Biologically and catalytically relevant reactions of small molecules (NO, O_2) activated on iron heme centers - models and mechanisms

Reactions involving small molecules, such as nitric oxide (NO) and dioxygen (O_2) play a very important role in a numerous vital, environmental and industrial processes. Both of these molecules require activation, which results in the increase of their reactivity by changing their redox properties. In biological systems, small molecules undergo activation through interaction with heme enzymes, proteins containing iron porphyrin e.g. P450 cytochromes, peroxidases. Activated molecule undergoes further reactions which are important for the processes associated with redox signaling or metabolic changes.

Activation of dioxygen on the metal center of enzymes leads to the production of highly reactive forms of enzymes that are capable of conducting oxidation of a variety of endo- and exogenous inert compounds, by incorporation of one or two oxygen atoms into the substrate molecule.

One of the pathways of nitric oxide action in living organisms is the S-nitrosylation, which is based on the binding of the nitrosonium ion (NO^+) to -SH group of cysteine and formation of -SNO. Recent discoveries show that this post-translational modification of proteins plays an equally important role to phosphorylation.

S-nitrosylation leads to activation/deactivation of many proteins and regulates many types of calcium channels. Both S-nitrosoalbumin and S-nitrosoglutathione leads to relaxation of smooth muscle cells within the vessel walls. Furthermore, S-nitrosothiols, because of their stability, are responsible for nitric oxide transport.

Research tasks in the scope of this project aim to discover and in some cases to expand the knowledge regarding the reactivity mechanisms of small molecules previously activated on iron heme centres. The project concentrates on the studies of reactivity of two small molecules, namely nitric oxide and dioxygen. In the case of nitric oxide, studies of the NO molecule transfer to the thiol groups containing molecules of biological importance e.g. glutathione and cysteine are planned. In the case of reactions following the activation of dioxygen, studies of oxidation mechanisms of selected organic substrates by heme enzymes models (iron(IV)oxo porphyrin), characterized by their high reactivity, will be performed. To fulfill both research tasks microperoxidase-11 (peptide containing a heme moiety connected with a chain of 11 amino acids) as well as water-soluble iron(III)porphyrins will be applied as functional heme enzyme models. In order to determine the mechanisms of the studied reactions, kinetic studies will be performed. Additionally, studies on the influence of temperature and pressure on the small molecules transfer reactions rates will allow formulating conclusions about the mechanisms of studied reactions. Identification of products from S-nitrosylation and oxidation reactions as well as yields calculation with the application of model heme systems will supplement the studies.

The reason behind undertaking this research topic is the drive to deepen the knowledge on the reaction mechanisms of small molecules (NO and O_2), whose activation occurs on the centres of metalloenzymes of catalytic and biological importance. Execution of this project will contribute to the science disciplines studying the functioning of living organisms and environmental issues. Due to the complexity of biological processes as well as high instability of the short lived intermediates of the catalyst, the elucidation of the reactivity mechanism of small molecules, activated on metal centers of enzyme at the molecular level, studied *in vivo* or *in vitro* still provides a challenge for researchers. The use of simple macrocyclic transition metal complexes as functional enzyme models (cytochrome P450, peroxidases) for activation of O_2 as well as functional models of centers responsible for NO bio-regulatory functions, allows for a greater understanding of the molecular basis of the mechanism of small molecules reactivity towards selected biologically relevant organic compounds. Knowledge of the molecular basis of mechanisms of reactions involving small molecules is still limited, yet it is extremely important for a better understanding of diverse processes both physiological and pathophysiological. Fulfillment of the project goals may allow us to gain control over complex processes, both physiological and pathophysiological associated with redox signaling or with metabolic processes, paving the way for the improvement of human health and effective combating of many diseases. The obtained results will contribute not only to a better understanding of processes occurring in living organisms and their environment, but also, in the longer term, will have a stimulating influence on the design of new compounds and processes of biomedical or environmental catalytic character.