A novel method for determination of inorganic oxyanions by electrospray ionization mass spectrometry using dehydration reactions

Hirochika Kojima,^a Shota Kurihara,^{a,c} Yoshito Watanabe,^{a,d} Koki Iwamaru,^a Kiichi Sato,^a Kin-ichi Tsunoda^{a*} and Hiroki Hotta^b

Novel methods for the determination of inorganic oxyanions by electrospray (ES) ionization mass spectrometry have been developed using dehydration reactions between oxyanions and carboxylic acids at the ES interface. Twelve oxyanions (VO_3^- , CrO_4^{2-} , MoO_4^{2-} , WO_4^{2-} , BO_3^{3-} , SiO_3^{2-} , SiO_4^{4-} , AsO_4^{3-} , AsO_2^- , SeO_4^{2-} , SeO_3^{2-} and NO_2^-), out of 16 tested, reacted with at least one of four aminopolycarboxylic acids, i.e. iminodiacetic acid (IDA), nitrilotriacetic acid (NTA), *trans*-1,2-diaminocyclohexane-*N,N,N',N'*-tetraacetic acid and triethylenetetramine-*N,N,N',N'',N''',N'''*-hexaacetic acid, at the ES interface to produce the dehydration products that gave intense mass ion responses, sufficient for trace analysis. As examples, trace determinations of Cr^{VI} and silica in water samples were achieved after online ion exchange chromatography, where the dehydration product of CrO_4^{2-} and NTA (m/z 290) and that of SiO_4^{4-} and IDA (m/z 192) were measured. The limits of detection of the respective methods were 17 nM (0.83 ng Cr/ml) for Cr^{VI} and 0.17 μM (4.8 ng Si/mL) for SiO_4^{4-} . Copyright © 2016 John Wiley & Sons, Ltd.

Additional supporting information may be found in the online version of this article at the publisher's web site.

Keywords: oxyanions; carboxylic acids; dehydration reaction; electrospray ionization mass spectrometry

Introduction

The determination of inorganic ions remains one of the oldest research themes in analytical chemistry. The current state of the art for such analyses is based on inductively coupled plasma (ICP) emission and mass spectrometry (MS) for metal ions and ion chromatography for anions. Although these techniques deliver impressive analytical performance, researchers in this field continue to seek improvements in sensitivity, selectivity and convenience. For instance, electrospray ionization MS (ESI/MS) has attracted a wide interest as testified in a number of recent studies.^[1–15]

Electrospray ionization MS is one of the most powerful analytical techniques for identification and quantitation of inorganic and organic species in various fields because of attractive features such as direct sampling of solution samples, soft ionization, high sensitivity and selectivity. A key disadvantage, however, is the susceptibility to sample matrix effects, which impacts adversely on quantitative analysis. For the determination of inorganic ions, therefore, ESI/MS has often been combined with a pre-separation step, whereby the analytes are first separated from the sample matrix using liquid chromatography (LC) and/or extraction techniques. The ion chromatography (IC)-ESI/MS system has been applied to determine various inorganic ions by a number of researchers as summarized in recent reviews.^[1–3] The use of ESI/MS and complexation-extraction techniques for sample pretreatments has been extensively developed by Minakata *et al.* for trace analysis.^[4–12]

For trace determination of metal ions using ESI/MS, a number of studies have been reported since the pioneering experiments of Horlick's group in the 1990s.^[13,14] However, few studies, until recently, have been applied to real samples, probably reflecting the

issue of sample matrix effects. Minakata *et al.* used diethyldithiocarbamate (DDC) and pyrrolidine dithiocarbamate (PDC) to ligate metal and metalloid ions and to extract the complexes into the organic phase. Methods were described for determinations of cobalt,^[4] platinum,^[5] molybdenum, ruthenium,^[6] hexavalent chromium,^[7] copper, silver and gold^[8] based on DDC and for determinations of arsenic(III) and arsenic(V)^[9] in clinical samples using PDC. A novel method was also proposed for trace metal analyses based on negative ion mode ESI/MS, where metal-aminopolycarboxylate (metal-APC) complexes, particularly those of *trans*-1,2-diaminocyclohexane-*N,N,N',N'*-tetraacetic acid (CyDTA), were measured after online separation of the complexes from sample matrices with a size exclusion column. This approach was used for determination of heavy metals in environmental samples.^[15–17] The group of Armstrong has devised more sensitive analytical methods for trace analysis using positive ion mode ESI/MS (or ESI/MS/MS) where the ion-pair formation of negatively charged

* Correspondence to: Kin-ichi Tsunoda, Department of Chemistry and Chemical Biology, Gunma University, Tenjin-cho, Kiryu 376-8515, Japan.
E-mail: tsunoda@gunma-u.ac.jp

a Department of Chemistry and Chemical Biology, Gunma University, Tenjin-cho, Kiryu 376-8515, Japan

b Department of Chemistry, Nara University of Education, Takabatake, Nara 630-8528, Japan

c Nippon Steel & Sumikin Eco-Tech Corporation, Kisarazu 292-0825, Japan

d Morioku Technology Co., Ltd., Meiwa 370-0718, Japan

metal–APC complexes and dicationic ion-pairing reagents were utilized. These approaches realized sensitivities for some metal ions that were comparable with ICP-MS.^[18,19]

In the case of anions, methods for the determination of perchlorate and perbromate ions in environmental samples by IC-ESIMS, as reported by Dasgupta and co-workers, are noteworthy because of their importance in environmental chemistry. A key feature of these methods is the formation of ion pairs of organic dications and perchlorate ion (or other inorganic anions), which are measured.^[20–22] Minakata *et al.* described the formation of gold(II) complexes followed by ion-pair extraction into an organic phase for determination of cyanide,^[10] thiocyanate^[11] and iodide^[12] in clinical samples. The concept of ternary complex formation for determination of halide and cyanide ions has been proposed by the authors, whereby the ternary complexes of group (III) elements with nitrilotriacetic acid (NTA) and halides and that of copper(II), 4-(2-pyridylazo)-resorcinol and cyanide permitted determinations of halides and cyanide, respectively.^[15,17,23] In particular, ultra-trace amounts of fluoride were determined using [AlF(NTA)][–].^[15]

For differential measurement of Cr species, HCrO_4^- (m/z 117) was directly monitored by ESIMS for Cr^{VI} , while Cr^{III} was detected as the Cr^{III} –CyDTA complex.^[24] The limits of detection (LODs) were $\sim 13 \text{ nmol/dm}^3$ for Cr^{VI} and 56 nmol/dm^3 for Cr^{III} . The proposed methods, applied to the measurement of chromate and trivalent chromium in conversion coatings on steel samples, gave results that were consistent with those by the diphenylcarbazide spectrophotometric method for Cr^{VI} and ICP-atomic emission spectroscopy (AES) for total Cr. During this study, it was noted that chromate ions reacted with various APCs at the electrospray (ES) interface to produce dehydrated products, which gave prominent MS signals. Also, the MS response was found to be linear with the Cr^{VI} concentration. The oxyanions, molybdate and orthosilicate were then tested, and it was noted that they also underwent dehydration reaction with APCs. Thus, the idea to use this dehydration reaction as a general reaction scheme for determination of oxyanions by ESIMS was conceived.

O'Hair's group has observed dehydration reactions at the ESIMS interface, where group VI oxyanions ($[\text{MO}_3(\text{OH})]^-$ and $[\text{M}_2\text{O}_6(\text{OH})]^-$, $\text{M} = \text{Mo}, \text{W}$) acted as catalysts for a two-step gas-phase catalytic cycle for the dehydration of acetic acid to ketene, where at the initial step, the condensation product of acetic acid, $[\text{MO}_3(\text{OCOCH}_3)]^-$ or $[\text{M}_2\text{O}_6(\text{OCOCH}_3)]^-$ was formed at the ES interface.^[25,26] The aforementioned workers also reported gas-phase reactions of group VI oxyanions and $[\text{VO}_2(\text{OH})_2]^-$ and $[\text{V}_2\text{O}_5(\text{OH})]^-$ with methanol.^[27,28] However, their interest in these studies appears to be limited to elucidation of reaction pathways and mechanisms of the gas-phase reactions and not the exploitation of the reactions for analytical purposes.

In this paper, we have tested the reactions of 16 oxyanions with four APCs and found that 12 oxyanions gave prominent MS signals. Next, the potential for trace measurement of these oxyanions was evaluated. The selective determination of trace amounts of inorganic oxyanions is generally difficult, and ESIMS is a good candidate for such a purpose. However, its application has been limited to specific oxyanions such as halogen species^[20–22] and phosphate.^[29] Also, it was found that a previous approach for measurement of Cr^{VI} was not appropriate for some oxyanions that have a low acidity.^[24] Moreover, this latter approach was unique in applying the gas-phase reaction at the ES interface to derivatize the oxyanions, which then makes it possible to perform trace analysis. Finally, methods for the determination of chromate and orthosilicate in waters based on the combination of IC and ESIMS were demonstrated.

Materials and methods

Reagents and chemicals

Each oxyanion standard solution was prepared by dissolving the pure compound in high-purity water as shown in Table S1. The oxyanion standards were purchased from Wako Pure Chemicals, Japan (analytical grade). Some of the standard solutions such as metasilicate (SiO_3^{2-}) and orthosilicate (SiO_4^{4-}) were cross-checked by ICP-AES using commercial elemental standard solutions. Iminodiacetic acid (IDA), NTA, CyDTA and triethylenetetramine-*N,N,N',N'',N''',N'''*-hexaacetic acid, supplied by Dojindo, Japan (analytical grade), were used as chelating agents. Acetic acid and halogenoacetic acids as well as some organic acids were also from Wako Pure Chemicals, Japan (analytical grade). Water was purified by a Millipore Milli-Q system (Millipore Corp., USA). The potassium salt of Co^{III} –EDTA complex, synthesized according to a published procedure,^[30] was added to sample solutions to evaluate the condition of the instrument, when indicated in the text.^[15] This addition did not show any observable effects on the signal intensities of the dehydration products.

Apparatus

An LC-ESI-quadrupole MS system, LCMS-2010 (Shimadzu Co., Japan), was used in flow injection mode. The schematic diagram of the instrument was shown in Fig. S1. The negative ion mode was used throughout. Unless stated otherwise, the instrumental conditions were as follows: ES voltage, -5.0 kV ; Q-array voltage, 0 V ; nebulizer gas (N_2) pressure, 0.1 MPa ; the curve desolvation line (CDL) temperature, 300°C ; and block heater temperature, 300°C . The CDL and the heater block are parts of the interface following the ES where desolvation of ions occurs. Sample solutions, introduced with a six-way loop injector whose sample loop volume was $5 \mu\text{l}$, were propelled with an LC pump (LC-10AD, Shimadzu Co. Japan). Pure water was used as a carrier solution (flow rate, 0.2 ml/min), unless otherwise stated. The ICP-AES instrument was a Spectroblue unit from Spectro (Kleve, Germany).

Results and discussion

Dehydration reaction of chromate and/or dichromate with carboxylic acids

In the context of method development and for direct measurement of HCrO_4^- (m/z 117) by ESIMS, it was found that chromate ion reacted with various APCs as well as some organic acids at the ES interface to produce dehydrated products, giving prominent MS signals (Table 1). As shown in the table, chromate and all the carboxylic acids tested gave intense signals due to the 1:1 dehydration products ($-\text{H}_2\text{O}$), although the signal for HCrO_4^- (m/z 117) was always observed, showing that chromate did not react completely with the carboxylic acids. The ratio of the signal of the dehydration product with NTA to that of HCrO_4^- (m/z 117) was highest, suggesting that the reaction efficiency of NTA with chromate was the highest for the combinations of chromate and carboxylic acids tested. Figure 1 shows the mass spectrum of a solution containing $100 \mu\text{M}$ of $\text{K}_2\text{Cr}_2\text{O}_7$, $500 \mu\text{M}$ of NTA and $40 \mu\text{M}$ of Co^{III} –EDTA, where the signal for the dehydration product was observed at m/z 290. A possible reaction scheme for NTA with chromate is shown in Scheme 1. As mentioned in the introduction, O'Hair's group observed similar reactions at the interface, where group VI oxyanions

Table 1. Dehydration reactions of chromate ion with various carboxylic acids

Carboxylic acid	Iminodiacetic acid	Nitrilotriacetic acid	EDTA-OH	EDTA	<i>Trans</i> -1,2-diaminocyclohexane- <i>N,N,N',N'</i> -tetraacetic acid	Malic acid	Citric acid	Oxalic acid
<i>m/z</i> of dehydration product (–H ₂ O)	232	290	377	391	445	233	291	189
Signal intensity (A) of HCrO ₄ [–] (<i>m/z</i> 117) (×10 ⁵ counts)	1.3	0.3	0.8	0.8	1.0	0.4	0.3	0.5
Signal intensity (B) of dehydration product (×10 ⁵ counts)	1.9	3.3	4.6	3.1	3.9	0.8	1.3	0.3
B/A	1.5	11	5.8	4.1	3.9	1.9	4.2	0.6

A solution containing 10 μM of K₂Cr₂O₇, 500 μM of each carboxylic acid, 1 mM of ammonium acetate and 40 μM of Co^{III}–EDTA was tested.

Figure 1. Mass spectrum for a solution containing 100 μM of K₂Cr₂O₇, 500 μM of nitrilotriacetic acid (NTA) and 40 μM of Co^{III}–EDTA. **Scheme 1.** Possible dehydration reaction of chromic acid and nitrilotriacetic acid.

([MO₃(OH)][–] and [M₂O₆(OH)][–], M = Mo, W) acted as catalysts in a two-step gas-phase catalytic cycle for the dehydration of acetic acid to ketene, although they reported that chromate hardly reacted with acetic acid.^[26] Our observations were clearly different from that of O'Hair *et al.* Moreover, other organic acids, i.e. citric acid, malic acid and oxalic acid, were also found to react with chromate as shown in Table 1, although signal intensities were lower than those of the APCs. To study the effect of the acidity of the carboxylic acid on the efficiency of the dehydration reaction, acetic acid and five halogenoacetic acids were examined. First, a solution containing 25 μM of chromate and 200 μM of acetic acid (pK_a 4.75), monochloroacetic acid (MCA) (pK_a 2.88), dichloroacetic acid (DCA) (pK_a 1.48) or trichloroacetic acid (TCA) (pK_a 0.7) was tested. The order for the intensities of the signals for the dehydration products

was acetic acid < MCA < DCA < TCA. Moreover, when a solution containing the three halogenoacetic acids (200 μM each) and chromate (25 μM) was tested, only the dehydration product of TCA gave a strong MS signal (*m/z* 261). Thus, it seemed that the higher the acidity of the carboxylic acid, the more reactive the acid was. This result was consistent with that of O'Hair's group; i.e. the order of the reactivity with [Mo₂O₆(OH)][–] was acetic acid > CF₃–CH₂OH > CH₃OH, depending on their acidities.^[25] They also proposed the mechanism of the dehydration reaction of [V₂O₅(OH)][–] and methanol based on their theoretical calculation study, which said that the reaction begins by the formation of an ion–molecule complex between [V₂O₅(OH)][–] and methanol; then, it is followed by the formation of a bridging oxo ligand deprotonating methanol with concomitant opening of the VO₂V ring (transition state).^[28] That is, the deprotonation process is one of the most important ones; thus, the acidities of carboxylic acids may affect their reactivities greatly. In contrast, different results were obtained with trifluoroacetic acid (pK_a –0.3), TCA and tribromoacetic acid (TBA) (pK_a 0.8) where almost the same intensities were noted for the three acids. Moreover, when a solution containing all three halogenoacetic acids (200 μM each) and chromate (25 μM) was tested, only the dehydration product of TBA gave a strong MS signal (*m/z* 395). These findings suggested that there was an optimum acidity of the carboxylic acid for this reaction, which should be quite low, probably around a pK_a value

of 1; the exact reason for this is not yet known. Although the gas-phase acidities of these acids might have some effects, we were not able to evaluate them because of lack of data on them. This may be one of the reasons why APCs gave higher intensities than other organic acids that did not contain a N atom.

Dehydration reaction of various oxyanions with APCs

As the dehydration reaction seemed not to be limited to chromate ion, dehydration reactions of 16 oxyanions with several APCs, i.e. IDA, NTA, CyDTA and triethylenetetramine-*N,N',N'',N'''*-hexaacetic acid, were next investigated. The test solutions contained 0–100 μM of each oxyanion, 500 μM of each APC and 40 μM of Co^{III} -EDTA as an internal standard. The internal standard did not affect the formation of dehydration products and was effective in compensating for the daily changes in instrument sensitivity. As for the pH of the test solutions, the pH values for solutions containing IDA were ~ 4 , and the others were ~ 9 . Table 2 summarizes the occurrences of the dehydration reaction for each test solution and specifies the LOD for the oxyanion (3σ of blank sample) when the reaction was used for the determination of the oxyanion. Moreover, the chemical forms of the supposed dehydration products of some oxyanions with IDA are shown in Fig. 2 as examples. It should be noted that the optimization of the measurement conditions for each combination was not performed; thus, the LOD would be improved, if reaction conditions were optimized. In fact, some of the combinations, i.e. chromate and NTA, orthosilicate and IDA, and molybdate and NTA, gave very high sensitivities. It is possible to classify the 16 oxyanions into three groups, i.e. group 1, metal elements; group 2, metalloid elements; and group 3, non-metal elements as follows:

Group 1 VO_3^- , CrO_4^{2-} , MoO_4^{2-} and WO_4^{2-} . All of the oxyanions in this group gave prominent MS signals for the dehydration products for all of the APCs tested. In particular, MoO_4^{2-} and WO_4^{2-} formed dehydration products that had lost two water molecules. Although O'Hair's group reported that CrO_4^{2-} did not react with acetic acid,^[26] this was not the case in this study, the dehydration product giving a strong MS signal as mentioned earlier. Moreover, although O'Hair's group reported the formation of the dehydration products with binuclear oxyanions ($[\text{M}_2\text{O}_6(\text{OH})]^-$, $\text{M} = \text{Mo}, \text{W}$, and $[\text{V}_2\text{O}_5(\text{OH})]^-$), we did not observe such products, probably because of differences in the respective measurement conditions. The MS signals of the dehydration products were sufficiently intense to be suitable for trace analyses. In this work, the dehydration product of NTA and CrO_4^{2-} was used for trace determination of Cr^{VI} in water samples (see below).

Group 2 BO_3^{3-} , SiO_3^{2-} , SiO_4^{4-} , AsO_4^{3-} , AsO_2^- , SeO_4^{2-} and SeO_3^{2-} . Although oxyanions of this group still formed dehydration products that may be useful for trace determinations, their reactivities seemed to be lower than those of group 1. Some of the APCs did not form dehydration products with some oxyanions, e.g. those of BO_3^{3-} , AsO_4^{3-} , AsO_2^- , SeO_4^{2-} and SeO_3^{2-} . It is speculated that complex formation involving the oxyanion and APC in the gas phase may occur prior to the dehydration reaction, and this step may be responsible for differences between the APCs. As shown in Table 2, direct measurement of some oxyanions of group 2 such as BO_3^{3-} , SiO_3^{2-} , SiO_4^{4-} and AsO_2^- was not possible because of low acidity; nevertheless, the dehydration

products did give high sensitivities. Thus, the use of these dehydration reactions for trace analysis may be important given that there are few alternative methods. There are two forms of oxyanions for Si, i.e. metasilicate (SiO_3^{2-}) and orthosilicate (SiO_4^{4-}). The dehydration product of metasilicate from which one water molecule is lost has the same m/z as that of orthosilicate from which two water molecules are lost, as shown in Table 2 and in Si-1 and Si-2 of Fig. 2. Thus, there was difficulty in differentiating between the two forms, which seemed to show only slight differences in sensitivities. In careful experiments using an ion-exclusion chromatography (IEC)-ESIMS system (see below), however, metasilicate and orthosilicate gave the same sensitivity where IDA was used as a carboxylic acid. This suggests that both silicates gave the same dehydration product, i.e. Si-1 or Si-2 in Fig. 2. Given that the main chemical form of silica in natural water is monomeric orthosilicate,^[30,31] the dehydration product of orthosilicate has mainly been studied in this paper, and an analytical method for silica in natural waters was developed as outlined later. In the case of the oxyanions of As and Se, there are two predominant species for each element, where the valencies of the central atoms are different from each other, i.e. AsO_4^{3-} and AsO_2^- and SeO_4^{2-} and SeO_3^{2-} . In these cases, the dehydration products give different m/z values; thus, we can distinguish them from each other, as shown in Table 2 and Fig. 2 (As-1 to As-4 and Se-1 and Se-2, respectively). In both cases, the oxyanions of the lower-valency species, i.e. arsenite (AsO_2^-) and selenite (SeO_3^{2-}), gave much higher sensitivities than those with higher valency, i.e. arsenate (AsO_4^{3-}) and selenate (SeO_4^{2-}), respectively. The higher valency of the central atom of the oxyanion species may cause a higher acidity (Table S2), in other words, a lower gas-phase basicity, therefore resulting in lower ability to accept proton from carboxylic acids (see above).^[28] Nevertheless, the dehydration products of arsenite (AsO_2^-) and arsenate (AsO_4^{3-}) with IDA gave high sensitivities; particularly, the 1:2 product of arsenite and IDA (m/z 337) from which two water molecules were lost (As-2 in Fig. 2) resulted in a very low LOD of 0.69 nM (0.052 ng As/mL) (Table 2). Accordingly, the development of speciation methods for arsenite and arsenate is planned.

Group 3 NO_3^- , NO_2^- , PO_4^{3-} , SO_4^{2-} and ClO_4^- . Oxyanions of this group did not react with APCs except for the combination of NO_2^- and IDA. Thus, the dehydration reaction may not be useful for the trace determination of these oxyanions except in the case of NO_2^- . These results may be due to the higher valencies of the central atom (M), which results in too low gas-phase basicity for reaction with carboxylic acids as discussed earlier for group 2 species. Although PO_4^{3-} did react with CyDTA at the highest temperature conditions of CDL, the MS signal was very weak. Thus, other measurement strategies such as direct measurement of the oxyanions^[29] or the application of ion-pair formation^[20–22] may be more effective for trace analysis. The possibility does, however, remain to exploit the dehydration reaction for trace determination of NO_2^- .

Table 2. Dehydration reactions of various oxyanions with aminopolycarboxylates (APCs)^a

		Direct ^b	Iminodiacetic acid	Nitrilotriacetic acid	<i>Trans</i> -1,2-diaminocyclohexane- <i>N,N,N',N'</i> -tetraacetic acid	Triethylenetetramine- <i>N,N,N',N'',N'',N'''</i> -hexaacetic acid
VO ₃ [−]	LOD (μM)	1.0	0.84	2.9	0.72	0.37
	<i>m/z</i> (−H ₂ O)	99 (VO ₃ [−])	214	272	427	575
CrO ₄ ^{2−}	LOD (μM)	0.013 ^b	0.84	0.016	0.16	0.67
	<i>m/z</i> (−H ₂ O)	117 (HCrO ₄ [−])	232	290	445	593
MoO ₄ ^{2−}	LOD (μM)	3.9	0.31	n.d.	n.d.	n.d.
	<i>m/z</i> (−H ₂ O)	163 (HMoO ₄ [−])	278	336	491	639
	LOD (μM)		0.31	0.060	1.23	2.3
	<i>m/z</i> (−2H ₂ O)		260	318	473	621
WO ₄ ^{2−}	LOD (μM)	1.0	0.88	n.d.	n.d.	n.d.
	<i>m/z</i> (−H ₂ O)	249 (HWO ₄ [−])	364	422	577	725
	LOD (μM)		1.6	5.4	1.9	1.6
	<i>m/z</i> (−2H ₂ O)		346	404	559	707
BO ₃ ^{3−}	LOD (μM)	n.d.	n.d.	n.d.	n.d.	0.69
	<i>m/z</i> (−2H ₂ O)	61 (H ₂ BO ₃ [−])	158	216	371	519
SiO ₃ ^{2−}	LOD (μM)	n.d.	0.014	3.4	1.1	3.7
	<i>m/z</i> (−H ₂ O)	77 (HSiO ₃ [−])	192	250	405	553
SiO ₄ ^{4−}	LOD (μM)	n.d.	n.d.	n.d.	10	2.1
	<i>m/z</i> (−H ₂ O)	95 (H ₃ SiO ₄ [−])	210	268	423	571
	LOD (μM)		0.011	n.d.	9.0	26
	<i>m/z</i> (−2H ₂ O)		192	250	405	553
AsO ₄ ^{3−}	LOD (μM)	0.95	n.d.	n.d.	1.5	1.0
	<i>m/z</i> (−H ₂ O)	141 (H ₂ AsO ₄ [−])	256	314	469	617
	LOD (μM)		0.035	n.d.	n.d.	n.d.
	<i>m/z</i> (−2H ₂ O)		238	296	451	599
	LOD (μM)		0.11	—	—	—
	<i>m/z</i> (−3H ₂ O)		353 ^c	—	—	—
AsO ₂ [−]	LOD (μM)	n.d.	0.034	0.27	n.d.	n.d.
	<i>m/z</i> (−H ₂ O)	107 (AsO ₂ [−])	222	280	435	583
	LOD (μM)		0.00069			
	<i>m/z</i> (−2H ₂ O)		337 ^d			
SeO ₄ ^{2−}	LOD (μM)	0.065	13	n.d.	n.d.	n.d.
	<i>m/z</i> (−H ₂ O)	145 (HSeO ₄ [−])	260			
SeO ₃ ^{2−}	LOD (μM)	1.2	0.16	n.d.	n.d.	n.d.
	<i>m/z</i> (−2H ₂ O)	129 (HSeO ₃ [−])	226			
NO ₃ [−]	LOD (μM)	113	n.d.	n.d.	n.d.	n.d.
	<i>m/z</i> (−H ₂ O)	62 (NO ₃ [−])	177	235	390	538
NO ₂ [−]	LOD (μM)	n.d.	0.49	n.d.	n.d.	n.d.
	<i>m/z</i> (−H ₂ O)	46 (NO ₂ [−])	161	219	374	522
PO ₄ ^{3−}	LOD (μM)	1.2	n.d.	n.d.	n.d.	n.d.
	<i>m/z</i> (−H ₂ O)	97 (H ₂ PO ₄ [−])	212	270	425	573
SO ₄ ^{2−}	LOD (μM)	0.37	n.d.	n.d.	n.d.	n.d.
	<i>m/z</i> (−H ₂ O)	97 (HSO ₄ [−])	212	270	425	573
ClO ₄ [−]	LOD (μM)	—	n.d.	n.d.	n.d.	n.d.
	<i>m/z</i> (−H ₂ O)	99 (ClO ₄ [−])	214	272	427	575

LOD, limit of detection; n.d., not detected.

^aA solution containing 0–100 μM of each oxyanion, 500 μM of each APC and 40 μM of Co^{III}–EDTA was tested. A 1:1 product (oxyanion:APC) was measured, unless otherwise stated.^bA solution containing 0–100 μM of each oxyanion and 40 μM of Co^{III}–EDTA was tested. Each oxyanion itself was measured.^cA 1:2 product (AsO₄^{3−}:IDA) from which three waters were removed was observed.^dA 1:2 product (AsO₂[−]:IDA) from which two waters were removed was observed.

Figure 2. Possible chemical structures of some dehydration products.

Determination of Cr^{VI} by post-column IC-ESIMS using dehydration reaction of chromate with NTA

A post-column IC-ESIMS system, which exploited the dehydration reaction of chromate ion with NTA, was used for the trace determination of Cr^{VI} , as shown in Fig. 3. For the post-column reaction, the optimized concentration of 500 μM NTA solution (flow rate, 0.3 mL/min) was added to the eluate (35 mM NH_4HCO_3 solution), and the dehydration product was monitored at m/z 290 in selected ion

Figure 3. Schematic of ion chromatography electrospray ionization mass spectrometry (ESI-MS) instrument. Experimental conditions for Cr^{VI} determination: eluate, 35 mM NH_4HCO_3 aqueous solution; post-column reagent, 500 μM nitrilotriacetic acid aqueous solution; column, anion exchange column (Dionex, AG4A-SC, 2.0-mm inner diameter (ID) $\times$ 50 mm). Experimental conditions for silica determination: eluate, pure water; post-column reagent, 100 μM iminodiacetic acid methanol–water (80:20 w/w) mixed solution; column, cation-exchange column (Tosoh TSKgel SuperIC-A/C (6.0-mm ID $\times$ 15 cm)) with a guard column (TSKgel guard column SuperIC-A/C, 4.6-mm ID $\times$ 2 cm).

monitoring (SIM) mode. An anion exchange column (AG4A-SC Dionex) was used to separate chromate ion from other anion and cation species. An example of a river water analysis is shown in Fig. 4, where sulfate ion was separated from chromate ion. Linear calibration for chromate was maintained up to 10 μM . At higher concentrations, the graph deviated slightly from linearity (Fig. S2). The LOD for chromate was 17 nM, whereas it was 62 nM when HCrO_4^- (m/z 117) was measured directly. The method was used for analysis of river samples (Kiryu River near the university), and although Cr^{VI} was not detected in the samples, analyte recoveries were $97 \pm 3.5\%$ and $98 \pm 3.9\%$ for spike additions of 5 and 10 μM of Cr^{VI} , respectively. These results demonstrated the potential of the present method for trace determinations of Cr^{VI} in real samples.

Determination of silica in water samples by ESIMS using the dehydration reaction of silica with IDA

As shown in Table 2 and Fig. 5, orthosilicate ion and IDA formed the dehydration product (m/z 192), from which two water molecules were lost, to give very high sensitivity for orthosilicate ion. Thus, this reaction was utilized to determine silica in water samples. Moreover, the dehydration product of the dimer of orthosilicate ($\text{H}_6\text{Si}_2\text{O}_7$) and IDA (m/z 270), from which two water molecules were lost, was also observed as shown in Fig. 5. This dimer probably does not exist in sample solutions but may form at the CDL, because the signal became very weak compared with the monomer product (m/z 192) when the CDL temperature was lower. Moreover, the monomer and the dimer gave the same retention time in IEC (see below).

The measurement conditions were as follows: a water methanol (v/v) ratio of 3:7 was found to be most suitable (Fig. 6a); the CDL temperature was the most important instrumental parameter, and the signal intensity increased with an increase in temperature (Fig. 6b). This result suggested that the dehydration reaction occurred mainly at the CDL, although the dissociation processes may also occur in the heater block region. A linear calibration curve for orthosilicate was obtained up to 1 μM ; at higher concentrations, the graph showed a curvature. The LOD for orthosilicate was 11 nM (0.31 ng Si/ml). Direct analyses of bottled mineral water samples were attempted, but we were not able to obtain reproducible results presumably because of the presence of matrix effects. Thus,

Figure 4. Chromatogram of chromate and sulfate ions in river water sample containing 5 μM of Cr^{VI} as spike. The dehydration product of chromate ion and nitrilotriacetic acid (m/z 290) was monitored in SIM mode. HSO_4^- (m/z 97) was also monitored.

Figure 5. Mass spectrum of a solution containing 50 μM Na_4SiO_4 , 500 μM iminodiacetic acid and 40 μM Co^{III} -EDTA.

Figure 6. Optimization of measurement conditions of electrospray ionization mass spectrometry for the detection of dehydration product of orthosilicate ion and iminodiacetic acid (m/z 192). (a) Effect of solvent constituents of sample solutions. Instrumental conditions; electrospray voltage, -5.0 kV; Q-array voltage, 0 V; nebulizer gas (N_2) pressure, 0.1 MPa; the curve desolvation line (CDL) temperature, 300°C ; block heater temperature, 300°C . (b) Effect of CDL temperature. Instrumental conditions; the same as above (except for CDL temperature).

IEC was used to separate silica from the sample matrix constituents,^[32,33] according to the procedure of Ikeda *et al.*^[32] The instrumental setup was basically the same as that of Fig. 3. The separation column was a polymethacrylate-based weakly acidic cation-exchange resin in the H^+ form, Tosoh TSKgel SuperIC-A/C (6.0-mm inner diameter $\times$ 15 cm) with a guard column

(TSKgel guard column SuperIC-A/C, 4.6-mm inner diameter $\times$ 2 cm). The eluate was pure water (flow rate, 0.3 ml/min).^[32] A methanol-water (80:20 w/w) solution containing the optimized concentration of 100 μM IDA (flow rate, 0.3 ml/min) was used as a post-column solution. The dehydration product of silicate and IDA was monitored at m/z 192 in SIM mode. Figure S3 shows the chromatogram of orthosilicate (m/z 192) and sulfate (HSO_4^- m/z 97) in SIM mode, where a model sample containing 5 mM NaCl, 2 mM MgCl_2 , 3 mM MgSO_4 , 1 mM KCl, 1 mM CaCl_2 and 5 μM Na_4SiO_4 was used to represent a typical sample matrix. The model sample gave a signal intensity of $97.1 \pm 5.7\%$ compared with that of 2.0×10^3 for 5 μM Na_4SiO_4 standard solution. On this basis, the IEC system was

Table 3. Determination of silica in water samples

Sample	Si/ μM			Hardness ^b (mg/l)
	The present method ^a	Inductively coupled plasma-atomic emission spectroscopy	Molybdenum yellow method	
Mineral water sample #1 ^c	372 ± 14	382	410	27
Mineral water sample #2 ^d	206 ± 20	204	221	281
Mineral water sample #3 ^e	113 ± 10	121	134	1200
River water sample ^f	204 ± 14	175	206	28

^aAverage of three determinations.

^bHardness of samples was obtained by determining Mg and Ca by inductively coupled plasma-atomic emission spectroscopy.

^cA dilution of 77 times.

^dA dilution of 45 times.

^eA dilution of 45 times.

^fA dilution of 35 times. The sample was obtained from Kiryu River.

effective in removing the matrix interferences present in the sample. The LOD was 0.17 μM for orthosilicate (4.8 ng Si/ml), and the calibration curve was linear up to 10 μM . This LOD was slightly higher than that of the literature (1.0 ng Si/ml) where a molybdenum blue method was used for post-column detection.^[33] However, the sensitivity of the present method should be high enough to determine silica in natural waters except for seawater samples. To analyze seawater samples, desalination may be necessary, and the development of such a system is now in progress. The present method was applied to the analysis of bottled mineral water samples and a river water sample, and, as shown in Table 3, the results were in good agreement with those of ICP-AES and the molybdenum yellow method.

To confirm that the dehydration reactions occur not only in the present instrument (Shimadzu LCMS2010) but also in other ESIMS systems, the dehydration reaction between orthosilicate and IDA was examined (any other system was not examined) using three further ESIMS systems, i.e. Nano Frontier from Hitachi High-Technologies Co., Japan; Model 6120 from Agilent Technologies, USA; and QTRAP 3200 from AB Sciex, USA. Although instrument optimizations were not attempted, prominent MS signals for the dehydration product (m/z 192) were realized in the three instruments. Thus, the proposed methods have generic potential, and trace measurement of oxyanions may be undertaken on various ESIMS platforms.

Conclusions

The oxyanions, VO_3^- , CrO_4^{2-} , MoO_4^{2-} , WO_4^{2-} , BO_3^{3-} , SiO_3^{2-} , SiO_4^{4-} , AsO_3^{3-} , AsO_2^- , SeO_4^{2-} , SeO_3^{2-} and NO_2^- , reacted with four APCs at the ES interface to produce dehydration products that gave intense ion responses. We assume that these dehydration reactions should take place in the gas phase, considering the works of O'Hair's group.^[25–28] However, it should be noted that we do not have any evidence to eliminate the possibility that the dehydration reactions take place in the liquid phase, and further studies should be necessary to clarify the mechanism of these reactions. Signal strength was sufficient to permit trace measurement of the oxyanions. In particular, the measurement of species that have relatively high pK_a values such as BO_3^{3-} , SiO_4^{4-} , AsO_2^- and NO_2^- would be significant given that direct measurement of these oxyanions by ESIMS is not possible. Moreover, simultaneous determination of several oxyanions should be possible by this method, as IDA, for example, reacts with various oxyanions as mentioned earlier. Methods for the determination of Cr^{VI} and silica in water samples were developed in combination with IC, where the dehydration products of CrO_4^{2-} and NTA (m/z 290) and SiO_4^{4-} and IDA (m/z 192) were measured, respectively. The LODs were 17 nM for Cr^{VI} and 0.17 μM for SiO_4^{4-} . There remain two outstanding problems with the present methodology. First, there is a need to improve method sensitivity. The optimization of chelating agent chemistry as well as the use of state-of-the-art instrumentation may result in sensitivity enhancement. Also, there is a need to improve the performance of the online matrix removal system. In this respect, we are developing an online electro dialysis system, which may make it possible to realize a more efficient and higher-throughput system compared with the present IC-based system.

Acknowledgements

This work was supported in part by a grant-in-aid for scientific research (B) (no. 20350033) and a grant-in-aid for scientific research

(B) (no. 26288065) from Japan Society for the Promotion of Science. We are grateful to Takamitsu Otake and Masahiko Numata of AIST, Hiromi Takiguchi of the University of Tokyo and Motohide Aoki and Tomonari Umemura of Tokyo University of Pharmacy and Life Sciences for allowing us to use the ESIMS facilities.

References

- [1] L. Barron, E. Gilchrist. Ion chromatography-mass spectrometry: a review of recent technologies and applications in forensic and environmental explosives analysis. *Anal. Chim. Acta* **2014**, 806, 27.
- [2] M. J. Keith-Roach. A review of recent trends in electrospray ionisation-mass spectrometry for the analysis of metal-organic ligand complexes. *Anal. Chim. Acta* **2010**, 678, 140.
- [3] R. Michalski, M. Jablonska, S. Szopa, A. Lyko. Application of ion chromatography with ICP-MS or MS detection to the determination of selected halides and metal/metalloids species. *Crit. Rev. Anal. Chem.* **2011**, 41, 133.
- [4] K. Minakata, M. Suzuki, O. Suzuki. Application of electrospray ionization tandem mass spectrometry for the rapid and sensitive determination of cobalt in urine. *Anal. Chim. Acta* **2008**, 614, 161.
- [5] K. Minakata, H. Nozawa, N. Okamoto, O. Suzuki. Determination of platinum derived from cisplatin in human tissues using electrospray ionization mass spectrometry. *J. Chromatogr. B* **2006**, 832, 286.
- [6] K. Minakata, M. Suzuki, O. Suzuki. Determination of molybdenum and/or ruthenium in urine using electrospray ionization mass spectrometry. *Anal. Biochem.* **2006**, 348, 148.
- [7] K. Minakata, M. Suzuki, O. Suzuki. Rapid and decisive determination of Cr^{6+} using electrospray ionization mass spectrometry. *Anal. Chim. Acta* **2005**, 539, 141.
- [8] K. Minakata, I. Yamagishi, H. Nozawa, K. Gonmori, K. Hasegawa, M. Suzuki, F. Horio, K. Watanabe, O. Suzuki. Simultaneous determination of coinage metals, copper, silver, and gold in tissues using electrospray ionization tandem mass spectrometry. *Forensic Toxicol.* **2012**, 30, 149.
- [9] K. Minakata, M. Suzuki, O. Suzuki. Simple and selective determination of arsenite and arsenate by electrospray ionization mass spectrometry. *Anal. Chim. Acta* **2009**, 631, 87.
- [10] K. Minakata, H. Nozawa, K. Gonmori, I. Yamagishi, M. Suzuki, K. Hasegawa, K. Watanabe, O. Suzuki. Determination of cyanide in blood by electrospray ionization tandem mass spectrometry after direct injection of dicyanogold. *Anal. Bioanal. Chem.* **2011**, 400, 1945.
- [11] K. Minakata, H. Nozawa, I. Yamagishi, K. Gonmori, K. Hasegawa, M. Suzuki, K. Watanabe, O. Suzuki. A rapid and decisive determination of thiocyanate in blood by electrospray ionization tandem mass spectrometry. *Forensic Toxicol.* **2012**, 30, 45.
- [12] K. Minakata, I. Yamagishi, S. Kanno, H. Nozawa, M. Suzuki, O. Suzuki. Determination of iodide in urine using electrospray ionization tandem mass spectrometry. *J. Chromatogr. B* **2010**, 878, 1683.
- [13] G. R. Agnes, G. Horlick. Electrospray mass spectrometry as a technique for elemental analysis: quantitative aspects. *Appl. Spectrosc.* **1994**, 48, 649.
- [14] D. A. Barnett, G. Horlick. Quantitative electrospray mass spectrometry of halides and halogenic anions. *J. Anal. At. Spectrom.* **1997**, 12, 497.
- [15] H. Hotta, T. Mori, A. Takahashi, Y. Kogure, K. Johno, T. Umemura, K. Tsunoda. Quantification of trace elements in natural samples by electrospray ionization mass spectrometry with a size-exclusion column based on the formation of metal-aminopolycarboxylate complexes. *Anal. Chem.* **2009**, 81, 6357.
- [16] H. Hotta, Y. Kogure, K. Tsunoda. Determination of divalent trace metals in soil sample using electrospray ionization mass spectrometry. *Anal. Methods* **2012**, 4, 1160.
- [17] H. Hotta, K. Tsunoda. Electrospray ionization mass spectrometry for the quantification of inorganic cations and anions. *Anal. Sci.* **2015**, 31, 7.
- [18] C. D. Xu, E. Dodliba, N. L. T. Padivitage, Z. S. Breitbach, D. W. Armstrong. Metal cation detection in positive ion mode electrospray ionization mass spectrometry using a tetracationic salt as a gas-phase ion-pairing agent: evaluation of the effect of chelating agents on detection sensitivity. *Rapid Commun. Mass Spectrom.* **2012**, 26, 2885.
- [19] E. Dodliba, C. D. Xu, E. Wanigasekara, D. W. Armstrong. Sensitive analysis of metal cations in positive ion mode electrospray ionization

- mass spectrometry using commercial chelating agents and cationic ion-pairing reagents. *Rapid Commun. Mass Spectrom.* **2012**, 26, 1005.
- [20] P. K. Martinelango, J. L. Anderson, P. K. Dasgupta, D. W. Armstrong, R. S. Al-Horri, R. W. Slingsby. Gas-phase ion association provides increased selectivity and sensitivity for measuring perchlorate by mass spectrometry. *Anal. Chem.* **2005**, 77, 4829.
- [21] P. K. Martinelango, P. K. Dasgupta. Dicationic ion-pairing agents for the mass spectrometric determination of perchlorate. *Anal. Chem.* **2007**, 79, 7198.
- [22] R. J. Soukup-Hein, J. W. Remsburg, P. K. Dasgupta, D. W. Armstrong. A general, positive ion mode ESI-MS approach for the analysis of singly charged inorganic and organic anions using a dicationic reagent. *Anal. Chem.* **2007**, 79, 7346.
- [23] H. Hotta, S. Kurihara, K. Johno, M. Kitazume, K. Sato, K. Tsunoda. New determination methods of halides and cyanide ions by electrospray ionization mass spectrometry based on ternary complex formation. *Anal. Sci.* **2011**, 27, 953.
- [24] H. Hotta, K. Yata, K. F. Bin Kamarudin, S. Kurihara, K. Tsunoda, N. Fukumoto, I. Kojima, S. Kinugasa. Determination of chromium(III), chromium(VI) and total chromium in chromate and trivalent chromium conversion coatings by electrospray ionization mass spectrometry. *Talanta* **2011**, 88, 533.
- [25] T. Waters, R. A. J. O'Hair, A. G. Wedd. Catalytic gas phase dehydration of acetic acid to ketene. *Int. J. Mass Spectrom.* **2003**, 228, 599.
- [26] R. A. J. O'Hair, G. N. Khairallah. Gas phase ion chemistry of transition metal clusters: production, reactivity, and catalysis. *J. Cluster Sci.* **2004**, 15, 331.
- [27] T. Waters, R. A. J. O'Hair, A. G. Wedd. Catalytic gas phase oxidation of methanol to formaldehyde. *J. Am. Chem. Soc.* **2003**, 125, 3384.
- [28] B. L. Harris, T. Waters, G. N. Khairallah, R. A. J. O'Hair. Gas-phase reactions of $[\text{VO}_2(\text{OH})_2]^-$ and $[\text{V}_2\text{O}_5(\text{OH})]^-$ with methanol: experiment and theory. *J. Phys. Chem. A* **2013**, 117, 1124.
- [29] M. M. Ivey, K. L. Foster. Detection of phosphorus oxyanions in synthetic geothermal water using ion chromatography-mass spectrometry techniques. *J. Chromatogr. A* **2005**, 1098, 95.
- [30] F. P. Dwyer, E. C. Gyarfas, D. P. Mellor. The resolution and racemization of potassium ethylenediaminetetra-acetatocobaltate (III). *J. Phys. Chem.* **1955**, 59, 296.
- [31] G. B. Alexander. The solubility of amorphous silica in water. *J. Phys. Chem.* **1954**, 58, 453.
- [32] M. Ikeda, M. Mori, K. Kurachi, W. Hu, K. Tanaka. Selective and simultaneous determination of phosphate and silicate ions in leaching process waters for ceramics glaze raw materials of natural origin by ion-exclusion chromatography coupled with UV-detection after postcolumn derivatization. *Anal. Sci.* **2006**, 22, 117.
- [33] N. Nakatani, W. Masuda, D. Kozaki, R. Goto, N. Nakagoshi, M. Mori, K. Hasebe, K. Tanaka. Simultaneous spectrophotometric determination of orthophosphate and silicate ions in river water using ion-exclusion chromatography with an ascorbate solution as both eluent and reducing agent, followed by postcolumn derivatization with molybdate. *Anal. Sci.* **2009**, 25, 379.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site.