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Chiral arsinic acid esters revealed by proton NMR spectroscopy†

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The unsymmetrically substituted arsinic acid ethylphenylarsinic acid, when dissolved in methanol-d_4 or ethanol-d_6, formed esters in which the chiral nature of the arsenic atom was clearly revealed by the diastereotopicity and resulting anisochrony of the protons of the methylene component of the ethyl group attached to arsenic. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: arsinic acid esters; chiral arsenic; NMR spectroscopy

INTRODUCTION

Recently, methylphenylarsinic acid (Fig. 1, **1**) was found in groundwater and in rice plants at two sites in Japan.[1] Probably it had been formed by microbial methylation of phenylarsonic acid that had found its way into the environment through wastes from the manufacture of chemical warfare agents more than 60 years ago.[2,3] When such unsymmetrically substituted arsinic acids, containing pentavalent arsenic, are reduced and bound by sulfur ligands, the resulting trivalent arsenic is chiral; configuration about the arsenic atom is tetrahedral and the lone-pair constitutes the fourth arm of the tetrahedron.[4] We have used NMR spectrocopy to investigate the stereochemical properties of such reduced and derivatised unsymmetrically subsituted arsinic acids.[5] The pentavalent arsenic atom in arsinic acids is also tetrahedrally configured[6] but, in solution, unsymmetrically subsituted arsinic acids do not contain chiral arsenic because the proton will migrate rapidly between the two oxygens bound to arsenic and render them equivalent.

Arsonic acids dissolved in alcohols are rapidly esterified and the reaction can be pushed to completion if the water that is formed can be removed azeotropically.[7,8] Esters of arsinic acids have been made in similar manner.[9,10] If an unsymmetrically substituted arsinic acid is dissolved in an alcohol, the ester of the alcohol will be formed, and the arsenic atom in the ester molecule will be expected to be chiral. In ^{1}H NMR, spectroscopy groups that would be expected to be equivalent and display isochrony in achiral molecular environments can be rendered diastereotopic and possibly anisochronous when attached to, or close to, chiral centres.[11] Thus, substituents rendered diastereotopic by attachment to chiral arsenic might be expected to display anisochrony.

Methylphenylarsinic acid esterified in deuterated alcohols suitable for NMR spectroscopy lacks potentially anisochronous substituents. However, the methylene protons of the ethyl group in ethylphenylarsinic acid (**2**) derivatives will be diastereotopic and possibly anisochronous if the arsenic atom is chiral. In solutions where the acid is unreacted, the rapid migration on the NMR time scale of the acidic proton between the oxygen atoms bound to arsenic will ensure that the arsenic atom is achiral. However, when dissolved in alcohols the resulting esters would be expected to contain stable chiral arsenic and this might be revealed in anisochony of the two protons of the methylene of the ethyl group bound to arsenic. This paper reports the results of our investigations into the possibility of diastereotopicity and anisochrony in esters (**3, 4**) of ethylphenylarsinic acid and the revealed chirality of pentavalent arsenic in the molecules.

EXPERIMENTAL

Chemicals

Iodoethane, phenylarsine oxide and solvents and reagents used in the synthesis of ethylphenylarsinic acid were obtained from Wako Pure Chemicals, Osaka, Japan. D_2O

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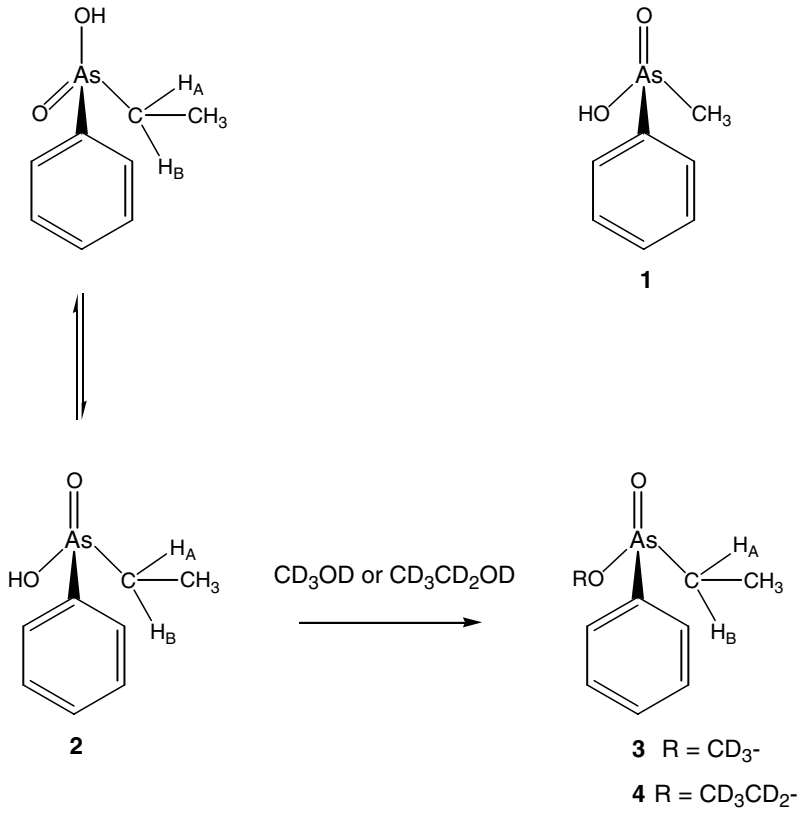

Figure 1. Structures of **1**, methylphenylarsinic acid and **2**, ethylphenylarsinic acid, showing that the structural consequence of the rapidly migrating proton on the oxygen atoms bound to arsenic is achiral arsenic; **3**, methyl-d_3 ethylphenylarsinate; **4**, ethyl-d_5 ethylphenylarsinate. In both **3** and **4** the arsenic atom is chiral.

and $CDCl_3$ were purchased from Isotec, Miamisburg, OH, USA; methanol-d_4 was from Cambridge Isotope Laboratories, Andover, MD, USA; and ethanol-d_6 was from Merck, Darmstadt, Germany.

Ethylphenylarsinic acid (**2**) was synthesized by the reaction of iodoethane with phenylarsine oxide and purified through its silver salt[11,12] and by column chromatography on Sephadex LH-20 (820 × 26 mm) Elution was with methanol and therefore the ethylphenylarsinic acid eluted as its methyl ester; the acid was regenerated by evaporation of the methanol.

Mass spectrometry

FAB MS, both positive and negative modes, were measured on a Jeol JMS-700 GC/MS (Jeol, Tokyo, Japan) using aqueous solutions of ethylphenylarsinic acid, and employing glycerol as the matrix. FAB MS positive mode [M + H] = 215: negative mode [M − H] = 213.

NMR spectrocopy

NMR spectra were recorded for approximately 20 mM solutions of ethylphenylarsinic acid in D_2O, methanol-d_4, $CDCl_3$ and ethanol-d_6 on a Jeol ECA 800 spectrometer (Jeol, Tokyo, Japan) operating at 800 MHz (^{1}H) or 200 MHz (^{13}C). Shifts are reported relative to external TMS. Typical parameters for ^{1}H NMR were: spectral width, 15 kHz; number of data points, 16.4K; 0.917 Hz per point ^{1}H digital resolution; acquisition time, 1.09 s; relaxation delay, 1 s; pulse width, 7.6 μs (45°); number of scans, 64–256. Typical parameters for ^{13}C NMR were: spectral width, 63 kHz; number of data points, 32.8K; 1.92 Hz per point ^{13}C digital resolution; acquisition time, 0.52 s; relaxation delay, 1.4 s; pulse width, 2.38 μs (30°); number of scans, 512–1024. Parameters for HMQC spectra were: data points, x-points = 1024, 11.7 Hz per point, y-points = 256, 133.6 Hz per point; acquisition time, x-acquisition = 85.3 ms, y-acquisition = 7.48 ms; relaxation delay, 1.5 s; x pulse, 17.5 μs; y pulse, 7.15 μs; number of scans, 4.

Simulated ^{1}H NMR spectra were generated with WINDNMR-Pro Version 7.1.11.[13]

RESULTS AND DISCUSSION

NMR data are presented in Table 1 and Figs 2 and 3. Figure 2 shows partial proton NMR spectra, the region in which the ethyl methylene resonates, of ethylphenylarsinic acid

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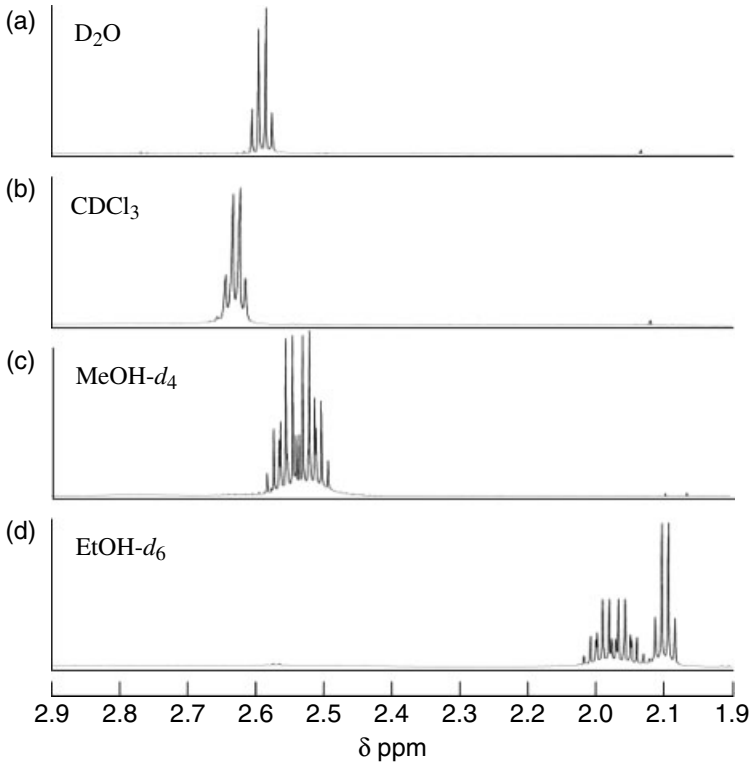

Figure 2. Partial ^{1}H NMR spectra of ethylphenylarsinic acid and/or its esters in (a) D_2O; (b) $CDCl_3$; (c) methanol-d_4; and (d) ethanol-d_6. Only those parts of the spectra showing the resonances of the methylene component of the ethyl group attached to arsenic are shown. Spectra in D_2O and $CDCl_3$ show only the presence of the acid; the spectrum in methanol-d_4 shows only the methyl-d_3 ester, whereas that in ethanol-d_6 shows the presence of both acid (AB quartet, approximately 40%) and ethyl-d_5 ester (approximately 60%).

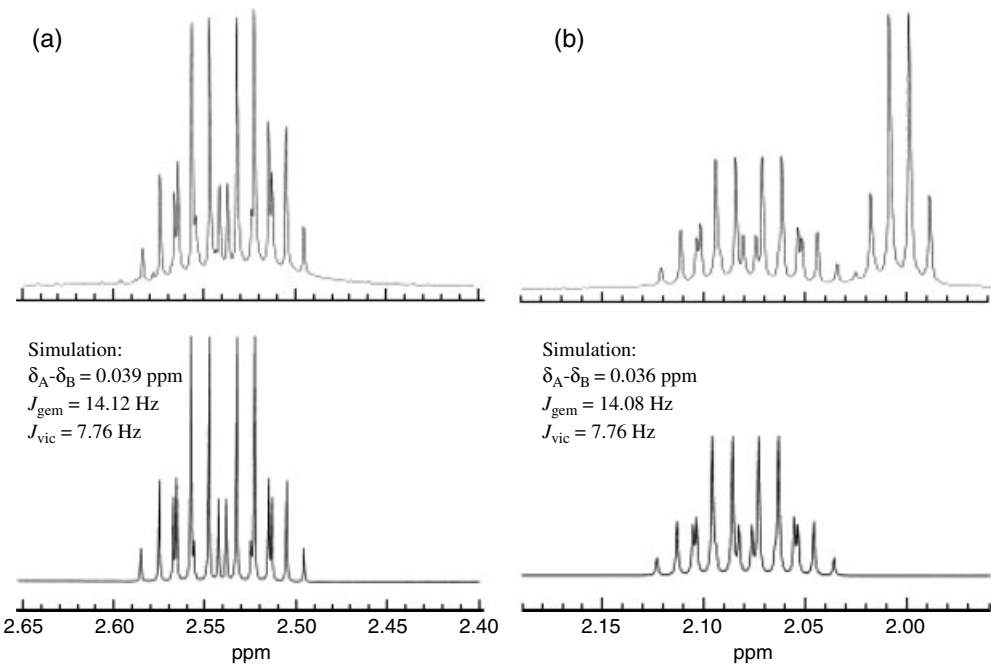

Figure 3. Partial ^{1}H NMR spectra of ethylphenylarsinic acid and/or its esters in (a) methanol-d_4 and (b) ethanol-d_6. Expansions of resonances shown in Figure 1 together with simulated spectra generated using WINDNMR-Pro version 7.1.11[12] are presented. Parameters used for generating the simulated spectra are shown in the figure.

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Table 1. ^{1}H and ^{13}C NMR data[a] for ethylphenylarsinic acid and its methyl-d_3 and ethyl-d_5 esters

		Acid							Ester						
				Aromatic H or C[b]						Aromatic H or C[b]					
	Solvent	CH_3	CH_2	*o*-	*m*-	*p*-	C-As[c]	CH_3	CH_2	*o*-	*m*-	*p*-	C-As[c]
^{1}H data	D_2O	1.332 t J = 8.2 Hz	2.598 q J = 8.2 Hz	7.828 d J = 7.4 Hz	7.697 t J = 7.4 Hz	7.773 t J = 7.4 Hz	—	—	—	—	—	—	—
	$CDCl_3$	1.342 t J = 8.2 Hz	2.635 q J = 8.2 Hz	7.796 d J = 7.4 Hz	7.542 t J = 7.4 Hz	7.619 t J = 7.4 Hz	—	—	—	—	—	—	—
	MeOH-d_4	—	—	—	—	—	—	1.273 t J = 7.76 Hz	2.518 (Fig. 3a) J_{gem} = 14.12 Hz J_{vic} = 7.76 Hz 2.058 (Fig. 3b) J_{gem} = 14.08 Hz J_{vic} = 7.76 Hz	2.557 (Fig. 3a) J_{gem} = 14.12 Hz J_{vic} = 7.76 Hz 2.094 (Fig. 3b) J_{gem} = 14.08 Hz J_{vic} = 7.76 Hz	7.773 d J = 7.3 Hz 7.412 d J = 7.4 Hz	7.610 t J = 7.3 Hz 7.220 t J = 7.4 Hz	7.677 t J = 7.3 Hz 7.248 t J = 7.4 Hz	—
	EtOH-d_6	0.888 t J = 7.8 Hz	2.004 J = 7.8 Hz	7.420 d J = 7.4 Hz	7.186 t J = 7.4 Hz	7.281 t J = 7.4 Hz	—	0.892 t J = 7.76 Hz					
^{13}C data	D_2O	5.58	25.91	130.15	129.89	133.74	*	—	—	—	—	—	—
	$CDCl_3$	6.51	27.15	130.74	129.65	133.48	129.89	—	—	—	—	—	—
	MeOH-d_4	—	—	—	—	—	—	5.10	24.68	130.58	129.59	133.39	130.17
	EtOH-d_6	7.75	28.22	132.51	131.47	134.99	*	7.68	27.50	132.78	131.73	135.36	*

[a] For ^{1}H data, integration of resonances was consistent with their assignments.
[b] Assignments of aromatic ^{13}C signals were aided by HMQC experiments.
[c] In ^{13}C spectra, signals for C-As were not always discernible (indicated by as asterisk).

in D_2O, $CDCl_3$, methanol-d_4 and ethanol-d_6. Clearly those spectra taken in methanol-d_4 and ethanol-d_6 differ from those spectra taken in D_2O and $CDCl_3$ in having more complex signals for the ethyl methylene protons. It is also evident that these complex resonances result from the non-equivalence of the methylene protons. Figure 3 also shows the simulated spectra generated by WINDNMR software[13] with differences in chemical shifts of 0.039 ppm (31.06 Hz) for the methylene protons of the ethyl group for the spectrum recorded in methanol-d_4, and 0.036 ppm (29.06 Hz) for the spectrum recorded in ethanol-d_6.

The asymmetric environment giving rise to such diastereotopic methylene protons could only arise in this case from the chirality of the arsenic atom. In D_2O and $CDCl_3$ there is no NMR evidence of chirality; in these cases the oxygen substituents on the arsenic atom will be equivalent, rendered so by the rapid movement on the NMR timescale of the proton (or, specifically in this case, the deuteron) between the oxygen atoms bound to arsenic.

In alcohol, methanol or ethanol, the ethylphenylarsinic acid (**2**) was esterified and the oxygens bound to arsenic were rendered non-equivalent. Thus the four groups bound to tetrahedral arsenic were all different, the arsenic became chiral and the methylene protons of the ethyl group were rendered diastereotopic, and this was clearly seen in the proton NMR spectra. Although the spectrum indicated that esterification of ethylphenylarsinic acid by its dissolution in methanol was virtually complete (no signals attributable to the free acid were discernable), it was evident that formation of the ethyl ester (**4**) in ethanol-d_6 was only about 60% complete and this did not increase after maintaining the solution at room temperature for 24 h. Figure 3(b) shows the resonances of the methylene of the ethyl group of the free acid (2.06 ppm) as well as those of the ethyl ester. The simulated spectrum shows only the spectrum of the methylene protons of the ethyl ester.

Although the environmental pollutant methylphenylarsinic acid (**1**) lacks any potentially diastereotopic group to reveal chiral arsenic after it has been esterified (or otherwise derivatised), it will exhibit analogous stereochemistry to that described here for ethylphenylarsinic acid (**2**). The toxicological consequences of this for cellular toxicity are currently unclear.

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