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Synthesis of phenyl arsenic analytical standards related to contaminated well water in Kamisu, Ibaraki, Japan

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To facilitate, by the provision of internal standards, the liquid chromatographic and mass spectrometric analysis of diphenylarsinic acid in well water and other samples related to an incident of environmental contamination in Kamisu, Ibaraki, Japan, syntheses of the analogous perdeuterated and mono-*meta*- and di-*meta*-methylated acids were undertaken. The acids were synthesized by cleavage of the triarylarsines by sodium in liquid ammonia. The triarylarsines were made from the reaction of arsenous chloride and sodium with the appropriate aryl-bromo compound. Properties of the compounds are given. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: diphenylarsinic acid; phenylarsonic acid; diarylarsinic acids; triarylarsines; deuterated arsenic compounds; synthesis; analysis

INTRODUCTION

Arsenic at high concentrations was discovered in well water used for drinking and other domestic purposes by some householders in the town of Kamisu in Ibaraki Prefecture, Japan.[1] Analysis showed that the arsenic was present almost entirely as diphenylarsinic acid[1] and was thus very unlikely to have a natural origin. The source of this compound to the ground water supplying the well is unknown, although the most likely explanation is that arsenical war gases or their precursors were dumped and buried in the area during, or immediately following, the World war II. There is no record of such a disposal. Although dumping of war-gas-related materials seems the most likely source of the compounds, there is also the possibility that the arsenic results from an old industrial dump.

Analysis of environmental samples (water and soil) and the monitoring of exposed and potentially exposed persons (hair, blood and urine samples) has involved gas chromatography–mass spectrometry (GC–MS) and liquid chromatography–inductively coupled plasma mass spectrometry (LC–ICP-MS).[1] GC–MS requires deuterated analytes for use as internal standards. However, LC–ICP-MS, in which the ICP-MS serves as an arsenic-specific detector for LC, requires as internal standards compounds that are expected to produce an identical response in the detector to the analyte, but with a chromatographic retention time sufficiently different from that of the analyte for their peaks to be clearly separated and thus allow their individual quantification.

LC–ICP-MS analysis of diphenylarsinic acid in water samples is conveniently carried out on a column that, although nominally facilitating separation of analytes by size exclusion or gel permeation, relies substantially, in the absence of a buffered eluent, on hydrophobicity.[1] Thus, it was expected that analogues of diphenylarsinic acid in which the non-polar aromatic portion was increased by the addition of alkyl groups might serve as the required internal standards.

Here, we describe the syntheses of a number of triaryarsines and the conversion of tri(3-methylphenyl)arsine and tri(3,5-dimethylphenyl)arsine to di(3-methylphenyl)arsinic acid and di(3,5-dimethylphenyl)arsinic acid respectively. The properties of these compounds, including NMR data, are given. In addition, we describe a convenient synthesis of diphenylarsinic acid-d_{10} and measure the pK_a values of diphenylarsinic acid and phenylarsonic acid by ^{1}H NMR titration.

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EXPERIMENTAL

Chemicals

Arsenous chloride and 5-bromo-*m*-xylene were obtained from Aldrich Chem. Co., Milwaukee, WI, USA. Liquid ammonia was from Sumitomo Seika Chemicals Co. Ltd, Osaka, Japan. Phenylarsonic acid was from Tokyo Kasei Organic Chemicals, Tokyo, Japan. All other chemicals used were reagent grade and obtained from Wako Pure Chemical Industries, Osaka, Japan. Solvents were HPLC grade, also from Wako, and were not purified further. Melting points were measured on an As-One ATM-01 melting point apparatus (As-One Co. Ltd, Osaka, Japan) and are uncorrected.

NMR spectroscopy

^{1}H NMR spectra were recorded in $CDCl_3$ or D_2O on a JEOL ECA 800 spectrometer (JEOL, Tokyo, Japan) operating at 800 MHz. Chemical shifts for spectra taken in D_2O are reported in δ (ppm) values relative to HDO, which was taken as δ 4.800 relative to tetramethylsilane (TMS) δ 0.000. For spectra taken in $CDCl_3$, chemical shifts are relative to internal $CHCl_3$, which was taken as 7.250 relative to TMS. ^{13}C NMR spectra were recorded at 200 MHz in $CDCl_3$ or D_2O. Chemical shifts are reported relative to internal $CDCl_3$ (δ 77.300 relative to TMS) for spectra recorded in $CDCl_3$, or relative to external TMS (δ 0.000) for spectra recorded in D_2O.

Mass spectrometry

Electron impact and fast atom bombardment mass spectra were measured on A JEOL JMS-700 GC/MS (JEOL, Tokyo, Japan).

Synthesis

Diphenylarsinic acid

Diphenylarsinic acid was prepared by the method of Campbell,[2] which involved the oxidation with hydrogen peroxide of diphenylarsinosodium obtained by the cleavage of triphenylarsine with sodium in liquid ammonia. Tripharsine (10 g, 0.03 mol) gave diphenylarsinic acid as white crystals (4.4 g, 51%); m.p. 171 °C (lit.[3] 174 °C). Charcoal (Darco G-60) treatment and recrystallization from water did not raise the melting point. ^{1}H NMR (800 MHz, D_2O), see Fig. 1.

Triphenylarsine-d_{15}

The method of Shriner and Wolf[4] was adapted for the synthesis of deuterium-labelled triphenylarsine. Arsenous trichloride (6 g, 0.03 mol) and bromobenzene-d_5 (14 g, 0.09 mol) was reacted with freshly cut sodium (4.6 g, 0.2 mol) in benzene (32 ml). Triphenylarsine was obtained as an off-white solid (8.6 g, 85%). Recrystallization from 95% ethanol gave lustrous white rhomboidal plates (m.p. 60 °C (lit.[4] (unlabelled compound) 61 °C)]. ^{13}C NMR and mass spectrometry (MS) data are given in Table 1.

Diphenylarsinic acid-d_{10}

Diphenylarsinic acid-d_{10} was prepared by hydrogen peroxide oxidation of diphenylarsinosodium, obtained by the cleavage of triphenylarsine-d_{15} with sodium in liquid ammonia.[2] Triphenylarsine-d_{15} (5 g, 0.016 mol) yielded diphenylarsinic acid as white crystals (m.p. 172 °C, 2 g, 50%). Treatment with charcoal (Darco G-60) and recrystallization from water gave white needles but, as for the unlabelled compound, did not raise the melting point. MS data are given in Table 1.

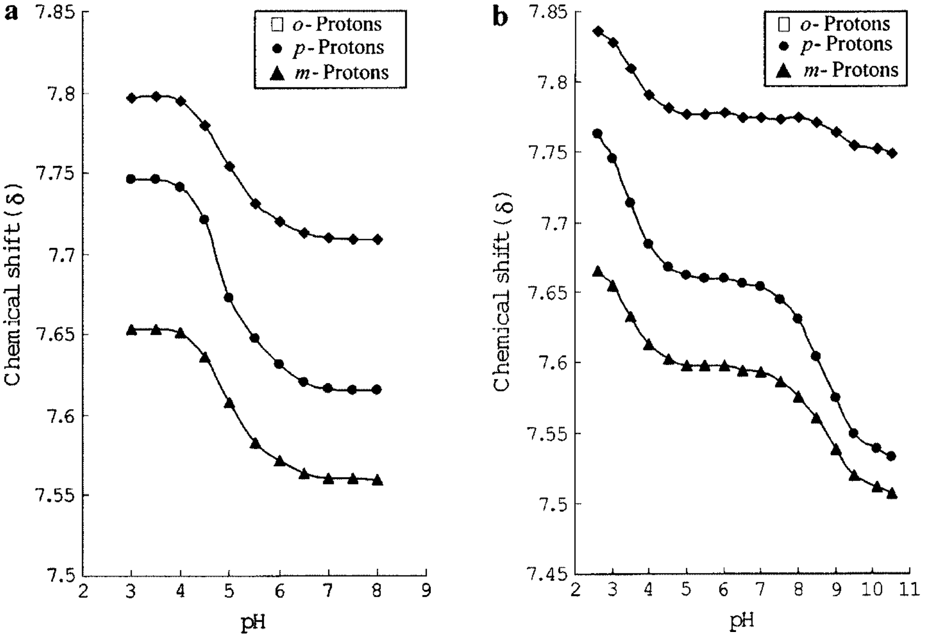
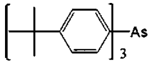
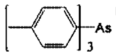
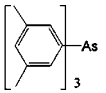
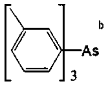
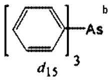


Figure 1. ^{1}H NMR chemical shift of aromatic protons *versus* pH: (a) diphenylarsinic acid; (b) phenylarsonic acid.

Table 1. Triarylarsines

Structure	m.p. (°C)	^{13}C NMR shifts[a]								HR-MS	
		C1 (C–As)	C2	C3	C4	C5	C6	Me	Other	Required	Observed
	>250, sublimes from ~200	136.75	133.75	125.86	151.53	125.86	133.75	31.39	34.90	474.2268	474.2286
 [b]	148–150[c]	136.79	129.69	133.91	138.43	129.69	133.91	21.57	—	—	—
	143	139.93	131.68	138.14	130.40	138.14	131.68	21.61	—	390.1329	390.1315
 [b]	95[d]	139.93	130.97	138.38	128.72[b]	134.72	129.49[b]	21.73	—	—	—
 [b]	60[e]	139.70	133.57 (t)	128.42 (t)	128.21 (t)	128.42 (t)	133.57 (t)	—	—	321.1331	321.1324

[a] t: triplet.

[b] Assignments uncertain relative to each other.

[c] 145 °C, Ref. 5.

[d] 96 °C, Ref. 6.

[e] 61 °C, Ref. 4 for unlabelled compound.

Triarylarsines

Tri(4-methylphenyl)arsine, tri(4-*tert*-butylphenyl)arsine, tri-(3-methylphenyl)arsine and tri(3,5-dimethylphenyl)arsine were prepared from 4-bromotoluene, 1-bromo-4-*tert*-butylbenzene, 3-bromotoluene and 5-bromo-*m*-xylene respectively, as described above for triphenylarsine-d_{15}. In each case, 25 g of the bromo-compound was reacted. All products were crystallized from ethanol. ^{1}H NMR (800 MHz, $CDCl_3$) tri(4-methylphenyl)arsine, δ 2.330 (s, 9H, 3 × Me), 7.120 (d, $J = 8.2$ Hz, 6H, 3 × H3,5), 7.210 (d, $J = 8.2$ Hz, 6H, 3 × H2,6); tri(4-*tert*-butylphenyl)arsine, δ 1.310 (s, 27H, 9 × Me), 7.278 (d, $J = 8.2$ Hz, 6H, 3 × H3,5), 7.345 (d, $J = 8.2$ Hz, 6H, 3 × H2,6); tri(3-methylphenyl)arsine, δ 2.295 (s, 9H, 3 × Me), 7.086 (m, 3H, 3 × H2), 7.127 (m, 3H, 3 × H6), 7.199 (m, 6H, 3 × H2,4); tri(3,5-dimethylphenyl)arsine, δ 2.258 (s, 18H, 6 × Me), 6.949 (m, 3H, 3 × H4), 6.966 (m, 6H, 3 × H2,6). ^{13}C NMR data and other properties of the triarylarsines are given in Table 1.

Attempted synthesis of di(4-methylphenyl)arsinic acid and di(4-tert-butylphenyl)arsinic acid

The attempted syntheses of di(4-methylphenyl)arsinic acid and di(4-*tert*-butylphenyl)arsinic acids by cleavage of the appropriate triarylarsines with sodium in liquid ammonia failed completely. No reaction occurred, and the starting arsine was fully recovered in each case.

Di(3-methylphenyl)arsinic acid and di(3,5-dimethylphenyl)arsinic acid

Cleavage of tri(3-methylphenyl)arsine and tri(3,5-dimethylphenyl)arsine with sodium in liquid ammonia, and oxidation of the products with hydrogen peroxide, as in the synthesis of diphenylarsinic acid, yielded the expected di(3-methylphenyl)arsinic and di(3,5-dimethylphenyl)arsinic acids, each in about 50% yield. Both compounds were recrystallized from aqueous ethanol. ^{1}H NMR (800 MHz, D_2O) di(3-methylphenyl)arsinic acid, δ 2.393 (s, 6H, 2 × Me), 7.476 (m, 4H, 2 × H2,6), 7.539 (m, 2 × H4,5); di(3,5-dimethylphenyl)arsinic acid, δ 2.345 (s, 6H, 2 × Me), 7.303 (m, 2H, 2 × H4), 7.332 (m, 4H, 2 × H2,6). Other properties of these compounds are given in Table 2.

^{1}H NMR 'pH' titration of diphenylarsinic and phenylarsonic acids

Citrate (up to pH 5.5), phosphate (pH 6 to 8), borate (pH 8.5 and 9), and carbonate (pH 9.5 to 10.5) buffers at 0.1 M concentration were used.

RESULTS AND DISCUSSION

Diphenylarsinic acid-d_{10}, di(3-methylphenyl)arsinic acid and di(3,5-dimethylphenyl)arsinic acid were successfully synthesized by cleavage of the respective triphenylarsines with sodium in liquid ammonia as recommended by Campbell *et al.*[2] for the preparation of unlabelled diphenylarsinic acid. The yield of diphenylarsinic acid and other diarylarsinic acids from the chosen method was not high but was in excess of 50%. Importantly, the reaction was quick, simple and clean and gave a white crystalline product that had a purity of greater than 98%. A single crystallization gave the pure product in each case. However, attempts to synthesize *para*-alkylphenylarsinic acids (methyl and *tert*-butyl) by the same method failed entirely; there was no reaction, and the starting triarylarsine was recoverable in both cases.

The retention time (8.0 min) of di(3-methylphenyl)arsinic acid on the LC–ICP-MS system used for the analysis of diphenylarsinic acid in water samples (Table 2) was satisfactory for it to serve well as an internal standard; consequently, it was not necessary to pursue the synthesis of other alkylated phenylarsinic acids. The retention time (22.0 min) of di(3,5-dimethylphenyl)arsinic acid was too long for it to be useful.

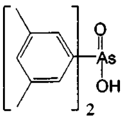
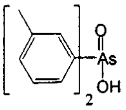
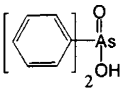
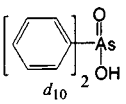
The plot of the ^{1}H NMR chemical shift versus pH for the protons in diphenylarsinic acid (Fig. 1) allows approximate pK_a values to be obtained by inspection. For diphenylarsinic acid it can be seen that the pK_a for

$$Ph_2As(O)OH \longleftrightarrow Ph_2As(O)O^- + H^+$$

is 5.0. The comparable plot for phenylarsonic acid is also shown, and the pK_a values for

$$PhAs(O)(OH)_2 \longleftrightarrow PhAs(O)(OH)O^- \longleftrightarrow PhAs(O)(O)_2{}^{2-}$$

Table 2. Diarylarsinic acids

Structure	m.p. (°C)	HR-MS Required	HR-MS Observed	Chromatographic retention time (min)[b]
	231–232	319.0679	319.0678	22.0
	146–148	291.0366	291.0373	8.0
	171[a]	—	—	4.5
	172[a]	273.0681	273.0708	—

[a] 174 °C, Ref. 3.

[b] Asahipak GS 220 7C (7.6 × 100 mm); eluent buffer: 25 mM malonic acid–tetramethylammonium hydroxide adjusted to pH 6.8, flow rate 1 ml min^{-1}.

can be seen to be about 3.8 and 8.7. Literature[7] values are 3.47 and 8.48.

The 'pH' values of the buffers (made up in D_2O) are for the equivalent buffers in H_2O, and there will be some small difference from the nominal values. The pK_a values will assist in the processing of water samples for analysis and will be of use in the understanding of the environmental behaviour of diphenylarsinic acid in groundwater.

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