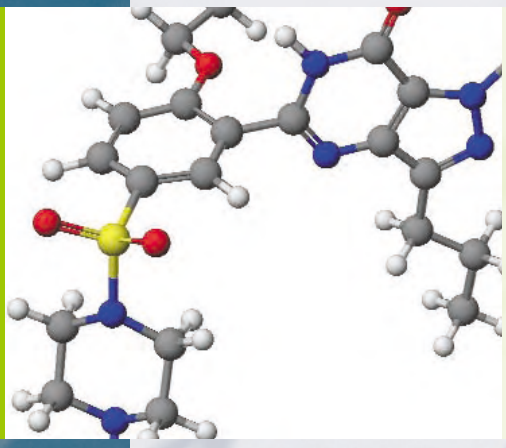
THE POSSIBILITIES ARE INFINITE FUJITSU



CAChe® Software

Professional desktop modeling, prediction, and structure-property analysis for the experimental chemist

PREDICT
CONFIRM
AUTOMATE

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CAChe® Software

- In silico prediction, modeling, and analysis package designed for the experimental chemist
- Wide range of graphic views and modeling techniques from molecular mechanics through rigorous electronic structure methods
- Model and analyze single molecules or collections, gathering data through property-driven interface in which you designate properties and CAChe chooses the best calculation method
- CAChe handles all atoms including metals

CAChe® (Computer-Aided Chemistry) is a richly equipped desktop graphical modeling package designed to help the experimental chemist shorten time to discovery by bringing powerful analytic capabilities to the desktop or laptop, thus enabling "on the fly" simulations.

Designed by chemists for use by chemists, CAChe incorporates a wide range of modeling and analysis techniques, including many developed and validated by experts in computational chemistry. Experimental chemists who need answers about realistic molecular systems can use CAChe effectively without becoming experts in the details of computational techniques. CAChe facilitates access to its methods through a graphical interface that helps scientists construct and test models. Its property-driven interface intuitively guides the experimental scientist through varying calculation methods and offers alternatives to balance accuracy and computational requirements.

Property-Driven Interface

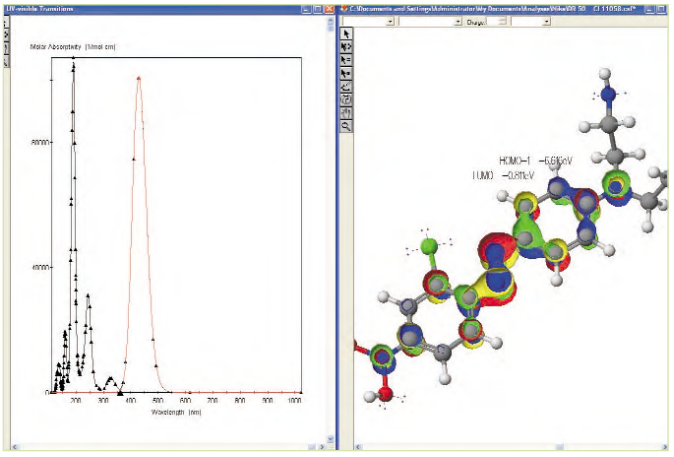
The chemist approaches CAChe through multiple integrated views. ProjectLeader, a 2-D workspace, offers a tabular, spreadsheet-like organization of molecules and their properties. The 3-D workspace shows structure displays with a wide range of molecular graphics techniques including surfaces and annotations. Modeling a single molecule is valuable, but real chemistry often involves studying collections or libraries of molecules to understand why their properties differ and how these differences are related to structural features, and thus to know which molecules to study next. Computations can be performed on the desktop or on a networked server.

Statistical Modeling with QSAR

CAChe combines experimental data with over 100 descriptors to develop QSAR protocols, and additional descriptors can be defined within the system.

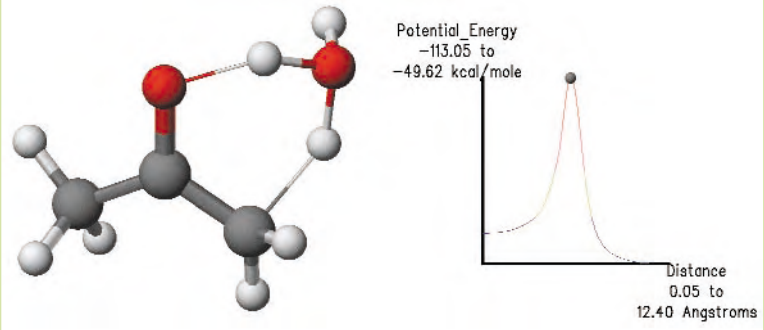
As the scientist selects descriptors, CAChe shows their definitions and offers alternative calculation methods in addition to a standard or default procedure. Once CAChe has guided the scientist in choosing properties and calculation methods, the software goes to work in the background, automatically filling in the ProjectLeader table while freeing up the scientist to do other work. Calculations which are time-consuming may be sent off to computational resources such as Fujitsu's BioServer™ for faster processing.

The user then chooses the type of regression analysis to be performed, and the variables for the QSAR regression. Various strategies



UV/Vis spectral analysis of an azo dye computed with CAChe. The compound's color results from a combination of activity at several major peaks. Selecting a peak highlights the responsible orbital transitions in the model. Highest Occupied MOs (HOMO) are blue and green. Lowest Unoccupied MOs (LUMO) are yellow and red.

can be compared and evaluated based on their correlation coefficients, cross-validation scores, and predicted values. From the QSAR/QSPR model results, properties can be predicted for new compounds, including those lacking experimental data or which have never been synthesized. CAChe models can also be calibrated to account for systematic modeling biases and to increase the confidence of predictions.



Water-catalyzed keto-enol tautomerization with 6-membered ring transition state. CAChe's reaction path plot animates the reaction and shows that water catalyzes this reaction by lowering the activation energy barrier.

Model Building

Model systems can be generated and manipulated fully within CAChe, or imported from a variety of commonly used file formats such as PDB (Brookhaven Protein Data Bank), MOL files, SD files, and the output of popular chemical drawing programs. Batch 2D to 3D conversions are also provided. Once the model is in the CAChe workspace, the scientist can edit it, correct or alter its geometry, invert chiral centers, and superimpose molecules. Especially valuable is the Beautify command with its many options including Comprehensive, which corrects valence, hybridization, geometry, and ring structure in a single step.

Geometric features of models can be rendered with a range of display methods such as ball and stick, tubular, and ribbons. Further analytical data and features such as measurements (e.g., bond lengths and angles, distances), surfaces, and orbitals can be added. Optional stereoscopic 3D visualization speeds the comprehension of spatial relationships.

For protein studies, model building is facilitated by sequence editing, insertion, and mutation with automatic 3D display. Proteins can be colored according to various criteria, and protein sequences can be aligned. Ligand pocket surfaces, manual docking of ligands, and an optional automated docking procedure help elucidate binding features.

Computational Methods

CAChe has the unique ability to apply a wide range of computational models, from molecular mechanics through rigorous *ab initio* electronic structure techniques, to all types of molecular systems, from small organic molecules, to inorganics, polymers, materials systems, and whole proteins.

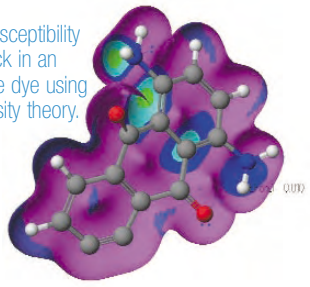
Molecular mechanics and dynamics calculations can be performed on organic and inorganic molecules containing all elements of the periodic table using augmented MM2 and MM3 force fields. Force field parameters can be modified by the user. CAChe includes CONFLEX for automated global minimum searching and systematic generation of low-energy conformers for molecules of any shape, including ring systems.

Electronic structure methods in CAChe include Extended Hückel theory (for all elements), ZINDO (primarily for UV-visible spectra), MOPAC, and DGauss (density functional theory). MOPAC2002, a refinement of MOPAC developed by Fujitsu scientists, covers all main group elements and many metals, with an extensive choice of models including PM5, AM1, PM3, MINDO/3, and MNDO. It also includes the COSMO solvent model and d-orbitals for transition metals. MOPAC2002's linear scaling method, Mozyme, can geometry optimize large systems such as proteins of 20,000 atoms, with or without a solvent field. CAChe's quantum chemistry methods facilitate the study of kinetics and thermodynamics, and the prediction of many physical and chemical properties.

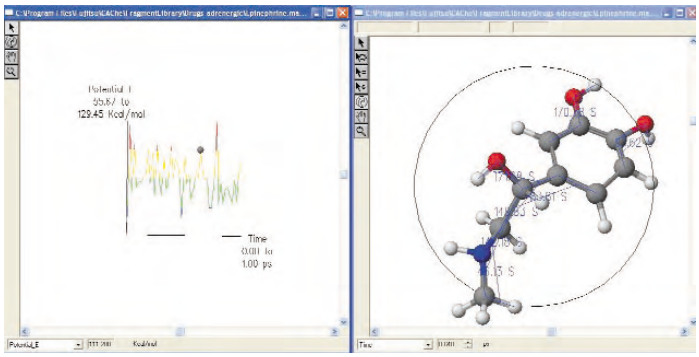
CAChe can also transparently run and visualize results for the third party program, Gaussian™ (requires separate installation of Gaussian).

The ActiveSite™ option with FastDock™ automated ligand docking provides for rigid or flexible ligands to be docked into rigid proteins or proteins with flexible sidechains. With its Lamarckian genetic algorithm and enhanced potential of mean force (PMF) scoring function, this technique has been shown to achieve high-quality docking geometries with reliability over a range of examples.

Information-based design has become a standard part of scientific research because it provides more knowledge earlier in the research process, leading to better-informed decisions. Research guided by increased information is both more efficient, pruning away unproductive avenues earlier, and more effective, providing a better basis for choosing new lead compounds at the outset. CAChe, with its intuitive, property-driven user interface and rich set of methodologies, is the ideal tool to enhance the productivity of the experimental scientist.



Bull's eyes show susceptibility to electrophilic attack in an aminoanthroquinone dye using Fukui's frontier density theory.



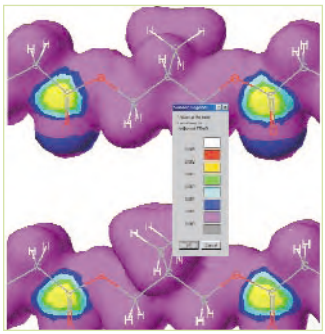
In this view the potential energy of varying conformers of epinephrine can be assessed.

Case Studies

Predicting Polymer Stability

Journal of Coatings Technology Vol. 67, No. 847, August '95 by Carl J. Sullivan & Charles F. Cooper, ARCO Chemical Company.

By calculating reactivity indices with CAChe, ARCO Chemical Co. was able to show that its new polyester coating was just as resistant to radical attack as the competitor's more-expensive polyester.[1] In CAChe, susceptibility to radical, electrophilic, or nucleophilic attack can be tabulated quantitatively by atom or, displayed graphically on the van der Waals surface of the molecule, as shown below. The Fukui indices indicating susceptibility to radical attack for ARCO's polyester were in agreement with the accelerated weathering tests and helped disprove the competitor's claims that the cheaper polyester would degrade faster in sunlight.

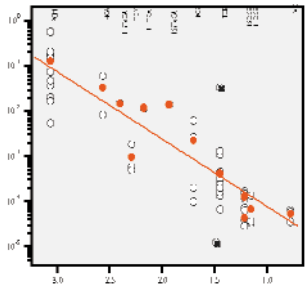


Surface coloring indicates that the susceptibility to radical attack is virtually identical for ARCO's methyl-propane diol-based polyester (top) and the competitor's more expensive neopentyl diol-based polyester (bottom)

Environmental Remediation

Correlation Analysis of Rate Constants for Dechlorination by Zero-Valent Iron, Environmental Science and Technology, 1998, 32, 3026-3033; M.Scherer, B.Balko, D.Gallagher, P.Tratnyek

The ability to predict environmental remediation rates of potential new agrochemicals, provides for the possibility to screen against potentially untreatable pollutants before they are even synthesized. Paul Tratnyek and coworkers at Oregon Graduate Institute[2] have developed a quantitative structure-property relationship (QSPR) with the CAChe WorkSystem that has been shown to predict decomposition rates of organochlorine compounds by metallic iron turnings, with useful accuracy. The energy of the lowest unoccupied molecular orbital (E_{LUMO}) calculated by MOPAC, was shown to correlate inversely with the rate constant (LogK) for the compound's dehalogenation with a correlation coefficient, $r^2 = 0.85$. Now, a few seconds calculation can save the need for days of synthesis and experimental testing.



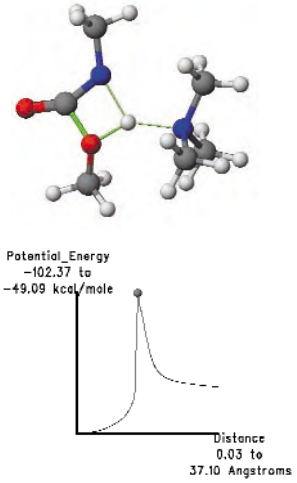
Plot of ELUMO (horizontal axis) versus LogK (vertical)

Synthesis Design

Malwitz, N., Reaction Kinetic Modeling from PM3 Transition State Calculations, J. Phys. Chem., Vol 99, No. 15, 1995 p. 5291

To save the time and expense of pilot scale testing, Sealed Air Corp. turned to the CAChe WorkSystem to find ways to improve the yield and lower energy costs for their polyurethane synthesis process.[3] Nelson Malwitz was able to model the effects of changing substituents, solvent, temperature, and catalyst on the kinetics and thermodynamics of the urethane polymerization reaction and, explore alternative reaction pathways.

In addition to finding improved reaction conditions in a fraction of the time and expense of the experimental pilot-scale approach, they discovered new insights about the way the catalyst works that might facilitate the design of a better catalyst in the future.



Four-membered ring transition state with trimethylamine catalyst, and reaction path plot.

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