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Four-Coordinate As^{III}-N,S Complexes: Synthesis, Structure, Properties, and Biological Relevance

Vivian C. Ezeh, Ashis K. Patra, and Todd C. Harrop*

Department of Chemistry, The University of Georgia, 1001 Cedar Street, Athens, Georgia 30602

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Air-stable four-coordinate As^{III} complexes, [As(L4)Cl] (**1**) and [As(L4)I] (**2**), were prepared using a rearranged form of the deprotonated benzothiazoline ligand, 2-(pyridin-2-yl)-2,3-dihydrobenzo[*d*]thiazole. Complexes **1** and **2** have been characterized by FTIR, ^{1}H NMR, UV−vis, and elemental microanalysis. The solid-state structure of **2** was also solved. The unusual and rare four-coordinate geometry of **2** elucidates possible binding modes and properties of N,S-ligated As^{III} that may be encountered in biology.

Arsenic (As) is a ubiquitous element in the earth's crust, and its presence poses an environmental health hazard.[1] Compounds of As found in the environment are broadly classified as either organic (e.g., organoarsenicals like roxarsone[2]) or inorganic [e.g., arsenite = $As(OH)_3$] with common oxidation states of 3+ and 5+. It is the As^{III}-containing compounds, however, that are regarded as the most toxic form and inhibit a variety of enzymes by forming strong As−S bonds with Cys-SH residues.[3] In addition As^{III} histidine N-ligation is inferred as part of the As-extrusion pump, denoted as ArsAB, present in *E. coli*.[3a] This protein displays simultaneous N,S-chelation in an Sb^{III}-coordinated derivative, and metalloid binding results in activation of the detoxification pathway.[3a] Despite its biological precedence and implications on health, there still remains a general lack of small-molecule As^{III} complexes[4] in biological coordination environments. This void presents a need to understand the fundamental coordination chemistry of As^{III} with relevant ligand constructs. In our pursuit of suitable bioinspired chelators for As^{III} and also to understand As detoxification in biology, we have initiated research on the fundamental coordination chemistry and properties of this metalloid with N,S ligands. Herein, we report the synthesis and reactivity of an unusual and rare type of coordination motif for the As^{III} ion formed via a well-defined ligand redox rearrangement of the N,S-containing benzothiazoline ligand, L1H [where L1H is 2-(pyridin-2-yl)-2,3-dihydrobenzo[*d*]thiazole and H represents a dissociable proton; Chart 1]. The L1H ligand has been used as a tridentate anionic ligand in several transition-metal complexes where the benzothiazoline form (L1H) rearranges to the Schiff base ($L2^-$) when treated with a mild base (Chart 1).[5] Another less encountered rearrangement of L1H is the disproportionation to the benzothiazole (L3) and the ring-open-reduced molecule ($L4H_2$; Chart 1). This type of rearrangement has been observed in reaction with other transition metals[6,7] but not with metalloids such as As^{III}.

When a violet THF solution of a racemic mixture of $L1^-$ (deprotonated with NaH) was treated with 0.5 mol equiv of $AsCl_3$ (Scheme 1), a yellow-orange solution results with the formation of an off-white precipitate (identified as NaCl). Characterization of the resulting compound reveals equal formation of the benzothiazole (L3) and [As(L4)Cl] (**1**) in 38% yield (Scheme 1). On the basis of spectroscopic data (vide infra), the As^{III} ion is coordinated by the most reduced and dianionic form of the N_2S ligand ($L4^{2-}$). The stoichiometry of the reaction indicates that 2 equiv of $L1^-$ is required for the reaction since it serves as an internal reductant to form the dianionic $L4^{2-}$. In fact, this ligand-based redox chemistry has been observed before with L1H in the reductive formation of Re^V-N,S complexes.[7] In this reaction, excess L1H acts as the reductant for both the

*To whom correspondence should be addressed. E-mail: tharrop@chem.uga.edu.

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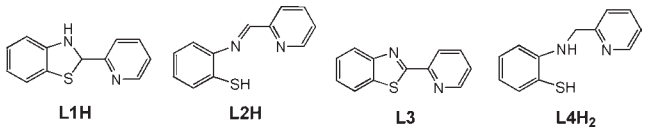
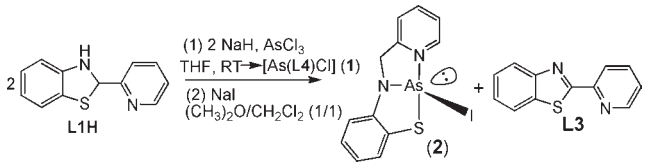
Chart 1. N,S Ligands Derived from L1H



Scheme 1. Synthetic Route toward **2**



metal ion and the ligand itself, forming the benzothiazole L3 (oxidized form) in the process. Because As^{III} is not reduced in the reaction, it reveals that disproportionation is probably triggered by the presence of NaH; however, the mechanistic details are yet to be established.

Complex **1** was identified by spectroscopic and microanalytical techniques (see the Supporting Information, SI); however, growing single crystals of **1** proved difficult. Performing a salt metathesis of **1** with NaI resulted in near stoichiometric isolation of the corresponding iodide complex, [As(L4)I] (**2**), in 88% yield (Scheme 1). Diffraction quality crystals of **2** revealed the four-coordinate (4C) nature of the complex (Figure 1). This coordination number is quite unusual, and only a handful of other 4C As^{III} complexes have been structurally characterized to date.[8] Indeed, As^{III}-SR complexes generally do not exhibit this type of geometry and tend to be three-coordinate.[4,9] The equatorial plane consists of N1, I1, and the lone pair, whereas the axial positions are occupied by S1 and N2 (Figure 1 and Scheme 1). The bond distances (As1—N1 = 1.846 Å; As1—N2 = 2.411 Å) are comparable to the relatively scarce number of known arsenic(III) amide[8a,9a] and As^{III}—Py[9a,c] complexes. The structure of **2** indicates that As−peptido−N coordination in biology is also possible. The As−S distance (As1—S1 = 2.292 Å) is similar to other arsenic(III) thiolate small molecules[4,9a] and peptides.[3b−d] Analogous to **1** and **2**, the As-extrusion protein ArsA also exhibits a similar coordination environment with His-N, Cys-S, and Cl ligands in a distorted trigonal-planar arrangement.[3a] This structure provides snapshots of the As-detoxification pathway. Unfortunately, the low resolution (2.3 Å) of the structure does not allow for a direct comparison with the metric parameters of **2**. Complex **2** establishes, however, that simultaneous N,S-coordination in an environment similar to that of ArsA is possible and also quite stable (vide infra).

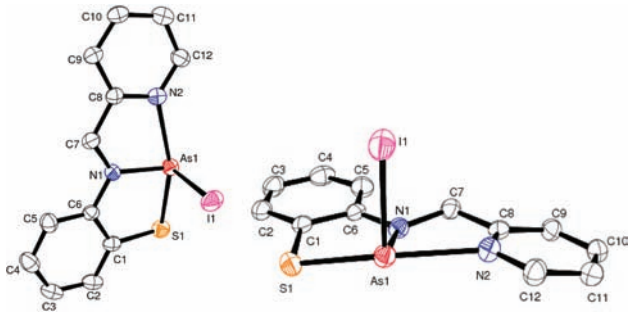


Figure 1. ORTEP diagram of **2** showing 30% thermal probability ellipsoids. Two orientations of the complex are displayed. H atoms are omitted for clarity. Selected bond distances (Å) and angles (deg) for **2**: As1−I1, 2.737(2); As1−N1, 1.846(5); As1−S1, 2.292(2); As1−N2, 2.411(6); N1−As1−S1, 87.71(2); N1−As1−I1, 97.86(2); S1−As1−N2, 162.69(2); N1−As1−N2, 76.64(2).

The spectroscopic properties of solutions of **1** and **2** support the structure obtained from the X-ray analysis. As predicted for As^{III} ($[Ar]3d^{10}4s^2$), complexes **1** and **2** are diamagnetic ($S = 0$), making them suitable for NMR characterization. The ^1H NMR spectrum ($CDCl_3$, 298 K) of **1** displays a singlet at 5.16 ppm that integrates for the two protons of the methylene $-CH_2-$ group. This resonance is shifted upfield to 4.83 ppm in **2**, revealing a more shielded environment about the methylene protons due to the presence of the less electronegative I^- anion. Although the two protons on this carbon are chemically distinct, they appear equivalent in solution, resulting from the conformational fluctuation of the molecule on the NMR time scale at 298 K. The molecular ion peak was not observed in the ESI-MS of the complexes. Instead, the intense ion fragment of $m/z = 289.0$ was observed, resulting from the loss of halogen from the complex, e.g., $[M-X]^+$.

Although the color of many As^{III} complexes is reported in literature accounts, very few report the quantitative UV−vis spectra of these systems. The 298 K UV−vis spectrum of **1** in a non-donor solvent such as CH_2Cl_2 displays an intense peak at 310 nm ($\varepsilon = 4600\ M^{-1}\ cm^{-1}$) with a shoulder at 260 nm (Figure S4 in the SI). The UV−vis spectrum of **1** recorded in MeCN reveals similar spectral features with a decrease in ε, suggesting that the complex remains 4C even in donor solvents (see the SI). The spectrum of **2** in CH_2Cl_2 at 298 K has one peak in common with **1** ($\lambda_{max} = 294$ nm; $\varepsilon = 2830\ M^{-1}\ cm^{-1}$) in addition to a distinct low-energy peak ($\lambda_{max} = 382$ nm; $\varepsilon = 4800\ M^{-1}\ cm^{-1}$). In contrast, the UV−vis spectrum of **2** in THF at 298 K (Figure S6 in the SI) is much less intense, with the lower-energy peak blue-shifted from the CH_2Cl_2 spectrum with two low-intensity maxima at 294 nm ($\varepsilon = 780\ M^{-1}\ cm^{-1}$) and 362 nm ($\varepsilon = 510\ M^{-1}\ cm^{-1}$). This change suggests solvent coordination and/or iodide displacement when **2** is dissolved in coordinating solvents.[10] The peaks at 310 nm for **1** and 294 nm for **2** (both in CH_2Cl_2) are

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(10) Although the UV−vis spectrum of **2** in THF, MeCN, and CH_2Cl_2 reveal differences that suggest a change in the coordination sphere, one cannot rule out whether I^- is still coordinated in the donor solvents. λ_{max} for the assigned iodine-to-arsenic charge-transfer band remains the same in all solvents. We expect this band to vanish with the appearance of a new band if only $L4^{2-}$ and solvent were coordinated. Thus, performing the UV−vis experiments in MeCN or THF cannot rule out the absence of the As−I bond but does imply a new coordination sphere presumably due to solvent ligation.

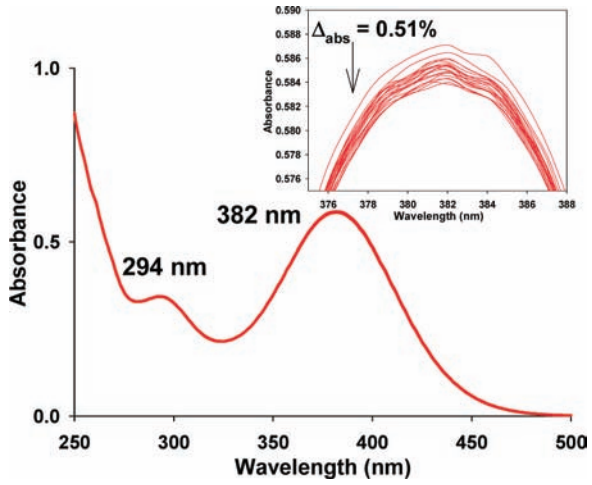

Figure 2. UV−vis spectral changes of a 0.12 mM CH_2Cl_2 solution of **2** upon direct purging of O_2(g) at 298 K (traces recorded at 3 min intervals; total time = 1 h). Inset: expansion of the λ = 382 nm peak and its changes over time (Δ_{abs} = 0.003 = 0.51% change). The arrow shows the direction of change.

tentatively assigned as S-to-As charge transfer. This assignment is supported by the UV−vis spectra of analogous As^{III} alkylthiolate complexes such as [As(GS)$_3$] (where GS is glutathione: λ_{max} = 280 nm, $\varepsilon \sim 2000$ M^{-1} cm^{-1} in a pH 7.0 buffer)[3b,c] and [As(H_{-3}dte)] (where H_{-3}dte is dithioerythritol: λ_{max} = 266 nm, $\varepsilon \sim 510$ M^{-1} cm^{-1} in a pH 6.4−8.9 buffer).[4a] The halogen-to-As charge-transfer band appears to overlap with the S-to-As band in **1**, whereas it is distinct for **2** (λ_{max} = 382 nm in CH_2Cl_2). These high-energy absorptions account for the resulting yellow/orange color of the two complexes and the similar color reported for As^{III}-SR complexes reported at biological sites.[3]

The As^{III} complexes also demonstrate remarkable stability under aerobic conditions. When solutions of **1** or **2** are purged with O_2(g) for 5 min or exposed to ambient aerobic atmosphere, no significant change in the ESI-MS, ^{1}H NMR, or UV−vis (see the SI) is observed over 1 h. Complex **1** appears to be much more stable than **2**, with virtually no change in its UV−vis spectrum in MeCN or CH_2Cl_2 (see the SI). Although complex **2** is stable in non-donor solvents (Δ_{abs} = 0.51% in CH_2Cl_2; Figure 2), it appears less stable in donor solvents like THF (Δ_{abs} = 5%; Figure S3 in the SI), suggesting greater lability of the coordination sphere in **2** due to the weaker coordination of I^- versus Cl^- in **1**. Thus, high-oxidation-state As^V or sulfur-oxidized SO_x species do not readily form, and the complexes are stable under these conditions. Furthermore, cyclic voltammetric experiments on **2** revealed no redox waves over a broad potential range of +2.0 to −2.0 V (vs Ag/AgCl in THF at room temperature), supporting the observed oxygen inertness and aerobic stability. Dissolution of the complexes in pH 7.2 water (phosphate buffer), however, resulted in an insoluble oil that is presumably due to hydrolysis of the complex to form As(OH)$_3$ along with protonated and insoluble ligand. Collectively, it appears that biological N,S donors stabilize the As^{III} oxidation state to a significant extent.

In conclusion, we have synthesized and extensively characterized new 4C As^{III} complexes **1** and **2** formed via a well-defined ligand-redox rearrangement. These complexes represent rare examples of structurally characterized 4C As^{III} complexes and are the first such examples in biologically relevant mixed N,S-coordination spheres. Additionally, these systems appear to be stable in air and present a potential ligand construct to integrate into As-based chemosensors. Our aim is to utilize this ligand as a receptor in the design of As^{III} sensors analogous to those known for other toxic heavy metals like Hg^{II} [11] and Pb^{II}.[12] These studies are in progress in our laboratory.

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Supporting Information Available: Experimental details and characterization of complexes including UV−vis, ^{1}H NMR, X-ray tables, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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