Computer Software Review

CAChe 6.1 WorkSystem Pro plus Active Site Add-On. CAChe Group, Fujitsu America, Inc., 15244 Greenbriar Parkway, Beaverton, OR 97006. http://www.cachesoftware.com/. Contact CAChe group for pricing information.

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CAChe 6.1 WorkSystem Pro plus Active Site add-on for windows is a powerful molecular modeling package suitable for both beginners and experienced users. The package makes available both molecular mechanics- and quantum mechanics-based methods that are applicable to a variety of computational problems across a broad spectrum of disciplines. The package works with Intel Pentium processors running Windows 98, Me, 2000, or XP and requires a minimum of 128 MB RAM. A 1200 MHz Intel Pentium III processor with 256 MB RAM was used in this evaluation.

Installation of the software is straightforward using the automated protocol. The initial layout is a workspace window with the most basic of capabilities in the form of selective radio buttons, although more sophisticated options can be accessed through the drop-down menus. CAChe handles a variety of chemical species ranging from small molecules to large biomolecules. Construction of a chemical structure is simple and can be done either by sketching it directly onto the interface or by opening a previously generated molecule from a number of file formats, including chemical sample files (CSF), MOL2, PDB, XSF, SKC, and others. All chemical features such as type of element, hybridization, charge, and coordination states can be individually set and verified either manually or automatically. Molecules can be saved as CSF, on which a variety of computational experiments can be performed. The availability in CAChe 6.1 of a broad range of computational tools allows the end user to design specific computational experiments to address most issues of interest. Computation of a wide range of properties such as geometry, heat of formation, infrared (IR) and UV−visible spectra, current energy, electron density, HOMO/LUMO shape and energies, molecular orbitals, electrostatic isopotentials, susceptibility, superdelocalizability, dipole, quadrapole and octupole moments, polarizability, bond orders, atom partial charges, and NMR chemical shifts is possible. Reaction properties including optimization, identification of stationary states (ground and transition states), mapping, and characterizing of reaction paths can be addressed with the available quantum mechanical methods. Additional features allow for evaluation of atom, bond, and conformational properties.

Molecular mechanical (MM2, MM3) and quantum mechanical methods, including semiempirical (MOPAC, ZINDO) and density functional theory (DGauss) programs, can be used for optimizing geometries. For calculations of electronic structures and properties, ExtHückel, MOPAC, ZINDO, and DGauss methods are available. In MOPAC, AM1 and PM3 Hamiltonians are available, and solvent effects can be computed using COSMO. Accurate high level computations can be carried out using hybrid density functionals B88-LYP, B88PW91, and D-VWN with a variety of split-valence basis sets (DZVP, TZVP STO-3G, 3-21G,3-21G*,6-31G,6-31G*,6-31G**) and pseudopotential (PPC). For very large molecules, including biological macromolecules, MOZYME, a method available in MOPAC, can be used for calculations of electronic structure. CAChe includes a visualization tool for viewing properties such as electron density, molecular oribitals, electrostatic potential, superdelocalizability, and amplitudes from absorption spectra that may be computed using quantum mechanical methods. Though the stand-alone CAChe 6.1 WorkSystem Pro has some limitations with regard to available quantum mechanical methods, an interface to the program *Gaussian* provides access to all the capabilities of this well-know quantum package. Generation of molecular dynamical trajectories is limited to the NVT (constant temperature) and NVE (constant energy) ensembles using the Verlet algorithm based on MM2 and MM3 force fields. Other methods such as constant pressure and constant surface tension are currently not available.

Inclusion of the Active Site add-on for CAChe 6.1 WorkSystem Pro adequately met the requirements for studying large biomolecules with particular focus on drug discovery. Visualization capabilities include display of proteins, rendering features for various representations, such as ribbon diagrams, etc., and display of surfaces, such as accessible surface area maps, protein sequences, hydrophic and hydrophilic regions, and hydrogen bonds, to list a few. Figures generated by the program can be directly printed from the workspace; however, they cannot be exported in any alternate format. Manipulation of the protein sequence through deletion, insertion, joining of chains, or mutation of residues can be made directly in the sequence viewer, and the effects of modification can be visualized on the workspace window. Homology modeling tools for building new peptides or proteins are also available. Preparation of a crystal structure or homology model of a protein for modeling studies can be performed readily by selecting specific chains, setting the protonation states of ionizable residues, standardizing ligands, and defining the active site for docking and other initial manipulations. For docking studies, the active site pocket display feature that has a color scheme to identify hydrogen bond donors, acceptors, and hydrophobic regions is useful. For proteins that lack a bound ligand, identification of active sites is assisted by crevice surface mapping to locate possible binding pockets along with a facility for sequence alignment of homologous proteins based on active site residues. It is also possible to perform knowledge-based docking to a homologous protein that has a bound ligand functioning as a template. The ligands and side-chain atoms of the residues at the active site can be treated as either fixed or flexible during the docking experiment. The Active Site add-on also provides enhanced docking capabilities through automated docking and scoring of ligands or compound libraries using a genetic docking algorithm with a potential of mean force (PMF). Docking, calculation of

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properties, and analysis of compound libraries with 2D structures saved in .mol, .sd, or .sdf for virtual screening applications can be done using the Project Leader component of CAChe. However, automatic generation of multiple isomeric forms of the compounds in the libraries is not available. Multiple linear regression, stepwise regression, an algebraic equation editor for customization, and a scatter plot graphing tool are available for statistical analysis of the data generated.

Setting up a new experiment in CAChe 6.1 is easy and is guided by the menu box that has various selectable options as well as brief descriptions of the function of each chosen option. This feature is particularly useful for new or casual users. The procedures to calculate the property of interest can be further edited using the procedure editor, which provides the flexibility for expert users to design optimal experiments through specific modifications or by combining various procedures. Experiments designed by expert users can be saved and distributed for repetitive execution. One of the attractive features of the software is its ease of use; it does not require extensive experience in modeling. The software manuals are very informative, particularly the manuals on "Getting Started". It is advisable for new users to go through the exercises described in the manuals relevant to their area of interest prior to use of the software. The support features include online help and resources with explanations of the various options in the package. In the final analysis, CAChe 6.1 WorkSystem Pro plus Active Site add-on is a very comprehensive molecular modeling package that is equally suitable for studying small molecules with high accuracy or for high-throughput studies, such as docking of virtual libraries.

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