

Illustrating Computational Solvent Screening: Prediction of Standard Gibbs Energies of Reaction in Solution

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Prediction of thermodynamic properties of new compounds or mixtures is industrially important, especially when processes are established or alternatives for existing processes are evaluated. Of particular importance is the equilibrium constant, derived from the standard Gibbs energy of reaction in solution. Up to date, experimental determination is challenging, mirrored by a lack of data available. A straightforward computational way for the prediction using quantum mechanics and statistical thermodynamics is presented. The use of three standard quantum chemical methods for the determination of the ground state energies enables a comparison in terms of accuracy and computational cost. The results show that the two most laborious methods coupled cluster with single and double excitations and perturbative triple excitations and MP2 lead to comparable accuracy, whereas the fastest method density functional theory leads to considerable deviations. Hence, the method of choice for the prediction of standard Gibbs energies of reaction in solution with good accuracy at medium computational cost is MP2 combined with conductor-like screening model for real solvents COSMO-RS. © 2008 American Institute of Chemical Engineers AIChE J, 54: 2729–2734, 2008

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Introduction

In the chemical industry, continuously new chemicals are demanded and new processes have to be installed. Hence, the percentage of reactions for which the thermodynamics are known constantly decreases. Solvation processes are of special interest because product design as well as product de-

velopment depend on solubility or partition behavior of compounds between different phases. To know how one can influence processes in solution the standard Gibbs energies of reaction in solution are of great interest. Experimental values as well as electrochemical potentials are sparsely found in literature. The reason for this lack is that either the measurements are considered routine although advanced techniques and laborious protocols are needed for reliable data, or the direct measurement is impossible. Beyond that, the knowledge of standard Gibbs energies of reaction in solution $\Delta G_r^{\text{solution}}$ paves the way to a straightforward and cost-effective computational solvent screening.

Additional Supporting Information may be found in the online version of this article.

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Theoretical Background

Computational chemistry is a rapidly emerging subfield of theoretical chemistry which constantly gains importance in chemical engineering applications. Not only predictions for gas phase reactions but especially the calculation of thermodynamic properties in solution are what chemical engineers are interested in. Starting point of the calculation of thermodynamic properties is in each case quantum mechanics which is used to calculate a large variety of molecular properties of isolated molecules in vacuo.

Quantum mechanics

The ultimate goal of most quantum chemical approaches is to find a solution of the time-independent, nonrelativistic Schrödinger equation. This differential equation cannot be solved analytically for more than one-electron systems. Furthermore, the direct numerical integration is not tractable. As a result, a large number of approximate methods have evolved to solve the Schrödinger equation. This work focuses upon important examples for electronic structure methods, electron correlation methods, and density functional theory (DFT). One of the most basic theories is the Hartree-Fock theory,^{1–3} an electronic structure method where the electron correlation is neglected. This approximation is the corner stone of almost all conventional orbital based quantum chemical methods. The underlying molecular orbital picture was, and still is, the most important theoretical concept for the interpretation of reactivity and molecular properties. A further development are electron correlation methods that consequently lead to more accurate results, many times at higher computational costs. Here, most widely used electron correlation methods are the Møller-Plesset perturbation theory of n th order (MP n)⁴ and coupled cluster theory.^{5,6} In the MP n theory the perturbation theory is applied to the calculation of the correlation energy. The most frequently used variations are MP2^{7–10} and MP4.¹¹ Perturbation methods add all types of corrections to a given order, whereas coupled cluster methods include all corrections of a given type to infinite order.¹² An important variation is coupled cluster with single and double excitations and perturbative triple excitations (CCSD(T)).^{13,14} A completely different approach to quantum chemistry in comparison to the mentioned orbital-based methods with or without electron correlation is the DFT.^{15,16} Instead of working with wavefunctions, DFT makes use of the electron density as fundamental variable because Hohenberg and Kohn¹⁶ could prove that the ground-state electronic energy is determined completely by the electron density. Hence, DFT methods utilize empirical functionals connecting electron density and energy. DFT is a ground state theory that incorporates both exchange and correlation effects. Among the different methods that exist within DFT, hybrid methods such as Becke three-parameter hybrid functional (B3LYP) are commonly used because of the often good accuracy and computational economy.

Continuum solvation models

Hence, different quantum chemical methods allow a more or less accurate calculation of properties of molecules in the gas phase. However, a large part of chemical reactions takes

place in solution and does not regard isolated molecules. As a large number of solvent molecules have to be considered and numerous parameters are needed, direct calculation of molecules in solution is difficult. Molecular dynamics^{17,18} or Monte-Carlo methods,^{19,20} both rely on the availability of suitable force fields, lead to high accuracy results at high computational costs. Group contribution methods such as UNIFAC²¹ and continuum solvation models,²² e.g., (COSMO-RS),²³ are computationally less demanding at the cost of accuracy. To find an easy-to-handle approach, group contribution methods as well as continuum solvation models are applicable. Within this work, the continuum solvation model COSMO-RS was chosen, a truly predictive and generally applicable method that does not depend on experimental parameters. Hence, it also allows the prediction of properties of compounds that have never been synthesized before.

COSMO-RS is used as a bridge from single molecule properties (screening charge densities) to macroscopic properties of pure systems and mixtures. It combines an electrostatic theory of locally interacting molecular surface descriptors, available from quantum mechanics, with a statistical thermodynamics methodology. The theory of COSMO-RS is described elsewhere.²⁴ For each molecule, a quantum chemical geometry optimization combined with a COSMO calculation has to be carried out. These calculations can usually be done overnight on a single CPU, but they might get time-consuming when moving to bigger molecules of more than about 100 atoms. However, these calculations have to be done only once per molecule and can be stored in a database for further use. The subsequent COSMO-RS calculations using a statistical thermodynamics approach, which lead to the prediction of thermodynamic properties such as excess Gibbs energies and partition coefficients, only take a few seconds. Consequently, COSMO-RS is a valuable tool for screening purposes, e.g., for a solvent screening using a solvent database.

Computational Methods

The molecules were assembled using the software Gauss-View (version 3.09; Gaussian, Wallingford).²⁵ The geometry optimizations and the frequency calculations for each molecule were carried out using the B3LYP/triple zeta valence polarization (TZVP) method using the software Gaussian.²⁶ On top of that the calculations lead to a term accounting for thermal correction to the Gibbs free energies of reaction in the gas phase. This term was added to the gas phase energies. The latter were calculated via single point calculations using the software Gaussian²⁶ and the different quantum-chemical methods B3LYP/TZVP, MP2/TZVP, and CCSD(T)/correlation consistent polarizable valence triple zeta (CC-PVTZ). The standard state for the Gaussian calculations is a pressure of 1013 hPa and a temperature of 298.15 K. The calculations of the gas phase energies for COSMO-RS and the energies in a conductor were performed using TURBOMOLE (version 5.8; COSMOlogic GmbH, Leverkusen, Germany)^{27–30} with RI-BP86 functional and TZVP basis set. The energies of solvation were calculated using the software COSMOtherm (version C2.1, release 01.05; COSMOlogic GmbH).^{23,31} The different basis sets used for the calculations in the gas and the liquid phase were chosen according to the

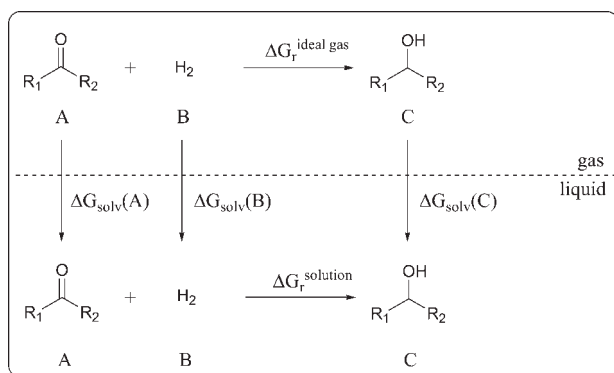


Figure 1. Hess cycle for the computational derivation of the standard Gibbs energy of reaction in solution $\Delta G_r^{\text{solution}}$.

recommendation of COSMOlogic, the distributor of COSMOtherm. Standard state for the calculation of Gibbs free energy of solvation ΔG_{solv} is the fluid hypothetical ideally diluted at 1 molar concentration. All quantum-chemical calculations were carried out at the Center for Computing, RWTH Aachen University, Germany.

Results and Discussion

The overall aim of our work was to establish an easy-to-handle procedure for the calculation of standard Gibbs energies of reaction in solution $\Delta G_r^{\text{solution}}$. Based on a Hess cycle in Figure 1, $\Delta G_r^{\text{solution}}$ can be calculated by adding up the values for the Gibbs free energies of reaction in the gas phase $\Delta G_r^{\text{ideal gas}}$ and the Gibbs free energies of solvation ΔG_{solv} . Experimental data for the Gibbs free energies of reaction in the gas phase can be found in literature.³² By contrast there is a huge lack of experimental data for the standard Gibbs energy of reaction in solution. Adkins et al.³³ measured standard reaction Gibbs energies in toluene for reduction reactions of differently substituted ketones to alcohols, with which our data will be compared. All experimental and calculated values can be found in the Supporting Information.

Gibbs free energy of reaction in the gas phase $\Delta G_r^{\text{ideal gas}}$

When performing a quantum chemical geometry optimization, the equilibrium geometry of the studied molecule and its energy is obtained. This is the energy of the molecule in vacuum, at 0 K and without zero point energies (ZPE) of the internal vibration modes of the molecule. To take the ZPE and finite temperatures into account, all internal modes are assumed to be harmonic oscillators. The force constants of these oscillators have to be computed, which are the second derivatives of the energy with respect to the internal coordinates. Then the ZPEs of these modes are obtained and translational, rotational (based on the geometry of the molecule) and vibrational contributions to internal energy, enthalpy and entropy need to be computed by statistical mechanics.³⁴ These contributions are necessary to go from the energy, which is a result of the Schrödinger equation, to the Gibbs free energy of reaction of a molecule in the gas phase at a finite temperature. From these data, the standard Gibbs

energy of reaction in the gas phase can be computed and compared with the experimental data. It is important to note that the force constants are second derivatives and therefore computationally much more demanding than mere energies. Fortunately, the corrections are relatively small compared to the quantum chemical energies. Therefore, the most efficient approach is to choose a simpler method for the thermodynamic corrections and a more sophisticated method for the quantum chemical energy. Because the geometry is usually less sensitive to inaccuracies of the method than the energy but at the same time computationally more demanding, the geometry is often calculated by a simpler method as well.

For the calculation of the Gibbs free energy of reaction in the gas phase $\Delta G_r^{\text{ideal gas}}$, energies in the gas phase and a term accounting for thermal correction were summed up. The method used for the calculation of the latter one is DFT. Three different quantum chemical methods were compared for the calculation of the energies: DFT, MP2, and CCSD(T). Here, the accuracy in the calculations rises with $\text{DFT} < \text{MP2} < \text{CCSD(T)}$ (Figure 2). For $\Delta G_r^{\text{ideal gas}}$, the average differences between calculation and experiment are 3.4 kJ/mol for CCSD(T), 8.5 kJ/mol for MP2, and 17.5 kJ/mol for DFT. In terms of computational costs, the trend is the same as for the accuracy because DFT scales with molecular size n^{2-4} , MP2 with molecular size n^5 , and CCSD(T) with molecular size n^7 . So DFT is the fastest method with the lowest accuracy, and CCSD(T) is the most time-consuming method leading to the highest accuracy. Because of the high computational costs of CCSD(T), only few calculations could be accomplished with this method. Therefore it is generally not applicable for calculations where molecules with more than ~12 atoms are considered.

Gibbs free energy of solvation ΔG_{solv}

The Gibbs free energies of solvation can be calculated from the Henry coefficients. For the calculation of latter ones the COSMO-RS theory and the COSMOtherm program^{23,31} were used. As no literature data were available, the calcu-

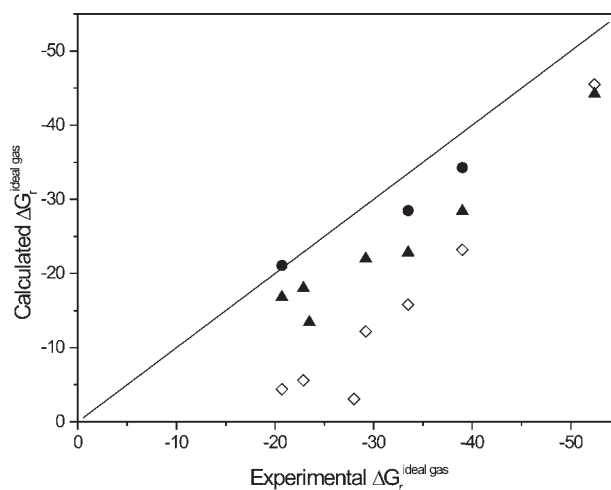


Figure 2. Parity plot for the Gibbs free energy of reaction in the gas phase $\Delta G_r^{\text{ideal gas}}$ in kJ/mol. (\diamond) DFT, (\blacktriangle) MP2, (\bullet) CCSD(T).

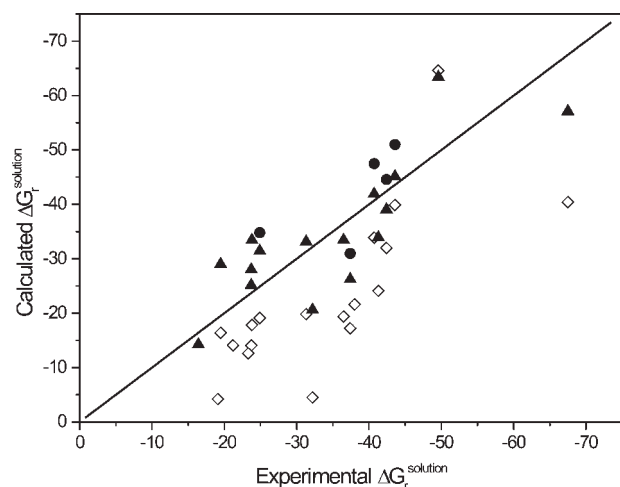


Figure 3. Parity plot for the standard Gibbs energy of reaction in solution $\Delta G_r^{\text{solution}}$ in kJ/mol.

Calculated $\Delta G_r^{\text{solution}}$ obtained by addition of calculated $\Delta G_r^{\text{ideal gas}}$ and calculated ΔG_{solv} . (◇) DFT, (▲) MP2, (●) CCSD(T).

lated values for ΔG_{solv} cannot be compared with experimental values.

Standard Gibbs energy of reaction in solution $\Delta G_r^{\text{solution}}$

Following the Hess cycle depicted in Figure 1, the calculation of the standard Gibbs energies of reaction in solution is possible by adding up the values for the Gibbs free energies of reaction in the gas phase $\Delta G_r^{\text{ideal gas}}$ and the Gibbs free energies of solvation ΔG_{solv} . The results are shown in Figure 3. Surprisingly, the quantum chemically most laborious method CCSD(T) as well as the second laborious methods MP2 lead to similar results in terms of accuracy: For the standard Gibbs energy of reaction in solution the difference between calculation and experiment is 6.5 kJ/mol for CCSD(T), 6.1 kJ/mol for MP2, and 13.2 kJ/mol for DFT. This is due to fortunate error cancelation effects caused by the combination of COSMOtherm and MP2. DFT leads to less accurate results but at the lowest computational costs. To judge the contribution of COSMO-RS to the error for $\Delta G_r^{\text{solution}}$, a comparison for the calculation of $\Delta G_r^{\text{solution}}$ was carried out (Figure 4): On the one hand, $\Delta G_r^{\text{solution}}$ was calculated by addition of calculated $\Delta G_r^{\text{ideal gas}}$ and calculated ΔG_{solv} , and on the other hand, $\Delta G_r^{\text{solution}}$ was calculated by addition of experimental $\Delta G_{r,\text{exp}}^{\text{ideal gas}}$ and calculated ΔG_{solv} . As expected, COSMO-RS shows a systematical error in the calculation of ΔG_{solv} . This is in line with the results for the normalization (see later). This effect explains also why the MP2 results in solution are more accurate than the CCSD(T) results.

Application example: solvent screening for maximum conversion in biphasic reaction systems

Sample reaction is the asymmetric substrate-coupled biocatalytic reduction of acetophenone to (*R*)-phenylethanol in a biphasic reaction system with one reactive phase. The solvent used in the reactive phase is water with isopropanol as reduc-

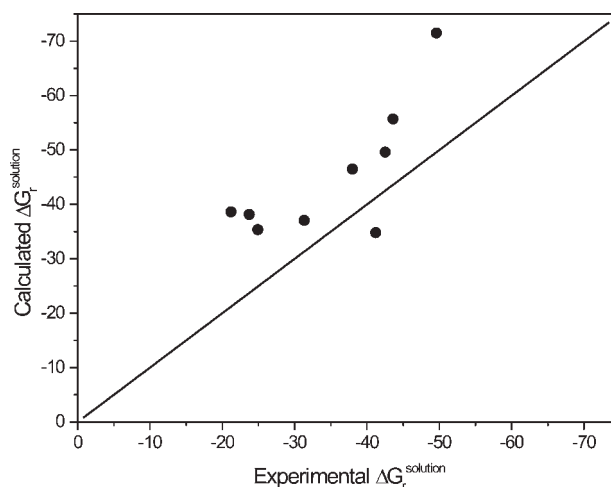


Figure 4. Parity plot for the standard Gibbs energy of reaction in solution $\Delta G_r^{\text{solution}}$ in kJ/mol.

Calculated $\Delta G_r^{\text{solution}}$ obtained by addition of experimental $\Delta G_{r,\text{exp}}^{\text{ideal gas}}$ and calculated ΔG_{solv} .

ing agent. Possible solvent candidates assessed are *n*-hexane, *n*-heptane, MTBE, DIPE, toluene, as well as the ionic liquids [BMIM][BTA] and [BMIM][PF₆]. Before the actual screening can be started a precise definition of the target is important. In this case, our aim is to maximize equilibrium conversion and yield. The calculation and prediction of equilibrium conversion and yield in biphasic reaction mixtures with only one reactive phase is possible using the mathematical derivation introduced in Refs. 35–37 as a basis. For an ab-initio solvent screening the calculation of the partition coefficients of all substrates and products is necessary as well as the calculation of the equilibrium constant in the reactive water phase. The partition coefficients were calculated using COSMOtherm,³⁸ and the equilibrium constant was calculated

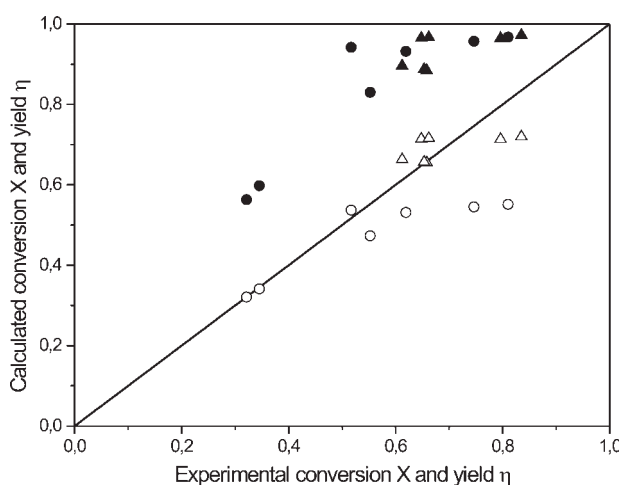


Figure 5. Parity plot for conversion X and yield η .

(▲) Conversion, (●) yield, (△) normalized conversion, (○) normalized yield; the latter ones were normalized to one experimental result, here to the median of experimental conversion and yield, respectively.

according to the method presented within this publication. Figure 5 shows the results for the experimental and ab-initio predicted conversion X and yield η for the biocatalytic reduction of acetophenone to (*R*)-phenylethanol for the different solvents mentioned earlier. The solvent MTBE is the best solvent for the second phase in terms of conversion and yield, predicted and experimentally verified.^{36,37} Hence, a reasonable ranking of the solvents is possible and the general trends predicted are correct. Nevertheless, the absolute values for predicted conversion and yield might differ substantially from the experimental values. Thus, to achieve quantitative values, the predicted values for conversion and yield were normalized to one experimental result, here to the median of experimental conversion and yield for the system hexane/water (Figure 5). This procedure gives satisfactory absolute values within the experimental error using a minimum of one experimental point for conversion and yield, each.

Conclusion

A straightforward computational way for the prediction of standard Gibbs energies of reaction in solution $\Delta G_r^{\text{solution}}$ was presented using quantum mechanics as well as the statistical thermodynamics as implemented in COSMO-RS. After a quantum chemical geometry optimization the Gibbs free energies in the gas phase $\Delta G_r^{\text{ideal gas}}$ including the ZPE are determined. The Gibbs free energies of solvation ΔG_{solv} are calculated using the COSMOtherm program. From these values the standard Gibbs energies of reaction in solution $\Delta G_r^{\text{solution}}$ can be calculated according to a Hessian cycle simply by adding up $\Delta G_r^{\text{ideal gas}}$ and ΔG_{solv} . For the calculation of the gas phase energies, three different quantum-chemical methods are compared. CCSD(T) leads to accurate results but at high computational costs. The second laborious method MP2 leads to results with similar accuracy than CCSD(T). The fastest method DFT leads to results with the largest error. Generally, as a matter of fact, the computational costs rise with the level of complexity of the investigated molecules. Overall, the user has to make the decision between accuracy and computational costs. With the general availability of the quantum chemical programs, the presented method for the prediction of standard Gibbs energies of reactions in solution is generally applicable. The results overall show that, where no comparable data are available from literature, the COSMO-RS combined with off-the-shelf quantum mechanical methods can be used to predict trends for the standard Gibbs energies of reaction in solution $\Delta G_r^{\text{solution}}$. Although the absolute values predicted might differ substantially from the experimental values, general trends are predicted correctly as shown in the application example. Here, the correction of predicted values by scaling with single experimentally derived points leads to quantitative values within the experimental error.

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Notation

B3LYP = Becke three-parameter hybrid functional
 CC-PVTZ = correlation consistent polarizable valence triple zeta
 CCSD(T) = coupled cluster theory with single, double, and perturbative triple excitations
 COSMO = conductor-like screening model
 COSMO-RS = conductor-like screening model for realistic solvation
 DFT = density functional theory
 MP n = Møller-Plesset perturbation theory of n th order
 n = number of electrons
 TZVP = triple zeta valence polarization
 $\Delta G_r^{\text{ideal gas}}$ = Gibbs free energy of reaction in the gas phase
 $\Delta G_{r,\text{calc}}^{\text{ideal gas}}$ = calculated Gibbs free energy of reaction in the gas phase
 $\Delta G_{r,\text{exp}}^{\text{ideal gas}}$ = experimental Gibbs free energy of reaction in the gas phase
 $\Delta G_r^{\text{solution}}$ = standard Gibbs energy of reaction in solution
 ΔG_{solv} = Gibbs free energy of solvation
 X = conversion
 η = yield

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