

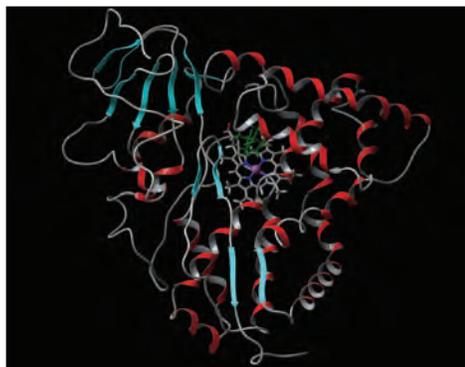
# QSite

A high-performance QM/MM program

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QSite applies quantum mechanics to the reactive center of a protein active site and molecular mechanics to the rest of the system. Its accuracy allows detailed understanding of reactions involving proteins, making it a powerful tool for lead optimization.

## The Advantages of QM/MM methods



Cytochrome P450cam (P450cam), taken from *Pseudomonas putida*, has long provided a paradigm for structural understanding of cytochrome P450s, a ubiquitous protein family with functions including the synthesis and degradation of physiologically important compounds, e.g. steroids and prostaglandins, and of many xenobiotics, e.g. drugs and procarcinogens.

The heme molecule is represented here by multi-colored tubes near the center of P450cam. The iron atom at the center of the heme is shown as a sphere, while the camphor molecule nearby is shown in green tubes.

Insight into reactive chemistry is crucial to understanding the mechanism of drug receptor interactions in systems where the ligand is covalently bound to the receptor. For example, it's necessary to study the transition states between bound and unbound forms in order to design antibiotics that are not subject to inactivation by beta lactamases. Classical molecular mechanics (MM) methods cannot describe the electronic changes during a reaction, and are ill-equipped to address ligand-receptor interactions in systems containing metals.

Ab initio quantum mechanics (QM) is required to study reactive chemistry or interactions involving transition metals in a protein environment. However, even with today's computer technology, full QM calculations of entire proteins are still intractable.

Mixed QM/MM calculations provide the ideal solution by separating out the reactive core, which can be accurately described with QM, while treating the remainder of the complex more efficiently with MM. While QM/MM may not be needed for every structure-based drug design project, many important systems cannot be effectively addressed by any other computational means. QM/MM is therefore a key component in the arsenal of computational drug discovery.

## QSite: Maximizing Performance for Pharmaceutical Research

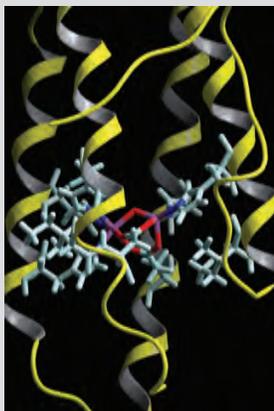
QSite enjoys several advantages over other QM/MM programs:

- **High performance:** QSite outperforms other QM/MM programs because it takes advantage of Jaguar, long recognized as the industry leader in QM calculations
- **Advanced technology:** QSite's innovative approach to the QM/MM interface specifically addresses protein systems and interactions between QM and MM regions. QSite also models crucial solvation effects.
- **Transition metal convergence:** QSite achieves unparalleled accuracy in metalloproteins thanks to Jaguar's advanced capabilities; it reliably and efficiently converges to the correct ground state of transition metal containing systems.
- **Wave function choices:** QSite offers different levels of theory to evaluate the QM region: Hartree Fock, DFT, and local MP2. This allows the user to choose the best balance between computational cost and accuracy.
- **Easy-to-use interface:** The Maestro interface makes it easy to set up calculations. Users can specify QM and MM regions through simple point-and-click operations.

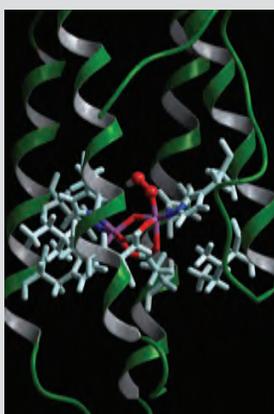
## Performance-Driven Technology

QSite delivers its benefits through a number of technological innovations:

- **Treatment of QM region:** Top-performing Jaguar is QSite's QM engine. Its advanced transition metal initial guess wave function algorithm makes QSite uniquely suited for studying metal-containing protein systems. The unrestricted spin formalism can be used for modeling open-shell systems. Transition state searches can be carried out using several search algorithms.
- **Treatment of MM region:** QSite uses the OPLS-AA force field for the MM calculations. A continuum dielectric model of aqueous solvation that treats the QM and MM regions simultaneously simulates important solvent effects.
- **Treatment of QM/MM interface:** For proteins, QSite employs frozen orbitals and specialized correction parameters to ensure a smooth transition between the QM and MM regions. Interactions between regions are fully accounted for via Coulomb and van der Waals energy terms. Proteins, DNA, RNA, and other polymeric systems can be modeled using QSite's hydrogen-capping method.
- **Reduced computational cost:** During geometry optimization, the structure of the MM region is adiabatically optimized after each QM step to further speed computations.
- **Advanced calculation setup and analysis:** QSite automatically applies special interface parameters, making it simple to set up calculations. Computed results, such as molecular orbitals and electron densities, can be visualized within Maestro.



Above and below are the deoxy and oxy forms of Hemerythrin, respectively. The active sites are shown in tubes while the protein backbone is represented by ribbons. The oxy form below also exhibits the dioxygen that binds reversibly to Hemerythrin as spheres bonded to the iron atom on the right.



The QSite-predicted *in vivo* free energy of binding of -5.2 kcal/mol is in remarkably good agreement with the experimental value of -7.3 kcal/mol, derived from the equilibrium constant of  $(2.5 \pm 0.5) \times 10^5 \text{ M}^{-1}$  obtained from stopped-flow experiments carried out in solution.

## Reactive Chemistry in Proteins

Hemerythrin (Hr) proteins function as dioxygen carriers in many marine species. The task of binding  $\text{O}_2$  reversibly requires that the free energies of the oxy and deoxy forms of Hr be within a few kcal/mol of each other at room temperature. Examining this reaction therefore requires extremely precise energy calculations.

QSite has been successfully applied in a study of reversible dioxygen binding to Hemerythrin. Its quantitative account of the electrostatic stabilization of the oxy form greatly improved agreement with the experimental data. Moreover, QSite directly computed the nonpolar component of the interaction without requiring any data-fitting or estimation. QSite provided accurate energetic contributions from both metal coordination and protein environment.

## Evaluation Copies

To request an evaluation copy of QSite, please contact [info@schrodinger.com](mailto:info@schrodinger.com). Our staff of support scientists will be happy to assist you in giving QSite a thorough trial.

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### A Coordinated Family of Products

Schrödinger offers a coordinated family of drug discovery solutions. QSite is part of Schrödinger's structure-based analyses, which contain four integrated modules:

- **Glide:** High-throughput ligand-receptor docking for fast library screening
- **Liaison:** Ligand-receptor binding free energies for lead optimization
- **QSite:** Mixed QM/MM for reactive chemistry at the enzyme active site
- **Strike:** Statistical modeling and QSAR for developing structure-activity relationships

Glide can be employed during lead discovery to dock candidate compounds, followed by Liaison or QSite to obtain more accurate structures and/or binding affinities during lead optimization.

Additionally, **MacroModel** can be instrumental in preparing both ligand and protein structures, and **QikProp** can predict accurate ADME properties for all lead compounds.

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

### Additional Information:

[www.schrodinger.com](http://www.schrodinger.com)

[info@schrodinger.com](mailto:info@schrodinger.com)

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120 West 45th Street  
29th Floor  
New York, NY 10036

101 SW Main Street  
Suite 1300  
Portland, OR 97204

3655 Nobel Drive  
Suite 430  
San Diego, CA 92122

Dynamostraße 13  
68165 Mannheim  
Germany

Quatro House, Frimley Road  
Camberley GU16 7ER  
United Kingdom

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