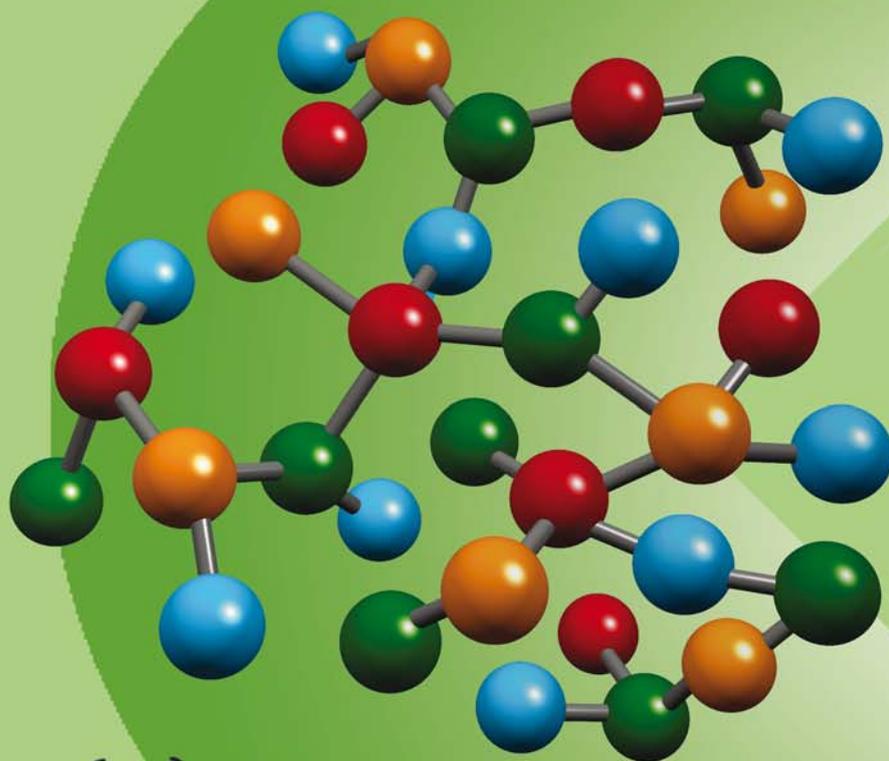


1.0

USER MANUAL



CADDLE[®]

Impressum

Copyright

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The Old Vicarage
132 Bedford Road
Kempston
BEDFORD, MK42 8BQ
United Kingdom

www.ceposinsilico.com

Manual

David Whitley, Timothy Clark

Layout

www.eh-bitartist.de





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1 INTRODUCTION

CADDLE.® is a new molecular modeling suite that runs entirely on a remote or local web server and that requires no software installation at all on the user's desktop. All that is required is a suitable browser (please see this [web page](#) for a list of supported browsers). This innovative architecture allows schools, colleges, university department or companies to install CADDLE.® on a single central server in order to make it available to all users. This flexibility does not come at the cost, for instance, of reduced graphics quality. The molecular visualization offered in CADDLE.® was developed by Cepas InSilico's partner **Molcad GmbH** and offers the state-of-the-art visualization that Molcad users expect. CADDLE.® is conceived to link with a number of modeling programs, the first of which is Cepas InSilico's **EMPIRE™**, a modern, parallel semiempirical molecular orbital (MO) program.

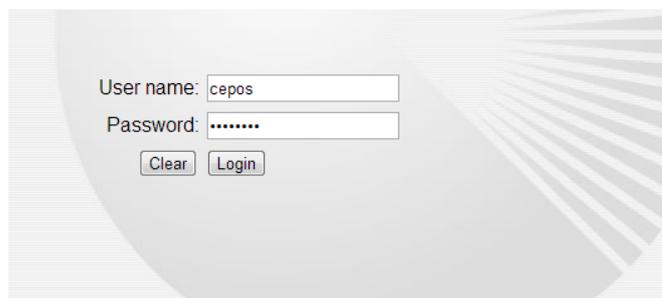


2 THE PRINCIPLES BEHIND CADDLE.®

The CADDLE.® workflow is based on a series of *projects*, each of which contains one or more molecules and a set of calculations performed on those molecules. Initially, *projects* are assigned to the user who created them but can later be shared with other users. Molecules can be added to *projects* or new *projects* created and earlier calculations on a given project can be retrieved for further analysis (including visualization of molecular properties or orbitals). *Projects* are administered using the *Projects* tab on any of the CADDLE.® pages. Calculations are performed by selecting a compute engine (for instance *EMPIRE*) from the main menu and the results are then visualized in the browser directly. No dedicated visualization program is required. Both the molecular and the visualization calculations are performed on the web server (which may be a central high-performance server or the local desktop machine) so that the calculations can be scheduled optimally by CADDLE.®. Visualization is achieved by calculating three-dimensional WebGL scenes that can be manipulated (rotated, translated, zoomed) using a suitable web browser. Not all web browsers are equally suitable and we recommend that you test your combination of machine and browser (click here for the [test web page](#)). CADDLE.® includes a user-management facility; the CADDLE.® administrator can add or delete CADDLE.® users, change passwords *etc.*

3 GETTING STARTED

If your system manager has set up CADDLE.® to require user names and passwords, your first view of CADDLE.® when you access the URL provided by your system administrator will be the login page shown in **Figure 1**, which is self-explanatory.

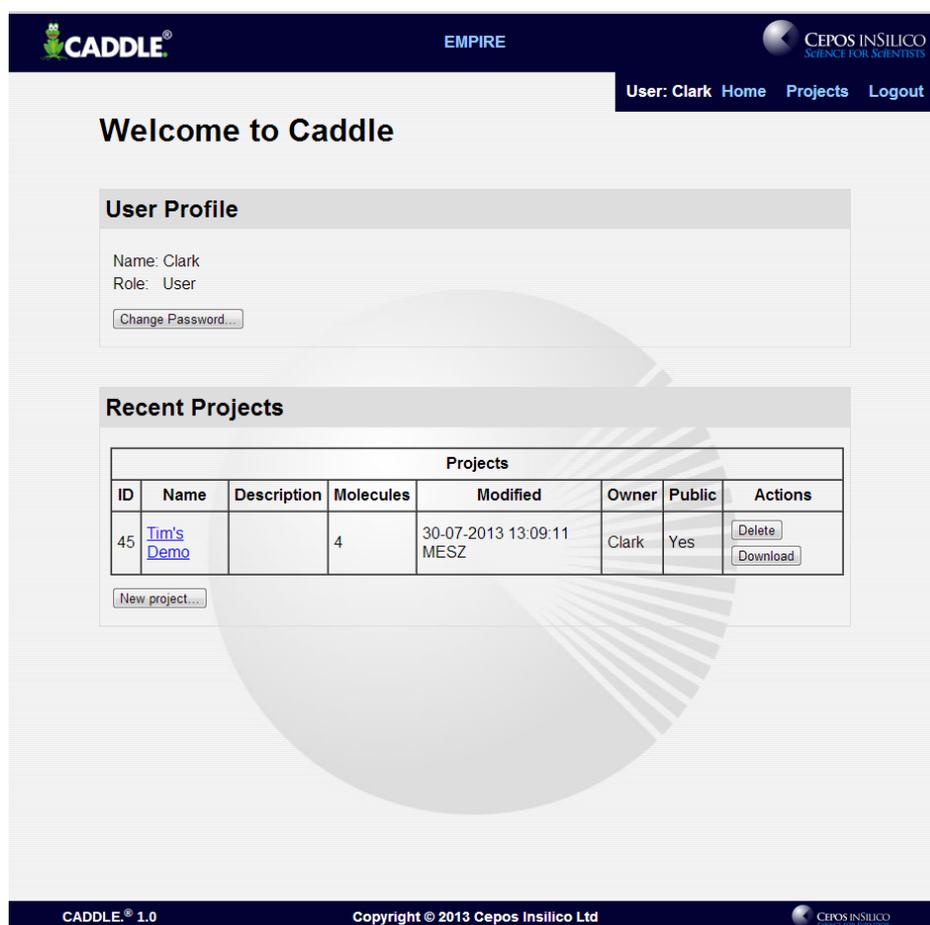


User name:

Password:

Figure 1 An excerpt from the CADDLE.® login page

Once you have logged into the system, CADDLE.® displays your personal **Home** page, which contains some user details, a link to change your CADDLE.® password and a list of recent **projects** (see **Figure 2**). The personal menu bar at the top right of the page provides links to view all available **projects**, to access the online help and to logout from CADDLE.®.



CEPOS INSILICO
SCIENCE FOR SCIENTISTS

EMPIRE

User: Clark Home Projects Logout

Welcome to Caddle

User Profile

Name: Clark
Role: User

Recent Projects

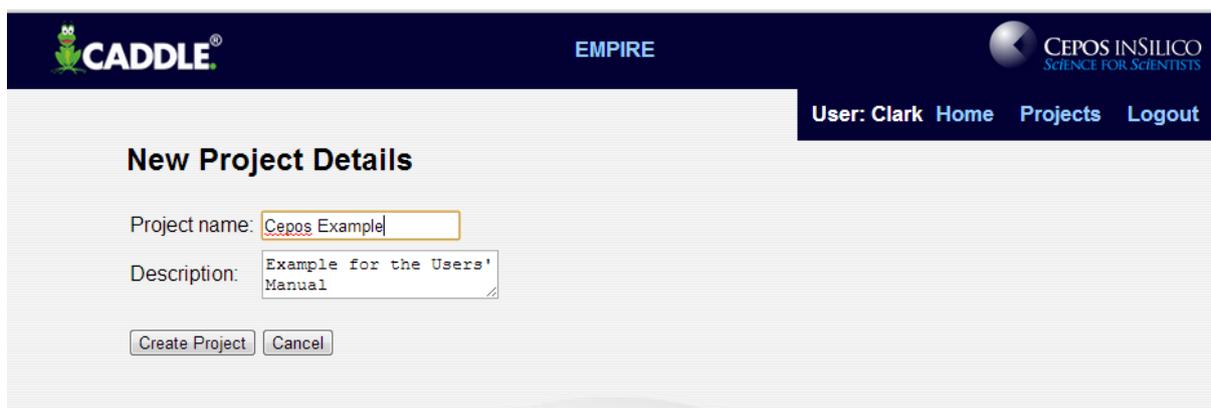
Projects							
ID	Name	Description	Molecules	Modified	Owner	Public	Actions
45	Tim's Demo		4	30-07-2013 13:09:11 MESZ	Clark	Yes	<input type="button" value="Delete"/> <input type="button" value="Download"/>

CADDLE.® 1.0 Copyright © 2013 Cepos Insilico Ltd

Figure 2 The CADDLE.® home page

3.1 Creating a new project

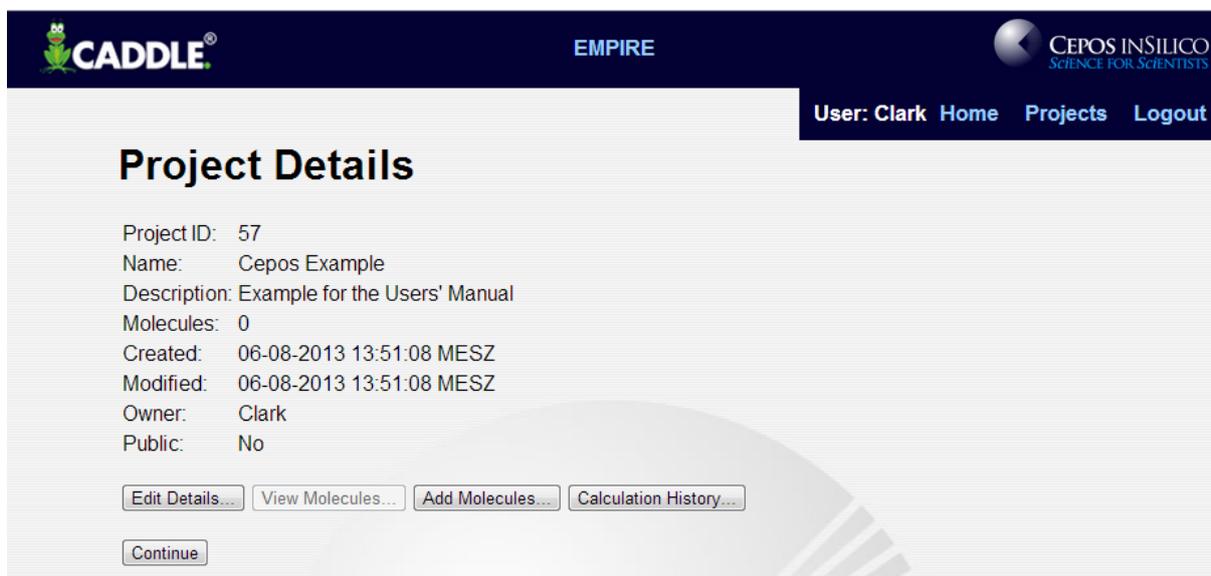
To create a project, select the **New Project** button below the list of recent **projects** on the **Home** page (see **Figure 2**). As explained in the introduction, a project may be either a list of compounds that will all be treated in the same way or it may also be a single molecule. Enter the details of the new project (a name and an optional brief description) in the appropriate boxes, as shown in **Figure 3**, then click the **Create Project** button to add the project to CADDLE.®.



The screenshot shows the 'New Project Details' form in the CADDLE.® interface. The header includes the CADDLE.® logo, 'EMPIRE', and 'CEPOS INSILICO SCIENCE FOR SCIENTISTS'. A user navigation bar shows 'User: Clark Home Projects Logout'. The form contains two input fields: 'Project name' with the value 'Cepos Example' and 'Description' with the value 'Example for the Users' Manual'. Below the fields are 'Create Project' and 'Cancel' buttons.

Figure 3 Creating a new CADDLE.® project

A **Project Details** page is then displayed (see **Figure 4**). Select the **Add Molecules** button to access the molecule input page, which provides three ways to add molecules to the project (see **Figure 5**.)



The screenshot shows the 'Project Details' page for the 'Cepos Example' project. The header is identical to Figure 3. The main content area displays the following project information: Project ID: 57, Name: Cepos Example, Description: Example for the Users' Manual, Molecules: 0, Created: 06-08-2013 13:51:08 MESZ, Modified: 06-08-2013 13:51:08 MESZ, Owner: Clark, and Public: No. At the bottom, there are buttons for 'Edit Details...', 'View Molecules...', 'Add Molecules...', 'Calculation History...', and 'Continue'.

Figure 4 A CADDLE.® project details page

CADDLE.® EMPIRE CEPOS INSILICO
SCIENCE FOR SCIENTISTS

User: Clark Home Projects Logout

Add molecules to the project

Add molecules from a file

Upload a structure-data file (.sdf) or a list of SMILES strings with optional molecule names (.smi).

Specify data file: No file chosen

Build 3D structure:

Add hydrogens:

Add molecules as SMILES

Enter one molecule per line, with each line containing a SMILES string and an optional molecule name.

Specify molecules:

Add molecules from sketches

Figure 5 The CADDLE.® molecule input page

3.2 Reading molecules from a file

Molecules can be read as input for the project from structure-data (SDF) files or from lists of SMILES strings. SMILES input files should contain one SMILES per line, followed by an optional molecule name, and must have a **.smi** file extension. Molecules entered in SMILES format will have hydrogens added and 3D coordinates generated automatically by CADDLE.®. For molecules entered in SDF format, CADDLE.® can read two-dimensional structures and convert them to 3D automatically or it can read 3D structures produced by another program without changing them. In order to read a list of molecular structures from a file, select the **Add molecules from a file** option, choose the input file in the file browser and request the appropriate options to generate 3D coordinates or add hydrogens, as shown in **Figure 5**. CADDLE.® will load the molecules into the current project when you click the **Save Molecules to Project** button.

3.3 Defining molecules using SMILES

A single molecule or a list of molecules can also be loaded directly into CADDLE.® using SMILES notation. To do this, select the **Add molecules as SMILES** option and type (or cut-and-paste) a list of SMILES strings into the text entry area. Enter one SMILES per line, with an optional molecule name. In this case, the 3D coordinates will be generated by CADDLE.®. Once again, clicking the **Save Molecules to Project** button loads the molecule(s) into CADDLE.®.

3.4 Sketching molecules

The third method for inputting molecules into CADDLE.® is to use the built-in 2D sketcher. In order to access the sketcher, select the **Add molecules from sketches** option and click the **sketch molecule** button shown in **Figure 5**. This brings up the Sketcher window shown in **Figure 6**.

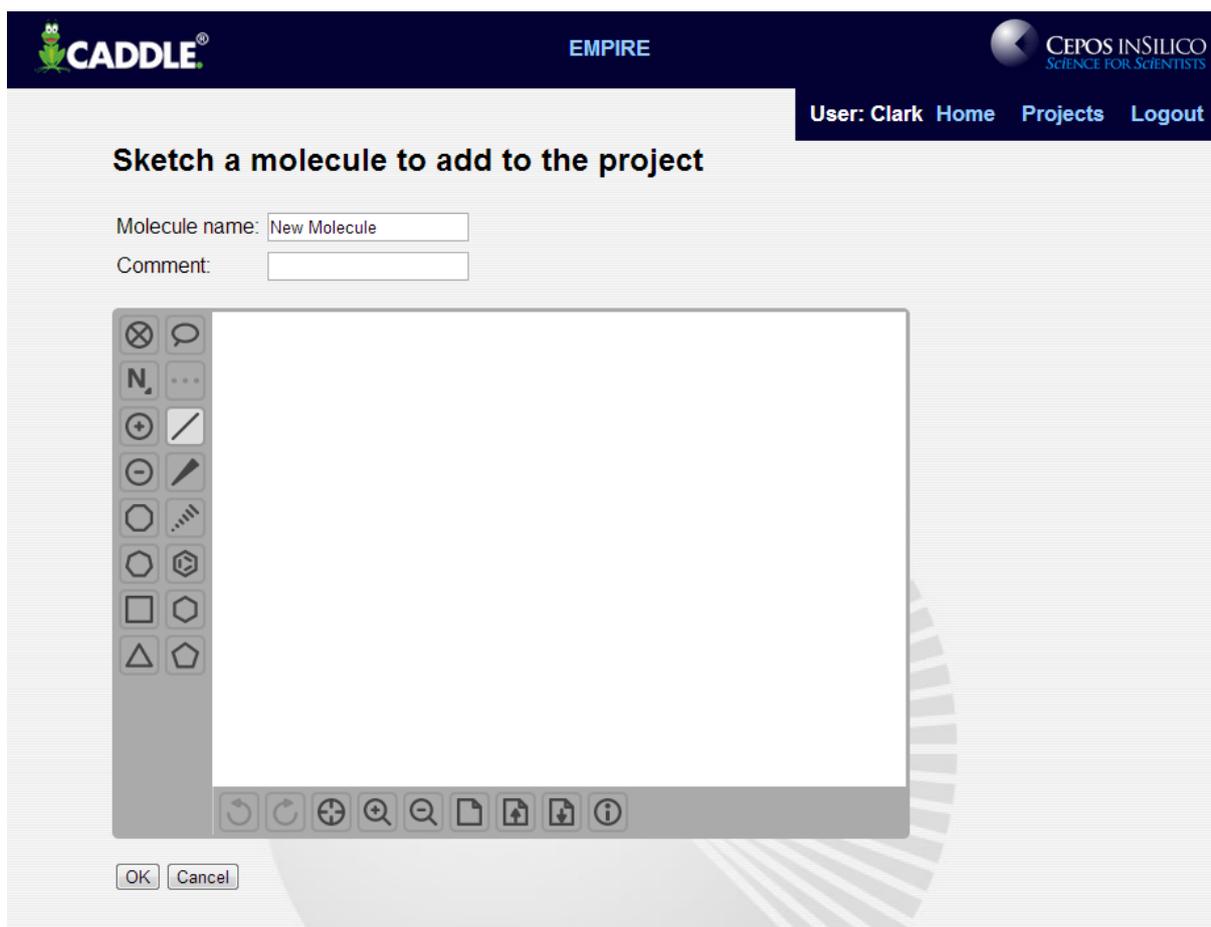


Figure 6 The CADDLE.® 2D sketcher

Using the sketcher is very intuitive. Ring systems can be added by selecting the appropriate symbol on the left hand side of the sketcher window, single bonds by selecting the bond symbol and then clicking

on the atom to which the bond is to be added and double bonds by selecting the bond symbol and clicking on an existing single bond. Further details on using the sketcher are provided in the online help.

When the molecule sketch is complete, click **OK** (Figure 7) to exit the sketcher and return to the molecule input page, where the sketched molecule is shown as a small 2D structure (see Figure 8). Further molecules can be sketched in the same way and they will be added to the list of sketched molecules. As for the other methods of adding molecules to the *project*, clicking the **Save Molecules to Project** button loads the sketched molecule(s) into CADDLE.®.

The screenshot displays the CADDLE.® 2D sketcher interface. At the top, the CADDLE.® logo is on the left, 'EMPIRE' is in the center, and the CEPOS INSILICO logo with the tagline 'SCIENCE FOR SCIENTISTS' is on the right. Below the logo is a navigation bar with 'User: Clark Home Projects Logout'. The main heading is 'Sketch a molecule to add to the project'. Below this are two input fields: 'Molecule name: Aspirin' and 'Comment:'. The central area is a sketching canvas with a toolbar on the left containing various drawing tools (lines, polygons, rings, etc.) and a bottom toolbar with navigation and editing icons. The canvas shows a 2D chemical structure of Aspirin (acetylsalicylic acid), consisting of a benzene ring with a carboxylic acid group (-COOH) and an acetoxy group (-O-C(=O)-CH₃) attached at adjacent positions. The oxygen atoms and the hydroxyl hydrogen are highlighted in red. At the bottom left of the sketcher are 'OK' and 'Cancel' buttons.

Figure 7 A molecular structure created using the CADDLE.® 2D sketcher

Add molecules to the project

Add molecules from a file

Upload a structure-data file (.sdf) or a list of SMILES strings with optional molecule names (.smi).

Specify data file: No file chosen

Build 3D structure:

Add hydrogens:

Add molecules as SMILES

Enter one molecule per line, with each line containing a SMILES string and an optional molecule name.

Specify molecules:

Add molecules from sketches

Sketched Molecules		
Name	Comment	Sketch
Aspirin		

Figure 8 The CADDLE.® molecule input page with the molecule added from the 2D sketcher

3.5 Viewing input structures

Once the molecules have been added to the project, their input structures can be viewed using the **View molecules** link on the project details page (Figure 4). The input structures are then displayed in the **Molecule Browser**, shown in Figure 9.

The screenshot shows the CADDLE molecule browser interface. At the top, there is a navigation bar with the CADDLE logo, the word 'EMPIRE', and the CEPOS INSILICO logo. Below this, a user menu shows 'User: Clark' with links for 'Home', 'Projects', and 'Logout'. The main content area is titled 'Molecule Browser' and 'Project 57: Cepas Example'. It displays 'Molecule 1 of 1' with the following properties: Name: Aspirin, Atoms: 21, Charge: 0, Electrons: 68, and Orbitals: 34 doubly occupied; 0 singly occupied. A 3D ball-and-stick model of the Aspirin molecule is shown in a central window. To the right of the model is a 'Display Style' menu with radio buttons for 'Wireframe', 'Sticks' (which is selected), 'Ball and stick', and 'Space filling', along with an 'Update' button. Below the 3D viewer are navigation buttons: 'First', 'Previous', 'Next', 'Last', and 'Continue'.

Figure 9 The CADDLE.® molecule browser

The structures of the molecules can be viewed in the interactive 3D viewer window and the structures rotated, shifted or zoomed using the mouse button combinations shown in **Table 1**.

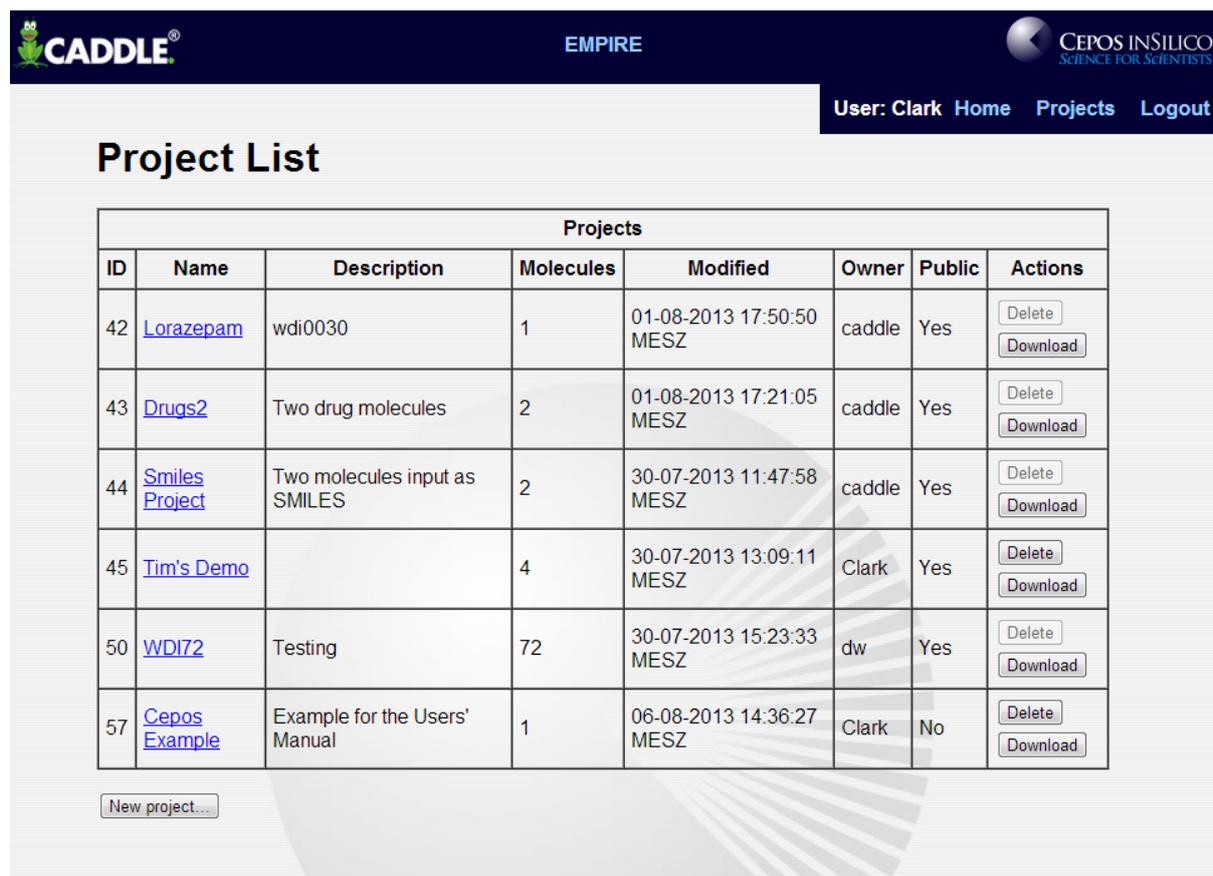
Table 1 Mouse commands for the molecule viewer in common web browsers. For an up-to-date summary of suitable browsers, see the [test web page](#)

Action	Chrome	Firefox	Internet Explorer	Safari
Rotate	Left button	Left button	Left button	Left button
Translate	Central button or <ctrl> right button	<ctrl> right button	<ctrl> right button	<ctrl> right button
Zoom	Mouse wheel or right button	Mouse wheel or right button	Mouse wheel or right button	Right button

Molecules can be displayed as wireframe, stick, ball and stick or space-filling depictions by selecting the appropriate option and then clicking **Update**.

3.6 Accessing an existing project

Existing **projects** may be accessed from the list of recent projects on the **Home** page, or by selecting the **Projects** link on your personal menu bar, which produces a list of all your projects, together with projects made publicly available by other users (see **Figure 10**). From the project list the input structures of a project's molecules may be downloaded as an SDF file and the project may be deleted by its owner.



The screenshot shows the CADDLE project browser interface. At the top, there is a navigation bar with the CADDLE logo, the word "EMPIRE", and the CEPOS INSILICO logo. Below the navigation bar, there is a user menu showing "User: Clark Home Projects Logout". The main content area is titled "Project List" and contains a table of projects. The table has columns for ID, Name, Description, Molecules, Modified, Owner, Public, and Actions. Below the table is a "New project..." button.

Projects							
ID	Name	Description	Molecules	Modified	Owner	Public	Actions
42	Lorazepam	wdi0030	1	01-08-2013 17:50:50 MESZ	caddle	Yes	<input type="button" value="Delete"/> <input type="button" value="Download"/>
43	Drugs2	Two drug molecules	2	01-08-2013 17:21:05 MESZ	caddle	Yes	<input type="button" value="Delete"/> <input type="button" value="Download"/>
44	Smiles Project	Two molecules input as SMILES	2	30-07-2013 11:47:58 MESZ	caddle	Yes	<input type="button" value="Delete"/> <input type="button" value="Download"/>
45	Tim's Demo		4	30-07-2013 13:09:11 MESZ	Clark	Yes	<input type="button" value="Delete"/> <input type="button" value="Download"/>
50	WDI72	Testing	72	30-07-2013 15:23:33 MESZ	dw	Yes	<input type="button" value="Delete"/> <input type="button" value="Download"/>
57	Cepos Example	Example for the Users' Manual	1	06-08-2013 14:36:27 MESZ	Clark	No	<input type="button" value="Delete"/> <input type="button" value="Download"/>

Figure 10 The CADDLE.® project browser

To select a project, click on its name in the project list. This will display the **Project Details** page (**Figure 4**), which allows the project owner to edit the project details, add molecules to the project, view the project molecules and access previous calculations.

3.7 Editing project details

The **Edit Details** button on the **Project Details** page produces the **Project Editor** shown in **Figure 11**. This allows the project name, description and visibility to be changed. Specifying a project to be **Public** grants read-only access to the project to all CADDLE.® users. A project that is not **Public** is visible only to the user who created it.

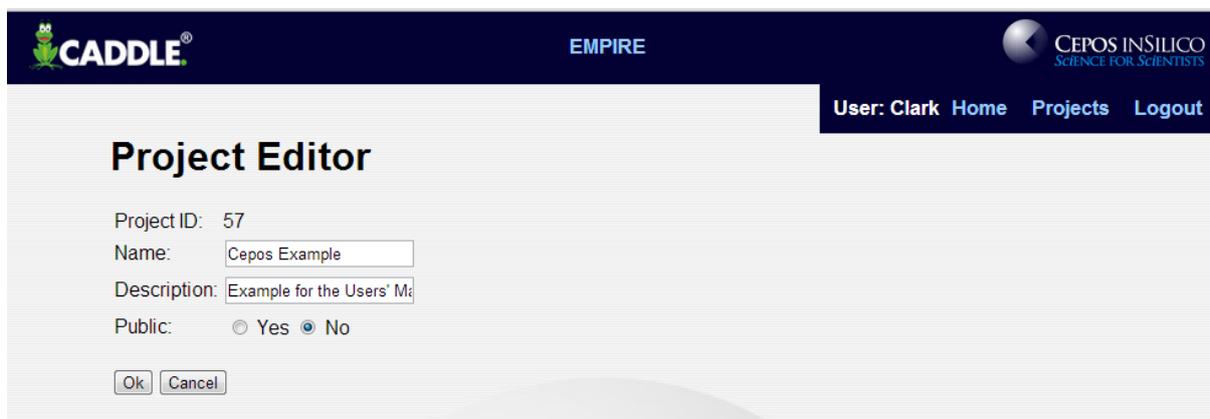


Figure 11 The CADDLE.® project editor

3.8 Viewing previous calculations

The **Calculation History** button on the **Project Details** page retrieves a list of previous calculations for the project (see **Figure 12**). To display the results of a specific calculation, click the calculation's ID in the first column of the table. The calculation list also allows the output files for a calculation to be downloaded or a calculation to be deleted.

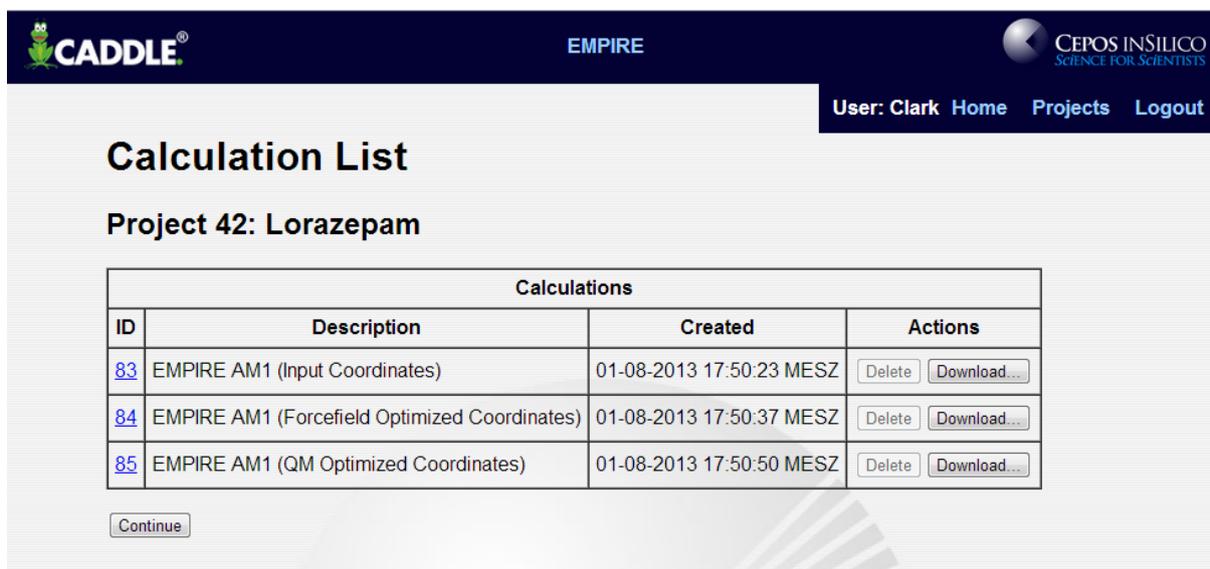


Figure 12 The CADDLE.® project calculation list

4 EMPIRE™ CALCULATIONS

EMPIRE™ is Cepas InSilico's new parallel semiempirical molecular orbital [1] program. To run a calculation, select the **EMPIRE** link in the main CADDLE.® menu to display the project selection page (**Figure 13**). Select a project for the calculation from the drop-down list and click **Next** to move to the EMPIRE control page shown in **Figure 14**.

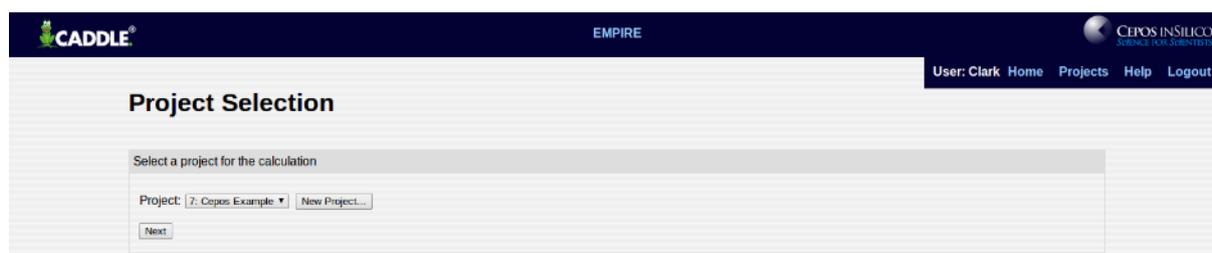


Figure 13 The project selection page

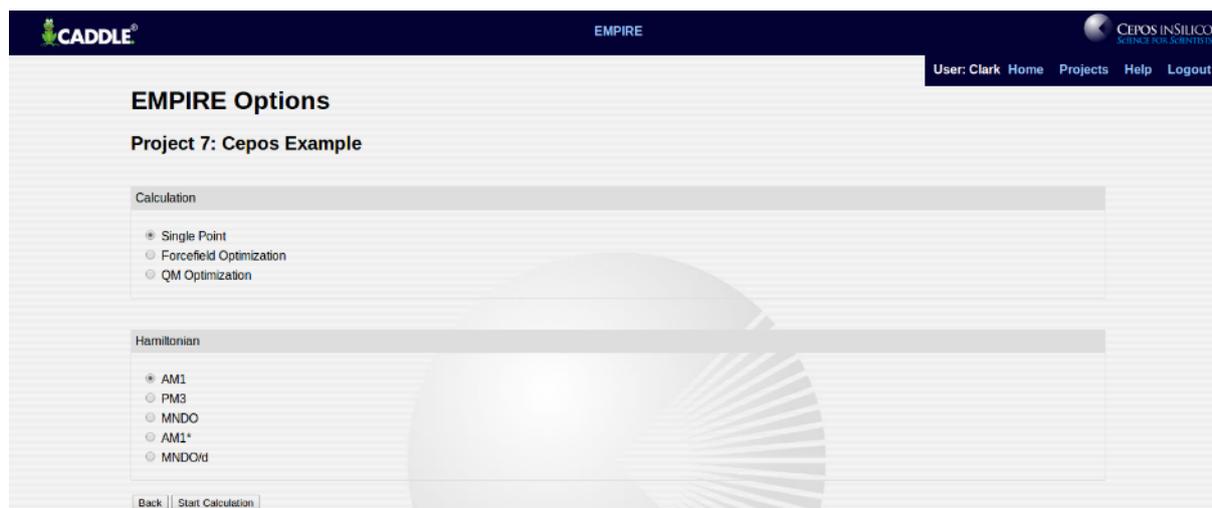


Figure 14 The EMPIRE™ control window

All molecules in the **project** are calculated in the same way, so that the **EMPIRE** options are limited to the choice of Hamiltonian (computational method) to be used (currently AM1 [2], PM3 [3], MNDO [4], AM1* [5] and MNDO/d [6]) and the geometry to be used. Calculations can be performed on the input geometry without optimization (single point), on the optimized geometry obtained using the Merck Force Field [7] or the structures can be fully optimized using the semiempirical Hamiltonian.

Clicking the **Start calculation** button sends the calculations to the server. The results will appear on the **EMPIRE Browser** page automatically as soon as the calculations are finished. Details and options for the EMPIRE™ program are available in the **EMPIRE™ Users' Manual**.

5 VISUALIZATION

High quality visualization of the results of the calculations in a web browser is a major feature of CADDLE[®]. The results from an EMPIRE[™] calculation are displayed in an **EMPIRE Browser** page, shown in **Figure 15**.

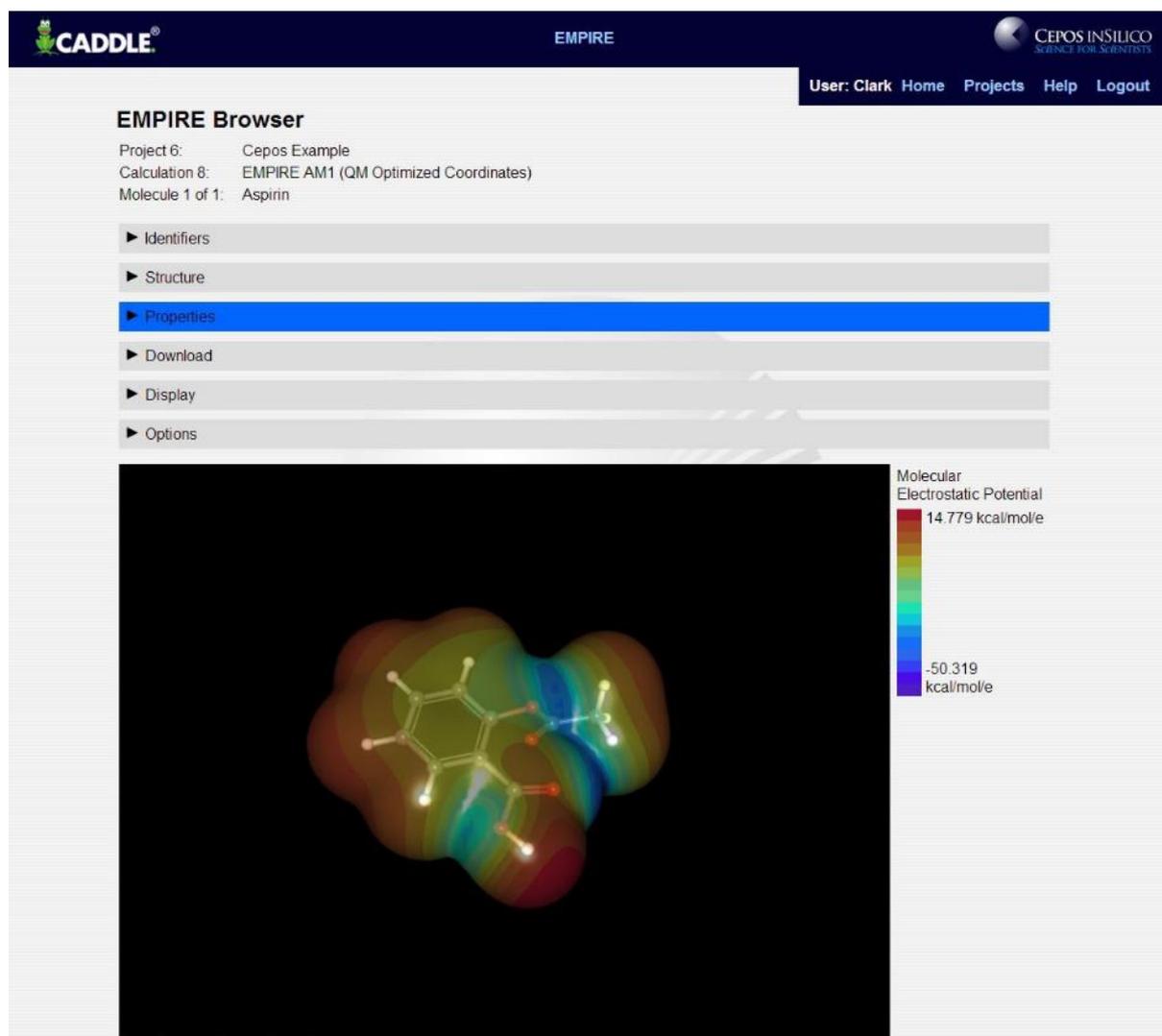


Figure 15 The EMPIRE[™] browser window

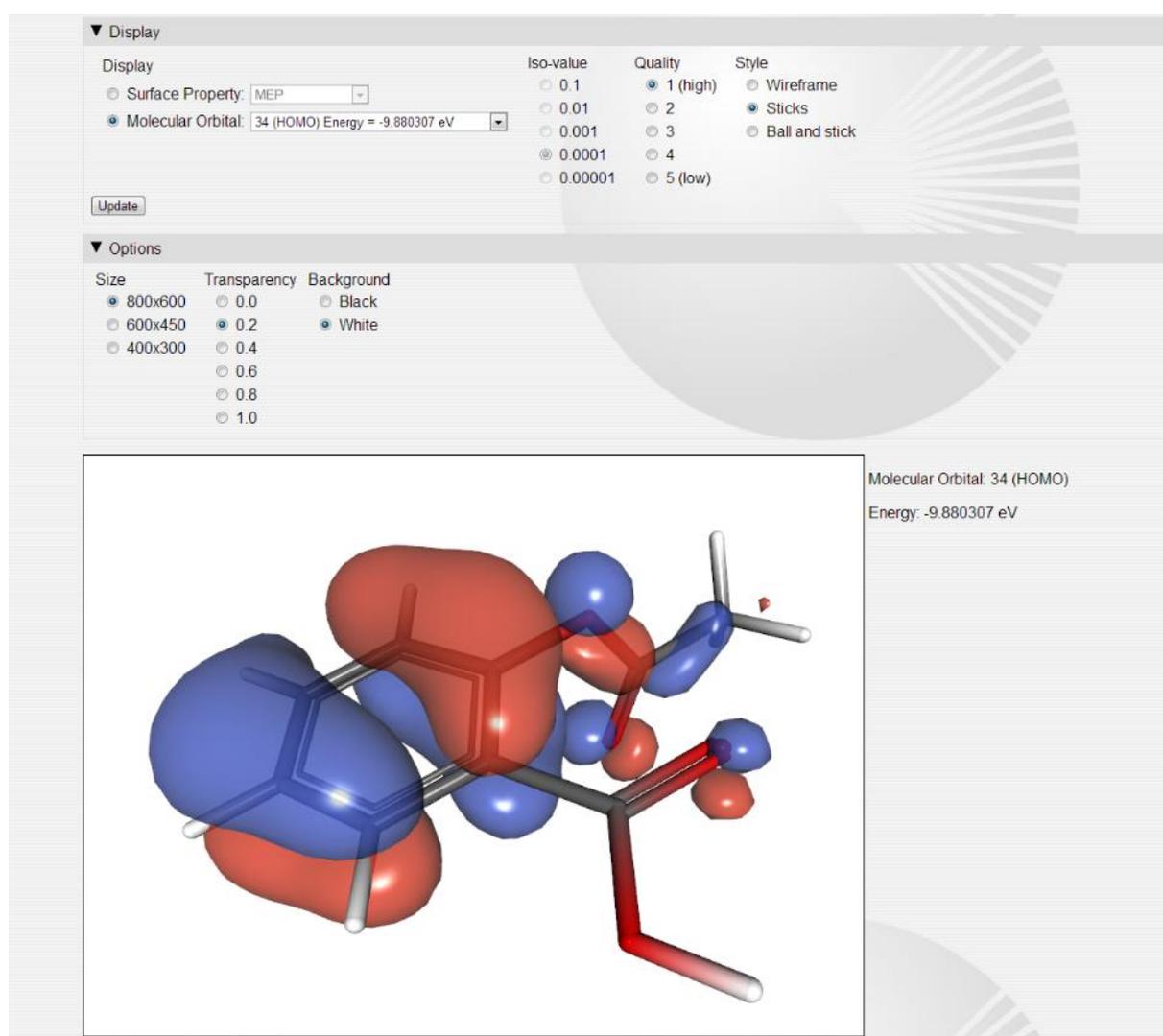
Most of the information on the **EMPIRE[™] Browser** page is contained in expanding sections whose contents are displayed when the section header bar is clicked. These sections include the molecule identifiers, a summary of the molecule's structural information and a list of properties calculated by EMPIRE[™].

The **Download** section contains a list of output files from the EMPIRE[™] calculation. These files can be downloaded to the user's computer in a zip archive by selecting the files required and clicking the **Download** button. The content of these files is described in the **EMPIRE[™] Users' Manual**.

The **Display** section controls the contents of the interactive 3D viewer, which displays either a local property (the molecular electrostatic potential [8], the local ionization energy [9], the local electron affinity [10], electronegativity [10a] or hardness [10a]) projected onto an isodensity surface [11] for each molecule, or a molecular orbital. In each case the molecular structure may be displayed as a wireframe, sticks or ball-and-sticks model. The quality of the surface drawn can also be specified. It is recommended that, initially, low quality surfaces are drawn for local properties and high quality surfaces for molecular orbitals. Changes to the options in this section take effect when the **Update** button is clicked.

The **Options** section controls the size, transparency and background color of the 3D display. These options are applied immediately to the 3D viewer.

Figure 16 shows an orbital display for aspirin with the **Display** and **Options** sections expanded.



The screenshot displays the software's control panels and the 3D molecular model. The **Display** section includes:

- Display:**
 - Surface Property: MEP
 - Molecular Orbital: 34 (HOMO) Energy = -9.880307 eV
 - Update button
- Iso-value:**
 - 0.1
 - 0.01
 - 0.001
 - 0.0001
 - 0.00001
- Quality:**
 - 1 (high) [selected]
 - 2
 - 3
 - 4
 - 5 (low)
- Style:**
 - Wireframe
 - Sticks [selected]
 - Ball and stick

The **Options** section includes:

- Size:**
 - 800x600 [selected]
 - 600x450
 - 400x300
- Transparency:**
 - 0.0
 - 0.2 [selected]
 - 0.4
 - 0.6
 - 0.8
 - 1.0
- Background:**
 - Black
 - White [selected]

The 3D viewer shows a molecular orbital visualization of aspirin. The molecular structure is rendered in a stick style. The orbital is represented by red and blue lobes. Text to the right of the viewer reads: "Molecular Orbital: 34 (HOMO) Energy: -9.880307 eV".

Figure 16 An orbital display demonstrating the use of the **Display** and **Options** facilities

6 SUPPORT

6.1 Contact

Questions regarding CADDLE.® should be sent directly to:

support@ceposinsilico.com

6.2 Cepos InSilico GmbH

Computer-Chemie-Centrum (CCC)
Nägelsbachstr. 25
91052 Erlangen
Germany

support@ceposinsilico.com

Tel. +49 (0)9131 970 4910

Fax. +49 (0)9131 970 4911

www.ceposinsilico.com/contact



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Table 1 Mouse commands for the molecule viewer in common web browsers. For an up-to-date summary of suitable browsers, see the test web page 12



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