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Comprehensive characterisation of bismuth thiosalicylate complexes: models for bismuth subsalicylate

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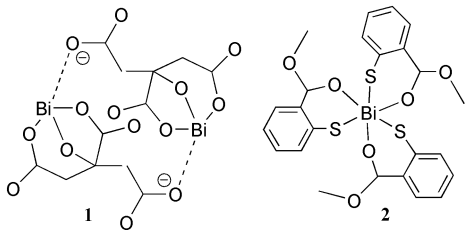
ESI-MS identification of bismuth methylthiosalicylate complexes and isolation of tris(methylthiosalicylato)bismuth(III) demonstrates the importance of thiolates as anchors for hetero-bifunctional ligands and provides models for the medicinally relevant bismuth subsalicylate.

Pepto-Bismol and De-Nol are trade names for globally marketed gastrointestinal medications that contain '*bismuth subsalicylate*' (BSS) and '*colloidal bismuth subcitrate*' (CBS), respectively. These preparations are the culmination of a 250 year medicinal history for bismuth compounds,[1–6] however, their modes of bioactivity are not understood. Numerous reports of solid state structures for CBS[3] indicate a complicated structural chemistry with the dimeric unit **1** as a common feature.† In contrast, the low solubility of BSS has precluded structural characterisation.

Complexes of bismuth with anions of various hydroxycarboxylic acids (tartaric,[7,8] lactic,[9] malic[8]) and other compounds,[10–13] have been examined as potential models for the medicinal agents. Recognising the high thermal and hydrolytic stability of the sulfur–bismuth bond, we have modeled BSS more directly using thiosalicylate derivatives and have identified complexes by *in situ* electrospray ionisation mass spectrometry (ESI-MS). In addition, we report the first comprehensive characterisation of a bismuth–methylthiosalicylate complex **2**.



Solutions containing $BiCl_3$ with methylthiosalicylate (MTS), potassium methylthiosalicylate (KMTS) or thiosalicylic acid (TSA) in ethanol‡ were injected directly into the electrospray source of a VG Micromass Quattro triple quadrupole mass spectrometer at a flow rate of 300 μl min^{-1}, with a source temperature of 383 K and skimmer cone voltage of 50 V. Spectral data are summarised in Table 1, including reaction stoichiometry and assignments. Mass assignments are supported by the appropriate isotopic distributions of sulfur and by MS/MS spectra obtained using argon as a collision gas with a collision energy of 50 eV. The argon pressure was sufficient to reduce the intensity of the main beam by 1%.

ESI-MS of mixtures containing $BiCl_3$ with MTS or KMTS at various stoichiometric combinations (1:1, 1:2; Bi:S) show prominent peaks at *m*/*z* 749, 733 and 543 assigned to **2K**, **2Na** and **3**,§ respectively. A representative spectrum is provided in Fig. 1. The tris-**2** and bis-thiolate **3** complexes are consistent with previously isolated aminothiolate derivatives, the solid state structures for which are confirmed by X-ray crystallography.[14] Fig. 2 shows an ESI-MS of reaction mixtures containing $BiCl_3$ with TSA at various stoichiometric combinations (1:1, 1:2; Bi:S). Peaks at *m*/*z* 515 and 361 are assigned to bis- (**5**) and mono-thiolate **6** complexes, respectively. Tris(methylthiosalicylate)bismuth(III) $(\mathbf{2})_2$ has been isolated¶ and shown to adopt a dimeric arrangement in the solid state,‖ in contrast to the complicated hexanuclear structure reported for the thiosalicylate derivative.[15] The ligand bridged dimeric structures of **7**[16–20] and **1**[21] involve pendant linkages, while $(\mathbf{2})_2$ associates through μ-thiolate bridges (Fig. 3).

The prominence of the tris-, bis-, and mono-thiosalicylate bismuth complexes in the mass spectra and the solid state structure of $(\mathbf{2})_2$ are consistent with the established series of tris-**8**, bis- **9**, and mono-thiolate **10** complexes observed for thiolate hetero-bifunctional ligands with weakly donating functional-

Table 1 Prominent peaks (*m*/*z*), relative peak intensities (%) and assignments observed for *in situ* ESI-MS of reaction mixtures containing $BiCl_3$ with MTS, KMTS or TSA in ethanol

		Relative intensity (%)			
m/*z*	Assignment	MTS	KMTS	MS/MS *m*/*z*	Assignment
749	**2K**		15	373	**4K**
733	**2Na**	5	40	543	**3**
				357	**4Na**
543	**3**	20	100	407	$C_8H_6BiO_2S_2^+$
407	$C_8H_6BiO_2S_2^+$	15	10	209	Bi^+
373	**4K**		20		
357	**4Na**	100	50		
		TSA			
515	**5**	25		361	**6**
				317	$C_6H_4BiS^+$
				209	Bi^+
361	**6**	50		317	$C_6H_4BiS^+$
				209	Bi^+
317	$C_6H_4BiS^+$	100		209	Bi^+
209	Bi^+	15			

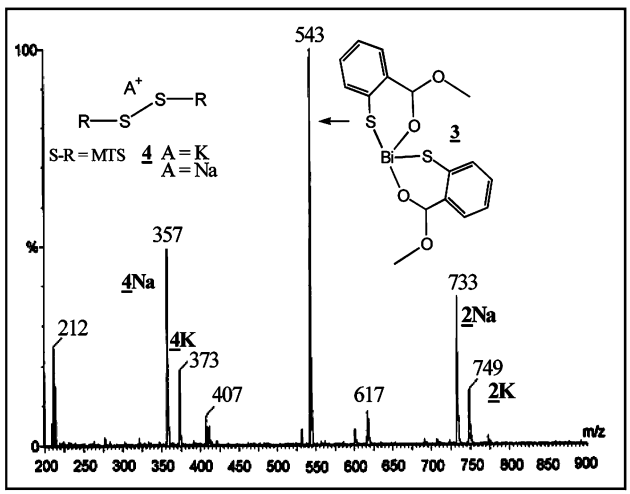


Fig. 1 Representative ESI-MS of a solution containing $BiCl_3$ and KMTS in ethanol.

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ities.[14,21,22] The results reemphasise the dominating influence of bismuth–sulfur bonds in the chemistry of bismuth.

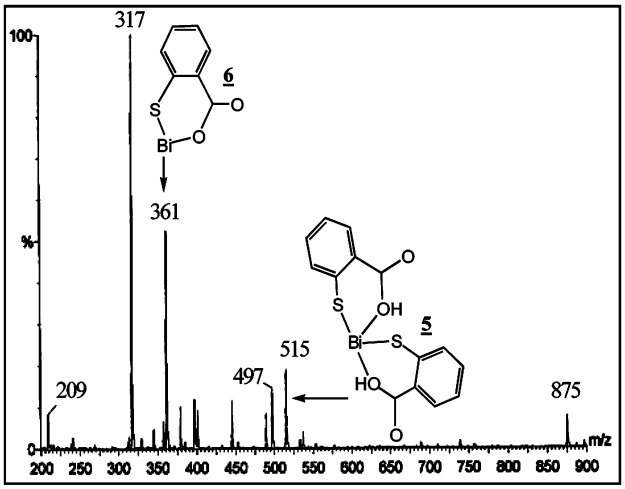
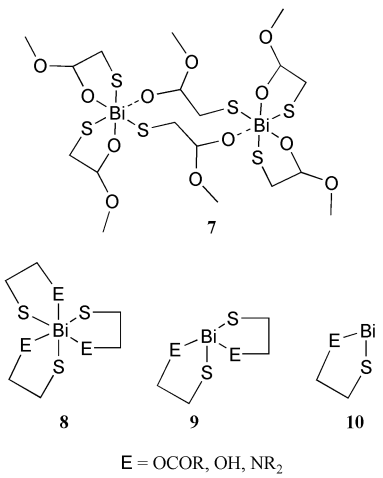


Fig. 2 Representative ESI-MS of a solution containing $BiCl_3$ and TSA in ethanol.



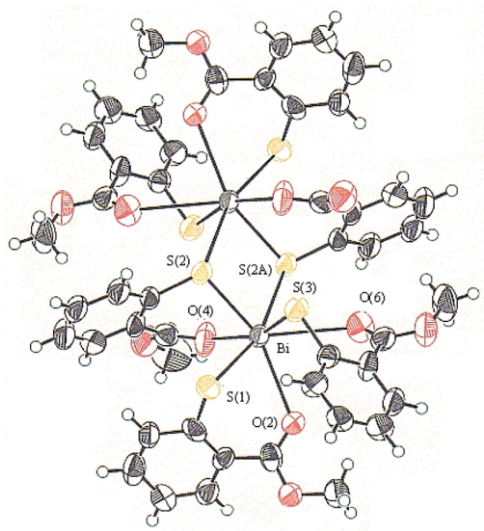


Fig. 3 Crystallographic view of $(\mathbf{2})_2$. Thermal ellipsoids are drawn to 50% probability. Selected bonds lengths (Å): Bi–O(2) 2.84(1), Bi–O(4) 2.72(2), Bi–O(6) 3.08(2), Bi–S(1) 2.606(5), Bi–S(2) 2.597(5), Bi–S(3) 2.602(6), Bi–S(2A) 3.277(5).

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Notes and references

† Molecular drawings illustrate connectivity only; drawings of these complexes aimed at describing bonding features (*e.g.* Lewis) are not meaningful or are misleading.

‡ $BiCl_3$, MTS, KMTS or TSA were added to ethanol (100 mL) and the yellow reaction mixture was stirred for at least 6 h. The filtrate was collected by suction filtration.

§ Molecular drawings of ions assigned to peaks in ESI-MS represent monocationic species.

¶ Isolation of $(\mathbf{2})_2$: a solution of methylthiosalicylate (MTS) (21.4 mmol) and KOH (22.3 mmol) in ethanol (50 mL) was added dropwise to a stirred slurry of $BiCl_3$ (7.29 mmol) in ethanol (50 mL) under nitrogen. The product was removed by suction filtration and recrystallized from DMF (yellow needles). Yield: 64%; mp 141 °C; Anal. Calc. (Found): C, 40.57 (40.48); H, 2.98 (3.21%); IR (cm^{-1}): 1716 (9), 1699 (6), 1675 (3), 1582 (18), 1456 (11), 1437 (8), 1423 (16), 1310 (12), 1291 (7), 1274 (5), 1248 (1), 1194 (20), 1134 (15), 1129 (17), 1112 (13), 1054 (2), 1037 (19), 749 (10), 743 (4), 303 (14).

‖ *Crystal data* for **2**: $C_{24}H_{21}BiO_6S_3$, M = 710.59, triclinic, space group $P\bar{1}$ (no. 2), yellow needles, a = 12.683(5), b = 14.118(4), c = 8.123(2) Å, α = 105.19(2), β = 105.29(2), γ = 104.22(3)°, V = 1274.2(9) $Å^3$, D_c = 1.852 g cm^{-3}, Z = 2, T = 23.0 °C, R = 0.068, R_w = 0.074. Measurements were made on a Rigaku AFC5R diffractometer, Cu-Kα radiation (λ = 1.54178 Å) and a 12 kW rotating anode generator. The structure was solved by direct methods (SHELXL97) and refined by full matrix least squares on F using 2642 reflections with $I > 3.00\sigma(I)$. CCDC reference number 183155. See http://www.rsc.org/suppdata/cc/b2/b203110h/ for crystallographic data in CIF or other electronic format.

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