Metallocryptands

Arsenic–π Interactions Stabilize a Self-Assembled As_2L_3 Supramolecular Complex**

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The self-assembly of supramolecular coordination compounds has resulted in structures with a diverse range of properties, shapes, sizes, and stoichiometries, including helicates (M_2L_2, M_2L_3, etc.), triangles (M_3L_3), squares (M_4L_4), rings (e.g., M_6L_6), and polyhedra (M_4L_4, M_4L_6, M_6L_6, M_8L_{12}, etc.).[1] These assemblies almost exclusively contain metals with square-planar, tetrahedral or octahedral coordination geometries. Metals that can exhibit more peculiar coordination geometries have typically been avoided as components for a supramolecular design strategy,[2] most likely because of their variable coordination spheres. Herein we describe a supramolecular design strategy for forming arsenic-based assemblies, which relies on the self-assembly of arsenic(III) with thiol ligands—and hence the reversibility and lability of arsenic–sulfur bonds—and we report the first member of this class, [As_2**L**$_3$] (H_2**L** = α,α′-dimercapto-*para*-xylene). The design strategy incorporates the unusual, yet predictable trigonal-pyramidal coordination geometry of As^{III} featuring a stereochemically active lone pair when coordinated by sulfur-based ligands (Figure 1 a).[3–6]

We selected arsenic(III) as a design component because of its unusual coordination geometry and a general lack of specific and powerful chelators for this highly toxic ion.[7] Arsenic compounds are legendary for their toxicity, and hydrated As^{III} is recognized as a known human carcinogen. Arsenic is abundant in the earth's crust and is all-too-frequently present as an environmental health hazard;[8–10] however, specific chelators for environmental and in vivo remediation and sensing applications are lacking. Furthermore, the stereochemically active lone pair of As^{III} adds a novel feature to the targeted supramolecular assemblies: for instance, lone pairs directed into the cavity would provide a unique soft, Lewis-basic cavity environment (Figure 1 b).[11]

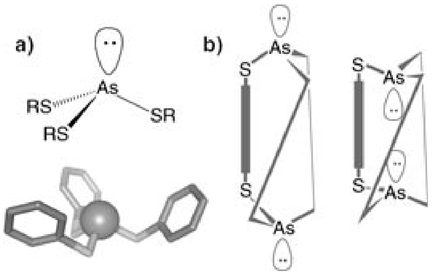
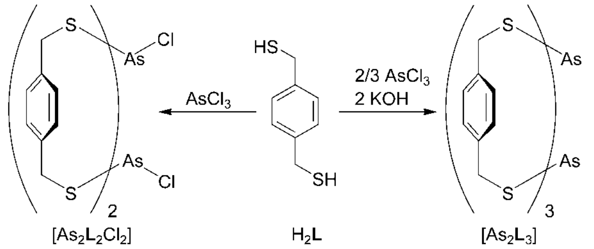


Figure 1. a) Top: Representation of the preferred trigonal coordination geometry of As^{III} with sulfur-based ligands; the stereochemically active lone pair on arsenic is highlighted. Bottom: Structure of [As(thiophenol)$_3$] from a single crystal X-ray structure analysis adapted from the Cambridge Structure Database showing an example of this trigonal coordination geometry. b) Two examples of how this As^{III} coordination geometry could be used to form As_2L_3 assemblies with rigid, twofold symmetric dithiolate ligands (solid rods). The arsenic lone pairs can be directed either into or out of the cavity.

Figure 1 illustrates the design strategy for forming C_{3h}-symmetric [As_2L_3] assemblies, which is based on rigid, twofold symmetric dithiols capable of acting as bridging ligands. Dithiol ligand H_2**L**[12] (Scheme 1) was the initial bridging ligand investigated, because it is easily prepared and thiolates show a well-known affinity for As^{III}.[12] Using a ligand such as H_2**L** allows for two possible orientations of the arsenic lone pairs: *into* or *out of* the cavity of the complex. Molecular models (CAChe, MM3) indicated that the lone pairs would be directed into the cavity with an As–As distance of about 6 Å.[13]



Scheme 1. Synthesis of [As_2L_3] assemblies.

H_2**L**, synthesized by a literature procedure,[12] forms a yellowish white solid in 52% yield when treated with stoichiometric amounts of $AsCl_3$ and KOH in THF/methanol mixtures. The product has very simple ^1H and ^{13}C NMR spectra, indicative of formation of the desired high-symmetry C_{3h} complex, and the parent ion peak [H{As_2**L**$_3$}]$^+$ is present in the electrospray ionization mass spectrum. Interestingly, [As_2**L**$_3$] also forms in the absence of any base; however, the dominant product under these conditions is a mixture of [As_2**L**$_2Cl_2$] macrocycles (Scheme 1), which are presumably kinetically stable intermediates on the self-assembly pathway to forming [As_2**L**$_3$].[14]

A single crystal X-ray diffraction study performed on crystals grown by diffusing pentane into a $CHCl_3$ solution of [As_2**L**$_3$] at −4 °C confirms the solid-state structure of the supramolecular assembly (Figure 2).[15] [As_2**L**$_3$]·$CHCl_3$ crystallizes in space group *C2/c* with eight molecules per unit cell. Therefore, one complex makes up the asymmetric unit and the discrete structure has no crystallographic symmetry. However, [As_2**L**$_3$] has very nearly C_{3h} symmetry. Consistent

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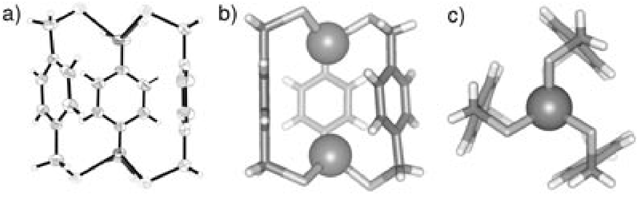

Figure 2. Structure of [$As_2\mathbf{L}_3$] in the crystal. a) ORTEP representation with 50% thermal ellipsoids. b) and c) Wireframe representations with arsenic atoms shown as space-filling spheres, the view in (c) is along the pseudo-threefold axis of the assembly showing the twist directions of the methylene groups being of opposite configurations at the two arsenic centers.

with predictions from molecular models, the arsenic lone pairs indeed are directed into the cavity of the complex. The two As^{III} ions are coordinated in a tripodal fashion by the three thiolate ligands, with the stereochemically active lone pairs directed at each other in the cavity.

The arsenic atoms in [$As_2\mathbf{L}_3$] are quite a bit closer together than molecular models indicated; they are separated by 5.03 Å (models predicted 6 Å). The average As–S distance is 2.25 Å and the angles between the mean planes of the phenyl rings are 57.3°, 64.2°, and 58.6° showing the complex has very nearly threefold symmetry. Furthermore, the As–C_{Aryl} distances are quite short, with six close contacts between 3.18 and 3.33 Å, suggesting an attractive interaction between the phenyl rings of the ligands and the arsenic ions helps stabilize the assembly.

Previous work by Schmidbaur et al. has shown that As^{III} and other heavier main group elements with stereochemically active lone pairs can form close contacts with arene rings in the solid state.[16–18] To analyze this attractive interaction, DFT calculations were performed on the $AsCl_3$–benzene dimer.[19] These studies revealed a lower limit for the binding energy of 7.4 $kcal\,mol^{-1}$ for the arsenic–arene interaction, with C–As distances of 3.2–3.4 Å. Furthermore, although the preferred geometry of the interaction orients the arsenic lone pair at a 68° angle to the phenyl ring, this structure is only 0.5 $kcal\,mol^{-1}$ more stable than the two C_{3v}-symmetric arrangements. This suggests that, while this interaction is quite strong, its geometry is flexible. Calculations at a higher level of theory to include dispersion energy (Moeller–Plesset and coupled cluster) are currently underway as are efforts to quantify the strength of this interaction in solution.

Figure 2c shows that the orientation of the methylene groups provides a "twisted" arrangement of the sulfur atoms around the arsenic atoms. These twists have opposite directions at the two arsenic centers in one complex, which results in a *meso* static structure with C_{3h} symmetry. The ^1H NMR spectrum ($CDCl_3$) of [$As_2\mathbf{L}_3$] shows one singlet in the aromatic region for the phenyl rings of the ligands and one singlet for the methylene protons, both shifted relative to the signals of the free ligand. That the methylene resonance is a singlet shows that the twisted orientations interconvert quickly on the NMR timescale, otherwise the methylene protons would be inequivalent because they are diastereotopic with one proton closer to the arsenic center than the other. Therefore, the [$As_2\mathbf{L}_3$] structure determined in the solid state is stable in solution on the NMR timescale. Furthermore, the NMR spectrum does not change down to −80°C, indicating that none of the possible dynamic solution behavior of this assembly is frozen out at this temperature. This is markedly different from the behavior of analogous organic π-prismands and bicyclophanes. Gleiter et al. reported that torsional motion in related nitrogen-based systems is frozen out at −20°C and the rotation of the π systems ceases at −82°C.[20]

[$As_2\mathbf{L}_3$] is remarkably robust in solution, suggesting this self-assembled compound is indeed the thermodynamic product of the reaction between As^{III} and $H_2\mathbf{L}$. No ligand exchange occurs between [$As_2\mathbf{L}_3$] and excess ligand on the NMR timescale, [$As_2\mathbf{L}_3$] is air- and water-stable, and it is even stable to a variety of competing metal ions (including Ag^I, Cu^I, Pd^{II}, and Zn^{II}). Remarkably, even extended heating in $CHCl_3$ at reflux in the presence of an excess of trifluoroacetic acid or *p*-toluenesulfonic acid gave neither decomposition nor protonation of [$As_2\mathbf{L}_3$] according to ^1H NMR spectroscopy.

The robustness of the [$As_2\mathbf{L}_3$] assembly is exciting for several reasons. Firstly, this provides the first proof of principle for the design strategy to form supramolecular assemblies using As^{III} as a building block, and reveals that the coordination chemistry of arsenic–sulfur interactions is sufficiently labile to allow for the self-assembly of discrete species to occur. This is an unusual use of arsenic(III) as a metalloid in coordination chemistry, rather than as a phosphine ligand analogue. Secondly, the intriguing observation that the arsenic lone pairs are oriented into the cavity of the complex hints at exciting host–guest applications. Because guests in encapsulation complexes experience a nonpolar, asymmetric environment, providing functionality to them in a synthetic receptor is challenging. Exposing functional groups to the cavities of synthetic receptors has also been referred to as "endohedral" and "introverted" functionality, and the presence of the arsenic lone pairs inside the cavity is an excellent first step in introducing functionality to a guest from its host shell.[11b,21]

That [$As_2\mathbf{L}_3$] forms in a nonoptimized yield of 52% suggests this reaction indeed occurs by a self-assembly mechanism. It is quite unlikely that six arsenic–sulfur bonds would spontaneously form to yield a discrete species as a kinetic product, and in fact the yields of the stepwise syntheses of related organic π-prismands are much lower.[20] The isolation of an intermediate [$As_2\mathbf{L}_2Cl_2$] macrocycle in the absence of base sheds light on the mechanism of this self-assembly reaction. Presumably, this stable macrocycle, which is preorganized for an incoming ligand **L** to bridge the two arsenic ions to form [$As_2\mathbf{L}_3$], forms as one of the many possible intermediates. Favorable arsenic–π interactions likely add further stability to the resulting assemblies and suggest that this interaction may help preorganize the arsenic atoms near the sulfur atoms to facilitate formation of the As–S bonds.

We have presented a self-assembled inorganic analogue of the bicyclophanes and,[22] specifically, the π-prismands.[20,23] The self-assembly strategy allows for increased yields in the macrobicyclization reaction and is a proof of principle of the design strategy to form arsenic-based supramolecular assemblies from simple, identical starting compounds. The success of this strategy augurs well for the formation of larger arsenic-based capsules resulting from expanded two- and threefold symmetric ligands. We are pursuing these studies, as well as attempting to prepare host–guest complexes of $[\mathrm{As}_2\mathbf{L}_3]$.

Experimental Section

General: All NMR spectra were measured using a Varian INOVA 300-MHz spectrometer. Single crystal X-ray diffraction studies were performed on a Bruker SMART APEX diffractometer. Mass spectra were recorded on an Agilent 1100 LC/MSD mass spectrometer.

$[\mathrm{As}_2\mathbf{L}_3]$: $\mathrm{H}_2\mathbf{L}$ (0.763 mmol, 130 mg) was added to a degassed solution of THF (80 mL) and KOH (2.43 mmol, 136 mg) in MeOH (24 mL). This solution was heated to 50 °C and AsCl_3 was added dropwise. The reaction was stirred under N_2 for 2.5 h. The resulting white precipitate was removed by filtration and the filtrate was dried in vacuo (yield 87 mg, 52 %). Crystals suitable for X-ray diffraction were grown by pentane diffusion into a chloroform solution of AsCl_3 and $\mathrm{H}_2\mathbf{L}$ at $-4\,°\mathrm{C}$. $^1\mathrm{H}$ NMR (300 MHz, CDCl_3, 25 °C): $\delta = 7.09$ (s, 12 H, CH), 3.81 ppm (s, 12 H, CH_2); $^{13}\mathrm{C}$ NMR (75 MHz, CDCl_3, 25 °C): $\delta = 137.5$ (C), 128.9 (CH), 35.0 ppm (CH_2); API-ES MS: m/z (MH,%): 655.2 ($[\mathrm{H}\{\mathrm{As}_2\mathbf{L}_3\}]^+$ 654.9 calcd, 23 %), 715.2 ($[\mathrm{H}\{\mathrm{As}_2\mathbf{L}_3\} + \mathrm{AcOH}]^+$, 714.9 calcd, 27 %).

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[15] Crystallographic data for $[\mathrm{As}_2\mathbf{L}_3]\cdot\mathrm{CHCl}_3$: crystal size $0.41 \times 0.27 \times 0.10$ mm; $T = -120(2)\,°\mathrm{C}$; monoclinic, space group $C2/c$ (no. 15), $a = 34.9159(11)$, $b = 8.8957(3)$, $c = 23.0878(7)$ Å; $V = 6152.2(3)$ Å^3, $Z = 8$, $\mu = 2.857\ \mathrm{mm}^{-1}$, $F(000) = 3104$, $\rho_{\mathrm{calcd}} = 1.67\ \mathrm{g\,mL^{-1}}$, $2\Theta_{\max} = 56.58°$. Of the 15036 reflections which were collected, 6780 were unique ($R_{\mathrm{int}} = 0.014$). Final $R1 = 0.033$ for 6070 data for $I > 2\sigma(I)$ (325 paramaters, 0 restraints); for all 6780 data, $wR2 = 0.093$, $GOF = 1.017$; max/min residual electron density $+1.680/-0.949\ \mathrm{e\,Å^{-3}}$. CCDC 238936 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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