**3D-QSAR: a better tool for predicting partition coefficients influenced by molecular steric effects?**

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Partition processes play a crucial role in, e.g., the environmental fate, the distribution in organisms, and the behaviour in engineering systems, of the chemicals. For the description of partition processes, two cases can be distinguished: 1) the partitioning between two homogeneous phases like octanol and water and 2) the partitioning between a homogenous phase like water and a heterogeneous material with particular binding sites like cyclodextrin (CD) and serum albumin. The case 2 partitioning is influenced by the complementarity of the 3D structure of the solute and the binding sites, which causes a molecular steric effect.

The aim of our study was to determine whether a 3D quantitative structure activity relationship (3D-QSAR) would be a suitable tool to explain such molecular steric effects. We investigated two diverse and consistent experimental partitioning data sets: a) alpha-CD-water partition coefficients for 70 neutral chemicals measured for this work and b) bovine serum albumin (BSA)-water partition coefficients for 83 neutral and 32 ionic organic chemicals from previous studies. All data were measured in our laboratory. Neutral chemicals were measured with headspace or passive sampling experiments and organic ions were measured with equilibrium dialysis experiments.

We conducted several 3D-QSAR analyses (i.e., comparative molecular field analyses) for the two data sets to evaluate the influences of different molecular alignments and interaction fields on the results. For each data set, five chemicals with the highest partition coefficients were used to generate a template structure on which all other chemicals were aligned. The data were split to training and test sets, and the models were always evaluated with the data that were not used for model calibration. The standard deviation of the prediction was 0.5 log units on average. For cyclodextrin, the unique binding pocket structure was available, and using that as a template led to an even better result. This error range is comparable to that of the polyparameter linear free energy relationship (pp-LFER) approach, which has been widely used for the prediction of partition coefficients but does not consider the steric effects on the binding. A remarkable advantage of the used 3D-QSARs over pp-LFER is that the 3D-QSARs correctly reproduced the experimental trends for several isomers that show a large difference in BSA-water partition coefficients, e.g., 1-naphtoic acid (log *K*BSA/water exp. 2.81, calcd. 2.45) and 2-napththoic acid (log *K*BSA/water exp. 4.36, calcd. 3.81). Hence, we conclude that 3D-QSARs are a promising tool to account for molecular steric effects in partition processes of organic contaminants.