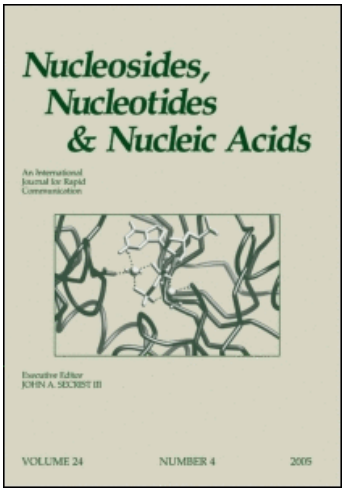

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REACTIONS OF NUCLEOSIDE HYDROGENPHOSPHONATES WITH DIPHENYL CHLOROPHOSPHATE AND STERICALLY HINDERED AROMATIC ACYL CHLORIDES

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Abstract

The final product of the reaction of H-phosphonate monoesters with diphenylchlorophosphate was found to be the corresponding dichlorophosphite. Sterically hindered aromatic acyl chlorides react with H-phosphonate diesters affording C-phosphonate derivatives.

Recently, we have explored nucleoside hydrogenphosphonate chemistry with the aim of developing an efficient method for the synthesis of oligonucleotides based on the use of nucleoside hydrogenphosphonate monoesters as starting materials[1-4]. As a part of these investigations, mechanistic studies concerning activation of H-phosphonate monoestes[5,6] and reaction of H-posphonate diesters[7] with various condensing reagents have been carried out. The overall picture of the reaction of H-phosphonate esters with condensing agents seems to be rather clear but it is far from complete. Thus, we undertook additional basic studies in H-phophonate chemistry which may clarify some points of interest.

RESULTS AND DISCUSSION

Reaction of H-phosphonate monoesters with diphenylchlorophosphate

Our previous studies[6] on the reaction of chlorophosphates with with nucleoside H-phosphonate monoesters showed that when diphenylchlorophosphate (DPCP) or bis-oxazolionephosphinic chloride (OXP) are used as condensing reagents, formation of a new class of heterocyclic compounds, i.e. 2,4,6-trinucleoside-1,3,5,2,4,6-trioxatriphosphorinanes (trinucleoside trimetaphosphites) **2** was observed. However, during the activation process, a relativly strong nucleophile, i.e. chloride anion, is generated and this, as we showed for nucleoside phosphorodiesters[8], may react with activated phosphorus compounds forming P-Cl bond.

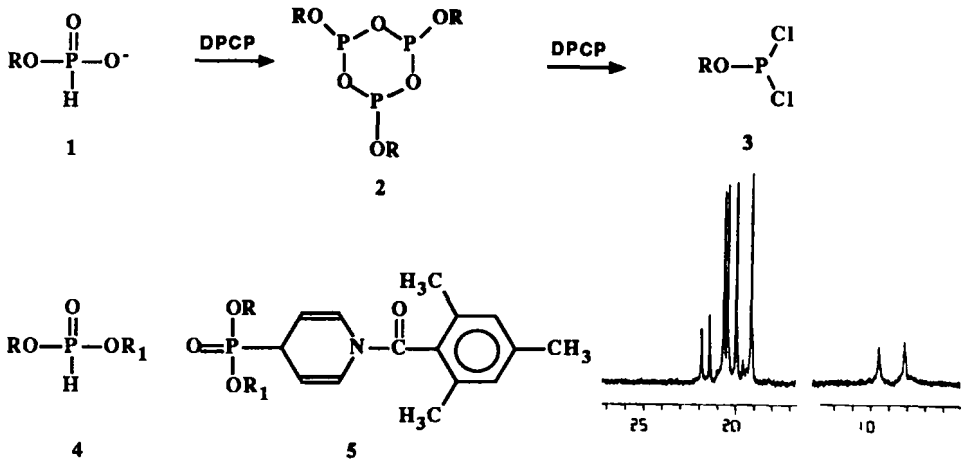
To find out if this is valid also for tervalent phosphorus derivatives, a reaction of 5′-O-dimethoxytritylthymidine 3′-hydrogenphosphonate **1a** with of DPCP in pyridine has been investigated, using 6 equiv. of a condensing agent instead of 3 equiv. as in our previous studies[6]. ^{31}P NMR analysis of the reaction mixture showed that the activation pathway is the same as with 3 equiv. of DPCP, and a familiar pattern characteristic for trinucleoside trimetaphosphite **2a** (11 resonances in the range of 110-120 ppm)[6] was observed. However, under the present reaction conditions, signals from **2a** gradually disappeared during ca 30 min. and a new resonance at 173.8 ppm (singlet), appeared. The chemical shift indicated the presence of a tervalent phosphorus derivative containing a P-Cl bond and the splitting pattern[9] suggested that the new signal arose from a symmetrical compound having one nucleoside residue. Thus, the most likely structure consistent with these data is that of the nucleoside dichlorophosphite **3a.** A similar pathway of activation was also observed for ethyl H-phosphonate **1b**, and a singlet at 175.6 ppm in the ^{31}P NMR spectrum was assigned to ethyl dichlorophosphite **3b**.

Assignement of signals in the ^{31}P NMR spectra to dichlorophosphites **3** was further substantiated by comparison with the spectra of compounds **3a** and **3b**,which were produced *in situ* from PCl_3 and 5′-O-dimethoxytritylthymidine and ethanol respectively.

The mechanism for conversion of trimetaphosphites **2** into dichlorophosphites **3** is unknown but it is likely to be similar to that suggested by us for the reaction of **2** with alcohols[6]. Two subsequent nucleophilic attacks of chloride ion on the same phosphorus center should result in ring opening followed by formation of **3** and a pyrophosphonate. The latter probably is activated again by DPCP and regenerates trimetaphosphite **2**. Such an assumption is in agreement with findings that **3** is formed faster when an excess of chlorophosphate is present.

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

In all methods of oligonucleotide synthesis, which involve activation of a nucleotidic component by a condensing reagent, the latter may react also with a nucleosidic component lowering the yield of condensation. To reduce the extent of such undesire reactions, sterically hindered condensing reagents, e.g. 2,4,6-triisopropylbenzenesulfonyl chloride, are often used, since they can discriminate more efficiently between weaker and stronger nucleophiles. Thus, we decided to check if sterically hindered aromatic acyl chlorides offer any advantages over other acyl chlorides. First, the acylation of an internucleotidic H-phosphonate bond by a condensing reagent was investigated. To this end, equimolar amounts of H-phosphonate monoester **1a** and 3′-O-benzoylthymidine in pyridine were allowed to react with 5 equiv. of mesitoyl chloride for 16 hr. The ^{31}P NMR spectrum of the reaction mixture showed that all starting material disappeared, but instead of the expected two singlets from dinucleoside



1a,2a,3a,4,5, R = dmt-T, R1 = -T-OBz ;
1b,2b,3b, R = ethyl

Fig.1. ^{31}P-NMR spectrum of 4+mesitoyl chloride

H-phosphonate **4**, two groups of resonances centered at ca 16 ppm (7 signals) and at ca 20 ppm (6 signals) were observed. None of these signals showed large coupling constants characteristic for the P-H bond. Interestingly, a similar reaction with benzoyl chloride afforded compounds which have been identified as H-phosphonate diesters.

To find out if any of these signals could be assign to compound(s) formed from the dinucleoside H-phosphonate diester **4** and mesitoyl chloride, the former was produced *in situ* using pivaloyl chloride as a coupling agent, and then, 3 equiv. of mesitoyl chloride was added. ^{31}P NMR spectra recorded at various time intervals showed a clean conversion of dinucleoside H-phosphonate diester **4** into compound(s) which gave rise to 6 resonances at ca 20 ppm (Fig.1.), identical in intensities and pattern to those observed in the previous reaction.

Chemical shift values and the number of signals exluded acylphosphonates as a possible reaction product and indicated rather on mixture of (sp^3)C-phosphonates. Since at this stage no other conclusion could be drawn, than that the reaction is not a simple acylation of H-phosphonate diester by mesitoyl chloride, some additional experiments on diethyl and diphenyl H-phosphonates were carried out. These experiments revealed that : (i) pyridine (or its derivatives) is an indispensable component of the reaction mixture, (ii) always two compounds, in different ratio are formed, (iii) both compounds have only one hydrogen on carbon bound to phosphorus, (iv) both componds contain a coupling agent residue, (v) only one compound is formed when pyridine is replaced by γ-picoline, (vi) products of the reaction are resistant to hydrolysis. On the basis of these results we tentativly assigned 6 resonances at 20 ppm observed in the ^{31}P NMR spectra (Fig 1.) of the reaction of dinucleoside H-phosphonate diester **4** with mesitoyl chloride in pyridine to a mixture of dinucleoside 1-mesitoyl-1,4(1,2)-dihydropyridine-4(2)phosphonates **5**.

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9. Chemical shift is reported relative to 2% H_3PO_4 in D_2O (inner tube). Compound **3a**: 173.8 ppm (d, $^3J_{PH}$ = 13.6 Hz); compound **3b**: 175.6 ppm (t, $^3J_{PH}$ = 8.6 Hz).
10. Reaction of PCl_3 with 5′-O-dimethoxytritylthymidine in pyridine produced a mixture of **3a** (173.8 ppm, d, $^3J_{PH}$ =14.6 Hz), bis(5′-O-dimethoxytritylthymidine) chlorophosphate (164.9 ppm, t, $^3J_{PH}$ = 10.4 Hz) and tris(5′-O-dimethoxytrityl thymidine phosphate (138.4 ppm, $^3J_{PH}$ = 7.4 Hz). Reaction of PCl_3 with ethanol in pyridine produced **3b** (175.4 ppm, t, $^3J_{PH}$ = 8.3 Hz) and triethylphosphite (138 ppm, h, $^3J_{PH}$ = 7.9 Hz).