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Determination of alkylphosphonic acids by microcolumn liquid chromatography with gradient elution coupled on-line with flame photometric detection

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Abstract

Microcolumn liquid chromatography with gradient elution and on-line flame photometric detection has been used for the selective and rapid determination of non-volatile alkylphosphonic acids, which are hydrolysis products of nerve agents, in aqueous samples. A make-up of water was used to maintain stable introduction of the eluent during a gradient run. The detection limits are strongly dependent on quenching, which is determined by the mass flow of methanol in the eluent. Large-volume injections of 100 μl of aqueous solutions of short- and long-chain alkylphosphonic acids resulted in detection limits in the range 6–800 ng/ml. The repeatability of the retention times and analyte response – peak area or peak height – were 0.7–0.9% and 4–11%, respectively. The method was successfully applied to a local tap water sample and an aqueous soil extract.

Keywords: Warfare agents; Detection, LC; Flame photometric detection; Large-volume injections; Alkylphosphonic acids

1. Introduction

In recent years, there has been a growing interest in the analysis of chemical warfare agents (CWAs) as well as their precursors, manufacturing by-products and degradation products. This is mainly because of the entering into force of the Chemical Weapons Convention (CWC) in 1997, which prohibits the development, production, stockpiling and use of CWAs. Analysis of CWAs and related compounds may play a key role in the verification of the treaty. Recently, an extensive review [1] was published which gives an overview of the state-of-the-art of the analytical methods used for these purposes and future trends.

The most frequently used methods for analysis of the non-volatile highly polar organophosphorus hydrolysis products of nerve agents (alkylphosphonic acids) in aqueous samples are based on gas chromatography (GC) in combination with flame photometric detection (FPD) [2], Fourier transform infrared spectrometry (FT-IR) [3], atomic emission detection (AED) [4], mass spectrometry (MS) and/or tandem mass spectrometry (MS–MS) [5–7].

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However, all GC-based methods require time-consuming sample preparation and derivatization prior to analysis. In so-called ''alleged-use'' investigations, and especially when many samples are involved the time delay may become unacceptably long. Besides, derivatization may lead to the formation of artefacts and low recoveries because of the possible presence of interfering compounds. Recent developments based on rapid hyphenated methods such as liquid chromatography (LC) and capillary electrophoresis (CE) coupled with a variety of (tandem) MS detection techniques [8–12] are therefore of great importance for identification purposes. CE with indirect UV [13–16] or conductivity [16,17] detection is a suitable method for the rapid screening of short- and long-chain alkylphosphonic acids within one run, with aqueous buffer systems, no need of an organic additive and minimal sample pre-treatment. Ion chromatography (IC) can also be used for the analysis of alkylphosphonic acids [18–20]. Recently, LC coupled with evaporative light scattering detection (ELSD) has been proposed [21].

Since 1988, the TNO Prins Maurits Laboratory (TNO–PML) has devoted much attention to the direct determination of alkylphosphonic acids, by means of LC–thermospray MS [22], micro-LC (μLC) with phosphorus-selective FPD [23,24] or thermionic detection [25] and CE–FPD [26]. The μLC–FPD coupling with isocratic elution proved to be easily applicable in many analyses dealing with the short-chain alkylphosphonic acids, but the higher alkylphosphonic acids ($>C_3$) could not be determined in the same run because they are strongly retained. A single μLC–FPD method using gradient elution should eliminate these problems and permit the rapid screening for all alkylphosphonic acids. In the present paper such a method is presented. A make-up flow was used to keep the boiling point and surface tension of the eluent essentially constant, to effect a stable operation of the interface during a gradient run. After a suitable column and an optimised gradient had been selected, analytical data were obtained, with special attention to the effect of quenching on the detector sensitivity and limits of detection (LODs), defined as signal/noise=3. Finally, the suitability of the system was studied by analysing several aqueous samples.

2. Experimental

2.1. Materials

Analytical-grade formic acid, methanol and phosphoric acid (PA) were purchased from Merck (Darmstadt, Germany), ammonium formate, ethylphosphonic acid (EPA) and *n*-propylphosphonic acid (nPrPA) were obtained from Aldrich (Steinheim, Germany). Methylphosphonic acid (MPA), isopropylphosphonic acid (iPrPA), ethyl methylphosphonic acid (EMPA), isopropyl methylphosphonic acid (IMPA), isopropyl ethylphosphonic acid (IEPA) and pinacolyl methylphosphonic acid (PMPA) were synthesised at TNO–PML. Certified non-contaminated soil was obtained from Bedrijfslab Grond-en Gewasonderzoek (Oosterbeek, The Netherlands). Throughout the study, deionised water (Milli-Q water purification system; Millipore, Milford, MA, USA) was used. All solvents and solutions were filtered prior to use over 0.45-μm pore size filter disks from Millipore.

2.2. Instrumentation

The μLC–FPD system is shown schematically in Fig. 1. A Phoenix 20 CU (CE Instruments, Milan, Italy) syringe pump (pump 1) and a Phoenix 20 CU

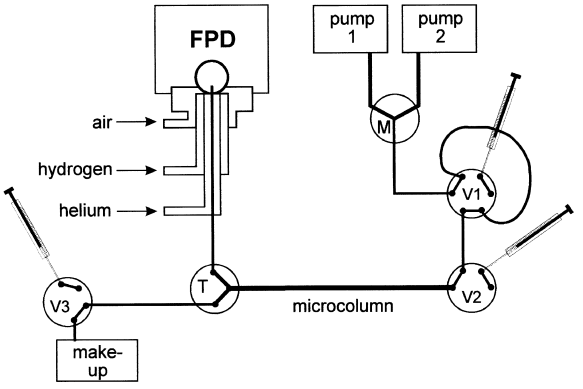


Fig. 1. μLC–FPD set-up. Column: 18.5 cm×320 μm I.D.×450 μm O.D., 10 μm PRP-X100. Gas flow-rates: hydrogen, 600 ml/min; helium, 40 ml/min; air, 300 ml/min. For further details, see Experimental section. The scheme has not been drawn to scale.

slave pump (pump 2) were connected via a Valco mixing chamber (VICI, Schenkon, Switzerland) (M) with a Valco six-port valve (V1) having an external injection loop of polyether ether ketone (PEEK) tubing (Alltech, Breda, The Netherlands). This six-port valve was connected to a Valco microinjection valve with a 60-nl internal volume (V2). The fused-silica (Supelco, Bellefonte, PA, USA) column (18.5 cm×320 μm I.D.×450 μm O.D.) was slurry-packed with 10 μm PRP-X100 (Hamilton, Reno, NV, USA) copolymer. The column outlet was inserted in a laboratory-made PEEK T-piece (T), together with the outlet of a Phoenix 20 CU make-up pump, which was connected via a Valco microinjection valve with a 60-nl internal volume (V3), allowing flow-injection optimisation of the interface and detector. An introduction capillary (25 cm×100 μm I.D.×170 μm O.D.) leads from the T-piece through the interface into the flame of the Model 380 FPD system (CE Instruments). The interface is described in detail elsewhere [23].

Data collection and processing of the FPD output was performed using Atlas 98 (LabSystems, Altrincham, UK). The data-sampling rate was set at 6.25 Hz. Bond lengths were calculated using SPARTAN (Wavefunction, Irvine, CA, USA), and bond orders using GAMESS_US (Iowa State University, Ames, IA, USA) software.

2.3. Sample preparation

A 100-ml standard solution of a mixture of alkylphosphonic acids in water was prepared. The structures of the test compounds and their concentrations in the standard solution are shown in Table 1. A standard solution in local tap water was prepared in the same way.

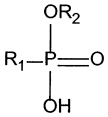
An amount of 10 g soil was put in an Erlenmeyer flask, and spiked with 2 ml of the alkylphosphonic acid standard solution. The spiked soil was thoroughly stirred and left under a gentle stream of nitrogen at room temperature for 1 day. Subsequently, the spiked soil was extracted with 10 ml of water according to a TNO–PML standard operation procedure [27]. After 10 min of ultrasonication the liquid was decanted into a centrifuge tube. An additional 10 ml of water were added to the soil and after 10 min of ultrasonication, decanted into another centrifuge tube. The extracts were centrifuged for 10 min at 10 000 rpm and, subsequently, combined. Finally, the extracts were filtered over 0.45-μm pore size filter disks from Millipore.

3. Results and discussion

3.1. Choice of the separation column, gradient and make-up

In earlier work, it was concluded that in μLC–FPD with isocratic elution, PRP-X100 is a suitable packing material for the separation of lower alkylphosphonic acids, while PRP-1 should be used for the separation of higher alkylphosphonic acids ($>C_3$) [28]. Because of the hydrophobic as well as strong anion-exchange properties of PRP-X100, it should be possible to separate both short- and long-chain alkylphosphonic acids ($pK_{a1}<3$) in one run on

Table 1
Structures and concentrations in the standard solution of the studied compounds

Structure	Compound name	Acronym	R_1	R_2	Concentration (μg/ml)
	Methylphosphonic acid	MPA	CH_3	H	2.5
	Ethylphosphonic acid	EPA	C_2H_5	H	5.0
	Isopropylphosphonic acid	iPrPA	C_3H_7	H	10.0
	n-Propylphosphonic acid	nPrPA	C_3H_7	H	10.0
	Ethyl methylphosphonic acid	EMPA	CH_3	C_2H_5	10.0
	Isopropyl methylphosphonic acid	IMPA	CH_3	C_3H_7	12.5
	Isopropyl ethylphosphonic acid	IEPA	C_2H_5	C_3H_7	12.5
	Pinacolyl methylphosphonic acid	PMPA	CH_3	C_6H_{13}	50.0

that packing material by using gradient elution. From earlier results it was concluded that below 0.1 *M* formate concentration, ion-exchange plays a predominant role. Polar hydrolysis products like MPA can be nicely separated with such eluents and with ammonium ion concentrations up to 0.2 *M* and a pH in the range of 2 to 8. MPA and ubiquitous inorganic phosphate (PA), however, are only separated completely in the absence of ammonium ions. The more hydrophobic, monovalent alkylphosphonic acids are strongly retained under these circumstances. For formate concentrations of over 0.1 *M*, retention due to ion-pair formation is more likely, and ion-pair LC with organic modifiers will probably allow the separation of these higher alkylphosphonic acids. In other words, a gradient starting with an aqueous formic acid solution with, next, an increase of the formic acid as well as the ammonium concentration, in combination with an organic modifier, should offer a screening method for all alkylphosphonic acids in a single run.

Unfortunately, the current μLC–FPD system cannot be used under these conditions because the present interface can only be operated if isocratic elution is used. Changing the eluent composition changes the boiling point and surface tension of the eluent. Consequently, the optimum position of the introduction capillary in the interface, which is dependent on these parameters, varies during a gradient run. Because this position is fixed in the current interface, introduction instability and subsequent loss of sensitivity and irreproducible results may be expected, and were indeed observed in initial experiments. Secondly, quenching of the phosphorus emission by organic compounds is the main disadvantage of FPD. Collision-induced quenching will reduce analyte detectability with the degree of quenching being dependent on the mass flow of organic molecules [29]. In LC the situation is more serious than in GC, and the percentage of organic modifier should be minimised. Since the proposed gradient requires the addition of a modifier, a certain loss of sensitivity is unavoidable.

To improve the stability of the interface during gradient elution, the post-column addition of a make-up flow to limit the variation of the boiling point and surface tension is a possible solution. For obvious reasons, water is the first choice. The flow-rate of the make-up flow is determined by that of the eluent, and the maximum flow that can be handled by the interface used, e.g., 5–15 μl/min. To keep the variation of the boiling point and surface tension as small as possible, the make-up flow should be maximised.

3.2. Optimisation of the gradient and make-up

The LC gradient was optimised with the diluted aqueous standard mixture of the alkylphosphonic acids as test sample. It contained highly polar divalent alkylphosphonic acids, MPA, EPA, nPrPA and iPrPA, more hydrophobic monovalent alkyl methylphosphonic acids, EMPA, IMPA and PMPA, and IEPA.

For the analysis of environmental and industrial samples it is important to separate the polar analytes of interest, e.g., MPA and EPA, from PA, which may be present in such samples. Since MPA and PA are only separated completely from each other on PRP-X100 in the absence of ammonia with 0.13 *M* formic acid in water as eluent, this eluent (A) was taken as the initial solution in the gradient programme. A 10-μl injection of a mixture containing 5 μg/ml of MPA, PA and EPA with isocratic elution by eluent A at 8 μl/min, confirmed the baseline separation of the analytes, with retention times of 5.10, 5.45 and 6.40 min, respectively.

With the higher alkylphosphonic acids, acetonitrile could not be used as the modifier because of the possible formation of toxic hydrogen cyanide in the flame of the detector. Methanol, which is known to cause the same degree of quenching as does acetonitrile, was selected instead [23]. Initially, 0.3 *M* aqueous ammonium formate–methanol (98:2, v/v), at a flow-rate of 8 μl/min, was chosen as the second eluent (B). Water was used as make-up at 7 μl/min. All alkylphosphonic acids were baseline separated using a 2-min isocratic run of eluent A and, next, a 10-min gradient up to 100% eluent B with a final 10-min hold. However, PMPA did not elute under these conditions, and therefore the percentage of methanol in eluent B was increased to 50%, which caused the elution of PMPA. Unfortunately, excessive tailing was observed for the late eluting compounds. Peak shapes improved upon changing eluent B to 0.3 *M* ammonium formate–methanol (30:70,

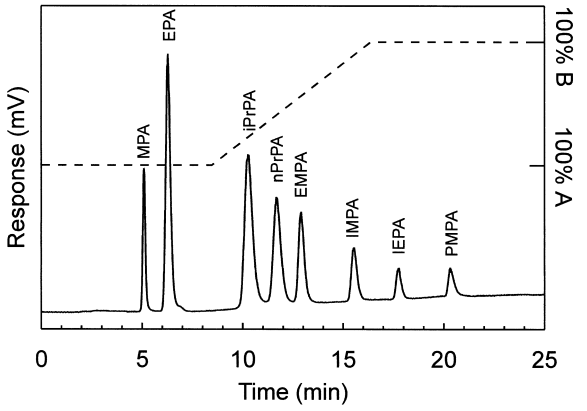


Fig. 2. Gradient elution μLC–FPD of a 10-μl injection of a standard solution of alkylphosphonic acids in water. For structures and concentrations, see Table 1. Gradient profile indicated by dashed line: 8.5 min isocratic 0.13 *M* formic acid, next an 8-min gradient up to 0.3 *M* ammonium formate–methanol (30:70, v/v), and finally an 8.5 min hold; flow-rate, 8 μl/min. Make-up, water at 7 μl/min.

v/v). Fig. 2 shows a 10-μl injection of the standard solution using a much shorter, i.e., 0.5-min, isocratic run of eluent A and, next, an 8-min gradient up to 100% eluent B with a final 8.5-min hold. The effective gradient program is delayed some 8 min because of the extra volume of the injection loop between the mixing chamber and the top of the column. Clearly, all tested compounds are baseline separated, even the structural isomers, iPrPA, nPrPA and EMPA. The composition of this gradient was maintained in further experiments.

The effect of the make-up flow was studied by varying the flow-rate from 0 to 10 μl/min, while using the above gradient at 8 μl/min. Without using a make-up, introduction instability immediately became apparent during the gradient part of the LC run, and caused high and irregular noise, as well as bad peak shapes for the later eluting compounds. When an increasing volume of water was added, the noise gradually decreased and analyte peak shapes improved. The best results were obtained with make-up flows in the range of 5–7 μl/min. When the total carrier stream exceeded 15 μl/min, the baseline started to become irregular again, probably because the current interface cannot handle such high flow-rates.

3.3. Quenching

The degree of quenching caused by a modifier can be calculated by plotting the intensity ratio, ∅, as defined by Sugiyama et al. [29]:

$$\varnothing = \frac{\mathrm{FPD_m}}{\mathrm{PFD_0}} \tag{1}$$

as a function of the mass flux of that modifier. In the present study, the FPD responses without modifier, FPD_0, were determined by flow-injection analysis (FIA) of the test compounds, while the FPD responses with modifier, FPD_m, were calculated from the μLC–FPD chromatograms. The peak areas were converted to the detector sensitivity, $Q_{i,n}$, of each compound *n* (pg P/s) to compare the FIA ($i=0$) and the μLC results ($i=$m) by means of:

$$Q_{i,n} = \frac{2N_i c_{i,n} V_i P_n}{A_{i,n}} \tag{2}$$

where N_i is the noise (mV), $c_{i,n}$, the concentration of compound *n* (pg/nl), V_i, the injection volume (nl), P_n, the amount of phosphorus in the molecule of compound *n* (total mass of *P* in *n*/molecular mass of *n*), and $A_{i,n}$, the peak area of compound *n* (mVs). The intensity ratio of *n* can then be calculated to be:

$$\varnothing_n = \frac{Q_{\mathrm{m},n}}{Q_{0,n}} \tag{3}$$

The detrimental influence of the increasing percentage of methanol on the analyte responses can be read from Fig. 3, where $\varnothing_n$ is plotted as a function of the mass flux of methanol in a gradient run after a 10-μl injection of the standard solution. As was expected, the largest effect was observed for the later eluting compounds, while no quenching occurred for MPA and EPA. At the maximum concentration of methanol, PMPA has an ∅ of 0.015, which means a loss of sensitivity of two orders of magnitude. Quenching which cannot be avoided with the present set-up may, in principle, be reduced by using a dual-flame FPD system, or by exchanging the positions of the hydrogen and air entrances to create a hydrogen-hyperventilated flame. Unfortunately, both solutions are rather complicated because the principle of the introduction of liquid is dependent on the temperature and position of the detector flame, which are

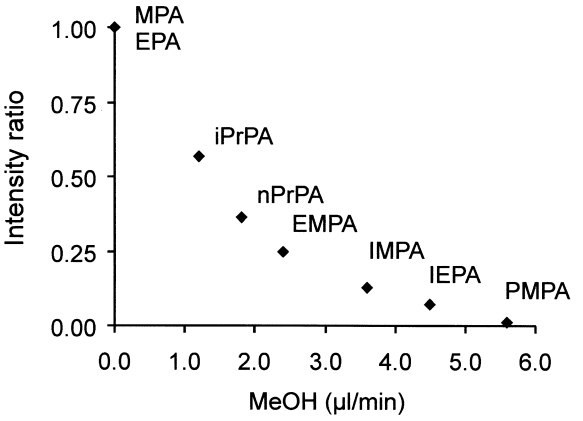


Fig. 3. Influence of the mass flux (µl/min) of methanol on intensity ratio (Eq. (3)). Conditions as in Fig. 2.

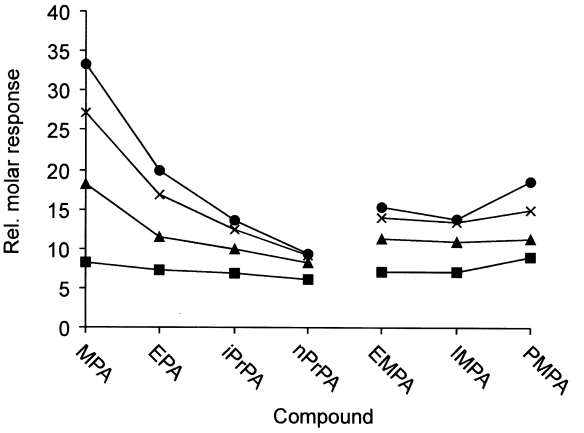


Fig. 4. Influence of the hydrogen-to-oxygen ratio on the molar responses of the alkylphosphonic acids. Air flow-rate: ■, 250 ml/min; ▲, 300 ml/min; ×, 350 ml/min; ●, 400 ml/min. Hydrogen flow-rate, 600 ml/min. Molar responses relative to those at air flow-rate of 200 ml/min. Conditions as in Fig. 2.

totally different in those situations compared with the current system. The use of an eluent–jet interface [30] would be an interesting alternative because it decouples the introduction of the liquid from the detector–flame part of the set-up. This approach should enable a separate optimisation of both modules. Work in this area is currently in progress.

The influence of the hydrogen-to-oxygen ratio on the analyte responses during gradient elution was studied by varying the air flow in the range of 200–400 ml/min with a 600 ml/min hydrogen flow. The effect of decreasing the hydrogen-to-oxygen ratio from 15 to 7.5 results in an increase of the flame temperature and energy available for the dissociation of molecular species. On the other hand it is well known that the FPD response is dependent on the characteristic emission of the HPO* molecule that is formed in relatively cool hydrogen-rich hydrogen–air flames.

Fig. 4 shows the molar responses at the different air flows calculated relative to the molar responses when using an air flow of 200 ml/min. Rather remarkably, the effect on the divalent alkylphosphonic acids was much larger than on the monovalent alkyl alkylphosphonic acids, with a decrease from MPA via EPA and iPrPA to nPrPA. The different results obtained for each of the divalent acids clearly show a trend, which suggests a structure-related change of the response factor when decreasing the hydrogen-to-oxygen ratio from 15 to 7.5. This change is probably related to the C_n–P bond dissociation energy which decreases with increasing *n*. Support is provided by the differences calculated for the bond order and bond length of MPA and EPA. Ab initio ($3-21G^{(*)}$) calculation showed the bond lengths of MPA and EPA to be 1.7713 Å and 1.7739 Å, respectively, and the C_n–P bond orders, 0.969 and 0.952, respectively. Both results strongly suggest that the C_n–P bond is stronger in MPA or, in other words, that the dissociation energy is higher than that of EPA. The mutual differences in dissociation energy decrease with an increasing number of carbon atoms, which results in a decreasing change in the molar response going from EPA to nPrPA. The absence of a significant difference in molar responses observed for the monovalent alkyl methylphosphonic acids can probably be explained by the fact that the formation of HPO* intermediates is determined by the energy of the P–C_n bond, rather than that of the PO–C_n bond. Structure-related effects on the phosphorus-selective FPD response have been reported in the literature [31–33].

3.4. Analytical performance

In µLC, injection volumes usually are limited to

about 10 μl. In order to increase analyte detectability (expressed in units of concentration), larger injection volumes were also tested and, somewhat surprisingly, no problems were encountered up to 100 μl. It was only for still higher injection volumes that the first three peaks (MPA, EPA and iPrPa) started to become distorted. Of course, with a 100-μl injection, the effective gradient is delayed for a long period of time, viz. some 20 min. The detector sensitivity represented as pg P/s, and the LODs of all test compounds at this injection volume are summarised in Table 2. The widely different LODs, 6–800 ng/ml, reflect the increasing quenching as well as the decreasing amount of phosphorus present in later-eluting compounds. However, the LODs easily meet the performance criteria established by the Organisation for the Prohibition of Chemical Weapons for their proficiency tests, which are held to evaluate the capability of laboratories to analyse chemicals relevant to the CWC. Test samples such as water, soil, rubber and organic liquids, are spiked with relevant chemicals at levels of 1–10 μg/g or even higher (and verification analyses are primarily qualitative [34]). The repeatability of the retention times and the analyte responses were determined from five successive 10-μl injections of the standard solution. The relative standard deviations (RSDs) were in the ranges 0.7–0.9% and 4–11% for the retention times and the responses – peak area or peak height – respectively. The higher RSDs for the analyte responses were found for the compounds eluting on the slope of the gradient. Most probably, they reflect small disturbances of the liquid introduction because of the changing composition of the eluent. However, all results are fully acceptable for screening purposes.

Table 2
LODs and detector sensitivity of the alkylphosphonic acids in μLC–FPD[a]

Compound	LOD (μg/l)	Detector sensitivity (pg P/s)
Methylphosphonic acid	6	5
Ethylphosphonic acid	8	5
Isopropylphosphonic acid	40	5
n-Propylphosphonic acid	55	10
Ethyl methylphosphonic acid	70	15
Isopropyl methylphosphonic acid	100	30
Isopropyl ethylphosphonic acid	160	60
Pinacolyl methylphosphonic acid	800	200

[a] Injection volume, 100 μl. For details, see text.

3.5. Applications

To study the applicability of gradient μLC–FPD for the detection of alkylphosphonic acids in real-life samples, local tap water and a certified soil were spiked with the standards. Local tap water was spiked to the same final concentration as the standard solution in deionised water used in the previous experiments (2.5–50 μg/ml). A 10-μl injection of the spiked tap water yielded a chromatogram that was closely similar to that of the standard solution shown in Fig. 2. The same was true for the chromatogram recorded for a 100-μl injection of tap water with a 10-fold lower spiking level of 0.25–5.0 μg/ml.

As for the soil, 10 g of the spiked soil (0.5–10 μg/g) was extracted with 20 ml of water. Subsequently, 10-, 20- and 100-μl samples of this extract were analysed by μLC–FPD without further sample preparation. All compounds could be detected if 20 μl were injected, with PMPA, not unexpectedly, only slightly above the LOD. A typical chromatogram obtained for a 100-μl injection of the aqueous soil extract is shown in Fig. 5. Next to the spiked compounds, no additional peaks were observed, which illustrates the selectivity of the present method.

4. Conclusions

A wide range of non-volatile alkylphosphonic acids can be analysed selectively in a single run by μLC–FPD with gradient elution and the post-column addition of water as a make-up to maintain stable introduction of the eluent. Injection volumes for real-life samples can be as high as 100 μl, which results in LODs of 6–800 ng/ml, depending on the degree of quenching by the organic modifier used, methanol, that is, on the elution time of the analyte. Further research will be focused on the use of an eluent–jet interface combined with a hydrogen-hyperventilated flame or a dual-flame FPD system to

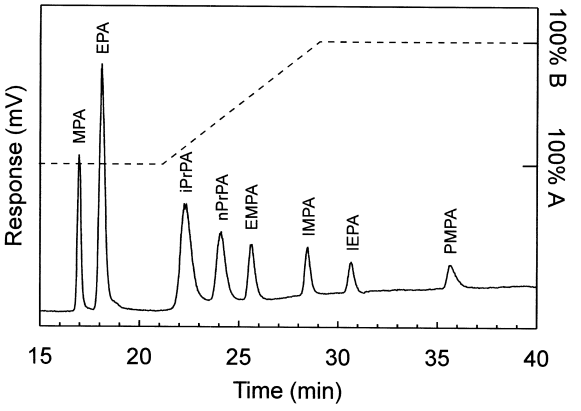


Fig. 5. Gradient elution μLC–FPD of a 100-μl injection of a 20-ml aqueous extract of a soil spiked with 0.5–5.0 μg/g of alkylphosphonic acids. Gradient profile indicated by dashed line: 20.5 min isocratic 0.13 *M* formic acid, next an 8-min gradient up to 0.3 *M* ammonium formate–methanol (30:70, v/v), and finally an 11.5 min hold; flow-rate, 8 μl/min. Make-up, water at 7 μl/min.

reduce quenching and improve the LODs of the later eluting compounds.

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