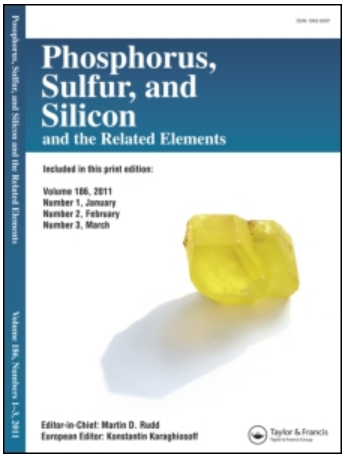


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# Synthetic, Mechanistic And Biological Aspects of Phosphorus-Sulfonic Acids Anhydrides. Direct Evidence for The $S_N1$ (P)-Ionic Mechanism in Phosphorus Chemistry

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# SYNTHETIC, MECHANISTIC AND BIOLOGICAL ASPECTS OF PHOSPHORUS-SULFONIC ACIDS ANHYDRIDES. DIRECT EVIDENCE FOR THE $S_N1(P)$-IONIC MECHANISM IN PHOSPHORUS CHEMISTRY

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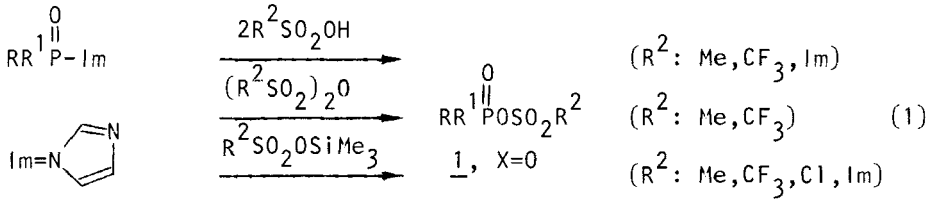
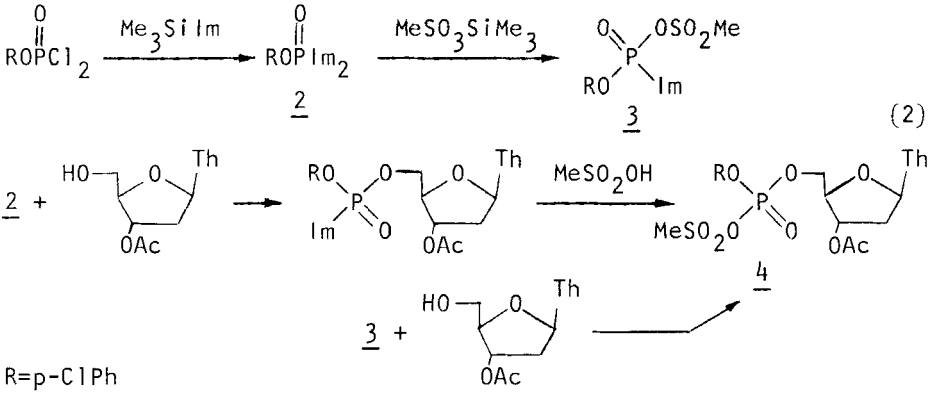
Special attention in this Laboratory has been recently given towards the chemistry of phosphorus-sulfur acids anhydrides $RR^1P(X)\text{-}O\text{-}SO_2\text{-}R^2$ (X=O,S,Se) **1**.

Synthesis of phosphorus-sulfur acids anhydrides **1**. Satisfactory methods of synthesis of **1** have been devised only recently.[1] Among methods which are intended to be published in full in due course, the methods given bellow are of special interest.

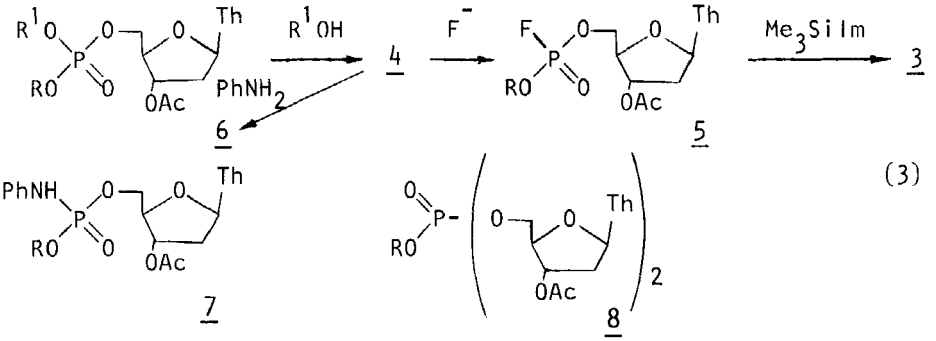



(1)

The most interesting synthetic applications are in the field of nucleotides.



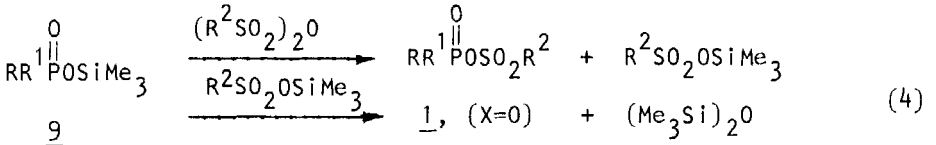
We observed that imidazolides of phosphorylated nucleosides can be readily converted into mixed anhydrides. They are excellent intermediates for the preparation modified nucleotides. These possibilities are illustrated in the scheme (2) and (3). The anhydrides 4 have been converted in stereoselective way into the corresponding fluoridates 5, phosphates 6 and amidates 7. The fluoridate 5 reacts with the nucleoside to form the dinucleotide 8.



(3)

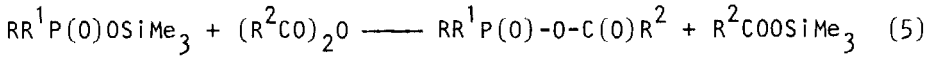
Several other modifications of nucleotides via phosphorus-sulfonic acids anhydrides are under study.

Another important approach towards the anhydrides 1 (X=O) is based on silyl esters of phosphorus acids 9 which are available either by direct silylation of synthetic or naturally occuring phosphates or by transylitation of the corresponding alkyl phosphates.



(4)

The method of activation of phosphorus acids silyl esters has been extended to the mixed phosphorus-carboxylic acid anhydrides.



(5)

Activation of the silyl esters of nucleoside phosphates according to schemes (4) and (5) is under study in this Laboratory.

The mixed anhydrides 1 are phosphorylating reagents and our results

do not confirm the statement that structures such as 1 are sulfonating rather than a phosphorylating reagents.[2]

P$^{III}$-phosphorus-sulfonic acids anhydrides. The imidazolides 10 react smoothly with $R^2SO_2OH$ to afford a novel class of tricoordinate phosphorus anhydrides, the phosphino-sulfonates.[3]

$$\underset{10}{RR^1P\text{-}Im} \xrightarrow{2R^2SO_3H} \underset{11}{R^1RP\text{-}OSO_2R^2} + Im\text{-}R^2SO_3H \qquad (6)$$

The anhydrides 11 are readily oxidized by air and add elemental sulfur or selenium giving products identical with the anhydrides 1 (X=O,S,Se). Under suitable structural circumstances the anhydrides 11 undergo a novel type of rearrangement 11 —— 12.

$$11 \longrightarrow \underset{12}{RR^1P(O)\text{-}SO_2R^2} \xrightarrow{HOH} RR^1P(O)H + HOSO_2R^2 \qquad (7)$$

The structure of 12 was confirmed by $^{31}P$ NMR spectroscopy and by identification of the appropriate products of hydrolysis. It is of significance that phosphinoyl sulfinates 12 readily undergo oxidation to give anhydrides 1 (X=O). This observation is relevant to the recent studies of Cassida and Segall on the oxidative conversion of the phosphinoyl sulfide 13 by peracids as a model for the enzymatic oxidation of 13. The following hypothetical steps have been suggested.[2]

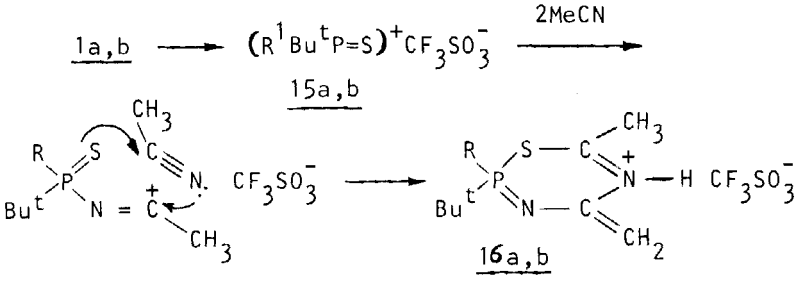
$$\underset{13}{RR^1P(O)\text{-}SR^2} \xrightarrow{MCPBA} \underset{14}{RR^1P(O)S(O)\text{-}R^2} \longrightarrow RR^1P(O)O\text{-}S\text{-}R^2 \xrightarrow{MCPBA}$$

$$RR^1P(O)O\text{-}SO\text{-}R^2 \xrightarrow{MCPBA} 1\ (X=O)$$

Our work strongly suggests a different sequence of events, involving formation of 14, its oxidation to 12 and final oxidation to the mixed anhydride 1 (X=O).

Chemical evidence for the $S_N1(P)$ ionic mechanism. We were able to synthesize two model anhydrides 1a (X=S, R=Bu$^t$, $R^1$=Ph, $R^2$=$CF_3$) and 1b (X=S, R=$R^1$=Bu$^t$, $R^2$=$CF_3$) including optically active

1a and have found that 1a and 1b dissolved in dry MeCN undergo a quantitative reaction with two moles of the MeCN leading to the compounds 16a,b which structure was established by $^{1}H$ and $^{13}C$ NMR.




The addition leading to 16a was completed in 70 h while 16b was formed nearly ten times faster. Only a dissociative mechanism for the solvolysis of 1 with the formation of the ion pair 15 can explain such a difference in reactivity of 1a and 1b towards acetonitrile. Any $S_N2(P)$ type process leading to 16b would be slower than in the case of 16a because of immense steric hindrance caused by the two t-butyl groups.

Consequently we have examined the reaction of optically active 1a with acetonitrile. The adduct 16a formed was optically active but its thermal decomposition in anisole at 90°C led to the anhydride 1a which was almost completely racemized. It is likely that racemisation takes place in both processes: formation of the adduct 16a and its further decomposition. The high degree of racemisation observed for 1a after thermal decomposition of the adduct 16a indicates that the thiophosphacylium cation 15a is formed as a planar weakly solvated species.

The nucleotide part of these studies were done in collaboration with Prof. F.Cramer (Göttingen).

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