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Linear coordination of Hg(II) by cysteamine

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Abstract

Combination of the hydrochloride salt of cysteamine (**1**) with $HgCl_2$ in water affords the unique compound, $[Hg\{S(CH_2)_2NH_3\}_2](Cl)_2$ (**2**) in which the S–Hg–S angle is nearly linear. The ammonium portion of the molecule forms short hydrogen bonding contacts with the sulfur atoms. A related S···H bond is observed in the structure of the free ligand **1** indicating that such bonding does not require the presence of a metal. The compounds were characterized with spectroscopic (^1H NMR, IR) and physical techniques (Mp, CH-analysis) as well as X-ray diffractometry.

Keywords: Cysteamine; Cysteine; Sulfur; Hydrogen bonding

1. Introduction

The affinity of the amino acid cysteine for soft heavy metals is exploited in many metal binding proteins. For example, cysteine is found in the binding sites of the mercury metalloregulatory proteins, MerR [1] and MerP [2]. Due to the abundance and importance of cysteine in biological systems a great deal of research has been conducted to understand how the amino acid interacts with metals [3].

By comparison, the chemistry of cysteamine ($HS(CH_2)_2NH_2$), having the same sulfur-containing unit as cysteine, has not been examined in as much depth. This is despite the fact that cysteamine is a fairly common medicinal agent. It is approved by the US Food and Drug Administration for the treatment of the painful disease, cystinosis where its effect is to break up excess intracellular cysteine as a soluble cysteine–cysteamine complex that can be subsequently excreted [4]. It is also one of the best radioprotective agents [5].

Recently, a small-molecule model of the binding site for MerP has been prepared which incorporates two cysteamine units. The ligand, benzene (or pyridine) diaminoethanethiol (BDET) irreversibly binds mercury (and other metals) from aqueous sources, is totally insoluble, and does not release the bound metal under harsh conditions [6]. The nature of the interaction between free cysteamine and mercury has not yet been established and so little can be inferred about the remarkable stability of the BDET–Hg complex. The purpose of the work presented herein is to obtain some insight into the BDET–Hg interaction.

$[Hg\{S(CH_2)_2NH_3\}_2](Cl)_2$ (**2**), is prepared by combining cysteamine-hydrochloride (**1**) with $HgCl_2$ in

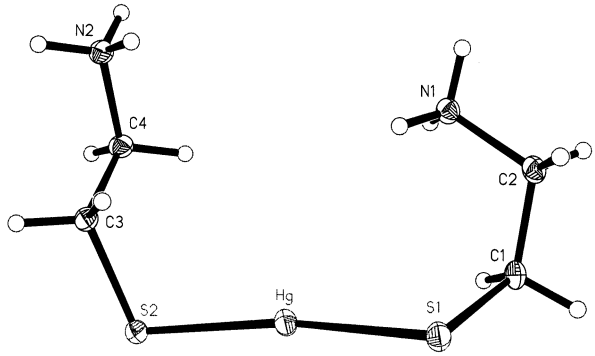

Fig. 1. ORTEP view of $[Hg(SCH_2CH_2NH_3)_2](Cl)_2$ (**2**). Selected bond distances (Å) and angles (°): Hg–S(1) 2.3330(9), Hg–S(2) 2.3380(9), S(1)–C(1) 1.832(3), C(1)–C(2) 1.512(4), C(2)–N(1) 1.489(4), S(2)–C(3) 1.830(3), C(3)–C(4) 1.518(4), C(4)–N(2) 1.499(4); S(1)–Hg–S(2) 168.53(3), Hg–S(l)–C(1) 105.5(1), S(1)–C(1)–C(2) 114.0(2), C(1)–C(2)–N(1) 113.0(3), Hg–S(2)–C(3) 100.6(l), S(2)–C(3)–C(4) 112.1(2), C(3)–C(4)–N(2) 108.8(2).

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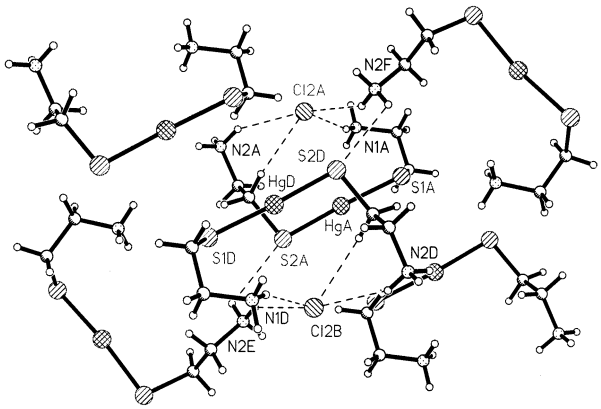

Fig. 2. Packing diagram of $[Hg(SCH_2CH_2NH_3)_2](Cl)_2$ (**2**) showing the hydrogen bond networks.

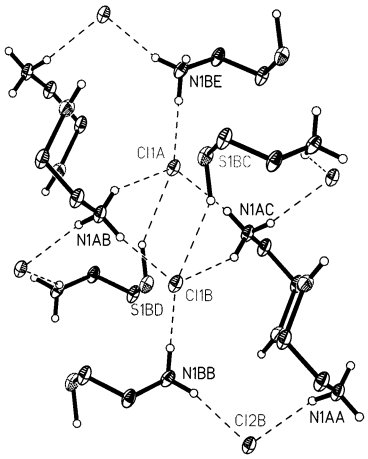

Fig. 3. ORTEP view of $[SHCH_2CH_2NH_3]Cl$ (**1**). Selected bond distances (Å) and angles (°): S(1)–H(1) 1.248, S(1)–C(1) 1.814(5), C(1)–C(2) 1.525(7), C(2)–N(1) 1.486(6); S(1)–C(1)–C(2) 114.4(4), C(1)–C(2)–N(1) 112.4(4).

water. After cooling for 2 weeks at 4 °C colorless X-ray quality crystals form in near quantitative yield. In the structure the Hg atom is coordinated to two sulfurs in a nearly linear fashion (168.53(3)°) and there are no secondary contacts to the mercury atom (Fig. 1). The structure is unique in that other related compounds feature either bridging and/or chelating cysteamine units [7]. For instance, the structures of soft metals bound by cysteamine and related molecules feature predominantly bidentate S-N coordination [8,9]. When employing cysteamine hydrochloride metals such as Cu [10] and Ag [11] form clusters with bridging (μ_2, μ_3 and μ_4) sulfur atoms. The only exception, and closest precedent to (**2**) is a rhenium-oxo compound which is coordinated by a single μ_1, cysteamine [12].

In general, structurally characterized molecules possessing a linear S–Hg–S geometry are rare [13]. This unit is observed in the cysteine compound, $Hg\{SCH_2CH(NH_3)COO\}$ $\{SCH_2CH(NH_3)COOH\}Cl{\cdot}0.5$ H_2O (**3**) (S–Hg–S = 170°) [14], and in $Hg\{SCN)_2$–Rb(SCN) (S–Hg–S = 154) [15]. The groups in $[MeHgSCMe_2CH(NH_3)](CO_2^-)$ (**4**) are also linear (C–Hg–S = 178°, Hg–S = 2.35 (**1**) Å) [16]. Most other Hg compounds that are linear have close secondary contacts [17,18]. This is true, for example, in $Hg\{SSi(O^tBu)_3\}_2$ (S–Hg–S = 180°, Hg–O ~ 2.8 Å) [19] and $Hg[(SPh)(OAc)]_2$ (S–Hg–S = 162°, Hg–O ~ 2.4–2.9 Å) [20]. Remarkably, the Hg–S distances in all of these compounds, including **2** are essentially the same at ~2.4 Å.

A unique feature that has been identified in **2**, in contrast to other synthetic mercury thiolates, is the presence of short S···H contacts (Fig. 2) [21]. The S···N distance is 3.26 Å (between S2A and N1D) implying a short hydrogen bond distance of ~2.2 Å (with the N–H fixed at 0.920 Å). This type of contact, although rare, has been found to be important in the structures of ferredoxins [22]. The common feature for **2** and the ferredoxins is the fact that the hydrogen bonding occurs in conjunction with the sulfur (either cysteamine for **2** or cysteine for the ferredoxin models) bound to the metal. It is possible that such a contact exists in MerP but the known structures are not of sufficient resolution to determine this.

In order to explore whether sulfur–hydrogen bond contacts are unique to the structure of **2** and possibly require a metal to be present, the structure of **1** was determined (Fig. 3). Hydrogen bonding is, indeed, observed for **1**, but between the S–H and a chloride. The S1BD···Cl1A distance is 3.78 Å implying a hydrogen bond contact of 2.75 Å (with an S–H distance of 1.25 Å (the hydrogens were found as peaks in the Fourier Difference map and then fixed in place)). The ammonium groups are hydrogen bonded to the chlorides (2.3–2.8 Å) but not to the sulfurs as in **2**. Clearly, chloride is the organizing force for the hydrogen bonding contacts in **1**.

2. Conclusion

With a linear S–Hg–S unit and S···H hydrogen bonding compound **2** may be viewed as a potential soluble model of the binding site of MerP in which two cysteine units coordinate a mercury atom in a linear manner [4]. It is possible that this is also occurring in the BDET–Hg complex [6]. Additionally, there is growing evidence that hydrogen bonding may be common in metal thiolate compounds. Compound **2** is the first mercury thiolate to demonstrate such bonding.

3. Experimental

3.1. General considerations

NMR data were obtained on JEOL-GSX-400 and -270 instruments operating at 270.17 and 399.78 MHz

and are reported relative to $SiMe_4$ and are in ppm. Elemental analyses were obtained on a Perkin–Elmer 2400 Analyzer. IR data were recorded as KBr pellets on a Matheson Instruments 2020 Galaxy Series spectrometer and are reported in cm^{-1}. X-ray data for **1** and **2** were collected on a Nonius Kappa-CCD unit using Mo Kα radiation. The structures were refined using the Siemens software package SHELXTL 4.0. All of the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were put into calculated positions. Absorption corrections were not employed. Further details of the structure analyses are given in Table 1.

Isolation of $(SHCH_2CH_2NH_3)Cl$ (**1**): cysteamine hydrochloride (0.57 g, 5 mmol) was dissolved in hot 1-$C_4H_{10}O$ (15 ml) and filtered. The solution was allowed to stand for 2 weeks at 4 °C during which time colorless crystals formed in quantitative yield. Other alcohols, such as iso-C_3H_8O and *n*-C_3H_8O could be employed in a similar manner. Yield: 0.40 g (70%); m.p. 64–66 °C. ^1H NMR (D_2O, 200 MHz): δ 2.83 (t, 2H, CH_2N), 3.21 (t, 2H, CH_2S), 4.80 (s, residual water in the D_2O, HS, NH). IR (KBr; ν cm^{-1}): 3410w, 2955s, 2718w, 2660w, 2558w, 2504w, 1598s, 1499s, 1444m, 1423m, 1379s, 1321m, 1279m, 1244m, 1130s, 1079s, 1041s, 979m, 898s, 858s, 787w, 660w, 455m. *Anal.* Calc. for C_2H_8ClNS: C, 21.14; H, 7.10; N, 12.33; S, 28.22. Found: C, 21.33; H, 7.25; N, 12.19; S, 28.47%.

Preparation of $[Hg(SCH_2CH_2NH_3)_2](Cl)_2$ (**2**): to a stirring solution of cysteamine hydrochloride (1.14 g, 10 mmol) in deionized water (15 ml) was added mercury(II) chloride (1.36 g, 5 mmol). The resulting solution was allowed to stand for 2 weeks at 4 °C during which colorless crystals formed in near quantitative yield. Yield: 1.72 g (81%); m.p. 218–220 °C (dec.). ^1H NMR (D_2O, 400 MHz): δ 3.23 (m, 4H, CH_2N), 3.27 (m, 4H, CH_2S), 4.80 (br s, residual water in the D_2O and NH). ^{13}C NMR (D_2O, 100 MHz): δ 25.2 (CH_2S), 43.3 (CH_2N). IR (KBr; ν cm^{-1}): 3445w, 2991s, 2904s, 2720w, 2606w, 2532w, 2410w, 1604s, 1566s, 1491s, 1477s, 1420w, 1405m, 1366w, 1315m, 1264s, 1249m, 1134m, 1094m, 1077m, 1034m, 1015w, 933s, 882m, 802w, 787m, 724w, 653w, 453w. *Anal.* Calc. for $C_4H_{14}Cl_2HgN_2S_2$: C, 11.28; H, 3.32; N, 6.58; S, 15.06. Found: C, 11.39; H, 3.25; N, 6.70; S, 14.98%.

Table 1
Summary of X-ray data for compounds **1** and **2**

Chemical formula	C_2H_8ClNS	$C_4H_{14}Cl_2HgN_2S_2$
Formula weight	113.60	425.78
Temperature (K)	145(1)	145(1)
Crystal system	triclinic	monoclinic
Color/shape	colorless cube	colorless cube
Space group	$P\bar{1}$	$P2_1/c$
a (Å)	8.540(4)	7.746(1)
b (Å)	8.659(4)	12.138(1)
c (Å)	8.990(4)	12.023(1)
α (°)	107.12(3)	
β (°)	117.08(3)	103.61(1)
γ (°)	90.00(3)	
V (Å^3)	558.6(2)	1098.7(2)
Z	4	4
D_{calc} (g cm^{-3})	1.351	2.574
Absorption coefficient (mm^{-1})	0.900	14.823
Reflections	3277	4925
Independent	1912 unique ($R_{int} = 0.0417$)	2528 unique ($R_{int} = 0.0295$)
$R[F>4\sigma(F)]$	0.0634	0.0194
R(all data)	0.0634	0.0240

4. Conclusion

The presence of S···H contacts in **1** and **2** suggests that the thiol and sulfide form of the MerP protein are capable of hydrogen bonding. This hydrogen bonding is well-known in iron sulfide containing proteins but not established for either the MerP or MerR proteins. This may be due, in part, to the relative paucity of information on the later two proteins. Out of the synthetic mercury-sulfides known, including **3** and **4**, none are reported to have S···H contacts. Thus, compound **2** is unique in this regard.

5. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 15748 and 157479 for compounds **1** and **2** which includes full tables of bond lengths and angles, full atom-labeled ORTEP views, unit cell views and observed and calculated structure factor tables are available upon request. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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