Schrödinger software. To set this variable, enter the following command at a shell prompt:

csh/tcsh: `setenv SCHRODINGER` *installation-directory*

bash/ksh: `export SCHRODINGER=`*installation-directory*

Once you have set the `SCHRODINGER` environment variable, you can run programs and utilities with the following commands:

```
$SCHRODINGER/program &
$SCHRODINGER/utilities/utility &
```

You can start the Maestro interface with the following command:

```
$SCHRODINGER/maestro &
```

It is usually a good idea to change to the desired working directory before starting the Maestro interface. This directory then becomes the working directory.

Windows:

The primary way of running Schrödinger applications on a Windows platform is from a graphical interface. To start the Maestro interface, double-click on the Maestro icon, on a Maestro project, or on a structure file; or choose Start → All Programs → Schrodinger-2015-2 → Maestro. You do not need to make any settings before starting Maestro or running programs. The default working directory is the Schrodinger folder in your Documents folder.

If you want to run applications from the command line, you can do so in one of the shells that are provided with the installation and have the Schrödinger environment set up:

- Schrödinger Command Prompt—DOS shell.
- Schrödinger Power Shell—Windows Power Shell (if available).

You can open these shells from Start → All Programs → Schrodinger-2015-2. You do not need to include the path to a program or utility when you type the command to run it. If you want access to Unix-style utilities (such as `awk`, `grep`, and `sed`), preface the commands with `sh`, or type `sh` in either of these shells to start a Unix-style shell.

Mac:

The primary way of running Schrödinger software on a Mac is from a graphical interface. To start the Maestro interface, click its icon on the dock. If there is no Maestro icon on the dock,

you can put one there by dragging it from the SchrodingerSuite2015-2 folder in your Applications folder. This folder contains icons for all the available interfaces. The default working directory is the Schrodinger folder in your Documents folder (`$HOME/Documents/Schrodinger`).

Running software from the command line is similar to Linux—open a terminal window and run the program. You can also start Maestro from the command line in the same way as on Linux. The default working directory is then the directory from which you start Maestro. You do not need to set the `SCHRODINGER` environment variable, as this is set in your default environment on installation. To set other variables, on OS X 10.7 use the command

`defaults write ~/.MacOSX/environment` *variable* `"`*value*`"`

and on OS X 10.8, 10.9, and 10.10 use the command

`launchctl setenv` *variable* `"`*value*`"`

1.3 Starting Jobs from the Maestro Interface

To run a job from the Maestro interface, you open a panel from one of the menus (e.g. Tasks), make settings, and then submit the job to a host or a queueing system for execution. The panel settings are described in the help topics and in the user manuals. When you have finished making settings, you can use the Job toolbar to start the job.

You can start a job immediately by clicking Run. The job is run on the currently selected host with the current job settings and the job name in the Job name text box. If you want to change the job name, you can edit it in the text box before starting the job. Details of the job settings are reported in the status bar, which is below the Job toolbar.

If you want to change the job settings, such as the host on which to run the job and the number of processors to use, click the Settings button. (You can also click the arrow next to the button and choose Job Settings from the menu that is displayed.)

You can then make the settings in the Job Settings dialog box, and choose to just save the settings by clicking OK, or save the settings and start the job by clicking Run. These settings apply only to jobs that are started from the current panel.

If you want to save the input files for the job but not run it, click the Settings button and choose Write. A dialog box opens in which you can provide the job name, which is used to name the files. The files are written to the current working directory.

The Settings button also allows you to change the panel settings. You can choose Read, to read settings from an input file for the job and apply them to the panel, or you can choose Reset Panel to reset all the panel settings to their default values.

You can also set preferences for all jobs and how the interface interacts with the job at various stages. This is done in the Preferences panel, which you can open at the Jobs section by choosing Preferences from the Settings button menu.

Note: The items present on the Settings menu can vary with the application. The descriptions above cover all of the items.

The icon on the Job Status button shows the status of jobs for the application that belong to the current project. It starts spinning when the first job is successfully launched, and stops spinning when the last job finishes. It changes to an exclamation point if a job is not launched successfully.

Clicking the button shows a small job status window that lists the job name and status for all active jobs submitted for the application from the current project, and a summary message at the bottom. The rows are colored according to the status: yellow for submitted, green for launched, running, or finished, red for incorporated, died, or killed. You can double-click on a row to open the Monitor panel and monitor the job, or click the Monitor button to open the Monitor panel and close the job status window. The job status is updated while the window is open. If a job finishes while the window is open, the job remains displayed but with the new status. Click anywhere outside the window to close it.

Jobs are run under the Job Control facility, which manages the details of starting the job, transferring files, checking on status, and so on. For more information about this facility and how it operates, as well as details of the Job Settings dialog box, see the *Job Control Guide*.

1.4 Citing QSite in Publications

The use of this product should be acknowledged in publications as:

QSite, version 6.7, Schrödinger, LLC, New York, NY, 2015.

QSite Tutorial

This chapter contains a tutorial designed to help you quickly become familiar with QSite using the Maestro interface. In this chapter, you will perform a QSite geometry minimization on a protein-ligand complex. Density functional theory (DFT) will be used to treat the QM region, which will consist of the ligand only. This is a straightforward example of using QSite to model a stationary state. QSite can also be useful in modeling enzymatic systems involving transition states or metal atoms, which can be poorly treated by empirical force fields.

Requirements: To do these exercises, you must have access to an installed version of Maestro and QSite. For installation instructions, see the *Installation Guide*.

2.1 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 `qsite` 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:

csh/tcsh: `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-2015-2 → Maestro.

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

If it is not on the dock, drag it there from the SchrodingerSuites2015-2 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 QSite Tutorial 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.

2.2 Importing the Complex

Use the following steps to import the protein-ligand complex in the file `qsite-1tpb.mae`.

1. Click the Import button on the Project toolbar.

   

   The Import panel opens.

2. Choose Maestro or Common from the Files of type option menu.

3. Navigate to your working directory (if necessary) and select the file `1tpb.mae`.

4. Click Open.

   The 1TPB receptor-ligand complex is included in the Workspace.

This complex has already been prepared for use in QSite. Normally you would need to prepare the complex using the Protein Preparation Wizard panel—see Chapter 2 of the *Protein Preparation Guide* for more information.

2.3 Setting Up the Display

Given the number of atoms in the typical receptor-ligand complex, it can be hard to identify the ligand. In this exercise you will locate the ligand and set up the display to view only the ligand and the protein residues close to it.

1. From the Undisplay toolbar button menu, choose Protein.

   

   The protein is undisplayed, and only the ligand remains visible.

2. From the Within toolbar button menu, choose +4 Å.

   

   The residues around the ligand are now displayed.

3. Click the Fit to Workspace toolbar button.

   

   The view zooms in so that the structure fills most of the Workspace.

4. From the Tube toolbar button menu, choose Molecules.

   

5. Click on an atom in the ligand molecule.

   The ligand is now displayed in the tube representation, and is clearly distinguished from the protein residues.

6. From the Color all atoms by scheme toolbar button menu, choose Element.

   

2.4 Selecting the QSite Job Type

Follow the instructions below to open the QSite panel and set the job type.

1. In the main window, choose Applications → QSite or Tasks → Minimization → QM-MM.

   The QSite panel opens.

2. In the Potential tab, ensure that OPLS_2005 is selected in the Force field option menu, and deselect Use non-bonded cutoffs (this stabilizes the minimization for this small receptor).

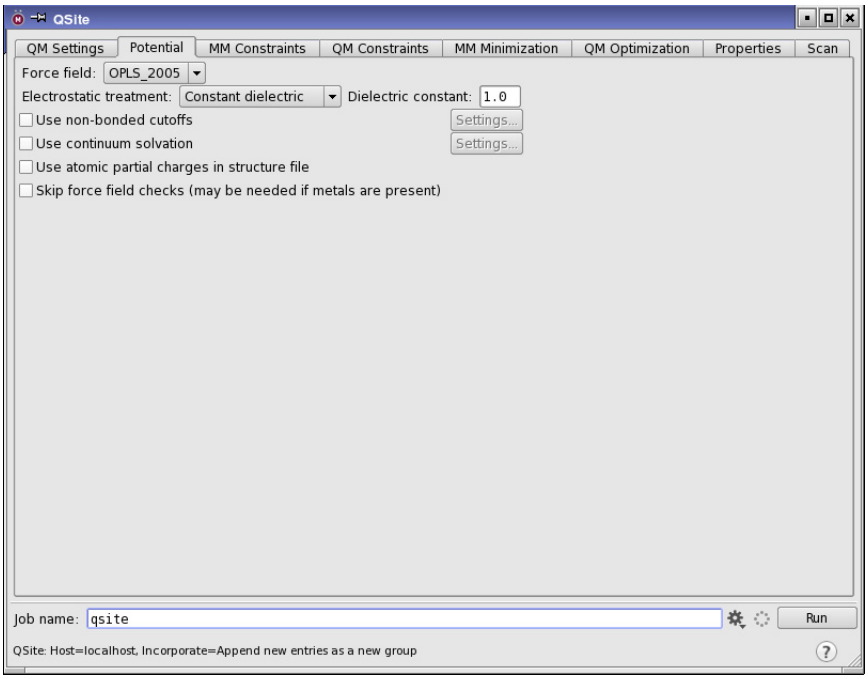

Figure 2.1. The Potential tab of the QSite panel.

3. In the QM Optimization tab, ensure that Minimization is selected in the Method option menu.

2.5 Defining a QM Region

You can select a ligand molecule, a lone ion, or a metal for the QM region by simple picking. To select entire residues from protein chains, you must make backbone cuts or use hydrogen caps. It is often useful to make side chain cuts, adding only the side chain rather than the entire residue to the QM region. This exercise demonstrates QM region definition by ligand picking.

1. In the QM Region subtab of the QM Settings tab, ensure that the Pick option is selected.

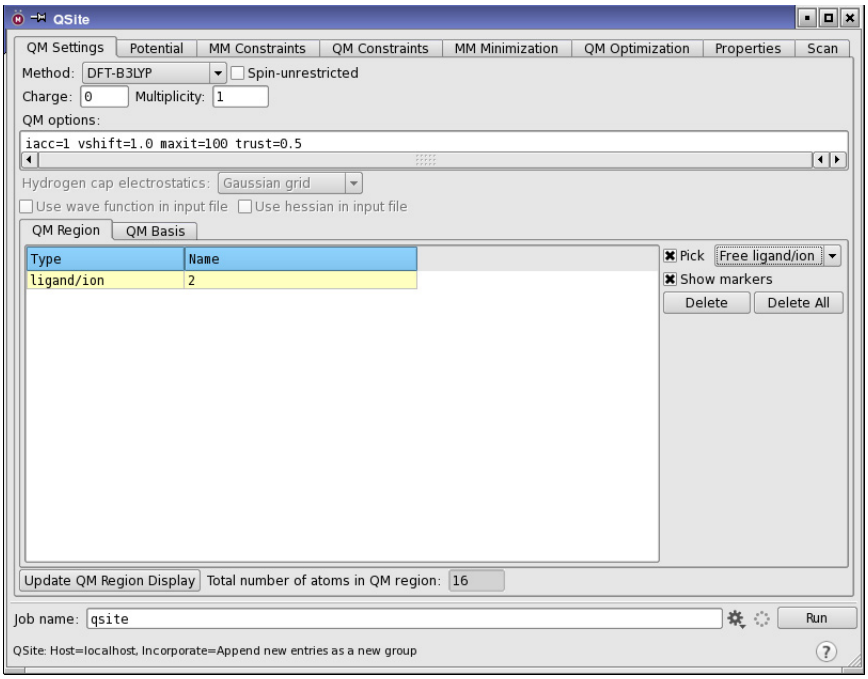

Figure 2.2. The QM Settings tab with the ligand picked.

2. Choose Free ligand/ion from the Pick option menu.
3. Pick an atom in the ligand.

   Markers in cyan are superimposed on the ligand molecule to indicate that it has been selected for the QM region. In the table, the type of cut and the name of the residue or ion are listed. In this case, the name is the molecule number. The cyan color indicates that the row for this cut is selected in the table.

QM region size is the most influential factor in QSite calculation speed. It is therefore not advantageous to work with smaller model proteins.

2.6 Running the QSite Job

1. Change the job name to `qsite_tutorial`.
2. Click Run.

   The job starts. You can view its progress in the Monitor panel.
3. Close the QSite panel.

This job runs for several hours. If you wish to examine the results without waiting for the job to finish, you may simply import the output structure file, `qsite-1tpb.01.mae`, from your working directory.

The following files appear in your current Maestro working directory (*qsite-workdir*) before the job starts:

`qsite_tutorial.in`	QSite input file
`qsite_tutorial.mae`	Maestro structure file

When the job is complete, these files are written:

`qsite_tutorial.out`	QSite output file
`qsite_tutorial.log`	Log file as displayed in the Monitor panel
`qsite_tutorial.01.in`	QSite restart file
`qsite_tutorial.01.mae`	Maestro structure file with optimized structure

2.7 Examining Results

In the next two exercises, you will examine the results of the calculation. If you decided not to run the job, you can import the results from your working directory, as follows:

1. Click the Import structures toolbar button.

   

   The Import panel is displayed.
2. Choose Maestro from the Files of type option menu.
3. Select the file `qsite-1tpb.01.mae`.
4. Click Open.

2.7.1 Comparing Input and Output Structures

1. Click the Table toolbar button

   

   The Project Table panel opens. The output structure has been appended to the project as an entry, with properties QM/MM Energy, QM Basis, QM Method, and Job Name (and others). By default, the output structure is included in the Workspace.

2. Control-click the check box in the In column for the original structure.

   The original structure is included in the Workspace as well.

3. Choose Molecule Number from the Color all atoms by scheme button menu

   

   Each of the four molecules in the Workspace (two receptors and two ligands) is now distinctly colored, and you can see what changes have occurred in the optimization. There have been substantial movements of some of the protein residues.

4. Choose Element from the Color all atoms by scheme toolbar button menu.

   

   Corresponding atoms in the two entries are now colored identically.

2.7.2 Comparing Ligand-Receptor Interactions

In this exercise you will compare the hydrogen bonding interactions between ligand and receptor in the input complex and the output complex. Some of the hydrogen bonds are around the limit at which Maestro displays them, so the settings will be changed.

1. Choose Maestro → Preferences.

   The Preferences panel opens.

2. In the tree on the left, click Criteria, under Non-bonded interactions.

3. In the H-Bonds section, if the value in the Maximum distance text box is less than 2.6, increase it to 2.6, or click the Maestro button to use the Maestro default of 2.8.

4. Include only the input entry in the Workspace.

5. Add the output entry to the Workspace (use control-click).

6. Click the HBonds button, on the Measurements toolbar.

7. Check that H-Bonds and Ligand-Receptor are selected, and select Display.

   Hydrogen bonds are now displayed between each ligand and its protein atoms. Halogen Bonds is also selected by default, but that does not affect this exercise.

8. Click the Tile toolbar button.

   You can now see the two structures side-by-side. You might want to enlarge the Maestro main window to fill your screen, so you can see the details clearly.

9. Choose Residue Information from the Label All toolbar button menu.

   The alpha carbon atoms are labeled with the PDB residue name and number. This allows you to see which residues are close to the ligand.

   In the output structure, the hydroxamate hydroxyl has rotated to form two new hydrogen bonds, to SER 211 and HIS 95 (Figure 2.3). ASP 165 has moved out, and SER 211 has moved around to form one hydrogen bond, and HIS 95 has moved in to form the second.

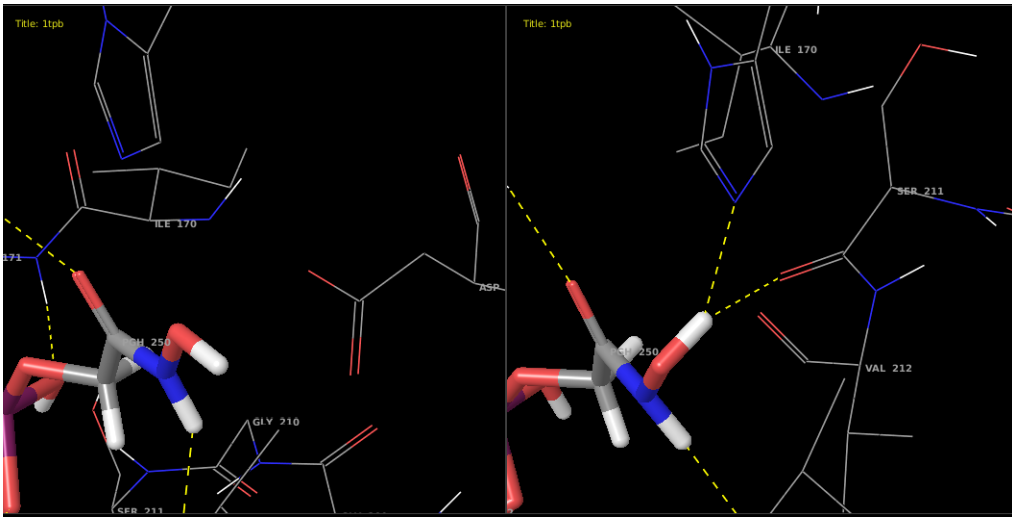

Figure 2.3. Input (left) and output (right) structures, showing H-bond to hydroxamate

You might have to rotate the structures to locate a good view of the hydrogen bonds, as shown in the figures.

10. Rotate the view so you can see the phosphate and these two glycines clearly.

    The hydrogen bonds to the phosphate from GLY 232 seems to have gone in the output structure. You can check this by measuring the distance.

11. Choose Distance from the Measure toolbar button menu.

12. Click the H on GLY 232 and the nearest O of the phosphate in the output (right) structure.

    The distance is more than 3 Å, so this hydrogen bond, if it still exists, is likely to be very weak.

Note: Small differences may occur between your results and the results supplied with the installation.

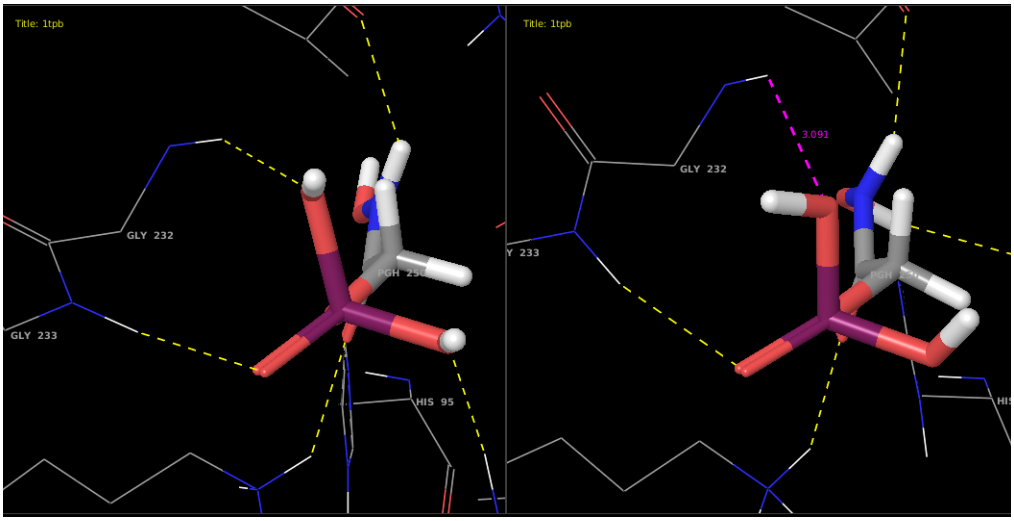

Figure 2.4. Input (left) and output (right) structures, showing H-bonds to phosphate.

Protein Preparation

The quality of QSite results depends on reasonable starting structures. Schrödinger offers a comprehensive protein preparation facility in the Protein Preparation Wizard, which is designed to ensure chemical correctness and to optimize protein and protein-ligand complex structures for use as input. For QSite, the entire system (both MM and QM regions) must be prepared so as to satisfy the requirements of Impact and the OPLS_2005 force field, while the QM region must satisfy the requirements of Jaguar. It is strongly recommended that protein structures imported from non-Maestro sources, such as PDB structures, be treated with the protein preparation facility in order to achieve best results.

For the molecular mechanics simulations using Impact with OPLS force fields, structures must be all-atom (explicit hydrogens) and there must be no covalent bonds between ligand atoms and protein atoms, including protein metal atoms. Bond orders and formal charges must be correct.

For Jaguar calculations on the QM region, structures must be three-dimensional and correct (have reasonable starting bond orders and formal charges).

3.1 Protein Preparation Procedure

A typical PDB structure file consists only of heavy atoms, can contain waters, cofactors, and metal ions, and can also be multimeric. The structure generally has no information on bonding or charges. Terminal amide groups can also be misaligned, because the X-ray structure analysis cannot usually distinguish between O and NH_2. For QSite calculations, which use an all-atom force field, atom types and bond orders must be assigned, the charge and protonation states must be corrected, side chains reoriented if necessary, and steric clashes relieved.

This section provides an overview of the protein preparation process. The entire procedure can be performed in the Protein Preparation Wizard panel, which you open from the Workflows menu on the main toolbar. This tool and its use is described in detail in Chapter 2 of the *Protein Preparation Guide*.

After processing, you will have files containing refined, hydrogenated structures of the ligand and the ligand-receptor complex. The prepared structures are suitable for use with QSite. In most cases, not all of the steps outlined need to be performed. See the descriptions of each step to determine whether it is required.

You may on occasion want to perform some of these steps manually. Detailed procedures are described in Chapter 3 of the *Protein Preparation Guide*.

1. Import a ligand/protein cocrystallized structure, typically from PDB, into Maestro.

   The preparation component of the protein preparation facility requires an identified ligand.

2. Simplify multimeric complexes.

   For computational efficiency it is desirable to keep the number of atoms in the complex structure to a minimum. If the binding interaction of interest takes place within a single subunit, you should retain only one ligand-receptor subunit to prepare for QSite. If two identical chains are both required to form the active site, neither should be deleted.

   - Determine whether the protein-ligand complex is a dimer or other multimer containing duplicate binding sites and duplicate chains that are redundant.
   - If the structure is a multimer with duplicate binding sites, remove redundant binding sites and the associated chains by picking and deleting molecules or chains.

3. Locate any waters you want to keep, then delete all others.

   These waters are identified by the oxygen atom, and usually do not have hydrogens attached. Generally, all waters (except those coordinated to metals) are deleted, but waters that bridge between the ligand and the protein are sometimes retained. If waters are kept, hydrogens will be added to them by the preparation component of the protein preparation job. Afterwards, check that these water molecules are correctly oriented.

4. Adjust the protein, metal ions, and cofactors.

   Problems in the PDB protein structure may need to be repaired before it can be used. Incomplete residues are the most common errors, but may be relatively harmless if they are distant from the active site. Structures that are missing residues near the active site should be repaired.

   For the MM calculations, metal ions in the protein complex cannot have covalent bonds to protein atoms. The MacroModel atom types for metal ions are sometimes incorrectly translated into dummy atom types (Du, Z0, or 00) when metal-protein bonds are specified in the input structure. Furthermore, isolated metal ions may erroneously be assigned general atom types (GA, GB, GC, etc.).

   Cofactors are included as part of the protein, but because they are not standard residues it is sometimes necessary to use Maestro's structure-editing capabilities to ensure that multiple bonds and formal charges are assigned correctly.

   - Fix any serious errors in the protein.

- Check the protein structure for metal ions and cofactors.
- If there are bonds to metal ions, delete the bonds, then adjust the formal charges of the atoms that were attached to the metal as well as the metal itself.
- Set charges and correct atom types for any metal atoms, as needed.
- Set bond orders and formal charges for any cofactors, as needed.

5. Adjust the ligand bond orders and formal charges.

   If the complex structure contains bonds from the ligand or a cofactor to a protein metal, they must be deleted. Impact models such interactions as van der Waals plus electrostatic interactions. Impact cannot handle normal covalent bonds to the ligand, such as might be found in an acyl enzyme.

   If you are working with a dimeric or large protein and two ligands exist in two active sites, the bond orders have to be corrected in both ligand structures.

6. Run a restrained minimization of the protein structure.

   This is done with `impref`, and should reorient side-chain hydroxyl groups and alleviate potential steric clashes.

7. Review the prepared structures.

   - If problems arise during the restrained minimization, review the log file, correct the problems, and rerun.
   - Examine the refined ligand/protein/water structure for correct formal charges, bond orders, and protonation states and make final adjustments as needed.

3.2 Checking the Protein Structures

After you have completed the protein preparation, you should check the completed ligand and protein structures.

3.2.1 Checking the Orientation of Water Molecules

You only need to perform this step if you kept some structural waters. Reorienting the hydrogens is not strictly necessary, as their orientation should have been changed during refinement, but it is useful to check that the orientation is correct.

If the orientation is incorrect, reorient the molecules by using the procedure outlined in Section 3.9 of the *Protein Preparation Guide*.

When you have corrected the orientation of the retained water molecules, you should run a refinement on the adjusted protein-ligand complex.

3.2.2 Checking for Steric Clashes

You should make sure that the prepared site accommodates the co-crystallized ligand in the restraint-optimized geometry obtained from the structure preparation.

Steric clashes can be detected by displaying the ligand and protein in Maestro and using the Contacts button on the Measurements toolbar to visualize bad or ugly contacts. Maestro defines bad contacts purely on the basis of the ratio of the interatomic distance to the sum of the van der Waals radii it assigns. As a result, normal hydrogen bonds are classified as bad or ugly contacts. By default, Maestro filters out contacts that are identified as hydrogen bonds, and displays only the genuine bad or ugly contacts.

If steric clashes are found, repeat the restrained optimization portion of the protein preparation procedure, but allow a greater rms deviation from the starting heavy-atom coordinates than the default of 0.3 Å. Alternatively, you can apply an additional series of restrained optimizations to the prepared ligand-protein complex to allow the site to relax from its current geometry.

3.2.3 Resolving H-Bonding Conflicts

You should look for inconsistencies in hydrogen bonding to see whether a misprotonation of the ligand or the protein might have left two acceptor atoms close to one another without an intervening hydrogen bond. One or more residues may need to be modified to resolve such an acceptor-acceptor or donor-donor clash.

Some of these clashes are recognized by the preparation process but cannot be resolved by it. The preparation process may have no control over other clashes. An example of the latter typically occurs in an aspartyl protease such as HIV, where both active-site aspartates are close to one or more atoms of a properly docked ligand. Because these contact distances fall within any reasonable cavity radius, the carboxylates are not subject to being neutralized and will both be represented as negatively charged by the preparation process. However, when the ligand interacts with the aspartates via a hydroxyl group or similar neutral functionality, one of the aspartates is typically modeled as neutral.

If residues need to be modified, follow these steps:

1. Place the refined protein-ligand complex in the Workspace.
2. Examine the interaction between the ligand and the protein (and/or the cofactor).
3. Use your judgment and chemical intuition to determine which protonation state and tautomeric form the residues in question should have.
4. Use the structure-editing capabilities in Maestro to resolve the conflict (see Section 3.8 of the *Protein Preparation Guide* for procedures).

5. Re-minimize the structure.

It is usually sufficient to add the proton and perform about 50 steps of steepest-descent minimization to correct the nearby bond lengths and angles. Because this optimizer does not make large-scale changes, the partial minimization can be done even on the isolated ligand or protein without danger of altering the conformation significantly. However, if comparison to the original complex shows that the electrostatic mismatch due to the misprotonation has appreciably changed the positions of the ligand or protein atoms during the protein-preparation procedure, it is best to reprotonate the original structure and redo the restrained minimization.

Running QSite From Maestro

QSite performs mixed quantum mechanical/molecular mechanical (QM/MM) calculations, using Jaguar for the QM calculations and Impact for the MM calculations. Ligands and other specified regions of a protein complex can be studied using QM, while MM is used for the rest of the molecule.

At each step of a QM geometry optimization, Impact calculates energy terms for MM-QM region interactions; if MM minimization was also specified, it is also performed at each QM step. The next QM step takes into account the new MM atom distribution and energy terms. If a single-point QM calculation is selected, the current QM/MM energy is calculated without MM minimization.

The speed of QSite is largely determined by the size of the QM region. Therefore there is no advantage to making a smaller model protein. You can run calculations on systems with up to 90000 atoms or 90000 bonds (the limit set by Impact).

Cartesian constraints may be placed on atoms in both the QM and the MM regions. See Section 4.4 on page 33 for a description of the two types of constraints. Frozen-atom constraints can be applied to atoms in both regions. Constrained atoms can be specified for MM-region atoms, but are ignored if applied to QM-region atoms.

In general, a QSite calculation can only be performed using a single entry. If you want to run a QSite job using the Workspace structure as input, and that structure includes multiple entries, combine them into a single entry using the Merge option from the Entry menu in the Project Table panel. The merged entry should be the only entry included in the Workspace when you start the job. One exception to this is when setting up a transition-state search. In this case you may select up to three Project Table entries, depending upon the algorithm that is selected for performing the search. See Section 4.7 for more information about transition-state searching.

4.1 The QSite Panel

QSite calculations can be set up and run using the QSite panel. To open the QSite panel, choose QSite from the Applications menu. The panel has eight tabs:

- QM Settings—specify the QM region and other QM options.
- Potential—choose settings for the MM potential energy function.
- MM Constraints—set up atom constraints for atoms in the MM region.
- QM Constraints—set up constraints for atoms in the QM region.

- MM Minimization—set up energy minimization of the MM region.
- QM Optimization—select and set up the job task.
- Properties—specify the properties to be generated at the end of the job.
- Scan—set up a job to scan one or more coordinates.

These tabs are described in later sections of this chapter. Below the tabs there is a standard Job toolbar, which is described in detail in Section 1.3 on page 3. The items on the Settings button menu that are specific to QSite are described below.

- Read—reads a QSite input file and imports the associated structure. It opens a file selector in which you can navigate to the desired input file.
- Write—writes out all the files required for the job but does not run the job. Once the files required for the job are written by Maestro, the job can be run from the command line in a terminal window using the syntax:

  `$SCHRODINGER/qsite` *job-options jobname*

  where *jobname*`.in` is the input file for the job in question, and job-options is a list of options for the job. The log output is written to *jobname*`.log`.

  Type `$SCHRODINGER/qsite` for a usage summary of the `qsite` command, or see Chapter 5 for information on running QSite from the command line.

Input for QSite single point jobs, minimization jobs, scans, and standard transition state searches is taken from the Workspace. LST and QST transition state searches are a special case: here, the input is specified in the QM Optimization tab.

4.2 The QM Settings Tab

The QM Settings tab is used to enter information for the QM job and to define the QM region.

QM job information includes the quantum-mechanical method to be used, the charge and spin multiplicity of the QM system, and other keywords and options that may be required by Jaguar.

The QM region can be defined by one of the following methods:

- Selecting the ligand, metal ions, or other disconnected species (not covalently bonded to the protein).
- Specifying *cuts* between certain covalently-bonded atoms in connected peptide residues. QSite cuts are specially parameterized frozen-orbital boundaries between the QM and MM regions. They can be placed between an alpha carbon and a side chain (side-chain cuts) or between an alpha carbon and the backbone to one side (backbone cuts, which must be made in pairs to add the residues between them to the QM region).

Cuts in a protein-ligand complex must be between atoms in peptide residues. Covalently-bound ligands can be included in the QM region, but only along with attached protein atoms. The QM region must extend at least as far as the first permissible cut between protein atoms.

- Specifying cuts between atoms for which the QM region is capped with hydrogen atoms.

  Hydrogen caps can be placed on any atom designated to be in the QM region, provided that it is singly-bonded to an atom in the MM region, and that any two such MM atoms are separated in the MM region by at least three bonds. This option offers much more flexibility in the selection of the QM region. The MM atom is replaced with a hydrogen atom in the QM calculation, which leaves a chemically well-defined structure with no dangling bonds.

The QM Settings tab features are described below.

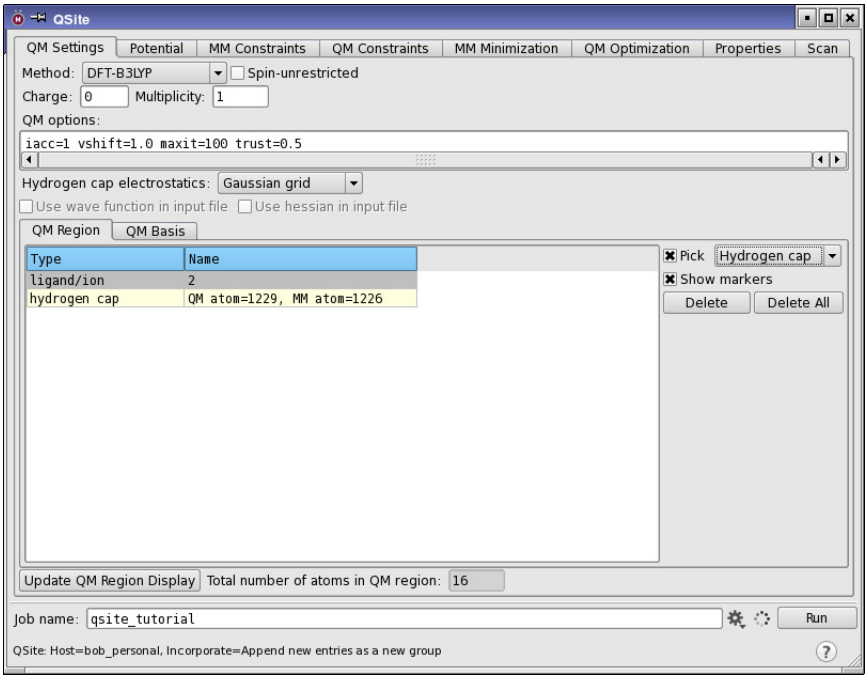

Figure 4.1. The QM Settings tab of the QSite panel, showing the QM Region subtab.

4.2.1 General Settings

Method

The options for the QM method include several density functional theory methods (DFT-B3LYP, DFT-PWB6K, DFT-M06, DFT-M06-2X, DFT-M06-L, DFT-M06-HF, DFT-M05, DFT-M05-2X), Hartree-Fock (Hartree-Fock), local Møller-Plessett perturbation theory (Local MP2), and several semiempirical methods of NDDO type (RM1, AM1, PM3, MNDO, MNDOd). The DFT-User defined option is selected when an input file is read that specifies a functional other than those available from this menu. Otherwise this option is not available. For more information on the functionals, see Section 3.3 of the *Jaguar User Manual*. For information on the semiempirical methods, see the *Semiempirical NDDO Guide*.

If you choose the Hartree-Fock method or a DFT method for a closed-shell system, you can calculate excited states with the CIS or the TDDFT method by including the relevant keywords from Section 9.5.8 of the *Jaguar User Manual* in the QM options text box or the input file. This can only be done for a QM region defined with hydrogen caps or defined by a ligand.

Spin-unrestricted option

Select this option to perform a spin-unrestricted open-shell calculation. This option is only available with the Hartree-Fock and DFT-B3LYP methods. Otherwise, open-shell calculations will be performed with the restricted open-shell methods.

Charge

This is the net charge of the QM region of the system. Maestro updates the charge to a reasonable value whenever a new residue or ion is added to the QM region. If a discrepancy appears, edit the value. If this value does not match the sum of the formal charges of the atoms in the QM region, Maestro displays a warning message, but allows you to proceed.

Multiplicity

This is the spin multiplicity of the QM region of the system: 1 for singlet, 2 for doublet, etc. Edit the value if necessary. If there is a discrepancy between the total charge and the multiplicity, the Jaguar calculation halts with an error message. The charge and multiplicity of the QM region must be mutually consistent. By default, open-shell calculations are spin-restricted. If you want to perform a spin-unrestricted HF or DFT calculation, select Spin-unrestricted.

QM options

This text box can contain any Jaguar keywords such as print settings, non-default convergence criteria, and so on. Each such option is of the form keyword=value (with no embedded blanks).

Multiple keyword-value pairs can be specified, separated by one or more blank spaces. By default, the following QM options appear in the box:

```
iacc=1 vshift=1.0 maxit=100
```

You can remove or modify these options as appropriate. See Chapter 9 of the *Jaguar User Manual* for more information on Jaguar keywords.

Hydrogen cap electrostatics

This option menu allows you to choose how atoms in the MM region in the vicinity of a hydrogen cap are treated when calculating their electrostatic interaction with the QM region. It is only available when you are using hydrogen caps to define part or all of the QM region.

- Gaussian grid—Use Gaussian charge distributions to represent the potential of the atoms near the cap, and MM point charges for the rest of the MM region. The charge distributions are represented on a grid.
- Gaussian charges—Use Gaussian charge distributions to represent the potential of the atoms near the cap, and MM point charges for the rest of the MM region. Cannot be used for excited states or for properties that require a CPHF calculation.
- Point charges—Use modified point charges to represent the potential of the atoms near the cap, and MM point charges for the rest of the MM region.
- None—Ignore electrostatic interactions between the QM and MM regions near the hydrogen caps. Van der Waals interactions are still included.

Use wave function in input file
Use Hessian in input file

These options allow you to read the wave function and the Hessian from the input file, and make use of them in the calculation. This capability is useful when restarting a calculation.

4.2.2 QM Region Subtab

In this subtab, you set up the QM region. The total number of atoms in the QM region is displayed below this subtab. To define the region, choose a type of cut from the Pick option menu, and pick atoms to define the cut. If you want to delete a cut, select it in the table and click Delete. To start over with the selection of cuts, click Delete All.

QM region table

The cuts that define the QM region are listed in the table. The Type column gives the cut type, and corresponds to the choice made from the Pick option menu to define the cut. The Name column identifies the cut:

- Side chain—Residue name and number
- Entire residue—Residue name and number
- Free ligand/ion—Molecule number
- Hydrogen cap—QM atom=number, MM atom=number

When you have finished picking to define a cut or a set of QM atoms, table rows are added for each cut or atom set. To delete a cut, select the cut in the table and click Delete.

Pick option and menu

Select this option to pick the location of one or more cuts, and choose the type of cut from the option menu. Note that a residue can be an amino acid residue, a free ligand or solvent molecule, or an ion. The items on the option menu are:

- Side chain

  Choose this option to add only the side chain of an amino acid residue to the QM region, leaving the backbone in the MM region. Pick an atom in the side chain you want to include. The side chain is marked in sienna if Show markers is selected. A cut is made between the alpha carbon and the beta carbon of that residue. All of the atoms in the side chain are part of the QM region.

  Side-chain cuts can be made in any peptide residue other than alanine (ALA), glycine (GLY), and proline (PRO). To incorporate side chains from these residues in the QM region, you must select the entire residue by using a backbone cut. Side-chain cuts can be made in positively-charged histidine (HIP) as well. Side-chain cuts are not permitted if the side chain has been modified within 3 atoms of the alpha carbon atom.

- Entire residue

  To add entire amino acid residues to the QM region, choose this option and then pick two atoms that are not alpha carbons and are at least three backbone bonds apart. The residues containing these two atoms and the residues in between are included in the QM region. The cut between MM and QM atoms is made between the alpha carbon and the backbone atom bonded to it. When you pick the first atom it is marked with a purple cube. After picking the second atom, all of the backbone and side chain atoms between the two cuts are marked in sienna if Show markers is selected.

  If you click twice on the same atom in an amino acid residue, then the QM/MM cuts will be set as small as possible so as to place that entire residue in the QM region.

  Backbone cuts can be made in any peptide residue, including glycine, proline, and their adjacent residues, and including positively-charged histidine (HIP). An exception is that backbone cuts on PRO residues cannot be made between the N atom and the Cα atom.

There must be at least 3 bonds between pairs of QM-MM cuts that are made along the protein backbone. This ensures that the QM/MM boundaries are kept far enough apart that they do not interfere with one another. This means that the smallest QM region that contains all of the atoms of an amino acid residue would necessarily contain an extra carbonyl group and an extra N-H bond from the neighboring residues.

A backbone cut cannot be placed between an amino acid residue and an end cap. The end cap must be included in the QM region. To do this you may click on any atom in an end cap, and on any other atom in an amino acid residue further up the chain. In this case only one cut will actually be made, and all atoms from the cut to the end of the chain will be placed into the QM region.

The cuts made with this choice use the frozen-orbitals method for defining the terminus of the QM region.

- Free ligand/ions

  Entire free ligands, metal ions, or other species not covalently bound to the protein can be added to the QM region by this method, which does not make any cuts between atoms. Select this option, then pick a metal ion or an atom in the ligand molecule to add it to the QM region. Molecules are marked in sienna, and single atoms or ions are marked in cyan, if Show markers is selected.

  Ligands that are covalently bound to the protein cannot be added using this method, because this method does not make parametrized cuts between bonded atoms. To add covalently-bound ligands to the QM region, make either a pair of backbone cuts to select the residue to which the ligand is bound, or make a side-chain cut.

- Hydrogen cap

  To define cuts that are capped by hydrogen atoms rather than atoms with frozen orbitals, select this option and then pick the QM atom followed by the MM atom on either side of the cut. The QM atom and the MM atom must be joined by a single bond. The MM atom is replaced by a hydrogen atom in the QM calculation. The QM region usually requires two or more cuts. The markers in the Workspace are not updated after making this kind of cut. Instead, you must click Update QM Region Display to display the markers for the QM region (provided Show markers is selected).

  Once you have created a hydrogen cap, the Hydrogen cap electrostatics option menu in the general section becomes available, and you can choose the electrostatic treatment of MM atoms near the cap.

Note: If the structure contains a metal atom, it should be either included in the QM region or it should be frozen, if it is in the MM region, along with its ligands or ligand residues.

Show markers option

If this option is selected, markers are displayed in the Workspace to indicate the QM region. Ball-and-stick markers are superimposed on the QM region atoms. The markers are colored sienna. The markers that correspond to the selected rows in the QM region table are colored cyan. For hydrogen caps, an arrow is superimposed on the bond where the cap will be placed, pointing to the MM atom that will be replaced with a hydrogen atom.

4.2.3 QM Basis subtab

In this subtab you can view and change the basis set associated with each atom in the QM region.

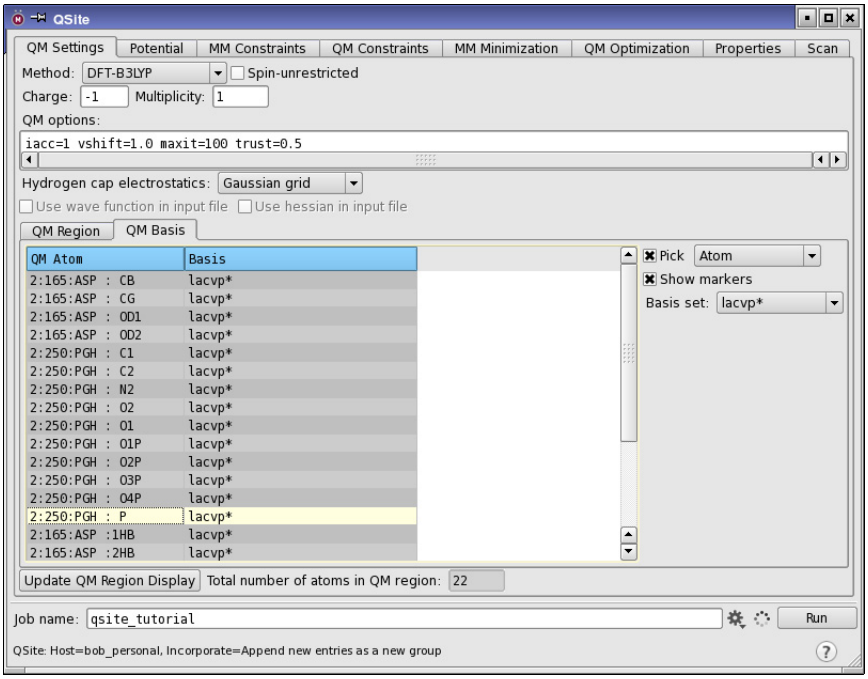

Figure 4.2. The QM Settings tab of the QSite panel, showing the QM Basis subtab.

Basis set table

This table lists the basis set used for each QM atom. The atom is identified in the QM Atom column, and the basis set used is given in the Basis column. You can select multiple rows and apply a basis set to the selection.

Pick option and menu

Select this option to pick atoms for which you want to change the basis set. Three of the options on the menu are the same as in the QM Region tab, and work in the same way. The Hydrogen cap option is not present; instead there is an Atom option that enables you to pick individual atoms. The atoms you pick are marked with green axes if Show markers is selected, and they are also selected in the basis set table.

Show markers option

When this option is selected, the atoms that are selected in the table or picked are marked with green axes.

Basis set option menu

Choose the basis set for the selected rows in the basis set table from this option menu. By default, the basis set used for the entire QM region is LACVP*, which uses 6-31G* for non-transition metals. This is the basis set used in the parameterization of the frozen orbital cuts.

Note: The inclusion of frozen-orbital cuts enforces the use of 5D for the d functions.

4.3 The Potential Tab

The Potential tab provides options for the definition of the potential energy functions used in the molecular mechanics part of the calculation. One of these (continuum solvation) affects the QM potential energy as well.

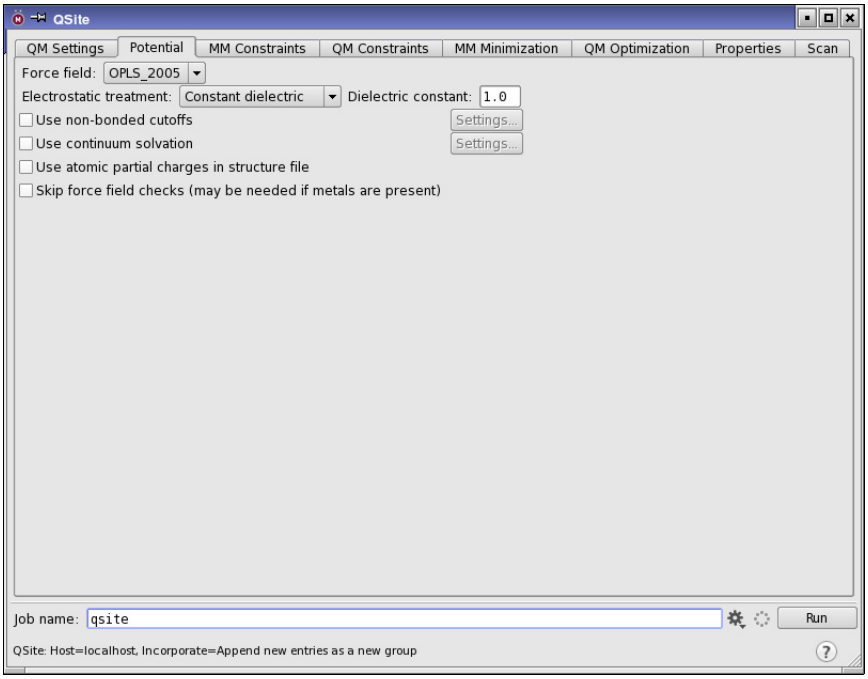

Figure 4.3. The Potential tab of the QSite panel.

Force Field

The available force field is OPLS_2005.

Electrostatic treatment

This option menu offers two methods for calculating the electrostatic component of the molecular mechanics energy:

- Constant dielectric

  This option calculates the electrostatic interaction between atoms *i* and *j* as:

  $$E_{ele} = 332.063762\ q_i q_j/(\varepsilon\ r_{ij})$$

  A constant dielectric is appropriate for a vacuum (gas-phase) calculation or when an explicit or implicit solvent model is used.

- Distance dependent dielectric

  This option calculates the electrostatic interaction between atoms *i* and *j* as:

  $$E_{ele} = 332.063762\ q_i q_j / \varepsilon\ r_{ij}^2$$

  A distance-dependent dielectric is sometimes used as a primitive model for the effect of solvent. In this model, the electrostatic interaction between a pair of atoms falls off rapidly as the distance between the atoms increases. Continuum and explicit solvent models are much better at accounting for solvent effects than a distance-dependent dielectric.

The variables in the above formulae are defined as follows:

- E_{ele} is the electrostatic interaction in kcal/mol
- q_i and q_j are the partial atomic charges on atom *i* and *j*
- r_{ij} is the distance in Å between atoms *i* and *j*
- ε is the Dielectric constant (see below)

Dielectric constant

This text box specifies the dielectric constant ε used in the electrostatic calculations.

In molecular-mechanics calculations it is often impractical to include the nonbonded (electrostatic and van der Waals) interactions between every pair of atoms. For large systems, many such pairs are separated by a great distance and contribute little to the interaction energy. Judicious truncation of the non-bonded interactions between widely separated pairs of atoms is an important strategy for reducing the resources needed for calculations on large systems.

At present only residue-based cutoffs are supported for calculations set up in Maestro. This means that all atoms within complete residues that have any pair of atoms within the cutoff distance will be included in the non-bonded interaction list. The list is updated periodically as the geometry changes, because residues may move inside or beyond the cutoff radius.

Use non-bonded cutoffs

Select this option to truncate nonbonded interactions. Click Settings to open the Truncation panel. There are two settings that can be changed:

- Update neighbor-list frequency (# steps): The number of steps after which the neighbor list will be updated. The default is 10 steps (in the MM part of the calculation). Larger values will speed up the calculation, at the possible expense of accuracy.
- Residue-based cutoff distance: All atoms in complete residues that have any pair of atoms within this distance are included in the nonbonded interaction list. The default is 12 Å. This value should be increased to avoid convergence problems, to a value like 30 Å. Smaller values will speed up the calculations, but could miss important long-range electrostatic interactions between formally charged atoms.

Use continuum solvation

Select this option and click Settings to open the Continuum Solvation dialog box. The only available solvation method in QSite, for both the MM and the QM solvation functions, is the Poisson–Boltzmann Solver (PBF); selecting Use continuum solvation automatically sets both solvation functions to PBF (in the Jaguar input file, `isolv=2`). The Surface Generalized Born (SGB) and Analytic Generalized Born (AGB) methods are not available for QSite calculations. The Continuum Solvation panel options available for PBF are as follows:

- PBF resolution

  The Poisson–Boltzmann solver involves a finite-element calculation on a grid. The grid spacing controls the accuracy of the PBF calculation and the time required. The default, Low resolution, suffices for most protein work. If needed, greater accuracy can be achieved by choosing Medium or High resolution.

- PBF displacement threshold

  This text box specifies how far (in Å) any atom may move from the coordinates used in the previous PBF calculation before a new PBF calculation must be performed. If no atom has moved this distance, the previously calculated PBF energy and forces are used.

This option affects both MM and QM calculations. Do not select Use continuum solvation if you intend to run the QM (Jaguar) calculation using multiple processors (parallel processing); when QSite jobs with solvation are run in parallel, erroneous energies result.

If you want to use explicit water solvent rather than continuum solvation, you can add the water molecules using the Soak application of Basic Impact, followed by an equilibration, also using Basic Impact. See Chapter 5 of the *Impact User Manual* for more information on Soak.

Use atomic partial charges in structure file

With this option, you can choose to use the atomic partial charges that are stored in the input structure file, rather than the partial charges that are assigned by the force field.

This option should only be used when the QM region consists of one or more non-covalently bound molecules. If you use this option for a system in which you make frozen orbital cuts or hydrogen caps, the resulting structure and properties will generally be erroneous. The handling of frozen orbitals involves a parameterization for the potential about the frozen bond, which relies on particular values for the partial charges of the atoms near the QM/MM interface. In general the charges in the Maestro structure file will not be appropriate for use with frozen orbitals. ESP charges written to the output Maestro file from jobs with frozen orbitals or hydrogen caps are only for the QM atoms and will not usually add up to the appropriate molecular charge.

Skip force field checks

By default, Impact performs a number of tests during atom typing to guide selection of optimal force-field parameters for the atoms in the input structure. The tests are applied to both the MM and the QM regions. For transition metals, force-field parameters are more limited than for the common p-block elements, so when the structure contains transition metals, these atom typing tests can fail and cause the job to halt. The force field is not used if the metals are in the QM region. By selecting this option, the force-field checks are bypassed, and the metal atoms do not cause the job to fail.

4.4 The MM Constraints Tab

The MM Constraints tab is used to apply constraints to the Cartesian coordinates of selected atoms in the MM region. Specified atoms can be frozen at their input coordinates (frozen-atom constraints), or they can be constrained to remain near their initial coordinates by applying a harmonic force.

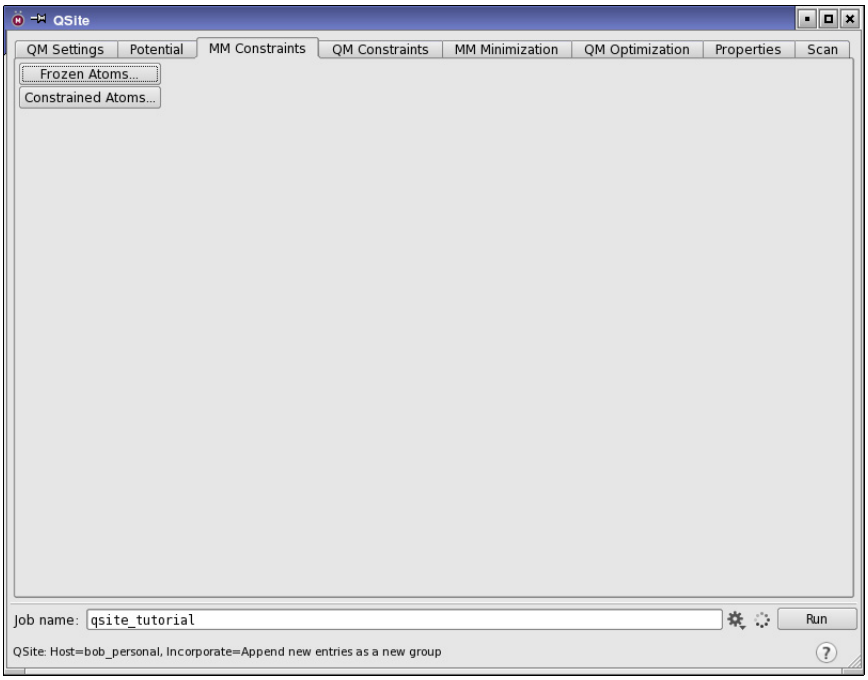

Figure 4.4. The MM Constraints tab of the QSite panel.

Atom constraints in QSite for atoms in the MM region must be set in the MM Constraints tab.

The Constraints tab contains two buttons, Frozen Atoms and Constrained Atoms. These buttons open the Frozen Atoms and Constrained Atoms panels. These panels have a similar structure. The panel features are described below.

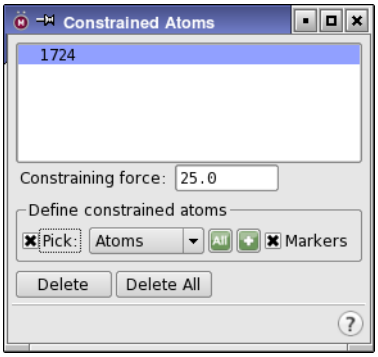

Figure 4.5. The Constrained Atoms panel.

Atoms list

The upper portion of each panel is a text area that lists the atom number of each atom that has been selected to be frozen or constrained. The currently selected atom is highlighted.

Picking tools

This section, labeled Define frozen atoms or Define constrained atoms, contains standard picking controls: a Pick check box and menu, which is set to Atoms by default, and an Atom selections button, which provides a range of predefined atom selections and access to other tools for atom selection. If you deselect the Pick check box, you can use the Select atoms tool in the Workspace to select atoms, then use the Atom Selections button to add those atoms to the list.

The picking tools section also contains a Markers option, which is selected by default. Atoms to be frozen are marked with a red cross and a "padlock" icon in the Workspace. Atoms to be constrained are marked with a brown cross and a "spring" icon in the Workspace display.

To distinguish the selected frozen or constrained atom, Maestro colors the marker turquoise.

Constraining force

The Constraining force text box sets the value of the harmonic force constant applied to the selected constrained atoms. The same force constant is used for all atoms. The default is 25.00 kcal/(mol $Å^2$).

Deletion buttons

The constraint on the currently selected atom can be removed by clicking Delete. The atom is then removed from the atoms list. To remove all constraints of this type, click Delete All. The atoms list is then cleared.

4.5 The QM Constraints Tab

The QM constraints tab is used to set constraints on geometric parameters in the QM region. It provides the same capabilities as in the Optimization tab of the Jaguar panel. For full details, see Section 4.2 of the *Jaguar User Manual*. Briefly, you can set constraints on distances, angles, and dihedrals, and set Cartesian constraints. These constraints freeze the internal or Cartesian coordinates. For Cartesian coordinates, you can only freeze the entire atom, not individual coordinates. You can also make constraints dynamic, which means that the optimization will constrain the parameter to reach the target value specified at convergence. Harmonic constraints are not available in the QSite panel, but can be set by using Jaguar keywords.

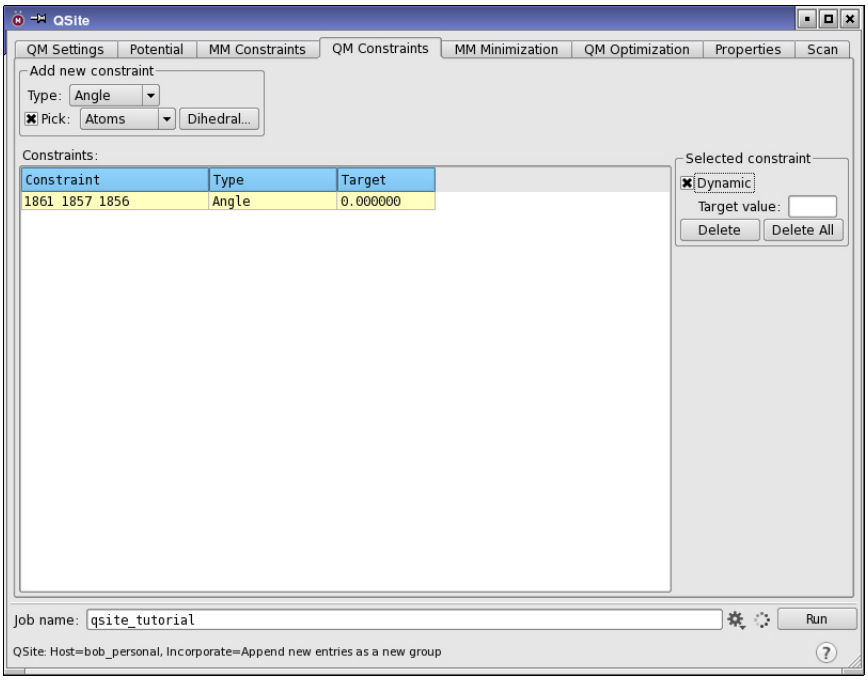

Figure 4.6. The QM Constraints tab of the QSite panel.

To set a constraint, choose the parameter type from the Type menu, select Pick (if it is not already selected), choose Atoms or Bonds from the Pick menu, then pick the atoms in the

Workspace for the constraint. The constraints are marked in the Workspace with a spring icon and lines to indicate the atoms involved and the type of constraint.

To make a constraint in the Constraints table dynamic, select the table row, then select Dynamic in the Selected constraint section next to the table and enter the value that you want the constraint to converge on in the Target value text box. This value is copied to the Target column of the table.

To delete one or more constraints, select them in the table and click Delete in the Selected constraint section. To delete all constraints, click Delete All.

4.6 The MM Minimization Tab

The MM Minimization tab specifies settings for Impact energy minimization of the MM region of the molecule. If the QM method chosen in the Optimization tab is Single point, these settings are not used, and no MM minimization is performed. The options available in this tab are described below.

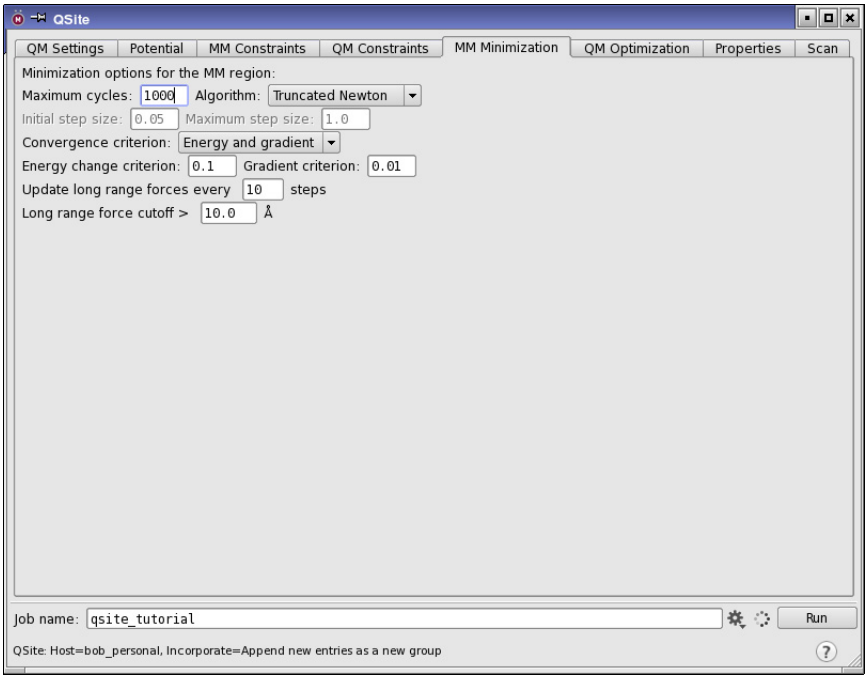

Figure 4.7. The MM Minimization tab of the QSite panel.

Maximum cycles

Set the maximum number of cycles for the minimization calculation in this text box. The minimization terminates if it has not converged by this point. The default value of this setting is 100 iterations, but you can specify any value greater than or equal to zero. “Zero cycles” is a special case; it instructs Impact just to evaluate the energy for the current coordinates.

Algorithm

Choose the minimization algorithm from this option menu. The choices are:

- Truncated Newton (TN). This is a very efficient method for producing optimized structures. A short conjugate gradient pre-minimization stage is performed first to help improve the convergence of the Truncated Newton algorithm.
- Conjugate gradient. This is a good general optimization method and is the default method.
- Steepest descent. This can be a good method for initiating a minimization on a starting geometry that contains large steric clashes. Convergence is very poor towards the end of minimization, where the conjugate gradient algorithm should be used.

Initial step size

Specifies the initial step size of the minimization cycle for conjugate gradient and steepest descent minimizations in this text box. The default value is 0.05, but any positive value is allowed.

Maximum step size

Specify the maximum step size of the minimization cycle for conjugate gradient and steepest descent minimizations in this text box. If the step size exceeds this value, the minimization will halt. The default value is 1.00 Å, but any positive value is allowed. The maximum step size is the maximum displacement allowed for an atom in any step of a minimization calculation.

Convergence criterion

Choose the quantities used for the convergence criteria from this option menu. Either or both of two criteria—energy change and gradient—can be specified. The options control the availability of the Energy change criterion and Gradient criterion text boxes.

Energy change criterion

Specify the value of the energy change criterion in this text box. The default value is 10^{-7} kcal/mol, but any positive value is allowed. The criterion is satisfied if two successive energies differ by less than the specified value.

Gradient criterion

Specify the value of the gradient criterion in this text box. The default value is 0.01 kcal/(mol Å), but any positive value is allowed. The criterion is satisfied if the norms of two successive gradients differ by less than the specified value.

Update long range forces every *n* steps.

Specify the frequency with which long range forces are updated for Truncated Newton minimizations in this text box. Between these intervals, estimates of these forces are used. Every 10 steps is the default; smaller numbers (more frequent updates) can be used to improve convergence, but will make the optimization slower. Larger numbers for n may speed the calculation, but the maximum recommended value is 20.

Long range force cutoff > *d* Angstroms.

Specify the distance beyond which forces are considered long range, and are therefore updated every *n* steps, for Truncated Newton minimizations in this text box. The default value is 10.0 Å.

4.7 The QM Optimization Tab

The QM Optimization tab specifies the type of QM (Jaguar) calculation to be performed and provides information needed to set up the calculation. For transition state optimizations additional structures (reactant, product, and transition state guess structures) can be given to guide the search. QSite geometry optimizations use internal coordinates by default; to force Cartesian coordinate optimization, run QSite from the command line, using the option `intopt=0` in the **gen** section of the input file. If you want to save the intermediate geometries in the output structure file (including the MM region), you can select Save all structures in output Maestro file. This option can generate a large amount of output. The options available in this tab are described in the following sections.

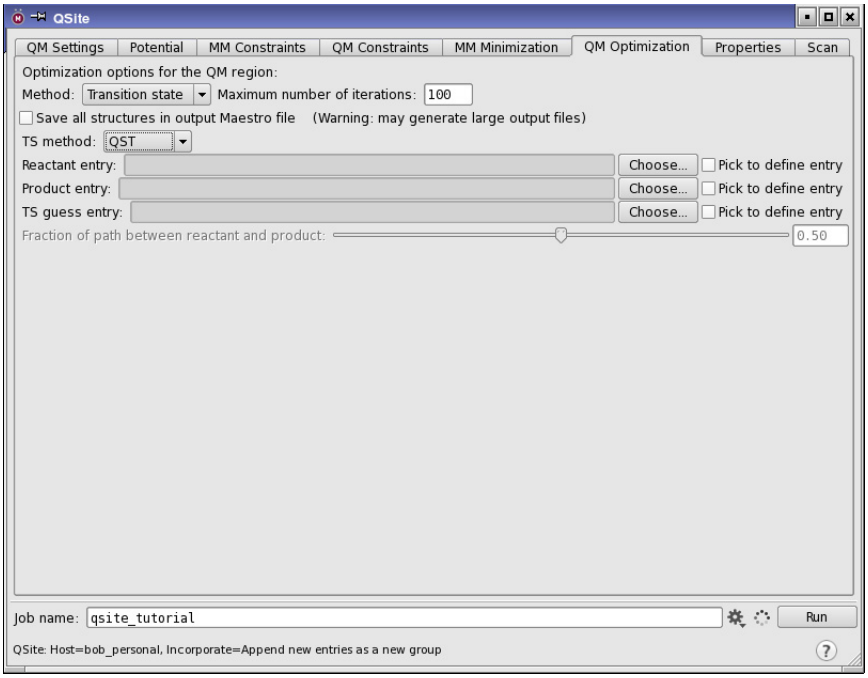

Figure 4.8. The QM Optimization tab with TS method QST selected

4.7.1 Calculation Type

The Method menu controls the QM calculation type. The options are:

- Single point—Calculate the QM energy for the structure as it stands. No QM geometry optimization or MM minimization is performed. When Single point is selected, other options in this tab are unavailable. Settings in the Minimization and Constraints tabs are ignored. This is the default QM method.
- Minimization—Locate a minimum-energy structure by geometry optimization. If you want to optimize only the QM region, simply set the number of minimization steps to 0 in the MM Minimization tab. There is no need to explicitly freeze all of the MM atoms.
- Transition state—Locate a transition state structure by geometry optimization. The remaining controls in the tab define the initial guess for the transition state geometry, and are described in the next subsection.

For minimization and transition-state calculations, you can specify the number of optimization iterations in the Maximum number of iterations text box. The default is 100 iterations.

4.7.2 Transition State Searches

If you select Transition state from the Method menu, the default option for TS method is Standard. The following three methods for transition-state optimization are supported in QSite, corresponding to well-known ab initio techniques. See Section 4.3 and Section 7.4 of the *Jaguar User Manual* for detailed information about these methods:

- Standard: The standard transition-state optimization method is useful if you have only a single initial guess structure (in the Workspace) for the transition-state. It attempts to find the saddle point closest to the starting structure by maximizing the energy along the lowest-frequency mode of the Hessian and minimizing the energy along all other modes.
- LST: *Linear Synchronous Transit* is useful if you have initial guess structures for the reactant and the product and want QSite to look for a transition-state structure by interpolating between them. LST uses a quasi-Newton method to search for the optimum transition-state geometry, choosing a transition-state guess structure based on the interpolation value you set using the Fraction of path between reactant and product slider. By default it is set at 0.50, directing QSite to choose an interpolated transition-state guess structure midway between the reactant and the product. If you want to pick a guess structure closer to the reactant, move this slider toward 0.00. For a guess structure closer to the product, move the slider toward 1.00
- QST: *Quadratic Synchronous Transit* is useful if you have initial guess structures for the reactant, the product, and the transition state. QST uses a quasi-Newton method to optimize the transition-state geometry. This is the recommended method.

The structures that define the transition state initial guess can be specified in the Reactant entry, Product entry, and TS guess entry sections. You can select the entry by typing in the entry name from the Project Table, by clicking Choose and selecting the entry from a list, or, if the structure is in the Workspace, by selecting Pick to define entry and clicking on any atom in the structure.

The structures used in a transition state search *must* all have the same QM region, atom numbering, labeling, and connectivity. This means that the bonds may look unphysically stretched, but they are not relevant to the QM part of the calculation, so this is not a problem. We recommend the following procedure for setting up your structures:

1. Optimize the structure of the reactant in a configuration in which it is ready to react. This should not be the minimum energy, but somewhere on the reactant side of the transition state, and might require some constraints.
2. With this structure, use the build tools to modify the structure to somewhere on the product side of the transition state, and optimize it. This makes sure you have the same atom numbers and labels. *Do not break or form any bonds*.

3. Repeat for the transition state guess, if using QST.

If bonds should be broken or formed in the reaction but you did not actually break them, add a **connect** section to the input file, in which all bonds that are broken or formed are specified. This ensures that the bonds that are broken or formed are included in the internal coordinates used to drive the search, and usually results in faster convergence and more reliable location of the transition state. See Section 9.4 of the *Jaguar User Manual* for information on this section.

You can also run an IRC calculation, by setting up the transition state search, and then adding the **irc** keyword to the **gen** section with the appropriate value, and removing the **qst** and **igeopt** keywords. You can add keywords in the QSite panel, but to remove keywords you must edit the input file. See Section 4.5 and Section 9.5.11 of the *Jaguar User Manual* for more information.

4.8 The Properties Tab

In this tab, you can set options for the calculation of QM properties at the end of the QSite job. The Properties tab is essentially the same as in the Jaguar panel. For detailed information on the properties and the use of the tab, see Section 3.8, Section 3.9, and Section 3.10 of the *Jaguar User Manual*. This section describes features that are unique to QSite.

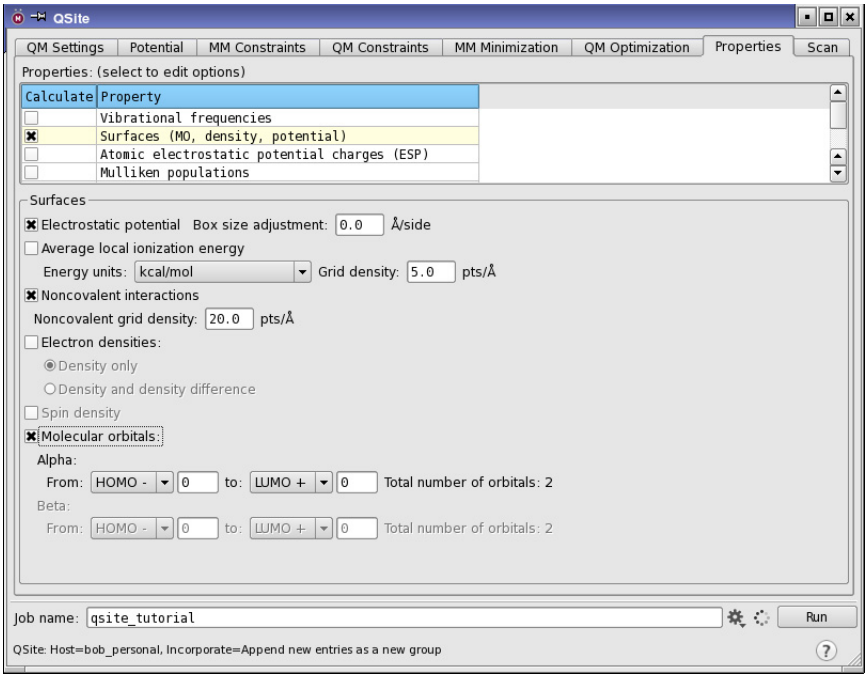

Figure 4.9. The Properties tab

As in Jaguar, the list of available properties depends on the method selected. QSite has access to semiempirical methods, for which various properties can also be calculated—see the *Semiempirical NDDO Guide* for details.

In addition to restrictions on the properties due to the method, there are also restrictions that are based on the nature of the QM/MM boundary. Properties that are not available due to the definition of the QM region are dimmed in the Properties table of the tab. Specifically, frequencies, NMR shielding constants, and polarizabilities are not available if there are frozen-orbital cuts. Also, the Pulay SQM scaling of frequencies is not available at all.

Properties are calculated from the QM orbitals, but frozen orbitals from frozen-orbital cuts are ignored. For example, if you request a surface for the HOMO, the surface is generated for the highest-energy occupied orbital that is not frozen. The QM orbitals include effects from the MM region, but the MM region is not explicitly included in any of the properties.

Note: Properties for atoms that are within a few bonds of frozen-orbital cuts or hydrogen caps are likely to be unreliable and should be treated with caution. This is because the representation of the wave function near the cuts does not accurately represent the wave function of the full system.

4.9 The Scan Tab

In this tab, you set up the coordinates for a relaxed or a rigid coordinate scan. Whether the scan is relaxed or rigid depends on the method selection in the QM Optimization tab: selecting Single point from the Method option menu performs a rigid scan, selecting Minimization performs a relaxed scan.

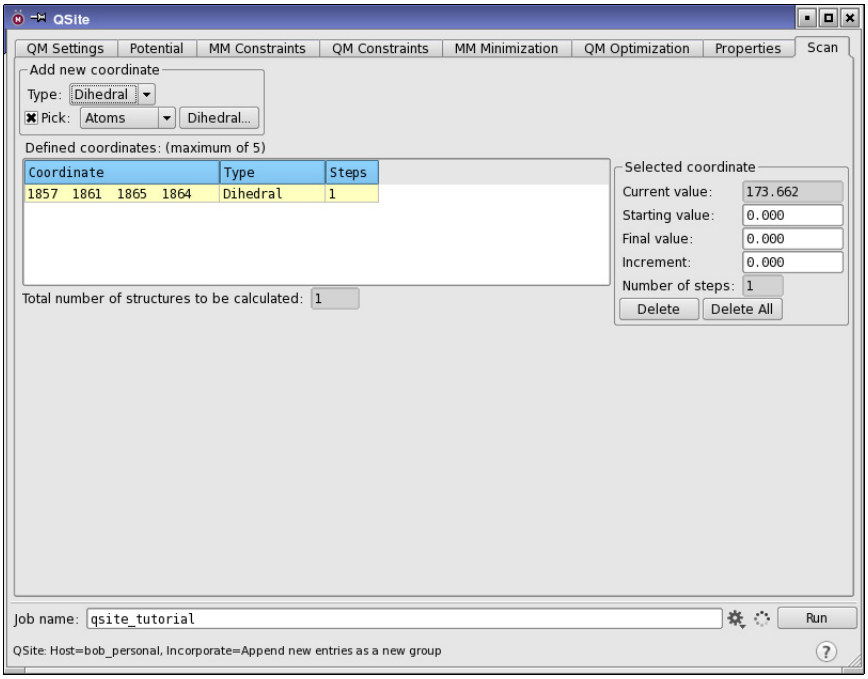

Figure 4.10. The Scan tab

To add a new scan coordinate:

1. Choose a coordinate type from the Type option menu
2. Choose Atoms or Bonds from the Pick option menu
3. Pick the atoms or bonds in the Workspace.

The order of picking of the coordinates determines which atoms are moved in the scan: the last atom picked is the moving atom, and the first atom picked remains stationary. If you are picking bonds, they must be contiguous. The last atom (the moving atom) is the atom in the last bond picked that is not part of the previous bond picked.

The choice you make from the Type option menu determines the number of atoms to pick. The Z-matrix must be in the appropriate form for the coordinate type: Cartesian for Cartesian coordinates, and Z-matrix for distances, angles, and dihedrals. The coordinate types are:

- Cartesian-X—X coordinate of an atom. Pick one atom.
- Cartesian-Y—Y coordinate of an atom. Pick one atom.
- Cartesian-Z—Z coordinate of an atom. Pick one atom.
- Distance—Distance between two atoms. Pick two atoms or one bond. If you pick atoms, they need not be bonded to each other.
- Angle—Angle between three atoms. Pick three atoms or two bonds. If you pick atoms, they need not be bonded to each other.
- Dihedral—Dihedral angle between four atoms. Pick four atoms or three bonds. If you pick atoms, they need not be bonded to each other.

The choices available on the Pick option menu are Atom for Cartesian coordinates, and Atom and Bond for all other types of coordinates. The atoms are marked in the Workspace as you pick them, and each coordinate is marked in the Workspace and entered in the Defined coordinates table as it is completed. If you want to select a protein dihedral angle, click Select. A dialog box is displayed, in which you can select a standard dihedral from a list.

The Defined Coordinates table displays information on the scan coordinates. You can select a single row to define the range and point spacing for the coordinate in the Selected Coordinate section. The table columns are:

- Coordinate—Atom numbers of the atoms that define the coordinate.
- Type—Coordinate type, from the Type option menu.
- Steps—Number of steps to take in the given coordinate. Calculated from the values provided in the Selected Coordinate section.

The total number of structures to be calculated is reported below the table, and is the product of the numbers in the Steps column.

To set up the range for a coordinate:

1. Select the coordinate in the Defined coordinates table
2. Enter values in the text boxes in the Selected coordinate section.

In the Selected Coordinate section, you can set the range of the scan and the spacing of the points along the scan coordinate for the coordinate that is selected in the table. These values are used to calculate the number of steps. The text boxes are described below.

- Current value—Current value of the coordinate in the input structure. Noneditable.
- Starting value—Initial value of the coordinate for the scan.
- Final value—Final value of the coordinate for the scan.

- Increment—Amount by which the coordinate is incremented at each scan step.
- Number of steps—Number of steps to take in the given coordinate. Calculated from the initial and final values and the increment.

You can delete coordinates by selecting them in the table and clicking Delete in the Selected coordinate section.

4.10 Running QSite Jobs

When you have set the options in the QSite panel tabs to the desired value, enter a name in the Job name text box and click Run to run the job with the current job settings. If you want to make job settings, click the Settings button to open the Job Settings dialog box. In this dialog box you can set up the job options, then submit the job to a host for execution. For details of the features of this dialog box, see Section 2.2 of the *Job Control Guide*.

When choosing job and host options, you should take note of the following points:

- QSite does *not* automatically assign new names to jobs or files. If files of the same name exist, a warning is displayed before any files are overwritten.
- You can use multiple processors for parallel processing of the QM part of the calculation, if the host has multiple processors.
- Do not use parallel processing for jobs that include continuum solvation treatment, as they will fail if you do.

When you have selected job options, click the Start button to run the job. QSite jobs can be monitored in the job Monitor panel.

If a QSite job needs to be restarted, it can be restarted from Maestro or from the command line.

To restart a job from the command line, run QSite with the restart file specified as the input:

```
$SCHRODINGER/qsite job-options jobname.01
```

The restart input file has an index number inserted into the file name: for the first restart it is *jobname*`.01.in`. Running with this file produces a restart file named *jobname*`.02.in`, and so on. Likewise, the output structure file has an index number inserted into the file name: for the first job it is *jobname*`.01.mae`. The index number is the same as for the restart file.

To restart a job from Maestro, open the QSite panel, and click Read. A file selector opens, in which you can navigate to and select the restart file. When you click OK, the structure is imported as well as the settings. You can select options in the QM Settings tab to read the wave function and the Hessian from the input file. You can then click Start to open the Start dialog box to restart the job.

4.11 QSite Output File

The output file from QSite contains a combination of the Jaguar output and the Impact output. Details of the Jaguar output are given in Chapter 6 of the *Jaguar User Manual*.

Near the top of the output, a table of mappings of Jaguar atom numbers to Maestro atom numbers is printed, from the `pre` program in Jaguar. This is because the Maestro atom numbers include the entire structure, and the Jaguar atom numbers include only the QM region. An example from the tutorial is given below.

```
Jaguar to Maestro atom number mapping:
--------------------------------------
         Jaguar   Maestro
         Atom #    Atom #
        --------  --------
             1      1856
             2      1857
             3      1858
             4      1859
             5      1860
             6      1861
             7      1862
             8      1863
             9      1864
            10      1865
            11      3730
            12      3731
            13      3732
            14      3733
            15      3734
            16      3735
```

Further down in the output from pre there is a list of counts of atoms, cuts, hydrogen caps, and so on. From the same tutorial example, this list is:

```
------------------------------------------------------------------------------
Total number of atoms:              3735
Number of atoms passed to Jaguar:     16
Number of atoms treated by QM:        16
Number of atoms treated by NDDO:       0
Number of hydrogen caps:               0
Number of NDDO hydrogen caps:          0
Number of frozen orbital cuts:         0
Number of constrained MM atoms:        0
Number of frozen MM atoms:             0
------------------------------------------------------------------------------
```

In the tutorial example, the QM region consists of a single free ligand. When there are hydrogen caps or frozen orbital cuts, then the number of atoms passed to Jaguar is greater than the number of atoms treated by QM or NDDO. This is because some of the atoms on the MM side of the boundary are passed in to guide Jaguar in parameter selection.

The energies reported by Impact and Jaguar contain additional terms. The MM energy breakdown includes 3 new terms (which are zero when the QM region consists of free ligands or ions). These are the stretching, angle-bending, and torsional terms for the atoms across the QM-MM interface. An example from the tutorial is given below.

```
Final Energy Reports:
-------------------------------------
 Total Energy of the system...... -1.17375E+04 kcal/mol
 Total Potential Energy.......... -1.17375E+04 kcal/mol
 Total Kinetic Energy............  0.00000E+00 kcal/mol
 Temperature of the system.......        0.000 K
 Bond Stretch Energy.............  1.32773E+02 kcal/mol
 Angle Bending Energy............  4.98316E+02 kcal/mol
 Torsion Angle Energy............  8.06200E+02 kcal/mol
 Restraining Energy for Torsions.  0.00000E+00 kcal/mol
 1,4 Lennard Jones Energy........  1.08765E+03 kcal/mol
 1,4 Electrostatic Energy........  7.11491E+03 kcal/mol
 Lennard Jones Energy............ -1.85269E+03 kcal/mol
 Electrostatic Energy............ -1.95423E+04 kcal/mol
 H-bond Energy...................  1.76228E+01 kcal/mol
 QM/MM Stretch Energy............  0.00000E+00 kcal/mol
 QM/MM Bend Energy...............  0.00000E+00 kcal/mol
 QM/MM Torsion Energy............  0.00000E+00 kcal/mol
```

The MM energy terms are passed to Jaguar and are labeled as A0 in the SCF energy breakdown. The interaction of the MM point charges with the nuclei and electrons in the QM region are included in the QM energy terms: the nuclear repulsion energy includes the QM nuclear–MM point charge terms, and the one-electron energy includes the QM electron-MM-point charge terms. The terms included in the nuclear repulsion energy are negative when the MM point charges are negative, because the MM point charges represent the atomic partial charges, not the nuclear charge. An example of the QM energy components is given below:

```
 Energy components, in hartrees:
   (A0) QSite MM terms.............      -18.70492456555
   (A)  Nuclear repulsion..........      668.01850190086
   (E)  Total one-electron terms.....  -2601.82844589834
   (I)  Total two-electron terms.....   1006.51789124588
   (J)    Coulomb...................    1101.39831318806
   (K)    Exchange+Correlation.......     -94.88042194219
   (L)  Electronic energy..........  -1595.31055465247  (E+I)
   (N)  Total energy...............    -945.99697731715  (A0+A+L)
```

4.12 Troubleshooting

This section contains information on various conditions that you might encounter, and offers some suggestions to work around or fix the problems.

4.12.1 mmlewis Warnings or Atom Typing Failures

By default, Impact performs a number of tests during atom typing to guide selection of optimal force-field parameters for the atoms in the input structure. The tests are applied to both the MM and the QM regions. For transition metals, force-field parameters are more limited than for the common p-block elements, so when the structure contains transition metals, these atom typing tests can fail and cause the job to halt. If this happens, you can select Skip force field checks in the Potential tab, or add the setting `notestff=1` to the **mmkey** section of your input file and rerun the job from the command line. The `notestff=1` setting directs Impact to skip the extra atom typing tests, and this may allow your job to run.

Specifically, if there are metal atoms in your structure and you see warnings like:

```
mmlewis warning: Problems were identified with the following atoms:
mmlewis warning: 4471 4476
mmlewis warning: Now attempting to fix the lewis structure.
```

or if your job halts with this error:

```
Impact: FATAL mmlewis_apply(): Unable to handle mol 9
Impact: FATAL mmlewis_apply(): Error in handling of full CT
%IMPACT-I(foldmain): calling opls2005 atomtyping ...
%IMPACT-I(foldmain): parameter assignment not performed
%IMPACT-E (die): At line 9
%IMPACT-E: CREATE: Molecule unsuitable for current force field. To
process this molecule, you must first fix the structure.
```

then you should select Skip force field checks in the Potential tab, or set `notestff=1` in the **mmkey** section of your input file, and rerun the job.

Note that these warnings or errors could also mean that there really is a problem with your structure which you should fix. For example, some atoms may have atom types that are inconsistent with their connectivity or formal charge, or there may be atoms that are superimposed.

4.12.2 Convergence Problems

For difficult to converge QSite cases, the following recommendations may help:

- Do not use non-bonded cutoffs (clear the Use non-bonded cutoffs box in the Potential tab). Using non-bonded cutoffs leads to energy jumps when the number of non-bonded

interactions changes, as residues or atoms cross the cutoff boundary. This causes convergence problems, and the energies obtained are not comparable between jobs unless the number of non-bonded interactions happens to be the same. Turning off the use of cutoffs increases the time taken for the job. An alternative is to use a distance-dependent dielectric in Impact.

- Do not use loose Impact convergence criteria. In the MM Minimization tab the default is an RMS gradient of 0.01, so values much larger than that would be considered loose. Even if you are running a quick job, using loose convergence criteria for Impact side is likely to be counterproductive, as the MM region will not be able to move enough to be stable with respect to the QM region and the adiabatic approximation will not then be valid.

Running QSite from the Command Line

Although you will normally set up QSite jobs using the controls and settings in the Maestro GUI, you can submit jobs either from Maestro or from the command line. The same is true for the Protein Preparation facility. Advantages of running from the command line include:

- The command-line scripts can run all full-featured jobs written using the QSite and Impact panels in Maestro, and also allow you to override specific run-time values that are not accessible through the Maestro interface.
- Command-line scripts allow you to run jobs when you want.
- Command-line scripts can be modified and jobs can be re-run without reconfiguring and reloading job settings in Maestro.
- Some job options are available only when you run QSite from the command line.

The `SCHRODINGER` environment variable must be set to run jobs. You can define `SCHRODINGER` as follows:

csh/tcsh: `setenv SCHRODINGER` *installation-directory*

bash/ksh: `export SCHRODINGER=`*installation-directory*

Unless otherwise specified, Schrödinger applications and utilities run under the Schrödinger Job Control facility and are automatically run in the background. For more information on the Job Control facility, see the *Job Control Guide*.

5.1 QSite Files

QSite jobs have a single input file, which is like the Jaguar input file. The input for the QM part of the calculation is included as regular Jaguar sections with their keywords. The input for the MM part is embedded in an **mmkey** section, and consists of keywords that correspond to the Impact commands. The QM region is defined in a separate **qmregion** section.

The Write button in the QSite panel writes the input files needed for a job. See Section 4.1 on page 21 for more information.

A typical QSite job has one input file (*jobname*`.in`), one or more structure files (*jobname*`.mae`, *jobname*`.pdb`, or *jobname*`.sdf`), and after execution, several output files. Table 5.1 contains descriptions of the various file types.

Table 5.1. QSite input and output files

File name	Description
jobname.mae	Maestro format structure file. The output Maestro file contains an index number, like the restart file: *jobname*.*nn*.mae. However, if *jobname* already contains an index number, it is incremented in the output Maestro file name.
jobname.log	QSite log file. The .log file captures standard error messages in text form. Includes both Jaguar and Impact log information.
jobname.in	The input file for a QSite calculation. Includes both Jaguar and Impact input. At various points in the job, an input file (restart file) containing the latest geometry and settings is written. This file is named *jobname*.*nn*.in, where nn is a two-digit number starting with 01. This number is incremented if *jobname* already contains an index number.
jobname.out	QSite output file. Includes both Jaguar and Impact output.

Like Jaguar, QSite writes a restart file at various stages of the calculation. The restart input file has an index number inserted into the file name: for the first restart it is *jobname*.01.in. The output Maestro structure file also includes the index number: its name is *jobname*.01.mae. Running QSite with this first restart file produces a restart file named *jobname*.02.in and a Maestro file named *jobname*.02.mae.

5.2 The qsite Command

The qsite command provides both the means to submit QSite jobs and to interact with the Job Control facility to query and control the progress of a job. To run a job, the syntax is:

```
$SCHRODINGER/qsite [run-options] jobname[.in]
```

The .in suffix for the input file, *jobname*.in, is optional: if it is not specified, it is added.

The qsite command also has its own commands for querying Job Control about jobs, controlling jobs, and obtaining some other information. The syntax is as follows:

```
$SCHRODINGER/qsite command command-options
```

The available commands are listed in Table 5.2.

Table 5.2. Syntax for qsite commands.

Command	Description
`jobs` [*name* | *status*]	Show status of the specified QSite jobs or list the jobs that have the specified status.
`kill` {*name* | *status*}	Kill the QSite jobs with the specified job name or job status.
`stop` {*name* | *status*}	Stop the QSite jobs with the specified job name or job status at the end of the current calculation stage.
`purge` [*name*]	Remove records for the specified jobs from the job database. If no *name* is given, all completed jobs are purged.
`help`	Display usage message
`machid`	Report the hardware and software configuration. This command gives the same output as the `$SCHRODINGER/machid` command.
`platform`	Report information on the hardware platform. This command gives the same output as the `$SCHRODINGER/platform` command.
`sysreq`	Report any system requirements for QSite and whether they are met.

5.3 The QSite Input File

The input file for QSite combines the input required for Jaguar and the input required for Impact. The file is in the same format as the Jaguar input file, and the input sections that relate to the QM part of the calculation are the same as in the Jaguar input file. For details on these sections, see Chapter 9 of the *Jaguar User Manual*. There are no **zmat**, **zmat2**, or **zmat3** sections are in the input file, because all structures needed for a QSite job are in the associated Maestro file. Instead, the input file contains a `MAEFILE:` pointer to a valid Maestro structure file.

In addition to the Jaguar sections, there are two sections, **qmregion** and **mmkey**, for defining the QM region and for setting parameters for the MM part of the calculation. These sections are described below. As in the Jaguar keyword tables, the value given in bold italics is the default value.

5.3.1 Additions to the gen Section

In addition to the Jaguar keywords, there are some QSite-specific keywords that can be added to the **gen** section. These keywords are described in Table 5.3.

Table 5.3. Additional gen section keywords

Keyword	Value	Description
hcapeschg	0	Ignore electrostatic interactions between the QM and MM regions entirely in the vicinity of a hydrogen cap. Van der Waals interactions are still included.
	1	Use modified point charges to represent the potential of the atoms near the cap, and MM point charges for the rest of the MM region.
	2	Use Gaussian charge distributions to represent the potential of the atoms near the cap, and MM point charges for the rest of the MM region. Cannot be used with CIS/TDDFT or CPHF calculations. You should use `hcapeschg=3` instead.
	3	Use Gaussian charge distributions to represent the potential of the atoms near the cap, and MM point charges for the rest of the MM region. The potential for the Gaussians is represented on a grid.
impversion	`medium`	Use the default impact version (8000 atoms/bonds). Default.
	`huge`	Use the large impact version (40,000 atoms/bonds).
	`extrahuge`	Use the largest impact version (90,000 atoms/bonds).
mmqm	***0***	Do not run QSite. This is the default.
	1	Run QSite. This setting must be added for QSite calculations.
qsallerg	0	Do not include MM-MM frozen atom interactions in the energy.
	1	Include MM-MM frozen atom interactions in the energy.

If you want to print the forces for both the QM and the MM atoms, you can set `ip191=2`. The forces are printed out in a table labeled “Full QM/MM forces”. The output file is likely to be large because it contains the Cartesian gradients for all atoms in the system. You can calculate the forces without optimizing the geometry by setting `igeopt=-1`. In QSite, this setting automatically sets `ip191=2`. Forces for atoms at or near the boundary should be treated with caution.

5.3.2 The qmregion Section

The **qmregion** section contains specifications that define the QM region, in terms of frozen-orbital cuts, free ligands, ions, or cofactors, and hydrogen caps. The specifications are made in a free-format table, using the keywords given in Table 5.4. The first five keywords can be combined in any fashion, provided they define a valid cut or free molecule. The hydrogen cap keywords **hcapqm** and **hcapmm** must be used together.

Table 5.4. Keywords used in the qmregion section.

Keyword	Description
molid	Molecule number.
chain	Chain name. This keyword is optional, and can be used to distinguish chains if more than one is present.
resnum	Residue number and insertion code.
qmatom	QM atom for a cut. Can be specified with the PDB atom name or the atom number, optionally prefixed by the atom name and an underscore.
mmatom	MM atom for a cut. Can be specified with the PDB atom name or the atom number, optionally prefixed by the atom name and an underscore. If omitted, all atoms in the molecule are taken to be in the QM region.
hcapqm	QM atom for cuts made by the hydrogen cap (link atom) method. The atom can be specified by the Maestro atom number, optionally prefixed by the atom name and an underscore. Must be given with **hcapmm**.
hcapmm	MM atom for cuts made by the hydrogen cap (link atom) method. The atom can be specified by the Maestro atom number, optionally prefixed by the atom name and an underscore. Must be given with **hcapqm**.
theory	Type of theory to use in the QM region. Allowed values are: `qm`—use Jaguar for quantum-mechanical calculations `nddo`—use semiempirical NDDO module for calculations

A sample **qmregion** section is given below. This is a rather artificial example that contains all possible types of specification of the QM/MM boundary.

```
&qmregion
molid chain resnum qmatom mmatom
  2     A    455a    CA     N
  2     A    277     C      CA
  2     B    1211    CB     CA
molid
  7
qmatom
```

```
 774
O_422
qmatom mmatom
 237    238
N_222  C_1285
hcapqm hcapmm
 852     853
C_125   C_61
&
```

The first two specification lines in the example above describe backbone cuts. The third is a side-chain cut, and the fourth specifies an entire molecule. The fifth specification line is equivalent to the fourth: `qsite` follows the connectivity from the atom indicated until the connectivity runs out. The next two specification lines can be used to specify the locations of cuts which may not be in amino acid residues. This syntax could be used for nucleic acid cuts, for example, although the first syntax would also work for amino acid cuts. For generalized cuts Maestro atom numbers are the only way to define the location of a cut. The last two specification lines define hydrogen caps.

5.3.3 The mmkey Section

The **mmkey** section includes keywords for specifying the MM potential (corresponding to choices in the Potential tab of the QSite panel), for controlling the MM minimization (MM Minimization tab), and for constraints (MM Constraints tab). MM potential keywords are listed in Table 5.5, and MM minimization keywords are listed in Table 5.6. There is one keyword for constraints, **buf_force_const**, which is the force constant for constrained atoms, and has a default value of 25.0. Detailed information about the parameters that are set can be found in Section 4.3 on page 30 and Section 4.6 on page 36.

Table 5.5. Potential energy keywords for the mmkey section

Keyword	Value	Description
dielectric	*real number*	Dielectric constant. Default: 1.0.
estatics	`nodist` | `dist`	Electrostatic treatment: use a constant (`nodist`) or a distance-dependent (`dist`) dielectric. Default: `nodist`.
nb_cutoff_dist	*real number*	Residue-based cutoff distance, in angstroms. Default: 12.0.
nb_update_freq	*integer*	Frequency with which the neighbor list is updated, in steps. Default: 10.
notestff	`0` | `1` | `yes` | `no`	Turn off consistency checks (`notestff=1` or `yes`) when performing atom typing. These checks can prevent a valid structure from being accepted, when the structure contains atoms in the QM region that are not recognized in the force field. The value is case-insensitive. Maestro use `YES` or `NO`. Default: `0` or `no`.
pbf_disp	*real number*	PBF displacement threshold. Default: 0.1
pbf_resolution	`low` | `med` | `high`	PBF resolution Default: `low`.
qsite_ff	`opls2005`	Force field. Default: `opls2005`.
solvation_method	`pbf`	Solvation method (turns on solvation and chooses the solvation model) Default: not present.
use_mae_charges	`0` | `1`	Use atomic partial charges from the input structure (Maestro) file if set to 1. If set to 0, the force field is used to determine the atomic partial charges. Only use when the QM region consists of one or more non-covalently bound molecules—see page 32 for details. Default: `0`.
use_nb_cutoff	`0` | `1`	Use non-bonded cutoffs. Default: `0`.

Table 5.6. Keywords for MM minimization in the mmkey section

Keyword	Values	Description
init_step_size	*real number*	Initial step size. Default: 0.05
rms_gradient	*real number*	Gradient threshold. Default: 0.01.
converge_on	`energy` | `gradient` | `eandg`	Specify quantities that will be tested for convergence: energy, gradient, or both. Default: `eandg`.
deltae	*real number*	Energy change threshold. Default: 0.1.
max_step_size	*real number*	Maximum step size. Default: 1.0
maxcycles	*integer*	Maximum number of minimization cycles. If zero, no minimization is performed. Default: 1000.
opt_method	`conjugate` | `steepest` | `tnewton`	Optimization algorithm. The three choices are conjugate gradient, steepest descent, and truncated Newton. Default: `tnewton`.
tn_force_cutoff	*real number*	Long range force cutoff. Default: 10.0.
tn_force_update	*integer*	Interval between long range force updates, in steps. Default: 10.

5.3.4 The mopac Section

This section is used to specify keywords for semiempirical NDDO calculations on the QM region. The keywords are the same as in the semiempirical NDDO input file—see Section 3 of the *Semiempirical NDDO Guide*. In the **mopac** section, they must be assigned values of 1 (true) or 0 (false). Thus, for each keyword in a semiempirical NDDO input file, the **mopac** section would include these keywords and set their values to 1.

QSite Technical Notes

The study of reactive chemistry in a protein environment is an extremely challenging problem for computational chemistry. The only methods that can produce reliable results (particularly for structures containing transition metals) are those of ab initio quantum chemistry. However, such methods are computationally intensive and scale poorly (~N^2–N^3 for self-consistent-field based approaches such as density functional theory) with the number of atoms N, making it impractical to apply them to an entire protein. An attractive solution is use a mixed quantum mechanics/classical molecular mechanics (QM/MM) method such as QSite. Such methods treat the reactive core of the system quantum mechanically and model the remainder via a classical molecular-mechanics force field.

6.1 QM/MM for Protein Active Sites

QSite is specifically designed to treat protein active sites. It combines Schrödinger's powerful Jaguar program for ab initio electronic structure calculation with molecular-mechanics calculations that use the OPLS-AA force fields of Jorgensen and coworkers. The speed of Jaguar—augmented by an MPI-based parallel implementation—makes it possible to study realistic representations of the active site with the large QM regions (typically 100–200 atoms in applications we have pursued) that are in many cases necessary to obtain chemically realistic results. Hartree-Fock (HF), density functional (DFT), and local MP2 (LMP2) methods are available for the QM/MM region, although geometry optimization has been implemented only for the first two of these methods. We have found DFT methods to be particularly useful for studying protein active-site reactive chemistry.

QSite provides QM/MM interface parameters for all 20 amino acids in their various protonation states. This ensures that you will be able to construct a QM region tailored specifically to your needs. Maestro provides an easy and reliable way to set up the QM/MM interface via pointing and clicking with the mouse on residues of the protein active site. Protein preparation can be carried out using the procedure described in Chapter 3. This technology makes setting up a new QM/MM job a task that can be carried out effectively and straightforwardly.

One key use of QSite is to study ligand binding to transition-metal-containing enzymes such as zinc matrix metalloproteases. Conventional molecular-mechanics force fields usually model ligand interactions with protein metals in a primitive fashion, i.e., as a van der Waals body and a charge site. Jaguar contains specialized methods for treating transition metals that include a novel initial-guess methodology and variable-energy-shift algorithms to converge difficult

cases. The combination of Jaguar's ability to handle large systems efficiently and to accelerate the SCF convergence yields a methodology of unprecedented power and flexibility. No other commercially available program can provide the kind of chemical insight and quantitative description for metal-containing enzymes that QSite offers. As described below, QSite also allows reactive processes to be modeled and transition states to be located. For applications such as these, QSite is an essential part of a comprehensive computational strategy for structure-based drug design.

6.2 QM/MM Transition State Modeling

Jaguar and QSite can perform transition state (TS) searches by using a quasi-Newton method to find the TS nearest the initial geometry [1]. Alternatively, Jaguar can employ a Linear/Quadratic Synchronous Transit (LST/QST) approach, which is also known as Synchronous Transit Quasi-Newton (STQN), to guide the search along the reaction pathway between specified reactant and product geometries [2]. This latter approach is clearly superior and has now been extended for use in QSite.

Through the Maestro GUI, you can enter one of the following:

1. Initial guess for the TS (a simple TS search is then used)
2. Reactant, product, and TS guess (QST is used, with the entered guess used as the initial TS geometry)
3. Reactant and product geometries (LST is used, but an initial TS geometry is generated automatically)

For case 3, the automatic generation is done by interpolating between the reactant and product structures for only the atoms seen by the QM program, Jaguar (these atoms include those in the QM region plus a small number of MM atoms located at the QM/MM interface). This procedure includes a least-squares fit of the interfacial MM atoms in the interpolated geometry to the respective atoms in each of the reactant and product geometries. The interpolated TS QM region plus interfacial MM atoms are then inserted into the pure MM structure of the best-fitting case (reactant or product) using the transformation found from the least-squares fitting.

The LST/QST guided search (for cases 2 or 3) then proceeds as it does for Jaguar by first restricting the optimizer to search along the circular curve connecting the reactant, TS, and product structures. Again, only the QM plus interfacial MM atoms seen explicitly by Jaguar are used. The pure MM atoms are adiabatically minimized at each step. Once the optimizer approaches (or finds) a maximum-energy TS structure along this reactant-product curve, the TS search proceeds along the Hessian eigenvector that is most similar to the tangent to the circular curve. This process continues until a saddle point with one negative eigenvalue (corresponding to an imaginary frequency) is found.

In contrast, a simple transition state search (case 1) just involves the attempt by the optimizer to maximize the energy along the lowest-frequency eigenvector of the Hessian and to minimize along all other modes. Again, only the QM and interfacial MM atoms are included in the determination of the Hessian, as all pure MM atoms are adiabatically minimized at each TS search step.

6.3 How QSite Works

Most approaches for developing robust and accurate QM/MM methods have been based on "link atom" approaches, in which QM and MM fragments are capped by hydrogens. These methods face nontrivial problems in constructing an accurate description of the QM/MM interface, particularly for polar systems, where the treatment of electrostatic interactions can be highly problematic. While progress has been made, we do not believe that a fully satisfactory link-atom methodology is available. QSite takes an alternative approach in which frozen localized molecular orbitals are used to build the QM/MM interface. This methodology has recently been reviewed favorably [3]. As far as we are aware, QSite is the first ab initio frozen-orbital methodology with analytical gradients for which accuracy for structures and conformational energetics of a polar system has been demonstrated.

The details of QSite's frozen-orbital interface technology is provided in References 4-6 at the end of this chapter. The key aspects are:

- The frozen orbital itself is obtained by Boys localization of the quantum chemical wavefunction for one of a series of small template molecules. The orbital must be translated and rotated as the molecular geometry changes, and its interaction with both the QM and MM regions must be properly represented. The charge distribution must be empirically corrected to reproduce the fully quantum chemical result. QSite does this by placing a charge in the middle of the frozen bond. QSite not only includes appropriate energy expressions for this representation but also the analytical gradients that are critical to applications that involve geometry optimization.
- The QM and MM regions interact via two mechanisms: Coulomb interaction between MM charges and the QM wavefunction, and van der Waals interaction between QM and MM atoms (both of which employ van der Waals parameters).
- Specialized correction terms are used for stretches, bends, and torsions involving the atoms directly associated with the frozen-orbital interface. These terms are fit to reproduce quantum-chemical conformational energies of the template molecules. Again, QSite has gradients for all of these terms as well as energy expressions.

The torsional correction parameters were determined from a library of high-quality QM calculations on rotamer states for dipeptides. Beginning with roughly 300 geometries obtained via

conformational search using OPLS-AA, the structures were optimized at the HF/6-31G** level and single point LMP2/cc-pVTZ (-f) relative energies were computed. Finally, one-dimensional torsional profiles were generated at the same level of theory for all minima and relevant torsional degrees of freedom (~2000 QM data points in all). Alanine tetrapeptide conformations, generated via the same protocol, were used to test transferability. In addition, a database consisting of hydrogen-bonded pairs of small-molecule side-chain analogues was constructed. About 200 such pairs were used to determine van der Waals radii for QM atoms that yield accurate hydrogen bonding energetics between QM and MM donors and acceptors. These data sets are considerably more extensive, and of higher quality, than any that have been used previously in developing or testing QM/MM models of peptides and proteins.

Both DFT and Hartree-Fock parameter sets have been developed. The LMP2 version of the theory has been implemented for use in "single-point" calculations. It has not yet been fully parameterized, but can be used to compare structures and energies when there is little change in the protein geometry in the vicinity of the frozen orbital interfaces. Details of the parameter optimization methodology are provided in the previously cited references.

QSite makes use of a tight coupling between Jaguar and Impact. Key features of the implementation are as follows:

- QSite adiabatically minimizes the MM region after each QM geometry step. Without this, the number of QM steps would become prohibitively large and would place the calculations out of range for all but the most powerful supercomputers.
- QSite can run the rate-limiting QM part of the code on parallel processors so that reasonable throughput can be achieved for the relatively large (100–200 atom) QM regions that can be necessary to reliably model active-site reactive chemistry.
- QSite incorporates a Poisson-Boltzmann continuum-dielectric treatment of aqueous solvation. This treatment is capable of handling the QM and MM regions simultaneously and includes an analytic gradient, so that geometry optimization in solution can be performed. Inclusion of solvation will be critical in some (but not all) applications, an obvious case being calculation of pK_a values of ionizable protein side chains or of ligand groups that interact with the protein.

Maestro makes it easy to set up a QSite calculation. For example, its QSite interface can be used to readily identify the QM residues of the protein via mouse clicks, and to specify whether the QM/MM "cut" is to be placed in the backbone or side chain. The 6-31G* basis set is used in the interface region, but other basis sets can be used elsewhere. For example, the geometry can be optimized with the 6-31G* basis set, and a large, high quality basis set can then be used in a reactive region to determine accurate single-point energies. We have used this strategy very successfully in our QM-based modeling of the protein methane monooxygenase [7] and expect it to work for a wide range of active-site modeling applications.

6.4 Parametrization Validation

6.4.1 Deprotonation Energies

Chemical reaction energetics provide one important measure of how well a QM/MM model reproduces accurate quantum mechanics. Below we examine a simple reaction—removal of a proton from the QM region. Table 6.1 compares differences between the QM and QM/MM deprotonation energies for the capped peptides we have examined and lists the distance between the proton to be removed and the frozen interface orbital. When this distance is greater than ~5 Å (a distance that one would want to maintain between a reactive chemical event and the QM/MM interface in any event) the error is less than 0.4 kcal/mole. This error is negligible when compared to total reaction energies of hundreds of kcal/mole and is small even in comparison to the intrinsic error HF or DFT calculations make relative to experiment. (DFT does quite well with a large basis set, but still makes errors on the order of 1–2 kcal/mole for small-molecule deprotonation energies). When the reactive event is very close to the frozen bond, the errors can be somewhat larger but are still very reasonable.

Table 6.1. B3-LYP/6-31G QM/MM absolute deprotonation energy differences relative to fully QM B3-LYP/6-31G* values. (*) denotes the deprotonated QM leucine residue (H of Cδ). The line through the capitalized residue denotes the QM/MM boundary. This residue is mostly in the QM region and the cut is made between N and Cα.*

Peptide MM Region	Peptide QM Region	Frozen orb.-H dist. (Å)	Error (kcal/ mole)
ace - ala - **L**	**EU*** - nma H1	4.1	0.70
ace - ala - **L**	**EU*** - nma H2	4.3	0.52
ace - ala - **L**	**EU*** - nma H3	4.3	0.53
ace - ala - **A**	**LA** - leu* - nma H1	5.2	0.40
ace - ala - **A**	**LA** - leu* - nma H2	5.5	0.34
ace - ala - **A**	**LA** - leu* - nma H3	6.3	0.29
ace - ala - **A**	**LA** - ala - leu* - nma H1	8.7	0.20
ace - ala - **A**	**LA** - ala - leu* - nma H2	9.7	0.15
ace - ala - **A**	**LA** - ala - leu* - nma H3	8.2	0.23
ace - ala - ala - ala - ala -ala - **L**	**EU*** -ala - nma H1	4.1	1.21
ace - ala - ala - ala - ala -ala - **L**	**EU*** -ala - nma H2	4.3	0.93
ace - ala - ala - ala - ala -ala - **L**	**EU*** -ala - nma H3	4.3	0.82

6.4.2 Conformational Energies

Conformational energies afford a second critical test of the quality of the QM/MM methodology. Table 6.2 summarizes the RMS deviations between the QM/MM or MM (OPLS-AA) and the purely QM results for the relative energetics of the side-chain rotamer data set used to parameterize QSite. The QM/MM results generally are at least as good as those from the OPLS-AA force field, and in many cases are much better. The QM/MM rotamer structures also display good fidelity to the QM structures.

6.4.3 Other Comparisons

QSite has also been shown to accurately reproduce patterns in quantum-mechanical hydrogen-bond dimerization energies and to reproduce LMP2/cc-pVTZ(-f) relative conformational energies for the alanine dipeptide more accurately than does a molecular force field such as OPLS-AA (see Ref. 6).

Table 6.2. RMS deviations (kcal/mole) of rotamer side chain conformational energies for HF/6-31G QM-MM, B3LYP/6-31G* QM-MM and OPLS-AA relative to cc-pVTZ(-f) LMP2*

Residue	QM-MM (QM=HF)	QM-MM (QM=DFT)	OPLS-AA
Phe	0.18	0.14	0.18
His	1.14	1.10	1.05
Asn	0.38	1.36	2.29
Val	0.21	0.41	0.62
Trp	0.71	0.25	0.75
Tyr	0.37	0.29	0.40
Leu	0.77	0.90	0.40
Met	1.10	1.21	1.82
Gln	1.48	1.03	2.70
Glu	2.61	2.69	3.34
Cys	0.61	0.62	3.52
Lys	1.44	1.29	4.22
Ile	1.03	0.56	1.19
Asp	1.11	1.91	2.51
Arg	1.67	3.50	2.90

6.5 An Illustrative Application

Cytochrome P-450 is an enzyme whose variants are ubiquitously distributed across a wide variety of organisms. A human version of the enzyme in the liver is of great importance pharmaceutically because it is involved in a significant fraction of toxicity and drug metabolic pathways. While a high-resolution structure of a form of the human enzyme relevant to questions of toxicology and metabolism does not yet exist, such structures are likely to be produced in the next few years (either experimentally or via homology modeling). This will open the possibility of computer modeling of these critical processes.

It is very difficult to study the chemistry of ligand binding of cytochrome P450 with conventional molecular-modeling techniques. The existence of a reactive metal center, and the centrality of the reactive chemistry in the interaction of the enzyme with various drug candidates, mandate a quantum-chemical treatment of the active site. On the other hand, the protein structure is clearly important in selectivity, binding affinity, and reaction kinetics, and cannot be incorporated to any great degree with conventional quantum-chemical techniques. QSite is well suited to addressing this problem with relatively modest computational resources. Its application to a problem in cytochrome P450 chemistry [6] is recounted below.

1. Structure and QM Region

   The particular systems studied are available as entries 1phf and 1akd in the PDB archives. The former has a coordinating phenylimidazole ligand, while the latter is the so-called substrate-free state with a non-coordinating camphor ligand located near the heme.

2. P-450 and Phenylimidazole Ligand

   The 1phf structure has a 4-phenylimidazole complexed with Fe. On the opposite side of the heme, Fe is coordinated to a cysteinate sulfur ($R\text{-}S^-$). Thus, the Fe is in a six-fold coordination site and is assumed to be Fe^{3+}, given the S^- formal charge and the two negative charges distributed over the four coordinating nitrogens in the heme ring system. The net spin state is either a doublet, with the Fe-S moiety low-spin coupled as in the coordinated dioxygen state of P-450, or a high-spin quartet. There are 7075 atoms in the system.

   The QM region is the full heme ring, the Fe, the full coordinating cysteine residue including residues on either side of the cysteine, and the 4-phenylimidazole. The two QM-MM cuts were made in the residues adjacent to the coordinating cysteine. The net charge of the QM region is –2 from the two carboxylate groups on the heme. There are 125 total quantum atoms and 1138 6-31G* basis functions. The QM method used was B3LYP DFT. The outer shell of the protein was frozen during the optimization, leaving 3960 of the 7075 atoms free to optimize. This procedure is commonly used to avoid irrelevant energy differences caused by re-arrangements of the outer parts of the protein.

3. P-450 and Camphor

   The specification of this system (1akd) is identical to that above, but with a quantum camphor molecule replacing the phenylimidazole ligand. The camphor is not directly bound to the Fe but, like the phenylimidazole ligand, has forced water out of the heme-binding region. The main purpose of running this system was to find the lowest spin state of the substrate-free P-450.

4. Preliminary results

   The P-450 optimization was run on 6 SGI-R10000 nodes in about a 1 week of wall-clock time. The calculation took ~30 QM-MM geometry-optimization cycles. Approximately 10 hours was spent on the initial MM minimization in which the QM region is frozen. The final geometry has an RMS deviation of 0.6 Å with respect to the non-hydrogen atoms of the crystal structure, a reasonable level of accuracy. In a general study of a system like this, the initial cost of this minimization would be amortized over similar runs in which the QM region would be perturbed (by changing the ligand, for example) since these subsequent runs would have a good initial geometry.

   As an initial calibration of the energetics we optimized the doublet and quartet spin states of the system. The doublet was found to be 14 kcal/mol lower in energy. This is in accord with qualitative EPR data [8] that indicates that Fe is in a low-spin state when a six-fold Fe^{3+} coordination site involves dative bonding to the ligand. The substrate-free system with the camphor above the heme ring was found after full QM-MM optimization to have a high-spin quartet ground state with the doublet 15 kcal/mol higher in energy. This ordering of spin states is also in agreement the experimental ordering [9].

6.6 References

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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/, In particular, you can use the Knowledge Base, http://www.schrodinger.com/kb, to find current information on a range of topics, and the Known Issues page, http://www.schrodinger.com/knownissues, to find information on software issues.

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 the lower right corner of 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 the Help panel. The button may have text or an icon:

  

- Choose Help → Online Help or press CTRL+H (⌘H) to open the default help topic.
- When help is displayed in the Help panel, use the navigation links in the help topic or search the help.
- Choose Help → Documentation Index, to open a page that has links to all the 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*.
- New software features: choose Help → New Features.
- 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.

Web:	http://www.schrodinger.com/supportcenter
E-mail:	help@schrodinger.com
Mail:	Schrödinger, 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone:	+1 888 891-4701 (USA, 8am – 8pm Eastern Time)
	+49 621 438-55173 (Europe, 9am – 5pm Central European Time)
Fax:	+1 503 299-4532 (USA, Portland office)
FTP:	ftp://ftp.schrodinger.com

Generally, using the web form is best because you can add machine output and upload files, if necessary. You will need to include the following information:

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

Gathering Information for Technical Support

The instructions below describe how to gather the required machine, licensing, and installation information, and any other job-related or failure-related information, to send to technical support. Where the instructions depend on the profile used for Maestro, the profile is indicated.

For general enquiries or problems:

1. Open the Diagnostics panel.
   - **Maestro:** Help → Diagnostics
   - **Windows:** Start → All Programs → Schrodinger-2015-2 → Diagnostics
   - **Mac:** Applications → Schrodinger2015-2 → 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. Upload the file specified in the dialog box to the support web form.

   If you have already submitted a support request, use the upload link in the email response from Schrödinger to upload the file. If you need to submit a new request, you can upload the file when you fill in the form.

If your job failed:

1. Open the Monitor panel, using the instructions for your profile as given below:
   - **Maestro/Jaguar/Elements:** Tasks → Monitor Jobs
   - **BioLuminate/MaterialsScience:** Tasks → Job Monitor
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, and an information dialog box with the name and location of the file opens. You can highlight and copy the name of the file.
5. Upload the file specified in the dialog box to the support web form.

   If you have already submitted a support request, use the upload link in the email response from Schrödinger to upload the file. If you need to submit a new request, you can upload the file when you fill in the form.

6. Copy and paste any log messages from the window used to start the interface or the job into the web form (or an e-mail 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-2015-2 → Diagnostics
   - **Mac:** Applications → SchrodingerSuite2015-2 → 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. Upload the file specified in the dialog box to the support web form.

   If you have already submitted a support request, use the upload link in the email response from Schrödinger to upload the file. If you need to submit a new request, you can upload the file when you fill in the form.
4. Upload the error files to the support web form.

   The files should be in the following location:

- **Windows:** `%LOCALAPPDATA%\Schrodinger\appcrash`
  (Choose Start → Run and paste this location into the Open text box.)
  Attach `maestro_error_`*`pid`*`.txt` and `maestro.exe_`*`pid_timestamp`*`.dmp`.
- **Mac:** `$HOME/Library/Logs/CrashReporter`
  (Go → Home → Library → Logs → CrashReporter)
  Attach `maestro_error_`*`pid`*`.txt` and `maestro_`*`timestamp_machinename`*`.crash`.
- **Linux:** `$HOME/.schrodinger/appcrash`
  Attach `maestro_error_`*`pid`*`.txt` and `crash_report_`*`timestamp_pid`*`.txt`.

If a Maestro panel failed to open:

1. Copy the text in the dialog box that opens.
2. Paste the text into the support web form.

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