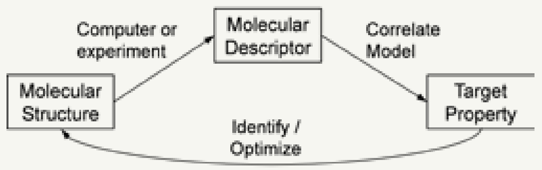
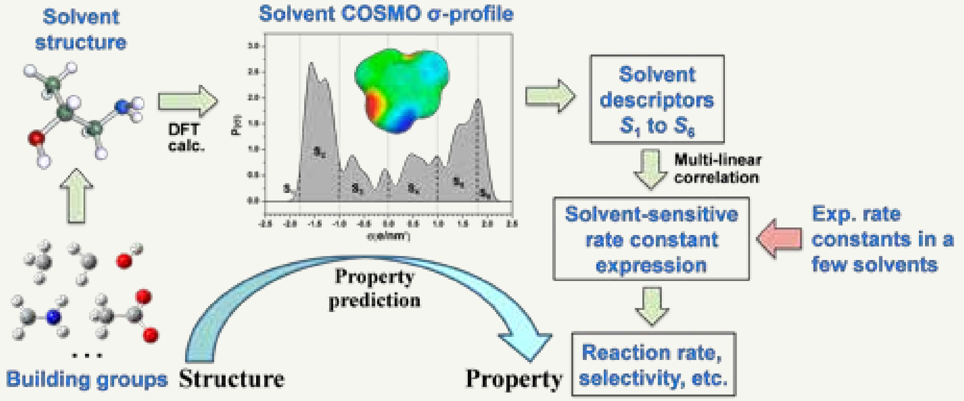
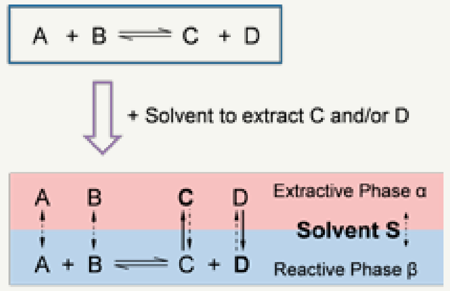


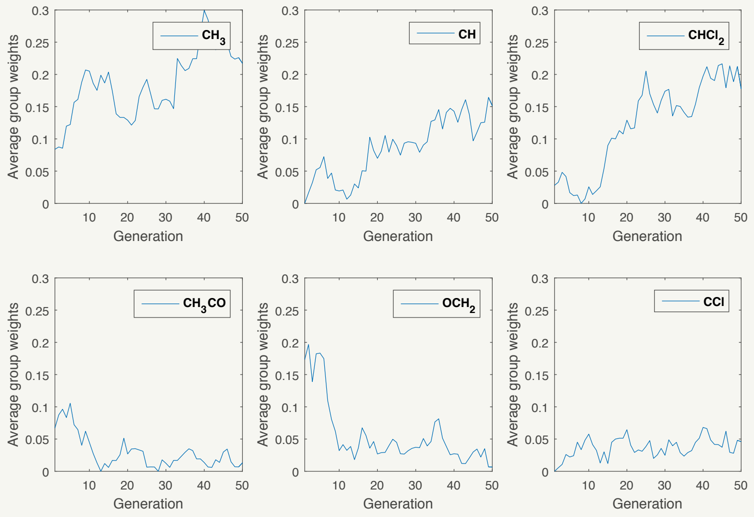
+ **Figure 1:**
Computeraided molecular design (CAMD) methodology.



+ **Figure 2:**
Framework of the proposed solvent design methodology.



+ **Figure 3:**
Scheme of solvent-aided extractive reaction.



+ **Figure 4:**
Evolution of average group weights over many generations.

Computer-Aided Molecular Design of Solvents for Chemical Reactions

Solvents are widely used as reaction media in liquid phase reactions. It has been proven that the variation of the type of solvent can dramatically change the reaction rate and equilibrium conversion. Despite that, so far there have been only few works addressing the optimal selection or design of solvents for chemical reactions. Since solvents can influence the reaction kinetics and thermodynamics, the PSE group developed two Computer-Aided Molecular Design (CAMD) approaches: a) a method for the optimal design of solvents to increase reaction rates for irreversible reactions and b) a method for improving equilibrium conversions of reversible reactions. The two methods are briefly described in the following.

The task of CAMD is to design molecules possessing specific and desirable properties. As depicted in Figure 1, a standard CAMD procedure consists of two subproblems. The forward problem relates molecular structures to molecular properties through certain molecular descriptors. The reverse problem determines molecular structures that possess the optimal properties based on the established structure-property relationship models.

For CAMD of reaction solvents, we introduced a new type of solvent molecular descriptor and used these descriptors for correlating the effect of solvents on chemical reaction rates. Later, we formulated and solved an optimization-based molecular design problem to identify the best solvent structure. As illustrated in Figure 2, starting from a given set of molecular building groups, different solvent structures were generated. Through DFT calculations based on the COSMO solvation model, we obtained the σ-profile, i.e. the screening charge density distribution, of each solvent molecule. Due to its molecule-specific nature, the σ-profile can be regarded and used as a molecular fingerprint. Consequently, we partitioned the σ-profile into six sections and used the areas underneath the curve sections as solvent molecular descriptors. By correlating experimental reaction rate constants measured in few known solvents with their descriptors, we parameterized a QSPR (Quantitative Structure Property Relationship) model which describes the solvent effect on the rate of the investigated reaction. Based on this model and an additionally developed group contribution method for estimating the descriptors from solvent molecular building blocks, one can reversely optimize solvent structures in terms of the combination of groups for identifying an optimal solvent featuring the highest reaction rate or another best rate-related property, such as the reaction selectivity. The solvent design method has been applied successfully to two Diels-Alder reactions[1], [2].

Due to the fact that solvents as reaction media can change the equilibrium of a chemical reaction, the PSE group developed a CAMD methodology for finding optimal solvents to the equilibrium conversion via a “extractive reaction” strategy. Therein, a suitable solvent is added to the reaction mixture to selectively extract products into a separate phase, thus allowing for higher product yields. The concept of a solvent-supported extractive reaction is depicted in Figure 3. The design problem can be described as follows: Given a liquid reaction mixture composed of a known amount of reactants A and B under a specified temperature and pressure, determine which solvent and by which amount it should be added to the mixture in order to achieve a maximum equilibrium conversion of the reaction.

The above-mentioned solvent design task leads to a challenging optimization problem containing continuous and binary decision variables. For a given solvent structure and composition, we used a rate-based dynamic method for calculating the combined chemical and liquid-liquid phase equilibria. A genetic algorithm (GA)-based CAMD method was developed to optimize the solvent structure and composition for maximizing the reaction equilibrium conversion. The method has been applied successfully on an esterification reaction where 1,1-dichloro-2-methylpropane and 1,1-dichlorobutane were found to be the best solvents.[3]. In this GA-based molecular design approach, the structural groups can be regarded as genes that constitute the molecules. Just as promising genes have more chances of being retained while non-promising genes are gradually eliminated in natural selection, the appearance frequency of a group in a generation behaves in a similar way. Figure 4 shows the evolution of average group weights in a generation. As can be seen, favorable groups (such as CH_3, CH, and $CHCl_2$) accumulate in the evolution. The weights of unfavorable groups (such as CH_3CO and OCH_2) generally decrease with increasing number of generations. Some group weights (such as CCl) do not change much at all during the evolution. These observations are consistent with the final solvent design results.

I **Dr.-Ing. Teng Zhou**

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Author **Dr.-Ing. Teng Zhou**

Dr.-Ing. Teng Zhou obtained his master degree in 2012 from East China University of Science and Technology in Shanghai, China. In 2016 he received his Ph.D. degree from Otto-von-Guericke University Magdeburg. Within the PSE group, Teng Zhou is developing systematic methods for reaction solvent design and integrated solvent and process design. He published five first-author articles and earned several important awards, including the CAST Directors’ Award 2015 granted by the American Institute of Chemical Engineers (AIChE). At the PSE chair of Otto-von-Guericke University Magdeburg, he works as an assistant lecturer for the graduate course Advanced Process Systems Engineering (APSE).

zhout@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/pse