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Determination of haloacetic acids in water by liquid chromatography-electrospray ionization-mass spectrometry using volatile ion-pairing reagents

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A method for the determination of nine haloacetic acids (HAAs) in drinking water was developed using liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) employing volatile ion-pairing reagents. The separation and sensitivity of all the compounds were optimized using three volatile amines (di-*n*-butylamine, *N*,*N*-dimethyl-*n*-butylamine and tri-*n*-butylamine) and optimized conditions were obtained with 5 mmol l^{-1} dibutylamine (DBA). The sample preparation of this method was very simple involving filtration of the sample and the addition of 100 mmol l^{-1} DBA. With DBA as ion-pairing reagent and propan-2-ol as mobile phase modifier, a water sample spiked with 0.1–100 ng ml^{-1} of nine HAAs could be determined by LC-ESI-MS using time-scheduled selected ion monitoring. The correlation coefficients for all target analytes were higher than 0.999. The detection limits ranged from 24 to 118 pg ml^{-1}. The repeatability and reproducibility were in the range 1.5–9.1% and 5.9–12.4%, respectively.

Introduction

Haloacetic acids (HAAs), especially the chloroacetic acids monochloroacetic acid (MCAA), dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA), are known to be formed from dissolved humic matter during disinfection of drinking water with chlorine.[1–4] Of the chlorination by-products in drinking water, volatile chlorinated organic compounds, such as trihalomethanes,[1,5] have received almost exclusive attention. However, awareness that bromoacetic acids and mixed bromochloroacetic acids, including monobromoacetic acid (MBAA), dibromoacetic acid (DBAA), tribromoacetic acid (TBAA), bromochloroacetic acid (BCAA), dichlorobromoacetic acid (DCBAA) and dibromochloroacetic acid (DBCAA), exhibit serious human health hazards has increased. The presence of bromide ions and MCAA may lead to MBAA, DBAA, TBAA and mixed BCAAs, and their presence in water has been reported in recent years.[6–8] Moreover, these HAAs have been found in various environments, such as river water,[9–11] rain water,[9,12,13] waste water,[9,10] seawater[10,11] and even in conifer needles.[12]

Because of the very high toxic and carcinogenic risks of some HAAs,[14] fast and accurate analytical methods for these substances are needed to monitor their concentration, behaviour and distribution in surface water, drinking water and groundwater. The EPA has established, in the first stage of the Disinfectants/Disinfection By-Products (D/DBP) Rules,[15] a maximum contaminant level (MCL) of 60 μg l^{-1} for the sum of five HAAs: MCAA, DCAA, TCAA, MBAA and DBAA. Most of the methods used to determine HAAs, including EPA Methods 552[16] and 552.2,[17] involve gas chromatography (GC) with electron capture detection (ECD)[16–20] and mass spectrometry (MS).[21,22] However, for GC methods, a prior derivatization step using diazomethane, acidic methanol or BF_3–methanol is necessary because of the low volatility and high polarity of HAAs. A further extraction step, including liquid–liquid extraction,[16] solid phase extraction[17,22] and solid phase microextraction,[21] is necessary because derivatization cannot be performed in water solution. Methylation of HAAs directly in water followed by analysis using a headspace sampler has been reported.[23]

New strategies to avoid extraction and derivatization in HAA analysis are desirable to increase simplicity and reduce the analysis time. Alternative methods based on high performance liquid chromatography (HPLC) have been proposed.[24–26] These procedures do not require extraction or derivatization and employ a conventional reversed phase C_{18} column with ion-pairing reagent to separate HAAs. However, UV wavelengths required to detect HAAs are influenced by interference in real samples and hence indirect UV detection[25] or electrochemical detection[26] have been used. In addition, the detection limits are much higher than those of the GC-ECD technique. Further, for a more exact identification of target compounds, MS, which provides structural information, is the method of choice. Unfortunately, coupling of conventional ion-pair chromatography to MS is obstructed by contamination of the interface by the involatile tetraalkylammonium salts used as mobile phase modifiers. Another disadvantage of tetraalkylammonium salts as mobile phase modifiers in liquid chromatography (LC)-electrospray ionization (ESI)-MS is their tendency to form cluster ions with anionic analytes, which can reduce sensitivity in the selected ion monitoring (SIM) mode.[27] For the coupling to MS, a volatile ion-pairing reagent is preferred to enhance the retention and peak shape. Triethylamine is suited for this purpose, since it does not interfere with MS detection in concentrations normally applied for HPLC. It has consequently been used in several applications for LC-MS, for the analysis of nucleotides and oligonucleotides,[28] as well as for the analysis of linear alkylbenzene sulfonates (LASs).[29] Very polar compounds, such as MCAA, MBAA and DCAA, generally require more efficient ion-pairing reagents than triethylamine to obtain reasonable retention. Thus, aliphatic amines may be suitable to provide the necessary retention for LC-ESI-MS, but their suitability as ion-pairing reagents for HAAs has not been investigated. We therefore investigated the applicability of three

aliphatic amines, dimethylbutylamine (DMBA), dibutylamine (DBA) and tributylamine (TBA), as ion-pairing reagents for the LC-ESI-MS analysis of HAAs. In this study, the retention behaviour and influence of the concentration of these amines on the MS sensitivity of nine HAAs were studied. Further, a large volume injection (500 μl) on LC-ESI-MS was applied for the analysis of the nine HAAs because this procedure does not require the extraction and concentration of natural samples. The potential of the final method is demonstrated by its application to the analysis of drinking water.

Experimental

Chemicals

MCAA, MBAA, DCAA, DBAA, BCAA, DCBAA, DBCAA, TCA and TBAA were obtained as individual products from Hayashi Pure Chemicals Osaka, Japan. The purity of these compounds was higher than 99% and they were in liquid form. Stock solutions containing all HAAs at 1 mg ml^{-1} were prepared in pure water, stored in the dark at 4 °C and diluted to the desired concentrations prior to use. *N*,*N*-Dimethyl-*n*-butylamine (DMBA), tributylamine (TBA) and dibutylamine (DBA) were purchased from Tokyo Kasei (Tokyo, Japan). Propan-2-ol and acetonitrile were obtained from Wako Chemicals (Osaka, Japan). All other chemicals were of reagent grade. Pure water was purified with a Milli-Q system (Millipore, Tokyo, Japan).

Sample preparation

Drinking water was collected in 100 ml glass bottles. A 900 μl aliquot of the sample was filtered through a 0.2 μm nylon filter and transferred to a 2 ml glass vial. For the analysis of drinking water, there is no need to filter the sample. However, to verify the potential of the final method for environmental water, sample filtration was performed. Finally, 0.1 mol l^{-1} DBA (100 μl) was added to the vial.

Apparatus

Liquid chromatography-mass spectrometry. An HP 1100 series liquid chromatograph (Hewlett-Packard, Waldborn, Germany), consisting of a vacuum solvent degassing unit, a binary high-pressure gradient pump, an automatic sample injector and a column thermostat, was used for LC-MS analysis. Further, a model HP 1100 series diode array detector (DAD) (Hewlett-Packard, Waldborn, Germany) was connected on line with the MS detector. Flow injection analysis (FIA) was performed using an LC system without an analytical column, followed by injection of 5 μl of the HAA standard mixture at 1 mg l^{-1} to study the effect of the concentration and type of amine as ion-pairing reagent. This mixture was prepared by mixing the stock solutions and diluting 1 : 1000 in pure water. LC separation was performed on a 150 × 2.1 mm id column packed with 5 μm Inertsil ODS3 (GL Science, Tokyo, Japan) using linear gradient elution for 20 min with a mobile phase of acetonitrile–water containing 5 mmol l^{-1} adjusted to pH 7 with acetic acid (from 10 + 90 to 50 + 50 v/v). The flow rate was 200 μl min^{-1}. Propan-2-ol was added after DAD at a flow rate of 50 μl min^{-1} *via* a tee by an isocratic pump (Hewlett-Packard, Waldborn, Germany). The injection volume was 500 μl.

An HP 1100 series MSD single quadrupole instrument equipped with an orthogonal spray-ESI (Hewlett-Packard, Palo Alto, CA, USA) was used for MS. The nebulizer gas and drying gas (350 °C) was nitrogen generated from pressurized air in a Whatman model 75-72 nitrogen generator (Whatman, Haverhill, MA, USA). The gas and fragmentor voltage for in-source fragmentation were optimized using an analytical column with the HAA standard mixture at 100 mg l^{-1}. The nebulizer gas, drying gas and fragmentor voltage were set at 60 psi, 10 l min^{-1} and 40 V, respectively. Further, skimmer 1, skimmer 2 and entrance lens voltages in the ion source of the MSD were automatically optimized by a calibrant delivery system using a calibration standard at 0.1 ml min^{-1} and set to 23 V, 47 V and 57 V, respectively. LC-MS determinations were performed by operating the MSD in the negative ion mode. Post-column addition of propan-2-ol to the column effluent was performed to decrease the surface tension, facilitating the ionization of the compounds and resulting in an increase in sensitivity. As a result, the sensitivity of the target analytes was enhanced by a factor of two. Mass spectra were acquired over the scan range *m*/*z* 70–500 using a step size of 0.1 u and a scan speed of 0.5 scan s^{-1}. Quantitative analysis was carried out using single ion monitoring (SIM) of base ion peaks at *m*/*z* 93 (MCAA), 127 (MBAA), 139 (DCAA), 173 (BCAA), 217 (DBAA), 117 (TCAA), 163 (DCBAA), 207 (DBCAA) and 250 (TBAA) with a dwell time of 250–500 ms per ion. Internal standards were not used because the injection volume using the autosampling device was very accurate and the effect of the matrix for signals of all target analytes was very small. To verify the presence of target analytes in drinking water, the halogen isotopic ions of all target analytes were monitored.

Results and discussion

Mobile phase optimization

Influence of the ion-pairing reagent on the sensitivity of haloacetic acids. Sensitivity in ESI-MS is strongly dependent on the composition of the mobile phase, such as the concentration, type of ion-pairing reagent and the pH value. To study the influence of the concentration and the type of amine as ion-pairing reagent on the peak area of all HAAs, eluents containing various concentrations of DMBA, DBA and TBA were used for flow injection without an analytical column. The deprotonation ions of MCAA, MBAA, DCAA, BCAA and DBAA and the decarboxylated ions of TCAA, DCBAA, DBCAA and TBAA were monitored in the SIM mode. These results are shown in Fig. 1. For all ions and the three amines, the peak area tended to decrease with increasing amine concentration, namely between 0 and 5 mmol l^{-1}. This significant decrease seems to be due to the formation of cluster ions with anionic analytes. In order to obtain maximum sensitivity, the concentration of ion-pairing reagent should be kept as low as feasible for sufficient chromatographic retention. Despite the general trend of decreasing intensity with increasing amine concentration, an increase in ion intensity was found by increasing the TBA concentration from 0 to 1 mmol l^{-1} for all HAAs. This effect was found by Stom *et al*.[30] in the ESI-MS analysis of aromatic sulfonates. This phenomenon, however, is not fully understood and requires further investigation. On the other hand, the ion intensities using the three amines were not significantly altered for seven HAAs (excepting DCAA and TBAA) between 5 and 20 mmol l^{-1}, and the intensities of all HAAs showed a maximum value with 1 mmol l^{-1} of TBA. However, a 10-fold difference in ion intensity was observed for TBAA at 5 mmol l^{-1} of the three amines and the ion intensity of TBAA was extremely low when using TBA. From these results, TBA seems to be the best volatile ion-pairing reagent at an amine concentration of 1 mmol l^{-1}, and DBA and DMBA are suitable volatile ion-pairing reagents at a concentration above 5 mmol l^{-1}.

Further, according to accepted theory, ions preformed in solution are a major source of ions in ESI. The influence of the

mobile phase pH on ion formation was studied for DBA only because the type of amine does not affect ion formation. Only TBAA was not detected at pH 4 since the pK_a value of TBAA is above 4. For the other HAAs, the ion intensities were not significantly altered between pH 4 and pH 10 since their pK_a values are very low. Thus a pronounced pH effect on the ionization efficiencies was not expected in the pH range investigated here, except for TBAA. A pH value of 7 was selected for the final separation conditions used for quantification to prevent the acid-catalysed oxidation of amines.

Retention behaviour of haloacetic acids. For the retention behaviour of all HAAs, the HAA standard mixture at 1000 ng ml^{-1} was analysed with the SIM mode using the three amines as ion-pairing reagents. Firstly, TBA was used as ion-pairing reagent at an amine concentration of 1 mmol l^{-1}. However, monohaloacetic acids and dihaloacetic acids eluted in the dead volume. Thus, in this investigation, the three amines were used at an amine concentration of 5 mmol l^{-1}. Fig. 2 shows the separation of the nine HAAs using TBA, DBA and DMBA at 5 mmol l^{-1} at pH 7. All amines provided sufficient retention for dihaloacetic acids and trihaloacetic acids. However, the more polar monohaloacetic acids (MCAA and MBAA) were poorly retained with DMBA. These compounds eluted in the dead volume and did not separate (Fig. 2a). Thus, DMBA exhibited the highest sensitivity, but this amine was not suitable in the analysis of all HAAs. On the other hand, with TBA and DBA, these compounds exhibited strong retention under the same conditions (Fig. 2b and 2c). With TBA, monoacetic acids were retained most strongly, but the separation of MCAA and MBAA was not significantly improved and TBAA could not be detected. From the results of the separation and sensitivity of the nine HAAs, DBA was selected as ion-pairing reagent for the final LC-ESI-MS method of HAAs.

Evaluation of ESI performance

The investigation of the performance of the LC-ESI-MS technique using volatile ion-pairing reagents for the analysis of the nine HAAs is very important because ion-pairing reagents form complexes with the target analytes and the intensities of the HAAs are influenced by the ESI parameters. This investigation was carried out under chromatographic conditions using linear gradient elution with a mobile phase of acetonitrile–water containing 5 mM DBA (which was the best volatile ion-pairing reagent for the separation of all HAAs) at a flow rate of 0.2 mL min^{-1}. The main operating parameters which have an impact on the performance of ESI are the fragmentor voltage (capillary exit voltage), nebulizer gas pressure and drying gas flow rate. The effect of these parameters on the MS response was investigated.

In a first step, ESI performance at different fragmentor voltages was investigated. The fragmentor voltage is applied to the exit of the capillary and affects the transmission and fragmentation of sample ions. In general, the higher the fragmentor voltage, the more fragmentation will occur. In compounds that do not fragment readily, higher fragmentor voltages often result in better ion transmission. The fragmentor voltage gives the ions a push which helps them to traverse the relatively high pressure region between the exit of the capillary and the skimmer. Thus, at higher voltage values, maximum structural information is obtained. However, the optimum fragmentor voltage is compound dependent and, for this reason, an accurate evaluation of the fragmentor voltage of each of the compounds studied in this work was performed using a reversed phase column and 5 mmol l^{-1} DBA as ion-pairing reagent. In Fig. 3, the intensities of the deprotonated ions and the decarboxylated ions for all HAAs are shown as a function of the fragmentor voltage. For monohaloacetic acids (MCAA and MBAA) and dihaloacetic acids (DCAA, DBAA and BCAA), the deprotonated ions were observed as the base peak at less than 40 V and presented maximum sensitivities. At higher fragmentor voltage, the sensitivities for the deprotonated ions

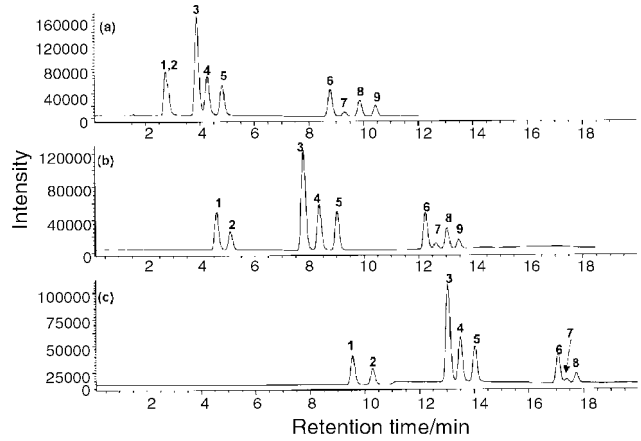

Fig. 2 Optimization of chromatographic conditions using DMBA, DBA and TBA as ion-pairing reagents. Eluent A (water) and B (acetonitrile) containing 5 mmol l^{-1} amine. Linear gradient from 10% B to 50% B in 20 min, 15 min re-equilibration. (a) DMBA; (b) DBA; (c) TBA. 1, MCAA; 2, MBAA; 3, DCAA; 4, BCAA; 5, DBAA; 6, TCAA; 7, DBCAA; 8, DCBAA; 9, TBAA.

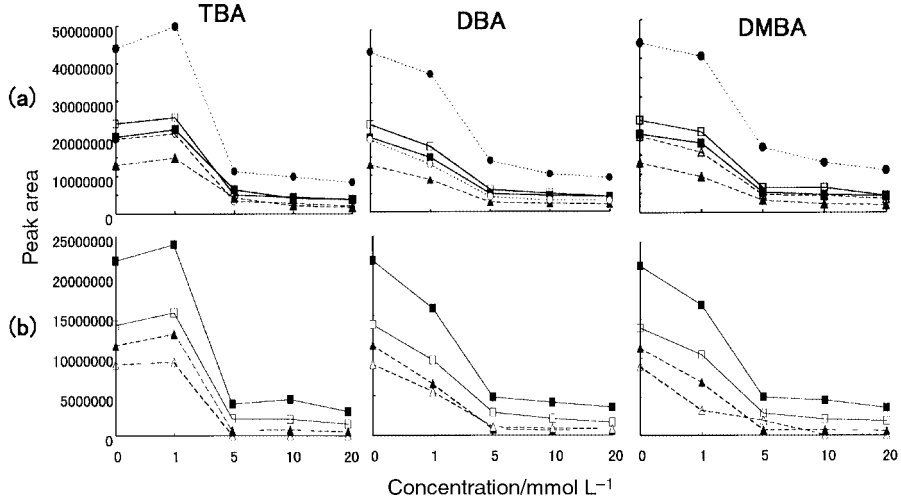

Fig. 1 Influence of amine concentration on ionization efficiencies as measured by flow injection of (a) mono- and dihaloacetic acids and (b) trihaloacetic acids. (a) ■, MCAA; ▲, MBAA; ●, DCAA; □, BCAA; ○, DBAA; (b) ■, TCAA; ▲, DBCAA; □, DCBAA; △ TBAA.

decreased and the sensitivities for the decarboxylated ions increased. On the other hand, for trihaloacetic acids (DCBAA, DBCAA, TCAA and TBAA), the sensitivities of the deprotonated ions were very low and the decarboxylated ions were observed as the base peak at 20 V. Further, the base peak presented its maximum sensitivity in the mass spectra of all HAAs at 40 V. Other ions (dimer ions) were observed in the mass spectra of monohaloacetic acids and dihaloacetic acids. From the above results, the fragmentor voltage of all HAAs was set at 40 V and Table 1 shows the typical mass spectra of the nine HAAs at 40 V. The isotopic ions derived from chlorine or bromine were the ions of maximum abundance.

In a second step, ESI performance at different drying gas flow rates was investigated at a fragmentor voltage of 40 V. All HAA signals showed no variation at a drying gas flow rate between 4 and 13 l min^{-1}. Therefore, this parameter was maintained at 10 l min^{-1}.

The third step is to optimize the nebulizer gas pressure. The fragmentor voltage and drying gas flow rate were set to 40 V and 10 l min^{-1}, respectively. As shown in Fig. 4, a high nebulizer gas pressure was found to ensure the best sensitivity for all HAAs, whereas at lower values a signal intensity reduction was observed. We have previously described different results for the influence of nebulizer gas pressure: a strong variation in the intensity of the analytes was not observed when this parameter was varied from 20 psi to 60 psi.[31] However, in the current study, the intensity of the analytes can be influenced by the amines (volatile ion-pairing reagents) due to of the formation of ion-pairs with the cationic analytes that appear 'neutral' to the electrospray process. Further, the intensities at 60 psi were almost equal to the intensities observed when not using the ion-pairing reagent. It can therefore be presumed that the higher nebulizer pressure breaks the 'neutral' ion-pairs of HAAs and improves the suppression of the intensity of the analytes.

Table 1 Relative intensities (RI) of the main ions formed in ESI-MS of haloacetic acids [*m/z* (RI, %) fragmentor voltage: 40 V]

Haloacetic acid	$(M - H)^-$	$(M - COOH)^-$	$(2M - H)^-$
Monochloroacetic acid	93(100)		187(19)
Monobromoacetic acid	137(100)		277(23)
Dichloroacetic acid	127(100)		257(21)
Bromochloroacetic acid	173(100)		345(19)
Dibromoacetic acid	217(100)	173(18)	435(15)
Trichloroacetic acid		117(100)	
Dichlorobromoacetic acid		163(100)	
Dibromochloroacetic acid		207(100)	
Tribromoacetic acid		251(100)	

Large volume injection with ion-pairing reagent

In this study, a large volume injection method with no sample concentration was investigated to simplify the sample preparation. When the injection volume was varied from 10 to 500 μl, the intensities of all HAAs increased as the injection volume increased. However, the chromatographic peak widths increased and the separation between the monohaloacetic acids decreased. This peak broadening seems to result from the dilution of the mobile phase by the large sample volume. To counteract this dilution of the mobile phase by the sample, a 0.1 mol l^{-1} DBA solution was added to the sample (900 μl) and this sample was injected (500 μl). As a result, the peak widths of the monohaloacetic acids decreased and became almost equal to those at an injection volume of 10 μl with no ion-pairing reagent. Therefore, for a large volume injection (500 μl), 0.1 mol l^{-1} DBA (100 μl) was added to the sample (900 μl).

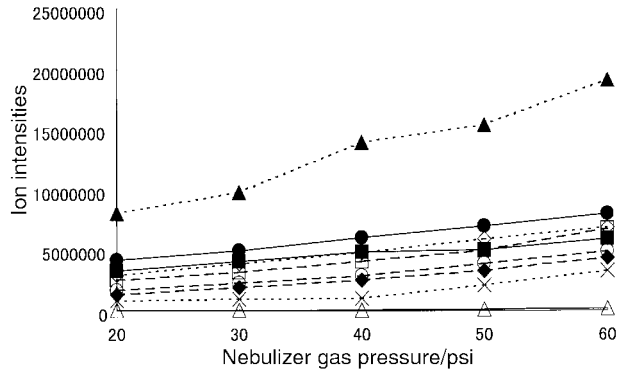

Fig. 4 Effect of nebulizer pressure on peak area. Concentration: 10 ng ml^{-1}; for other conditions, see Experimental. ■, MCAA; ◆, MBAA; ▲, DCAA; ● BCAA; □, DBAA; ◇, TCAA; △, DBCAA; ○, DCBAA; ×, TBAA.

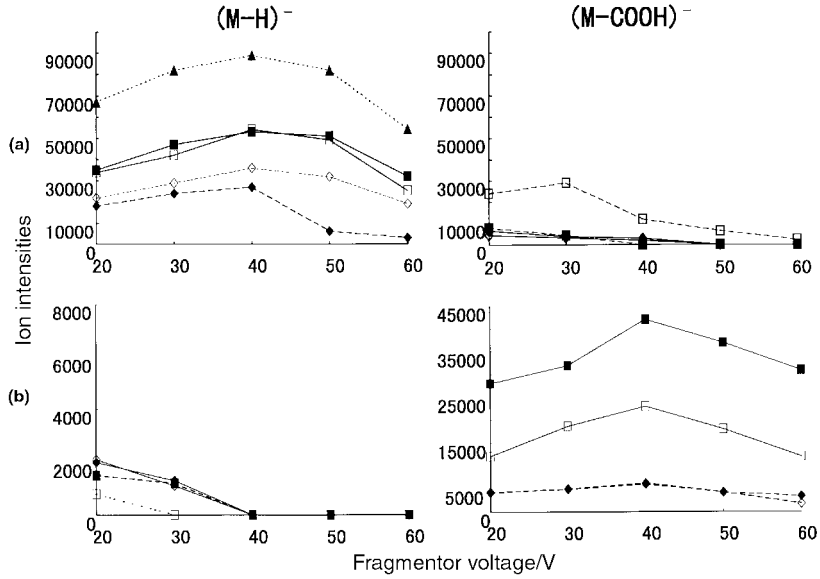

Fig. 3 Dependence of ionization and fragmentation on fragmentor voltage for haloacetic acids. (a) ■, MCAA; ◆, MBAA; ▲, DCAA; □ BCAA; ◇, DBAA; (b) ■, TCAA; ◆, DBCAA; ◇, DCBAA; □, TBAA.

Linearity, detection limits and precision of the LC-ESI-MS system

In order to achieve optimum sensitivity, all experiments were carried out under SIM conditions and the deprotonated ions or decarboxylated ions were selected for all HAAs. The calibration curve was determined by external calibration in the concentration range 0.1–100 ng ml^{-1} in injection solutions, corresponding to 90 pg to 90 ng. As shown in Table 2, the linearity was very good for all HAAs with correlation coefficients (r^2) greater than 0.999. The sensitivity of this analytical procedure was evaluated in terms of the minimum quantification limit (MQL) defined as 10 times the standard deviation[32] with a real sample such as drinking water. Since this parameter depends on the spiking concentration, the US Environmental Protection Agency (EPA) guidelines were used. These guidelines require that the ratio of the spiking concentration to the estimated MQL should be lower than 5:1. If the ratio is greater, the spiking concentration should be reduced until the criterion is achieved. According to the above-mentioned criterion, the spiking concentration selected in the drinking water was 100 pg ml^{-1} for all HAAs. Firstly, drinking water in our office was analysed. A few HAAs were detected at trace levels because HAAs are chlorination by-products. However, the amount of detected target analytes was much less than the spiked amount, and hence the nine HAAs were spiked in this real sample at 0.1 ng ml^{-1}. The MQLs of the HAAs by this method were in the range 24–118 pg ml^{-1}. These MQLs were much lower than for HPLC with indirect UV detection[25] and electrochemical detection,[26] but slightly higher than for GC-ECD[17] and GC-MS.[22] However, this LC-ESI-MS method is the only technique which can determine all nine HAAs simultaneously. The intra-day precision (repeatability) was estimated by injecting standard solutions containing all HAAs at 200 pg ml^{-1} five times during a working day. The inter-day precision (reproducibility) was evaluated by analysing the same sample three times over three working days. The repeatability and reproducibility for all HAAs ranged from 1.5% to 12.4%. The quantitative results of all HAAs in the spiked river water at 1 ng ml^{-1} using external standards are also shown in Table 2 and the SIM chromatogram of this sample is shown in Fig. 5. These experimental results correlate well with those expected (< 20%) and no significant interference peaks were observed.

Conclusions

An important advantage of using LC-ESI-MS for the determination of the HAA content of drinking water is that this method does not involve any sample preparation (extraction or derivatization) and hence there is no need to consider the

Table 2 Detection limits, linearity, precision of haloacetic acids

Nonylphenol oligomer	r^2	Detection limits[a]/ ng ml^{-1}	Quantitative[b] results/ ng ml^{-1}	Instrument precision (RSD, %)	
				Repeatability[c]	Reproducibility[d]
Monochloroacetic acid	0.9993	0.089	1.12	4.5	9.3
Monobromoacetic acid	0.9995	0.096	1.05	5.3	9.1
Dichloroacetic acid	0.9992	0.024	1.07	1.5	5.9
Bromochloroacetic acid	0.9994	0.088	1.15	4.2	8.3
Dibromoacetic acid	0.9991	0.091	1.18	6.1	7.8
Trichloroacetic acid	0.9995	0.083	1.15	4.9	6.6
Dichlorobromoacetic acid	0.9993	0.113	1.03	9.4	11.3
Dibromochloroacetic acid	0.9992	0.074	1.17	5.2	7.7
Tribromoacetic acid	0.9991	0.118	0.98	9.1	12.4

[a] Detection limit is the minimum quantification limit defined as 10 standard deviations for the spiked drinking water at 0.1 ng ml^{-1}. [b] Quantitative result was calculated with the spiked drinking water at 1 ng ml^{-1} [c] Repeatability was calculated on the basis of five replicates at 0.2 ng ml^{-1} within one day. [d] Reproducibility was calculated on the basis of one sample analysed each day for three days at 0.2 ng ml^{-1}.

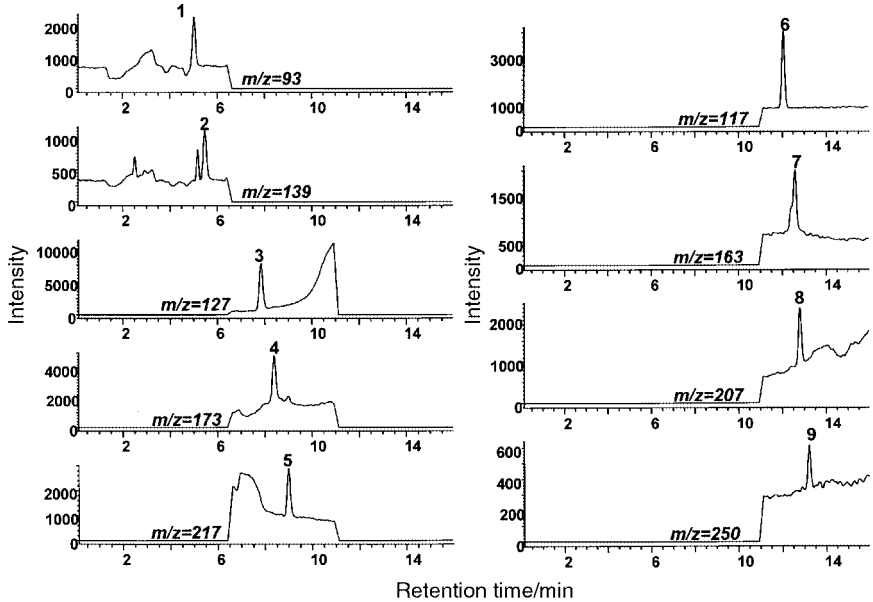

Fig. 5 Typical SIM chromatogram obtained by LC-ESI-MS of drinking water spiked at 1 ng ml^{-1}. 1, MCAA; 2, MBAA; 3, DCAA; 4, BCAA; 5, DBAA; 6, TCAA; 7, DBCAA; 8, DCBAA; 9, TBAA.

recovery or reaction yield. Moreover, a mass spectrometric detector has been successfully coupled to ion-pair LC through ESI, which enhances the identification capability of the method.

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