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Studies on Aryl H-Phosphonates. 3. Mechanistic Investigations Related to the Disproportionation of Diphenyl H-Phosphonate Under Anhydrous Basic Conditions

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Abstract: Diphenyl H-phosphonate undergoes under anhydrous reaction conditions a base-promoted disproportionation to triphenyl phosphite and phenyl H-phosphonate. On the basis of ^{31}P NMR data the most likely mechanism for this transformation was proposed. In order to substantiate these findings and to get a deeper insight into the chemistry of aryl H-phosphonate esters, we carried out also some studies on activation of phenyl and diphenyl H-phosphonates with various condensing agents. We found that aryl *vs* alkyl esters of phosphonic acid often follow different reaction pathways during the activation, and this can most likely be traced back to higher electrophilicity of the phosphorus centre and to higher reactivity of the P-H bonds in aryl H-phosphonate derivatives. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Reaction of H-phosphonate monoesters with a hydroxylic component promoted by a condensing agent provides an efficient synthetic route to the corresponding H-phosphonate diesters[1-3]. From these, a variety of phosphate analogues, some of them of considerable medicinal importance, are easily accessible *via* oxidation with suitable agents[4]. This methodology proved to be successful and sometimes superior to the well established phosphoramidite and phosphotriester approaches in the preparation of various phosphorus-containing natural products and their analogues, *e.g.*, oligonucleotides[5], phospholipids[6], phosphorylated sugars[7,8], phosphorylated peptides[9].

As a part of our studies in H-phosphonate chemistry we have recently embarked on investigations of aryl H-phosphonates[10-12] as starting materials and intermediates for the preparation of organic phosphorus compounds. We have developed simple and efficient synthetic methods for nucleoside H-phosphonate monoesters[10], alkyl H-phosphonates[11], and H-phosphonamidates[12] by making use of the high susceptibility of

the phosphorus centre in aryl H-phosphonate diesters towards nucleophilic substitution[13]. During these studies it became apparent that chemical reactivity of aryl H-phosphonates was significantly different from that of alkyl H-phosphonates. This, in principle, may be advantageous from a synthetic point of view, since some additional reaction pathways, not available to simple alkyl H-phosphonates, can become accessible to these compounds. However, it is also possible that the higher reactivity of aryl H-phosphonates may contribute to some instability of these compounds under reaction conditions ultimately leading to the formation of side products. To be able to predict the chemical behaviour of aryl H-phosphonates under various experimental conditions and to extend further their synthetic applications, a more detailed knowledge of the basic chemistry of these esters of phosphonic acid was necessary.

We have noticed on several occasions[10] that reaction mixtures resulting from transesterification of diphenyl H-phosphonate with alcohols in pyridine were contaminated with variable amounts of triphenyl phosphite (0-5%) and phenyl H-phosphonate (5-10%). The presence of the latter could in principle be due to spurious water, however, to account for the formation of the former one, a special mechanism has to be invoked. We found that these two compounds were formed simultaneously under anhydrous conditions in pyridine and most likely were the products of the disproportionation of diphenyl H-phosphonate[10]. A similar observation concerning the instability of diphenyl H-phosphonate in the presence of diisopropylethylamine has also been reported recently[14].

Dialkyl H-phosphonate diesters when heated with their alkali metal salts in inert solvents undergo a disproportionation which superficially resemble that of diphenyl H-phosphonate. In this reaction dialkyl alkylphosphonates and alkyl H-phosphonate monoesters are formed from the corresponding n-alkyl derivatives[15], or trialkyl phosphites and alkyl H-phosphonate monoesters from sec-alkyl H-phosphonate diesters[16]. The postulated mechanism[16] invokes dealkylation of an H-phosphonate diester by dialkyl phosphite anion. The latter is an ambident nucleophile and undergoes apparently P-alkylation by n-alkyl H-phosphonate diester or O-alkylation by sec-alkyl H-phosphonates yielding, together with H-phosphonate monoesters, alkylphosphonates or trialkyl phosphites, respectively.

Inasmuch as nucleophilic substitution proceeds very slowly at an aromatic carbon, it is rather unlikely that transformation of diaryl H-phosphonates to the corresponding triaryl phosphites and aryl H-phosphonate monoesters involves a mechanism similar to that for alkyl H-phosphonates, *i.e.*, dearylation of diaryl H-phosphonate by a diaryl phosphite anion. For this reason we assumed that this reaction probably occurs *via* a mechanism which is characteristic for aryl H-phosphonate derivatives. In this paper we describe our ^{31}P NMR studies directed towards elucidation of the mechanism of this transformation. We also carried out some studies on activation of phenyl H-phosphonate monoester and diphenyl H-phosphonate with various condensing agents in order to substantiate our mechanistic investigations and to get a deeper insight into aryl H-phosphonate chemistry.

RESULTS AND DISCUSSION

Stability of diphenyl H-phosphonate under various experimental conditions

Diphenyl H-phosphonate **1a** was dissolved in pyridine and the ^{31}P NMR spectrum monitored. Besides the major resonance due to **1a** (δP = 1.19 ppm) a small signal at 128.3 ppm (< 2%) was observed. Gradual changes occurred in time in the spectrum and after 24 h the reaction mixture consisted of **1a** (~30%) and two additional compounds resonating at 128.3 (~30%) and at 1.08 ppm (~40%). The latter ones have been tentatively identified on the basis of the ^{31}P NMR data (see Table 1) as triphenyl phosphite **3** and phenyl H-phosphonate **2a,** respectively. The reaction proceeded further until a complete disappearance of the starting material (3-4 days) occurred. The postulated reaction products **2a** and **3** were isolated from this reaction mixture and their structures proved by spectral compared with the authentic samples.

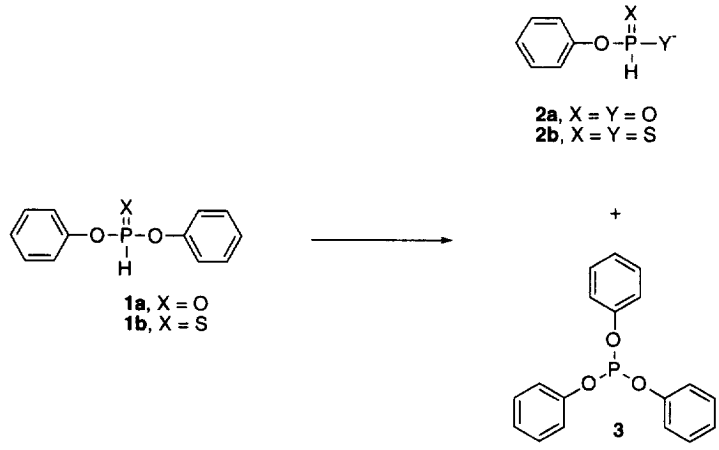
In acetonitrile the H-phosphonate **1a** was stable, however, the addition of pyridine (15 equiv.) initiated a slow transformation to **2a** and **3** (< 5% after 10 min). The reaction was rapid in the presence of triethylamine (TEA, 15 equiv.) and went to completion within few minutes.

The above transformation (Scheme 1) can thus be described as a base catalyzed disproportionation and tentatively summarized as follows:

$$2\ (PhO)_2P(H)O \xrightarrow{base} (PhO)_3P + PhOP(H)O_2H$$

Ratio of the products **3** to **2a** varied from ~1:1 up to ~1: 1.8 in different experiments. Usually, the longer the reaction time, the more differed the ratio from the expected value of 1:1. These we ascribed to spurious water which generated **2a** *via* hydrolysis of the starting material **1a**. In agreement with these, addition of 2 equiv. of water to a pyridine solution of diphenyl H-phosphonate **1a** caused its complete hydrolysis to the monoester **2a** before the first ^{31}P NMR spectrum could be recorded (~3 min.).

Scheme 1



The disproportionation of diphenyl H-phosphonate **1a** to the corresponding phosphite triester **3** and the H-phosphonate monoester **2a** was found to be practically an irreversible process. Both **3** and **2a** were completely stable and even after prolonged time (72 h) did not undergo any reaction (separately or with each other) neither in neat pyridine nor in pyridine in the presence of TEA or DBU.

We probed also stability of dialkyl H-phosphonates under similar reaction conditions. To this end, diethyl H-phosphonate was kept for 72 h in neat pyridine or in pyridine with 2 equiv. of a tertiary base (TEA or DBU). After this time, the ^{31}P NMR spectra revealed only presence of the starting material (δ_P = 7.5 ppm) and small amounts (< 8%) of ethyl H-phosphonate monoester. No signals which could be assigned to products of the disproportionation of diethyl H-phosphonate, *i.e.*, diethyl ethylphosphonate or triethyl phosphite, were detected.

Disproportionation of 1a in pyridine in the presence of triethylamine

Up to this point we had no clue whatsoever concerning a possible mechanism of the disproportionation of diphenyl H-phosphonate **1a** since no intermediates could be observed by ^{31}P NMR spectroscopy during the course of the reaction. Only occasionally a tiny transient signal at ~124 ppm appeared at the early stages of the reactions in pyridine. We assumed that it may come from an intermediate, but its low intensity prevented any spectroscopic or chemical analysis.

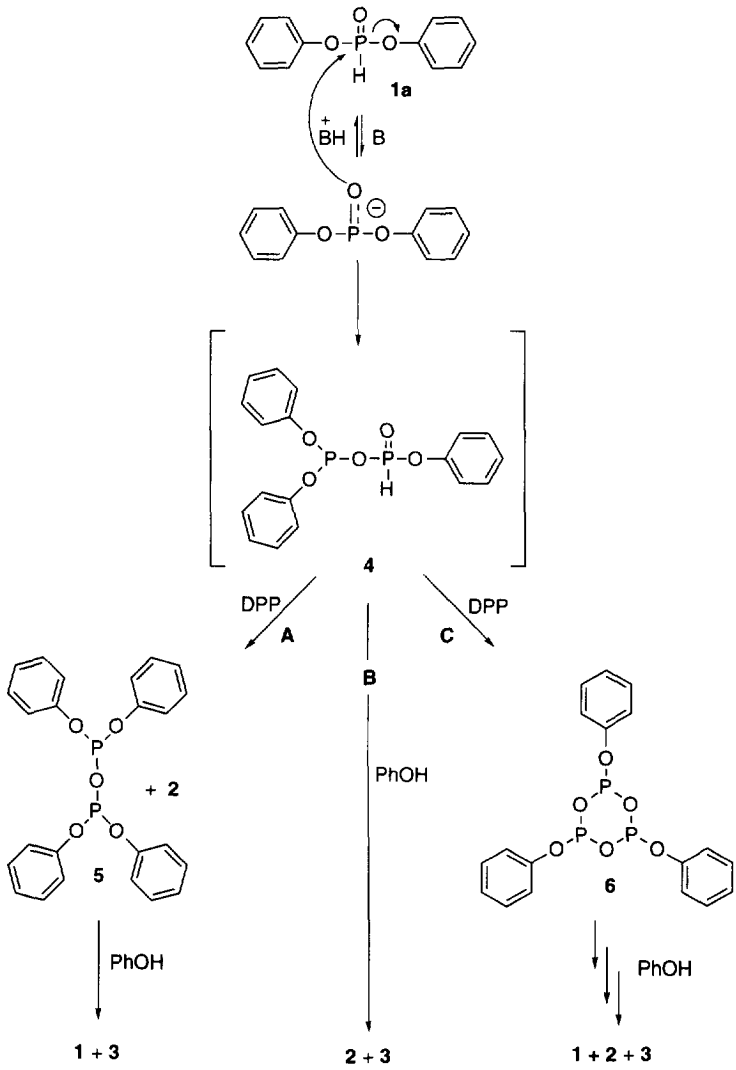
Since the disproportionation of the diaryl H-phosphonate **1a** in pyridine most likely is a multistep reaction with the first step being rate determining, we searched for conditions under which some of a distant reaction step would be slow, and thus a transient accumulation of an intermediate, detectable by ^{31}P NMR spectroscopy, could occur. At first we investigated the disproportionation of **1a** in acetonitrile, because its rate can be conveniently controlled by increasing concentration of added tertiary base. When **1a** in acetonitrile was treated with incremental amounts of TEA (5 equiv.) and the ^{31}P NMR spectrum monitored, the resonances corresponding to the products **2a** and **3** appeared (ratio ~1:1) while that from the starting material became broad. No intermediate absorptions could be detected during the course of the reaction.

An analogous reaction in pyridine in the presence of TEA afforded the awaited intermediate. Addition of 0.5 equiv. of TEA to a pyridine solution of **1a** caused the reaction to go to ~60% completion within 5 min as judged from the disappearance of the starting material. Besides resonances due to **1a** (broad signal, ~40%), **2a** (~18%), and **3** (~12%), a singlet at 124.4 ppm (~28%) was detected. Time-dependent changes in the ^{31}P NMR spectrum of the reaction mixture suggested that the intermediate at ~124.4 ppm was gradually converted to the products **3** and **2a**. The relative intensities of the signals related to **3**, **2a**, and the intermediate at ~124.4 ppm underwent changes from the initial value of ~1.0 : 1.5 : 2.3 (after 5 min) to ~1.0 : 1.1 : 0.3 (after 35 min), while the amount of unreacted starting material **1a** remained practically unchanged. When more amine (1-2 equiv.) was used, the reaction was faster (~80% completion after 5 min), but followed the same pattern consisting of the rapid formation of the intermediate resonating at ~124.4 ppm followed by its gradual conversion to the products **2a** and **3**.

A plausible mechanism for the disproportionation of diphenyl H-phosphonate 1a

To propose a credible mechanism for the disproportionation of **1a** to triphenyl phosphite **3** and phenyl H-phosphonate **2a** one has to take into account characteristic chemical features of diaryl H-phosphonates. These most likely stem from the presence of electron withdrawing substituents (two phenyl groups) which makes the phosphorus centre in **1a** more electrophilic and enables abstraction of the phosphorus-bound hydrogen even by a weak base (*e.g.*, pyridine).

Scheme 2



The resultant ambident phosphonate anion (Scheme 2) may then attack, in the absence of other nucleophiles, the electrophilic phosphorus centre in another molecule of **1a** with expulsion of the phenoxide. If the rules

concerning reactivity of ambident anions toward sp^3 carbon [17] apply also to the phosphorus centre, then attack by oxygen atom of the phosphonate anion should be favoured[18] and lead to formation of an intermediate **4** (Scheme 2) Since in the ^{31}P NMR spectra of the reaction mixtures in pyridine no signals related to **4**[19] were observed, we assumed that the postulated intermediate probably collapsed rapidly under these reaction conditions to the products **2a** and **3** *via* attack of phenol on the phosphite centre of **4** (Scheme 2, pathway B). However, in pyridine in the presence of TEA the nucleophilicity of phenol should be lowered and **4** may thus preferentially react with the phosphonate anion affording another intermediate, tetraphenyl pyrophosphite **5**, and phenyl H-phosphonate **2a**. The former one, in the reaction with phenol should produce triphenyl phosphite **3** and regenerate the starting material **1a** (Scheme 2, pathway A).

One can envisage, however, that the primary intermediate **4** undergoes activation with TEA and that the produced phosphonate anion reacts with diphenyl H-phosphonate to form an intermediate, which upon cyclization affords 2,4,6-triphenyl-1,3,5,2,4,6-trioxatriphosphinane (triphenyl trimetaphosphite) **6**. This, analogously to trialkyl trimetaphosphites[20], may produce **2a**, **3**, and the starting material **1a**, in a series of reactions involving phenol as a nucleophile (Scheme 2, pathway C). Due to the low reactivity of phenol under the reaction conditions, the postulated secondary intermediate, **5** or **6**, may accumulate and give rise to a signal in the ^{31}P NMR spectrum in the region of chemical shifts of tervalent compounds (~120 ppm).

The reaction pathways in Scheme 2 are compatible with the experimental data and explain why the disproportionation is catalysed by bases. In neat pyridine, the postulated intermediate **4** is formed in the rate determining step and since its concentration is most likely low, the disproportionation proceeds slowly (*via* one or more reaction pathways). Strong bases (*e.g.*, TEA) speed up formation of **4** *via* a more efficient generation of the phosphonate anion from **1a**, and also facilitate further reaction of **4** with diphenyl H-phosphonate, either *via* pathway A or C. Due to high concentration of the secondary intermediate, **5** or **6**, the reaction may proceed relatively fast, even that nucleophilicity of phenol under the reaction conditions is low.

Since the initial intermediate in the disproportionation of **1a** was assumed to be the mixed anhydride **4**, it was probable that the pathways A, B and C represented parallel ways for its decomposition to the products **2a** and **3**. For the reaction in neat pyridine it was difficult to assess the relative contribution of these reaction pathways. However, in the presence of TEA it seemed that one of the pathways (A or C) for the disproportionation prevailed. To find the main route for the disproportionation of **1a** in the presence of strong bases, we tried to assign the observed resonance at ~124.4 ppm (singlet) in the ^{31}P NMR spectrum (*vide supra*) to the postulated intermediates **5** or **6**.

The two phosphorus centers in the pyrophosphite **5** are chemically equivalent. Due to $^4J_{PH} \sim 0$ they are also magnetically equivalent and thus, for this compound a singlet at ~120 ppm should be expected. The other intermediate, the trimetaphosphite **6**, should also resonate in the same region of chemical shifts, however, the appearance of the spectrum is more difficult to predict in this instance. For a symmetrical structure with equivalent phenyl groups (C_{3v}) only one signal (a singlet) should be observed, while for a structure with nonequivalent substituents (C_s), a doublet and a triplet (intensities 2:1) were expected. Alkyl[20] and *o*-substituted

aryl[21] trimetaphosphites in solution usually form structures with C_s symmetry, but for the corresponding phosphonate analogues, both type of structures were observed[22]. Thus, with no ^{31}P NMR data available for **6**, at this stage we could not exclude the intermediacy of this compound in the disproportionation of diphenyl H-phosphonate **1a**.

The particular chemical reactivity of diphenyl H-phosphonate that we postulated to account for the observed disproportionation of **1a**, should be even more pronounced in the reactions of **1a** with reagents having electrophilic carbon or a phosphorus centre. To this end we investigated reactions of phenyl and diphenyl H-phosphonates with condensing agents (pivaloyl chloride and diphenyl phosphorochloridate) in order to explore the basic chemistry of aryl H-phosphonates and, hopefully, to produce some of the postulated intermediates in a different way.

Reactions of phenyl and diphenyl H-phosphonates with pivaloyl chloride

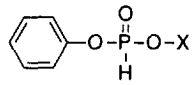
Pivaloyl chloride (PV-Cl) is a well established reagent in H-phosphonate chemistry[4]. Its usefulness as a condensing agent stems from the fact that it activates phosphonic acid[23] and alkyl H-phosphonate monoesters[3,24] to form the corresponding mixed anhydrides or acyl phosphites, but is unreactive towards dialkyl H-phosphonates[25]. For diaryl H-phosphonates, assuming a facile generation in pyridine of the phosphonate anions, however, the latter should not be the case. Indeed, when diphenyl H-phosphonate **1a** was subjected in pyridine to a reaction with PV-Cl (2 equiv.), the major resonances observed in the ^{31}P NMR spectrum were those at 1.2 (~30%), 128.4 (~30%) and 126.1 (~30%) ppm. These were assigned to the starting material **1a**, triphenyl phosphite **3**, and the acyl phosphite **9a**, respectively. The identity of **9a** (Scheme 3) was proved by converting it to compounds with known structures. Thus, addition to the reaction mixture of ethanol (3 equiv.) or phenol (3 equiv.) caused an immediate disappearance of the signal related to **9a** and formation of ethyl diphenyl phosphite **9b** (δ_P ~130.3 ppm) or **3**, respectively. Since the starting material **1a** contained phenol (see the Experimental Part), this also explained the formation of triphenyl phosphite **3** during the course of activation. The presence of a small signal at ~124.4 ppm (< 3%) indicated that the acyl phosphite **9a** might to some extent react with **1a** forming most likely **5**.

Phenyl H-phosphonate **2a** (triethylammonium salt) reacted in pyridine with PV-Cl (2 equiv.) in a predictable way[25] producing as a major product (~90%) a compound resonating at 125.3 ppm. This intermediate was tentatively identified as the diacyl phenyl phosphite **8a**. The two other signals of equal intensities in the ^{31}P NMR spectrum, at 132.8 and 126.2 ppm, were found to be due to triacyl phosphite **10**[23] and diphenyl acyl phosphite **9a**, respectively. The origin of these signals is not clear. It is possible, however, that compounds **10** and **9a** may be formed as a result of a partial decomposition of **2a** or may arise from **8a** in the ligand exchange process catalysed by pyridine.

The correctness of the structural assignments of **8a** and **10** was probed by addition of phenol (5 equiv.) to the reaction mixture. This resulted in a rapid disappearance of the resonances related to **8a**, **9a** and **10**, and formation of triphenyl phosphite **3**. In a separate experiment an analogous reaction mixture was treated with

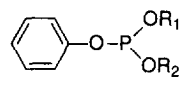
incremental amounts of phenol (2 equiv.) and the ^{31}P NMR spectrum monitored. The absorption at ~125.3 ppm due to **8a** gradually decreased while that at 126.1 ppm for **9a** began to grow until it became the major one. Simultaneously, the signal at 128.3 related to **3** appeared and it became the main signal (> 90%) when the addition of all the phenol was complete. As expected, treatment of the reaction mixture containing mainly **8a** with ethanol (3 equiv) produced as a major product (> 90%) diethyl phenyl phosphite **8b** (δ ~134.2 ppm). It is worth noting that during the activation of phenyl H-phosphonate **2a** with PV-Cl no resonances which could be assigned to the trimetaphosphite **6** were observed.

Scheme 3



7

7a, X = C_2H_5
7b, X = P(O)(H)OPh
7c, X = P(O)(H)OC_2H_5
7d, X = $C(O)C(CH_3)_3$
7e, X = $CH(CH_3)_2$



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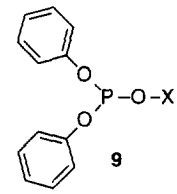
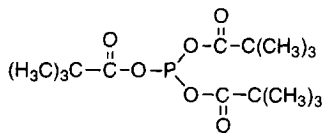
8a, $R_1 = R_2 = C(O)C(CH_3)_3$
8b, $R_1 = R_2 = C_2H_5$

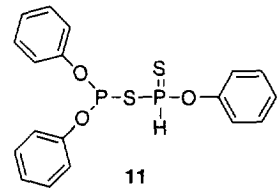


9

9a, X = $C(O)C(CH_3)_3$
9b, X = C_2H_5
9c, X = P(O)$(OPh)_2$



10



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With limited amounts of PV-Cl (0.5-1 equiv.) phenyl H-phosphonate **2a** afforded a mixture of the bisacyl phosphite **8a** and the starting material. This indicates that, similarly to alkyl H-phosphonate derivatives, the monoactivated species **7d** reacts in pyridine faster with PV-Cl than the parent H-phosphonate monoester does. However, when the activation was carried out in acetonitrile in the presence of 2-4 equiv. of pyridine or quinoline, the monoacyl H-phosphonate **7d** was formed as a major species (~85%, δ_P ~-0.7 ppm). It reacted rapidly with the added phenol (2 equiv.) to form **1a** or with isopropanol[26] producing phenyl isopropyl H-phosphonate (**7e**, δ_P ~3.9 ppm).

Reactions of phenyl and diphenyl H-phosphonates with diphenyl phosphorochloridate

Diphenyl phosphorochloridate (DPCP) is known as a reagent which activates alkyl H-phosphonate monoesters[1,27,28] but is unreactive towards dialkyl H-phosphonates[25,29]. When the activation process is carried out in pyridine in the absence of an alcohol, the only intermediates detected by ^{31}P NMR spectroscopy are those that do not contain as integral parts the condensing agent moieties[20]. This is most likely due to the high leaving

ability of the diphenyl phosphate group that can be easily substituted by other nucleophiles. We expected that some of the intermediates formed upon reaction of DPCP with phenyl and diphenyl H-phosphonates should thus be identical with those postulated in Scheme 2 (*e.g.*, the intermediates **5**, and **6**). This would enable us to delineate the main reaction pathway for the disproportionation of **1a** in pyridine in the presence of TEA.

To this end diphenyl H-phosphonate **1a** in pyridine was treated with DPCP (1 equiv.) and the ^{31}P NMR spectrum monitored. Within a few minutes the reaction went to 75% completion producing **3** (25%) and an intermediate resonating at ~124.4 ppm (~50%). The primary product of this activation should be the mixed anhydride **9c** with an easy to identify pattern of ^{31}P NMR signals. However, this kind of an intermediate was expected to undergo in pyridine a rapid reaction with **1a** producing a symmetrical pyrophosphite. For this reason we assigned the signal at ~124.4 ppm to the tetraphenyl pyrophosphite **5**. This was confirmed by probing the chemical reactivity of the intermediate at 124.4 ppm with phenol or ethanol. Addition of excess of phenol (5 equiv.) caused an immediate disappearance of the signal assigned to **5** and the formation of almost equal amounts of **3** and **1a**. The reaction with ethanol also afforded the expected phosphite **9b** together with products of transesterification of **1a** (**7a** and diethyl H-phosphonate). Similarly to the reaction of **1a** with PV-Cl, formation of **3** during the course of activation was also most likely in this instance due to the presence of phenol in the starting material **1a** (see the Experimental Part).

In a series of separate experiments we found that chemical reactivity (reaction with phenol and ethanol) of the intermediate at 124.4 ppm observed during the disproportionation of **1a** in pyridine in the presence of TEA was the same as that produced in the reaction of **1a** with DPCP. Since these intermediates also had identical chemical shifts in ^{31}P NMR spectroscopy (as found by mixing samples of the two reaction mixtures) we tentatively concluded that the disproportionation of **1a** under these reaction conditions proceeds to a significant extent *via* the pathway A (Scheme 2).

To provide further support for the intermediacy of **5** in the disproportionation of diphenyl H-phosphonate we wanted to prove that the signal at 124.4 ppm cannot be due to trimetaphosphite **6**. We therefore carried out ^{31}P NMR studies on the activation of phenyl H-phosphonate **2a** with DPCP. In pyridine a variety of intermediates can be formed from alkyl H-phosphonate monoesters[20] and DPCP. However, they usually rapidly collapse to the corresponding trimetaphosphites[20], which are the only reactive species detected by ^{31}P NMR spectroscopy under the reaction conditions.

Monitoring of the activation process by ^{31}P NMR spectroscopy revealed that addition of DPCP (1 equiv.) to a pyridine solution of **2a** caused immediate formation of a major resonance at ~113.3 ppm (singlet). On the basis of its chemical shift we assigned the signal to the expected trimetaphosphite **6**. This compound, similarly to trialkyl trimetaphosphites[20], was not stable under the reaction conditions and underwent gradual conversion (within ~1 h) to the symmetrical pyrophosphite **5** (δ_P ~124.4 ppm) and triphenyl phosphite **3**. Excess of the condensing agent apparently speeded up this transformation, since with 2 equiv. of DPCP signals from **6** and **5** were already present in the first ^{31}P NMR spectrum. After ~30 min, only a singlet due to **3** and several other resonances at -10 – -22 ppm remained. Since some of the high field signals were splitted due to $^2J_{PP}$ couplings,

apparently a complex transformation (most likely polycondensation) was taking place in time. No attempt was made to elucidate the nature of these reactions.

Table 1. ^{31}P NMR data of the substrates **1** and some products and intermediates[a]

Cmpd	δ (ppm)	$^1J_{PH}$ (Hz)	$^3J_{PH}$ (Hz)	Cmpd	δ (ppm)	$^1J_{PH}$ (Hz)	$^3J_{PH}$ (Hz)
1a	1.19	736.0 (d)	-	**6**[b]	113.21 112.87	-	$^2J_{PP}$ =7.4 (d) $^2J_{PP}$ =7.4 (t)
1a[b]	2.07	738.8 (d)	-	**7a**	4.63	711.6 (d)	9.8 (t)
1b	63.38	666.5 (d)	-	**7d**	-0.67	754.1 (d)	-
2a[c]	1.08	633.6 (d)	-	**7e**	3.87	712.9 (d)	8.5 (d)
2a[d]	-0.95	611.6 (d)	-	**8a**	125.29	-	-
2b	86.92	533.4 (d)	-	**8b**	134.15	-	7.6 (q)
3	128.34	-	-	**9a**	126.14	-	-
3[b]	129.70	-	-	**9b**	130.27	-	6.7 (t)
5	124.40	-	-	**10**	132.78	-	-
6	113.33	-	-				

[a] Spectra in pyridine; [b] Spectrum in acetonitrile; [c] Pyridinium salt; [d] Triethylammonium salt

The assignment of a singlet at ~113.3 ppm to the trimetaphosphite **6** implied the C_{3v} symmetry for this intermediate. We also succeeded in generation the isomer of **6** with the C_s symmetry. To this end the activation of phenyl H-phosphonate **2a** with DPCP (1 equiv.) was carried out in acetonitrile in the presence of 6 equiv. of pyridine and the ^{31}P NMR spectrum monitored. Two signals, at 113.2 and 112.9 ppm, with relative intensities of ~2:1 and with the expected $^2J_{PP}$ couplings (a doublet and a triplet, respectively), were the major resonances observed. Since in pyridine, the reactive species of type **6** may undergo a ring opening-closure, it is likely that the trimetaphosphite with the C_{3v} symmetry represents the ground state structure[30], while the formation of C_s trimetaphosphite 6 in acetonitrile (with pyridine) may be kinetically controlled. Recently, similar observations have been reported for a cyclic phosphonic acid anhydride, namely, triphenyltrimetaphosphonate[22].

Other experiments related to the identification of the postulated intermediates involved in the disproportionation of diphenyl H-phosphonate 1a.

The chemical identity of the pyrophosphite **5**, the postulated intermediate in the disproportionation of diphenyl H-phosphonate **1a**, was authenticated further by its *in situ* generation from diphenyl phosphorochloridite and **1a** (see the Experimental Part). The reactivity of **5** (*e.g.*, reactions with phenol and

alcohols, *vide supra*) was found to be the same irrespective of the means by which the intermediate was generated.

In an analogous experiment involving diphenyl phosphorochloridite and phenyl H-phosphonate **2a** we attempted also to form *in situ* the mixed anhydride **4**. After reacting equimolar amounts of these two reagents in acetonitrile in the presence of TEA (4 equiv.) no signals which could be related to **4** were detected by ^{31}P NMR spectroscopy. Instead, only the trimetaphosphite **6** [(δ_P ~112.7 (t) and 113.1 (d) ppm] and the pyrophosphite **5** (δ_P ~124.8 ppm) were formed. This agrees with our assumption that high reactivity towards nucleophiles of the mixed anhydride **4** prevented its detection by ^{31}P NMR spectroscopy.

In the postulated mechanism for the disproportionation of **1a** (Scheme 2) we assumed as an initial step a nucleophilic attack of diphenyl phosphonate anion on diphenyl H-phosphonate. In this context one may argue that the product of the disproportionation, phenyl H-phosphonate **2a**, should also react with the starting material **1a** affording diphenyl H-pyrophosphonate **7b**. Most likely this is so, but **7b** cannot be detected under the reaction conditions due to its immediate reaction with phenol which restores **1a** and **2a**. This point was clarified further by reacting diphenyl H-phosphonate with ethyl H-phosphonate monoester. In this instance an intermediacy of the mixed anhydride **7c** could be inferred from the formation of ethyl phenyl H-phosphonate **7a**. Indeed, a reaction of **1a** (1 equiv.) with ethyl H-phosphonate (δ_P ~3.4 ppm, $^1J_{PH}$ = 615.0 Hz) in pyridine resulted in the formation of two compounds, which were identified by comparison with authentic samples as phenyl H-phosphonate **2a** and the ethyl phenyl H-phosphonate **7a** (see Table 1). Addition of TEA (3 equiv.) to the reaction mixture caused a slow formation of diphenyl ethyl phosphite **9b** (~15% after 25 min) which indicated that **7a** may undergo a similar to diaryl H-phosphonates disproportionation under basic conditions.

To validate our findings concerning the mechanism of the disproportionation of diaryl H-phosphonates we carried out some preliminary studies on diphenyl H-phosphonothioate **1b**. If the same mechanism applies, one should expect the formation of phenyl H-phosphonodithioate **2b** and triphenyl phosphite **3** as products of the disproportionation. The formation of species **2b** with two sulfurs bound to phosphorus might serve as a proof that the disproportionation proceeded *via* a binuclear phosphorus intermediate **11** with sulfur in the bridging position. This intermediate, which is analogous to the mixed anhydride **4**, should undergo similar transformations as those depicted in Scheme 2 for its oxygen congener. Indeed, under anhydrous conditions in neat pyridine **1b** (δ_P ~63.4 ppm) underwent a disproportionation which was faster than that for its oxygen congener (~50% completion within 25 min) and which produced equimolar amounts of the anticipated H-phosphonodithioate **2b** (δ_P ~86.9 ppm) and triphenyl phosphite **3**.

Conclusions

Diphenyl H-phosphonate undergoes under anhydrous basic conditions a disproportionation to triphenyl phosphite **3** and phenyl H-phosphonate **2a**. The reaction is base catalysed and probably involves as an initial step a nucleophilic attack of diphenyl phosphonate anion on diphenyl H-phosphonate. A resulting intermediate (most likely **4**) may then react with phenol affording the final products of the disproportionation (path B in

Scheme 2), or alternatively, be converted into another intermediate **5** on the way to **2a** and **3** (path A). In pyridine in the presence of triethylamine apparently the latter pathway prevails.

It was also found that diphenyl H-phosphonothioate **1b** in pyridine underwent a similar disproportionation to that of **1a**, affording **3** and phenyl H-phosphonodithioate **2b**. Formation of the latter one provides a strong support for the postulated intermediacy of **11** in the rearrangement of **1b** and also substantiate our assumption about the involvement of a binuclear phosphorus intermediate of type **4** in the disproportionation of diphenyl H-phosphonate **1a**.

EXPERIMENTAL PART

Materials and Methods

Pyridine, quinoline, and triethylamine (TEA) were refluxed with CaH_2 and then distilled and stored over molecular sieves (4 Å) or CaH_2 (TEA). Acetonitrile (Merck) was stored over molecular sieves (4 Å). Diphenyl H-phosphonate **1a** (containing ~10% of phenol) and triphenyl phosphite **3** were commercial grade (Aldrich). Pivaloyl chloride (Aldrich) and diphenyl phosphorochloridate (Aldrich) were distilled before use. Phenyl H-phosphonate (obtained as below) was converted before reactions into the triethylammonium salt by addition of triethylamine to the ammonium salt of **2a** and repeated evaporation of the added pyridine. Ethyl H-phosphonate[11] and diphenyl H-phosphonothioate[31] **1b** have been synthesised according to published procedures.

The reference compounds used for the identification of some reaction products or intermediates were obtained as follows. Phenyl H-phosphonodithioate **2b** was prepared *via* reaction of **2a** with PV-Cl (2 equiv.) in pyridine, followed by addition of excess of 1M hydrogen sulfide in dioxane[32]; the intermediate **5** was generated *in situ* in acetonitrile by reacting diphenyl phosphorochloridite[33] and **1a**; ethyl phenyl H-phosphonate **7a** was produced *via* transesterification[11] of **1a** with ethanol; tripivaloyl phosphite **10** was prepared[23] in the reaction of phosphonic acid with PV-Cl.

The ^{31}P NMR experiments were performed in 10-mm tubes on a Jeol GSX-270 FT spectrometer using 0.2 mmol of phosphorus-containing compounds (1) in 2 mL of a solvent (pyridine or as indicated in the text). 2% H_3PO_4 in D_2O was used as external standard (coaxial inner tube). Amounts of triethylamine, condensing agents, and other additives were as indicated in the text. The values of the chemical shifts for the intermediates produced *in situ*, in some experiments varied (±1 ppm) depending on the reaction conditions.

Preparation of phenyl H-phosphonate, ammonium salt (2a).

This is a modification of the literature procedure[34].

To a solution of diphenyl H-phosphonate **1a** (10 mmol, 2.0 mL) in pyridine (10 mL) water (1 mL) and after 10 min. conc. aqueous ammonia (1 mL) were added. The reaction mixture was concentrated to dryness and traces of pyridine and water were removed by repeated evaporation of added isopropanol. The oily residue was suspended in a small volume of isopropanol (5-10 mL) and excess of diethyl ether was added. The

resulting crystals were filtered off and washed with diethyl ether. To remove phenol completely, the crystalline product was suspended in methylene chloride, vigorously shaken, filtered off, and dried under vacuum. Yield: 1.61 g (89%). mp. 145-146°C (after recrystallization from EtOH-Et_2O).

For the ^{31}P NMR data, see Table 1.

^1H NMR (CD_3OD, δ in ppm) 6.97 (1H, d, $^1J_{PH}$ = 633.8 Hz, P-H), 7.32 - 7.04 (5H, m, aromatic protons), 8.75 (4H, bs, NH_4^+).

^{13}C NMR ($CDCl_3$, δ in ppm) 153.17 (d, J_{PC} = 7.4 Hz, C-1), 130.45 (C-3), 124.71 (C-4), 121.78 (d, J_{PC} = 5.5 Hz, C-2).

HRMS (FAB): calculated for $C_6H_6O_3P$ (M-NH_4^+) 157.0055, found (M-NH_4^+) 157.0059.

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