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Analytical sensitivity of arsenobetaine on atomic spectrometric analysis and the purity of synthetic arsenobetaine[†]

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Arsenobetaine is one of the main organoarsenic compounds that exist in living organisms. Determination errors in total arsenic analyses for organoarsenic compounds occur because analytical sensitivities depend upon the chemical forms of the compounds. However, information on the analytical sensitivity of arsenobetaine by ICP-MS and ICP-AES and the purity of commercially available arsenobetaine standards is lacking. BCR CRM 626 (arsenobetaine solution) is a certified reference material from IRMM with a certified concentration of arsenobetaine. The sensitivity and behavior of arsenobetaine on ICP-MS and ICP-AES were investigated using the BCR arsenobetaine. The analytical sensitivity and behavior of arsenobetaine using ICP-MS and ICP-AES were also investigated using a commercially available synthetic arsenobetaine, and were compared with results for BCR-AB based on a Japan calibration service system (JCSS) arsenic standard solution. In the results, arsenic determined directly in arsenobetaine showed about 15% greater sensitivity in analysis by ICP-MS and ICP-AES than did inorganic (JCSS) arsenic. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: organoarsenic compounds; arsenobetaine; purity; atomic spectrometric analysis; determination sensitivities of arsenic compounds; speciation; SI traceability

INTRODUCTION

Arsenic (As) exists in the natural environment as various chemical species. These are widely distributed although the concentrations are usually low. Arsenic, in its inorganic forms, exists in two oxidation numbers such as As(III) and As(V). These, together with organic forms of arsenic, exhibit a range of toxicities. The main naturally occurring chemical forms of As are the inorganic ions As(III) and As(V). However, methylated forms are also found, particularly in living organisms. The toxicity of the naturally occurring organoarsenic compounds and As(V) is low for humans, but As(III) is highly toxic. Therefore, it is important to know not only the total concentration of As in environmental and biological samples but also the identity and abundance of the species that are present. Hence, many speciation methods using HPLC-ICP-MS and ICP-AES have recently been reported for arsenic.[1–14] Arsenobetaine (AB) is one of the major arsenic species, found chiefly in marine animals, but also in some terrestrial organisms. When biological tissue samples are prepared for analysis, arsenobetaine is often the main target analyte. For total arsenic analysis of solid or powdered samples, pretreatment is necessary to decompose the samples before the determination step, and some decomposition techniques of arsenobetaine have been reported.[15–20] However, AB is difficult to completely decompose to inorganic arsenic, and some AB often persists and is not decomposed by the pretreatment. The chemical forms of decomposed As have seldom been examined prior to analysis.

Widely used analytical techniques for determining total arsenic in environmental and biological samples include inductively coupled plasma mass spectrometry (ICP-MS),

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inductively coupled plasma atomic emission spectrometry (ICP-AES) and electrothermal atomic absorption spectrometry (ETAAS), sometimes in combination with a hydride generation (HYD) system.[21–23] Inorganic arsenic is almost used to make standard solutions in the determination of total arsenic. However, there is a lack of information on the sensitivity of such ICP-MS and ICP-AES analyses when they specifically target arsenobetaine and whether the behavior of arsenobetaine is different from that of inorganic arsenic. Thus it is possible that, when arsenobetaine is contained in sample solutions, determination errors may occur, and accurate determination of arsenic will be difficult.

The National Research Council of Canada (NRCC) developed certified reference materials (CRMs) DORM 1 and DORM 2,[24] and the Institute for Reference Materials and Measurements (IRMM) developed BCR CRM 627 for arsenic speciation. The CRMs have been used to study arsenic speciation.[25–29] Although a CRM for BCR CRM 626 arsenobetaine[30] as an organoarsenic standard solution is available, there have been few reports of its use.

Generally, reports of arsenic speciation have been based on the commercially available standards, methylarsonic acid [MMAA, $(CH_3)AsO(OH)_2$], dimethylarsinic acid [DMAA, $(CH_3)_2AsO(OH)$], trimethylarsine oxide [TMAO, $(CH_3)_3AsO$], tetramethylarsonium iodide [TeMA, $(CH_3)_4AsI$], arsenocholine bromide [AsC, $(CH_3)_3As^+CH_2CH_2OH\ Br^-$] and arsenobetaine [AB, $(CH_3)_3As^+CH_2COO^-$]. However, in many cases, the purity of those reagents is defined as 95–100%, but a precise purity evaluation has not been reported. Thus in the analysis of arsenic in environmental and biological samples the precise determination of arsenobetaine is difficult.

Because the analytical sensitivities of inorganic arsenic and arsenobetaine may be different, complete decomposition of arsenobetaine to inorganic arsenic is very difficult and requires specific conditions. Reference materials certified for arsenic compounds and establishment of a precise determination technique for arsenobetaine are very important because they are urgently needed for quality control. In addition, precision controls on analytical procedures and ensuring traceability in SI units can be difficult. Thus, in the preparation of biological and environmental samples that contain arsenobetaine the precision of the analysis needs investigation.

In this work, the sensitivity of ICP-MS and ICP-AES analyses for arsenobetaine, and the behavior of arsenobetaine in such analyses, when compared with inorganic arsenic, have been investigated with the object of increasing the precision of analyses for total arsenic and for arsenic species. In addition, the purity of a commercial synthetic arsenobetaine reagent (powder), available for purchase in Japan, was evaluated.

EXPERIMENTAL

Apparatus

An ICP-AES Optima 4300DV instrument (Perkin Elmer, Yokohama, Japan) equipped with a concentric glass nebulizer and a cyclonic chamber, and an ICP-MS 7500c instrument (Agilent, Tokyo, Japan) equipped with a micro mist nebulizer and a Scott chamber were used for arsenic measurement. An AAnalyst 800 (Perkin Elmer) was used for electrothermal atomic absorption spectrometry. The AAnalyst 800 spectrometer was equipped with a graphite atomizer using a THGA graphite tube (GFAAS). High-performance liquid chromatography, an ICP-MS (Agilent 7500c; HPLC-ICP-MS) system, was used for speciation of arsenic compounds. The column employed was a CAPCELL PAK C_{18} MG S3 ODS (Shiseido Co. Ltd, Tokyo, Japan). The mobile phase consisted of 10 mmol l^{-1} sodium butanesulfonate, 4 mmol l^{-1} tetramethylammonium hydroxide, 4 mmol l^{-1} malonic acid and 0.05% (v/v) methanol (pH 3.0). A digital hot plate HP30A1 (Iuchi Ltd, Osaka, Japan) was used for wet digestion.

Reagents

Inorganic arsenic standard solution

A Japan calibration service system (JCSS) arsenic standard solution (1011 mg l^{-1} ± 0.6%, Kanto Chemical Industries, Ltd, Tokyo, Japan) was prepared by diluting the As_2O_3 reagent in water of pH 5.0 (HCl). The main chemical form in this solution was confirmed to be As(III) by HPLC-ICP-MS [99.5% of As(III), 0.5% of As(V)]. In addition, the concentration of arsenic in the JCSS standard solution is SI traceable. The solution was diluted with 1% HNO_3 for use in the experiments.

Certified reference material for arsenobetaine [AB, $(CH_3)_3As^+CH_2COO^-$][30]

A BCR CRM 626 arsenobetaine solution (BCR-AB) supplied by the Institute for Reference Materials and Measurements (IRMM) was diluted with water and used in the experiments. The certified value of arsenobetaine is 1031 ± 6 mg kg^{-1}. The CRM does not have a certified or reference value of the total arsenic and other arsenic compounds.

Commercial arsenobetaine

Synthetic arsenobetaine commercially available in Japan was examined. The purity of arsenobetaine was stated as 100% by the manufacturers. A solution to test the purity of this arsenobetaine was prepared as follows. Precisely 0.10 g (as As) of the commercial synthetic arsenobetaine was dissolved in water to make 100 g of solution (commercial AB solution; 1000 mg kg^{-1} as As, 2377 mg kg^{-1} as AB). The commercial AB solution was diluted to be 10 mg kg^{-1} with water, and the AB solution was used in experiments to determine its purity.

The acids used were of PMA-grade (Wako Pure Chemical Industries Ltd, Osaka, Japan); others used were of ultrapure grade (Kanto Chemical Industries Ltd). Ultrapure-grade

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water purified with a Milli Q-Labo filter (Nippon Millipore Ltd, Tokyo, Japan) was used throughout. Yttrium (Y) was used for internal standard element on the determination by ICP-MS and ICP-AES.

Procedure

All preparation in this work employed a gravimetric preparation method for SI traceability. The outline of the procedure in the work is shown in Fig. 1.

Speciation of arsenic compounds in the arsenobetaine solutions by HPLC-ICP-MS

The BCR-AB and commercial AB solutions were diluted with water, and aliquots of the solutions were analyzed by HPLC-ICP-MS. The analytical conditions are given in Table 1.

Analytical sensitivity and behavior of arsenobetaine

The BCR-AB and the commercial AB solution (without pretreatment) were determined by ICP-MS and ICP-AES

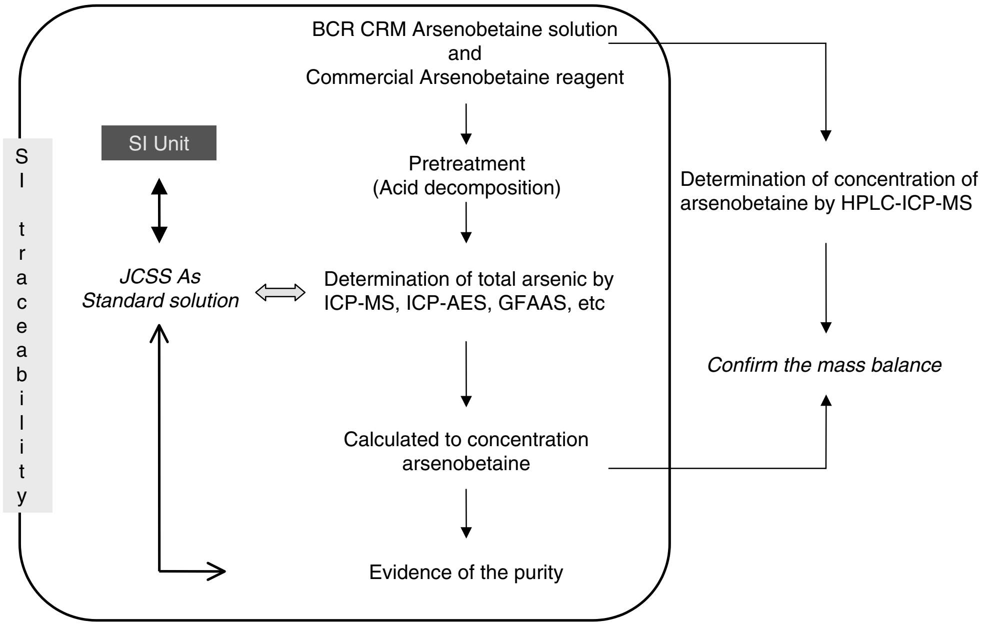

Figure 1. Outline of the procedure in the work.

Table 1. Instrumental and analytical parameters

ICP-MS	Agilent7500c		
Plasma conditions			
	Incident R_f power	1.5	kW
	Reflected power	<2	W
	Outer gas flow rate	Ar 15	$l\ min^{-1}$
	Intermediate gas flow rate	Ar 0.9	$l\ min^{-1}$
	Carrier gas flow rate	Ar 0.8	$l\ min^{-1}$
	Make-up gas flow rate	Ar 0.4	$l\ min^{-1}$
Sampling conditions			
	Nebulizer	Micro mist	
	Spray chamber	Scott type	
	Sampling depth	7	mm from work coil
Collision			
	Reaction mode	He 2.0	$ml\ min^{-1}$
Measured m/z			
	As	75	

Chromatographic system: column, CAPCELL PAK C_{18} MG S3 ODS column (diameter 4.6 mm × length 150 mm); elute, 10 mmol l^{-1} sodium butanesulfonate–4 mmol l^{-1} tetramethylammonium hydroxide–4 mmol l^{-1} malonic acid–0.05% (v/v) methanol (pH 3.0) mixed solution.

based on the JCSS arsenic standard solution as the calibration standard solution.

Evaluation of purity by measuring arsenic following wet digestion (for SI traceability)

To decompose the arsenobetaine in the BCR-AB and in the commercial AB solution, a mixture of HNO_3, $HClO_4$ and H_2SO_4 was used. A precisely weighed portion (3 g) of the 10 ppm BCR-AB or commercial AB solution was placed in a Pyrex glass vessel, to which a mixture consisting of 10 g of HNO_3, 5 g of $HClO_4$ and 3 g of H_2SO_4 was added. After digestion on a hot plate (maximum heating temperature 320 °C) to decompose the arsenobetaine, the sample was evaporated to dryness. The residue was dissolved in 0.3 g HNO_3 and made up to 30 g solution with water. This solution was used for the determination of total arsenic in the BCR-AB or commercial AB solution by ICP-MS, ICP-AES, GFAAS and HPLC-ICP-MS based on the JCSS arsenic standard solution. The concentration of arsenic was converted to an arsenobetaine concentration, and the purity of arsenobetaine measured. A blank test for acid decomposition procedure was also performed but no arsenic contamination was revealed.

RESULTS AND DISCUSSION

Speciation of arsenic compounds in the BCR-AB solution by HPLC-ICP-MS

The BCR-AB is certified for its concentration of arsenobetaine, but information on other compounds that might be present and on total arsenic are lacking. The speciation of the 10 ppm (as As) BCR-AB solution was carried out using HPLC-ICP-MS. Chromatograms are shown in Fig. 2. Two peaks, corresponding to dimethylarsinic acid (DMAA) and trimethylarsine oxide (TMAO), besides that of AB, were evident. The signal intensities for DMAA and TMAO were approximately 0.01 and 0.3%, respectively, of that of AB. However, when using analytical solution samples that were diluted with water to the ppb level, the concentrations of arsenic of the impurities were not detected.

Calibration curves of BCR-AB and JCSS As standard solution

Calibration curves were obtained for both ICP-MS and ICP-AES using the BCR-AB and the JCSS As standard solution. The concentration of arsenic in the BCR-AB was calculated from the quantities of AB using the arsenic atomic weight (74.92) and the arsenobetaine molecular weight (178.06). The results are shown in Fig. 3.

For ICP-MS, the slope of the calibration curve of BCR-AB was approximately 15% higher than that of the JCSS arsenic standard solution. For ICP-AES, the slope of the calibration curve of BCR-AB was approximately 16% higher than that of the JCSS arsenic standard solution. The results show that analytical sensitivities for arsenic using these methods depend upon the chemical forms of arsenic.

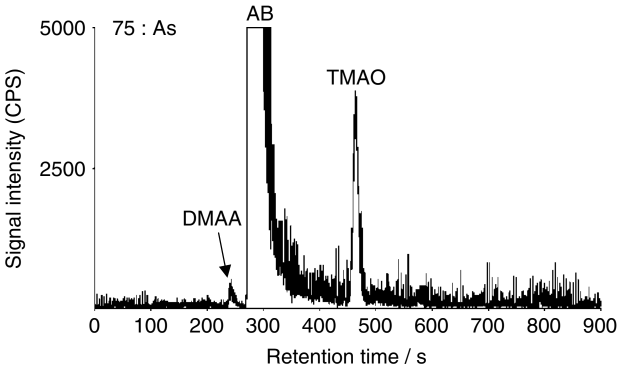

Figure 2. Speciation of arsenic compounds in the BCR arsenobetaine solution by HPLC-ICP-MS. DMAA, dimethylarsinic acid (content 0.01%); AB, arsenobetaine; TMAO, trimethylarsine oxide (content 0.29%).

Therefore, when arsenobetaine is determined based on JCSS arsenic (inorganic arsenic) standard solution using either ICP-MS or ICP-AES, it is suggested that the AB determined value is overestimated by approximately 15%, and influence was occurred by depending on chemical species.

Determination of total arsenic in BCR-AB solution following acid decomposition

BCR-AB was decomposed to inorganic arsenic by wet digestion using the procedure outlined above to yield only As(V), as shown by HPLC-ICP-MS. Other arsenic compounds were not detected.

The concentration of arsenic in the acid-digested solution was determined by ICP-MS and by ICP-AES based on the JCSS arsenic standard solution. The concentration of arsenic was calculated from the atomic weight of arsenic and the molecular weight of AB using the certified value of arsenobetaine in the BCR-AB solution. Recoveries based on the expected (theoretical) value and the actual measured value by both ICP-MS and ICP-AES are given in Table 2. The recoveries for ICP-MS and ICP-AES were approximately 101 and 103%, respectively, i.e. the measured values were in good agreement with the theoretical values. The results indicated that, when AB is determined by ICP-MS or ICP-AES, based on the JCSS arsenic standard solution (inorganic arsenic), prior acid digestion of the AB is necessary.

The concentrations of arsenic in the digest were also determined by GFAAS and HPLC-ICP-MS based on the JCSS arsenic standard solution, and the recoveries were approximately 100% (Table 2). Thus, if AB is decomposed to inorganic arsenic, there is no analytical error resulting from the chemical form of the arsenic or the instrument used for the analysis.

The influence of organic matter on the determination of arsenic by ICP-MS and ICP-AES was investigated to

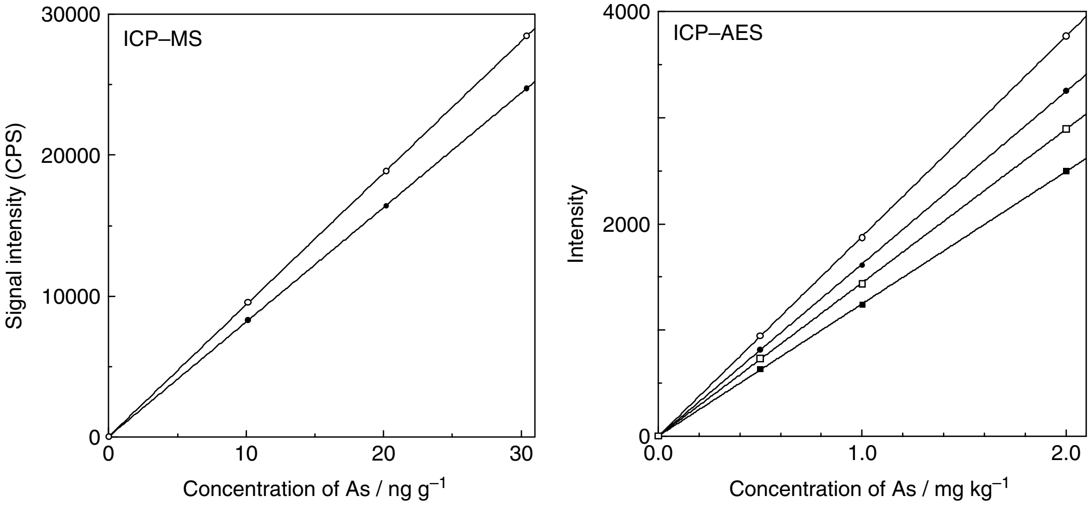

Figure 3. Calibration curves on ICP-AES and ICP-MS. ICP-MS, (●) JCSS As solution, (○) BCR arsenobetaine solution, $m/z = 75$, internal element Y; ICP-AES: (●, ■) JCSS As solution, (○, □) BCR arsenobetaine solution, analytical line, (●, ■) 188.98 nm, (○, □) 193.70 nm, internal element Y.

determine if this was a cause of the error that apparently depended on the chemical form of the arsenic. Acetic acid and methanol were chosen for this experiment because of hydrophilicity and the CH_3-base in their structure. Therefore, those organic matters were added to the sample as a model solution. Results are shown in Fig. 4. For ICP-AES, the intensities of signals for both inorganic arsenic and AB increased with increasing spiked amounts of acetic acid. However, when inorganic arsenic and AB were spiked with the same amounts of acetic acid, the disparity in their sensitivities was not different from that of unspiked samples. The differences in their sensitivities, which did not relate the spiked amounts of acetic acid, were constant.

The effect of important instrumental parameters such as RF power, carrier gas flow rate, plasma and gas flow rate on the analysis was also investigated. However, the analytical sensitivities for inorganic arsenic and AB did not converge. Therefore, one possible reason why AB showed greater sensitivity in ICP-AES than inorganic arsenic is because of spectral interference resulting from its carbon content.

The effect of acetic acid and varying the instrumental parameters on the analysis of the compounds by ICP-MS was also examined. No increase in sensitivity was observed in ICP-MS analysis, as might be expected if the increase in sensitivity noted for ICP-AES resulted from the presence of carbon in the AB molecule. Again, when the analysis conditions were varied there was no convergence in the analytical sensitivities for inorganic arsenic and AB. This suggested that the difference resulted from the production of molecular species of AB in the plasma.

Table 2. Recoveries of based on the theoretical value and the actual measured value

Analytical method	Recovery
ICP-AES	103.1%
ICP-MS	101.2%
HPLC-ICP-MS	100.6%
ETAAS	100.9%

Evaluation of the purity of a commercial synthetic arsenobetaine and speciation of the commercial arsenobetaine by HPLC-ICP-MS

The chemical form of the arsenic in a solution of a commercial synthetic arsenobetaine containing, nominally 10 ppm of arsenobetaine, was analyzed by HPLC-ICP-MS. The chromatogram is shown in Fig. 5. A signal that corresponded to TMAO was evident as well as that of arsenobetaine. The signal intensity for TMAO was approximately 0.3% that of arsenobetaine. Other arsenic-containing impurities were not seen. Therefore, the commercial synthetic AB is of high purity with regard to total arsenic.

Determination of commercial synthetic AB based upon the JCSS arsenic standard solution

Analysis of the commercial synthetic AB by ICP-MS and ICP-AES and based on the JCSS arsenic standard, gave purities of 100 and 99%, respectively. However, these values assumed that the interferences were the same in the analysis of the commercial synthetic AB as they were for the BCR-AB.

Determination of arsenic in commercial synthetic arsenobetaine following acid decomposition

Results of the chemical form with the wet digestion of the AB are shown in Fig. 6 and the results of determination of

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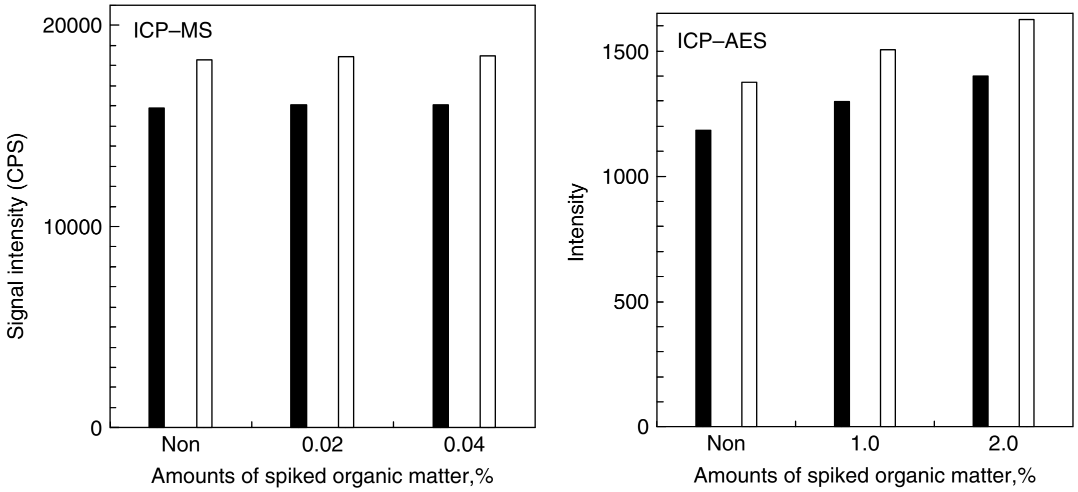

Figure 4. Influence of organic matter on the determination of arsenic by ICP-MS and ICP-AES. ICP-MS: (■) JCSS As solution, (□) BCR arsenobetaine solution, $m/z = 75$, internal element Y; ICP-AES: (■) JCSS As solution, (□) BCR arsenobetaine solution, analytical line, 188.98 nm, internal element Y.

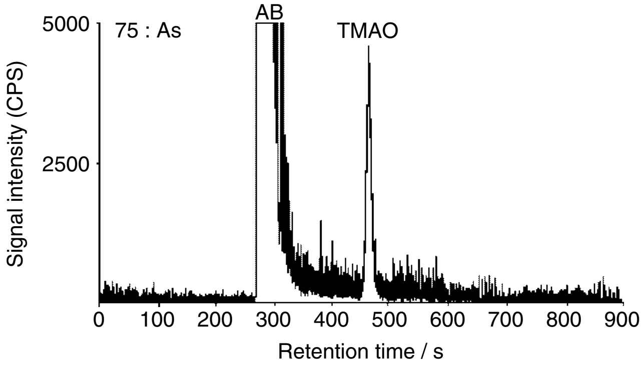

Figure 5. Speciation of arsenic compounds in the commercial synthetic arsenobetaine solution by HPLC-ICP-MS. AB, arsenobetaine; TMAO, trimethylarsine oxide (content 0.30%).

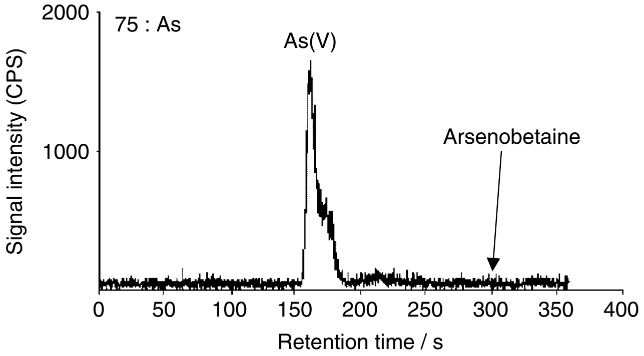

Figure 6. Chromatogram of the arsenic compound in the prepared commercial synthetic arsenobetaine solution by HPLC-ICP-MS after wet digestion.

arsenic in the acid-digested solution by several instruments are shown in Fig. 7 and Table 3.

The quantity of arsenic in the commercial synthetic AB was approximately 85% of the expected (theoretical) amount. Therefore, it can be assumed that the purity of the commercial synthetic AB is approximately 85%.

Analysis of the AB sample was also carried out by instrumental neutron activation analysis (INAA), a technique with a different measurement principle from that of atomic spectrometric analysis. INAA does not depend on the chemical form of an element because it measures the nuclides in the atomic nucleus. The recovery of arsenic by INAA was 85.6 ± 0.8% of the theoretical value, and was thus in good agreement with the results of the atomic spectrometric analyses.

Table 3. Determination result and the recovery of arsenic in the prepared commercial synthetic arsenobetaine solution

Theoretical (mg kg^{-1})	Mean (mg kg^{-1})	Recovery (%)
9.999	8.469	84.7

To further evaluate the purity of the commercial synthetic AB, thermo-gravimetric–differential thermal analysis (TG-DTA, Seiko Instrument Inc., EXSTAR 600 TG/DTA 622) and elemental analysis were performed. A solution of the commercial synthetic AB was also examined by proton nuclear magnetic resonance spectroscopy (^{1}H-NMR). The results are shown in Table 4.

TG-DTA showed that the amount of free water in the AB was approximately 5.0%. Arsenobetaine is very hygroscopic and therefore very difficult to weigh. Thus, assurances are required that precautions have been taken in weighing it out.

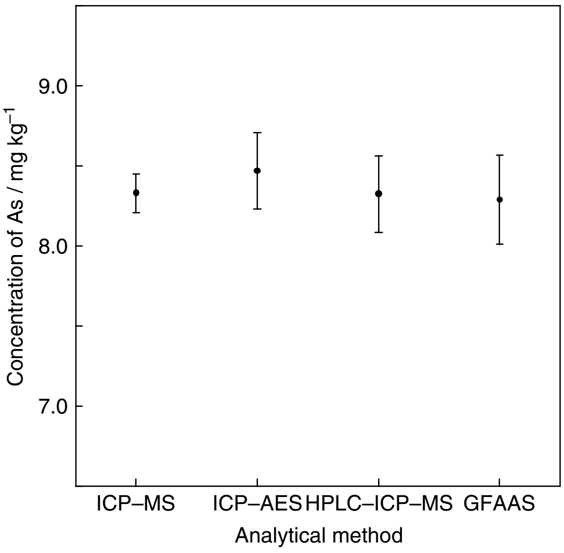

Figure 7. Results of concentration of arsenic in the prepared commercial synthetic arsenobetaine solution by atomic spectrometric analysis.

Table 4. Measurements of impurities in the commercial synthetic arsenobetaine powder

Element	(in powder) (%)	Composition relating for As	Excess
C	32.29 ± 0.43	28.2%	4.1%
H	7.13 ± 0.33	5.7%	1.5%
O	19.88 ± 0.09	15.0%	4.9%
Halogen (as Cl)	0.99 ± 0.01		
S	ND		
TG-DTA	H_2O	5.07%	
Arsenobetaine in organic matter		^{1}H-NMR	99.4%

It seems that 5% moisture as revealed by thermogravimetric analysis is reasonable; also it will be closely related to the purity, when treated as powdered AB. Moreover, synthetic arsenobetaine crystallizes as the mono-hydrate. Therefore, its molecular formula is really $Me_3As^+CH_2COO^- : H_2O$.[25]

Elemental analysis revealed carbon (C), 32%, hydrogen (H), 7% and oxygen (O), 20%. These values were approximately 4% high for C, 2% high for H and 5% high for O. In addition, the halogen elements, estimated as chlorine (Cl), were present at a level of about 1%. A brominated compound, ethyl bromoacetate, can be used in the synthesis of AB. The reaction sequence is as follows [equations (1) and (2)].[30–32]

$$(CH_3)_3As + CH_2COOEt,\ Br^- + \}X + OH^- \longrightarrow$$
$$(CH_3)_3As^+CH_2COO^- + EtOH + \}X^+OH$$
$$\}X^+OH:\ \text{anion exchange resin}$$

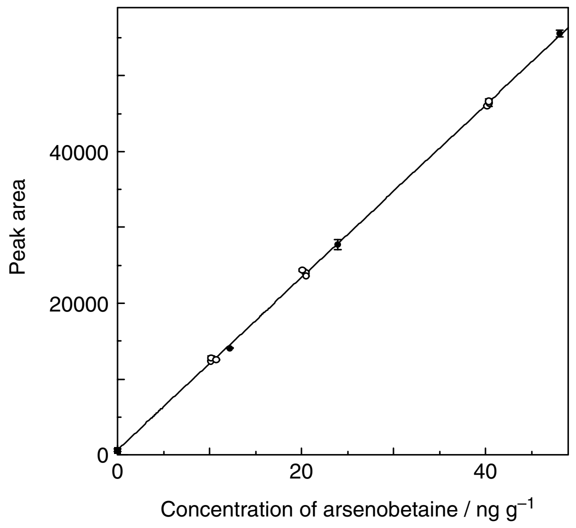

Figure 8. Calibration curve by using two type arsenobetaine solution by HPLC-ICP-MS. (■) Blank; (●) commercial synthetic arsenobetaine solution; (○) BCR arsenobetaine solution.

The 600 MHz ^{1}H NMR spectrum, taken in CD_3OD, of the commercial synthetic AB showed some additional peaks in the methyl region. When these assumed methyl peaks are taken into consideration, i.e. allowing only for organic impurities, the purity of the arsenobetaine was estimated to be about 99.6%.

Based on the results of these investigations and the results obtained by estimating the amount of arsenic in the reagent by subtraction (35.64%), the purity of the commercial synthetic AB was 101.0%. In addition, N, F, Na, S, Si, Zr and I impurities represented less than 0.001%. Other impurities were undetected. The purity of the commercial synthetic AB was calculated from the quantity of arsenic revealed by analysis, and speciation of an undigested solution by HPLC-ICP-MS, as for the BCR-AB.

The two AB solutions, BCR-AB and commercial synthetic AB, were diluted to provide a range of concentrations. Calibration curves were constructed using the values from both solutions obtained from peak areas and AB concentrations by HPLC-ICP-MS. The correlation coefficient between the two sets of values was 0.999_7 (Fig. 8). Therefore, it was concluded that the arsenic analysis based on the JCSS arsenic standard solution, and after acid decomposition of the commercial synthetic AB, was precise.

CONCLUSIONS

Analytical sensitivity depended on the chemical form of the arsenic compound being analyzed. AB showed approximately 15% greater sensitivity than inorganic arsenic. When ICP-AES was used, there was an influence of carbon, and when AB was determined by based on JCSS As by

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ICP-MS, it showed approximately 15% error; however, the influence has not yet been clarified. The errors may have occurred by hygroscopic means in treating the powdered reagent. On the other hand, analytical error occurred from influences on the instrument analysis depending on the chemical species. In fact, the sensitivities of BCR-AB from certified material were different from JCSS As standard solution at the same concentrations.

Therefore, when SI traceability is necessary, it is difficult to apply the JCSS arsenic standard solution to the analysis of AB. However, when the procedure and methods proposed here are used, the amount of AB in the reagent can be estimated more accurately by measuring the arsenic against the JCSS arsenic standard solution after the AB has been decomposed to inorganic arsenic compounds by wet digestion. In addition, traceability according to the International System of Units can be secured by analyzing the AB against the JCSS arsenic standard solution.

Commercially available synthetic AB may be of a lower purity than is claimed and an exact purity evaluation was necessary. Pure AB is necessary for reliable speciation analysis. In addition, the BCR-AB solution was slightly contaminated with DMAA and TMAO and it is likely that these compounds were generated during the synthesis of arsenobetaine.

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