

A Computational Approach to Solvent Selection for Biphasic Reaction Systems

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Diplom-Chemikerin

Martina Peters

aus Bitburg

Berichter: Universitätsprofessor Dr. rer. nat. Walter Leitner
Universitätsprofessor Dr.-Ing. Andreas Pfennig

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Abstract

Biphasic reaction systems with a reactive and a non-reactive phase are widespread in technical applications. The non-reactive phase serves as a reservoir of dissolved substrates at high concentrations and allows for the extraction of the product during the reaction. The proper choice of the phase combination will have manifold influence on catalytic parameters such as activity, selectivity, and stability, but also on maximum conversion or yield. To optimize such biphasic reactions, conversion and yield constitute concise targets of practical relevance for a rational solvent screening which requires thermodynamic information on coupled reactions and phase equilibria as input. Usually, the experimental determination of these data requires considerable laboratory effort.

To minimize the experimental effort and to enlarge the dataspace for optimization, an *in silico* solvent screening for maximum conversion and yield in different biphasic catalyzed reactions is evaluated. The primary target of the investigations is in biocatalytic applications as these benefit greatly from the addition of organic non-reactive media to the reactive aqueous phase. The conductor-like screening model for realistic solvation (COSMO-RS) is used for the prediction of solute partitioning between organic solvents and a reaction medium. Although the calculated results show significant absolute deviations, COSMO-RS still predicts the correct trends for the partition coefficients of solutes in different solvents. Furthermore, a combination of statistical thermodynamics and classical quantum mechanics is used for the prediction of the reaction equilibria. The calculated overall reaction equilibrium using the calculated partition coefficients and the calculated equilibrium constants again results in the prediction of the best solvent combination regarding conversion and yield. Extending the approach with numerical simulations provides a more detailed insight into the reaction system.

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Nomenclature

Symbols

A	free energy, interfacial area
a	segment surface area
A,B,C,D	compounds A, B, C, D
E	energy
c_i	concentration of compound i
G	Gibbs free energy
H	enthalpy
J	mass transfer flux
K	equilibrium constant
k_i	mass transfer coefficient of compound i
m	factor accounting for partitioning in biphasic media
n	molar amount
P_i	partition coefficient of compound i
P^∞	infinite dilution partition coefficient
P_s	σ -profile
R	partition coefficient ratio of product and substrate, general gas constant
S	cosubstrate / substrate ratio $S = \frac{n(B)_0}{n(A)_0}$
T	temperature
U	internal energy
V	phase volume ratio $V = \frac{V_N}{V_R}$
X	equilibrium conversion

x	mole fraction
z	number of electrons
α	electrostatic misfit energy coefficient
$\alpha, \beta, \gamma, \delta$	partition coefficients of compounds A,B,C,D
γ_i	activity coefficient of compound i
ϵ	dielectric constant
η	equilibrium yield
μ_i	chemical potential of compound i
σ	surface charge density
Φ	electrostatic potential
v	molar volume

Indices, superscripts, subscripts

acc	acceptor
aq	aqueous phase
c	combinatorial
calc	calculated
calc, <i>ab initio</i>	calculated by <i>ab initio</i> methods
don	donor
E	excess
eff	effective
eq	equilibrium conditions
exp	experimental
hb	hydrogen bonding
i	compound i
N	non-reactive phase
org	organic phase

ow	octanol/water
r	reaction
R	reactive phase
res	residual
S	solvent
solution	solution
solv	solvation
0	initial conditions
∞	infinite dilution

Abbreviations

B3LYP	Becke-Lee-Yang-Parr three parameter hybrid functional
BAL	benzaldehyde lyase
BMIM	1-butyl-3-methylimidazolium
BP86	Becke-Perdew functional of 1986
CAMD	computer-aided molecular design
CC	coupled cluster theory
CCSD(T)	coupled cluster theory with single, double and perturbative triple excitations
cc-pVTZ	correlation-consistent polarized valence triple zeta basis
COSMO	conductor-like screening model
COSMO-RS	conductor-like screening model for realistic solvation
CPU	central processing unit
CSM	continuum solvation model
DFT	density functional theory
DIPE	di- <i>iso</i> -propyl ether
DMBA	3,5-dimethoxy-benzaldehyde
DMF	dimethyl-formamide

EOS	equation of state
FDH	formate dehydrogenase
GC	gas chromatography
HF	Hartree-Fock theory
HPLC	high-performance liquid chromatography
<i>LB</i> -ADH	alcohol dehydrogenase from <i>Lactobacillus brevis</i>
LLE	liquid-liquid equilibrium
MIBK	methyl- <i>iso</i> -butyl-ketone
MO	molecular orbital
MP n	n^{th} -order Møller–Plesset perturbation theory
MTBE	methyl- <i>tert</i> -butyl ether
NADP $^{+}$	nicotine amide adenosine dinucleotide phosphate, oxidized form
QM	quantum mechanics
RI	resolution of identity
rms	root mean square
SHOP	Shell higher olefin process
TMB	(<i>R</i>)-3,3',5,5'-tetramethoxy-benzoin
TZVP	triple zeta valence polarization
UNIFAC	universal functional activity coefficient
ZPE	zero point energy

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1. Introduction

Well then, my dear listeners, let us proceed with fervor to another problem! Having sufficiently analyzed in this manner the four resources of science and nature, which we are about to leave (i.e. fire, water, air, and earth) we must consider a fifth element which can almost be considered the most essential part of chemistry itself, which chemists boastfully, no doubt with reason, prefer above all others, and because of which they triumphantly celebrate, and to which they attribute above all others the marvelous effects of their science. And this they call the solvent (menstruum).

Hermannus Boerhaave (1668-1738),
De mentruis dictis in chemia, in:
Elementa Chemiae (1733)^[1-3]

Boerhaave accentuated that solvents can be considered to be the *fifth element which can almost be considered the most essential part of chemistry itself* in the above citation. This reflects the particular importance of solvents in chemistry. In the earlier days, alchemists searched for the universal solvent, the *Mentruum universale* as Paracelsus called it. Although scientists failed in the search for the universal solvent, they conducted new experiments, discovered new reactions and new compounds. It was still a long way to the understanding of fluid phases that we have today. Nevertheless, solvents have been widely applied from early on, both in academia as well as in industry.

1.1. Industrial applications of solvents

The industrial production of chemical compounds relies predominantly on catalytic reactions. While in heterogeneously catalyzed gas phase processes solvents do not have to be considered, they play an important role in homogeneously catalyzed transformations in liquid phase as they influence the rates and selectivities of catalytic reaction as well as catalyst stabilities. Also important is the fact that well designed multiphase solvent systems can eliminate the classical drawback of homogeneous catalysis, which is the separation of the reaction products from the catalyst. In many cases it is this disadvantage that prevents otherwise highly selective and efficient homogeneously catalyzed reactions to be applied in industrial practice, as the separation problem cannot be solved in an economically justifiable way. Prominent examples of industrial multiphase reactions are the Shell higher olefin process (SHOP) and the Ruhrchemie/Rhône-Poulenc process.^[4] Recent developments have also lead to various processes in the pharmaceutical industry that are based on multiphase catalysis, such as the production of Ibuprofen.^[5] Biocatalytic reactions are of particular interest for the investigation of multiphase systems as they offer the advantages of ideal product selectivity and a strong thermodynamic limitation.

What are the promising advantages biphasic reaction media can offer for homogeneous catalysis and biocatalysis? Firstly, the product may easily be removed and purified by phase separation. This furthermore enables the avoidance of unintended consecutive reactions leading to increased selectivity.^[6] Secondly, the retention of the dissolved catalyst in the reactive phase allows the catalyst to be reused. If conversion is sufficiently high, additional separation steps after the reaction can be avoided.^[7–9] Thirdly, possible inhibitory effects on the catalyst can be suppressed if substrate and product concentrations can be kept low in the reactive phase. Fourthly, being of importance for limited substrate solubility in the reactive phase, e.g. aqueous solution for biocatalysis, the second phase acts as a reservoir for the reactants allowing one to obtain preparative quantities in reasonable concentrations. Finally, the overall reaction equilibrium may be shifted.^[10]

The advantages of biphasic reaction media are utilized for a broad variety of reactions and solvents.^[9] Besides water and organic solvents,^[11–16] fluorinated solvents,^[17] ionic liquids,^[18–21] and supercritical solvents like supercritical carbon dioxide are applied in

multiphase catalysis with homogeneous catalysts as well as with biocatalysts.^[22,23] Overall, the increasing interest in biphasic reaction systems in biocatalysis is displayed by the increasing number of publications in this field.^[11,24–27]

1.2. Molecular models for fluid phases

Since solvents are widely applied in chemical industry, a distinct knowledge of fluid-phase behavior is of crucial importance for chemical transformations as well as process engineering. Hence, models for fluids in equilibrium are a prerequisite for any scientific process analysis. Although fluid models can be constructed entirely on the macroscopic level based on experimental data, this approach is limited to few systems for which enough data is available. However, the vast majority of technically relevant processes deals with complex fluid systems that cannot be analyzed experimentally in sufficient detail with reasonable effort. In such cases one must turn to the microscopic basis of matter and design a theory, based on the complex molecular properties of fluids, that requires only few experimental data or even is fully predictive.^[28]

1.2.1. Constraints for fluid-phase models

Fluids owe their properties and their particular behavior not only to the properties of single molecules but also to the energetic interactions between them. Related to the order of interactions between the molecules, one distinguishes three different states of matter, the gaseous, the solid and the liquid (Figure 1.1).

The gas phase is remarkably simple. At low to moderate pressures, molecules may be treated as isolated, non-interacting species. This facilitates theoretical modeling enormously since the system of interest is entirely defined by the single molecules.^[29] In a solid, on the other hand, molecules are closely packed and their motion is restricted to small vibrations around space-fixed positions. Thus, a solid is highly ordered. In liquid systems, the interactions between the molecules are on the one hand too strong to be treated by the kinetic theory of gases, and on the other hand too weak to be treated by the laws of solid state physics. Thus, the liquid is neither a microscopically homogeneous

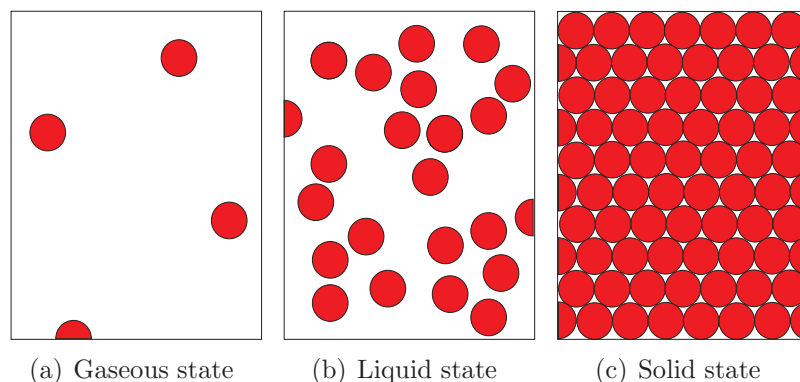


Figure 1.1.: Three different states of matter (a) gaseous, (b) liquid, (c) solid.

medium in which the dissolved material diffuses in order to distribute itself evenly and disorderly, nor does it possess a translatory order resembling a crystal lattice. Nevertheless, the long-range ordering in a crystal is somewhat analogous to the local ordering in a fluid. Thus, neither of the two models can be applied to fluids without limitations. In between the two models there is such a wide spectrum of imaginable and experimentally established variants that it is difficult to develop a generally valid model for all fluid systems. Due to the complexity of liquids, it is the least-known of all aggregate states. Therefore, the experimental and theoretical examination of the structure of liquids belongs to the most difficult tasks of modern chemistry and engineering.^[3]

The complexity of fluids is displayed by the various disciplines needed for the development of a fluid model system, namely classical mechanics, electrodynamics, quantum mechanics, classical and statistical thermodynamics.^[28] The description of the molecular energy is the basis of fluid-phase models. It depends on the relation between molecular geometry and molecular energy described by classical mechanics. However, it also depends on the force fields the molecules are moving in, created by the electrical properties of the molecules and consequently described by electrodynamics. Quantum mechanics is used to specify molecular geometry and molecular charge distribution as origin of the force fields. Statistical thermodynamics links the molecular energy of a system and its macroscopic properties. By using this link the molecular model leads to numerical data for the thermodynamic functions, from which the macroscopic behavior of a fluid can be calculated by the laws of classical thermodynamics.

1.2.2. Inter- and intramolecular potential energy

For a single molecule, the energy can be expressed in terms of its mechanical degrees of freedom. The energy can be calculated out of the molecular geometry, represented by various moments of inertia, the atomic masses and the properties related to the intramolecular force fields, such as vibration frequencies and the barriers to internal rotation. The energy of a single molecule constitutes one part of the total energy of a molecular system, referred to as the kinetic part. Molecules have a potential part that needs to be considered as well if different conformers exist or reactions occur.

Defining a fluid, a potential part is added, originating from the intermolecular potential energy of a molecular system. In general, all degrees of freedom such as translation, rotation and internal motions will be influenced by adjacent molecules. This interaction with the molecular environment can be expressed in terms of the forces acting between the molecules, which in turn are derived from the intermolecular potential energy. So, although the simple equations for the kinetic energies associated with the various degrees of freedom continue to be valid, they have to be supplemented by an expression for the intermolecular potential energy in terms of the molecular configuration of the system.

1.2.3. Fundamental equations

The most fundamental equations of thermodynamics are the first and the second law of thermodynamics. A combination of these equations leads to a thermodynamic relation that generally describes all thermodynamic properties of a system. For a defined system this fundamental thermodynamic relation may be expressed in terms of the internal energy:

$$dU(S, V, N_i) = TdS - pdV + \sum_i \mu_i dN_i. \quad (1.1)$$

Using the Legendre transform, this fundamental thermodynamic equation for the internal energy can be transformed into fundamental equations for additional thermodynamic potentials. Hence, in addition to the internal energy the most important fundamental

equations expressed in term of enthalpy H , free energy A and Gibbs free energy G are:

$$dH(S, p, N_i) = TdS + Vdp + \sum_i \mu_i dN_i. \quad (1.2)$$

$$dA(T, V, N_i) = -SdT - pdV + \sum_i \mu_i dN_i. \quad (1.3)$$

$$dG(T, p, N_i) = -SdT + Vdp + \sum_i \mu_i dN_i. \quad (1.4)$$

Due to the natural variables they depend on, A and G are the only thermodynamic potentials for which the influence of all natural variables on the reaction system can be measured experimentally. The difference between these expressions is:

$$dG(T, p, N_i) - dA(T, V, N_i) = pV. \quad (1.5)$$

Consequently, as an approximation, if pV is very small as typically assumed in many fluid phase models, A and G are interchangeable. This explains why in literature there is often no clear distinction between A and G .

1.2.4. Implicit models for condensed phases

Different approaches exist for the description of fluid phases, e.g. continuum models. Their overall basis is a model in which a number of the degrees of freedom of the constituent particles are described in a continuous way, usually by means of a distribution function. Continuum models were developed more than a century ago. But only lately, the merging with the quantum mechanical description of molecules opened up new perspectives for the study of solvation effects.^[30] The most important, fundamental quantity describing the interaction of a solute with a surrounding solvent is the Gibbs energy of solvation, ΔG_{solv} , caused by electrostatic effects. This is equal to the free energy change for a molecule leaving the gas phase and entering the condensed phase.^[29]

1.2.4.1. Continuum solvation models

Continuum models differ in the way they describe the degrees of freedom of the constituent particles in a continuous way. One approach is to neglect the atomic structure of the solvent and replace its electrostatic properties by those of a dielectric continuum. The polarization of the medium and the back-polarization of the solute are the electrostatic response to placing the solute molecule in the solvent and thus a measure of the electrostatic interactions between solvent and solute. The macroscopic effect of this electrostatic interaction energy is calculated by a particular branch of continuum models, referred to as continuum solvation models. Since the first application of this approach,^[31] many different versions of the model have appeared.^[30,32–34] They all have in common that a cavity is constructed that represents the geometry of the solute molecule and that the solvent is represented by an infinitely extended dielectric continuum outside this cavity. The electric field, arising from the nuclei as well as from the electrons of the solute molecule, is screened by the polarization of this continuum. The effect of this polarization can be represented by the surface charge density distribution it produces on the inner surface of the cavity. Also, the screening charges back-polarize the solute and thus change its charge distribution. In a continuum solvation model the electrostatic interactions between solute and solvent molecules in a real solution, resulting from the interactions between the molecular charge densities, are thus modeled by a rather localized system, the charges of the solute in the solvent interacting with the associated charged surface of the cavity.^[29]

1.2.4.2. Quantum mechanics

The starting point for the calculation of thermodynamic properties using modern continuum solvation models is in each case quantum mechanics which is used to calculate a large variety of molecular properties of isolated molecules in vacuo. The ultimate goal of most quantum chemical approaches is to find a solution of the time-independent, non-relativistic 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, for example electronic structure methods, electron correlation methods and density functional theory.

One of the most basic theories is the Hartree-Fock (HF) theory,^[35–37] an electronic structure method where electron correlation is neglected. This approximation is the cornerstone 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, usually at higher computational costs. Here, most widely used electron correlation methods are the Møller-Plesset perturbation theory of n^{th} order (MP n),^[38] and the coupled cluster theory (CC).^[39,40] In the MP n theory the perturbation theory is applied to the calculation of the correlation energy. The most frequently used variations are MP2^[41–44] and MP4.^[45] Perturbation methods add all types of corrections to a given order, whereas coupled cluster (CC) methods include all corrections of a given type to infinite order.^[46] An important variation is CCSD(T) (coupled cluster with single and double excitations and perturbative triple excitations).^[47,48]

A completely different approach to quantum chemistry in comparison to the mentioned orbital based methods with or without electron correlation is the density functional theory (DFT).^[49,50] Instead of working with wavefunctions, DFT makes use of the electron density as fundamental variable because Hohenberg and Kohn could prove that the ground-state electronic energy is completely determined by the electron density.^[50] 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 density functional theory, hybrid methods such as B3LYP (Becke three parameter hybrid functional) are commonly used due to its good accuracy and computational economy.

Quantum chemical methods allow a calculation of thermodynamic properties of molecules in the gas phase, depending on the method of choice with more or less accurate results. To move from the quantum mechanic prediction of gas phase properties to fluid-phase properties, continuum solvation models are useful tools.

1.2.4.3. COSMO

Among continuum solvation models in literature, one is of particular practical usefulness, namely COSMO (conductor-like screening model). In this model, the continuum chosen to represent the solvent is an infinitely extended electrical conductor with $\epsilon \rightarrow \infty$.^[51] This choice leads to a remarkably simple expression for the screening charges and the screening energy, because the resulting electrostatic potential Φ is zero for every point r on the surface of the cavity in the conductor:

$$\Phi(r) = 0. \quad (1.6)$$

Because the electrical conductor screens the charges perfectly, it is intuitively clear that all electrostatic effects vanish behind the electrically conducting surface, including the electrostatic potential. The disadvantage using this assumption is that it is only exact for a molecule in a conductor, not for a solvent with a finite dielectric constant ϵ . An approximate correction for non-conducting media offers the approach to scale the ideal screening charge densities σ^* :

$$\sigma = f(\epsilon)\sigma^* = \frac{\epsilon - 1}{\epsilon + x}\sigma^*. \quad (1.7)$$

For many problems, x can be calculated exactly, it is always $0 \leq x \leq 2$. For COSMO $x = \frac{1}{2}$ was chosen, the relative error is less than $\frac{1}{2}\epsilon$. Some concerns were raised initially that this *post facto* correction for the dielectric behavior is only appropriate for media having reasonably high dielectric constants (such as water), but a systematic study indicated non-polar solvents to be equally amenable to a treatment by the COSMO model.^[29,52] Since its original description at semi-empirical level, COSMO has been generalized to *ab initio* and density functional levels of theory as well.^[53]

An important point is the construction of the cavity around the solute. In COSMO, the cavities are constructed by modeling a solute molecule by a fused sphere geometry and choosing the radii as the spheres representing the atoms by fitting to experimental data; quite common is the use of 1.2 times the corresponding van der Waals radii.^[54] Furthermore, the segmentation of the cavity surface must be done properly for reliable results. In a practical COSMO calculation the number of surface segments typically ranges

from about one hundred for diatomic molecules to a few thousand for drug molecules. COSMO calculations have been incorporated into various quantum-chemical computer packages, so that the results can be generated without bothering about every detail of their production.^[54] The thermodynamic energy of solvation obtained from COSMO will in general be no more than a crude approximation of the true experimental value. This is to be expected because the macroscopic dielectric constant cannot accurately reproduce the local electrostatic interactions between solute and solvent molecule. Results of a COSMO calculation are the charge density distribution over the surface of the cavity and the energy of the solute in the conductor, including the back-polarization effect. The difference between the energy of the solute in the conductor and in the gas phase reflects the electrostatic intermolecular interactions. It is not a molecular potential energy, but rather has been shown to be approximate to the electrostatic part of the thermodynamic free energy of solvation.

Figure 1.2(a) shows the molecular structure of water, and Figure 1.2(b) shows a qualitative picture of the screening charge density distribution on the inner surface of a cavity for a H_2O molecule in an electrical conductor. There is an accumulation of negative screening charges (blue) around the positively charged hydrogen atoms, whereas the negatively charged oxygen atom is screened by positive charges (red).

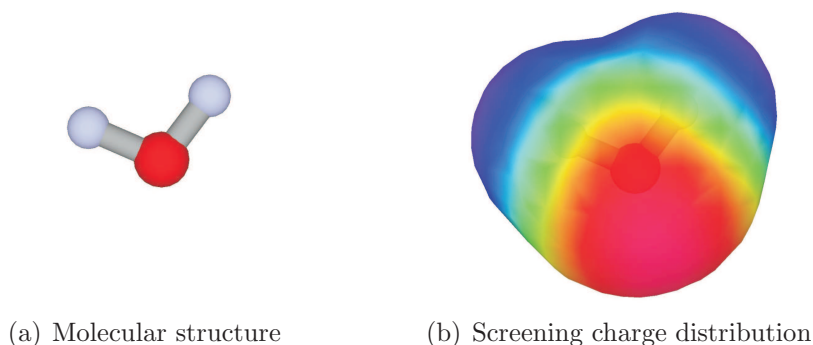


Figure 1.2.: (a): Molecular structure and (b): screening charge distribution of H_2O with red: positive surface charge, blue: negative surface charge, yellow and green: almost neutral surface charges.

All in all, COSMO represents the first realistic approximation to electrostatic solvation

effects. Although not generally reliable or sufficiently accurate, it is a good starting point for a realistic semi-empirical model of the molecular potential energy in liquid mixtures beyond the continuum solvation approximation.

1.2.5. Excess function models

Moving beyond computation of the electrostatic component of the solvation free energy, excess function models are used to describe properties of liquid mixtures with reference to the pure component properties. But due to the complexity of liquids, liquid models are used for a simplified treatment of mixing effects.

1.2.5.1. Basics of excess function models

Any molecular model for the excess free energy A^E is made up of two separate contributions, a repulsive A_{rep}^E and an attractive A_{att}^E :

$$A^E = A_{\text{rep}}^E + A_{\text{att}}^E. \quad (1.8)$$

The repulsive term accounts for molecular size and shape effects, hence it introduces the molecular geometry. The attractive part is associated with attractive intermolecular forces. Since mixing effects of industrially relevant systems usually occur at high densities, a reasonable approximation is that the molecular system is represented by a space-filling arrangement of molecules interacting *via* surface contacts. This crude approximation implies that pressure-dependent effects cannot be calculated using these simplified liquids models. In addition, a distance dependency is suppressed which means that only temperature dependencies can be taken into consideration. Because the intermolecular interactions are formulated in terms of pair contacts, they will depend on the local structure in the liquid. Thus, an essential part of any molecular model for the excess functions in liquid mixtures is a model for the relation between the unknown local compositions and the known bulk compositions in terms of the intermolecular potential energy, hence the short-range non-randomness (Figure 1.3).

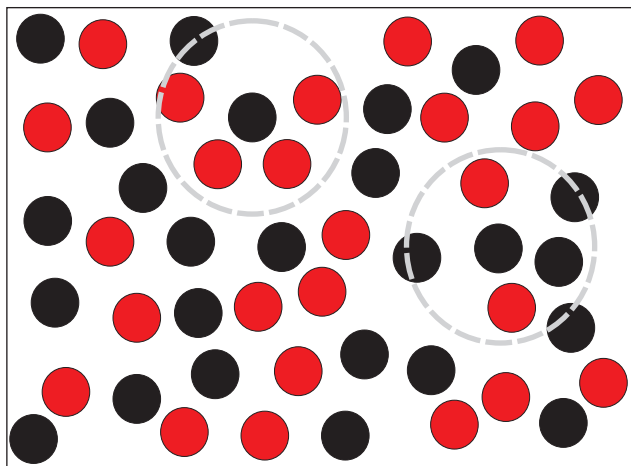


Figure 1.3.: The concept of local composition: Although the bulk composition of red and black balls is 1:1, the local compositions, exemplary accentuated by gray circles, differ.

Nevertheless, simplified liquid models are useful representations of the intermolecular potential energy of fluid phases. Two different approaches will be presented (Figure 1.4), group interaction models based on the lattice picture (Figure 1.4(a)) and surface charge interaction models based on the polyhedral surface picture (Figure 1.4(b)).

1.2.5.2. Group interaction models - UNIFAC

Group interaction models are based on the liquid model in the lattice picture as shown in Figure 1.4(a). They calculate the intermolecular energy as the sum of independently interacting functional groups according to the free segment approximation. At present, UNIFAC is one of the most popular group interaction models.^[55,56] The functionality of UNIFAC is exemplary shown in Figure 1.5 for a mixture of hexane and butanone. Both molecules are broken up into their functional groups; hexane is broken up into $-\text{CH}_2$ and $-\text{CH}_3$, and butanone is broken up into $-\text{CH}_3$, $-\text{CH}_2$ and $-\text{COCH}_3$. This leads to specific group frequencies for the pure components. The intermolecular energy in the mixture is calculated from a summation over all pair contact energies between the different functional groups in the mixture. The interaction energies cannot be calculated yet from quantum mechanics and hence must be determined by fitting to experimental

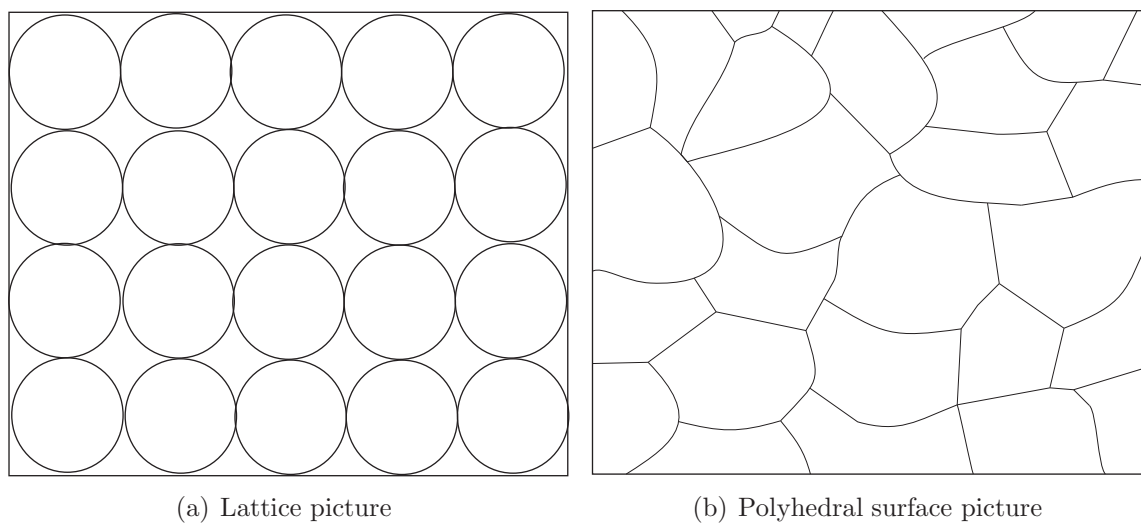


Figure 1.4.: Liquid model in the lattice and the polyhedral surface picture; circles and polyhedrons represent molecules in the liquid phase.

data. UNIFAC relies on a large database and a large number of functional groups, leading to a high predictive capacity for the macroscopic behavior of fluids. Fortunately, the number of functional groups is much smaller than the number of chemical compounds that can be synthesized from them.^[28]

Despite the high predictive capacity of UNIFAC, it suffers from several general drawbacks:

- *Non-randomness:* Since the local composition might differ strongly from the bulk composition, a model for the relation between local and bulk composition is essential. UNIFAC uses an approximation to the solution of the Guggenheim quasi-chemical approximation.
- *Free segment approximation:* By using the free segment approximation, all geometrical information is neglected and just the statistical information about the group frequencies is considered. As a consequence, UNIFAC suffers from the inability to distinguish between any type of isomers consisting of identical groups unless taken into account by particular group definitions.
- *Segmentation:* Since there is no theoretical basis for the choice of the functional

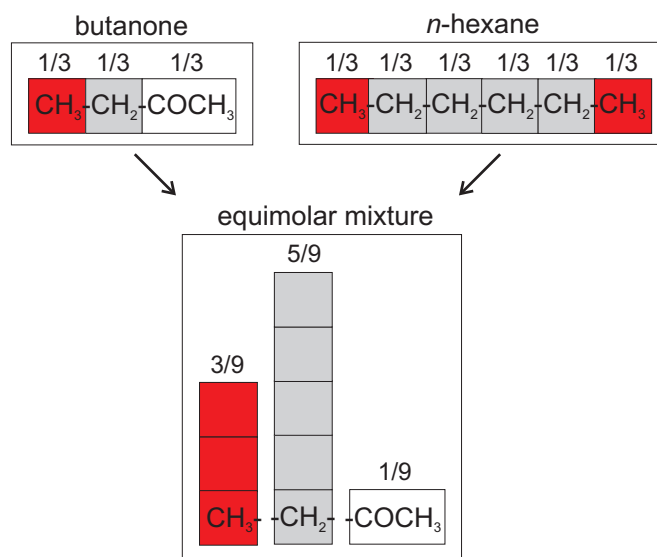


Figure 1.5.: Frequency profile of functional groups in the 1:1 mixture of butanone and hexane.^[28]

groups, different scientific groups might use different segmentations and consequently yield different results.

- *Parameterization:* Since the interaction energies between different functional groups cannot yet be calculated using quantum mechanics, UNIFAC depends on experimental data for these values. Consequently, it is only applicable for molecules that consist of already parameterized groups.
- *Temperature dependency:* With the original basic UNIFAC, no temperature dependency could be considered; the parameters needed to be fitted to experimental data. Newer, modified UNIFAC versions, as usually used today, can take temperature dependent parameters into account.^[57]

In summary, a group contribution method like UNIFAC is a highly predictive method for fluid-phase behavior of molecules whose functional groups have already been parameterized. It does not, however, represent a realistic picture of the intermolecular interaction resulting from the surface properties of the molecule.

1.2.5.3. Surface charge interaction models - COSMO-RS

Surface charge interaction models are an alternative approach to the intermolecular potential energy in liquids. Here, the results of COSMO calculations are used to model real solvents. The screening charges obtained from COSMO calculations can be used as a basis to establish the intermolecular potential model due to electrostatic effects in real solvents. This generalization of COSMO is referred to as COSMO for realistic solvation (COSMO-RS). In COSMO-RS, the interactions between molecules are visualized to occur between surface segments of polyhedral surfaces contacting each other in a space-filling manner according to the polyhedral surface picture (Figure 1.4(b)). Each surface segment is associated with a characteristic electrostatic surface charge density.

The COSMO-RS replaces the conductor by real solvent molecules which overcomes the limitations of continuum models. A new reference state is created, defined as that of a molecule being ideally screened electrostatically by solvent molecules as if it was dissolved in a conductor. With the creation of the new reference state, the conductor is removed without changing the electrostatic energy of the solute molecule. The intermolecular contacts in this reference state occur *via* pairwise interactions of surface segments of solute and solvent molecules with COSMO surface charge densities. The COSMO reference state for a solute is defined by a situation where all interacting surface segments of the solute are matched electrostatically in such an ideal manner by solvent molecules.

In real liquid mixtures, most surface pairs will not meet the perfect fit. This results in a less perfect screening of the solute molecule by the solvent molecules. Removing the ideal conductor between them is associated with a change in electrostatic energy, referred to as a misfit energy. It is this misfit energy that is responsible for deviations from the COSMO reference state due to local electrostatic effects and it is thus necessary for calculating excess functions. The misfit energy can be computed from the conductor-like screening charges.

Figure 1.6 shows the liquid model adapted to take into account surface charge interactions in the framework of space-filling polyhedral segments. Surface segments are paired, ideally there is no single segment. If a single surface segment occurs, it can be neglected in the range of a large number of segments. Every pair of segments is characterized by

the surface area of a segment a_{eff} and the total surface charge density σ_{tot} . The latter is the sum of the local screening charge densities, $\sigma_{\text{tot}} = \sigma + \sigma'$. When $\sigma = -\sigma'$ it is called an *ideal contact*. With $\sigma \neq -\sigma'$ the screening charge densities do not cancel out and the energy of this non-ideal pair is called *misfit energy*:

$$E_{\text{misfit}}(\sigma, \sigma') = a_{\text{eff}} \frac{\alpha}{2} (\sigma + \sigma')^2, \quad (1.9)$$

where α is an electrostatic misfit energy coefficient for converting a charge into an energy, and a_{eff} , the surface area of the segment, transforms the charge densities into charges. Both are adjustable parameters of the model.

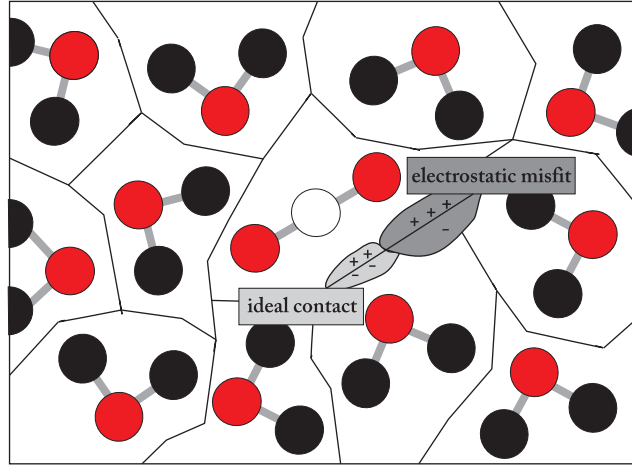


Figure 1.6.: COSMO-RS interaction model.

Although local electrostatic effects in the fluid are quite well modeled by the misfit energy, there will be further contributions of electrostatic origin to the intermolecular potential energy of liquids. If the absolute values of the screening charge densities of two interacting surface segments are large enough and of opposite sign, an energy contribution to the description of *hydrogen bonds* has to be considered:

$$E_{\text{hb}} = a_{\text{eff}} c_{\text{hb}} \max[0, \sigma_{\text{acc}} - \sigma_{\text{hb}}] \min[0, \sigma_{\text{don}} + \sigma_{\text{hb}}] \quad (1.10)$$

where σ_{hb} and c_{hb} are fitted parameters.

To move from mixtures of segments to real solvent, a crucial simplification is possible by

invoking the free segment approximation. Then, the geometrical information contained in the COSMO files is irrelevant and statistical information about the frequencies of particular charge densities in a molecule, the so-called σ -profiles, is sufficient. The σ -profile of a molecule is obtained by a suitable statistical averaging of the charge density distribution over the effective contact areas. It is basically a histogram in which discrete σ -values are related to associated surface areas.

The σ -profiles are useful tools to gain qualitative insight into a molecular system. Figure 1.7 exemplary shows the σ -profiles of water, hexane, toluene and benzene. The σ -profile of water is very broad which reflects its strongly polar character. Furthermore, the σ -profile is almost symmetrical, which means that the negative peak of the σ -profile results in almost ideal screening of the positive peak. Hence, water molecules are not likely to form non-ideal pairs and the surface segments have a high affinity to each other. As a consequence, water has a rather high boiling point. In contrast, hexane has a σ -profile which is rather narrow but high. Due to the differences in the σ -profiles it is obvious that water and hexane do not show a high miscibility. In contrast, benzene and toluene show a high mutual solubility represented by their similar σ -profiles.^[28]

Continuing with the transformation of the molecule concentrations to segment concentrations, the σ -profile of a whole system $P_s(\sigma)$ is the sum of the mole fraction weighted σ -profile of all components:

$$P_s(\sigma) = \sum x_i P'(\sigma). \quad (1.11)$$

The chemical potential of a segment is given by the following equation which has to be solved iteratively:

$$\mu_s(\sigma) = -\frac{RT}{a_{\text{eff}}} \left[\int P_s(\sigma') \exp \left(\frac{a_{\text{eff}}}{RT} (\mu_s(\sigma') - E_{\text{misfit}}(\sigma, \sigma') - E_{\text{hb}}(\sigma, \sigma')) \right) d\sigma' \right]. \quad (1.12)$$

The move from a segment to molecules is described by the following equation, which assembles the chemical potential of a component i in a solvent S by a combinatorial term and a residual term

$$\mu_s^i = \mu_{\text{c},S}^i + \mu_{\text{res},S}^i = \mu_{\text{c},S}^i + \int P'(\sigma) \mu_s(\sigma) d\sigma. \quad (1.13)$$

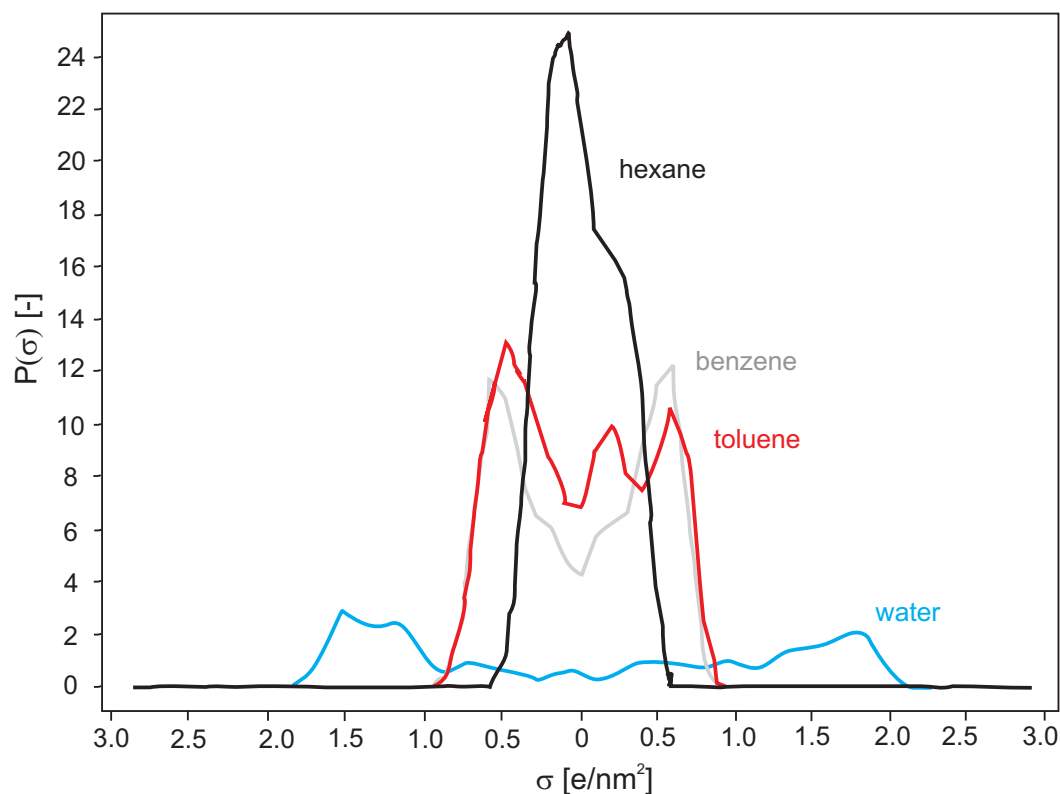


Figure 1.7.: σ -profiles of different molecules.

The combinatorial term $\mu_{c,S}^i$ takes shape and size effects of solvent molecules and solvate molecules into account. The residual term $\mu_{res,S}^i$ describes the interactions between solvate i and solvent S .

For each molecule, a quantum chemical geometry optimization combined with a COSMO calculation has to be carried out just once. These calculations can usually be done overnight on a single CPU, but they might get time-consuming when moving to molecules with more than 100 atoms. The results can be stored in a database for further use. Note that a conformer analysis is important because it can lead to energetic changes. The subsequent COSMO-RS calculations using a statistical thermodynamics approach, leading 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. The overall

workflow of the calculation of mixture equilibrium data is illustrated in Figure 1.8.

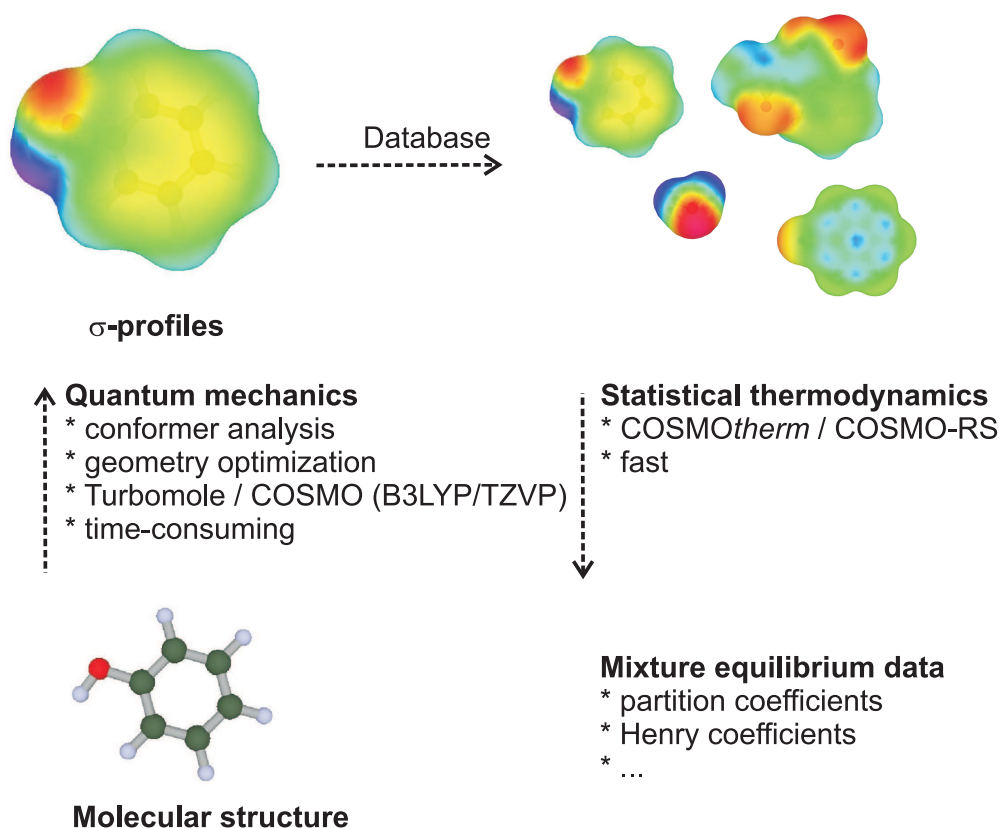


Figure 1.8.: Workflow of the calculation of mixture equilibrium data.

Nevertheless, COSMO-RS has several disadvantages that limit a general applicability.

- *No density dependence:* Being a simplified liquid model based on the polyhedral surface interactions, COSMO-RS approximates the molecules in a liquid to be densely packed. Consequently, it is not possible to calculate pressure dependencies.
- *Non-randomness:* For the relation between bulk and local composition, COSMO-RS uses an iterative solution to the quasi-chemical approximation of Guggenheim; the iterative solution is identical with the one used in other models, such as GEQUAC.
- *Free segment approximation:* A crucial simplification within COSMO-RS is the use of the free segment approximation. The geometrical information is neglected

and just the statistical information about the frequencies of the screening charge densities are important, the so-called σ -profiles. By this, COSMO-RS cannot distinguish stereoisomers. But in contrast to UNIFAC, a discrimination of structural isomers is possible (e.g. ethanol and dimethylether).

- *Dissociation*: The tendency of molecules to dissociate cannot automatically be covered by COSMO-RS.

In the future, predictive models based on polyhedral surface charge distributions will play an important role for the prediction of mixture equilibrium data. Due to an increasing computer power, these methods are likely to become one of the most important branches of progress. At present, highly parameterized group contribution methods are often more accurate.^[28]

1.3. Applications of fluid-phase models

Due to their predictive power, fluid-phase models are widely applied in the chemical industry. For COSMO-RS and UNIFAC, chemical engineering simulations have become the most important area of applications. Both are often used as thermodynamic models in process simulations. COSMO-RS is also commonly applied by the pharmaceutical industry for drug development or direct product design. UNIFAC as well as COSMO-RS are used for industrial solvent screenings.

Fluid phase models are also used in algorithms, such as in the computer-aided molecular design (CAMD) approach.^[58] Here, up to date, UNIFAC and further developments of UNIFAC are used for the prediction of pure compound and mixture properties.^[59] In addition to that, the CAMD approach also screens for intrinsic molecular properties such as melting point, boiling point or toxicity. All these parameters are also important for the choice of suitable solvent combinations. The method still suffers from disadvantages: apart from the general problems of group contribution methods, the CAMD approach does not take molecular conformations into account up to date. Regardless, the CAMD approach is a valuable tool for a fast and effective industrial solvent selection.

In general, for a more sophisticated prediction of fluid-phase properties, equations of state (EOS) are used.^[60] Especially, if the fluid phase over a large region of pressure or density is considered, excess function models are no longer applicable. In theory, an equation of state model is generally applicable and does not have theory based limitations like excess function models. Nevertheless, in practice, a generally applicable equation of state has not yet been found. Specific EOS are used for specific applications. Although equations of state are computationally more demanding than excess function models, they are at the same time very accurate if not correlative.

For an even more sophisticated investigation of fluid phases, Molecular Dynamics^[61,62] or Monte-Carlo Methods^[63,64] can be used. Both rely on the availability of suitable force fields. They lead to highly accurate results if appropriate force-field are available at high computational costs. But up to date, computers are not fast enough for an efficient use of these methods for everyday problems in the chemical and pharmaceutical industry.

1.4. Objective

To use biphasic reaction conditions effectively, a distinct knowledge of the equilibrium thermodynamic boundaries is of great value. In order to obtain reliable data, a large number of time-consuming and expensive experiments is necessary. To minimize the amount of experimental work but also to reduce the environmental impact, a computational approach to solvent selection according to maximum equilibrium conversion and product yield is proposed as depicted in Figure 1.9.

The first step in a computational solvent selection is the selection of a *target reaction system* as discussed in **Chapter 2**. The reaction system examined is a biphasic reaction system with only one reactive phase. For the idealized reaction system, an analytical solution is derived in order to calculate and predict equilibrium conversion and product yield.

In the second step, a suitable *target reaction* is chosen. Biocatalytic reactions are good model reactions for biphasic reaction systems with one reactive phase as they offer the advantages of ideal product selectivity and a strong thermodynamic limitation. Two

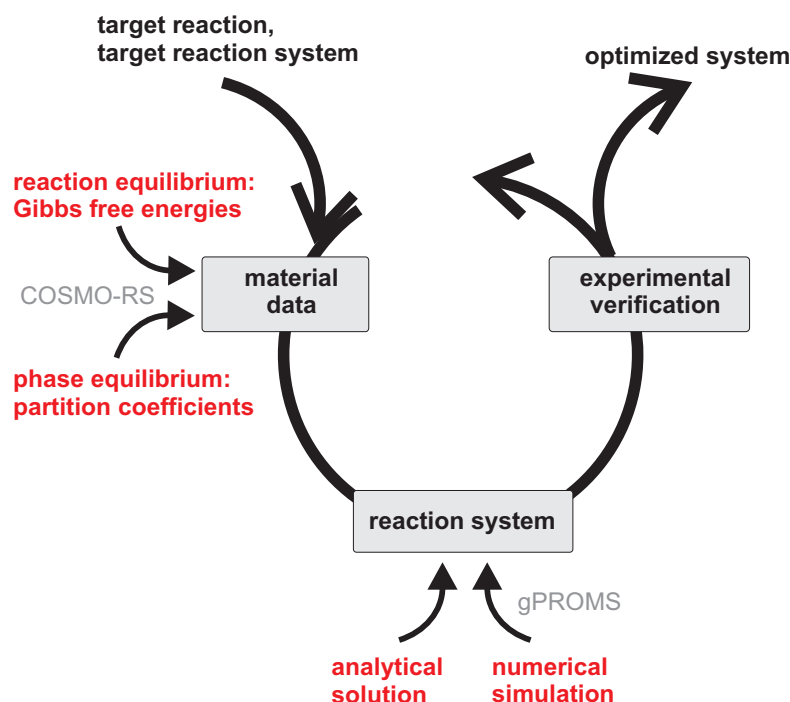


Figure 1.9.: Computational approach to solvent selection.

biocatalytic reactions are examined here: The first reaction is an enantioselective substrate coupled cofactor regeneration where acetophenone is reduced to (*R*)-phenylethanol while 2-propanol is oxidized to acetone. The catalyst used is an alcohol dehydrogenase from *Lactobacillus brevis* (*LB*-ADH). The second reaction is the enantioselective carbon-carbon coupling of 3,5-dimethoxy-benzaldehyde (DMBA) to (*R*)-3,3',5,5'-tetramethoxybenzoin (TMB) using the enzyme benzaldehyde lyase (BAL).

For the selected target reactions, material-specific data needs to be collected such as partition coefficients and equilibrium constants. In **Chapter 3**, the calculation of partition coefficients using the conductor-like screening model for real solvents (COSMO-RS) is discussed. This method is used because it offers the possibility of an *ab initio* prediction of the phase equilibria. Moreover, a method for the *ab initio* prediction of equilibrium constants using a combination of quantum mechanics and statistical thermodynamics is the topic of **Chapter 4**. Subsequent to that, the calculated material data needs to be inserted into the mathematical model derived in **Chapter 2**.

The last step in the computational solvent screening is an experimental validation. Calculated and experimentally obtained conversion and yield of the target reaction in different solvent combinations are compared. Finally, the optimal solvent in terms of equilibrium conversion and product yield for the target reaction in an idealized target reaction system can be identified. This is shown throughout the thesis in **Chapter 2 - Chapter 5**.

Apart from conversion and yield, there are of course many more parameters that determine an optimal solvent, e.g. price, toxicity, temperature dependence, long-term stability. The computational screening for maximum equilibrium conversion and product yield is meant to be a starting point for a final solvent selection. For a more detailed study of the reaction system, a further investigation of the target reaction system using numerical simulation tools is of great value as presented in **Chapter 5**.

2. Mathematical analysis of biphasic reaction systems

2.1. Introduction

Various parameters determine the choice of a suitable solvent, such as enantiomeric excess, toxicity, long-term stability, price and so forth. From a practical point of view, conversion and yield are important targets for process optimization. Consequently, within this thesis, these are the parameters chosen to determine a suitable solvent.

For an *ab initio* prediction of conversion and yield in biphasic systems, the first step is a mathematical analysis of the thermodynamic equilibrium. Subsequently a parameter study and a sensitivity analysis will be carried out. Finally, the validity of the derived model will be tested in an experimental validation.

2.2. Materials and methods

2.2.1. Computational

Algebraic transformations were carried out using Maple 10 (The Mathworks). Graphs have been created using PSTricks. All calculations were performed by the author of this thesis.

2.2.2. Experimental

All experiments were carried out by M. Eckstein as part of her PhD thesis^[65] and by Julia Lembrecht (both Technical Chemistry, University of Rostock, Germany) as part of her diploma thesis. Experimental details are described elsewhere.^[66,67]

2.3. Results and discussion

A general reaction scheme, which applies to the majority of reactions in biphasic systems, is the bimolecular reversible reaction with partitioning of all reactants (Figure 2.1). The catalyst is restricted quantitatively to the reactive phase (index: R). The second phase acts as a reservoir for the reactants and the extracted products and is thus defined as non-reactive phase (index: N). For a detailed description of equilibrium conversion X and yield η , seven different parameters have to be taken into account:

- partition coefficients $\alpha, \beta, \gamma, \delta$
- phase volume ratio $V = \frac{V_N}{V_R}$
- co-substrate excess $S = \frac{n(B)_0}{n(A)_0}$
- equilibrium constant K .

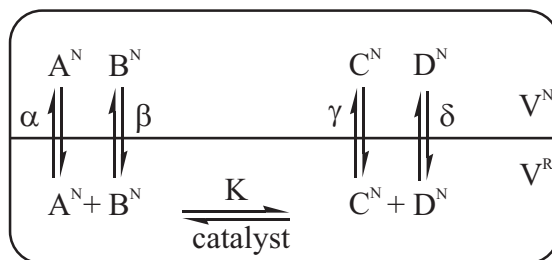


Figure 2.1.: Bimolecular reaction with partitioning of all reactants; A and B are the substrates, C and D the products; indices R and N indicate reactive and non-reactive phase, respectively; K is the equilibrium constant; V is the phase volume ratio; $\alpha, \beta, \gamma, \delta$ are the partition coefficients.

The whole system was idealized in order to identify the general underlying trends. The partition coefficients express the reactant's affinity to the non-reactive phase. The partition coefficient of compound A is given by the ratio of the concentration of compound A in the reactive phase $[A]^R$ and in the non-reactive phase $[A]^N$ as $\alpha = \frac{[A]^N}{[A]^R}$, with β , γ , and δ accordingly. Partition coefficients were regarded as constant and independent of each other. Activity coefficients and selectivity were set to unity. Initially, no products were present. Selectivity towards the products was taken as unity.

2.3.1. Mathematical description

For the idealized system an analytical expression describing the thermodynamic conversion X of a bimolecular reaction with partitioning of all reactants in a biphasic system as a function of the seven previously mentioned parameters was derived. A closed solution for the recoverable, thus technically relevant, amount of product in the non-reactive phase expressed as yield η was also derived. By this, the values can be calculated directly avoiding numerical simulations. Furthermore, with the analytical solutions at hand, derivatives with respect to all the variables are in principle available.

The analytical solution was derived by expressing the conversion of the limiting substrate A by the molar amounts $n(A)$ and $n(C)$

$$X := \frac{n(A)_0 - n(A)}{n(A)_0} = \frac{n(C)}{n(A)_0} \quad (2.1)$$

with the initial total molar amount of compound A as $n(A)_0$.

The equilibrium constant K is given by the mass action law and in the idealized system by the ratio of the concentrations of all reactants in the reactive phase

$$K = \frac{[C]^R[D]^R}{[A]^R[B]^R}. \quad (2.2)$$

Applying the relevant mass balance equations

$$n(A)^R + n(A)^N = n(A)_0 (1 - X) \quad (2.3)$$

$$n(B)^R + n(B)^N = n(A)_0 (S - X) \quad (2.4)$$

$$n(C)^R + n(C)^N = n(A)_0 X \quad (2.5)$$

$$n(D)^R + n(D)^N = n(A)_0 X. \quad (2.6)$$

The molar amounts of the reactants in the reactive phase are given by the mass balances

$$n(A)^R = \frac{n(A)^N}{\alpha V} = \frac{(n(A)_0) (1 - X)}{(\alpha V + 1)} \quad (2.7)$$

$$n(B)^R = \frac{n(B)^N}{\beta V} = \frac{(n(A)_0) (S - X)}{(\beta V + 1)} \quad (2.8)$$

$$n(C)^R = \frac{n(C)^N}{\gamma V} = \frac{(n(A)_0) X}{(\gamma V + 1)} \quad (2.9)$$

$$n(D)^R = \frac{n(D)^N}{\delta V} = \frac{(n(A)_0) X}{(\delta V + 1)}. \quad (2.10)$$

Thus, the expression the equilibrium constant of the system can be written as

$$K \frac{(\gamma V + 1) (\delta V + 1)}{(\alpha V + 1) (\beta V + 1)} = \frac{X^2}{(1 - X)(S - X)}. \quad (2.11)$$

Factor m is defined as factor of the effective concentrations in the reactive phase as

$$m := \frac{(\gamma V + 1) (\delta V + 1)}{(\alpha V + 1) (\beta V + 1)}. \quad (2.12)$$

For single phase systems ($V = 0$, thus $m = 1$) equation (2.11) has been solved numerically^[68] as well as analytically.^[69] Solving equation (2.11) with respect to X for biphasic systems with $mK \neq 1$ gives

$$X = \frac{mK \left((S + 1) - \sqrt{(1 - S)^2 + 4S(mK)^{-1}} \right)}{2(mK - 1)}. \quad (2.13)$$

Note that for $mK = 1$ it can be shown that $X = S/(1 + S)$ is the continual completion in analogy to the monophasic case.^[69] Reinsertion of equation 2.12 gives the analytical expression for the conversion X

$$X = \frac{\frac{(\gamma V+1)}{(\alpha V+1)} \frac{(\delta V+1)}{(\beta V+1)} K \left((S+1) - \sqrt{(1-S)^2 + 4S \left(\frac{(\gamma V+1)}{(\alpha V+1)} \frac{(\delta V+1)}{(\beta V+1)} K \right)^{-1}} \right)}{2 \left(\frac{(\gamma V+1)}{(\alpha V+1)} \frac{(\delta V+1)}{(\beta V+1)} K - 1 \right)}. \quad (2.14)$$

In practice, the amount of product in the non-reactive phase is of particular interest as it is equal to the amount of recoverable product. With the mass balance for the desired product C (equation 2.9) the limiting yield η can be defined as

$$\begin{aligned} \eta &= \frac{n(C)^N}{n(A)_0} = \frac{\gamma V}{(\gamma V + 1)} X \\ &= \frac{\frac{\gamma V(\delta V+1)}{(\alpha V+1)(\beta V+1)} K \left((S+1) - \sqrt{(1-S)^2 + 4S (mK)^{-1}} \right)}{2 (mK - 1)}, \end{aligned} \quad (2.15)$$

where $\frac{\gamma V}{(\gamma V+1)}$ is the selectivity factor for the extraction efficiency.

Solving equation 2.11 with respect to S with $0 < X < 1$ and $0 < \eta < 1$ gives

$$S(X) = X \left(1 + \left(\frac{1}{(X^{-1} - 1) mK} \right) \right) \quad (2.16)$$

and with rearrangement of equation 2.15

$$S(\eta) = \eta (1 + (\gamma V)^{-1}) \left(1 + \frac{1}{\eta (1 + (\gamma V)^{-1}) mK} \right). \quad (2.17)$$

This gives S as a function of the desired target variables, thus enabling the calculation of the initial amounts of substrates needed at minimum to reach a desired value of X or η . Similar separation of variables to obtain either a solution for V or the partition coefficients is not possible.

The first and second order derivatives of the equations are complex and reveal no physi-

cally reasonable extreme points, neither by direct calculation nor by numerical inspection. Consequently, a parameter study with the analytical expressions was carried out to show their influences and interdependencies. The boundaries were chosen to exemplify the general trends within physically reasonable limits. In the following sections, the influences of K , S , V and the partition coefficients $\alpha, \beta, \gamma, \delta$ on X and η will be discussed.

2.3.2. Equilibrium constant K

The equilibrium constant K is an intrinsic property of the reaction system and is not easily accessible for optimization. The influence of K follows the intuitive trend that rising K leads to an increase in X and η (Figure 2.2). The sensitivity of X and η to other reaction parameters increases with decreasing K . In other words, reactions with smaller thermodynamic driving forces can be influenced more easily.

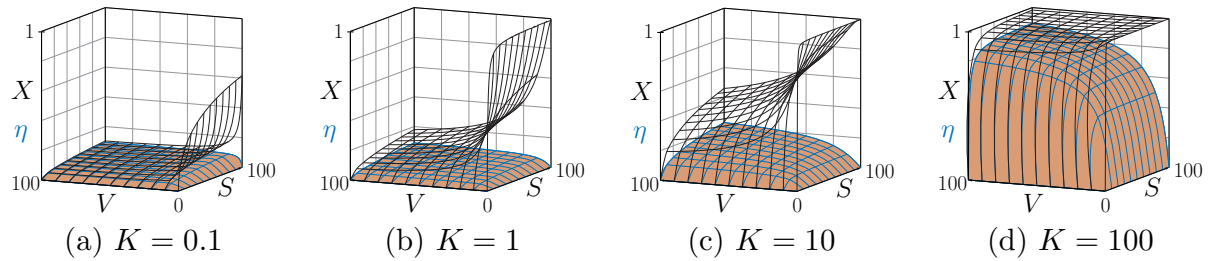


Figure 2.2.: Conversion X and yield η as a function of S and V for different K ; $\alpha = \beta = 1$, $\gamma = \delta = 0.01$.

An example: With increasing equilibrium constant K the conversion X rises. However, at different levels of K the influence of phase volume ratio V and co-substrate excess S are different. At low K it is obvious that increasing S leads to monotonous but convex increase of X . For increasing V a monotonous but concave behavior may be observed. The higher the value of K the less significant these influences become.

2.3.3. Partition coefficients $\alpha, \beta, \gamma, \delta$

In biphasic reaction systems, many different partition coefficient combinations are possible. Their influences are complex and interconnected. For the variation of one partition coefficient at a time, the influence on X and η depends on whether substrates or products are considered: An increase of α or β decreases X and η while, opposite to that, an increase of γ or δ increases X and η .

However, the independence of partition coefficients is an unlikely scenario. In the majority of catalytic reactions, changes in the molecules are small and partition properties are interconnected. The ratio and absolute values of the partition coefficients dominate the influence of V . Here, practically relevant cases were chosen which reflect the interconnection of the chemical nature of the reactants and which demonstrate general trends. As obvious from equations 2.18-2.20 and as shown in Figure 2.3, the three cases are

- (a) that most of the substrates are contained in the non-reactive phase,
- (b) that all substrates and products are equally distributed,
- (c) that most of the products are contained in the non-reactive phase:

$$(a) \begin{cases} \alpha \approx \beta > \gamma \approx \delta \\ \alpha > \gamma; \beta \approx \delta \\ \alpha \approx \gamma; \beta > \delta \end{cases} \quad \begin{matrix} \max X \text{ for } S \uparrow V \downarrow \\ \\ \end{matrix} \quad \& \quad \begin{matrix} \max \eta \text{ for } S \uparrow V \uparrow \\ \\ \end{matrix} \quad (2.18)$$

$$(b) \begin{cases} \alpha \approx \beta \approx \gamma \approx \delta \\ \alpha \approx \gamma; \beta \approx \delta \end{cases} \quad \begin{matrix} \max X \text{ for } S \uparrow V - \\ \\ \end{matrix} \quad \& \quad \begin{matrix} \max \eta \text{ for } S \uparrow V \uparrow \\ \\ \end{matrix} \quad (2.19)$$

$$(c) \begin{cases} \alpha \approx \beta < \gamma \approx \delta \\ \alpha < \gamma; \beta \approx \delta \\ \alpha \approx \gamma; \beta < \delta \end{cases} \quad \begin{matrix} \max X \text{ for } S \uparrow V \uparrow \\ \\ \end{matrix} \quad \& \quad \begin{matrix} \max \eta \text{ for } S \uparrow V \uparrow \\ \\ \end{matrix} \quad (2.20)$$

In the following, the influences of the phase volume ratio V and the co-substrate excess S on X and η for these different partition coefficient combinations will be shown.

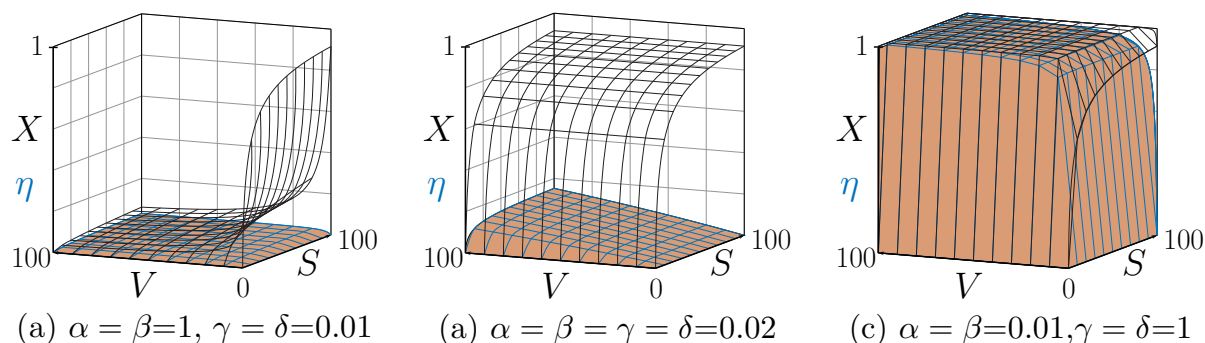


Figure 2.3.: Dependency of conversion X and yield η on partition coefficients.

2.3.4. Co-substrate excess S

The excess of co-substrate influences the conversion in a way that rising S leads to increasing X (Figure 2.4, upper row). The same holds true for the influence of S on η (Figure 2.4, lower row). The sensitivity of X and η as a function of S is mainly influenced by K and the partition coefficients. It is large if most substrates are contained in the non-reactive phase ($\alpha = \beta > \gamma = \delta$, Figure 2.4(a) and Figure 2.4(d)). This sensitivity decreases if all reactants are equally distributed ($\alpha = \beta = \gamma = \delta$, Figure 2.4(b) and Figure 2.4(e)). S has the lowest influence for good product extraction ($\alpha = \beta < \gamma = \delta$, Figure 2.4(c) and Figure 2.4(f)).

2.3.5. Phase volume ratio V

The influence of V is interdependent with the influence of the partition coefficients. A well behaved system with respect to X and η can be expected if the products are well soluble in the reactive phase and the products are easily extracted (see above). In practice such systems are rarely found, as the partition coefficients for substrate and product will be related, especially if overall changes in the molecules are small.

The influence of V on X and η for fixed values of S is shown in Figure 2.5. For high affinity of the substrates to the non-reactive phase ($\alpha = \beta > \gamma = \delta$, Figure 2.5(a)), increasing V will decrease X , whereas for good extraction of the products ($\alpha = \beta <$

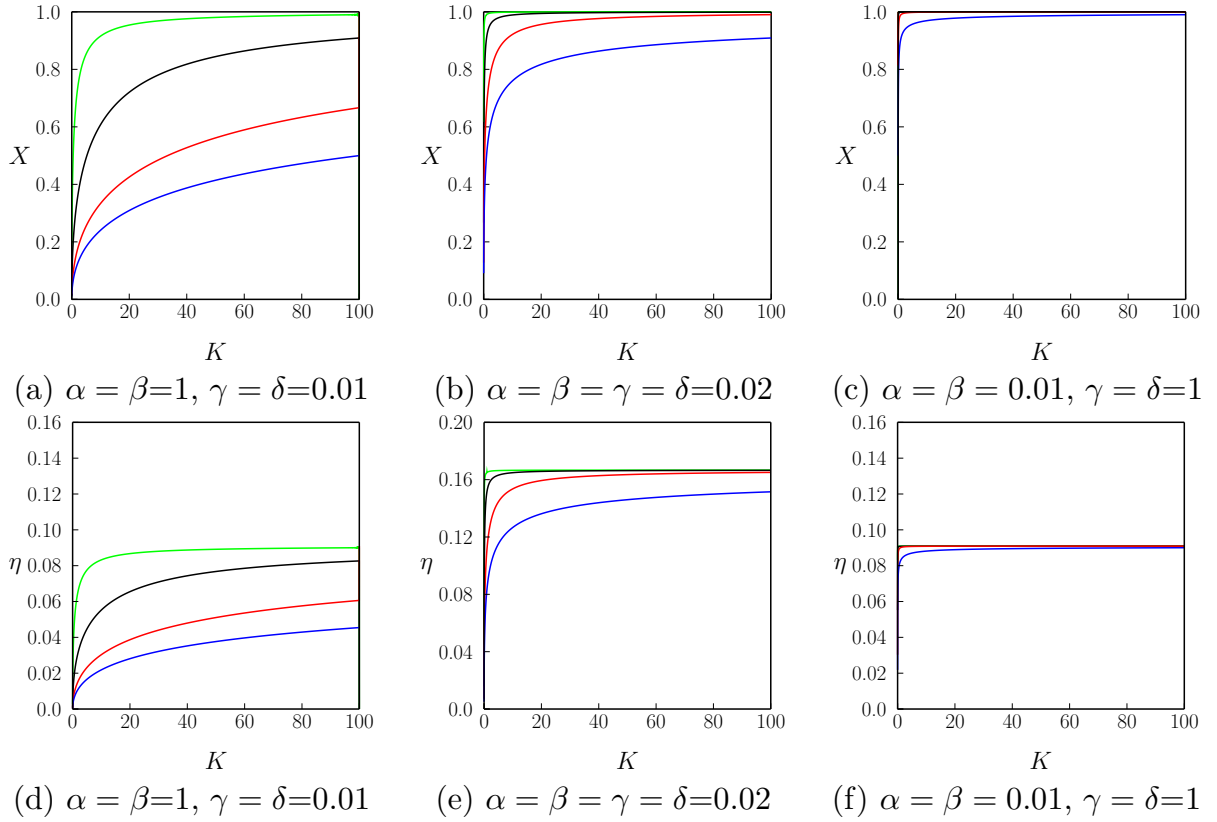


Figure 2.4.: (a)-(c): Influence of S on X , (d)-(f): influence of S on η (note the difference in ordinate scaling); ((a)-(f) for $V=10$; blue: $S=1$, red: $S=2$, black: $S=10$, green: $S=100$).

$\gamma = \delta$, Figure 2.5(c)) an increase in V will increase X . If all reactants partition equally (Figure 2.5(b)), V has no influence on X and marks a turning point of the general behavior. This is depicted in Figure 2.5(b) by the change in the order of the colored lines. With regard to η , no such reversal of trends is apparent (Figure 2.5, lower row). Here, for high affinity of the substrates to the non-reactive phase, η increases with increasing V ($\alpha = \beta > \gamma = \delta$, Figure 2.5(c)). For good product extraction ($\alpha = \beta < \gamma = \delta$, Figure 2.5(f)), η increases with increasing V .

Even though X may decrease with rising V due to lower availability of the products in the reactive phase, η generally increases with increasing V . As m approaches unity when V takes much greater values than the partition coefficients, X and η converge for large

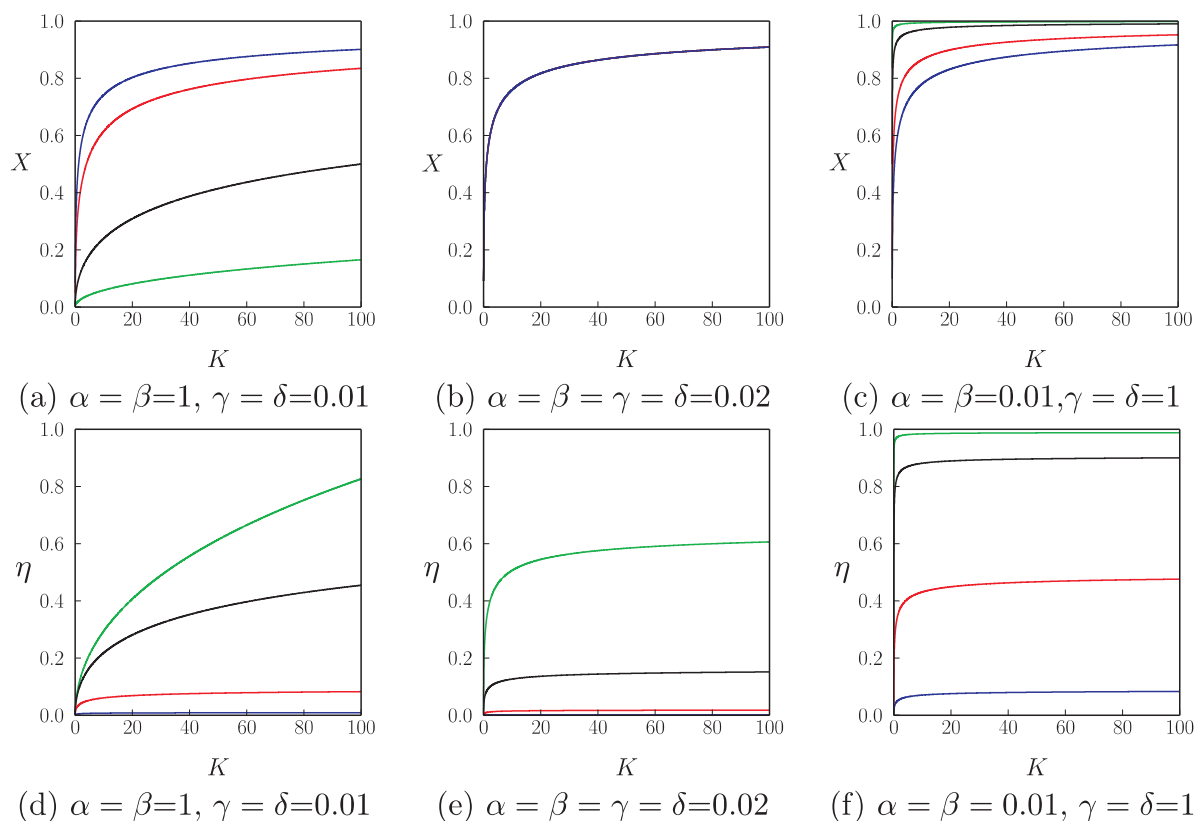


Figure 2.5.: (a)-(c): Influence of V on X , (d)-(f): influence of V on η ; ((a)-(f) for $S=1$; blue: $V=0.1$, red: $V=1$, black: $V=10$, green: $V=100$).

values of V . This can be either by simultaneous increase of η and decrease of X or by both X and η approaching unity for high values of V .

2.3.6. Experimental validation

To show whether the simplifications made in the development of the mathematical expression are acceptable, calculated conversion and yield are compared to experimental values. For the calculations, experimental data such as partition coefficients are inserted into the mathematical expression. Scheme 2.1 shows the model reaction, the enantioselective reduction of acetophenone to (*R*)-1-phenylethanol with 2-propanol, catalyzed by alcohol dehydrogenase from *Lactobacillus brevis* (*LB*-ADH). This model reaction was

examined with respect to equilibrium conversion X and equilibrium yield η in several biphasic reaction media.^[66,67] Different solvents such as alkanes, ethers, toluene, cyclohexanone, and ionic liquids were used as the non-reactive phase in combination with water as the reactive phase.



Scheme 2.1: Model reaction is the enantioselective reduction of acetophenone to (*R*)-1-phenylethanol using 2-propanol and acetone; the catalyst used is *LB*-ADH.

The results are depicted in Figure 2.6. Calculated X_{calc} and η_{calc} are in all cases lower than experimentally obtained values, but the general trends are predicted correctly. The relative deviations between experiment and calculation of X_{calc} and η_{calc} lie in between 1%–5% of the experimental results and are thus in a reasonable range. Consequently, the error contribution of the underlying ideality assumption does not account too much.

While the partition coefficients are intrinsically linked to the solvents and reactants, S and V are independent parameters. For methyl-*tert*-butyl ether (MTBE) as non-reactive phase, $K = 0.426$ and the partition coefficients for acetophenone, 2-propanol, (*R*)-1-phenylethanol and acetone were experimentally determined to be $\alpha = 66.9$, $\beta = 1.1$, $\gamma = 32.1$, $\delta = 1.1$.^[66,67] The reaction system can be classified as case (a) (equation 2.18 on page 31). Thus, following the general guidelines valid for this model, X and η can be maximized by an increase in S and a decrease in V . The smaller V is chosen, the smaller S is necessary for the desired conversion. This prediction matches the results obtained experimentally, investigating the equilibrium conversion X with changing V at a fixed S (Table 2.1). To obtain sensitive data for demonstration issues, a low value of $S = 2$ was chosen. As expected, in *n*-hexane the influence of V is more pronounced as the partition coefficients of acetophenone ($\alpha = 17.5$) and (*R*)-1-phenylethanol ($\gamma = 1.1$) differ stronger compared to MTBE.

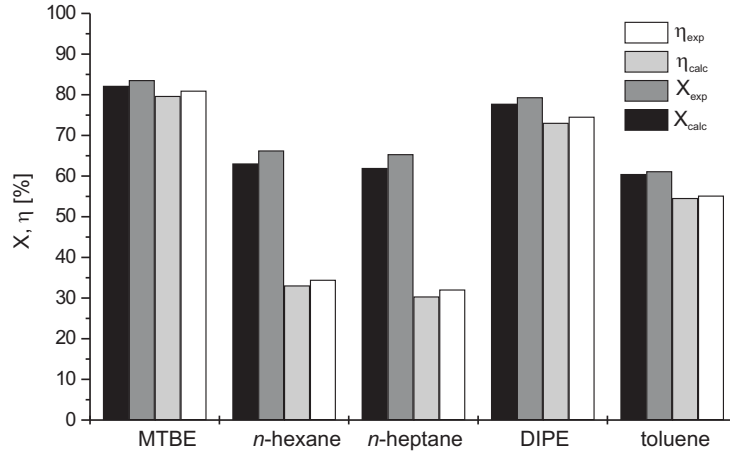


Figure 2.6.: Comparison of calculated and experimentally measured^[66,67] equilibrium conversion X and equilibrium yield η for different solvent combinations for the reduction of acetophenone to (*R*)-1-phenylethanol at 30 °C.

Table 2.1.: Equilibrium conversion X_{calc} and experimentally obtained values X_{exp} in % as function of V for $S = 2$.

Solvent	V	X_{calc}	X_{exp}
MTBE	0.1	44.7	48.6
	0.5	43.1	46.4
	1	42.8	45.9
	10	42.6	44.6
<i>n</i> -hexane	0.1	40.4	41.0
	0.5	28.7	30.1
	1	25.4	27.1
	10	24.1	28.2

Iso-conversion and iso-yield lines can be calculated for desired values of X and η according to equations 2.16 and 2.17, respectively. With fixed X and η , S and V are dependent on

each other, following the general trends (Figure 2.7). Generally, each particular system has to be judged on an individual basis as it is dependent on both the absolute values for the partition coefficients and their combination.

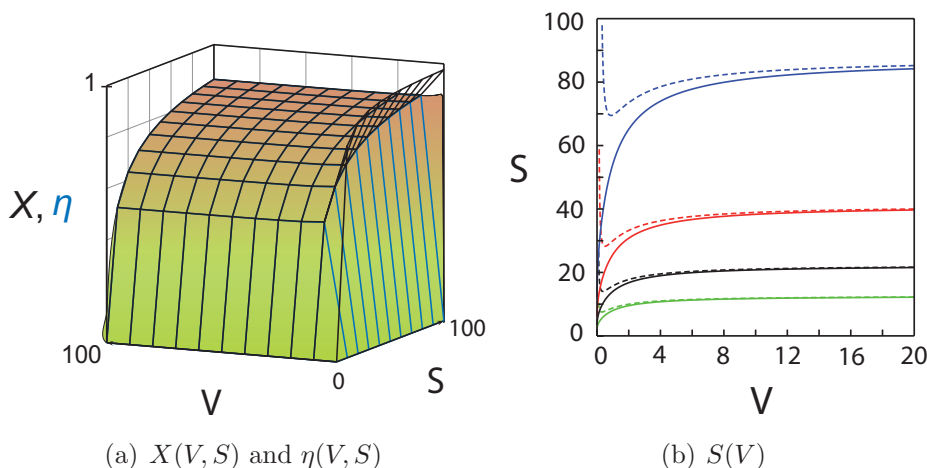


Figure 2.7.: (a): Conversion X and yield η as function of S and V , (b): iso-conversion and iso-yield lines of S and V for the experimental system from literature^[66,67] with solid: X , dashed: η , and in top down order: blue: 0.85, red: 0.75, black: 0.65, green: 0.55.

Increasing the substrate ratio to $S = 20$ with a fixed phase volume ratio of $V = 1$, X increases from 27% to 66% in the presence of *n*-hexane and from 46% to 84% when MTBE is used (Table 2.1 and Table 2.2). A further increase in substrate ratio S leads to preparative useful equilibrium conversions (e.g. for $S = 200$ and $V = 1$ in MTBE/aqueous buffer, $X_{\text{exp}} = 98.0\%$ and $X_{\text{calc}} = 97.7\%$).

To find a suitable non-reactive phase, the equilibrium conversion and the product yield were compared for different solvents (Table 2.2). For $S = 20$ the highest equilibrium conversions are achieved in the presence of MTBE and di-*iso*-propyl ether (DIPE). The equilibrium product yield η is only slightly lower than X , because the partition coefficients of the product (*R*)-1-phenylethanol are high for both systems: $\gamma(\text{MTBE}) = 32.1$ and $\gamma(\text{DIPE}) = 15.7$. In contrast, using *n*-hexane or *n*-heptane, the partition coefficients of (*R*)-1-phenylethanol are close to unity: $\gamma(\textit{n-hexane}) = 1.1$ and $\gamma(\textit{n-heptane}) = 1.0$. Then, not only conversion is lower, but η is only half of X for $V = 1$.

Table 2.2.: Calculated equilibrium conversion X_{calc} , calculated equilibrium yield η_{calc} and experimentally obtained values in % for $S = 20$ and $V = 1$.

Solvent	X_{calc}	X_{exp}	η_{calc}	η_{exp}
MTBE	82.2	83.6	79.7	81.0
<i>n</i> -hexane	63.1	66.3	33.1	34.5
<i>n</i> -heptane	62.0	65.4	30.4	32.1
DIPE	77.8	79.4	73.1	74.6
toluene	60.5	61.2	54.6	55.2
cyclohexanone ^[a]	83.9	-	81.6	-
[BMIM][(CF ₃ SO ₂) ₂ N]	51.2	64.9	41.0	51.7
[BMIM][PF ₆]	66.1	66.2	61.8	61.9

^[a] No exp. result due to enzyme deactivation

For the application of cyclohexanone the calculation yields $X = 84\%$. However, no experimental data could be obtained for this system due to the lack of enzyme stability. This example demonstrates that the mathematical expression cannot cover the influence of factors like (bio-)catalyst stability in the biphasic mixture.

Finally, X and η obtained by calculation can be compared to experimental data X_{exp} and η_{exp} . In general, both values are in good agreement (Figure 2.8). The observation that experimental results are slightly higher than calculated data may be due to the neglected activity coefficients. The differences between the calculated and experimentally determined conversion and product yield are highest for the ionic liquids where the experimental error for the partition coefficients is highest. This shows that the underlying database is, of course, critical for correct predictions.

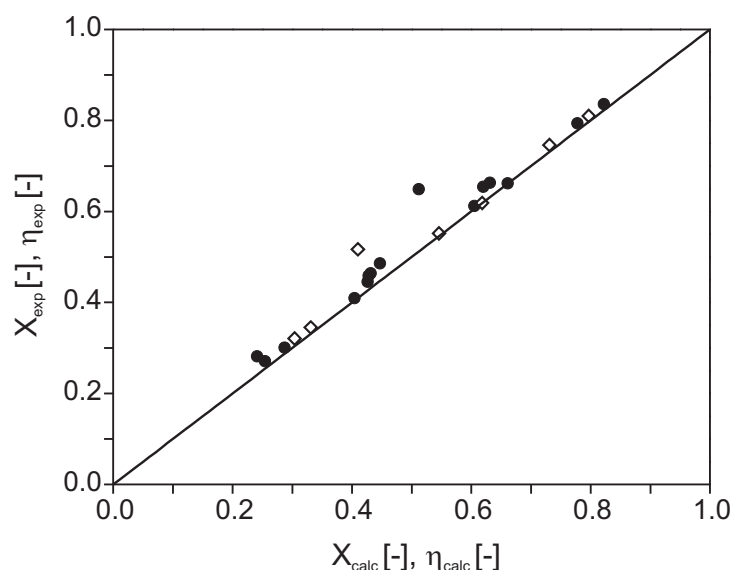


Figure 2.8.: Parity plot of calculated and experimental^[66,67] results for X and η ; $\bullet$ represent X , $\diamond$ represent η .

2.4. Conclusion

A mathematical description for conversion and yield in an idealized catalyzed biphasic reaction system was discussed. With this exact expression it is possible to generalize the influence of different parameters such as partition coefficients, phase volume ratio, co-substrate excess and equilibrium constant. Overall, a prediction of equilibrium conversion and yield is possible. Due to the interdependencies of the different parameters, case by case consideration is necessary.

For a given system the degrees of freedom are reduced to co-substrate excess S and phase volume ratio V . Iso-conversion and iso-yield lines for co-substrate excess S and phase volume ratio V are helpful tools for experimental planning. Following this methodology, conversion and yield could be improved for the model reaction, the enantioselective reduction of acetophenone from $X_{\text{exp}} = 61.2$ in toluene to $X_{\text{exp}} = 83.6$ in MTBE. As a given system can only be influenced within the thermodynamically imposed boundaries, knowledge and prediction of this experimental frame enables to reveal and adequately discuss other relevant influences.

3. Calculating partition coefficients using COSMO-RS

3.1. Introduction

To pave the way to an *ab initio* solvent screening for biphasic systems, prediction of solvent dependent parameters is a prerequisite. After the analysis of the thermodynamic situation of the system in the previous chapter, investigation of the phase equilibria is the target of this chapter. The performance of COSMO-RS for the prediction of equilibrium partitioning of enzyme-catalyzed oxidoreductions in biphasic media will be tested. At first, the quantitative performance for a specific reaction and solvent and then for a set of substrates and solvents is evaluated. The results are used for a solvent screening of a defined reaction based on equilibrium conversion as optimization target.

3.2. Materials and methods

3.2.1. Computational

The software GaussView (Version 3.09, Gaussian Inc., Wallingford, US) was used to assemble all molecules. The DFT/COSMO (Conductor-like screening model^[51]) calculations were performed using TURBOMOLE (Version 5.7.1, COSMOlogic, Leverkusen, Germany) with the BP86 density functional and a TZVP basis set combination.^[54]

For the following statistical thermodynamics, the software *COSMOtherm* (Version C2.1-0104/C2.1-0105, COSMOlogic, Leverkusen, Germany) was used based on the conductor-like screening model for realistic solvation (COSMO-RS).^[53,70] Partition coefficients at infinite dilution are a direct result of *COSMOtherm* calculations:

$$P_i^{21} = \frac{\exp(\mu_i^1 - \mu_i^2)}{RT} \frac{v^1}{v^2}. \quad (3.1)$$

In chemical engineering partition coefficients are usually reported in mole fractions, while in chemistry the unit of choice is usually mol/l. Although a partition coefficient is dimensionless in both conventions, it differs by the ratio of the molar volumes of the two solvents.^[71] The ratio of the molar volumes was estimated from the COSMO volumes since only ambient temperatures and pressures were considered here. The mutual solubility of the solvents was taken into account using an experimental data collection.^[72] These calculations at infinite dilution have been performed by the author of this thesis. All quantum chemical calculations were carried out on the high performance computer cluster of the Center for Computing and Communication, RWTH Aachen University, Germany.

The equilibrium partitioning at finite concentrations, however, was determined iteratively using the activity coefficients calculated by *COSMOtherm*. In contrast to the calculations at infinite dilution, no experimental data on phase composition could be inserted into the calculations. The iteration was carried out until activity coefficients were constant:

$$\gamma_i^1 x^1 = \gamma_i^2 x^2. \quad (3.2)$$

The resulting molar fractions x_i^2 and x_i^1 of both phases could then be used to calculate the volumetric equilibrium concentrations. These calculations at finite concentrations were performed by W. Eberhard, Biochemical Process Engineering, RWTH Aachen University, Germany, as part of his PhD thesis.

The calculations of equilibrium conversion were performed both with COSMO-RS calculated partition coefficients at infinite dilution and with experimentally determined partition coefficients. These calculations were performed by the author of this thesis.

3.2.2. Experimental

Experimental determination of partition coefficients at finite dilution was performed by W. Eberhard, Biochemical Process Engineering, RWTH Aachen University, Germany, as part of his PhD thesis. For the measurement of concentration dependent partition coefficients at 25°C (measurement range between 1.5mM and 350 mM), quantities of water, solvent and substrate were filled into screw capped glass vials. The headspace was minimized to reduce the loss of volatile material. The vials were repetitively shaken and left for one week. Samples were taken from the organic phase and analyzed by GC. For formic acid, the aqueous phase was sampled from an upside-down vial in order not to penetrate the organic phase during sampling and the equilibrium concentration was determined using HPLC. All measurements were carried out at least 7-fold.

Infinite dilution partition coefficients and equilibrium conversions were experimentally determined by M. Eckstein as part of her PhD thesis^[65] and by Julia Lembrecht (both Technical Chemistry, University of Rostock, Germany) as part of her diploma thesis. All infinite dilution partition coefficient measurements were carried out at least 7-fold.

For the determination of partition coefficients of acetophenone and 1-phenylethanol, substrate solutions for each compound were prepared in the desired solvents. In screw-capped vials the aqueous phase was covered with the same amount of organic phase. The samples were shaken (30°C, 400 rpm). The mixtures were stored in a water bath (30°C, 3 days). Samples were taken from each phase and analyzed by GC.

For the measurement of partition coefficients of acetone and 2-propanol the procedure is different. Since the analytical method to quantify 2-propanol and acetone is based on HPLC applying an aqueous eluent, samples could only be measured out of the aqueous phase. Therefore, substrate solutions were prepared in water and buffer, respectively, and the aqueous phase was covered with the desired organic solvents. To determine partition coefficients of acetone and 2-propanol, samples were taken from the aqueous phase before and after the addition of organic solvent and were measured by HPLC. The partition coefficients P could then be calculated following the decline of concentration in the aqueous phase.

For the measurement of equilibrium conversion and yield, an aqueous solution (2.5 mL)

of LB-ADH, NADP⁺ (0.1 mmolL⁻¹) and 2-propanol was covered with the organic solvent containing acetophenone (20 to 80 mM). The mixture was shaken in a vertical shaker (30°C, 200 rpm). Samples were withdrawn from the non-reactive organic phase and analyzed by GC. To get to values for conversion and yield, mass balances of acetophenone and 1-phenylethanol were corrected by their partition coefficients. Complete experimental details are described elsewhere.^[66,67]

3.3. Results and discussion

3.3.1. Alcohol dehydrogenase catalyzed reductions

The biocatalytic asymmetric reduction of acetophenone to (*R*)-1-phenylethanol using LB-ADH as biocatalyst (Figure 2.1 on page 35) is a typical example for a reaction where a biphasic system is particularly advantageous. Interesting substrates typically exhibit a low solubility in water, whereas the alcohol dehydrogenases are considerably more effective in aqueous environment. Therefore, aqueous-organic^[11,73,74] and aqueous-ionic liquid systems^[20,75] are in use. The addition of an immiscible solvent to the reaction system will influence the overall reaction equilibrium by partitioning of all substrates and products between the non-reactive organic and the reactive aqueous phase (Figure 2.1 on page 26).

The design and optimization of the reaction system requires the knowledge of the partitioning of all substrates and products between both phases. For a biocatalytic esterification in aqueous-organic two-phase systems, it was previously found that non-ideal partitioning occurs.^[76] Therefore, calculations and measurements of concentration-dependent partition coefficients were performed.

3.3.2. Calculation of concentration-dependent partition coefficients

The first system investigated was the reduction of acetophenone and a functionalized derivative (2-chloroacetophenone) to the corresponding alcohols in the biphasic reaction

medium *n*-hexane/water. The formate dehydrogenase (FDH) coupled cofactor regeneration with formic acid as co-substrate yielded gaseous carbon dioxide as co-product, thus driving the reaction equilibrium to the desired product. The predicted concentration dependent phase equilibria, those at infinite dilution and experimental data points for the distribution of acetophenone, 1-phenylethanol, 2-chloroacetophenone and formic acid in *n*-hexane/water are given in Figure 3.1.

As indicated by the experimental values, the solutes show a non-linear concentration-dependent distribution between the organic and the aqueous phase. For acetophenone (Figure 3.1(a)), COSMO-RS predictions for finite concentrations are both qualitatively and quantitatively in good agreement. The solubility limit in the aqueous buffer phase is reached at around 15 mM. For the corresponding reaction product, 1-phenylethanol (Figure 3.1(b)), however, larger deviations between the prediction and the experimental data occur. The same, even stronger effect can be observed for the chloro-substituted acetophenone (Figure 3.1(c)). In both cases, a more hydrophobic character of the substances is predicted than determined experimentally. A similar overestimation of octanol/water partition coefficients for alcohols and chloro-substituted compounds has been observed previously.^[77] Even the deviation of up to factor 10 lies within the previously published prediction accuracy. For formic acid (Figure 3.1(d)), however, the predicted and experimental values deviate within two orders of magnitude. In the same plot the prediction of the formic acid concentration is not distinguishable from the ordinate. Only in the insert in Figure 3.1(d) can it be seen that the aqueous formic acid concentration differs from infinity. The deviations here can be attributed to the formation of dimers of the acid in the organic phase.^[76,78] The mere statistical approach of COSMO-RS is not capable of representing this associating behavior of a chemical compound. The consideration of conformers in case of alcohols and of dimers in case of carboxylic acids during the quantum mechanical calculation of the molecular surface will most probably lead to better quantitative results.

One source of error in the prediction of partition coefficients is the mutual solubility of the solvents. This cannot be taken into account in the calculation of finite partition coefficients using COSMO-RS leading to a significant error. Opposite to that, in the COSMO-RS calculation of infinite dilution partition coefficients the mutual solubility can be considered. This is possible either *via* direct calculation of liquid-liquid

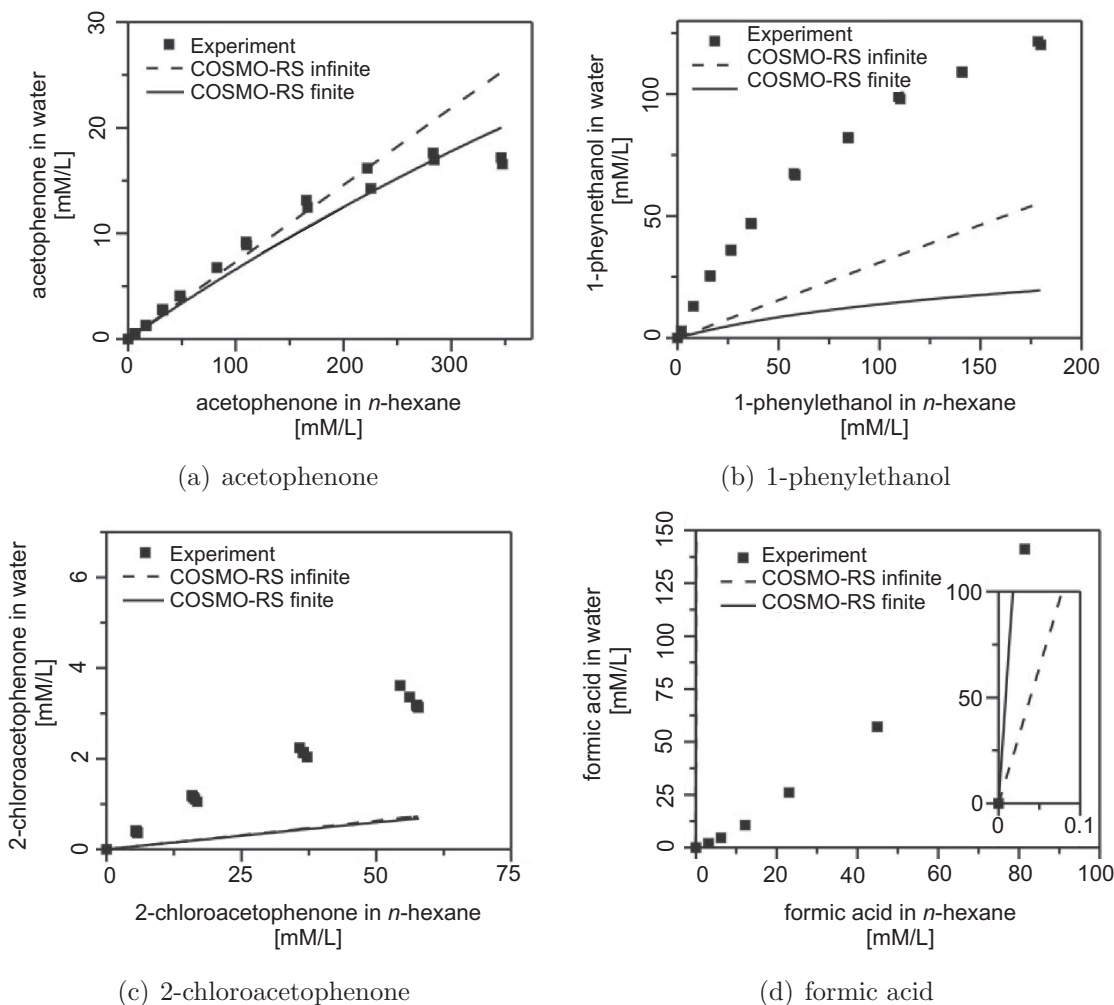


Figure 3.1.: Concentration-dependent equilibrium partitioning of single compounds in *n*-hexane/water biphasic systems at 25°C for (a): acetophenone, (b): 1-phenylethanol, (c): 2-chloroacetophenone, (d) formic acid; ■ indicate experimental data points, solid lines refer to COSMO-RS calculations for finite dilution, dashed lines refer to infinite dilution. For formic acid (d), the predicted values are not distinguishable from the ordinate, only the insert shows that aqueous formic acid concentrations differ from infinity.

equilibria or by using experimental data. For acetophenone and 1-phenylethanol in *n*-hexane/water at 30°C for example, the partition coefficients at infinite dilution calculated using COSMOtherm’s LLE calculation are slightly lower (17.232 and 6.842) than those

calculated using the experimental LLE (19.231 and 8.621).

Although the prediction of partitioning at finite dilution better represents the qualitative behavior of the solute partitioning between the aqueous and *n*-hexane phase, the prediction of partitioning at infinite dilution is equal (for 2-chloroacetophenone) or superior (in all other cases) in quantitative terms. Therefore, only infinite dilution partition coefficients were predicted for further studies. A similar approach was chosen previously for the prediction of partitioning using UNIFAC.^[79]

3.3.3. Calculation of infinite dilution partition coefficients

A set of experimentally determined partition coefficients was compared to the COSMO-RS predicted partition coefficients at infinite dilution. In order to eliminate the systematic error of formic acid, the chosen solutes now cover substances used in the reduction of aliphatic ketones and acetophenone derivatives with a substrate-coupled cofactor regeneration using isopropanol as co-substrate in several biphasic solvent combinations (*n*-hexane, *n*-heptane, MTBE, toluene, cyclohexanone, each coupled with water). In the experimentally covered concentration range from 10 mM to 100 mM, the partition coefficients did not vary, but remained constant. Therefore, they are considered a good approximation to infinite dilution. The numerical values for the experimental data can be found in the original literature.^[65–67]

Figure 3.2 shows a logarithmic parity plot of the predicted infinite dilution partition coefficients over three sets of experimentally determined data. The first data set covers substrates and products of the acetophenone reduction using 2-propanol as co-substrate in several solvent systems.^[66] The second set covers linear ketones and some acetophenone derivatives and their corresponding alcohols in MTBE/water biphasic systems.^[65] The third data set covers the same compounds as the second, but in a *n*-hexane/water biphasic system.^[67] A certain bias towards overestimation of the partition coefficients towards hydrophobicity as mentioned above can be observed. The lower 95% boundary corresponds to factor 2.5 units ($0.4 \log(P^\infty)$) deviation, and the upper 95% boundary to factor 8 ($0.9 \log(P^\infty)$ units). A calculation of the root mean square (rms) deviation results in $0.25 \log(P^\infty)$ units. Even the COSMO-RS parameterization data set has a higher

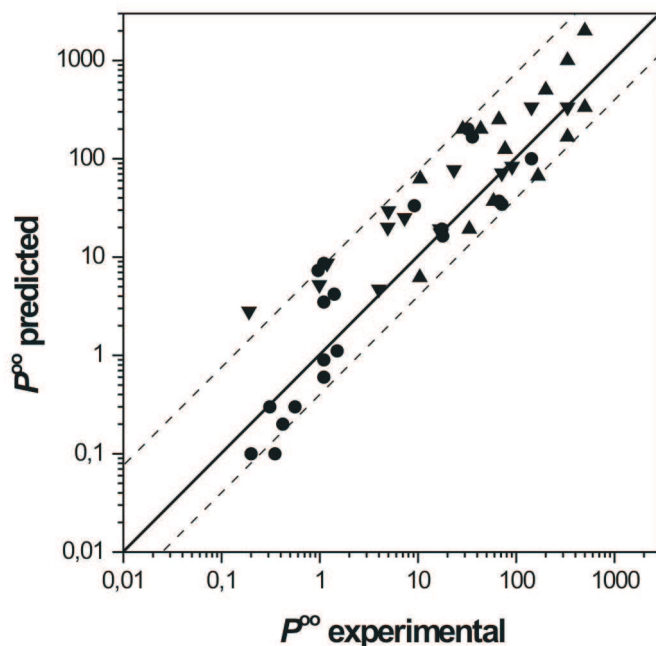


Figure 3.2.: Comparison of experimental and COSMO-RS predicted infinite dilution partition coefficients P^∞ at 30°C for single selected substrates and products in organic/aqueous biphasic reaction systems; ● indicate the data points corresponding to reference^[66], ▲ those of^[65], and ▼ those of^[67], the thick solid line indicates parity; the thin dashed lines enclose 95% of the data points; please note the logarithmic scaling.

rms deviation of 0.34 $\log(P^\infty)$ units.^[80] The prediction of the octanol-water partition coefficient $\log P_{ow}$ for more than 60 compounds resulted in a slightly inferior deviation of 0.43 $\log P_{ow}$ units (rms).^[77] In comparison to the prediction accuracy (0.64-0.83 $\log P_{ow}$ units rms) of two UNIFAC versions,^[77] the predictive power of COSMO-RS becomes apparent.

3.3.4. Solvent screening: partition coefficients

The screening of solvent combinations for one specific oxidoreduction reaction is now carried out by again predicting infinite dilution partition coefficients using COSMO-RS. To reduce the prediction error, experimental data was used for the mutual solubility of the solvents.^[72] The investigated reaction is the *LB*-ADH catalyzed reduction of acetophenone to (*R*)-1-phenylethanol using the 2-propanol coupled regeneration with acetone as co-product (Figure 2.1 on page 35). An overview about partition coefficient prediction for all solutes across several solvents is given in Figure 3.3. The solvents cover a representative range of organic solvents which are often used for enzyme catalyzed biphasic reaction systems.

Figure 3.3 indicates that the prediction of partition coefficients of ketones in several solvent combinations is more successful than that of the corresponding alcohols. The predicted partition coefficients at infinite dilution of acetophenone (Figure 3.3(a)) and acetone (Figure 3.3(d)) have a relative error of less than 30% with respect to the measured partition coefficients. Nearly quantitative prediction is obtained for acetophenone in linear alkane/water solvent combination. A bias to underestimate the infinite dilution partition coefficients of ketones can be observed for all solvent combinations. In contrast to the ketones, the infinite dilution partition coefficients of (*R*)-1-phenylethanol are overestimated for all solvent combinations (Figure 3.3(b)). Only the partitioning of the very small 2-propanol molecule is in good agreement in toluene and even underestimated in linear alkanes (Figure 3.3(c)). The prediction accuracy for the studied reaction system is within one order of magnitude on a linear scale. Looking at the sequence of partition coefficients for one solute across several solvent combinations, COSMO-RS is capable of predicting the correct trends. Nevertheless, care should be taken for protic solvents, since their ability to form hydrogen bonds is to date not sufficiently covered by COSMO-RS.

3.3.5. Solvent screening: equilibrium conversion

Having identified correct trends for infinite dilution partition coefficients for all reactants, the solvent combinations may now be compared with respect to the target function of maximum conversion (equation 2.13 on page 28). The reaction equilibrium constant

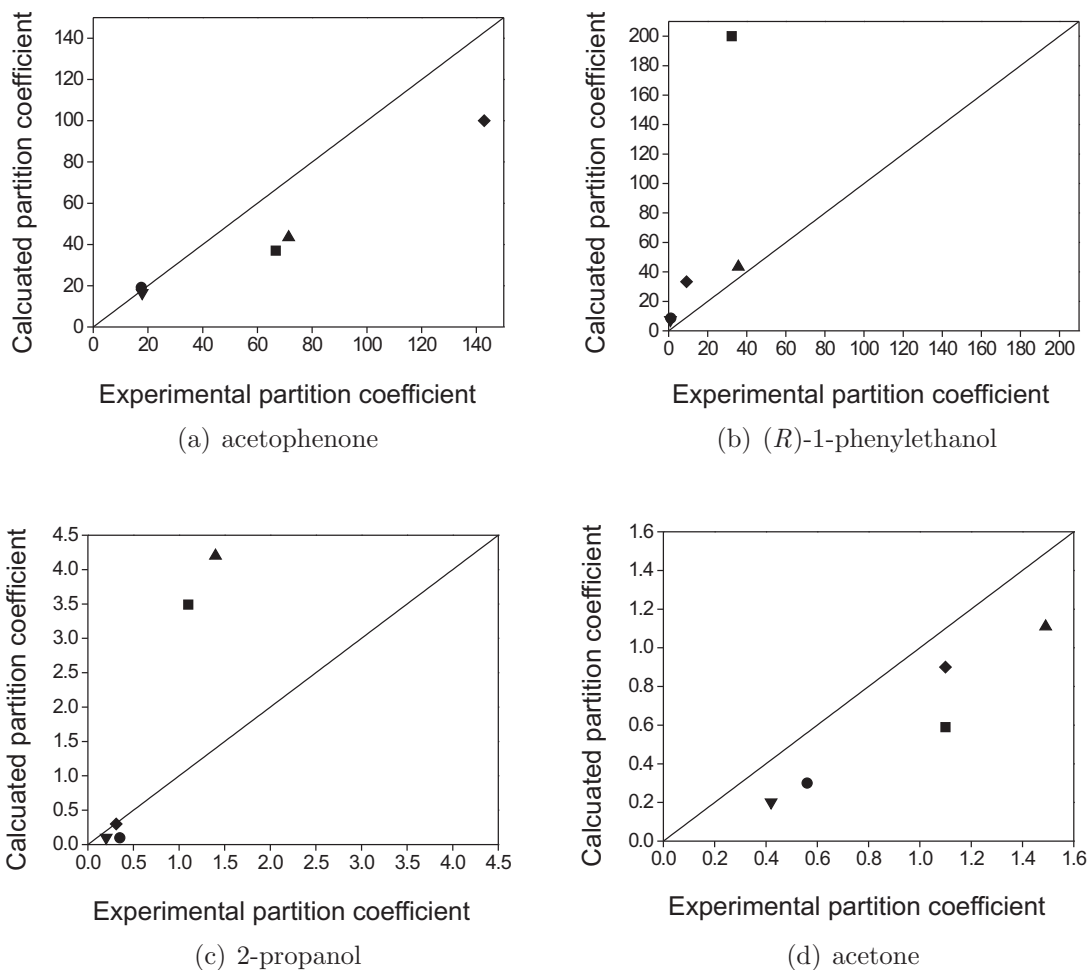


Figure 3.3.: Experimental and COSMO-RS predicted infinite dilution partition coefficients of single compounds at 30°C of (a): acetophenone, (b): (*R*)-1-phenylethanol, (c): 2-propanol, and (d): acetone in various organic solvent/water systems with ●: *n*-hexane/water, ▼: *n*-heptane/water, ■: MTBE/water, ▲: cyclohexanone/water, ◆: toluene/water. Note the difference in scaling.

K ($=0.426$ at 30°C) is intrinsically defined by the aqueous reaction environment. The substrate ratio $S = 20$ and the phase volume ratio $V = 1$ are kept constant across all solvent combinations. Thus, the maximum conversion may be calculated using the predicted partition coefficients at infinite dilution $X_{calc,ab\ initio}$, and compared with both

the calculated conversion using the experimentally determined partition coefficients X_{calc} and the experimental equilibrium conversion X_{exp} (Figure 3.4).

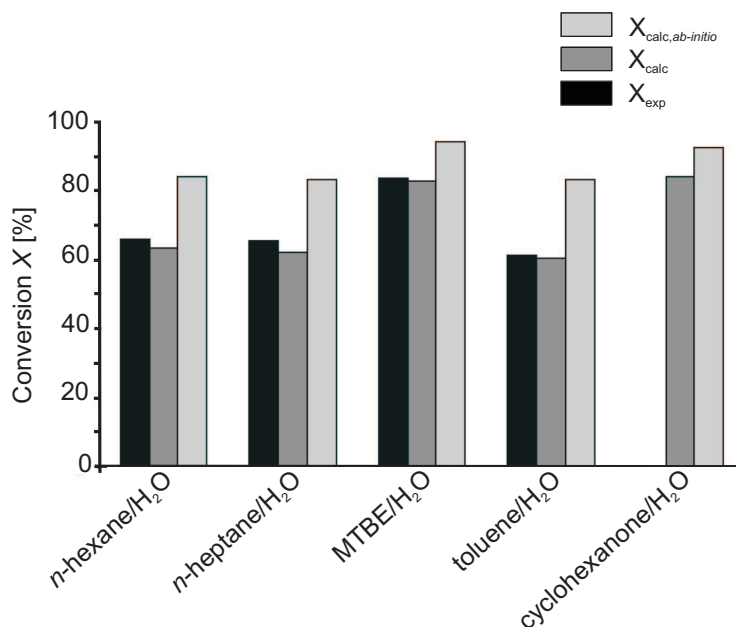


Figure 3.4.: Equilibrium conversion of the reduction of acetophenone to (*R*)-1-phenylethanol by oxidizing 2-propanol in various organic solvent/water systems with $K = 0.426$; $S = 20$; $V = 1$; black bars indicate experimental values X_{exp} ,^[66,67] dark grey bars represent the calculated conversion based on experimentally determined partition coefficients X_{calc} , light grey bars show the calculated conversion based on the COSMO-RS predicted partition coefficients at infinite dilution $X_{calc,ab-initio}$; for the cyclohexanone/water system no experimental data could be obtained.

The screening target theoretical conversion as calculated based on predicted infinite dilution partition coefficients $X_{calc,ab-initio}$ shows a systematic deviation of roughly +20% from the corresponding experimental data (Figure 3.4). The analogously calculated conversion using experimentally determined partition coefficients X_{calc} , however, is in good agreement with the directly measured X_{exp} . Therefore, it appears that the error contribution of the underlying ideality assumption in equation 2.13 on page 28 does not have a major effect. Although this assumption is in contrast to the non-ideal partitioning of

the investigated reaction systems (Figure 3.1), the influence on the maximum conversion is negligible in comparison to the deviation in the predicted partition coefficients. The error contribution may be explained by analyzing equation 2.12 on page 28. The overall reaction equilibrium constant is corrected by an expression containing the phase volume ratio and the partition coefficients. The overestimation of (*R*)-1-phenylethanol partition coefficients contributes strongest to the factor m , thus resulting in an overestimated overall reaction equilibrium constant mK . This again leads to a higher calculated equilibrium conversion.

Even if the absolute values for predicted conversions deviate in analogy to the prediction of individual partition coefficients, the overall trends are again represented well. One reason for this is that errors may cancel out in a reaction situation where functional groups such as ketones and alcohols are retained during the reaction. The highest experimentally determined conversion was successfully identified by the highest predicted conversion as shown in Table 3.1. The table also underlines that the ranking order of X_{exp} and $X_{calc,ab initio}$ for the systems *n*-heptane/water and toluene/water differ from each other. However, the difference lies within the first decimal place representing the limit of the predictions.

Table 3.1.: Ranking order of equilibrium conversion of the reduction of acetophenone to 1-phenylethanol by oxidizing 2-propanol in various organic solvent/water systems; bold red figures indicate a difference in the ranking order compared to X_{exp} .

Solvent combination	X_{exp}	X_{calc}	$X_{calc,ab initio}$
MTBE/water	83.5	82.8	93.9
<i>n</i> -hexane/water	65.8	63.2	83.9
<i>n</i> -heptane/water	65.3	62.0	83.0
toluene/water	61.2	60.5	83.2
cyclohexanone/water	0.0	83.9	92.3

Looking at the solvent combination cyclohexanone/water in Table 3.1, however, the second highest conversion was predicted both using predicted and experimentally deter-

mined partition coefficients, but was not reached experimentally since the enzyme did not retain sufficient activity in this solvent combination. This is an often observed effect for solvents of moderate hydrophobicity,^[81] also for oxidoreduction reactions.^[11] It brings the alternative solvent screening targets back into mind: Enzyme activity, selectivity, and stability. Thus, the thermodynamic screening may indeed be performed *in silico*, but an experimental validation of the top solvent candidates is mandatory. Even with a final confirmation run, the *in silico* screening approach will still save considerable laboratory effort because it allows to identify targets for further development and optimization.

3.4. Conclusion

For the design of biocatalytic biphasic reaction systems, the knowledge of partition equilibria for all reactants in suitable solvent systems is helpful for process modeling as well as for the targeted solvent screening. The quantum mechanical and statistical thermodynamics-based tool COSMO-RS was evaluated with respect to this quantitative task, i.e. prediction of finite and infinite dilution partition coefficients for modeling purpose and the qualitative task of solvent screening for maximum conversion.

Although non-ideal equilibrium partitioning was well predicted, the infinite dilution partition coefficients calculations still lead to smaller overall deviations from the experimental values than finite dilution partition coefficient calculations. Consequently, the more sophisticated approaches to overall reaction equilibrium calculations taking the changing reactant partitioning during the reaction into account (non-ideal equilibrium partitioning) seem exaggerated at the current stage. For the selected components the experimental data were systematically better represented than by other tools, but an improvement of the quantitative performance would still be highly desirable for a more in-depth process design.

For qualitative tasks like solvent screening, however, the quality of prediction seems sufficient since the ranking order of solvents for a chemical compound regarding infinite dilution partition coefficients was predicted correctly. Based on these data, the theoretical conversion could be calculated, resulting in the selection of suitable solvents for the asymmetric biphasic reduction of acetophenone to (*R*)-1-phenylethanol. A ranking

of solvents in view of theoretical conversion was achieved, systematic deviations in predicted partition coefficients for individual compounds neutralize in the reaction context. The experimental validation of this choice will remain necessary with respect to solvent tolerance of the catalyst and solvation effects that influence the catalytic performance, such as activity, specificity, and selectivity.

4. Calculating equilibrium constants

4.1. Introduction

The last step to the *ab initio* solvent screening is an *in silico* prediction of the equilibrium constant of a reaction. Therefore, the investigation of solvation processes is a prerequisite. In order 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 found only sparsely 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.^[67] In the context of this thesis, 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 for equilibrium conversion and yield.

4.2. Materials and methods

4.2.1. Computational

The molecules were assembled using the software GaussView (Version 3.09, Gaussian Inc., Wallingford, US).^[82] The geometry optimizations and the frequency calculations for each molecule were carried out using the B3LYP/TZVP method using the software Gaussian 03.^[83]

On top of that the calculations led 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 Gaussian and the different quantum chemical methods B3LYP/TZVP, MP2/TZVP and CCSD(T)/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) with RI-BP86 functional and TZVP basis set.^[84–86]

The energies of solvation were calculated using the software COSMO*therm* (Version C2.1, Release 01.05, COSMOlogic GmbH, Leverkusen, Germany).^[80,87] The different basis sets used for the calculations in the gas and the liquid phase were chosen according to the recommendation of COSMOlogic, the distributor of COSMO*therm*. Standard state for the calculation of Gibbs free energy of solvation ΔG_{solv} is the fluid hypothetical ideally diluted at 1 M concentration. All quantum chemical calculations were performed by the author of this thesis and carried out on the high performance computer cluster of the Center for Computing and Communication, RWTH Aachen University, Germany.

4.2.2. Experimental

The experimental data for $\Delta G_{\text{r}}^{\text{ideal gas}}$ were taken from literature,^[88] the experimental data for $\Delta G_{\text{r}}^{\text{solution}}$ were taken from literature as well.^[89]

4.3. Results and discussion

The overall aim was to establish an easy-to-handle procedure for the calculation of standard Gibbs energies of reaction in solution $\Delta G_{\text{r}}^{\text{solution}}$. Based on a Hessian cycle in Figure 4.1, $\Delta G_{\text{r}}^{\text{solution}}$ can be calculated by summing 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} :

$$\Delta G_r^{\text{solution}} = \Delta G_r^{\text{ideal gas}} + \sum \Delta G_{\text{solv}}(i). \quad (4.1)$$

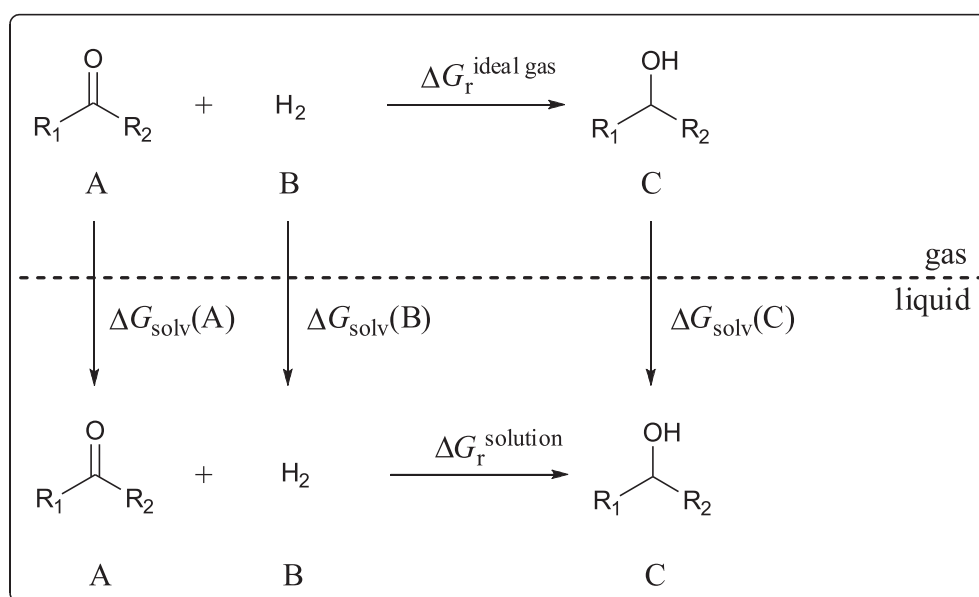


Figure 4.1.: Hessian cycle for the computational derivation of the standard Gibbs energy of reaction in solution $\Delta G_r^{\text{solution}}$ for the reduction of ketones with different residues R₁ and R₂ to the corresponding alcohols.

Experimental data for the Gibbs free energies of reaction in the gas phase can be found in literature.^[88] By contrast there is a huge lack of experimental data for the standard Gibbs energy of reaction in solution. Adkins *et al.* measured standard reaction Gibbs energies in toluene for reduction reactions of differently substituted ketones to alcohols to which the data will be compared.^[89] Experimental and calculated values can be found in the appendix in Table B.1 on page 99 – Table B.6 on page 104.

4.3.1. Gibbs free energy of reaction in the gas phase

When performing a quantum chemical geometry optimization, the equilibrium geometry of the studied molecule and its energy are 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 2nd 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.^[28] These contributions are necessary to proceed from the energy, which is a result of the Schrödinger equation, to the $\Delta G_r^{\text{ideal gas}}$ at a finite temperature.

From this data, the standard Gibbs energy of reaction in the gas phase can be computed and compared to experimental data. It is important to note that the force constants are 2nd 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. Since 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 $\Delta G_r^{\text{ideal gas}}$, energies in the gas phase and a term accounting for thermal correction were summed up:

$$\Delta G_r^{\text{ideal gas}} = E^{\text{gas phase}} + G_{\text{thermal correction}}. \quad (4.2)$$

The method used for the calculation of the latter 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 4.2 and in the appendix Tables B.1, B.2, B.3). For $\Delta G_r^{\text{ideal gas}}$, the magnitude of

the average differences between calculation and experiment is 3.4 kJ/mol for CCSD(T), 8.5 kJ/mol for MP2 and 17.5 kJ/mol for DFT.

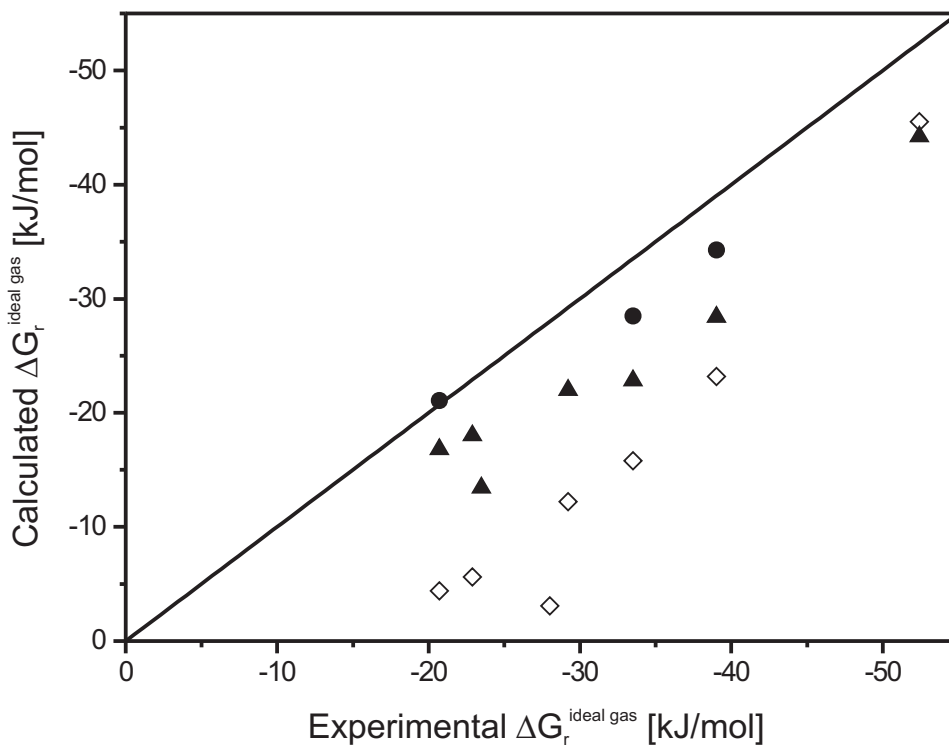


Figure 4.2.: Parity plot for the Gibbs free energy of reaction in the gas $\Delta G_r^{\text{ideal gas}}$ in kJ/mol; ◇ : DFT, ▲ : MP2, ● : CCSD(T); experimental data taken from literature.^[88]

In terms of computational costs the trend is the same since DFT scales with molecular size $z^2 - z^4$, MP2 with molecular size z^5 and CCSD(T) with molecular size z^7 . So DFT is the fastest method with the lowest accuracy, CCSD(T) is the most time-consuming method leading to the highest accuracy. Table 4.1 highlights these trends for selected compounds. Due to the high computational costs of CCSD(T) only few calculations could be accomplished with this method. Therefore it is generally not applicable for calculations of molecules with more than approximately 12 atoms.

Table 4.1.: Comparison of job CPU time in s for the calculation of Gibbs free energies of reaction in the gas phase $\Delta G_r^{\text{ideal gas}}$; CPU time for geometry optimizations at B3LYP/TZVP and single point energy calculations at B3LYP/TZVP, MP2/TZVP or CCSD(T)/cc-pVTZ summed up.

molecule	calculation time for $\Delta G_r^{\text{ideal gas}}$ in s		
	B3LYP/TZVP	MP2/TZVP	CCSD(T)/cc-pVTZ
C ₂ H ₄ O (acetaldehyde)	120	180	21000
C ₃ H ₆ O (acetone)	480	660	152880
C ₄ H ₈ O (isobutanal)	1140	1620	323460
C ₅ H ₁₀ O (3-pentanone)	9120	10080	857220

4.3.2. Gibbs free energy of solvation

The Gibbs free energies of solvation ΔG_{solv} can be calculated from Henry coefficients. For the calculation of Henry coefficients, COSMO-RS was used.^[80,87] Table 4.2 highlights the speed of this kind of calculations. The calculated values for ΔG_{solv} cannot be compared to experimental values because no literature data is available for the specific reduction reactions in toluene considered here.

Table 4.2.: Comparison of job CPU time in s for the calculation of Gibbs free energies of solvation ΔG_{solv} ; geometry optimizations and single point energy calculations at BP86/TZVP.

molecule	calculation time for ΔG_{solv} in s
	BP86/TZVP
C ₂ H ₄ O (acetaldehyde)	8
C ₃ H ₆ O (acetone)	16
C ₄ H ₈ O (isobutanal)	16
C ₅ H ₁₀ O (3-pentanone)	40

4.3.3. Standard Gibbs energy of reaction in solution

Following the Hessian cycle depicted in Figure 4.1, the calculation of $\Delta G_r^{\text{solution}}$ 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} according to equation (4.1). The results are shown in Figure 4.3 and in Tables B.4, B.5, B.6 in the appendix. Surprisingly, the quantum chemically most laborious method, CCSD(T), as well as the second most laborious method, MP2, leads to similar results in terms of accuracy: For the standard Gibbs energy of reaction in solution the magnitude of 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. The good result for MP2 might be 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.

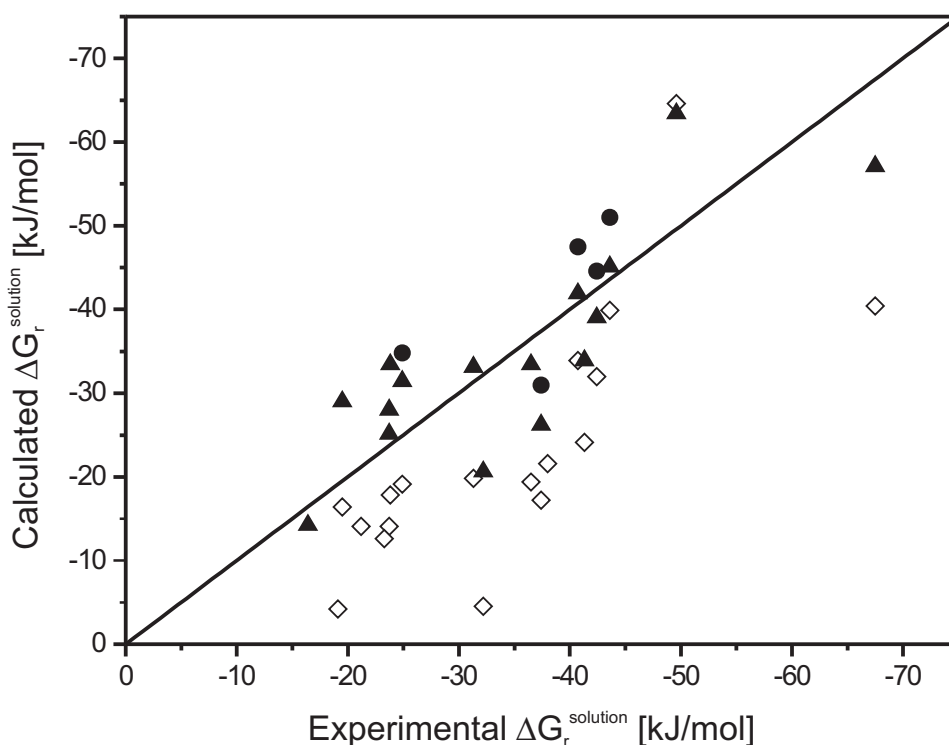


Figure 4.3.: Parity plot for the standard Gibbs energy of reaction in solution $\Delta G_r^{\text{solution}}$ in kJ/mol; $\diamond$: DFT, $\blacktriangle$: MP2, $\bullet$: CCSD(T); experimental data taken from literature.^[89]

4. Calculating equilibrium constants

To get an overview about the computational cost for the calculation of $\Delta G_r^{\text{solution}}$, Table 4.3 summarizes the overall computational time.

Table 4.3.: Comparison of job CPU time in s for the calculation of Gibbs free energies of reaction in the gas phase $\Delta G_r^{\text{ideal gas}}$, Gibbs free energies of solvation ΔG_{solv} and Gibbs free energies of reaction in solution $\Delta G_r^{\text{solution}}$; exemplarily shown for CCSD(T)/cc-pVTZ single point energy calculation method.

molecule	calculation time in s			
	$\Delta G_r^{\text{ideal gas}}$	ΔG_{solv}	ΔG_{solv}	$\Delta G_r^{\text{solution}}$
	CCSD(T)/cc-pVTZ	BP86/TZVP	COSMO $_{\text{therm}}$	Σ
C ₂ H ₄ O (acetaldehyde)	21000	8	2	21010
C ₃ H ₆ O (acetone)	152880	16	2	152898
C ₄ H ₈ O (isobutanal)	323460	16	2	323478
C ₅ H ₁₀ O (3-pentanone)	857220	40	2	857262

Moreover, to judge the contribution of COSMO-RS to the error for $\Delta G_r^{\text{solution}}$, a comparison was carried out (Figure 4.4): On the one hand, $\Delta G_r^{\text{solution}}$ was calculated by addition of calculated $\Delta G_{r, \text{calc}}^{\text{ideal gas}}$ and calculated ΔG_{solv} :

$$\text{Ab-initio calculated } \Delta G_r^{\text{solution}} = \Delta G_{r, \text{calc}}^{\text{ideal gas}} + \Delta G_{\text{solv}}. \quad (4.3)$$

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} :

$$\text{Semi-empirically calculated } \Delta G_r^{\text{solution}} = \Delta G_{r, \text{exp}}^{\text{ideal gas}} + \Delta G_{\text{solv}}. \quad (4.4)$$

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 below).

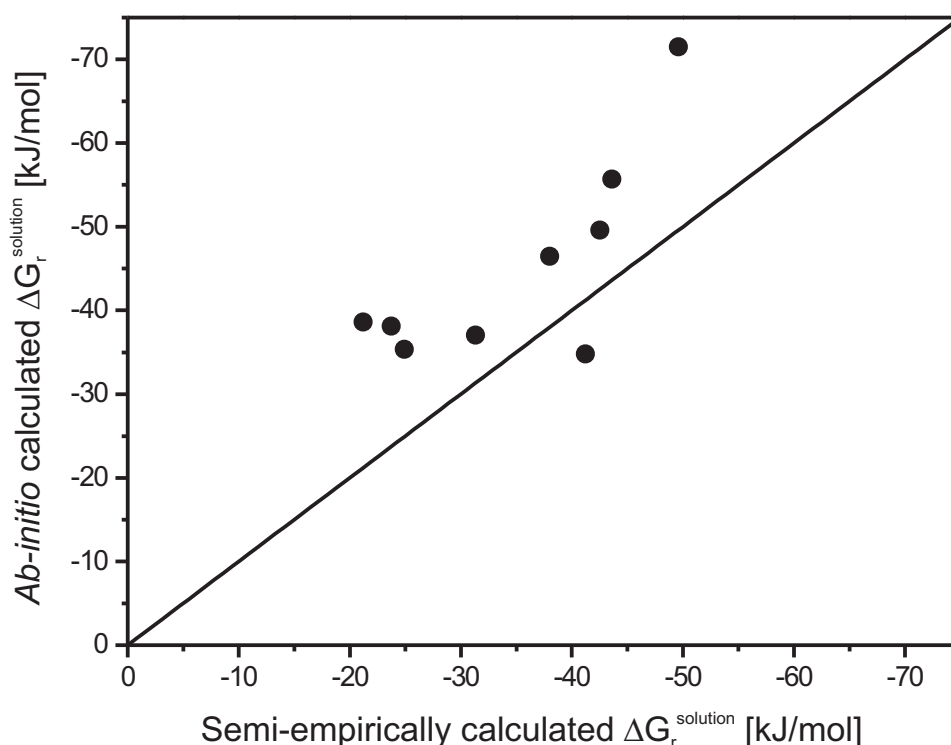


Figure 4.4.: Parity plot for the standard Gibbs energy of reaction in solution $\Delta G_r^{\text{solution}}$ in kJ/mol; semi-empirically calculated $\Delta G_r^{\text{solution}}$ obtained by addition of experimental $\Delta G_{r,\text{exp}}^{\text{ideal gas}}$ [88] and calculated ΔG_{solv} (equation (4.3)), *ab initio* calculated $\Delta G_r^{\text{solution}}$ obtained by addition of calculated $\Delta G_{r,\text{calc}}^{\text{ideal gas}}$ and calculated ΔG_{solv} (equation (4.4)).

4.3.4. Experimental validation

The model reaction is the asymmetric substrate-coupled biocatalytic reduction of acetophenone to (*R*)-phenylethanol (Figure 2.1 on page 35) in a biphasic reaction system with one reactive phase. The solvent used as reactive phase is water. Possible solvent candidates assessed are: *n*-hexane, *n*-heptane, MTBE, DIPE, toluene as well as the ionic liquids [BMIM][BTA] and [BMIM][PF₆].^[65,66]

Before the actual screening can be started a precise definition of the target is important, here, the maximization of 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 Chapter 2 as a basis. For an *ab initio* solvent screening the calculation of partition coefficients of all reactants is necessary as well as the calculation of equilibrium constant in the reactive water phase. The partition coefficients were calculated using COSMOtherm,^[90] the equilibrium constant according to the method presented within this chapter.

Experimentally, the equilibrium constant was determined to be 2.15 kJ/mol, the calculation yields 0.43 kJ/mol. There is a huge deviation in the absolute value, but the positive sign for the equilibrium constant could be calculated correctly. Figure 4.5 shows the results for experimental and *ab initio* predicted conversion X and yield η for the biocatalytic reduction of acetophenone to (*R*)-phenylethanol for the different solvents mentioned above. The solvent MTBE is the best solvent for the second phase in terms of conversion and yield, predicted and experimentally verified.^[66,67] 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, in order 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 (Figure 4.5). This procedure gives satisfactory values within the experimental error using a minimum of one experimental point for conversion and yield, respectively.

4.4. 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 quantum chemical geometry optimizations, the Gibbs free energies in the gas phase $\Delta G_r^{\text{ideal gas}}$ including the zero point energies were determined. The Gibbs free energies of solvation ΔG_{solv} were calculated using the COSMOtherm program.

From these values the standard Gibbs energies of reaction in solution $\Delta G_r^{\text{solution}}$ could be calculated according to a Hessian cycle by adding up $\Delta G_r^{\text{ideal gas}}$ and ΔG_{solv} . For

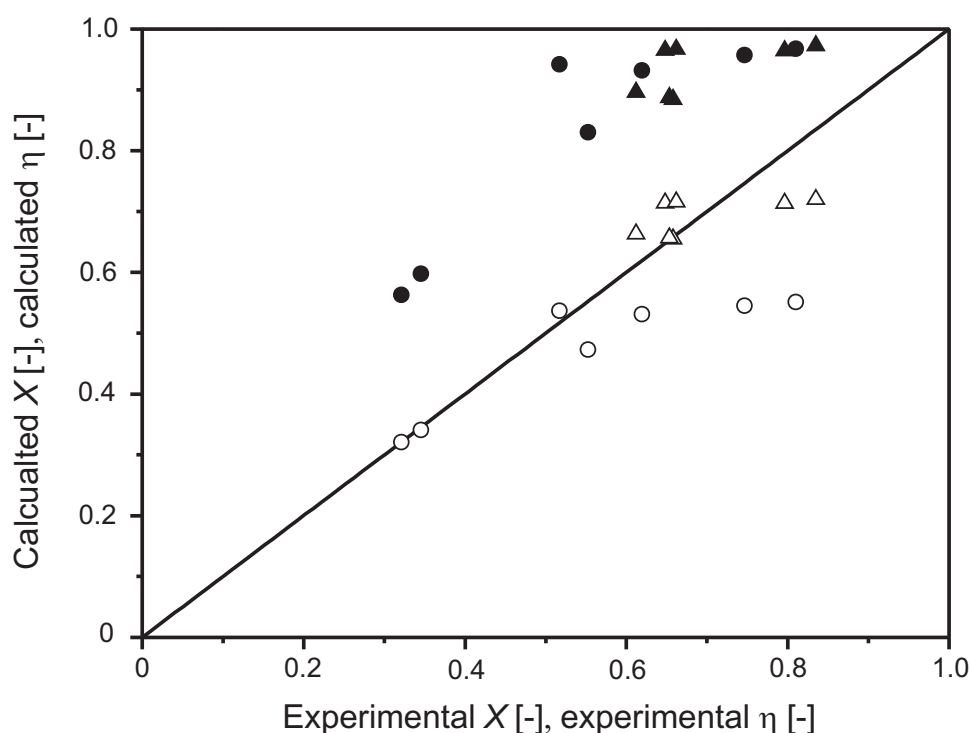


Figure 4.5.: Parity plot for conversion X and yield η ; $\blacktriangle$ =conversion, $\bullet$ =yield; $\triangle$ =normalized conversion, $\circ$ =normalized yield; the latter ones were normalized to one experimental result, here to the median of experimental conversion and yield, respectively; experimental results from literature^[66,67].

the calculation of the gas phase energies, three different quantum chemical methods were compared. CCSD(T) led to accurate results but at high computational costs. The second most laborious method MP2 led to results with similar accuracy to CCSD(T). The fastest method DFT led to results with the largest error. 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, 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. For

a further refinement and validation of the method more reliable experimental data is needed.

Moving beyond the prediction of $\Delta G_r^{\text{solution}}$ to a computational solvent screening, a prediction of general trends was possible, exemplarily shown for equilibrium conversion and product yield. Due to the error in the calculation of $\Delta G_r^{\text{solution}}$, the absolute values for conversion and yield differed substantially from experimental values. Correction of predicted values by scaling with a single experimental point led to quantitative values within the experimental error. This is often an economically more reasonable way than an exclusively experimental investigation.

5. Combining COSMO-RS with dynamic modeling for solvent screening

5.1. Introduction

In the previous chapters, a computational approach to solvent selection was established. With the method presented so far, a general solvent screening for equilibrium conversion and yield is possible. But X and η are just the first screening targets. In reality, there are many more parameters that determine a suitable solvent combination for a reaction. Hence, a further investigation of the reaction system is necessary, typically carried out experimentally. To reduce the amount of experiments a computational approach is presented combining *ab-initio* COSMO-RS calculations with subsequent *a posteriori* dynamic modeling, hence dynamic modeling based on experimental data. With sufficient experimental data, e.g. the decrease of the initial substrate concentration with time, mass transfer coefficients and partition coefficients can be modeled. Furthermore, the dependency of these coefficients on process parameters such as temperature and solubilizer can be modeled.

5.2. Materials and methods

5.2.1. Computational

Quantum mechanical geometry optimizations were performed using TURBOMOLE (Version 5.7.1, COSMOlogic, Leverkusen, Germany) with BP86 parameterization and a TZVP basis set.^[84–86,91] The statistical thermodynamics calculations were performed using the COSMOtherm software (Version C2.1-0106, COSMOlogic, Leverkusen, Germany).^[92] The calculations were performed by the author of this thesis. All quantum chemical calculations were carried out on the high performance computer cluster of the Center for Computing and Communication, RWTH Aachen University, Germany.

The dynamic modeling was carried out by M. Zavrel, Department of Biochemical Engineering, RWTH Aachen University, Germany, as part of his PhD thesis. For the purpose of dynamic modeling the software package gPROMS (Version 3.0.4, Process System Enterprise Ltd., London, UK) was used. The dynamic model contains the following three equations:

$$\frac{dc_{i,\text{org}}}{dt}V_{\text{org}} = \dot{n}^i. \quad (5.1)$$

$$\frac{dc_{i,\text{aq}}}{dt}V_{\text{aq}} = -\dot{n}^i. \quad (5.2)$$

$$\dot{n}^i = k_i A (P_i c_{i,\text{aq}}(t) - c_{i,\text{org}}(t)) \quad (5.3)$$

According to the two-film theory, the mass transfer resistance in both boundary layers has to be considered.^[93] Therefore, k_i is defined as:

$$\frac{1}{k_i} = \frac{1}{k_{i,\text{org}}} + \frac{P_i}{k_{i,\text{aq}}} \quad (5.4)$$

However, this term contains only constants and can thus be combined to one single parameter in order to reduce the number of unknown parameters.^[94]

For the parameter estimation, the initial concentrations, the mass transfer area and the phase volumes had to be known as well as initial guesses for the mass transfer coefficients k_i and the partition coefficients P_i . Due to the high correlation between the mass transfer coefficient and the partition coefficient that equals -1 for DMBA and TMB, the concurrent estimation of both parameters is difficult. That is why in a first step only the mass transfer coefficient was estimated while for the partition coefficient the value obtained by HPLC was used (52.5 for DMBA, 89.8 for TMB).^[95] In the second step, both parameters were estimated concurrently.

5.2.2. Experimental

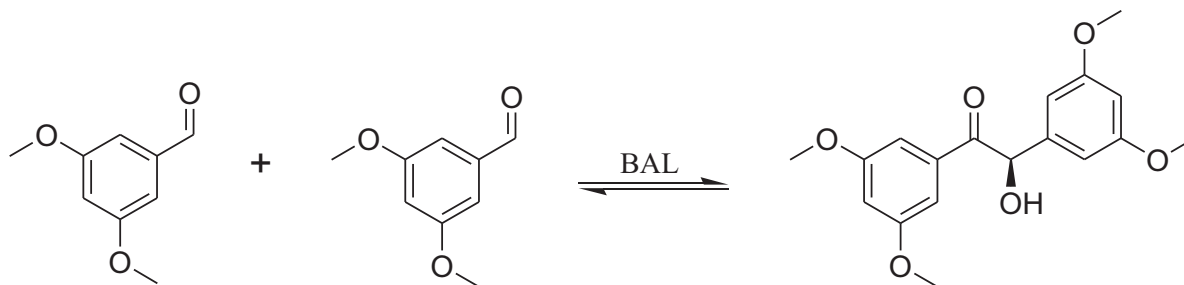
Experiments were carried out by T. Schmidt, Department of Biotechnology, RWTH Aachen University, Germany, as part of his PhD thesis.^[95] Details regarding the specific reaction set-up can be found in his PhD thesis. For mass transfer experiments the aqueous phase consisted of a 50 mM KPi buffer and 25 % (v/v) DMF. The latter was added to increase the solubility of the aromatic compounds. The pH value was set to 8.5 and the ionic strength to 100 mM. The solvents *n*-hexane and MIBK were used as organic phases, respectively. The mass transfer experiments were performed at 25°C in a continuously stirred tank reactor. Both phases were stirred individually using two independent stirrers and their volumes were equal. The dynamic measurements were conducted using a spectrophotometer that recorded the extinction in the aqueous phase. In all experiments no enzyme was present. For the analysis, high-performance liquid chromatography (HPLC) was used.

5.3. Results and discussion

5.3.1. Benzaldehyde lyase catalyzed carbon-carbon coupling

So far, bimolecular reactions with partitioning of all reactants were investigated. However, there are many more types of reactions that are of great industrial interest. The reaction studied here is the enantioselective carbon-carbon coupling of two 3,5-dimethoxy-

benzaldehyde (DMBA) molecules to (*R*)-3,3',5,5'-tetramethoxy-benzoin (TMB) using the enzyme benzaldehyde lyase (BAL, EC 4.1.2.38) (Scheme 5.1). This benzoin formation is of commercial interest since chiral hydroxy-ketones are important building blocks of drugs and natural products.^[96] A mechanistic model for this reaction has recently been derived by Zavrel.^[97]



Scheme 5.1: Enantioselective carbon-carbon coupling of 3,5-dimethoxy-benzaldehyde (DMBA) to (*R*)-3,3',5,5'-tetramethoxy-benzoin (TMB) catalyzed by BAL.

From a thermodynamic point of view, a well-suited solvent for this reaction type will continuously push the substrate into the reactive phase while it pulls the product from the reactive to the non-reactive phase. In other words, the substrate partition coefficient will be low and the product partition coefficient will be high. Consequently, a factor R was introduced (equation 5.5), defined as the ratio of the product partition coefficient divided by the substrate partition coefficient:

$$R = \frac{P_{\text{product}}}{P_{\text{substrate}}}. \quad (5.5)$$

This factor describes the ability of the solvent in the non-reactive phase to shift the substrate into the reactive phase and to extract the product out of it. There are of course more parameters that influence maximum conversion and extractable yield obtainable in a biphasic system, but among these factors, the ratio of partition coefficients R is of great importance: By increasing R , both conversion and extractable yield are maximized.^[98]

A general problem of various reactions of preparative and industrial interest is that their ratio of partition coefficients is disadvantageous. Furthermore, to use the tool of biphasic reaction systems effectively for reaction engineering purposes, a distinct knowledge of R is

required. To obtain reliable data for R , a large number of time-consuming and expensive experiments are necessary. To overcome the effort of numerous experiments for reaction optimization in biphasic systems, a systematic approach to solvent selection for biphasic systems is presented.

The proposed systematic approach to solvent selection combining COSMO-RS with dynamic modeling and guided experiments is illustrated in Figure 5.1. Starting point are quantum mechanical geometry optimizations and COSMO calculations. The subsequent COSMO-RS (conductor-like screening model for realistic solvation)^[70,92,99] calculations that allow a first *ab-initio* solvent screening consist of two major steps: the first selection step is the calculation of liquid-liquid equilibria (LLE). If the solvents do not show a miscibility gap at reaction temperature with the solvent used as reactive phase, here water, they are eliminated in the first step.

Those solvents that actually show a miscibility gap with water enter into the second selection step, the calculation of partition coefficients at infinite dilution and are ranked accordingly. COSMO-RS can predict general trends for partition coefficients, but the prediction of absolute values is difficult.^[66,90] Hence, an experimental validation is carried out to check the COSMO-RS solvent ranking.

Experimental data also serves as starting point for the subsequent *a posteriori* dynamic modeling. The dynamic model is fitted to experimental data to model partition coefficients and mass transfer coefficients. The influence of process parameters such as temperature and solubilizer content, which can significantly influence the overall mass transfer, can also be modeled.

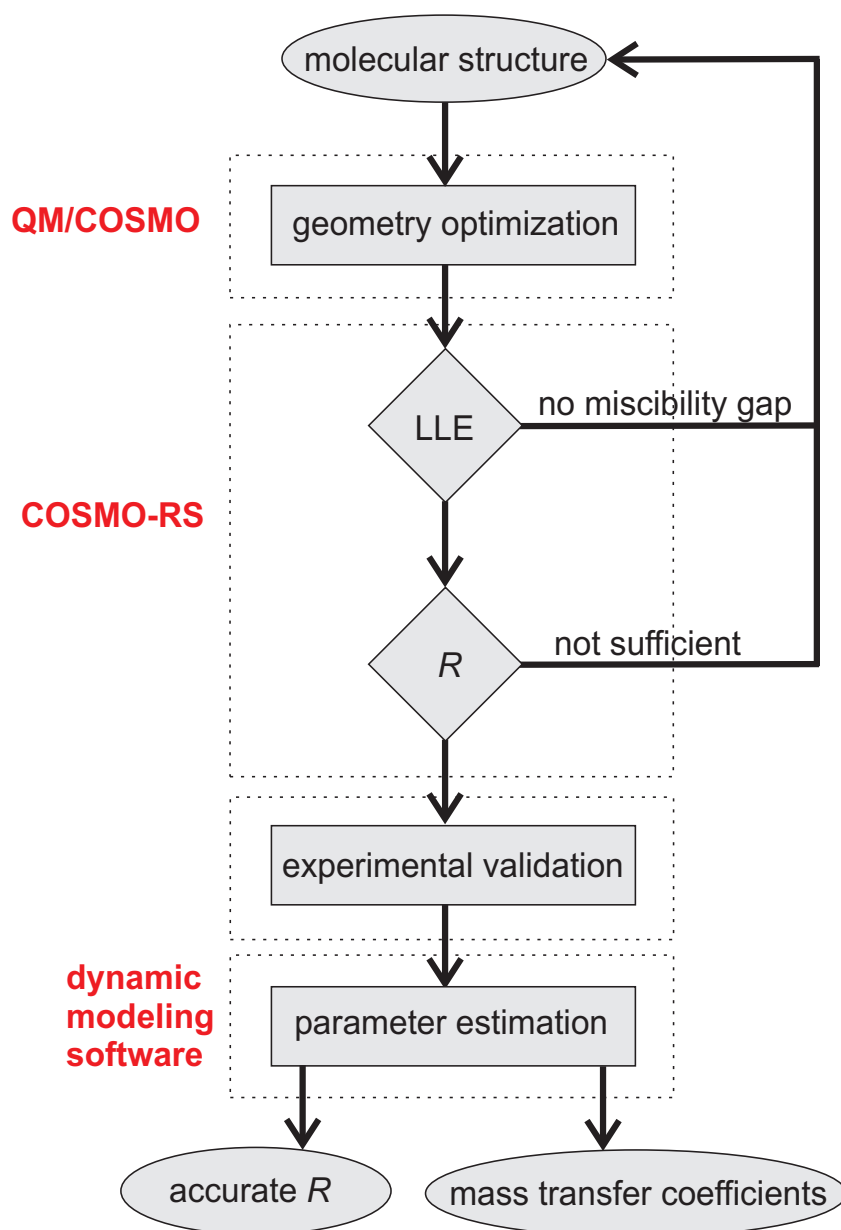


Figure 5.1.: Systematic approach to solvent selection combining COSMO-RS and dynamic model with guided experiments.

5.3.2. COSMO-RS

For the solvent screening using COSMO-RS more than 30 solvents have been tested as non-reactive phase (Table 5.1). The solvents have been chosen so that a wide range of solvent polarity is covered. Out of these, 11 solvents did not pass the first hurdle, the LLE calculation, since they did not show a miscibility gap with water at reaction temperature (25 °C). For the remaining solvent combinations, partition coefficients were calculated for the substrate DMBA and the product TMB between aqueous and organic phase. The solvent combinations were assessed according to their factor R which is a good first indicator of solvent suitability for the reaction system of interest. To validate the COSMO-RS predictions, MIBK with large factor R and n -hexane with small factor R were investigated experimentally and are discussed in the following sections.

Table 5.1.: Solvents with COSMO $_{therm}$ calculated miscibility gap with water at 25 °C, ranked according to the factor R .

solvent	$R = P_{\text{product}}/P_{\text{substrate}}$	solvent	$R = P_{\text{product}}/P_{\text{substrate}}$
<i>cis</i> -decalin	2.59	benzene	15.53
cyclohexanone	2.79	2-pentanone	16.51
<i>n</i> -heptane	3.02	piperidine	16.69
2-propanol	3.28	anisole	16.84
<i>n</i> -hexane	3.35	1-butanol	19.78
cyclohexane	3.56	MTBE	19.83
pentane	3.84	acetophenone	20.39
1-propanol	5.25	1-hexanol	23.32
tetrahydrofuran	5.54	MIBK	24.14
toluene	12.41	1-pentanol	24.15
ethoxybenzene	14.20	diethylether	24.42
ethylacetate	14.33		

5.3.3. Dynamic modeling

COSMO-RS can only predict thermodynamic properties at equilibrium. For the prediction of dynamic behavior of a reaction system an *a posteriori* dynamic modeling is promising. To estimate the parameters, the initial concentrations, the mass transfer area and the phase volumes have to be given as well as initial guesses for the mass transfer coefficients k_i and the partition coefficients P_i . First, only the mass transfer coefficient was estimated while the measured HPLC value was used for the partition coefficient. Second, both parameters were estimated concurrently. The results are the estimated values of partition coefficients and mass transfer coefficients with their standard deviations.

Figure 5.2 illustrates the fit of the dynamic model to experimental data using MIBK. The experiment started with 5 mM DMBA in the aqueous phase and 0 mM DMBA in the organic MIBK phase. No enzyme was used in the experiment. The aqueous phase also contained the solubilizer DMF to enhance the solubility of the aromatic compounds. The DMBA concentration in the aqueous phase was recorded using absorption measurements.

After fitting the dynamic model to experimental data, partition coefficients can be modeled in the reaction system. Despite the high correlation between mass transfer coefficients and partition coefficients, the obtained parameter estimates can be considered reliable since the obtained values for the partition coefficients are close to those obtained by HPLC (52.5 for DMBA and 89.8 for TMB):^[95] The partition coefficients modeled by the dynamic model are 52.37 ± 0.13 for DMBA and 84.36 ± 0.99 for TMB, resulting in a factor R of 1.611 ± 0.023 . This is a significantly lower value than the one obtained by the COSMO-RS predictions resulting in a factor R of 24.14. One of the main reasons for that is that in the COSMO*therm* calculations, opposite to the dynamic modeling, the solubilizer DMF could not be taken into account.

Figure 5.3 illustrates the fit of the dynamic model to the experimental results using *n*-hexane as organic phase. The initial experimental concentration of DMBA in the aqueous phase was 15 mM DMBA and 0 mM DMBA in the organic *n*-hexane phase. No enzyme was used in the experiment. The aqueous phase contained DMF as solubilizer. In the aqueous phase, the DMBA concentration was recorded using absorption measurements.

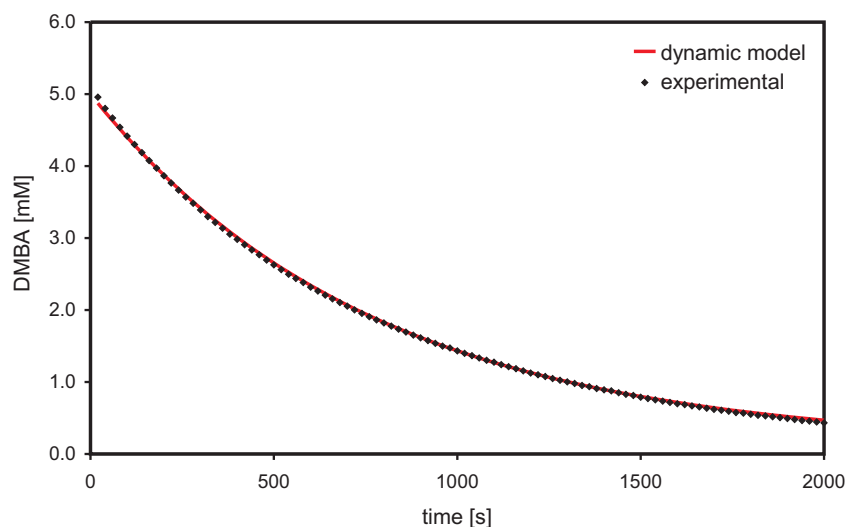


Figure 5.2.: Fit of the dynamic model to experimental results; the experiment was started with a DMBA concentration of 5 mM in the aqueous phase, and 0 mM in the organic phase (MIBK); the DMBA concentration in the aqueous phase was recorded using absorption measurements.

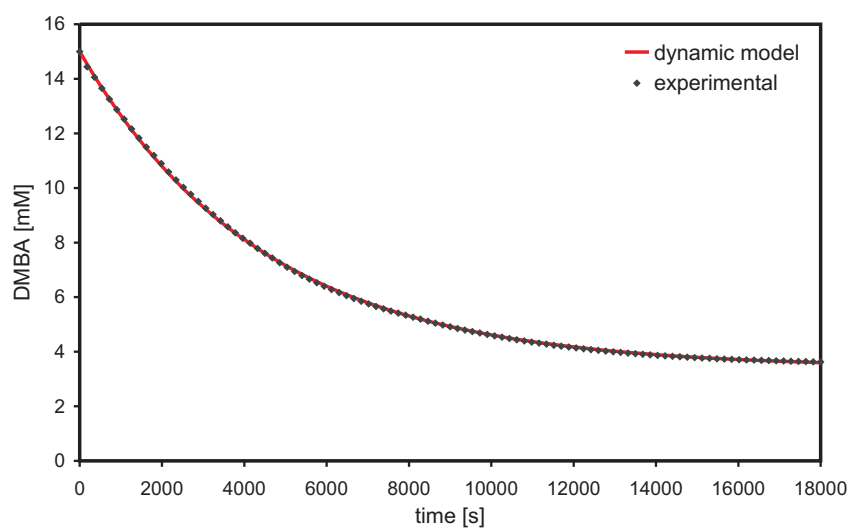


Figure 5.3.: Fit of the dynamic model to experimental results; the experiment was started with a DMBA concentration of 15 mM in the aqueous phase, and 0 mM in the organic phase (*n*-hexane); the DMBA concentration in the aqueous phase was recorded using absorption measurements.

The partition coefficients for DMBA and TMB are in this system dynamically modeled to be 3.41 ± 0.04 and 0.36 ± 0.01 , respectively, R equals 0.106 ± 0.004 . COSMO-RS predictions resulted in a factor R of 3.35. Consequently, for the reaction system of interest *n*-hexane is not a suitable organic phase to obtain high yields.

However R can generally be altered by process parameters such as temperature and volume fraction of the solubilizer DMF. Figure 5.4 illustrates the influence of the temperature on the single partition coefficients and on the factor R . The partition coefficients show only slight changes whereas the factor R can significantly be increased with increasing temperature.

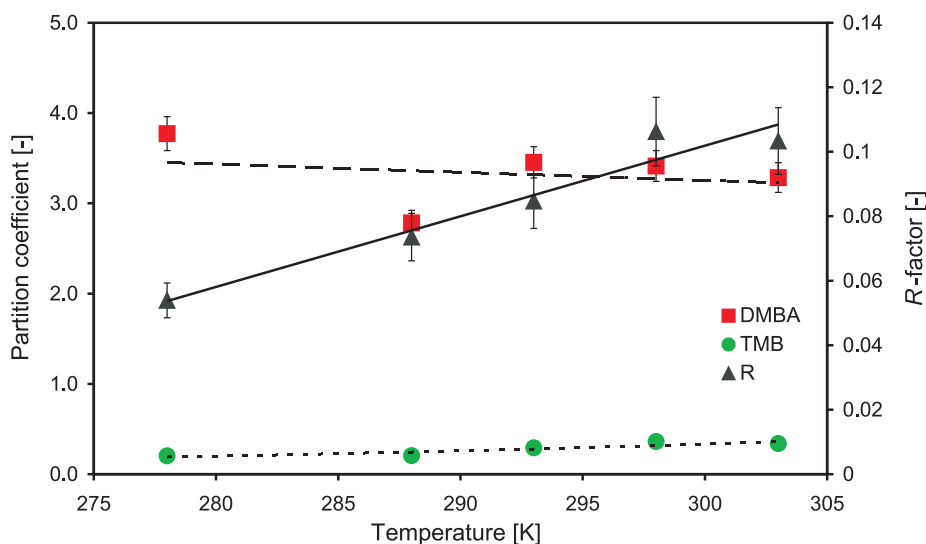


Figure 5.4.: Influence of temperature on partition coefficients (DMBA: ■; TMB: ●) and on the R -factor (▲).

More pronounced is the effect of the solubilizer DMF shown in Figure 5.5. DMF increases the equilibrium concentration of both reactants in the aqueous phase. However, the decrease of the product partition coefficient is more pronounced than the substrate partition coefficient. As a result, the factor R can be increased by reducing the amount of solubilizer in the aqueous phase. Concluding, a process using *n*-hexane as extraction

solvent should be operated at high temperatures and with as little as possible solubilizer DMF.

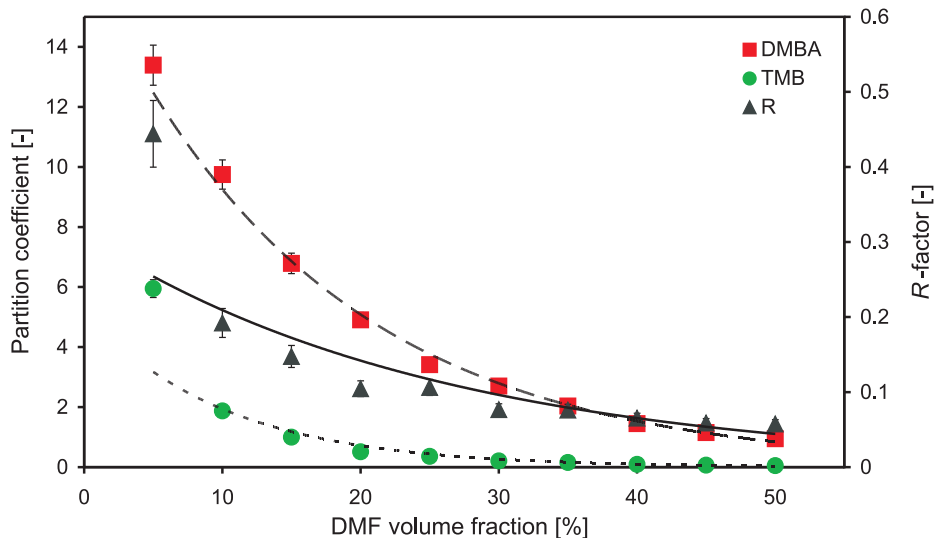


Figure 5.5.: Influence of the solubilizer DMF on partition coefficients (DMBA: ■; TMB: ●) and on the R -factor (▲).

If the factor R of MIBK and n -hexane are compared it becomes obvious that, despite the fact that their absolute values are not predicted accurately, the overall trend is verified. The predicted ratio of the R factors of MIBK and n -hexane by COSMO-RS is 7.16, while the ratio of R factors determined by the dynamic modeling is 14.63. Consequently, MIBK turned out to be a more suitable solvent for the reaction in terms of partition coefficients.

The mass transfer coefficients in MIBK at 298 K for the substrate DMBA with a 95% confidence interval are modeled to be $k_{\text{DMBA}} = 5.39 \cdot 10^{-07} \frac{\text{m}}{\text{s}} \pm 1.33 \cdot 10^{-09} \frac{\text{m}}{\text{s}}$. For the product TMB the mass transfer coefficients with a 95% confidence interval are estimated to be $k(\text{TMB}) = 2.81 \cdot 10^{-07} \frac{\text{m}}{\text{s}} \pm 3.33 \cdot 10^{-09} \frac{\text{m}}{\text{s}}$. This seems reasonable since the substrate DMBA should diffuse faster through the interface than the larger product TMB.

Certainly, there are many more parameters than partition coefficients and mass transfer coefficients that have an influence on the final solvent choice for an industrial process,

such as enzyme stability, safety aspects, price and availability. Mostly, solvent selection in industry is a compromise.

5.4. Conclusion

A systematic approach to solvent selection for biphasic aqueous-organic reactions was presented. The model reaction was the enantioselective carbon-carbon coupling of two 3,5-dimethoxy-benzaldehyde (DMBA) molecules to (*R*)-3,3',5,5'-tetramethoxy-benzoin (TMB).

In the first step, COSMO-RS was used as a fast and effective solvent screening tool. The accuracy of the calculated results was sufficient for a first solvent screening. Although no reliable absolute values could be predicted, the method was nevertheless a valuable tool at least as long as the solubilizer is neglected. The second step, where a dynamic model was fitted to experimental data, led to a more detailed and exact study of the model system. Furthermore, not only the mass transfer coefficients and the partition coefficients could be modeled but also the dependency on process parameters such as temperature and solubilizer content, which might significantly affect the mass transfer as demonstrated.

6. Conclusion and Outlook

Solvent selection is a key requirement for the successful implementation of environmentally benign but economically competitive processes in chemical production. Up to date, a suitable solvent for an industrial process is chosen by many time-consuming and cost-intensive experiments. For multiphase systems the interaction of the phases multiplies the complexity and the expenses for the choice of the best combination. To minimize the cost of experimental work, to enlarge the dataspace but also to reduce the environmental impact, a computational solvent screening procedure based on thermodynamic properties is a promising alternative (Figure 6.1).

The basic target reaction system investigated in this thesis was the biphasic reaction system with one reactive phase. Due to the possibility of integrating downstream processing and facilitating product separation, biphasic reaction systems are of high industrial relevance. Nevertheless, their exact mathematical description is complex. And the further combination of biphasic systems with a reaction taking place in the reactive phase renders an additional challenge.

Suitable model reactions for biphasic systems are biocatalytic reactions, as they offer the advantages of ideal selectivity towards the product. Furthermore, they are strongly limited by thermodynamics. Two biocatalytic reactions were examined here: On the one hand the enzymatic substrate coupled cofactor regeneration where acetophenone is enantioselectively reduced to (*R*)-phenylethanol while 2-propanol is oxidized to acetone, on the other hand the enzymatic enantioselective carbon-carbon coupling of two 3,5-dimethoxy-benzaldehyde (DMBA) molecules to (*R*)-3,3',5,5'-tetramethoxy-benzoin (TMB).

In order to judge the potential of different biphasic reaction systems, conversion X and yield η were applied as dimensionless measures for reaction progress and maximum re-

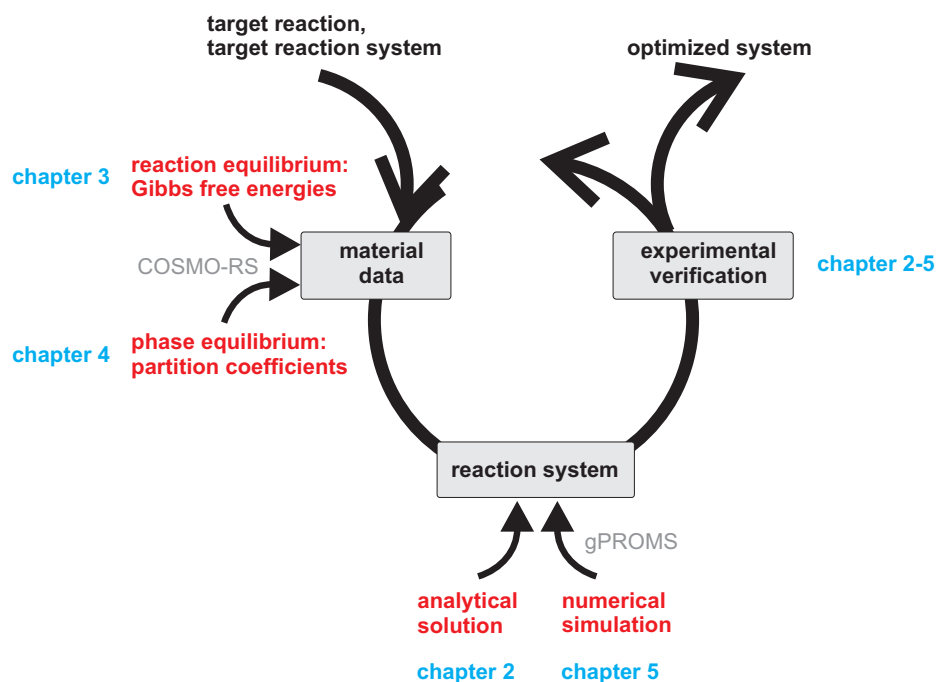


Figure 6.1.: Conceived and realized workflow for a computational approach to solvent selection.

coverable product. A derived mathematical description of the idealized biphasic reaction system covered the key parameters that influence conversion and yield. The direct algebraic solution worked well for experimentally determined partition coefficients and equilibrium constants. It allowed an estimation of the thermodynamic boundaries of the reaction system. Furthermore, a quantification of chemists' intuitive guesses on biphasic reaction systems was possible.

To be independent of experimental values of partition coefficients and equilibrium constants, their *ab initio* prediction was evaluated successively. Using a quantum-mechanical geometry optimization at B3LYP/TZVP level and a subsequent COSMO-RS calculation, a qualitative prediction of partition coefficients was possible. One of the great advantages of this approach was that, besides known compounds, also virtual compounds not synthesized before could be subject to calculations, and their application potential could be evaluated.

The *ab initio* prediction of equilibrium constants in solution was made possible but

proved to be much more complicated than the partition coefficient calculation. A generally applicable workflow was set up, applied here to the reduction of differently substituted ketones in toluene. In the calculations, the first step was a quantum-mechanical geometry optimization at B3LYP/TZVP level. For the subsequent single-point calculations, different quantum-chemical methods have been evaluated, in fact, in the order of increasing complexity and increasing computational cost: DFT (density functional theory), MP2 (2nd-order Møller–Plesset perturbation theory) and CC (coupled-cluster theory). Fortunately, for the equilibrium constant calculation, MP2 as being a method with medium complexity and medium computational demand led to results with similar accuracy as CC, the most complex and computationally most demanding method. Overall, this allowed a prediction of equilibrium constants or standard Gibbs energies of reaction in solution, respectively. This is especially important for equilibrium limited reactions.

For an evaluation of the overall process, a reduction to the dimensionless figures conversion X and yield η was made on the basis of *ab initio* data. Although at some stages deviations between experimental and calculated partition coefficients or equilibrium constants occurred, the overall results for conversion X and yield η were very promising. The ranking according to the *ab initio* predictions was in line with the experimental data. Normalizing to one experimental data point rendered the absolute data to mirror the experimental data fairly well. The investigations did not only reduce the amount of experiments but also led to a deeper understanding of reactions in biphasic reactions systems.

In order to benchmark the developed approach to computational solvent screening in biphasic reaction systems and to increase the overall predictive power of the method, reliable experimental data is needed. This is important for the testing and adjusting of the developed mathematical description and for extending this approach to other reactions, for example condensation reactions.

Reliable experimental data is also needed to verify and refine the computational tools used within this thesis such as COSMO-RS. The method leads to remarkably good results for molecules that do not have a too large structural variety. If more sophisticated substrates are to be considered in the solvents selection process, COSMO-RS still runs

into problems. This has been shown in a cooperation with *Shell Global Solutions, Amsterdam, The Netherlands*. In this project, activity coefficients of about 2000 ionic liquids have been screened for an industrial application. It could be shown that for ionic liquids the *ab initio* prediction of activity coefficients using COSMO-RS works very well, but the prediction of liquid-liquid-equilibria is still difficult. Since the calculation of the latter is always the first step in partition coefficient calculation, large errors might be the consequence. Up to date, the structural diversity of ionic liquids is not satisfactorily covered by COSMO-RS, especially the various intermolecular interactions. Moreover, first approaches to the prediction of polymeric properties are established but still challenging, and there is still room for further improvement.

Reliable experimental data is also needed to enhance the calculation of equilibrium constants of reactions in solution. Here, solvent dependent equilibrium constants for different types of reaction would be of great importance. With a further development of computer power, complex quantum-mechanical methods might become more and more attractive in the future.

For the determination of reliable experimental data, an automatization and miniaturization of the experiments would be a great advantage. Especially for the measurement of partition coefficients, the combination with robotics would have a major impact on the further development of the method and the computational tools.

The analytical mathematical description of the biphasic reaction system with one reactive phase is only accurate for strongly idealized reaction systems. To improve the method and to be able to treat non-ideal reaction systems, the combination with numerical simulation tools is the logical consequence. Briefly touched upon within this thesis, the combination with numerical simulation tools also enables the treatment of dynamic effects and does not necessarily stay with the static picture. For example, it allows a treatment of solubilizer which up to date cannot be treated satisfactorily using COSMO-RS. For the future, this might also link thermodynamic and kinetic investigations of reaction systems.

One of the major goals on the way towards computational solvent screening is an automated computational approach as this enables a fast and effective screening. In a cooperation with *Bayer MaterialScience, Leverkusen, Germany* within a project at the

CAT Catalytic Center at RWTH Aachen University, Germany, an automated solvent screening method was set up. For an industrial application, in total about 20000 solvent combinations could be investigated computationally. Including this approach in a software tool would enable fast screening processes.

Extending the idea of a computational solvent screening to other industrial problems such as crystallization is also possible. In a cooperation with a leading European pharmaceutical company, a solvent screening for crystallization processes has been carried out. First results look promising and raise expectations for future investigations.

Summarizing, the modeling of fluid phases is very complex and still deserves intensive study by interdisciplinary research teams. For the future, more experimental data are needed to optimize and benchmark computational tools and derived computational methods. The overall goal would be to establish a quantitative structure-activity relationship. The future development of more computer power is probably a major step towards an effective usage of computational tools. The first important steps have been made and have yielded promising results.

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Appendix

A. Computational details

A.1. Hardware

All quantum chemical calculations were carried out on the high performance computer cluster of the Center for Computing and Communication, RWTH Aachen University, Germany.

A.2. Software

The software packages and tools used for the calculations within this thesis are the following:

- Maple 10 (The Mathworks)
- GaussView (Version 3.09)
- Gaussian (Version 03)
- TURBOMOLE (Versions 5.7.1/5.8)
- COSMOtherm (Versions C2.1-0104/C2.1-0105/C2.1-0106)
- gPROMS (Version 3.0.4)

Computational details can be found in the respective chapters.

A.2.1. Workflow of a geometry optimization

The commands in the following geometry optimization workflow are only valid for calculations carried out on the high performance computer cluster of the Center for Computing and Communication, RWTH Aachen University, Germany.

A.2.1.1. Building of a molecule

- to initialize GaussView03/GaussView41 type `module load gaussview`
- generate molecular coordinates with GaussView
- save coordinates as cartesians in a *.com file

A.2.1.2. Definition of calculation parameters

Convert coordinates

- to initialize Turbomole 5.9.1 type `module load turbomole`
- type `x2t *.com > coord`

Turbomole tool "define":

- type `define`, <enter>, insert a title, <enter>

Reading of the molecular geometry:

- type `a coord`, verify the coordinates have been read successfully
- do not use `desy`, use C_1 symmetry
- use `ired` unless you optimize a linear molecule
- run a Force-Field optimization: `ff`, <enter>, `m 100`, <enter>, <enter>. The result should say "UFF ended normally, UFF geometry optimization converges!"
- `*` <enter>

Definition of the basis set:

- type `b` <enter> `all TZVP` <enter> to use Ahlrichs TZVP basis for all atoms
- `*` <enter>

Definition of MOs:

- type `eht` <enter> to use the Extended Hückel Theory
- enter charge if necessary
- press <enter> after all questions to use default values

Definition of the calculation parameters:

- for a DFT calculation with the BP functional and RI approximation type
`dft` <enter> `on` <enter> <enter> `ri` <enter> `jbas` <enter> `b` <enter>
`all def-TZVP` <enter> `*` <enter> `on` <enter> <enter>
- type `*` <enter> to finish the Turbomole tool "define", check "define ended normally"

Turbomole tool "cosmoprep":

- type `cosmoprep`
- press <enter> eight times
- type `r all o`
- type `*` <enter>
- enter a name for the *.ccf file

B. Calculating equilibrium constants

B.1. Gibbs free energy of reaction in the gas phase

Table B.1.: Gibbs free energies of reaction in the gas phase $\Delta G_r^{\text{ideal gas}}$ in kJ/mol for reduction of a ketone to an alcohol; only the ketone is given in the table. Computational method for the calculation of $\Delta G_r^{\text{ideal gas}}$ is CCSD(T)/cc-pVTZ, computational method for the added term accounting for the thermal correction to $\Delta G_r^{\text{ideal gas}}$ is B3LYP/TZVP.

ketone	experiment ^[88]	calculation		
	$\Delta G_{r, \text{exp}}^{\text{ideal gas}}$	$\Delta G_{r, \text{calc}}^{\text{ideal gas}}$	abs. error	rel. error
formaldehyde	−52.4	-	-	-
acetaldehyde	−39.0	−34.3	4.7	−0.1
acetone	−20.7	−20.1	0.6	0.0
isobutanal	−33.5	−28.5	5.0	−0.2
2-butanone	−23.5	-	-	-
furfural	−29.2	-	-	-
3-pentanone	-	-	-	-
cyclohexanone	−22.9	-	-	-
benzaldehyde	-	-	-	-
average over absolute values		-	3.4	0.1
$\text{abs. error} = \Delta G_{r, \text{calc}}^{\text{ideal gas}} - \Delta G_{r, \text{exp}}^{\text{ideal gas}}$				
$\text{rel. error} = \frac{\Delta G_{r, \text{calc}}^{\text{ideal gas}} - \Delta G_{r, \text{exp}}^{\text{ideal gas}}}{\Delta G_{r, \text{exp}}^{\text{ideal gas}}}$				

Table B.2.: Gibbs free energies of reaction in the gas phase $\Delta G_{\text{r}}^{\text{ideal gas}}$ in kJ/mol for reduction of a ketone to an alcohol; only the ketone is given in the table. Computational method for the calculation of $\Delta G_{\text{r}}^{\text{ideal gas}}$ is MP2/TZVP, computational method for the added term accounting for the thermal correction to $\Delta G_{\text{r}}^{\text{ideal gas}}$ is B3LYP/TZVP.

ketone	experiment ^[88]	calculation		
	$\Delta G_{\text{r, exp}}^{\text{ideal gas}}$	$\Delta G_{\text{r, calc}}^{\text{ideal gas}}$	abs. error	rel. error
formaldehyde	−52.4	−44.2	8.2	−0.2
acetaldehyde	−39.0	−28.4	10.6	−0.3
acetone	−20.7	−16.8	3.9	−0.2
isobutanal	−33.5	−22.8	10.7	−0.3
2-butanone	−23.5	−13.4	10.2	−0.4
furfural	−29.2	−22.0	7.2	−0.2
3-pentanone	-	-	-	-
cyclohexanone	−22.9	−18.0	4.9	−0.2
benzaldehyde	-	-	-	-
average over absolute values		-	8.5	0.3
abs. error = $\Delta G_{\text{r, calc}}^{\text{ideal gas}} - \Delta G_{\text{r, exp}}^{\text{ideal gas}}$				
rel. error = $\frac{\Delta G_{\text{r, calc}}^{\text{ideal gas}} - \Delta G_{\text{r, exp}}^{\text{ideal gas}}}{\Delta G_{\text{r, exp}}^{\text{ideal gas}}}$				

Table B.3.: Gibbs free energies of reaction in the gas phase $\Delta G_{\text{r}}^{\text{ideal gas}}$ in kJ/mol for reduction of a ketone to an alcohol; only the ketone is given in the table. Computational method for the calculation of $\Delta G_{\text{r}}^{\text{ideal gas}}$ is B3LYP/TZVP, computational method for the added term accounting for the thermal correction to $\Delta G_{\text{r}}^{\text{ideal gas}}$ is B3LYP/TZVP.

ketone	experiment ^[88]	calculation		
	$\Delta G_{\text{r, exp}}^{\text{ideal gas}}$	$\Delta G_{\text{r, calc}}^{\text{ideal gas}}$	abs. error	rel. error
formaldehyde	−52.4	−45.5	7.0	−0.1
acetaldehyde	−39.0	−23.2	15.8	−0.4
acetone	−20.7	−4.4	16.3	−0.8
isobutanal	−33.5	−15.8	17.7	−0.5
2-butanone	−23.5	−12.2	17.0	−0.6
furfural	−29.2	0.7	24.4	−1.0
3-pentanone	-	−5.6	17.3	−0.8
cyclohexanone	−22.9	−3.1	24.9	−0.9
benzaldehyde	-	-	-	-
average over absolute values		-	17.5	0.6
$\text{abs. error} = \Delta G_{\text{r, calc}}^{\text{ideal gas}} - \Delta G_{\text{r, exp}}^{\text{ideal gas}}$				
$\text{rel. error} = \frac{\Delta G_{\text{r, calc}}^{\text{ideal gas}} - \Delta G_{\text{r, exp}}^{\text{ideal gas}}}{\Delta G_{\text{r, exp}}^{\text{ideal gas}}}$				

B.2. Standard Gibbs energy of reaction in solution

Table B.4.: Standard Gibbs energies of reaction in solution $\Delta G_r^{\text{solution}}$ in kJ/mol for reduction of a ketone to an alcohol; only the ketone is given in the table. Computational method for the calculation of $\Delta G_r^{\text{ideal gas}}$ is CCSD(T)/cc-pVTZ.

ketone	experiment ^[88]	calculation		
	$\Delta G_{r, \text{exp}}^{\text{ideal gas}}$	$\Delta G_{r, \text{calc}}^{\text{ideal gas}}$	abs. error	rel. error
acetaldehyde	−43.6	−51.0	−7.4	0.2
acetone	−24.9	−34.8	−9.9	0.4
isobutanal	−42.5	−44.6	−2.1	0.1
2-butenal	−37.4	−31.0	6.4	−0.2
2,2-dimethyl-propionaldehyde	−40.7	47.5	−6.8	0.2
average over absolute values		−	6.5	0.2
$\text{abs. error} = \Delta G_{r, \text{calc}}^{\text{ideal gas}} - \Delta G_{r, \text{exp}}^{\text{ideal gas}}$				
$\text{rel. error} = \frac{\Delta G_{r, \text{calc}}^{\text{ideal gas}} - \Delta G_{r, \text{exp}}^{\text{ideal gas}}}{\Delta G_{r, \text{exp}}^{\text{ideal gas}}}$				

Table B.5.: Standard Gibbs energies of reaction in solution $\Delta G_r^{\text{solution}}$ in kJ/mol for reduction of a ketone to an alcohol; only the ketone is given in the table. Computational method for the calculation of $\Delta G_r^{\text{ideal gas}}$ is MP2/TZVP.

ketone	experiment ^[88]	calculation		
	$\Delta G_{r, \text{exp}}^{\text{ideal gas}}$	$\Delta G_{r, \text{calc}}^{\text{ideal gas}}$	abs. error	rel. error
formaldehyde	−49.6	−63.4	−13.8	0.3
acetaldehyde	−43.6	−45.1	−1.5	0.0
acetone	−24.9	−31.4	−6.5	0.3
isobutanal	−42.4	−39.0	3.5	−0.1
2-butenal	−37.4	−26.2	11.3	−0.3
1-methoxy-2-propanone	−36.5	−33.4	3.1	−0.1
2-butanone	−23.7	−28.0	−4.3	0.2
cyclopentanone	−23.8	−33.4	−9.7	0.4
2,2-dimethyl-propionaldehyde	−40.7	−41.9	−1.2	0.0
furfural	−41.2	−33.9	7.4	−0.2
1,3-dimethoxy-propan-2-one	−67.5	−57.1	10.4	−0.1
2-methyl-2-butanone	−23.7	−25.1	−1.4	0.1
cyclohex-2-enone	−16.4	−14.2	2.2	−0.1
cyclohexanone	−31.3	−32.1	−0.9	0.0
4-heptanone	−19.5	−29.0	−9.5	0.5
4-methoxy-cyclohexanone	−32.2	−20.6	11.6	−0.4
average over absolute values		−	6.1	0.2
$\text{abs. error} = \Delta G_{r, \text{calc}}^{\text{ideal gas}} - \Delta G_{r, \text{exp}}^{\text{ideal gas}}$ $\text{rel. error} = \frac{\Delta G_{r, \text{calc}}^{\text{ideal gas}} - \Delta G_{r, \text{exp}}^{\text{ideal gas}}}{\Delta G_{r, \text{exp}}^{\text{ideal gas}}}$				

Table B.6.: Standard Gibbs energies of reaction in solution $\Delta G_r^{\text{solution}}$ in kJ/mol for reduction of a ketone to an alcohol; only the ketone is given in the table. Computational method for the calculation of $\Delta G_r^{\text{ideal gas}}$ is B3LYP/TZVP.

ketone	experiment ^[88]	calculation		
	$\Delta G_{r, \text{exp}}^{\text{ideal gas}}$	$\Delta G_{r, \text{calc}}^{\text{ideal gas}}$	abs. error	rel. error
formaldehyde	−49.6	−64.6	−15.0	0.3
acetaldehyde	−43.6	−39.9	3.7	−0.1
acetone	−24.9	−19.1	5.8	−0.2
isobutanal	−42.5	−32.0	10.5	−0.2
2-butenal	−37.4	−17.2	20.3	−0.5
1-methoxy-2-propanone	−36.5	−19.4	17.0	−0.5
cyclopentanone	−23.7	−17.8	6.0	−0.3
2,2-dimethyl-propionaldehyde	−40.7	−33.9	6.9	−0.2
furfural	−41.2	−24.1	17.2	−0.4
1,3-dimethoxy-propan-2-one	−67.5	−40.4	27.1	−0.4
3-pentanone	−21.2	−14.1	7.1	−0.3
2-methyl-2-butanone	−23.8	−14.1	9.6	−0.4
3,3-dimethyl-2-butanone	−23.3	−12.6	10.8	−0.5
cyclohex-2-enone	−16.4	0.7	17.1	−1.0
cyclohexanone	−31.3	−19.8	11.5	−0.4
4-heptanone	−19.5	−16.4	3.1	−0.2
4-methoxy-cyclohexanone	−32.2	−4.5	27.7	−0.9
benzaldehyde	−38.0	−21.6	16.4	−0.4
indan-1-one	−14.1	5.0	19.0	−1.3
1-(4-methoxy-phenyl)-ethanone	−19.1	−4.2	14.9	−0.8
average over absolute values		−	13.2	0.5
$\text{abs. error} = \Delta G_{r, \text{calc}}^{\text{ideal gas}} - \Delta G_{r, \text{exp}}^{\text{ideal gas}}$				
$\text{rel. error} = \frac{\Delta G_{r, \text{calc}}^{\text{ideal gas}} - \Delta G_{r, \text{exp}}^{\text{ideal gas}}}{\Delta G_{r, \text{exp}}^{\text{ideal gas}}}$				

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Johann Wolfgang von Goethe (1749-1832)

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D. Curriculum vitae

PERSONAL

Name	Martina Peters
Date of birth	January 14, 1980
Place of birth	Bitburg, Germany
Nationality	German

EDUCATION

04/2007 - 07/2007	Research stay, Shell Global Solutions, Amsterdam, The Netherlands, Prof. ir. Jan Harmsen
12/2005 - 12/2008	Doctoral thesis, Institute of Technical and Macromolecular Chemistry, RWTH Aachen University, Germany, Prof. Dr. Walter Leitner
05/2005 - 10/2005	Diploma thesis, Institute of Technical and Macromolecular Chemistry, RWTH Aachen University, Germany, Prof. Dr. Walter Leitner
04/2000 - 10/2005	Chemistry studies, RWTH Aachen University, Germany and University of Colorado at Boulder, USA
10/1999 - 09/2000	Biology studies, RWTH Aachen University, Germany
09/1992 - 06/1999	Secondary school, St.-Willibrord Gymnasium, Bitburg, Germany