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Abbreviations

2D: Two dimensional
3D: Three dimensional
AM1: A semiempirical quantum chemical method
BP-SVP / BP-TZVP: Becke-Perdew\textsuperscript{1,2,3} (BP) functional for density functional theory calculations with a split valence plus polarization function (SVP) or triple valence plus polarization function (TZVP) basis set. The necessary parameterization file does always correspond to one functional and basis set. The term “BP-TZVP parameterization” is thus sometimes used and refers to the COSMOtherm parameterization not the basis set specification.
CAS-Number: The Chemical Abstracts Services registration number is a unique identifier for compounds.
COSMO: COnductor like Screening MOdel
COSMO-RS: COnductor like Screening MOdel for Real Solvents
DB: Database, usually used for the COSMOtherm compound databases.
DFT: Density Functional Theory: A quantum chemical theory used in several software packages for molecular or lattice calculations.
HB: Hydrogen Bond
IL: Ionic Liquid
LFER: Linear Free Energy Relationship
LLE: Liquid Liquid Equilibrium
MW: Molar Weight
QC / QM: Quantum Chemical / Quantum Mechanical
QSPR: Quantitative Structure Property Relationship, also QSAR (A = activity)
\(\sigma\) (sigma): The COSMO screening charge
SLE: Solid Liquid Equilibrium
SMILES: Simplified Molecular Input Line Entry Specification, notation to describe molecules e.g. methane is “C” ethane is “CC” and ethanol is “CCO”
SMS: Sigma Match Similarity
VLE: Vapor Liquid Equilibrium
1 A Quick Start

This chapter is intended as a quickstart guide and addresses the basic steps needed to start a COSMOtherm calculation. All steps are described in more detail in separate chapters. The general procedure for a COSMOtherm calculation involves two steps: compound selection and property input. The Graphical User Interface has panels and dialogues for these steps. The most customary procedures are described in this chapter.

1.1 Compounds

A COSMOtherm calculation requires screening charge distributions of the molecules involved in the system in question. The screening charge distribution can be taken from the screening charge surface of the molecule, as calculated in a quantum chemical COSMO calculation. The result of the COSMO calculation is stored in a COSMO file with the extension .cosmo or .ccf.

In principle, COSMO files can be generated on almost any quantum chemical level. For applications in standard chemical and engineering thermodynamics, we recommend to use the TZVP or the TZVPD-FINE levels. Both levels are based on molecular structures retrieved from DFT calculations, but the TZVPD-FINE level involves additional QM energy calculations with the TZVPD basis set. Generally, COSMOtherm calculations on the TZVP level are faster, while the TZVPD-FINE level gives slightly better results. Depending on the number of compounds involved, the computer power available, and the accuracy required, other levels can be better suited for other purposes.

COSMOtherm reads the compound information from the COSMO file(s) of the compound and transforms the screening charge surface into a screening charge distribution, called $\sigma$-profile. Information about the molecular structure is generally not required and is discarded. Because $\sigma$-profiles for conformers of one compound may differ depending on the molecular structure, conformers have to be calculated individually. If COSMO files of several conformers exist for a compound, they will be combined into a single compound. For detailed information on the selection of conformers for COSMO calculations and on the conformer treatment in COSMOtherm refer to section 5.5.
On start-up, there are two tabs in a COSMOthermX workplace window: COMPOUNDS and PROPERTIES. Compounds can be selected from the COMPOUNDS tab. There are two ways to do this:

- from one of the databases, selecting the required level and clicking the FROM DATABASE button.
- from a directory on your computer system, clicking the FROM FILE button.

To select a compound from one of the databases, select a level, e.g. TZVP, and open the database which lists all available compounds. The database dialog has several functionalities:

- By default, compounds from all embedded databases of the selected level will be listed. Databases can be selected or deselected using the checkboxes in the SELECT DBS TO SEARCH line. A mouse-over will show the location of the database directory.
- Compounds can be tagged for selection by checking the box in the first column. All tagged compounds will be transferred to the compound section in the main window when the GET SELECTION button is pressed.
- Double-clicking a compound will also transfer the compound to the compound section in the main window.
- Clicking on a column header will sort the databases according to that column.
- By default, all conformers of a compound will be selected. However, the box in the USE CONF. column can be untagged: in that case only the lowest-energy conformer will be transferred to the compound section.
- In case a specific conformer other than the lowest energy conformer is needed, first select the complete conformer set. Close the database dialog and highlight the conformer set in the compound section. Use the right mouse button to open the compound context menu and select DECOMPOSE CONFORMER SET. Then delete the unwanted conformers from the compound section by highlighting them and pressing the "Del" key.
- Database tables are searchable. Enter a search string (name, formula, CAS-Number, smiles code) and process the search by pressing SEARCH, or SEARCH SMILES.

To select compounds from a place in your directory tree, click on the FILE MANAGER button. Go to the directory where the COSMO files of the required compounds are located and highlight the files. Several files can be highlighted by keeping the "Ctrl" or "Shift" key pressed while clicking on the file names. To
transfer the highlighted COSMO files to the compound section, press the SELECT button on the left side of the FILE MANAGER window. In case the parameterization is not discernible from the COSMO file you will be asked to choose a parameterization to fit the selected files. Make sure that you use an adequate parameterization, i.e. the one corresponding to the DFT functional and basis set used in the quantum chemical COSMO calculation.

Selected compounds are listed in the compound section. For detailed information on additional options for the compound list please refer to chapter 5.

1.2 Property input

Once the compounds are selected, change to the PROPERTIES tab and select the property you want to calculate. Each property panel comprises fields for the adjustable settings. Settings required for all property calculations are the temperature and the composition of the system. The composition of the system can be set in three ways: if it consists of one compound only, just tick the box in the PURE column. If the system is composed of several compounds, the mole or mass fraction numbers can be set compound-wise in the corresponding fields. Alternatively, the sliders in the compound lines can be used to set the mole or mass fractions. Depending on the property, other input, e.g. the composition of a second phase, might be required.
When all parameters have been set, press the ADD button at the bottom of the input preparation panel to finish the property input. It is possible to prepare input for several COSMOtherm calculations in a single job. To run a job, press the RUN button. Jobs can be saved and run with jobnames. If a jobname is not used, jobs are run as temporary jobs, and input and output files are deleted when COSMOthermX is closed. Job input files can also be saved permanently before running with the SAVE AS button.

1.3 Workplace

It is possible to open several workplace windows inside the main frame. Several jobs can be set up and run at the same time. When a job has finished, calculation results are displayed in separate tabs in the workplace window. To open a new workplace, use NEW JOB from the FILE menu or simply click on the shortcut icon from the toolbar.

If the view is changed to CLASSIC STYLE, the Job list is minimized into the toolbar. The workplace window is enlarged to cover the main window and the COMPOUNDS and PROPERTIES tabs are arranged side by side.
\section{COSMO-RS: Theory, technical details and accuracy}

\subsection{COSMO-RS theory}

COSMO-RS is a predictive method for thermodynamic equilibria of fluids and liquid mixtures that uses a statistical thermodynamics approach based on the results of quantum chemical calculations. The underlying quantum chemical model, the so called “CONductor-like Screening MOdel” (COSMO)\textsuperscript{4}, is an efficient variant of dielectric continuum solvation methods. In COSMO calculations the solute molecules are calculated in a virtual conductor environment. In such an environment the solute molecule induces a polarization charge density $\sigma$ on the interface between the molecule and the conductor, i.e. on the molecular surface. These charges act back on the solute and generate a more polarized electron density than in vacuum. During the quantum chemical (QC) self-consistency algorithm, the solute molecule is thus converged to its energetically optimal state in a conductor with respect to electron density. The molecular geometry can be optimized using the same methods for calculations in vacuum. The time consuming QC calculation has to be performed only once for each molecule of interest.

The polarization charge density of the COSMO calculation (also called screening charge density), which is a good local descriptor of the molecular surface polarity, is used to extent the model towards “Real Solvents” (COSMO-RS)\textsuperscript{5,6}. The (3D) polarization density distribution on the surface of each molecule $i$ is converted into a distribution-function, the so called $\sigma$-profile $p'(\sigma)$, which gives the relative amount of surface with polarity $\sigma$ on the surface of the molecule. The $\sigma$-profile for the entire solvent of interest $S$, which might be a mixture of several compounds, $p_S(\sigma)$ can be built by adding the $p'(\sigma)$ of the components weighted by their mole fraction $x_i$ in the mixture.

$$p_S(\sigma) = \sum_{i \in S} x_i p'(\sigma)$$ \hspace{1cm} (1)

The most important molecular interaction energy modes, i.e. electrostatics ($E_{\text{misfit}}$) and hydrogen bonding ($E_{\text{HB}}$) are described as functions of the polarization charges of two interacting surface segments $\sigma$ and $\sigma'$ or $\sigma_{\text{acceptor}}$ and $\sigma_{\text{donor}}$, if the segments are located on a hydrogen bond donor or acceptor atom. Electrostatic energy arises from the misfit of screening charge densities $\sigma$ and $\sigma'$, as illustrated below.
The less specific van der Waals ($E_{vdW}$) interactions are taken into account in a slightly more approximate way.

$$E_{misfit}(\sigma, \sigma') = a_{eff} \frac{\alpha'}{2} (\sigma + \sigma')^2$$  \hspace{1cm} (2)

$$E_{HB} = a_{eff} c_{HB} \min(0; \min(0; \sigma_{donor} + \sigma_{HB}) \max(0; \sigma_{acceptor} - \sigma_{HB}))$$  \hspace{1cm} (3)

$$E_{vdW} = a_{eff} (\tau_{vdW} + \tau'_{vdW})$$  \hspace{1cm} (4)

Eqs. 2-4 contain five adjustable parameters, an interaction parameter $\alpha'$, the effective contact area $a_{eff}$, the hydrogen bond strength $c_{HB}$, the threshold for hydrogen bonding $\sigma_{HB}$, and the element specific vdW interaction parameter $\tau_{vdW}$. In order to take the temperature dependency of $E_{HB}$ and $E_{vdW}$ into account, temperature dependent factors are applied, each with one adjustable parameter.\(^7\)

The transition from microscopic molecular surface charge interactions to macroscopic thermodynamic properties of mixtures is possible with a statistical thermodynamic procedure. The molecular interactions in the solvent are fully described by $p_S(\sigma)$, and the chemical potential of the surface segments can be calculated solving a coupled set of non-linear equations.

$$\mu_S(\sigma) = -\frac{RT}{a_{eff}} \ln \left[ \int p_S(\sigma^\prime) \exp \left( \frac{a_{eff}}{RT} \left[ \mu_S(\sigma^\prime) - E_{misfit}(\sigma, \sigma^\prime) - E_{HB}(\sigma, \sigma^\prime) \right] \right) d\sigma^\prime \right]$$  \hspace{1cm} (5)

The $\sigma$-potential $\mu_S(\sigma)$ is a measure for the affinity of the system $S$ to a surface of polarity $\sigma$. The vdW energy, which does not appear in Eq. (5), is added to the reference energy in solution (energy of the COSMO calculation). The chemical potential of compound $i$ in the system $S$ (the solvent) can now be calculated by integration of $\mu_S(\sigma)$ over the surface of the compound.

$$\mu^i_S = \mu^i_{c,S} + \int p^i(\sigma) \cdot \mu_S(\sigma) d\sigma$$  \hspace{1cm} (6)

To take into account size and shape differences of the molecules in the system an additional combinatorial term, $\mu^i_{c,S}$, which depends on the area and volume of all compounds in the mixture and three adjustable parameters is added. For information on the exact expression for the combinatorial term refer to the COSMOtherm Reference Manual. The chemical potential can be used to calculate a wide variety of thermodynamic properties, e.g. the activity coefficient:

$$\gamma^i_S = \exp \left\{ \frac{\mu^i_S - \mu^i_i}{RT} \right\}$$  \hspace{1cm} (7)

where $\mu^i_S$ is the chemical potential in the solvent $S$, and $\mu^i_i$ is the chemical potential of the pure compound $i$.

For a more detailed introduction to COSMO and COSMO-RS, refer to the COSMOtherm Reference Manual and the cited literature.
2.2 Quality levels and parameterizations

COSMOtherm reads the input for the compounds directly from COSMO files. At least one COSMO file (.cosmo) or compressed COSMO file (.ccf) has to be selected as compound input. Note that COSMO file names with blanks are not supported by COSMOthermX.

COSMO files delivered with COSMOtherm are available on various quantum chemical levels. The quality, accuracy, and systematic errors of the electrostatics resulting from the quantum chemical COSMO calculations depend on the quantum chemical method as well as on the basis set. COSMOtherm is therefore parameterized separately for each supported method / basis set combination. All of the parameterizations are based on molecular structures quantum chemically optimized at the given method / basis set level. Recommendations for which method to use depend upon the required quality and the intended usage of the predictions.

The application of COSMOtherm in chemical and engineering thermodynamics (e.g. prediction of binary VLE or LLE data, activity coefficients in solution or vapor pressures) typically requires high quality of property predictions of mixtures of small to medium sized molecules (up to 25 non-Hydrogen atoms). For this type of calculations the TZVP or TZVPD-FINE levels are recommended. The TZVP level encompasses a full Turbomole BP-RI-DFT COSMO optimization of the molecular structure using the TZVP basis set, in the following denoted BP-TZVP, and the corresponding parameter file BP_TZVP_C30_1701.ctd. The TZVPD-FINE level, introduced in 2012, is based on a Turbomole BP-RI-DFT COSMO single point calculation with TZVPD basis set on top of an optimized BP/TZVP/COSMO geometry. The COSMO single point calculation is using the TZVPD basis set with diffuse basis functions and a novel type of molecular surface cavity construction (fine grid marching tetrahedron cavity, FINE), which creates a COSMO surface whose segments are more uniform and evenly distributed compared to the standard COSMO cavity. The gas phase energy files of this level are optimized on Turbomole BP-RI-DFT level with TZVP basis set, followed by a single point BP-RI-DFT calculation with the TZVPD basis set. The associated BP_TZVPD_FINE_C30_1701.ctd parameter set additionally incorporates the HB2012 hydrogen bonding term and a novel van der Waals dispersion term based on the “D3” method of Grimme et al., which shows improved thermodynamic property prediction results for compound classes where the classical COSMO-RS hydrogen bonding term showed weaknesses, e.g. with secondary and tertiary aliphatic amines and polyether compounds. On the TZVPD-FINE level, the wider realm of organic liquid and gas phase thermodynamics is predicted with the same quality or slightly better as the standard TZVP and DMOL3_PBE methods. Therefore, the TZVPD-FINE level is considered to be the “best quality” calculation method currently available. Note that the BP-TZVPD-FINE level is subject to ongoing revision and improvement. Thus, the actual predictions of the FINE level may differ more strongly from parameterization to parameterization, than the other, standard parameter sets. Moreover, the FINE level is computationally somewhat more demanding than the other standard methods, which concerns the quantum chemistry calculation as well as the COSMOtherm calculation itself. Nevertheless, users should feel encouraged to try this level: it probably fits their special demands in property prediction better than the standard levels BP-TZVP-COSMO and DMOL3-PBE, in particular if the mentioned compound classes are involved.

If the DMOL3 program package is to be used instead of TURBOMOLE, a prediction quality comparable to that of the TZVP level can be reached with the DMOL3 level. COSMO calculations for the DMOL3 program package employ full COSMO and gas phase geometry optimization with the PBE DFT functional and the
numerical DNP basis set. For the corresponding COSMOtherm parameterization use the DMOL3_PBE_C30_1701.ctd parameter file.

Screening a large number of compounds, e.g. prediction of solubility of compounds in various solvents, typically requires a predictive quality that is somewhat lower than for chemical engineering applications. The molecules involved are often larger (>100 atoms) and an overall large number of compounds has to be computed by quantum chemistry. Thus a compromise between computational demands and quality of the predictions has to be made: A very good compromise is the optimization of molecular geometry on the computationally very cheap semiempirical MOPAC AM1-COSMO level\textsuperscript{11} with a subsequent single point COSMO calculation on Turbomole BP-RI-DFT COSMO level using the small SVP basis set. This method is named BP-SVP-AM1 in the following, and the corresponding parameterization is available in the BP_SVP_AM1_C30_1701.ctd parameter file.

For more information on available quantum chemical levels and parameterizations refer to the COSMOtherm Reference Manual, section 3.

Please note that starting with version C3.0 Release 17.01 of the COSMOtherm program, the unit conversions and fundamental physical constants used in the COSMOtherm parameterizations (Avogadro constant $N_A$, Boltzmann constant $k$, Elementary charge $e$, Electron mass $m_e$, Planck constant $h$, and Electric constant $e_0$) were updated according to the latest NIST/CODATA recommendations\textsuperscript{12}. In older parameterization files, the original values of the physical constants and unit conversions have been retained, to ensure downward compatibility of the predictions with these parameter sets.

### 2.3 Accuracy and Limitations

The main advantage of COSMO-RS is that it uses quantum chemically generated charge density surfaces to describe each molecule and its interactions with other molecules. It is therefore universally applicable without using group parameters or any system-specific adjustments. Electronic group effects such as inductive and mesomeric influences on the polarity are automatically incorporated, as well as intramolecular interactions such as hydrogen bonding. Multifunctional and complex compounds are treated as well as simple organic molecules.

COSMOtherm is an implementation of an advanced variation of COSMO-RS. Still, due to the approximations made within COSMO-RS and the limits of quantum chemistry, predictions are not perfect. The standard error resulting from the COSMOtherm validation applies to a broad range of organic chemistry, but some compound classes are generally described better than others. In order to provide a well-balanced prediction throughout all organic chemistry and all predicted properties, fitting to certain compound classes is not reasonable, since it will usually reduce the accuracy for other compound classes. In the development of COSMOtherm we therefore aim on identifying the physical origin of systematic errors to find a solution within the COSMO-RS framework. Only by directly addressing the physical origins of the errors a general improvement without special adjustments can be achieved.
Some of the present limitations to property prediction with COSMOtherm come from COSMO-RS theory itself. In COSMOtherm however, these limitations are not as pronounced as in less advanced implementations of COSMO-RS:

- COSMO-RS is an equilibrium theory. Non-equilibrium properties cannot be predicted directly.
- COSMO-RS is a theory of incompressible liquids. System which cannot be treated with this approximation (gases, solids and critical systems) have to be treated with additional (external) information. The gas phase is treated as ideal. COSMO-RS cannot predict fugacity.
- After the QM calculations are done, COSMO-RS neglects the 3D geometry (except in extensions as Flatsurf and COSMomic). Larger systems with internal cavities are therefore beyond COSMO-RS. Furthermore, effects like cooperative binding cannot (yet) be taken into account.
- Long range Coulomb interaction is not described by COSMO-RS. While this is not a problem for pK\textsubscript{a} prediction or ionic liquids, treatment of diluted electrolytes requires an additional (external) Debye-Hückel contribution. While salt-in or salt-out effects can be predicted to a certain extent, activity coefficients of small ions in water are beyond the theory.
- The properties of strong (hydrogen) bonds (e.g. formed by OH\textsuperscript{-} or atomic metal-ions in solvent water) are not fully taken into account. This may lead to problems in systems that are near the Brönsted-limit of high ionic strength, e.g. resulting in physically wrong behavior such as “salting in”.

Please note that errors in COSMOtherm are not normal distributed. Some compound classes are described better than others (alcohols vs. amines). This has been mostly corrected with the TZVPD-FINE level. Furthermore, best predictions are made at room temperature. Deviations increase for low or high temperatures.

Generally, errors for quantities ranging over several decades, like pK\textsubscript{a}, ln(\gamma), logP, or ln(Pressure), are best expressed in ln- or log-units. As shown for the vapor pressure example below, absolute or relative errors in mbar are asymmetric and not very useful.

<table>
<thead>
<tr>
<th>prediction [mbar]</th>
<th>RMSE = 0.68 ln-units</th>
<th>Range [mbar]</th>
<th>Deviation [mbar]</th>
<th>Dev. [%]</th>
<th>Chance to be better</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 1 RMSE</td>
<td>0.68</td>
<td>1.96</td>
<td>255 to 980</td>
<td>-245 to 480</td>
<td>-49% to 96%</td>
</tr>
<tr>
<td>500 2 RMSE</td>
<td>1.35</td>
<td>3.86</td>
<td>130 to 1930</td>
<td>-370 to 1430</td>
<td>-74% to 286%</td>
</tr>
<tr>
<td>500 3 RMSE</td>
<td>2.03</td>
<td>7.59</td>
<td>66 to 3795</td>
<td>-434 to 3295</td>
<td>-87% to 659%</td>
</tr>
<tr>
<td>500 4 RMSE</td>
<td>2.70</td>
<td>14.91</td>
<td>34 to 7455</td>
<td>-466 to 6955</td>
<td>-93% to 1391%</td>
</tr>
</tbody>
</table>

Predictions of infinite dilution activity coefficients (IDAC) of various UNIFAC variants and two COSMO-SAC versions were compared by Gerber and Soares\textsuperscript{13}. We used the same dataset to evaluate the COSMOtherm predictions.

Two different data sets have been used for the study of infinite dilution activity coefficients. The first set consists of organic solvents only, while the second set contains organic solvents and water. Some important chemical functionalities are not included in both sets, among them amines, aniline, thiol compounds, imines, cyano groups, and nitro groups. Bi- or poly functional molecules are also not included, e.g amino acids, diols, glycerols, halogenated acids.
### Dataset overview

<table>
<thead>
<tr>
<th></th>
<th>non-water dataset</th>
<th>water dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total data points</td>
<td>386</td>
<td>359</td>
</tr>
<tr>
<td>Temperature range / [K]</td>
<td>293 K</td>
<td>283 K</td>
</tr>
<tr>
<td></td>
<td>393 K</td>
<td>373 K</td>
</tr>
<tr>
<td>Substances</td>
<td>50</td>
<td>257</td>
</tr>
<tr>
<td>Gamma ∞</td>
<td>0.54</td>
<td>76.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.74E+09</td>
</tr>
<tr>
<td>Chemical diversity</td>
<td>very low</td>
<td>low to medium</td>
</tr>
</tbody>
</table>

Results for COSMO-SAC and UNIFAC have been taken from the publication by Gerber and Soares. Only the best UNIFAC variants of that paper are presented here. Two COSMO-SAC variants are included in the comparison, the published literature variant (lit.) and a variant with adjusted (adj.) parameters. COSMOtherm results have been calculated using the BP_TZVPD_FINE_C30_1501 parameterization.

<table>
<thead>
<tr>
<th>Methods</th>
<th>IDAC results for the non-water DB</th>
<th></th>
<th>IDAC results for the water DB</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># points</td>
<td>AAD</td>
<td>RMSE</td>
<td>Max dev</td>
</tr>
<tr>
<td>UNIFAC (1)</td>
<td>374</td>
<td>0.28</td>
<td>0.39</td>
<td>1.74</td>
</tr>
<tr>
<td>UNIFAC (2)</td>
<td>386</td>
<td>0.12</td>
<td>0.17</td>
<td>0.88</td>
</tr>
<tr>
<td>COSMO-SAC-D (lit.)</td>
<td>361</td>
<td>0.59</td>
<td>0.81</td>
<td>2.77</td>
</tr>
<tr>
<td>COSMO-SAC-D (adj.)</td>
<td>361</td>
<td>0.48</td>
<td>0.57</td>
<td>3.10</td>
</tr>
<tr>
<td>COSMOtherm</td>
<td>386</td>
<td>0.35</td>
<td>0.53</td>
<td>3.42</td>
</tr>
</tbody>
</table>

AAD: absolute average deviation, RMSE: root mean square error

It is noteworthy, that while the COSMOtherm calculations include all data points of both sets, the COSMO-SAC data have only been published for reduced sets. The UNIFAC (1) calculations were also done for subsets of the non-water dataset and the water dataset, respectively, and the UNIFAC (2) calculations for the water dataset were done for 114 points only.

UNIFAC shows the best RMSE among the compared methods when used on mono-functional organic solvents with limited chemical diversity. With respect to overall accuracy however, COSMOtherm outperforms UNIFAC and COSMO-SAC. Even the adjusted version of COSMO-SAC has higher AAD and RMSE values than COSMOtherm.
3 COSMOTHERM and COSMOTHERMX

COSMOTHERM is a command line/file driven program which can be run directly from a UNIX or DOS shell. It allows for the calculation of any solvent or solvent mixture and solute or solute system at variable temperature and pressure. COSMOTHERM uses the chemical potentials derived from COSMO-RS theory to compute all kinds of equilibrium thermodynamic properties or derived quantities, e.g.:

- Vapor pressure
- Free energy of solvation
- Activity coefficients
- Partition coefficients
- Solubility and solid-liquid equilibria (SLE).
- Liquid-liquid equilibrium (LLE) and vapor-liquid equilibrium (VLE)
- Phase diagrams, azeotropes, miscibility gaps, excess enthalpies and excess free energies
- pKₐ of acids and bases
- Various QSPR models
- Reaction constants
- Liquid extraction equilibria

COSMOTHERMX is a Graphical User Interface to the COSMOTHERM command line program. It allows for the interactive use of the COSMOTHERM program, i.e. selection of compounds, preparation of property input, program runs and display of calculation results.
3.1 Flowchart of a property calculation with COSMOthermX

Start

Select compounds from the Databases or the File Manager

Found all compounds?

Yes

Select settings for property calculations

Add

Another property?

Yes

Add compounds to database

No

Use the New Molecule Wizard to generate COSMO files and/or gas phase structures.

TURBOMOLE

Run
3.2 The main window

In the default view, the main window has a Job List frame on the left and space for several resizable workplace frames in the major section. At startup, a workplace window has a panel for the compound list (COMPONENTS) with database access and another panel for property input preparation (PROPERTIES).

The COSMOthermX main window has several menus, some of them also available from shortcut icons in the toolbar:

File:
- NEW JOB: Create a new input file in a new workplace window.
- OPEN JOB: Open an existing input file from a file browser dialog. Select a file from the directory or type the filename into the “File name” text field and press “Open”.
- SAVE: Save the input file to the current directory with the actual name.
- SAVE AS...: Choose a directory and a name for the input file to be saved.
- CLOSE JOB: The job selected from the job list is removed from the list. All input and output files of the job are kept.
- DELETE JOB: The job selected from the job list will be deleted, together with all input and output files of the job.
- QUIT: Exit the program.

Edit:
- COPY: Copy text from a text editor window or compounds from a workplace.
- PASTE: Paste selected text to a text area, respectively compounds to a workplace.
FIND: Find a search string in a text output.

SELECT ALL: Select text from a text output.

EDIT INPUT FILE: Open the actual input file in a text editor window. The input file can be changed manually, e.g. for additional input in the compound lines (further information: COSMOTHERM Reference Manual). The input file can be saved or COSMOTHERM can be run. Note that not all changes can be read in when the input file is re-opened with COSMOTHERM X.

OPEN WORKPLACE: Open a new workplace window.

Compounds:

SVP: Select compounds from the compound databases or the file system, or load a compound list. Level is set to SVP.

TZVP: Select compounds from the compound databases or the file system, or load a compound list. Level is set to TZVP.

TZVPD-FINE: Select compounds from the compound databases or the file system, or load a compound list. Level is set to TZVPD-FINE.

DMOL3: Select compounds from the compound databases or the file system, or load a compound list. Level is set to DMOL3.

FILE MANAGER: A compound can be selected from an arbitrary directory.

LOAD COMPOUND LIST: A list of previously saved compounds can be loaded with this option. The saved concentrations of the compounds will also be loaded but not automatically applied.

SAVE COMPLETE COMPOUND LIST: With this option it is possible to save the complete compound list to a file for later use. The concentrations are also saved. To save only the selected compounds to a list use the SAVE TO COMPOUND LIST option from the compound list context menu has to be used.

RESTORE LIST CONCENTRATIONS: Apply the saved list concentrations after loading a compound list. The saved concentrations of the compounds will not be applied automatically when a list is opened.

NEW MOLECULE: This option allows for searching for a compound by name, CAS-Number, SMILES or structure in the New Molecule tool. It also offers the possibility to generate a new structure with TURBOMOLE or COSMOconf (if installed).

Run:

RUN: The actual input file is saved automatically with the current file name and COSMOTHERM is run.

RUN (EXTERNAL) INPUT: A COSMOTHERM calculation can be run with an external input file, without opening it in the GUI. Any valid COSMOTHERM input file can be run.

STOP RUNNING JOBS: Running COSMOTHERM Jobs can be selected and stopped.

Result:

OPEN: COSMOTHERM output files and table files as well as COSMOmic files can be selected from a directory. Alternatively, type the filename into the “File name” text field and press “Open”.

© COSMOlogic
SHOW RESULTS: Output and table files of the active job will be opened in separate tabs of the workplace window.

VIEW AS .XLS: The table file of the active job will be opened in a spreadsheet program (if available)
VIEW AS TEXT: The table file of the active job will be opened in a text editor.
SAVE AS .XLS(X): The table file of the active job will be saved in MS Excel format.
SHOW EXTENDED OUTPUT: By default, only the summary table with a truncated number of columns is displayed in a table editor. With this option, the complete results table will be displayed.
HIDE EXTENDED OUTPUT: The summary table will be displayed. The number of columns is truncated to allow for a concise representation of results.
SAVE OUTPUT FILE AS: The output file can be saved in text format.

Extras:
GLOBAL OPTIONS: A panel with general calculation options, including options for gas phase energy input, units, COSMOtherm output print options, additional output files and program control. For a detailed description see below.
PROPERTY OPTIONS: A panel with special options applied to specified property calculations only. For individual property calculations, print options for output and table files can be set, program control settings can be changed, and compound specific options can be set. The PROPERTY OPTIONS dialog is used to apply options to a certain property calculation only. Thus, it is possible to use different options in a single COSMOtherm run. For a detailed description see below.
CONFORMER OPTIONS: This dialog allows users to apply options to compound conformers individually or collectively. Options can be given in the text area of the respective conformer.
VIEWER SETTINGS: Change atom / bond color, show or hide label, change sphere / cylinder smoothness and so on.
PREFERENCES: Opens the PREFERENCES dialog where some settings are already specified: Paths for the COSMOtherm executable and the CTDATA directory of the COSMOtherm installation are set, and the parameter files for the quantum chemical levels are specified. Additionally, you can set paths for the Adobe Acrobat Reader and a web browser. If you intend to use COSMO metafiles (extension .mcos) for the fragment approach, you should also specify the fragment directory. When the path for the QSPR property directory is set QSPR coefficient files (extension .prop) can be read from there. For details see below.
DATABASES: Opens the PREFERENCES dialog with the COMPOUNDS tab. The databases that come with the COSMOtherm release are specified here. Additional databases can be added with ADD DATABASES. For detailed information on adding your own databases, refer to the section “COSMO files and Databases”.
IMPORT SETTINGS: Settings from other COSMOthermX versions can be imported.
Tools:
COSMOVIEW: Opens the COSMOview tool which allows for the visualization of .wrl files generated by COSMOtherm. For more information, please refer to the section “Using COSMOview”.

COSMOWEIGHT: Opens the COSMOweight tool. For information on atom weighting and the COSMOweight tool, please refer to section 8.3.

COSMOBASE EDITOR: Opens the COSMObase Editor which allows for creating and administration databases of compound COSMO, gas phase energy and Vapor Pressure / Property files. For details, refer to the section “The COSMObase Editor”.

View:
CLASSIC STYLE: Arrange frames similarly to the view in previous COSMOthermX versions (up to version C30_1301). The Compounds panel is moved internally to a separate frame on the left side of the Properties panel. The Job list is disconnected from the main frame.

DEFAULT STYLE: Restore the default arrangement of frames in the main window. The Job list is expanded in the main window and the Compounds and Properties panels are arranged in tabs in the workplace window.

LAPTOP STYLE: The Job list is disconnected from the main frame and the workplace window is enlarged to fill the complete main frame.

 TILE WINDOWS: Arrange workplace windows in tiles in the main window.

CASCADE WINDOWS: Arrange workplace windows in a cascade in the main window.

License:
IMPORT LICENSE: Opens a file browser for the selection of a license file. Use to change from demo mode to full COSMOtherm.

CHECK LICENSE: Display license information in a text viewer window.

Help:
PHYSICAL CONSTANTS: Displays information about some physical constants and conversion factors.

OPEN EXAMPLE: Opens a file browser in the COSMOtherm Examples subdirectory. Example input files can be opened and run in COSMOthermX. For an overview of available example input files refer to Appendix C: Example Input .

COSMOHERM MANUAL: Open the COSMOtherm Reference Manual with the Adobe Acrobat Reader.

COSMOHERM USER GUIDE: Open the COSMOthermX User Guide (this document) with the Adobe Acrobat Reader.

COSMOMIC MANUAL: Open the Manual for the COSMOMIC extension.

CHECK FOR UPDATES: Check online for available updates.

ABOUT: Information about the current COSMOthermX version is displayed.
LICENSE AGREEMENTS USED: A list of external libraries and software tools employed and the corresponding license terms.

RESET PREFERENCES: The COSMOlogic AppData subdirectory is deleted and the configuration is reset to the installation status.

### 3.3 Job list

By default, the Job list is held separately in a retractable frame on the left side of the main window. Jobs opened via the OPEN button in the main window will be listed in the job list and opened in a workplace window. The job status is depicted by a status icon.

- In preparation 📒
- Running ⌛
- Finished successfully ✅
- Error ⚡
- Stopped ⏹

A right mouse button click on a job in the compound list opens a context menu with several options for the highlighted job. All jobs in the job list (jobs saved in previous sessions and temporary or saved jobs from the current session) can be closed, opened in a workplace window, or deleted individually. When deleted, all files and job directories belonging to the respective job are deleted from the file system. VIEW JOB DIRECTORY will open a file manager with the path of the job directory. CLOSE ALL JOBS will remove all jobs from the job list but retain the files belonging to the jobs. MANAGE JOBS will open the context menu for the highlighted job.

### 3.4 The Workplace Window

Each workplace window belongs to a specific job in the Job list and displays the settings used for that job. When opened with the NEW JOB option, a job’s workplace window has tabs for compound selection and property prediction. When a job has run, results (output file, summary table file, other files depending on the job type and settings) will be displayed in separate tabs in the workplace window of the respective job.

The elements in the workplace window can be arranged in different styles. In the DEFAULT STYLE, the Job list is kept in a retractable frame on the left side of the main window. The workplace window is floating and the tabs COMPOUNDS and PROPERTIES are arranged back-to-back.

If the view is changed to CLASSIC STYLE, the Job list is minimized into the toolbar. The workplace window is maximized to fill the main window and the COMPOUNDS and PROPERTIES tabs are arranged side by side.

LAPTOP STYLE is designed for small displays. The Job list is retracted and the workplace window is maximized with the tabs COMPOUNDS and PROPERTIES arranged back-to-back.
3.5 Preferences

The Preferences dialog allows users to customize COSMOTHERM X settings.

![Preferences dialog](image)

**General:**

**DO NOT LOAD PREVIOUSLY SAVED JOBS ON START UP:** COSMOTHERM X starts with an empty job list.

**CHECK FOR UPDATES AUTOMATICALLY:** Specify an interval at which to check for updates regularly.

**SHOW IONIC LIQUID DBU PROJECT INFO:** A message box with information about the IONIC LIQUID PROPERTIES calculation will be displayed.

**SWITCH OFF JAVA EXCEPTION WARNING:** The user can be alerted to Java exceptions by a button in the upper right corner of the COSMOTHERM X window. When a Java exception occurs, the button will change color from green to red.

**USER DIRECTORY:** If you intend to save input files the specified user directory will be used as starting point for the file select dialog if the corresponding checkbox is ticked. After saving a file, the last used directory will be used as long as COSMOTHERM X is not closed.

**DATA DIRECTORY:** If a path is set and the checkbox activated, the FILE MANAGER, the OPEN file dialog in COSMOView and other OPEN / SAVE dialogs involving compound handling will use this path on first start.

**.PDF READER PATH:** A path to a pdf reader can be set.

**Appearance:**

**LAYOUT STYLE:** Switch between Default, Classic and Laptop style for COSMOTHERM X.

**FONT TYPE:** Change font type and size.

**SHOW EXTENDED INFO OF COMPOUND:** If selected, further information about compounds will be listed in the compound section of the workplace window, e.g. the number of conformers constituting a compound.

**COMPOUND DATABASE VIEW:** The fields in the COMPOUND DATABASE VIEW dialog apply to the database tables.

**SHOW FILE TREE (FILE MANAGER):** Changes the way the file browser displays the directories on the system in the FILE MANAGER.
**Jobs:**

**COSMOThERM EXECUTABLE PATH:** Path for the COSMOtherm command line executable.

**CTDATA DIRECTORY:** Path for the CTDATA directory. The parameter files are stored in the CTDATA directory.

**QSPR PROPERTY DIRECTORY:** Path for the directory where the QSPR coefficient files are stored.

**FRAGMENT DIRECTORY (CFDB):** A directory where cosmo files constituting *mcos* files are stored.

**COSMOQUICK INSTALLATION DIRECTORY:** Path for the COSMOquick installation to be used when starting a fragmentation run from the New Molecule wizard.

**TMOLEX INSTALLATION DIRECTORY:** Path for the TmoleX installation to be used when starting quantum chemical calculation from the New Molecule wizard.

**COSMOCONFX INSTALLATION DIRECTORY:** Path for the COSMOconfX installation to be used when starting conformers searches from the New Molecule wizard.

The fields in the **PARAMETERIZATION** section indicate which parameter file is used in combination with the databases of a certain level. A preferred level for COSMOtherm property predictions can be selected in the **LEVEL PREFERENCE** section. A unit system for calculation output can be selected in the **UNITS** section. In the Options section, **DELETE TEMPORARY SCREENING FILES** can be checked if temporary files from screening calculations, e.g. solubility screening should not be kept after the calculation is finished. Input and output concentration systems can be changed from MOLE FRACTION to MASS FRACTION or SURFACE FRACTION in the **CONCENTRATIONS** section.

**Processing:**

**SHOW MEMORY USAGE:** When enabled, the amount of memory used will be displayed in the menu bar in COSMOthermX.

**CPUS TO USE:** COSMOthermX will use the indicated number to distribute the separate jobs for screenings. Note that it is recommended to set at least one CPU less than available on the machine.
Compounds:
Compound databases are specified here. The databases that come with the COSMOtherm release are specified here. Additional databases can be added with ADD DATABASES. For detailed information on adding your own databases, refer to the section “COSMO files and Databases”.

Favorites:
Customize the FAVORITES group in the properties selection panel. A maximum of six properties can be selected as FAVORITES.

Results:
OPEN OUTPUT FILE FOR EVERY RESULT: The .out file of COSMOtherm will be opened in a separate tab in the workplace window.

OPEN ERRORLOG FILE FOR EVERY RESULT: Errors and warnings from .out and .tab files will be collected into a .err file and displayed in a separate tab in the workplace window.

SHOW EXTENDED OUTPUT BY DEFAULT: With this option, the complete results table will be displayed. Usually only the summary table with a truncated number of columns is displayed in a table editor, and extended output is displayed only when the corresponding checkbox in the table file panel is selected.

SHOW PDB (COSMOMIC): The micelle structure from the pdb file will be displayed as a wireframe model.

HIDE HYDROGENS IN PDB VIEWER: Hydrogen atoms will not be displayed.

Remote Jobs:
Settings for quantum chemical calculation using Turbomole and COSMOconf on remote computers can be supplied in the REMOTE JOBS panel. Remote jobs require command line installations of COSMOconf and TURBOMOLE (Version 6.4 or newer) on the remote computer. Note that COSMOconfX supports only Linux systems as remote machines. When a job is run on a remote machine, the input data are transferred there. On finishing, the results are copied back from the remote system to the local machine.

At the top of the REMOTE JOBS panel settings for external machines can be created or imported.
Clicking the ADD NEW MACHINE button opens a dialog where information required for the remote system can be entered. Once defined, the machine settings can be saved and used to start jobs on the remote machine.

**MACHINE/IP:** Machine name or IP address of the remote machine.

**USER:** Login name of the user.

**PASSWORD:** Password of the login defined above. The password will be held in memory but not saved to disk. Once the GUI is closed, all passwords are unset. It is recommended to use CHECK PASSWORD SETTINGS after typing a password.

**GROUP NAME:** The machines can be organized by groups. A new machine will either be assigned to an existing group or a new group will be opened.

**Expert Settings:** Additional login parameters for ssh and scp can be set.

**WORK DIRECTORY:** Already existing directory that will be used for the COSMOconf calculations. Please note that the user needs read and write permissions for this directory on the remote system.

**TURBOMOLE DIRECTORY:** Path to the TURBOMOLE installation. This path is named $TURBODIR in the TURBOMOLE documentation.

**COSMOCONF DIRECTORY:** Path to COSMOconf installation (amongst others, this directory contains the cosmosconf_job_wrap.pl and the install script).
NUMBER OF CPUs FOR JOB(s): No definition needed. The value will be taken from the number of CPUs definition of the run button.

CHECK REMOTE SYSTEM EVERY ... MIN: Time interval for the checks of the remote jobs. Because the remote system needs to be connected and some data need to be transferred, it is recommended to use moderate values like the 1 minute default.

TURBOMOLE VERSION: The TURBOMOLE version can be chosen. Optional.

USE QUEUING SYSTEM: In order to activate the use of a queuing system the USE QUEUING SYSTEM checkbox of the machine settings needs to be checked.

Because of the diversity of modern queuing systems this section cannot provide useful default values. The SUBMIT WITH and CHECK STATUS fields contain the commands for job submission and status check. The latter one will be used by the GUI in order to get information about the job status. On the right hand side of the panel there are two textboxes that can be used to add code to the shell script that will be submitted. Please note that sh (/bin/sh) is used automatically, i.e. do not give a #!/bin/ line. Furthermore, the TURBOMOLE and COSMOconf paths are set automatically. The SCRIPT AFTER JOB EXECUTION text area is useful if you like to do some post-processing on the remote machine.

A script for a serial run using the PBS queuing system could read like:

```
#Name of your run :
#PBS -N COSMOconf-job
#Number of nodes to run on:
#PBS -l nodes=1
#
#Export environment:
#PBS -V
#Change to the input file directory
cd $PBS_O_WORKDIR
```
A minimal script for Univa Grid Engine™ would read like below. In this example, it is important to change the directory to the directory where the input files are.

```bash
## Execute this script in the same directory where it was
## submitted and where the input files are
#$ -cwd
## Merge the standard out and standard error to one file
#$ -j y
```

The panel has two check boxes that trigger the export of parallel TURBOMOLE settings (PARNODES and PARA_ARCH). If more than one CPU is required, both options are checked by default. PARNODES will be set to the NUMBER OF CPUs FOR JOB(s). If, for any reasons, other parallel TURBOMOLE settings should be used, it is possible to uncheck the default and put the new settings into the SCRIPT BEFORE JOB EXECUTION section of the submit script. Nevertheless, if parallel TURBOMOLE should be used the number of nodes has to be indicated. An appropriate entry in the SCRIPT BEFORE JOB EXECUTION section of the submit script is essential.

Please note: the “FINE level COSMO” calculations have not been parallelized yet. All job definitions containing the FINE level will be started as serial jobs automatically.

The checkbox ADD–NP NUMBER OF CPUS allows for the use of the multi-thread perl parallelization instead of the TURBOMOLE MPI parallelization. In this case the user needs to ensure that only one node with multiple cores is used. The current implementation will not spread tasks over various nodes.

### 3.6 Global Options, Property Options and Conformer Options

There are different types of options in COSMOtherm. Global options comprise options that are applied universally to all compounds and property calculations, as well as general file handling options. Some options can also be set for property calculations or compounds individually instead of generally. Property options are options that are applied to the specified property calculation only, while conformer options refer to options applied individually for specified conformers or conformer sets.

#### Global Options

The GLOBAL OPTIONS dialog lists options for gas phase energy input, units, COSMOtherm output print options, additional output files, program control and QSRR options. A text area allows for additional COSMOtherm keywords to be entered. The dialog can be opened from EXTRAS or directly from the icon bar in the main window.

GLOBAL OPTIONS apply for the complete COSMOtherm run, i.e. all temperature / mixture / property lines in the input. It is also possible to save the global option settings to a file and to load previously saved global options.

#### Gas phase estimation:

USE ENERGY FILE: The gas phase energy is required for certain properties (e.g. the calculation of the chemical potential in the gas phase). It can be taken from a gas phase quantum chemical calculation (.energy file) or empirically estimated by COSMOtherm. If possible, the quantum chemical calculated value of the
gas phase energy should be used. Energy files from COSMObase use Hartree units. If this option is checked COSMOTHERM will use the energy file if no adequate pure compound properties are available.

**USE COMPOUND PROPERTY FILE:** For some properties experimental vapor pressure data can be used. The relevant pure compound property data are taken from the .vap file. The Antoine or Wagner coefficients might be used in this case.

**Units and concentrations:**
The units for the general COSMOTHERM output of the calculated properties can be chosen here. Settings from the GLOBAL OPTIONS dialog precede settings from the PREFERENCES.

**Print options for the COSMOTHERM output and table files:**
- **PRINT COMPOUND/MIXTURE NUMBER:** Write compound / mixture number to the right side of the output file. This may be useful for efficient processing of the output file.
- **PRINT CONFORMER INFO:** If a compound input consists of several conformers this option causes the output of the calculated COSMOTHERM mixture information to be written for each individual conformer. By default, only the results for the mixed compound are written to the output file.
- **SUPPRESS PURE COMPOUNDS INFO:** Pure compound information will not be written to the output file.
- **SUPPRESS MIXTURE OUTPUT IN .OUT FILE:** Mixture information will not be written to the output file.
- **PRINT 15 DIGIT LONG NUMBERS TO .OUT-FILE:** Print all real numbers in scientific exponent number format with 15 significant digits to the output file.
- **PRINT FULL LENGTH ATOMIC WEIGHT STRING:** Print complete atomic weight or real weight string to the compound section of the output file. If you toggle this option, the line for the atomic weights may become very long.
- **PRINT MOLECULAR SURFACE CONTACTS:** Print statistics of molecular surface contacts for all compounds in all mixtures to the output file. For a detailed description see section 5.7 of the COSMOTHERM Reference Manual.
- **PRINT DETAILED SEGMENT MOLECULE CONTACTS:** Print statistics of the molecular surface contacts for all segments of all compounds in all mixtures to the output file and to the contact statistics table file name.contact. Refer to the COSMOTHERM Reference Manual, section 5.7, for details.
- **PRINT FULL COMPOUND NAMES IN TABLE ENTRIES:** Print full compound and/or molecule names to all tables in the table file and the sigma-moments file. By default the compound/molecule names are cropped after 20 characters.
- **PRINT ADDITIONAL COMPOUND INFORMATION TO .OUT (LEVEL1):** Print additional debug information to the output file. Currently this option toggles the printing of the following additional information: 1) Molecular symmetry point groups. 2) Molecule principal moments of inertia. 3) Zwitterion information. 4) If the PRINT CONFORMER INFO [wconf] option is also given, the conformer weight prefactors are printed to the mixture conformer output.
- **PRINT ADDITIONAL COMPOUND INFORMATION TO .OUT (LEVEL2):** Print additional debug information to the output file (second level). Currently this option toggles the printing of the following additional information: 1) All
debug information as produced by the LEVEL1 option. 2) in combination with the the PRINT CONFORMER INFO [wconf] option, for each molecule the atom-wise contributions to the interaction energy terms (chemical potential \( \mu_i \), total mean interaction energy \( H_{\text{tot}} \), misfit interaction energy \( H_{\text{mis}} \), H-Bond interaction energy \( H_{\text{Hb}} \) and van der Waals interaction energy \( H_{\text{vdW}} \)) are printed to the conformer mixture section of the output file. 3) Molecule principal moments of inertia eigenvectors. 4) Number of irreducible representations of molecular symmetry point groups.

PRINT "NA" (NOT AVAILABLE) TO TABLE INSTEAD OF BLANK SPACE: Empty fields in tables are indicated with NA. Useful for processing of table files in spreadsheet programs.

Additional output files:

\( \sigma \)-MOMENTS (.mom): Write the \( \sigma \)-moments of all processed compounds in tabulated form to filename.mom. In addition some other molecular information will be written to filename.mom, including volume \( V \), molecular weight, dielectric energy \( E_{\text{die}} \), average energy correction \( dE \), van der Waals energy in continuum \( E_{\text{vdw}} \), ring correction energy \( E_{\text{ring}} \) and the standard chemical potential of the molecule in the gas phase with respect to the ideally screened state \( \mu^{\text{QSPR}}_{\text{gas}} = E_{\text{COSMO}} - E_{\text{gas}} + dE + E_{\text{vdw}} + E_{\text{ring}} - \mu_{\text{gas}}RT \), using \( T = 25^\circ C \). Please note that \( \mu^{\text{QSPR}}_{\text{gas}} \) is only used as special QSPR descriptor and is only loosely connected to the gas phase chemical potential used otherwise). Refer also to sections 5.4 and 5.5 of the COSMOtherm Reference Manual.

ATOMIC \( \sigma \)-MOMENTS (.moma): Write the atomic \( \sigma \)-moments of all processed compounds to filename.moma. If this option is used, \( \sigma \)-moments will be calculated for each atom of the compounds.

\( \sigma \)-PROFILES (.prf): Write the \( \sigma \)-profiles of all processed compounds to file filename.prf. A summary of the \( \sigma \)-profiles will be written in tabulated form to the table file filename.tab.

\( \sigma \)-POTENTIALS (.pot): Write the \( \sigma \)-potentials of all calculated mixtures to filename.pot. A summary of the \( \sigma \)-potential information will be written in tabulated form to the table file filename.tab.

GENERATE VRML (GEOMETRY): Create VRML files name_mol.wrl of the molecular geometry of all compounds. The files will be written to the job directory in the next COSMOtherm run.

GENERATE VRML (\( \sigma \)-SURFACE): Create VRML files name_sig.wrl of the molecular COSMO surface charges of all compounds. The files will be written to the directory of the selected input file in the next COSMOtherm run.

VRML, the “Virtual Reality Modeling Language”, is a script language allowing for the interactive examination of virtual three-dimensional objects. VRML files are usually identified by the extension .wrl. All VRML files generated by COSMOtherm can be viewed by the internal VRML viewer of COSMOtherm, offering advanced functionality like colour correction and charge picking. For more information refer to the section ‘Using COSM0view’.

Otherwise, VRML files can be viewed with common World-Wide-Web browsers such as Mozilla Firefox or Microsoft Internet Explorer if an appropriate VRML browser plug-in has been installed. Plug-ins are freely available, e.g. the Cortona VRML client (http://www.cortona3d.com/cortona3d-viewers).

MOLECULAR GEOMETRY IN BROOKHAVEN-PDB FORMAT: Write molecular structure in .pdb format.

MOLECULAR GEOMETRY IN BROOKHAVEN-MOL FORMAT: Write molecular structure in .mol format.

MOLECULAR GEOMETRY IN MDL/ISIS-SDF FORMAT: Write molecular structure in .sdf format.

MOLECULAR GEOMETRY IN MSI-CAR FORMAT: Write molecular structure in .car format.
**Molecular geometry in Tripos/Sybyl-ML2 format:** Write molecular structure in `.ml2` format.

**Molecular geometry in XMOL-XYZ format:** Write molecular structure in `.xyz` format.

**Program control settings:**

- **Switch off combinatorial contrib. to chemical potential:** Switch off combinatorial contribution to the chemical potential for the complete COSMOTHERM run.

- **Switch on polymer combinatorial term [combi=elbro]:** Use free volume combinatorial contribution of Elbro for chemical potential. Recommended for property calculations involving macromolecular compounds.

- **Use sum of fragment energies as metatfile energy:** (Expert use only) Use the sum of the fragment COSMO file energies in the calculation of the total free energy (by default a zero value is used instead). Details on the usage of atomic weights and COSMO-metafiles are explained in COSMOTHERM Reference Manual.

- **Use compound boiling points in vapor pressure prediction:** The pure compound boiling points as given in the compound input section can be used as a reference points for scaling vapor pressure predictions.

- **Use compound vapour pressures $P^0_T$ (in vapor pressure prediction):** Use the temperature dependent experimental pure compound vapor pressure $P^0_{exp}(T)$ (as given in the compound input section or read from a compounds vapor-pressure property file) as a reference point for scaling the vapor pressure prediction. Valid for pure compound and mixture vapor pressure predictions.

- **Compute derivatives of chemical potential:** Compute the values of the temperature and composition derivatives of the chemical potentials of all compounds in all mixtures and print them to the output file. See COSMOTHERM Reference Manual for further information.

- **Compute observable partial enthalpies:** Enthalpy values in the output files will be replaced by the thermodynamically correct observable $H_i$ as computed by eq. 5.6-4 from the COSMOTHERM Reference Manual.

- **Switch off temp. dependency of hydrogen bond contrib.:** Switch off temperature dependency of the hydrogen bond contribution to the total interaction energy of the compound for the complete COSMOTHERM run.

- **Switch off temp. dependency of van der Waals contrib.:** Switch off temperature dependency of the van der Waals contribution to the total interaction energy of the compound, active for the complete COSMOTHERM run.

- **Switch off hydrogen bonding:** Switch off hydrogen bonding (HB) contribution to the chemical potential.

- **Switch off van der Waals contributions:** Switch off van der Waals (vdW) interaction energy contribution to the chemical potential.

- **Use “external” quantum chemical energies (gas):** Use the external quantum chemical gas phase energies and vibrational zero point energies as given in the energy file for the Boltzmann-weighting of conformers. See COSMOTHERM Reference Manual for details.

- **Allow negative free energy of fusion:** Allow for negative values of $\Delta G_{fus}$. For more information, refer to the COSMOTHERM Reference Manual.
USE HEAT CAPACITY OF FUSION ESTIMATE: The heat capacity of fusion is approximated as $\Delta C_{p_{\text{fus}}} = \Delta S_{\text{fus}} = \Delta H_{\text{fus}} / T_{\text{melt}}$. The value of $\Delta G_{\text{fus}}(T)$ thus obtained can be used to compute the solubility of solid compounds or salts as well as solid-liquid-equilibria.

SWITCH OFF USAGE OF GAS PHASE CONFORMER MINIMUM ENERGY: Switch off the usage of gas phase minimum conformer energies in single-conformer calculations.


CHANGE THRESHOLD FOR THE ITERATIVE SELF-CONSISTENCY: Change threshold for the iterative self-consistency cycle for the determination of the chemical potential. A smaller value leads to higher accuracy of the COSMOtherm results but also to a longer computational time due to an increasing number of iterations. Default value: $10^{-8}$.

ALLOW CHARGED META-FILES (.MCOS): Optional for the use of COSMO-metafiles or atomic weights: Allow charged metafiles. Details on the usage of atomic weights and COSMO-metafiles are given in the COSMOtherm Reference Manual.

ALLOW WRONG (NONMATCHING) PARAMETER SET: Allow the usage of a parameter set that does not match the computation level of the COSMO files used. Note that COSMOtherm predictions typically will not be reasonable any more if parameterization and quantum chemical computation level do not match.

ALLOW MIX OF COMPRESSED AND UNCOMPRESSED COSMO-FILES IN CONFORMER BLOCKS: Allow the usage of compressed (.ccf) and uncompressed COSMO files in the same conformer block. Mixing compressed and uncompressed COSMO files can lead to inconsistent conformer energies. Hence a slight bias on the conformer distribution might be introduced into the COSMOtherm predictions.

CHANGE THE MAXIMUM NUMBER OF PHASES ALLOWED TO $L_{\text{mx}}$: Change the number of phases allowed in a multi-component multi-phase extraction equilibrium calculation. $L_{\text{mx}}$ is expected to be an integer number. Note that an increase of $L_{\text{mx}}$ increases the memory requirements of COSMOtherm.

DISABLE SYMMETRY CONTRIBUTION TO CONFORMER WEIGHTS: Switch off the usage of symmetry information in the distribution of molecules among conformer sets. Details on the use of symmetry in conformer sets are given in the COSMOtherm Reference Manual.

ENABLE SYMMETRY CONTRIBUTION TO CHEMICAL POTENTIAL: A symmetry contribution $RT \ln(N_{\text{irrep}})$ will be added to the liquid and gas phase chemical potentials of each molecule present. $N_{\text{irrep}}$ is the symmetry number (the number of irreducible representations of the symmetry point group) of the molecule. For details, refer to the COSMOtherm Reference Manual.

Fine tuning of COSMO-RS parameters:
Several options for adjusting the parameters of the COSMO-RS method to specific requirements. For detailed information, refer to the COSMOtherm Reference Manual.

Command line keywords for the selected options will be printed to the text area below the options section. Additional keywords can also be entered here.
Property Options

While options from the GLOBAL OPTIONS dialog apply for all temperature / mixture / property lines in the input, settings from the PROPERTY OPTIONS dialog can be applied to individual temperature / mixture / property lines. To apply options to a certain property calculation, the settings for the calculation have to be added to the property section first. After this has been done, open the PROPERTY OPTIONS dialog from EXTRAS / PROPERTY OPTIONS. Select a temperature / mixture / property line from the list in the PROPERTY OPTIONS dialog and tick the checkboxes for the required options. Keywords entered in the text area next to the property list will also be used for the selected temperature / mixture / property lines. Note that multiple temperature / mixture / property lines can be selected using the Ctrl or Shift keys.

Print options for the COSMOtherm output and table file:
SUPPRESS MIXTURE OUTPUT IN .OUT-FILE: Mixture information will not be written to the output file.
PRINT FULL COMPOUND NAMES IN TABLE ENTRIES: Print full compound and/or molecule names to all tables in the table file and the sigma-moments file. By default the compound/molecule names are cropped after 20 characters.
CONCENTRATION OUTPUT UNIT: The unit for concentration information in the output files can be changed from mole fraction based to mass fraction based or surface fraction based.

Program control settings:
SWITCH OFF COMBINATORIAL CONTRIB. TO CHEMICAL POTENTIAL: Switch off combinatorial contribution to the chemical potential for the complete COSMOtherm run.
SWITCH ON POLYMER COMBINATORIAL TERM [COMBI=ELBRO]: Use free volume combinatorial contribution of Elbro for chemical potential. Recommended for property calculations involving macromolecular compounds.
DO NOT CHECK FOR CHARGE NEUTRALITY: Overrides the check for charge neutrality of a given mixture composition and allows you to compute non-neutral mixtures.
COMPUTE DERIVATIVES OF CHEMICAL POTENTIAL: Compute the values of the temperature and composition derivatives of the chemical potentials of all compounds in all mixtures and print them to the output file. See COSMOtherm Reference Manual for further information.
COMPUTE OBSERVABLE PARTIAL ENTHALPIES: Enthalpy values in the output files will be replaced by the thermodynamically correct observable $H_i$ as computed by eq. 5.6-4 from the COSMOtherm Reference Manual.
SWITCH OFF TEMP. DEPENDENCY OF HYDROGEN BOND CONTRIB.: Switch off temperature dependency of the hydrogen bond contribution to the total interaction energy of the compound for the complete COSMOtherm run.
**Switch off temperature dependency of van der Waals contributions**: Switch off temperature dependency of the van der Waals contribution to the total interaction energy of the compound, active for the complete COSMOTHERM run.

**Switch off hydrogen bonding**: Switch off hydrogen bonding contribution to the chemical potential.

**Switch off van der Waals contributions**: Switch off van der Waals (vdW) interaction energy contribution to the chemical potential.

**Select compounds printed in .out file**:
Write to the COSMOTHERM output file the evaluated information only for the selected compounds. Helps to shorten the output file if not all evaluated information is required by the user.

**Extended Options: Switch of combinatorial contribution for specific compounds**:
The combinatorial contribution is switched off for the selected compounds only.

**Conformer Options**
In the CONFORMER OPTIONS dialog users can set options applying for conformer sets or individual conformers. Keywords for options can be given in the text area corresponding to the respective conformer set or conformer. Compounds for which options are to be set can be selected from the pull-down menu.
4 Results and Postprocessing

4.1 Input and Output Files

Files and directories produced by COSMOTHERM and COSMOTHERMX are:

- The command line input file .inp
- The XML input file .inpx.
- Subdirectories for all jobs.
- The regular output file with the extension .out
- The summary table file .tab
- If the corresponding options are set:
  - \( \sigma \)-profiles .prf
  - \( \sigma \)-potentials .pot
  - \( \sigma \)-moments .mom
  - Atomic \( \sigma \)-moments .moma

The summary table file will be displayed in a separate tab in the workplace window. The number of columns is truncated by default to allow for a concise representation of results. The complete results table will be displayed when the SHOW EXTENDED OUTPUT checkbox is ticked. If the print options for \( \sigma \)-profiles or \( \sigma \)-potentials have been set, the data for the \( \sigma \)-profiles or \( \sigma \)-potentials will also be displayed in the table editor in separate tabs. Moreover, there will be tabs where \( \sigma \)-profiles or \( \sigma \)-potentials can be plotted.

There are different options available for the current .tab file. They can be selected either from the shortcut icons or from a context menu.

The regular output file .out will only be opened in a separate tab of the workplace window if the corresponding option in the PREFERENCES dialog is checked.

4.2 Results Filter

The COSMOTHERM table file can be filtered for results of certain compounds or for certain properties. Rows and Columns can be selected from a subtable and combined to a single table.

In the first step, the subtable to be used has to be selected from the pulldown menu in the DEFINE FILTER section. Then, table rows and columns have to be selected. The SELECT TABLE ROWS and SELECT TABLE COLUMNS buttons open a preview of the selected subtable. Rows (or columns, respectively) can be selected from
this table by a simple mouse click. For selecting several rows or columns, keep the "Ctrl" or "Shift" key pressed while clicking on the respective row or column.

<table>
<thead>
<tr>
<th>Nr</th>
<th>Compound</th>
<th>mu</th>
<th>log(10)µ</th>
<th>E_COSMO+δE_Mu</th>
<th>H_int</th>
<th>H_MF</th>
<th>H_HB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H2O</td>
<td>-2.77896</td>
<td>0.73473</td>
<td>-47993.27528</td>
<td>-7.13688</td>
<td>0.26559</td>
<td>-6.51685</td>
</tr>
<tr>
<td>2</td>
<td>1-octanol</td>
<td>-2.13772</td>
<td>1.98789</td>
<td>-2.45403E+05</td>
<td>-10.75151</td>
<td>3.055</td>
<td>-5.693</td>
</tr>
<tr>
<td>3</td>
<td>cdH</td>
<td>-1.04873</td>
<td>6.05457</td>
<td>-1.17917E+06</td>
<td>-5.32272</td>
<td>2.23217</td>
<td>0.00000E+00</td>
</tr>
<tr>
<td>4</td>
<td>ethanol</td>
<td>-2.44237</td>
<td>1.65529</td>
<td>-97338.52526</td>
<td>-8.1749</td>
<td>1.2624</td>
<td>-6.01786</td>
</tr>
<tr>
<td>5</td>
<td>diethylether</td>
<td>-0.85585</td>
<td>4.4796</td>
<td>-1.46685E+05</td>
<td>-5.80912</td>
<td>2.04535</td>
<td>-2.58052</td>
</tr>
<tr>
<td>6</td>
<td>methanol</td>
<td>-2.31039</td>
<td>1.33217</td>
<td>-72657.1732</td>
<td>-8.07288</td>
<td>0.91</td>
<td>-6.37196</td>
</tr>
<tr>
<td>7</td>
<td>propanone</td>
<td>-0.95967</td>
<td>2.37852</td>
<td>-2.12163E+05</td>
<td>-5.93545</td>
<td>1.46023</td>
<td>-3.35244</td>
</tr>
<tr>
<td>8</td>
<td>cd3</td>
<td>-0.72666</td>
<td>4.81884</td>
<td>-8.0074E+05</td>
<td>-4.35005</td>
<td>1.09471</td>
<td>-0.58530</td>
</tr>
<tr>
<td>9</td>
<td>dimethylsulfide</td>
<td>-3.35491</td>
<td>-3.59594</td>
<td>-1.27220E+05</td>
<td>-11.7693</td>
<td>1.60105</td>
<td>-8.70107</td>
</tr>
<tr>
<td>10</td>
<td>1-butanol</td>
<td>-2.39497</td>
<td>1.99647</td>
<td>-1.46933E+05</td>
<td>-8.6734</td>
<td>1.94871</td>
<td>-5.67875</td>
</tr>
<tr>
<td>11</td>
<td>benzene</td>
<td>0.71447</td>
<td>4.93131</td>
<td>-1.45791E+05</td>
<td>-3.04552</td>
<td>1.96836</td>
<td>0.00000E+00</td>
</tr>
</tbody>
</table>

The selected subtable type, row numbers and column headers are then transferred to the SELECTION OVERVIEW section in the Filter tab. Pressing APPLY FILTER generates a new subtable from this selection.
5  Compounds

Apart from the menu and shortcut bars, the COSMOthermX main window has two sections. In the default view, the section on the left is reserved for the Job list. The workplace window belonging to the job has two tabs labelled COMPOUNDS and PROPERTIES. The COMPOUNDS tab contains a list of selected compounds. At the bottom of this section, there are buttons to open the FILE MANAGER, database files or the NEW MOLECULE option from which compounds can be selected.

5.1  Compound selection

The compound selection panel of the COSMOthermX workplace window offers various functionalities for compound selection. There are four radio buttons referring to the different supported levels. With the FROM DATABASE button the databases of the corresponding level are opened in tabulated form. Inside the FILE MANAGER or the databases, a list of compounds can be highlighted by using the “Ctrl” or “Shift” keys together with the mouse.

![Compound Selection Panel]

Options for compound handling are:

MANAGE COMPOUNDS: Opens the context menu for the highlighted compound.

UP AND DOWN BUTTONS: Compound can be moved up and down the list.

CLEAR COMPOUNDS: Clear all compounds from the selection window. Note that individual compounds can be removed using the Delete key.

Supported levels can be selected using the radio-buttons:

SVP: COSMO files are calculated on the BP/SVP quantum chemical level, based on AM1 molecular structures.

TZVP: COSMO files are calculated on the BP/TZVP quantum chemical level.
TZVPD-FINE: COSMO files are calculated as single points using the BP-DFT functional and the TZVPD basis set with the novel fine grid marching tetrahedron cavity (FINE), based on BP/TZVP structures. For details refer to section 2.2.

DMOL3: COSMO files are calculated on the PBE/DNP quantum chemical level with the DMOL3 program.

Compounds can be loaded from databases, from the computer file system, or as compound lists.

FROM DATABASE: The databases of the corresponding level, as specified in the PREFERENCES dialog, are opened in tabulated form.

FROM FILE: Opens a file browser and enables you to choose COSMO files of any quantum chemical level directly from the file system. Make sure that you use an adequate parameterization for the COSMO files. If you do not plan to use any compounds other than those provided with your COSMOTHERM installation, it is more convenient and fail-safe to use the database button. Also note that COSMO files with names containing blanks cannot be used in COSMOTHERM.

COMPOUND LIST: A list of previously saved compounds can be loaded with this option. The saved concentrations of the compounds will also be loaded but not automatically applied. Please select SET DEFAULT CONCENTRATIONS from the COMPOUNDS menu for this feature.

Furthermore, using the NEW MOLECULE tool, it is possible to search compounds in all databases by name, SMILES, CAS-Number, 2D structure and 3D structure. It is also possible to generate a 3D structure from SMILES strings and to start COSMO calculations with TURBOMOLE directly. A detailed description is given in section 5.4.

5.2 The compounds context menu

A right mouse button click on one or more compounds inside the compound list opens a context menu with several options for the highlighted compound. The context menu is also available in the database search and the NEW MOLECULE tool and may vary by applicability. Options are:

- compound properties
- decompose conformer sets / combine to conformer sets
- open COSMO file
- open energy file
- remove from list
- view gas phase geometry
- view cosmo geometry
- view sigma surface
- view sigma profiles / potentials
- export geometry
- save selection to compound list
- edit weight string
- edit .mcos file
- show existing files
COMPONENT PROPERTIES: Pure compound property data can be edited with this option. Data entries in the dialog come from the .vap file of the compound. There are data groups for vapor pressure related data and free energy of fusion related data. The additional data group provides fields for UNIQUAC parameters, boiling point temperature, critical point data, CAS registry number, dielectric constant, pKa and macromolecular properties. Properties printed in black indicate that data entries are available, while for properties in gray no data exist so far. Data fields can be edited by pressing the pen button. Data fields can be selected by ticking the checkboxes or with the SELECT ALL and DESELECT ALL buttons. With APPLY, only the selected entries will be used for the current job. SAVE TO VAP will save all available data permanently to the .vap file. Note that if applied to database compounds SAVE TO VAP will change the corresponding .vap files in the database. The use of the saved pure compound property can be switched on and off in the GLOBAL OPTIONS dialog. By default, the data are used where possible.

COMBINE TO CONFORMER SET / DECOMPOSE CONFORMER SET: If several compounds are highlighted and this option is selected from the context menu, the highlighted compounds will be treated as conformers of a single compound. A name for the compound can be specified. If a single compound is selected, the option will appear as DECOMPOSE CONFORMER SET and construct individual compounds of the different conformers of the selected compound. Note that this option is only available in the compound list.

OPEN COSMO FILE: Opens the .cosmo or .ccf file of the compound in a text editor.
**OPEN ENERGY FILE**: Opens the `.energy` file of the compound in a text editor.

**REMOVE FROM LIST**: Deletes a compound from the compound list, same as “Del” key.

**VIEW GASPHASE GEOMETRY**: 3D ball-and-stick model of the molecular gas phase geometry.

**VIEW COSMO GEOMETRY**: 3D ball-and-stick model of the molecular geometry from the `.cosmo` file.

**VIEW SIGMA-SURFACE**: 3D preview of the molecular σ-surface. This graphic has a lower resolution than the graphic you get from a VRML of the σ-surface in a VRML viewer.

**VIEW SIGMA-PROFILES /-POTENTIALS**: The σ-profiles and the σ-potentials of the selected compounds are plotted.

**CONVERT SELECTION**: The selected files can be converted into a variety of other file types like `.xyz`, `.pdb` or `.m12`.

**SAVE COMPLETE COMPOUND LIST**: The selected files can be written to a list which can be used for further processing. If the complete compound list should be saved, the SAVE COMPOUND LIST option from the FILE menu can be used alternatively. The compound concentrations are also saved. Please note: The saved concentrations of the compounds will not be loaded automatically when a list is opened. Please select RESTORE LIST CONCENTRATIONS from the EXTRAS menu to apply the saved list concentrations after loading a compound list.

**EDIT WEIGHT STRING**: Opens the `.cosmo` or `.ccf` file in the COSMOweight tool and allows for the setting of a weight string and correction charges which will be written to the compound list of the input file. The weight string will not be saved to the `.cosmo` or `.ccf` file. Compounds with weight strings will be displayed with a different symbol in the compound list.

**EDIT .MCOS-FILE**: Opens the `.cosmo`, `.ccf` or `.mcos` file in the COSMOweight tool and allows for the creation or modification of a `.mcos` file.

Note that the options EDIT WEIGHT STRING and EDIT .MCOS-FILE are available only in the compound list and only if the conformer treatment is deactivated. Refer to the section “Atom weighting” for information on the use of the COSMOweight tool.

**SHOW EXISTING FILES**: Opens a list of available files.

The options **VIEW COSMO GEOMETRY**, **VIEW GASPHASE GEOMETRY**, **VIEW SIGMA-SURFACE** and **VIEW SIGMA-PROFILES /-POTENTIALS** from the context menu require a COSMOtherm run in the background. Output files of the runs are written to temporary files which will be removed when the display windows are closed. For the 3D ball-and-stick model of the molecular geometry or the σ-surface of the molecule, σ-profiles or σ-potentials to be written to permanent files check the corresponding checkboxes in the GLOBAL OPTIONS dialog.

### 5.3 Selecting compounds from databases

After clicking on the FROM DATABASE button a window for the compound search and selection appears. Inside the window compounds from the implemented databases of the chosen level will be listed. By default, checkboxes for all implemented databases are selected. The database table can be sorted with respect to columns. For some compounds, there are several conformers with different σ-profiles to be...
considered. By default, all available conformers are selected. You can uncheck the selection to use only the lowest energy conformer. In case a specific conformer other than the lowest energy conformer is needed, first select the complete conformer set. Close the database dialog and highlight the conformer set in the compound section. Use the right mouse button to open the compound context menu and select **DECOMPOSE CONFORMER SET**. Then delete the unwanted conformers from the compound section by highlighting them and pressing the "Del" key. Alternatively, the specific conformer can be selected using the **FILE MANAGER**.

The database tables can also be searched for compounds. It is possible to enter a search string (name, formula, CAS-Number, SMILES string) or open a text file with a list of compound names which will then be searched for in the database. The search is processed in the selected databases only.

The **SEARCH LIST** option enables compound search from compound lists in .txt file format. The compound list can be opened from a file browser. The compound list is then displayed in the left part of the **SEARCH LIST** dialog, while search results are displayed on the right side. Compounds can be selected or skipped, databases to be searched can be selected, and the search string can be modified, similarly to the handling in the main database table.
5.4 New Molecules

The NEW MOLECULE tool is a universal tool for adding compounds to your calculation. It also offers some advanced search options for the databases.

The NEW MOLECULE tool makes use of free external tools, which have not been developed by COSMOlogic. Although we tested them carefully, we cannot guarantee that all offered functionality will operate smoothly under all possible circumstances. The NEW MOLECULE tool can be used for setting up COSMOtherm calculations in many cases involving compounds that are not readily available from the COSMO databases.

The following list gives an overview of the general options:

- Search all databases by names, CAS-Number, SMILES.
- Search the free Internet database ChemSpider by compound name.
- Draw two dimensional or three dimensional structures. Use structures to start quantum mechanical COSMO calculations or generate a SMILES string for database search.
- Load structures from files.
- Convert SMILES or two dimensional structures to three dimensional structures. This option is only available in the search results window.
- Modify an existing molecule to generate a new one.

Start Search:

Inside the first window, the name, CAS-Number or SMILES can be given to start the corresponding database search. Alternatively a structure can be drawn or a molecule taken from file. If a quantum mechanical COSMO calculation has been started previously, you can also go to the QM Results panel directly.

The search for name, SMILES, CAS-Number or a drawn 2D structure will always lead to the DB Search Results window. A 2D structure is converted to a SMILES string beforehand.
The above search for ethanol led to a number of perfect hits (green) and near hits (yellow). The right column shows in which database the compound was found. After selecting a compound from the results list, several options are available:

- Use one of the structures for a quantum mechanical COSMO calculation to obtain a `.cosmo` file for a different parameterization level.
- Use structure for 2D or 3D editing, useful if only similar molecules have been found.
- Add the molecule to the compound list for the COSMOtherm calculation.
- The Internet database ChemSpider can be used to find a SMILES for a given name. This option is only available if the search was started by compound name.
- If the search was started by SMILES or a drawn structure, you can also choose to convert the SMILES to a 3D structure.

In case that a drawn 3D structure or a molecule file should be used for the search, the 3D molecule editor will open. Only two options are available after a 3D geometry has been build or opened from file. Either use the structure for a quantum mechanical COSMO calculation or restart the search with a SMILES generated from the 3D structure. The latter option is useful to search the databases for a given 3D Structure.

**Start quantum mechanical calculations:**

If the requested compound could not be found inside the database or not with the needed basis set level (e.g. TZVP), a QM calculation is necessary to generate the appropriate `.cosmo` file. The QM Calculation panel can either be accessed from the DB Search Results or from the 3D editor.
Inside the QM Calculation panel you can choose:

- the type of calculation (gas phase only, COSMO only, or gas phase and COSMO).
- the output file type. .cosmo or .ccf are available for COSMO calculations. Selecting .mcos will start a fragmentation run with COSMOfrag instead of a quantum chemical calculation.
- the quantum chemical level, corresponding to the parameterization levels (TZVP, TZVPD-FINE, or SVP).
- A single conformer optimization or a conformer search. Note that depending on the molecular size and structural features (e.g. number of rotatable bonds), a conformer search can be time consuming. Furthermore, the conformer search requires a COSMOconf installation.

With START CALCULATION (NETWORK) the QM calculation can also be done on a remote machine (Linux only).

After the QM calculation is finished you can transfer the molecules to your compound list or to one of the databases. The QM Results panel can be directly accessed from the Starting window. Note that for later use in COSMOtherm, blanks should not be used in compound names.

Both options for quantum chemical calculations (USE START CONFORMATION ONLY and CONFORMER SEARCH) require a Turbomole installation. The CONFORMER SEARCH option additionally requires a COSMOconf installation. If Turbomole and COSMOconf can be found on your system upon installation of COSMOthermX, the paths will be set automatically. Paths for both programs can be edited in the corresponding text areas in the QM CALCULATION panel, or in the JOBS panel of the PREFERENCES dialog.

Calculations on the local machine can be started without further settings. The only parameter that can be changed is the maximum number of CPUs to be used on the local machine (see EXTRAS -> PREFERENCES). Surplus jobs will be queued.

Remote jobs require a TURBOMOLE installation and, if the CONFORMER SEARCH option is selected, a COSMOconf installation on the remote computer. Only Linux systems are supported as remote machines.

When a job is run on a remote machine, the input data are transferred there. On finishing, the results are copied back from the remote system to the local machine. For large molecules this may take a few seconds.

Because the work environment of a remote Linux system cannot be known by the GUI, the user has to define the settings. The remote system configuration menu can be opened via the START CALCULATION (NETWORK) button or via the EXTRAS – PREFERENCES menu. For details refer to section 3.5.
Example 1: Generate a new cosmo file Glycofurol

- Open the NEW MOLECULE tool and enter glycofurol into the name field,
- press enter or the SEARCH BY NAME button to see if the substance is already inside your databases.
- Let’s assume it is not there and try the SEARCH THIS NAME IN CHEMSPIDER button. A tutorial for using ChemSpider is also available directly within the NEW MOLECULE tool.
- ChemSpider will find the SMILES O(CCO)CC1OCCC1 for glycofurol. Enter it into the corresponding field and CONTINUE WITH THIS STRUCTURE/SMILES.
- Now a structure search based on the SMILES string will be performed.
- Assuming that the structure can again not be found in the database the GENERATE 3D STRUCTURE FROM SMILES option is your last resort.
- The 3D Structure will be generated and a new COSMO calculation can now be conducted by choosing USE FOR QM CALCULATION.
5.5 Conformers

Molecules often can adopt more than one conformation. For COSMO-RS, only conformers with different σ-profiles are relevant. For each of these conformers, an individual COSMO file is required for the compound input. If compounds are selected from the databases and the checkbox in the USE CONF. column is checked, all existing conformer COSMO files will be selected automatically. If the ACTIVATE CONFORMER TREATMENT checkbox in the compound section is checked, the conformers will be weighted internally by COSMOtherm using their COSMO energies and their chemical potentials.

If you intend to use your own COSMO files for conformers please be aware that in order to be identified as conformers by COSMOthermX automatically, the names of the files must follow a convention. It is also possible to define conformers of a compound manually without following the name convention as described in section 2.5 of this document. Select the corresponding compounds from the databases of the FILE MANAGER, highlight them in the compound list using the Control key and the left mouse button, and choose COMBINE TO CONFORMER SET from the right mouse button menu. Note that this option is available only if the conformer treatment is activated.

A useful option for calculations involving conformers from the GLOBAL OPTIONS dialog is the print option PRINT CONFORMER INFO (wconf). For more information on conformer input refer to the COSMOtherm Reference Manual, section 2.2.2.

5.6 Visualization of σ-surfaces, σ-profiles, and σ-potentials

The 3D screening charge distribution on the surface of a molecule $i$ can be used to qualitatively describe the molecule. Polarity, hydrogen bonding and lipophilicity or hydrophilicity can be visualized on the molecular surface. The surface screening charges can be converted into a distribution function, the σ-profile $p(\sigma)$, which gives the relative amount of surface with polarity $\sigma$ on the surface of the molecule. The σ-potential, as calculated from eq. 5, can also be visualized.

Example 2: COSMO charge surface visualization, σ-profile and σ-potential.

A: Visualization “on the fly”

The COSMO charge surface, the σ-profile and the σ-potential of a compound can be visualized from the FILE MANAGER or the databases:

- Highlight a compound with a left mouse button click.
- With a right mouse button click you can choose VIEW SIGMA SURFACE or VIEW SIGMA PROFILE/POTENTIAL from the context menu.
- A COSMOtherm calculation is run in the background and a window displaying the chosen property will pop up.
- Note that no files are written permanently.
B: Visualization using permanent files for $\sigma$-profiles (.prf), $\sigma$-Potentials (.pot), and $\sigma$-surface (.wrl)

- Select the compounds you would like to visualize.
- In the EXTRAS/GLOBAL OPTIONS/ADDITIONAL OUTPUT FILES menu, check GENERATE VRML ($\sigma$-SURFACE) for the COSMO charge surface visualization.

- Check $\sigma$-PROFILES (.prf) and $\sigma$-POTENTIALS (.pot) for the generation of the $\sigma$-profile and $\sigma$-potential files.
- The $\sigma$-surface will be written to a separate VRML file with the extension .wrl, which can be used for visualization in COSMOview or external VRML viewers.
- The $\sigma$-profiles and $\sigma$-potentials will be written to separate output files with the extensions .prf and .pot.
- .prf and .pot files can be used for post-processing in spreadsheet programs like Microsoft Excel or Open Office.

For more information on COSMOview, please refer to section 8.1. $\sigma$-Profiles and $\sigma$-potentials can be plotted in a spreadsheet program. For further information on $\sigma$-profiles and $\sigma$-potentials refer to the COSMOtherm Reference Manual, chapter 5.
6 Property input

The property panel in the workplace window shows the range of properties that can be calculated automatically by COSMOtherm. The properties are grouped according to application areas. To customize the FAVORITES group click on the CUSTOMIZE button or open the PREFERENCES dialog. For each property you can adjust parameters like temperature, composition etc. Input settings from the property panels are transferred to the property section with the ADD button. Changes in the PROPERTY OPTIONS have to be done after the property line is added to the property section. The COSMOtherm calculation is started from the RUN button in the property section, from the RUN menu or from the shortcut bar.

By default, COSMOtherm produces two sorts of output files: The COSMOtherm output file filename.out and a file filename.tab which contains the calculated property information in tabulated form. These files will automatically be displayed in separate tabs in the workplace window after the calculation has finished. Additional output files will be written if the corresponding options in EXTRAS/GLBAL OPTIONS are activated. These output files may contain \( \sigma \)-moments (.mom), atomic \( \sigma \)-moments (.moma), \( \sigma \)-profiles (.prf), or \( \sigma \)-potentials (.pot).

The explanations, examples and the results in this User Guide refer to the full version of COSMOtherm. Some examples cannot be calculated with the DEMO/EDU version. The example results might be calculated with different versions of COSMOtherm and can deviate numerically from the current version, due to differences in the parameterizations involved.
6.1 Phase definition

By default, the solvent phase definition in the property panels is set to mole fraction, but can be changed to mass fraction with the corresponding radio button. Pure compound phases can be defined using the PURE checkboxes in the corresponding compound lines. Mixed phases can be defined either giving the relative numbers in the corresponding fields or using the sliders in the compound lines.

In all property panels the phase definition subsections have a context menu. With a right mouse button click, phase compositions can be copied and pasted into another property panel.

Instead of adding a job with a single defined phase composition to the property section, it is also possible to add a series of jobs with varying phase compositions using the LOAD LIST dialog. Concentration series can be loaded from .txt, .csv, or .xls files. The delimiter used in the .txt and .csv files is a semicolon. Lines in the concentration series source file should consist of two blocks: the first with numbers for compound identification (e.g. 2 referring to the second compound), followed by the second block with concentration numbers. The blocks are separated by two subsequent semicolons (in a .txt or .csv file) or an empty column (in a .xls file). Concentration entries in the .xls format can be taken from subsequent cells or semicolon-separated numbers in the same cell. Each line in the source file corresponds to a property calculation where the settings are taken from the property panel with phase compositions taken from the actual line of the source file. All text following the hash sign # in the source file is considered a comment and will be ignored. The lines in the following table all lead to the same property calculation:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>0.5</th>
<th>0.5</th>
<th># comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1;2;0.5;0.5</td>
<td># same as first line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1;2</td>
<td>0.5;0.5</td>
<td># same as first line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1;2;</td>
<td>0.5;0.5</td>
<td>Same line without hash sign. Changing the cell implies the second ;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1;2;</td>
<td>0.5;0.5; same as above</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1;</td>
<td>0.5;0.5; same as first line - concentrations are applied to compounds in descending order</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An example for a series of mixtures with varying concentrations can be taken from the following:

```plaintext
2; 3; 1; ; 0.0; 0.9; 0.1 # mixture 1
2; 3; 1; ; 0.1; 0.8; 0.1 # mixture 2
2; 3; 1; ; 0.2; 0.7; 0.1 # mixture 3
2; 3; 1; ; 0.3; 0.6; 0.1 # mixture 4
2; 3; 1; ; 0.4; 0.5; 0.1 # mixture 5
2; 3; 1; ; 0.5; 0.4; 0.1 # mixture 6
2; 3; 1; ; 0.6; 0.3; 0.1 # mixture 7
2; 3; 1; ; 0.7; 0.2; 0.1 # mixture 8
2; 3; 1; ; 0.8; 0.1; 0.1 # mixture 9
2; 3; 1; ; 0.9; 0.0; 0.1 # mixture 10
```

The Load List option can also be used to setup a property calculation with two phases. In this case, the files containing the phase definition should hold four blocks, two for each phase: the compound identification block and the concentration block for the first phase, followed by the compound identification block and the concentration block for the second phase. Each of the blocks should conform
to the definition above, and the blocks should be separated by an empty column (in a .xls file) or two subsequent semicolons (in a .txt or .csv file), respectively.

An example for a series of two-phase mixtures:

| 2; 3; | 0.0; | 1.0; | 1; 4; 5; | 0.1; | 0.2; | 0.7 |
| 2; 3; | 0.1; | 0.9; | 1; 4; 5; | 0.1; | 0.2; | 0.7 |
| 2; 3; | 0.2; | 0.8; | 1; 4; 5; | 0.1; | 0.4; | 0.7 |
| 2; 3; | 0.3; | 0.7; | 1; 4; 5; | 0.1; | 0.2; | 0.7 |
| 2; 3; | 0.4; | 0.6; | 1; 4; 5; | 0.1; | 0.2; | 0.7 |

6.2 Mixture: Calculation of compound properties in mixture

The Mixture option toggles the COSMOtherm calculation of interaction energy terms at the given temperature and composition. For all compounds in the compound list, the following terms will be calculated:

- Chemical potential \( \mu \), of the compound in the mixture from eq (6).
- Log10(partial pressure [mbar])
- Free energy of the molecule in the mixture (E_COSMO+dE+Mu)
- Total mean interaction energy in the mix (H_int): The mean interaction enthalpy of the compound with its surrounding, i.e. the interaction enthalpy of the compound which can be used to derive heats of mixing and heats of vaporization.
- Contributions to the total mean interaction energy:
  - Misfit interaction energy in the mix (H_MF).
  - H-Bond interaction energy in the mix (H_HB)
  - VdW interaction energy in the mix (H_vdW)
  - Ring correction

For details on the calculation of the energy terms and contributions please refer to the COSMOtherm Reference Manual, section 1.1.

Furthermore, COSMOtherm allows for the computation of the contact probability of molecules and molecule surface segments in arbitrary mixtures. The checkbox COMPUTE CONTACT STATISTICS in the EXTENDED OPTIONS dialog can be checked to obtain a more detailed contact interaction statistics of all segments of molecules A and B. For more information on the calculation of contact statistics please refer to the COSMOtherm Reference Manual.
6.3 Vapor pressure

COSMO-RS allows for the estimation of pure compound vapor pressures. The energy of the gas phase $E_{i\text{gas}}$ is required for the calculation of the chemical potential in the gas phase, $\mu_{i\text{gas}}$. $E_{i\text{gas}}$ can be taken from a gas phase quantum chemical calculation or empirically estimated by COSMOTHERM. If possible, the quantum chemically calculated value of $E_{i\text{gas}}$ should be used: Check USE ENERGY FILE in GLOBAL OPTIONS (this is the default setting).

The vapor pressure option enables the computation of vapor pressures for a given temperature or a temperature range and a fixed mixture concentration. The number of points in a temperature range can be up to 100, default value is 10. Since the strength of COSMOTHERM vapor pressure prediction is in the temperature dependency of the vapor pressure, and not in the prediction of the absolute vapor pressure at a given temperature, it is possible to scale the vapor pressure prediction using a pair of reference temperature and pressure. Data can be entered in the USE REFERENCE DATA TO SCALE VAPOR PRESSURE PREDICTION subsection of the EXTENDED OPTIONS dialog.

For each temperature and compound in the mixture the partial vapor pressures, the chemical potential of the compound in the gas phase and its enthalpy of vaporization are computed and written to the COSMOTHERM output file. The total vapor pressure of the mixture is written to the COSMOTHERM table file in tabulated form $p_{\text{VAP}}$ vs $T$. In addition the total chemical potentials of the liquid $\mu_{\text{liquid (tot)}}$ and of the gas phase $\mu_{\text{gas (tot)}}$, as well as the heat of vaporization of the mixture $\Delta H_{\text{vap}}$ are written to the COSMOTHERM table file. If the given temperature is below a compound’s melting point, COSMOTHERM will compute the partial and total vapor pressure of the subcooled melt. However, if experimental data on a compound’s solid state properties are available ($T_{\text{melt}}$ and $\Delta G_{\text{fus}}(T)$), COSMOTHERM will compute the compound’s partial sublimation pressures ($p_{i\text{Sub}} / 1 \text{ bar} = \exp \left[ \frac{- \Delta G_{i\text{fus}}}{RT} \right]$), and write the computed partial sublimation pressures and the according enthalpies of sublimation to the COSMOTHERM output and table files.

If three or more temperature points were calculated in a vapor pressure curve, the total vapor pressure will be fitted to Antoine’s vapor pressure equation $\ln(p) = A - \frac{B}{C + T}$, where $T$ is the temperature in [K] and $A$, $B$ and $C$ are coefficients. The coefficients are written to the COSMOTHERM output and table files.

Note that since the Vapor Pressure option in COSMOTHERM is intended for the prediction of vapor pressures data from .vap files are not used even if this is indicated in the options. However, if vapor pressure data are available from a .vap file, they will be printed to the last column of the table file for comparison.
Example 3: Calculation of a vapor pressure curve

- In the **COMPONENTS** tab of the workplace window, open the TZVPD-FINE DB and select methanol.
- Make sure that “Energy file” in the **GLOBAL OPTIONS** is checked.
- In the **PROPERTIES** tab of the workplace window, select **VAPOR PRESSURE**.

![Example of the COSMOthermX interface for vapor pressure calculation](image)

- Set the temperature range from 0°C to 70°C and the mole fraction as pure methanol.
- Pressing **ADD** transfers the selected vapor pressure settings to the property panel at the bottom.
- Start the calculation by pressing **RUN**.

The total vapor pressures can be read from the output file and from the table file which will open in a separate window after the calculation has finished.
6.4  Boiling point

This option enables the iterative optimization of the equilibrium temperature for a given vapor pressure. The temperature of the system is varied and for each temperature the vapor pressure is calculated. This is repeated until the COSMOtherm prediction of the total vapor pressure and the specified pressure in the input file is below a certain threshold. During the procedure, the partial vapor pressures of the compounds are written to the COSMOtherm output file. When the required threshold is met, i.e. convergence is reached, the total vapor pressure of the mixture is written to the COSMOtherm table file.

6.5  Flash point

The flash point option allows for the automatic computation of the flash point (FP) of pure compounds and mixtures. The flash point $T_{FP}$ corresponds to a saturation pressure $p_{FP}$, which by definition is the theoretical lower flammability limit at the FP. The prediction of the pure compound's $T_{FP}$ is a variational minimization procedure using the pure compound's vapor pressure $p_i^0(T)$. $p_i^0(T)$ can be predicted by COSMOtherm or, for mixtures, computed from experimental vapor pressure data as provided in the COMPOUND PROPERTIES dialog. Non-combustible substances, e.g. water or CO$_2$, should be tagged as inert in a mixture flash point calculation.

The only descriptor involved in the flash point prediction is the molecular hard-sphere area $a_i$, which is read from the compound COSMO file. For details on the equations and fit parameters involved, please refer to the COSMOtherm Reference Manual and the corresponding publication.\textsuperscript{14}

6.6  Activity coefficient calculation

The activity coefficients of different compounds in the selected solvent or solvent mixture can be calculated in the ACTIVITY COEFFICIENT panel. For the calculation of the activity coefficient at infinite dilution, the mole or mass fraction of the compound of interest has to be set to zero in the composition of the solution. The chemical potentials $\mu_j^{(P)}$ of all pure compounds $j$ and the chemical potentials $\mu_i^{(L)}$ in the liquid phase (compound $i$ or compound mixture, respectively) are calculated. The activity coefficients are then calculated as $\ln(\gamma_j) = (\mu_j^{(P)} - \mu_j^{(P)}) / RT$.

It is also possible to calculate the activity coefficients at a given finite concentration. This is achieved by setting the mole or mass fraction of the compound of interest to the required value in the composition of the solvent. The compound in question is thus treated as part of the solvent.

By checking the EXTENDED OPTIONS a reference state for the activity coefficient can be chosen.

Example 4: Calculate the activity coefficient of aspirin in water

- In the COMPOUNDS panel, open the TZVPD-FINE DB and select aspirin and water.
- By default, all aspirin conformers are selected from the database.
- In the PROPERTIES panel, select ACTIVITY COEFFICIENT and set the temperature to 25 °C,
- Set the water mole fraction to 1.0 (check PURE).
- Transfer the selection to the property section with the ADD button and run the program.
6.7 Henry law coefficient calculation

This option allows for the computation of Henry law coefficients $H^{(i)}$ in compound $i$. The chemical potentials $\mu_j^{(p)}$ of all pure compounds $j$ and the chemical potentials $\mu_j^{(l)}$ at infinite dilution in compound $i$ are calculated. Then the Henry law coefficients $H_j^{(i)}$ for all compounds $j$ are calculated from the activity coefficients and the vapor pressures of the compounds are written to the COSMOtherm output and table files. It is also possible to calculate the Henry law coefficients at a given finite concentration, i.e. in a mixture of solvents.

The Henry law coefficient depends on the pure compound vapor pressure. For each compound, there are several possibilities to calculate or approximate this property. In order of increasing accuracy you might:

- Use the COSMOtherm approximation of the vapor pressure using the approximated gas phase energy of the compound. This is the default if no *.energy file is present and requires no additional input.
- Use the COSMOtherm approximation of the vapor pressure using the exact gas phase energy of the compound from the *.energy file. This option is set by default. (GLOBAL OPTIONS: check ENERGY FILE)
- Use the Wagner, DIPPR, or Antoine equation $\ln(p_j^0) = A - B / (T + C)$ to compute the vapor pressure at the given temperature. If available, data for these equations will be read from the *.vap file if the VAPOR PRESSURE / PROPERTY FILE option is checked in the GLOBAL OPTIONS. Data can also be entered in the COMPOUND PROPERTIES dialog from the context menu of the compound list.
- Enter the exact value of the vapor pressure for this temperature via the COMPOUND PROPERTIES dialog from the context menu of the compound list.

Windows displaying the output and table files will open after the calculation has finished.

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The Henry Law Coefficient option also allows for the calculation of the Gibbs free energy of solvation in different reference frameworks.

6.8 Gas solubility

With this option the solubility of a gas in a solvent or solvent mixture can be calculated in an iterative procedure. For each compound \( j \) the mole fraction \( x_j \) is varied until the partial pressure of the compound \( p_j = p_j^0 \cdot x_j \cdot \gamma_j \) (with the activity coefficient \( \gamma_j \) and the pure compound vapor pressure \( p_j^0 \)) is equal to the given reference pressure \( p \).

Like the calculation of the Henry Law Coefficient, the calculation of a gas solubility requires the knowledge of the pure compound vapor pressure. For options to give the pure compound vapor pressure please refer to the Henry law coefficient calculation section.

Example 5: Gas solubility of methane in water

- In the COMPOUNDS tab of the workplace window, open the TZVP DB and select water and methane.
- In the Properties tab, select GASES,
- Set the temperature to 25 °C, and the pressure to 1013.25 mbar.
- Set the solvent composition to pure water.
- Transfer the settings to the property section by pressing ADD and run the program.

Windows displaying the output and table files will open after the calculation has finished.
6.9 Solubility of multiple solutes in a solvent or solvent mixture

The **MULTIPLE SOLUTES** option allows for the automatic computation of the solubility of a liquid or solid compound \( j \) in a solvent \( i \). Within the calculation all compounds in the compound list are considered solutes, even the solvents themselves. This approach is optimized for the calculation of many solutes in a limited number of solvents or solvent mixtures. If the solubility of a single solute in a large number of solvents should be calculated the **MULTIPLE SOLVENTS** panel offers an appropriate solution.

There are three different methods for the solubility calculation. By default, the JOB TYPE is set to SLE/LLE. With this method, COSMOtherm attempts to solve the actual solid-liquid (SLE), and, if present liquid-liquid (LLE), or solid-liquid-liquid (SLLE) equilibrium conditions for each solute with the given solvent or solvent mixture. The equilibrium conditions that are solved for are described in sections 2.3.7.2 and 2.3.7.3 of the COSMOtherm Reference Manual. Note that, compared to the two other methods available, the explicit solution of the phase equilibrium conditions requires considerably more computational time. However, the solubilities thus computed are actual solutions of the phase equilibrium conditions of the system. Complex phase situations like a SLLE case can be resolved correctly by this option.

Alternatively, the solubility can be calculated from:

\[
\log_{10}(x_j) = \log_{10}\left[\exp(\left(\mu^\text{pure}_j - \mu^\text{solvent}_j - \Delta G_{j,fus}) / RT\right)\right]
\]

COSMOtherm can directly calculate the chemical potentials required: \( \mu^\text{pure} \) of all pure compounds \( j \) and the chemical potentials \( \mu^\text{solvent} \) at infinite dilution. The free energy of fusion \( \Delta G_{fus} \) is zero for liquid compounds and has to be given or estimated for solid compounds. The computed solubility \( x^{(0)}_j \) is a zeroth order approximation, which is valid only for small concentrations of the solute. The simple zeroth order approximation is used if the NON-ITERATIVE method is selected. For large solubilities \( x_j > 0.1 \), \( x^{(0)}_j \) is a poor approximation, but \( x_j \) can be refined iteratively by resubstitution of \( x^{(0)}_j \) into the solubility calculation. This procedure can be repeated until the differences in the computed value of \( x_j \) are below a certain threshold. This procedure is turned on by checking the ITERATIVE calculation type in the solubility panel.

As mentioned above the Gibbs free energy of fusion \( \Delta G_{fus} \) has to be taken into account for solid solutes. \( \Delta G_{fus} \) can be read from the vapor pressure / property file or from the compound line in the compound input section of the COSMOtherm input file. A temperature dependent heat of fusion can also be calculated if the compounds enthalpy or entropy of fusion (\( \Delta H_{fus} \) or \( \Delta S_{fus} \)) and melting temperature are known. This will be done automatically if the USE HEAT CAPACITY OF FUSION ESTIMATE checkbox in the EXTENDED OPTIONS is checked. To add \( \Delta G_{fus} \) (or \( \Delta H_{fus} \) or \( \Delta S_{fus} \) and \( T_{\text{melt}} \)) to the compound input lines open the COMPOUND PROPERTIES dialog for the compound. Alternatively, \( \Delta G_{fus} \) can be estimated by COSMOtherm using a QSPR approach. QSPR parameters are read from the parameter file, if possible, but can also be given explicitly in the EXTENDED OPTIONS dialog. Since one of the QSPR parameters is the chemical potential of the compound in water, water has to be included in the compound list even if it is not present in the system. For further information refer to the COSMOtherm Reference Manual, section 2.3.4.

The output of the solubility option is in logarithmic mole fractions, \( \log_{10}(x) \). Additionally, the mass based solubility is written to the table file. By default the normalized mass fraction solubility is computed. Definitions 1 and 2 are unnormalized mass based solubilities. Definition 1 is an approximation derived for small solubilities. The definition applied for the mass based solubility can be changed in the EXTENDED OPTIONS.
Mass fraction: \( w_j = x_j \cdot \frac{MW_j}{x_j \cdot MW_j + (1-x_j) \cdot MW_{\text{solvent}}} \)  (popular in chemistry, default)

Definition 1: \( w_j = x_j \cdot \frac{MW}{MW_{\text{solvent}}} \)  (popular in drug solubility screening)

Definition 2: \( w_j = x_j \cdot \frac{MW_j}{(1-x_j) \cdot MW_{\text{solvent}}} \)  (popular in engineering)

For further information about the definition of the mass based solubility, refer to the COSMOtherm Reference Manual, section 2.3.

The decadic logarithm of the molar solubility (\( \log_{10}(S \ [\text{mol/l}]) \)) will be written to an additional column in the table file. To calculate the solubility in the more commonly used g/L units the densities have to be known and will therefore be estimated by COSMOtherm. Please note, that this estimation introduces an additional error to the results.

In aqueous systems, acidic or basic solutes can dissociate. The dissociated species typically have properties different from the property of the undissociated compound, thus affecting the apparent solubility of the compound.\(^{15}\) The effect of the dissociated compound approximatively can be taken into account by applying a dissociation correction to the partition coefficient. Additional input for this suboption can be given in the COMPUTE DISSOCIATION CORRECTION subsection of the solubility panel. For the calculation of the dissociation correction either input of the solute pKa value or a cosmo file of the dissociated solute is required. Note that input in this section is only enabled if pure water is selected as solvent.

**Example 6: Solubility of glycol in hexane**

For comparison, we will calculate the solubility of glycol in hexane using the three different methods available in the MULTIPLE SOLUTES panel.

- In the **COMPONENTS** tab of the workplace window, open the TZVP DB and select glycol and hexane.
- In the **PROPERTIES** tab, select MULTIPLE SOLUTES,
- Set the temperature to 25 °C and the state of the solute to LIQUID.
- The Job type is set to SLE/LLE by default.
- Check **PURE** in the “Solvent” paragraph for hexane.
- Add the settings to the property section by pressing the **ADD** button.
- Change the Job type to **ITERATIVE**, then add the settings to the property section again.
- Change the Job type to **NON-ITERATIVE**, add the settings to the property section again.
- Run the calculation.
The COSMOtherm output and table files will pop up after the calculation has finished. Results for the different methods can be read from the corresponding tabs.

### 6.10 Solvent screening: Multiple solvents

The MULTIPLE SOLVENTS option works similarly to the MULTIPLE SOLUTES option and is based on the same thermodynamics. It is especially adjusted to fit solvent screening purposes, i.e. to predict the solubility of one solute in a list of solvents. It is also possible to define a solvent mixture grid for the screening. For solid compounds, a relative screening option is available in addition to the absolute solubility. As the Gibbs free energy of fusion $\Delta G_{\text{fus}}$ is one of the largest error sources for the solubility of solids in general, the relative screening option avoids this error by neglecting $\Delta G_{\text{fus}}$. The result is a relative solubility ranking. The numbers thus given contain all relevant information about solute-solvent interactions, which means that they represent trends of the solubility in different solvents, but they are no absolute solubility values.

The calculated solubilities are printed to the table file in logarithmic mole fractions, $\log_{10}(x)$, and as a mass based solubility. By default, the normalized mass fraction solubility is computed. Definition 1 is an approximation to the default definition 2 for low solubilities. The definition applied for computation of the mass based solubility can be changed in the EXTENDED OPTIONS:

**Mass fraction:**

$$ w_j = x_j \cdot \frac{\text{MW}_j}{\sum x_i \cdot \text{MW}_i} $$

(frequently used in chemistry, default)

**Definition 1:**

$$ w_j = x_j \cdot \frac{\text{MW}_j}{\text{MW}_{\text{solvent}}} $$

(frequently used in drug solubility screening)
Definition 2: \[ w_j = x_j \cdot \frac{MW_j}{(1-x_j)MW_{solvent}} \] (frequently used in engineering)

For further information about the definition of the mass based solubility, refer to the COSMOTHERM Manual.

**Solubility of salts**

Besides neutral compounds, COSMOTHERM can also calculate the solubility of salts in solvents or solvent mixtures. A salt compound \( A^- C^+ \) is always treated by means of its anion \( A^- \) and cation \( C^+ \). To obtain the solubility of a salt, the chemical potentials of the individual ions \( A^- \) and \( C^+ \) and the free energy of fusion \( \Delta G_{fus} \) of the salt \( A^- C^+ \) have to be determined. The salt solubility is then computed from the mean chemical potentials of the ions and the free energy of fusion. COSMOTHERM will calculate a temperature dependent free energy of fusion if the enthalpy or entropy of fusion \( \Delta H_{fus} \) or \( \Delta S_{fus} \), respectively) and the melting temperature \( T_{melt} \) are known. Note that the value of a salt’s free energy of fusion \( \Delta G_{fus}^{AC} \) (as computed from salt enthalpy or entropy of fusion and melting point) by default is considered to be the “total” or “net” free energy of fusion of the salt. This means that the given salt free energy of fusion value is scaled by the total stoichiometry of the salt in a salt solubility (or salt SLE) computation.

For the calculation of a salt solubility, the anion and cation constituting the salt have to be defined. This can be done by clicking on the DEFINE SALT checkbox. The SALT DEFINITION dialog allows for setting anion and cation, their stoichiometric parameters, and the free energy of fusion data. Note that \( \Delta G_{fus} \) can be entered directly or, alternatively, the enthalpy or entropy of fusion \( \Delta H_{fus} \) or \( \Delta S_{fus} \), respectively) and the melting temperature \( T_{melt} \) can be entered. If the heat capacity of fusion \( \Delta C_p_{fus} \) is entered, it will be used to describe the temperature dependency of the Gibbs free energy of fusion.

The computed mass and mole fraction salt solubility can be compared directly to experimental data.

In contrast to most other options the screening cannot be done in a single COSMOTHERM run. Therefore, the graphical user interface generates a summary input file with the extension .inpx and writes the required COSMOTHERM input files (.inp) into a job directory named after the job name. The individual jobs will be run separately and the results will be summarized in a results table.

**Liquid solutes and relative solubility of solid compounds**

The use of the solvent screening option is straightforward in these cases. Select the solute, choose NON ITERATIVE (INFINITE DILUTION) or ITERATIVE (FINITE CONCENTRATION) type of calculation and add all solvents or solvent mixtures to the Property Section. Please note, that the RELATIVE SCREENING is always calculated in infinite dilution (NON ITERATIVE).

The result may look like below:
In addition to the logarithm of the solubility in mole fractions the solubility is also printed in gram per gram solvent (default definition, see also Solubility). Other data, including the chemical potential of the pure solute $\mu^\text{pure}$, the chemical potential in the solvent $\mu^\text{solvent}$, are displayed when the SHOW EXTENDED OUTPUT checkbox is ticked.

Solvent screening for salts works in almost the same manner as for liquid or solid compounds. For liquid salts solubility screening is straightforward: Define the salt, choose a NON ITERATIVE (infinite dilution) or ITERATIVE (finite concentration) type of calculation and add all solvents or solvent mixtures to the property section. For solids salts the free energy of fusion $\Delta G_{\text{fus}}$ of the salt A\textsuperscript{+}C\textsuperscript{−} has to be known, as described above.

To illustrate the meaning of relative solubility the following screenshot shows a solvent screening for benzoic acid in different solvents at 25°C. The plot can be generated automatically in the GRAPH SCREENING tab of the tab file panel.
The logarithm of the best solubility is set to 0 and all other solvents are given relative to the best solvent. In the above example tetrahydrofuran (THF, No. 7) is the best solvent. A solvent with a log10(x_RS) value of -1.00 yields a solubility which is decreased by a factor of 10 compared to THF. In this example the relative solubility of benzoic acid in water (No. 10, log10(x)=3.41) is about 2000 times worse.

**Absolute solubility for solid compounds**

When the absolute solubility of a solid solute should be computed, the free energy of fusion cannot be neglected. Solvent screening for solid salts works in almost the same manner as for neutral solid compounds.

After selecting the corresponding options (State of solute is SOLID, and ABSOLUTE VALUES checked) three different options for the estimation of ΔG_{fus} appear:

- An experimental reference solubility in one of the solvents or solvent mixtures can be used to determine ΔG_{fus} of the solute. If the reference solvent is chosen carefully, i.e. it is known, that COSMOtherm results are usually in good agreement with experimental data for this solvent, this option might give results closest to measurements due to error cancellation. If, however,
COSMOtherm fails to make good predictions for the reference solvent, the errors might add up instead of canceling. To enter the reference solubility data click on PROVIDE DATA. The reference solubility can be given in mass fraction, mole fraction or mg/g solvent according to definition 2.

In rare cases the reference solvent leads to a negative \(\Delta G_{\text{fus}}\). This unphysical value is by default allowed for by applying ALLOW NEGATIVE FREE ENERGY OF FUSION in the GLOBAL OPTIONS dialog. If this option is not set, COSMOtherm will use \(\Delta G_{\text{fus}} = 0.0\) instead. The original reference solubility cannot be reproduced then and all resulting solubilities will be shifted.

- An experimentally measured value for \(\Delta G_{\text{fus}}\) or (or \(\Delta H_{\text{fus}}\) or \(\Delta S_{\text{fus}}\) and \(T_{\text{melt}}\)) can read from the property (.vap) file of the solute. If no data for \(\Delta G_{\text{fus}}\) are available in the .vap file of the solute, it be entered directly. The accuracy of this method depends on extrapolation of \(\Delta G_{\text{fus}}\) at the melting point to the temperature where the solution is calculated.
- A quantitative structure property relationship (QSPR) can be used to estimate \(\Delta G_{\text{fus}}\). The predictive accuracy of this option is generally the least accurate of the three choices.

Screening of solvent mixtures

A range of solvent mixtures can be defined by start and end composition and the total number of mixtures required. Start and end compositions can be pure solvents or solvent mixtures. For each component of the solvent mixture, the concentration is evenly distributed between the respective concentrations in the start composition and in the end composition.

Automatic optimization of solvent mixtures

To find the best solvent is one of the standard tasks of COSMOthermX. In addition to the established methods to screen solvents and solvent mixtures a new method has been implemented to automatically optimize a given solvent mixture. This method has been integrated into the MULTIPLE SOLVENTS panel and can be used in combination with standard solvent screening. The automatic optimization features
• Optimization of any solvent systems consisting of more than one solvent towards maximum solubility of a given solute.
• Optimization towards maximum mole fraction or mass fraction solubility.
• Numerical gradient based algorithm for fast convergence.

The automatic optimization is limited to single compound solutes, i.e. salts cannot be treated. Optimizations are done locally only; global solvent optimization cannot be done. Furthermore, solvent mixtures are always considered as miscible by COSMOtherm; features such as miscibility gaps are not taken into account.

There are different ways to define the mixture to be optimized:
• If non-zero concentrations are given for more than one solvent, only those solvents will be optimized. All other compounds in the compound list will be ignored.
• If a single solvent is set to “pure”, all solvents from the compound list will be added to the solvent with zero concentration. This option is only useful if the compound list contains only solvents of the needed mixture.
• Predefined mixtures and composition series as starting points for the solvent optimization can be loaded from .txt, .csv, or .xls files using the LOAD LIST dialog.

The following options can be enabled for the solvent optimization:
• PROTOCOL will add all intermediate optimization steps to the output table
• OPTIMIZE LOG(X) will maximize the mole fraction solubility
• OPTIMIZE W_SOLUB will maximize the mass based solubility, according to standard COSMOtherm definition (definition to use can be changed in EXTENDED OPTIONS).

Furthermore, there are additional options in the EXTENDED OPTIONS:
• MAXNO. OF STEPS: For each optimization the maximum number of steps is limited. If no convergence occurs the calculation will stop. Default is 50.
• CONVERGENCE: If the algorithm does not find a larger log(solubility) than in the last optimization step by a minimum difference of "convergence", the results is converged. The convergence threshold of 0.0 means convergence is reached if no larger solubility is found. As the solubility is only calculated at discrete steps (STEPSIZE parameter) the accuracy is only determined by the stepsize if convergence is zero. A larger number might cause faster convergence, but a certain circumstances also a premature break. If the solubility does only change very slightly between two optimization steps, the algorithm might stop. Default 0.0.
• STEPSIZE (GRADIENT): A numerical gradient will be calculated for each optimization step. The stepsize in mole fraction is the starting modification of x to generate a gradient. In certain cases the value might be changed internally by the algorithm. The default is 0.02. It should be small enough so no maxima are overseen and the gradient points into the right direction, but large enough to produce numerically significant changes in log10(x_solub).
• STEPSIZE: After the gradient has been calculated the algorithm will go several steps into the direction of the gradient. The basic stepsize is defined here. The algorithm will do multiple steps with different step sizes such as (2xstepsize, 3xstepsize, 0.5xstepsize) to conduct a primitive line
search. Larger numbers might lead to faster convergence and less accurate results and lower numbers to slower convergence and possibly more precise results (dependent on convergence parameter). Default 0.1

Example 7: Estimated solubility improvement of the cocrystal systems carbamazepine – niacinamide and carbamazepine – oxalic acid in water

When dealing with cocrystals, a useful quantity which may be estimated using COSMOtherm is the solubility of the cocrystal. For the cocrystal solubility the same equations as for the salt solubility can be used. For the solubility of a cocrystal/salt the following equation (eq. 2.3.1a from the COSMOtherm manual) is valid:

$$\log_{10}(x_{AB}^{SOL}) = \left[ \left( \mu_{AB}^{(0)} - \mu_{AB}^{(v)} - \max(0, \Delta G_{fus}) \right) / V_{tot} \right] / (RT \ln(10))$$

In this case $x_{AB}^{SOL}$ is the solubility of the AB cocrystal with stoichiometry m:n, referring to one mole of cocrystal (salt). $\mu_{AB}^{(0)} - \Delta G_{fus}$ is the chemical potential of the cocrystal AB and $\mu_{AB}^{(v)}$ is the chemical potential of AB in the solvent, and $V_{tot} = m+n$. Please refer to the COSMOtherm manual for further details.

- In the COMPOUNDS tab of the workplace window, open the TZVP Database and select the following compounds: carbamazepine, niacinamide (=nicotinamide) and water.
- In the PROPERTIES tab, select MULTIPLE SOLVENTS.
- The temperature is set to 25 °C by default.
- Set state of solute to LIQUID. As we do not know the free energy of fusion $\Delta G_{fus}$, we neglect it in this case, setting the solute state to liquid (which means $\Delta G_{fus} = 0$). Of course we will not get absolute solubility values anymore, but we still can predict solubility trends with this approximation.
- Tick the DEFINE SALT checkbox. Set carbamazepine and niacinamide as compounds in the salt definition section, using 1 as stoichiometric values for both components. Close the SALT DEFINITION dialog by clicking OK.
- Set the calculation type to NON ITERATIVE.
- In the DEFINE SOLVENT section, specify water as PURE.
- Add the system carbamazepine-nicotinamide (CBZ-NCT, 1:1) to the property section by pressing the ADD SOLVENT button.
- Start the solubility calculation via the RUN button.
- Repeat the calculation for the carbamazepine and oxalic acid in water, using 2:1 stoichiometric settings for the salt definition.
In a true predictive calculation the stoichiometry of the potential crystal would of course be unknown, and one should start from a 1:1 ratio.

After the calculation has finished, we obtain for the logarithmic mole fraction solubility of the CBZ-NCT cocrystal $\log_{10}x = -1.85$ and for CBZ-OX $\log_{10}x = -2.84$ (for the different and sometimes intricate definitions of solubility please refer to the COSMOTHERM Reference Manual). The solubility of the component CBZ itself in the CBZ-OXA cocrystal is thus twice as large, because we have a 2:1 stoichiometry and the logarithmic mole fraction is approximately $\log_{10}x = -2.56$. The solubility of CBZ-NCT remains unchanged as we have 1:1 stoichiometry.

Results plotted below were calculated using a previous COSMOTHERM parameterization (BP_TZVP_C30_1201.ctd). Results obtained with the current parameterization may differ numerically. Comparing the calculated logarithmic solubilities with experimental literature data for some carbamazepine cocrystals results in the following plot:
The cocrystal system CBZ-NCT shows the highest improvement in solubility as compared to the solubility of the pure drug carbamazepine. Please note that no correction for dissociation of the acids or the API was applied. The data for the remaining cocrystals of Good et al. is shown below with the solubility of the cocrystal ($\log_{10}(x_{CC})$), the solubility of carbamazepine itself ($\log_{10}(x_{CBZ})$) and the experimental ratio of the solubility of carbamazepine within the cocrystal to the solubility of pure carbamazepine ($\log_{10}(x_{CC}/x_{CBZ})$).

<table>
<thead>
<tr>
<th>API</th>
<th>coformer</th>
<th>$\log_{10}(x_{CC})$</th>
<th>$\log_{10}(x_{CBZ})$</th>
<th>$\log_{10}(x_{CC}/x_{CBZ})$, exp</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbamazepine</td>
<td>nicotineamid (NCT)</td>
<td>-1.93</td>
<td>-1.93</td>
<td>2.182</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>oxalic acid (OXA), 2:1</td>
<td>-2.86</td>
<td>-2.56</td>
<td>0.752</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>glutaric acid (GTA)</td>
<td>-2.33</td>
<td>-2.33</td>
<td>2.070</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>saccharin (SAC)</td>
<td>-3.14</td>
<td>-3.14</td>
<td>0.416</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>succinic acid (SUC), 2:1</td>
<td>-2.80</td>
<td>-2.49</td>
<td>0.717</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>malonic acid (MLN), 2:1</td>
<td>-2.78</td>
<td>-2.47</td>
<td>1.409</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>salicylic acid (SLC)</td>
<td>-3.24</td>
<td>-3.42</td>
<td>0.296</td>
</tr>
</tbody>
</table>

Example 8: Prediction of the solubility of NaCl in several solvents

- In the **COMPOUNDS** tab of the workplace window, open the TZVP Database and select methanol, ethanol, 1-octanol, Na⁺ (na_cation), and Cl⁻ (cl_anion).
- In the **PROPERTIES** tab select **MULTIPLE SOLVENTS**.
- The temperature is set to 25 °C by default.
- Tick the **DEFINE SALT** checkbox. Define the salt composition in the “Salt definition” box: Check the checkboxes in the cl and na compound lines. The stoichiometric coefficients are set to 1 automatically.
- Also in the **DEFINE SALT** dialog, specify experimental data for calculation of $\Delta G_{fus}$: Enter the value for the enthalpy of fusion (28.16 kJ/mol) and the melting point temperature (800.7 °C). Click OK.

- Set the state of solute to **SOLID**, and select **ABSOLUTE VALUES**.
- **USE EXPERIMENTAL $\Delta G_{fus}(T)$ DATA FROM SALT DEFINITION** is selected by default.
6.11 Partition coefficient calculation (log P / log D)

Partition coefficients of solute \( j \) between solvents \( i_1 \) and \( i_2 \) are defined as \( P_{1,2} = c_2 / c_1 \), with \( c_1 \) and \( c_2 \) being the concentrations of solute \( j \) in \( i_1 \) and \( i_2 \), respectively. The calculation of the partition coefficient \( \log P \) is accomplished via computation of the chemical potentials \( \mu_j^{(1)} \) and \( \mu_j^{(2)} \) of all compounds \( j \) in infinite dilution in pure compounds \( i_1 \) and \( i_2 \), respectively:

\[
\log_{10}(P_{1,2}) = \log_{10}[\exp((\mu_j^{(1)} - \mu_j^{(2)})/RT) \cdot V_1/V_2]
\]  

(8)

The ratio of molar \( V_1/V_2 \) (also called volume quotient) will be estimated from the COSMO volumes by default, unless a value is entered in the LOG P / LOG D panel. In case the COMPUTE OCTANOL-WATER PARTITION option is selected, the ratio of molar volumes and the phase compositions will be set automatically. With the THERMODYNAMIC PARTITION option, the ratio will be set to 1, which corresponds to a logP definition by mole fractions. The input of a volume quotient will be necessary if the experimental density of at least one of the two solvent phases differs substantially from a linear interpolation form the individual phase compounds. In this case the estimate from the COSMO volumes, based on the assumption of an incompressible liquid, will be poor. Furthermore, the mutual solubility of the solvents in each other has
to be taken into account when computing $\mu_j^{(1)}$ and $\mu_j^{(2)}$. It is possible to give finite concentrations in the solvent mixture section.

In systems with one aqueous phase it is possible that acidic or basic solutes dissociate in the water phase. The dissociated species typically have partition properties different from the partition property of the undissociated compound, thus affecting the apparent partition coefficient of the compound.\textsuperscript{15} The effect of the dissociated compound approximatively can be taken into account by applying a dissociation correction to the partition coefficient. Additional input for this suboption can be given in the COMPUTE DISSOCIATION CORRECTION (LOGD) subsection of the logP panel. For the calculation of the dissociation correction either input of the solute pKa value or a cosmo file of the dissociated solute is required.

**Example 9: Prediction of octanol / water partition coefficients**

- In the COMPOUNDS tab of the workplace window, open the TZVPD-FINE Database and select water, 1-octanol and aspirin.
- In the PROPERTIES tab select the LOGP/LOGD option.
- The temperature is set to 25 °C by default.
- Select the COMPUTE OCTANOL-WATER PARTITION OPTION: Correct phase compositions are set automatically, as well as the ratio of molar concentrations. As you can see the WET OCTANOL phase contains 0.274 mole fractions of water.
- ADD your settings to the property section and run the program.

The partition coefficients can be read from the output and table files.
6.12 Calculation of pK\textsubscript{A}

The pK\textsubscript{A} of a solute $j$ can be estimated from the linear free energy relationship (LFER),

$$pK_A = c_0 + c_1(\Delta G_{\text{neutral}}^j - \Delta G_{\text{ion}}^j)$$

(9)

where $\Delta G^j$ are the free energies of the neutral and the ionic compounds.

The pK\textsubscript{A} option allows for the computation of the pK\textsubscript{A} value of a compound in a solvent $i$ (usually water). The free energies $\Delta G^j$ in the solvent at infinite dilution are computed and the pK\textsubscript{A} is estimated from the above LFER. Thus, to obtain a pK\textsubscript{A} value it is necessary to do quantum chemical COSMO calculations of a molecule in its neutral and in its ionic state. Since the LFER is valid for both anions and cations it is possible to estimate acidity as well as basicity. The LFER parameters $c_0$ and $c_1$ are read from the COSMO\textsubscript{therm} parameter file by default.

pK\textsubscript{A} prediction by COSMO\textsubscript{therm} is not restricted to aqueous acid pK\textsubscript{A}. However, both aqueous base pK\textsubscript{A} prediction and pK\textsubscript{A} in solvents other than water require reparameterization of the pK\textsubscript{A} LFER parameters. LFER parameters for aqueous base pK\textsubscript{A}, pK\textsubscript{A} in solvents dimethylsulfoxide (DMSO) and acetonitrile at room temperature are shipped within the COSMO\textsubscript{therm} parameter files. Please note, that the solvent has to be set corresponding to the selected option for the LFER parameters. LFER parameters for solvent-solute systems other than those provided by COSMO\textsubscript{therm} or for temperatures other than room temperature can be set by selecting the EXTENDED OPTIONS checkbox to enter the LFER parameters.

For the computation of higher states of ionization, the neutral and singly charged ionic species have to be replaced by higher ionized species.

Example 10: Calculation of the aqueous pKA of pyrrolidine

- In the COMPOUNDS tab of the workplace window, open the TZVPD-FINE Database and select the solvent (water), and the neutral and ionic compounds (pyrrolidine, pyrrolidine-cation).
- Select the pK\textsubscript{A} option in the PROPERTIES tab.
- Set the temperature, 25 °C, and set water as the solvent.
- Use the pK\textsubscript{A} parameters for bases in water.
- Set the neutral and ionic compounds from the menus.
Note that it is possible to reset the compounds and also add them to the input. In that case, COSMOTHERM will do more than one property calculation and write the results to the output and table files. Since we have chosen room temperature and water as solvent for the calculation, no further settings are necessary. If you want to use your own LFER parameters, input is possible via the EXTENDED OPTIONS option. Save the input file and run the calculation. The COSMOTHERM output and table files will open after the calculation has finished.

The table file lists the computed pKa of the conjugated acid (experimental pKa for Pyrrolidine = 10.27).

### 6.13 Vapor liquid-equilibria (VLE) and liquid-liquid equilibria (LLE)

COSMOTHERM allows for the computation of phase diagrams (VLE and LLE) of binary, ternary or higher dimensional (“multinary”) mixtures. In COSMOTHERMX, these options are accessible from the VAPOR-LIQUID and LIQUID-LIQUID buttons in the property selection. It is possible to calculate phase diagrams at fixed pressure (isobaric) or at fixed temperature (isothermal). The pressure or temperature has to be given in the input. The program automatically computes a list of concentrations covering the whole range of mole fractions of the binary, ternary or multinary mixture. At each point the following properties are calculated:

- the excess properties $H^e$ and $G^e$,
- the chemical potentials $\mu_i + RT \ln(x_i)$
- the activity coefficient $\gamma_i$
- the total vapor pressure of the system $p^{(tot)}$
- and the concentrations of the compounds in the gas phase $y_i$
The total pressures used in the computation of a phase diagram are obtained from

$$p^{(\text{tot})} = \sum_i p_i^0 x_i \gamma_i$$

(10)

The $p_i^0$ are the pure compound vapor pressures for compounds $i$. $x_i$ are the mole fractions of the compounds in the liquid phase and $\gamma_i$ are the activity coefficients of the compounds as predicted by COSMOtherm. Ideal behavior in the gas phase is assumed. Thus, the computation of phase diagrams requires the knowledge of the pure compound’s vapor pressure $p_i^0$ at a given temperature. There are several possibilities to calculate or approximate this property, as described in the Henry Law Coefficient section. By default, the COSMOtherm approximation of the vapor pressure, using the approximated gas phase energy of the compound, is employed, unless the use of energy files or vapor pressure / property files is specified in the GLOBAL OPTIONS. For other options, experimental data can be entered in the COMPOUND PROPERTIES dialog from the compound list context menu.

Vapor mole fractions $y_i$ are obtained from the ratio of total vapor pressures and partial vapor pressures $p_i = p_i^0 x_i \gamma_i$:

$$y_i = \frac{p_i^0 x_i \gamma_i}{p^{(\text{tot})}}$$

(11)

Phase diagrams can be calculated either at a fixed given temperature or at a fixed given pressure with variable temperatures. In an isobaric calculation, COSMOtherm will compute the mixture properties and vapor pressure for each concentration at different starting temperatures and iteratively converge to the temperature corresponding to the given pressure.

By default, phase diagram calculations are done on a grid of 29 (for a binary) and 231 (for a ternary) mole fraction concentration points. The default grid values span the complete concentration range of the two and three dimensional binary and ternary phase space. The concentrations of the VLE default grid are defined in mole fractions, which are unevenly spaced: the concentrations steps in the grid are becoming smaller if a compound approaches infinite dilution. This specific grid accounts for the fact that properties such as activity coefficients $\gamma_i$ or concentrations in the vapor phase $y_i$ typically show their strongest changes at low $x_i$ concentrations. Thus being uneven the default VLE grid tries to cover the phase space of the computed properties as comprehensive and effective as possible. When the SEARCH LLE POINT suboptions are used, the default grid values are modified automatically, as described in more detail in the COSMOtherm Reference Manual. The default grid can also be modified with the CHANGE CONCENTRATION GRID suboptions in the VLE/LLE panel.

For binary phase diagram calculations, options for automatic post-processing are provided, such as fitting of the computed activity coefficients to activity coefficient models or azeotrope detection.

**Ionic Liquid Phases**

COSMOtherm also offers the possibility to compute phase diagrams of binary or ternary mixtures of an Ionic Liquid (IL) phase with additional solvent phases. In ternary calculations, up to 3 ionic liquid phases can be defined.

Because in COSMO-RS theory any Ionic Liquid (or dissolved salt) phase has to be treated by means of the individual ions forming the IL (or salt), a phase diagram computation has to be conducted in the form of
a multicomponent phase diagram with the boundary condition of the anion and cation concentrations forming the IL (or salt) having a fixed ratio according to the IL (salt) stoichiometry. This means that within COSMOtherm, the IL (salt) is treated by means of the individual ions, but on output, the results of the individual ion’s properties are combined to form a single IL (or salt) phase, i.e. in the output of COSMOtherm the “laboratory binary” definition is used for binary calculations involving Ionic Liquids. For information about the conversion from the “pseudo-binary” framework to the “laboratory-binary” framework refer to Appendix A of this document or to sections 2.3.7.3 and 5.9 of the COSMOtherm Reference Manual. Note that isobaric phase diagram calculations including an Ionic Liquid phase are unfeasible in COSMOtherm.

To define an IL phase in COSMOthermX, tick the DEFINE IONIC LIQUID PHASE checkbox in the COMPONENTS definition block of the VLE/LLE panel. The ions constituting the IL and the stoichiometry should be indicated in the list of compounds appearing upon ticking the checkbox.

Composite Phases

Furthermore, it is also possible to define each of the solvent phases as a composite with a given mixture composition. Implicitly this approach assumes that the physical and thermodynamic properties of the given mixture phases are additive with respect to the contributions of the mixtures components. Using mixture phases thus defined, COSMOtherm can perform a “pseudo-binary” multicomponent phase diagram computation. This means that within COSMOtherm, the mixture phase is treated by means of its individual components at the given mixture ratio, but on output, the results of the individual compound properties are combined to form a single mixture phase. It is possible to include neutral components as well as ions into such a composite phase as long as the resulting mixture is charge neutral. The mixtures of the composite phases are not allowed to overlap, neither with another pure compound phase, nor with another composite / mixture phase.

A mixture phase can be defined by ticking the DEFINE MIXTURE PHASE checkbox in the COMPONENTS definition block. The components of the mixture phase and their relative amount has to be indicated in the compound list of the respective phase.

Miscibility Gaps

Miscibility gaps in binary, ternary and multinary mixtures can be searched for automatically. The liquid-liquid equilibrium properties are calculated from

\[ x' I y' I = x'' II y'' II \]  \hspace{1cm} (12)

where superscripts \( I \) and \( II \) denote the two liquid phases. If the SEARCH LLE POINT option is used, the COSMOtherm table file will be modified according to any miscibility gap that has been detected. In case of a binary mixture, the binodal LLE point (eq. 14) and the spinodal LLE point, that distinguishes the unstable region of the liquid mixture from the metastable region, will also be printed in the table file. In ternary and multinary mixtures it is necessary to define a starting composition and end composition. A given number of points between these compositions is then used a starting point for the tie point search. If no good guess for the starting and end compositions is available, several concentrations should be tried. Please be aware that no guarantee can be given that all points are found.
Optionally, COSMOtherm can do a renormalization of LLE points accounting for thermodynamic fluctuations in the liquid mixture. This will be done if the COMPUTE RENORMALIZED LLE checkbox is checked. For details refer to the COSMOtherm Reference Manual.

Example 11: Calculate the solubility of aniline in water

- In the COMPOUNDS tab of the workplace window, open the TZVPD-FINE Database and select the compounds, aniline and water (h2o.cosmo).
- In the PROPERTIES tab, select LIQUID-LIQUID.
- Pre-set conditions of the LLE are isothermal, 25 °C for the temperature, and binary for the type of the system.
- Water and aniline are automatically set as 1st and 2nd components. To change components, select them from the pull-down boxes.
- Check SEARCH LLE POINT.
- Create the property input by pressing the ADD button and run COSMOtherm.
When the calculation has finished the COSMOtherm output and table files will open in separate tabs. The data of the binary phase diagram are tabulated in the .tab file, and can also be plotted in a plot tool. Go to the “graphics” tab at the bottom of the table file panel. Choose a quantity from the left menu and plot it. Use the shift or Control keys to select another quantity for the same plot. A right mouse-button click in the plot opens a menu which allows you to add properties of the same or other table files, e.g. to compare VLEs at different temperatures, or to change the quantity on the x-axis.

Equation-of-State models

Equation-of-State (EOS) models can be used to extend the applicability of the LLE and VLE calculation to systems near or beyond the critical point. Two different EOS models can be chosen from the Use EQUATION-OF-STATE (EOS) MODEL option, the Peng-Robinson or the Soave-Redlich-Kwong EOS models. Furthermore, mixing rules and various binary interaction parameters can be chosen.

6.14 Solid liquid equilibria

With the SOLID-LIQUID option, COSMOtherm will compute a range of mixtures and search for possible concentrations of solidification. The solid-liquid equilibrium properties are calculated from

$$
\mu^\text{Solid}_i = \mu^\text{Liquid}_i + RT \cdot \ln(x_i)
$$

The SLE search assumes that there is a simple eutectic point in the binary mixture. Complicated systems with several phase transitions in the solid state cannot be predicted by the SLE option. Since COSMO-RS is a theory for liquids only, the Gibbs free energy of fusion of the compound, $\Delta G_{\text{fus}}$, has to be taken into account for the solid-liquid equilibrium of a solid compound with a solvent. COSMOtherm will calculate a temperature dependent free energy of fusion if the compounds enthalpy or entropy of fusion ($\Delta H_{\text{fus}}$ or $\Delta S_{\text{fus}}$ are
$\Delta S_{fus}$, respectively) and melting temperature ($T_{melt}$) are known. These data can be read from the .vap file or you can use the COMPOUND PROPERTIES dialog from the compound context menu to enter the data. Note that the value of a salt’s free energy of fusion $\Delta G^0_{fus}$ (as computed from salt enthalpy or entropy of fusion and melting point) by default is considered to be the “total” or “net” free energy of fusion of the salt. This means that the given salt free energy of fusion value is scaled by the total stoichiometry of the salt in a salt solubility or salt SLE computation.

SLE calculations are done on an even spaced grid of 325 mixture concentrations, followed by an iterative refinement. Note that therefore, the calculation will take some time. The default grid can be modified to mass fraction or surface fraction with the CHANGE CONCENTRATION GRID suboptions. Furthermore, the heat capacity of fusion can be used to improve the calculated temperature dependency.

**Ionic Liquid Phases**

Like in a VLE/LLE binary calculation, it is possible to compute solid-liquid phase equilibria (SLE) for pseudo-binary solutions with an Ionic Liquid or salt phase. The predicted mole fraction concentration of the ionic liquid or salt is converted to the "laboratory-binary" framework (i.e. the salt is considered to be one single compound) when printed to the table file.

**Composite Phases**

Furthermore, it is also possible to define each of the solvent phases as a composite with a given mixture composition, under the same conditions as in the case of vapor-liquid or liquid-liquid equilibria.

**Example 12: Solid-liquid equilibrium curve of toluene and ethylbenzene**

- In the COMPOUNDS tab of the workplace window, open the TZVPD-FINE Database and select toluene and ethylbenzene. For both compounds the necessary data for $\Delta G_{fus}$ are already contained in the database.
- In the PROPERTIES tab, select SOLID-LIQUID.
- To calculate a temperature series enter 140 K as starting temperature and 178 as end temperature. Use as many points as you like (beware that too many points will need a lot of calculation time).
- Toluene and ethylbenzene are automatically set as components.
• Add the settings to the property selection window and run the program.

The computed SLE points are stored in the .tab file for each calculated temperature. To visualize the calculated eutectic point, change to the GRAPH BIN tab. In the upper list, select all temperatures. Then select SLE(1) and SLE(2) in the lower property list and use the PLOT button. The individual SLE points for each temperature are also printed in each card of the .tab file.
6.15 FlatSurf: surface activity

With the FlatSurf option, the surface interaction energy of all compounds is computed at the interface of the two solvents or solvent mixtures. This is possible under the idealized assumption of a flat interface. The position of the solute at the interface is described by the distance \( z \) of the solute center from the interface, and orientation \( \Gamma \) of a fixed solute axis with respect to the surface normal direction. For such a given position of the compound a certain part of the molecular surface segments will be imbedded in phase \( S \) and the rest in phase \( S' \). By sampling all relevant positions and orientations the minimum of the free energy of the solute at the interface of \( S \) and \( S' \) can be found. The search for the optimal association of \( X \) at the interface can be extended to conformationally flexible molecules when the free energy differences between different solute conformers are taken into account. The minimum of the free energy of the solute at the flat interface of \( S \) and \( S' \) and the total free energy of the solute at the flat interface of \( S \) and \( S' \) can both be used as significant and thermodynamically rooted descriptors for the determination of surface activity in a solution. More details about the method can be found in the COSMOtherm Reference Manual.

COSMOtherm can use the experimental interfacial tension of the two solvent phases to improve the computed FlatSurf energies. This is possible with the \texttt{IFT=value} keyword. The value of the interfacial tension is expected to be in \([\text{mN/m}]\). Values for interfacial tensions of various solvent-solvent or air-solvent combinations can be found e.g. in the CRC Handbook of Chemistry and Physics\textsuperscript{17}.

To visualize the immersion and geometric partition of a solute in the two phases the option “Create Flatsurf VRML charge surface” can be checked. With this option, a VRML file will be written where the immersion depth \( z \) of the solute between the two solvent phases is represented graphically on the charge surface in the form of a black and white ring. The black part of the ring points towards FlatSurf solvent phase 1 and the white part of the ring points towards FlatSurf solvent phase 2. Thus the ring indicates how the solute molecule is immersed in the two phases. The example on the right shows the immersion of a phenol molecule in a water (upper part) and a hexane phase (lower part).

**Example 13: Calculate the air-water surface partition energy**

- In the \texttt{COMPOUNDS} tab of the workplace window, open the TZVP Database and select water, benzene and chlorobenzene.
- For air, select the \texttt{vacuum.cosmo} file from the TZVP database.
- Select \texttt{FLATSURF} in the \texttt{PROPERTIES} tab.
- Check \texttt{PURE} for water in phase 1 and for vacuum in phase 2.
- Enter the value for the interfacial tension at the air-water interface (72.8 mN/m) into the appropriate field.
• To visualize the immersion of the solute between the two phases, check CREATE FLATSURF VRML SIGMA SURFACE.
• Add the settings to the property selection window and run the program.

The table file for the FLATSURF option consists of two separate tables: one table for FlatSurf interaction Phase 1 to Interface, and one table for FlatSurf interaction Phase 1 to Interface. For each compound, the following descriptors are written to the tables:

• \( \mu_{SS',res}^{Gmin} \): maximum of the free energy gain of the solute X going from phase 1 or phase 2, respectively, to the interface of S and S'. (Please note, that going from phase 1 to the interface makes a difference to going from phase 2 to the interface)
• \( G_{SS'}^{X} (G_{tot}) \): total free energy gain of the solute X going from phase 1 or phase 2, respectively, to the interface of S and S';
• \( a_{SS'}^{X}(Across,mean) \)
• \( a_{SS'}^{X}(Asurf,mean) \)
• \( a_{SS'}^{X}(Asurf,min) \) contact area of the solute X with phase 2 or phase 1, respectively, at the free energy minimum;
• \( a^{X}(Acomp) \): initial area of the COSMO-surface of solute X;
• \( V_{SS'}^{X}(Vsurf,mean) \): the mean volume of the solute X at the flat interface;
• \( V_{SS'}^{X}(Vsurf,min) \): the contact volume of the solute X with phase S at the free energy minimum;
• \( V^{X}(Vcomp) \): the initial volume of the COSMO-file of solute;
• \( z_{min}^{X}(Depth) \): distance of the center of solute X from the interface at the free energy minimum.
• \( z_{max}^{X}(Depth_{z}) \): the maximum z-coordinate of the distance of the center of solute X from the interface at the free energy minimum.

COSMOtherm will write the name of the specific conformer to the table output which was able to achieve the lowest value of \( \mu_{SS',res}^{X} (G_{min}) \). I.e. from the list of all conformers of a compound the one with the lowest minimum free energy values at the flat interface of S and S’ will be listed. In contrast, \( G_{SS'}^{X}(G_{tot}) \),
the total free energy gain of the solute X at the flat interface, is the thermodynamic average according to the interface partition sum of all conformers in a conformer set.

6.16 Interfacial Tension

The Interfacial Tension panel implements a model for predicting interfacial tension, requiring no experimental input. The model is applicable to liquid/liquid systems of arbitrary compositions. For detailed information, please refer to the corresponding publication.\textsuperscript{18} Since the phases should have equilibrium concentrations corresponding to the employed level of COSMOTHERM, a preceding calculation of the liquid-liquid equilibrium is mandatory and will be done automatically if the corresponding checkbox (AUTOMATIC PHASE EQUILIBRIUM) is checked. Alternatively, phase compositions from an LLE or Liquid Extraction calculation can be provided manually. Note that for algorithmic reasons, mole fraction concentrations of all compounds in the phase compositions have to be larger than 0.

Example 14: Interfacial Tension for a binary water / heptane system

Since the prediction of the IFT requires equilibrium phase concentrations for both phases, an automatic Liquid Extraction calculation will be performed as a preparatory step.

- In the COMPOUNDS tab of the workplace window, open the TZVPD-FINE Database and select h2o and n-heptane.
- In the Properties tab, select INTERFACIAL TENSION from the partitioning property group.
- Enter the temperature (25 °C).
- Check the PURE checkboxes for water in phase 1 and for n-heptane in phase 2.
- Select the AUTOMATIC PHASE EQUILIBRIUM option.
- Transfer the settings to the property section with the ADD button and run the program.
6.17 Density

The Density option uses the corrected molar liquid volume \( \tilde{V}_i \) of the pure compounds to calculate the pure compound liquid density \( \rho_i \) for all given compounds according to

\[
\rho_i = \frac{MW_i}{\tilde{V}_i N_A}
\]

where \( MW_i \) is the molecular weight of the compound and \( N_A \) is Avogadro’s constant. The corrected molar liquid volume \( \tilde{V}_i \) is computed from a Quantitative-Structure-Property-Relationship (QSPR) which includes seven generic QSPR parameters and one element specific parameter.

Generally, the QSPR model is valid for a specific temperature only, because it does not include a temperature dependency term. The QSPR parameters and element specific surface area parameters that can be read from the COSMOtherm parameterization files were derived from room temperature data. Optimized element specific surface area parameters are available for elements H, N, C, O, F, S, Cl, Br and I. For other elements reasonable guesses for the element specific surface area parameters are provided.

It is possible to specify user-defined values for the density/volume QSPR parameters and the element specific surface area parameters. Check the “Extended Options” checkbox to enter the parameters manually. Please refer to the COSMOtherm Reference Manual, section 2.3.12, for more details.

If several conformers of one compound are present, COSMOtherm will compute the density descriptors of all individual conformers. Subsequently a thermodynamic average of the conformer descriptors at the given temperature condition will be calculated, from which the averaged density of the compound is predicted.

The computation of the liquid density of a pure Ionic Liquid (IL) compound can be done from the individual ions that form the specific IL. The composition of the IL has to be defined in the input. The IL is then pieced together from its anion(s) and cation(s). If the IL option is used, COSMOtherm will compute the density of the given IL compound only (this is unlike the regular density option for individual compounds, which always computes the densities of all compounds present).

Example 15: Liquid density and liquid molar volume of pure compounds

- In the COMPOUNDS tab of the workplace window, open the TZVP Database and select h2o, 1-butanol, butanone, diethylether, chcl3, chlorobenzene, benzene, toluene, and octane.
- In the Properties tab, select DENSITY.
- Enter the temperature (25 °C).
- Transfer the settings to the property section with the ADD button and run the program.

The calculated densities and volumes can be read from the table file.
6.18 Viscosity

The pure compound liquid viscosity is another property that can be calculated from QSPR. The descriptors for the liquid viscosity are the compound surface area as read from the COSMO file $A_i$, the second $\sigma$-moment of the compound $M_r^2$, the number of ring atoms in the compound $N^\text{ring}$ and the pure compound’s entropy times temperature $T S_m$ which is computed from the difference of the total enthalpy of mixture of the pure compound $H_i$ and the chemical potential of the pure compound $\mu_i$: $T S_m = \{H_i - \mu_i \}$. This QSPR model, like the Density QSPR model, does not include a temperature dependency term, so that the model is valid at a specific temperature only. All parameterizations include the viscosity QSPR parameters for room temperature. User-defined values for the QSPR parameters can be specified manually within the EXTENDED OPTIONS.

For a compound with several conformers COSMOtherm will compute the viscosity descriptors of all individual conformers, followed by a thermodynamic averaging of the conformer descriptors at the given temperature condition to predict the averaged viscosity of the compound.

6.19 Similarity

With this option, COSMOtherm will calculate a molecular similarity of two compounds based on $\sigma$-profiles or $\sigma$-potentials. There are three possible methods which can be used for a similarity calculation, and which can be combined in a single calculation:

**$\sigma$-profile similarity factor $S_{ij}$.** The $\sigma$-profile similarity factor $S_{ij}$ is calculated as the normalized overlap integral of the $\sigma$-profiles $p_i(\sigma)$ and $p_j(\sigma)$ of the two compounds $i$ and $j$:

$$S_{ij} = \left( \int_{-\infty}^{+\infty} p_i(\sigma)p_j(\sigma) d\sigma \right) / \left( A_i A_j \right)$$

(14)

$S_{ij}$ will be small if the overlap between the compounds $\sigma$-profiles is small. In addition, the similarity factor given by eq. (14) is corrected by a factor $S'^{n}_{ij}$ taking into account the difference in the apparent hydrogen bonding donor and acceptor capacities of the two compounds and by a factor $S'^{A}_{ij}$ taking into account size differences between the two compounds $i$ and $j$.

**$\sigma$-potential similarity factor $S'^{\sigma}_{ij}$.** COSMOtherm can also calculate a $\sigma$-potential based similarity factor for two compounds. This method is useful for comparing solvents. The COSMOtherm $\sigma$-potential similarity factor $S'^{\sigma}_{ij}$ is defined as the sum of the differences between the two pure compound $\sigma$-potentials $\mu_i(\sigma)$ and $\mu_j(\sigma)$:

$$S'^{\sigma}_{ij} = \exp \left( \sum_{m=0.02}^{-m=0.02} \mu_i(\sigma_m) - \mu_j(\sigma_m) \right)$$

(15)

$S'^{\sigma}_{ij}$ will be small if the overlap between the compounds $\sigma$-potentials is small. The $\sigma$-potential can also be weighted by the $\sigma$-profile of a third compound. Then the computed similarity is a solute-specific $\sigma$-potential similarity (see section 2.3.10 of the COSMOtherm Reference Manual).

**Sigma-Match Similarity SMS$'^{\sigma}_{ij}$.** Alternatively, COSMOtherm allows for the calculation of a molecular $\sigma$-profile similarity by the “Sigma-Match Similarity” (SMS) algorithm\(^{19}\).
The similarity factors $S_{i,j}$, $S^p_{i,j}$ and $SMS_{i,j}$ are printed to the mixture output section of the COSMOtherm output file below the compound output block of the first compound for which the similarity factors are calculated and, additionally, to the COSMOtherm table file. If several conformers are present for a compound, the $\sigma$-profile based similarity factor will be computed for all possible combinations of the conformers and the overall compound similarity factor is averaged from the computed conformer similarity factors. It is possible to enter a solvent mixture, in which the different conformers are weighted. In benzene a different conformer might be relevant than in water, consequently the SMS can give different results if the conformers are weighted according to their abundance in water or benzene.

### 6.20 Critical Properties

Some critical properties of pure compounds can be calculated in this panel, namely the critical temperature $T_C$, the critical volume $V_C$, the critical pressure $p_C$, and some critical-point related auxiliary properties. All critical point properties are computed via QSPR-type correlations using descriptors computed on-the-fly by COSMOtherm. Details for the calculation are described in the COSMOtherm Reference Manual.

### 6.21 Liquid extraction

This option allows for the automatic computation of a multi-component multi-phase liquid-liquid extraction equilibrium. The mole or mass based equilibrium partitioning of an arbitrary number of compounds between a given number of liquid or, optionally, solid (precipitation) and gaseous (evaporation) phases, can be computed. The functionality of the option is described in the figure below for two liquid phases:

![Liquid extraction diagram](image)

The two predefined phases I and II may be mixtures of compounds including ionic liquids or dissolved salts. Phases I and II are assumed to be immiscible and to separate in thermodynamic equilibrium. In the above example, phase I has a high water concentration and phase II is an ionic liquid. Compounds methanol, acetone, H2O and the ions are distributed between the two phases. Please note, that all compounds including water and the ionic liquid are equilibrated.

All compounds are distributed among the two phases according to their partition equilibrium constants:

$$K^X_i = \exp \left( \frac{\mu_i^I - \mu_i^II}{RT} \right)$$

Since all chemical potentials themselves do depend on the composition of the phases, the final equilibrium distribution has to be solved iteratively. Starting from the given concentrations a set of new concentrations is calculated. In the next step the new concentrations are used to calculate the refined
chemical potentials and thus another refined set of concentrations. This procedure is repeated until the concentrations of the two phases do not change any more. Thus the thermodynamic equilibrium, the mass balance and, if ions are present, the charge neutrality condition (as a boundary condition of the mass balance) of the two phases are solved simultaneously in an iterative self consistent manner until the system converges to a thermodynamic and mass equilibrium of two neutral phases.

Unlike almost all of the other COSMOtherm computations, the liquid extraction can be done in the framework of the absolute amounts of substance, namely compound mole numbers (N) or compound masses (W). These options can be chosen alternatively to the common options of mole fraction and mass fraction.

In addition to the two starting phases in the LIQUID EXTRACTION panel, it is also possible define further liquid phases as solvent phases in the phase definition block. Furthermore, when absolute mole numbers or masses are used to define the liquid phases, one or several solutes can be added to the predefined phases from an external “solute” reservoir (EXTENDED OPTIONS). The additional “solute” is considered completely dissolved in the two phases I and II. This option may be helpful if it is not clear in advance, which phase will be preferred by a given compound when added to the system.

By default all phases are assumed to be liquid phases. It is, however, possible to define one of the phases defined in the phase definition block as a solid (precipitation) or gaseous (evaporation) phases. Solid phases can also be defined as salts, composed of cosmo files of the corresponding ions. All salts will precipitate into the phase that is defined as solid unless they are forced to precipitate into their own separate salt phases.

In the COSMOtherm output file the equilibrium constants \( k_x \) and the equilibrium concentration \( x_k \) are printed. The table file gives the final absolute compositions of the phases in mole (N), gram (W) and the concentrations as mole fraction (x). If mass or mole fractions have been used as input, absolute mole numbers and masses are excluded from the output.

Example 16: Three-phase equilibrium between water, hexane, and \([\text{bmim}+]\)[pf6-] with an additional solute

- In the COMPOUNDS tab of the workplace window, open the TZVP Database and select h2o, hexane, propanone, 1-butyl-3-methyl-imidazolium(+) and pf6(-).
- In the PROPERTIES tab, select LIQUID EXTRACTION.
- Enter the temperature (25 °C).
- Set the phase compositions: Set the mole number for phase 1 to 35 mole of water, for phase 2 to 50 mole of hexane and for phase 3 to 15 mole of water, 25 mole of the cation 1-butyl-3-methyl-imidazolium and 25 mole of the anion pf6.
- Check the EXTENDED OPTIONS checkbox and enter 1 mole of propanone in the ADDITIONAL SOLUTE section.
• Transfer the settings to the “Property Selection” window with the Add button and run the program.

6.22 Reaction

The REACTION panel basically allows to calculate the equilibrium constant ($K_{\text{reac}}$), the free energy ($\Delta G_{\text{reac}}$) and the enthalpy ($\Delta H_{\text{reac}}$) of a given reaction in an arbitrary solvent or solvent mixture. For a hypothetical reaction $A + B \rightarrow C + D$ the free energy is defined as:

$$\Delta G_{\text{reac}} = G_C + G_D - (G_A + G_B)$$

and the reaction equilibrium constant is defined as:

$$K_{\text{reac}} = \exp(-\Delta G_{\text{reac}} / RT)$$

In a standard calculation the values for $G_A$, $G_B$, $G_C$, and $G_D$ are computed from the DFT gas phase energies modified by the free energy of solvation ($\Delta G_{\text{solvation}}$) as calculated by COSMOtherm.
\[ G_A = E_{A,\text{DFT}} + \Delta G_{A,\text{solvation}} \]

In each calculation the solvent and both sides of the reaction have to be specified. If neither products nor educts are part of the solvent / solution, a reaction in infinite dilution is calculated. If products or educts are part of the solvent their concentration is taken into account, but remains constant. Using the standard approach, a relative ranking of the reaction equilibrium in different solvents can be established from calculating the same reaction in different solvents or solvent mixtures, which makes it possible to determine the solvent suited best for a given reaction. For an absolute estimate of the reaction enthalpy or free energy higher level quantum mechanical energies are necessary. In general, the standard DFT energies are not accurate enough for absolute predictions of a reaction energy.

In the EXTENDED OPTIONS dialog the computation of the solvent-independent activity equilibrium constant \( K_a \) can be enabled, optionally with a reference activity equilibrium constant. Also optionally, it is possible to use a given reference pressure \( p \) for the computation of the reaction equilibrium. Furthermore, entering high precision energies from external quantum mechanical calculations, zero point energies and experimental values for \( \Delta G_{\text{solvation}} \) and \( H_{\text{vap}} \) is allowed for. Please refer to the manual for a detailed description.

The result table file contains the individual values for the free energy, the enthalpy, the chemical potential in solvent, the free energy of solvation, enthalpy of interaction, enthalpy of vaporization and the external values for quantum mechanical or zero point energy.

Example 17: Solvent choice for a simple ester reaction

- In the COMPOUNDS tab of the workplace window, open the TZVPD-FINE database and select the educts and products of the reaction: methanol, formic acid, methylformate and water.
- Select some solvents: ethanol, ch2cl2 and THF.
- In the PROPERTIES tab, select REACTION.
- Set the Reaction Solvent to PURE for ethanol.
- Use the pre-set temperature (25 °C). Enter methanol and formic acid with stoichiometry 1 into the reactant definition and methylformate and water with stoichiometry 1 into the product definition.
- Transfer the settings to the property section with the ADD button.
- Reset the Reaction Solvent to pure CH\(_2\)Cl\(_2\) and transfer the settings to the property section with the ADD button.
- Reset the Reaction Solvent to pure THF and transfer the settings to the property section with the ADD button.
- Run the program.

By varying the solvent composition, it can now easily be seen that the reaction free energy, and thus the equilibrium constant critically depend upon the choice of the solvent.
6.23 Cocrystal screening with COSMOthermX

Cocrystals are organic crystals consisting of a drug (active pharmaceutical ingredient, API) and a coformer, which may improve physical and chemical properties compared to the pure drug crystal itself. COSMOtherm can also be used for computational cocrystal screening and for estimation of cocrystal solubilities.

To compute the likelihood of cocrystal formation the excess enthalpy $H_{\text{ex}}$ can be used. We start from a virtually subcooled liquid of the cocrystallization components and neglect the long-range interactions in the crystal. It has been shown that this approximation gives rather good results on a set of potential cocrystal formers. The excess enthalpy $H_{\text{ex}}$ (mixing enthalpy) is obtained when mixing the pure component A and B to yield the subcooled cocrystal liquid $A_mB_n$: 
\[ H_{ex} = H_{AB} - x_m H_{pure,A} - x_n H_{pure,B} \]

\( H_{AB} \) and \( H_{pure} \) represent the molar enthalpies in the pure reference state and in the m:n mixture, with mole fractions \( x_m = m/(m+n) \) and \( x_n = n/(m+n) \). The excess enthalpy \( H_{ex} \) of an API and conformer pair gives a good estimate of the propensity to cocrystallize.

Technically, three calculations are necessary to obtain \( H_{ex} \): one for each of the pure components A and B, and one mixture calculation for A and B with the given stoichiometry in the subcooled liquid consisting of the mixture of A and B. Subsequently, COSMOtherm will calculate \( H_{ex} \) via:

\[
H_{AB} = x_m H_{AB}^A + x_n H_{AB}^B \\
H_{ex} = x_m H_{AB}^A + x_n H_{AB}^B - x_m H_{pure,A} - x_n H_{pure,B}
\]

In a similar way the free energy of mixing \( G_{mix} \) for the compound A\_mB\_n will be calculated automatically:

\[
G_{mix} = x_m H_{AB}^A + x_n H_{AB}^B - x_m H_{pure,A} - x_n H_{pure,B} + RT(\ln x_m + \ln x_n)
\]

**Example 18: Cocrystal formation in a 1:1 mixture of 4-pyridinecarbonitrile and 1,3,5-trihydroxybenzene**

For the calculation of \( H_{ex} \) for the compounds 4-pyridinecarbonitrile (4-cyanopyridine, 4-pyridinecarbonitrile.cosmo), compound A, and 1,3,5-trihydroxybenzene (1,3,5-trihydroxybenzene0.cosmo and 1,3,5-trihydroxybenzene1.cosmo), compound B, with the TZVP parameterization (BP_TZVP_C30_1701.ctd) proceed as follows:

- In the COMPOUNDS tab of the workplace window, open the TZVP database and select the two components into your compound list.
- In the PROPERTIES tab, select COCRYSTAL.
- Set the API field to 4-pyridinecarbonitrile and the stoichiometry to 1:1.
- Click ADD ALL COFORMERS to transfer the settings to the property section and run the calculation.

When the calculation has finished, the results table will open, showing the results of the calculation.
The excess enthalpy for the mixture 4-pyridinecarbonitrile/1,3,5-trihydroxybenzene is highly negative, indicating that it will likely form a cocrystalline compound.

<table>
<thead>
<tr>
<th>No.</th>
<th>API</th>
<th>Coformer</th>
<th>Hex</th>
<th>G_mix</th>
<th>H_HB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4-pyridine</td>
<td>1,3,5-trihydroxybenzene</td>
<td>-2.79678</td>
<td>-1.23601443</td>
<td>-2.265115</td>
</tr>
</tbody>
</table>

For the system 4-pyridinecarbonitrile/1,3,5-trihydroxybenzene the free energy of mixing at the TZVP level is $G_{\text{mix}} = -1.2$ kcal/mol. Different cocrystal systems may now be ordered according to their excess quantities, here $H_{\text{ex}}$ will give a slightly better ranking than $G_{\text{mix}}$.

Alternatively, the VLE/LLE panel may be used to obtain a phase diagram of the system. In the VLE/LLE approach excess quantities are calculated at once for several compositions, which makes this procedure more time consuming.

Another useful quantity which may be estimated using COSMOtherm is the solubility of the cocrystal. For the cocrystal solubility the same equations as for the salt solubility can be used. Please refer to Example 7: Estimated solubility improvement of the cocrystal systems carbamazepine – niacinamide and carbamazepine – oxalic acid in water.

### 6.24 COSMOmeso: Flory-Huggins and DPD Parameter with COSMO-RS

In the COSMOmeso panel, Flory-Huggins $\chi$ and DPD $\Delta a$ Parameter can be calculated. The beads have to be prepared in the same way as other COSMO files. Since the parameters are binary interaction parameters two beads have to be defined.

For the given temperature and mole fraction, the Flory-Huggins interaction parameter $\chi$ is determined from the COSMO-RS chemical potentials using the calculated $\ln(\gamma)$ value according to:\(^{22}\)

$$\ln(\gamma) = \ln(1-\phi) + (1-1/r)\phi + \chi \phi^2$$

with $\phi$ being the volume fraction of the polymer (bead 1) and $r$ the volume ratio of bead 1 / bead 2.

COSMOtherm also allows for the calculation of the DPD parameter $\Delta a$ according to:\(^{22,23}\)

$$\Delta a (p=3, a=25) = \chi / 0.292$$

or

$$\Delta a (p=5, a=25) = \chi / 0.689$$

The relative bead concentration is set to 1:1 by default. This can be changed in the EE if desired.
6.25 Ionic Liquid Screening

The IONIC LIQUID SCREENING panel enables the calculation of capacity and selectivity of Ionic Liquid solvents. The calculated solvent capacity \( C_1^\infty \) corresponds to the non iterative (infinite dilution) solubility of a solute in the Ionic Liquid solvent, and is a good first solubility guess for a fast screening procedure. The selectivity, i.e. the fraction of the capacities of two different solutes in the same IL solvent, can be calculated with the SELECTIVITY SCREENING suboption.

The IONIC LIQUID SCREENING has been implemented for the BP-TZVP level of theory. Note that .mcos files for the ions should not be used. Neutral solutes can be represented by .mcos files.

6.26 Ionic Liquid Properties

The IONIC LIQUID PROPERTIES panel allows for the computation of a range of properties of Ionic Liquids using a QSAR approach. The QSARs have been implemented for singly charged ions and the BP-TZVP level of theory, and some depend on specific COSMOTHERM parameterizations.

The TEMPERATURE DEPENDENT DENSITY and TEMPERATURE DEPENDENT LIQUID ENTROPY options require .energy files that provide gas phase frequency data at the BP-TZVP level. For information on the file format definition refer to the COSMOTHERM Reference Manual, section 2.2.1. Missing information will lead to empty tab file entries. The prediction of the CRITICAL MICELLE CONCENTRATION is based on different interaction terms of ions and water. Therefore, water \((\text{h2o.cosmo})\) needs to be loaded to the compound list.

6.27 Environmental / Safety

In contrast to other panels in COSMOTHERM, the ENVIRONMENTAL / SAFETY panel enables the calculation of a collection of physico-chemical properties, which are of importance for environmental and safety considerations, for a group of single (pure) compounds. Most of the properties can also be computed separately. For a description of these properties, refer to the corresponding sections in this document. Special to the ENVIRONMENTAL / SAFETY panel are the calculation of the flash point (FP) and the atmospheric lifetime. Note that usage of .mcos files is not recommended.

**Flash Point:** Flash point temperatures are estimated from a correlation of the compound saturation pressure and the COSMOTHERM vapor pressure estimation. The FP’s prediction quality can be improved if the temperature dependent experimental vapor pressure of the experimental boiling point temperature are used in the Compound Properties dialog.\(^{14}\)

**Atmospheric life time:** Since the atmospheric life time of organic compounds is mainly determined by the reaction with OH-radicals, it can be estimated based on the OH-radical reactivity \( k_{\text{OH}} \) of the compound. A molecular orbital based prediction method MOOH for \( k_{\text{OH}} \) has been published already in 1992, based on semi-empirical AM1 calculations. Recently Schüürmann et al.\(^{24}\) showed that the MOOH method is still up to date and at least as accurate (\(\sim 0.35\) log-units) as the generally accepted increment method by Atkinson, with the advantage of having smaller maximum deviations, i.e. being more robust. The calculations are done with our MOOH implementation in MOPAC7, using the lowest energy gas-phase conformation provided.\(^{25,26}\)

**Interfacial tension:** IFT predictions of compounds with water at room temperature. The IFT model predictions are based on empirical models which utilize the mutual solubilities of the solute and water in terms of the tie points of the liquid-liquid-equilibrium. Thus each IFT computation involves a binary LLE computation in COSMOTHERM. The IFT model predictions are based on the assumption of a liquid solute
and a phase separation with water. This implies that for compounds that are solid or gaseous at room temperature, the virtual liquid LLE is computed by COSMOtherm. If no phase separation is predicted, no IFT can be computed. The column for the IFT prediction will be left empty in this case. Three different IFT models can be used.
7 COSMO files and databases

There are several ways to make COSMO files available in COSMOthermX:

- Add a database prepared for use in COSMOtherm,
- Generate a new database using your own COSMO files and add it to COSMOthermX,
- Add COSMO files to existing databases accessible in COSMOthermX,
- Select COSMO or compressed COSMO files from any directory on your system using the FILE MANAGER.

COSMO or compressed COSMO files from quantum chemical calculations can be selected from any directory on your system using the FILE MANAGER in the compound section of COSMOthermX. Make sure that you select the appropriate parameterization for the .ccf/.cosmo files.

For larger amounts of compounds, however, it is more convenient to collect them into a database. The COSMObase editor tool has been designed to administrate databases of compound files and is described in detail in section 8.2.

For all options involving compound files generated by yourself there are a few prerequisites you have to meet for the COSMOtherm calculations to run correctly.

- Ensure that all COSMO files you want to use come from the same quantum chemical level. .cosmo and .ccf files can be mixed inside the databases as long as they come from the same quantum chemical level.
- Gas phase energies, which should be used if properties involving a gas phase (VP, VLE, Henry law constant, gas solubility) are calculated and experimental vapor pressure data are not available, should be saved into a gas phase energy (.energy) file. The gas phase energies must be calculated at the quantum chemical level that has been used for the COSMO calculations, e.g. BP-TZVP for gas phase calculations and BP-TZVP-COSMO for COSMO calculations. The default unit for gas phase energies is [Hartree].
- Experimental vapor pressure data or other experimental data can be saved into a Vapor Pressure / Property (.vap) file. Create the .vap file manually using any text editor, or use the COMPOUND PROPERTIES menu from the right mouse button context menu for a selected compound to enter property data for a compound and save the .vap file permanently. Vapor Pressure / Property and energy files should be located in the same directory as the COSMO files.
7.1 Embedding a COSMObase

COSMObase, COSMObaseIL and COSMObaseFF are collections of compound COSMO and gas phase energy files for usage in COSMOtherm. COSMObase is a general compound database containing over 7000 common compounds and solvents, including their most important conformations. COSMObaseIL is a collection of over 200 commonly used ionic liquid cations and anions. The possibility to freely combine cations and anions results in several thousand ionic liquids. COSMObaseFF holds over 2000 typical fragrance and flavor compounds and their conformations.

You can add a COSMObase to COSMOthermX in the EXTRAS/DATABASE SETTINGS dialog. When you select ADD DATABASE, a file browser dialog will open where you can select the database file. After pressing the SELECT button, the selected database file name, database info and (in case the selected file is a .cdb file) the parameterization to be used with this database are displayed automatically in the ADD DATABASE dialog. The database label refers to the label under which the database will be shown in the database view. All added databases will be available with the button corresponding to the parameterization in the compound section of COSMOthermX. E.g. for a newly added COSMObase where the parameterization was indicated to be TZVP a checkbox labeled by the Database label will be available for selection when the TZVP level is used for compound selection from the databases.
8 Tools

8.1 COSMOview

COSMOview can be used to display sigma surfaces of molecules or molecular structures. It is included in COSMOthermX and can be accessed via TOOLS/COSMOVIEW from the main menu.

COSMOview displays one molecule per window or one window with multiple frames. In the multiframe mode rotation and zoom can be done for all frames in parallel. The number of frames can be set with a right mouse button click on the box in the bottom right corner of the COSMOview window. If a molecule with weight string is displayed, the sigma surface of atoms with weight 0 is displayed in grey. If .sms files from a COSMOsim3D calculation are loaded, the window also features sliders to adjust the surface transparency based on the local sms values.

The following options can be selected from the menu bar:

OPEN: Open a previously generated VRML. Alternatively, open a VRML file by right-clicking a compound and selecting view sigma surface or VIEW MOLECULE from the context menu.

SAVE: Graphics can be saved, optionally with a transparent background.

RESET CAMERA: Reset the camera to its initial position.

LINK CAMERA: In a multiframe window, apply camera movements (rotation and zoom) to all frames. By default, cameras in a multiframe window are linked.

ARRANGE ALL WINDOWS: The arrangement of multiple COSMOview windows can be changed automatically.

SETTINGS: Change color, labels, atom settings, bond settings and so on.

DISPLAY SIGMA SURFACE: If a surface is loaded, it can be hidden and shown again.

DISPLAY MOLECULE: The molecular structure can be hidden and shown again.

DISPLAY WIREFRAME: Instead of closed object surfaces it is possible to show only the wire frame. This option works for surfaces, atoms and bonds.

USE CHARGE DENSITY PICKER: To get an idea of the quantitative surface charge density at a given point, you can activate the charge picking mode and move the cursor over the $\sigma$-surface. A slider at the right-hand side will display the charge density at the spot you are pointing on. However these values can only be approximated and are not guaranteed to be entirely precise. This is mainly an effect of interpolation between the reduced grid size compared to .cosmo files. Please also note that since COSMOview uses
an internal color correction, the legend produced will not be applicable to images obtained by other means than COSMOview, e.g. third-party browser plug-ins.

DISPLAY INFO: Filename and COSMO energy are displayed in the COSMOview window.

Movement: Molecules can be moved using the mouse buttons. Rotate the molecule by dragging the mouse with the left button pressed. If you move the mouse quickly, you can give the molecule a spin to have it turn by itself. Zoom in and out with the right mouse button pressed or simply by turning the mouse wheel.

8.2 COSMObase Editor

The COSMObase editor was developed to administrate databases of compound files (COSMO, gas phase energy, and Vapor Pressure / Property files). New databases can be generated, and existing databases can be extended with new compound files or experimental data. The COSMObase editor will perform consistency checks for every database generated and every compound added to a database. This procedure ensures a high quality of the COSMO file databases. A database of COSMO files consists of a database directory containing the compounds COSMO, gas phase energy and Vapor Pressure / Property files and a database file with information about conformers, CAS number and experimental data, if available. In the database directory the compound files may also be sorted alpha-numerically in subdirectories. With the COSMObase Editor a new format for database files is introduced. Based on the general .xml format, the .cdb format allows for extended compound information and conformer handling. In the COSMObase, COSMObaseL and COSMObaseFF, the .cdb format replaces the .csv format used in COSMOtherm until version C30_1301. The COSMObase editor has several menus in the menubar:

File:

NEW DATABASE: Create a new database. Entries for the name, directory and path for the new database are required in the respective fields.

OPEN DATABASE (.CDB): Open an existing database in .cdb format. Database files can be selected from a file browser. If the COSMObase Editor is started from inside COSMOthermX, databases from the Database Settings dialog are also listed here.

OPEN RECENTLY USED: Open a recently used database listed in the extension menu.

CONVERT .CSV FILE: Open a database .csv file and convert to .cdb format. Database files can be selected from a file browser. Since databases in .cdb format may also differ in conformers and other compound information, the database conversion additionally requires a new database directory to be created.

EXPORT TO .CSV: Export an existing database from .cdb to .csv format

IMPORT PROPERTIES: Opens a .csv file with tabulated property information for compounds.

CLOSE: Close the COSMObase Editor.

Edit:
**ADD COSMO FILES:** Add COSMO files to an existing database. If gas phase energy files and a Vapor Pressure / Property file for the compound are available in the same directory and with the same filename, they will also be added.

**ADD DIRECTORY:** Add all compound files from a directory to an existing database.

**ADD DATABASE:** Add a complete database with database file and database directory to an existing database.

**EDIT INFO:** Edit the database Info field displayed for currently loaded databases.

**DELETE SELECTED ENTRIES:** For the selected compound, entries in the database file and files from the database directory will be deleted.

**OPEN IN VIEWER:** The selected compound is visualized with COSMOview.

**Tools:**

**SHOW LOG FILES:** The log file of the COSMObase Editor will be opened in a text editor window.

**SHOW DB STATUS:** Opens the status messages in a text viewer window.

**Extras:**

**OPTIONS:** Opens a settings dialog with information about last used database and directories, license directory and log directory. Furthermore, the user can set options for the maximum number of conformers and the output level.

**Help:**

**ABOUT COSMOBASEEDITOR:** Information about the current COSMObase editor version is displayed.

**Generating a new database:** In principle, generating a new database is a two-step procedure. First, the database file and directory are created. In the second step, the empty file and directory are filled with data and compound files, respectively.

A new database is created in the COSMObase editor from the NEW DATABASE option in the FILE menu. The CREATE NEW DATABASE dialog requires entries for the name, directory and location of the new database to be created. The path where the database file and directory are to be stored and the appropriate parameterization for the new database have to be indicated. The version entry is optional, and the remaining fields are filled automatically. On finishing this dialog, the COSMObase editor will create a new, empty directory and .cdb file for the database.

Options to load compounds into the new database are ADD COSMO FILES, ADD DIRECTORY or ADD DATABASE from the EDIT menu or the buttons on the right side of the COSMObase editor window.

For adding compound files for several compounds to a database (ADD DIRECTORY), collect all compound
files intended for the database in a single directory. If there are gas phase energy (.energy) or Vapor Pressure / Property files (.vap) for the compounds, also copy them into this directory. Ensure that all COSMO files are calculated on the same quantum chemical level, and that the gas phase energy files come from corresponding gas phase calculations. For conformers of a compound to be identified as conformers, the compound files have to be named with the same filename followed by a defined string _c and a digit, e.g. ethanol_c0.cosmo, ethanol_c1.cosmo, ethanol_c0.energy and so on. Note there is only one Vapor Pressure / Property files (.vap) per compound, e.g. ethanol.vap. If the filenames are used correctly, the compound files will be treated as conformers of a single compound automatically. By default, the COSMObase editor can handle up to 10 conformers, i.e. with digits 0-9 in the COSMO file names. Settings for the maximum number of conformers to accept can be changed in the EXTRAS/OPTIONS dialog. When a directory with compound files is selected for adding to a new database, the COSMObase editor will check the compounds for consistency and create conformer information for the .cdb file. If checks fail or require the user to make a definite decision, messages are collected and query boxes will appear cumulatively at the end of the procedure.

Databases created by this option can be used in COSMOthermX in the same way as the COSMObase. To make such a database accessible from inside COSMOthermX, you can add your database in the database settings dialog as described for the COSMObase.

**Extending existing databases:** To extend databases with new compounds, use the ADD COSMO FILES or ADD DIRECTORY options from the Edit menu or the shortcut buttons.

In the file browser dialog, go to the directory where the compound files (.cosmo, .energy and .vap files) are located. Select the compounds or directory you want to add and click OPEN. The compound files will be checked automatically for matching parameterization. As for the generation of a new database, messages from failed consistency checks are collected and query boxes will appear cumulatively at the end of the procedure.

### 8.3 COSMOweight

Due to the additive nature of σ-profiles it is possible to approximately describe molecules which are not contained in a database or which are simply too large to be calculated by adjusting the ‘importance’ of other molecules’ atoms or even blending together multiple secondary molecules. The result of this process is either stored in a so-called weight string (for a single molecule) or in a COSMO metafile with the extension .mcos (for a molecule blended together from multiple molecules). For more information about atom weighting please refer to the COSMOtherm manual. As the manual generation of weight strings usually involves quite a lot of counting and double checking, COSMOthermX includes COSMOweight, an interactive graphical tool, which can greatly improve your working speed when dealing with medium-sized molecules.
COSMOweight displays a ball-and-stick-model of the selected compound, where disabled atoms will be displayed in black, whereas atoms with higher importance than 1 will be labeled with their weight factor. For a description of navigation in 3D-space have a look at section 8.1 COSMObas.

General functionalities of COSMOweight are:
- Resetting all weights to their initial value of 1 is possible by pressing the “Set to 1” button.
- Setting all weights to 0 is possible by pressing the “Set to 0” button.

COSMOweight can be operated in a navigation mode and a selection mode. Switch between the modes with the “Selection mode” button. The following functionalities are available in navigation mode:
- Atom weights are increased by left-clicking and decreased by right-clicking single atoms.
- Rotate the molecule with the left mouse button.

In selection mode, you can:
- Select a group of atoms with the left mouse button.
- For a selected atom or atom group, assign the weight by typing the number on your keyboard.
- Alternatively, change the weight for the selected atom(s) in the REAL WEIGHT text area at the bottom of the COSMOweight window.

Please note that COSMOweight will sometimes display warning messages related to the structure of the molecule being edited. These are only supposed to help spotting chemical and/or logical mistakes - the structure itself is not used in any COSMOtherm calculation.

**Using COSMOweight to edit weight strings:** Right-click a compound in your compound list and select EDIT WEIGHTSTRING. Assign the weights according to your needs, using the options described above.

**Using COSMOweight as a meta file editor:** This mode can either be accessed by right-clicking an .mcos file in your compound list and selecting EDIT .MCOS FILE, by selecting one or more .cosmo or .ccf files from your compound list, right-click and select EDIT .MCOS FILE or via TOOLS/COSMOWEIGHT. In the latter case, open an existing .mcos file by clicking OPEN or start from scratch by adding a first molecule. Additionally to editing single weight strings you can add further or remove molecules as well as switch between them in the tabbed pane. When you are done, click SAVE to generate a .mcos file.

**Saving .mcos files:** In the SAVE dialog, there are different options to save the .mcos file. These options control where COSMOtherm will look for the .cosmo and .ccf files (henceforth “source files”) used for the .mcos file.

**INTERNAL:** This is the default option. Source files are written in separate sections to the .mcos file. The resulting .mcos files are larger but are completely transferable to any system.

**ABSOLUTE:** The absolute paths of the source files are written to the file, which means, that your sources can be spread over different directories and volumes and you are able to move your .mcos file wherever you please. However, if the source files themselves are moved, or - more importantly - you try to use the .mcos file on another computer with a different folder hierarchy, you will run into problems.

**RELATIVE TO FILE:** Source files will have to be located in the folder where you save the .mcos file or in subfolders. You can move this kind of .mcos file to different directories, even different computers, if you also copy the source files.
RELATIVE TO FRAGMENT DIRECTORY: This option gives you ultimate portability while still avoiding the need to copy data. All source files used have to be located in the folder set as “fragment directory (CFDB)” in the PREFERENCES dialog. You can move the .mcos file everywhere, as long as you keep with your FRAGMENT DIRECTORY settings. If you use a lot of metafiles, this is the most convenient way of handling the .mcos files. If you did not set a fragment directory, this option will be disabled. Please note that, you may want to set your fragment directory to the COSMO-DATABASE folder or one of its subfolders. The .mcos-files shipped with COSMOthermX will not work unless you either disable the use of a fragment directory or set the database with parameterization as a fragment directory, e.g. <COSMOTHERM_HOME>/DATABASE-COSMO/BP-SVP-AM1>.

Problems when using .mcos files: If COSMOtherm or COSMOweight complain about missing files when using previously saved .mcos files, you are likely trying to open a kind of .mcos file which is saved:

- RELATIVE TO FRAGMENT DIRECTORY: Please check if a fragment directory in COSMOthermX is correctly set and enabled.
- RELATIVE TO FILE: Make sure that no fragment directory is set in COSMOthermX
- ABSOLUTE: Please check the path. If the file was saved on a different computer or the path was changed, the file cannot be found.
Appendix A: Systems with Ionic Liquid (IL) compounds

Ionic Liquids are organic salts consisting of bulky ions with usually strongly delocalized charges and low melting points. Many IL compounds are liquid at room temperature. While in an experimental setting, an Ionic Liquid is usually treated as one single compound, a thermodynamically consistent solvent modeling approach will treat the ions independently in an electroneutral mixture. The “independent ion” treatment of Ionic Liquids in the modeling context results in different total mole numbers in the system, and, consequently, in different mole fractions of the compounds, compared to the “one compound” IL approach. Thus, for comparing modeling results to experimental results, a re-scaling of property data that depend on the mole fraction is necessary.

As an example, consider a mixture of an organic compound and an IL consisting of anion and cation with 1:1 stoichiometry. This system is treated as a binary mixture within the experimental setting and as a ternary mixture within COSMOtherm. The different definitions lead to different mole fractions of the compounds in the system: In a system consisting of 2 moles 1-octanol and 3 moles [bmim][PF6], the mole fraction of 1-octanol is calculated from a binary mixture of 1-octanol and IL, resulting in \( x_{\text{1-octanol}} = \frac{2}{3+2} = 0.4 \) in the framework of the “one IL compound”. In the framework of the “independent ions”, however, the mole fraction of 1-octanol is calculated from a ternary mixture of 1-octanol, [bmim]\(^+\) and [PF\(_6\)]\(^-\), resulting in \( x_{(1\text{-octanol})} = \frac{2}{3+3+2} = 0.25 \).

Since many property definitions depend on the mole fraction of a compound, the different approaches will also influence the values of properties. To be able to compare results from modeling to experimental results, the calculated property values have to be re-scaled. Generally, the partial pressure is related to the activity coefficient \( \gamma_i \) by \( p_i = x_i \gamma_i p_0 \). In our example, the following relations apply:

\[
p_i = x_i^{\text{bin}} \gamma_i^{\text{bin}} p_0 \quad \text{in the binary framework as used in laboratory}
\]

\[
p_i = x_i^{\text{tern}} \gamma_i^{\text{tern}} p_0 \quad \text{in the ternary framework as used in COSMOtherm}.
\]

In the mixture from the example above, the observed partial pressure \( p_i \) of 1-octanol must be independent of the mole fraction definition. Thus, it follows that

\[
x_i^{\text{bin}} \gamma_i^{\text{bin}} = x_i^{\text{tern}} \gamma_i^{\text{tern}}
\]

which can be re-arranged to

\[
\gamma_i^{\text{bin}} = x_i^{\text{tern}} \gamma_i^{\text{tern}} / x_i^{\text{bin}}
\]

In the limit of infinite dilution activity coefficients (\( x_i \rightarrow 0.0 \)). The mole fraction of each ion (\( x_{\text{cation/anion}} \)) inside a pure IL is 0.5 (1:1 stoichiometry) in the ternary definition. Within this limit the equation simplifies to:

\[
\gamma_{i,x \rightarrow 0}^{\text{bin}} = 0.5 \gamma_{i,x \rightarrow 0}^{\text{tern}} \quad (\text{only for infinite dilution} \ \gamma)
\]
In an electroneutral mixture of anion and cation, as used in COSMOtherm, the mole fractions of ionic liquid ions with 1:1 stoichiometry are

\[ n_{\text{ion}} = n_{\text{cation}} = n_{\text{anion}} = n_{\text{IL}} \]

In COSMOtherm three types of mole fraction definitions are used.

- The “laboratory-binary” definition for solute \( i \) (\( S_i \)):
  \[ x_{\text{Si}}^{\text{bin}} = \frac{n_{S_i}}{\sum_i n_{S_i} + n_{\text{IL}}} \]

- The “ternary” definition\(^1\) for solute \( i \) (\( S_i \))
  \[ x_{\text{Si}}^{\text{tern}} = \frac{n_{S_i}}{\sum_i n_{S_i} + 2n_{\text{ion}}} \]

- The “pseudo binary” definition (used in the COSMOtherm table files). This definition is used to preserve the column structure of the table files. The solute (\( S_i \)) mole fractions are the same as in the “ternary” definition, while the “pseudo-binary” mole fraction of the IL is the sum of the mole fractions of the ions.
  \[ x_{\text{Si}}^{\text{pbin}} = x_{\text{Si}}^{\text{tern}} \quad x_{\text{IL}}^{\text{pbin}} = \sum x_{\text{ion}}^{\text{tern}} \]

The transformation of the “ternary” mole fraction of a solute \( S_i \) in an IL mixture (IL with 1:1 stoichiometry) to the “laboratory-binary” definition reads:

\[ x_{\text{Si}}^{\text{bin}} = \frac{\sum x_{\text{Si}}^{\text{tern}} x_{\text{ion}}^{\text{tern}}}{\sum x_{\text{Si}}^{\text{tern}} + x_{\text{ion}}^{\text{tern}}} \]

The derived equations can be used to calculate laboratory binary results from COSMOtherm ternary results for 1:1 IL’s.

In general COSMOtherm will give ternary results as this is the native COSMOtherm definition. All properties calculated with ILs have to be checked for possible scaling effects. Examples are:

- Partition/Log(P): According to the definition of \( \log(p) \) [(mol/l)/(mol/l)] re-scaling is not necessary as long as the solute is not an IL. The transformation of mole fraction to liter will automatically do

---

\(^1\) Historically this term has been chosen for mixtures of one IL and one solute. Although it might be a bit misleading, we will stay with the expression even for mixtures with more than three components.
the scaling.
If thermodynamic units \([x/x]\) are used a mole fraction scaling has to be applied.

- Solubility: If a solute is solved in an IL, the resulting solubility \(x\) has to be re-scaled, as it is automatically given in the “ternary” definition.
  If the IL is the solute, the SALT SOLUBILITY option can be used directly. Provide a \(\Delta G_{ fus}\) of 0 (liquid state). The result is automatically converted to the “laboratory binary” definition.
- Henry constant: The Henry constant is directly connected to the activity coefficient and the re-scaling as described above applies.
- Vapor pressure: For computing the vapor pressure, only the \(x\)-axis (mole fraction) values have to be rescaled.

Some panels automatically provide a re-scaled result to enable easy comparison to experimental data:

- SALT SOLUBILITY and SALT SOLUBILITY SCREENING provide the solubility of a Salt in a solvent, the \(\log(x)\) is automatically provided in laboratory binary.
- LLE (binary and ternary LLE) calculations of a mixture between IL and solute provide binary and ternary results for the LLE points. The mole fraction of the IL is given as pseudo binary values. All other table data are within ternary definition.
  The multinary option does not allow an IL definition and will not provide any automatic rescaling.
- SLE results will be printed out in binary and ternary definition.
- IONIC LIQUID SCREENING will give laboratory-binary capacities.

The results table will generally provide information about the used definitions and units within the explanation text.

**Example 19:** Calculate the infinite dilution activity coefficients of water in IL (1-butyl-3-methylimidazolium_cation + PF6_anion)

- In the COMPOUNDS tab of the workplace window, open the TZVP database and select water and the ions 1-butyl-3-methylimidazolium_cation and PF6_anion.
- In the PROPERTIES tab, select ACTIVITY COEFFICIENT.
- The temperature is set to 25 °C by default.
- In the solvent definition section set the mole fractions of both ionic compounds to 0.5.
Click ADD to transfer the settings to the property section and run the calculation.

After running the program, take the result \( \ln(\gamma) = 2.44 \) or \( \gamma = 11.44 \) and multiply it with 0.5: \( \gamma = 5.72 \) or \( \ln(\gamma) = 1.74 \)

**Example 20: Calculate a LLE of water in IL (1-butyl-3-methyl-imidazolium_cation + PF6_anion)**

- In the COMPONDS tab of the workplace window, open the TZVP database and select water and the ions 1-butyl-3-methyl-imidazolium_cation + PF6_anion.
- In the PROPERTIES tab, select LIQUID-LIQUID.
- Default settings are isothermal for the phase diagram condition, 25 °C for temperature, and binary for the system.
- In the Components definition section set water for the 1st component.
- Tick the DEFINE IONIC LIQUID PHASE checkbox for the 2nd component. Set the USE checkboxes for 1-butyl-3-methyl-imidazolium_cation and PF6_anion. The stoichiometry is set to 1 for both components automatically.
- Check the SEARCH LLE point checkbox.
- Click ADD to transfer the settings to the property section and run the calculation.
The results table will automatically calculate the LLE in binary and ternary definition. If only the LLE is of interest no further calculations are needed.

If the ln(γ) curve from the LLE calculation should be plotted, the ln(γ) and the mole fraction have to be scaled according to the above derived equations:

\[ x_i^{\text{binary}} = \frac{x_i^{\text{ternary}}}{x_i^{\text{ternary}} + x_i^{\text{cation/anion}}} \quad \text{and} \quad \gamma_i^{\text{binary}} = \gamma_i^{\text{ternary}} \left( x_i^{\text{ternary}} + x_i^{\text{cation/anion}} \right) \]
Appendix B: Treatment of Polymers

Due to their size, polymers are composed of independently calculated fragment molecules in COSMOtherm. For the COSMOtherm calculation, the polymer repeat unit is taken from the fragment molecule using atom weight factors as described in section 8.3. Since the chemical potential of the polymer is calculated from a monomer (or larger) repeat unit, the corresponding solvent area and volume do not reflect the real surface area and volume of the polymer. The combinatorial contribution to the chemical potential should therefore be switched off in the GLOBAL OPTIONS or PROPERTY OPTIONS dialog.

If the polymer compound is treated as a liquid solvent of monomeric (or larger) repeat units, COSMOtherm allows for the calculation of activity coefficients and solubilities of gaseous and liquid compounds in polymers. This approximation is only valid for non-crystalline polymers. Furthermore, polymer swelling cannot be taken into account, because the employed relations are valid only for low solute load. As the molecular weight and volume of the polymer are neglected, the computed activity coefficient or solubility cannot be interpreted in a quantitative way, but in terms of relative activity/solubility of different solutes in the polymer solvent. This issue is explained in more detail in section 5.3.2 of the COSMOtherm Reference Manual.

Quantitative prediction of polymer properties is possible with two modifications in the underlying COSMO-RS theory. First, because the polymer is represented by a small molecular fragment (e.g. by a monomeric repeat unit), the absolute prediction of the polymer properties needs to take into account the apparent molecular weight of the polymer, $\text{MW}_{\text{polymer}}$. Second, the combinatorial contribution to the chemical potential, which was derived from molecular size and shape considerations (see section 1.1 of the COSMOtherm Reference Manual) has to be replaced by a special combinatorial term that accounts for free volume effects and thus can handle macromolecules. Of the numerous free volume terms that were published in the chemical engineering literature it was found\(^\text{27}\) that the free volume method of Elbro et al.\(^\text{28}\) is particular useful in combination with COSMO-RS. If dealing with macromolecules in an absolute and quantitative way, it is therefore recommended to switch on the free volume combinatorial contribution of Elbro et al.\(^\text{28}\) This can be done as a global command in the CALCULATIONS OPTIONS dialog or locally, for a certain property only, in the PROPERTY OPTIONS dialog (open the CALCULATIONS OPTIONS dialog and switch to the PROPERTY OPTIONS tab).

The input of polymer-related properties required for calculations utilizing the Elbro combinatorial term, namely $\text{MW}_{\text{polymer}}$, can be done in the COMPOUND PROPERTIES dialog, which can be opened from the compounds context menu. The Polymer Properties section offers a field for the molecular weight and other properties. $\text{MW}_{\text{polymer}}$ will be used by COSMOtherm to scale up the molecular weight of the given molecular fragment to match the actual/apparent polymer weight using the atomic weights concept. Furthermore, a compound can also be flagged as polymer with the corresponding checkbox. Please note that the flag does not affect the results of the COSMOtherm calculation. It simply is used as an identifier, which allows COSMOtherm to refer to the given compound as a polymer in the output and in potential warning or error messages.

In case the direct input of free volume, molar volume, or density for all compounds may not be convenient or possible the free volumes can be estimated. The estimation method is a two-step procedure which utilizes the room-temperature QSPR density estimate for neutral compounds as described in section 2.3.12 of the COSMOtherm Reference Manual.
Example 21: Activity Coefficient Calculation in a Macromolecular Solvent

In this example, the activity coefficients of three gaseous solutes in PDMS (polydimethylsiloxane) are computed. Experimental density and molecular weight values are provided for the polymer compound only. Free volumes or densities for the solute compounds have to be estimated, which is done in a two-step procedure. As a first initialization step a DENSITY calculation is done for all compounds. In order to save the densities and molar volumes thus computed for later use, the PREPARE DENSITY FOR LATER USE IN POLYMER [COMBI=ELBRO] CALCULATIONS checkbox in the EXTENDED OPTIONS has to be checked. This suboption triggers the conversion of the computed densities to free volumes and storing of the computed free volumes for later use by property computations involving the combi=ELBRO option. For more details please refer to section 5.3.2 of the COSMOTHERM Reference Manual.

- Open the TZVP database from the COMPOUNDS tab, and select PDMS.
- Now select the gaseous solutes, ethane, propane and butane.
- With a right mouse-button click on PDMS in the compound section, open the compound context menu and select COMPOUND PROPERTIES. Scroll down to the ADDITIONAL DATA block and edit the POLYMER PROPERTIES data fields (Click on the pen icon). Tick the checkbox defining the compound as a polymer and set the density to 0.97 g/mL. Enter the molecular weight as 6800 g/mol. Check the POLYMER PROPERTIES checkbox and close the COMPOUND PROPERTIES dialog by clicking the APPLY button.

- In the PROPERTIES tab, select DENSITY. Click the EXTENDED OPTIONS checkbox and then the PREPARE DENSITY FOR LATER USE IN POLYMER [COMBI=ELBRO] CALCULATIONS checkbox.
- Click ADD to transfer the calculation settings to the property section.
- Go back to the NEW PROPERTY tab in the PROPERTIES panel and select ACTIVITY COEFFICIENT.
- Use the default temperature (25 °C) and tick the PURE checkbox for PDMS in the solvent composition section.
- Click ADD to transfer the calculation settings to the property section.
- Open the PROPERTY OPTIONS dialog: Select PROPERTY OPTIONS from the EXTRAS Menu. Select the last line in the property settings list, which should be the activity coefficient line (Gamma=...). Then, tick the PROGRAM CONTROL SETTINGS checkbox and tick the checkbox SWITCH ON POLYMER COMBINATORIAL TERM. Leave the dialog with OK.
- Run the program.

![Image of solvent composition settings](image_url)
Appendix C: Example Input Files

ABRAHAM-PARAMETER-QSPR-SVP
Estimation of the five Linear Free Energy Parameters of Abraham using sigma-moment QSPR.
The estimated Abraham parameter values can be found in the compound output section of output-file ABRAHAM-PARAMETER-QSPR-SVP.out and in the sigma-moment-file ABRAHAM-PARAMETER-QSPR-SVP.mom.

ABRAHAM-PARAMETER-QSPR-TZVP
Estimation of the five Linear Free Energy Parameters of Abraham using sigma-moment QSPR.
The estimated Abraham parameter values can be found in the compound output section of output-file ABRAHAM-PARAMETER-QSPR-TZVP.out and in the sigma-moment-file ABRAHAM-PARAMETER-QSPR-TZVP.mom.

ABRAHAM-PROPERTY-QSPR-SVP cannot be processed by graphical user interface
The estimated Abraham parameter values and the computed Abraham property can be found in the compound output section of output-file ABRAHAM-PROPERTY-QSPR-SVP.out and in the table-file ABRAHAM-PROPERTY-QSPR-SVP.tab.

ABRAHAM-PROPERTY-QSPR-TZVP cannot be processed by graphical user interface
Estimation of the five Linear Free Energy Parameters of Abraham using sigma-moment QSPR and estimation of several different Solvent-Water Partition Coefficient logP(Solvent-Water) using Abraham coefficients.
The estimated Abraham parameter values and the computed Abraham property can be found in the compound output section of output-file ABRAHAM-PROPERTY-QSPR-TZVP.out and in the table-file ABRAHAM-PROPERTY-QSPR-TZVP.tab.

CAS-NUMBER
Computation of a binary phase diagram using CAS Registry Number as molecule identifier.
COSMOtherm a priori prediction of pure compound vapor pressures (using molecules gas phase energies) is used in the computation of the binary phase diagram.
CAS-NUMBER-CONFORMER cannot be processed by graphical user interface
Computation of a binary phase diagram using CAS Registry Number as molecule identifier. For each compound all conformers that are present in the database are used to compute the binary phase diagram.
COSMOtherm a priori prediction of pure compound vapor pressures (using molecules gas phase energies) is used in the computation of the binary phase diagram.

COCRystal-SCREEN cannot be processed on the command line
Cocrystal screening with 4-pyridinecarbonitrile as API and 16 potential coformers.

CONFORMER.inp
Computation of Conformer Equilibrium.

CONFORMER-AUTOc.inp
Computation of Conformer Equilibrium.

CONFORMER-QUASI.inp
Computation of the relative stability of different isomers using conformer formalism. It is assumed that the thymine isomers are in quasi-equilibrium, so that they can be treated as conformers.
The computed relative stabilities of the conformers can be found in the mixture output section of output-file CONFORMER-QUASI.out and in tabulated form in CONFORMER-QUASI.tab. Note that the thymine_c0.cosmo tautomer is dominant in polar (bulk thymine and water) as well as in unpolar (hexane) solutions.

CONTACT-MAP.inp
Computation of a molecular surface segment contact statistics.
The computed molecular contact probabilities can be found in the mixture output section of output-file CONTACT-MAP.out. The computed segment contact probabilities can be found in the newly created files "name.contact". For further information on the definition of molecular surface contacts, please read the COSMOtherm Reference Manual.

CONTACT-MAP-VRML.inp
Computation and Visualization of all contact statistics in equimolar mix of water and propanone. Create a VRML visualization of a precomputed molecular surface segment contact statistics file.
This input file creates a VRML visualization of the surface segment contact map computed by the CONTACT-MAP.inp example input file. The computed molecular VRML-file "propanone_map.wrl" can be found in the output directory.
For further information on the visualization of molecular surface contact maps, please read the COSMOtherm Reference Manual.

COSMOMESO cannot be processed on the command line
Automatic DPD parameter calculation for water and celluloseacetate.

COSMOmic-dmpc
COSMOmic calculation of solute methanol in micelle DMPC (micelle file COSMOmic-dmpc.mic).
Note that the file paths for the micelle cosmofiles required by the COSMOmic-dmpc.mic micelle file are given in the COSMOmic-dmpc.mic file. The computed micelle partition properties of the solute can be found in the COSMOmic results file COSMOmic-dmpc.xml. The XML-format COSMOmic results file can be visualized by COSMOthermX.
COSMOmic-dppc
COSMOmic calculation of several solutes in micelle DPPC (micelle file COSMOmic-dppc.mic).
Note that the file paths for the micellecosmofiles required by the COSMOmic-dppc.mic are read from the global fdir input given in this input file. The computed micelle partition properties of the solutes can be found in the COSMOmic results file COSMOmic-dppc.xml. The XML-format COSMOmic results file can be visualized by COSMOthermX.

COSMOmic-popc
COSMOmic calculation of several solutes in micelle POPC (micelle file COSMOmic-popc.mic).
Note that the file paths for the micellecosmofiles required by the COSMOmic-popc.mic are read from the global fdir input given in this input file. The computed micelle partition properties of the solutes can be found in the COSMOmic results file COSMOmic-popc.xml. The XML-format COSMOmic results file can be visualized by COSMOthermX.

COSMOmic-SDS
COSMOmic calculation of several solutes in spherical micelle SDS (micelle file COSMOmic-SDS.mic).
Note that the file paths for the micellecosmofiles required by the COSMOmic-SDS.mic are read from the global fdir input given in this input file. The computed micelle partition properties of the solutes can be found in the COSMOmic results file COSMOmic-SDS.xml. The XML-format COSMOmic results file can be visualized by COSMOthermX.

DATABASE
Computation of a list of molecules from a database.
Calculation of the solubility of drug-like solids with automatic procedure. The heat of fusion of all solutes is estimated by a solubility QSPR procedure.
This input is equivalent to SOLUBILITY-QSPR-BP-TZVP.inp. COSMOFILES.txt is a simple ASCII-file holding the names of the molecular COSMO-files that shall be processed.
Experimental solubilities of the compounds given in COSMOFILES.txt:

<table>
<thead>
<tr>
<th>Compound</th>
<th>log10(x_solub)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,5-diphenylhydantoin</td>
<td>-5.73</td>
</tr>
<tr>
<td>Aspirin</td>
<td>-3.46</td>
</tr>
<tr>
<td>Atenolol</td>
<td>-3.04</td>
</tr>
<tr>
<td>Naproxen</td>
<td>-5.63</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>-5.60</td>
</tr>
</tbody>
</table>

DENSITY
Estimation of pure compounds liquid density rho and molar volume V using density QSPR.

DENSITY-IL
Estimation of the density Rho and molar volume V of Ionic Liquid [em2im][tf2n] using density QSPR.
The experimental density of (em2im)[1]-{tf2n}[1] is Rho ~ 1.50 [g/cm3]

ENVIRON-SCREEN cannot be processed on the command line
Environmental/Safety Screening: Calculation of physico-chemical properties of importance for environmental and safety considerations for some pure compounds.

FLASHPOINT-MIX
Computation of flash points for compound mixtures, using cosmo files from the FINE level with the BP_TZVPD_FINE_C30_1701 parametrization.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure is read from the compounds vapor pressure and property files.

FLASHPOINT-PURE
Computation of pure compound flash points using cosmo files from the FINE level with the BP_TZVPD_FINE_C30_1701 parametrization.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure is read from the compounds vapor pressure and property files.

FLATSURF
Computation of FlatSurf property with automatic procedure.

FLATSURF-AIR-WATER
Computation of Air-Water surface partition energy with automatic FlatSurf procedure.

FLATSURF-EQPHASES
Computation of FlatSurf properties with automatic phase equilibration.

FRAGMENT
Computation of Octanol-Water Partition Coefficient logPOW and water solubility for various drug-like compounds. Solutes are built from COSMO-metafiles (i.e. from fragments of smaller molecules). For comparison also the complete (not fragmented) COSMO-files of the solutes are used to compute the logPOW and solubility properties.

GAMMA
Computation of Infinite-Dilution Activity Coefficient with automatic procedure.

GAMMA-IONICLIQUID
Computation of Infinite-Dilution Activity Coefficient of different solutes in an Ionic Liquid solvent system using the automatic GAMMA procedure. Please also refer to the COSMOtherm Reference Manual.

Experimental Data:
Please note: To be consistent with experimental measurements for Ionic Liquid activity coefficients, it is necessary to scale the COSMOtherm predictions of activity coefficients with a factor of 0.5, which is equivalent to adding the amount ln(0.5) = -0.69 to the calculated values of ln(gamma). This issue is explained in the COSMOtherm Reference Manual.

<table>
<thead>
<tr>
<th>Compound</th>
<th>ln(gamma_Exp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>3.23</td>
</tr>
<tr>
<td>Octane</td>
<td>4.01</td>
</tr>
<tr>
<td>Benzene</td>
<td>0.09</td>
</tr>
<tr>
<td>Toluene</td>
<td>0.50</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.72</td>
</tr>
<tr>
<td>1-butanol</td>
<td>1.36</td>
</tr>
<tr>
<td>Propanone</td>
<td>-0.77</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>-0.10</td>
</tr>
</tbody>
</table>

GAMMA-SALT
Computation of Mean Ionic Activity Coefficient of a salt using automatic procedure.
GAMMA-SOLVENT-MIXTURE
Computation of Activity Coefficient in a solvent mixture using automatic procedure.

GEO
Create molecular structure files for output of the molecular geometries. The molecular structure files can be found in the output directory.

GHYDRATION
Computation of Gibbs Free Energy of Solvation $G_{solv}$ in Solvent water (i.e. Gibbs Free Energy of Hydration) with automatic procedure.

GHYDRATION-IONS
Computation of Gibbs Free Energy of Solvation $G_{solv}$ in Solvent water (i.e. Gibbs Free Energy of Hydration) with automatic procedure for several anions and cations.

GRADIENTS
Computation of analytic first derivatives of the chemical potential in respect to mixture and temperature for the example of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties.
Experimental data (Wagner equation coefficients) is given in the compound input area of the input file.
The computed phase diagram data can be found in the mixture output section of output-file GRADIENTS.out and in the table-file GRADIENTS.tab. The computed temperature and mixture gradients can be found in the mixture output section of output-file GRADIENTS.out. On the definition and interpretation of the chemical potential derivatives, see the COSMOtherm Reference Manual.
The acetone - methylenechloride system shows a minimum boiling-point azeotrope at $T=50 \, ^\circ\mathrm{C}$.
Experimental data for the azeotropic point: $x_1 = 0.58$

HENRY-LAW-CONSTANT
Computation of Henry law constants $k_H$ with automatic procedure.

H-PARTIAL
Computation of observable partial enthalpies for the example of a simple mixture and an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties.
Experimental data (Wagner equation coefficients) is given in the compound input area of the input file.
The computed phase diagram data can be found in the mixture output section of output-file GRADIENTS.out and in the table-file GRADIENTS.tab. The computed temperature and mixture gradients can be found in the mixture output section of output-file GRADIENTS.out. On the definition and interpretation of the chemical potential derivatives, see the COSMOtherm Reference Manual.
The acetone - methylenechloride system shows a minimum boiling-point azeotrope at $T=50 \, ^\circ\mathrm{C}$.
Experimental data for the azeotropic point: $x_1 = 0.58$

IL-PROPERTY-SCREEN cannot be processed on the command line
Computation of some properties of Ionic Liquids, using a QSAR approach.

IL-SELECTIVITY-SCREEN cannot be processed on the command line
Calculation of the selectivity, i.e. the fraction of the capacities of two different solutes in the same IL solvent.
IL-SOLUB-SCREEN *cannot be processed on the command line*
Calculation of the solvent capacity in IL solvents. The calculated solvent capacity $C^{\infty}$ corresponds to the non iterative (infinite dilution) solubility of a solute in the IL solvent, and is a good first solubility guess for a fast screening procedure.

INTERFACIAL-TENSION *cannot be processed on the command line*
Computation of the interfacial tension on the water-tetrachlorcarbon interface with automatic calculation of the liquid-liquid equilibrium.

LIQUID-EXTRACTION
Computation of Multi-Component-Two-Phase (liquid extraction) equilibria.
Experimental value for the heat of fusion of the salt sodium chloride is used.
Iteratively computes the equilibrium concentrations of all given compounds in two or three phases I, II, and III. The computed equilibrium concentrations in terms of compound mole numbers (N), compound masses (W) and mole fractions (x), can be found in the mixture output section of output-file LIQUID-EXTRACTION.out and in the table-file LIQUID-EXTRACTION.tab.

LIQUID-SOLID-EXTRACTION
Computation of Multi-Component-Two-Phase (liquid extraction) equilibria
Experimental value for the heat of fusion of the salt sodium chloride is used.
Iteratively computes the equilibrium concentrations of all given compounds in two liquid phases I and II and a solid phase III. The computed equilibrium concentrations in terms of compound mole numbers (N), compound masses (W) and mole fractions (x) can be found in the mixture output section of output-file LIQUID-SOLID-EXTRACTION.out and in the table-file LIQUID-SOLID-EXTRACTION.tab.

LLE-ANILINE-WATER-BINODAL-SPINODAL
Computation of a binary phase diagram with miscibility gap: Both the thermodynamic (*BINODAL*) and the metastable (*SPINODAL*) miscibility gaps (point of liquid-liquid equilibria) are detected with an automatic procedure.
The computed phase diagram data can be found in the mixture output section of output-file LLE-ANILINE-BINODAL-SPINODAL.out and in the table-file LLE-ANILINE-WATER-BINODAL-SPINODAL.tab. The computed LLE concentrations of the miscibility gap can be found at the end of the mixture output section of output-file LLE-ANILINE-WATER-BINODAL-SPINODAL.out and in the table-file LLE-ANILINE-WATER-BINODAL-SPINODAL.tab.
The aniline-water system shows a miscibility gap at T=323.15 K.
Experimental data for the (binodal) miscibility gap:
\[ x_1' = 0.003, \ x_2' = 0.997 \]
\[ x_1'' = 0.56, \ x_2'' = 0.44 \]

LLE-ANILINE-WATER
Computation of a binary phase diagram with miscibility gap: The miscibility gap (point of liquid-liquid equilibria) is detected with an automatic procedure. This option will perform a search for the phase equilibrium on the coarse grid of the 31 concentration points computed by the "binary" option with a subsequent iterative search for the point of phase equilibrium.
The aniline-water system shows a miscibility gap at T=323.15 K.
Experimental data for the (binodal) miscibility gap:
\[ x_1' = 0.003, \ x_2' = 0.997 \]
LLE-BINARY-LOOP
Computation of a binary phase diagram with miscibility gap: The miscibility gap (point of liquid-liquid equilibrium) is detected with an automatic procedure using the option "LLE". This option will perform a search for the phase equilibrium on the coarse grid of the 31 concentration points computed by the "binary" option with a subsequent iterative search for the point of phase equilibrium. The renormalization procedure of the computed LLE values to compensate for thermodynamic fluctuation near the critical points is used (i.e. near the regions where the LLE closes). See the COSMOtherm Reference manual for details.
The 3-picoline - water system shows a temperature dependent miscibility gap with a "closed loop" pattern, i.e. an upper as well as a lower critical solution.
Experimental data for the (binodal) miscibility gap:
Temperature (UCST and LCST):
LCST = 49.4 °C
UCST = 152.5 °C

LLE-BINARY-LOOP-OPT
Computation of a binary phase diagram with miscibility gap: The miscibility gap (point of liquid-liquid equilibrium) is detected with an automatic procedure using the option "LLE". This option will perform a search for the phase equilibrium on the coarse grid of the 31 concentration points computed by the "binary" option with a subsequent iterative search for the point of phase equilibrium. The renormalization procedure of the computed LLE values to compensate for thermodynamic fluctuation near the critical points is used (i.e. near the regions where the LLE closes). The upper and lower critical solution temperatures (UCST and LCST) are optimized automatically. See the COSMOtherm Reference manual for details.
The 3-picoline - water system shows a temperature dependent miscibility gap with a "closed loop" pattern, i.e. an upper as well as a lower critical solution.
Experimental data for the (binodal) miscibility gap:
Temperature (UCST and LCST):
LCST = 49.4 °C
UCST = 152.5 °C

LLE-BINARY-MIX
Computation of an isothermal pseudo-binary phase diagram with an aqueous salt solution phase.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties.

LLE-BUTANOL-WATER-ISOBAR
Computation of an isobaric (fixed pressure) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties.

LLE-BUTANOL-WATER-ISOTHERM
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties.

LLE-EOS-ISOBAR
Computation of an isothermal binary phase diagram with miscibility gap using an Equation-Of-State (EOS) method.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties.
Experimental pure compound critical point data is used in the computation of the EOS model.
LLE-EOS-ISOTHERM
Computation of an isothermal binary phase diagram with miscibility gap using an Equation-Of-State (EOS) method. Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental pure compound critical point data is used in the computation of the EOS model.

LLE-IONIC-LIQUID-1-OCTANOL
Computation of an isothermal pseudo-binary phase diagram with Ionic Liquid (IL) phase. Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties.

LLE-IONIC-LIQUID-1-OCTANOL-CONF
Computation of an isothermal pseudo-binary phase diagram with Ionic Liquid (IL) phase. Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties.

LLE-IONIC-LIQUID-WATER
Computation of an isothermal pseudo-binary phase diagram with Ionic Liquid (IL) phase. Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties.

LLE-MULTINARY
Computation of a 4-dimensional phase diagram with miscibility gap: The miscibility gap (point of liquid-liquid equilibrium) is detected with an automatic procedure using the option "LLE". This option will perform a search for the phase equilibrium on the given grid of 11 concentration points using an iterative search procedure for the tie lines of the phase equilibria.

The computed phase diagram data can be found in the mixture output section of output-file LLE-MULTINARY.out and in the table-file LLE-MULTINARY.tab. The computed LLE tie points (i.e. concentrations of the miscibility gap) can be found in the mixture output section of output-file LLE-MULTINARY.out and in the table-file LLE-MULTINARY.tab.

Please note that the MULTINARY LLE option will produce two tables:
1) a table with the usual multinary phase diagram properties (x, HE, GE, ptot, mu+RTlnx, gamma, y) on the given grid points, i.e. the starting points of the LLE searches.
2) a special LLE table, that holds the mole fraction concentrations of the phase separation x' and x'', gamma and y at these points, as well as the temperature and pressure.

LLE-TERNARY
Computation of a ternary phase diagram with miscibility gap: The miscibility gap (point of liquid-liquid equilibrium) is detected with an automatic procedure using the option "LLE". This option will perform a search for the phase equilibrium on the default TERNARY-LLE grid of 33 concentration points using an iterative search procedure for the tie lines of the phase equilibria.

The computed phase diagram data can be found in the mixture output section of output-file LLE-TERNARY.out and in the table-file LLE-TERNARY.tab. The computed LLE tie points (i.e. concentrations of the miscibility gap) can be found at the end of the mixture output section of output-file LLE-TERNARY.out and in the table-file LLE-TERNARY.tab.

Please note that the TERNARY LLE option will produce two tables:
1) a table with the usual ternary phase diagram properties (x, HE, GE, ptot, mu+RTlnx, gamma, y) on the given grid points, i.e. the starting points of the LLE searches.
2) a special LLE table, that holds the mole fraction concentrations of the phase separation x' and x'', gamma and y at these points, as well as the temperature and pressure.
LLE-TERNARY-IONIC-LIQUID

Computation of a ternary phase diagram with miscibility gap: The miscibility gap (point of liquid-liquid equilibrium) is detected with an automatic procedure using the option "LLE". This option will perform a search for the phase equilibrium on the given grid of 11 concentration points using an iterative search procedure for the tie lines of the phase equilibria. In this example the third of the three ternary phases is a Ionic Liquid (IL) phase, where the IL is formed from the [C4mim] Anion and the [PF6] cation.

The computed phase diagram data can be found in the mixture output section of output-file LLE-TERNARY-IONIC-LIQUID.out and in the table-file LLE-TERNARY-IONIC-LIQUID.tab. The computed LLE tie points (i.e. concentrations of the miscibility gap) can be found at the end of the mixture output section of output-file LLE-TERNARY-IONIC-LIQUID.out and in the table-file LLE-TERNARY-IONIC-LIQUID.tab. Please note that the TERNARY LLE option with a Ionic Liquid will produce three tables:

1) a table with the usual ternary phase diagram properties (x, HE, GE, ptot, mu+RTlnx, gamma, y) on the given grid points, i.e. the starting points of the LLE searches.
2) a special LLE table, that holds the mole fraction concentrations of the phase separation x' and x'', gamma and y at these points, as well as the temperature and pressure.
3) an additional IL-LLE table, which holds the information presented in table 2) converted to the laboratory (Lx) frame, where the IL is treated as a single compound.

LLE-TERNARY-ISOBAR

Computation of a ternary phase diagram with miscibility gap: The miscibility gap (point of liquid-liquid equilibrium) is detected with an automatic procedure using the option "LLE". This option will perform a search for the phase equilibrium on the default TERNARY-LLE grid of 33 concentration points using an iterative search procedure for the tie lines of the phase equilibria.

The computed phase diagram data can be found in the mixture output section of output-file LLE-TERNARY-ISOBAR.out and in the table-file LLE-TERNARY-ISOBAR.tab. The computed LLE tie points (i.e. concentrations of the miscibility gap) can be found at the end of the mixture output section of output-file LLE-TERNARY-ISOBAR.out and in the table-file LLE-TERNARY.tab. Please note that the TERNARY LLE option will produce two tables:

1) a table with the usual ternary phase diagram properties (x, HE, GE, ptot, mu+RTlnx, gamma, y) on the given grid points, i.e. the starting points of the LLE searches.
2) a special LLE table, that holds the mole fraction concentrations of the phase separation x' and x'', gamma and y at these points, as well as the temperature and pressure.

LOGD

Computation of Octanol-Water Partition Coefficient "logD" (logPOW with Dissociation Correction). The computed logD values can be found in the mixture output section of output-file LOGD.out and in the table-file LOGD.tab. Please note that the computation of logD (i.e. the dissociation correction to a Partition Coefficient) is possible only for partitions of systems with one water phase (such as logPOW). See section 2.3.5 of the COSMOtherm User's Manual for further details on logD.

LOGKHSA-QSPR

Estimation of Human Serum Albumin partition coefficient logKHSA using sigma-moment QSPR. The estimated logKIA values can be found in the compound output section of output-file LOGKHSA-QSPR.out and in the sigma-moment-file LOGKHSA-QSPR.mom. No mixture input is required for the sigma-moment QSPR estimation of logKHSA.

LOGKIA-QSPR

Estimation of Intestinal Absorption Coefficient logKIA using sigma-moment QSPR.
The estimated logKIA values can be found in the compound output section of output-file LOGKIA-QSPR.out and in the sigma-moment-file LOGKIA-QSPR.mom. No mixture input is required for the sigma-moment QSPR estimation of logKIA.

LOGKOC-QSPR
Estimation of Organic Carbon (Soil)-Water Partition Coefficient logKOC using sigma-moment QSPR.
The estimated logKOC values can be found in the compound output section of output-file LOGKOC-QSPR.out and in the sigma-moment-file LOGKOC-QSPR.mom. No mixture input is required for the sigma-moment QSPR estimation of logKOC.

LOGPBB-QSPR
Estimation of Blood-Brain Partitioning Coefficient logPBB using sigma-moment QSPR.
The estimated logPBB values can be found in the compound output section of output-file LOGPBB-QSPR.out and in the sigma-moment-file LOGPBB-QSPR.mom. No mixture input is required for the sigma-moment QSPR estimation of logPBB.

LOGP-EQPHASES
Computation of 2-propanethiol-Water Partition Coefficient logP with automatic phase equilibration.

LOGPOW
Computation of Octanol-Water Partition Coefficient logPOW with automatic procedure.
LOGPOW-DRUGS
Computation of Octanol-Water Partition Coefficient logPOW for drug-like compounds using automatic procedure.
LOGPOW-QSPR
Estimation of Octanol-Water Partition Coefficient logPOW using sigma-moment QSPR.
The estimated logPOW values can be found in the compound output section of output-file LOGPOW-QSPR.out and in the sigma-moment-file LOGPOW-QSPR.mom. No mixture input is required for the sigma-moment QSPR estimation of logPOW.

LOGPOW-VRML
The molecular VRML-files can be found in the output directory. No mixture input is required for the sigma-moment QSPR estimation of logPOW and the creation of VRML files. VRML, the 'Virtual Reality Modeling Language' is a script language allowing interactively the examination of virtual three-dimensional objects (see http://www.vrml.org). VRML files usually identified name.wrl can be viewed with common World-Wide-Web browsers such as Netscape or Microsoft Internet Explorer if an appropriate VRML browser plug in has been installed. Such plug-ins are available freely e.g. the Silicon Graphics Cosmo Player (http://www.ca.com/cosmo/) or the Cortona VRML client (http://www.parallelgraphics.com/products/cortona).

META-BINARY
Computation of a binary phase diagram using a COSMOtherm meta-file.
Experimental pure compound vapor pressures are used in the computation of the multinary phase diagram properties. Experimental data is read from "name.vap" files via command "vpfile" in the global command section.

METAFILE
Computation of a multinary phase diagram using a COSMOtherm meta-file.
Experimental pure compound vapor pressures are used in the computation of the multinary phase diagram properties. Experimental data is read from "name.vap" files via command "vpfile" in the global command section.

**MIXTURE**
Computation of a simple mixture: aspirin at infinite dilution in solvent water.

**PCCP**
Estimation of pure compound critical property (PCCP) data.

**PKA**
Computation of the acidity pKA of a compound with automatic procedure.
Experimental value for the pka of x-chlorophenol in water at T=25°C:
pKA(2-chlorophenol) 8.29
pKA(3-chlorophenol) 8.78
pKA(4-chlorophenol) 9.14

**PKA-BASE**
Computation of the basicity pKA of a compound with automatic procedure.
Experimental value for the base pka at T=25°C:
pKa(pyridine) 5.14
pKa(pyrrolidine) 11.27

**PKA-DMSO**
Computation of pKA acidity in solvent DMSO with automatic procedure.
Experimental value for the DMSO pKA at T=25°C:
pKa(benzoicacid) 11.1
pKa(3-chlorophenol) 15.8

**POLYMER-ABSOLUTE**
Computation of activity coefficient of several small gas compounds in the polymer compound PDMS (polydimethylsiloxane). The polymer solvent is built from a COSMO-metafile: the repeat unit of the polymer scaled by the polymer's molecular mass is used to describe the polymer properties. In addition, a special combinatorial term for polymer applications (Elbro-term) is used. Unlike the fragment approach used in the example-input POLYMER-RELATIVE.inp, the approach presented here allows for the absolute prediction of systems involving polymers. This issue is explained at more detail in section 5.3.2 "Treatment of Polymers" of the COSMOtherm users manual and the article "Prediction of Solubilities and Partition Coefficients in Polymers Using COSMO-RS", C. Loschen, A. Klamt, Ind. Eng. Chem. Res. 2014, 53, 11478. http://dx.doi.org/10.1021/ie501669z

**POLYMER-ABSOLUTE-FINE**
See POLYMER-ABSOLUTE-FINE, but calculation on the FINE level.

**POLYMER-RELATIVE**
Computation of activity coefficient of several small gas compounds in the polymer compound PDMS (polydimethylsiloxane). The polymer solvent is built from a COSMO-metafile: only the repeat unit of the polymer is used to describe the polymer properties. This implies that the true molecular weight and size of the polymer is neglected. Thus the computed activity coefficient cannot be interpreted in a quantitative way, but in terms of relative activity/solubility of the different solutes in the polymer solvent. This issue is explained in more detail in the
COSMOTHERM Reference Manual. Note that the workflow for computing absolute properties of systems containing polymers is demonstrated in input POLYMER-ABSOLUTE.inp.

**PSUB**
Computation of a pure compounds vapor pressure over a given temperature range including solid state (i.e. sublimation pressure).

**PVAP**
Computation of a pure compounds vapor pressure over a given temperature range.

**PVAP-REFERENCE**
Computation of a pure compounds vapor pressure over a given temperature range.

**PVAP-REFERENCE-MIX**
Computation of a mixtures vapor pressure over a given temperature range.

**QSPR-MIX** cannot be processed by graphical user interface
Estimation of Octanol-Water Partition Coefficient logPOW using sigma-moment QSPR.

**REACTION**
Computation of the reaction equilibrium constant K and reaction energy G(react) and H(react) for the isomerization reaction of 5-methyl-4-nitrobenzofuroxane to 7-methyl-4-nitrobenzofuroxane (unimolecular Boulton-Katritzky rearrangement) in different solvents.
High quality DFT based COSMO-files (BP-TZVP-COSMO) are used. High level CCSD(T) quantum chemistry data and vibrational zero point energies of the reacting species are used to refine the results. The computed equilibrium constant K(react), reaction Gibbs free energy G(react), and reaction enthalpy H(react) values can be found in the mixture output section of output-file REACTION.out and in the table-file REACTION.tab.

**SALT-SOLUB-SCREEN-SOLID-REFERENCE**
A solubility screening for a salt solute (ammonium chloride), using a reference solubility to determine the free energy of fusion DGfus.

**SIMILARITY**
Determine chemical similarity and sigma potential similarity between different compounds.

**SLE-IONIC-LIQUID**
Computation of the solubility curve (SLE) and eutectic point of a neutral compound and a Ionic Liquid (IL) / salt compound with automatic procedure.
Experimental data for the temperature dependent heat of fusion is used for both molecules. The eutectic point can be interpolated graphically from the computed SLE using the COSMOTHERMX graphical user interface via loading the table output file SLE-IONIC-LIQUID.tab.

**SLE-OPT-EUTECTIC**
Computation of the solubility curve (SLE) and eutectic point of two solids with automatic procedure. Experimental data for the temperature dependent heat of fusion is used for both molecules. The eutectic point can be
interpolated graphically from the computed SLE using the COSMOthermX graphical user interface via loading the table output file SLE-OPT-EUTECTIC.tab.

**SLE-TOLUENE-ETHYLBENZENE**
Computation of the solubility curve (SLE) and eutectic point of two solids with automatic procedure. Experimental data for the temperature dependent heat of fusion is used for both molecules. The eutectic point can be interpolated graphically from the computed SLE using the COSMOthermX graphical user interface via loading the table output file SLE-TOLUENE-ETHYLBENZENE.tab.

**SLE**
Computation of the solubility curves (SLE and LLE) of a solid solute in water with automatic procedure. Experimental data for the temperature dependent heat of fusion is used for solid aspirin. Solvent compound water is assumed to be liquid. The SLE(T) and LLE(T) curves can be plotted in COSMOthermX graphical user interface via loading the table output file SLELE.tab.

**SOLUBILITY-DISSOCIATION**
Computation of compound solubility with dissociation correction. Experimental value for the heat of fusion of solute naphthalene is used. The computed log(x_Solubility) values can be found in the mixture output section of output-file SOLUBILITY-SOLID.out and in the table-file SOLUBILITY-SOLID.tab. Please note that the dissociation correction to a solubility is possible only for solvent pure water. See section 2.3.4 of the COSMOtherm User Manual for further details on the dissociation correction applied.

**SOLUBILITY-GAS**
Computation of the solubility of a gas in a liquid solvent with automatic procedure.

**SOLUBILITY-LIQUID**
Computation of the solubility of a liquid with automatic procedure.
Experimental value for the solubility of water in 1-octanol at T=25°C:
\[ x_{h2o}=0.274 \quad \log(x_{h2o})=-0.562 \]

**SOLUBILITY-QSPR-BP-SVP-AM1**
Computation of the solubility of drug-like solids with automatic procedure. The heat of fusion of the solutes is estimated by a solubility QSPR procedure.
Experimental data:
- Phenytoin \( \log10(x_{solub}) = -5.73 \)
- Aspirin \( \log10(x_{solub}) = -3.46 \)
- Atenolol \( \log10(x_{solub}) = -3.04 \)
- Naproxen \( \log10(x_{solub}) = -5.63 \)
- Nortriptyline \( \log10(x_{solub}) = -5.60 \)

**SOLUBILITY-QSPR-BP-TZVP**
Computation of the solubility of drug-like solids with automatic procedure. The heat of fusion of the solutes is estimated by a solubility QSPR procedure. Please note: The solubility QSPR procedure which estimates the solutes heat of fusion is toggled automatically if no experimental data for the heat of fusion is given in the compound input section. The solubility QSPR parameters are read from the COSMOtherm parameterization file. See section 2.3.4 of the COSMOtherm user manual.
Experimental data:
Phenytoin \[ \log_{10}(x_{\text{solub}}) = -5.73 \]
Aspirin \[ \log_{10}(x_{\text{solub}}) = -3.46 \]
Atenolol \[ \log_{10}(x_{\text{solub}}) = -3.04 \]
Naproxen \[ \log_{10}(x_{\text{solub}}) = -5.63 \]
Nortriptyline \[ \log_{10}(x_{\text{solub}}) = -5.60 \]

**SOLUBILITY-SALT**

Computation of the solubility of a salt with automatic solubility calculation procedure. Experimental value for the heat of fusion of the salt sodium chloride is used.

**SOLUBILITY-SLE**

Computation of the solubility of a solid in a solvent mix using SLE search procedure. Experimental value for the heat of fusion of solute naphthalene is used.

**SOLUBILITY-SOLID**

Computation of the solubility of a solid with automatic procedure. Experimental value for the heat of fusion of solute naphthalene is used. Experimental value for the solubility of naphthalene in acetone at \( T=40^\circ\text{C} \):

\[ \log(x_{\text{solub}})= -0.423 \quad x_{\text{solub}}=0.378 \]

**SOLUBILITY-SOLID-REFERENCE**

Computation of the enthalpy and free energy of fusion \( \Delta H_{\text{fus}} \) and \( \Delta G_{\text{fus}} \) using a given reference solubility.

**SOLUB-SCREEN-SOLID-REFERENCE**

A solubility screening for a solid solute using a reference solubility to determine the free energy of fusion \( \Delta G_{\text{fus}} \).

**SOLUB-SOLVENT-MIX-GRID**

A solubility screening in a range of solvent mixtures, using a grid to determine the mixture compositions.

**SOLUB-SOLVENT-MIX-OPT**

An automatic solvent mixture optimization.

**TBOIL**

Computation of the normal pressure boiling point of a compound. Experimental Boiling Point \( T_{\text{Boil}} = 337.9 \) K for \( p_{\text{vap}}(T_{\text{Boil}}) = 100 \) kPa

**TRIVIALNAME-CONFORMER**

Computation of a binary phase diagram using database trivial names as molecule identifier. For each compound all conformers that are present in the database are used to compute the binary phase diagram.

**TRIVIALNAME**

Computation of a binary phase diagram using database trivial names as molecule identifier.

**VISCOSITY**

Estimation of pure compounds liquid viscosity \( \eta \) using viscosity QSPR.

**VLE-ACETONE-CHCL3-ISOBAR**

Computation of an isobaric (fixed pressure) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental data (Wagner equation coefficients) is given in the compound input area of the input file.

**VLE-ACETONE-CHCL3-ISOTHERM**
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental data (Wagner equation coefficients) is given in the compound input area of the input file.

**VLE-BUTANOL-HYDROGEN-CONFORMER**
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure at the given temperature is given in the compound input area of the input file via the vpinp=value command (see below).

**VLE-BUTANOL-HYDROGEN-GRID**
Computation of isothermal binary phase diagrams on different concentration grids.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure at the given temperature is given in the compound input area of the input file via the vpinp=value command (see below).

**VLE-BUTANOL-HYDROGEN**
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure at the given temperature is given in the compound input area of the input file via the vpinp=value command (see below).

**VLE-DIETHYLETHER-METHANOL**
Computation of an isothermic binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. The experimental data is given in the compound input area of the input file. Note: Experimental pure compound vapor pressures taken from Lide, Ed. "CRC Handbook of Chemistry and Physics", 70th ed. (2000).

**VLE-EOS-ISOBAR**
Computation of an isobaric binary phase diagram at critical conditions using an Equation-Of-State (EOS) method. Experimental critical data and pure compound vapor pressures are used in the computation of the EOS model phase diagrams. The experimental data is read from the Vapor-pressure/Property files of the compounds. Note that at extrapolation temperatures of 525 and 550 K, the given binary system is supercritical at large propanone concentrations. Graphically, this is reflected in the fact that the phase diagram at these temperatures is detached from the y-axis of the x,y-vs.-ptot phase diagram plot.

**VLE-EOS-ISOTHERM**
Computation of an isothermal binary phase diagram at critical conditions using an Equation-Of-State (EOS) method. Experimental critical data and pure compound vapor pressures are used in the computation of the EOS model phase diagrams. The experimental data is read from the Vapor-pressure/Property files of the compounds. Note that at an extrapolation temperature of 525 K, the given binary system is supercritical at at large propanone concentrations. Graphically, this is reflected in the fact that the phase diagram at these temperatures is detached from the y-axis of the x,y-vs.-ptot phase diagram plot.
VLE-ETHANOL-TRIETHYLAMINE-BP-TZVPD-FINE
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure at the given temperature is given in the compound input area of the input file.

VLE-ETHANOL-WATER-BP-SVP-AM1
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure at the given temperature is given in the compound input area of the input file.

VLE-ETHANOL-WATER-BP-TZVPD-FINE
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure at the given temperature is given in the compound input area of the input file.

VLE-ETHANOL-WATER-BP-TZVP
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure at the given temperature is given in the compound input area of the input file.

VLE-ETHANOL-WATER-DMOL3
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure at the given temperature is given in the compound input area of the input file.

VLE-HEXANE-BENZENE
Computation of an isothermal binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental data is read from "compound.vap" files via command "vpfile" in the global command section.

VLE-METHANOL-WATER-1
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure at the given temperature is given in the compound input area of the input file.

VLE-METHANOL-WATER-2
Computation of an isothermal (fixed temperature) binary phase diagram.
Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure data is read from "compound.vap" files via command "vpfile" in the global command section. The vapor pressure/property files "compound.vap" hold experimental vapor pressure data in the form of coefficients for Wagners vapor pressure equation.

VLE-METHANOL-WATER-3
Computation of an isothermal (fixed temperature) binary phase diagram.
The generic COSMOtherm prediction method for pure compound vapor pressures is used to estimate the vapor pressure of the two pure compounds. This estimation method relies on the energy difference between the quantum chemical cosmo calculation (energy in cosmo/ccf-file) and the quantum chemical gas phase energy. The gas phase energy is read from "compound.energy" files using the "efile" option (see below). In addition, the vapor pressures thus computed are scaled in order to match their experimental normal boiling point as a reference temperature and pressure (i.e. Tref = Tboil at pref = 1 atm).

**VLE-METHANOL-WATER-4**
Computation of an isothermal (fixed temperature) binary phase diagram. The generic COSMOtherm prediction method for pure compound vapor pressures is used to estimate the vapor pressure of the two pure compounds. This estimation method relies on the energy difference between the quantum chemical cosmo calculation (energy in cosmo/ccf-file) and the quantum chemical gas phase energy. The gas phase energy is read from "compound.energy" files using the "efile" option.

**VLE-METHANOL-WATER-5**
Computation of an isothermal (fixed temperature) binary phase diagram. The empirical COSMOtherm estimate for pure compound vapor pressures is used to estimate the vapor pressure of the two pure compounds. Normally this is the most inaccurate estimation method for vapor pressures that COSMOtherm provides.

**VLE-MULTINARY1**
**VLE-MULTINARY2**
**VLE-MULTINARY3**
Computation of a high-dimensionality (multinary) phase diagram. Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental data is read from "compound.vap" files via command "vpfile" in the global command section.

**VLE-MULTINARY-IONICLIQUID**
Computation of a high-dimensionality (multinary) phase diagram with Ionic Liquid. Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental data is read from "compound.vap" files via command "vpfile" in the global command section.

**VLE-OCTANE-ACETICACID-IEI**
Computation of an isothermal (fixed temperature) binary phase diagram of a reactive species (acetic acid which dimerizes in octane solution dependent on the solute concentration). The dimerization reaction is described by the interaction energy index (IEI) formalism of COSMOtherm (see COSMOtherm Reference Manual). Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental data (Wagner equation coefficients) is given in the compound input area of the input file.

**VLE-PROPANONE-METHANOL-AZEOTROPE**
Computation of a binary phase diagram and subsequent optimization of its Azeotrope point. Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure data is read from "compound.vap" files via command "vpfile" in the global command section.

**VLE-PROPANONE-WATER-GAMMA-FIT**

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Computation of a binary phase diagram and subsequent fitting of the computed activity coefficients to different variants of NRTL, UNIQUAC and Wilson equations.

Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental vapor pressure data is read from "compound.vap" files via command "vpfile" in the global command section.

The computed phase diagram data can be found in the mixture output section of output-file VLE-PROPANONE-WATER-GAMMA-FIT.out and in the table-file VLE-PROPANONE-WATER-GAMMA-FIT.tab. The computed coefficients for the NRTL, UNIQUAC and Wilson equations can be found at the end of the mixture output section of the output-file VLE-PROPANONE-WATER-GAMMA-FIT.out.

VLE-TERNARY

Computation of an isothermic ternary phase diagram.

Experimental pure compound vapor pressures are used in the computation of the binary phase diagram properties. Experimental data is read from "compound.vap" files via command "vpfile" in the global command section.
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