

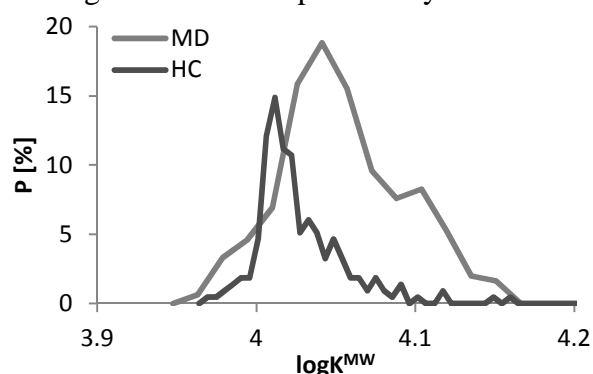
Micelle/water partition coefficients using COSMO-RS: Conformational Study

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In the field of chemical engineering and life sciences, the prediction of phase equilibria in complex multicomponent systems is of growing interest. One of the most popular and effective methods here is the COSMO-RS model, which allows for the predictions based only on the chemical structure of the system components. As shown by our group, the results depend strongly on the choice of conformations. For small molecules, sets of minimum energy conformations from the common conformational analysis made in vacuum give adequate results. Large flexible molecules however may have a huge number of conformations and the prediction results vary significantly for different conformations. Therefore, the reliable conformations of large flexible molecules, which afford reproducible results and lead to stable *a-priori* predictions on phase equilibria, should be identified.

In this work, the partitioning of small solutes (alkanes, alcohols, etc.) in the micellar solution of the non-ionic surfactant Triton X-100 (TX100) in water is studied as an example. Micelles hereby are treated as a macroscopic phase being in equilibrium with the aqueous surrounding (pseudo-phase approach), so that the partitioning of a solute between these coexisting pseudo-phases is determined by the thermodynamic equilibrium and thus the micelle/water partition coefficient (K^{MW}) can be calculated based on the solute limiting activity coefficients in the two pseudo-phases. For any small solute molecule with the limited number of conformations, the same set of the minimum energy conformations was used in all calculations. However, both pseudo-phases also contain large flexible amphiphilic molecules, for which adequate conformations have to be found. The conformations of TX100 were generated using two methods: the force-field-based energy-minimization method (hyperchem HC) and the condensed phase molecular dynamics (MD, Gromacs). The HC conformational search was carried out in vacuum, while the MD simulations were made in water and in octanol (the model solvent for micellar pseudo-phase) to account for the solvent effects. The conformations obtained by both methods were then used to calculate K^{MW} of the solutes using COSMO-RS and their influence on the latter was studied.

The figure shows the probability distribution of the logarithmic K^{MW} of octanol calculated by



COSMO-RS for different single conformations. The maxima observed in the distributions indicate that some of the conformations occur more often than the others and thus will lead to the more reproducible values of K^{MW} , i.e., are reliable for K^{MW} . However, using this method to identify reliable conformations, great calculation efforts have to be made. Thus, it would be advantageous to be able to select such conformations directly from the conformational space obtained from MD or HC, even before

performing the time-consuming DFT/COSMO geometry optimization calculations. Such a selection should be based on physical parameters. In this study, we consider two of them, the radius of gyration and conformation specific energy as well as their combination. It has been shown that if the selection is made from the 20% most probable conformations of any of criteria, the outliers in the probability distributions of K^{MW} are avoided. If both criteria are considered simultaneously, a single surfactant conformation can be identified that leads to the most probable result for K^{MW} . Thus, the probability-based methodology leads to reliable and stable *a-priori* predictions of solute partitioning in micellar systems as well as of phase equilibria in general.

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