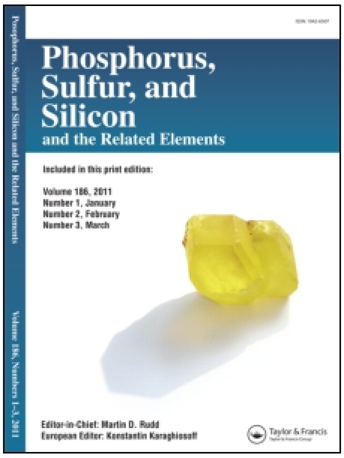

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New Aspects of Trivalent Phosphorus Acid Amide Chemistry

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NEW ASPECTS OF TRIVALENT PHOSPHORUS ACID AMIDE CHEMISTRY

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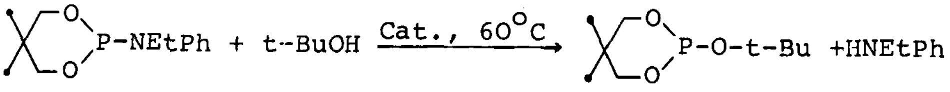
It is known that trivalent phosphorus acid amides (TPAA) in the presence of amine hydrohalides and other weak acids readily phosphorylate proton-containing nucleophiles. This reaction has received wide acceptance in the synthetic practices including the production of oligonucleotides. At the same time, little is known about its chemistry.

The phosphorylation route was studied in a series of experiments. The intermediate haloanhydride formation of the corresponding trivalent phosphorus acids was not observed. This is very important because according to some published data the formation of such intermediates is a must.

To get a deeper insight into the hydrochloride catalysis problem, we started with the establishment of the kinetics of the process. One approach was to study the dependence of the alcoholysis rate on the strength of the used acid. The experiment was made in the system N-ethylanilidoneopentylenephosphorous acid - tertiary butyl alcohol:



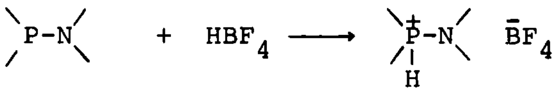
The used catalysts were hydrochlorides of dimethylamine, diethylamine, trimethylamine, triethylamine, ethylbenzylamine, diethylbenzylamine, N-ethylaniline and N,N-diethylaniline. A dependence of the catalytic coefficient logarithm (K_c), considering the catalyst activity, on salt acidity was observed. The obtained data were analyzed by Brönsted's equation which for the process under study is represented as follows:

$$\lg K_c = \lg G_a - \alpha pK_a,$$

where pK_a is the catalyst acidity; G_a and α are the constants characterizing the reaction series. The α value can be used for estimating the degree of proton transfer from the ammonium salt to the phosphamide in the catalytic complex. The derived α value was found to be about 0.05 suggesting the occurrence of the general acid catalysis. In this case the proton is transferred along the reaction coordinate from the ammonium salt to the phosphamide by about 5-10%. Thus the catalytic route takes place not via the phosphamide substrate protonation, i.e. formation of a phosphonium or phosphammonium salt, as suggested earlier, but rather by formation of a complex composed of the substrate and catalyst. It should be noted that the established dependence has some exceptions. Imidazole and N-methylimidazole hydrochlorides catalyze the phosphorylation process much more vigorously than could be expected. The interaction of the TPAA with such substances is likely to be multiaspect. This problem is under discussion at the present time.

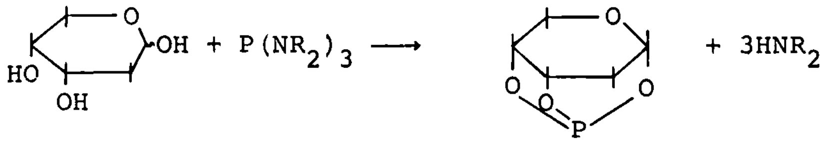
One conclusion following from the conception underlying the appearance of H-complexes is that the interaction of the racemic TPAA with optically active amine hydrohalides can yield optically active diastereomeric phosphorylation intermediates. Therefore a racemic ethyl anilide of 1,3-butylenephosphorous acid was reacted with 1,2; 5,6-di-isopropylidene-α-D-glucofuranose (the molar ratio of reagents 2:1) in the presence of hydrochlorides of racemic and antipodean (+), (-) α-phenylethylamines. The ^{31}P NMR method was used to show that in the case of the racemic catalyst approximately equal amounts of the two diastereomers are formed. With the use of the laevorotatory amine hydrochloride the amount of one of the diastereomers exceeds that of the other by 10%. The dextrarotatory amine hydrochloride will give approximately the same predominant amount of the other diastereomer. Thus, the use of optically active catalysts was shown to provide stereoselectivity in phosphorous acid amide phosphorylation.

The paper also discusses the possibility of the activation of the TPAA by their complete protonation. It is shown that tris-diethylamide, tris-piperidide of phosphorous acid as well as diethylamide diisopropyl- and pyrrolideditertbutylphosphinous acid form with equimolecular amounts of borofluorhydric acid mainly borofluorides of the corresponding amidophosphoniums:



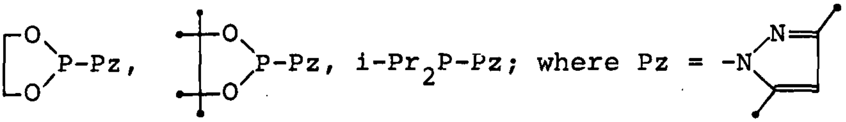
The salts were isolated in a pure form and characterized by ^{1}H and ^{31}P NMR spectra (δ ^{31}P 39-69 ppm, doublet $^1J_{PH}$ 504-630 Hz), which confirms their structure. As demonstrated by their NMR spectra at higher temperatures or in solutes prototropic processes can occur.

The method of TPAA acid activation was useful in finding solution to a number of new synthetic phosphorylation problems, especially in a series of polyfunctional natural compounds. Thus mutarotating sugars with three or four hydroxyl groups, react in the presence of amine hydrochlorides with phosphorous acid triamides, preferable imidazolides, yielding bicyclophosphites, e.g., that of 2-desoxy-α-D-ribopyranose:



In this case the acid catalysis allows to decrease the reaction temperature and thereby avoid the side processes, i.e. splitting of the phosphite-glycoside bond by amine generated in the course of phosphorylation. In addition, using the acid activation was a valuable tool in solving some other urgent problems. Thus, the acids were established to catalyze phototropic processes in p,Π-conjugated

TPAA. For example, pyrazolides of the type



in the presence of 5 mol% of 3,5-dimethylpyrazole hydrochloride, undergo degenerative rearrangements even at 28°C. Related catalytic processes were observed when using phosphorylated imidazoles and amidines.

The advances in TPAA conversions are firmly based on the methods of synthesis of new substances and their effective purification from acid impurities by interphase hydroxyl anion transfer technique.

In conclusion, the phenomenon of acid TPAA catalysis, discovered at our laboratory, was interpreted on the basis of kinetic and structural data. The general conclusions derived have made it possible to offer novel applications of this catalysis.