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GROUP TRANSFER REACTIONS VIA PENTAVALENT PHOSPHORUS INTERMEDIATES.

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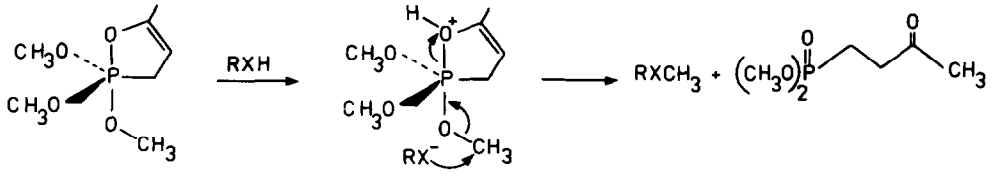
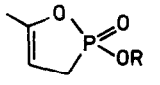
In previous communications[1,2] it was demonstrated that apical protonated P(V) intermediates play an essential role in the reaction of acidic substances with P(V) oxyphosphoranes. A typical example is given in scheme I.



1 SCHEME I

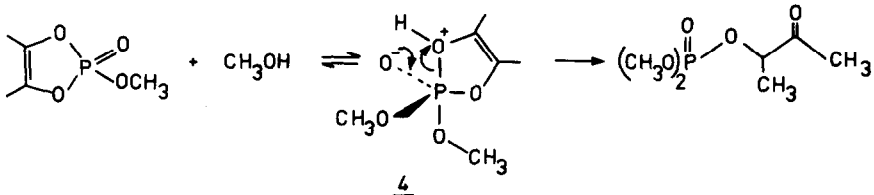
At room temperature the P(V) oxaphospholene 1 alkylates carboxylic acids, phenols and thiols, instantaneously. In order to obtain more reactive P(V) intermediates for group transfer reactions, we studied the reactions of P(IV) oxaphospholens (2, 3) with nucleophilic reagents.



2 R = CH_3

3 R = $C(CH_3)_2$H

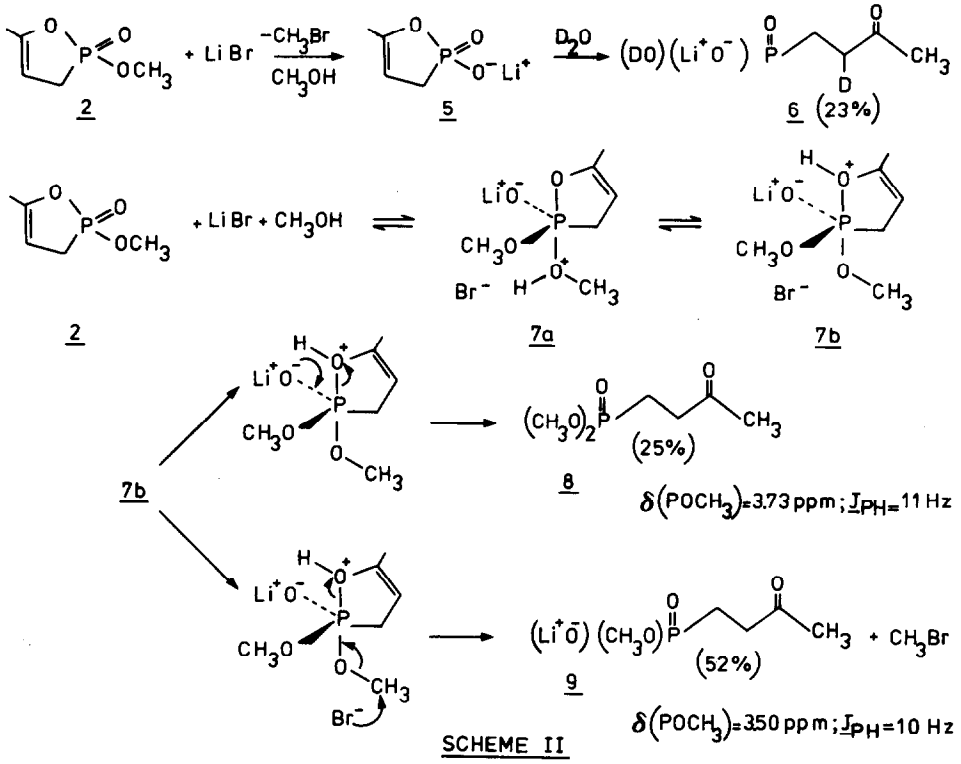
As has been established by Ramirez et al.[3,4,5], alkyl cyclic enediol phosphates are powerful phosphorylating compounds affording acyclic triesters upon reaction with alcohols. These nucleophilic displacement reactions proceed via phosphorane intermediates in a trigonal bipyramidal configuration (TBP), e.g. 4:



4

Decomposition of these intermediates is always accompanied by P=O bond formation from the equatorial anionic oxygen atom with simultaneous departure of the apical protonated ligand. Now it will be demonstrated that pentavalent phosphorus intermediates related to 4 can even participate in group transfer reactions in the

presence of metal ions. Apparently this is caused by the interaction of the metal ion with the equatorial anionic oxygen ligand, thus promoting the stability of the trigonal bipyramidal configuration. When 2 was allowed to react with methanol in the presence of one equivalent of LiBr suspended in ether, 52% of group transfer occurred, i.e. methyl transfer to the bromide anion with the concomitant formation of 9[6]. The reaction was carried out at room temperature for the period of one hour. After evaporation of the solvent, the residue was dissolved in D_2O and investigated by ^1H NMR. The overall results, including the mechanism for the product formation, are depicted in scheme II.

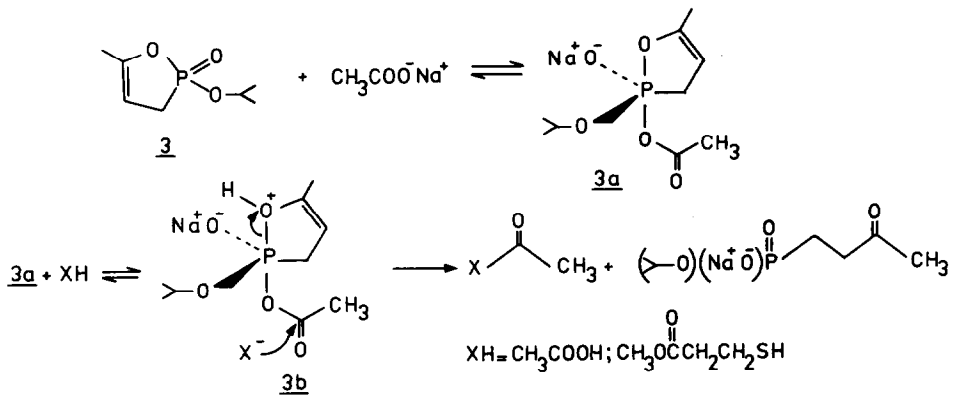


SCHEME II

The formation of 5 is a result of a concurrent dealkylation reaction of 2 with LiBr which, under the experimental conditions, takes place to an extent of 23%. Quenching of the reaction mixture with D_2O results in the formation of 6. This reaction was verified by means of a control experiment in the absence of methanol: a mixture of 200 mg of 2 and 117 mg of LiBr in 25 ml of dry ether gives after 24 hr of stirring at room temperature, evaporation of the solvent and quenching with 3 ml of D_2O 80% of 6 and 20% of 3-oxobutyl phosphonic acid methyl ester ($(DO)(CH_3O)P(O)CH_2CHDCOCH_3$; $\delta(POCH_3)$=3.70 ppm). The latter product is obtained from a direct reaction of 2 with D_2O. Compounds 8 and 9 were identified by addition of authentic samples of pure material. For the preparation of 8 a solution of 1 g of 2 and 0.25 g of methanol in 5 ml benzene was refluxed for 6 hr. After evaporation of the solvent and distillation of the residue pure 8 was

obtained: bp 89-90° (0.05 mm). Refluxing of a solution of 500 mg of 2 and 60.8 mg of water in 5 ml benzene during 15 min resulted in the formation of pure 3-oxobutyl phosphonic acid methyl ester. The lithium salt 9 was obtained quantitatively by addition of one equivalent of Li_2CO_3, followed by evaporation of the solvent and drying in vacuo: mp 170-175°. Quantitative analyses of the products 6, 8 and 9 were made by integration of the methoxy groups relative to the CH_3CO and PCH_2 groups. The amount of 6 was also determined by the amount of Li_2CO_3, necessary to neutralize the acid. Under the experimental conditions 5 does not react with methanol to yield 9 and 8 is not dealkylated by LiBr. Thus the formation of 9 can only be explained by a methyl transfer to Br^- via a pentavalent phosphorane intermediate of structure 7b as illustrated in scheme II. It is noteworthy that the reaction rate of 2 with methanol is increased remarkably due to the presence of LiBr. This catalysis probably results from an interaction of the lithium cation with the phosphoryl oxygen of the P(IV) compound, thus facilitating nucleophilic attack at phosphorus. In addition LiBr may act as a nucleophilic catalyst, i.e. LiBr reacts with 2 yielding a P(V) adduct, which in turn reacts with methanol via a P(VI) intermediate to the P(V) adduct 7a. A similar mechanism has been proposed for the catalysis of P(IV) dioxaphospholens with alcohols by amines, phenoxide and acetate ions[7,8].

Group transfer can be accomplished quantitatively in the reaction of 3 with acetate, in the presence of a proton donor like acetic acid (see scheme III)[6,9].



SCHEME III

Compound 3 was allowed to react with one equivalent of sodium acetate in ether, resulting in the formation of intermediate 3a. A similar intermediate is postulated by Ramirez et al. in a recent publication[8]. One equivalent of acetic acid was added as the acid moiety to react with 3a according to scheme III. After three days of reaction at room temperature, acetic anhydride was formed quantitatively. Similarly, methyl 3-mercaptopropionate could be acetylated by 3 and sodium acetate. After seven days of reaction, the resulting mixture was chromatographed over SiO_2 (ethyl acetate as eluent) affording pure methyl 3-acetylmercaptopropionate in 95% yield. The spectroscopic properties (IR, ^1H NMR) were identical to

those of authentic material prepared from methyl 3-mercaptopropionate and acetylchloride/triethylamine in ether. Aminoacetylation of 3-mercaptopropionate could be accomplished with sodium N-acetylglycine and 3. Chromatography over SiO_2 (ethylacetate as eluent) affords 95% of pure thio ester of N-acetylglycine (mp 81.5-82.5°). Apparently, group transfer can be achieved quantitatively if the exocyclic apical ligand is a better leaving group than the protonated endocyclic oxygen. The interaction of the sodium cation with the equatorial anionic oxygen of the P(V) intermediates 3a and 3b is essential in order to suppress P=O bond formation from the anionic oxygen and removal of the carboxylate anion. In addition, the high electronegativity of the apical oxonium oxygen and the apical acetyl group , stabilizes the TBP configuration to a great extent[10,11,12]. The presence of an equatorial anionic oxygen results in a relatively high basicity of the apical ring oxygen atom, which accounts for the fact that even weak acids like thiols can be acetylated or aminoacetylated[6].

The results of this investigation may lead to a better insight into several enzyme catalyzed reactions involving phosphorus compounds. The acetylation of methyl 3-mercaptopropionate with the aid of acetate or sodium N-acetylglycine and oxaphospholene 3 resembles the enzymatic acetylation of co-enzyme A with acetyl-AMP and the aminoacetylation of t-RNA synthetases, respectively[6,2]. These findings suggest that the essential step in the enzymatic acetylation of the -SH group is the phosphorylation of the enzyme by (amino)acetyl-AMP, resulting in the formation of a TBP intermediate in which the acetyl group and the phosphorylated site of the enzyme are situated in the apical positions.

Acknowledgement

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References

1. W.G. Voncken and H.M. Buck, Rec. Trav. Chim., 93, 14 (1974)
2. W.G. Voncken and H.M. Buck, Rec. Trav. Chim., 93, 210 (1974)
3. F. Ramirez and I. Ugi, Bull. Soc. Chim. France, 453 (1974)
4. F. Ramirez and J.F. Marecek, J. Org. Chem., 40, 2849 (1975)
5. F. Ramirez, S.L. Glaser, P. Stern, Tetrahedron, 29, 3741 (1973)
6. W.G. Voncken, Thesis, Eindhoven (1976)
7. F. Ramirez, J.F. Marecek, H. Okazaki, J. Am. Chem. Soc., 97, 7181 (1975)
8. F. Ramirez and J.F. Marecek, Tetrahedron Letters, 42, 3791 (1976)
9. W.G. Voncken, S.A.J. de Leeuw, H.M. Buck, Contributed Paper, Vth International Conference on Organic Phosphorus Chemistry, Gdansk, Poland, Sept. 1975
10. R. Hoffmann, J.N. Howell, E.L. Muetterties, J.Am. Chem. Soc., 94, 3047 (1972)
11. E.L. Muetterties and R.A. Schunn, Quart. Rev. Chem. Soc., 20, 245 (1966)
12. D. Gorenstein and F.H. Westheimer, J. Am. Chem. Soc., 92, 634 (1970)