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DETERMINATION OF ORGANOPHOSPHORUS ACIDS BY THERMOSPRAY LIQUID CHROMATOGRAPHY–MASS SPECTROMETRY

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SUMMARY

The determination of thirteen organophosphorus acids, hydrolysis products of nerve agents and pesticides, by a combination of ion-pair liquid chromatography on a reversed-phase C_{18} column and thermospray mass spectrometry was investigated. Ammonium acetate and three tetraalkylammonium salts with different alkyl groups (methyl, ethyl and *n*-butyl) were applied as ion-pair reagents. All the organophosphorus acids could be eluted using water or water–methanol mixtures. Capacity factors (k') were measured for some selected acids using water as eluent.

The recorded thermospray mass spectra using ammonium acetate as electrolyte gave the $[M + NH_4]^+$ ion as a predominant peak, whereas with the tetraalkylammonium salts cluster ions were found. This difference in ionization mechanism was also reflected in the sensitivity. An amount of 100 pg of dimethylthiophosphoric acid could be detected by selected ion monitoring using ammonium acetate, whereas with tetramethylammonium hydroxide the amount was 5 ng. To obtain lower detection levels preconcentration could be achieved with a Sep-Pak C_{18} cartridge pretreated with a tetra-*n*-butylammonium salt.

INTRODUCTION

Alkyl-substituted organophosphorus acids are the primary hydrolysis products of physiologically active organophosphorus compounds such as nerve agents and pesticides. With a few exceptions the first group of substances contain a methyl group directly linked to a phosphorus atom, leading to alkylmethylphosphonic acids after hydrolysis. organophosphorus pesticides are mainly (thio)phosphates which hydrolyse to dialkyl(thio)phosphoric acids. In recent years various analytical procedures for the determination of these hydrolysis products in environmental and biological samples have been developed. Generally, these procedures are based on the isolation of the organophosphorus acids from the aqueous phase followed by derivatization and determination by gas chromatography (GC) using phosphorus-specific or mass spectrometric (MS) detection.

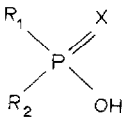
Direct analysis of these acids in aqueous solution by reversed-phase liquid chromatography (LC) seems more straightforward. However, sensitive detection is a

problem because these acids do not contain ultraviolet (UV)-absorbing or fluorescing groups. This has been overcome by precolumn derivatization into compounds with UV[1] or fluorescence properties[2]. Combining LC with a phosphorus-specific GC detector is another approach[3,4]. This detection problem can also be solved by using a mass spectrometer as an LC detector. A compound such as nitric acid with similar detection limits to the organophosphorus acids has successfully been determined by thermospray (TSP)–LC–MS[5]. In the investigation described here a combination of tetra-*n*-butylammonium (TBA) hydroxide and ammonium acetate was used as ion-pair reagent in chromatography on a reversed-phase C_{18} column.

Organophosphorus acids are relatively strong acids and exist as anions at neutral pH. Until now conventional ion chromatography has offered limited possibilities for the determination of these organophosphorus acids[4,6]. Some experiments on the determination of phosphonic acids used in the detergent industry by ion-pair chromatography on a reversed-phase C_{18} column have been reported[3]. Hence, a study was started to investigate the determination of a number of hydrolysis products of nerve agents and organophosphorus pesticides (Table I) by ion-pair TSP–LC–MS on conventional C_{18} columns. Recently, in the course of this study, the determination of four hydrolysis products of nerve agents by ion-pair reversed-phase chromatography on a polystyrene–divinylbenzene (PSDVB) column has been published[6]. TBA hydroxide was used as the ion-pair reagent and detection was carried out by means of a conductivity detector after suppression of the TBA ions. These cations are mostly applied during ion-pair chromatography of anions on reversed-phase columns. However, tetraalkylammonium ions with smaller alkyl groups and even the ammonium ion itself have been used as counter ions, in particular for the determination of anions containing hydrophobic groups[7]. Therefore ammonium acetate, generally used in

TABLE I

ORGANOPHOSPHORUS ACIDS USED AS TEST COMPOUNDS



No.	*Acid*	R_1	R_2	*X*	*MW*
1	Methylphosphonic	OH	CH_3	O	96
2	Dimethylphosphoric	CH_3O	CH_3O	O	126
3	Ethylmethylphosphonic	C_2H_5O	CH_3	O	124
4	Dimethylthiophosporic	CH_3O	CH_3O	S	142
5	Ethylmethylthiophosphonic	C_2H_5O	CH_3	S	140
6	Isopropylmethylphosphonic	$(CH_3)_2CHO$	CH_3	O	138
7	Diethylphosphoric	C_2H_5O	C_2H_5O	O	154
8	Diethylthiophosphoric	C_2H_5O	C_2H_5O	S	170
9	Cyclopentylmethylphosphonic	C_5H_9O	CH_3	O	164
10	Diisopropylphosphoric	$(CH_3)_2CHO$	$(CH_3)_2CHO$	O	182
11	Cyclohexylmethylphosphonic	$C_6H_{11}O$	CH_3	O	178
12	Diisopropylthiophosphoric	$(CH_3)_2CHO$	$(CH_3)_2CHO$	S	198
13	Pinacolylmethylphosphonic	$(CH_3)_3CCH(CH_3)O$	CH_3	O	180

TSP–LC–MS as an electrolyte for the ionization of organic molecules, could also serve as an ion-pair reagent in chromatography.

This paper describes the effects of ammonium acetate and tetraalkylammonium salts with different alkyl groups (methyl, ethyl and *n*-butyl) on the chromatographic behaviour and on the TSP ionization of organophosphorus acids.

EXPERIMENTAL

Chemicals

Ammonium acetate (A.C.S. reagent grade) was obtained from Aldrich (Milwaukee, WI, U.S.A.). Tetramethylammonium hydroxide was purchased from Sigma (St. Louis, MO, U.S.A.), tetraethylammonium hydroxide (20% solution in water) from Aldrich (Steinheim, F.R.G.) and tetra-*n*-butylammonium hydroxide (40% solution in water) from BDH (Poole, U.K.). Glacial acetic acid (UCB, Leuven, Belgium), used to adjust the pH of the eluent as indicated, and methanol (Merck, Darmstadt, F.R.G.) were of analytical-reagent grade. Polyethylene glycols (PEG-200 and PEG-400) were purchased from Fluka (Buchs, Switzerland). For all purposes water was purified in a Milli-Q water purification system (Millipore, Bedford, MA, U.S.A.). Organophosphorus acids were prepared in the laboratory and gave satisfactory elemental analyses and spectral (IR, NMR and mass) data. Standard solutions of the acids were prepared in water, with the exception of pinacolylmethylphosphonic acid, which was dissolved in water–methanol (80:20, v/v). The solutions were diluted to the appropriate concentrations with water before use.

Liquid chromatography

The LC system included the following components: a Waters Model 590 solvent delivery system (Waters Assoc., Milford, MA, U.S.A.), a Valco injector (Bester, Amsterdam, The Netherlands) with a 10-μl sample loop and a stainless-steel column (250 mm × 5 mm I.D.) which was packed in the laboratory with LiChrosorb C_{18}, 5-μm particles (Merck). The connection between the column and the TSP interface consisted of a low-dead-volume tee, a Valco injector with a 5-μl sample loop for flow injections and a 2-μm screen filter (Waters Assoc.). A second high-pressure pump (Waters Model 501) combined with a pulse damper (Touzart et Matignon, Vitry sur Seine, France) was connected to the low-dead-volume tee for post-column addition of an ammonium acetate solution or for the introduction of the mass axis calibration mixture.

A flow-rate of 1.5 ml/min was used in all experiments, except during post-column addition. In this instance a flow-rate of 1.2 ml/min was maintained through the column, while 0.3 ml/min of a 0.3 *M* ammonium acetate solution was added at the end of the column.

Capacity factors (k') were calculated by using the hold-up time of ^2H_2O, which was injected into an eluent of pure water at a flow-rate of 1.5 ml/min. Detection of the ^2H_2O signal was carried out after post-column addition of ammonium acetate. Retention times of the acids were measured after equilibration of the LC system. Column loading, especially with the TBA salt, required at least 30 min to reach a steady state.

Mass spectrometry

A Nermag (Rueil Paris, France) R 10-10 C quadrupole instrument, equipped with a TSP ion source (Nermag), was coupled with the LC system via a Vestec TSP interface (Vestec, Houston, TX, U.S.A.). The mass spectrometer was operated in the positive ion mode, with the filament off. Mass axis (m/z) calibration from m/z 60 to 800 was performed with a mixture of PEG-200 and PEG-400. Maximal sensitivity was tuned in the mass range of the expected ions.

The scan range used was dependent on the application, whereas the scan time was dependent on the mass range and varied between 0.6 and 0.9 s. During single ion monitoring experiments the integration time was set at 0.2 s. The TSP vaporizer temperature was optimized for the particular kind of analysis and was normally in the range 190–240°C. The ion block temperature was maintained at 240°C during experiments with ammonium acetate. This temperature was raised to 280°C when tetraalkylammonium salts were applied.

Preconcentration of pinacolylmethylphosphonic acid

Sep-Pak C_{18} cartridges (Waters Assoc.) were prewashed with 10 ml of methanol and 5 ml of water. To equilibrate the C_{18} phase, 20 ml of a 10 mM solution of TBA hydroxide (adjusted to pH 6.0) were forced through the cartridge at a flow-rate of approximately 10 ml/min. A volume of 50 ml of a solution of pinacolylmethylphosphonic acid (2.5 ng/ml) in 10 mM TBA hydroxide (previously adjusted to pH 6.0) was forced through the pretreated cartridge. After drying both ends of the cartridge with a tissue, 2 ml of methanol were used to elute the ion pair. This solution was evaporated to 200 μl by gently blowing nitrogen over the liquid surface. The recovery was determined by comparing the signal obtained after LC–MS analysis of this concentrated solution with that of an appropriate standard solution.

RESULTS AND DISCUSSION

Ammonium acetate as ion-pair reagent

The effect of the ammonium acetate concentration on the capacity factor (k') of three organophosphorus acids was measured (Fig. 1). Without ammonium acetate a negative k' value was obtained, indicating that the acids did not penetrate the pores of the silica particles when using pure water as the eluent. This phenomenon had been observed before on C_{18} columns and was explained by an electrostatic exclusion mechanism[8]. Above the concentration level of 0.02 M no substantial enhancement of the k' values was noticed. Generally, a concentration of 0.1 M ammonium acetate is used during TSP–LC–MS analysis, providing optimal ionization of the analyte[9]. Therefore, further experiments were carried out at this concentration level.

The reconstructed ion chromatograms (RIC) obtained after analysing mixtures of organophosphorus acids are presented in Figs. 2 and 3. Although the more hydrophilic acids (1–4) eluted very fast, separation was still complete. In order to analyse acids with longer alkyl chains the addition of an organic solvent was necessary. Pinacolylmethylphosphonic acid (13), the hydrolysis product of the nerve agent soman, is the most hydrophobic of the compounds studied. By means of a mixture containing 30% methanol this acid eluted within 12 min at the chosen flow-rate. If all the acids need to be analysed in one LC run, gradient elution will be necessary; this will be the subject of a future investigation.

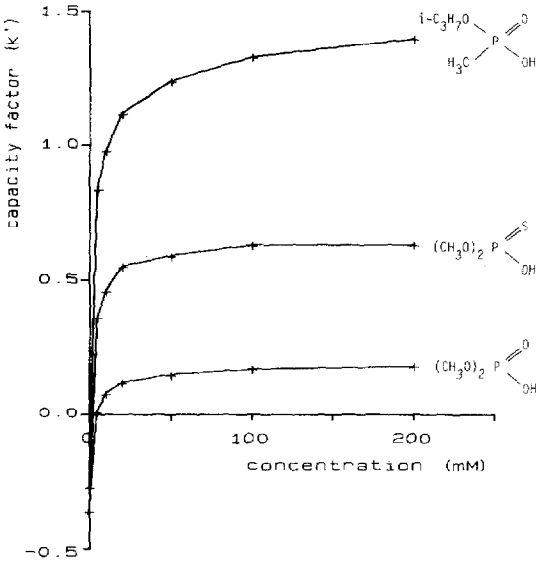


Fig. 1. Effect of ammonium acetate concentration on the capacity factors (k') of three acids. Eluent, water containing the indicated amount of counter ion (pH 5.8).

The influence of the pH of the mobile phase on the retention behaviour was investigated. Small but significant changes in the retention times were found between pH 4.5 and 7.0. The retention times of thiophosphoryl acids decreased at lower pH, whereas methylphosphonic acids showed the opposite behaviour. This different retention behaviour might be attributed to the differences in pK_a values. Thiophosphoryl acids (pK_a < 1) are stronger acids than methylphosphonic acids (p$K_a \approx$ 2). By selecting an appropriate pH a separation could be achieved of ethylmethylthiophosphonic acid (5) and isopropylmethylphosphonic acid (6), the hydrolysis products of

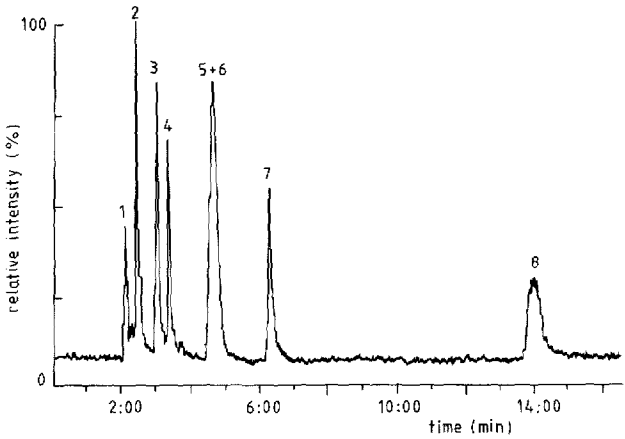


Fig. 2. Reconstructed ion current chromatogram. Eluent, 0.1 M ammonium acetate (pH 6.8). Analyte concentration, 2–3 ng/μl. See Table I for compound numbers.

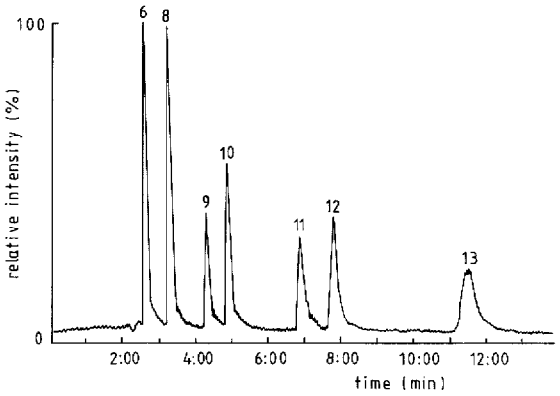


Fig. 3. Reconstructed ion current chromatogram. Eluent, water (0.1 *M* ammonium acetate)–methanol (70:30) (pH 6.8). Analyte concentration, 4–6 ng/μl. See Table I for compound numbers.

the nerve agents VX and sarin, respectively. At pH 6.8 both acids coeluted (Fig. 2), whereas at pH 5.0 baseline separation was achieved.

Tetraalkylammonium salts as ion-pair reagents

The major disadvantage of the use of ammonium acetate as an ion-pair reagent is the small k' values obtained for the more hydrophilic organophosphorus acids. By using tetraalkylammonium salts these values could be enhanced. With tetramethylammonium (TMA) ions a small enhancement of the k' values was achieved. However, the use of tetraethylammonium (TEA) ions led to a k' value above 1 for dimethylphosphoric acid (Fig. 4). For the three selected acids a rapid increase was

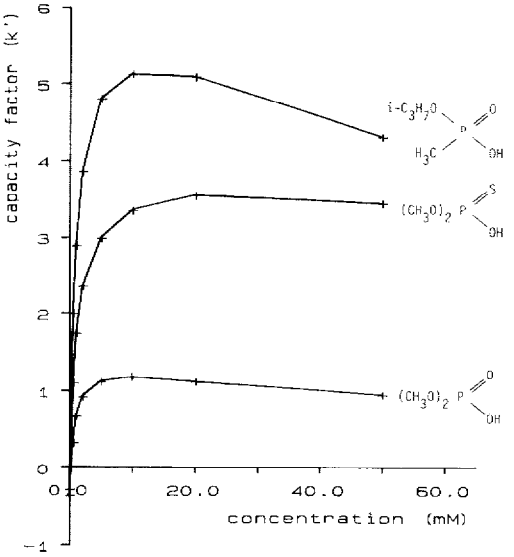


Fig. 4. Effect of TEA hydroxide concentration on the capacity factors (k') of three acids. Eluent, water containing the indicated amount of counter ion (pH 5.2).

observed, leading to a maximal k' value at a counter-ion concentration of around 10 mM, followed by a gradual decrease at higher concentrations. This concentration dependence of the k' value has been described theoretically[10].

A different behaviour was observed for the more hydrophobic TBA ions, which were strongly adsorbed on the C_{18} stationary phase. Consequently, the nature of the column after preconditioning was changed and resembled an ion-exchange resin[10]. The effect of the TBA ion concentration on the k' value of dimethylphosphoric acid is presented in Fig. 5. A relatively high concentration (> 10 mM) was necessary to elute this acid. The elution of acids with larger alkyl groups was only possible after the addition of methanol. In Table II the retention times of twelve monovalent organophosphorus acids obtained using a water–methanol mixture are presented. The effect of increasing the TBA ion concentration on the retention was the opposite of that with the use of water as the eluent. When using water–methanol, increased salt concentrations led to increased retention times. The acids with the smaller alkyl groups were well separated. However, the retention times became long for the more hydrophobic acids such as pinacolylmethylphosphonic acid.

Attempts were made to determine methylphosphonic acid using TBA ions. The determination of this bivalent acid on a PSDVB column has been described[6] using, in addition to TBA hydroxide, sodium carbonate as a modifier to shorten the retention time. However, it was impossible to obtain a reasonable peak shape for this acid on a C_{18} column. Very broad peaks were obtained in the pH range tested (3.0–6.0). Probably this acid can only be measured at a pH far above the second dissociation constant (pK_{a_2} in water *ca.* 6.5). Unfortunately, C_{18} columns cannot be used at high pH values.

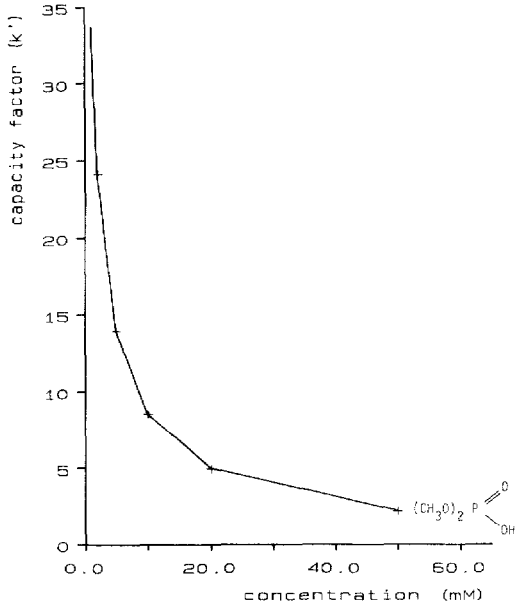


Fig. 5. Effect of TBA hydroxide concentration on the capacity factor (k') of dimethylphosphoric acid. Eluent, water containing the indicated amount of counter ion (pH 5.2).

TABLE II

EFFECT OF THE TBA ION CONCENTRATION ON THE RETENTION TIMES OF TWELVE ORGANOPHOSPHORUS ACIDS

Column, 250 × 5 mm I.D., 5-μm LiChrosorb C_{18}; eluent, water–methanol (60:40), pH 5.0; flow-rate, 1.5 ml/min.

No.	*Acid*	*Retention time (min)*	
		1 mM	*5 mM*
2	Dimethylphosphoric	3.15	4.05
3	Ethylmethylphosphonic	3.35	4.38
4	Dimethylthiophosphoric	3.37	4.48
5	Ethylmethylthiophosphonic	4.07	5.42
6	Isopropylmethylphosphonic	4.17	5.53
7	Diethylphosphoric	4.26	6.09
8	Diethylthiophosphoric	5.02	8.00
9	Cyclopentylmethylphosphonic	7.12	11.17
10	Diisopropylphosphoric	7.52	12.54
11	Cyclohexylmethylphosphonic	12.10	19.38
12	Diisopropylthiophosphoric	13.15	23.16
13	Pinacolylmethylphosphonic	20.52	33.00

The use of tetraalkylammonium salts (especially TBA salts) at high concentrations had some drawbacks. The C_{18} column degraded fairly rapidly, resulting in a reduction of the number of plates. Further, partial or complete blockage of the TSP interface occurred, probably owing to silica material originating from the degrading column. Although the use of TBA salts did not lead to an extremely contaminated ion source, the salt was difficult to eliminate. Changing to another mobile phase required extensive rinsing of the whole LC–MS system with methanol. Even then the TBA ion at m/z 242 could still be found in the TSP mass spectra after several weeks. Strong memory effects from alkylammonium salts have been reported before[11].

Positive ion TSP mass spectra

The ammonium adduct ion $[M + NH_4]^+$ was a predominant peak in the positive ion TSP mass spectra of the organophosphorus acids recorded during the LC–MS analysis using ammonium acetate as electrolyte. The spectra correspond to those obtained for organophosphorus pesticides which also showed strong $[M + NH_4]^+$ ions[9]. The ratio between the ammonium adduct ion and the protonated molecular ion $[M + H]^+$ varied for the acids studied. In acids with small alkyl groups the $[M + H]^+$ ion was relatively small (Fig. 6), but became more abundant in acids with larger alkyl groups (Fig. 7). No great difference in the $[M + NH_4]^+/[M + H]^+$ ratio was found between phosphoryl and thiophosphoryl compounds containing the same alkyl groups. The $[M + NH_4]^+/[M + H]^+$ ratio depended on the temperature of the vaporizer and to a minor extent on the ion source block. Normally, owing to contamination of the capillary tip after a number of analyses, the vaporizer temperature was increased to obtain the same stable signal. An increase in the vaporizer temperature reduced the $[M + NH_4]^+/[M + H]^+$ ratio. Variations of a factor 3 in these ratios were observed over the temperature range used. Therefore, the spectra presented

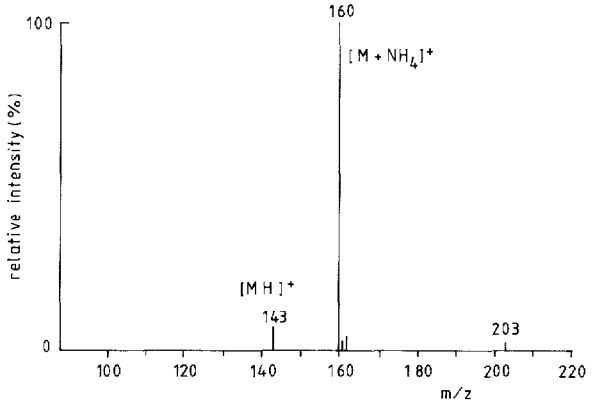


Fig. 6. TSP mass spectrum of dimethylthiophosphoric acid. Eluent, 0.1 *M* ammonium acetate.

should be regarded only as typical examples. A small ion corresponding to the addition of acetic acid to the $[M + H]^+$ ion was sometimes noticed, *e.g.*, *m/z* 203 in the TSP mass spectrum of dimethylthiophosphoric acid (Fig. 6). Fragments derived from methylphosphonic acid (*m/z* 97 and 114) were noticed in the TSP mass spectrum of pinacolylmethylphosphonic acid (Fig. 7). The intensities of these fragments increased with increasing ion source block temperature, indicating that decomposition of this compound can take place.

Two kinds of ions were formed during TSP–LC–MS analysis of the organophosphorus acids using tetraalkylammonium salts as electrolytes. In addition to an ion due to the addition of the cation to the acid ($[M + C]^+$), a cluster ion, $[A][C]_2^+$ (A = anion, C = cation), was found. Higher cluster ions were not observed. This $[A][C]_2^+$ ion was of moderate intensity in the TSP mass spectra recorded with TMA salts, but became predominant using TEA and TBA salts (Fig. 8). The cation adduct ion $[M + C]^+$ corresponds to the $[M + Na]^+$ ion frequently found in the TSP mass

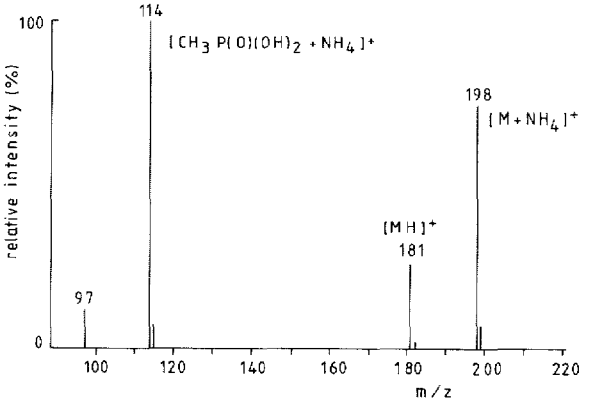


Fig. 7. TSP mass spectrum of pinacolylmethylphosphonic acid. Eluent, water (0.1 *M* ammonium acetate)–methanol (70:30).

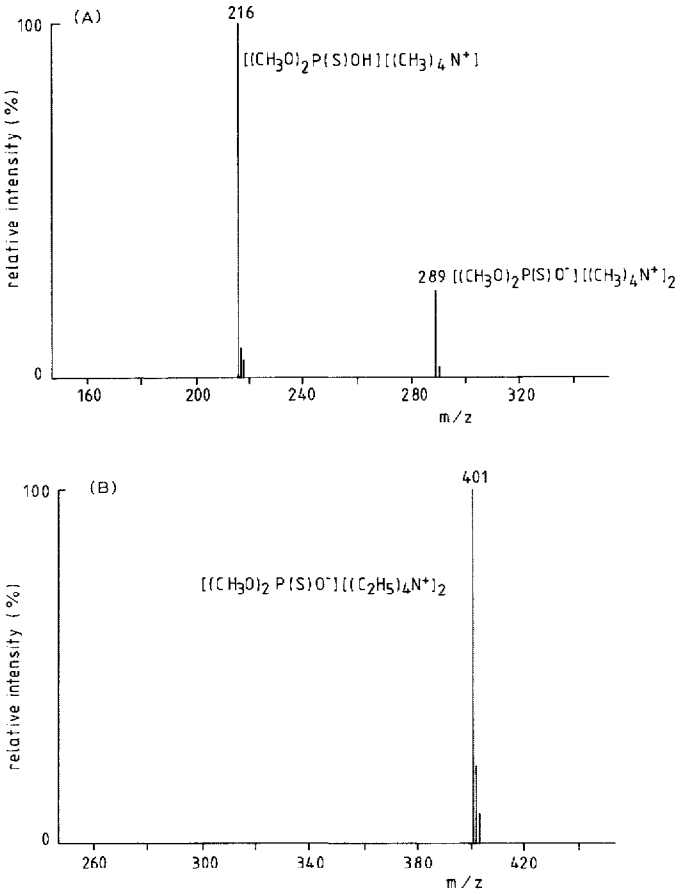


Fig. 8. TSP mass spectrum of dimethylthiophosphoric acid obtained using 5 m*M* TMA hydroxide (A) and TEA hydroxide (B) (pH 5.2).

spectra of polar organic compounds and whose formation has recently been discussed in nucleotides[12]. A similar $[A][C]_2^+$ cluster ion has been found in the TSP and fast atom bombardment (FAB) mass spectra of sodium butanesulphonate[13]. In both spectra the major peak was assigned to the cluster ion $[C_4H_9SO_3][Na]_2^+$. As observed previously[12,13], the similarity between TSP and FAB mass spectra is supported by the results obtained here with the organophosphorus acids. Recently, the same kinds of ions have been detected in the FAB mass spectra of several alkylammonium salts[14,15].

Sensitivity considerations

An advantage of the use of ammonium acetate as an ion-pair reagent is the high water content of the eluent, which is the most preferential situation in TSP ionization[16]. To demonstrate the sensitivity achieved in the positive ion detection mode, the signal-to-noise (S/N) ratio obtained after injecting an amount of 100 pg of di-

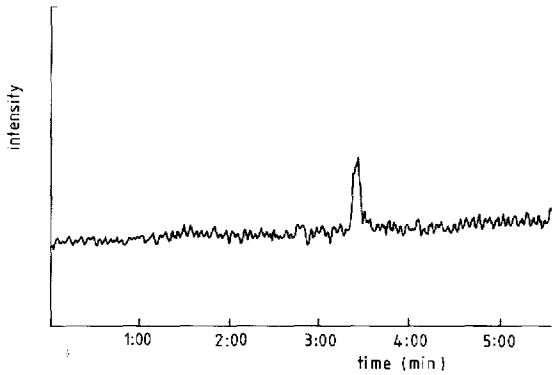


Fig. 9. Selected ion monitoring at *m/z* 160, the ammonium adduct ion of dimethylthiophosphoric acid (100 pg). Eluent, 0.1 *M* ammonium acetate (pH 6.8).

methylthiophosphoric acid is shown in Fig. 9. Selected ion monitoring (SIM) was applied to the ammonium adduct ion. Owing to peak broadening at longer retention times and the addition of methanol to the eluent (resulting in a decrease in the TSP ionization), the minimal amount detected was higher for acids containing longer alkyl chains. For instance, to achieve a detectable signal with SIM for pinacolylmethylphosphonic acid an amount of 1 ng had to be injected.

The sensitivity using tetraalkylammonium salts as electrolytes was much reduced in comparison with ammonium acetate. The S/N ratio obtained after injecting an amount of 5 ng of dimethylthiophosphoric acid using an eluent containing 5 m*M* of TMA hydroxide was similar to that shown in Fig. 9, indicating a reduction in sensitivity by a factor of 50. Although the absolute intensity of the TMA adduct ion was enhanced on increasing the salt concentration, the noise was also increased and consequently no improvement in the S/N ratio was achieved. This phenomenon was also observed on increasing the ammonium acetate concentration[9].

The TSP ionization of dimethylthiophosphoric acid by mixtures of 0.1 *M* ammonium acetate and various concentrations of tetraalkylammonium salts was investigated. After reducing the salt concentration to 0.1 m*M* the formation of the $[M + NH_4]^+$ ion was favoured instead of the above-mentioned cluster ions. At this low concentration TBA ions could still interact with the organophosphorus anions during elution through a C_{18} column. By post-column addition of ammonium acetate the acids could be detected as the $[M + NH_4]^+$ ions formed in the TSP ion source. In this way 1 ng of dimethylthiophosphoric acid could be determined with a similar S/N ratio to that shown in Fig. 9, using a mobile phase consisting of 0.1 m*M* TBA hydroxide–methanol (70:30).

This reduced sensitivity in comparison with the experiments using only ammonium acetate as the mobile phase (Fig. 9) must mainly be attributed to the reduced ionization efficiency of water–methanol mixtures[16].

Although the results obtained for the determination of organophosphorus acids are promising, further research will be necessary. Generally, the measured sensitivity is insufficient for analysing real samples of environmental or biological origin. An SIM detection limit of around 1 ng leads to a minimum detectable concentration of 20 ng/ml when using a relatively large injection volume of 50 μl. Future improve-

ments to the equipment (incorporation of negative ion detection and a repeller in the TSP source) may lead to lower detection limits. Experiments at the Nermag application laboratory pointed to an increase in sensitivity by a factor of 4 for pinacolylmethylphosphonic acid[17]. However, to detect organophosphorus acids in aqueous solution below a concentration level of 1 ng/ml, preconcentration will be necessary. Preconcentration of organophosphorus acids by means of an ion-exchange resin or a polymeric adsorbent such as XAD-4 has been reported[18,19]. On the basis of the results obtained here with ion-pair chromatography, Sep-Pak C_{18} cartridges can also be used for preconcentration. Pinacolylmethylphosphonic acid was trapped quantitatively from a volume of 50 ml of water with a Sep-Pak C_{18} cartridge using TBA salts. The ion pair formed was removed from the cartridge with methanol. After evaporation of the methanol a preconcentration factor of greater than 100 was easily achieved. The overall recovery of the procedure described was around 90%.

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