MAGNETIC RESONANCE IN CHEMISTRY, VOL. 33, 971–976 (1995)

NOTE

^{31}P NMR—Structure Correlations for Phosphonocarboxylic Acids and Esters

Sabine Olagnon-Bourgeot and Francine Chastrette*
Laboratoire de Chimie Organique Physique et Synthétique, Université C. Bernard Lyon I,
43 Boulevard du 11 novembre 1918, 69622 Villeurbanne, France

Didier Wilhelm
Société Française, Hoechst, CRA, 48 bis Av. G. Monmousseau, 92240 Stains, France

^{31}P chemical shift–structure correlations were established from methyl and ethyl esters of simple phosphonocarboxylic acids. The influence of solvent, acidity, function and neighbourhood of phosphorus was studied. The correlations could be extended and led to the identification of esters obtained when a series of phosphonocarboxylic acids were reacted with alcohols—reactions which were designed as models of cellulose cross-linking by these acids.

KEY WORDS NMR; ^{31}P NMR; structure–δ correlations; phosphonocarboxylic acid esters; esterification

INTRODUCTION

^{31}P NMR has been used for years and many data are recorded.[1–4] Sensitive to chemical environment in the molecule, the chemical shift may provide a good tool for structural analysis. We used this tool to evaluate theprogress of the esterification in a series of phosphonocarboxylic acids currently studied as cellulose cross-linking agents.[5]

It is generally agreed that no general correlation can be seen between ^{31}P δ values and molecular structure, as electron density depends on a variety of factors such as electronegativity of substituents, extent of π bonding, related to the degree of occupation of d-orbitals of phosphorus atom, bond angles, and solvent.[4,6,7]

In the work presented here we studied the variation of ^{31}P chemical shift in a series of phosphonic and phosphonocarboxylic acids and derived esters as a function of the nature of the phosphonic function (acid, mono- or diphosphonate), the framework of the molecule, the medium and the presence of esterified or non-esterified carboxylic functions in the vicinity. First, from simple acids and alcohols taken as models, correlations were established between chemical shifts and phosphonic functions and their neighbourhood. These correlations were then applied to identify species found in reaction mixtures of esterification reactions involving alcohols such as 2-tetrahydropyranylmethanol (**2**) and phosphonocarboxylic acids of the general formula **1**:

$$\mathrm{HOOC{-}(CH_2)_n{-}CH(PO_3H_2){-}Y}$$

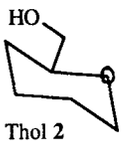
1

1a $n = 0$, Y = H
1b $n = 1$, Y = H
1c $n = 1$, Y = COOH
1d $n = 2$, Y = COOH

* Author to whom correspondence should be addressed.

CCC 0749–1581/951209710–60

Received 20 February 1995
Accepted (revised) 18 May 1995



Thol **2**

RESULTS

As a variety of acids and fully esterified species were available, the study of the influence of the function first required the preparation of monophosphonates. No ^{31}P δ values of monophosphonates have been recorded to our knowledge, while a number of δ values are known for diphosphonates.[4,7,8] We also needed phosphonic acids and esters containing carboxylic acid or ester functions in the vicinity at various positions.

First we realized syntheses of esters derived from simple acids **1a** and **1b** in order to obtain, besides acids and diphosphonates, a series of methyl, ethyl (or Thyl, from Thol, **2**) partial esters, some of which had not yet been described (**1a–7a**, **1b–7b**):

1a $\mathrm{HOOC{-}CH_2{-}PO_3H_2}$ [a]
1b $\mathrm{HOOC{-}(CH_2)_2{-}PO_3H_2}$ [a]
3a $\mathrm{ROOC{-}CH_2{-}PO_3H_2}$ [a]
3b $\mathrm{ROOC{-}(CH_2)_2{-}PO_3H_2}$ [a]
4a $\mathrm{HOOC{-}CH_2{-}PO(OH)OR}$ [a]
4b $\mathrm{HOOC{-}(CH_2)_2{-}PO(OH)OR}$ [a]
5a $\mathrm{ROOC{-}CH_2{-}PO(OH)OR}$
5b $\mathrm{ROOC{-}(CH_2)_2{-}PO(OH)OR}$
6a $\mathrm{HOOC{-}CH_2{-}PO(OR)_2}$ [a]
6b $\mathrm{HOOC{-}(CH_2)_2{-}PO(OR)_2}$ [a]
7a $\mathrm{ROOC{-}CH_2{-}PO(OR)_2}$ [a,b]
7b $\mathrm{ROOC{-}(CH_2)_2{-}PO(OR)_2}$ [a,b]

(R = Me, Et, Th)

[a] Already described molecules (R = Me or Et).
[b] Already recorded ^{31}P δ values (R = Me or Et).

Actually we were unable to prepared all the required esters as pure samples. Most of them were obtained as main components of mixtures where they could be unambiguously characterized by ^{1}H and chiefly ^{13}C NMR.

To complete the correlation, other types of molecules (according to function and vicinity) were then evidenced in reaction mixtures issued from the esterification of **2** by acids **1c** and **1d** for which Y = COOH. As main components of reaction mixtures, some of them could be characterized as above, but in a few cases their structures were extrapolated from ^{31}P chemical shift–structure correlations.

Table 1 displays the chemical shifts values and assignments obtained in this work. Assignments made only by ^{31}P correlations are pointed out.

DISCUSSION

Variation of δ(^{31}P) with phosphonic function: the functional rule

Ethanephosphonic acid and esters illustrate (Table 2) a rule which applies to the whole set of acids under study, whatever the solvent: δ(phosphonic acid) < δ(monophosphonate) < δ(diphosphonate); for example 29.4, 31.7 and 34.4 for acid and ethyl esters in DMSO (δ in ppm). The ^{31}P shielding increases according to the degree of esterification, with increments of at least 2 ppm. This rule will be referred to as the *functional rule.* It may be ascribed to the deshielding attracting effect of —OR compared to that of —OH.

Table 2. Variation of δ ^{31}P with function F in the ethanephosphonic series[a,b]

	Solvent: DMSO		Water		Thol	
Molecule	δ	$\Delta\delta_F$	δ	$\Delta\delta_F$	δ	$\Delta\delta_F$
Et—$PO(OH)_2$	29.7	0	32.8	0	31.2	0
Et—PO(OH)(OR)	31.7^{Et}	+2.0				
	32.1^{Th}	+2.4	34.1^{Th}	+1.3	32.5^{Th}	+1.3
Et—$PO(OR)_2$	33.2^{Et}	+3.5	37.0^{Et}	+4.2	33.4^{Et}	+2.2

[a] Values (ppm) of chemical shifts δ and functional increments $\Delta\delta_F$.
[b] Thol and R: see Table 1, note b.

Table 1. δ ^{31}P variation with function, solvent, framework Z and carboxylic neighbourhood N_C for acids Z—PO_3H_2 and their esters[a,b]

		—$PO(OH)_2$			—PO(OH)OR			—$PO(OR)_2$		
z—	N_c	DMSO	Water	Thol	DMSO	Water	Thol	DMSO	Water	Thol
Me—		26.5	29.8	28.4				33.2^{Me}	37.8^{Me}	33.2^{Me}
Et—		29.7	32.8	31.2	31.7^{Et} 32.1^{Th}	34.1^{Th}	32.5^{Th}	33.2^{Et}	37.0^{Et}	33.4^{Et}
COOH | CH_2—	α COOH	16.2	16.9	17.4	$18.6^{Th\,d}$		$19.0^{Th\,d}$	22.8^{Et}	23.89^{Et}	22.54^{Et}
	α COOR	15.1^{Th}		16.5^{Th}	17.7^{Th}		18.1^{Th}	21.5^{Th}		
COOH | CH_2	β COOH	26.2	28.4	28.4	29.0^{Me} 29.0^{Th}	31.4^{Me}	29.9^{Me} $29.9^{Th\,d}$	33.4^{Me} 30.7^{Et}	36.4^{Me}	33.7^{Me} 31.1^{Et}
CH_2—	β COOR[c]	25.6^{Me} 25.7^{Et} 25.5^{Th}		27.9^{Me} 27.9^{Th}	28.5^{Me} 28.5^{Th}		29.4^{Me} 29.4^{Th}	33.0^{Me} 30.4^{Et}	35.9^{Me} 33.0^{Et}	33.2^{Me} 30.6^{Et}
COOH |	α,β COOH	17.1	16.5	19.5	19.3^{Th}		21.5^{Th}			
CH_2	α COOR	16.0^{Th}		18.5^{Th}	$18.3^{Th\,d}$		$20.4^{Th\,d}$			
CH—	β COOR	16.5^{Th}		19.1^{Th}	$18.8^{Th\,d}$		$20.8^{Th\,d}$			
COOH	α,β COOR	15.5^{Th}		18.0^{Th}	$17.7^{Th\,d}$		$20.0^{Th\,d}$	23.8^{Me} $21.6^{Th\,d}$	26.6^{Me}	24.1^{Me} $22.3^{Th\,d}$
COOH |	α,γ COOH	18.8			19.9^{Th}–21.0^{Th}					
$(CH_2)_2$	α COOR	$17.8^{Th\,d}$								
CH—	γ COOR	$18.7^{Th\,d}$			19.9^{Th}–21.0^{Th}					
COOH	α,γ COOR	$17.7^{Th\,d}$			19.9^{Th}–21.0^{Th}					
Anhydrides Z—PO(OR)—O—Z' Z = Et Z' = PO(OEt)(Et)								27.0		26.9
Z = Et Z' = C(O)Me								31.0		30.70

[a] Values of chemical shifts δ (ppm) from phosphoric acid as external reference.
[b] Thol: 2-tetrahydropyranylmethanol. R: methyl (Me), ethyl (Et) or 2-tetrahydropyranylmethyl (Th). For esters the nature of R is shown by the exponent.
[c] In mixtures close signals are clearly distinguishable for various R.
[d] Assignments from δ ^{31}P–structure correlations only.

Interestingly, the nature of the alkyl group is important for esters: shifts up to 2.5 ppm can be seen between ethyl and methyl diphosphontes (Table 1).

The spectra of related anhydrides (Table 1, bottom), which may be viewed as substituted disphosphonates, showed that ^{31}P was much shielded in their case.

Variation of $\delta(^{31}P)$ with framework

This variation, very important as expected, could prevent the application of the above rule in cases of mixtures of phosphonic acids (Table 1), which is not the case in our study. For example, δ varies from 16.2 to 29.2 ppm in DMSO for acids **1**.

Variation of $\delta(^{31}P)$ with solvent

In the present work, spectra were recorded in DMSO, water or **2** (Thol).

Table 3 shows that in most cases DMSO is the most shielding of the three solvents, while water is the most deshielding, with the exception of phosphonoacetic and -succinic acids **1a** and **1c**. On the other hand, Thol seems to line up with DMSO for diphosphonates and with water for acids, with the same exceptions as above.

The difference between DMSO and water may be ascribed to H-bonding, for which the former is a good acceptor and the latter a good donor. Both solvents are expected to behave in the same way neither towards phosphonates which are not H bond donors nor towards phosphonic acids, as is indeed the case with α-carboxylic phosphonic acids **1a** and **1b**, where a strong chelation can compete with intermolecular H-bonding.

The difference between water and Thol towards phosphonates might be ascribed to steric bulk which would impede H-bonding with Thol. Hence DMSO and Thol behave in the same way toward diphosphonates.

Further experiments, especially with monophosphonates, are necessary to confirm these interpretations.

Variation of $\delta(^{31}P)$ with acidity

As expected, a number of ^{31}P chemical shift values were considerably lowered in a basic medium, as observed for acids and monophosphonates (and not for diphosphonates), due to the formation of salts. The phosphorus nucleus is shielded by the oxanion's unbonded electrons (the increment can be as high as -6 to -8 ppm). Intermediate values of δ were found when OH functions were only partly neutralized, due to chemical equilibrium in solutions. As a result, the functions could not be recognized in a basic medium and we eventually had to acidify before analysing the reaction mixtures.

Actually, after careful examination, correlations could be established and used in acidic medium. Table 4 allows a comparison, for spectra recorded in acidic medium with and without added HCl, first of the variation Δ_{Δ}^{ac} of the chemical shift of a specific acid, then of the variation $\Delta_{\Delta}{}^{H}$ of the chemical shift difference between the acid and its esters. The result depends on the series. For phosphonosuccinic acid **1c**, acidification made no difference; for phosphonoacetic acid **1a** the observed variations were of the same order of magnitude: in both series the same correlation pertain. On the

Table 3. Variation of δ ^{31}P with solvent S for acids $Z—PO_3H_2$ 1 and their esters[a,b]. $\Delta\delta_s = \delta_s — \delta_{DMSO}$ solvent increment for a specific species in solvent S

		—PO(OH)$_2$			—PO(OH)OR			—PO(OR)$_2$		
		DMSO	Water	Thol	DMSO	Water	Thol	DMSO	Water	Thol
Z—	N_C	δ	$\Delta\delta_S$	$\Delta\delta_S$	$\Delta\delta_F$[c]	$\Delta\delta_S$	$\Delta\delta_S$	$\Delta\delta_F$[c]	$\Delta\delta_S$	$\Delta\delta_S$
Me—		26.7	3.3	1.9				6.7^{Me}	4.6^{Me}	0^{Me}
Et—		29.7	3.1	1.5	2.0^{Et} 2.4Th	2.0Th	0.4Th	3.8^{Et}	3.8^{Et}	0.2^{Et}
COOH | CH_2—	α COOH	16.2	0.7	1.2	2.4Th		0.4Th			
	α COOR	15.1Th		1.4Th	2.6Th		0.4Th	6.6^{Et} 6.4Th	1.1^{Et}	0.3^{Et}
COOH | CH_2	β COOH	26.2	2.2	2.2	2.8^{Me} 2.8Th	2.4^{Me}	0.9^{Me} 0.9Th	7.2^{Me} 4.5^{Et}	2.0^{Me}	0.3^{Me} 0.4^{Et}
| CH_2—	β COOR[c]	25.7^{Et} 25.6^{Me} 25.5Th		2.3^{Me} 2.4Th	2.8^{Me} 2.9Th		0.9^{Me} 0.9Th	4.2^{Et} 6.8^{Me}	2.6^{Et} 2.9^{Me}	0.2^{Et} 0.2^{Me}
COOH |	α,β COOH	17.1	−0.6	2.4	2.2Th		2.2Th			
CH_2	α COOR	16.0Th		2.5Th	2.3TH		2.1Th			
| CH—	β COOR	16.5Th		2.6Th	2.3Th		2.0Th			
| COOH	α,β COOR	15.5Th		2.5Th	2.2Th		2.3Th	4.5Th 6.7^{Me}	2.8^{Me}	0.7Th 0.3^{Me}

a Values (ppm) of chemcal shifts δ and solvent increment $\Delta\delta_S$ (all $\Delta\delta$ values are positive).
[b] For Z, S and N_C see Table 1. R and Thol: see Table 1, note b.
[c] For mono- and diphosphonates in DMSO (reference solvent) the *functional shifts* $\Delta\delta_F$ between esters and the corresponding acid *in DMSO* are indicated.

Table 4. Variation of δ ^{31}P with acidity for acids Z—PO_3H_2 1 and their esters[a,b,c] $\Delta\delta_H = \delta_{H\ species} - \delta_{H\ acid}$ functional acidity increment for a species with HCl added

		—PO(OH)$_2$			—PO(OH)OR)			—PO(OR)$_2$		
Z—	N_C	$\Delta\delta_{H^0}$ without HCl	$\Delta\delta_H$ with HCl	Δ_Δ^{ac}	$\Delta\delta_{H^0}$ without HCl	$\Delta\delta_H$ with HCl	Δ_Δ^H	$\Delta\delta_{H^0}$ without HCl	$\Delta\delta_H$ with HCl	Δ_Δ^H
COOH | CH_2—	α COOH	0	0	0.5	$+2.4^{Th,Et}$	$+2.0^{Et,Th}$	0.4			
	α COOR	−1.1	−1.3	0.2	$1.5^{Th,Et}$	$0.9^{Th,Et}$	0.6	6.6^{Et} 5.3^{Th}		
COOH | CH_2	β COOH	0	0	0.6–1	$2.75^{Th,Me}$	$1.65^{Th,Me}$	1.1			
| CH_2—	β COOR	$-0.65^{Th,Me}$	$-0.8^{Th,Me}$	0.15	$2.25^{Th,Me}$	$1.7^{Th,Me}$	0.55	6.8^{Me}	6.4^{Me}	0.4
								4.2^{Et}	4.0^{Et}	0.2
COOH | CH_2	α,β COOH	0	0	0.1	2.3					
| CH—	α or β COOR	-1.15^{Th}	-1.1^{Th}	⩽0.1	1.15^{Th}	1.0^{Th}	⩽0.1			
| COOH		-0.55^{Th}	-0.5^{Th}	⩽0.1	1.7^{Th}	1.7^{Th}	⩽0.1			
	α,β COOR	-1.6^{Th}	-1.7^{Th}	⩽0.1	0.5^{Th}	0.6^{Th}	⩽0.1	6.7^{Et}	6.7^{Et}	0

[a] Solvent: DMSO. Values (ppm) of functional acidity increments $\Delta\delta_H$ and variations of increments Δ_Δ. For values of δ without HCl, see Table 1.
[b] For Z, S and N_C see Table 1. R = Me, Et or Th: see Table 1, note b.
[c] H^0: without HCl added. For acids $\Delta\delta_H = 0$ and Δ_Δ^{ac} indicates the difference observed when HCl is added. For esters Δ_Δ^H indicates the variation of the functional shift between ester and acid due to addition of HCl: $\Delta_\Delta^H = \Delta\delta_H - \Delta\delta_{H^0}$ ($\Delta\delta_{H^0} = \Delta\delta_F$, see Tables 1 and 2).

contrary, for phosphonopropionic acid **1b** two different although close sets of values had to be used.

On the other hand, δ values of mono- and diphosphonates were not affected by the quantity of phosphonic acid present in the solutions.

In conclusion, the *functional rule* could be applied whatever the acidity, provided pertinent values were used.

Variation of δ(^{31}P) with the carboxylic neighbourhood

As we were involved in the esterification of phosphonocarboxylic acids, the evaluation of the effect of the carboxylic functions esterification on ^{31}P chemical shifts was of the utmost importance. Would the variations of δ values make unusable the above functional rule? Or would they be small but characteristic enough to become an analytical criteria? The question arose from a previous study[9] of polycarboxylic acids, esters and anhydrides whose ^{13}C chemical shift of C=O and adjacent alkyl could not be used as an analytical tool, due to variations which were of the same order of magnitude for functions and environment.

Table 5. Variation of δ ^{31}P with carboxylic neighbourhood N_C for acids Z—PO_3H_2 and their esters.[a,b] $\Delta\delta_{NC} = \delta_{(\alpha,\beta,\gamma)COOR} - \delta_{(\alpha,\beta,\gamma)COOH}$

	carboxylic neighbourhood increment for a specific species		
N_C	$-PO_3H_2$	—PO(OH)(OR)[b]	—PO(OR)$_2$[b]
α COOR	−1	−0.9	
β COOR	−0.6	−0.5	−0.5
γ COOR	−0.1		
α,β COOR	−1.6	−1.6	
α,γ COOR	−1.1		

[a] Average values (ppm) of $\Delta\delta_{NC}$ in DMSO or Thol. For δ values see Table 1.
[b] R = Me, Et, Th: see Table 1, note b.

The variations due to the esterification of the carboxylic function were deduced from Table 1. For monocarboxylic phosphonic acids **1a** and **1b**, related monophosponates and the only case studied for diphosphonates, the variations are characteristic of the relative positions of COOR and phosphorus, respectively −0.5 and −1 ppm (±0.1 ppm) for α and β positions. Although the esters were not all characterized by other methods, the additivity of the effect appeared clearly for phosphonosuccinic acid and its monophosphonates and led to assignments recorded on Table 1. The results can be extended to phosphonoglutaric acid provided a very small variation (−0.1 ppm) due to esterification in the γ position is taken for granted. Table 5 displays the average values.

In conclusion, the functional rule always applies and the carboxylic esterification is clearly observable. Thus the determination of percentages of esterification, which was one of the aims of our study, has been possible in all cases for the phosphonic function and, either precisely or at least within rather narrow limits, for carboxylic functions.[9]

These results could be extended to analyse the complicated pattern of esters of diols whose signals were assigned by means of the above correlations. Thus the reactivities of two alcohols viewed as simple models of the cellulose structure could be compared.[9]

EXPERIMENTAL

Spectra

^{1}H and ^{13}C spectra and ^{1}H-decoupled ^{31}P spectra were recorded at ambient temperature with a Bruker AM-300 spectrometer operating respectively at 300 and 75 MHz using TMS as internal standard and at 121.5

MHz using 85% phosphoric acid as external standard. For ^{31}P 30° pulses were used and spectra were acquired over 0.786 s (64 K). The spectra had a digital resolution of 0.32 Hz per point. For the precise determination of ^{31}P δ values, in each series the specific phosphonic acid was used as internal reference for its esters in a given solvent and as external reference for comparison between solvents. Phosphonopropionic acid in DMSO (δ = 26.2 ppm) was used as external reference for comparison between series. Concentrations of phosphonic derivatives were about 0.2 mol l^{-1}; no significative variations were observed when concentrations varied from 0.1 to 0.4 mol l^{-1}. For spectra recorded with HCl, 4–12 drops of concentrated acid were added in a 2 ml volume.

Compounds

Ethanephosphonic, methanephosphonic and the corresponding methyl or ethyl diphosphonates were commercially available. Phosphonopropionic acid **1b** and its fully esterified ethyl ester were commercially available. Other phosphonocarboxylic acids **1** and fully esterified methyl or ethyl phosphonocarboxylates were known and either kindly provided by Société Française Hoechst (**1a** and ethyl ester; **1b** and ethyl ester; **1c** and methyl ester; **1d**) or obtained by standard methods (**7b**, R = Me).[10] Known partial esters were obtained as described by selective esterification of acids, selective hydrolysis of full esters or hydrolysis or alcoholysis of anhydrides (**3a**, **4a**, R = Et;[12] **6a**, R = Et;[13] **3b**, R = Et;[14] **4b**, R = Me, Et;[11] **6b**, R = Me, Et).[11,15] Ethyl ethanepyrophosphonate and acetoxyphosphonate (Table 1, bottom) were obtained as reported.[16] As yet unrecorded NMR data of the above known acids and esters are reported at the end of the Experimental (see 'Miscellaneous').

^{31}P δ values, established as discussed, are displayed in Table 1.

Methyl 3-phosphonopropanoate 3b (R = Me). 3-Phosphonopropanoic acid (23 mmol, 3.5 g) and methanol (20 ml) were stirred for 20 min with acetyl chloride (1.6 ml) at room temperature. After evaporation of solvents, white crystals were obtaind (pF 99–101 °C, quantitative yield). IR (cm^{-1}): 3000–2200, 1734, 1257, 1200–1000. NMR (ppm, DMSO) ^{1}H: 1.76–1.87 (m, 2H); 2.43–2.52 (m, 2H); 3.60 (s, 3H); 10.58 (s, OH). ^{13}C: 22.75 (CH_2, J_{CP} = 139.2 Hz); 27.45 (CH_2, J_{CP} = 3.2 Hz); 51.50 (CH_3); 172.46 (C=O, J_{CP} = 17.9 Hz). ^{31}P: 25.6.

The ethyl homologous carboxylate[14] was obtained as 60% of a mixture containing 40% of the remaining acid and spectra were recorded without isolation (δ ^{31}P: 25.7 ppm).

3-Diethoxyphosphorylpropanoic acid 6b (R = Et[11,15]). Ethyl 3-diethoxyphosphorylpropanoate (4.2 mmol, 1 g), THF (5 ml) and aqueous potassium hydroxide (4.2 mmol of a 8.4 M solution) were stirred 15 h at room temperature. After evaporation, dissolution in a $KHSO_4$ saturated solution, extraction with ethyl acetate, drying and evaporation, the expected diester was obtained mixed with 30% of the remaining known triester (total yield 0.9 g). IR (cm^{-1}): 3410, 1730, 1250, 1050. NMR (ppm, DMSO) ^{1}H: 1.23 (t, J_{HH} = 7.1 Hz, 6H) 1.90–2.04 (m, 2H); 2.35–2.49 (m, 2H); 3.98 (q, J_{HH} = 7.1 Hz, 4H). ^{13}C: 16.18 (CH_3, d, J_{CP} = 5.7 Hz); 20.17 (CH_2, d, J_{CP} = 141.9 Hz); 27.06 (CH_2, d, J_{CP} = 3.9 Hz); 61.09 (CH_2, d, J_{CP} = 6.2 Hz); 172.98 (C=O, d, J_{CP} = 16 Hz). ^{31}P: 30.7.

Under the same conditions the methyl homologous diphosphonate[11] was obtained in only 11% yield (δ ^{31}P: 33.0 ppm, DMSO).

3-Hydroxymethoxyphosphorylpropanoic acid 4b (R = Me).[11] When water was added to 2,5-dioxo-2-methoxy-1,2-oxaphospholane (prepared and distilled with 10% of methyl 3-dimethoxyphosphorylpropanoate as described,[17] NMR data *vide infra*) and spectra recorded, the monophosphonate was, as expected, the only species observed (90%) apart from the initially present triester (10%). NMR (ppm, D_2O) ^{1}H: 1.68–1.85 (m, 2H); 2.23–2.41 (m, 2H); 3.36 (d, J_{HP} = 10.9 Hz, 3H). ^{13}C: 20.62 (CH_2, d, J_{CP} = 140.1 Hz); 27.24 (CH_2, d, J_{CP} = 4.2 Hz); 52.69 (CH_3, d, J_{CP} = 6.1 Hz); 176.9 (C=O, d, J_{CP} = 16.4 Hz). ^{31}P: 31.4.

Methyl 3-hydroxymethoxyphosphorylpropanoate 5b (R = Me). 2,5-Dioxo-2-methoxy-1,2-oxaphospholane (11.1 mmol) and water (0.2 ml) were stirred for 2 h at room temperature. Methanol (10 ml) and acetyl chloride (0.9 ml) were added. After stirring for 20 h at room temperature and evaporating, the spectra showed the presence of the expected diester (50%) along with the known remaining carboxylate and triester. IR (cm^{-1}): 3400–2300, 1735–1710, 1180. NMR (ppm, DMSO) ^{13}C: 20.55 (CH_2, d, J_{CP} = 140.3 Hz); 27.07 (CH_2, d, J_{CP} = 3.6 Hz); 51.14 (CH_3, d, J_{CP} = 6 Hz); 51.4 (CH_3, s); 171.9 or 171.2 (C=O, d, J_{CP} = 16.2 or 16.99 Hz. ^{31}P: 28.5.

2'-Tetrahydropyranyl 3-phosphononopropanoate 3b (R = Th). 3-Phosphonopropanoic acid (4.2 mmol, 0.65 g), 2-tetrahydropyranylmethanol (10 ml) and acetyl chloride (0.3 ml) were stirred for 22 h at room temperature. Reactants in excess were distillated (0.7 mmHg) and the residue was analysed. The expected carboxylate (yield 83% from NMR) was obtained mixed with initial alcohol and the corresponding acetate. IR (cm^{-1}): 3400–2300, 1735, 1250. NMR (ppm, DMSO) ^{1}H: 1.08–1.24 (m, 1H); 1.37–1.54 (m, 4H); 1.74–1.89 (m, 2H); 2.42–2.51 (m, 2H); 3.19–3.49 (m, 2H); 3.82–3.86 (m, 1H); 3.90–3.95 (m, 2H); 9.1 (s, OH). ^{13}C: 22.52 (CH_2, s); 22.80 (CH_2, s): 22.82 (CH_2, d, J_{CP} = 139.4 Hz); 25.47 (CH_2, s); 27.60 (CH_2, d, J_{CP} = 3 Hz); 66.8 (CH_2, s); 67.3 (CH_2, s); 74.7 (CH, s); 171.9 (C=O, d, J_{CP} = 18.6 Hz). ^{31}P: 25.5.

A series of esters were obtained by esterification of acids **1** by alcohol **2**.

Typical procedure. Thol (32 mmol), acid (3.2 mmol) and eventually sodium hydride (3.2 mmol) were stirred for 5, 30 or 60 min at 180 °C. After vacuum distillation of excess Thol ($eb_{0.7}$ = 65 °C), solvent was added and spectra of esters were recorded (NMR: ppm solvent DMSO).

***3a, R = Th.** ^{31}P: 15.1. ^{1}H: 1.02–1.30 (m, 1H); 1.36–1.58 (m, 4H); 1.66–1.79 (m, 1H); 2.80 (d, J_{HP} = 21.3 Hz, 2H); 3.16–3.52 (m, 2H); 3.81–4.02 (m, 3H); 7.65 (s, OH). ^{13}C: 22.42 (CH_2, s); 25.39 (s, CH_2); 27.49 (CH_2, s); 36.24 (CH_2, d, J_{CP} = 125.5 Hz); 67.09 and 67.21 (CH_2, 2s); 74.58 (CH, s); 166.70 (C=O, d, J_{CP} = 6.4 Hz).

***5a, R = Th.** ^{31}P: 17.7. ^{1}H: 1.25 (m); 1.43–1.59 (m, 8H); 1.76 (m, 2H); 2.95 (d, J_{HP} = 21.2 Hz, 2H); 3.32–3.45 (m, 4H); 3.72–3.93 (m, 5H), 5.5 (s, OH). ^{13}C: 22.42 ($2CH_2$, s); 25.39 ($2CH_2$, s); 27.19 (CH_2, s); 27.42 (CH_2, s); 34.60 (CH_2, d, $J_{C,P}$ = 126.2 Hz); 67.21 (CH_2, s); 67.94 (CH_2, s); 74.55 (CH, s); 75.69 (CH, s); 166.31 (C=O, s).

***4b. R = Th.** ^{31}P: 29.0. ^{13}C: 173.28 (C=O, d, J_{CP} = 18.1 Hz).

***5b, R = Th.** ^{31}P: 28.5. ^{1}H: 1.05–1.28 (m, 2H); 1.44–1.69 (m, 8H); 1.76–1.95 (m, 4H); 2.40–2.50 (m, 2H); 3.20–3.52 (m, 4H); 3.74–3.97 (m, 5H); 8.03 (s, OH). ^{13}C: 21.13 (CH_2, d, J_{CP} = 140.2 Hz); 22.40 ($2CH_2$, s); 25.36 (CH_2, s); 25.41 (CH_2, s); 27.13 (CH_2, s); 27.25 (CH_2, d, J_{CP} = 3 Hz); 27.39 (CH_2, s); 66.94 (CH_2, d, J_{CP} = 2.4 Hz); 67.17 ($2CH_2$, s); 67.25 ($2CH_2$, s); 74.60 (CH, s); 75.78 (CH, d, J_{CP} = 6.4 Hz); 171.75 (C=O, d, J_{CP} = 17.8 Hz).

***Esters of 1c, R = Th**

α-Carboxylate. ^{31}P: 16.0. ^{13}C: 169.0 (C=O, d, J_{CP} = 5.8 Hz); 172.5 (C=O, d, J_{CP} = 19.2 Hz).

β-Carboxylate. ^{31}P: 16.5. ^{13}C: 22.46 (CH_2, s); 25.40 (CH_2, s); 27.41 (CH_2, s); 31.70 (CH_2, s); 42.59 (CH, d, J_{CP} = 123.8 Hz); 67.06 (CH_2, s); 67.27 (CH_2, s); 74.64 (CH, s); 170.28 (C=O, d, J_{CP} = 5.3 Hz); 171.23 (C=O, d, J_{CP} = 19.4 Hz).

α, β-Dicarboxylate. ^{31}P: 15.5. ^{13}C: 22.40 ($2CH_2$, s); 25.35 ($2CH_2$, s); 27.04 (CH_2, s); 27.60 ($2CH_2$, s); 31.70 (CH_2, s); 42.61 (CH, d, J_{CP} = 122.8 Hz); 67.16–68.33 ($4CH_2$); 74.54 (CH, s); 74.51 (CH, s); 169.0 (C=O, d, J_{CP} = 5.6 Hz); 170.8 (C=O, d, J_{CP} = 18.8 Hz).

Monophosphonate α,β-dicarboxylate. ^{31}P: 17.7. ^{13}C: 22.44 ($3CH_2$, s); 25.38 ($3CH_2$, s); 27.04–27.60 ($3CH_2$, s + 2d). 31.74 (CH_2, s); 41.31 (CH, d, J_{CP} = 125.3 Hz); 41.23 (CH, d, J_{CP} = 125.0 Hz); 67.07–68.30 ($6CH_2$); 75.78 and 74.55 (3CH, 2s); 168.6 (C=O, d, J_{CP} = 5.5 Hz); 170.6 (C=O, d, J_{CP} = 15.5 Hz).

***Esters of 1d, R = Th**

α-Carboxylate. ^{31}P: 17.8. ^{13}C: 169.44 (C=O, d, J_{CP} = 5.0 Hz); 173.65 (C=O, s).

γ-Carboxylate. ^{31}P: 18.7. ^{13}C: 22.46 (CH_2, s); 22.58 (CH_2, s); 25.40 (CH_2, s); 27.51 (CH_2, s); 31.74 (CH_2, d, J_{CP} = 13.9 Hz); 45.55 (CH, d, J_{CP} = 124.9 Hz); 66.68 (CH_2, s); 67.23 (CH_2, s); 74.68 (CH, s); 170.8 (C=O, d, J_{CP} = 5.1 Hz); 172.1 (C=O, s).

α,γ-Carboxylate. ^{31}P: 17.7. ^{13}C: 22.46 ($2CH_2$, s); 22.62 (CH_2, s); 25.39 ($2CH_2$, s); 27.42 ($2CH_2$, s); 31.75 (CH_2, d, J_{CP} = 13.9 Hz); 45.58 (CH, d, J_{CP} = 124.9 Hz); 66.93–67.29 ($4CH_2$); 74.68 (CH, s); 169.43 (C=O, d, J_{CP} = 5.0 Hz); 172.05 (C=O, s).

Miscellaneous NMR data (ppm, solvent DMSO except otherwise indicated)

**Ethanephosphonic acid.* ^{31}P: 29.7. ^{1}H: 1.02 (t × d, J_{HP} = 19.1 Hz, J_{HH} = 7.6 Hz, 3H); 1.52 (q × d, J_{HP} = 25.5 Hz, J_{HH} = 7.6 Hz, 2H); 10.4 (s, OH). ^{13}C: 6.92 (CH_3, d, J_{CP} = 6.2 Hz); 20.21 (CH_2, d, J_{CP} = 138.9 Hz).

Phosphonoacetic acid* ***1a.* ^{31}P: 16.2. ^{1}H: 2.88 (d, J_{HP} = 21.3 Hz, 1H); 2.89 (d, J_{HP} = 21.2 Hz, 1H). ^{13}C: 37.5 (CH_2, d, J_{CP} = 125.0 Hz); 173.2 (C=O, d, J_{CP} = 6.0 Hz).

Phosphonopropionic acid* ***1b.* ^{31}P: 26.2. ^{1}H: 1.69–1.81 (m, 2H); 2.33–2.42 (m, 2H); 9.92 (s, OH), ^{13}C: 22.6 (CH_2, d, J_{CP} = 138 Hz); 27.5 (CH_2, d, J_{CP} = 3 Hz); 173.2 (C=O, d, J_{CP} = 18 Hz).

Phosphonosuccinic acid* ***1c.* ^{31}P: 17.1. ^{1}H: 2.55 (d × d × d, J_{HP} = 8.8 Hz, J_{HH} = 17.4 Hz and 3.1 Hz, 1H); 2.75 (d × d × d, J_{HP} = 6 Hz, J_{HH} = 11.6 Hz and 17.4 Hz, 1H); 3.0 (d × d × d, J_{HP} = 23.5 Hz, J_{HH} = 11.6 Hz and 3.1 Hz, 1H); 8.8 (s, OH). ^{13}C: 31.8 (CH_2, s); 42.7 (CH, d, J_{CP} = 123.4 Hz); 170.2 (C=O, d, J_{CP} = 5.3 Hz); 172.6 (C=O, d, J_{CP} = 18.9 Hz).

Phosphonoglutaric acid* ***1d.* ^{31}P: 18.8. ^{1}H: 1.94 (m, 2H); 2.22 (d × d, J_{HH} = 16.4 Hz and 7.5 Hz, 1H); 2.32 (d × d, J_{HH} = 16.4 Hz and 7.4 Hz, 1H); 2.72 (d × t, J_{HP} = 23.0 Hz, J_{HH} = 7.4 Hz, 1H); 10.69 (s, OH). ^{13}C: 22.5 (CH_2, d, J_{CP} = 3.6 Hz); 32.06 (CH_2, d, J_{CP} = 14.1 Hz); 45.62 (CH, d, J_{CP} = 124.9 Hz); 170.8 (C=O, d, J_{CP} = 5.1 Hz); 173.7 (C=O, s).

Ester* ***7b.* R = Me: ^{31}P: 33.0. ^{1}H = 2.03 (t × d, J_{HH} = 7.5 Hz, J_{HP} = 20 Hz, 2H); 2.50 (t × d, J_{HH} = 7.5 Hz, J_{HP} = 13.6 Hz, 2H); 3.61 (d, J_{HP} = 1 Hz, 3H); 3.62 (s, 3H); 3.65 (d, J_{HP} = 1 Hz, 3H). ^{13}C: 19.11 (CH_2, d, J_{CP} = 141.6 Hz); 26.84 (CH_2, d, J_{CP} = 3.8 Hz); 51.73 (CH_3, s); 52.19 ($2CH_3$, d, J_{CP} = 6.3 Hz); 172.11 (C=O, d, J_{CP} = 16.4 Hz). Mass spectrum (*m/e*, %): 196 (M^+: 100), 161 (1); 164 (32); 137 (38); 110 (68); 109 (59); 105 (10); 93 (28); 87 (17); 80 (21); 79 (53); 59 (11); 55 (84); 47 (20); 31 (10); 28 (20); 27 (19).

Ester* ***4b.* R = Et, sodium salt (D_2O): ^{31}P: 29.20. ^{1}H: 1.21 (t, J_{HH} = 6.4 Hz, 3H); 1.83–194 (m, 2H); 2.34–2.42 (m, 2H); 3.60 (d, J_{HP} = 10.3 Hz, 3H). ^{13}C: 25.15 (CH_2, d, J_{CP} = 135.0 Hz); 34.04 (CH_2, d, J_{CP} = 4.0 Hz); 54.19 (CH_3, d, J_{CP} = 5.6 Hz); 184.84 (C=O, d, J_{CP} = 19.0 Hz).

Ester* ***4b.* R = Me, sodium salt (D_2O): ^{31}P: 27.7. ^{1}H: 1.21 (t, J_{HH} = 6.4 Hz, 3H); 1.72–1.83 (m, 2H); 2.06–2.43 (m, 2H); 3.84–3.99 (m, 2H). ^{13}C: 16.01 (CH_3, s); 23.28 (CH_2, d, J_{CP} = 135.2 Hz); 31.38 (CH_2, s); 60.73 (CH_2, s); 182.2 (C=O, d, J_{CP} = 19.5 Hz).

**Ethyl ethanemonophosphonate.* ^{31}P: 31.7. ^{1}H: 1.02 (t × d, J_{HP} = 19.3 Hz, J_{HH} = 7.6 Hz, 3H); 1.21 (t, J_{HH} = 7.0 Hz, 3H); 1.60 (q × d, J_{HP} = 17.5 Hz, J_{HH} = 7.6 Hz, 2H); 3.93 (d × q, J_{HP} = 14.6 Hz, J_{HH} = 7.0, 2H); 6.36 (s, OH). ^{13}C: 6.70 (CH_3, d, J_{CP} = 6.4 Hz); 16.37 (CH_3, d, J_{CP} = 6.0 Hz); 18.83 (CH_2, d, J_{CP} = 139.4 Hz); 60.0 (CH_2, d, J_{CP} = 5.9 Hz).

**2-Tetrahydropyranyl ethanemonophosphonate.* ^{31}P: 32.1. ^{1}H: 1.01 (t × d, J_{HP} = 18.9 Hz, J_{HH} = 7.7 Hz, 3H); 1.13–1.78 (m, 8H); 3.33 (m, 2H); 3.75 (d × d, J_{HP} = 7.1 Hz, J_{HH} = 5.2 Hz, 1H); 3.81–3.88 (m, 2H); 7.98 (s, OH), ^{13}C: 6.68 (CH_3, d, J_{CP} = 6.5 Hz); 18.67 (CH_2, d, J_{CP} = 139.6 Hz); 22.44 (CH_2, s); 25.48 (CH_2, s); 27.31 (CH_2, s); 66.91 (CH_2, d, J_{CP} = 5.9 Hz); 67.18 (CH_2, s); 75.88 (CH, d, J_{CP} = 6.6 Hz).

**Diethyl ethanepyrophosphonate.* IR: 1270, 1050, 950. ^{31}P: 27.0 (d). ^{1}H: 1.01 (t × d, J_{HP} = 10.4 Hz, J_{HH} = 7.6 Hz, 6H); 1.27 (t, J_{HH} = 7.0 Hz, 6H); 1.91 (q × d, J_{HH} = J_{HP} = 18.0 Hz, 4H); 4.13 (m, 4H). ^{13}C: 6.05 ($2CH_3$, s + d, J_{CP} = 7.0 Hz); 15.88 ($2CH_3$, s + d, J_{CP} = 6.0 Hz); 19.2 ($2CH_2$, d, J_{CP} = 148.4 Hz and d × d, J_{CP} = 148.4 Hz, J_{CP} = 6.1 Hz); 61.92 ($2CH_2$, d × d, J_{CP} = 51 Hz, J_{CP} = 3.3).

**Diethyl acetoxyphosphonate.* IR: 1760, 1270, 1050. ^{31}P: 31.0. ^{1}H: 1.08 (t × d, J_{HP} = 15.9 Hz, J_{HH} = 7.7 Hz, 3H); 1.26 (t, J_{HH} = 7.1 Hz, 3H); 1.92 (q × d, J_{HP} = 8.9, J_{HH} = 7.7 Hz, 2H); 2.20 (d, J_{HP} = 1.0 Hz, 3H); 4.06–4.21 (m, 2H). ^{13}C: 5.85 (CH_3, d, J_{CP} = 7.0 Hz); 15.88 (CH_3, d, J_{CP} = 6.0 Hz); 18.93 (CH_2, d, J_{CP} = 136.4 Hz); 21.77 (CH_3, d, J_{CP} = 4.3 Hz); 62.01 (CH_2, d, J_{CP} = 7.2 Hz); 166.26 (C=O, d, J_{CP} = 8.9 Hz).

**2,5-Dioxo-2-methoxy-1,2-oxaphospholane.* IR: 1810, 1735, 1260, 1050. ^{31}P: 42.2. ^{1}H: 2.35–2.55 (m, 2H); 3.04–3.15 (m, 2H); 3.80 (d, J_{HP} = 11.6 Hz, 3H). ^{13}C: 19.45 (CH_2, d, J_{CP} = 110.2 Hz); 30.94 (CH_2, d, J_{CP} = 7.5 Hz); 53.58 (CH_3, d, J_{CP} = 6.8 Hz); 167.38 (C=O, d, J_{CP} = 26.6 Hz).

REFERENCES

1. G. Mavel, *Prog. NMR Spectrosc.* **1**, 251 (1966).
2. M. M. Crutchfiels, C. H. Dungan, L. H. Letcher, V. Mark and J. R. Van Wazer, *Topics in Phosphorus Chemistry*, Vol. 5. Interscience, New York (1967).
3. G. Mavel, *Annual Reports on NMR Spectroscopy*, Vol. 5b, Academic Press, New York (1973).
4. D. G. Gorenstein, *Prog. NMR Spectrosc.* **16**, 1 (1983).
5. D. Wilhelm and I. Fietier, European Patent 0484196A1 (1992).
6. K. Troev, *Rev. Heteroatom Chem. (Tokyo)* **8**, 165 (1993).
7. J. Hahn, W. G. Bentrude, W. N. Setzer and L. D. Quin, *Phosphorous-31 NMR Spectroscopy in Stereochemical Analysis*, Vol. 8. Plenum, New York (1987).
8. G. A. Gray, *J. Am. Chem. Soc.* **93**, 2132 (1971).
9. S. Olagnon-Bourgeot, Thesis, Université Lyon I, France (1994).
10. A. N. Pudovik, *Zh. Obshch. Khim.* **22**, 473 (1952). A. N. Pudovik and I. V. Konovalova, *Synthesis* 81 (1979).
11. V. S. Tsivunin and N. I. D'yakonova, *Zhur. Obsch. Khim.* **40**, 1995 (1970).
12. P. Nylen, *Chem. Ber.* **57**, 1023 (1924).
13. P. Coutrot, M. Snoussi and P. Savignac, *Synthesis* 133 (1978). P. Savignac, M. Snoussi and P. Coutrot, *Synth. Commun.* **8**, 19 (1978).
14. P. Nylen, *Chem. Ber.* **59**, 1119 (1926).
15. T. Janecki and R. Bodalski, *Synthesis* 506 (1989).
16. D. G. Coe, B. J. Perry and R. K. Brown, *J. Chem. Soc.* 3604 (1957). A. N. Pudovik and A. A. Muratova, *Zh. Obshch. Khim.* **30**, 2624 (1960).
17. T. K. Gazizov, Y. M. Mareev, V. S. Vinogradova, A. N. Pudovik and B. A. Arbuzov, *Izv. Akad. Nauk SSSR*, Ser. Khim. no. 6, 1259 (1971).