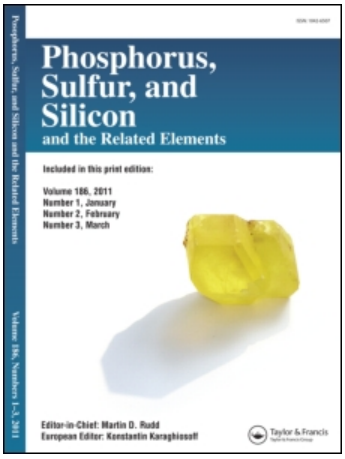

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CHARACTERIZATION AND PROPERTIES OF SOME DIALKYL-1-(*N,N*-DIALKYLAMINO)-ALKYLPHOSPHONATES AND THEIR HYDROCHLORIDE SALTS

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CHARACTERIZATION AND PROPERTIES OF SOME DIALKYL-1-(*N*,*N*-DIALKYLAMINO)-ALKYLPHOSPHONATES AND THEIR HYDROCHLORIDE SALTS

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Several new dialkyl-1-(*N*,*N*-dialkylamino)alkylphosphonates were synthesized[1a] as well as their hydrochloride salts. These compounds, along with two previously reported compounds, have been characterized by spectroscopic methods as well as elemental analysis. Spectral analysis indicates that the molecules assume an oriented posture in solution which can influence their reactivity. Additionally, the hydrochloride salts of the diethyl-1-(*N*,*N*-dimethylamino)alkylphosphonates have shown anti-viral activity.

Key words: Aminoalkylphosphonate; phosphonate; NMR; HCl salt; phosphonate esters; hydrogen-bonding.

INTRODUCTION

Phosphonic acid esters are important synthetic precursors to phosphonic acids. Traditionally, phosphonic acid esters have been purified by distillation[1a] or more recently by chromatographic techniques.[1b] Distillation becomes more difficult as the covalently bonded carbon species becomes larger and chromatographic techniques are not always feasible due to the strong hydrogen-bonding toward the column materials experienced by some phosphonic acids. Synthesis of the analogous phosphonic acid ester often affords a compound which is much easier to purify using conventional techniques. Facile hydrolysis of the ester can be accomplished through a variety of methods[2,3] yielding the desired phosphonic acid.

The 1-aminoalkyl(aryl)phosphonic acids and their esters are of importance due to their close structural similarity to α-amino acids. The potential for biological activity of these analogs is yet to be fully assessed, however several 1-aminoalkylphosphonic acids have been shown to be enzyme inhibitors in amino acid metabolism.[4] Currently several compounds of this type and other structurally similar species are being used in agriculture, and as such renewed interest in the mechanism of environmental degradation of 1-aminoalkylphosphorus species is currently being investigated.[5,6]

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Due to unexpected reactions encountered in subsequent studies using these compounds, it became necessary to gain a better understanding of their solution structure. This could allow us to determine whether the reactivities observed might be attributed to differences in structure. With these goals in mind, a comprehensive spectral study was undertaken and samples were examined for biological activity.

EXPERIMENTAL SECTION

Materials: Dimethylphosphite (Aldrich), diethylphosphite (Aldrich), and bis(2-propyl)phosphite (Aldrich) were used as received. Paraformaldehyde (Baker), acetaldehyde (Alfa), propionaldehyde (Aldrich-gold label), and diethylamine (Fisher) were also used without further purification. Anhydrous hydrogen chloride and anhydrous dimethylamine were obtained from Matheson. The dimethylamine was condensed and collected at −78°C. The condensed materials were then transferred to a chilled (−25°C) weighing vessel for accurate delivery of known amounts of material.

Biological Testing: Inhibition of virus-induced cytopathogenic effect (CPE) was used to indicate antiviral activity. Antiviral tests using a thymidine kinase positive strain (MacIntyre) of herpes simplex virus type 1 (HSV/1) were run in African green monkey kidney cells (MA-104). Influenza A, strain A/NWS/33, antiviral tests were run in the Madin Darby canine kidney cell line (MDCK). In these systems 18–24 hr monolayers of cells, in 96-well tissue culture plates, were exposed to 7 concentrations of each compound, ranging on one-half log dilutions from 1000 to 1 μg/ml. Virus was added to the cells within 15 min of addition of the compound and the compound was left on the cells. After approximately 72 hr of incubation at 37°C, the degree of CPE inhibition and of compound cytotoxicity were observed microscopically. The CPE was scored on a basis of O = no CPe to 4 = 100% CPE and a virus rating (VR) was calculated for each compound, as previously described.[7] Results of herbicidal testing will be reported in a subsequent publication.

Instrumental: ^{1}H and $[^{1}H]^{13}C$ NMR spectra were recorded on a Varian XL-300 or a JEOL FX-90Q operating at 300 MHz and 90 MHz respectively for ^{1}H and 75.44 mHz and 22.49 MHz respectively for ^{13}C. The spectra were routinely obtained in $CDCl_3$ or D_2O using TMS (tetramethylsilane) and sodium 3-(trimethylsilyl)-1-propane-sulfonic acid respectively as internal standards. The $[^{1}H]^{31}P$ NMR spectra were obtained on a JEOL FX-90Q operating at 36.19 MHz, with the chemical shifts reported in ppm relative to external 85% H_3PO_4.

Infrared spectra were run as KBr disks, neat on salt plates, or in $CHCl_3$ using NaCl solution cells on a Perkin–Elmer 1750 FT–IR. Elemental analyses were performed by M–H–W Laboratories, Phoenix, AZ 85018.

General Method for the Synthesis of Dialkyl-1-(*N,N*-dialkylamino)alkylphosphonates:

Modifying the general procedure described by Fields,[1a] one equivalent of the dialkylamine was rapidly weighed out in a chilled flask and quickly transferred to a pre-chilled (−78°C for dimethylamine, 0°C for diethylamine) round bottom flask equipped with a stir bar, condenser, and oil bubbler. One equivalent of the dialkylphosphite was then transferred to the rapidly stirred amine and the mixture allowed to equilibrate with the surrounding low temperature bath (approx. 10–15 mins). One equivalent of the aldehyde (acetaldehyde or propionaldehyde) was dissolved in an equal volume of benzene or in the case of paraformaldehyde, was suspended in a volume of benzene. This mixture[8] was then slowly added to the rapidly stirred, chilled reaction mixture. When addition was complete, the cold bath was removed and the flask was allowed to warm to room temperature. Stirring was continued for an additional 1–2 hrs.[9] The resulting product mixture was dried overnight with anhydrous sodium sulfate or anhydrous sodium carbonate. The drying reagent was filtered off followed by removal at reduced pressure of the benzene and any unreacted starting materials. The resulting product was purified by vacuum distillation. The dialkyl-1-(*N,N*-dialkylamino)-alkylphosphonates produced from this procedure are soluble in most organic solvents and water.

General Method for the Synthesis of the Dialkyl-1-(*N,N*-dialkylamino)-alkylphosphonate Hydrochloride Salts:

The phosphonate was dissolved in anhydrous diethyl ether and anhydrous hydrogen chloride gas was slowly bubbled through the rapidly stirred solution until no more product appeared. The hydrochloride separated out of solution as a white solid or as a pale-yellow oil. The solids were isolated by filtration, washed with several aliquots of anhydrous ether, followed by drying *in vacuo* (10^{-3} torr) overnight. The oils were isolated by decanting off the acidified ether, followed by several washings with anhydrous ether. The oily product was then dried overnight *in vacuo* (10^{-3} torr). Oils of the dimetylamine derivatives usually solidified under this treatment. The diethylamine derivatives

all produced ester hydrolysis side-products which were very difficult to separate from the hydrochloride, and as such they were characterized as mixtures. These hydrochloride salts were soluble in water, alcohol, chloroform, and methylene chloride. They also showed a slight solubility in tetrahydrofuran and were insoluble in anhydrous diethyl ether.

Using the general procedures described, the following compounds resulted from the stated reactants.

$(C_2H_5O)_2P(O)CH_2N(CH_3)_2$ (**1**).[10] Diethylphosphite, dimethylamine, and paraformaldehyde were used to synthesize **1** in 80% yield. B.p. 57°C/0.05 mm. IR (neat) cm^{-1} 1260 (P═O), 1045 (P—O). $[^1J]^{31}P$ NMR, ^1H NMR, and $[^1H]^{13}C$ NMR spectral data are reported in Tables I–III respectively. Anal. Calcd. For $C_7H_{18}NO_3P$: C, 43.06; H, 9.31; N, 7.18. Found: C, 42.87; H, 9.31; N, 7.42.

$(C_2H_5O)_2P(O)CH(CH_3)N(CH_3)_2$ (**2**). Compound **2** was synthesized using diethylphosphite, dimethylamine, and acetaldehyde. Care must be exercised during the aldehyde addition as the reaction can be quite exothermic. Yield of the purified product was 35%. B.p. 57°C/0.05 mm. IR (neat) cm^{-1} 1250 (P═O), 1040 (P—O). See Tables I–III for $[^1H]^{31}P$, ^1H, $[^1H]^{13}C$ NMR data, respectively.

$(C_2H_5O)_2P(O)CH(C_2H_5)N(CH_3)_2$ (**3**). As with compound **2**, care must be taken when adding the propionaldehyde to the chilled diethylphosphite/dimethylamine mixture (*vide supra*). Compound **3** was isolated in 60% yield. B.p. 60°C/0.025 mm. IR (neat) cm^{-1} 1241 (P═O), 1035 (P—O). See Tables I–III for NMR spectral data. Anal. Calcd. for $C_9H_{22}NO_3P$: C, 48.41; H, 9.95; N, 6.27. Found: C, 48.33; H, 9.98; N, 6.38.

$(CH_3O)_2P(O)CH_2N(C_2H_5)_2$ (**4**). A suspension of paraformaldehyde was combined with dimethylphosphite and diethylamine, producing **4** in 92.3% yield. B.p. 96°C/3 mm. IR (neat) cm^{-1} 1260 (P═O), 1040 (P—O). NMR spectral data are summarized in Tables I–III.

$(C_2H_5O)_2P(O)CH_2N(C_2H_5)_2$ (**5**).[11] Compound **5** was made from paraformaldehyde, diethylphosphite, and diethylamine in 88.5% yield. B.p. 96°C/3 mm. IR (neat) cm^{-1} 1260 (P═O), 1043 (P—O). The NMR spectral data are summarized in Tables I–III.

$(2\text{-}C_3H_7O)_2P(O)CH_2N(C_2H_5)_2$ (**6**). Bis(2-propyl)phosphite, diethylamine, and paraformaldehyde were combined to give **6** in 86% yield. B.p. 86–9°C/1 mm. IR (neat) cm^{-1} 1260 (P═O), 1069 (P—O). NMR data are summarized in Tables I–III.

$(C_2H_5O)_2P(O)CH_2N(CH_3)_2 \cdot HCl$ (**7**). The product was isolated in 95% yield. IR (KBr disk) cm^{-1} 1242 (P═O), 1032 (P—O), broad (N/H). IR (50% $CHCl_3$) cm^{-1} 1257 (P═O), 1019 (P—O), 2253 (N—H). See Table VI for additional IR data. $[^1H]^{31}P$, ^1H, and $[^1H]^{13}C$ NMR are summarized in Tables I, IV, and V respectively. Anal. Calcd. for $C_7H_{19}ClNO_3P$: C, 36.29; H, 8.28; N, 6.05. Found: C, 36.34; H, 8.23; N, 6.10.

$(C_2H_5O)_2P(O)CH(CH_3)N(CH_3)_2 \cdot HCl$ (**8**). Compound **8** was isolated in 95% yield. IR (KBr disk) cm^{-1} 1241 (P═O), 1018 (P—O), broad (N—H). Tables I, II, and V summarize the NMR data. Anal. Calcd. for $C_8H_{21}ClNO_3P$: C, 39.10; H, 8.63; N, 5.70. Found: C, 38.90; H, 8.65; N, 5.66.

$(C_2H_5P)_2P(O)CH(C_2H_5)N(CH_3)_2 \cdot HCl$ (**9**). Compound **9** was synthesized in 95% yield. IR (KBr disk) cm^{-1} 1236 (P═O), 1019 (P—O), broad (N—H). NMR data for the compound are summarized in Tables I, IV, and V. Anal. Calcd. for $C_9H_{23}ClNO_3P$: C, 41.61; H, 8.94; N, 5.39. Found: C, 41.62; H, 8.73; N, 5.34.

$(CH_3O)_2P(O)CH_2N(C_2H_5)_2 \cdot HCl$ (**10**). A mixture of products including the hydrochloride salt was obtained as a pale yellow, viscous oil. Compound **10** was estimated to be in 38% yield by $[^1H]^{31}P$ NMR spectroscopy. The residual components of the product mixture are believed to be ester hydrolysis products.[12] See Table I for $[^1H]^{31}P$ NMR data.

$(C_2H_5O)_2P(O)CH_2N(C_2H_5)_2 \cdot HCl$ (**11**). Compound **11** was also obtained in a mixture of products in a pale yellow, viscous oil. The yield of the hydrochloride was estimated to be 89% by $[^1H]^{31}P$ NMR spectroscopy; other components appear to be due to ester hydrolysis.[12] See Table I for $[^1H]^{31}P$ NMR data. $[^1H]^{13}C$ NMR ($CDCl_3$/TMS) ppm: 16.10 (d, $\mathbf{CH_3}CH_2O$, $J_{CCOP} = 6.0$ Hz); 63.36 (d, $\mathbf{CH_2}O$, $J_{COP} = 6.7$ Hz); 43.47 (d, $\mathbf{PCH_2}$, $J_{CP} = 154.0$ Hz); 49.39 (d, $\mathbf{NCH_2}$, $J_{CNCP} = 2.2$ Hz); 9.75 (s, $NCH_2\mathbf{CH_3}$). ^1H NMR ($CDCl_3$/TMS) ppm: 1.52[0] (t, $\mathbf{CH_3}CH_2O$, $J_{HCCH} = 7.2$ Hz); 4.25[1] (m, $\mathbf{CH_2}O$); 3.47[3] (m, $\mathbf{PCH_2}$ overlapping $\mathbf{NCH_2}$); 1.40[0] (t, $NCH_2\mathbf{CH_3}$, $J_{HCCH} = 7.2$ Hz).

(2-$C_3H_7O)_2P(O)CH_2N(C_2H_5)_2$·HCl (**12**). The product **12**, was observed in a pale yellow, viscous oil[12] in 80% yield, as estimated by $[^1H]^{31}P$ NMR spectroscopy. See Table I for $[^1H]^{31}P$ NMR data. ^1H NMR ($CDCl_3$/TMS) ppm: 1.39[4] (d, $(CH_3)_2CHO$, J_{HCCH} = 6.3 Hz); 4.82[4] (m, **CHO**); 3.42[3] (m, pCH_2 overlapping NCH_2); 1.52[4] (t, NCH_2CH_3, J_{HCCH} = 7.2 Hz). $[^1H]^{13}C$ NMR ($CDCl_3$/TMS) ppm: 23.73, 23.70 (d, $(CH_3)_2CHO$, J_{CCOP} = 4.0, 4.9 Hz); 72.82 (d, **CHO**, J_{COP} = 6.8 Hz); 44.08 (d, PCH_2, J_{CP} = 155.1 Jz); 49.47 (d, NCH_2, J_{CNCP} = 1.7 Hz); 9.88 (s, NCH_2CH_3).

RESULTS AND DISCUSSION

Unlike ^1H NMR chemical shift data, there appears in ^{31}P NMR to be no simple correlation between chemical shift and electronegativity of the substituents. Instead, ^{31}P NMR chemical shifts appear to be a function of a combination of effects including substituent electronegativity, π-electron overlap, and σ-bond angle. Consequently, attempts to develop a general predictive theory for ^{31}P NMR chemical shift data have proven to be unsatisfactory.[13] In general, structural correlations appear to be valid only with structurally similar compounds. The bulk of structural studies have focused on chemical shift relationships in phosphate ester systems, and several of the observations made in those systems appear to carry over into our phosphonate system.

In Table I we observe what appears to be an anomalous trend in compounds **1–3**. As the length of the alkyl group covalently attached to the phosphorus increases, the chemical shift implies a relative decrease in shielding. If one views this change in alkyl group size as an increase in alkyl substitution at the α-carbon with a concomitant increase in electron-releasing capability, one would expect an increase in shielding and the opposite trend to occur. However, an additional factor can account for this change. The steric bulk at the α-position has increased and this would be expected to change the bond angles, i.e. the hybridization of

TABLE I

$[^1H]^{31}P$ NMR chemical shifts of dialkyl-1-(*N*,*N*-dialkylamino)-alkylphosphonates and their hydrochloride salts

Compound	Structure	δ, ppm[a]
1[b]	$(C_2H_5O)_2P(O)CH_2N(CH_3)_2$	24.84
2	$(C_2H_5O)_2P(O)CH(CH_3)N(CH_3)_2$	27.53
3	$(C_2H_5O)_2P(O)CH(C_2H_5)N(CH_3)_2$	28.35
4	$(CH_3O)_2P(O)CH_2N(C_2H_5)_2$	28.27
5[c]	$(C_2H_5O)_2P(O)CH_2N(C_2H_5)_2$	25.88
6	$(2\text{-}C_3H_7O)_2P(O)CH_2N(C_2H_5)_2$	24.06
7	$(C_2H_5O)_2P(O)CH_2N(CH_3)_2$·HCl	15.45
8	$(C_2H_5O)_2P(O)CH(CH_3)N(CH_3)_2$·HCl	19.14
9	$(C_2H_5O)_2P(O)CH(C_2H_5)N(CH_3)_2$·HCl	18.75
10[d]	$(CH_3O)_2P(O)CH_2N(C_2H_5)_2$·HCl	19.89
11[d]	$(C_2H_5O)_2P(O)CH_2N(C_2H_5)_2$·HCl	15.62
12[d]	$(2\text{-}C_3H_7O)_2P(O)CH_2N(C_2H_5)_2$·HCl	13.50

[a] Spectra were taken in $CDCl_3$ with 85% H_3PO_4 as an external reference, using a JEOL FX-90Q operating at 36.19 MHz.

[b] This compound previously reported by K. Moedritzer.[10]

[c] This compound previously reported by E. Fields.[11]

[d] These compounds were characterized as mixtures and could not be isolated as pure compounds due to the formation of products from hydrolysis of P—OR.

the phosphorus. It has been observed in phosphate diesters that a decrease in O—P—O bond angle results in a downfield shift.[14] Steric effects also appear to be the dominate factor in our compounds, with the electron-releasing nature of the substituents playing a lesser role. Compounds **4–6** substantiate this observation, since an increase in the O—P—O angle would occur with increasing ester bulk, causing an upfield ^{31}P shift and this is the trend observed.

Examining the data summarized in Table II, one observes for compounds **1–3** that the CH_2 and CH_3 of the ethyl esters both give two sets of signals indicating that the ester groups within the molecule are not equivalent. However, the differences in environment of the ester become smaller as the size of the covalently bonded alkyl group grows larger. In compound **1**, $\Delta\delta$ is 0.06 ppm for CH_3, the difference drops to 0.006 ppm for **2**, and 0.002 ppm for **3**. This trend implies that the esters have fewer conformational options and as such are assuming similar environments. This observation supports the interpretation of the ^{31}P NMR chemical shift data that there is a decrease in the O—P—O bond angle. Such a decrease would be expected to limit the number of structural conformations that the esters could assume.

For compounds **1–3**, the *N*-CH_3 groups also are non-equivalent, but show an opposite trend to that observed for the esters. That is, as the alkyl group becomes larger the difference in the two chemical shift values increase. The values for $\Delta\delta$ are 0.003 ppm, 0.005 ppm, and 0.007 ppm for compounds **1–3** respectively. This trend suggests a dependency of *N*-CH_3 δ values on steric bulk. An increase in steric bulk at the α-position would be expected to reduce the ability of the *N*-dimethyl group to freely rotate around the α-C—N bond, thus making some conformations more stable than others. The variety of energetically favorable conformations available to the *N*-dialkyl group would be expected to decrease with increased steric hindrance and this is the trend observed.

In compounds **4–6**, the general absence of a distinct difference in *N*-alkyl chemical shift values, i.e. only **5** shows the non-equivalent *N*-CH_2 groups whereas **4** and **6** give only broadened peaks, implies that smaller differences in environment are present in the *N*-alkyl groups in these compounds. The ester groups in compounds **4–6** show behavior similar to that of their *N*-alkyl groups. The CH_3 group in **5** and **6** gives a single chemical shift, while the OCH protons result in distinct shifts with $\Delta\delta$'s of 0.004 ppm and 0.005 ppm for compounds **4** and **5** respectively. These data imply that the esters are in very similar conformations. The trends exhibited in the chemical shift values for the α-protons for **4–6** give an expected increase in shielding as the ester groups increase in size. The lack of change in J_{HCP} in these compounds indicates that the O—P—C—H dihedral angle is not changing, implying that the compounds are in similar orientations.

In compounds **1** and **5**, in which an increase in *N*-alkyl group size occurs, the hydrogen on the α-carbon shows a decrease in shielding, an apparent anomalous result if related to expected changes in electron density based on electron releasing capability of the alkyl groups. This decrease in shielding experienced by the hydrogens on the α-carbon implies a change in the N—CP bond network manifested through a change in the hybridization on the nitrogen. Further indication that the *N*-alkyl groups are affecting the N—C—P bond network is reflected in the difference in J_{HCP} values. This difference implies that the

TABLE II

Phosphonate ^1H NMR chemical shifts[a] (multiplicities)[b]/J, coupling constants[c]

Compound	HCCOP	HCOP	HCP	HCCP	HCCCP
1	1.32[0](t) 1.38[0](t)/ 7.2(HCCH)	4.15[4](d of q)/ 8.7(HCOP) 4.15[8](d of q)/ 8.1(HCOP) 7.2(HCCH)	2.74[4](d)/ 11.7(HCP)		
2	1.33[3](t), 1.33[9](t)/ 6.9(HCCH)	4.15[5](m)	2.99[0](d of q]/ 18.0(HCP) 7.5(HCCH)	1.26[4](d of d)/ 17.55(HCCP) 7.5(HCCH)	
3	1.33[2](t) 1.33[0][t]/ 7.2(HCCH)	4.12[5](m)	2.74[5](m)	1.73[8](m)	1.03[0](t)/ 7.2(HCCH)/ 1.5(HCCCP)
4		3.79[2](d), 3.78[8](d)/ 10.5(HCOP)	2.87[7](d)/ 10.8(HCP)		
5	1.33[1](t)/ 7.2(HCCH)	4.15[3](d of q)/ 7.8(HCOP), 4.14[8](d of q)/ 7.2(HCOP), 7.2(HCCH)	2.85[8](d)/ 10.8(HCP)		
6	1.33[1](d)/ 6.0(HCCH)	4.74[2](m)	2.81[6](d)/ 10.8(HCP)		

[a] All spectra were taken in $CDCl_3$ with TMS (tetramethylsilane) as an internal standard using a Varian XL-3 are reported in ppm.

[b] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet b = broad.

[c] Coupling constants are reported in Hz ± 0.3 Hz.

TABLE III

Phosphonate [^{1}H] ^{13}C NMR chemical shifts[a] (multiplicities)[b]/J, coupling constan

Compound	CCOP	COP	CP	CCP	CCCP
1	16.48(d)/ 6.1(COOP)	61.78(d)/ 7.2(COP)	54.95(d)/ 163.3(CP)		
2	15.78(d)/4.8(CCOP), 15.75(d)/6.4(CCOP)	61.11(d)/6.9(COP), 60.29(d)/8.8(COP)	56.10(d)/ 150.9(CP)	8.37(d)/ 2.7(CCP)	
3	16.15(d), 16.08(d)/3.8(CCOP)	60.23(d)/6.8(COP), 60.34(d)/7.7(COP)	63.23(d)/ 136.3(CP)	19.59(d)/ 6.1(CCP)	11.85(d)/ 12.7(CCCP)
4		52.20(d)/ 7.1(COP)	47.73(d)/ 164.0(CP)		
5	16.19(bd)/ 5.6(CCOP)	61.55(d)/ 7.0(COP)	48.57(d)/ 163.7(CP)		
6	23.90(d)/2.3(CCOP), 23.77(d)/4.5(CCOP)	70.01(d)/1.5(COP), 69.96(d)/5.5(COP)	49.48(d)/ 164.7(CP)		

[a] All spectra were taken in $CDCl_3$ with TMS (tetramethylsilane) as an internal standard using a 75.44 MHz. Values are reported in ppm.

[b] s = singlet, d = doublet, b = broad.

[c] Coupling constants are reported in Hz ± 0.08 Hz.

O—P—C—H dihedral angle is influenced by the steric requirements of the *N*-alkyl group thereby giving somewhat different J_{HCP} value in **1** and **5**. As expected, this influence is of much less importance than that of the substituents on the α-carbon.

Table III summarizes the $[^1H]^{13}C$ NMR data. Like ^1H NMR data, the phosphonates containing the more sterically demanding groups (**2**, **3**, and **6**) show two sets of chemical shifts for the two carbons of the ester groups, indicating an oriented environment. These data support the conclusion from the ^1H NMR that the ester groups are non-equivalent. In the other less sterically hindered cases (**1**, **4**, and **5**), the presence of two sets of proton shifts for the ester protons would suggest the presence of diastereotopic behavior in the protons rather than nonequivalency of the ester itself.

Although ^{31}P–^{13}C coupling constants have been shown to be highly dependent on structure,[15] most of the correlation studies involving phosphonates have been done on cyclic esters rather than acyclic compounds and therefore must be used with discretion in acyclic systems. It has been noted[16] that an increase in alkyl substitution or steric bulk at the α-position will cause a reduction in J_{CP}. This is thought to reflect a decrease in the *s*-character of the P—C bond leading to an increase in bond length or PCX bond angle (X = H, R). We see this trend in compounds **1–3**, as the α-hydrogen is replaced by a methyl group or an ethyl group in **1** giving a concomitant decrease in the coupling constant of 12.4 and 27.0 Hz respectively. A decrease in *s*-character in the P—C bond and the resulting weakening of the P—C bond would agree with the increased susceptibility to P—C bond cleavage we have seen in some reactions with these compounds.[17]

Also of interest is the magnitude of J_{CNCP} which indicates an extended electronic network through the α-carbon and nitrogen. This network appears to be quite susceptible to changes in hybridization at the α-carbon. Substitution on the α-carbon itself results in a J_{CNCP} change from 11.1 Hz (**1**) to 7.0 Hz (**2**) and 4.1 Hz (**3**). Changes in the hybridization of nitrogen, as is seen in compounds **1** and **5**, result in a much smaller change in J_{CNCP}, i.e. 11.1 Hz (**1**) to 9.1 Hz (**5**). Changes in the ester group, as is demonstrated in compounds **4–6**, produce only insignificant changes in J_{CNCP}.

Table IV and V show the large solvent effects experienced by several of the hydrochlorides, **7–9**. In general, the ^1H NMR spectra in $CDCl_3$ show an oriented structure with the CH_3 on the ester and the N-CH_3 giving two sets of peaks. The $\Delta\delta$ for N-CH_3 becomes larger as the bulk of the α substituent increases, i.e. 0.0002 ppm (**7**) 0.063 ppm (**8**), and 0.230 ppm (**9**). A similar trend is observed for the HCCOP chemical shift data, but as expected the magnitude of the changes in $\Delta\delta$ are much smaller. The data summarized in Table V for ^{13}C NMR spectra reinforce this observation. In the $CDCl_3$ data, with an increase in bulk at the α-position, the N-CH_3 chemical shifts (**8** and **9**) show an unusual broadening in the peak, as well as large $\Delta\delta$. Another observation can be made, that the trends in J_{CP} observed in the parent phosphonates have been notably changed in the hydrochlorides since the latter show little differentiation in the coupling constant.

The phosphonate hydrochloride, possessing both electron rich and electron poor regions, seems admirably suited to hydrogen bonding. The question of

TABLE IV

Phosphonate hydrochloride: ^{1}H NMR chemical shifts[a] (multiplicities)[b]/*J*, coupling

Compound	HCCOP	HCOP	HCP	HCCP
7[d]	1.39[8](t) 1.39[6](t)/7.2(HCCH)	4.25[7](m)	3.46[2](d)/12.9(HCP)	
7[e]	1.37[3](t), 1.37[1](t)/7.2(HCCH)	4.28[8](m)	3.82[4](d)/13.8(HCP)	
8[d]	1.40[2](bt), 1.39[8](bt)/6.9(HCCH)	4.23[6](m)	3.60[1](d of q)/13.8(HCP)/ 7.2(HCCH)	1.75[0](d of d)/15.3(HC 7.3(HCCH)
8[e]	1.37[2](t), 1.36[6](t)/7.2(HCCH)	4.29[6](m)	3.99[8](d of q)/16.8(HCP)/ 7.2(HCCH)	1.56[1](d of d)/16.8(HC 7.2(HCCH)
9[d]	1.40[5](t), 1.40[0](t)/7.2(HCCH)	4.25[5](m)	3.50[9](m)	2.39[1](m) 2.00[9](m)
9[e]	1.38[8](t), 1.38[2](t)/7.2(HCCH)	4.31[6](m)	3.81[5](m)	2.03[6](m)

[a] All spectra were taken using a Varian XL-300 operating at 300 MHz.
[b] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad.
[c] Coupling constants are reported in Hz ± 0.3 Hz.
[d] Spectrum was taken in $CDCl_3$ with TMS as an internal reference.
[e] Spectrum was taken in D_2O with $NaO_3S(CH_2)_3Si(CH_3)_3$ as an internal reference.

TABLE V

Phosphonate hydrochlorides: [^{1}H] ^{13}C NMR chemical shifts[a] (multiplicities)[b]/*J*, coupling

Compound	CCOP	COP	CP	CCP	C
7[d]	16.37(d)/ 6.2(CCOP)	63.62(d)/ 7.4(COP)	50.18(d)/ 152.5(CP)		
7[e]	18.20(d)/ 5.6(CCOP)	67.80(d)/6.7(COP)	53.52(d)/ 151.9(CP)		
8[d]	16.42(d)/ 4.3(CCOP)	63.68(d)/7.3(COP), 63.41(d)/7.0(COP)	56.89(d)/ 152.0(CP)	12.37(d)/ 2.8(CCP)	
8[e]	18.23(d)/ 5.7(CCOP)	68.01(d)/6.9(COP) 67.97(d)/7.8(COP)	59.13(d)/ 154.9(CP)	10.44(d)/ 3.3(CCP)	
9[d]	16.43(d)/3.4(CCOP) 16.36(d)/1.6(CCOP)	63.55(d)/5.7(COP) 63.08(d)/7.1(COP)	63.43(d)/ 149.0(CP)	21.58(d)/ 3.2(CCP)	11.70(d 2.8(C
9[e]	18.28(d)/2.0(CCOP) 18.21(d)/2.2(CCOP)	67.95(d)/7.2(COP), 67.85(d)/7.2(COP)	65.17(d)/ 151.3(CP)	20.18(d)/ 2.2(CCP)	12.78(d 4.2(C

[a] All spectra were taken using a Varian XL-300 operating at 75.44 MHz.
[b] s = singlet, d = doublet, b = broad.
[c] Coupling constants are reported in Hz ± 0.08 Hz.
[d] Spectrum was taken in $CDCl_3$ with TMS as an internal reference.
[e] Spectrum was taken in D_2O with $NaO_3S(CH_2)_3Si(CH_3)_3$ as an internal reference.

TABLE VI

Infrared study of hydrogen bonding in **7**

% Concentration[a]	N—H (cm^{-1})	P=O (cm^{-1})
KBr pellet	—	1242
50	2253	1257
10	2255	1253
2.5	2256	1253
1.0	2257	1253
0.5	2257	1252
0.01	2260	1250

[a] $CHCl_3$ solvent.

hydrogen bonding, its presence or absence as well as the question of intramolecular vs. intermolecular hydrogen-bonding could best be evaluated by an IR study.[18] The results of this study, Table VI, show that the P=O is experiencing hydrogen-bonding with the N—H proton. The concentration studies, by showing very little change in the N—H and P=O absorptions, indicate that the hydrogen bonding is intramolecular, giving the molecule the conformation in Figure 1.

Preliminary results of the anti-viral testing are summarized in Table VII. The

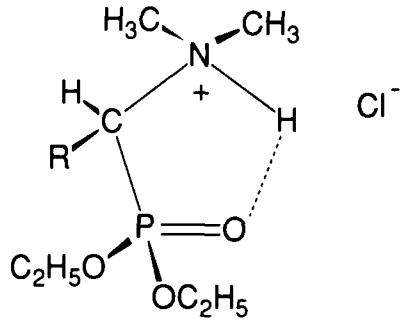

FIGURE 1 Proposed structure for the intramolecularly hydrogen-bonded diethyl aminoalkylphosphonate hydrochloride salts.

TABLE VII

Results of Anti-viral Testing

Compound	Virus Rating		Minimum cytotoxic dose (μg/ml)	
	Type 1 Herpes	Influenza A	MA104[b]	MDCK[b]
1	0.0	0.2	1000	n.s.[a]
2	0.0	0.5	1000	1000
3	0.0	0.5	320	1000
4	0.0	0.0	n.s.[a]	n.s.[a]
6	0.0	0.0	n.s.[a]	1000
7	0.5	0.1	1000	n.s.[a]
8	1.0	0.1	1000	100
9	0.1	0.0	1000	1000

[a] No cytotoxicity seen.
[b] Cell lines, see experimental section for details.

viral ratings are reported as normalized values which have been referenced to compounds of known anti-viral activity.[19] A virus rating of 0.5 indicates slight or no antiviral activity; 0.5–0.9, moderate activity; and 1.0, strong activity. Generalizations relating structure to activity using these limited data would be highly speculative. Further testing of these compounds are planned with the results to be reported in a subsequent publication.

ACKNOWLEDGMENT

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REFERENCES AND NOTES

1. a. The phosphonates reported here were synthesized using a modification of the method described by E. K. Field, *J. Am. Chem. Soc.*, **74,** 1528 (1952). b. J.-L. Montero, J.-L. Clavel and J.-L. Imbach, *Tet. Lett.*, **28** 1163 (1987).
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8. The order of addition of the reactants, i.e. the addition of the aldehyde to the phosphite/amine rather than the addition of the amine to a phosphite/aldehyde mixture, must be maintained in order to minimize the number of side-products produced in the reaction. It should also be noted that the addition of the aldehyde can often be accompanied by a rapid rise in the temperature of the reactant mixture as a result of the exothermicity of the reaction to form the 1-aminoalkylphosphonate. Care should therefore be taken during this addition.
9. During this warmup and the subsequent period of stirring, the reaction mixture may experience a rise in temperature as the reaction proceeds. This temperature rise does not appear to decrease the yield of the reaction and recent experimental data indicate that additional heating may increase the yield in some cases.
10. Compound has had ^{31}P NMR data reported as a private communication by K. Moedritzer in *Topics in Phorus Chemistry*, **5,** 227 (1967). However no synthetic details nor other physical data have been published.
11. This compound has been previously reported by Fields (*vide supra*), however only limited physical data were reported (B.p. and elemental analysis).
12. These compounds were characterized as mixtures as the pure compound could not be isolated from the reaction mixture. Data from work in progress suggest that the other products in the reaction mixture are the result of ester hydrolysis side-reactions. This side-reaction most likely appears with **10–12**, because of the increased exposure time of the phosphonate to HCl, a result of increased solubility of these particular phosphonates as compared to their dimethyl counterparts.
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