

## Abstract:

Cytochromes P450 (CYP) are monooxygenases participating reactions of the Phase I in xenobiotic biotransformations. Better and more detailed knowledge of heme - protein interaction is crucial for understanding of function of these enzymes; in particular, of their regulation.

We analyzed orientations of both heme vinyl side-chains in all X-ray structures of CYP enzymes available in the PDB data bank. For two mammalian forms, CYP 2A4 and 3A4, a more detailed analysis of the heme contacts with the apoprotein was performed, based on identification of the amino acid side chains in the vicinity. In addition to spatial information, dissociation constants and Coulombic interaction of polar residues in proximity to the heme were calculated using the PropKA web server. Deviations of the heme from planarity in both forms of P450 was investigated using the normal coordinate analysis (NSD server).

Distribution of torsion angles of vinyls in position 2 and 4 of the heme shows that the side-chain at position 2 is conformationally more restricted in most P450 forms studied.

Comparison of all forms shows that the range of attainable values of torsional angles is very wide, practically unrestricted, and that the actual conformations of the heme moiety are probably determined more by the interaction with the protein, than by any internal restrictions of the heme itself. The observed variability likely reflects the diversity of CYP enzyme group. Contacts of the heme in CYP 2B4 and in 3A4 differ considerably, their common feature observed is the Arg:propionate electrostatic interaction. However, in detail also this interaction is different in both forms. Heme vinyls interact exclusively with nonpolar residues of the apoprotein. The normal coordinate analysis of the out-of-plane heme deformations reveals, that in both forms the most prominent mode is the saddling (sad) mode. The amplitude of the deformation in the published structures, however, differs significantly.

The results point to the great variability of P450 enzymes and indicate the influence of heme - protein interaction on the structure and function of the heme.

(In Czech)

