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Michael addition reactions of ethenylidenebisphosphonates

David W. Hutchinson * and David M. Thornton

Department of Chemistry, University of Warwick, Coventry CV4 7AL (Great Britain)

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Abstract

Tetraethyl and tetraisopropyl ethenylidenebisphosphonates can undergo facile Michael-type addition reaction with nitrogen, phosphorus or sulphur nucleophiles (but not with oxygen or carbon nucleophiles) to give C-substituted methylenebisphosphonates. In the case of sulphur nucleophiles, the products can be readily isolated and de-esterified to give the corresponding bisphosphonic acids, which are potential inhibitors of the replication of influenza virus A.

Introduction

The conjugate addition of alkyl- and vinyl-copper complexes to diethyl ethenylphosphonate [1] occurs in good yield (70–90%) under mild conditions yielding C-substituted dialkyl phosphonates [2]. We now report that tetraalkyl ethenylidenebisphosphonates (**1**) [3] will react with nitrogen, phosphorus or sulphur nucleophiles at moderate temperatures to give high yields (ca. 90%) of addition products (C-substituted methylene bisphosphonates) (**3**) which may be of value as complexing agents for metals. No Michael addition could be observed with oxygen or carbon nucleophiles.

While C-alkylated methylenebisphosphonates can be synthesised by the alkylation of sodium, lithium, or thallium(I) salts of methylenebisphosphonates [4–6], direct alkylation is often not suitable for the preparation of methylenebisphosphonates with reactive groups attached to the central carbon atom. We believe that the Michael addition reactions described here can be used to prepare a wider range of C-substituted methylenebisphosphonates than has been available hitherto.

Although the products of the addition reaction are formed in almost quantitative yield (as inferred from ^{1}H or ^{31}P NMR measurements) when the ethenylidenebisphosphonate esters (**1**) are treated with nitrogen, sulphur or phosphorus

* To whom correspondence should be addressed.

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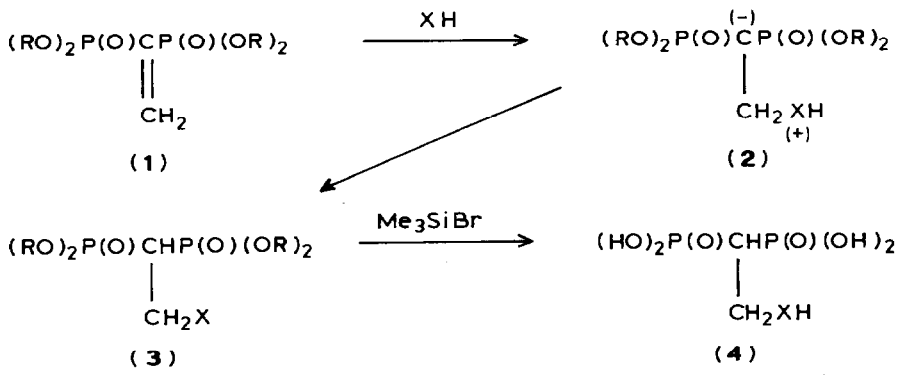

Scheme 1

nucleophiles in chloroform at 20–45 °C (Scheme 1), only the adducts formed from sulphur nucleophiles can be readily isolated. The sulphur adducts can easily be de-esterified with bromotrimethylsilane [7,8] and isolated as crystalline tris(cyclohexylammonium) salts of the C-substituted methylenebisphosphonic acids (**4**). The inhibitory effects of these acids on the RNA transcriptase of influenza virus A [9] is under investigation and will be reported elsewhere.

Results and discussion

While the Michael addition of nucleophiles to α,β-unsaturated carbonyl compounds is well known [10], the addition of nucleophiles to tetraalkyl ethenylidenebisphosphonates (**1**) has not been reported hitherto. By analogy to that involving unsaturated carbonyl compounds, our reaction probably proceeds via the formation of a zwitter-ion (**2**) in which the negative charge on the bridge carbon atom is stabilised by delocalisation over the two phosphoryl groups. We have observed by NMR spectroscopy that this type of addition in solution on a small scale with amines, thiols or phosphites gives quantitative yields of the adducts **3** (Table 1). Unlike amines and thiols, dialkyl phosphites only take part in the addition reaction in the presence of one equivalent of base (diisopropylamine) with the formation of a new carbon–phosphorus bond. There was no ^{31}P NMR evidence for P–O bond formation. When the Michael reactions were carried out on a 2 g scale, only minor side products could be detected by ^{31}P NMR spectroscopy in addition to starting material **1**. Reactions involving thiols gave fewer side products (as judged by ^{31}P NMR spectroscopy) than those involving amines or phosphites. For example, treatment of a solution of **1** (R = Et) with thiophenol for 24 h at 45 °C resulted in > 97% Michael addition (from ^{31}P NMR) (Table 2). We were unable to observe Michael addition reactions with oxygen nucleophiles under a variety of conditions. Water, methanol, phenol and acetic acid all failed to react with **1** (R = Et) over 72 h. Treatment of the latter with alkoxide or hydroxide ion led to de-esterification before Michael addition could be observed. The addition of water to **1** (R = Et) catalysed by a strong acid (20% DCl) did not take place over 72 h. We were also unable to observe addition reactions with carbon nucleophiles. Tetraisopropyl methylenebisphosphonate (both in the presence and absence of added base) failed to react with **1** (R = Et), possibly owing to steric hindrance at the central carbon atom of the

Table 1

Michael addition reactions of ethenylidenebisphosphonate tetraesters

Reactant [a]	Time (min) for complete reaction	^{31}P NMR chemical shift of adduct (ppm)	NH_3/CI (m/z) $(M^3+H)^+$
Tetraethyl ester			
Nitrogen nucleophiles			
Diethylamine	< 5	23.8	374
Morpholine	< 5	22.4	388
Imidazole	< 5	19.6	369
Cyclohexylamine	< 5	22.9	400
Aniline	12 h	22.0	394
Ethylenediamine [b]	< 5	22.6	661 [b]
2,2,6,6-Tetramethylpiperidine	No reaction after 72 h		
Diisopropylamine	No reaction after 72 h		
Sulphur nucleophiles			
Thiophenol	60	21.2	411
2-Mercaptoethanol	720	21.7	379
Ethanethiol	60	21.6	363
Propane-1-thiol	70	21.7	377
Dodecane-1-thiol	150	21.7	504
Phosphorus nucleophiles			
Diethyl phosphite	No reaction after 72 h		
Diethyl phosphite +	180	23.0d (J 26.9 Hz)	439
Diisopropylamine (1 equiv.)		28.7t (J 26.9 Hz)	
Diisopropyl phosphite	No reaction after 72 h		
Diisopropyl phosphite +		25.9dd (J 30.24 Hz)	467
Diisopropylamine (1 equiv.)		22.3d (J 30 Hz)	
		22.3d (J 24 Hz)	
Tetraisopropyl ester			
Nitrogen nucleophiles			
Diethylamine	< 5	21.2	430
Morpholine	< 5	20.5	444
Imidazole	< 5	17.5	425
Cyclohexylamine	< 5	20.9	457 [c]
Sulphur nucleophiles			
Thiophenol	240	19.2	468 [c]
2-Mercaptoethanol	40	19.7	435

[a] All reactions were carried out in $CDCl_3$ as described in the text. [b] Reaction at both amino groups. [c] The actual masses of the $(M+H)^+$ peaks are 456.5 and 467.5, respectively. The computer of the mass spectrometer records masses to the nearest integer.

methylenebisphosphonate. When **1** (R = Et) was treated with butyllithium, a number of products were formed, but none had the NMR characteristics of a Michael adduct. The Michael Reaction is, in principle, reversible [10,11] and when X was a good leaving group, we found that the adduct was too unstable to be isolated by distillation or chromatography. In these cases ready elimination of XH occurred, with regeneration of the starting material **1**. For example, flash chromatography of tetraethyl C-(diethylamino)methyl methylenebisphosphonate on silica followed by evaporation of the eluate fractions gave an almost quantitative yield of **1** (R = Et).

Table 2

Preparative scale (2 g) Michael addition reactions of tetraethyl ethenylidenebisphosphonate (isolated yields are given in parentheses; all reactions were allowed to proceed for 24 h.)

Reactant	Temperature (°C)	% by ^{31}P NMR (162.0 MHz)		
		Starting Material	Michael Addition	Others
$(C_2H_5)_2NH$	20	3	94	3
C_6H_5SH	45	2	97 (91)	1
$C_{12}H_{25}SH$	45	3	97 (92)	0
$(C_2H_5O)_2POH$	45	3	92	5

The comparative stability of the Michael adducts formed between **1** and thiols may be due to the greater stability of the zwitter ions **2** which would inhibit the reverse reaction. Differences in the stabilities of the adducts could readily be demonstrated by ^1H NMR spectroscopy. When C-(thiophenyl)methyl methylenebisphosphonate was dissolved in methanol-d_4 there was no change in the NMR spectrum at room temperature during 24 h. On the other hand, when C-(diethylamino)methyl methylenebisphosphonate was dissolved in methanol-d_4 rapid exchange of the proton on the bridge carbon atom occurred, and this was confirmed by mass spectrometric analysis of the methanolic solution. As might be expected, the rates of exchange and elimination were slower in a non-polar solvent (deuterated chloroform) than in a polar solvent (deuterated methanol). When the reaction between **1** (R = Et) and aniline was carried out in chloroform, it required 400 min for completion, whereas in methanol the addition was over in 30 min (Table 3).

The effect of the basicity of the attacking nucleophile was examined with a series of 4-substituted anilines. Basic anilines with a high pK_a for their conjugate acid e.g. 4-methoxyaniline (pK_a 5.3) were found to react rapidly with **1**. On the other hand, anilines with low basicity and a low pK_a for their conjugate acid e.g. 4-nitroaniline (pK_a 1.0) reacted very slowly with **1** in methanol. Thus, the presence of a high electron density on the nitrogen atom of the attacking nucleophile is an important factor in determining the rate of these additions.

Thiols were found to add to **1** only slowly in chloroform solution, but the reactions were extremely clean and gave high yields. The products were colourless oils, and could easily be separated from excess thiol or traces of starting material by chromatography on silica. The tetraisopropyl ester **1** (R = i-Pr) reacted more slowly

Table 3

Effect of basicity of aromatic amines on the rate of Michael addition reactions of tetraethyl ethenylidenebisphosphonate

$4\text{-}XC_6H_4NH_2$ X =	pK_a	Solvent	Time for complete reaction
OCH_3	5.3	MeOH-d_4	< 5 min
H	4.3	$CDCl_3$	400 min
H	4.3	MeOH-d_4	27 min
Br	3.8	MeOH-d_4	220 min
NO_2	1.0	MeOH-d_4	90 h

with sulphur nucleophiles than **1** (R = Et) presumably owing to greater steric hindrance.

Hydrolysis of the bisphosphonate adducts **3** (X = SR) by concentrated hydrochloric acid [12] does not give good yields of the corresponding acids **4** (X = SR), but treatment of these compounds with bromotrimethylsilane followed by hydrolysis of the resulting tetra(trimethylsilyl) esters with aqueous methanol gave the free acids **4** (X = SR) in good yield [7,8]. In each case, the crude free acid was treated with an excess of cyclohexylamine in methanol to yield the tris(cyclohexylammonium) salt which was purified by recrystallisation.

Experimental

Unless otherwise stated, all NMR spectra were recorded for solutions in $CDCl_3$. ^1H NMR spectra were recorded at 220 MHz on a Perkin–Elmer R34 spectrometer with tetramethylsilane (TMS) as internal reference. ^{31}P NMR spectra were recorded at 36.43 MHz on a Bruker WH90 spectrometer or at 162.0 MHz on a Bruker WH400 spectrometer. With both instruments, 85% H_3PO_4 was used as external reference (downfield shifts positive). ^{13}C NMR spectra were recorded at 100.62 MHz on a Bruker WH400 spectrometer with TMS as external reference. Broad band decoupling was employed for all ^{31}P and ^{13}C NMR spectra. All chemical shifts are expressed in ppm and all coupling constants are expressed in Hz.

Electron impact and ammonia chemical ionisation [13] mass spectra were recorded on an MS80 mass spectrometer fitted with a DS55 data system (Kratos Analytical Instruments Ltd).

Syntheses of phosphonates

(a) Tetraethyl ethenylidenebisphosphonate (1, R = Et). This was prepared as described by Degenhardt and Burdsall [3] in 65% yield as a colourless oil, b.p. 120–121°C (0.2 mmHg); δ(H) 1.32 (12Ht, *J*(HH) 7.1), 4.12 (8Hm), 6.97 (2Hdd, *J*(HP) 33.8, *J*(HP) 37.8); δ(^{31}P) 13.0 (s) ($CDCl_3$); δ(^{13}C) 148.5 (s), 131.5 (t) (*J*(CP) 166.6), 62.0 (t) (*J* 2.8), 15.7 (t) (*J* 3.3). NH_3/CI $m/z = 301$ $(M + H)^+$, 319 $(M + NH_4)^+$. EI accurate mass $M^{+\cdot}$ calc. for $C_{10}H_{22}O_6P_2$ 301.0970, found 301.0970.

(b) Tetraisopropyl ethenylidenebisphosphonate (1, R = i-Pr). This was prepared in an analogous manner to **1** (R = Et) except that in the first stage of the preparation the mixture was heated for 11 days. Vacuum distillation at the end of the preparation gave **1** (R = i-Pr) as a colourless oil in 33% yield, b.p. 114–115°C (0.15 mmHg), ^1H NMR δ 1.35 (24Hdd, *J* 6.1, *J* 7.2), 4.75 (4Hm), 6.96 (2Hdd, *J*(HP) 38.3, *J*(HP) 34.4); ^{31}P δ 11.3(s). NH_3/CI $m/z = 357$ $(M + H)^+$. Accurate mass $(M + H)^+$, calc. for $C_{14}H_{31}O_6P_2$ 357.1637, found 357.1641.

Michael addition reactions

(a) NMR scale experiments

To tetraethyl ethenylidenebisphosphonate (75 mg, 0.25 mmol) in $CDCl_3$ (250 μl) was added a solution of diethylamine (0.45 mmol) in $CDCl_3$ (250 μl). After rapid mixing, the solution was kept at 45°C and the progress of the reaction followed by ^1H NMR spectroscopy. When no further change in the ^1H NMR spectrum could be

detected, the ^{31}P NMR spectrum was recorded. The solvent was removed by blowing nitrogen through the solution and the ammonia CI mass spectrum of the residue was recorded. A similar procedure was used for other Michael addition reactions except that when dialkyl phosphites were used as nucleophiles, one equivalent of diisopropylamine was added.

(b) Preparative scale reactions

Tetraethyl C-(thioalkyl)methyl methylenebisphosphonates (3, R = Et; X = SR) (general procedure). The alkanethiol (2 equiv., 13.3×10^{-3} mol) * was added by syringe to a solution of **1** (R = Et) (2.0 g, 6.66×10^{-3} mol) in freshly distilled $CHCl_3$ (15 cm^3). The solution was kept at 40 °C for 24 h, after which no starting material could be detected by TLC on silica. Removal of solvent in vacuo yielded a colourless oil, which was purified by flash chromatography on silica, with methanol/diethyl ether (1/20 v/v) as eluant to give **3** (R = Et; X = SR) in ≈ 90% yield. The characteristics of the Michael adducts are given below.

(c) De-esterification procedures

Tris(cyclohexylammonium) C-(thioalkyl)methyl methylenebisphosphonates (4, X = SR). The bisphosphonate esters **3** (R = Et, X = SR) (0.5 g) were treated with bromotrimethylsilane (2.5 molar excess) at room temperature for 60 h, then the solvent was removed in vacuo, the residue shaken with water (5 cm^3) and freeze-dried to yield a colourless oil. This was dissolved in methanol (10 cm^3) and an excess of cyclohexylamine added. The resulting precipitate was recrystallised from methanol/water (2/1)/diethyl ether to give the tris(cyclohexylammonium) salts of **4** (X = SR) in 66% yield. The characteristics of these salts are given below.

(d) Characteristics of ester adducts

Tetraethyl C-(thioethyl)methyl methylenebisphosphonate (3, R = Et, X = SEt). ^1H NMR δ 1.30 (3Ht, J(HH) 7.8), 1.40 (12Ht, J(HH) 7.2), 2.63 (2Hq, J(HH) 7.8), 2.64 (1Htt, J(HH) 5.8, J(HP) 29.8), 3.11 (2Htd, J(HH) 5.8, J(HP) 17.2), 4.27 (8Hm, J(HH) 7.2, J(HP) 7.2); ^{31}P NMR δ 21.65 (s). NH_3/CI m/z 363 $(M + H)^+$. Analysis: Found, C, 39.51; H, 7.93; S, 8.53; P, 15.09. $C_{12}H_{28}O_6P_2S$ calc.: C, 39.78; H, 7.79; S, 8.85; P, 17.10%.

Tetraethyl C-(thio-1-propyl)methyl methylenebisphosphonate (3, R = Et, X = n-Pr). ^1H NMR δ 1.00 (3Ht, J(HH) 7.8), 1.38 (12Ht, J(HH) 7.5), 1.64 (2Hm, J(HH) 7.8), 2.56 (2Ht, J(HH) 7.8), 2.57 (1Htt, J(HH) 6.4, J(HP) 25.6), 3.08 (2Htd, J(HH) 6.4, J(HP) 16.7), 4.23 (8Hm, J(HH) 7.5, J(HP) 7.5); ^{31}P NMR δ 21.7(s). NH_3/CI m/z 377 $(M + H)^+$. Analysis: Found: C, 40.83; H, 8.13; S, 7.95; P, 15.04. $C_{13}H_{30}O_6P_2S$ calc.: C, 41.48; H, 8.03; S, 8.52; P, 16.46%.

Tetraethyl C-(thio-1-dodecyl)methyl methylenebisphosphonate (3, R = Et, X = $SC_{12}H_{25}$). ^1H NMR δ 0.90 (3Ht, J(HH) 6.4), 1.28 (18Hm), 1.46 (12Ht, J(HH) 7.2), 1.60 (2Hm), 2.57 (2Ht, J(HH) 7.2), 2.60 (1Htt, J(HH) 6.4, J(HP) 24.4), 3.06 (2Hdt, J(HH) 6.4, J(HP) 16.7), 4.22 (8Hm, J(HH) 7.2, J(HP) 7.2). ^{31}P NMR δ 21.7 (s). NH_3/CI m/z 504 $(M + H)^+$. Analysis; Found: C, 52.35; H, 9.63; S, 6.24; P, 11.86. $C_{22}H_{48}O_6P_2S$ calc.: C, 52.58; H, 9.63; S, 6.38; P, 12.32%.

* Owing to the low boiling point (35 °C) of ethanethiol, 8 equivalents were added.

Tetraethyl C-(thiophenyl)methyl methylenebisphosphonate (3, R = Et, X = SPh). ^{1}H NMR δ 1.35 (12Htd, J(HH) 7.5, J 2.8), 2.67 (1Htt, J(HH) 5.8, J(HP) 24.4), 3.48 (2Htd, J(HH) 5.8, J(HP) 15.8), 4.22 (8Hm, J(HH) 7.5, J(HP) 7.5), 7.20–7.50 (5Hm). ^{31}P NMR δ 21.2 (s). ^{13}C NMR δ 15.9 (d, J 6.1), 29.8 (t, J 4.6), 37.6 (t, J(CP) 131.2), 62.3 (dd, J 6.4, J 18.2), 126.2 (s), 128.6 (s), 129.6 (s), 135.2 (s). NH_3/CI m/z 411 $(M + H)^+$. Analysis; Found: C, 46.54; H, 7.02; P, 14.10; S, 7.29. $C_{16}H_{28}O_6P_2S$ calc.: C, 46.83; H, 6.88; P, 15.09; S, 7.81%.

(e) Characteristics of tris(cyclohexylammonium) salts of the bisphosphonic acids (3)

Unless otherwise stated, all NMR spectra were measured for the salts in solution in D_2O. All the ^{1}H NMR spectra contained peaks due to cyclohexylammonium residues at 1.10–1.50 (5Hm), 1.65 (1Hm), 1.80 (2Hm), 2.00 (2 Hm) and 3.15 (1Hm) in addition to the peaks mentioned below.

Ethenylidene bisphosphonate. ^{1}H NMR δ 6.22 (2Hdd, J(HP) 33.3, J(HP) 35.6), ^{31}P NMR δ 11.7 (s). Analysis: Found: C, 49.37; H, 9.12; P, 11.90; N, 8.00. $C_{20}H_{45}N_3O_6P_2$ calc.: C, 49.57; H, 9.15; P, 12.79; N, 8.67%.

C-(Thioethyl)methyl methylenebisphosphonate (4, X = SC_2H_5). ^{1}H NMR δ 1.25 (3Ht, J(HH) 7.6), 2.08 (1Htt, J(HH) 7.5, J(HP) 21.1), 2.62 (2Hq, J(HH) 7.6), 2.98 (2Htd, J(HH) 7.8, J(HP) 17.2), ^{31}P NMR δ 18.0(s). Analysis: Found: C, 47.54; H, 8.98; N, 7.72; P, 11.08; S, 5.49. $C_{22}H_{51}N_3O_6P_2S$ calc.: C, 48.25; H, 9.39; N, 7.67; P, 11.31; S, 5.85%.

C-(Thio-1-propyl)methyl methylenebisphosphonate (4, X = SC_3H_7). ^{1}H NMR δ 0.98 (3Ht, J(HH) 7.5), 1.65 (2Hm, J(HH) 7.8, J(HH) 7.5), 2.06 (1Htt, J(HH) 7.8, J(HP) 22.2), 2.60 (2Ht, J(HH) 7.8), 3.00 (2Htd, J(HH) 7.8, J(HP) 16.0), ^{31}P NMR δ 18.0(s). Analysis: Found: C, 49.16; H, 9.23; N, 7.61; P, 10.63; S, 5.60. $C_{23}H_{53}N_3O_6P_2S$ calc.: C, 49.18; H, 9.51; N, 7.48; P, 11.03; S, 5.71%.

C-(Thiophenyl)methyl methylenebisphosphonate (4, X = SC_6H_5). ^{1}H NMR δ 2.16 (1Htt, J(HH) 7.2, J(HP) 20.0), 3.44 (2Htd, J(HH) 7.2, J(HP) 15.6), 7.25–7.55 (5Hm), ^{31}P NMR δ 18.0(s). Analysis: Found: C, 52.26; H, 8.67; N, 6.78; P, 9.96; S, 5.14. $C_{27}H_{51}N_3O_6P_2S$ calc.: C, 53.36; H, 8.46; N, 6.91; P, 10.19; S, 5.28%.

C-(Thio-1-dodecyl)methyl methylenebisphosphonate (4, X = $SC_{12}H_{25}$). NMR spectra were recorded in solution in 80% MeOH-d_4/16% D_2O/4% DCl. ^{1}H NMR δ 0.90 (3Ht, J(HH) 6.9), 1.30 (18Hm), 1.65 (2Hm), 2.58 (1Htt, J(HH) 6.7, J(HP) 23.3), 2.63 (2Ht, J(HH) 6.9), 3.06 (2Htd, J(HH) 6.7, J(HP) 16.7), ^{31}P NMR δ 19.6 (broad s). Analysis: Found: C, 55.58; H, 10.16; N, 6.17; P, 8.93; S, 4.43. $C_{32}H_{71}N_3O_6P_2S$ calc.: C, 55.87; H, 10.40; N, 6.11; P, 9.00; S, 4.66%.

Ethenylidene bisphosphonic acid. ^{1}H NMR δ 6.67 (2Hdd, J(HP) 35.6, J(HP) 37.8), lit. [3] δ 6.44 (2Ht, J 36.1), ^{31}P NMR δ 12.5 (s), lit. [3] δ 11.1. Analysis: Found: C, 12.59; H, 3.44. $C_2H_6O_6P_2$ calc.: C, 12.78; H, 3.22%.

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