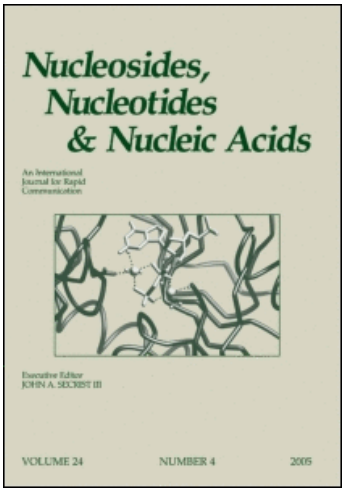

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ACTIVATION OF NUCLEOSIDE HYDROGENPHOSPHONATES BY USE OF ARYL SULFONYL CHLORIDES

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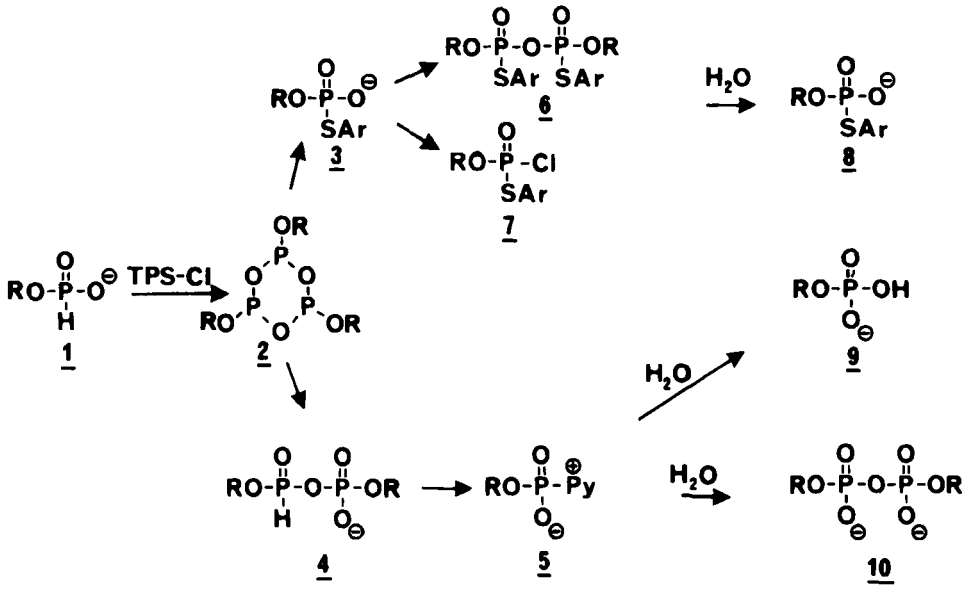
Abstract. The reaction of nucleoside 3'-hydrogenphosphonates with 2,4,6-triisopropylbenzenesulfonyl chloride (TPS-Cl) has been studied using ^{31}P NMR spectroscopy, and a general scheme of transformations occuring during this activation process is proposed.

In our studies on the internucleotidic bond formation via H-phosphonate intermediates[1], we found that nucleoside 3'-hydrogenphosphonates can be activated inter alia by aryl sulfonyl chlorides and formed dinucleoside-(3'-5')-hydrogenphosphonate diesters in the presence of a nucleoside with a free hydroxyl group.

A characteristic of this reaction is extremly rapid H-phosphonate diester formation when nucleoside hydrogenphosphonate is activated by TPS-Cl in the presence of hydroxylic component. When, however, the latter is added after a few minutes to the preactivated nucleoside H-phosphonate, practically no H-phosphonate diester formation is observed[1].

Because the formation of internucleotidic bond via H-phosphonate intermediates is a promising approach to oligonucleotide synthesis[2], we wish to get a deeper insight into H-phosphonates chemistry and have now investigated the activation reaction of nucleoside hydrogenphosphonates by TPS-Cl, using FT ^{31}P NMR spectroscopy.

It was found that nucleoside 3'-H-phosphonate 1 reacts with TPS-Cl producing trimetaphosphite 2, which is oxidized by TPS-Cl and the products of its reduction to metaphosphate 5 and phosphorothioate 3.



SCHEME 1

These, in turn, undergo several subsequent reactions, affording after hydrolysis nucleoside 3'-phosphate 9, a symmetrical disubstituted pyrophosphate 10, and nucleoside S-aryl 3'-phosphorothioate 8. A simplified reaction pathway for the activation of nucleoside 3'-H-phosphonate 1 by TPS-Cl is suggested in Scheme 1.

Formation of trimetaphosphite 2 seems to be critical for the oxidation reaction. In agreement with this, we could not detect any oxidation (within 1 h) or formation of trimetaphosphite 2 in acetonitrile without pyridine (or another base). Pyridine can participate on different stages of the reaction, however, its most important role in the oxidation of H-phosphonate monoesters by TPS-Cl, is probably, to facilitate the formation of trimetaphosphite 2.

Fast oxidation of nucleoside H-phosphonates by TPS-Cl explains our previous findings that preactivation of H-phosphonate, followed by addition of nucleoside, fails to produce the corresponding H-phosphonate diester.

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