Studies on the Activation Pathway of Phosphonic Acid using Acyl Chlorides as Activators

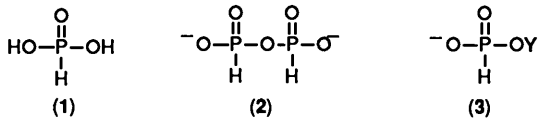
Jacek Stawinski* and Mats Thelin
Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, 106 91 Stockholm, Sweden

The activation pathway of phosphonic acid with acyl chlorides has been investigated with the aim of evaluating the synthetic utility of the intermediates involved for the preparation of hydrogen-phosphonate (H-phosphonate) monoesters. It is found that, depending on the amount of condensing reagent used, three distinctive intermediates are potentially formed, namely the pyrophosphonate (**2**), the phosphono-acyl mixed anhydride (**3a**), and the triacyl phosphite (**4a**). Their chemical reactivities towards oxygen nucleophiles indicate that the most suitable intermediate for H-phosphonate monoester synthesis is the pyrophosphonate (**2**).

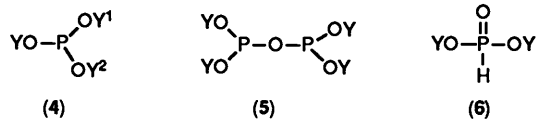
The reaction of alcohols with phosphonic acid in the presence of a condensing agent is potentially the most straightforward method for the preparation of H-phosphonate monoesters. However, since H_3PO_3 is a dibasic acid, it can, in an activation process, afford several intermediates of different reactivities. Some of them may react with alcohols to give H-phosphonate monoesters, but one can envisage several others which may afford H-phosphonate diesters, phosphite triesters, or other derivatives. Further complications may arise due to activation and subsequent transformations of the desired product, H-phosphonate monoester, under the reaction conditions. In addition, some reactions involving the P–H bond of phosphonic acid may also occur when a reactive condensing agent is used for activation. It has been shown, *e.g.* by Nicholson *et al.*[1] that phosphonic acid reacts with acetic anhydride to produce 1-hydroxyethylidenebis(phosphonic acid), together with some other products.

To eliminate this additional activation pathway involving the P–H bond of phosphonic acid, sterically hindered acyl chlorides (pivaloyl and adamantanecarbonyl) have been selected for the present studies.

The reaction of phosphonic acid with nucleosides has been briefly investigated by Hata *et al.*[2] for the purpose of H-phosphonate monoester synthesis. The authors reported that, under various reaction conditions, the desired nucleoside H-phosphonate monoesters were always formed together with substantial amounts (30–40%) of dinucleoside H-phosphonate diesters. Our interest in H-phosphonate chemistry prompted us to study this reaction in order to identify the intermediates involved, and to evaluate their possible usefulness in the preparation of H-phosphonate monoesters.



(1) (2) (3)



(4) (5) (6)

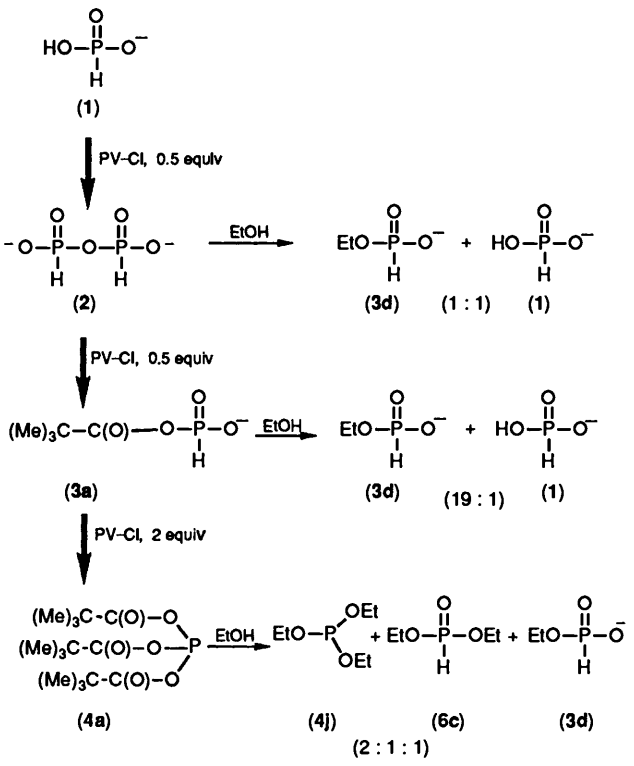
(**3a**) Y = pivaloyl
(**3b**) Y = adamantanecarbonyl
(**3c**) Y = dmt-T
(**3d**) Y = ethyl
(**4a**) Y = Y^1 = Y^2 = pivaloyl
(**4b**) Y = Y^1 = Y^2 = ada mantanecarbonyl
(**4c**) Y = pivaloyl, Y^1 = Y^2 = adamantanecarbonyl
(**4d**) Y = adamantanecarbonyl, Y^1 = Y^2 = pivaloyl
(**4e**) Y = dmt-T, Y^1 = Y^2 = pivaloyl
(**4f**) Y = dmt-T, Y^1 = Y^2 = adamantanecarbonyl
(**4g**) Y = dmt-T, Y^1 = pivaloyl, Y^2 = adamantanecarbonyl
(**4h**) Y = ethyl, Y^1 = Y^2 = pivaloyl
(**4i**) Y = Y^1 = dmt-T, Y^2 = pivaloyl
(**4j**) Y = Y^1 = Y^2 = ethyl
(**5**) Y = pivaloyl
(**6a**) Y = pivaloyl
(**6b**) Y = dmt-T
(**6c**) Y = ethyl

Results

When phosphonic acid (**1**) in pyridine was treated with 0.5 equiv. of pivaloyl chloride (Scheme 1), the ^{31}P NMR spectrum (recorded after 2 min) showed complete disappearance of the signal from phosphonic acid (δ_P 3.34 ppm, $^1J_{PH}$ 627.4 Hz) and formation of a new resonance at −6.57 ppm ($^1J_{PH}$ 637.0 Hz). The chemical shift and the stoicheiometry of the reaction indicated formation of the pyrophosphonate (**2**). Upon addition of an excess of ethanol to the reaction mixture, the intermediate afforded equimolar amounts of ethyl H-phosphonate (**3d**) (δ_P 4.50 ppm) and phosphonic acid (**1**), as one may have anticipated for the reaction of the pyrophosphonate (**2**).

With 1 equiv of pivaloyl chloride, phosphonic acid (**1**) in pyridine reacted to produce an intermediate which, in the ^{31}P NMR spectrum, gave rise to a signal at −3.21 ppm ($^1J_{PH}$ 651.8 Hz). The same intermediate was also formed from the *in situ* produced pyrophosphonate (**2**), upon addition of 0.5 equiv. of pivaloyl chloride (based on phosphonic acid used for formation of pyrophosphonate). The chemical shift value and the stoicheiometry of the reaction indicated the presence of a mixed anhydride of type (**3a**). In accordance with such a structure, the intermediate reacted with an excess of ethanol to produce ethyl H-phosphonate monoester (**3d**) and *ca.* 5% of phosphonic acid.

Addition of 3 equiv. of pivaloyl chloride to phosphonic acid (**1**) in pyridine resulted in the formation of an intermediate with a chemical shift of 132.67 ppm in the ^{31}P NMR spectrum. The absence of a $^1J_{PH}$ coupling constant and the value of the chemical shift pointed to the presence of a trivalent phosphorus species. When pivaloyl chloride was added in a stepwise manner, the ^{31}P NMR spectrum showed formation of the mixed anhydride (**3a**) (1 equiv. of PV-Cl), which was almost completely converted into the intermediate giving a signal at 132.67 ppm, when the total concentration of pivaloyl chloride



Scheme 1. Activation pathway of phosphonic acid in pyridine and products obtained from various intermediates when treated *in situ* with an excess of ethanol (the ratio of products in parentheses).

reached *ca.* 2.5–3 equiv. The most likely structure for this intermediate is that of the triacyl phosphite (**4a**). However, instead of exclusive formation of triethyl phosphite upon addition of an excess of ethanol, a mixture of ethyl H-phosphonate (**3d**), diethyl H-phosphonate (**6c**) and triethyl phosphite (**4j**) in a ratio of *ca.* 1:1:2 was obtained. Various explanations can be put forward to account for the observed product distribution and are discussed below.

As shown above, any of the three intermediates (**2**), (**3a**), and (**4a**) can be produced as a single reactive species from phosphonic acid using various amounts of pivaloyl chloride. Because of substantial differences in chemical structures of the intermediates, it seemed relevant to evaluate the chemical reactivity of each of them. Reaction with an excess of ethanol, carried out for the sake of identification of the intermediates, did not provide reliable information about their synthetic usefulness for preparation of H-phosphonate monoesters. Thus, we decided to investigate reactions of the intermediates (**2**), (**3a**), and (**4a**) (produced *in situ* from phosphonic acid and appropriate amounts of pivaloyl chloride) with 1 equiv. of an alcohol (ethanol or a suitably protected nucleoside).

To this end, the pyrophosphonate (**2**) was allowed to react with 1 equiv. of ethanol in pyridine. The ^{31}P NMR spectrum showed that the reaction went to completion during *ca.* 15 min, affording equimolar amounts of ethyl H-phosphonate (**3d**) and phosphonic acid. When ethanol was replaced by 5′-*O*-(4,4′-dimethoxytrityl)thymidine (dmt-T), the reaction was considerably slower. After storage overnight, the ^{31}P NMR spectrum showed *ca.* 50–60% conversion to the H-phosphonate monoester (**3c**), while unchanged pyrophosphonate (**2**) was still present. However, when 3–5 equiv. of the pyrophosphonate (**2**) were used, the reaction with dmt-T went to completion within 3 h, affording (**3c**) and only small amounts (0–3%) of the H-phosphonate diester (**6b**) (TLC and ^{31}P NMR analysis).

Reaction of the mixed anhydride (**3a**) with 1 equiv. of a nucleoside (dmt-T) proved to be fast and was complete before the first ^{31}P NMR spectrum was recorded (*ca.* 2 min). However, in contradistinction to the reaction with an excess of ethanol [predominant formation of the H-phosphonate monoester (**3d**)], approximately equimolar amounts of the nucleoside H-phosphonate (**3c**), dinucleoside H-phosphonate (**6b**) and pyrophosphonate (**2**), were formed.

Fully activated phosphonic acid, in the form of triacyl phosphite (**4a**), was found to be at least as reactive as the mixed anhydride (**3a**) towards nucleosides. The ^{31}P NMR spectrum of the reaction mixture of the triacyl phosphite (**4a**) with 1 equiv. of dmt-T showed a predominant signal from the nucleoside bisacyl phosphite (**4e**) and presence of some dinucleoside acyl phosphite (**4i**), dinucleoside H-phosphonate diester (**6b**) and some starting material (**4a**). After hydrolysis, this reaction mixture afforded the nucleoside H-phosphonate monoester (**3c**) (*ca.* 68%), dinucleoside H-phosphonate diester (**6b**) (*ca.* 13%) and phosphonic acid (*ca.* 19%). The composition of the reaction mixture remained practically unchanged when a larger excess (2–3 equiv.) of (**4a**) (relative to nucleoside) was used. The undesired dinucleoside H-phosphonate diester (**6b**) was formed in substantially larger quantities (*ca.* 60%) when the reaction was carried out by adding 3 equiv. of pivaloyl chloride to the mixture of phosphonic acid and dmt-T in pyridine.

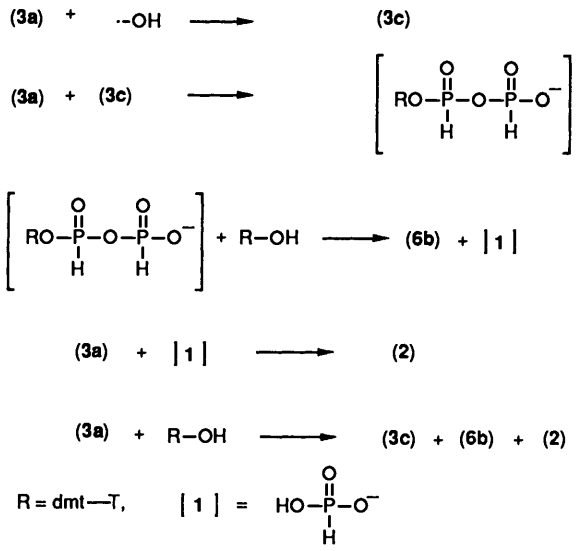
Discussion

There is no doubt that the first intermediate in the activation process of (**1**) by pivaloyl chloride, as observed by ^{31}P NMR spectroscopy, is the pyrophosphonate (**2**). Its ^{31}P NMR spectrum (AA′XX′ spin system) consists of a pair of asymmetric triplets and it is analogous to that of disodium pyrophosphonate.[3] Formation of the same intermediate was also observed when other coupling agents, *e.g.* adamantanecarbonyl chloride, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane, were used instead of pivaloyl chloride. Since hydrolysis of pyrophosphonate (**2**), as well as its reaction with ethanol, are considerably slower (a few hours *versus* a few minutes) when the triethylamine is added to the reaction mixtures, or when the triethylammonium salt of (**1**) is used, these seem to indicate acid catalysis[3] (by pyridinium hydrochloride) or involvement of the only partially ionized species of (**2**) in reactions with nucleophiles.

The second intermediate, observed by ^{31}P NMR spectroscopy in the activation process of phosphonic acid (**1**), was identified as the mixed anhydride (**3**), on the basis of its spectral properties and its chemical reactivity. This is most likely the primary intermediate formed during the activation of (**1**) with pivaloyl chloride but, apparently because of its high reactivity, it immediately reacts with (**1**) to form the pyrophosphonate (**2**). Thus, it cannot be detected by ^{31}P NMR spectroscopy as long as phosphonic acid (**1**) is present. On the other hand, the mixed anhydride (**3**) can exist in a reaction mixture together with the pyrophosphonate (**2**), when less than 1 equiv. of a condensing agent is used for activation.

The predominant formation of ethyl H-phosphonate and only small amounts of (**1**) (*ca.* 5%) upon reaction of (**3**) with an excess of ethanol is consistent with the assigned structure. The latter product can be formed due to moisture and/or presence of a small amount of the pyrophosphonate (**2**) in the reaction mixture. On the other hand, since the mixed anhydride (**3a**) has two electrophilic centres (phosphonyl and carbonyl), formation of small amounts of (**1**) in the above reaction may indicate a reaction of ethanol at the carbonyl group (acylation of ethanol).

In contradistinction to the reaction with an excess of ethanol, addition of 1 equiv. of the alcohol to the intermediate (**3a**)



Scheme 2. Reaction sequence of the mixed anhydride (**3a**) with 5′-*O*-dimethoxytritylthymidine (dmt-T).

resulted in formation of four compounds, phosphonic acid (**1**), pyrophosphonate (**2**), diethyl H-phosphonate (**6c**), and ethyl H-phosphonate (**3d**), in the ratio 1:1:1:6, respectively. In the reaction with 1 equiv. of dmt-T, approximately equimolar amounts of the diester (**6b**), monoester (**3c**), and pyrophosphonate (**2**) were formed. These results can be rationalized by assuming involvement of the mixed anhydride (**3a**) in the sequence of reactions shown in Scheme 2. It seems that for a moderately reactive hydroxylic component (*e.g.* a nucleoside), the first and second reactions occur at comparable rates. However, for more reactive alcohols (*e.g.* ethanol), the first reaction is apparently faster, and this results in a higher yield of the H-phosphonate monoester (**3d**) at the expense of the H-phosphonate diester (**6c**) and the pyrophosphonate (**2**).

Identification of the intermediate resulting from the activation of phosphonic acid with 3 equiv. of pivaloyl chloride posed some problems, due to the simplicity of its ^{31}P NMR spectrum (one singlet at 132.67 ppm). The reaction of the intermediate with ethanol afforded (**3d**), (**6c**), and (**4j**) in a 1:1:2 ratio. If one assumes that the pivalic acid anion, released during the reaction with ethanol, can deacylate acyl phosphites,[4] the composition of the reaction mixture can also be explained * by assigning structure (**4a**) to the intermediate at 132.67 ppm. Consistent with the assumed deacylation of triacyl phosphite, occurring during its reaction with an alcohol, was a substantial increase of phosphite triester formation, when the reaction was carried out in the presence of 4–5 equiv. of an acyl chloride. We could not, however, exclude on this basis another possible structure, *viz.* pyrophosphite (**5**). Theoretically, such a compound can be formed from (**1**) and 2.5 equiv. of pivaloyl chloride, and it should give a singlet in the same region of chemical shifts in the ^{31}P NMR spectrum as that of (**4a**). Thus, to differentiate between these two putative structures, it was necessary to investigate the system further. Both compounds, (**4a**) and (**5**), are symmetrical and can give only singlets in the ^{31}P NMR spectrum. However, if one carries out activation of phosphonic acid with two different acyl chlorides simultaneously, the pattern of signals in the ^{31}P NMR spectra of compounds of type (**4**) and (**5**) should be different. Assuming a similar reactivity of acyl chlorides, four compounds of type (**4**) should be formed, and the ^{31}P NMR spectrum should consist of four singlets. On the other hand, if the intermediate at 132.67 ppm has the structure (**5**), ten compounds should be formed. The unsymmetrical ones would have non-equivalent phosphorus atoms and thus they would exhibit characteristic AB coupling patterns in the ^{31}P NMR spectrum.

To check this hypothesis, phosphonic acid (**1**) in pyridine was treated with 1 equiv. of adamantanecarbonyl chloride to produce the mixed anhydride (**3b**) (δ −3.10 ppm, $^{1}J_{PH}$ 650.7 Hz), and then 2 equiv of pivaloyl chloride was added. The ^{31}P NMR spectrum of this reaction mixture showed four singlets with chemical shifts of 133.46, 133.24, 132.98, and 132.67 ppm (intensities respectively *ca.* 1:4:6:3). These results were consistent with the triacyl phosphite structure for the intermediate formed from phosphonic acid and 3 equiv. of acyl chlorides. In separate experiments, using various ratios of adamantanecarbonyl and pivaloyl chlorides, it was possible to assign the signals at 133.46, 133.24, 132.98, and 132.67 ppm to tri(adamantanecarbonyl) phosphite (**4b**), di(adamantanecarbonyl) pivaloyl phosphite (**4c**), dipivaloyl adamantanecarbonyl phosphite (**4d**), and tripivaloyl phosphite (**4a**), respectively. Additional support for the triacyl phosphite structure of the intermediate at 132.76 ppm is formation of the identical compound (^{31}P NMR data and a chemical reactivity) upon reaction of pivalic acid with phosphorus(III) chloride in pyridine or dioxane, in the presence of triethylamine. Compounds of similar structure, namely tribenzoyl phosphite[5] and triacetyl phosphite[6] have also been reported in the literature.

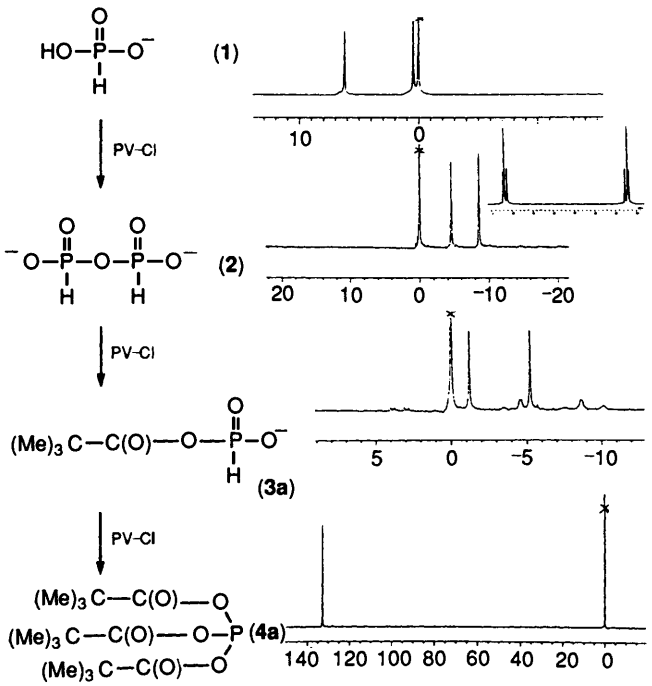
It is interesting to note that, after mixing tri(adamantanecarbonyl) phosphite (**4b**) (δ 133.46 ppm) and tripivaloyl phosphite (**4a**) (δ 132.67 ppm), four signals were also observed in the ^{31}P NMR spectrum. This indicates an acyl exchange process probably mediated by pyridine or pyridinium hydrochloride present in the reaction mixture. A similar phenomenon, namely formation of the mixed diacyl phosphite (**4g**), was also observed upon mixing of the two nucleoside bisacyl phosphites (**4e**) and (**4f**).

One point should be stressed concerning (**4a**) as an intermediate for the H-phosphonate monoester syntheses. Amounts of the major side product, the H-phosphonate diester (**6b**), in the reaction of (**4a**) with a nucleoside is substantially smaller (*ca.* 13%) when a nucleoside reacts with the *in situ* produced intermediate (**4a**), than when 3 equiv. of pivaloyl chloride is added to a pyridine solution of (**1**) and a nucleoside (*ca.* 60% of the H-phosphonate diester formation). This appears to indicate that, under the latter reaction conditions, the H-phosphonate esters are formed mainly *via* the mixed anhydride (**3a**), and not *via* (**4a**) as intermediate.

Conclusions

The activation pathway of phosphonic acid in pyridine using pivaloyl chloride can be summarized as in Scheme 3. Phosphonic acid reacts with an acyl chloride to form the mixed anhydride [*e.g.* (**3a**)], which is immediately trapped by the phosphonic acid anion to produce the pyrophosphonate (**2**). This is the first intermediate observed in the ^{31}P NMR spectrum. If more acyl chloride is present, the pyrophosphonate (**2**) undergoes further activation affording the mixed anhydride and, finally, the triacyl phosphite [*e.g.* (**4a**)]. Formation of (**4a**) is likely to proceed *via* the diacyl H-phosphonate (**6a**), but this

* The composition of the reaction mixture is probably kinetically controlled. If deacylation of a triacyl phosphite is faster than replacement of an acyl group by a hydroxylic component, formation of a phosphite triester may be completely eliminated. This may account for an observation reported by Hata *et al.*[2] that tribenzoyl phosphite reacts with nucleosides to yield a mixture of nucleoside H-phosphonate mono- and di-nucleoside H-phosphonate diesters in a ratio of 1:10.



Scheme 3. Activation pathway of phosphonic acid as observed by ^{31}P NMR spectroscopy (2% H_3PO_4 in D_2O as a reference).

Table. ^{31}P NMR data of some intermediates formed from phosphonic acid and pivaloyl chloride, and the products of their reactions with alcohols.

Compd.	Chemical shift (ppm)[a]	$^1J_{PH}$/Hz	$^3J_{PH}$/Hz
(1)	3.34	627.4	—
(2)	−6.57	637.0[b]	2.6[b] $^2J_{PP}$ 19.4[b]
(3a)	−3.21	651.8	—
(3b)	−3.10	650.7	—
(3c)	3.75	608.2	8.8 (dd)
(3d)	4.50	608.1	7.8 (dt)
(4a)	132.67	—	—
(4b)	133.46	—	—
(4c)	133.24	—	—
(4d)	132.98	—	—
(4e)	123.14	—	9.7 (d)
(4f)	124.06	—	9.8 (d)
(4g)	123.95, 123.23[c]	—	9.8 (d), 12.8 (d)
(4h)	122.60	—	6.9 (t)
(4i)	131.50	—	8.5 (t)
(4j)	137.80	—	7.9 (h)
(6b)	7.42	714.0	8.6 (dt)
(6c)	7.64	689.1	8.9 (dq)

[a] Chemical shifts relative to 2% H_3PO_4 in D_2O. [b] Calculated value for the spin system AA'XX'. [c] Two diastereoisomers.

intermediate is not visible in the ^{31}P NMR spectra, probably because it is immediately converted into the triacyl phosphite.

From a synthetic point of view, the most suitable intermediate for the H-phosphonate monoester preparations seems to be the pyrophosphonate (**2**). Its moderate chemical reactivity ensures smooth formation of H-phosphonate monoesters with only minimal amounts of H-phosphonate diesters. For less reactive alcohols, application of the much more reactive intermediate, the triacyl phosphite (**4a**) or (**4b**), would be advantageous. In such a reaction, however, the triacyl phosphite has to be formed *prior* to the addition of a hydroxylic component (preactivation), otherwise the formation of an H-phosphonate diester may become a predominant reaction. The mixed anhydrides [*e.g.* (**3a**) or (**3b**)] seem to be of less synthetic utility for the H-phosphonate monoester preparations, since a large excess of a hydroxylic component is required in order to prevent H-phosphonate diester formation.

Experimental

Materials and Methods.—Reactions were carried out in 10 mm NMR tubes and spectra were recorded on a JEOL GSX-270 FT spectrometer. For ^{31}P NMR experiments, 2% H_3PO_4 in D_2O was used as external standard (coaxial inner tube). The values of the chemical shifts for the intermediates produced *in situ*, in some experiments varied (±1 ppm) depending on the reaction conditions. The reference compounds (**4a–f**), (**6b**), (**6c**), (**3c**), and (**3d**) used for the identification of reaction products were prepared as previously described. TLC was carried out on Merck silica gel 60 F_{254} pre-coated plates using the following eluants: propan-2-ol–35% aq. ammonia–water (17:1:2 v/v; System A); chloroform–methanol (9:1 v/v, System B).

Pyridine, acetonitrile and triethylamine were refluxed with CaH_2 overnight and then distilled and stored over molecular sieves (4 Å) or CaH_2. Phosphonic acid, pivaloyl chloride, and adamantanecarbonyl chloride were commercial grade (Aldrich). The stock solution of 2 mol dm^{-3} H_3PO_3 in pyridine was prepared by evaporation of added pyridine to the appropriate amount of phosphonic acid and dissolving the residue in anhydrous pyridine. 5′-*O*-(4,4′-dimethoxytrityl)-thymidine[8] and 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane[9] were prepared by standard methods.

General Procedure for the Reaction of (**1**) *with Acyl Chlorides.*—Phosphonic acid (0.1 mmol) was dissolved in anhydrous pyridine (2 cm^3) and an activating agent (0.5–3 equiv. of pivaloyl chloride, adamantanecarbonyl chloride, or 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane) was added. The ^{31}P NMR spectra were recorded after mixing the reagents (for chemical shift values, see the Table).

General Procedure for the Reactions of (**2**), (**3a**), *and* (**4a**) *with Hydroxylic Components.*—To the reaction mixture, containing the *in situ* produced intermediate (**2**), (**3a**), or (**4a**) (0.1 mmol in pyridine, was added ethanol or 5′-*O*-dimethoxytritylthymidine (in quantities as specified in the text). The progress of the reactions was followed by recording ^{31}P NMR spectra at different time intervals and, if appropriate, also by TLC (for chemical shift values, see the Table).

Acknowledgements

We are indebted to Professor Per J. Garegg for his interest, to Professor D. Shugar for reading and correcting the manuscript, and to the National Swedish Board for Technical Development and the Swedish Natural Science Research Council for financial support.

References

1 J. B. Prentice, O. T. Quimby, R. J. Grabenstetter, and D. A. Nicholson, *J. Am. Chem. Soc.*, 1972, **94**, 6119.
2 M. Sekine, S. Narui, and T. Hata, *Tetrahedron Lett.*, 1988, **29**, 1037.
3 R. E. Mesmer and R. L. Carroll, *J. Am. Chem. Soc.*, 1966, **88**, 1381.
4 E. E. Nifant'ev and I. V. Fursenko, *Zh. Obshch. Khim.*, 1967, **37**, 511.
5 K. A. Petrov, E. E. Nifant'ev, and I. I. Sopikova, *Dokl. Akad. Nauk SSSR*, 1968, **151**, 859.

6 F. Nerdel and W. Burghardt, *Naturwissenschaften*, 1960, **47**, 178.
7 P. J. Garegg, T. Regberg, J. Stawinski, and R. Strömberg, *Nucleosides, Nucleotides*, 1987, **6**, 655.
8 H. Schaller, G. Weimann, B. Lerch, and H. G. Khorana, *J. Am. Chem. Soc.*, 1963, **85**, 3821.
9 R. L. McConnell and H. W. Coover, *J. Org. Chem.*, 1959, **24**, 630.

Paper 9/02819F
Received 3rd *July* 1989
Accepted 12th *December* 1989