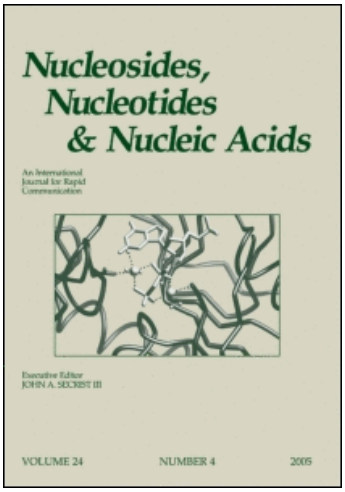

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Recent Studies in Nucleoside Phosphonate Chemistry

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RECENT STUDIES IN NUCLEOSIDE PHOSPHONATE CHEMISTRY

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Abstract

New activation pathways have been found for H-phosphonate monoesters subjected to a reaction with alkyl chlorophosphates or sterically hindered aromatic acyl chlorides. Studies on synthesis of nucleoside methylphosphonate diesters using a new condensing system are also discussed.

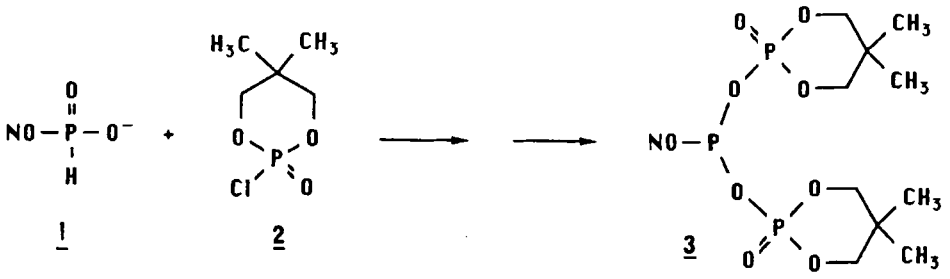
INTRODUCTION

Growing interest in H-phosphonate chemistry resulted in the recent years in developing a new method for the chemical synthesis of DNA and RNA fragments *via* H-phosphonate intermediates, as well as in application of this methodology in other fields of bioorganic chemistry[1]. Considering the importance of understanding of the underlying basic chemistry, we have carried out number of studies *inter alia* on the activation of H-phosphonate monoesters with various condensing agent and on coupling reaction[2]. Some findings from these studies concerning condensing agents proved to be also useful in the synthesis of nucleoside methylphosphonates.

RESULTS AND DISCUSSION

Activation of H-phosphonate monoesters with alkyl chlorophosphates

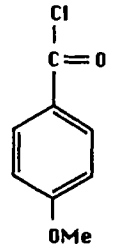
Recently we have reported that activation of nucleoside H-phosphonate monoesters with arene sulfonyl derivatives as well as with diphenyl chlorophosphate (DPCP) or bis(2-oxo-3-oxazolidynyl)phosphinic chloride (OXP) in pyridine, affords an intermediate, which has been identified by a ^{31}P NMR analysis and by chemical reactivity as 2,4,6-trinucleoside-1,3,5,2,4,6-trioxatriphosphorinane (trinucleoside trimetaphosphite)[2]. We have now found that this activation pathway is not the only one. Although the initial activation stage with alkyl chlorophosphates (e.g diethyl chlorophosphate or 5,5-dimethyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinane, **2**) is likely to be similar to that with e.g. diphenyl chlorophosphate, the final product is different and presumably it is the mixed anhydride of type **3**.



This tentative structural assignment is based on the following findings (i) the ^{31}P NMR spectrum of the reaction mixture of **1+2** consists of two signals at ca 112 ppm and at ca at -20 ppm with intensities of 1:1.75 (signals from **2** and from the products of its partial hydrolysis are not taken into account); (ii) activation with different condensing agents (e.g. **2** and diethyl chlorophosphate) afford different compounds (similar pattern in the ^{31}P NMR spectra but different chemical shifts); (iii) upon addition of excess of ethanol signals at 112 and at -20 ppm were replaced by two singlets at ca 138 and -3.8 ppm; (iv) with limited amount of ethanol, similar compounds as above are formed, but in addition, a new intermediate (signals at ca 130 ppm and at ca -20, partially overlapping with a signal from the starting material) is formed; (v) hydrolysis of the intermediate **3** affords the starting material **1** and phosphate and pyrophosphate derived form **2**

Reaction of H-phosphonate monoesters with sterically hindered aromatic acyl chlorides

Searching for the most suitable coupling agent for conversion of H-phosphonate monoesters into the H-phosphonate diesters, we investigated the activation of **1** with a series of aromatic acyl chlorides **4-6**. Reaction **1+4** in pyridine proceeded in a similar way as with pivaloyl chloride affording the corresponding bisacyl phosphite (^{31}P NMR, d=126.4 ppm, $^{3}J_{PH}$=9.7 Hz, d). However, when a sterically hindered acyl chloride **5** or **6** was used as activator, compounds which gave rise to several resonances at ca 12-18 ppm in the ^{31}P NMR spectra were formed (Spectrum 1, **1+5**) instead of a bisacyl phosphite. Addition of water to such a reaction mixture resulted in slow hydrolysis and the ^{31}P NMR spectrum after several hours showed only two singlets at ca 15 ppm. These finding can be explain assuming the activation pathway as on Scheme 1. Apparently, because of the steric hindrance at carbonyl group in **5**, the reaction centre is shifted to the carbon 2 and 4 of pyridine *via* formation of N-acyl pyridinium salt. The latter one may react with the mixed anhydride **7** forming C-phosphonate **8**. This activation pathway, however, is far too simple to explain even the ^{31}P NMR spectrum of the reaction mixture of **5** + ethyl hydrogenphosphonate (Spectrum 2). Thus, one has to assume formation also other related compound as 2-isomer of **8**, three kinds of pyrophosphonates and possibly, C-phosphonate diesters.



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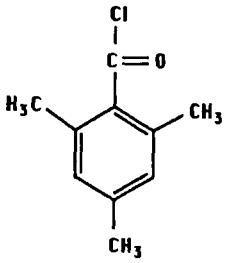

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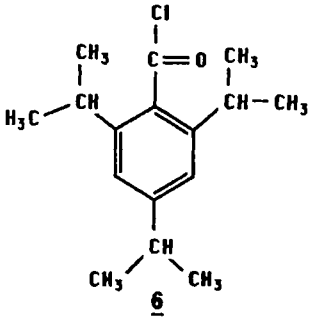

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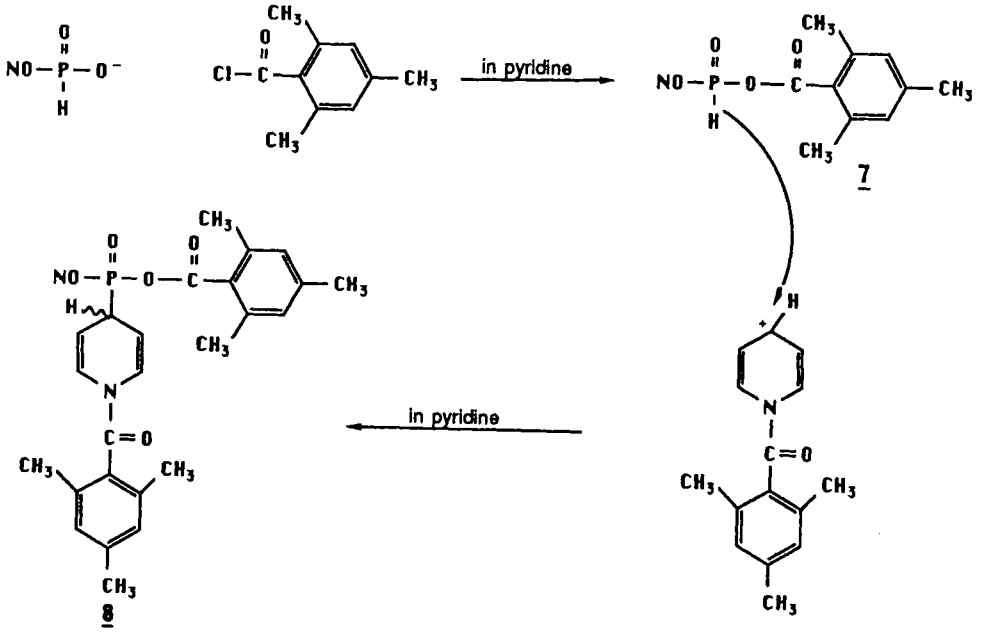
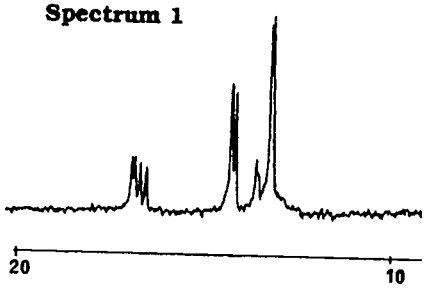
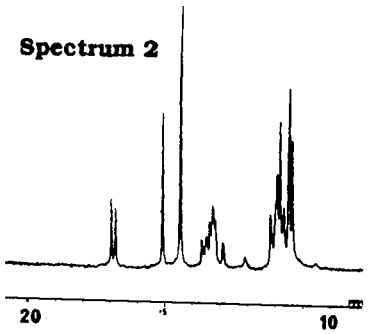
Scheme 1.

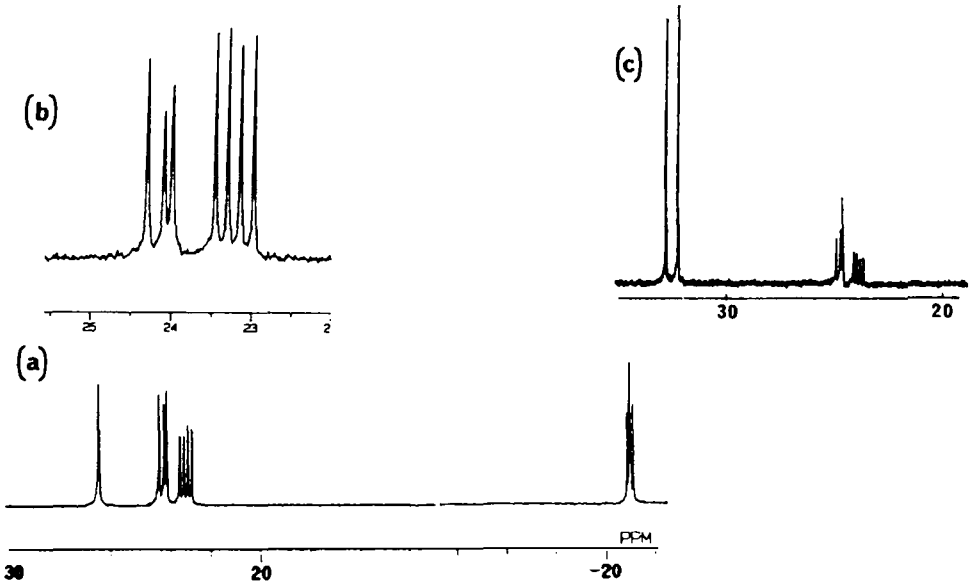


Spectrum 1



Spectrum 2





Scheme 2

Synthesis of nucleoside methylphosphonates

Low reactivity of nucleoside methylphosphonates in coupling reactions makes it difficult to design an optimal condensing system[3]. Investigating this problem we have found that coupling reaction to produce methylphosphonate diesters can be efficiently performed using the mild activating agent **2** in the presence of a powerful nucleophilic catalyst, 4-ethoxy-pyridine N-oxide[4].

^{31}P NMR spectra of the activation of DMT-T-$PCH_3(O)O^-$ with **2** showed formation of pyrophosphonates (ca 24 ppm) and a phosphono-phosphoric anhydride (ca 23 and -20 ppm) (Scheme 2, spectrum a and b). Both intermediates react with a hydroxylic component (e.g. HO-T-OBz, spectrum c, after 15 min) to produce a methylphosphonate diester in high yield.

Acknowledgements

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