**Partitioning of ionic organic chemicals to proteins: Influences of solute molecular structure**

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Equilibrium partition coefficients are an important input parameter for modelling environmental fate, bioaccumulation and toxicokinetics of a given target substance. While the partitioning behavior of neutral organic chemicals has been extensively studied, substantially large knowledge gaps exist for ionic organic chemicals (IOCs). A large body of evidence suggests that bioaccumulation of neutral chemicals is mainly controlled by the lipid fraction of an organism. For IOCs a large contribution of the protein fraction is expected, but until now sorption of IOCs to proteins has not been studied systematically. For mechanistic understanding and modeling of protein binding of IOCs a reliable and consistent data set is required. Therefore, in this study protein-water partition coefficients were measured for various organic anions and cations using an equilibrium dialysis approach. The data set includes many benzoic and naphthoic acids with diverse substitution patterns, and also pharmaceuticals and pesticides. Bovine serum albumin (BSA) and muscle protein (isolated from chicken breast filet) were chosen as model proteins to characterize low-specificity protein binding of IOCs. Using the data obtained, several correlation models were evaluated.

Strong association with BSA was measured for the anions tested, while generally weak binding of cations was observed. A remarkable finding is that binding to BSA seems to be highly influenced by the three dimensional structure and the substitution pattern of the molecules. For example 2-naphthoic acid has a logarithmic BSA-water partition coefficient (log *K*BSA/w) of 4.36, while log *K*BSA/w for 1-naphthoic acid is only 2.81. For chlorinated benzoic acids the following trends were found: 3-chlorobenzoic acid shows similar strong partitioning as 4-chlorobenzoic acid (log *K*BSA/w are 3.22 and 3.21, respectively), whereas 2-chlorobenzoic acid and 2,6-dichlorobenzoic acid only have log *K*BSA/w of 1.84 and 1.65, respectively. Additional data also confirm that substitution vicinal to the charged functional group leads to a significant decrease of binding to BSA. Conventional modeling approaches based on octanol-water partition coefficients (log *K*ow) or polyparameter linear free energy relationships (pp-LFERs) of neutral species fail to predict this behavior.

For the majority of the test substances partitioning to muscle protein is weaker than to BSA. The correlation between muscle protein-water partition coefficients (log *K*MP/w) and log *K*BSA/w measured in this study is weak. In contrast to BSA, no particular steric effects on the partitioning behavior were found for muscle protein. The data set for muscle protein correlates with log *K*ow calculated for the ionic species of the chemicals and with retention factors measured on a weak anion exchange column. The pp-LFER approach might also be an option to model partitioning of organic ions to muscle protein. In general the first modeling results suggest that empirical and theoretical descriptors that reflect the properties of ionic species tend to provide better correlations than those descriptors for neutral species.