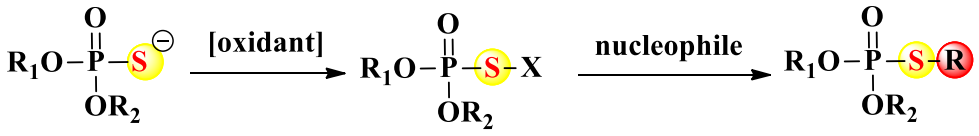
Description for the general public

Nucleic acids (DNA, RNA) are molecular carriers of genetic information which contain encoded data on the course of all life processes in all organisms. Nucleotides, which constitute the basic building blocks of these biopolymers, are of great interest to biochemistry, particularly after the double helix structure of DNA was solved by Watson and Crick in 1953. Since that time, intensive research has been carried out around the world on the role and influence of various modifications in nucleotides on DNA and RNA functions. Such nucleotide analogues can also be used as therapeutics, for example, in anti-HIV treatment or, in largely developing in the recent years, siRNA (short interfering RNA) strategy for silencing the expression of damaged genes. Interest in this class of chemical compounds is constantly growing due to their high biological potential. Searching for new modifications within the nucleotide structure is of interest for many scientists, and was also an inspiration for our research group to initiate this study.

In the course of the recently conducted in our laboratory experiments on nucleotide analogues, we have observed the formation of new derivatives with the P-S-N atom system. **The main goal of our project** is to explore the reaction conditions for the P-S-N or P-Se-N formation, which we call functionalization of heteroatoms (sulfur and selenium). Introducing modifications at heteroatoms, but not in the basic nucleotide backbone, allowed us to call this class of compounds the second generation of nucleotide analogues. A general diagram of the designed reaction of interest is shown in Fig.1.



R_1,R_2= a nucleoside moiety, alkyl, or combination; X= a part of oxidant; R= e.g. amine

Fig.1. Reaction scheme of the synthesis of the second generation of nucleotide analogues containing the P-S-N moiety.

In this project, we are going to focus our attention on some general aspects of the above reaction, which we consider to be crucial for understanding reactivity of heteroatoms in thio- and selenonucleotide analogues. First, in this synthesis of the second generation nucleotide analogues, we would like to investigate various oxidizing agents to find how these affect efficacy of the reaction. Then, we will examine the importance of structural features of a nucleophile used (among others, amines 1° and 2°) on the rate and yield of the product formation. Mechanistic and stereochemical studies on this reaction are also within our interest, and we plan to use for this purpose ^{31}P nuclear magnetic resonance spectroscopy.

We consider future studies (not being part of this project) on antiviral and anticancer potency of the obtained and physicochemically characterized new nucleotide analogues.

We expect that the obtained results will contribute to the broadening of our basic knowledge of bioorganic phosphorus chemistry, nucleotide analogues chemistry, and finding compounds with unknown yet biological properties.