

COSMOtherm Version 2.1

COSMOtherm is an advanced software tool that calculates the thermophysical properties of chemical compounds and mixtures. This program surpasses all similar software products in its ability to handle novel and complex compounds with unusual functional groups. COSMOtherm can predict the properties and attributes of complex compounds with unusual functional groups that are often encountered in the pharmaceutical, polymer and specialty chemical industries.

Thermodynamic properties which can be handled routinely include:

- vapor pressures
- boiling points
- activity coefficients
- excess enthalpy and entropy
- Henry's Law constants
- solubility
- log P
- pKa
- VLE/LLE/SLE
- density and viscosity for pure compounds

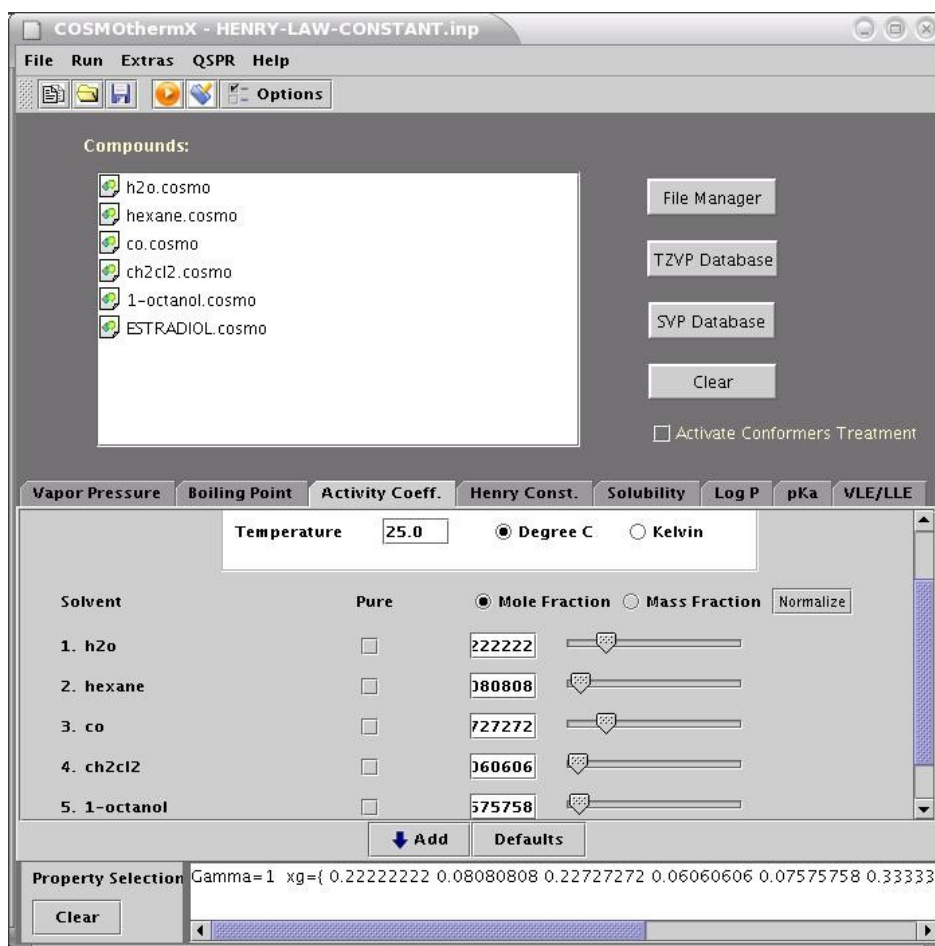


Figure 1. The COSMOtherm Graphical Interface

Other properties which COSMOtherm can predict are the free energy gain at a surface or interface between two different liquid phases. COSMOtherm can even provide estimations of general adsorption and physiological partitioning phenomena including blood/brain, intestinal and soil.

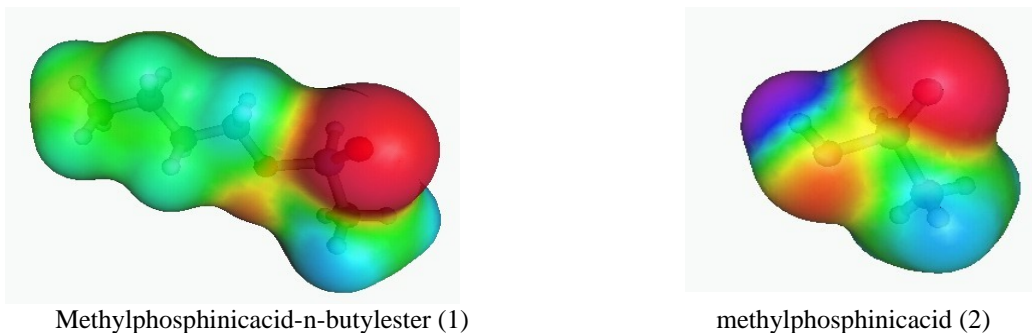


Figure 2. The screening charge density on the surface of two organic molecules based on their sigma-profiles.

These properties can be estimated for the over 4,000 chemical structures in **COSMObase**, the COSMOtherm database, and for their mixtures. The σ -profiles of new compounds may be added to the database and stored for future calculations. An external quantum chemistry program such as TURBOmole is used for this purpose. This method is often time-consuming but overall is almost always faster and less costly than laboratory testing.

COSMOtherm is a breakthrough product developed and updated by COSMOlogic GmbH & CoKG. Unlike programs which use group contribution or other fragment prediction methods and are limited to chemical structures for which empirical data exists, COSMOtherm is based on Electron Density Functional Theory (DFT) which is applicable to a much wider variety of chemical compounds. By a unique combination of DFT with continuum solvation theory and statistical thermodynamics, COSMOtherm extends the broad applicability of DFT to thermophysical property prediction. Almost any organic or inorganic compound containing H, C, N, O, Si, P, S, F, Cl, Br, I, As, and Se can be treated; with some restrictions other elements can be added as required. A 3-D map of the surface electron density distribution superimposed on a ball-and-stick model of each molecule can be displayed.

COSMOtherm's Graphical User Interface (GUI) and the Command Line Mode

The GUI is recommended for beginners. It is also useful when performing calculations which require only a small number of parameters to be entered. The GUI utilizes an automatic search function that simplifies the selection of compounds from COSMObase. Compounds may be selected by systematic or alternative name, CAS Registry Number or chemical formula. The GUI also facilitates access to databases of empirically-derived values such as Wagner and Antoine coefficients, UNIQUAC volume and area coefficients, enthalpy of fusion, melting points and critical point data. Calculated results are output to two screens: the Output Screen provides Run-Time program information and a Tab or Spreadsheet Screen, a tabular display of the requested results in an Excel compatible format. The GUI can also plot activity coefficients, phase equilibria and other output data.

Command line mode is useful for experienced users. It is the mode of choice for running batches of predictions which are more tedious to enter in GUI mode.

COSMOtherm runs on Windows operating systems starting with Windows 98 and on most versions of Linux.

COSMOtherm provides instant access to data essential for developing new products, improving chemical processes and solving environmental regulatory problems. Among COSMOtherm's many advantages are its applications to:

- ✓ Separation Processes
- ✓ Chemical Reaction Engineering
- ✓ Polymers
- ✓ Environmental Engineering
- ✓ Pharmaceuticals

Thanks to COSMOlogic's innovative methodology, the resources and time usually required to design and develop chemical products and processes can be reduced substantially and many engineering tasks that are critical to the chemical industry can be streamlined. The following detailed summaries, demonstrate COSMOtherm's essential role in R&D.

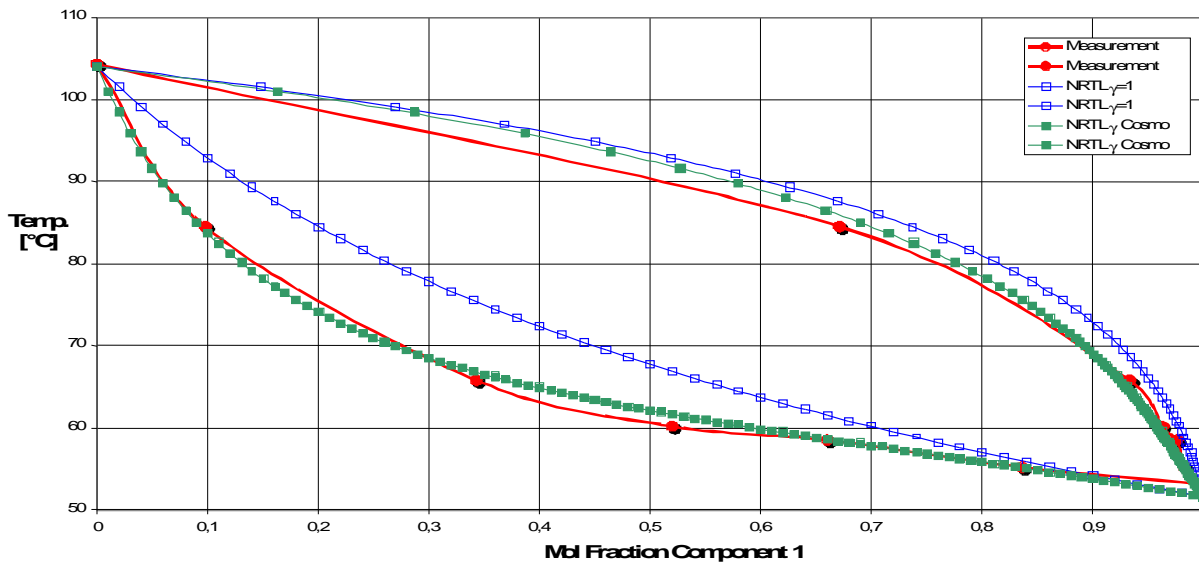


Figure 3. The VLE of methylphosphonicacid-n-butylester (1) / methylphosphonicacid (2).

Example by: Dr. Gordana Hofmann-Jovic, InfraServ Knapsack, Germany

• **SEPARATION PROCESSES.** COSMOtherm facilitates the development of separation processes such as distillation, solvent extraction and crystallization which absorb a large part of the cost of preparing a commercial product for market.

Distillation. When dealing with totally new compounds, it is often important to estimate VLE curves to see if the compound can be separated by distillation. Based on an example taken from industry, Figure 3 above shows how accurately COSMOtherm can predict the VLE of compounds over a wide range of temperatures and compositions.

In other engineering programs that are used for performing flash calculations to identify azeotropes and pinch points the user must choose from an often confusing variety of thermodynamic models and may miss complex azeotropes. In COSMOtherm the expertise is built in and much trial-and-error is avoided (see Figure 4).

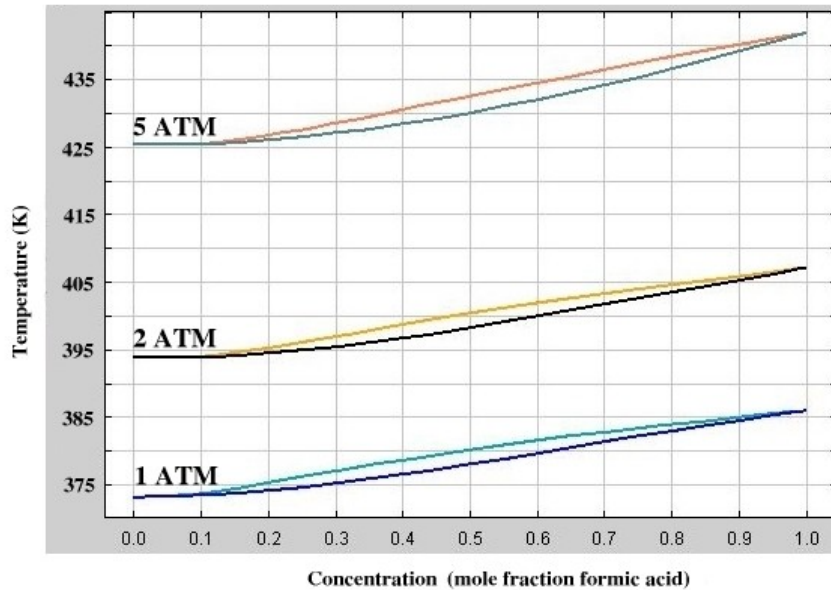


Figure 4. Identifying azeotropes and pinch points in Formic acid/water
COSMOtherm Identifies Minimum Boiling Point Azeotropes at .035 moles Formic Acid at 2 & 5 ATM

Furthermore, in complex distillation processes there is often a critical need to find suitable entrainers which can break an azeotrope. COSMOtherm is very useful for screening entrainers as it can predict the efficiency of such compounds. Highly innovative entrainers have been found in this way and some are already used in running processes.

Liquid-Liquid Extraction. Many separation and purification processes depend upon the ability of one solvent to extract compounds from other solvents. COSMOtherm is the only program currently available that does not rely on group contribution methods to predict a compound's solubility in different solvents as well as in different solvent mixtures. Therefore, COSMOtherm can predict solubility for a wider range of compounds, including those which are important in the specialty chemicals, pharmaceuticals and polymer industries (see below). When COSMOtherm is used to fine-tune solvent selectivity in processes that require selective extraction by using mixtures, the time and expense of experimental work can be reduced substantially. This applies as well to the purification of gases by solvent extraction.

Vapor-Liquid Extraction. Since COSMOtherm can predict selective solubilities, it can be a valuable tool for identifying suitable entrainers. It is therefore useful in the many cases where gas streams from a reactor contain significant fractions of low-boiling liquids.

Crystallization. The advantages which pertain to extraction also apply to crystallization, especially as part of the purification process. Most processes depend on the temperature-dependent solubility of the compound to be crystallized. When using COSMOtherm for calculations involving solids, this capability depends on the availability of an experimental ΔG^{fus} for the compounds. If the ΔG^{fus} is not available, a QSPR approach which has been fitted at 25°C can be used for estimations close to this temperature. This parameter and the relative solubility of the solute in different solvents are very useful for solvent selection. When data for a new compound is unavailable, it is often preferable to measure its solubility in any solvent, even a solvent that is not useful for the intended purpose. Once solubility has been measured in any given solvent, COSMOtherm can predict the solubility of the same compound in other solvents.

COSMOtherm's unique methodology for estimating the temperature-dependence of solubility, is more suitable for screening large sets of molecular structures for their solubility than are group contribution and other traditional methods (see Figure 5). This capability also facilitates the development of anti-solvents for use in separative crystallization processes.

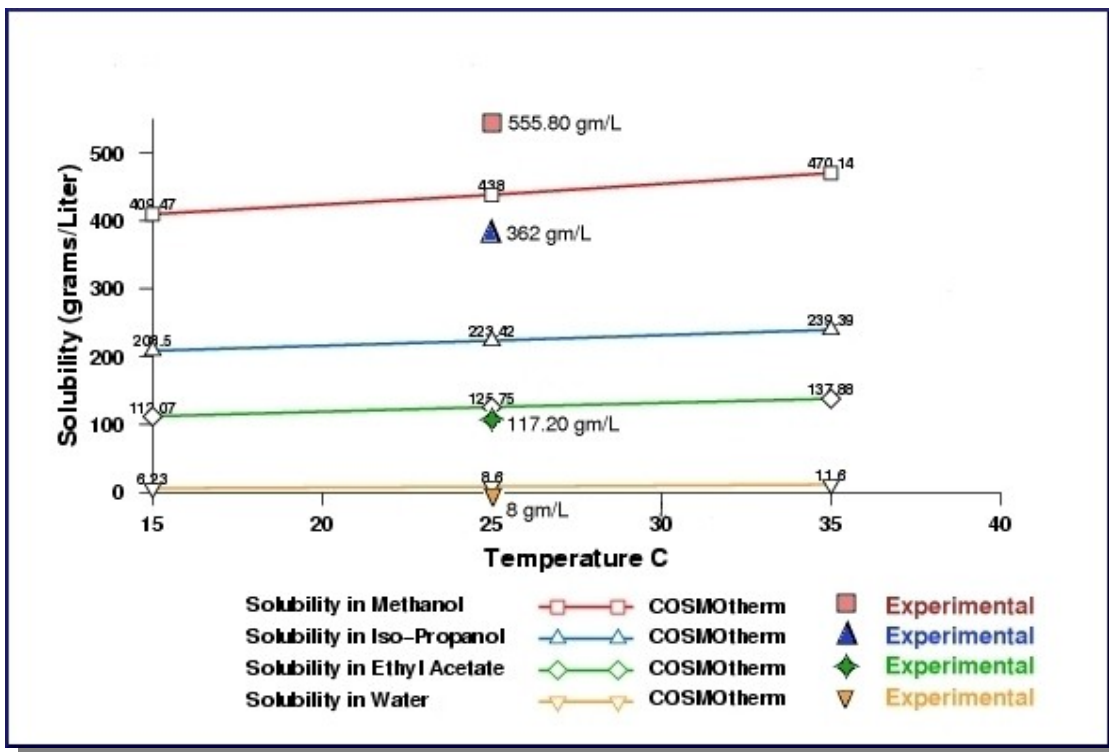


Figure 5. COSMOtherm Prediction of Solubility for 4-hydroxybenzoic acid

• **CHEMICAL REACTION ENGINEERING.** COSMOtherm's ability to estimate activity coefficients and the solubility of new compounds can be useful when applied to reactions which occur in the liquid phase. This application is very important in the design of new products and

for their development. COSMOtherm can also facilitate the selection of effective solvents for reactions which occur in solution by predicting the impact of a solvent on activity coefficients and equilibrium compositions.

• **POLYMERS.** COSMOtherm can provide vital information for developing polymer products. At present, this capability is limited to nonglassy polymers that can be treated as high viscosity liquids, to block co-polymers and, to polar polymers that exhibit a significant combinatorial effect. COSMOtherm can predict the relative solubility of gases, plasticizers and other additives in polymers. Since the permeability of polymer films depends on the solubility of a fluid compound in the polymer, this capability has many industrial applications, especially for the development of membranes. For example, membranes are often used for the selective separation of gases or solutes. COSMOtherm, is a valuable aid in polymer development projects because it can predict how changes in structure or in a functional group can modify the relative solubility and selectivity of a membrane for a gas or a solute.

• **ENVIRONMENTAL ENGINEERING.** In addition to its applicability to the improvement of purification processes for the development of new chemicals and drugs, COSMOtherm is an invaluable aid in the search for more environmentally friendly solvents. Since the solvent replacement is likely to be a mixture, COSMOtherm allows a wider range of potential candidates to be considered than is possible by other methods. Even "green solvents" such as ionic liquids can be treated. COSMOtherm is able to predict the solubility of almost any organic compound in almost any solvent.

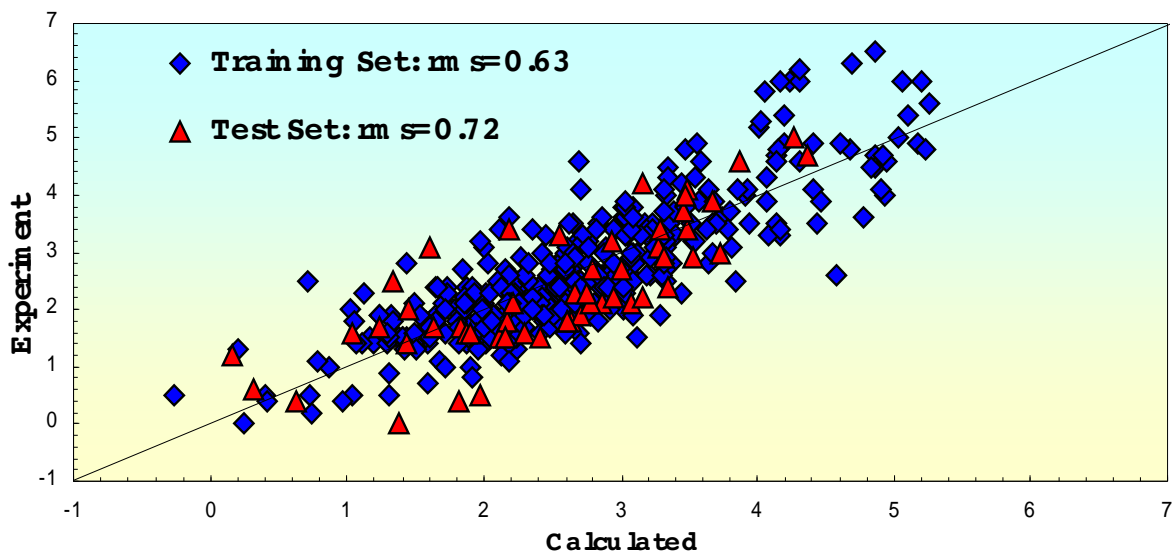


Figure 6. Prediction of soil-water partitioning $\log K_{oc}$

Log(K_{oc}) values of the training set (387 compounds) and a test set (53 compounds)

A. Klamt, F. Eckert, M. Diedenhofen, *Environ. Toxicol. Chem.* 21 (2002) 2562.

Other EHS applications of COSMOtherm include its use for the development of more effective processes for removing potential pollutants from effluents. Additionally, COSMOtherm's ability to predict very low vapor pressures as a function of operating conditions can help prevent the

escape of pollutants. Another important capability is the prediction of solubilities as low as ppb for organic compounds in water. This capability is important for identifying pollutants that are likely to enter the ground water. COSMOtherm can also predict the adsorption of organic pollutants in a wide range of soils by estimating the soil-adsorption coefficient K_{oc} (see Figure 6 above), the solubility of almost any organic compound in water and, many types of partition coefficients such as octanol/water.

Since COSMOtherm does not rely on group contribution methods, it can handle a much wider range of solvents and solutes than other programs can. COSMOtherm is also useful for estimating and cross-checking the values of vapor pressures, Henry's Law Constants and aqueous solubilities which are required for regulatory compliance. Although calculated values have little chance of being accepted by the authorities at present, it is often helpful to know properties in advance, even if only by "orders of magnitude" estimations. This is especially true when vapor pressures or solubilities are extremely low and experimental measurements are expensive and time-consuming.

• **PHARMACEUTICALS.** Among COSMOtherm's validated applications for drug research and development are water solubility, solubility in other solvents, solvent screening and, partition coefficients between different solvents including special partition properties such as log P (octanol/water), logBB and intestinal absorption.

Process Development. Because COSMOtherm can estimate solubilities in various solvents and solvent mixtures as a function of temperature, it can be applied in the development of efficient purification methods during drug production. This powerful tool can be of great value for developing better crystallization processes and for identifying selective solvents for purification as discussed above. COSMOtherm can also help solve the environmental problems of drug manufacture as explained in the Environmental Engineering section above.

Drug Discovery and Design. New drugs are usually designed with specific chemical structures in mind, however, certain parameters such as solubility or distribution coefficients have to be within limits before a drug candidate can be considered for further investigation. COSMOtherm can help determine how small structural modifications may help meet such limitations without impairing the desired functional groups.

Furthermore, COSMOtherm can predict ADME-properties such as logBB, intestinal absorption, human serum albumin binding, and water solubility using a more advanced approach than do most other QSAR tools. A recent enhancement to the program is an extension that includes enzymes. Now, drug receptor interactions can be investigated using this new COSMOtherm interaction model. Since COSMOtherm captures physiological partitioning and drug-receptor binding effectively, it has great potential for drug discovery applications.

Other Software and Hardware Products

COSMOfrag 2.0

The COSMOtherm database (COSMObase) can help identify structurally-similar compounds with desirable properties. At present, however, COSMObase includes σ -profiles for only 3800 compounds and each new compound requires many hours of processing before it can be added to COSMObase. When a large set of compounds with similar structures must be screened, it is too time consuming to create a σ -profile for each one when only a few may merit accurate estimation.

COSMOfrag, an auxiliary program to COSMOtherm which contains a database of over 40,000 drug-like compounds, addresses the special needs of the pharmaceutical industry to spot trends by evaluating the effects of structural changes on the final properties a compound. This advantage is achieved at the expense of accuracy, but COSMOfrag produces results that are sufficiently acceptable for screening purposes. COSMOfrag can also be applied to large-scale drug similarity searches by comparing the σ -profiles of targets and candidates to provide key information about pharmaceutical and physiological interactions.

COSMOfrag can handle almost any compound that can be put together from an arbitrary combination of structures because its database contains such a large number of substructures. This allows for the rapid screening of many thousands of compounds. The results for any specific compound can be checked and refined by using TURBOmole. A screening tool that helps provide good estimates without requiring experimental work gives the drug developer a big advantage in the search for new compounds or for the improvement of proven drugs.

COSMOsim

When used together with COSMOfrag, COSMOsim performs searches on large libraries of σ -profiles to identify new bioisosteric drug candidates by searching for candidates with similar surface polarities while disregarding their chemical structures. Its method is based on the observation that σ -profiles contain information predictive of most ADME properties such as, solubility, blood brain partition coefficients, intestinal absorption and many adsorption phenomena. Since σ -profiles are important factors in the surface interaction of molecules, they are also likely to carry a large part of the information needed for estimating the desolvation and for binding processes that are responsible for the inhibition of enzyme receptors by drug molecules. COSMOsim introduces a novel perspective to drug similarity searching and provides many innovative and complementary ideas for developing new and improved drugs.

TURBOmole

TURBOmole is a quantum chemical package recommended for use with COSMOtherm because of its speed and stability. Unlike other commercially available programs which can be used to create sigma-profiles, TURBOmole was specifically designed to handle molecules of industrial relevance – including those with large, complex structures, - within reasonable CPU-time and memory requirements. Linux and UNIX can be configured to utilize parallel processing to optimize CPU resources. A 'lite' Windows version is also available.

COSMOstation

COSMOstation is a high performance Linux computer optimized for running COSMOtherm. This 64-bit system can run COSMOtherm calculations at high speed as well as display complex 3-dimensional molecular models (VRML) in real-time. It comes preloaded with all necessary COSMOtherm and other applications - ready to run. It also contains all needed COSMOtherm support software and libraries for PERL development and Polyscan and can be pre-loaded with TURBOmole and COSMOfrag.

COSMOlogic SOFTWARE PRODUCTS from TDS

Product	Program Description
COSMOtherm, V2.1	Estimation of thermophysical properties from first principles.
COSMObase	A database of over 4,000 chemical structures that serve as input for COSMOtherm
COSMOfrag, V2.0	A rapid throughput tool for screening drugs for desired properties
COSMOsim	A search tool that identifies drugs that exhibit similar surface polarities
TURBOmole, V5.8	A quantum chemical package for creating σ --profiles

For an interactive COSMOtherm Demo or for more information please contact:



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