

# COSMOtherm

*as a Valuable Tool for  
Cocrystal Screening & Development*

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**COSMOtherm is a widely used versatile software tool for the prediction of thermodynamic properties in liquid systems. Recent studies reveal that it may be used for computational screening of co-crystals.**

Dr. Christoph Loschen & Dr. Andreas Klamt, COSMOlogic GmbH & Co. KG, Leverkusen, Germany

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## COSMOtherm as a Valuable Tool for Cocrystal Screening and Development

Christoph Loschen<sup>1\*</sup> and Andreas Klamt<sup>1,2\*</sup>

**Abstract:** COSMOtherm is a widely used versatile software tool for the prediction of thermodynamic properties in liquid systems. Only recently it has been shown that COSMOtherm as well can be used for accurate and efficient screening of cocrystallization cofomers. The excess enthalpy  $H_{ex}$  between an API-coformer mixture and the respective pure components as computed by COSMOtherm reflects the tendency of those two compounds to cocrystallize. Most likely due to its detailed and accurate description of all intermolecular interactions, COSMOtherm appears to be more accurate in conformer ranking than other specially developed procedures, which are focused on intermolecular hydrogen bonding. In combination with molecule libraries such as GRAS and EAFUS, automated calculations can be performed and novel, API-coformer pairs may be revealed. As a result, experiments may be focused on those cofomers which have an increased probability of cocrystallisation. In combination with additional capabilities of COSMOtherm (e.g. solubility prediction, solvent screening, accurate pKa calculation) such a rational approach will lead to more efficient cocrystal and product development. COSMOtherm based thermodynamics calculations can be easily performed with our graphical user interface COSMOthermX.

### Introduction

The transformation of active pharmaceutical ingredients (APIs) from their pure crystalline form into cocrystals has experienced increasing interest recently. A cocrystal of the API and an additional compound may show modified properties (such as solubility, dissolution rate, physical and chemical stability) as compared to the pure compounds.<sup>1,2</sup> The possibility to improve the bioavailability of the API and to create patentable intellectual property constitutes a

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1 COSMOlogic GmbH & Co. KG, Leverkusen, Germany

2 Institute of Physical and Theoretical Chemistry, University of Regensburg, Regensburg, Germany

\* Correspondence to: loschen@cosmologic.de, klamt@cosmologic.de

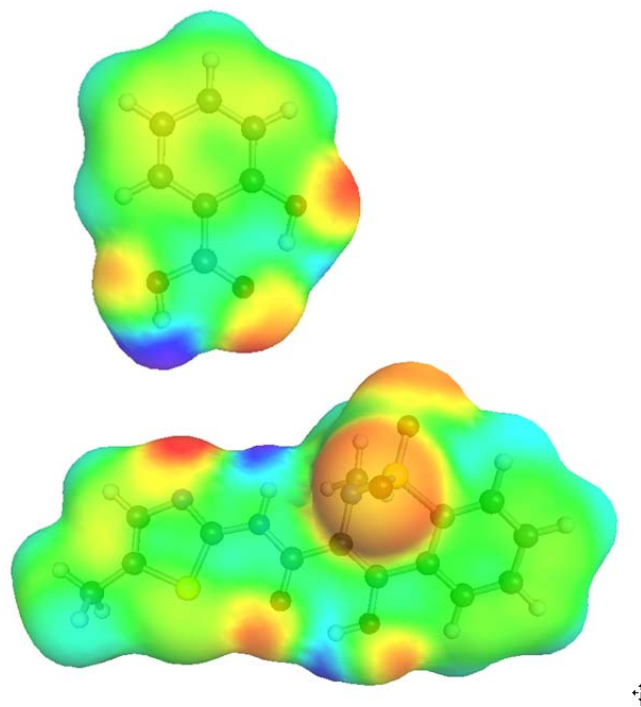
new and highly attractive route for drug development. In the following we will show how fluid phase thermodynamics computations may support such a development.

COSMO-RS (COnductor like Screening Model for Real Solvents) is a universal theory to predict the thermodynamic equilibrium properties of liquids, which was originally developed by A. Klamt at Bayer AG.<sup>3</sup> COSMO-RS thermodynamics is based on the statistical physics of interacting molecular surface segments. The polar and hydrogen bond interaction energies are quantified based on the surface screening charge densities, which result from a quantum chemical continuum solvation calculation. For details we refer the reader to the literature.<sup>3,4</sup> Due to its ability to treat mixtures at variable temperatures and to compute accurate solvation energies based on first-principles, it has become very popular in chemical engineering and in wide areas of physical and medicinal chemistry.

A complete computational modeling and prediction of the cocrystallization process is currently out of reach due to the complexity of the involved steps like nucleation and crystal growth. However, with COSMO-RS being a fluid phase thermodynamics model, we can compute a virtually liquid mixture of the cocrystallization components and obtain the excess enthalpy of stoichiometric m:n mixtures, typically 1:1 mixtures, created out of the pure components A and B:

$$H_{ex} = H_{AB} - mH_{pure,A} - nH_{pure,B}$$

$H_{pure}$  and  $H_{AB}$  represent the enthalpies in the pure reference state and in the m:n mixture respectively.  $H_{ex}$  contains *all* enthalpic contributions and is not limited to hydrogen bonding interactions, though those may be separated from the overall enthalpy by COSMOtherm. In our on-going studies we found that the excess enthalpy  $H_{ex}$  is a superior descriptor to the pure hydrogen bonding interaction. Compounds with  $H_{ex} < 0$  are strongly interacting in solution (equivalent to a negative deviation from Raoult's law) and prefer the mixture enthalpically over their pure liquids. In a set of sample calculation presented below we demonstrate that  $H_{ex}$  corresponds nicely with an increased probability of forming cocrystals. Since it is plausible to assume, that such liquid phase enthalpic preference will also pertain in a mixed crystal, i.e. in a cocrystal of the components, it is plausible to use the liquid phase excess enthalpy as a guide for cocrystal screening. Indeed, it may be shown, that  $H_{ex}$  is a dominant part of the free energy of cocrystal formation  $\Delta_f G_{cocr}$  out of the crystalline compounds A and B, a corresponding publication is in preparation.



**Figure 1:**  $\sigma$ -surfaces of meloxicam and salicylic acid as calculated with COSMOtherm. Positive segments of the molecular surface are marked blue (e.g. hydrogen bonding donors) whereas negative areas are marked red (e.g. hydrogen bonding acceptors).

### Computational Cocrystal Screening - Selecting the Most Promising Cofomers

In the following we will demonstrate the efficiency of the approach on the example of some experimental data. For a given set of compounds  $\sigma$ -surfaces which are already stored in our database COSMObase may be used and do not have to be computed therefore prior to the calculations. Still, this approach will increase the amount of time needed for a screening somewhat compared to the setting described in the next section. Therefore it is especially suited for refining for example the experimental setup for a smaller subset of compounds which are believed to be cocrystallisation candidates. In Table 1 the results for a screening based on the excess enthalpy as computed with the COSMOtherm program and a BP-SVP parameterization<sup>3</sup> is shown, where experimentally obtained cocrystals are highlighted in green.

**Table 1.** Cocrystal screening based on data of reference 5, experimentally obtained cocrystals are highlighted in green. For a better comparison same letters as in publication 6 have been used to designate the conformer compounds. **A:** 3-cyanophenol, **B:** 4-cyanophenol, **C:** 3-cyanopyridine, **D:** 4-cyanopyridine, **E:** bicalutamide, **F:** 1-hexadecanol, **G:** 1-naphtol, **H:** 4,4-biphenol, **I:** resorcinol, **J:** 1,3,5-trihydroxybenzene, **K:** 4-phenylpyridine, **L:** 4,4'-bipyridine, **M:** 4,4'-ethane-1,2-diylidipyridine, **N:** 1,2-di-4-pyridylethene, **O:** 1-naphtalenecarbonitrile, **P:** 1,3-benzenedicarbonitrile, **Q:** 1,4-benzenedicarbonitrile, **R:** 3 hydroxypyridine, **S:** 5-hydroxyisoquinoline. Enthalpies  $H_{ex}$  are given in kcal/mol.

A+Cof.	$H_{ex}$	B+Cof.	$H_{ex}$	C+Cof.	$H_{ex}$	D+Cof.	$H_{ex}$	E+Cof.	$H_{ex}$
<b>M</b>	-4.1	<b>M</b>	-3.7	<b>J</b>	-3.7	<b>J</b>	-3.6	<b>M</b>	-2.9
<b>N</b>	-3.7	<b>N</b>	-3.4	<b>H</b>	-3.3	<b>H</b>	-3.3	<b>N</b>	-2.6
<b>L</b>	-3.4	<b>L</b>	-3.1	<b>I</b>	-3.2	<b>I</b>	-3.2	<b>L</b>	-2.3
<b>K</b>	-2.5	<b>K</b>	-2.2	<b>G</b>	-3.1	<b>G</b>	-3.1	<b>J</b>	-1.7
<b>D</b>	-1.6	<b>D</b>	-1.4	<b>A</b>	-1.5	<b>A</b>	-1.6	<b>K</b>	-1.6
<b>C</b>	-1.5	<b>C</b>	-1.3	<b>B</b>	-1.3	<b>B</b>	-1.4	<b>H</b>	-1.4
<b>O</b>	-0.6	<b>G</b>	-0.6	<b>E</b>	-0.8	<b>E</b>	-0.9	<b>G</b>	-1.3
<b>G</b>	-0.5	<b>J</b>	-0.5	<b>R</b>	-0.8	<b>R</b>	-0.8	<b>I</b>	-1.3
<b>P</b>	-0.4	<b>H</b>	-0.4	<b>S</b>	-0.7	<b>S</b>	-0.8	<b>D</b>	-0.9
<b>Q</b>	-0.4	<b>O</b>	-0.4	<b>M</b>	-0.1	<b>M</b>	-0.1	<b>C</b>	-0.8
<b>J</b>	-0.4	<b>I</b>	-0.4	<b>N</b>	-0.1	<b>N</b>	-0.1	<b>O</b>	-0.2
<b>H</b>	-0.3	<b>P</b>	-0.3	<b>P</b>	0.0	<b>P</b>	0.0	<b>A</b>	-0.1
<b>I</b>	-0.3	<b>Q</b>	-0.2	<b>Q</b>	0.0	<b>Q</b>	0.0	<b>P</b>	0.0
<b>E</b>	-0.2	<b>R</b>	0.0	<b>L</b>	0.0	<b>L</b>	0.0	<b>Q</b>	0.0
<b>R</b>	-0.1	<b>E</b>	0.0	<b>D</b>	0.0	<b>C</b>	0.0	<b>B</b>	0.0
<b>S</b>	0.0	<b>A</b>	0.0	<b>K</b>	0.1	<b>K</b>	0.1	<b>R</b>	0.1
<b>B</b>	0.0	<b>S</b>	0.0	<b>O</b>	0.1	<b>O</b>	0.1	<b>S</b>	0.1
<b>F</b>	0.1	<b>F</b>	0.3	<b>F</b>	0.7	<b>F</b>	0.6	<b>F</b>	1.1
<b>A</b>	-	<b>B</b>	-	<b>C</b>	-	<b>D</b>	-	<b>E</b>	-

The experimental data is taken from the work of Bis et al.<sup>5</sup> and contains the API bicalutamide and other components containing pyridine, hydroxyl and cyano functional groups. All cocrystals

are ranked at the top of the list with only three false positive results, while a recently published specially developed cocrystal screening method had six wrong positives on exactly the same data set.<sup>6</sup>

In a similar way as potential cofomers are identified, solvents which tend to form solvates with the API may be found by calculation of the excess enthalpy.

**Table 2.** Excess enthalpy of solvents that form solvates with carbamazepine (reference 7).

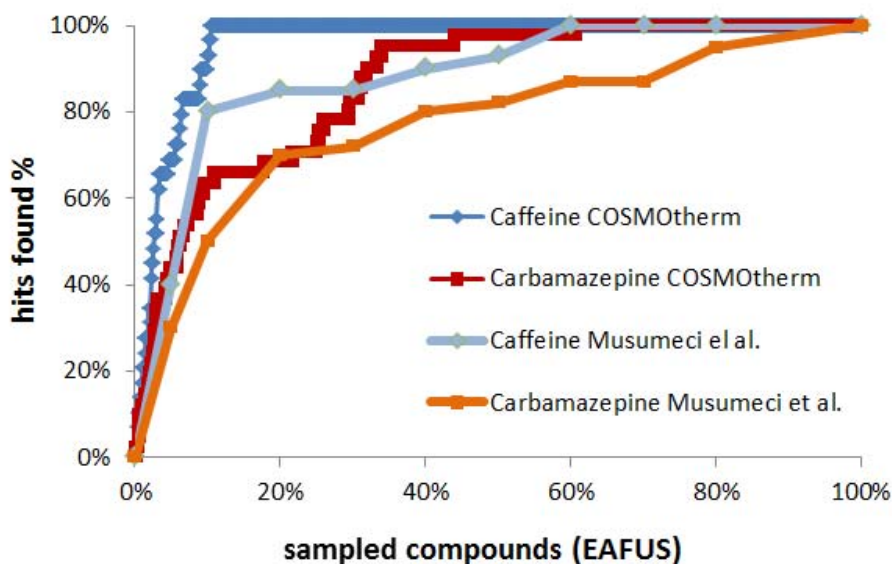
Solvent	H <sub>ex</sub> [kcal/mol]
formicacid	-2.2
aceticacid	-1.4
dimethylsulfoxide	-0.6
dimethylformamide	-0.4
h2o	-0.4
glycol	-0.1
propanone	-0.1
dioxane	-0.1
sulfolane	0.0

In Table 2 solvents forming solvates with carbamazepine are listed. Formic acid and acetic acid show a highly negative excess enthalpy and are both known to form especially persistent solvates with carbamazepine.<sup>7</sup>

### High Throughput Computational Cocrystal-Screening from Molecular Libraries – A Way to Find New Cofomers

The second scenario will show how we can identify possible cocrystallisation candidates (coformers) by ranking a large set of molecules according to their excess enthalpy H<sub>ex</sub> with the API. Some good sources for potential cofomers are FDA databases like GRAS (Generally Recognized As Safe) and EAFUS (Everything Added to Food in the US).<sup>8</sup> A subset of the compounds enlisted in these databases will be made available soon for COSMOtherm calculations (~ 2000 compounds). As a probe we have used the drugs caffeine and carbamazepine, an overview of their cocrystal cofomers can be found in reference 6. To increase the screening performance we use our module COSMOfrag, which allows for creating  $\sigma$ -surface out of SMILES string based on comparison with already existing  $\sigma$ -surfaces.<sup>9</sup> This significantly

speeds up the screening which is done for several hundred compounds within minutes. It has the advantage that data can be generated for compounds where no quantum chemical calculation has been made so far. Figure 2 shows an enrichment plot for both drugs which have been screened against the EAFUS list of compounds.

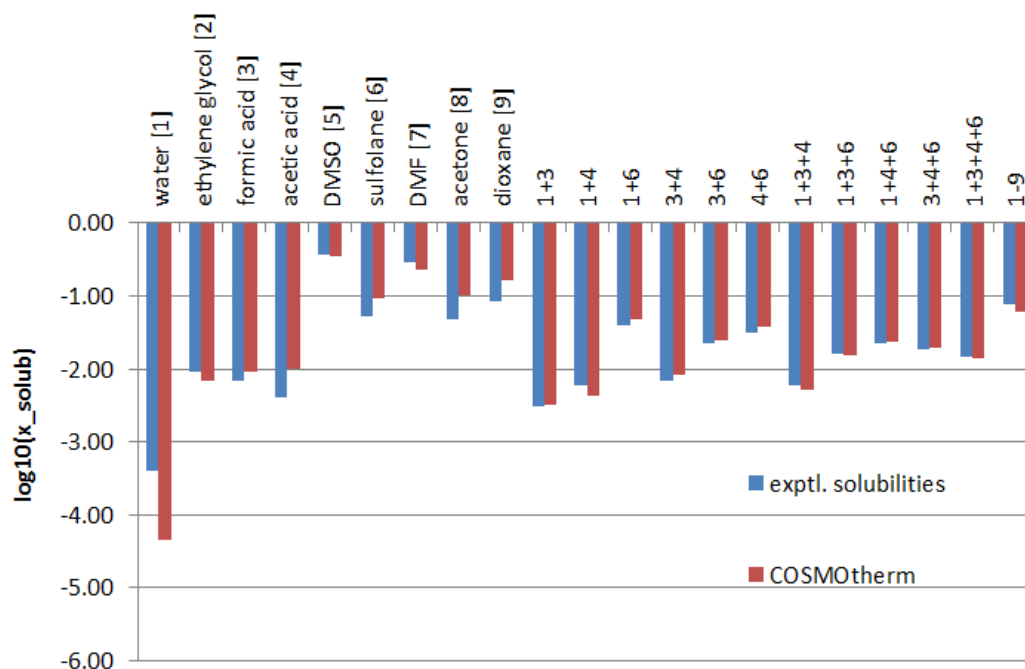


**Figure 2:** Computational cocrystal screening of caffeine and carbamazepine against a subset of the EAFUS list. Compounds have been sorted according to their excess enthalpy  $H_{ex}$ . For caffeine the search already contains all experimentally found cocrystals after having screened only 10% of the list. For carbamazepine still 80% of experimentally known cocrystals are found after having screened only 30% of the compounds. For comparison results of the computational cocrystal screening of reference 6 are given.<sup>10</sup>

For the case of caffeine we find in our ranked list all experimentally known hits already within the top 10%. For carbamazepine the ranking still gets 80% of the experimentally known cofomers into the top 30% of the list. Again, as demonstrated in Figure 2, this result seems to be superior compared to other recently published computational screening methods for cocrystals.<sup>6,11</sup> We like to emphasize that the approach can be performed within minutes *without* the need to perform any quantum chemical calculation beforehand.

## Solubility Predictions and Solvent Screening

Apart from cocrystal screening, the COSMOtherm software suite offers a rich selection of tools to support drug development. For example one of the strengths of COSMOtherm is the prediction of solubilities of organic compounds.<sup>12</sup> In Figure 3 the predicted solubility of saccharine which is a typical cocrystal candidate in a set of solvents and solvent mixtures is compared with experimentally determined solubilities.<sup>7</sup>



**Figure 3:** Solubility (decadic logarithm of solubility  $x$  in mol/mol) of the conformer saccharin in different solvents and solvent combinations. Experimental data taken from Reference 7. The solubility in glycole has been taken as a reference value.

The solubility in glycole has been taken as a reference value. The predictions reflect all trends correctly, even complex mixtures of solvents. Saccharine is known to form no solvates in these solvents. Complex equilibria in solution involving salt, solvate or cocrystal formation are more difficult to predict and the solubility computations may become less reliable. Additionally to solubility calculations, the software package COSMOtherm offers also the possibility to perform solvent screening to select the optimal solvent (or an anti-solvent) for a given compound. Other

features available with COSMOtherm are reliable pK<sub>a</sub> predictions and QSAR predictions based on  $\sigma$ -moments.

## Summary & Outlook

The software COSMOtherm offers a highly efficient and very promising way to preselect cocrystal conformers by computational screening, which appears to be more accurate in cofactor ranking than other currently available methods. This is achieved by the calculation of the excess enthalpy  $H_{\text{ex}}$  which may be interpreted as the tendency of the two components to associate in the mixture prior to cocrystallization. In addition, COSMOtherm offers several additional tools which are very supportive during drug development, for example solubility predictions in pure solvents and mixtures, pK<sub>a</sub> predictions and solvent screening. COSMOtherm is a software implementation based on COSMO-RS theory, which is well renowned for its reliable predictions regarding liquid phase thermodynamics. To alleviate the use of COSMOtherm the graphical user interface COSMOthermX is available where all calculations can be performed quite easily even by less experienced users. Please feel free to contact the authors directly to obtain supporting information on this work.

**COSMOtherm trainings and seminars** are available upon request: [info@cosmologic.de](mailto:info@cosmologic.de) or via phone: +49-2171-73168-0. Please visit us at [www.cosmologic.de](http://www.cosmologic.de).

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<sup>8</sup> <http://www.fda.gov/Food/FoodIngredientsPackaging/default.htm>

<sup>9</sup> Hornig, M. & Klamt, A. COSMOfrag: A Novel Tool for High-Throughput ADME Property Prediction and Similarity Screening Based on Quantum Chemistry, *Journal of Chemical Information and Modeling*, **2005**, *45*, 1169.

<sup>10</sup> Please note that it was not possible to retrieve the subset of compounds from the EAFUS list which used in reference 6. Therefore the sampled compounds used in both of the screenings shown in Figure 2 are not identical.

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