

COSMO-RS: An Alternative to Simulation for Calculating Thermodynamic Properties of Liquid Mixtures

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Abstract

The conductor-like screening model for realistic solvation (COSMO-RS) method has been established as a novel way to predict thermophysical data for liquid systems and has become a frequently used alternative to force field–based molecular simulation methods on one side and group contribution methods on the other. Through its unique combination of a quantum chemical treatment of solutes and solvents with an efficient statistical thermodynamics procedure for the molecular surface interactions, it enables the efficient calculation of many properties that other methods can barely predict. This review presents a short delineation of the theory, the application potential and limitations of COSMO-RS, and its most important application areas.

UNIFAC: universal quasichemical functional group activity coefficients model

Molecular dynamics (MD): a sampling technique in molecular simulations

Monte-Carlo (MC): a sampling technique in molecular simulations

INTRODUCTION

The liquid state is by far the most important for chemistry and biology in general and for chemical and biological engineering in particular. For reaction and separation purposes it provides the advantage of permanent, intensive molecular contacts with ever-changing partners. Furthermore, molecules of different species often can be mixed and brought into contact in the liquid phase if the solvents and mixtures are appropriately chosen. Therefore, biologists and chemical engineers prefer to do chemistry in the liquid state. And hence, an understanding of the interactions of molecules in liquid phases and knowledge of their liquid phase thermophysical properties, based on experiment or prediction, is an important prerequisite for any rational description and modification of chemical and biological processes.

Although accurate experimental data are still an important and without doubt the most reliable source for thermophysical data on liquids, good experiments are often expensive and time consuming, and as a result will ever be limited to a small subspace of possible combinations of solutes and pure or mixed solvents. Therefore, theoretical or computational methods and models are important supplements to the exploration of a larger space of new solutes and solvents. But unfortunately, the same attributes that make the liquid phase so preferable for biological and chemical engineering also make a theoretical description of it extraordinarily complicated. The properties of molecules in liquid systems are influenced by interactions with all fluctuating neighboring molecules, and calculation of these properties requires an efficient sampling and thermodynamic averaging of all the possible arrangements of solute and solvent molecules. Strictly speaking, the properties of molecules in solution need to be calculated as the combined thermodynamic and quantum mechanical expectation values of large ensembles of interacting molecules. Obviously, this is a hopelessly complex task, and therefore generations of researchers have tackled the problem with various degrees of simplification, empiricism, and pragmatism.

Many data-driven, empirical models have been developed, including:

- more or less theoretically founded data interpolation schemes, for example G^E -models such as Wilson, non-random two liquids (NRTL), or universal quasi-chemical (UNIQUAC), and equations of state (EoS), which are widely used in process simulations (1);
- linear solvation free energy relationship models such as the CLOGP (calculated logarithmic octanol-water partition coefficients) method (2), which is massively used in bio- and medicinal chemical research;
- and chemical engineering group-contribution methods such as UNIFAC (universal quasi-chemical functional group activity coefficients) (3).

These models allow for property predictions if sufficient experimental data are available for the compound of interest or for structurally similar compounds. But such methods do not catch the molecular details of the underlying compounds and usually fail for new situations, especially for new classes of chemical compounds.

Physical chemists, and to a smaller extent chemical engineers interested in a more fundamental description of the molecular interactions of molecules, therefore have developed atomistic simulation methods. These methods are based on force fields that are highly detailed but also highly parameterized schemes for the quantification of the different types of interactions that atoms can have. In combination with molecular dynamics (MD) or Monte-Carlo (MC) sampling techniques, this approach currently allows for the realistic simulation of liquid molecular ensembles and for the calculation of thermodynamic averages of energies, volumes, and many other properties (4–7). The strength of such molecular simulation techniques is the ability to model the systems of interest with molecular detail. Although especially the MC simulation techniques are rather efficient and mature, at least for pure systems, the largest drawback of these methods is the limited

accuracy and transferability of the force fields owing to the still too crude approximation of real molecules with their flexible electron distributions by ensembles of spherical atoms with mostly fixed point charges. One way out would be the replacement of the force fields by the much more fundamental and hence more generally applicable quantum chemistry (QC) methods, which have become feasible, but the system sizes and simulation times required for fluid phase simulations are still orders of magnitude too large for direct QC-based thermodynamic simulations.

Currently in QC, solvents are usually simulated by continuum solvation models (CSMs). These are based on the oversimplified but surprisingly successful approximation of the real solvent by a dielectric continuum of permittivity ϵ . Nowadays this approach is implemented in most QC programs to make use of the complete electrostatic information resulting from the molecular electron density (for a review of CSMs see Reference 8). Klamt & Schüürmann developed a technical modification of the dielectric CSMs, known as the conductor-like screening model (COSMO), which replaces the dielectric boundary conditions by a much simpler scaled-conductor boundary condition (9). COSMO has become popular owing to its considerable reduction of the numerical demands and increased numerical robustness. Nowadays a large part of the CSM calculations in QC are performed by applying COSMO or small improvements of it, such as the IEFPCM (integral equation formalism polarizable continuum model) or the SS(V)PE (surface and simulation of volume polarization method for electrostatics) (10, 11). CSMs are parameterized on the solvation energies of organic compounds, mostly for the solvent water. Usually each solvent needs to be parameterized separately. CSMs provide no concept for mixtures or for the description of temperature effects, and thus they are not suited for chemical engineering applications, in which temperature and composition variations are of crucial importance.

In 1995 Klamt introduced a novel combination of the COSMO model with statistical thermodynamics (12–14), which is called the conductor-like screening model for realistic solvation (COSMO-RS). COSMO-RS provides a novel, rather direct, and computationally efficient pathway from quantum chemistry to fluid phase thermodynamics that enables chemical and biochemical engineers to use the predictive power and broad applicability of modern QC methods for their needs. Many such engineers have taken up COSMO-RS enthusiastically, resulting in a large number of publications reporting successful applications in many different areas as well as in a few reimplementations of COSMO-RS, mostly by chemical engineering thermodynamics groups. This review will describe the basic steps of the COSMO-RS theory and its application potential.

THE CONDUCTOR REFERENCE STATE

From the perspective of dielectric theory, a vacuum with $\epsilon = 1$ and a conductor corresponding to a dielectric constant of $\epsilon = \infty$ are the ultimate extremes for the embedding of solutes. Whereas almost all computational chemistry methods start from the vacuum as reference, the COSMO-RS theory has introduced the state of molecules embedded in a conductor as a conceptually fruitful starting point for fluid phase simulations.

QC calculations combined with COSMO can calculate the state of a molecule in a conductor quite well. On the QC side the use of at least density functional theory (DFT) methods or Moeller-Plesset second order perturbation theory (MP2) ab initio theory is recommended because simpler levels, such as Hartree-Fock or semiempirical QC methods, do not provide sufficiently accurate electrostatics. The concept behind the QC/COSMO calculations required as input for COSMO-RS is rather simple. The calculations involve the following eight steps:

1. Choose a start geometry for the solute X under consideration.
2. A cavity defining the boundary of the conductor and divided in sufficiently small segments is constructed around the solute.

Quantum chemistry (QC): quantum mechanics applied to chemistry

CSMs: continuum solvation models

COSMO: conductor-like screening model

COSMO-RS: conductor-like screening model for realistic solvation

DFT: (electron-)density functional theory

MP2: Moeller-Plesset second order perturbation theory

OCE: outlying charge error

σ , σ' : the conductor polarization charge density on the surface of a molecule

3. An initial electron density is generated by the QC method.
4. The solute electrostatic potential arising from the atomic nuclei and the electron density is calculated on the grid of cavity segment centers.
5. The conductor screening charge density σ is calculated from the conductor boundary condition such that the total electrostatic potential arising from the solute and the polarization charges vanishes on the entire surface.
6. The polarization charges are included as external charges in the next step of the QC iteration, resulting in a modified electron density. Hence, Steps 4–6 are repeated until self-consistency is achieved.
7. A correction for outlying charge errors (OCEs) arising from the small portion of electron density outside the cavity is applied to the total energy and to the polarization charge densities.
8. The gradient of the total QC/COSMO energy is calculated analytically from the converged electron density and polarization charges, and a geometry step toward lower energy is performed. Steps 2–8 are iterated to self-consistency with respect to the solute geometry.

Finally, this algorithm yields the self-consistent state, i.e., the energy, the electron density, the polarization charge densities, and the geometry of the molecule in a virtual conductor. We will henceforth call this “the COSMO state.” All relevant information about the COSMO state is stored in a COSMO file.

In addition to the choice of the QC method, the ambiguous steps in the COSMO workflow are Step 2, the cavity construction, and the outlying charge correction in Step 7. The cavity usually is defined by the exterior of the atom-centered spheres. An important technical detail of the cavity construction is the method of smoothing along the crevices of intersecting spheres. Whereas such smoothing is essential for the numerical stability and physical consistency of the model, development of a robust smoothing algorithm yielding a continuous cavity is tricky. The details of the smoothing algorithms differ considerably, and this is a major source of differences in the results of different COSMO implementations. In addition, the OCE correction is treated differently in different implementations of COSMO. Although the COSMO algorithm is much less sensitive to the OCEs than other dielectric CSMs, in the context of COSMO-RS application of such OCE correction is strongly recommended. More details on cavity construction, smoothing algorithms, and OCE correction can be found in the book on COSMO-RS (13). In efficient implementations, QC/COSMO calculations usually only require approximately 20% more computation time than the corresponding gas phase calculations.

The conceptual value of the COSMO state as the reference state for molecules in the liquid phase was detected in the context of the COSMO-RS theory. In a perfect conductor all interactions are completely screened on the conductor interface, i.e., on the surface of the solute, by the conductor polarization charge density σ . Therefore, for an ensemble of molecules virtually swimming in a conductor, there are no intermolecular interactions. Hence, each molecule in the COSMO state can be considered individually. This decoupling makes the COSMO state an attractive, clean reference state.

THE MOLECULAR SURFACE INTERACTION CONCEPT OF COSMO-RS

In reality molecules are not swimming separately in a conductor bath but instead interact with each other. Starting from a reference ensemble of molecules swimming in a conductor in which each molecule has its COSMO energy and COSMO polarization charges, we can try to approximate a closely packed liquid system by the iterative introduction of molecular contacts. Thus, from

a thermodynamic point of view, COSMO-RS is based on a free enthalpy or Gibbs free energy concept of noncompressible fluids.

Let us first consider two molecules in the ensemble, A and B, which may be of the same or different types, and let us virtually reduce their distance until their COSMO surfaces touch each other, as schematically shown in **Figure 1**. Because there are no interactions between the conductor-screened molecules, there is no change in energy during their approximation. Only in the final step, when the molecules get in direct contact and the conductor between them is removed on a certain contact area a_{cont} , there is a sudden energy change because now the conductor screens the AB complex. Assuming that the dispersive interactions of A and B experienced through the contact area a_{cont} are the same as they were in the conductor, the energy change resulting from the contact can be split into two contributions arising from the electrostatics and from hydrogen bonding.

The electrostatic energy change is zero if the conductor polarization charge densities σ and σ' on the contact surface areas of A and B are exactly opposite, i.e., if $\sigma + \sigma'$ is zero, because then in total there is zero screening charge between the two molecules shortly before and after making the close contact. The electrostatic energy and the polarization charge densities on the remaining conductor surface do not change at all during such electrostatically optimal contact. In reality, the molecules in a liquid ensemble will indeed have a tendency to make contacts with oppositely polar surface pieces. But because of thermal fluctuations or a lack of appropriate partners, the sum of σ and σ' will not always be zero. Instead, some residual charge density, σ_{misfit} , must be taken into account. In general, the electrostatic energy difference between the AB complex and the individually screened molecules A and B that occurs during a contact of σ and σ' can be approximated as

$$E_{misfit}(\sigma, \sigma') \cong a_{cont} e_{misfit}(\sigma, \sigma') = \frac{1}{2} a_{cont} \alpha'_{misfit} (\sigma + \sigma')^2. \quad 1.$$

This is simply the energy required to neutralize the surface segment. The proportionality factor α'_{misfit} depends on the surface a_{cont} and takes into account the reduction in the neutralization energy arising from the electronic polarizability of the molecular environment. For most solvents the latter usually is well represented by an optical permittivity of 2.

If the two surface segments that make the contact belong to a hydrogen bond donating and accepting atom, respectively, in a second step the donor hydrogen atom will move closer to the acceptor and a hydrogen bond will be formed. The exact quantification of the energy gain that occurs with the formation of such a hydrogen bond requires a high level of quantum theory, and it would not be described accurately even by the DFT methods usually employed for COSMO calculations. Nevertheless, a bit more empirically, the hydrogen bond energy of a donor-acceptor contact gained after contact of the COSMO surfaces can be reasonably well quantified on the basis of the polarization charge densities σ and σ' of the contact segments because hydrogen bonds are formed only between surface segments of sufficiently strong and opposite polarities. Because the hydrogen bond energy increases with the polarity of both donor and acceptor, a simple expression such as

$$E_{bb}(\sigma, \sigma') \cong a_{cont} e(\sigma, \sigma') = a_{cont} c_{bb}(T) \min(0, \sigma\sigma' - \sigma_{bb}^2) \quad 2.$$

gives a reasonably accurate description of the hydrogen bond energy. The hydrogen bond threshold value σ_{bb} turns out to be in the range of 0.8–0.9 e nm⁻² (14). The coefficient c_{bb} depends on temperature, and this temperature dependence describes the entropy loss that goes along with the formation of a hydrogen bond, which results from the much stronger distance and orientation constraints of hydrogen bond contacts compared with the more floppy electrostatic contacts. Hence, strictly speaking, $E_{bb}(\sigma, \sigma')$ should be considered a hydrogen bond free energy. In summary, we have expressed the contact interaction energy of the conductor-embedded molecules A and B as

a_{cont} : the surface area of two molecules that is in contact with each other

a local interaction of the polarization charge densities σ and σ' of the two surface pieces of A and B that make the contact:

$$E_{\text{int}}(A, B) \cong E_{\text{int}}(\sigma, \sigma') = a_{\text{cont}} e_{\text{int}}(\sigma, \sigma') \cong E_{\text{misfit}}(\sigma, \sigma') + E_{\text{bb}}(\sigma, \sigma'). \quad 3.$$

With this expression for the first surface contact interaction energy, we can continue to create (virtually) one surface contact after another until intermolecular contacts replace the entire conductor. If we neglect the Coulomb interaction energy of all the misfit charge densities with each other, which usually is small as long as the misfit charge densities are not correlated, we have constructed a liquid-like model of an ensemble of densely packed molecules with a total interaction energy, which is expressed as a sum of local, pair-wise surface contact energies of COSMO polarization charge densities.

THE COSMO-RS STATISTICAL THERMODYNAMICS

Whereas the model considered above represents a single liquid-like configuration of our molecular ensemble, the only way to calculate the macroscopic thermodynamic properties of a liquid system is to apply statistical thermodynamics, i.e., to calculate thermodynamic averages over all possible configurations of the liquid. This is usually done by employing MC or MD techniques in the context of force field-based energy expressions. Such averaging always goes along with a loss of information. Motivated by the fact that the COSMO-RS energy expression, in contrast to force field energy expressions, does not explicitly depend on the full 3D geometry of the ensemble but is simply a sum of local surface contact energies, in COSMO-RS the complicated statistical thermodynamics of the nestled, 3D molecules is reduced to the much simpler statistical thermodynamics of independently pair-wise interacting surface pieces.

As preparation for this step, we introduce the concept of σ -profiles. The σ -profile $pX(\sigma)$ of a molecule X is the histogram of the molecular COSMO surface with respect to the polarization charge density σ , as shown schematically for the water molecule in **Figure 2**. A local average of σ is used to generate the polarization charge density, which is derived from the original polarization charge densities by averaging over the local neighbor segments using a Gaussian weight of width r_{av} . Although some reimplementations of COSMO-RS use a slightly larger averaging radius of 0.8 Å, we consider $r_{\text{av}} = 0.5$ Å to be the best value. The σ -profile of water shows two pronounced peaks with maxima at approximately -1.5 e nm^{-2} and $+1.5 \text{ e nm}^{-2}$, which result from the polar hydrogen atoms and the lone pair regions of the oxygen atom, respectively. In this picture we also introduce our color coding of the COSMO cavities with respect to σ , in which deep blue stands for a surface area with strongly negative polarization charge density σ , i.e., for strongly positively polar parts of the molecule; green for neutral parts of the surface; and red for strongly positive parts of the COSMO surface, i.e., strongly negative molecular surface regions. The sign inversion between the polarization charge density σ and the molecular polarity occurs because the conductor compensates for the molecular polarity through the opposite polarization charge density.

Figure 3 presents the σ -surfaces and σ -profiles of a few other compounds. The σ -profiles turn out to be valuable fingerprints of the molecular polarity. A detailed discussion of the various σ -profiles is given elsewhere (13).

Based on the individual σ -profiles of molecules, we define the σ -profile of a solvent or a mixture as

$$p_S(\sigma) = \frac{\sum_i x_i p^i(\sigma)}{\sum_i x_i A^i}, \quad 4.$$

$E_{\text{int}}(\sigma, \sigma')$:

interaction energy of surface segments with polarization charges σ and σ'

$e_{\text{int}}(\sigma, \sigma')$: surface-specific interaction energy of polarization charges σ and σ'

σ -profile [$pX(\sigma)$]:

the histogram of the molecular COSMO surface with respect to the polarization charge density σ of a molecule X

where x_i is the mole fraction of component i and A^i is the respective COSMO surface area. The surface normalization ensures that the same amount of surface always is considered in the statistical thermodynamics calculations. From this solvent σ -profile we can calculate a solvent σ -potential by integration over all potential partners σ' in the solvent S :

$$\mu_S(\sigma) = -\frac{kT}{a_{\text{eff}}} \ln \int p_S(\sigma) \exp \left\{ -\frac{a_{\text{eff}}}{kT} (e_{\text{int}}(\sigma, \sigma') - \mu_S(\sigma')) \right\} d\sigma. \quad 5.$$

$\mu_S(\sigma)$: the σ -potential of a solvent or mixture S

$p_S(\sigma)$: the σ -profile of a solvent or mixture S

Here the σ -potential $\mu_S(\sigma)$ is the specific chemical potential, i.e., the chemical potential per surface area, of a piece of surface of polarity σ in the solvent ensemble characterized by the solvent σ -profile $p_S(\sigma)$. In simple words, the σ -potential is a characteristic function of a solvent or mixture S that specifies how much it is attracted to a surface area of polarity σ . Equation 5 has been directly derived from the partition function of an ensemble of pair-wise interacting surface pieces of size a_{eff} . For a given interaction operator $e_{\text{int}}(\sigma, \sigma')$ it represents the exact statistical thermodynamics of such an ensemble. The effective contact area a_{eff} is a general parameter that represents the size of a thermodynamically independent contact. When optimized within a COSMO-RS parameterization (12, 14), it takes the quite reasonable value of $7.0 (\pm 0.5) \text{ \AA}^2$, corresponding to approximately six nearest-neighbor contacts for a molecule of the size of water.

Whereas the term $e_{\text{int}}(\sigma, \sigma')$ in Equation 5 represents the energetic costs of making a contact between σ and σ' , the appearance of $\mu_S(\sigma')$ in this location represents the cost in free energy that is required to release a piece of surface of polarity σ' from other contacts and make it available for contact with σ . Equation 5 was independently derived for ensembles of pair-wise interacting objects without any lattice concept. Later it was shown to be equivalent to the exact solution of a quasi-chemical lattice approach. Larsen & Rasmussen (15) published in 1986 a formal algorithm for the solution of the equation system of quasi-chemical lattice ensembles that is equivalent to Equation 5, but they did not introduce the conceptually helpful interpretation of segment chemical potentials.

The σ -potentials of some representative solvents are shown in **Figure 4**. The parabolic σ -potentials of hexane and benzene correspond to quasi-dielectric behavior, but with a significant and essential difference between hexane and benzene despite their almost identical macroscopic dielectric constant. This results from the broader σ -profile of benzene. The sharp decrease on the negative and positive ends in some σ -potentials reflects the hydrogen bond affinity with respect to donors and acceptors, respectively. The lower σ -potential of methanol compared with water in the donor range ($\sigma > 0.9 \text{ e nm}^{-2}$) reflects the larger donor affinity of methanol because it has only one hydrogen bond donor but two acceptor sites at its oxygen. As a consequence, the opposite can be observed for the acceptor affinity of methanol. Acetone exhibits a very strong hydrogen bond donor affinity but no affinity for acceptors because it does not have any donors that could form hydrogen bonds with acceptors. The σ -potential of nonpolar surfaces in water is much higher than in most other solvents. This reflects the hydrophobic effect of nonpolar molecular surfaces, which results from the extremely small amount of nonpolar surface area of water as well as the strong interactions of all polar surfaces in water. COSMO-RS in this way not only represents the hydrophobic effect in a natural way, but even correctly reproduces its entropic character, as has been shown in a study on the mutual solubilities of hydrocarbon compounds and water (16). We may conclude that σ -profiles and σ -potentials are extremely specific solvent and solute characteristics, respectively, that simultaneously describe solvent and solute behavior with respect to polar interactions, hydrogen bonding, and hydrophobic effects.

The final step in the COSMO-RS statistical thermodynamics procedure is the calculation of the chemical potential of a molecule X solvated in solvent S by the integration of the σ -potential,

i.e., by summation of the segment chemical potentials, over the surface of the solute X :

$$\mu_s^X = \int p^X(\sigma) \mu_s(\sigma) d\sigma + kT \ln \gamma_{comb}(X, S). \quad 6.$$

VLE: vapor-liquid equilibrium

SLE: solid-liquid equilibrium

This is a pseudochemical potential in the sense of Ben-Naim (17), i.e., the trivial mole fraction term $kT \ln(x)$ is omitted. In this article we will always use the expression “chemical potential” in this sense. The first term in Equation 6, which results from the interactions of solute X in solvent S and is described by the COSMO-RS σ -potential, would be considered the “residual part” of the chemical potential in the notation of the chemical engineering literature. The second term, the “combinatorial contribution,” describes the solute and solvent size dependence of the chemical potential, i.e., even in noninteracting liquids the chemical potential of a large molecule in one mole of small molecules is different from the chemical potential of a small molecule in one mole of large molecules, although this difference is small for typical solute-solvent size ratios up to a factor of 10. The COSMO-RS formalism itself would not describe such effects without a combinatorial term. Usually in COSMO-RS combinatorial terms rather similar to standard approaches from the chemical engineering literature are used for this purpose, as they are based on the surface areas and volumes of solute and solvent molecules. In the context of COSMO-RS, these areas and volumes are routinely taken from the COSMO cavities, which are available as a by-product of the COSMO calculation. The original size-correction term used in COSMO-RS versions up to the year 2000 (12, 14) was developed without the knowledge of the chemical engineering combinatorial terms and had a weak Gibbs-Duhem inconsistency, which was detected first by G. Krooshof (private communication, 2000), and later pointed out by Lin & Sandler (18).

Equation 6 is the central equation of the COSMO-RS approach. For incompressible liquids, it provides the chemical potential of an almost arbitrary solute X in an almost arbitrary liquid solvent or mixture as a function of temperature and concentration. Starting from the COSMO information on the pure compounds, it gives access to almost all thermodynamic liquid phase equilibrium properties of pure compounds and mixtures, e.g., activity coefficients, partition coefficients, enthalpies and entropies of mixtures, and many more. From a chemical thermodynamics point of view, the COSMO-RS concept derived in the previous sections is a free enthalpy or Gibbs enthalpy model of noncompressible fluids.

COSMO-RS GAS PHASE AND SOLID PHASE TREATMENT

As explained before, COSMO-RS is a theory about molecules in the liquid phase. But many important thermodynamic properties, such as vapor pressures, partial pressures, and Henry’s law constants, as well as vapor-liquid equilibrium (VLE) phase diagrams, refer to the gas phase, and many others, especially the solubilities of crystalline compounds, involve solid-liquid equilibria (SLE). For these cases COSMO-RS needs methods to estimate the involved free energy differences.

In contrast to simpler models such as UNIFAC, COSMO-RS can estimate the free energy of a compound in the ideal gas. The basic information necessary for this calculation is the quantum chemical energy difference between the vacuum reference state and the conductor reference state, i.e., the COSMO solvation energy at $\epsilon = \infty$. This includes all contributions to the free energy of phase transfer arising from the polarity and polarizability of the solute. We need to supplement this with a simple nonelectrostatic contribution representing dispersive or van der Waals (vdW) interactions, a small correction for ring structures, and a constant that connects the reference state in the ideal gas state, which we chose to be 1 bar, with the reference state in the liquid state, which we consider to be 1 mol/mol. In summary, we obtain

the expression:

$$\mu_{Gas}^X = E_{vac}^X - E_{COSMO}^X + c_{disp}(T) \sum_{\alpha} A_{\alpha}^X \tau_{el(\alpha)} - \omega n_{ring}^X + \eta_0(T). \quad 7.$$

Nevertheless, if the vapor pressure of the pure compound is available for compound X , which often is the case, it is strongly recommended to use the activity coefficients calculated by COSMO-RS in combination with the experimental vapor pressure for the evaluation of all VLE-related properties because this avoids the additional prediction error arising from Equation 7. Equation 7 does not take into account any gas phase nonidealities such as the dimerization of organic acids. If such are considered to be relevant, they need to be added externally starting from the ideal gas reference state.

The situation is similar, but somewhat worse, for SLE calculations, which require the chemical potential difference of the compound between the liquid and the crystalline phase. Despite remarkable recent progress (19), in general the prediction of the chemical potential of molecules in their crystalline phase is a rather unsolved task because it requires the prediction of the crystal structure and free energy of the potential polymorphs as an initial step. The prediction of the free energy differences between the liquid and solid state from first principles is currently impossible. Therefore, for SLE calculations with COSMO-RS the usage of an experimental estimate for the fusion free energy ΔG_{fus}^X based on the melting point and the heat of melting according to

$$\Delta G_{fus}^X(T) = -\Delta H_{fus}^X \left(1 - \frac{T}{T_{melt}^X}\right) + \Delta C p_{fus}^X (T_{melt}^X - T) - \Delta C p_{fus}^X T \ln \frac{T_{melt}^X}{T} \quad 8.$$

is strongly recommended. For high melting compounds, such as drugs and many fine chemicals, if possible the next order correction, including the heat capacity change of fusion $\Delta C p_{fus}^X$, should be used as well, but unfortunately this is rarely available from experiment. As a last resort, and owing to the practical importance of drug solubility predictions, a heuristic estimate of ΔG_{fus}^X based on COSMO-RS descriptors

$$\Delta G_{fus}^X(298K) \cong 12.2V_{COSMO}^X - 0.76N_{ringatom}^X + 0.54^* \mu_{water}^X \quad 9.$$

has been developed for usage in the context of solubility predictions of drug-like compounds (20). The three descriptors are the COSMO volume, the number of ring atoms, and the COSMO-RS chemical potential of the compound in water, representing size, rigidity, and a mixture of polarity and hydrogen bonding, respectively. This simple quantitative structure-property relationship (QSPR) expression gives a reasonably accurate and robust description of ΔG_{fus}^X at room temperature for many neutral drug and pesticide data sets, but because of its purely heuristic nature this approximation cannot claim general applicability. It also should not be considered part of the COSMO-RS method itself. In summary, for SLE calculations with COSMO-RS, one has the choice only between an often insufficient temperature extrapolation based on experimental melting information or heuristic methods such as the QSPR presented in Equation 9.

In combination with these estimates for the ideal gas and solid state chemical potentials, COSMO-RS can be used to calculate all kinds of VLE, liquid-liquid equilibrium (LLE), and SLE properties.

COSMO-RS PARAMETERIZATIONS AND IMPLEMENTATIONS

COSMO-RS requires several adjusted parameters, although far fewer than other models used in chemical engineering. For example, the mod-UNIFAC method (21) requires roughly 10,000 parameters, of which only approximately 50% are available. Furthermore, the COSMO-RS

ΔG_{fus}^X : Gibbs free energy of fusion, i.e., the free energy difference between a compound's crystalline and liquid states

QSPR: quantitative structure-property relationship

LLE: liquid-liquid equilibrium

parameters usually are at most element-specific and hence rather universally applicable. This may allow COSMO-RS to appear almost *ab initio* from a chemical engineer's perspective.

Indeed, not even the QC underlying COSMO-RS is parameter-free because usually DFT is employed to generate the COSMO files containing the COSMO polarization charge densities. DFT calculations require the choice of a density functional, and the commonly used DFT functionals include some empirical parameters. Because these are not fitted to fluid phase properties, they need not be considered parameters of COSMO-RS. Interestingly, the performance of almost all state-of-the-art density functionals with respect to the quality of the COSMO-RS predictions is quite similar. Semi-empirical QC methods such as AM1 (Austin Model 1), which was used in the first COSMO-RS publication, do not yield sufficient electrostatic quality and hence are considered less suitable for COSMO-RS calculations. Conversely, MP2-COSMO calculations have been tested and do yield comparable quality with respect to COSMO-RS results from DFT/COSMO calculations, but they are not recommended because of the higher computational demands. A further degree of freedom in the COSMO calculations is the choice of the basis set. Different classes of basis sets are used or favored in different QC programs. For these kinds of solvation calculations, basis sets of triple- ζ polarization level are a reasonable trade-off between accuracy and computation time. Larger basis sets usually do not yield better results.

Of strong influence on the quality of COSMO-RS predictions is the set of radii used for cavity definition in the QM/COSMO calculations. In the context of COSMO-RS, the COSMO radii usually are considered to be element-specific and independent of the local bonding pattern and charge status of an atom. All COSMO-RS parameterizations and implementations use the same set of COSMO radii, published in the first quantitative COSMO-RS paper (14), which were obtained from a computationally intensive optimization. These element-specific COSMO radii exhibit a rather systematic correlation with the Bondi radii (22) widely used in chemical engineering, namely that the COSMO radius is quite systematically $17(\pm 2)\%$ larger than the corresponding Bondi radius. This increase is understandable, as the COSMO radii represent average distances to the neighbor cavity instead of nearest neighbor atom distances.

Other details of the cavity construction in the COSMO step are of less crucial importance. The "solvent radius," which is usually set equal to the hydrogen COSMO radius, is just a technical parameter for the smoothing of the COSMO surface in the intersection region of the atomic spheres. The details of the smoothing algorithm can be important. σ -profiles generated from GEPOL cavities in the C-PCM algorithm (23, 24) exhibit significantly different features than σ -profiles derived from the standard COSMO implementations, but often these differences are smoothed out during the thermodynamic averaging.

Some of the quite well-defined parameters of COSMO-RS, such as the averaging radius r_{av} , the contact area a_{eff} , and the hydrogen bond threshold σ_{hb} have been discussed in the previous sections. The misfit energy coefficient α'_{misfit} is of high importance for COSMO-RS results. To first order it is quite reproducible and is in reasonable agreement with a crude estimate that can be derived from simple electrostatic arguments. But in detail it depends on the level of quantum chemistry used for the generation of the COSMO files, and it is able to compensate for small, systematic under- or overestimations of molecular polarities resulting from different quantum chemical methods and basis sets. The same is true for the hydrogen bond coefficient $c_{hb}(T)$.

Whereas the COSMO radii, the cavity construction details, and the averaging radii have not been altered since the first COSMO-RS parameterization (14), the other COSMO-RS parameters are often readjusted using a reasonably large set of experimental data of great solutes and solvent chemical diversity. For the COSMO $therm$ line of parameterizations (25), currently a data set consisting mostly of room-temperature partition coefficients, $\Delta G_{hydration}$, and vapor pressures is used; this is similar to, but approximately twice as large as, the data set used in the first quantitative

COSMO-RS parameterization (14). The temperature-dependent parameters are fitted only to vapor pressures because the largest amount of reliable temperature-dependent data is available for vapor pressure.

Apart from several more investigatory parameterizations on other QC levels, DFT functionals, and basis sets, the three main parameterizations supported by Klamt et al. are the BP-TZVP parameterization, the AM1-BP-SVP parameterization, and the DMol³ parameterization (25–28). The first is the standard, suggested for all problems in which the number and size of the involved compounds allow for a full DFT geometry optimization. The required DFT/COSMO geometry optimizations can be most efficiently performed with TURBOMOLE (29), but a few other QC programs allow for the generation of equivalent BP-TZVP-COSMO files of almost identical quality. The AM1-BP-SVP parameterization has been introduced for projects involving large numbers of larger, novel compounds in which the computational demands for full DFT/COSMO geometry optimizations for all compounds may be prohibitive. Therefore, the geometry optimization is performed on the semiempirical QC level using the AM1 method (30) together with COSMO within the MOPAC7 program (31), which is supplemented by some molecular modeling corrections for a few notorious geometry flaws in semiempirical methods. The AM1/COSMO geometries combined with single point BP-SVP DFT/COSMO calculations yield a rather good COSMO-RS parameterization, slightly less accurate than the BP-TZVP standard, but at only a few percent of the computation costs. DMol³-COSMO files were used in the first quantitative COSMO-RS parameterizations. Although these are computationally somewhat less efficient than our current TURBOMOLE BP-TZVP standard, in terms of accuracy the DMol³-COSMO files remain an excellent basis for COSMO-RS parameterizations.

Several reimplementations of COSMO-RS have been developed in recent years. The first was the reimplementation published by Lin & Sandler as COSMO-SAC (18), where SAC stands for “segment activity coefficients.” A second reimplementation was published by Grensemann & Gmehling as COSMO-RS(OI) (32). Banerjee et al. published another reimplementation of COSMO-RS along with several chemical engineering applications (33) with special emphasis on ionic liquids. The most recent reimplementation of COSMO-RS was published by Pye et al. (34). Although the reimplementations are based on different DFT-COSMO programs and methods and although some of them include minor modifications of the original COSMO-RS concept, all confirm the overall robustness and reproducible quality of the COSMO-RS concept. Nevertheless, some comparisons (35, 36) of the COSMO^{therm} parameterizations with available reimplementations indicate that the latter do systematically underestimate large infinite dilution activity coefficients, most likely owing to an underrepresentation of such cases in their parameterization data sets.

Within the line of COSMO-RS parameterizations available through the COSMO^{therm} program (25), several additional features have been introduced on top of the basic COSMO-RS concept. The most important of these are the self-consistent treatment of multiple conformations (see below), the introduction of a second polarization charge density averaged over a larger vicinity of a segment to take into account some correlation effects of the polarization charge densities, and the introduction of nonadditive vdW-interactions for some pairs of elements, especially fluorine interactions. The latter are crucial to describe the nonideal behavior and miscibility gaps in alkane-perfluoroalkane mixtures. To our knowledge, these improvements on the initial COSMO-RS concept are not available in the COSMO-RS reimplementations.

The overall accuracy of COSMO-RS, quantified as the root mean squared deviation (RMSD) of transfer free energies or enthalpies of neutral compounds, was ~ 1.7 kJ mol⁻¹ in the first quantitative DFT-based COSMO-RS parameterization and has improved to approximately ~ 1.3 kJ mol⁻¹ in recent COSMO^{therm} parameterizations. The relatively small improvements

achieved in recent years, together with estimates of the electrostatic accuracy of DFT methods, indicate that this is about the limit of accuracy that can be expected for COSMO-RS based on DFT/COSMO. The accuracy varies for different classes of solutes and solvents and for the properties considered. Obviously, transfer free energies and equilibrium constants between polar and nonpolar solvents, or polar solvents and molecules in the gas phase, are subject to larger errors than are activity coefficients in mixtures of similar liquids. Hydrogen bonding systems tend to show larger errors because of the more empirical nature of the hydrogen bond interaction expression compared with the misfit energy expression. Nevertheless, in general COSMO-RS is quite good at predicting the properties of aqueous systems.

In a recent validation the *COSMOtherm* implementation of COSMO-RS yielded an error of only 2.0 kJ mol⁻¹ (mean unsigned error) on a data set of almost 2,500 free energies of solvation (37) that had been collected for the parameterization of the SM8 solvation model (38). Although not trained on this data set, *COSMOtherm* still outperformed SM8 and the other solvation models tested. In addition, some data of questionable experimental quality were included in this data set and contributed considerably to the average error.

CONFORMATIONS

In the initial versions of COSMO-RS and the reimplementations published so far, each compound is represented by a single COSMO file. Although this is not a problem for rigid and for many small compounds, it becomes problematic for flexible molecules, which may have several or even a huge number of meta-stable geometries, called conformations. Especially if the relative orientation of polar functional groups differs in the conformations or if intramolecular hydrogen bonds can be formed, the energies and σ -profiles of such conformations can be significantly different. This may lead to the situation that the free energy of one conformation is lowest in one solvent and another conformation is lowest in a second solvent. Therefore, for a consistent treatment it is necessary to take into account not just one but an ensemble of conformations, including all those that may be of low free energy in polar or nonpolar solvents. Because the total free energy of each conformation in any solvent or mixture *S* is available within COSMO-RS as a sum of its DFT/COSMO energy in the conductor reference state and its individual pseudochemical potential according to Equation 6, the relative weight of each conformation follows from Boltzmann statistics, and all of the thermodynamic properties of a multi-conformational compound can be evaluated as the corresponding averages (13). Because the chemical potentials depend on the average σ -profile of a system *S*, and because the latter via the Boltzmann weights depends on the chemical potentials, an additional self-consistency loop is required for the thermodynamically consistent treatment of systems with multi-conformational compounds.

For molecules with several rotatable bonds, the search for the conformations required for a consistent treatment can be very demanding. Klamt and coworkers have recently developed an automated procedure named *COSMOconf* (39). In contrast to standard conformational search tools, *COSMOconf* is especially designed for finding the low energy conformations in both polar and nonpolar solvents. Arlt and coworkers have published another strategy for conformation generation and selection for COSMO-RS calculations that involves MC simulations (40).

AUXILIARY TOOLS AND TECHNICAL EXTENSIONS OF COSMO-RS

For the efficient usage of COSMO-RS, databases of precalculated COSMO files for common solvents and other common compound classes are valuable. The largest such database, which

includes multi-conformational COSMO files for almost 5000 compounds, is *COSMObase* (41), and its extension to ionic liquids, *COSMObaseIL*, contains the COSMO files for most widely used anions and cations used for ionic liquids. Another database of approximately 1800 σ -profiles has been developed in the context of COSMO-SAC (42), which is based on DMol³/COSMO calculations. For most compounds, this database takes into account only a single conformation per compound, and it is still not completely consistent in the choice of conformation.

As is true of any G^E-model, COSMO-RS is limited to incompressible, dense liquids. Several groups have presented combinations of COSMO-RS with EoS or hole theory (42–49), to extend its applicability toward critical or near-critical liquids. Currently experience is insufficient to decide which of these combinations is most generally applicable.

As described above, the COSMO-RS method was mainly developed for the prediction of fluid phase equilibrium properties of molecules in bulk, homogeneous liquids. Recently it has been extended to the simulation of molecules at liquid-liquid and liquid-vapor interfaces (13) by using the σ -potential $\mu_S(\sigma)$ of phase *S* for that part of the solute surface that is in phase *S*, and the σ -potential $\mu_{S'}(\sigma)$ of the other phase *S'* for that part of the solute surface that is in *S'*. By sampling all possible positions, orientations, and conformations, this leads to the partition sum of the solute at the interface and provides useful information about the binding of compounds to interfaces. Generalization of this idea to multiple phases and consideration of micellar systems as layered liquids led to the development of the *COSMOmic* extension (50) of COSMO-RS, which allows the prediction of free energies and the partition behavior of compounds in micellar systems. It has been validated on the biologically important case of biomembranes, i.e., aqueous 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) bilayers, where it not only well predicts without any adjusted parameters the biomembrane-water partition coefficients, but also provides efficient access to the free energy profiles of compounds that pass through the membrane, and thus provides important information about the cell permeability of drugs and other physiologically important compounds.

Although COSMO-RS is quite generally applicable to all partitioning problems involving chemically well-defined phases, a slightly more empirical extension, the σ -moment approach, was required to apply it to many important partitioning and adsorption problems in which one or both phases are less well defined. Although derived from theory, σ -moments have been shown to be strongly related to Abraham's empirical solvation parameter approach (51). The σ -moment approach has been successfully applied to such diverse problems as adsorption to activated carbon, blood-brain partitioning, intestinal absorption, soil-sorption, adsorption to cotton or hair, and many others (52–55).

Whereas in its original form COSMO-RS can be applied only to molecules of limited size that can be treated by quantum chemistry, two extensions have applied the method to large periodic structures such as thermoplastic polymers or crystal surfaces. One uses the periodic boundary conditions during the DFT/COSMO calculations as they are enabled in the DMol³ program (56). The other is the atom-weight technology implemented in the *COSMOtherm* code, which allows the COSMO screening charges of the relevant repeat unit to be cut out of the COSMO files of oligomers or surface clusters. Thus COSMO-RS can be applied to the prediction of solubilities in polymers and to the calculation of the free energies of crystal faces in solution (57).

To overcome the need for potentially time-consuming DFT/COSMO calculations, the *COSMOfrag* method (58) has been developed. In less than a second it generates an approximate σ -profile of a new compound from a huge database of precalculated COSMO files of diverse compounds, which can then be used for most COSMO-RS applications. *COSMOfrag* can be useful in large-scale screening applications such as those in drug design.

Because of their large information content and the general importance of σ -profiles for the physicochemical and physiological behavior of chemical compounds, it is often interesting, especially in drug design, to analyze or screen compounds with respect to σ -profile similarity. For this purpose a robust σ -profile similarity measure and a fast screening technology called COSMOsim (59) has been developed that allows efficient screening of millions of compounds. An extension of COSMOsim to 3D similarity is under development.

Although it is an almost straightforward application of COSMO-RS, it is worth mentioning the extension to the calculation of protonation and dissociation free energies and hence pK_a values in aqueous and nonaqueous solvents (60–62), which unfortunately requires some empirical scaling. Nevertheless, this extension can provide useful information about the protonation equilibria of demanding and complicated compounds, which often are of technical or physiological importance.

APPLICATION RANGE AND USER GROUPS

Since the original development of COSMO-RS, which was mainly focused on solvation free energies, vapor pressures, and partition coefficients (12, 14), it has been used for the prediction of a wide range of fluid properties by many different user groups. It is impossible to report all applications here. Therefore, we will try to give a representative overview.

The most important application area has become chemical engineering thermodynamics, as it is required for process design and development. Although out of the focus of the original developers, Clausen and Arlt opened this application area in 1998 with the pioneering application of COSMO-RS to the calculation of binary VLE diagrams (63, 64), which demonstrated the striking predictivity of COSMO-RS in such applications even though it was neither developed nor parameterized for binary mixtures. Shortly afterward, starting with BASF, DuPont, Bayer, and Degussa (65–68), many chemical engineering groups in chemical companies recognized the predictive potential of COSMO-RS, especially for more demanding compounds for which other methods fail, and they started to use it in chemical process design and development, especially for the screening and design of solvents and entrainers. The industrial usage of COSMO-RS achieved further impact through its success in the first Industrial Fluid Property Simulation Challenge (IFPSC) (69, 70), where COSMO-RS outperformed force field–based simulation methods in the prediction of previously unpublished VLE data. In the fifth IFPSC two COSMO-RS contributions, one using COSMO-SAC and the other COSMOtherm, were ranked first and second, respectively. In addition, the number of academic chemical engineering institutes using COSMO-RS for LLE, VLE, and SLE applications is continuously growing, as reflected by a broad variety of applications (e.g., 71–73).

Since 2002 COSMO-RS has gained attention in the field of ionic liquids, where it proved to be able to make reasonably accurate predictions of the activity coefficients of solutes in ionic liquids without any adjustments or reparameterization. Because all other methods are much harder to apply to ionic liquids, COSMO-RS is now widely used for the screening of suitable ionic liquids for certain separation and reaction problems (33, 74–82).

Beyond such more or less standard VLE, SLE, and LLE applications, COSMO-RS has been used for the simulation of more demanding separation and reaction systems, such as polymer membranes, activated carbon, micellar systems, and hyperbranched polymers, as well as for chromatographic separation processes such as high pressure liquid chromatography (HPLC), reverse phase HPLC, and supported ionic liquid phase (SILP) (53, 83–87). Many of these innovative applications have been developed by the Arlt group.

A second important application area and user group has developed in the field of consumer and personal care product research, i.e., in the area of cleaners, shampoos, soaps, perfumes, etc.

In this field COSMO-RS is used to calculate the solubilities and partition behavior of the various components in the often very complex liquid phases as well as to estimate the binding of the ingredients to target phases such as skin, hair, and cotton (55, 88, 89). In this context the σ -moment approach and the COSMOmic extension are often useful. Because many of the complex phases are often simulated with mesoscopic simulation techniques, such as the mesoscopic dynamics simulation method (MESODYN) or the dissipative particle dynamics (DPD) method (90), quite recently COSMO-RS has begun to be used for the estimation of the interaction parameters required for such simulations (91).

Another important application area is pharmaceutical and agrochemical research, in which COSMO-RS is used for solubility predictions, pK_a predictions, the determination of various physiological partition properties including σ -moment approaches, and drug similarity studies (20, 59, 60, 92, 93). Nevertheless, the technically most important application in this sector appears to be solvent screening in the early drug development phase, in which COSMO-RS can provide robust predictions of the relative solubility of a drug candidate in a large number of solvents and thus help to identify the most promising solvents for purification and recrystallization without time-consuming and often expensive experiments (94–96).

Finally, it is worth mentioning the application area of environmental research, which was an early starting point for the development of COSMO and COSMO-RS. Reasonable estimates of vapor pressures, partition coefficients, and pK_a values of very diverse compounds in often extremely complex environmental phases or at interfaces are of crucial importance for the estimation of the fate of chemical compounds entering the environment in various ways. Although simple classification and group contribution methods are still most widely accepted in this politically sensitive area, COSMO-RS is getting increasing attention in this context as a result of its broader, much more fundamental, and more general applicability to a wide range of environmentally relevant compounds and properties (97–101). An interesting example is the pK_a of the industrially and environmentally important perfluoro-octanoic acid (PFOA). Using COSMOtherm, Goss & Arp predicted a pK_a value of 0.7, whereas experiments and some classification methods suggested a value near 3 (102). More recent experiments appear to confirm the lower value of the COSMO-RS predictions, leading to a substantially different picture for the environmental transportation mechanism of PFOA.

LIMITATIONS

Despite its broad applicability, COSMO-RS, like any other model, obviously has its limitations. The most annoying and unexplainable limitation of COSMO-RS is its inability to correctly represent the interactions of secondary and tertiary amines with hydrogen bonding solutes or solvents.

Another important limitation is the accuracy of the chemical potential calculation, which even optimistically should not be expected to be better than 0.8 kJ mol^{-1} , without a perspective to become much more accurate in the near future. This clearly excludes COSMO-RS from many applications in process development that require much better accuracy. In the foreseeable future such high accuracies cannot be provided by any a priori predictive method but instead require group contribution or other empirical models that are specially parameterized on accurate experimental data for similar systems.

A general limitation is the already-mentioned restriction to incompressible liquids, which can only be overcome through combination with EoS or by a hole theory extension. Despite several successful applications to ionic systems (see, for instance, the example given in the Prediction of the Free Energy of Transfer of Ions sidebar, below), COSMO-RS is not capable of describing

PREDICTION OF THE FREE ENERGY OF TRANSFER OF IONS

In 2007 Frank Marken presented a demanding challenge for COSMO-RS. He wanted to compare the free energies of transfer of a diverse set of ions measured by voltammetry with the predictions made by COSMO-RS. The set of ions consisted of 18 anions, ranging from simple ions, such as Cl^- and BF_4^- , to highly flexible organic ions, such as singly, doubly, and triply charged citrate. The ion transfer from water to the organic solvent 4-(3-phenylpropyl)pyridine (PPP) was measured. The initial comparison exhibited an excellent correlation between the experimental and calculated transfer free energies, but a closer look disclosed a systematic overestimation of these energies by a factor of two. As a possible explanation of this overestimation we suggested the water content of the organic phase, of which the experimentalists were not aware. COSMO-RS predicted a considerable water content of 45 mol% for water-saturated PPP. An experimental determination yielded a slightly larger water content of 55 mol%. Including the water content of PPP into the COSMO-RS calculations of the free energies of transfer of the ions yielded a regression with the expected correct slope of the experimental versus calculated energies (103). Hence, COSMO-RS elucidated the crucial role of small water contents for the solvation of ions.

general electrolyte thermodynamics. This is partly because of the neglect of long-range ion-ion interactions and partly because of the extreme polarization charge densities σ appearing on small, highly charged ions, for which the approximations made in the relatively simple misfit and hydrogen bond interactions derived on neutral compounds may no longer be sufficiently accurate. As a general rule, COSMO-RS describes ionic systems better the more the charge on the ions is delocalized, i.e., the smaller the surface polarization charge densities are. This explains the success for ionic liquids, which usually have well-delocalized charges. Another limitation arises from the restriction to electrostatic, hydrogen bonding, and dispersive interactions; this excludes the treatment of many important transition metal complexes, which may interact with surrounding solvent molecules via orbital interactions or charge transfer.

Although COSMO-RS can straightforwardly treat single strong hydrogen bond interactions without the need for additional association corrections, COSMO-RS cannot by itself describe systems in which a geometrical coordination of strong interactions is of importance, as in carboxylic acid dimerization, complexation to crown ethers or other chelates, or drug-receptor binding. In many such cases, as well as in many cases of strong ions and metal complexes, the limitations of COSMO-RS can be overcome by including one or several of the solvent molecules in a solute-solvent cluster and then treating this by QM/COSMO first and by COSMO-RS in a second step. But such cluster-COSMO-RS applications require quantum chemical and thermodynamic expertise and are not recommended for occasional COSMO-RS users.

With respect to properties, COSMO-RS itself is restricted to fluid phase equilibrium properties and cannot describe any dynamic, transport or structural properties of liquid systems. Nevertheless, some of the equilibrium information derived from COSMO-RS may be useful in estimation of other properties, as has been shown in the case of viscosity and density predictions. Finally, it should be kept in mind that COSMO-RS usually is parameterized on room-temperature data and vapor pressure information. Hence, it is most accurate in the temperature range of -50°C to 200°C and should be used with caution outside this range.

CONCLUSIONS AND OUTLOOK

During the past 15 years the COSMO-RS method has become established as an additional research tool for the investigation of molecular thermodynamics in liquid systems, filling a gap between the

simplifying group contribution-based approaches and the demanding force field-based molecular simulation methods. Although COSMO-RS is a bit less accurate than group contribution methods based on experimental data in their core region, the special strengths of COSMO-RS are its robustness and its potential for extrapolation into new areas of chemistry and chemical engineering and toward properties not considered during the initial development of COSMO-RS. These strengths result from the theoretically sound combination of quantum chemistry with statistical thermodynamics. Owing to its predictive potential, COSMO-RS is an ideal tool for the generation and validation of new ideas and for the screening of new alternatives in the early stage of research projects.

Beyond the core application area of bulk fluid phase equilibria, many extensions toward a broader range of application areas have been developed. One direction is the σ -moment based QSAR extension for complex partition properties such as adsorption to activated carbon, blood-brain partitioning, and other medicinal and biochemical partition parameters. Other examples are the extensions toward inhomogeneous systems such as interfaces, micelles, and biomembranes; COSMOmic; the high throughput module COSMOfrag; and the related extension toward drug similarity screening, COSMOsim.

A special strength of COSMO-RS is its conceptual simplicity and graphicness. Starting from the molecular σ -surfaces resulting from the initial quantum chemical COSMO calculations, the relevant thermodynamic conclusions can be intuitively drawn from the σ -profiles and σ -potentials to yield entire phase diagrams. Because all the relevant interactions and thermodynamic phenomena, such as polar interactions, hydrogen bonding, hydrophobicity, entropy, and enthalpy, are covered within this simple concept, it is well suited as an educational tool for molecular thermodynamics, allowing students to qualitatively and quantitatively infer the pathway from molecules to phase diagrams and to understand why some molecules like each other, whereas others do not.

SUMMARY POINTS

1. Quantum chemical calculations on molecules in a virtual conductor (COSMO) yield valuable reference information for molecules in the liquid phase.
2. COSMO polarization charge densities can be used to quantify molecular surface interactions.
3. COSMO-RS statistical thermodynamics of surface pairs converts the surface interactions into chemical potentials, and these lead to all equilibrium-related liquid phase thermo-physical properties.
4. COSMO-RS is widely used in process design and development for solvent and solubility screening, including for ionic liquids.
5. COSMO-RS can also be used for the exploration of more advanced topics, such as pK_a prediction; partition behavior at liquid interfaces, in chromatographic systems, in micelles, and in biomembranes; partitioning and adsorption involving complex pseudophases; and even for similarity evaluation in drug design.
6. COSMO-RS provides a graphic bridge from molecules to liquid phase thermodynamic properties and phase behavior, which can be used for teaching molecular thermodynamics.

FUTURE ISSUES

1. For an overall improvement of the accuracy of COSMO-RS, a combination with a more accurate but still computationally affordable quantum chemical method than DFT is required.
2. More detailed and accurate σ -based expressions for the hydrogen bond interactions need to be developed.
3. A more sophisticated description of ion interactions, including long-range ion-ion interactions and better expressions for strong surface interactions, is required for a more general applicability of COSMO-RS to ionic and electrolyte systems.

DISCLOSURE STATEMENT

A.K. and F.E. are commercially developing and distributing the COSMO $_{therm}$ implementation of COSMO-RS at COSMO $_{logic}$ GmbH & Co. KG.

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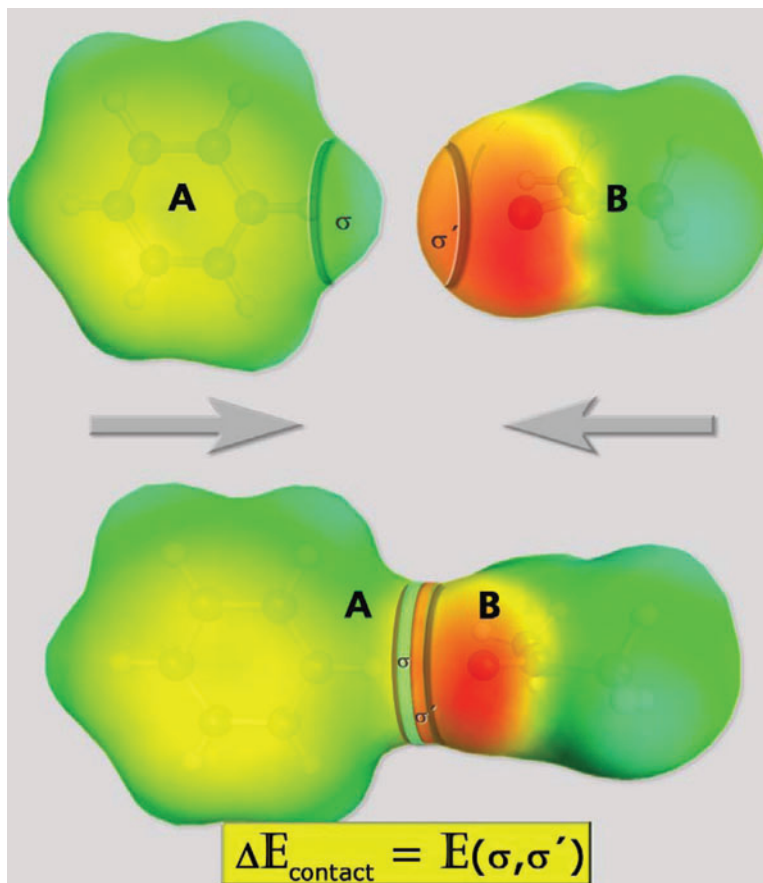


Figure 1

A schematic visualization of the COSMO-RS interaction concept.

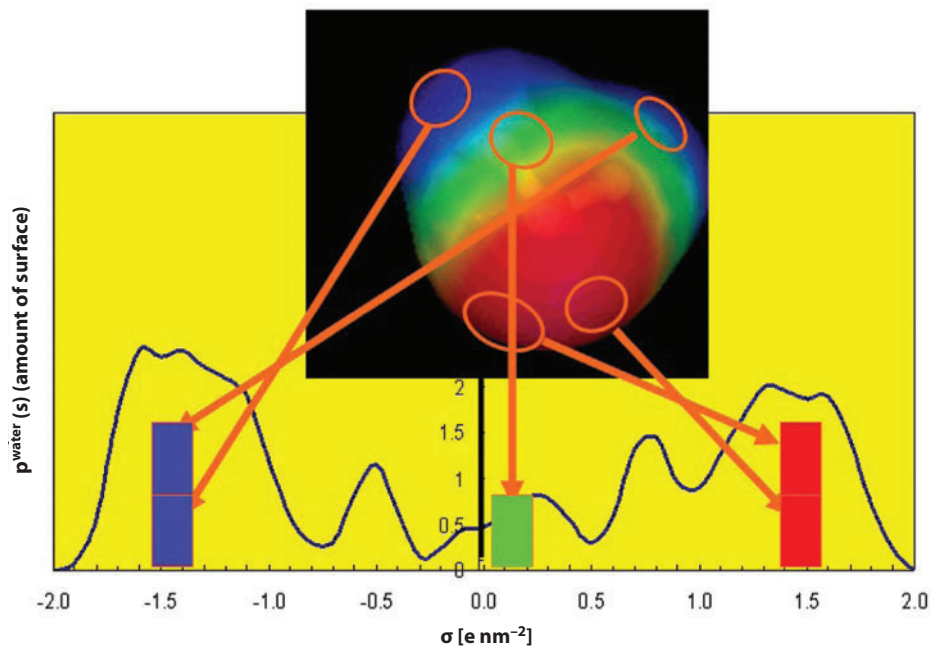


Figure 2

The σ -profile of water. Originally published in Reference 13. Copyright © Elsevier 2005.

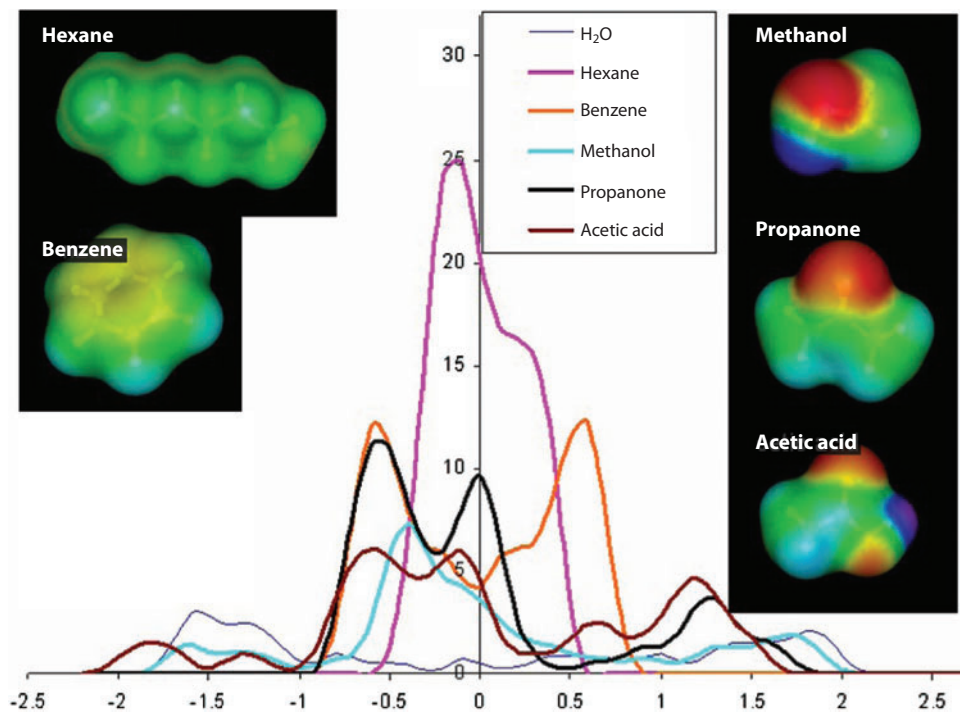


Figure 3

The σ -profiles of common compounds. Originally published in Reference 13. Copyright © Elsevier 2005.

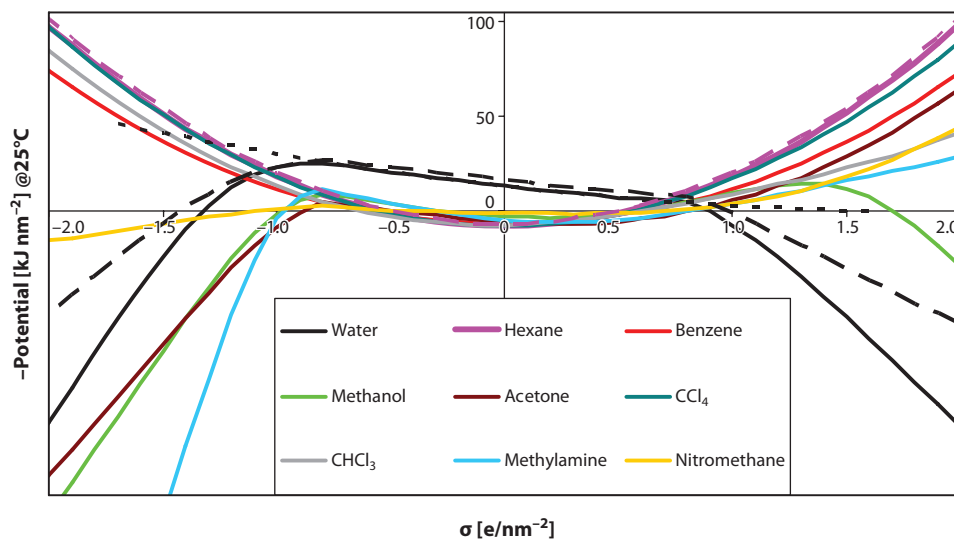


Figure 4

The σ -potentials of representative solvents at 25°C (and 100°C, dashed curve). Originally published in Reference 13. Copyright © Elsevier 2005.



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Errata

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