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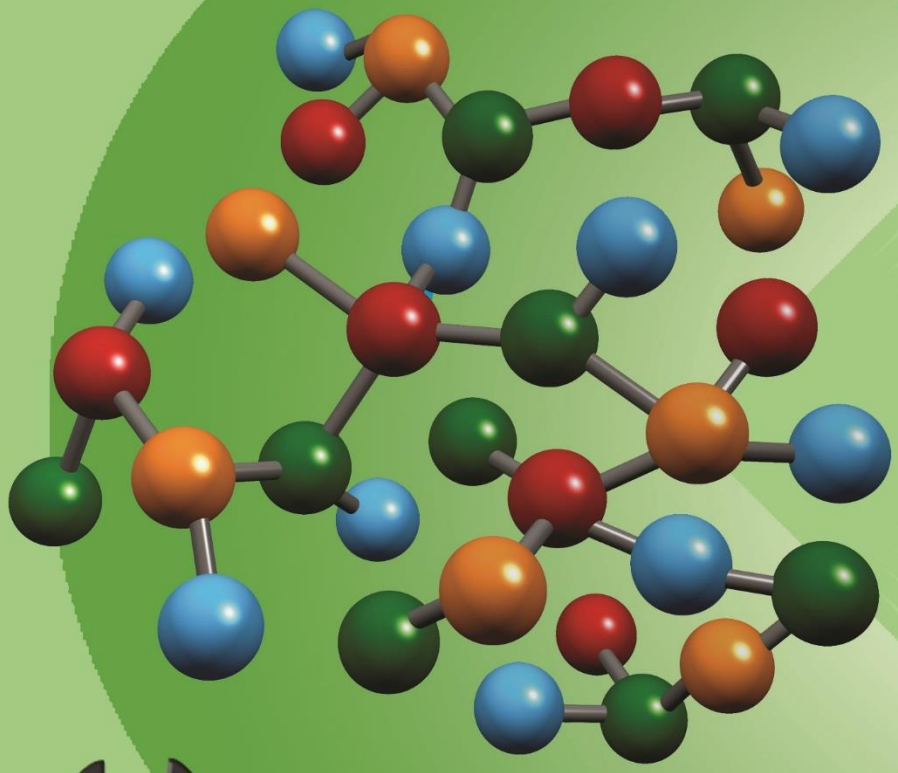
2.0

USER MANUAL



CADDLE®

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1 INTRODUCTION

CADDLE.® is a 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 web browser. This innovative architecture allows schools, colleges, university departments 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.® offers state-of-the-art visualization for molecules, properties projected onto isodensity surfaces and for molecular orbitals. CADDLE.® includes management facilities allowing CADDLE.® administrators to manage users and projects within the CADDLE.® system.

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. CADDLE.® includes a user-management facility; the CADDLE.® administrator can add or delete CADDLE.® users, change passwords *etc*.

3 GETTING STARTED

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.

Figure 1 An excerpt from the CADDLE.® login page. Clicking on the red box or hitting return logs the user in.

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 recently modified projects (see **Figure 1**).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.®.

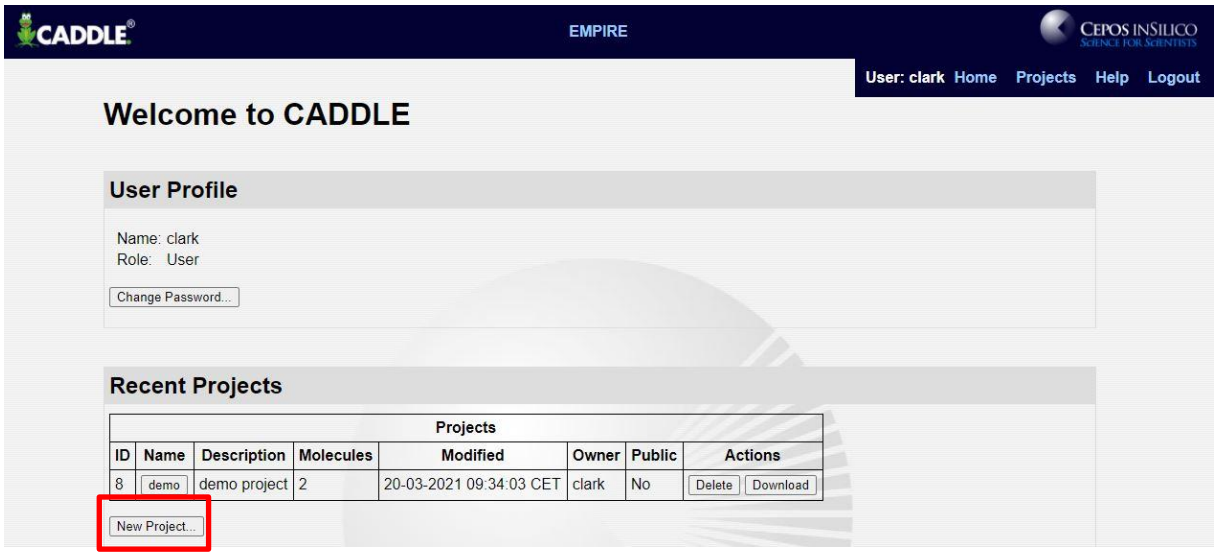

Figure 2 The CADDLE.® home page. Clicking on the red box opens the window to create a new project.

1.1 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 processed together 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®.

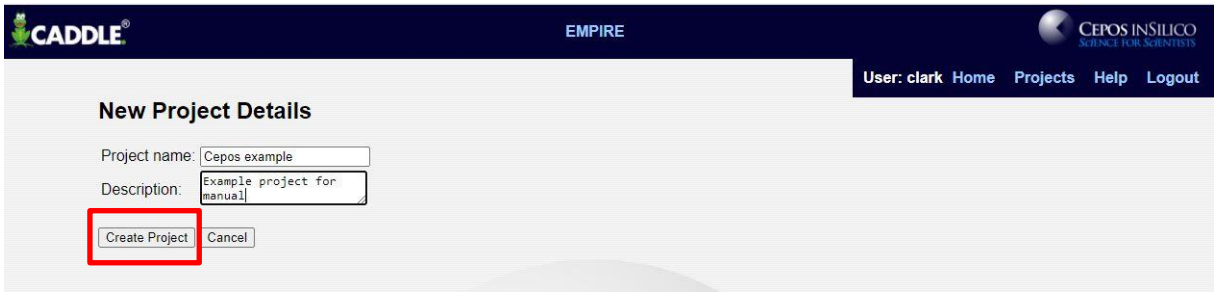

Figure 3 Creating a new CADDLE® project.

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**).

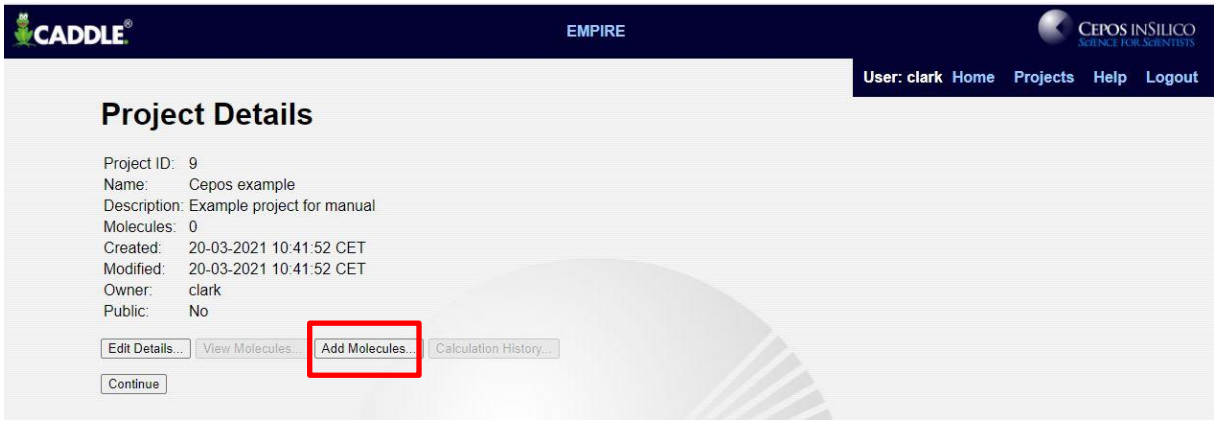

Figure 4 A CADDLE® project details page.

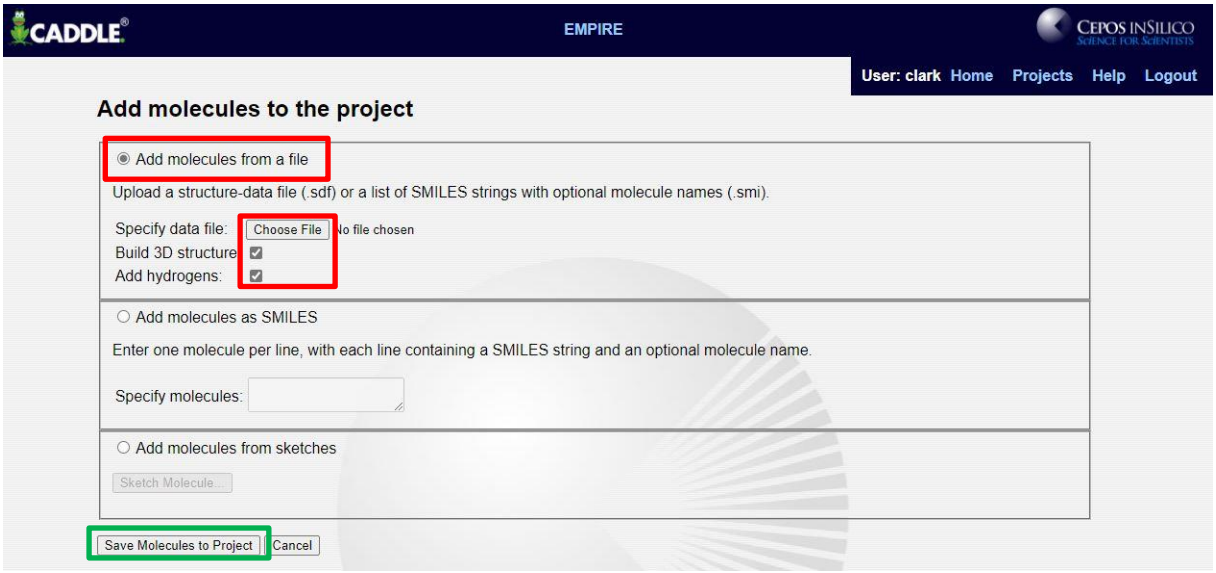

Figure 5 The CADDLE.® molecule input page. The red boxes show the options for reading a molecule from a file; click the green one to add the molecules to the project.

1.2 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.

1.3 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.®.

1.4 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 6**. This brings up the Sketcher window shown in **Figure 7**.

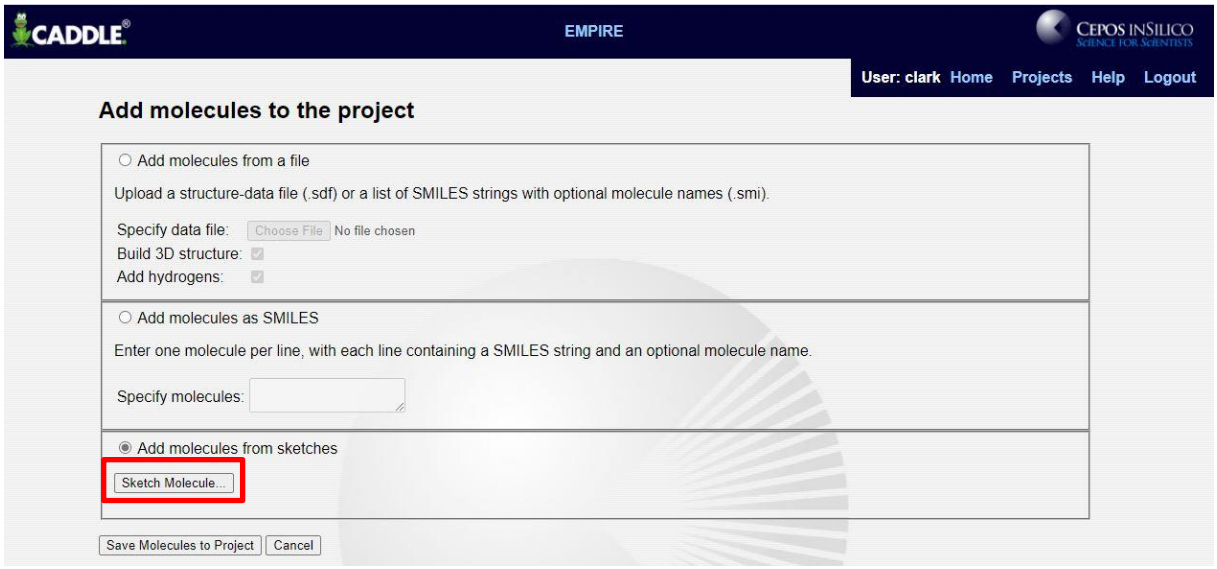

Figure 6 The CADDLE.® molecule input page; click the red box to open the molecule sketcher.

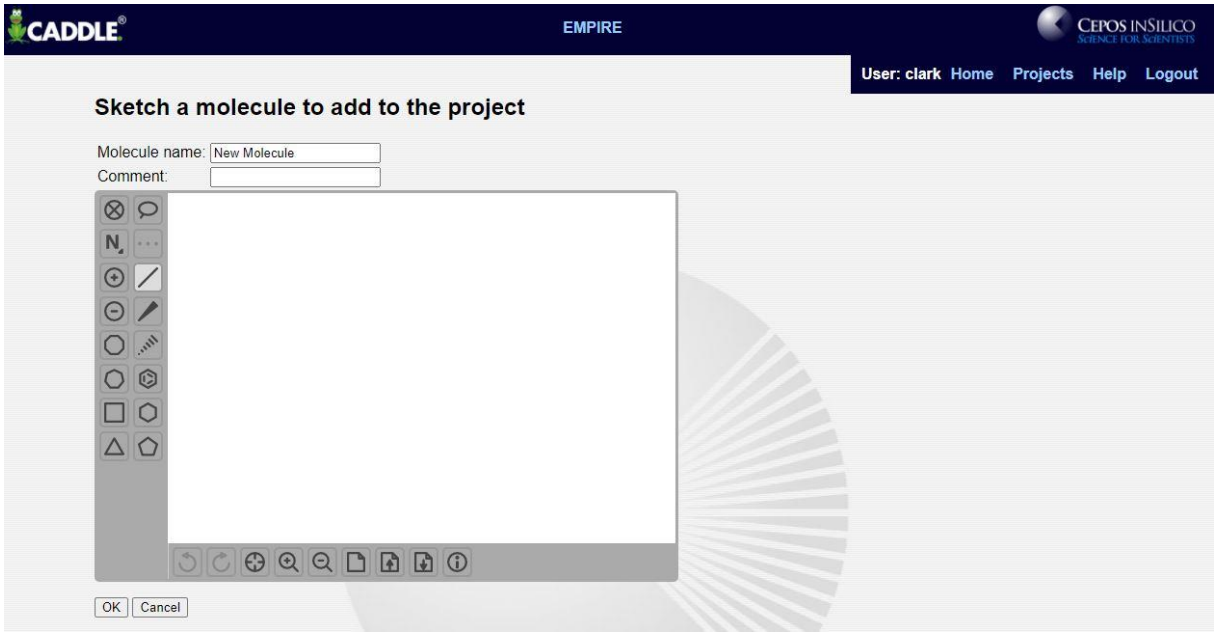

Figure 7 The CADDLE.® 2D sketcher.

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 8**) to exit the sketcher and return to the molecule input page, where the sketched molecule is shown as a small 2D structure (see **Figure 9**). 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.®.

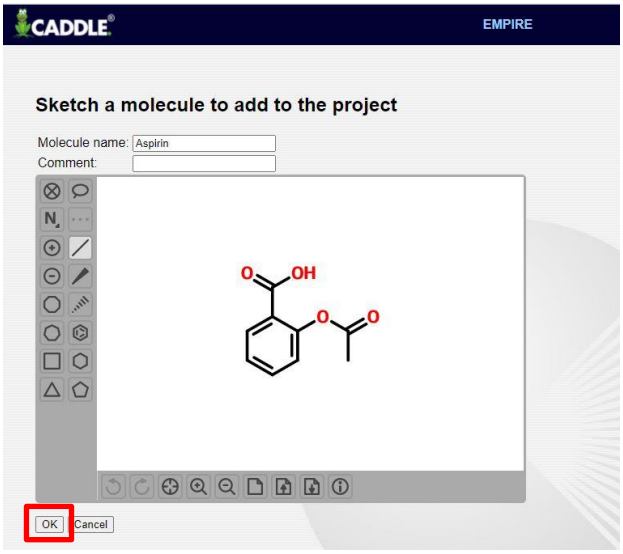

Figure 8 A molecular structure created using the CADDLE.® 2D sketcher; click on the red box to add the molecule to the project.

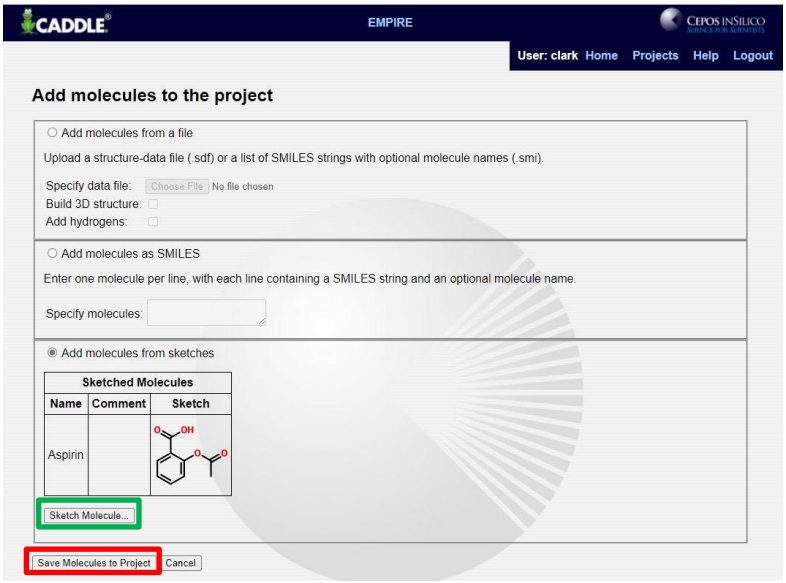

Figure 9 The CADDLE.® molecule input page with the molecule added from the 2D sketcher; click the red box to add the molecule(s) to the project or the green one to sketch another molecule.

In tablet and telephone browsers, it is possible to draw molecules in the sketcher but quite difficult to hit the atoms exactly when adding bonds. Zooming in as far as possible and using a pointing device both help.

1.5 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 10**.

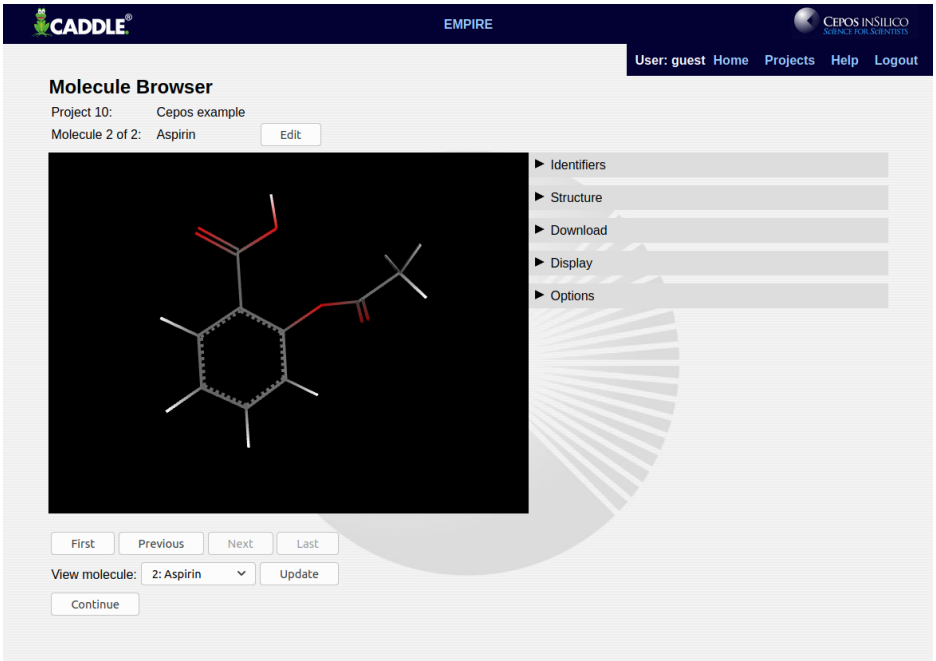

Figure 10 The CADDLE® molecule browser.

The molecule name may be changed by selecting the **Edit** button.

The structures of the molecules can be viewed in the interactive 3D viewer window and the structures rotated, shifted or zoomed using the following mouse-button combinations:

- Rotate: Hold down the left mouse button and move the mouse
- Translate: Hold down the center mouse button and move the mouse
- Zoom: Hold down the right mouse button and move the mouse or rotate the mouse wheel.

On tablet browsers such as Silk, the following mouse-button combinations apply:

- Rotate: Move one finger across the picture
- Translate: Move two fingers across the picture
- Zoom: Usual two-finger zoom gesture.

The navigation controls below the graphic allow the project molecules to be viewed sequentially via the First, Next, Previous and Last buttons. Specific molecules may be viewed directly by selecting them in the **View molecule** drop-down and clicking **Update**.

Molecules can be displayed as wireframe, stick, ball and stick or space-filling depictions by selecting the appropriate option in the Display tab and then clicking Update, as shown in **Figure 11**:

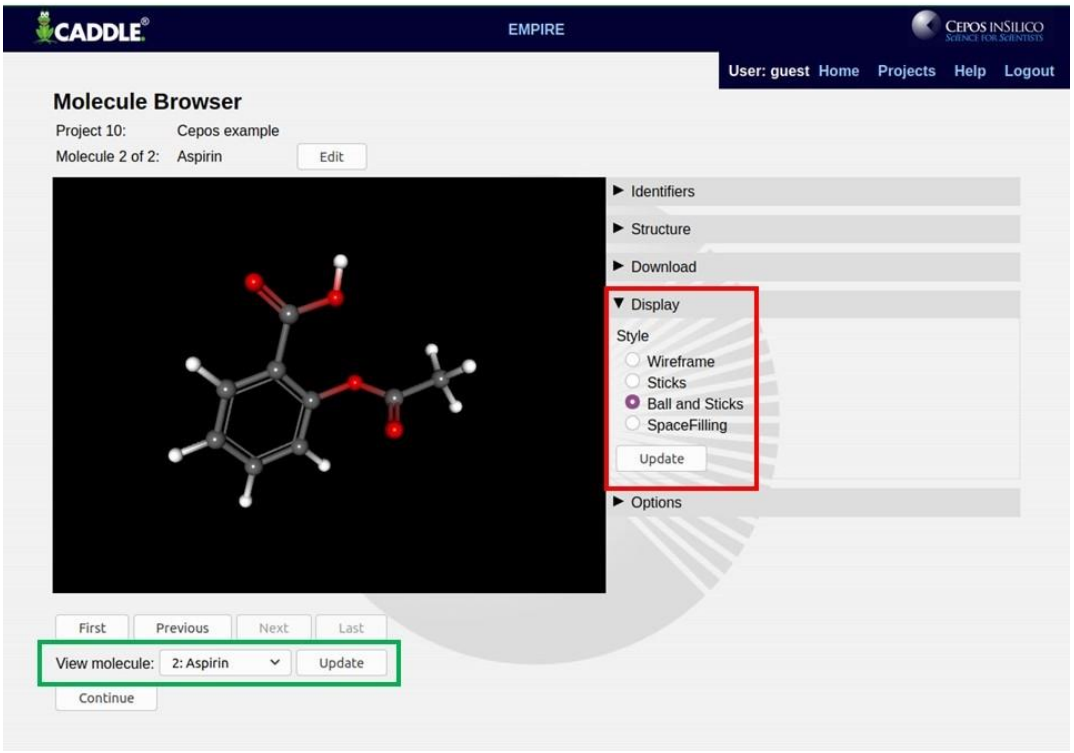

Figure 11 Selecting a display option in the CADDLE.® molecule browser: The display mode is selected in the red box. The selected mode becomes active when the Update box is clicked.

1.6 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 12**). 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.

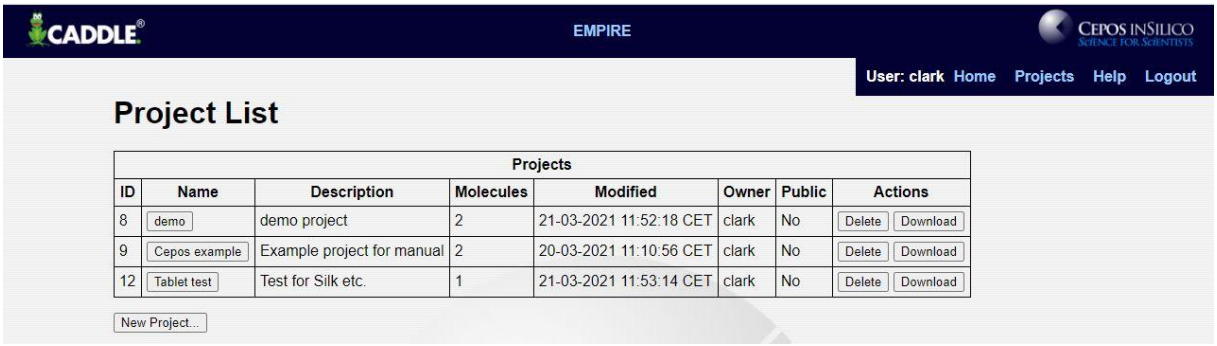

Figure 12 The **CADDLE.®** project browser

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.

1.7 Editing project details

The Edit Details button on the Project Details page produces the Project Editor shown in Figure 13. 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.

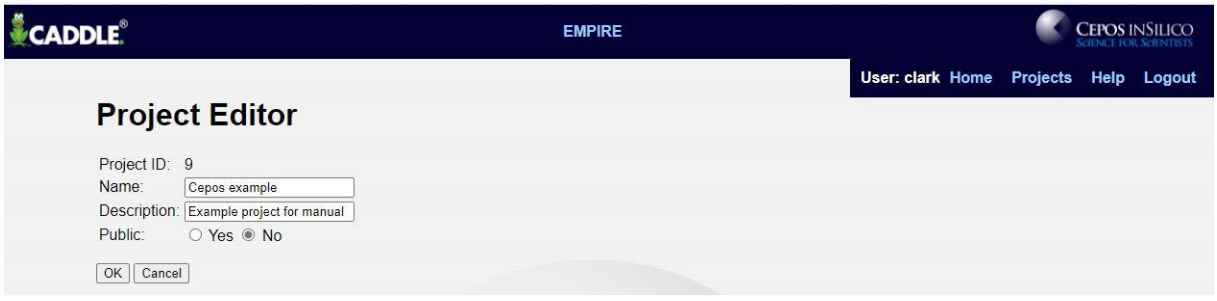

Figure 13 The CADDLE.® project editor.

1.8 Viewing previous calculations

The **Calculation History** button on the **Project Details** page (**Projects** → select project name from the list) retrieves a list of previous calculations for the project (see **Figure 14**). To display the results of a specific calculation, click the calculation's **ID** number 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.

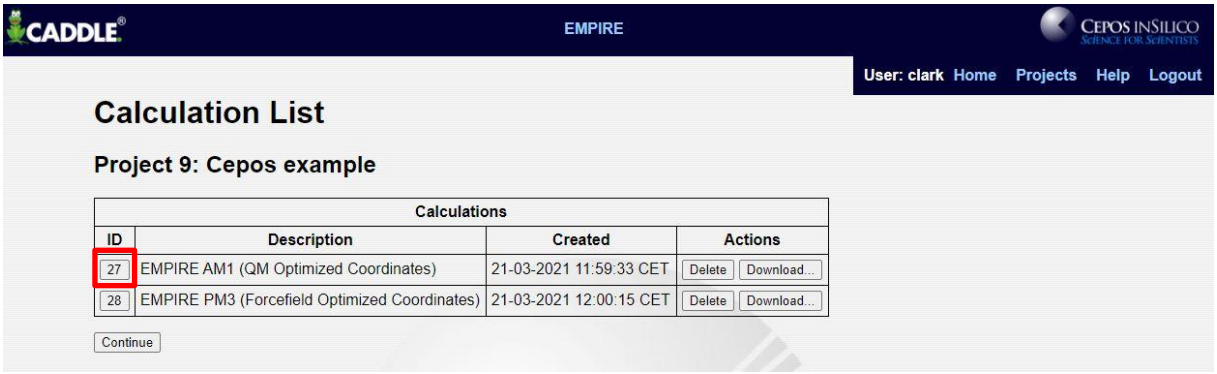

Figure 14 The CADDLE.® project calculation list; to select a project (e.g. 27) click the box in the "ID" column (marked red).

4 EMPIRE™ CALCULATIONS

EMPIRE™ is Cepos InSilico's parallel semiempirical molecular orbital [**1**] program. To run a calculation, select the **EMPIRE** link in the main CADDLE.® menu to display the **EMPIRE Options** page (**Figure 15**). Select a project for the calculation from the drop-down list and the **EMPIRE Options** from the three pull-down menus. The "**Start Calculation**" button is clicked to start the calculation for all molecules in the project on the server.

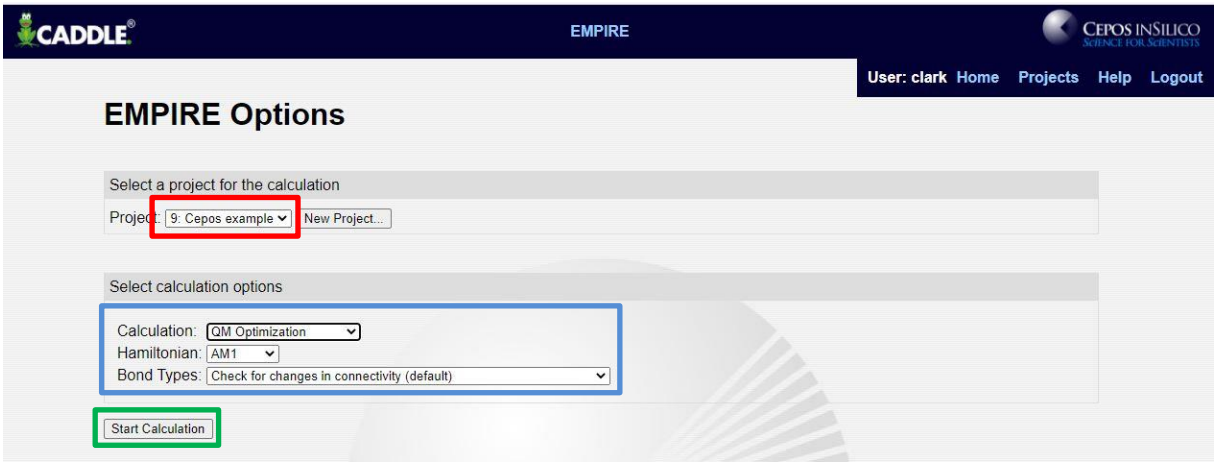

Figure 15 The project selection page: The project to be calculated is chosen in the red box, the calculation options in the blue one and the calculation started by clicking in the green box.

All molecules in the project are calculated in the same way, so that the **EMPIRE** options are limited to the choice of Hamiltonian (calculational method) to be used (currently AM1 [**2**], PM3 [**3**], MNDO [**4**], AM1* [**5**], MNDO/d [**6**] and PM6 [**7**]) 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 [**8**] 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 16**.

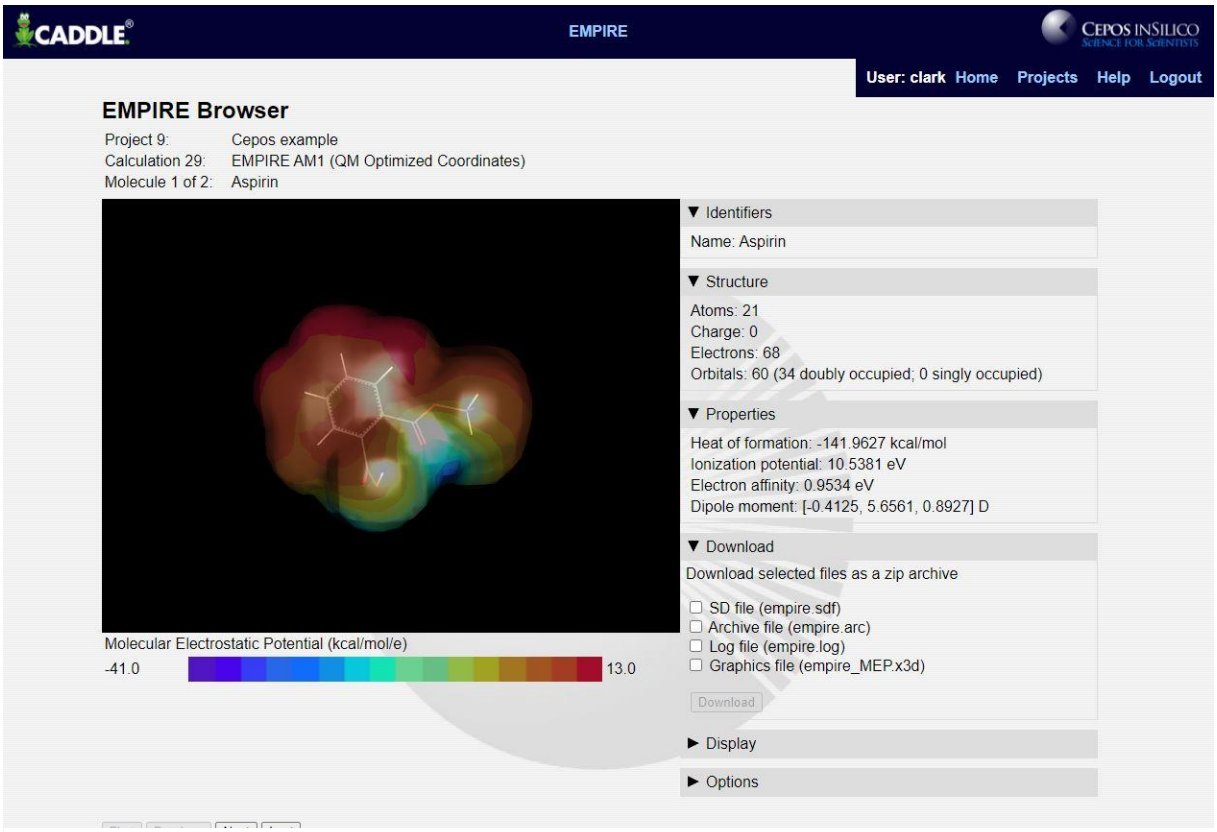

Figure 16 The EMPIRE™ browser window as it appears when the calculations are complete but with the pull-down menus “Identifiers”, “Structure”, “Properties” and “Download” open.

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 **Identifier** section contains the name of the molecule, which is also visible above the graphical display.

The **Structure** section contains the most important results of the EMPIRE™ calculation, the heat of formation, the ionization potential, the electron affinity and the dipole moment as the *x*-, *y*- and *z*-components of the vector.

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 contents of the 3D graphical display can also be downloaded as a standalone HTML file for display in a web browser or as an X3D file for display in a suitable graphics viewer.

The **Display** section controls the contents of the interactive 3D viewer, which displays either a local property (the molecular electrostatic potential [**9**], the local ionization energy [**10**], the local electron affinity [**11**], electronegativity [**11a**] or hardness [**11a**]) projected onto an isodensity surface [**12**] 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 17 shows an orbital display for aspirin with the **Display** and **Options** sections expanded.

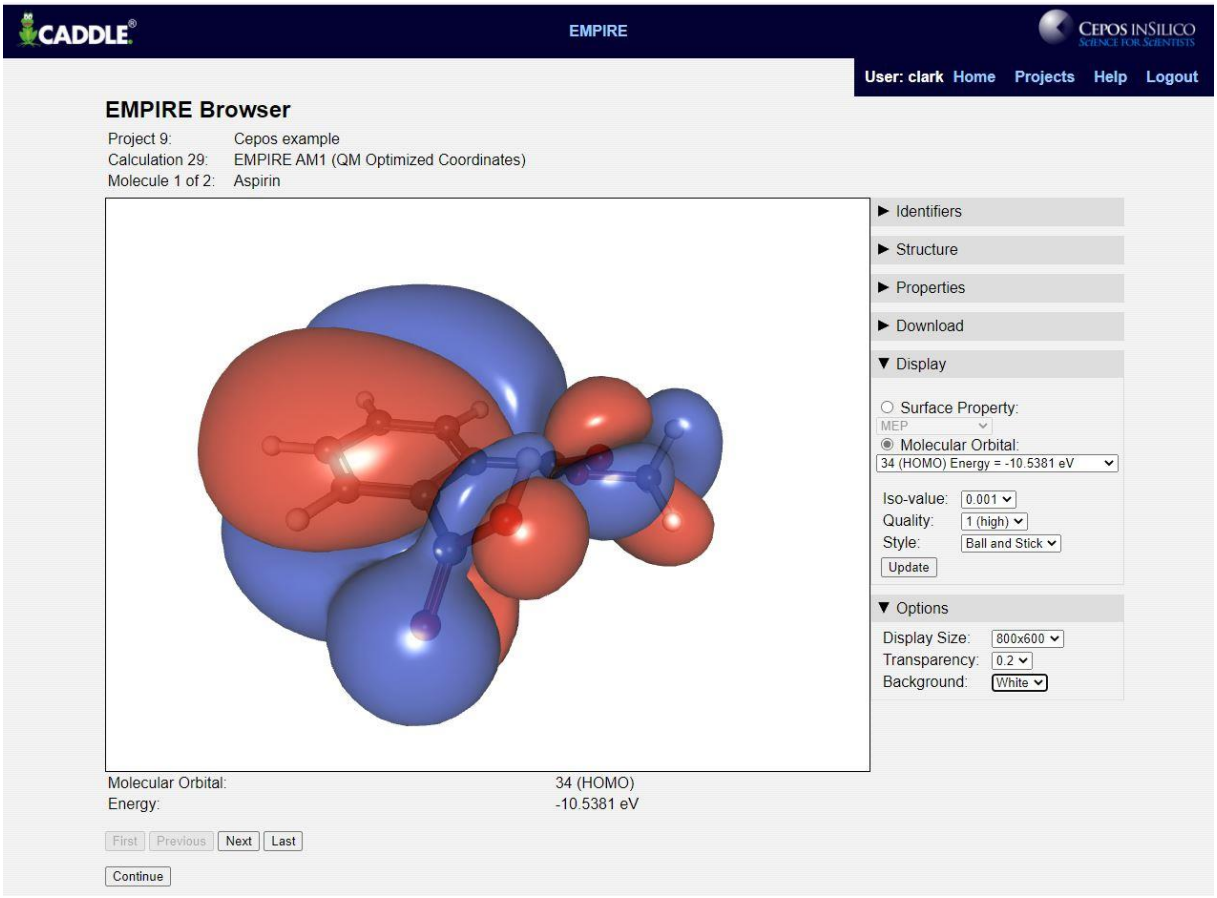

Figure 17 An orbital display demonstrating the use of the Display and Options facilities.

6 SUPPORT

1.9 Contact

Questions regarding CADDLE.® should be sent directly to:

support@ceposinsilico.com

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