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Trivalent phosphorus acid amides as phosphorylating agents for alcohols and amines

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Abstract. The principal results of studies on trivalent phosphorus acid amides (TPAA) as phosphorylating agents for alcohols, phenols, and amines are summarised and discussed. Problems concerning the catalysis and mechanism of the phosphorylation of proton-donating nucleophiles by TPAA are considered and new possibilities for the development of investigations on these lines are analysed. The preparative advantages of TPAA and the specific prospects for their use in fine organic synthesis and macromolecular chemistry are demonstrated. The bibliography includes 560 references.

I. Introduction

Phosphorylation, i.e. the introduction of a phosphorus-containing functional group in place of hydrogen atoms into a molecule of an organic nucleophile, is one of the most important problems in organophosphorus chemistry. Pentavalent and trivalent phosphorus reagents have been used traditionally in laboratory research and in industry. More attention was devoted initially to pentavalent phosphorus compounds and then in the subsequent period to trivalent phosphorus compounds. There were important reasons for such switching of interest. It was established that the use of trivalent phosphorus compounds ensures the maximum rates of phosphorylation and makes it possible to avoid side processes such as dealkylation and elimination. The usefulness of trivalent phosphorus reagents is also due to the creation of a modern strategy for the synthesis of organophosphorus compounds. According to the latter, in the first stage of the synthetic scheme the trivalent phosphorus reagents interact with nucleophiles to form only the key substances for subsequent reactions. When necessary, in the second stage of the scheme the key substances may be oxidised, iminated, and alkylated and may combine with sulfur, selenium, chlorine, etc. All these features lead to the formation of a large set of target compounds, including those which are inaccessible within the framework of the classical preparative methods based on the use of pentavalent phosphorus reagents.

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Among the phosphorylating agents which have come to be used vigorously during the last 10 – 15 years, mention should first be made of trivalent phosphorus acid amides (TPAA). Their advantages are ready availability, high reactivity, and the mild conditions in their preparative application. It is very important that the phosphorylating activity of these reagents can be increased significantly by catalysts, for example amine hydrochlorides.

By virtue of these qualities, TPAA are widely used nowadays for the solution of many problems in fine organic synthesis, for example for the preparation of higher oligonucleotides and other phosphorus-containing natural products and their analogues. Furthermore, they are used to obtain valuable high-molecular-mass compounds.

The number of communications describing phosphorylations by phosphoramides runs into thousands. Nevertheless, many important theoretical questions associated with their reactivity have still not been solved, although fairly numerous hypotheses concerning this topic have been put forward in the literature. Thus the phosphorylation mechanism has been elucidated only in broad outline, the relation between the structure and reactivity of the reagents has not been elucidated, and the role of solvation has been poorly investigated. Thus a clear contradiction has arisen between the breadth and depth of the investigation of the problem. In our view, further progress in the study of the phosphorylation of proton-donating nucleophiles by TPAA could be assisted by the writing of an analytical survey of literature data with emphasis on the latest advances. Bearing this in mind, the present review was prepared. In order to differentiate clearly the most important aspects of the problem, we made a selection from the published data and, instead of including data on the phosphorylation of all the proton-donating nucleophiles investigated, only those on the most popular nucleophiles are dealt with: alcohols, phenols, and amines. In the study of precisely these compounds, quantitative measurements have been made of the rates of phosphorylation and reliable results have therefore been obtained concerning both the synthetic aspects of the reactions and their mechanisms.

II. Phosphorylation of alcohols and phenols

The reaction of TPAA with alcohols and phenols was discovered at the very end of the 1950s independently in three laboratories simultaneously.[1-3]

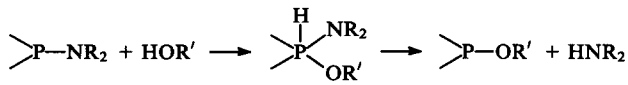
$$>P{-}NR_2 + HOR' \longrightarrow >P{-}OR' + HNR_2$$

This phosphorylation method has important synthetic advantages (see above), but much time was required for investigators to become 'used to it'. It appears that the new method being chemically unusual had an effect. Indeed, until its discovery it had no evident analogies: the amides of pentavalent phosphorus acids phosphorylate alcohols and phenols with a low effectiveness and only at a high temperature, while the amides of carboxylic acids (and even sulfenic acids[4]) altogether failed to interact with alcohols (on the other hand, the corresponding esters are smoothly converted into amides on treatment with ammonia and primary and secondary amines)†. The new method had not been resorted to for some time also because the synthetic problems in which its best aspect would be manifested had not been clearly formulated and included in the range of those dealt with by chemists concerned with organophosphorus chemistry. Nevertheless, this induction period was not wasted. During this period, studies were carried out which established the catalytic nature of the reaction and its principal features as well as the most promising ways of using it. Ultimately, the TPAA came to be firmly included among organophosphorus reagents and began to be used vigorously for the phosphorylation of labile natural products, in the creation of new types of polymers, and in the solution of other complex scientific problems. Bearing this in mind, the present section of the review has been subdivided into individual subsections devoted to the basic problems and questions in the phosphorylation of alcohols and phenols by TPAA and also in the modern synthetic use of this reaction.

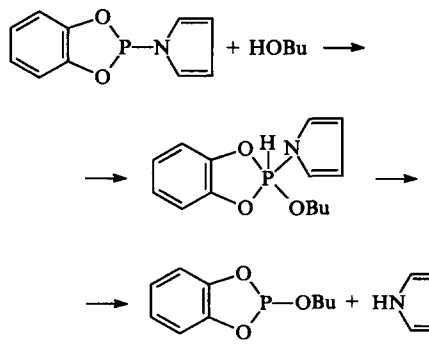
1. The mechanism of the phosphorylation reaction. Catalysis

a. History of the problem

In the first paper devoted to the alcoholysis and phenolysis of the simplest TPAA,[3] certain considerations concerning its mechanism were already put forward. Subsequently, this problem was dealt with by different investigators, but it was discussed only at a speculative level. A version of the mechanism of the 'addition–elimination' type was usually put forward in publications. Thus the intermediate formation of a hydrophosphorane, which decomposes with liberation of an amine, was postulated.[3]

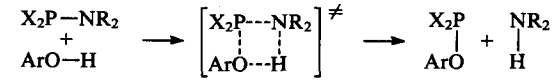


The principal features of this scheme were subsequently confirmed experimentally in a study with cyclic systems,[7–13] for example:[10]



A variant of this scheme is the hypothesis of the P-protonation of the phosphoramide by the alcohol with formation of a quasi-phosphonium adduct, which splits off the amine and is converted into an ester.[3,14–20] An alternative hypothesis is that the TPAA undergoes N-protonation.[3,17,19–23] None of these variants was confirmed experimentally.

At the same time, a view concerning the mechanism of the phenolysis of TPAA has been expressed in the literature according to which a four-centred transition state is formed.[24,25]



This hypothesis is supported by certain thermodynamic data (the activation energies and entropies). Unfortunately experimental errors were made in the relevant studies[25,26] which vitiated the conclusions reached.

When studies of the rates of phosphorylation were undertaken, it proved possible in a number of investigations to elucidate important problems concerning the chemistry of the reaction. Thus it was confirmed that the process is bimolecular for equimolecular proportions of the reactants[10,25,27–31] and that the medium[10,25,26,31] and temperature[32] influence the reaction. The interesting fact that the phosphorylation is inhibited following the accumulation in the medium of the amine produced in the course of the substitution reaction was established; apparently the inhibition is caused by the complex formation reaction between the amine and the alcohol, which reduces the rate of the main reaction.[10,29,31,33,34]

b. Catalysis of the phosphorylation by amine hydrohalides

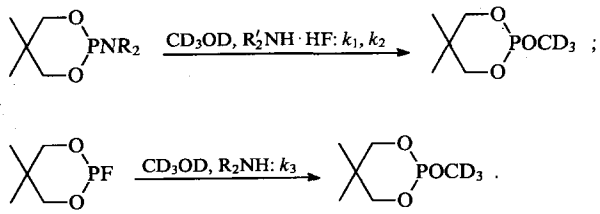
The study of the rate of alcoholysis of TPAA made it possible to determine the catalytic character of many reactions of this type. The catalytic effect was observed in 1965 on comparing the rates of phosphorylation of the simplest alcohols by phosphorus(III) acid amides freed from possible impurities and by phosphoramides which were obtained by the usual procedure and were contaminated by a certain amount of amine hydrochlorides (AHC).[35,36] The observed catalytic effect was subsequently confirmed in many laboratories,[10,18,22,25,28,37–41] the concentrations of the initial compounds and of the products of their reactions being usually determined by ^1H and ^{31}P NMR spectroscopy.[10,25,28,37–42]

The chemical aspect of the catalysis was the subject of prolonged discussion, the outcome of which has been described by Nifant'ev and Borisov.[43]

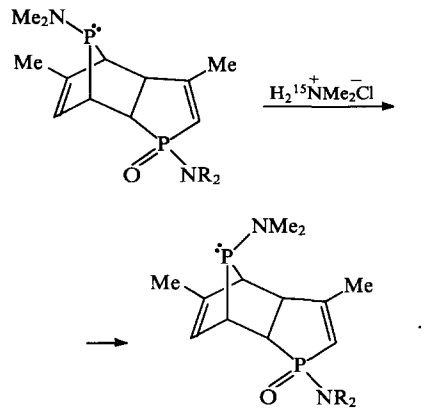
Two hypotheses were discussed. One of them was that acid substances protonate the phosphoramide at the phosphorus or nitrogen atom or at the phosphorus–nitrogen bond. As a result of such protonation, the phosphorus atom of the onium compound becomes more electrophilic and reacts with the alcohol more readily. According to the second hypothesis, the phosphoramide must be protonated at the nitrogen atom. The phosphorammonium cation produced is attacked by an anion (the chloride ion when AHC are used) and is converted into a mixed anhydride, which in fact constitutes the direct phosphorylating agent. The anhydride hypothesis was based on a known fact: on intense heating with diethylamine hydrochloride, phosphorous hexaethyltriamide affords the hydrochloride of *N,N,N',N'*-tetraethylphosphorodiamidite and diethylamine, which is distilled away from the reaction mixture. We may note that, after a lapse of time, the second hypothesis began to be considered by some investigators (see, for example, Refs 44–50) as fully wellfounded. At the same time, it became customary to resort to a speculative description of the mechanisms of the TPAA reaction instead of securing evidence for them. Nevertheless, the anhydride hypothesis was questioned[38,51–54] and was subsequently subjected to a specific criticism. Thus it has been demonstrated experimentally that the cleavage of the phosphoramide linkage in TPAA by amine hydrohalides is not a general phenomenon. For example, phosphorous hexaethyltriamide is cleaved much less effectively than the hexamethyltriamide, while higher amides do not interact

† The unusual character of alcoholysis by TPAA is due to the fact that this reaction had in fact been described twice[5,6] before its 'official discovery', but initially it had not been assessed as a novel and promising phosphorylation method.

preparatively with amine hydrohalides. On the other hand, the effectiveness of catalysis is high for all the amides indicated.[43] An even more interesting result was obtained on comparing the rates of deuteriomethanolysis of the imidazolide (k_1) and *N*-ethylanilide (k_2) of neopentylene phosphite in the presence of amine hydrofluorides and of deuteriomethanolysis of neopentylene phosphorofluoridite (k_3):

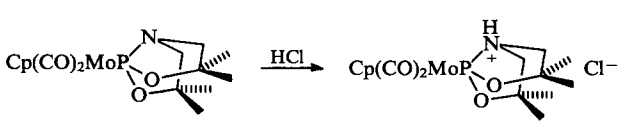


It was found that k_1 and $k_2 \gg k_3$.[55,56] It is significant that the catalytic activities of diethylamine hydrofluoride and other corresponding halides are comparable under standard conditions.[55,56] Such a situation would be impossible if the reaction pathway included a stage involving the formation and alcoholysis of phosphorohalidites. We shall complete the analysis of the hypothesis by quoting the data of Szewczyk and Quin,[57] who investigated the inversion at the phosphorus atom in the presence of dimethylamine hydrochloride enriched in the ^{15}N isotope:



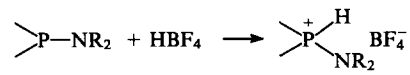
The authors observed the complete inversion of the phosphorus(III) acid amide centre only in the presence of a catalyst (15 h, 25 °C). It was established that the ^{15}N label does not appear in the phosphoramide. Thus the activation of the phosphoramide is associated with some kind of interaction of the substrate and the reagent which does not include an acid chloride formation stage. Otherwise, labelled dimethylamine would have appeared in the medium and its reaction with the acid chloride would have afforded phosphorous [^{15}N]dimethylamide.

The hypothesis of the protonation of TPAA to give onium compounds as a means of their activation for subsequent reaction with alcohols and other nucleophiles was revived at one time and was discussed in the literature. This possibility was specified in detail: the N-protonation pathway was initially considered to be the most probable.[22,23,44] Indeed, in a series of quantum-chemical studies on model >P–N< systems this pathway was specified as energetically preferable.[54,58,59] Nevertheless, convincing evidence for N-protonation in TPAA–AHC–alcohol systems was not obtained. At the same time, data secured in a successful experiment on the N-protonation of a metal complex derivative of one of the bicyclic TPAA were published:[60]



The lone pair of the phosphorus atom in the initial complex formed the phosphorus–molybdenum bond, which fact determines the course of the protonation.

Recently, many investigators indicated the probability of parallel P- and N-protonation[20,47–50] or selective P-protonation.[14,16,30] Evidence for this reaction pathway, obtained by IR[16,61–63] and NMR[20,64–67] spectroscopy, was quoted in the corresponding publications. A group of salts was recently synthesised by the reaction of TPAA with anhydrous fluoroboric acid.[68–72]



These salts are semicrystalline or crystalline. It was of interest that some of them are entirely stable on storage. The interaction of the salts with bases stronger than the initial phosphorus(III) acid amides leads to their deprotonation. By estimating the degree of the latter, it is possible to establish approximately the basicity of the TPAA.[71,72] The structures of certain initial phosphoramides and their quasi-phosphonium salts have been investigated by X-ray diffraction.[70–72] The structural parameters of these substances were determined. Among them, the anomalous shortening of the P–H bonds is striking. Conversely, it was established at the same time that the P–N bond in these salts is anomalously long. For example, its length in the fluoroborate of phosphinous di-*tert*-butylpyrrolide is 1.75 Å.[72] Additional studies demonstrated that treatment of solutions of the quasi-phosphonium salts with bases (B′), including TPAA, leads to the formation of dynamic complexes in which a proton migrates between two donor centres:[71,72]

$$(Et_2N)_3\overset{+}{P}H\overset{-}{B}F_4 + B' \longrightarrow [(Et_2N)_3P\text{---}H\text{---}B']^+BF_4^- ;$$

$B' = Et_3N, C_5H_5N, P(NEt_2)_3$.

Experiments were carried out on the alcoholysis of the salts and it was established[70–72] that they do not really react with alcohols‡.

Thus the hypothesis that the products of the protonation of TPAA are intermediates in the alcoholysis of phosphoramides is likewise not true. It was of interest to compare the tendencies of the products of the protonation and alkylation of TPAA to undergo alcoholysis, since these salt-like substances are isoelectronic. It was found that they all remain unchanged on treatment with alcohol§.[70,73]

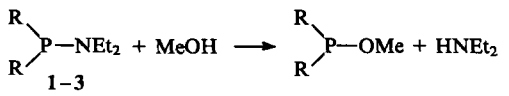
Further study of the alcoholysis of TPAA in the presence of AHC involved investigation of the rates of reaction in the presence of selected concentrations of various catalysts¶.

The quantitative characteristics of the effect of amine salts on the rate of alcoholysis of the amides **1–3** were established in preliminary experiments.[78]

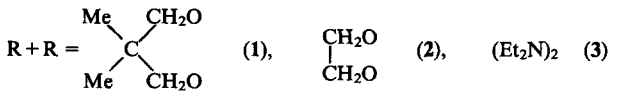
‡ Thus the P(III)–N bond length and the factors influencing it are not decisive criteria of the phosphorylating capacity, which has been occasionally implied.[24,48]

§ In this connection, we may note another important fact, namely that the phosphorammonium salts alkylated at the nitrogen atom undergo alcoholysis at the P–N bond.[74]

¶ For accurate kinetic studies of the acid-catalysed reactions of TPAA, the procedures for the removal of AHC impurities from TPAA already known[75,76] were supplemented by developing a purification procedure using phase transfer principles,[77] which made it possible to achieve a residual concentration of the chloride ions of 0.11×10^{-3} M. The residual content of chloride ions was monitored by potentiometric titration.[70,78] An attempt had been made previously[29] to monitor quantitatively the residual content of AHC and TPAA by a conductimetric method.



1–3



Thus the rate constants for the first stage of methanolysis were determined as a function of the content of the AHC in the ranges of concentrations corresponding to their amounts usually present in TPAA. The quantitative composition of the reaction mixture was determined by NMR spectroscopy — by integrating the ^{31}P signals. The pseudofirst-order rate constants (k_I^{ψ}) were determined from the decrease in the concentration of the initial amide by means of the linear plot of $-\ln([\gtrdot P-NEt_2]/[\gtrdot P-NEt_2]_0) = f(\tau)$, where $[\gtrdot P-NEt]_0$ is the initial concentration of the amide. The second-order rate constant was found from the values of k_I^{ψ} obtained by means of the equations $k_{II} = k_I^{\psi}/[MeOH]$.

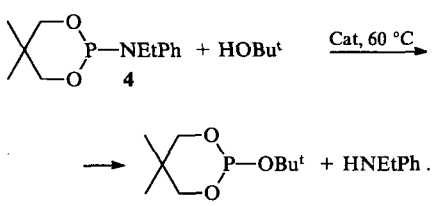
The results of the kinetic measurements can be represented by Eqns (1) and (2):[29]

$$-\frac{d\left[\gtrdot P-NEt_2\right]}{d\tau} = k_{II}\left[\gtrdot P-NEt_2\right][MeOH], \quad (1)$$

$$k_{II} = k_0 + k_c[Et_2\overset{+}{N}H_2], \quad (2)$$

where k_0 is the rate constant for the noncatalysed reaction, k_c a catalytic coefficient taking into account the activating effect of diethylamine hydrochloride, and $[Et_2\overset{+}{N}H_2]$ and [MeOH] are the concentrations of the salt and methanol, which remain constant during the reaction. The linearity of the dependence of k_{II} on the salt concentration demonstrated that the reaction is first order with respect to the catalyst. Thus the fundamental importance of the quantitative monitoring of the purity of the amides in the study of the alcoholysis of TPAA was established[70,78] and conditions were selected for the investigation of a crucial feature of the acid-catalysed reactions of TPAA — the nature of the interaction of AHC with TPAA.

For this purpose, a study was made of the influence of the nature of AHC on the catalytic activity in the alcoholysis of TPAA. The experiment was performed in the neopentylene *N*-ethylphosphoroanilidite–*tert*-butyl alcohol system.[70,79]



The catalysts employed were the hydrochlorides of diethylamine (**5**), dimethylamine (**6**), triethylamine (**7**), trimethylamine (**8**), benzyldiethylamine (**9**), benzylmethylamine (**10**), *N*,*N*-diethylaniline (**11**), and imidazole (**12**). The choice of the amide **4** and of the catalysts **5**–**12** was dictated by the fact that the basicity of the amines should be not less than that of the amine produced on alcoholysis, i.e. *N*-ethylaniline. Otherwise the catalyst would change during the reaction.

Graphical treatment of the data in accordance with equations (1) and (2) above showed that there is a linear relation between $\lg k_c$ and the acidity of the salts **5**–**12**. In the case of salts of secondary and tertiary amines, it is expressed by two independent straight lines (Fig. 1). The introduction of the statistical factor *S* (the number of protons bound to the nitrogen atom of the ammonium salt[80]) combines the two lines into one (Fig. 2).

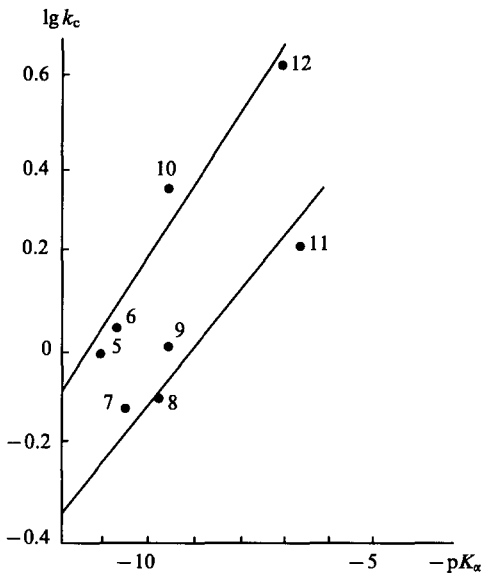


Figure 1. Dependence of $\lg k_c$ on the acidity of catalysts **5**–**12**.

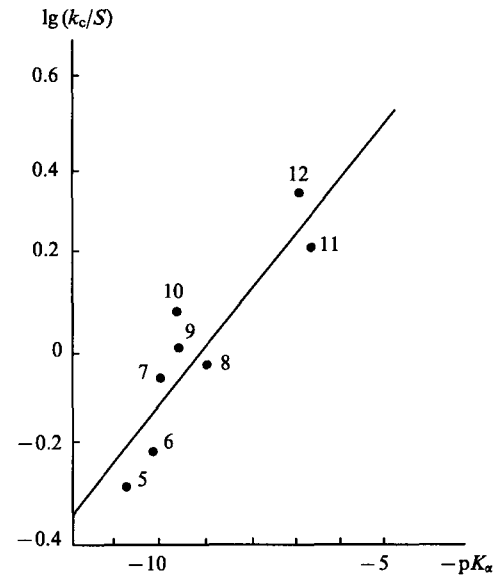
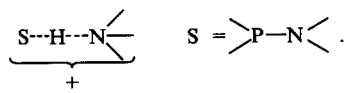


Figure 2. Dependence of $\lg (k_c/S)$ on the acidity of catalysts **5**–**12**.

The Brønsted equation (3) was used to analyse the results. For the process investigated, it was expressed in the following form:[81]

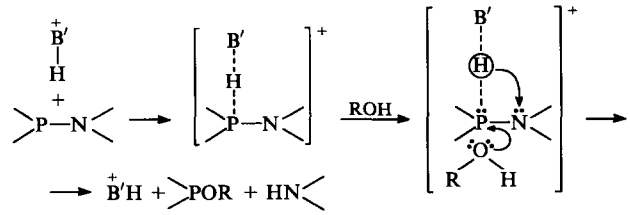
$$\lg\left(\frac{k_c}{S}\right) = \lg G_A - \alpha pK_a, \quad (3)$$

where G_A and α are constants characterising the reaction series. The slope α is a measure of the sensitivity of the reaction to the acid catalyst. It was found that $\alpha = 0.13$ ($r = 0.95$), which indicates *general acid catalysis* of the phosphorylation reaction. In this case, it is best to interpret α as an approximate measure of the change in the charge on the proton-donating or proton-accepting atom in the transition state.[82] Thus the catalytic process proceeds not via the protonation of the phosphoramide substrate (the formation of a phosphonium or phosphorammonium salt postulated previously) but via the formation of the catalytic hydrogen-bonded complex incorporating the substrate (S) and the catalyst as a whole:

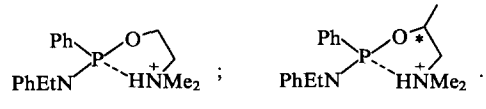


In contrast to the onium salts this complex is a proton-labile system, which apparently determines also its tendency to undergo alcoholysis.

Summarising the foregoing, one may conclude that the alcoholysis of TPAA in the presence of AHC includes stages involving the formation of the catalytic hydrogen-bonded complex. In the latter, the proton fulfills two functions: firstly, it activates the phosphorus atom in the electrophilic reaction, for example with an alcohol, and secondly, during the reaction the proton migrates from the phosphorus to the nitrogen atom, thereby assisting the dissociation of the P–N bond.[70–72]



An important stereochemical consequence follows from this: if a chiral catalyst is employed, then the catalytic hydrogen-bonded complex is also chiral. Therefore, when chiral catalysts are used, one may expect the manifestation of stereoselectivity in the phosphorylation reaction. Correspondingly, the interaction of the racemic 1,3-butylene *N*-ethylphosphoranilidite with 1,2;5,6-diisopropylidene-α-D-glucofuranose (in molar proportions of 2 : 1) was carried out in the presence of the racemic hydrochloride of α-phenylethylamine and its (+)- and (−)-enantiomers. It was shown by ^{31}P NMR that, when a racemic catalyst is used, approximately equal amounts of the two diastereoisomers are formed. When the hydrochloride of the laevorotatory amine is employed, 10% more of one of the diastereoisomers is obtained. The dextrorotatory hydrochloride ensures approximately the same preferential formation of the other diastereoisomer. Thus it has been shown[70,79] that the use of optically active catalysts can ensure stereoselectivity in the phosphorylation of TPAA. Subsequently this fact was used to attain a more effective 'contact' between the phosphoramide and the hydrochloride forming part of its composition (compound **13**), which ensured effective intramolecular catalysis resulting in a sharp increase in the rates of phosphorylation and in a significant stereoselectivity of the process following the inclusion of a chiral fragment in the composition of the 'catalytic' component of the phosphorus(III) acid amide **14**:[83]

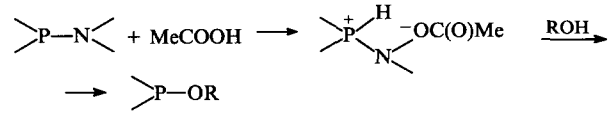


13 **14**

c. Phosphorylation in the presence of carboxylic acids and azoles

The discovery of the catalytic effect of AHC in the alcoholysis of TPAA led to the search for new ways of accelerating this type of phosphorylation. AHC and phenols are known to have comparable acid properties. Taking this into account, successful experiments were carried out on the phosphorylation of alcohols by TPAA in the presence of phenol.[84] The catalysis of the alcoholysis of TPAA by phenol was thus confirmed experimentally. Unfortunately this version of the catalysis is not promising in preparative terms, since the reaction resulted in the formation not only of the compounds sought but also of the corresponding phenyl esters.

The next stage in the development of the acid catalysis involved the study of the alcoholysis of TPAA in the presence of carboxylic acids, acceleration of phosphorylation by acetic acid being observed.[16,25,85] In a number of instances, the acceleration was very significant. Thus it has been shown[16] that phosphorous tripiperidide does not react with ethanol even on refluxing but, when acetic acid is added to the reaction mixture, phosphorylation occurs even at 20 °C. The formation of a quasi-phosphonium cation was initially postulated as the first stage.



Subsequent study of the catalytic effect of acetic acid showed that it not only accelerates but also alters the mode of certain reactions of phosphoramides. Thus the reaction of the amides with aliphatic mercaptans in the presence of acetic acid proceeds with dissociation of the P–N bond[85] and not via the addition of sulfur to the initial amides, noted in experiments without added catalyst.[86]

The mechanism of catalysis by carboxylic acids has been investigated only to a first approximation. It may be that the mechanism corresponding to the catalysis by AHC operates under certain conditions, but other variants are also possible. It has been shown[37] that the phenolysis of TPAA in the presence of carboxylic acids involves the formation of acyl phosphites, which were detected by ^{31}P NMR. Apparently the acyl phosphites phosphorylated phenol with formation of phenyl phosphites and carboxylic acids.[87,88] The latter again interact with TPAA, affording acyl phosphites, etc. At the present time, this mechanism is not well founded. We may draw attention to the fact that acyl phosphites can undergo not only phenolysis (alcoholysis) but also aminolysis with formation of carboxylic acid amides and hydrophosphoryl compounds.[87–93] Furthermore, it is essential to take into account also the neutralisation of the carboxylic acid by the secondary amines formed. Yet another important factor may be noted: there are data indicating the catalytic nature of the conversion of TPAA into acyl phosphites.[90,91,94] Hence, in the acyl phosphite variant, there may be two catalytic stages.

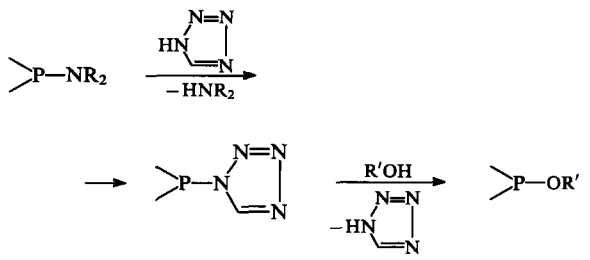
The alcoholysis of TPAA can also be catalysed by other acids, for example amidodithiocarbamic acids and also their ammonium salts.[95]

The search for new variants of the phosphorylation reaction led to the investigation of the activation of the alcoholysis with the aid of free azoles, which are weak N–H acids. These are usually 1*H*-tetrazole ($pK_a \approx 4.8$) (see, for example, Refs 96–99) and more rarely 1,2,4-triazole ($pK_a \approx 10$)[100,101] or azoles the acidity of which has been enhanced by the introduction of electronegative substituents into the azole ring (4,5-dichloroimidazole, 3-chloro-1,2,4-triazole,[100,102] 5-*p*-nitrophenyltetrazole, and certain others[103,104])†. The salts of azoles, mainly diisopropylammonium tetrazolide, are used for a similar purpose (see, for example, Refs 106–114). Very satisfactory results — complete phosphorylation in 2–3 min at 20 °C — have been achieved under the optimised conditions for the phosphorylation of complex systems. Because of this, the azolide variant has come to be especially widely used, including its employment in automatic synthesisers for the preparation of important oligonucleotides (see below).

The situation is less satisfactory as regards the understanding of the chemistry of the azolide variant of the phosphorylation reaction. It is significant that the amounts of azoles in relation to TPAA used in the experiments described were not catalytic but equimolar or even greater than equimolar. This makes it difficult to classify the reactions considered as catalytic. In view of the

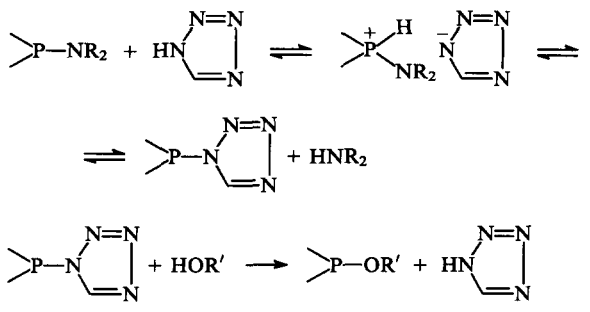
† The use of the last activator has been criticised.[105]

foregoing, we may note the observation in the ^{31}P NMR spectra of reaction mixtures containing an excess of tetrazole of a signal corresponding to the transamidation product—a phosphorus(III) tetrazolide, which is regarded as an intermediate.[115-117]



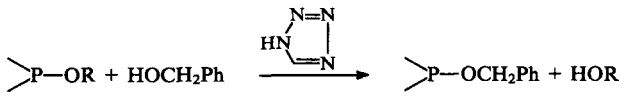
The possibility of the formation of phosphorus(III) tetrazolides has been the subject of certain special investigations, in which the role of the acidity of the activators was emphasised. According to the authors of these studies,[100,115,117,118] the activators are capable of protonating the initial TPAA. It is of interest that it has been possible to perform kinetic measurements in the TPAA—tetrazole system and to devise a scheme for the overall alcohol phosphorylation process (Scheme 1).[118]

Scheme 1



Unfortunately this scheme has not been analysed in depth. Two comments may be made on this question. The first is that the authors of the scheme do not prove but merely postulate the protonation of TPAA by tetrazole. The second is that the authors have not demonstrated that the phosphorus(III) tetrazolide is an 'on-going' and not a dead-end product in the system of stages involved in the phosphorylation of alcohols using the usual TPAA. The second comment is especially important in connection with the publication of data[119] on the transesterification of neutral phosphites in the presence of tetrazole (Scheme 2). There are also data concerning the activation of the transesterification of neutral phosphites by 1,2,4-triazole.[120]

Scheme 2



The reaction described is related to that discussed by ourselves because it too involves nucleophilic substitution at the trivalent phosphorus atom in the presence of tetrazole. However, it is difficult to postulate that the stage involving the conversion of the alkyl phosphite ester into the tetrazolide is obligatory, since in fact reactions of the opposite type are well known. Consequently, it is essential to analyse not only the tetrazolide but also other activation procedures. The authors of the present review believe that the most probable form of activation of the alcoholysis of an alkyl phosphite is the formation of a complex between this ester and tetrazole.

We shall return to the question of the phosphorylation of alcohols by TPAA in the presence of tetrazole. Taking into account the foregoing, we suggest that general acid catalysis may operate in this instance in the conversion of the dialkyl amides into the required esters or into tetrazolides. If, on the other hand, the tetrazolides prove to be intermediates in the synthesis of the esters, then they too probably require cooperation from tetrazole. The main factor in the catalysis in all these cases may be the formation and reaction of the corresponding tetrazole complexes. Unfortunately more far reaching kinetic studies with introduction of catalytic amounts of tetrazole into the reaction mixture have not yet been carried out. Nevertheless, a study has been published very recently on the application of triazole, indicating the existence of an acid catalytic stage in this process.[101]

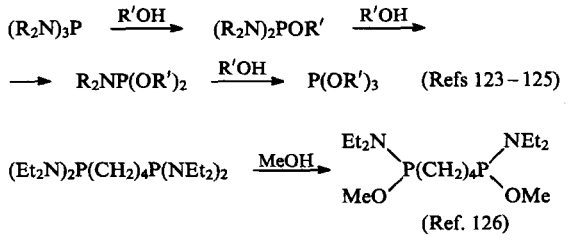
2. General characteristics of the phosphorylation of alcohols and phenols

The dependence of the phosphorylating capacity of TPAA on their structure and certain related problems will be considered in this subsection of the review. The second part of the subsection is devoted to the stereochemical features of the phosphorylation reaction.

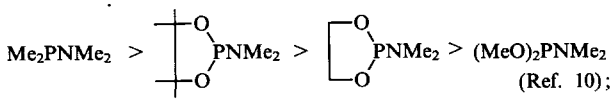
There have been few kinetic studies on the alcoholysis of TPAA and for this reason reliable correlations between the reactivity of phosphoramides and their structure have not so far been established. The situation is complicated also by the fact that in most of the published communications the problem of catalysis was overlooked and for this reason acid admixtures were not specially eliminated from the phosphoramides and a definite amount of a selected catalyst was not added to the substrate. Nevertheless, one can already speak of certain qualitative features, since the phosphoramides most often employed for phosphorylation have been usually obtained by a standard method in different laboratories and they were therefore contaminated by approximately equal amounts of identical activator impurities (these were most often AHC). The range of alcohols employed almost always comprised the most readily available standardised representatives.

Taking into account these comments, one may note that as a rule branched alcohols had a lesser tendency to undergo phosphorylation than linear alcohols, while secondary alcohols were inferior in this respect to the primary ones.[10,28,84] There exist data indicating a higher reactivity of phenols[10,24,25,28,84] and acid alcohols[84] in phosphorylation compared with the usual alcohols. However, it has been noted that the phosphorylation of phenols in bulk may be complicated by the formation of intermolecular hydrogen bonds, which, however, are ruptured on heating the phenol–TPAA system in aromatic solvents. The use of this procedure makes the phosphorylation of phenols more effective.[121] Intramolecular hydrogen bonds have a smaller inhibiting effect on phosphorylation; however, when these bonds are strengthened, as happens on passing from 8-hydroxyquinoline to 5,7-dibromo-8-hydroxyquinoline, the phosphorylation is impaired.[122]

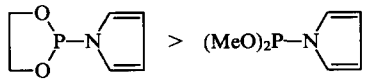
The influence of the TPAA structure on phosphorylation is expressed by more complex relations. It has been established that the amino-groups in phosphorous triamides can be substituted stepwise by alkoxy-groups.[123-126]



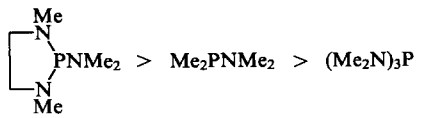
Consequently the full amides are more reactive than the amidoesters. Certain detailed features of the phosphorylation reactions have also been discovered, but these are based on a relatively narrow range of experimental data.[10,28] In terms of reactivity, amines can be arranged in the following sequence:

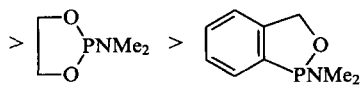


(Ref. 10);

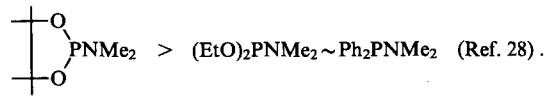


(Ref. 10);





(Ref. 28);



(Ref. 28).

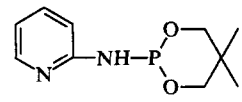
We may draw attention to the fact that the phosphorylating capacity of TPAA is in some way correlated with their basicity. One can apparently now state that the tendency of TPAA to form a complex with the acid catalyst plays a decisive role, i.e. that these substances are ready to form catalytic complexes.

The second aspect of the problem of the reactivity of TPAA, involving the elucidation of the role of substituents at the phosphorus atom, has been examined in greater detail. Thus it has been established for the reaction,

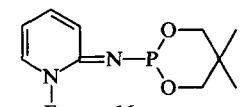


that the phosphorylating activity increases in the following sequence of substituents at the phosphorus atom:[28] $N(Pr^i)_2$ < NMe_2 < NMePh < NPh_2. The high phosphorylating activity of monophenyl- and diphenyl-amides, noted previously,[127] is striking. The phosphopyrrolides, which exhibit an increased resistance to alcoholysis, are an exception.[10,71,127,128] It has been shown[71] that this is associated with the passivity of the lone pair of pyrrole as regards the formation of a hydrogen bond and prototropism. We may note further that data have been published on the high phosphorylating capacity of the vinyl amides of trivalent phosphorus acids.[47] Summarising the foregoing, we may conclude that in phosphorylation there is an inverse relation between the tendency of the amino-group to leave the phosphorus atom and its basicity. It is of interest that, according to the data of Evdakov et al.,[25] the phenolysis of TPAA does not obey the rules presented above. Apparently such data should be subjected to additional analysis.

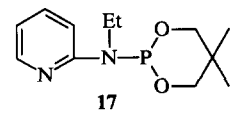
The observation of a high reactivity of anilides in alcoholysis led to the extension of the studies initiated to the field of related heterocyclic phosphoramides.[129,130] Thus phosphorylated 2-aminopyridine **15** and its two derivatives **16** and **17**, ethylated at different nitrogen atoms, have been subjected to methanolysis.[131,132]



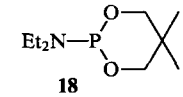
15



16



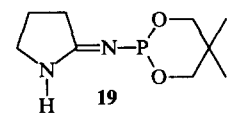
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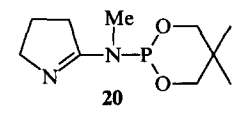
18

Study of the rates of methanolysis of these compounds made it possible to formulate several important conclusions. (1) The phosphoramides **15** and **17** are more reactive than *neopentylene N,N-diethylphosphoramidite* **18**. Thus the early observation that the reactivity of phosphoranilides is high has been reliably confirmed. (2) The phosphoramides **15** and **17** are more reactive than the phosphorimide **16**, so that the electronic structure in the P–N–C–N fragment is important for the alcoholysis of the P–N bond. (3) The phosphoramide **15**, the molecules of which contain secondary hydrogen atoms, is much more reactive than its *N*-ethyl derivatives **16** and **17**. Furthermore, compound **15** does not require a catalyst in alcoholysis, whilst compounds **16** and **17** do require it. This means that the reactions of compound **15** involve autocatalysis.[132]

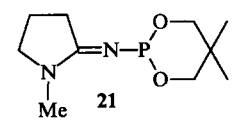
Thus it follows from the data presented that the tendency of TPAA to undergo alcoholysis can be effectively regulated by the structural features of these compounds. An even more interesting picture of this phenomenon has been observed in a study of the alcoholysis of phosphorylated 2-aminopyrrolines.[131,133,134] The rates of methanolysis of the three related derivatives **19**–**21** were compared in this instance and it was shown that compound **19** exhibits the greatest susceptibility to substitution.



19



20



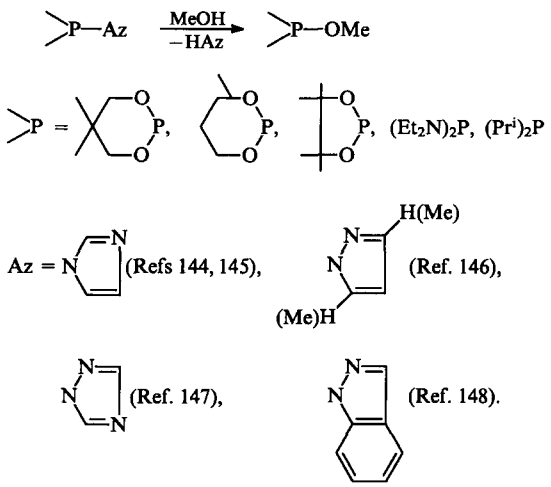
21

A distinctive feature of this compound is the presence of a mobile hydrogen atom. In this connection, we may note the greater reactivity of the pyrrolidine derivative **19** compared with that of the pyridine derivative **15**. This finding suggests an important role for prototropism in phosphorylation, which is more probable for the phosphopyrrolidine **19** than for the aromatic phosphopyridine **15**.

Comparison of compounds **20** and **21** revealed a relation which had already been discovered earlier for pyridines: the imine **21** is inferior in reactivity to the amide **20**. Nevertheless, comparison of the conditions in phosphorylation by these substances led to an unexpected observation — compound **21** does not require a catalyst in alcoholysis. Apparently, being one of the phosphorylated forms of an amidine, this compound exhibits a high reactivity and, together with an alcohol molecule, constitutes a catalytic complex for the phosphorylation reaction. Naturally, compound **19** is also a phosphorylated amidine but here the phosphorus atom is at the imine end of the amidine system, which lowers its basicity.

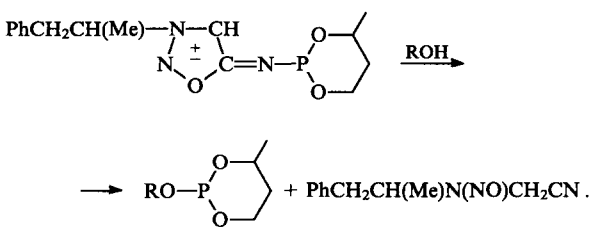
The interest in phosphorylated derivatives of heterocycles as phosphorylating agents for fine organic synthesis has become particularly marked nowadays in the study of phosphorazolides and related systems. Investigations on these lines began with the publication of the papers of Birkofer et al.[135] and Nifant'ev[136] and were vigorously continued in other studies[137–143] in which

phosphorimidazolides were identified as the most reactive preparations. The tendency has arisen recently to expand this research and to treat the results systematically. In this connection, we may note a series of communications on the synthesis of various phosphorazolides and their phosphorylating capacity.[144-148]



It has been established that the reactivity of phosphorus(III) acid azolides decreased significantly in this case in the series diester phosphorazolidites > phosphorous diamide azolides > phosphinazolidites and, depending on the nature of the azole, in the series imidazolide > pyrazolide > triazolide > benzimidazolide.[120] A very marked influence of the solvent polarity on the phosphorylating capacity of the phosphorus(III) acid azolides was unexpected. It decreased sharply on passing from acetonitrile to chloroform and even more so on passing to dioxane and benzene.[120] Azoles are known to exist in nonpolar solvents in the form of linear oligomers or cyclic trimers.[149,150] With increase in solvent polarity, these self-associated species can decompose and the catalytic function of azoles comes to the fore, which accelerates the alcoholysis.

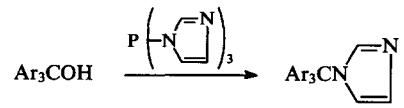
Continuing the consideration of the alcoholysis of heterocyclic phosphorus(III) acid amides and imides, we may point to the results of the phosphorylation of alcohols by phosphosydnone imine obtained in the following instance:[151,152]



This reaction has no special preparative advantages, but it is interesting because it is not accompanied by the accumulation of a nitrogenous base in the system, since the sydnone imine produced isomerises immediately to *N*-nitroso-1-phenylisopropylaminoacetonitrile. This product has optical properties differing strongly from those of phosphosydnone imine, so that it is easy to investigate the kinetics of its reactions by UV spectroscopy, including dilute solutions.

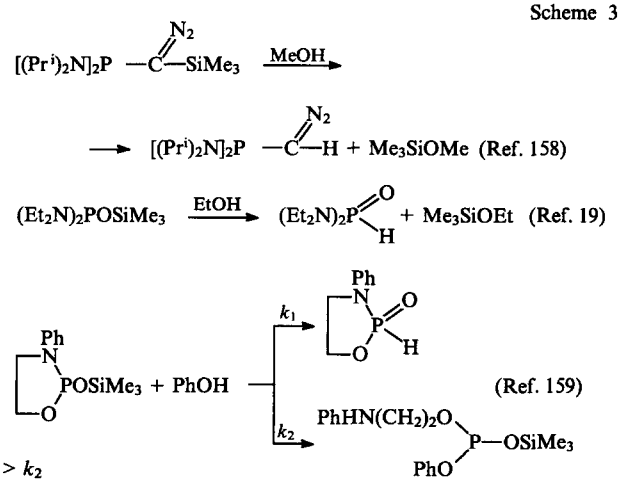
The first data have now been obtained also on the alcoholysis of the hydrazides,[153] hydroxyamides,[154] benzamidides,[155] and guanidides[156] of certian trivalent phosphorus acids. All these compounds exhibit an effective phosphorylating capacity, which intensifies with acid catalysts, but no characteristic features making them specially valuable have yet been noted.

The advantages of the phosphoramide phosphorylation method were indicated above: the mildness of the conditions and the absence of side reactions. This general rule has a few exceptions, which must be stated in the review. Thus it has been established that the phosphorylation of triarylcarbinols by phosphorous acid triimidazolide leads to triarylimidazolylmethanes and not to the expected product.[157]



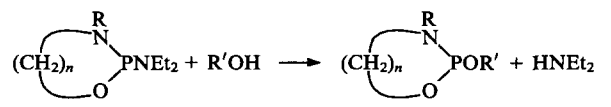
A deficiency of the phosphorus(III) acid amide method is also the unpredictability of the reactions of certain organoelement TPAA derivatives. Thus systems containing the C–Si[158] and O–Si[19,159] bonds can undergo cleavage at precisely these bonds on alcoholysis and phenolysis (Scheme 3)‡.

Scheme 3



We shall consider the influence of structural factors on the mode of alcoholysis and phenolysis of cyclic systems, the molecules of which contain both exophosphoramide and endophosphoramide bonds. There are literature data on the interaction of alcohols and phenols, in equimolar amounts relative to the substrate, with 2-dialkylamino-1,3,2-oxazaphospholane[162-165] and [the corresponding] phosphorinane.[166-170] These reactions lead mainly to the dissociation of the exocyclic bond (Scheme 4).

Scheme 4

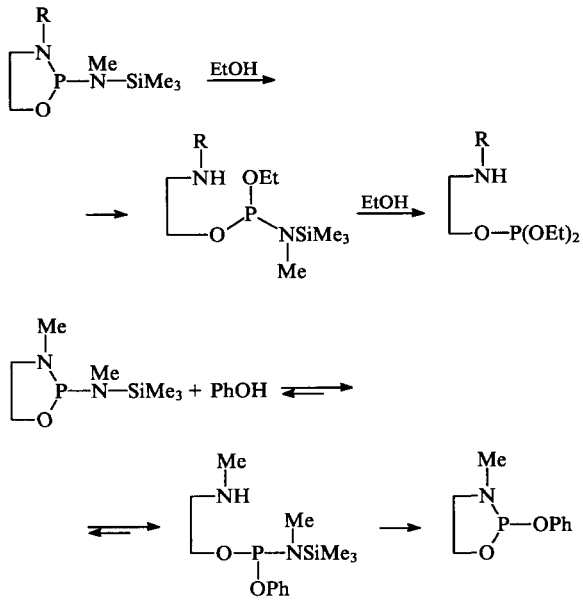


n = 2, 3; R,R′ = Alk, Ph

Oxazaphospholanes having a P–C exocyclic bond are much more reactive in the alcoholysis of the endocyclic P–N bond than the corresponding 2-alkoxy-derivatives, the introduction of an alkyl substituent in the 5-position in the oxazaphospholane ring resulting in a significant stability of the P–N bond.[171]

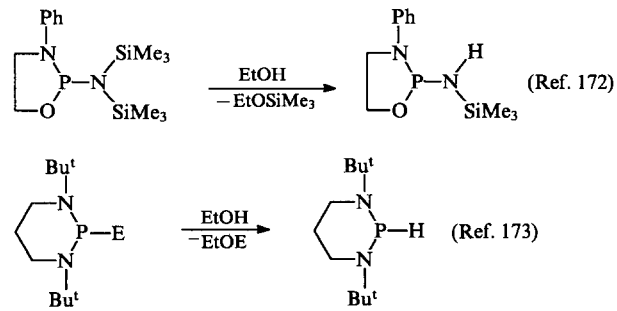
However, alcoholysis of oxazaphospholanes containing an exocyclic *N*-methyl-*N*-trimethylsilylamino-group begins with the rupture of the endocyclic P–N bond and only then of the exocyclic bond. In phenolysis, the ring is reformed in the second stage.[172]

‡ The acid catalyst (tetrazole) can, however, alter the mode of the reaction towards the dissociation of the P–N bond.[160,161]



When the molecules contain an exocyclic *N,N*-bistrimethylsilylamino-group[172] and trisubstituted P-silyl and P-germyl groups,[173] alcoholysis does not involve the cyclic skeleton of the molecules and begins with the dissociation of the N–Si and P–Si(Ge) exocyclic bonds (Scheme 5).

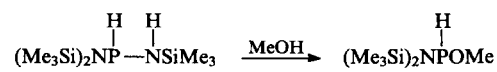
Scheme 5



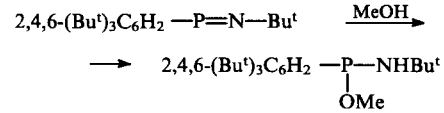
E = $SiEt_3$, $SiPh_3$, $GeEt_3$.

We may note the unusual nature of the alcoholysis of the P–N–Si acyclic systems. In the presence of two types of trimethylsilylamino-groups — secondary and tertiary — in the molecules of such TPAA, a secondary silylamino-group is the first to undergo alcoholysis (Scheme 6).

Scheme 6

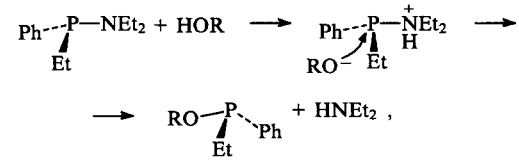


Finally, mention should be made of the possibility of the alcoholysis of the P=N π-bond in iminophosphine derivatives.[175,176]

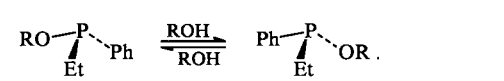


When an excess of the alcohol is used, there is a possibility of further alcoholysis, this time involving the P–N σ-bond.

The results of the study of the stereochemistry of substitution of the amino-group at the phosphorus(III) atom are difficult to interpret because it is essential to take into account the possibility of inversion at the phosphorus centre (especially at elevated phosphorylation temperatures) both in the initial TPAA and in the products of their reaction. Such inversion can occur readily under the influence of acid impurities[177,178] and other factors, for example owing to the presence of an excess of the alcohol (transesterification). Therefore the early studies, where the purity of the initial reactant was not rigorously monitored, must be treated with caution. This applies in the first place to the publications on the mechanisms of the reactions of optically active compounds, where the conclusions about their chemistry were reached solely on the basis of measurements of the angle of rotation of the reaction mixtures. As an example, we may point to a study[179] of the interaction of the optically active ethylphenylphosphinous diethylamide with methyl, ethyl, n-propyl, and isopropyl alcohols. A decrease in the angle of optical rotation was observed in these experiments. The above results were explained by two reactions. Firstly, by the substitution proper involving the inversion of the configuration at the phosphorus(III) atom:

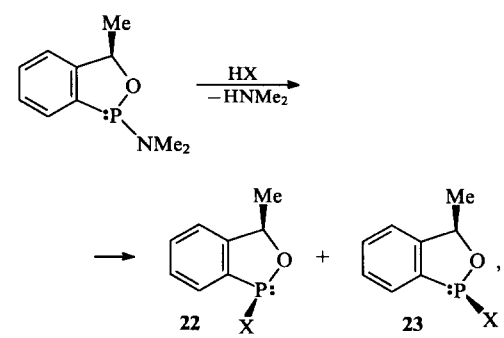


and secondly, by the racemisation effected by the excess alcohol:



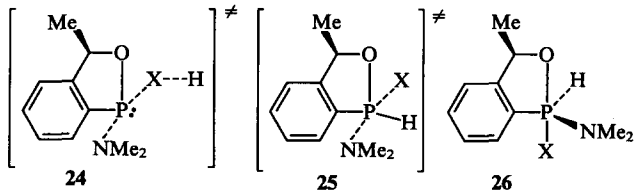
Under these conditions, retention of the configuration was observed in the reaction of *p*-cresol, which served as a basis for an explanation of the mechanism in terms of a four-membered transition state. In this connection, we emphasise that the authors[179] carried out the reaction with cresol for 1 h at 100 °C and were therefore unable to observe the primary inversion. Furthermore, the monitoring procedure they used enabled them to observe only the overall optical rotation of the mixture, while the influence of the initially inverted product might have been small owing to its insignificant amount.

More reliable results were obtained in the analysis of the stereochemical transformations of diastereoisomers by NMR spectroscopy. Thus, in the interaction of certain derivatives of phospholanes with phenol, Nielsen and Dahl[41,180] observed by ^1H NMR the initial inversion of the configuration of the phosphorus atom and the subsequent inversion in the reaction product. The latter led to the formation of a thermodynamically stable isomer (< 5 min). The data obtained in a study by ^1H and ^{31}P NMR of the nucleophilic substitution of a diastereoisomerically pure benzoxaphospholene, i.e.



where X = OMe, OBu^t, OPh, NMe_2, $N(CH_2)_5$, or NHPh, showed that the reaction with HX [X = OMe, OPh, $N(CH_2)_5$] at 25 °C in $CDCl_3$ proceeds with formation of two products, **22** and **23**, the product with the inverted configuration at the phosphorus atom being initially obtained preferentially. Subsequent reactions evidently lead to an equilibrium mixture of the diastereoisomers **22** and **23**. For X = OBu^t and NHPh, the rate of reaction is lower

than the rate of inversion and in this case an equilibrium mixture of compounds **22** and **23** was therefore immediately obtained. The authors believe that the $S_N2(P)$ type substitution mechanism at phosphorus(III) usually proposed (see, for example, Zavlin et al.[27]) is improbable because of the unfavourable diequatorial disposition of the phospholene ring in the transition states of two different types, **24** and **25**, and postulate the formation of a new type intermediate **26**.

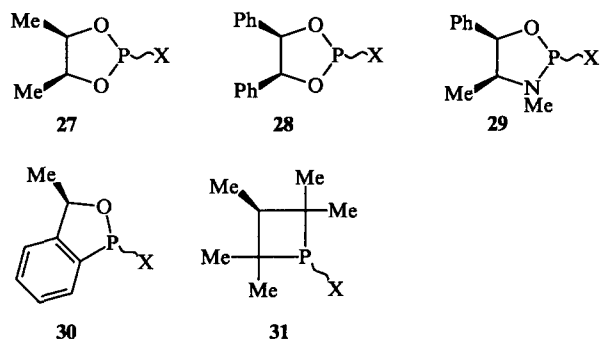


24 **25** **26**

Thus the stereochemical result of the reaction will depend on which pseudorotation (which is necessary to place the NMe_2 group in the axial position favourable for its elimination) in compound **26** has the lower energy barrier. In their analysis of possible pseudorotations, the authors conclude that the reaction proceeds with preferential inversion if the hydrogen is more apicophilic than NMe_2, which is known to be the case for phosphoranes of this kind.[181]

As a development of their research, Dahl and Nielsen investigated the stereochemistry of nucleophilic substitution in substrates **27–31** in their reactions with MeO^-, MeOH + NEt_3 (for compounds **27–31** with X = Cl), Et_2NH, PhOH, HCl, and MeOH (Scheme 7).[41]

Scheme 7

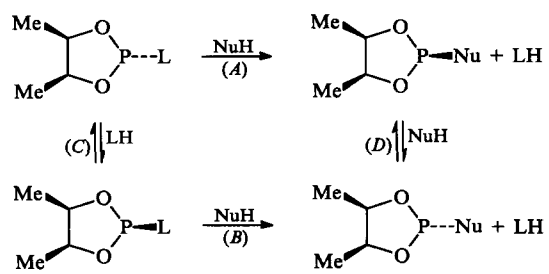


27 **28** **29**

30 **31**

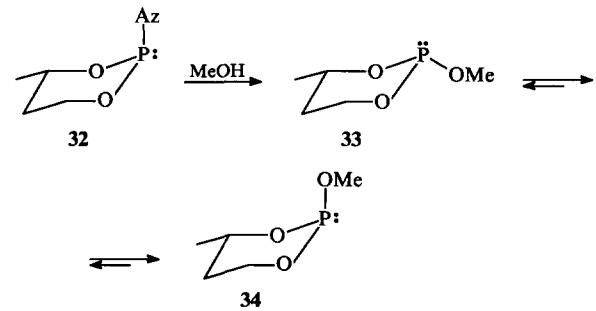
X = Cl (a), NMe_2 (b), NEt_2 (c), OMe (d), OPh (e), .

The majority of the compounds investigated were configurationally stable (with the exception of the compounds with X = Cl) at 25 °C only in a pure form and their isomerisation was readily accelerated by nucleophilic and acidic impurities (atmospheric moisture, alcohol, amines, acids, etc.). The scheme below reflects the different possibilities in the isomerisation of compounds **27–31**.



According to the authors, pure inversion is possible only when the substitution reactions (*A* and *B*) are much faster than the isomerisation reactions (*C* and *D*) (see also Horner and Jordan[179]). It was concluded that nucleophilic substitution in TPAA proceeds in most cases with complete inversion. We may note that this conclusion is to some extent arbitrary. Indeed, many cyclic compounds of trivalent phosphorus containing amino-groups are usually configurationally unstable and therefore the reactions of these substances are not stereoselective.

More clear-cut results were obtained in a study of the stereodynamics of the methanolysis of cycloasymmetric trivalent phosphorus acid (TPA) azolides **32**, which have been shown[145–148] to exist in the *trans*-configuration with the azolide substituent in the axial position.



32 **33** **34**

It has been demonstrated by ^{31}P NMR spectroscopy that, in contrast to TPA dialkylamides, alcoholysis takes place rapidly even at 20 °C (inversion of configuration) and a labile ester (isomer **33**) is formed and is then slowly converted into a stable ester—isomer **34**.

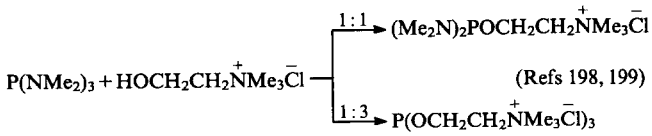
3. Trivalent phosphorus acid amides in fine organic synthesis

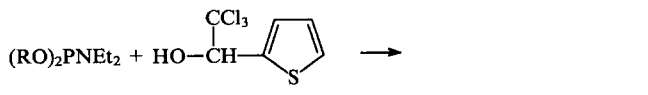
A considerable proportion of the publications on the chemistry of TPAA are devoted to problems of using these compounds in fine organic synthesis. This is due to their ready availability, high reactivity, convenience, and the mildness of the conditions under which they can be applied. The last fact permits specific phosphorylation of complex polyfunctional systems, avoiding at the same time isomerisations, dehydrations, and other unfavourable side reactions, which frequently occur in work involving phosphorochloridites and related reagents.

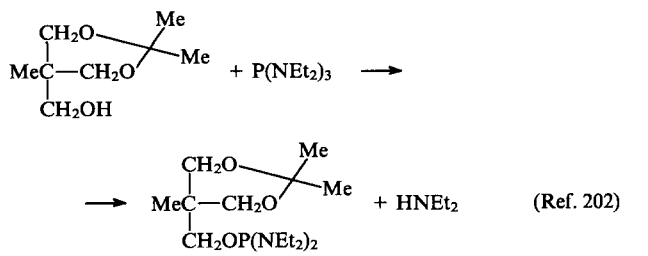
The principal synthetic results, arranged in terms of the types of hydroxy-compounds employed in phosphorylation will be examined below.

a. Phosphorylation of alkanols, phenols, and their functional derivatives

Phosphorylation of alkanols and phenols by TPAA is of a more general importance and is used to obtain the esters (amidoesters) of phosphorous, phosphonous, phosphinous, and hypophosphorous acids. This reaction was used initially to synthesise the simplest derivatives of compounds of the above classes and in this field has been recognised as not only convenient but also as preparatively useful[123–125] for purposes including the synthesis of sterically hindered phenol derivatives.[182,183] Subsequently the phosphoramide method came to be widely employed to obtain various functionalised systems, the molecules of which contain a trivalent phosphorus atom: phosphorylated aminoalcohols,[2,184–189] amidoalcohols,[190–197] cholines,[198,199] polyhalogenated alcohols,[200,201] partially acetalised triols,[167,168,183,184,202–211] etc. Certain examples are presented overleaf as an illustration.

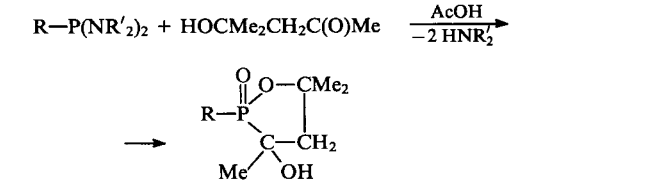




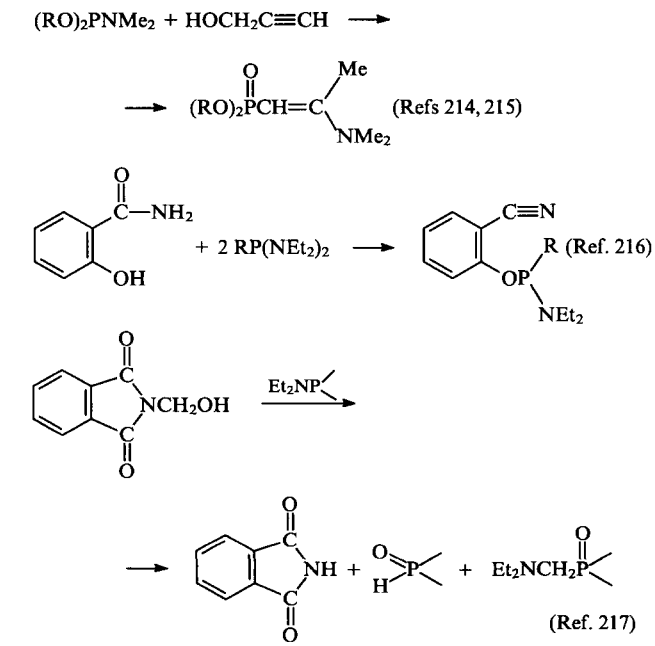


The phosphorylation of functionalised alcohols may be accompanied by additional reactions, which extend the possibilities of the classical synthesis and lead to simple procedures for the preparation of very interesting compounds (Scheme 8).[212,213-217]

Scheme 8

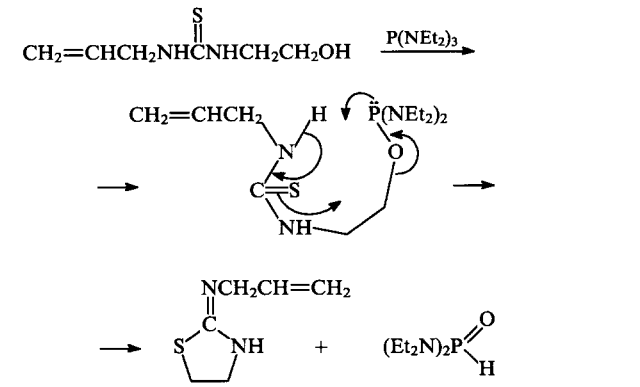


R = Alk2N, AlkO, Alk; R' = Alk (Ref. 213).

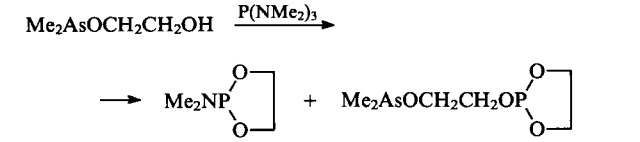


In a number of instances, phosphorylation leads to the creation of complex systems, which subsequently undergo the elimination of hydrophosphoryl compounds. In particular, it has been suggested that 2-allyliminothiazolidine be obtained in this way (Scheme 9).[218]

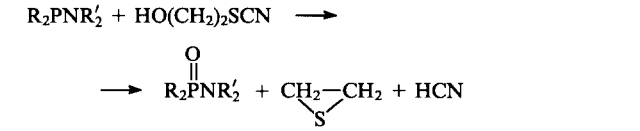
Scheme 9



The modes of the above reactions are treated quite clearly by the authors quoted. Nevertheless, some of the phenomena described in the literature have still not been adequately explained; these include, for example, the double phosphorylation of dimethylarsenylated ethylene glycol.[219]



Functionalised alcohols, capable of generating electrophilic species, may react with TPAA via a mechanism other than phosphorylation. For example, phosphoramides interact with thiocyanatoalcohols.[220]

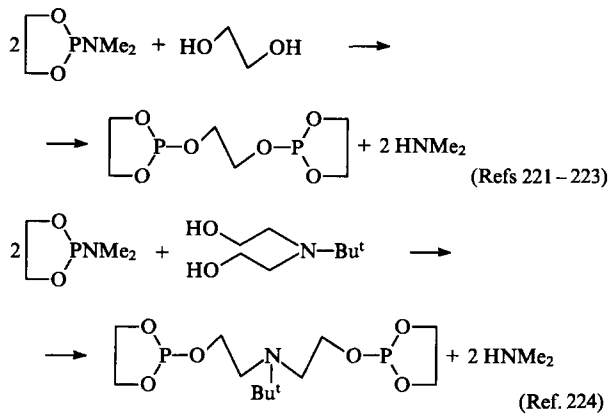


b. Phosphorylation of diols

Numerous publications have been devoted to the study of the reactions in the TPAA–diol system, which can be accounted for by the chemical diversity of the processes carried out and the importance of the products. The phosphorylation reaction is influenced by many factors: the nature of the reactants, their proportions, the reaction conditions, and also the characteristic features of the products. In many instances, this led to difficulties in the analysis of the results and then to erroneous conclusions. Subsequently these conclusions were revised.

It is possible to differentiate the following aspects of the phosphorylation of diols: (1) bisphosphorylation involving both hydroxy-groups of the diol and ending with the formation of a diphosphorous system; (2) monophosphorylation leading to phosphorylated hydroxy-compounds; (3) cyclophosphorylation and cyclooligophosphorylation. In addition, it is necessary to point out also the possibility of the combination of various aspects and also of polycondensations leading to polymeric esters. The last possibility will be examined separately.

The bisphosphorylation of glycols and dihydric phenols has been widely investigated. A series of studies devoted to the use of trivalent phosphorus acid monoamides in reactions with glycols in molar proportions of 1 : 2 have been published. They result in the formation of diesters, for example:[221-224]



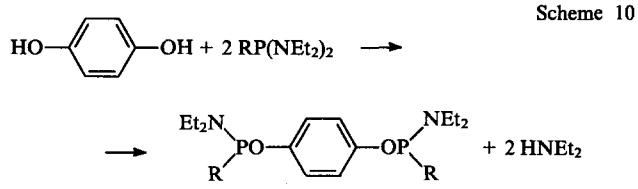
(Refs 221–223)

(Ref. 224)

We may note that the alternative method (the phosphorochloridite method) yields poor results owing to the interaction of the hydrogen chloride produced with the new reaction centre.

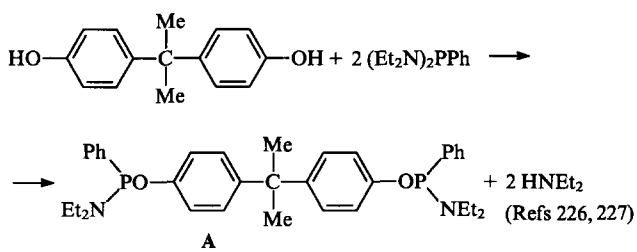
Many reactions with TPA diamides and triamides take place effectively (Scheme 10).[225–227]

Scheme 10



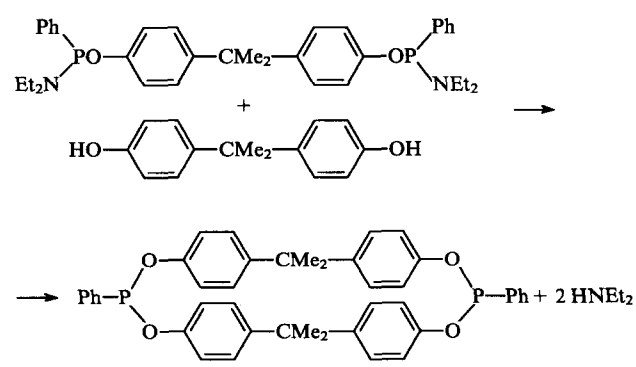
(Ref. 225)

R = NEt_2, OAlk



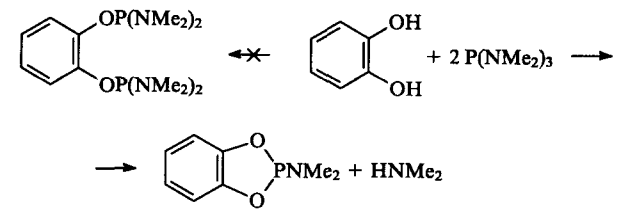
Compound A is interesting because, under the conditions discovered, it can react with an equimolar amount of 2,2-di-*p*-hydroxyphenylpropane (DIAN) and is converted into a phosphorus-containing cyclic system, which is the first representative of the new class of crown-ethers in the molecules of which arylene residues and trivalent phosphorus atoms alternate (Scheme 11).[226]

Scheme 11

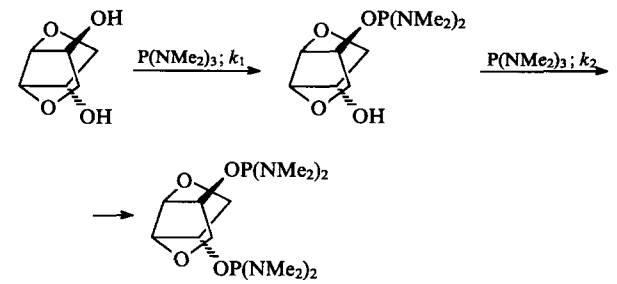


Cyclisation and not bicyclophosphorylation reactions are typical for experiments with diols in which the hydroxy-groups are close to one another in space. Half of the phosphoramide introduced into the reaction fails to react under these conditions. An example is provided by the phosphorylation of catechol and its derivatives by phosphorous acid hexaalkyltriamides (Scheme 12).[228–234]

Scheme 12



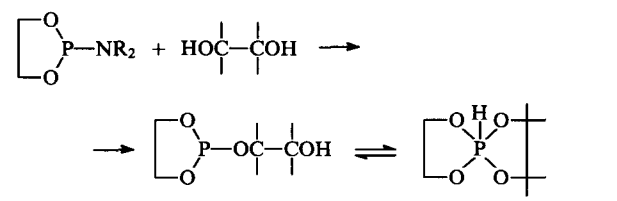
The interaction of phosphorous triamides with 1,4;3,6-dianhydromannitol merits special consideration. In this case, alcoholic hydroxyls in the initial compound are not quite so close in space as in catechol, so that phosphacyclisation is difficult.[235,236] On the other hand, the primary phosphorylation step leads to a novel situation: the free hydroxyl of the intermediate is apparently more reactive than the hydroxyl of the initial diol, the reactivity of which diminishes owing to the formation of intramolecular hydrogen bonds. The reactivity of the intermediate is manifested by the fact that in the interaction of even equimolar amounts of dianhydromannitol and phosphorous hexamethyltriamide results in the formation of mainly the bisphosphorylated product and residual unreacted dianhydromannitol remains.[237]



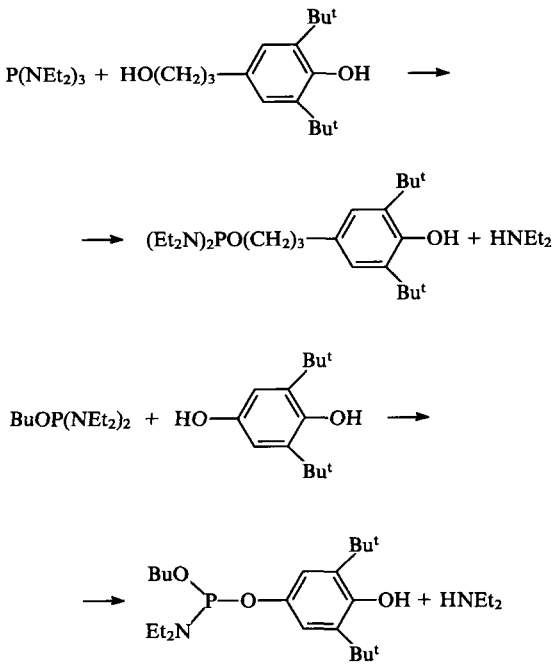
$k_2 \gg k_1$

Thus the geometrical characteristics of the initial diols may regulate significantly the nature of their phosphorylation.

The monophosphorylation of diols by an equimolecular amount of phosphorus(III) acid amides rarely affords satisfactory results. The group of reactions of cyclic TPAA with 1,2-diols has been investigated in greatest detail. The phosphoalcohols formed in this case as the primary product exhibited a tendency to undergo ring–chain tautomerism.



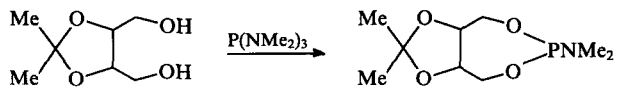
The position of the tautomeric equilibrium is determined by the structure of the compound, the solvent, and temperature. It is usually fully or largely displaced towards the formation of the form with pentacoordinate phosphorus — hydrospirophosphoranes. The history of this problem and the extent to which it has been investigated have been described in a series of reviews.[238–242] A different result was noted in the phosphorylation of diols the hydroxy-groups of which are of a different chemical nature: one of them is sterically exposed whilst the other is shielded. 4-(γ-Hydroxypropyl)-2,6-di-*tert*-butylphenol[243] and 2,6-di-*tert*-butylhydroquinone[210] may be included among these diols. In this case, phosphorous diamides and triamides interact regioselectively with an equimolecular amount of the diol.



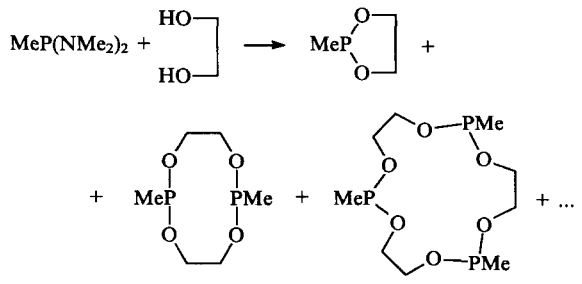
The phenyl phosphorodiamidites obtained are entirely stable. They can be distilled in a high vacuum and phosphorylate extraneous nucleophiles by virtue of their phosphoramide fragment.

The cyclophosphorylation and cyclooligophosphorylation of diols by TPAA has been comprehensively investigated. It has been shown that phosphorous diamides and tiramides effect the preparative phosphorous cyclisation of alkane-1,2 diols,[142,229,244-247] alkane-1,3-diols,[142,244,248,249] and alkane-1,4-diols[142,250-253] with formation of the corresponding 1,3,2-dioxaphosphacyclanes.

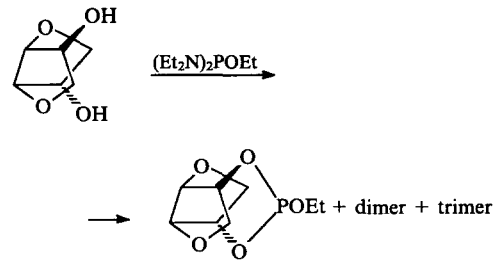
These phosphoramides cyclophosphorylate similarly also functional derivatives of diols,[254-257] for example, 2,3-isopropylidene-D-threitol.[257]



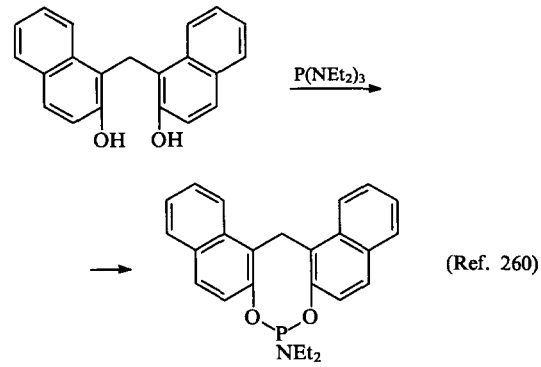
Many of the phosphacyclic compounds obtained in this way are used in the solution of stereochemical problems and in the synthesis of compounds of practical importance. It is very interesting that phosphorylation of alkane-1,2-diols and alkane-1,3-diols by phosphonous diamides leads to compositions comprising monocyclic and oligocyclic compounds which are in equilibrium, for example:[258]



It has recently been possible to extend the cyclophosphorylation reaction to 1,4;3,6-dianhydromannitol and to establish also the parallel formation of mono- and tri-cyclophosphorylated systems (this time phosphorous and not phosphonous).[236]

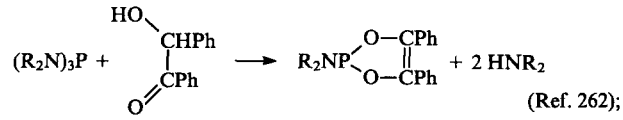


Normal cyclophosphorylation has been observed for catechols,[228-232] *o*-naphthalenediols,[259,260] and other dihydric phenols containing hydroxy-groups which are close in space.

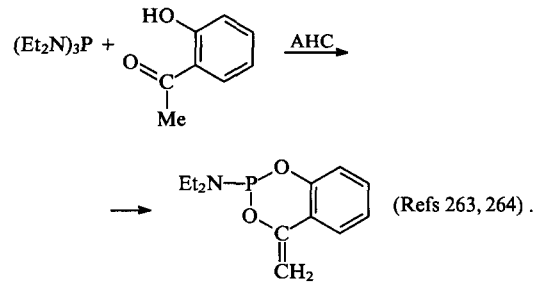


Aromatic heterocyclic *o*-diols—2,3-dihydroxypyridine[261] and 2,3-dihydroxyquinoxaline[259]—also form phosphacyclic compounds on reaction with TPAA. We may note, however, that the preparative conditions in these cyclisations are not identical. The latter diol is formed with considerable difficulty apparently owing to the great strength of its intermolecular hydrogen bonds.

The ready cyclophosphorylation of hydroxyketones, which readily react in their enolic forms when the hydroxy-groups are close together in space, also merits attention:[262]

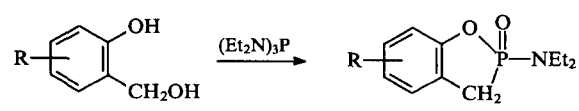


(Ref. 262);

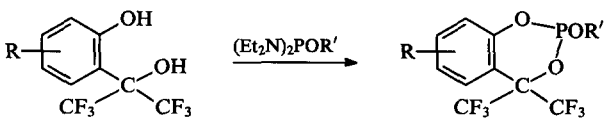


The last reaction is of interest because it leads to cyclisation only in the presence of amine hydrochlorides. Pure phosphoramides react with *o*-acetylphenol to form benzoxaphospholanes.[263,264]

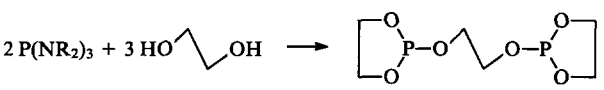
A number of investigators have attempted to cyclophosphorylate saligenin or related *o*-hydroxymethylphenols with formation of benzophosphorinanes. These attempts were unsuccessful: benzoxaphospholanes were obtained instead of the expected compound.[265]



It was postulated that the benzyl cations, formed readily after the primary phosphorylation, play a crucial role in such reactions. Taking this into account, bistrifluoromethyl derivatives of saligenins were used in the cyclophosphorylation reaction, which led to the successful synthesis of previously unknown benzodioxaphosphorinanes.[266]



In conclusion of the subject of the cyclophosphorylation of diols, we may point to interesting instances of the combination of reactions leading ultimately to the formation of cyclic diphosphites. An appropriate reactant ratio is needed for this purpose. Such combination is particularly successful with 1,2-diols, for example ethylene glycol.[221,222]

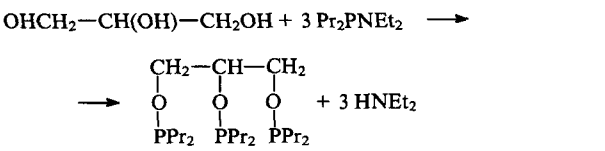


c. Phosphorylation of triols and higher oligools

TPAA were introduced into the range of popular phosphorylating agents during the period when the problem of the study of skeletal systems became of current interest in organic chemistry. It became necessary to develop specific procedures for the synthesis of phosphorus-containing skeletons. This was achieved in a series of leading scientific centres via the cyclophosphorylation of oligools by phosphorous and phosphonous amides. An extremely important feature is that, even in the first stages of the work involving the design and study of the properties of phospha-skeletal compounds, fundamentally important results were obtained, including the discovery of novel stereoelectronic interactions and other structural effects.

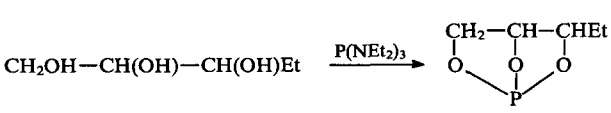
Studies on these lines are frequently experimentally complex and this is why there is still no well structured set of data. In view of this, we have arranged the published data in terms of a formal characteristic — the number of hydroxy-groups in the molecules of the phosphorylated oligools.

Phosphorylation of triols. The phosphorylation of glycerol with formation of open-chain triesters and phosphacyclic compounds has been described in the literature. Only one publication, reporting the interaction with dipropylphosphinous diethylamide, has been devoted to the triesters.[267]



It was noted that the phosphoramide employed exhibits in this case a lower reactivity than in the phosphorylation of other alcohols.

It is noteworthy that glycerol is a poor coreactant in the bicyclophosphorylation reaction using trifunctional derivatives of phosphorous acids. The instability of the target product, having a strained central unit, adds to the difficulties in phosphorylation under these conditions.[268] On the other hand, terminally substituted glycerols, for example pentane-1,2,3-triol, are smoothly bicyclophosphorylated with formation of stable esters.[269]



It may be that in this case the molecules of bicyclophosphites interact stereoelectronically with participation of terminal substituents, which alters the parameters of the valence bonds and hence diminishes the angular strain. Furthermore, an effect of the Thorpe–Ingold type may exert some influence in this instance.

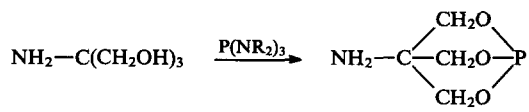
The related bicyclophosphites are obtained even more effectively on treating with phosphorous triamides linear triols having more widely separated hydroxyls: butane-1,2,4-triol,[270–273] pentane-1,2,5-triol,[274] and also related or branched systems — 1,1,1-tris(hydroxymethyl)methane[270] and 1,1,2-tris-(hydroxymethyl)ethane.[275]



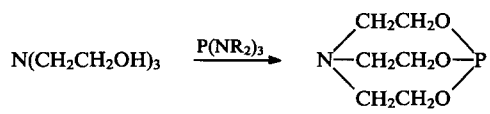
$n = 1, 2$

Stable skeletal bicyclophosphites, in the molecules of which 1,3,2-dioxaphospholane, 1,3,2-dioxaphosphorinane, and 1,3,2-dioxaphosphepane rings are condensed, are formed in all cases. Such skeletal systems have come to be widely used in fine organic synthesis and in coordination chemistry. They have attracted the attention also of physicochemical biologists[276] in connection with their ability to regulate membrane transport§.

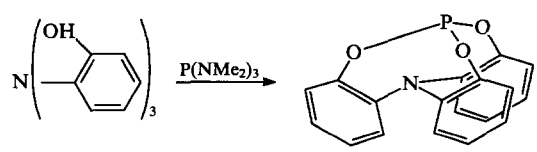
Phosphorous triamides can also interact with tris(hydroxymethyl)methylamine.[277]



A phosphorus-containing skeleton, the molecules of which contain two condensed six-membered rings and a free amino-group, is formed in this case. This aminoalkyl phosphite is a valuable ligand for the preparation of metal complex catalysts soluble in aqueous systems.[277] A formally, structurally similar, very labile system, which has been called phosphatrane, has been synthesised by the reaction of triethanolamine with phosphorous triamides.[278–282]



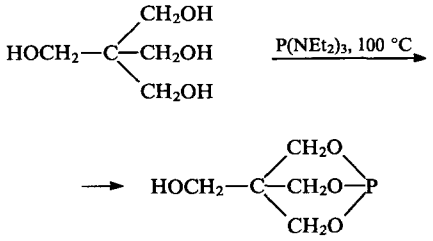
A skeletal amino-substituted phosphite, similar to that described above but containing *o*-phenylene groups and not ethylene groups as the main alkylene elements, has been synthesised by phosphorylating tris(*o*-hydroxyphenyl)amine with phosphorous hexamethyltriamide.[283]



This phosphite belongs to the class of rigid skeletal compounds of the 'cage' type. Its phosphorus and nitrogen atoms are not close to one another and do not therefore interact, as happens in phosphatrane. It is apparently of interest for the creation of supermolecular constructions.

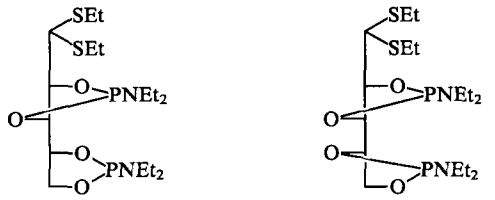
§The synthesis of phosphaskeletal compounds is examined in greater detail in the section devoted to carbohydrate phosphites.

Phosphorylation of tetraols. All the publications dealing with 'tetraols' were concerned only with the problem of cyclophosphorylation. Pentaerythritol may be specified in the first place as a promising substrate for cyclophosphorylation. This symmetrical tetraol is readily available and various syntheses have been planned on its basis. Some of them have already been achieved. Thus it has been reported that, when pentaerythritol is heated with an equimolecular amount of phosphorous hexaethyltriamide, a symmetrical skeletal phosphite is formed—4-hydroxymethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane.[270]

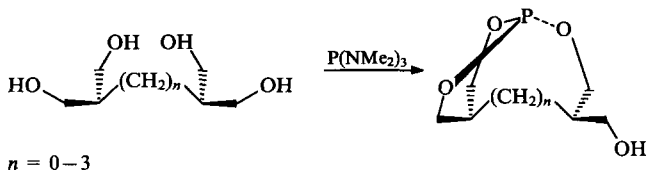


This compound is of great interest for subsequent reactions and also for use as a stabiliser of materials and as a ligand in the synthesis of metal complexes.

The 1,1-diethylthioacetals of aldopentoses—D-xylose and L-arabinose—are also bicyclophosphorylated with formation of compounds **35** and **36**.[284]

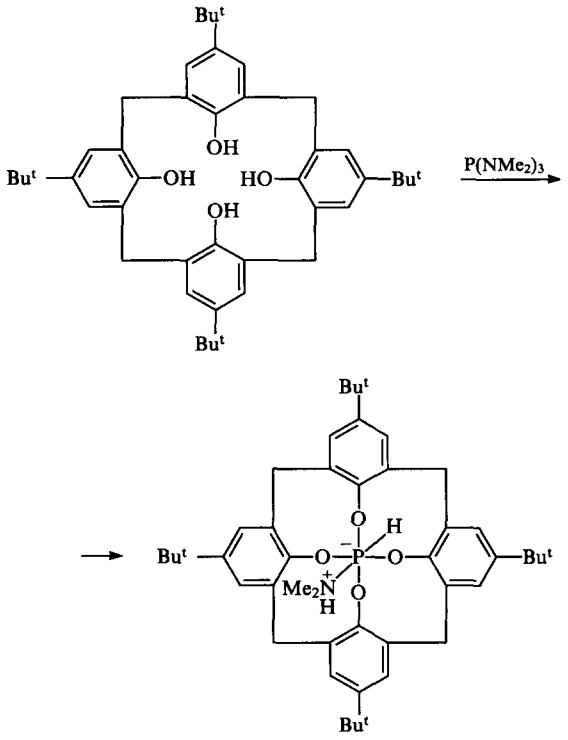


The group of α,α,ω,ω-tetrakis(hydroxymethyl)alkanes has been investigated in the reaction with an equimolecular amount of phosphorous hexamethyltriamide.[275]

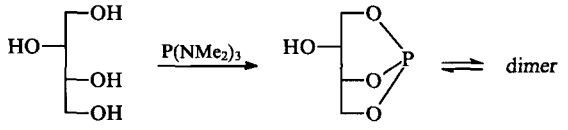


$n = 0-3$

The interaction of *p*-(*tert*-butyl)calix[4]arene with phosphorous hexamethyltriamide in equimolecular proportions is very interesting.[285] Triple phosphorylation of the calixarene occurs in this case and leads to the formation of a bicyclophosphite the phosphorus atom of which is very close to the phenolic hydroxyl which has not reacted. Owing to the spatial proximity of these groups, they readily react, which leads to the appearance of the phosphorane structure. The latter combines with a molecule of the dimethylamine produced. Naturally, the pathway described is only one of those possible in the reaction. A detailed study of this process can lead us to the discovery of new characteristics of the reactions of flattened skeletal phosphacyclic compounds.



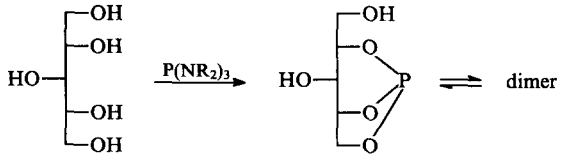
The phosphorylation of threitol, which is a conformationally labile tetraol, by TPAA is of a different kind. The interaction of equimolecular amounts of the reactants results in the initial formation of a mixture of products. Subsequently, it is converted into a 1,2,4-bicyclophosphite, which may dimerise reversibly.[286]



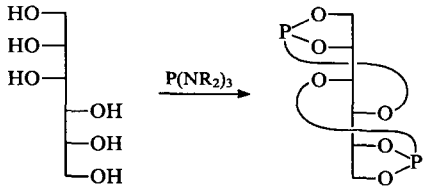
The entire information about these reactions has been obtained by ^{31}P NMR spectroscopy.[286]

Phosphorylation of higher polyols. The phosphorylation of higher polyols by TPAA leads to the formation of complex products[287-289] the structure of which has been reliably established only with the aid of NMR spectroscopy and X-ray diffraction.

Thus xylitol in contact with an equimolecular amount of phosphorous triamide behaves similarly to threitol.[286]



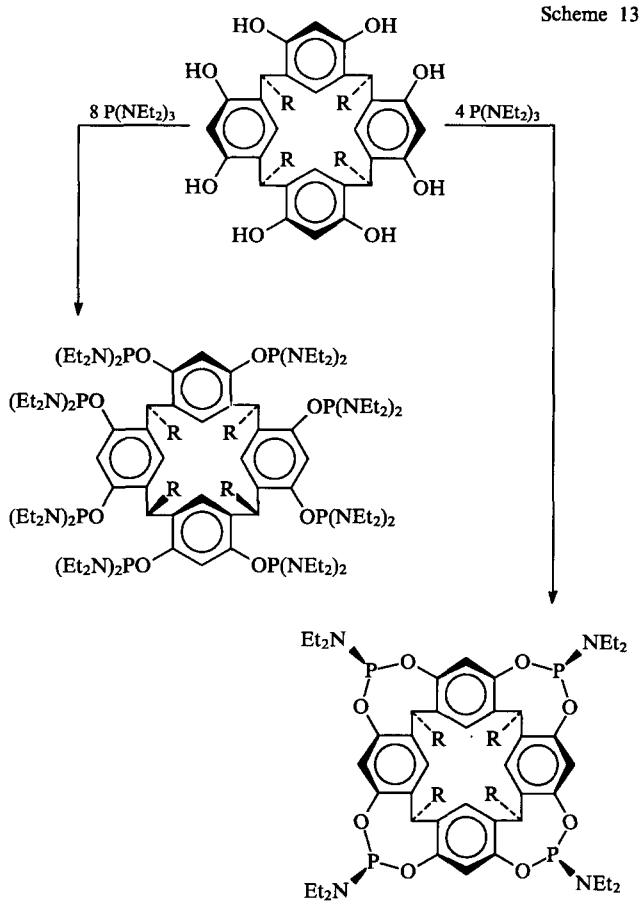
The reaction of mannitol with phosphorous triamide is more promising: in this case it was possible to obtain a bisbicyclophosphite—the product of the complete phosphorylation of the hexaol.[290]



We may note that a similar reaction with phosphorus trichloride affords much poorer results owing to the partial substitution of the hydroxyls by chlorine atoms. The structure and steric configuration of the compound obtained have been demonstrated by X-ray diffraction.[291]

Phosphorylation and cyclophosphorylation have been investigated also in the series of aromatic octaols in connection with the synthesis of ligands for the formation of supramolecular systems. Thus it has been shown[292,293] that octahydroxy[14]metacyclophane affords an octaamidophosphite on treatment with an eightfold molecular amount of phosphorous hexaethyltriamide, while treatment with a fourfold amount of this reagent gives rise to a tetracyclic derivative, which is the first reliably described representative of phosphorus-containing cavitands (Scheme 13).

Scheme 13



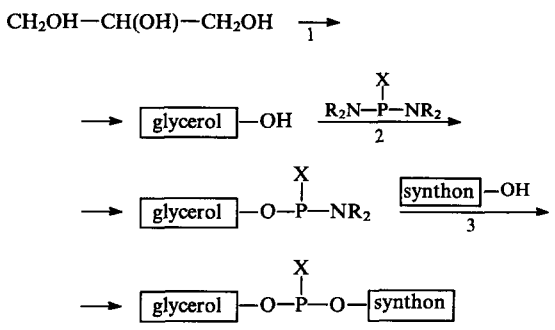
4. Trivalent phosphorus acid amides in the chemistry of natural products

The development of the methods of organophosphorus chemistry has in many respects determined the progress in physicochemical biology. Thus, by virtue of the active employment of trivalent phosphorus reagents, especially TPAA, fundamentally important results have been obtained during the last 10–15 years in the synthesis of oligonucleotides, phosphorylated sugars, phospholipids, and other phosphorus-containing natural products as well as their analogues as regards the phosphorus-containing functional groups. This has been reflected in the publication of a series of reviews in which problems of the employment of phosphoramides in the design of specific classes of natural products have been discussed.[294–304] The publication of these reviews helped us in writing the present review, because it obviated the need for a difficult task and for the exhaustive quotation of a large set of communications, which are of the same type from the standpoint of organophosphorus chemistry, and thus made it possible to draw the reader's attention to the principles of phosphoramide synthesis and the current trends in its employment.

a. The synthesis of phospholipids

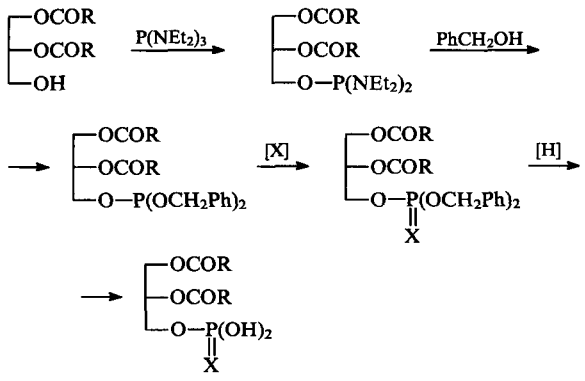
The commonest phospholipids in nature are glycerophosphates, especially phosphatidic acids and their various derivatives. These compounds perform exceptionally important biological functions and an enormous amount of attention has been devoted to their synthesis.[304–306]

We therefore begin the present section of the review with the consideration of the use of TPAA in the design of glycerophosphatides and their P-analogues. The strategy for these syntheses developed in recent years usually presupposes the carrying out of the following stages: (1) the synthesis of monohydroxy-derivatives of glycerol—either 1,2- or 1,3-acetals or 1,2- or 1,3-diacylates; (2) phosphorylation of glycerol derivatives via the alcoholysis of the phosphoramide linkage of a suitable TPAA; (3) oxidative and other necessary reactions leading to phosphatidic acids or other very simple phosphoglycerides, and construction of the complex phosphoglyceride by introducing into the glycerophosphite unit of an additional synthon as a result of the alcoholysis of the second phosphoramide linkage by a selected synthetic equivalent of this synthon.



This process is completed by oxidation reactions and the necessary reactions leading to the formation of the required complex glycerophospholipids.

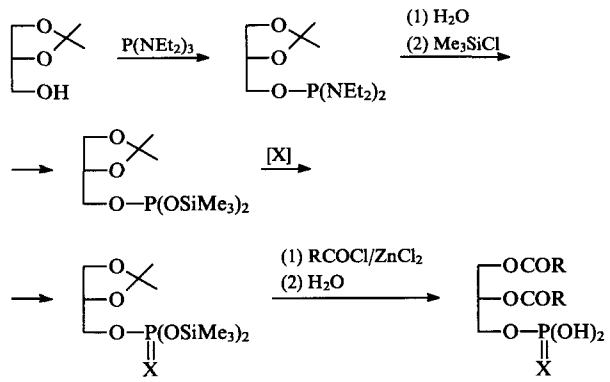
The general scheme presented above has now been embodied in numerous syntheses of various phospholipids and they have all been carried out on the basis of a narrow set of initial reagents and using convenient synthetic procedures.[304] We shall examine the syntheses of phosphatidic acids. These compounds can be obtained from 1,2- or 1,3-acylglycerols which are made to react with TPAA, this being followed by oxidation reactions and the removal of protecting groups, for example:[307,308]



X = O, S

The use of diacylglycerols in phosphorylation entails a risk, because the secondary amine produced can, generally speaking, add to the carbonyl group of acylates, which leads to their partial deacylation or isomerisation. Special studies were carried out which showed how it is possible to avoid these complications.[308,309] At the same time an analogous variant of the synthesis, based on the use of glycerol acetals instead of acylates, was proposed. Glycerol acetals are readily available compounds

which are convenient to handle. They are readily phosphorylated by TPAA without side reactions, after which they are converted by hydrolysis into diols. These are subsequently acylated. Unfortunately, this procedure is preparatively difficult and requires a scrupulous selection of conditions.[187] Therefore a much simpler and effective process has developed—direct acylation of acetals.[310–313] Subsequently the general scheme for the synthesis of phosphatidic acids was supplemented also by other improvements.[304]



X = O, S, Se

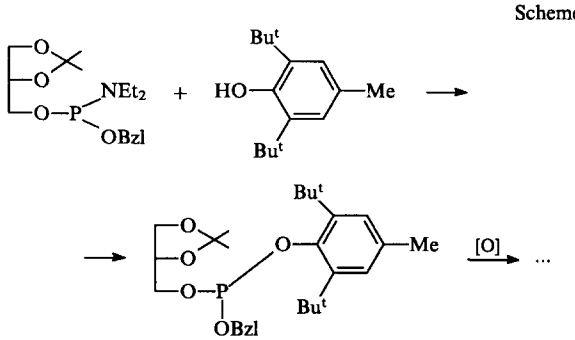
We emphasise that the proposed solution made not only phosphatidic acids but also their thio- and seleno-analogues really available. These analogues immediately began to be used successfully for the solution of important scientific problems, for example for the ^{31}P NMR study of phase transitions in lipid membranes.[314–315]

The use of the phosphoramidite synthesis is even more promising for the preparation of complex natural phosphatides and their analogues. For this purpose, glycerophosphoramidites are made to react[295,304] with aminoalcohols, glycerols, sugars, myoinositol, aminoacids, etc., which leads to the formation of the corresponding phosphatidic acid esters and amides¶. As an illustration, we present (above right) a scheme for the synthesis of 6′-(1,2-distearoylglycero-3-phospho)-D-galactose.[204,207]

Glycophospholipids containing D-glucose[185,207] and disaccharide (maltose)[316] residues were obtained in a similar way.

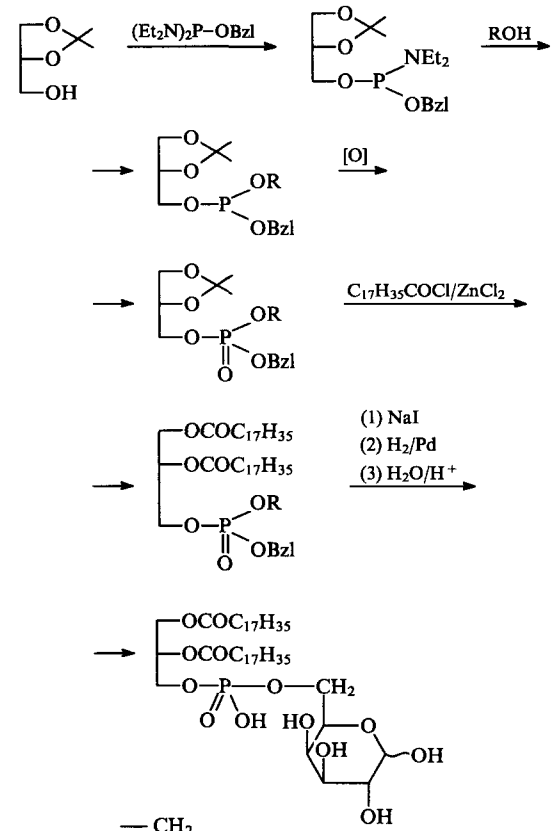
The method considered has been applied also to the synthesis of new constructions of fundamental importance, for example phosphatidyl derivatives of sterically hindered phenols (Scheme 14).[182,183] The preparations thus obtained are membranoaddressed bioantioxidants.

Scheme 14



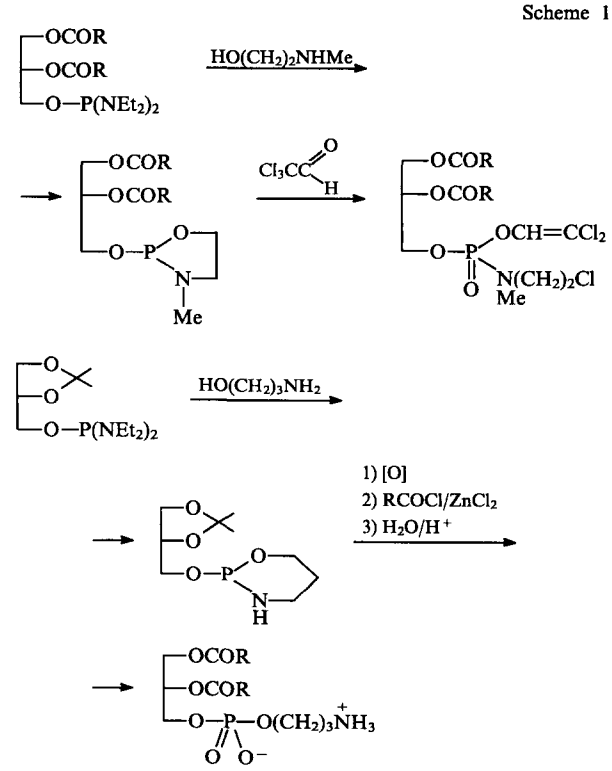
Reactions of glycerophosphorodiamidites with diols[188,206,317] and aminoalcohols[186,187] also merit attention. As in the phosphorylation of substituted glycerols by the amides of the

¶ In many cases an alternative approach may be useful. According to this procedure, the substituted glycerol incorporating sugar, aminoalcohol, etc. residues is phosphorylated by phosphoramidites.

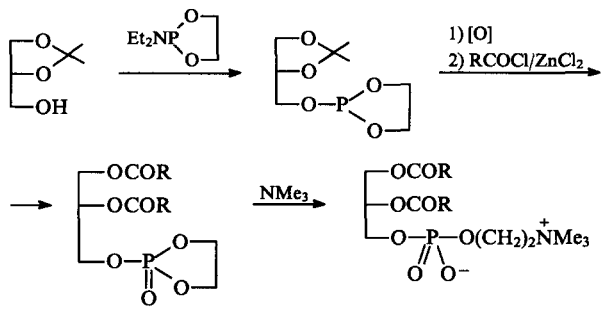


corresponding alkyl or alkylene phosphoramidites, various glycerophosphacyclanes are formed in such cases. There are good prospects for the use of phosphacyclanes for synthetic purposes (Scheme 15).

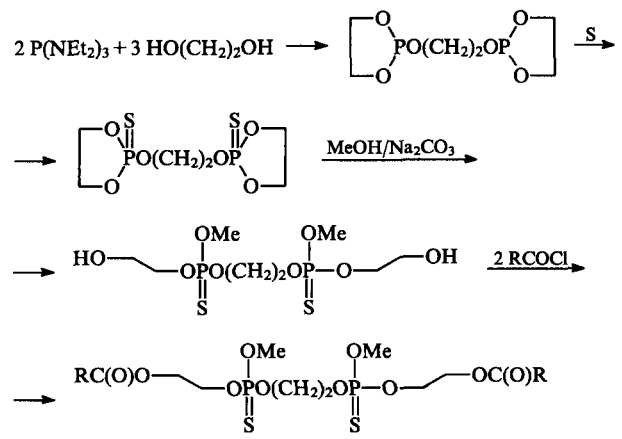
Scheme 15



During the study of such glycerophosphacyclic compounds, a promising reaction was discovered—alkylation of tertiary amines and other nucleophiles by alkylene cyclophosphites.[188, 206, 317–325] A simple method of synthesis of lecithins based on this reaction is presented below.

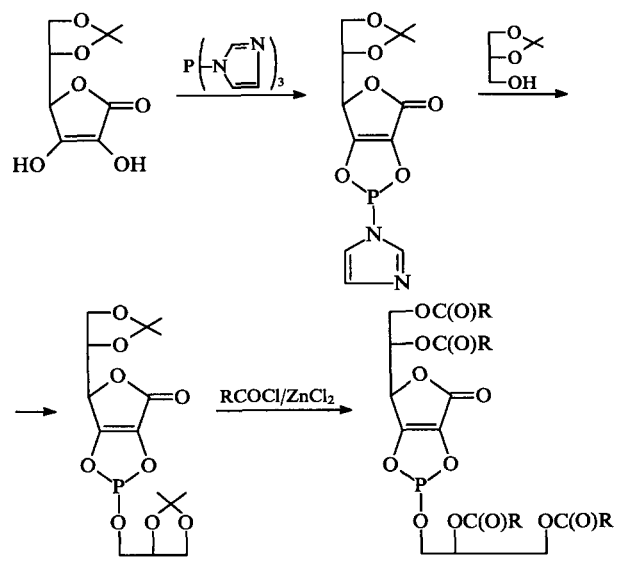


The successful development of glycerophosphoramidite syntheses stimulated research into the chemistry of diol phospholipids. A series of useful reactions leading both to the simplest diphosphites and to extremely complex substances which are difficult to obtain by other methods have been achieved.[326]



R = $C_{17}H_{35}$

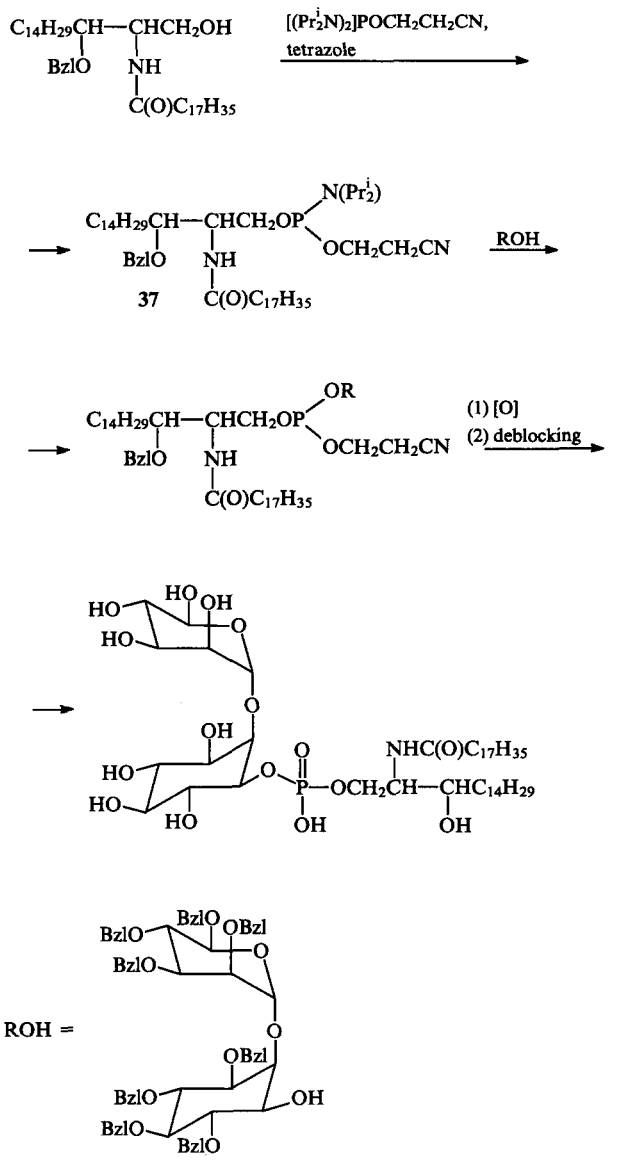
The synthesis of lipid systems from ascorbic acid is much more difficult.[327] For this purpose, 5,6-isopropylideneascorbic acid was cyclophosphorylated by phosphorazolidites, which act under mild conditions, to form an ascorbophospholene. The product was used subsequently as a phosphorylating agent in the reaction with 1,2-isopropylideneglycerol.



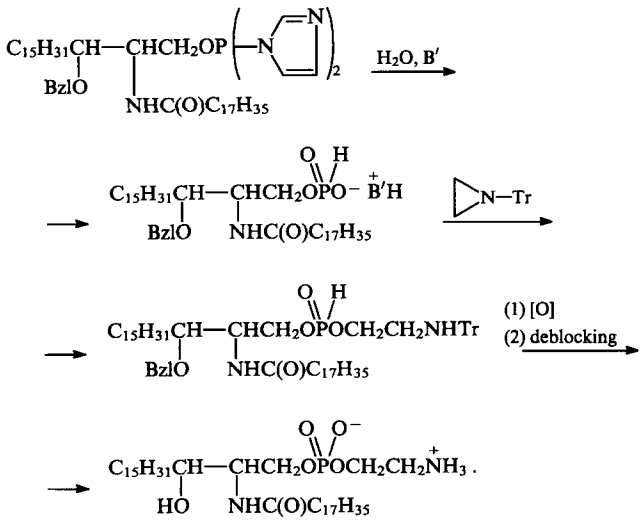
R = $C_{17}H_{35}$

Elegant studies have been carried out recently on the use of TPAA for the preparation of ceramidophosphoric systems. It was shown that the interaction of 3-benzoylceramide with β-cyanoethyl *N,N*-diisopropylphosphorodiamidite in the presence of tetrazole affords a phosphoramidite which can be converted by the methods mentioned above into extremely complex phosphate and phosphorothioate systems. As an illustration, we present the results of one of the latest studies[328] (Scheme 16).

Scheme 16



We may note that intermediate **37** and the corresponding phosphorodiamidite may be hydrolysed to form hydrophosphoryl compounds, which are phosphorous monoesters and diesters. These compounds are also promising for phospholipid syntheses: they have been introduced into a series of reactions, both those which have already proved useful in phospholipid practice[329, 330] and comparatively new ones, for example:[328]



Tr = CPh_3

b. Phosphorylation of nucleosides and the formation of an internucleotide linkage

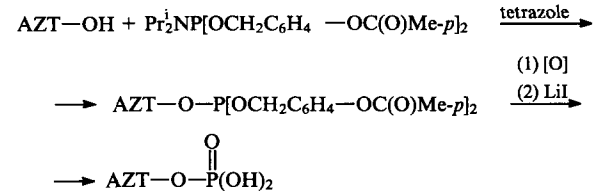
The methods of phosphate chemistry, intricately refined in many scientific centres, have been used for a long time for the phosphorylation of nucleosides, the formation of the internucleotide linkage, and the solution of other related problems. Nevertheless, owing to the low rates of phosphorylation, these methods do not meet the needs of modern research. Furthermore, the classical methods lead to poor results in the synthesis of thiophosphoryl and other nucleotide derivatives which are nonstandard in the phosphorus component. The employment of the highly reactive trivalent phosphorus derivatives and in the first place TPAA was seen as a method of overcoming the difficulties which have arisen.

The possibility, in principle, of resorting to amides of phosphorous, phosphonous, and phosphinous acids in order to phosphorylate nucleotides was demonstrated at the end of the 1960s and the beginning of the 1970s.[331,332] Unfortunately, time was needed to become accustomed to the new reagents and they have only now, i.e. much later, been introduced into laboratory practice. TPAA are nowadays widely employed in different chemical, molecular biological, and gene engineering aspects of nucleotide syntheses. It must be emphasised that TPAA are used not only for the synthesis of oligonucleotides but also of a wide variety of their P-analogues, which have extended the possibilities of research involving biopolymers.

The use of TPAA in the chemistry of nucleic acids has been described in a series of interesting monographs and reviews,[300-302,333] and in the present review we shall consider only the key aspects of the problem.

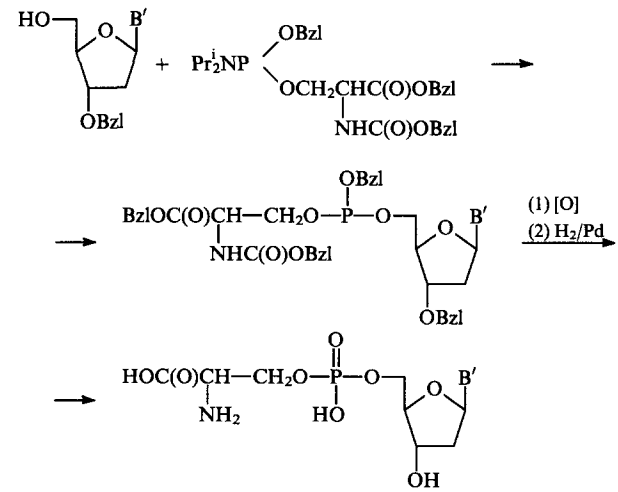
We may note that especially reactive phosphorazolides, such as the triazolides,[111,334-338] tetrazolides,[103,104,334,339-341] imidazolides†,[140-143,334,342] or the 'usual' TPAA, are frequently employed for the phosphorylation of deoxyribo- and ribo-nucleotides in the presence of acid activators — usually tetrazole,[300-302] diisopropylammonium tetrazolide,[106-114] 4,5-dichloroimidazole,[100,102] and certain others. In most studies, the phosphorylation is combined with oxidation reactions and manipulations involving protecting groups. As a rule, in contrast to the acid chloride method,[343] in the phosphoramide method the phosphorylation of nucleosides hardly involves their nitrogen-containing heterocycles. However, this version of the reaction is nevertheless possible in certain situations, which has been specially noted in the literature.[99,344]

We shall consider the most fruitful procedures for the phosphorylation of nucleosides using TPAA. In many instances, this reaction has served as the basis of the synthesis of nucleotides of especially great importance, for example the synthesis of phosphorylated azidothymidine (AZT):[345,346]

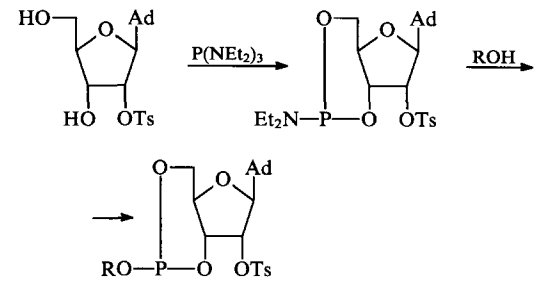


It has been suggested that nucleotide-sugars, including derivatives of sialic acids, which are of interest in the fight against AIDS, can be synthesised using TPAA.[347] In addition, it has been possible to synthesise compounds the molecules of which include the so called 'reporter' groups, for example aminoxyl radicals which assist in the performance of detailed structural studies on the functions of nucleotide compositions.[348,349]

Phosphorylation by TPAA which contain residues comprising aminoacids or other biomolecules have also attracted the attention of investigators. In this case, the synthesis leads to the formation of the link component of nucleoproteins or other complex systems. As an illustration we present the synthesis of the phosphoserine link.[350]



In view of the great importance of adenosine (thymidine) monocyclophosphates, studies have been made on the synthesis of their phosphite and phosphonite analogues.[332,351-357]

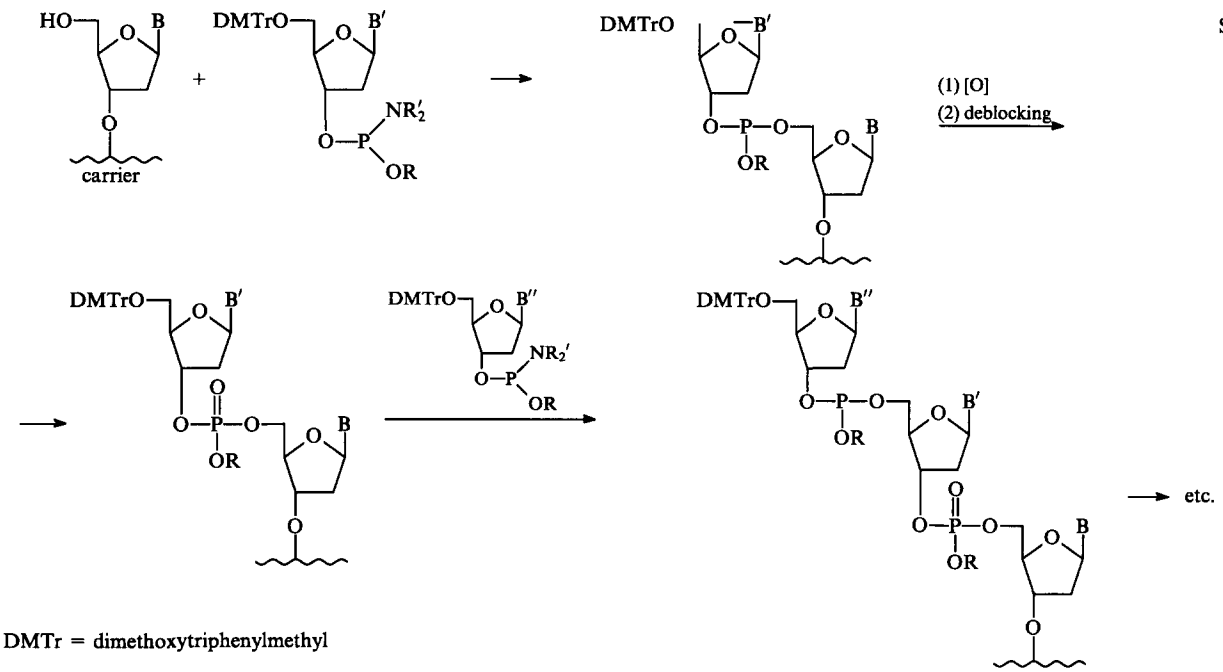


The compounds obtained were used in Arbuzov alkylation, oxidation, and other reactions.

Apparently most publications have been devoted to the use of phosphoramides to form the internucleotide linkage and especially for the synthesis of oligonucleotides by this procedure. The relatively easy and rapid methods for the synthesis of a wide variety of higher oligonucleotides have nowadays revolutionised a number of aspects of molecular biology and gene engineering.[300-302,333] The most widely used scheme for the synthesis of oligodeoxyribonucleotides is presented overleaf in a general form (Scheme 17).

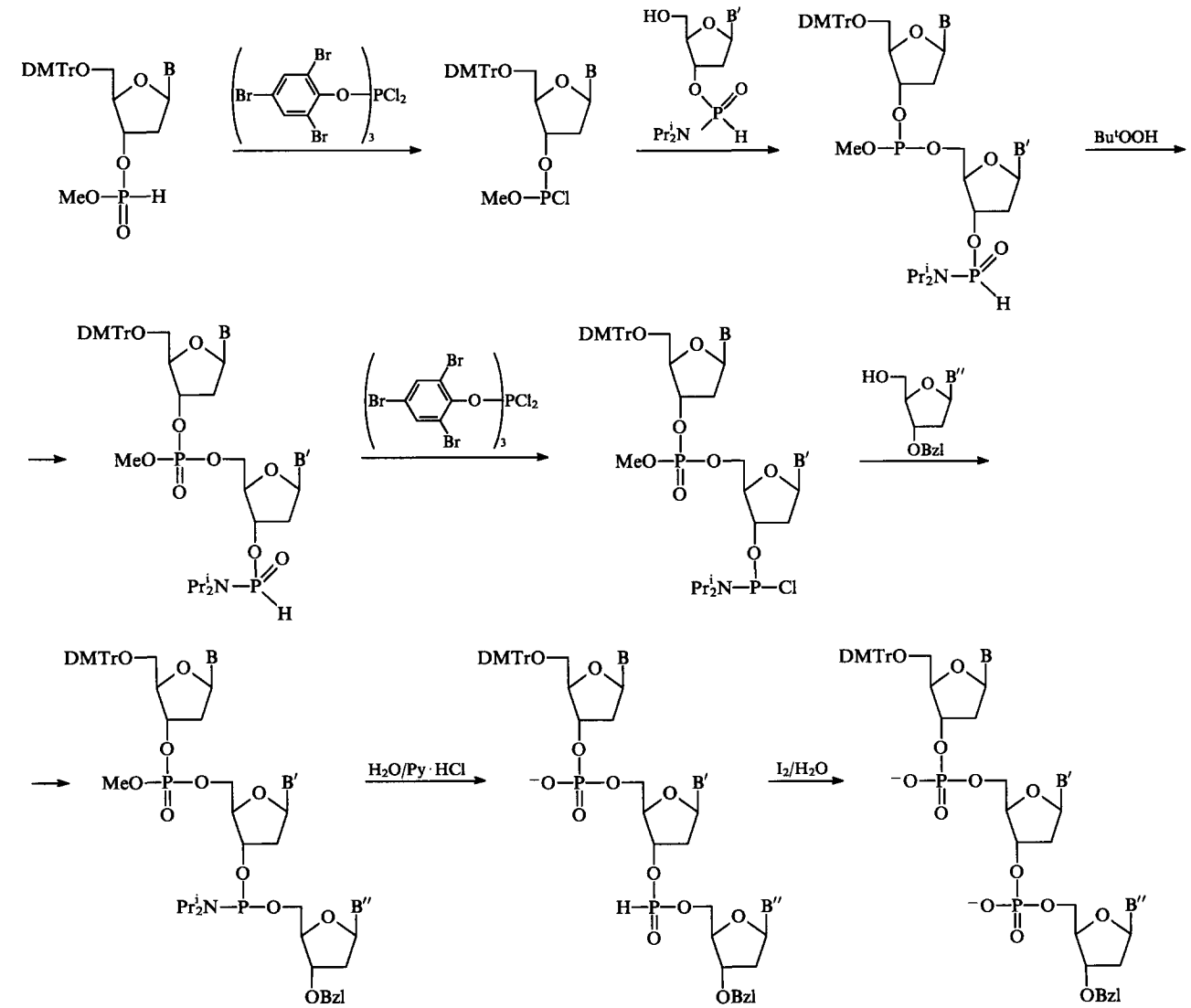
† The imidazolides are the most effective phosphorylating agents, but they are very sensitive to traces of moisture and are therefore unstable.

Scheme 17



DMTr = dimethoxytriphenylmethyl

Scheme 18



We may note that oligonucleotide condensations are most often carried out on solid carriers using automatic synthesisers which ensure a high process efficiency. It is sufficient to state that the typical phosphorylation step requires several minutes at 20 °C in these instruments. It is significant that nucleoside phosphoramidites, which are the principal reagents in the above condensations, have now become available as commercial preparations.[358, 359]

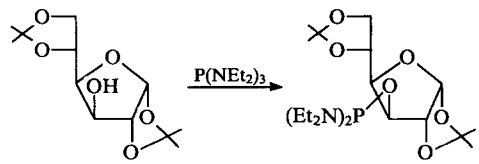
Oligoribonucleotides are also synthesised in accordance with a more complex programme.[104, 340, 359–361] It is very significant that, together with oligonucleotides, their phosphonate,[362–364] phosphoramidate,[106, 344, 365–367] phosphorothioate,[344, 365, 368–370] and phosphorodithioate[371–375] analogues can be obtained by the phosphoramidite method using the extensive procedures of the chemistry of trivalent phosphorus.

In molecular biology, the greatest interest attaches to solutions which make it possible to assemble from nucleoside phosphoramidites and diol oligomers [oligo(ethylene glycols) for example] complex constructions in which oligonucleotide and other chains are combined. A special review[302] published in 1993 was devoted to this current problem.

Finally, the phosphorylation of nucleosides by TPAA, supplemented by hydrolysis, sulfohydrolysis, or acidolysis, makes it possible to obtain primary[338, 376–383] and secondary[342, 367] nucleoside phosphites, phosphoramidites,[384] and phosphorothioites,[371] which are nowadays actively employed in a wide variety of hydrophosphoryl and thiophosphoryl syntheses. A new scheme for the synthesis of oligonucleotides with the aid of two different types of hydrophosphoryl compounds is presented (Scheme 18).[384]

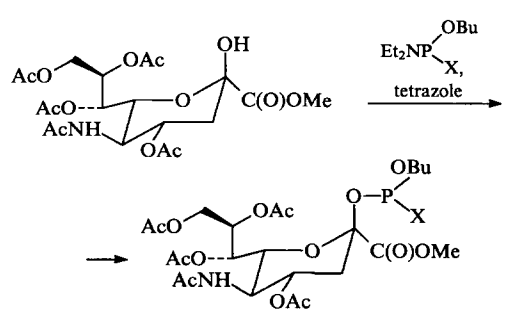
c. Phosphorylation of monosaccharides

Trivalent phosphorus acid esters and monosaccharides became the objects of independent systematic studies only after their synthesis began to be based on the phosphoramide method.[294, 298] TPAA of different nature readily phosphorylate monosaccharides the molecules of which contain a free alcoholic hydroxyl,[385, 390] for example, 1,2;5,6-diisopropylidene-D-glucofuranose.[386]



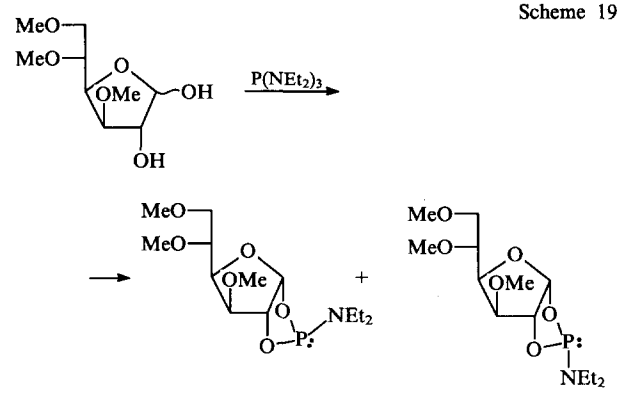
The products can be used subsequently as phosphorylating agents for various nucleophiles or can be introduced into a reaction with electrophiles (oxidants, alkyl halides, the simplest transition metal complexes, etc.).[185, 207, 391–393]

Monosaccharide derivatives are effectively phosphorylated also at the glycosidic hydroxyl,[394–396] whereupon the stereochemistry of the phosphorylated centre does not change during the reaction.[397] Such phosphorylation began to be extended to extremely complex systems in the most recent times. For example, β-sialyl phosphites and β-sialyl phosphoramidites have been obtained with the aid of TPAA.[347]

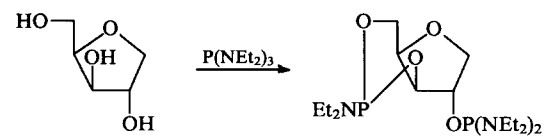


Treatment of monosaccharide derivatives containing two close hydroxyls can involve cyclophosphorylation. If one of the above hydroxyls is glycosidic, then stereochemical selection may take place (Scheme 19).[398]

Scheme 19

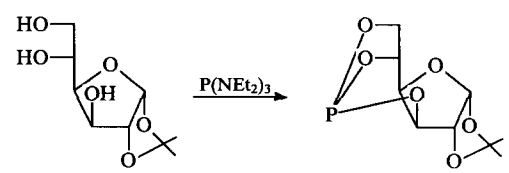


In this case, the selection concerns only the glycosidic and not the phosphoramide component of the system and therefore leads to the formation of two geometrical isomers the ratio of which may change on heating. The phosphorylation of triol systems takes place in different ways. Hydroxyls which are separated in space, as is the case in xylitan, are phosphorylated with formation of diphosphites.[392]

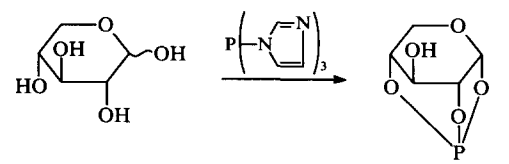


Such diphosphites began to be investigated as ligands for the preparation of chelate metal complex systems, which are likely to be used in enantioselective catalysis.[392, 393]

Monosaccharides—triols and tetraols with hydroxy-groups in close proximity—are phosphorylated particularly readily, being converted under these conditions into bicyclophosphites, for example:



(Ref. 399);



(Ref. 400).

As can be seen from the reaction presented, the latter case involves selective bicyclophosphorylation, the mode of which is determined by the steric characteristics of the sugar.

In the course of the development of the phosphoramide method for the bicyclophosphorylation of partly substituted and unsubstituted monosaccharides, a large group of skeletal systems was obtained. They proved to be interesting objects to study as regards stereochemistry, reactivity, and also practical use. The results of studies on the synthesis, steric organisation, and reactions of these new phosphaskeletal compounds have been recently summarised in a special review.[303]

d. Phosphorylation of other natural products

Aminoacids and peptides containing pentavalent phosphorus acid residues are widely investigated. Such studies involve the search for reactions based on new methods of organophosphorus chemistry.[401-403] The development of these investigations led to the study of the phosphorylation of carboxylic aminohydroxyacids by various TPAA, for example di(4-chlorobenzyl) *N,N*-diisopropylphosphoramidite[404] and benzyl bis(*N,N*-diisopropyl)phosphorodiamidite.[350,405] Subsequently the aminoacid phosphites obtained were introduced into oxidation reactions or were used as phosphorylating agents.

Steroid compounds have been relatively little studied in the phosphorylation reaction. It is noteworthy that studies were initiated recently on the phosphorylation of cholesterol and other steroids by various phosphorous amides.[95,406-409] Apparently there are good prospects for the synthesis from these derivatives of a wide variety of bioregulators, which can be addressed by means of the steroid component of the molecular system.

Simultaneously with steroids, α-tocopherol has been phosphorylated.[95,407,410,411] These studies are probably of interest for the development of research into bioantioxidants and other systems.

The specific phosphorylation of myoinositol[251-253,412-415] and its deoxy-derivatives[413,416] by phosphoramidite esters has clearly aroused interest recently. These studies were initiated mainly in connection with the development of effective methods of synthesis of complex phospholipids and the creation of cytostatic substances which are not targeted on DNA.[417]

TPAA have become the usual reagents for the phosphorylation of monosaccharides and other oligols in connection with the synthesis of the corresponding primary phosphites. The latter are successfully used nowadays in the synthesis of teichoic acids[418,419] and capsular polysaccharides.[420,421] Finally, TPAA have been used in the synthesis of a wide variety of biotin-containing phosphoramidites,[422-424] phosphoramidite derivatives of the alkaloid fagaronine,[425] and macrocyclic oligoester-oligodeoxynucleotide hybrid compounds in order to be able to 'recognise' DNA.[426] Unfortunately, the phosphorylation of alkaloids, a wide variety of plant phenols, terpenoids, and other polyfunctional natural products with the aid of TPAA has been scarcely investigated.

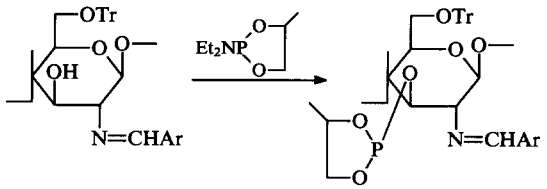
5. Trivalent phosphorus amides in the synthesis of phosphorus-containing polymers

TPAA have also begun to be used in macromolecular chemistry. The studies in this field can be divided into two aspects: (1) the introduction of phosphorus into hydroxylated polymers; (2) a polycondensation process with participation of diols and other oligools.

The first aspect has been investigated in greatest detail in relation to natural polymers. Thus it has been shown that anhydrous cellulose in a heterogeneous system is phosphorylated on heating to 80–120 °C by phosphorous hexaethyltriamide, various phosphoramidites, and also diethylphosphinous diethylamide.[427,428] In the reaction with the last reagent, it was possible to follow the degree of substitution and to achieve the degree of phosphorylation $\gamma = 180$. It is of interest that, in contrast to the initial cellulose, the phosphinite obtained is soluble in certain organic solvents.

The best phosphorylating agents proved to be the azolides of phosphorous and diphenylphosphinous acids, which modify cellulose at 20–50 °C with attainment of high degrees of phosphorylation.[429] The products obtained in the interaction with solutions of palladium chloride or bis(π-allylpalladium chloride) afford heterogeneous hydrogenation subcatalysts. Such systems exhibited a high catalytic activity in the hydrogenation of styrene under mild conditions.[429] A very important feature is that the above polymeric complexes are more effective than the complexes obtained using the chlorides of the corresponding trivalent phosphorus acids.[430]

The phosphorylation of chitosan derivatives soluble in organic solvents has been achieved very recently.[431]



The above communication is the first on the phosphorylation of chitosan in general. Among other natural hydroxylated polymers, only lignin was phosphorylated by TPAA.[432] The properties of the esters obtained have not been studied in detail.

There have been indications also of the phosphorylation by TPAA of synthetic hydroxylated oligomeric and high-molecular-mass resins[433-435] and poly(allyl alcohol).[436] The products synthesised have been investigated as regards the formation of polymeric pesticides and in other promising technical applications.[437]

The second aspect of the use of TPAA in macromolecular chemistry includes studies on the phosphorylation of glycols[244] and dihydric phenols[438] by equimolecular amounts of phosphonous diamides and alkyl phosphorodiamidites. Unfortunately, this outwardly simple instance of polycondensation is supplemented by the simultaneous formation of monophosphorus-containing rings[244] and the corresponding macrocyclic systems,[438] as a result of which the molecular masses of the products are low. Presumably the use of the latest generation phosphoramides, for example phosphorus(III) acid azolides, makes it possible to carry out the polycondensation effectively at low temperatures, avoiding thereby the conversion of linear systems into cyclic systems.

$$n\,R{-}P(NEt_2)_2 + n\,HOR'OH \longrightarrow$$

$$\longrightarrow -(-R'{-}O{-}\underset{\displaystyle R}{\overset{\displaystyle |}{P}}{-}O{-})_n + 2n\,HNEt_2$$

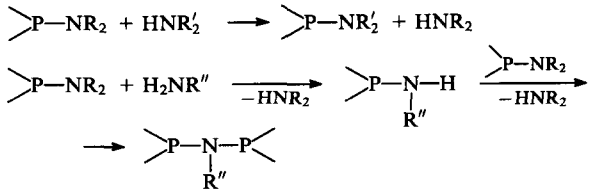
Hexitols[288] as well as methyl glucoside[439] have been used in polycondensations with TPAA. For selected reactant ratios, under the conditions discovered, oligomers and high-molecular-mass phosphorus-containing polymers were obtained in such cases. They are of practical interest, for example as additives to lubricants and as stabilisers.[440]

Overall, the field under consideration has not yet been adequately developed in view of the complications noted above and the fact that the attention of phosphorylation specialists has been to a large extent diverted to the striking problems posed by molecular biology and gene engineering. However, the logic of the development of the chemistry of trivalent phosphorus and macromolecular chemistry leads us to execute the tasks associated with the second stage in the development of the problem. This also arises from the needs of related sciences, especially coordination chemistry. Indeed, despite all the attention devoted to macromolecular ligands and complexes based on them, the very promising polyphosphite, phosphoramidite, and phosphonite ligands have been neglected nowadays. The optimum procedures for the synthesis of such ligands may be based primarily on the achievements in the chemistry of TPAA.

III. Phosphorylation of amines

The alcoholysis, phenolysis, and aminolysis of TPAA are in principle related reactions. Furthermore they are comparable as regards their effectiveness and experimental conditions. However, preliminary analysis of these reactions indicates also differences between them. Firstly, in contrast to the alcoholysis and phenolysis, the aminolysis can include not only single but also

double phosphorylation steps when secondary and primary amines are used as substrates‡. Secondly, the structures of the intermediates in the reactions enumerated differ significantly. In the alcoholysis and phenolysis, the leaving and entering groups are based on different atoms (nitrogen and oxygen), whilst in the case of aminolysis they are based on the same atoms. This situation hinders the elucidation of the pathway followed in the migration of the hydrogen forming part of the composition of the intermediate, this being particularly difficult when several hydrogen atoms, occupying different positions in space, are attached to the nitrogen atom.



These factors have apparently contributed to the delay in research into the transamination of TPAA behind the study of the corresponding reactions with alcohols and phenols. Nevertheless, the transamination methods already employed made it possible to solve a series of interesting and promising problems, especially in the chemistry of complex phosphacyclic compounds and nitrogen-containing natural products.

1. The history of the problem. Principal features of the reactions of trivalent phosphorus acid amides with amines

The first mentions of the possibility of the interaction of TPAA with amines leading to transamination date back to the end of the 1950s and the beginning of the 1960s.[135,441] Initial studies were on the simplest instances of transamination and were not associated with the solution of complex scientific problems. In the experiments, the low-boiling amine (usually diethylamine), which was one of the reaction products, was as a rule distilled away.[15,36,123,124,442–446] Approximately the same results were obtained in studies with the amides of phosphinous, phosphonous, and phosphorous acids.[447] The di- and tri-amides of these acids were used for complete and partial transamination. Mono- and polyfunctional amines of different chemical nature were selected as the substrates.

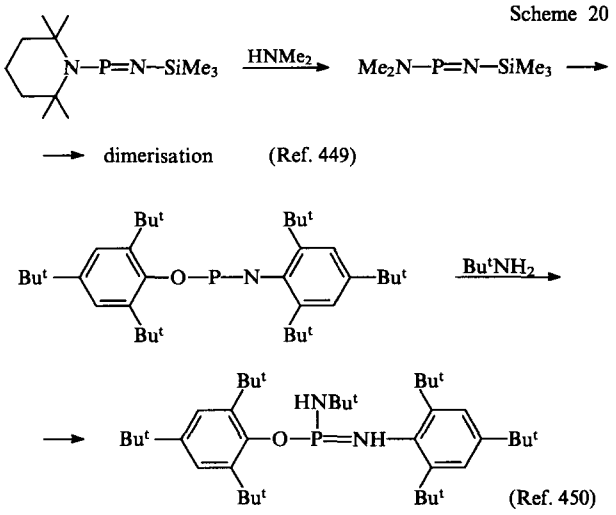
A high reactivity of the phosphoramide group was recorded in all the investigations. In this connection, we may note that even phosphorodifluoridous dimethylamide interacts with higher secondary amines via this group and not the phosphorofluoridite group.[448]



Studies on the interaction of primary and secondary amines with phosphenimidous compounds have been initiated recently. Various possibilities in the cleavage of the P–N σ- and π-bonds have been demonstrated in this connection: either substitution of a secondary amino-group[449] or the addition of an amine to the multiple bond (Scheme 20).[450] When an excess of the amine is used, more far reaching transamination processes can also occur.

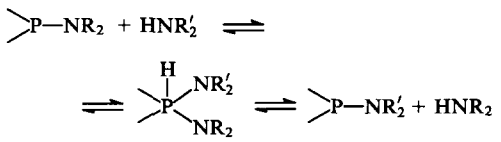
‡ Generally speaking, triple steps are also possible when ammonia is used as a substrate, but such reactions have so far been very little investigated.[441]

Scheme 20



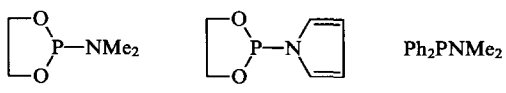
2. The chemistry of the transamination of trivalent phosphorus acid amides

On the basis of their own observations or merely on the grounds of general consideration, many investigators have expressed views concerning the dependence of the mechanism of the transamination of TPAA and of the rate of reaction on the structure of the reagent and the substrate. A mechanism involving addition of the phosphoramide to the amine with formation of a phosphorane and decomposition of the latter to the products detected has been proposed.[12,41,180,451,452]



Mechanisms involving a four-centre transition state[23,24] and direct nucleophilic substitution at phosphorus have also been discussed. The second variant is most common in the usual reactions. It has been related recently to the experimental observation of acid catalysis—the acceleration of the phosphorylation reaction by the addition of amine hydrochlorides[15,22,23,36,189] and acids.[38]

Convincing arguments in support of the nucleophilic substitution mechanism were first put forward in a study[33] in which the influence of the basicity of the entering and leaving amines on the rate of reaction was estimated. The authors investigated the interaction of ethylene *N,N*-dimethylphosphoramidite **38** with amines having different basicities and observed an increase in the rate of phosphorylation with increase in the basicity of the reacting amine. Thus, on passing from morpholine (pK_a = 8.70) to pyrrolidine (pK_a = 11.27), the rate increases, while in attempted reactions with *N*-methylaniline (pK_a = 4.85) and pyrrole (pK_a = −0.27), dimethylamine (pK_a = 10.77)§ is not displaced. Accordingly pyrrolidine displaces pyrrole more readily in experiments with ethylene phosphoropyrrolidite **39** than dimethylamine in experiments with the amide **38**.



38 **39** **40**

We may also point to the higher reactivity of the amide **38** than that of diphenylphosphinous dimethylamide **40**, which is consistent with the general principles of nucleophilic substitution at a trivalent phosphorus atom.[453] Unfortunately, the results of

§ The values of pK_a in water at 25 °C are quoted.

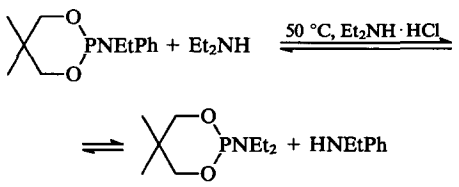
the transamination of the amide **38** were not obtained under equilibrium conditions, while those with the amide **39** were obtained under equilibrium conditions, so that strictly speaking their comparison is not valid. The difficulties in the interpretation of the results obtained with the pyrrolidite **39** have been noted also by other investigators.[31] We may note that the problem of the equilibrium nature of the transamination reaction has not been duly taken into account also in studies carried out in other laboratories (see, for example, Batyeva et al.[23]). Mosbo's study,[38] in which the transamination of the amino-derivatives of 1,3,2-dioxa- and 1,3,2-diaza-phosphorinanes was rigorously examined, is therefore especially important.



X = O, NMe; R = Et, $R_2 = (CH_2)_4$

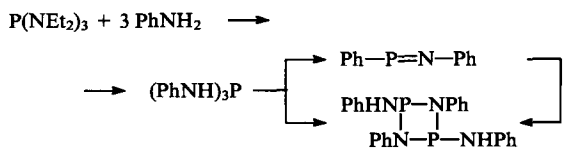
It was shown in this series of reactions that equilibrium can be attained when aminolysis is carried out in both forward and reverse directions. The conclusion that the high basicity of the amine substrate is important for the substitution reaction was confirmed. The results of this investigation do not confirm the necessity for the intermediate conversion of the initial amide into the corresponding acid chloride with subsequent phosphorylation by the chloride of the amine (substrate).[22,23,454]

The acid chloride concept has also been rejected in another study[189] where acid-catalysed aminolysis was investigated at the kinetic level.



The occurrence of catalysis was clearly demonstrated in this investigation and the dependence of the rate of reaction on the basicity of the amine was confirmed, but the influence of the solvent polarity on the rate of phosphorylation was not observed. In addition, the ability of the substrate, taken in excess, to inhibit the phosphorylation reaction was established. Thus, the study of the transamination of TPAA at the kinetic level established certain characteristics of this process, which distinguish it from the corresponding alcoholysis reactions.

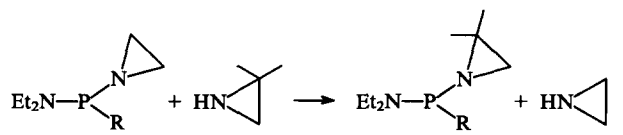
Comparison of the rates of phosphorylation and transamination of TPAA made it possible to make definite preparative recommendations. Thus it became clear that the best phosphorylating agents among the available phosphoramides are the anilides (*N*-alkylanilides).[127,189,209,447,455] We may note that the dialkylamides can react with aniline but only on heat treatment and with distillation of the dialkylamine evolved,[51,53] which shifts the equilibrium in the desired direction. The reaction considered is experimentally very complex and requires careful maintenance of constant phosphorylation conditions. Otherwise, elimination of self-phosphorylation reactions take place.[51,53,456-459]



The phosphorylation of dialkylamines by phosphorazolides merits attention.[145-148] The effectiveness of phosphorazolides increases in the sequence phosphinazolidite > phosphorodiamidous azolide > phosphorazolidite diester. The reverse reactions, i.e. the interaction of phosphorus acid dialkylamides with azoles, do not always take place. For example, they do not occur in the interaction of trivalent phosphorus acid diethylamides with imidazole.[145] The reason why this autocatalytic phosphorylation is impossible is the fact that the reaction involving the abstraction of a proton together with the imidazole residue by the intermediate is clearly preferred. We may note, however, that the problem of the chemical behaviour of phosphorus acid azolides, which are very unusual substances, has not yet been duly developed.

The rates of reactions of phosphorazolides under consideration depend definitely on the type of substituents at the phosphorus atom. Alkoxides ensure the maximum rates and alkyls the minimum rates,[145-148] which is also consistent with the concept of P-nucleophilic substitution. Nevertheless, a detailed description of the mechanism of the transamination of TPAA in the presence of acid catalysts is lacking in the literature. One may postulate that it is in principle analogous to the description of the alcoholysis of TPAA but differs by the migration of a proton between the linked nitrogen centres.

The problem of steric factors in the phosphorylation of TPAA has also been discussed in the literature, contradictory results being published. Thus the preferential phosphorylation of amines with less bulky substituents at the nitrogen atom has been reported.[38] On the other hand, the following reaction has been described:[445]

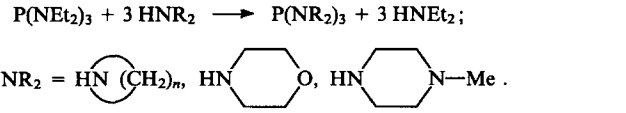


Thus our knowledge about the characteristic features of the transamination of TPAA requires further development.

3. The use of the transamination of trivalent phosphorus acid amides for the purposes of fine organic synthesis

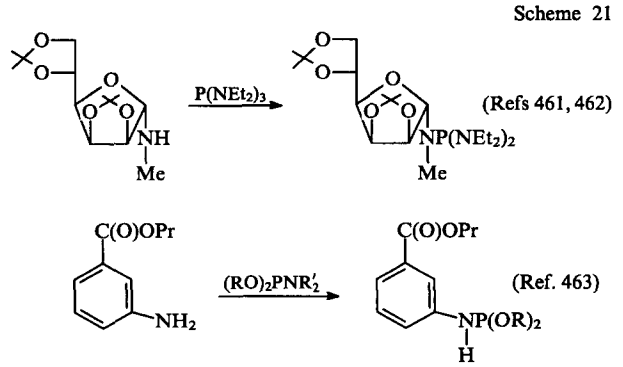
a. Phosphorylation of higher and functionalised primary and secondary amines

A useful preparative method of synthesis of higher and other complex phosphoramides is the aminolysis of the simplest representatives of substances of this class. Thus phosphorous hexamethyl(ethyl)triamides, which are readily available commercial products, perform the function of key substances in the synthesis of various more complex triamides, for example:[123,124,460]



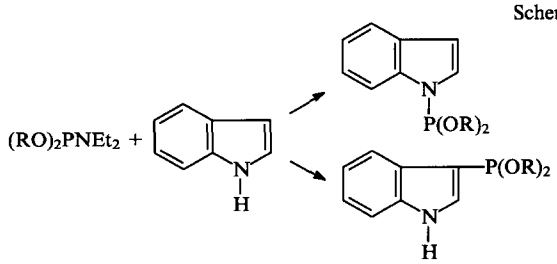
Complex asymmetric systems, including phosphorylated glucosylamines[461,462] and derivatives of *m*-aminobenzoic acid (Scheme 21),[463] can also be obtained in this way.

Scheme 21



Transamination may be supplemented by C-phosphorylation, as happened in experiments with indole (Scheme 22).[464] In the case of 3-mercaptoindole, phosphorylation can occur both at the nitrogen and at the sulfur depending on the conditions.[465]

Scheme 22



Higher primary α,ω-alkylenediamines are smoothly phosphorylated by *N,N*-dialkylphosphoramidites with formation of phosphorodiamidites which are difficult to obtain in other ways (Scheme 23).[447]

Scheme 23

$$2\,(RO)_2PNEt_2 + H_2N(CH_2)_6NH_2 \longrightarrow$$

$$\longrightarrow (RO)_2PNH(CH_2)_6NHP(OR)_2 + 2\,HNEt_2$$

For equimolecular reactants oligomeric or polymeric phosphoramidites may be formed.[442] This aspect has been investigated for cystamine.[444]

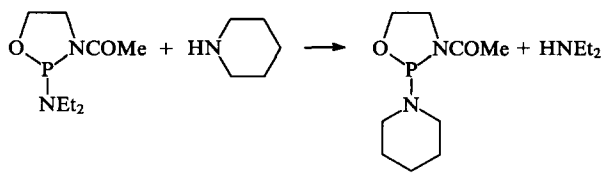
$$n\,RP(NEt_2)_2 + n\,H_2NCH_2CH_2SSCH_2CH_2NH_2 \longrightarrow$$

$$\longrightarrow -\left(\underset{\displaystyle R}{\overset{|}{P}}HNCH_2CH_2SSCH_2CH_2NH\right)_n-$$

R = Alk, OAlk, Et_2N.

When phosphorous hexaethyltriamide is used, it is possible to obtain network and not linear polymers. All these compounds are of interest as long-acting radioprotectors [radiation protectives? Ed.].

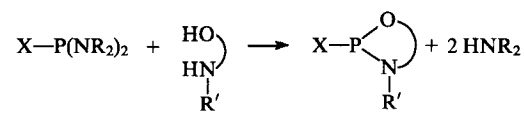
The result of transamination using phosphoramides with partially functionalised amino-groups, which are usually inert, is very interesting.[191]



There are data on the reactions of phosphoramides, the structures of which incorporate a polymeric amine having a N–P bond, with a nucleoside phosphite oligomer. It has been established that the oligonucleotide unit can be conveniently removed from the support in many instances by treatment with an excess of an amine, for example tetrazole.[466,467]

b. Phosphorylation of aminoalcohols and *o*-aminophenols

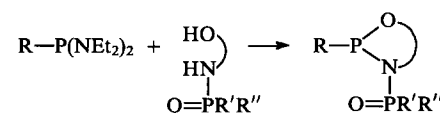
As mentioned above, the phosphorylation of tertiary aminoalcohols by treatment with TPAA leads to the formation of tertiary phosphoramidites and related compounds. The corresponding secondary aminoalcohols with functional groups in the 1,2- and 1,3-positions, including derivatives of 1,2-ethanolamine,[162,163,165,203,229,468–478] 1,3-propanolamine,[168,186,479–481] ephedrine,[473,482–486] prolinol,[484,487] etc. usually undergo phosphacyclisation on reacting with trivalent phosphorus acid diamides and triamides.



Aminomercaptans,[488] 1-alkylamino-1-deoxysugars,[489] and 3-imino-1-*N*-hydroxyethylpyrazoline[490] phosphacyclise in a similar manner.

Such reactions of aminoalcohols with TPAA are of extensive synthetic importance and are actively employed in the solution of many scientific and technical problems. We may point to the synthesis of phosphacyclic ligands for metal complex catalysis,[393,491,492] phospholipid systems (see the review by Nifant'ev and Predvoditelev[304]), and phosphacyclane derivatives of sugars.[303]

N-Phosphorylated aminoalcohols react similarly with TPAA.[194]

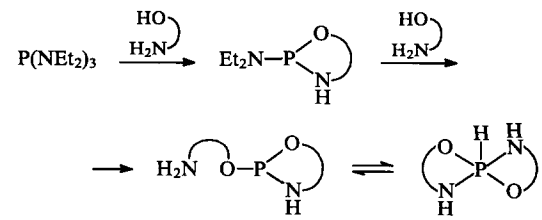


We may note that this scheme describes reactions for R = Alk or $NAlk_2$. When phosphorodiamidites are used, mono-*O*-phosphorylation turns out to be more probable.[194]

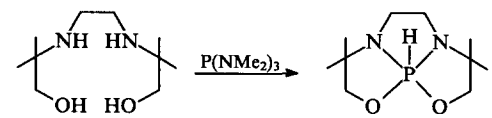
$$ROP(NEt_2)_2 + HO(CH_2)_3NHP(O)(OR')_2 \longrightarrow$$

$$\longrightarrow ROPO(CH_2)_3NHP(OR')_2$$

Many primary and certain secondary 1,2- and 1,3-aminoalcohols interact in a more complex manner with phosphorous triamides for a reactant molar ratio of 2 : 1; viz. 2-amino-1,3,2-oxazaphospholanes (phosphorinanes) are formed in the first stage of the synthesis and are then converted into phosphoramidites. The latter can be fully or partly converted into hydrospirophosphoranes (ring–chain tautomerism).[124,245,246,472,482,493–500]

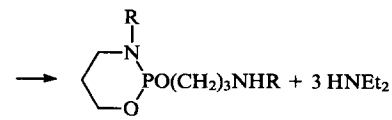


Similar, but this time tricyclic, hydrospirophosphoranes may be formed also in the phosphorylation of bisaminoethanols.[501]

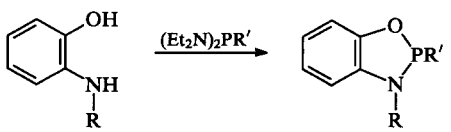


The ease of formation of the hydrospirophosphoranes is in many respects determined by the structure of the aminoalcohols. Vicinal, especially primary, aminoalcohols participate vigorously in this process. Secondary 1,3-aminoalcohols do not form spirosystems.[168]

$$P(NEt_2)_3 + 2\,HO(CH_2)_3NHR \longrightarrow$$

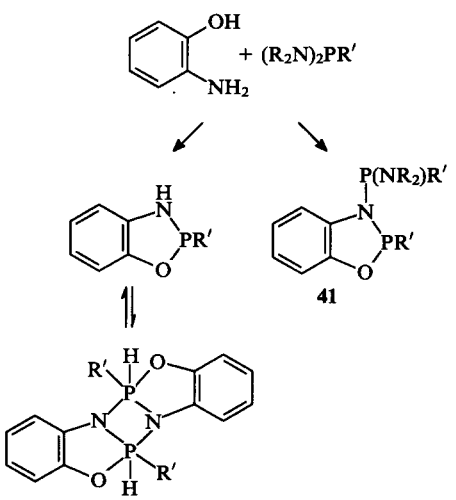


TPAA with two and three amino-groups effectively phosphorylate *o*-*N*-alkylaminophenols with formation of 4,5-benzo-1,3,2-oxazaphospholanes.[502,503]

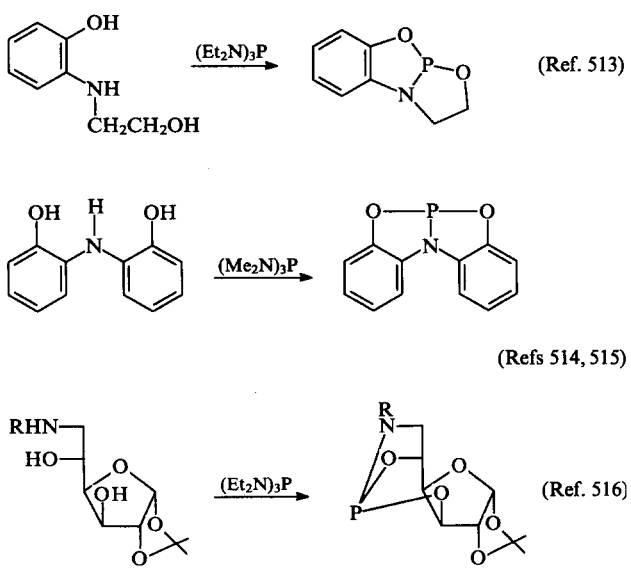


o-Aminothiophenols[229,504–507] and derivatives of *N*-acylaminophenols[508] are cyclophosphorylated in a similar manner.

Depending on the phosphorylation conditions and the reactant ratio, *o*-aminophenol itself can be either converted, in its reactions with trivalent phosphorous diamides, into a benzoxazaphospholane, which is capable of dimerising, or it affords a diphosphorus product.[509–512]



Aminophenols, namely *o*-(*N*-β-hydroxyethylamino)phenol[513] and di(*o*-hydroxyphenylene)amine[514,515] as well as 6-amino-6-deoxy-1,2-isopropylideneglucofuranose and 3-amino-3-deoxy-1,2-isopropylideneglucofuranose[516] are phosphorylated in an interesting manner. Rigid condensed systems are formed in such cases.



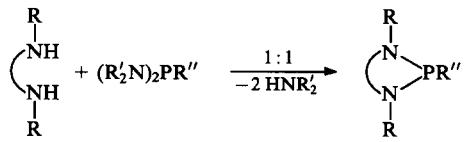
(Ref. 513)

(Refs 514, 515)

(Ref. 516)

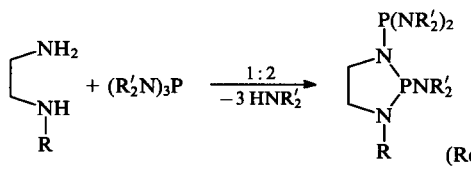
c. Phosphorylation of di, tri-, and tetra-amines

Alkylenediamines (1,2-alkylenediamine[517–519] and 1,3-alkylenediamine[520–522]), which include diprimary, primary-secondary, and disecondary representatives, are effectively phosphorylated by phosphorous and phosphonous diamides and triamides; in a few instances, the reaction has been achieved with 1,4-alkylenediamines.[523–527]

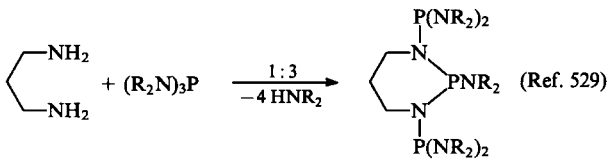


R = H, Alk.

When two or three molar amounts of the phosphoramide relative to the diamide are used, it is possible to obtain diphosphaheterocycles[518,519,528] and triphosphaheterocycles.[529]

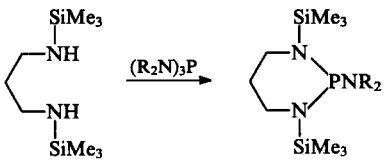


(Refs 518, 519, 528)

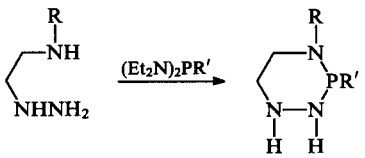


(Ref. 529)

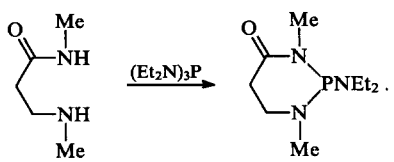
1,3-Disilylamines enter similarly into such reactions.[530]



It is interesting that β-aminoethylhydrazines can undergo the same phosphacyclisations, affording triazaphosphorinanes.[18]

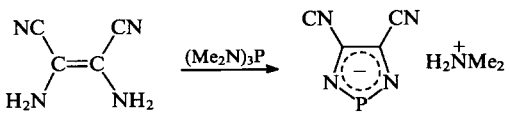


Certain aminoamides also enter into the phosphacyclisation reaction, for example:[531,532]

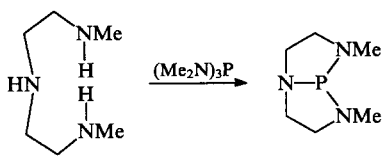


In the phosphacyclisation of diaminodicyanoethylene by phosphorous triamide, a stable anion may be formed—the isoelectronic 1,3,2-diazaphospholane (Scheme 24).[533]

Scheme 24



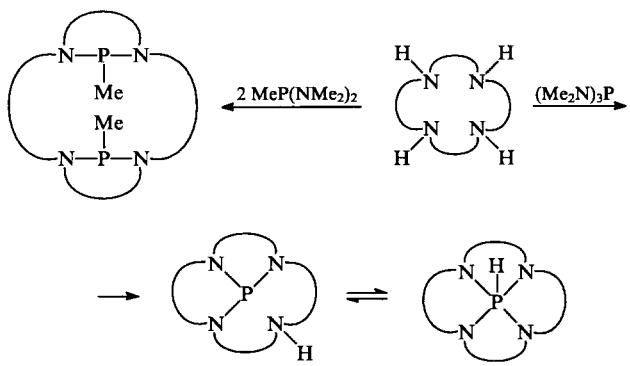
Mention must be made of the study of the phosphorylation of linear and alicyclic triamines and tetraamines, to which much attention has been devoted recently. It has been established that reaction of 2,5,8-triazanonane with an equimolar amount of phosphorous hexamethyltriamide affords a condensed bicyclic compound.[534]



The phosphorylation of trialkylenetriamines takes place similarly.[535-538]

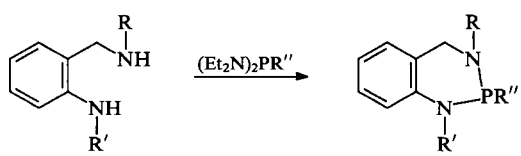


The phosphorylation of alkyenetetraamines has been studied even more extensively.[539-543]



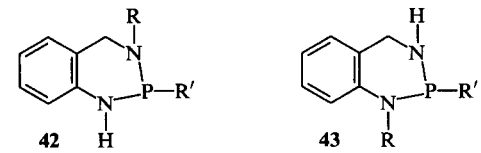
An interesting case of prototropism, leading to a symmetrical hydrospirophosphorane, has been observed in this series of studies. The position of the equilibrium described depends on the nature of the solvent and of the alkylene group linking the nitrogen atoms into a single system.

Aliphatic-aromatic diamines have been investigated even more vigorously in cyclophosphorylation by TPAA. Thus *N,N'*-dialkyl(aryl)-2-aminobenzylamines react with phosphorous diamides and triamides, forming readily and in high yields 1,3-disubstituted 4,5-benzo-1,3,2-diazaphosphorinanes.[544-547]



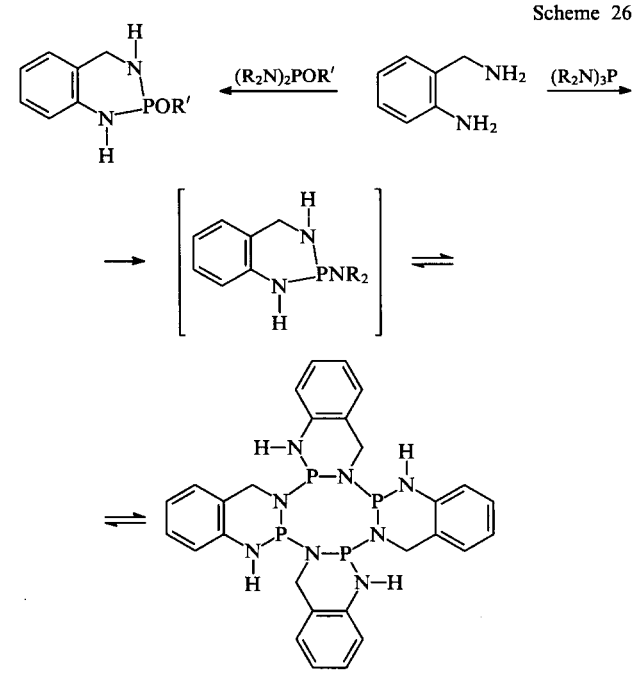
There are two types of 2-aminobenzylamines monosubstituted at the nitrogen atom. Each has been successfully phosphacyclised with formation of 4,5-benzo-1,3,2-diazaphosphorinanes of two classes—**42** and **43** (Scheme 25).[544-547]

Scheme 25



Unsubstituted 2-aminobenzylamine also reacts with TPAA. Phosphorodiamidite esters give rise in this case to 2-alkoxy-4,5-benzo-1,3,2-diazaphosphorinanes, while phosphorous triamides afford 2-dialkylamino-4,5-benzo-1,3,2-diazaphosphorinanes, which immediately undergo cyclotetracondensation (Scheme 26).[548]

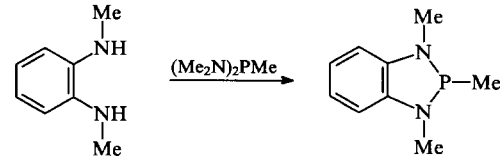
Scheme 26



The high efficiency (yield about 90%) and regiospecificity of the reaction [products containing only aminobenzyl nitrogen atoms in the tetraazaphosphacyanogen (tetraazatriphosphacyclooctane? Ed. of translation) ring] is striking. X-Ray diffraction data showed that a molecule of the product consists of a symmetrical crown in which the nitrogen atoms lie in a plane parallel to the plane of the phosphorus atoms. One can postulate that this and similar systems will be of considerable interest for the synthesis of new coordination systems.

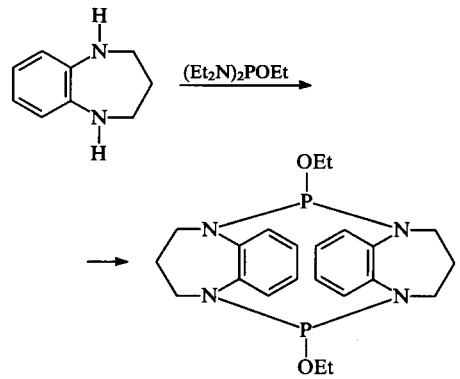
It is essential to note that as a rule all the phosphacyclisations examined above are more efficient than the corresponding reactions with phosphorous acid chlorides.

We shall now turn to the phosphorylation of aromatic diamines. Secondary *o*-diaminobenzenes interact readily with TPAA.[549]



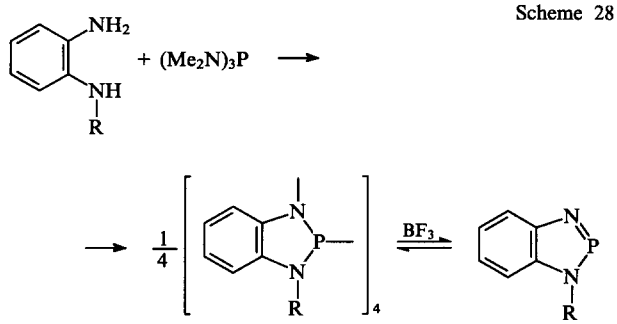
In the case of the cyclophosphorylation of *o*-phenylenediamine, in the molecules of which the nitrogen atoms are linked via a 1,3-propylene bridge, the process is more complex and leads to the formation of a diphosphorus system (Scheme 27).[550]

Scheme 27



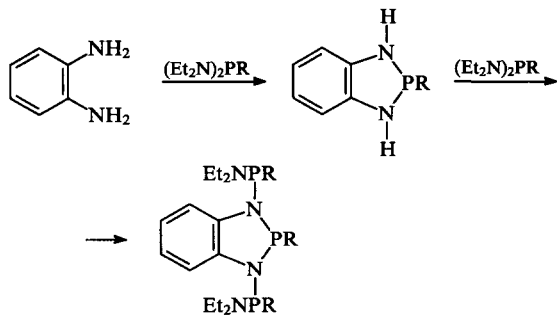
Primary-secondary diamines afford tetramers on reaction with phosphorous acid hexamethyltriamide (Scheme 28).[508,551-553]

Scheme 28

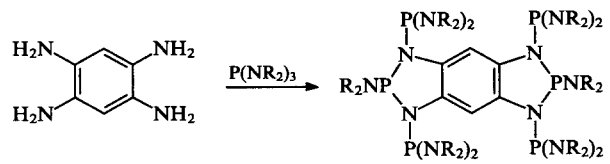


On heating with boron trifluoride, this tetramer decomposes. The monomer has been detected in solution by ^{31}P NMR spectroscopy.

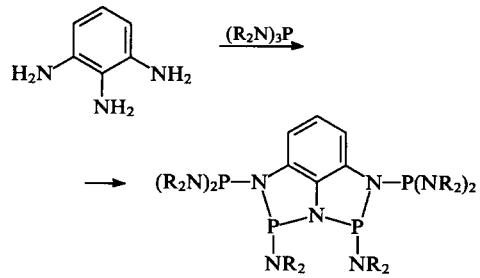
On phosphorylation with phosphorous diamides and triamides, unsubstituted *o*-phenylenediamine can give rise to the usual phosphacycles or the products of their additional phosphorylation at the nitrogen atom depending on the reaction conditions and the reactant ratio.[529,554-557]



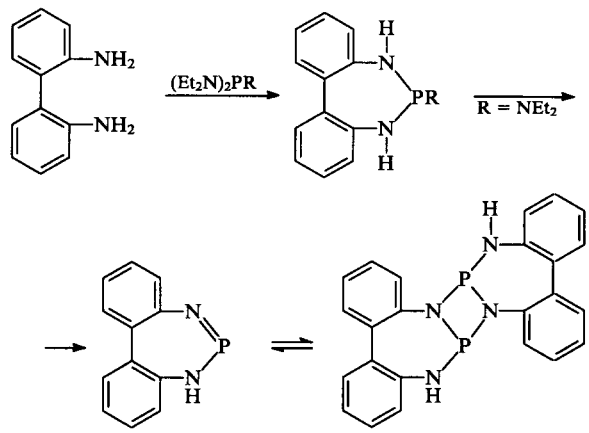
The second phosphorylation pathway has also been achieved in a study with 1,2,4,5-tetraminobenzene.[558]



We may also note that 1,2,3-triaminobenzene affords a phosphacyclic system of a different chemical nature in an analogous situation.[558,559]



The interaction of a more complex aromatic amine — *o,o'*-diaminobiphenyl — with phosphorous diamides and triamides affords 4,5,6,7-dibenzo-1,3,2-diazaphosphorinanes.[560]



R = OAlk, NEt_2

When R = NEt_2, the primary product can undergo the elimination of the amine with formation of a derivative of dicoordinate phosphorus, which apparently dimerises as a result of the regular 1,2;1,2-cycloaddition.[560]

IV. Conclusion

It is seen from the data presented that TPAA have found extensive application for the phosphorylation of alcohols, phenols, and amines of a wide variety of chemical types. Virtually all the types of these proton-donating nucleophiles have already served as substrates in the synthesis of derivatives of phosphorous, phosphonous, and phosphinous acids. The success of the syntheses is apparently due to the experimental formulation of the reactions and primarily the use of optimum catalysts (activators) and solvating agents.

The discovery of a high reactivity in TPAA brought modern organophosphorus chemistry closer to other chemical disciplines and eliminated the barriers which have traditionally arisen between them. The most important result of such a mutual approach has been a radical alteration in strategy for the synthesis of natural products, including the most complex of these, namely nucleic acids and phospholipids. Furthermore, there has been a change in the principles governing the design of phosphorus-containing skeletal compounds and other complex phosphorus heterocycles. There has been a revival also in other interdisciplinary fields.

Nevertheless, the considerable chemical potential of TPAA has not yet been fully realised. It is sufficient to state that studies on the application of these reagents in macromolecular chemistry, both for the modification of polyfunctional polymers and the polycondensation of oligools and amines, have been dealt with only in outline. Nevertheless we may state that certain fundamental problems, the solution of which will apparently lead to useful recommendations, have been found in this field.

It has now been established that, apart from the nucleophiles already named, TPAA can readily phosphorylate also other compounds—various derivatives of acids, mercaptans, phosphines, transition metal hydrides, etc. They give rise to interesting results in reactions of other types as well. All this makes TPAA valuable reagents for fine organic synthesis.

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