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High-yield synthesis of milligram amounts of isotopically enriched methylmercury ($CH_3{}^{198}HgCl$)

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Isotopically enriched $CH_3{}^{198}HgCl$ (MeHgCl) has been synthesized from commercially available elemental ^{198}Hg (96% isotopic purity). Elemental mercury is first converted to $HgCl_2$ and subsequently reacted with methylcobalamin to produce MeHgCl. The resulting MeHgCl is isolated from the reaction mixture by successive extractions with toluene and dried over Na_2SO_4. The product structure was verified using gas chromatography–mass spectrometry (GC–MS) and the isotopic composition was determined by GC–inductively coupled plasma MS. The yield obtained is 99%. The proposed method allows preparation of milligram quantities of MeHgCl in one step, minimizing the cost of this synthesis. Copyright © 2004 Crown in the right of Canada. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Mercury has been well known as an environmental pollutant for several decades. Environmental cycling of mercury is extremely complex, involving a variety of physical and chemical processes that affect its toxicity and mobility. Critical participants in this cycling include elemental mercury vapour (Hg^0), a common form in air, and methylated species. The dominant source of the most toxic species in the environment is methylation of inorganic mercury[1] to yield monomethylmercury (MeHg), which is able to enter the food chain, accumulating in, and contaminating, humans.

Analytical techniques for isolation of methylmercury are well documented. Various distillation techniques have been used for this purpose (vacuum, atmospheric pressure, steam and micro-distillation), but alkaline and acidic leaching are also employed to liberate methylmercury from many matrices. After extraction from solid matrices and derivatization, the methylmercury is frequently quantitated using hyphenated techniques. Gas chromatography, capillary electrophoresis[2] or liquid chromatography[3] can be interfaced with various detetctors. Sample introduction with these techniques can be further simplified and facilitated with use of solid-phase microextraction (SPME) coupled with headspace or aqueous-phase sampling. This approach has been used for the analysis of mercury species in fish tissues and river water samples, urine, biological tissues and soils.[4–6]

Typically, determination of methylmercury involves a succession of analytical steps. Recently, independent studies have shown that inorganic mercury can be accidentally methylated (to produce artifact methylmercury) during sample preparation, leading to erroneously high values in certain types of sample. The degree of artifactual methylation varies with sample matrix and sample preparation method used. In order to calculate the original levels of methylmercury, corrective measures, such as species-specific isotope dilution, have been applied and accurate and precise isotope dilution (ID) methodologies for MeHg have been devised.[7–17] ID-mass spectrometry (MS) is based on the addition of a known amount of an enriched isotope (contained in a material called the spike) to a sample.[18] After equilibration of the spike isotope(s) with the natural isotopes in the sample, MS is used to measure the altered isotopic ratio.[19] The endogenous concentration is directly derived from this ratio. A major advantage of the technique is that chemical separations, if required for accurate ratio measurement, need not be quantitative. In addition, ratios can be measured very reproducibly, and thus concentrations can be determined very precisely.

However, ID techniques require an isotopically enriched methylmercury standard, which is not commercially available and needs to be synthesized in the user laboratory.

Numerous methods for synthesis of isotopically enriched methylmercury have been employed. Toribara's method is based on the methylation of inorganic $^{203}Hg(II)$ by tetramethyltin. Isolation of $CH_3{}^{203}Hg(II)$ is then performed by successive benzene–water extractions.[20] It is commonly accepted that the methylated form of

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vitamin B12, methylcobalamin (MeCo) [CH_3–Co(III)–5,6-dimethylbenzimidazolyl cobamide], is one of the few responsible for mercury methylation in the environment. It has been demonstrated that chemical transmethylation by MeCo to inorganic mercury occurs within a few hours at 37 °C, pH 7, in the dark, under mild reducing conditions and in the absence of cell extract.[21] Imura *et al*.[21] reported that MeHg and dimethylmercury were formed in different ratios, depending on the molar ratio of the reactants and the reaction time. Dimethylmercury was obtained in good yield when $HgCl_2$ and MeCo were mixed in a molar ratio of 1 : 2. Dimethylmercury, formed during the reaction, was converted to methylmercury chloride by the addition of HCl after the reaction.

As noted by Naganuma *et al*.,[22] methylmercury is obtained by the reaction of MeCo with the ^{203}Hg(II) radioisotope and isolated by liquid chromatography. These multistep methods allow the preparation of a high-purity radioactive methylmercury, but they suffer several disadvantages, as both are rather time consuming (approximately 1 day) and the practical yield achieved (50–70%) results in the waste of 30–50% of the starting radioactive inorganic mercury. Rouleau and Block[23] combined several steps outlined in the methodologies of Naganuma *et al*.[22] and Toribara[20] to develop a much simpler and faster procedure that results in a yield >90%. This was based on the methylation of inorganic ^{203}Hg(II) by MeCo and isolation of $CH_3{}^{203}$Hg(II) from the reaction mixture in a single extraction step. This procedure provides excellent results, both qualitatively and quantitatively.

Demuth and Heumann[10] used the Rouleau protocol, wherein the synthesis was based on methylation of ^{201}Hg-enriched mercury chloride by MeCo. A mass of ^{201}HgO was dissolved in concentrated HCl to convert the oxide to mercury chloride, which was then dissolved in water. MeCo, dissolved in HCl, was then added and the mixture reacted for 1 h at room temperature. Adding a hexane–benzene mixture enabled extraction of methylmercury. This extraction procedure was repeated twice and the organic phases were combined in a glass tube, wherein they were blended with an Na_2CO_3 solution. The organic solvent was then evaporated at room temperature within 2–3 h by passing a flow of nitrogen over the extract. The isotopically enriched $Me^{201}Hg^+$ remained in the aqueous phase, with a synthesis yield of about 60%. A portion of this solution was diluted with water, transferred to a PFA bottle and stored at 4 °C for use as the stock spike solution.

Snell *et al*.[17] have reported the use of enriched ^{198}Hg for the preparation of dimethylmercury, methylmercury chloride and mercuric chloride standards, used for the determination of mercury species in natural-gas condensates and other organic samples by gas chromatography (GC)–inductively coupled plasma (ICP) MS and GC–high-field asymmetric waveform ion mobility spectrometry–MS. The synthesis procedure entailed the following: enriched mercury was dissolved in nitric acid in a borosilicate glass tube and the acid was evaporated to near dryness; concentrated hydrochloric acid was added, and the solution again heated until dry. Toluene was added, rapidly dissolving the resulting powder. This solution was taken as the ^{198}Hg-enriched mercuric chloride stock. Methylmercury chloride was then prepared using a dismutation reaction between the mercuric chloride and dimethylmercury stock solutions. Considering the high toxicity of dimethylmercury, this method was not suitable for the synthesis of MeHgCl in our work.

Other workers have suggested preparing enriched MeHgCl from mercury oxide (HgO). Hintelmann and Evans synthesized $CH_3{}^{201}Hg^+Cl^-$ from ^{201}HgO using tetramethyltin. Barshick *et al*.[25] used a more complicated synthesis employing numerous steps.

Rodríguez Martín-Doimeadios *et al*.[16] synthesized MeHgCl from commercially available mercury oxide (^{201}HgO) using MeCo co-enzyme as the methylating agent. Initial conditions were selected from Filipelli and Baldi's[24] work, but were adapted for maximum yield of methylmercury while avoiding formation of dimethylmercury. The optimization of the synthesis conditions for the *micro-scale* laboratory preparation of isotopically enriched MeHg was thus successfully established. The time required was less than 2 h and the final yield was about 90%. The resultant $Me^{201}HgCl$ was extracted with toluene and diluted in 2-propanol; working solutions were prepared fresh daily by diluting this 2-propanol stock solution with deionized water. The proposed method is faster than those previously reported in the literature, allowing work on a micro scale to minimize the consumption of expensive enriched isotope standard, as well as to control of unintentional formation of dimethylmercury.

The goal of this study was realization of high-yield synthesis of milligram amounts of MeHgCl. For this purpose, the procedures described by Rodríguez Martín-Doimeadios and co-workers[8,16] and Snell *et al*.[17] were modified to permit *macro*-scale synthesis.

EXPERIMENTAL

Instrumentation

A Hewlett Packard HP 6890 GC (Agilent Technologies Canada Inc., Mississauga, Ontario, Canada) fitted with a DB-5MS column (Iso-Mass Scientific Inc., Calgary Alberta, Canada) was used for the separation. Detection was achieved with an HP model 5973 mass-selective detector (MS). Typical GC–MS operating conditions are presented in Table 1.

A Perkin–Elmer SCIEX ELAN 6000 ICP-mass spectrometer (Concord, Ontario, Canada) equipped with a cross-flow nebulizer and custom-made quartz sample injector tube (0.9 mm i.d.) was used for elemental analysis. A double-pass Ryton® spray chamber was mounted outside the torch box and maintained at room temperature. Optimization of the ELAN 6000 and dead-time correction were performed as recommended by the manufacturer. A Varian 3400 gas chromatograph (Varian Canada Inc.,

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Table 1. Operating conditions for GC–MS

Column	DB-5MS 30 m × 0.25 mm i.d. ×0.10 μm d_f
Injection system	Split/splitless injector, splitless mode
Injector temperature (°C)	250
Oven temperature program	80 °C(1 min) $\xrightarrow[25\,^\circ C\,min^{-1}]{}$ 130 °C $\xrightarrow[3\,^\circ C\,min^{-1}]{}$ 150 °C $\xrightarrow[30\,^\circ C\,min^{-1}]{}$ 270 °C (5 min)
Carrier gas; flow rate (ml min^{-1})	Helium; 0.7
Transfer line temperature (°C)	280
MS	HP model 5973 mass-selective detector
SIM parameters	Measured ions, m/z: 292; 294
	Dwell times: 50 ms for each m/z
MS quad temperature (°C)	150
MS source temperature (°C)	250

Table 2. GC and ICP-MS operating conditions

GC	
Injection mode	Splitless
Injection volume (μl)	1
Injector temperature (°C)	250
Column	MXT-5 (20 m × 0.28 mm × 0.5 μm)
Carrier gas	He at 32 psi, 1.3 ml min^{-1}
Oven program	60 °C (1 min) to 200 °C at 20 °C min^{-1} to 270 °C at 30 °C min^{-1} (2 min)
Detector temperature (°C)	300
ELAN6000	
R.f. power (W)	1200
Plasma Ar gas flow rate (l min^{-1})	15.0
Auxiliary Ar gas flow rate (l min^{-1})	1.0
Ar carrier gas flow rate (l min^{-1})	0.30
Sampler cone (nickel) (mm)	1.00
Skimmer cone (nickel) (mm)	0.88
Lens voltage (V)	7.75
Scanning mode	Peak hopping
Points per peak	1
Dwell time (ms)	40
Sweeps per reading	1
Readings per replicate	5000
Number of replicates	1
Dead time (ns)	50

Georgetown, Ontario, Canada) equipped with an MXT-5 metal column (5% diphenyl, 95% polydimethylsiloxane, 20 m × 0.28 mm × 0.5 μm) was used for separations. The gas chromatograph was coupled to the ICP mass spectrometer using a home-made interface and transfer line, which is described in detail elsewhere. Typical GC and ICP-MS operating conditions are presented in Table 2. GC–ICP-MS was used to measure the isotopic composition of the synthesized $CH_3{}^{198}HgCl$.

Reagents

MeCo was purchased from Aldrich (St Louis, MO). Acetic acid was purified in-house by sub-boiling distillation of reagent-grade feedstock in a quartz still prior to use. Environmental-grade ammonium hydroxide was purchased from Anachemia Science (Montreal, Quebec, Canada). OmniSolv® methanol (glass distilled) was obtained from EM Science (Gibbstown, NJ, USA). High-purity deionized water (DIW) was obtained from a NanoPure mixed-bed ion-exchange system fed with reverse osmosis domestic feed water (Barnstead/Thermolyne Corp., IA, USA).

Sodium tetraphenylborate or sodium tetrapropylborate solutions, 1% m/v, were prepared daily by dissolving $NaBPh_4$ or $NaBPr_4$ (Strem, Bischeim, France) in DIW. A 2 mol l^{-1} sodium acetate buffer was prepared by dissolving an appropriate amount of sodium acetate (Fisher Scientific, Nepean, Ontario, Canada) in water and adjusting to pH 5 with acetic acid.

Methylmercury(II) chloride, >95% (assay), was purchased from Alfa Aesar (Ward Hill, MA, USA). Stock solutions of 1000–2000 mg l^{-1}, as mercury, were prepared in *iso*-propanol and kept refrigerated until used. Working standard solutions were prepared by dilution in methanol.

A ^{198}Hg-enriched liquid metal provided with isotopic composition and chemical impurities determination was obtained from Trace Sciences International Inc. (Toronto, Ontario, Canada). The isotopic composition was stated to be: ^{196}Hg (0.4%), ^{198}Hg (96.0%), ^{199}Hg (0.17%), ^{200}Hg (3.0%), ^{201}Hg (0.25%), ^{202}Hg (0.15%) and ^{204}Hg (<0.05%).

Caution! Organic and inorganic mercury compounds are highly toxic. Many of these compounds are readily absorbed through the skin and some types of protective gloves. These compounds are known to cause neurological damage and death and must be handled in areas with adequate ventilation, using proper personal-protection equipment. Anyone contemplating research with organometallic compounds is well advised to consult the material safety data sheets and or obtain the help of an industrial hygienist.

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Optimization procedure for methylmercury synthesis

Previous syntheses of MeHgCl have primarily been concerned with the generation of only microgram amounts of product. The goal of this study was to scale-up the synthesis and generate 10–20 mg of MeHgCl in one step. Elemental mercury was used as the starting material; natural mercury was used for optimization studies. An approach based on the combined procedures of Rodríguez Martín-Doimeadios *et al.*[16] and Snell *et al.*[17] was adopted. As production of milligram quantities of MeHgCl was desired, the amounts of all reagents were scaled up. Elemental mercury was first converted to $HgCl_2$. For this purpose, 10 to 50 mg of mercury was dissolved in 0.2 ml of nitric acid in a borosilicate glass tube and the solution was evaporated to near dryness on a hot plate, whereupon 0.2 ml of concentrated hydrochloric acid (in-house distilled) was added, and the solution again heated to dryness. 1 ml of hydrochloric acid was then added to dissolve the resulting powder rapidly. This solution was taken as the mercuric chloride stock solution ($HgCl_2$) to be used for methylation. 50 µl aliquots of this solution were transferred to glass vials and diluted with 10 ml of MeCo (1 to 10 mg l^{-1}) solution, which had been dissolved in sodium acetate buffer (2 mol l^{-1}, pH 5). The solution was left sitting in the dark at 37 °C for 1 h in a water bath. To stop the methylation reaction and convert any unintentionally formed dimethylmercury to methylmercury, the mixture was cooled at 4 °C, 1 ml of concentrated hydrochloric acid was added, and the solution was shaken for 5 min. The resultant MeHgCl was extracted three times using 0.5 to 3 ml volumes of toluene. The combined toluene extracts were dried over sodium sulfate. The products synthesized were derivatized with tetraphenylborate and analysed by capillary GC coupled to a mass spectrometer. Investigation of the reaction yield and identification of products was undertaken.

The volume of toluene and the ratio of methylcobalamin/mercury used were optimized, and the stability of the product synthesized was studied.

RESULTS AND DISCUSSION

Stability of $HgCl_2$ prepared

$HgCl_2$ was prepared on day zero (d_0, from liquid metal) and used for a series of syntheses on d_0, $d_0 + 8$ days, $d_0 + 14$ days. Each synthesis was performed under the same conditions (50 µl of $HgCl_2$, extraction with 3×0.5 ml of toluene) with MeCo freshly dissolved in buffer each time. Yields of MeHgCl synthesized from this solution after 8 days and 14 days decreased by 6% and 17% respectively. As shown by Snell *et al.*,[26] concentrations of $HgCl_2$ decrease quickly in organic solvents. Here, $HgCl_2$ was preserved in hydrochloric acid, but it appears not to be properly stabilized, even when stored in the refrigerator. Therefore, the synthesis of enriched MeHgCl (prepared from expensive enriched mercury) must be undertaken immediately after preparation of the enriched $HgCl_2$ in order to obtain maximum synthesis yield.

Optimization of toluene extraction volume

Synthesized MeHgCl was recovered from the aqueous phase using three successive extractions with toluene. Different volumes of toluene were tested, with Fig. 1 presenting the effect of this variable on yield. Each synthesis was performed in duplicate. Following derivatization (in duplicate for each synthesis), the analytes were injected for GC–MS and quantified by standard additions. It is evident that a volume of 6 ml (3×2 ml) is adequate for optimum recovery.

Optimization of amount of MeCo

Duplicate syntheses were conducted using 50 µl aliquots of the freshly prepared $HgCl_2$ solution (6.98 µmol of Hg) placed in a vial along with 10 ml of acetate buffer (2 mol l^{-1}) containing different amounts of MeCo (from 0.74 to 8.9 µmol of MeCo). The procedure previously described was applied and the resultant MeHgCl was extracted three times using 2 ml of toluene. The combined extract was dried over Na_2SO_4.

In order to measure the yield of MeHgCl, phenylation (in duplicate) was performed and the resultant Ph–MeHgCl was quantitated by GC–MS. The synthesis yield increased with the amount of MeCo added; the results are presented in Fig. 2. An optimum yield of 99% was obtained when using an MeCo : Hg molar ratio of about 1.3 : 1, corresponding to 8.5 mg of MeCo for 1 mg of mercury.

As the reaction mixture was treated with hydrochloric acid, unintentional formation of dimethylmercury was controlled[16] and any dimethylmercury inadvertently formed during the reaction was converted to MeHg.

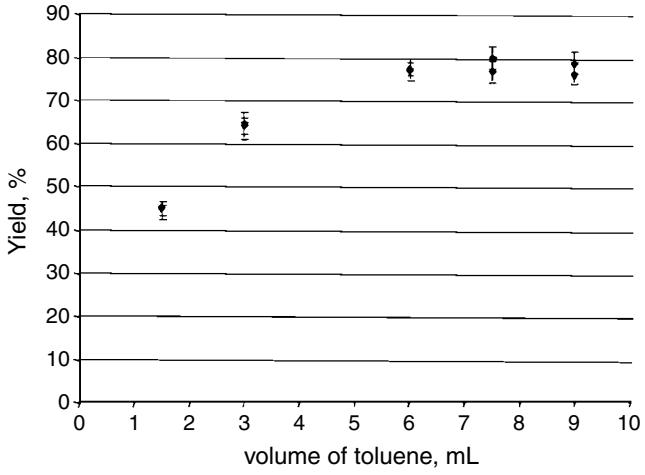

Figure 1. Synthesis yield as a function of volume of toluene [50 µl of $HgCl_2$ (24 mg ml^{-1}), 5 ml of buffer and 5 ml of MeCo (1 mg ml^{-1})]. Syntheses performed in duplicate; each synthesis product was derivatizated in duplicate and injected in duplicate.

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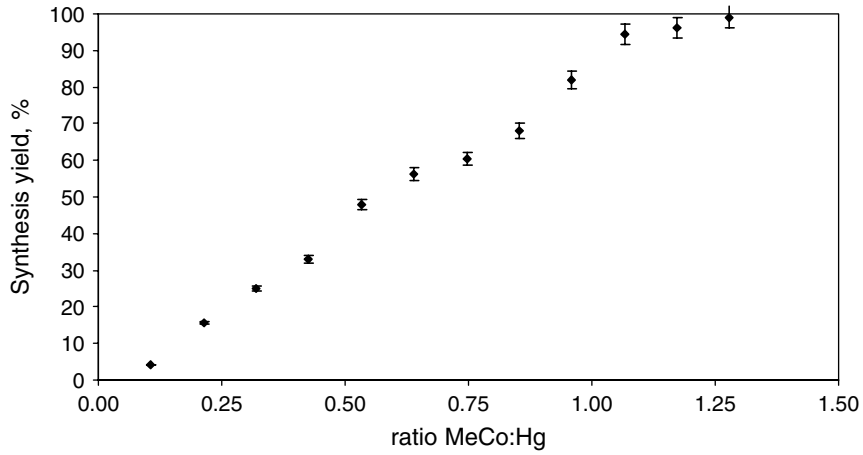

Figure 2. Effect of MeCo : Hg ratio on yield of MeHgCl. For the different ratios: syntheses performed in duplicate; each synthesis product was derivatized in duplicate and injected in duplicate.

Reproducibility of the optimized synthesis

In order to verify the reproducibility of this synthesis, 11 syntheses were performed on the same day using the same solution of freshly prepared $HgCl_2$. Using yield as a measure of reproducibility, an average value of 98% was obtained with a relative standard deviation of 5%.

Synthesis of enriched methylmercury

The optimized procedure applied to the synthesis of enriched MeHgCl is illustrated schematically in Fig. 3. After synthesis, the product was characterized by both GC–MS and GC–ICP-MS. The isotopic patterns obtained with GC–MS for natural and enriched methylmercury are presented in Fig. 4, clearly demonstrating that the methylmercury synthesized with ^{198}Hg was itself enriched.

In order to ensure preservation of the enriched methylmercury, several solvents and storage protocols were tested. The stability of MeHg is widely described in the literature, wherein studies have tested water, various organic solvents or acid solutions as media.

Stability of the enriched methylmercury

Devai *et al*.[27] have reported changes in MeHgCl concentration with time during storage in methylene chloride and noted the effects of storage temperature, which was not a significant factor affecting the change in MeHgCl concentration.

The temporal stability of methylmercury has also been evaluated in heptane, toluene and mixed hydrocarbon solutions.[26] Stock standard solutions of salts of the mercury species were prepared in various toluene mixtures and stored in the dark at 4 °C. However, the $HgCl_2$ concentration decreased considerably over 7 months. In contrast to $HgCl_2$, CH_3HgCl is stable even in the presence of Hg^0.

In studies designed to determine the stability of methylmercury in distilled water and acidified distilled water, Leermarkers *et al*.[28] found MeHgCl to be stable for at least 2 weeks

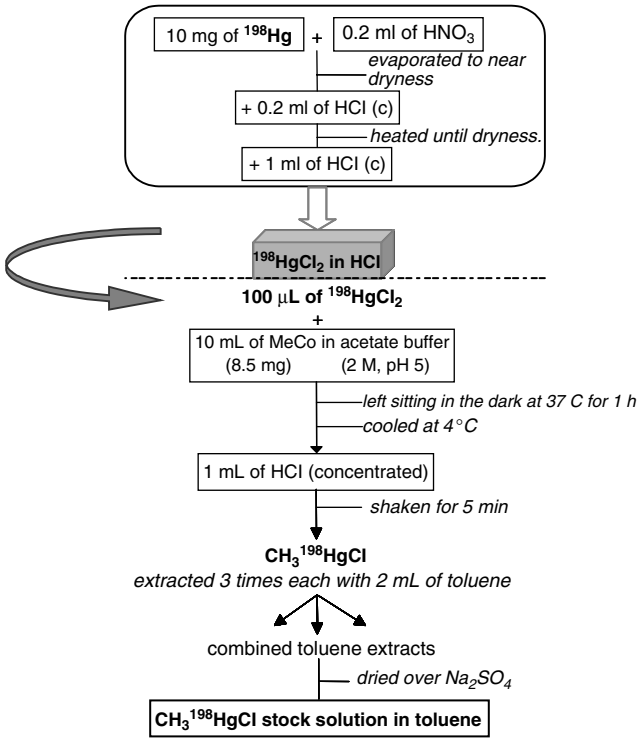

Figure 3. Procedure for synthesis of enriched methylmercury chloride.

in HNO_3-acidified distilled water. Stoeppler and Mathes[29] found considerable degradation of the compound in HNO_3-acidified seawater. In general, the stability of methylmercury in water depends upon pH, temperature and exposure to light. The stability of methylmercury in environmental samples also varies as a function of matrix. Methylmercury is sensitive to ultraviolet light and is somewhat volatile, so that over time its concentration may change, depending on the storage conditions.

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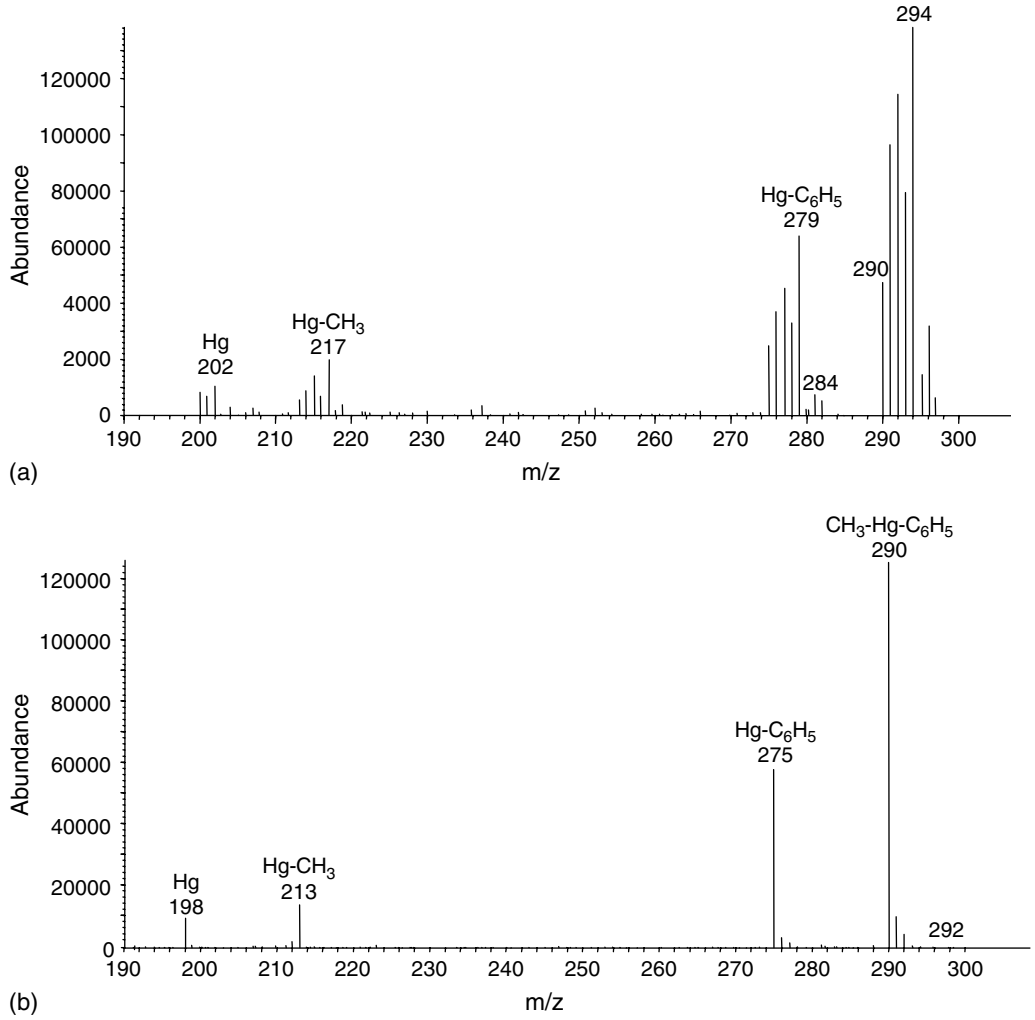

Figure 4. Isotopic pattern of (A) natural abundance methylmercury chloride and (B) enriched methylmercury chloride (^{198}Hg enriched) following phenylation and GC–MS detection.

Stock solutions of MeHgCl (1000 mg l^{-1}) of natural isotopic composition were prepared by dissolving methylmercury chloride in methanol.[30,31] Stock and working standard solutions dissolved in 1% HNO_3 and stored in the dark at 4 °C were shown to be stable for several weeks.[30] Working standards and calibration standards made by successive dilution in 0.1 mol l^{-1} hydrochloric acid remained stable for 1 month and for 1 week respectively.[31]

Quevauviller *et al.*[32] reported on the instability of several mercury compounds during their storage based on data from intercomparison exercises. No measurable effects of temperature were discerned. The stability was verified over 3 months based on the content of one bottle, and no significant changes were observed for MeHgCl solutions kept at ambient temperature. However, significant loss of mercury was noted after 100-fold dilution of the aqueous solution containing approximately 2 mg l^{-1} of MeHgCl.

Stability studies of MeHgCl[33] showed that, in the absence of light, the compound does not decompose to Hg^{2+}, even in the presence of 25% acids over a long period of time.

Rodríguez Martín-Doimeadios *et al.*[16] synthesized isotopically enriched MeHg and examined the stability of the solution over a period of 3 months to find a 20% degradation. It is clear that if this solution is to be used as a standard, then its concentration must be verified frequently.

Solutions containing 20 mg l^{-1} MeHgCl in hexane, toluene, *iso*-octane and *iso*-propanol were prepared and placed in freezer at −27 °C. After 2 months of storage, no evidence of degradation of MeHgCl was detected in any of the solvents (Fig. 5). Solutions containing 2 mg l^{-1} MeHgCl were prepared in methanol and *iso*-propanol and placed in a freezer at −27 °C, in a refrigerator at 4 °C and held at room temperature. After 1 month, no measurable degradation was detected in any of the solutions.

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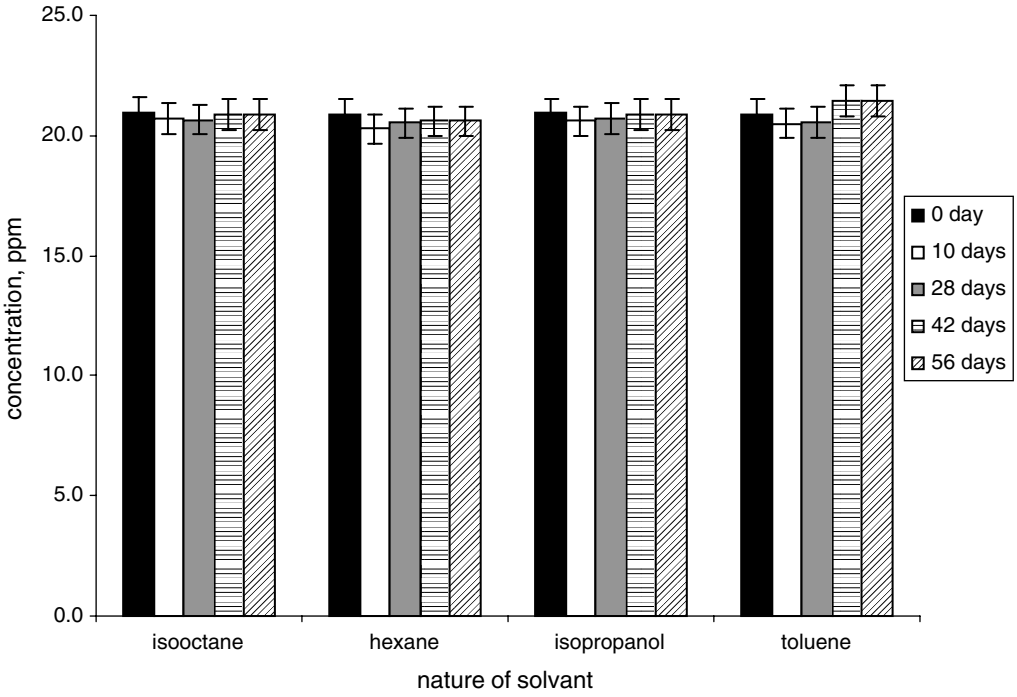

Figure 5. Stability of synthesized methylmercury in various solvents.

Following these initial stability experiments, and based on literature data, methanol was selected as the storage solvent for the methylmercury standard. Methanolic solutions of enriched MeHgCl (5 mg l^{-1}) were stored in nitrogen-purged, flame-sealed, amber glass vials. Long-term determination of the stability of this material is in progress.

Isotopic composition of the enriched methylmercury

The isotopic composition of the synthesized enriched MeHgCl was determined using GC–ICP-MS. For this purpose, a 0.1 ml volume of a 20 mg l^{-1} solution of enriched MeHgCl was derivatized with 1% $NaBPr_4$ in acetate buffer and extracted into 2 ml of *iso*-octane. 1 µl of the *iso*-octane extract was injected into the gas chromatograph for mercury isotope ratio measurements. The mass bias correction factors utilized for these ratio measurements were based on measurements of a natural-abundance methylmercury standard. The results are presented in Table 3.

Table 3. Isotope abundance data for mercury

Isotope	Accurate mass	Abundance (mol at%) Natural (IUPAC)[34]	Abundance (mol at%) Enriched spike[a]
^{196}Hg	195.965	0.15344	0.232 ± 0.012
^{198}Hg	197.967	9.968	96.20 ± 0.75
^{199}Hg	198.968	16.873	0.091 ± 0.010
^{200}Hg	199.968	23.096	3.08 ± 0.10
^{201}Hg	200.970	13.181	0.228 ± 0.011
^{202}Hg	201.971	29.863	0.124 ± 0.014
^{204}Hg	203.974	6.865	0.028 ± 0.004
Sum		100	100
Hg atomic weight		200.598	198.038

[a] Mean and one standard deviation ($n = 30$).

CONCLUSIONS

An improved synthesis protocol permits rapid, high-yield production of milligram amounts of methylmercury. The long-term stability of the product is currently under study and it is anticipated that an isotopically enriched methylmercury solution will shortly be made available as a reference calibration standard, certified for its isotopic composition and nominal MeHgCl concentration.

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