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Journal of Chromatography A, 825 (1998) 71–80

JOURNAL OF CHROMATOGRAPHY A

Identification of phosphonic acids by capillary electrophoresis–ionspray mass spectrometry

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Received 22 June 1998; received in revised form 26 August 1998; accepted 28 August 1998

Abstract

The identification of alkylphosphonic acids in spiked tap water has been investigated by on-line capillary electrophoresis–UV spectrometry–mass spectrometry (CE–UV–MS) in negative-ion mode. The 5 m*M* sorbic acid–ammonia electrolyte (pH 6.5) allows simultaneous indirect UV and MS (ionspray) detection. Several parameters (electrolyte pH, make-up chemical composition and make-up flow-rate) have been optimized and 5 mg/l limit of detection has been reached for these analytes in selected ion monitoring MS detection. MS–MS detection has also been investigated to reach a low detection limit (100 μg/l) for alkyl alkylphosphonic acids in spiked tap water. The mass spectra of these compounds exhibit a very abundant negative ion, $[M-H]^-$ (MS) with characteristic fragmentation (MS–MS) of acids and monoesters. Quantitative analysis achieved with CE–UV shows good correlation coefficients and allows accurate quantification of the analytes.

Keywords: Detection, electrophoresis; Ionspray; Water analysis; Warfare agents; Phosphonic acids; Sorbic acid; Alkylphosphonic acids

1. Introduction

Phosphonic acids (alkyl-ethyl/methylphosphonic acids and alkylphosphonic acids as described in Table 1) are hydrolysis products of nerve agents [1,2].

The analysis of these compounds has become very important in the last few years since the implementation of the Organization for the Prohibition of Chemical Weapons (OPCW) at the Geneva convention in 1992. The OPCW organizes exercises such as Round Robin Test or Official Proficiency Tests. The objective of these exercises is to verify the presence of Chemical Weapons Agents (CWAs) or key precursors and hydrolysis products in complex samples in order to develop and test existing or new procedures or methods and to gain experience in the verification tasks required by the implementation of the chemical weapons convention.

Analytical methods for the determination of alkylphosphonic acids described in the literature before 1998 have been exhaustively reviewed by several authors using gas chromatography (GC) [3–9], liquid chromatography (LC) [10–20], and capillary electrophoresis (CE) methods [21–26].

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0021-9673/98/$ – see front matter
PII: S0021-9673(98)00710-9

Table 1
Phosphonic acids and CID product ion spectra $(M-H)^-$

Name	Abbreviation	M_r	Precursor ion (m/z)	Product ion spectra m/z (% abundance)
Alkyl methylphosphonic acids				
Methyl methylphosphonic acid	MMPA	110	109	109 (100), 95 (5)
Ethyl methylphosphonic acid	EMPA	124	123	123 (100), 95 (5)
Isopropyl methylphosphonic acid	IMPA	138	137	137 (100), 95 (10)
Cyclopentyl methylphosphonic acid	CPMPA	164	163	163 (100), 95 (11)
Cyclohexyl methylphosphonic acid	CMPA	178	177	177 (100), 95 (6)
Pinacolyl methylphosphonic acid	PMPA	180	179	179 (100), 95 (7)
Alkyl ethylphosphonic acids				
Ethyl ethylphosphonic acid	EEPA	138	137	137 (100), 109 (15)
Isopropyl ethylphosphonic acid	IEPA	164	163	163 (100), 109 (20)
(1,2-Dimethylpropyl) ethylphosphonic acid	DEPA	180	179	179 (100), 109 (13)
Cyclohexyl ethylphosphonic acid	CEPA	192	191	191 (100), 109 (27)
Alkylphosphonic acids				
Methylphosphonic acid	MPA	96	95	95 (100), 79 (5)
Ethylphosphonic acid	EPA	110	109	109 (100), 79 (5)
Propylphosphonic acid	PPA	124	123	123 (100), 79 (5)
Butylphosphonic acid	BPA	138	137	137 (100), 79 (5)

In order to obtain structural information of chemical warfare agents, mass spectrometry (MS) has been coupled with separation methods particularly in GC–MS [3–6,8], LC–MS [27,28] and finally in CE–MS [29].

Up to now, curiously, the only method developed for alkylphosphonic acids in CE–MS is that by Kostiainen et al. [29] in negative ionization mode using volatile electrolytes such as ammonium acetate. The soft ionization mode of the ionspray (IS) interface allows minimal fragmentation with production of very abundant negative ions such as $[M-H]^-$ corresponding to the loss of one proton of each analyte.

The aim of this work is to develop a CE–MS and CE–MS–MS methodology to identify alkylphosphonic acids in different matrices such as tap water while avoiding the derivatization and preconcentration steps which are always difficult to manage correctly and time consuming.

2. Experimental

2.1. Chemicals

Electrolytes were prepared from analytical quality products; sorbic acid (98% purity) ammonia and *n*-pentanol were obtained from Fluka (Buchs, Switzerland).

Phosphonic acids were supplied by the CEB (Centre d'Etudes du Bouchet, Vert le Petit, France).

Standard mixture solutions of analytes and electrolytes were prepared in purified water (HPLC quality) obtained with an Elgastat UHQ II system (Villeurbanne, France).

All electrolytes were filtered before use through a polypropylene filter membrane with a 0.22 μm porosity (Prolabo, Paris, France).

2.2. CE conditions

Separations were carried out on a P/ACE 5000 apparatus (Beckman Instruments, Fullerton, CA, USA) using a fused-silica capillary of 85 cm (20 cm to the detector)×50 μm. Indirect UV detection was performed using a 254 nm UV filter; the detector time constant was 1 s and the data acquisition rate was 20 Hz.

The capillary was kept at constant temperature (25°C) by immersion in a cooling liquid circulating in the cartridge.

Analytes were injected at the anode by hydro-

dynamic injection under nitrogen overpressure (0.5 p.s.i; 1 p.s.i.=6894.76 Pa).

Data were collected using an IWT computer with an electrophoresis data calculation program (System Gold software, version 7.11, Beckman).

2.3. MS conditions

MS detection and fragmentation were carried out on an API 300 triple quadrupole mass spectrometer apparatus (Perkin-Elmer Sciex, Toronto, Canada) via an IS interface operating at room temperature.

Conditions were investigated using spray voltage (−4 kV), orifice voltage (−25 V), ring voltage (−400 V) and air as nebulizer gas.

A Harvard Model 22 syringe pump was used to deliver 5 μl/min make-up flow-rate.

Mass spectra were acquired using a dwell time of 1 ms per step of 0.2 u. A Macintosh computer was used for instrument control, data acquisition and data processing using LC_2 Tune software.

3. Results and discussion

The coupling between CE and MS requires the optimization of electrolyte composition commonly used in CE. As reported previously, many development methods by CE have been investigated for the analysis of alkylphosphonic acids, but none of them allowed these analytes to be detected simultaneously by indirect UV spectrometry and MS.

According to several authors [30–36], CE–MS coupling requires: (1) the use of volatile electrolyte systems to ensure compatibility with the mass spectrometer, (2) the addition of a make-up, sheath liquid to compensate the low flow-rate of the CE (nl/min) in order to increase the stability and the production of the spray, (3) the use of a nebulizer gas (pneumatic assisted nebulization such as IS) to stabilize the spray formation and (4) the optimization of the relative position between the CE capillary, the stainless steel of the sheath flow and the nebulizer gas.

We therefore decided to test the electrolyte system developed previously [1] with UV detection by using 5 m*M* sorbic acid–ammonia.

The use of sorbic acid seems inappropriate with MS detection because this acid is not considered as a volatile compound. In negative mode, sorbic acid gives an $[M-H]^-$ ion at m/z 111 (molecular mass, $M_r=112$), without any interference with any of the phosphonic ions studied (Table 1).

Moreover, the flow-rate of the CE capillary is about 10 nl/min whereas the make-up reaches about 1–10 μl/min. The dilution of the CE flow-rate allows for the use of sorbate anion.

The first step of our study was to determine the optimized buffer pH. This experiment was carried out on a model mixture (100 mg/l) containing five solutes (EMPA, IMPA, CPMPA, CMPA and PMPA, see Table 1).

The variation in the signal-to-noise ratio (S/N) versus the electrolyte pH values was studied. The electrolyte pH value was adjusted with an ammonia solution (1 *M*) between 5.25 and 8.33. S/N was calculated from the extract ion current corresponding to the analyte. For each alkylphosphonic acid, the signal-to-noise ratio increases from pH 5.25 (S/N= 200 for CMPA) and reaches a maximum value at pH 6.51 (S/N=950 for CMPA), with decreasing at higher pH value (S/N=250 for CMPA at PH 8.33). According to Wahl and Smith [37] signal intensity decreases with increasing ionic strength an electrolyte pH (*I* varied from 3.3 m*M* at pH 5.0 to 5 m*M* at pH 8.0).

In fact, at this pH value, both sorbic acid (pK_a= 4.75) and analytes (pK_a values were between 2.0 and 2.5 [38]) are totally dissociated so above pH 6.5 the electrophoretic mobility of analytes is independent of the pH. In contrast the electroosmotic mobility increases markedly which induces a decrease in the resolution between each solute; the resolution decrease more than 50% between pH 5.25 and 8.33.

pH 6.51 was therefore selected to give a high S/N value with a very acceptable resolution ($R_s>1$ except for CMPA/PMPA).

Since the nature, the composition and the flow-rate of the make-up liquid play a key role in IS mechanism, we have investigated its composition and flow-rate.

According to Bruins [35], the addition of an organic solvent to the make-up liquid via a coaxial addition reduces the surface tension of the analyte. The surface tension of solute droplets produced by IS is an important parameter. After droplet formation at

atmospheric pressure, the droplet undergoes size reduction by evaporation of the solvent, which induces an increase in the charge density at the droplet surface. The droplets then, become unstable and undergo deformation which leads to a high local electric field on the droplet surface. When this deformation becomes sufficient and the electrostatic charge repulsion between negative charges exceeds the surface tension, the droplet falls apart forming microdroplets, the process continues until the formation of gaseous ions.

The second step in optimization concerned the composition of the make-up liquid. Different alcohols were studied as make-up liquid with 5 m*M* sorbic acid electrolyte (pH 6.51). The higher S/N value was obtained by using pentanol as make-up liquid. The detection sensitivity was 100-times greater than with methanol or ethanol. These alcohols, along with isopropanol, are generally used to constitute the make-up [30,34–36]. As alcohols have a lower surface tension than water (respectively, between 22 to 26 dyne/cm for methanol to heptanol instead of 72 dyne/cm for water [39]) the surface tension of ionized droplets decreases with alcohol make-up liquids and the production of ions emitted from the microdroplet by ion evaporation increases.

The mechanisms of ion formation in gas phase are very complex, and future studies involve several physico–chemical parameters (viscosity, volatility, surface tension) to explain the better sensitivity obtained with pentanol as make-up liquid.

Lastly, the variation in the make-up flow-rate was studied (between 2.5 and 10 μl/min). According to Bruins [35] the IS efficiency would decrease with an increase in the flow-rate due to a smaller amount of ions formed in gas phase. Increasing the flow-rate at 10 μl/min decreases S/N for all the alkylphosphonic acid and leads to a constant noise background but increases the dilution of analytes in CE.

The optimum flow-rate seems to be in the 5.0–7.5 μl/min range, and the value of 5.0 μl/min was generally used [30–36].

Therefore, the separation of the three different families of alkylphosphonic acids (alkyl methylphosphonic acids, alkyl ethylphosphonic acids and alkylphosphonic acids) was realized under optimized conditions (pentanol as make-up liquid, 5 μl/min) as shown in Fig. 1.

The total ion current (TIC) of Fig. 1 shows that the separation is achieved in about 24 min with good resolution. This separation time is greater than those obtained in CE–UV due to the length of the capillary separation (85 cm instead of 60–70 cm commonly used in CE–UV). As expected [1], the migration order of these alkylphosphonic acids is inversely related to their hydrophobicity.

Before the separation coupling of CE with MS, we studied the behavior of these alkylphosphonic acids in mass spectrometry with IS ionization mode by infusion. Even if IS is a soft ionization mode, the fragmentation of these solutes exhibits selective fragment ions.

As reported Table 1, each of these alkylphosphonic acids gives characteristic fragment ions. For example, alkyl methylphosphonic acids give common product negative ions at m/z 95 $[CH_3P(O)(OH)O]^-$ due to the loss of the ester alkyl group. This corresponds also to the negative ions due to the ionization of MPA, see Table 1.

Concerning alkyl ethylphosphonic acids, the common product ion at m/z 109 $[C_2H_5P(O)(OH)O]^-$ is induced by the loss of the ester alkyl group and corresponds to the negative ion of EPA. Alkylphosphonic acids give common product ions at m/z 79 $[P(O)_2O]^-$ corresponding to the loss of the alkyl group (methyl ethyl, propyl or butyl).

These common product ions can be useful in CE–MS–MS to detect low levels of alkylphosphonic acids using MS–MS detection. The MS–MS detector is set to detect these fragments selectively as shown in Fig. 2. Fig. 2 reports the analysis of alkyl methylphosphonic acids in CE–MS–MS with extract ion current (XIC) recorded at m/z 95. The same results would be obtained with the alkyl ethylphosphonic acids and alkylphosphonic acids if the recorded XIC is set respectively, at m/z 109 and m/z 79.

3.1. Application to the analysis of two alkylphosphonic acids

This procedure has been applied to identify phosphonic acids contained in spiked tap water provided by the Third Official PTS/OPCW Proficiency Test Analysis (April 1997) [40] prepared by the Centre d'Etudes du Bouchet (France).

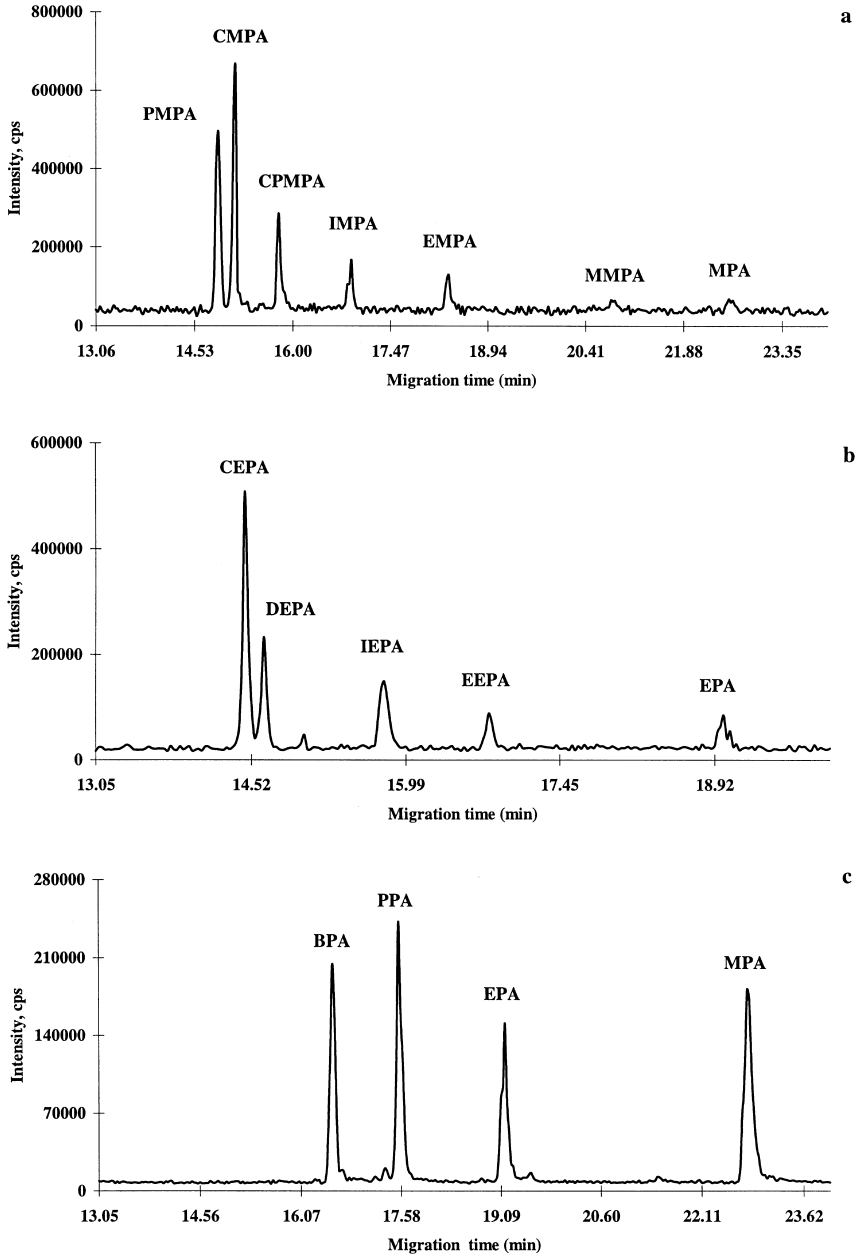

Fig. 1. CE–ionspray MS separations of alkylphosphonic acids (5 mg/l). (a) Alkyl methylphosphonic acids, (b) alkyl ethylphosphonic acids, (c) alkylphosphonic acids. CE conditions: fused-silica capillary dimensions, 85 cm (indirect UV detection set at 20 cm, 254 nm)×50 μm I.D.; electrolyte, 5 m*M* sorbic acid and ammonia, pH 6.5; applied voltage, +30 kV; temperature: 25°C; hydrodynamic injection, 5 s; analyte concentration: 5 mg/l; capillary conditioned step, 3 min with the electrolyte buffer. MS conditions: make-up, pentanol at 5 μl/min; nebulizer gas, air; ionspray voltage, −4 kV; orifice voltage, −25 V; ring voltage, −400 V.

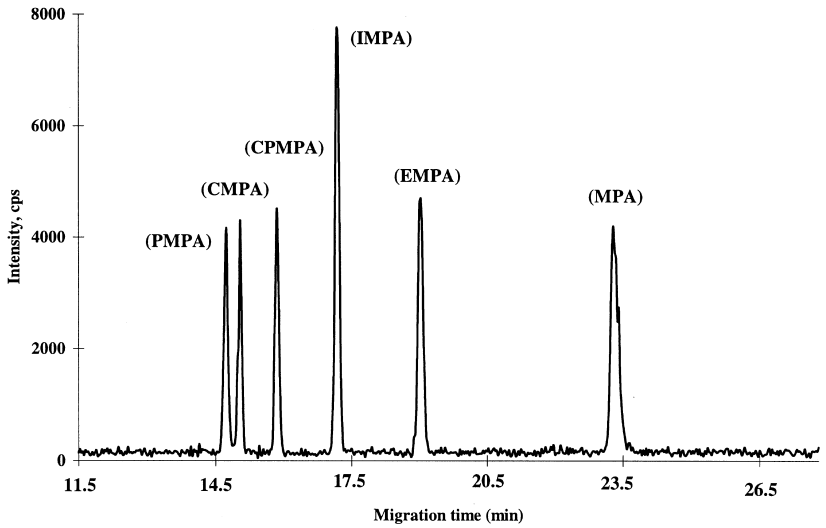

Fig. 2. CE–MS–MS analysis of alkyl methylphosphonic acids (5 mg/l). CE conditions as in Fig. 1; MS conditions as in Fig. 1 with collision energy set at 25 eV instead of 15 eV.

The mass spectra of the matrix and the blank have been recorded by infusion in Fig. 3a. The comparison between the two mass spectra shows two compounds with negative ions at m/z 123 (M_r=124) and m/z 207 (M_r=208). Fragments at m/z 97 and 111 were due to chemical compounds present in the matrix.

Then, on-line CE–UV–MS in negative ion mode was investigated under optimized conditions. The fingerprint of indirect UV detection in Fig. 3b indicates two solutes, even if we observed some baseline drift due to the matrix. Complete separation and resolution of two unknown compounds has been obtained even if the UV detection was performed on a 20 cm length capillary.

The MS detection was set at m/z 123 and 207. The two unknown compounds are correctly resolved with good S/N (respectively, 7200 and 3500 for m/z 123 and m/z 207) at 13.4 and 16.7 min (Fig. 3c).

Fragmentation studies have been undertaken in MS–MS in order to identify these two solutes (Fig. 4). By increasing in the collision energy from 15 eV to 25 eV (Fig. 4a), the intensity of the peak at m/z 207 decreases leading to an increase in the intensity of the peak at m/z 95, which corresponds to ion product characteristic of alkyl methylphosphonic acids (see Table 1). The loss of the alkyl group (m/z 122) gives a putative formula such as C_8H_{17}. The nature of the alkyl chain (linear or branched), required studies of fragmentation conditions and was identified as being a 2-ethylhexyl alkyl chain. So the first unknown compound at m/z 207 is 2-ethylhexyl methylphosphonic acid (EHMPA) [41].

Concerning the second compound, fragmentation studies (Fig. 4a) have shown the loss of an alkyl group at m/z 43 that corresponds to a C_3H_7 alkyl group. The fragmentation of m/z 123 increases the intensity of the peak at m/z 79, which is characteristic of the negative ionization of an alkylphosphonic acid (studies by LC–MS have determined that m/z 123 corresponds to the isopropylphosphonic acid [41]).

The CE–MS–MS electropherogram of this sample shows as expected an increase in the S/N, 16 000 compared to 7200 in MS and 18 000 compared to 3500 in MS for respectively, EHMPA and isopropylphosphonic acid, Fig. 4b.

Finally, quantitative analysis was achieved in CE–UV; the linear calibration curves in the 1–25 mg/l concentration range show a good correlation coefficient (r^2=0.9969 and 0.9979 for EHMPA and isopropylphosphonic acid, respectively). Concentrations are 13.2 mg/l and 9.1 mg/l for EHMPA and isopropylphosphonic acid, respectively and are close

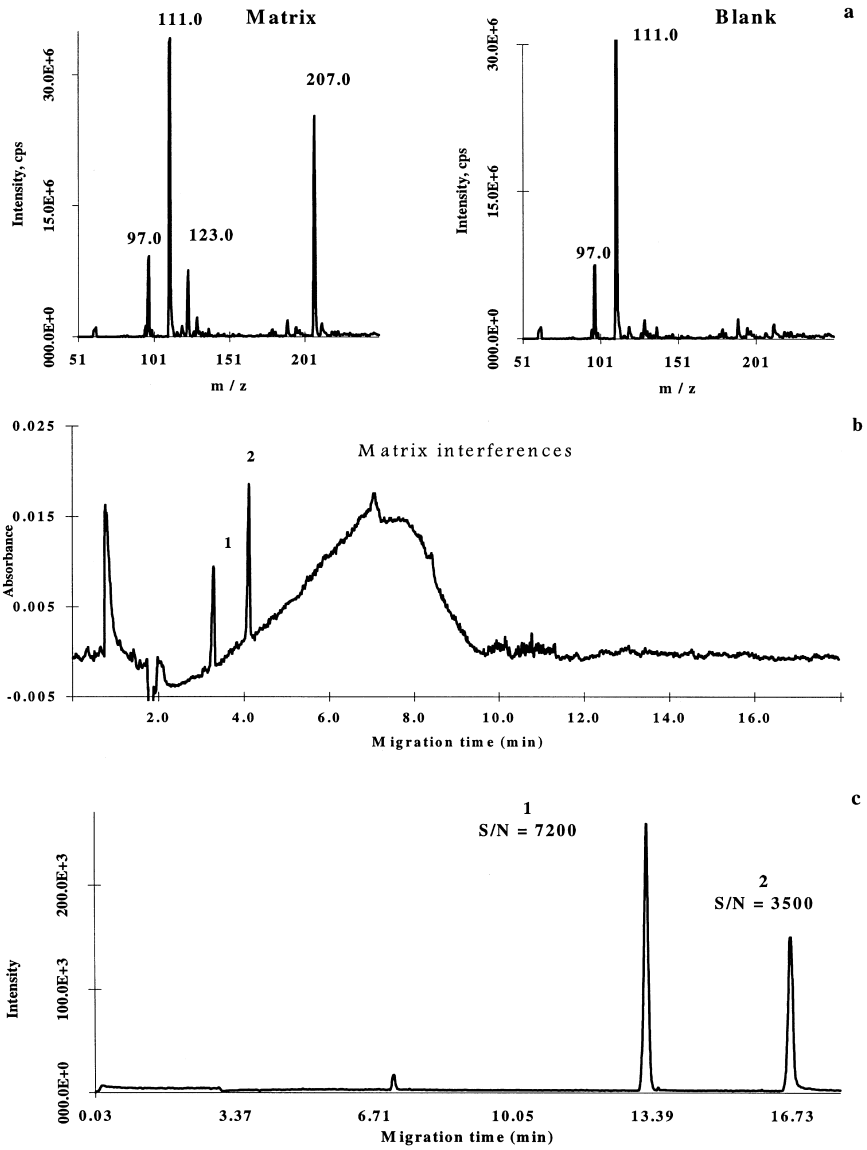

Fig. 3. MS, CE–UV and CE–MS analysis of the spiked tap water. (a) Mass spectra of the spiked tap water and of the blank, (b) CE–UV analysis of the spiked tap water, (c) CE–MS analysis of the spiked tap water. CE and MS conditions as in Fig. 1.

to the theoretical concentration (respectively, 12 mg/l and 8 mg/l).

The limit of detection (LOD) of this method (with diluted matrix method) shows very good results (Fig. 5). For a signal-to-noise ratio equal to 3, LOD was 132 μg/l (8.3 fmol injected) for EHMPA. Such LOD has never been reached during the CE analysis of phosphonic acids without derivatization of these solutes or preconcentration of the sample [1,2,21–26], but those LOD can be achieved also by LC–MS.

4. Conclusions

Structural identification and quantification of phosphonic acids have been achieved by on-line CE–

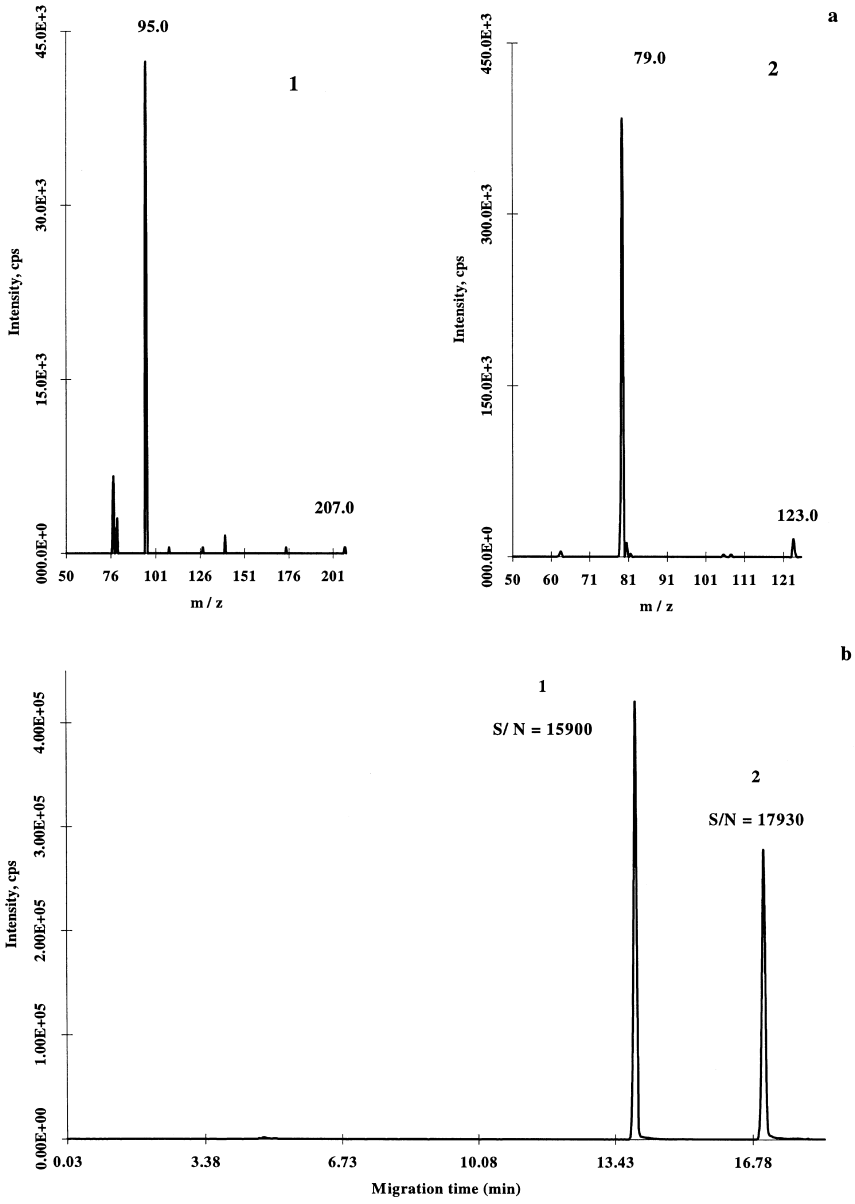

Fig. 4. MS–MS and CE–MS–MS analysis of the spiked tap water. (a) MS–MS fragmentation of the spiked tap water, (b) CE–MS–MS analysis of the spiked tap water, (c) CE and MS conditions as in Fig. 2.

UV–MS. An electrolyte system composed of 5 m*M* of sorbic acid–ammonia (pH 6.5) allows the simultaneous indirect UV and MS detection of these solutes. The non-volatile sorbic acid appears to be suitable as electrolyte in the CE–UV–MS–MS method of phosphonic acids determination provided pentanol was selected to compose the make-up liquid.

Under optimized (CE and MS) conditions, this procedure allows the separation of the main phosphonic acids with good selectivity, resolution and sensitivity.

The LODs obtained (about 100 μg/l) were very low.

This convenient methodology does not involve

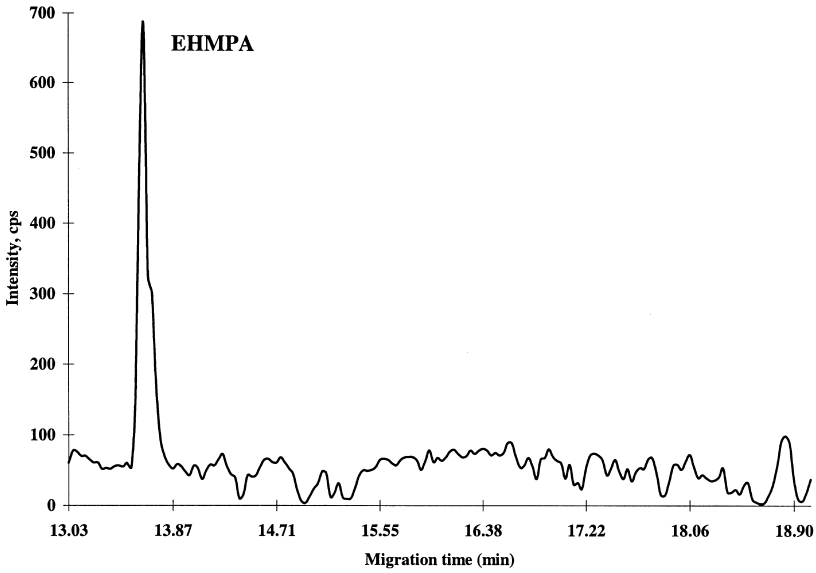

Fig. 5. LOD of the procedure (CE–MS–MS). CE and MS conditions as in Fig. 2.

any derivatization and preconcentration steps and can therefore easily be used in the routine analysis of phosphonic acids in CE–UV, CE–MS, CE–UV–MS and CE–UV–MS–MS methods.

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