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Towards a Structural Understanding of the Anti-Ulcer and Anti-Gastritis Drug Bismuth Subsalicylate**

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Bismuth subsalicylate (BSS), commonly marketed as colloidal suspensions under the commercial names of “Bismatrol”, and “Pepto-Bismol”, is one of several bismuth compounds regularly used for the therapeutic treatment of a variety of gastrointestinal ailments including duodenal and peptic ulcers, ulcerative colitis, and diarrhea.^[1–7] In conjunction with antibiotic compounds such as tetracycline, clarithromycin, and amoxicillin, BSS (as well as bismuth subcitrate (CBS) and ranitidine bismuth citrate) has been effective in the treatment and eradication of *Helicobacter pylori*, the bacterium linked to gastritis and ulceration implicated in the development of gastric cancer and gastric lymphoma.^[8–13] It is estimated that at least half of the world’s population is infected with *H. pylori* and, without treatment, it is present in its host for life.^[14–16] The medical and social impact of *H. pylori* was acknowledged by the award of the 2005 Nobel Prize in Physiology and Medicine to Marshall and Warren.

Despite the efficacy of these bismuth formulations, the mechanism of action of bismuth compounds in the body, either in their interaction with bacteria, the urease *H. pylori* produces, or the localized environment around gastric lesions, is largely unknown. As a first step there have been attempts to model the structures of BSS (and CBS) through the formation and structural elucidation of a variety of bismuth carboxylates.^[2,17,18] The most important of these are tris-substituted bismuth salicylate $[\text{Bi}(\text{Hsal})_3]$ ($\text{H}_2\text{sal} = (2\text{-HO})\text{C}_6\text{H}_4\text{COOH}$) “trapped” by chelating amines, for example, $[\text{Bi}(\text{Hsal})_3(\text{bpy})]_2 \cdot (\text{C}_7\text{H}_8)_2$, ($\text{bpy} = 2,2'\text{-bipyridine}$),^[19] bismuth thiosalicylate complexes,^[20] and the structurally uncharacterized $[\text{Bi}(\text{Hsal})_3]$ compound.^[21,22] These model compounds, however, do not address the “sub” part of subsalicylate which, as the name infers, requires partial hydrolysis of the BiL_3 species and concomitant hydroxide/oxide formation, resulting in the typical insolubility of these compounds. Since the hydrolysis or partial neutralization process is not easily

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controlled under heterogeneous conditions, BSS, as a pharmaceutical formulation, raises interesting compositional and structural questions. Its high degree of insolubility has made the definitive determination of its nature extremely difficult.

We report here the reproducible synthesis and characterization of two bismuth oxosalicylate clusters of high nuclearity, $[\text{Bi}_{38}\text{O}_{44}(\text{Hsal})_{26}(\text{Me}_2\text{CO})_{16}(\text{H}_2\text{O})_2] \cdot (\text{Me}_2\text{CO})_4$ (**1**) and $[\text{Bi}_9\text{O}_7(\text{Hsal})_{13}(\text{Me}_2\text{CO})_5] \cdot (\text{Me}_2\text{CO})_{1.5}$ (**2**). Our study provides structural insights into the nature of BSS and establishes a basis for more meaningful studies into its mode of action and biological activity.

Colorless crystals of **1** and **2** grew slowly over four to five days upon dissolution of $[\text{Bi}(\text{Hsal})_3]$ in reagent-grade acetone. The product from the solvent-free reaction of BiPh_3 with salicylic acid^[21] analyzes with relative consistency to be the $[\text{Bi}(\text{Hsal})_3]$ species. Hydrolysis at this stage is most likely precluded, or minimized, by the temperature of the reaction and the use of carefully dried reagents. $[\text{Bi}(\text{Hsal})_3]$ formed by this method is almost entirely soluble in warm acetone, and slow evaporation provides a reasonable yield of colorless crystals. Complete evaporation of the mother liquor results in a loss of integrity of the crystals as lattice and bound solvent is lost and the crystals become opaque.

Single-crystal X-ray diffraction on a variety of crystals from several reaction mixtures indicates that crystals of **2**, with nine bismuth atoms in the central oxide core, initially predominate with co-crystallization of a relatively small amount of the very large cluster **1**, which has 38 bismuth atoms. However, extended crystal growth times leads to a predominance of the larger cluster which appears to be the least soluble and most thermodynamically stable form. To date we have collected data on 15 crystals and as yet have not found any other cluster species by single-crystal X-ray diffraction. Powder XRD patterns on the bulk sample differed from those generated from the single-crystal data, most likely because of the loss of lattice and bound solvent molecules from **1** and **2**.

We assume that hydrolysis occurs as a result of water in the acetone and that the rate of hydrolysis and crystal growth determines the degree of oxide formation. Elemental analyses (C,H) on one fresh dried sample of crystalline material analyzed correctly for **1**. However, repeated analyses on several samples of the air-dried crystals provided inconsistent results, owing to the loss of acetone and/or H_2O . This is a strong indication, along with the crystallographic results, that a mixture of clusters is obtained and underscores the difficulty in comprehensive characterization.

MALDI mass spectrometry in acetone with 0.1% trifluoroacetic acid (TFA) confirms the presence of a Bi_9 cluster having the same nuclearity as the initial isolated cage, as well as other fragmentation species. This was the case whether an added matrix was used or not. The highest m/z values are for $[\text{Bi}_9\text{O}_7(\text{Hsal})_{10}(\text{Me}_2\text{CO})_3(\text{H}_2\text{O})_9]^{3+}$ (1233), $[\text{Bi}_9\text{O}_7(\text{Hsal})_{10}(\text{H}_2\text{O})_6]^{3+}$ (1157), and $[\text{Bi}_8\text{O}_6(\text{Hsal})_9(\text{Me}_2\text{CO})_2(\text{H}_2\text{O})]^{3+}$ (1045). Other prominent peaks are listed in the experimental description. ^1H and ^{13}C NMR spectra, recorded in dilute solutions in $[\text{D}_6]$ acetone, indicate just the salicylate ligand. At 30 °C all the proton signals are broad with no defined splitting, but four equal intensity resonances are observed for 2-

$\text{HOC}_6\text{H}_4\text{COO}^-$. Though there is some further broadening of the signals as the temperature is lowered, one ligand environment dominates. At -80°C the proton resonances become sharp, the splitting is more defined, and there is some movement in the chemical-shift values, but only one ligand environment is visible.

The crystal structures of **1** and **2** are shown in Figure 1a and Figure 1b, respectively. The oxide core of **1** adopts a well-defined octahedral cluster of edge-shared cubes at the crystallographic origin and resembles a small block of the fluorite structure when Bi–O contacts are included out to 3.1 Å, which is well within the sum (4.0 Å) of the van der

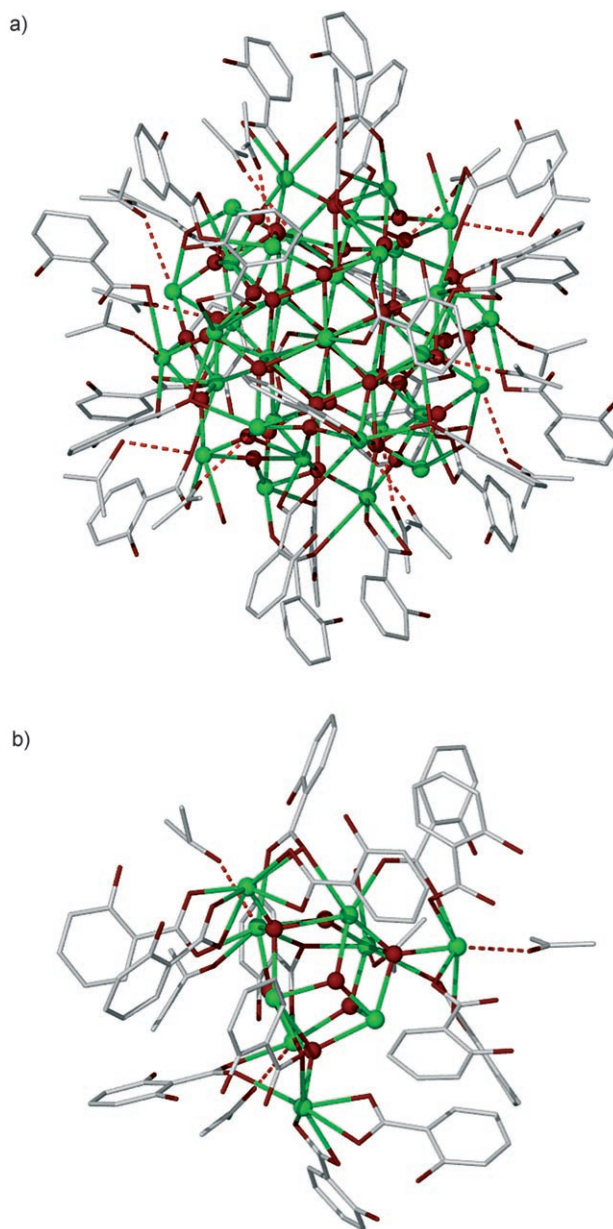


Figure 1. a) Molecular structure of $[\text{Bi}_{38}\text{O}_{44}(\text{Hsal})_{26}(\text{Me}_2\text{CO})_{16}(\text{H}_2\text{O})_2]$ (**1**) showing the shrouding of the $\text{Bi}_{38}\text{O}_{44}$ core (green = Bi, red = O) by 26 salicylate ligands (stick structures). b) Molecular structure of $[\text{Bi}_9\text{O}_7(\text{Hsal})_{13}(\text{Me}_2\text{CO})_5]$ (**2**) showing the shrouding of the Bi_9O_7 core (green = Bi, red = O) by 13 salicylate ligands (stick structures).

Waals radii for Bi and O.^[23,24] The cubes are almost regular though the location of each Bi atom in each cube is well displaced from the center, presumably as a result of the lone pairs of electrons. This arrangement corresponds to the high-temperature ($> 717^\circ\text{C}$) oxygen-deficient δ phase of Bi_2O_3 , the phase that has sparked significant interest in materials science recently owing to its extremely high oxide mobility.^[25] This phase contrasts with the formally lower-temperature β phase identified for the large silanolate cluster $[\text{Bi}_{22}\text{O}_{26}(\text{OSiMe}_2t\text{Bu})_{14}]$, which was isolated from the hydrolysis of $\text{Bi}(\text{OSiMe}_2t\text{Bu})_3$ in benzene.^[26] While inorganic ternary bismuth oxide clusters of high nuclearity are not unexpected,^[27–29] similar metal–organic compounds of bismuth, including those with ethoxide, trifluoroacetate, phosphonate, and citrate ligands are now apparent.^[30–34] In addition, Whitmire and co-workers have recently incorporated bismuth and salicylate anions and dianions into several structurally characterized heterobimetallic clusters containing Al or a series of transition metals,^[35–38] generally of low nuclearity.

Mehring and co-workers have proposed a set of rules to describe the growth pattern of bismuth oxo clusters, including homometallic oxo clusters containing 4, 9, 18, 20, and 22 bismuth atoms, in addition to several larger heterobimetallic clusters incorporating sodium which were derived from partial hydrolysis of bismuth silanolates.^[39] They deduced that the structural building block for the bismuth-rich clusters is the $[\text{Bi}_6\text{O}_8]^{2+}$ polyhedron, which has six octahedral Bi atoms with the eight O atoms located over all of the triangular faces. The structures of both **1** and **2** appear to conform to this. Thus, at the heart of the cluster in **1** is a central Bi_6 octahedron in which the six Bi atoms, $\text{Bi}(6, 9, 13)$ and symmetry equivalents, are bound to only oxide atoms. Surrounding this are four further Bi_6 octahedra, which share edges with each of the four equatorial edges of the central Bi_6 , thus forming a planar cross of five octahedra. Above and below this plane are four further Bi_6 octahedra, joined at a single vertex (i.e. each doubly edge sharing), which is also one of the axial Bi atoms of the central Bi_6 octahedron. Thus, each of these four octahedra shares four edges with neighboring Bi_6 octahedra. This accounts for all 38 Bi atoms (24 external and 14 internal). The Bi_9 clusters comprise a central Bi_6 octahedron but with only seven of the eight trigonal faces capped by an O atom, as shown in Figure 2a. The hole is covered by a $\mu_3\text{-}\eta^1\text{-}\eta^1\text{-}\eta^1$ -salicylate: $\text{Bi}(2, 5, 6)$ by $\text{O}(16, 17)$ and $\text{Bi}(11, 14, 16)$ by $\text{O}(61, 62)$. Three additional Bi atoms protrude from the core and are all connected through a bridging $\mu_4\text{-O}$ atom.

The cores of **1** and **2** are surrounded by 26 and 13 salicylate ligands, respectively. The bonding to the outlying Bi^{III} centers corresponds to highly complex bridging modes (see below) with no evidence of any interactions with the *ortho* hydroxy oxygen atoms. This is similar to the bonding in $[\text{Bi}(\text{Hsal})_3\text{-(bpy)}]_2\text{-(C}_7\text{H}_8)_2$ and in contrast to that in $[\text{Bi}(\text{Hsal})(\text{sal})\text{-(phen)}]_2\text{-(C}_7\text{H}_8)_2$ ^[19] (phen = 1, 10-phenanthroline). If one considers all Bi–O bond lengths in the structures up to 3.1 \AA , three broad categories become evident: very short bonds (shortest 2.06 \AA in **1** and 2.09 \AA in **2**) primarily found in the oxide core, and medium and long bonds resulting from asymmetric coordination of the carboxylate ligands. In **1** the coordination numbers of the Bi atoms are either six ($2 \times \text{Bi}$),

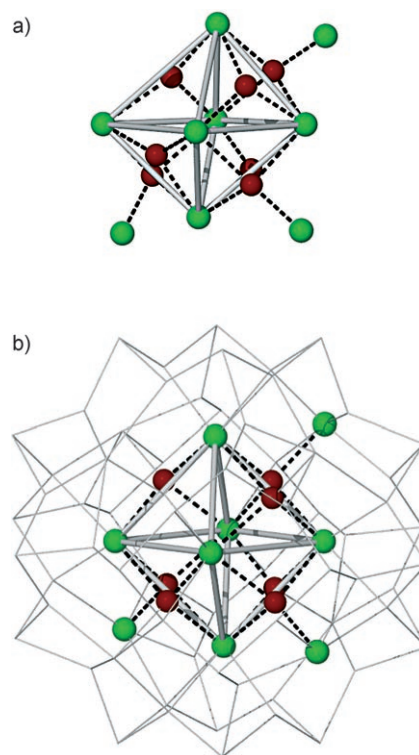


Figure 2. a) Structure of the Bi_9O_7 core of $[\text{Bi}_9\text{O}_7(\text{HSal})_{13}(\text{Me}_2\text{CO})_5]$ (**2**), showing the octahedral arrangement of the Bi atoms with seven octahedral faces capped by an oxygen atom. Three Bi atoms extend the core bound to a capping O atom. b) Structure of the $\text{Bi}_{38}\text{O}_{44}$ core of $[\text{Bi}_{38}\text{O}_{44}(\text{HSal})_{26}(\text{Me}_2\text{CO})_{16}(\text{H}_2\text{O})_2]$ (**1**), with Bi_9O_7 at the heart of the core; colors as in Figure 1.

seven ($10 \times \text{Bi}$), or eight ($7 \times \text{Bi}$). The bismuth atoms $\text{Bi}(6, 10, 13)$ and their symmetry equivalents bond only to core oxygen atoms and are all eight-coordinate. The three independent Bi atoms are bonded to 19 O atoms; $\text{O}(12)$ is bound to all three, and a further three oxygen atoms are bound to two such Bi atoms. $\text{Bi}(6, 9, 13)\text{--O}$ bond lengths range from $2.252(10)$ to $3.056(10)\text{ \AA}$ and do not include the shortest Bi–O bond lengths. Twelve of the remaining Bi atoms in the asymmetric unit each have three Bi–O core bond lengths shorter than 2.25 \AA , whilst the other four have three comparable with the shortest distance seen for $\text{Bi}(6, 9, 13)\text{--O}$ and at least one much shorter. The shortest $\text{Bi--O}_{\text{core}}$ bond length is $2.059(9)\text{ \AA}$, for $\text{Bi}(3)\text{--O}(6)$, and there are four others below 2.10 \AA . Eight Bi atoms, $\text{Bi}(2, 5, 10, 18)$ and their symmetry equivalents, are bound mainly to core O atoms with seven-coordinate $\text{Bi}(5)$ and eight-coordinate $\text{Bi}(10)$ each having six core O atoms.

Salicylate ligands are bonded to all Bi atoms except $\text{Bi}(6, 19, 13)$ and their symmetry equivalents. The variation in carboxylate bonding modes is extraordinary, even though, as stated earlier, binding of the OH group of Hsal^- does not occur. Thus, $\mu_4\text{-}\eta^1\text{-}\eta^1\text{-}\eta^1\text{-}\eta^1$, $\mu_3\text{-}\eta^2\text{-}\eta^2\text{-}\eta^1$, $\mu_3\text{-}\eta^2\text{-}\eta^1\text{-}\eta^1$, $\mu_3\text{-}\eta^1\text{-}\eta^1\text{-}\eta^1$, $\mu\text{-}\eta^2\text{-}\eta^1$ (with the CO_2 group perpendicular or coplanar with the $\text{Bi}\cdots\text{Bi}$ vector) and $\mu\text{-}\eta^1\text{-}\eta^1$, involving only one carboxylate oxygen, are all observed. The carboxylate bonding modes in **2** are less complex, with only $\mu_3\text{-}\eta^1\text{-}\eta^1\text{-}\eta^1$ and $\mu\text{-}\eta^2\text{-}\eta^1$ predominating. Surprisingly, none of the most common bonding

modes—simple chelation, O,O' bridging, and unidentate—are observed. The Bi–O_{Hsal} bond lengths cover a narrower range, 2.415(9)–3.066(10) Å, than the Bi–O_{core} bond lengths, and there are always at least three Bi–O_{core} bonds shorter than the shortest Bi–O_{Hsal} distance around each bismuth atom. In at least two cases where there is chelation to a bismuth atom (as part of a more complex carboxylate binding mode), the two Bi–O_{Hsal} distances differ by 0.5–0.6 Å. Two water ligands, Bi–O(23)_{H₂O} 2.647(10) Å, with a distance typical for Bi^{III}–OH₂,^[40] are attached to the Bi₃₈ cage. In addition, 16 acetone ligands are coordinated to the cage, four of which bridge two bismuth atoms unsymmetrically (0.13, 0.17 Å). The range of Bi–O distances, 2.815(10)–3.089(10) Å, is at the top end of the Bi–O bond lengths, and can be related to the ready loss of acetone and crystallinity on drying.

Of all the bismuth oxo coordination clusters observed thus far in the solid state, those with nine Bi atoms seem to occur most regularly. From Mehring's study [Bi₉O₇(OSiMe₃)₁₃] was characterized, while [Bi₉O₇(OC₆F₅)₁₃]^[41,42] and its thf solvate^[41] were obtained upon hydrolysis and elimination of bis(pentafluorophenyl) ether from dimeric [Bi(OC₆F₅)₃-(toluene)]₂.^[42] Apart from the obvious differences in the bonding modes of carboxylate with silanolate and phenolate, these clusters are essentially isostructural with **2** and display relatively high thermodynamic stability.

Interestingly, as Figure 2b graphically depicts, the core of **2** lies at the heart of **1**. This information, coupled with the presence of the Bi-coordinated solvent molecules in **1** and **2**, reveals a possible process for hydrolysis and core formation, and indicates that complex **2** gives rise to complex **1**. These structures provide an insight into the nature of bismuth subsalicylate and plausibly other basic bismuth medicinals which we propose are based on bismuth oxide cores. The capacity for cluster building, shown by the relationship between **1** and **2** and extrapolated to larger clusters, accounts for the near insolubility of these species.

Experimental Section

o-Hydroxybenzoic acid (salicylic acid) (0.44 g, 3.0 mmol) was ground together with BiPh₃ (0.44 g, 1.0 mmol) in a mortar and pestle and dried in vacuo. The mixture was heated at 120°C for 6 h and the resulting white powder dissolved in warm reagent-grade acetone and filtered. Slow evaporation of the solvent produced a crop of colorless crystals, which were separated by hand and identified as the oxosalicylate bismuth clusters **1** and **2** through single-crystal X-ray diffraction. Further analysis was conducted on the air-dried opaque material which was collected after complete solvent removal and washing with toluene. Yield 147 mg (air-dried, microcrystalline material) m.p. >240°C (decomp to gray powder). ¹H NMR (400.13 MHz, [D₆]acetone, 30°C): δ = 11.02 (1H, PhOH), 7.79 (1H, *o*-H), 7.35 (1H, *p*-H), 6.84, 6.67 ppm (2H, *m*-H). ¹³C NMR (100.62 MHz, [D₆]acetone, 30°C): δ = 206.9 (C=O), 162.3 (*q*-C), 136.3 (*p*-C), 131.7 (*o*-C), 119.8 (*m*-C), 118.2 (*m*-C), 116.3 ppm (*q*-C). Attenuated total reflectance (ATR) IR: $\tilde{\nu}$ = 3375 (w, br), 3050 (w, br), 1681 (w), 1619 (m), 1588 (m), 1522 (m), 1478 (s), 1143 (s), 1375 (s), 1336 (s, sh), 1303 (s), 1240 (s), 1216 (s), 1156 (s), 1141 (s) 1090 (m), 1029 (m), 860 (m), 808 (m), 750 (m), 701 (m), 663 cm⁻¹ (m). MS (MALDI, acetone + 0.1% TFA, no matrix): *m/z*: 1233 [Bi₉O₇-(Hsal)₁₀(Me₂CO)₅(H₂O)₉]³⁺, 1157 [Bi₉O₇-(Hsal)₁₀(H₂O)₆]³⁺, 1045 [Bi₈O₆-(Hsal)₉(Me₂CO)₂(H₂O)]³⁺, 887 [Bi₃-(Hsal)₇(Me₂CO)₂(H₂O)₄]²⁺,

767 [Bi₃O(Hsal)₅(Me₂CO)₂(H₂O)₅]²⁺, 716 [Bi(Hsal)₃Na(Me₂CO)-(H₂O)]⁺, 627 [Bi₅O₄(Hsal)₄(Me₂CO)₂(H₂O)₆]³⁺, 510 [Bi₂-(Hsal)₄-(H₂O)₃]²⁺, 417.9 [Bi₂]⁺, 208.9 [Bi]⁺. Elemental analysis for **1**–(H₂O and acetone) (%) calcd for C₁₈₂H₁₆₄O₁₂₂Bi₃₈: C 17.85, H 1.35; found C 17.97, H 1.13.

Crystalline samples of compounds **1** and **2** were mounted upon glass fibers in highly viscous oil at 123(2) K. Data were collected on Bruker ApexII Kappa CCD (**1**) and Enraf-Nonius Kappa CCD (**2**) diffractometers (graphite-monochromated MoK α X-ray radiation (λ = 0.71073 Å)) and corrected for absorption using the SADABS (**1**) and the DENZO-SMN packages (**2**). Structural solution and refinements were carried out using the SHELX suite of programs with the graphical interface X-Seed. Both structures were severely affected by the large heavy-atom content, and therefore data were not as precise as preferred. However, the connectivity of both structures is unambiguous. For compound **1**, all Bi atoms and salicylate ligands bound in the central core were refined anisotropically, while all other non-H atoms were refined isotropically. Examination of the anisotropic displacement parameters suggested rotational disorder in some of the aromatic rings, but this could not be adequately modeled with the current data. One aromatic ring C(37)–C(42) and some of the lattice acetone molecules were restrained with optimal geometries. For compound **2**, only the Bi atoms could sustain anisotropic refinement, and therefore all other non-H atoms were refined isotropically. Crystal data for **1**: C₂₄₂H₂₅₄Bi₃₈O₁₄₄, *M*_r = 13 407.86, 0.13 × 0.10 × 0.10 mm, orthorhombic, space group *Pbca* (No. 61), *a* = 31.302(1), *b* = 30.795(1), *c* = 31.584(1) Å, *V* = 30 409(11) Å³, *Z* = 4, ρ_{calcd} = 2.928 g cm⁻³, *F*₀₀₀ = 24 048, μ = 21.994 mm⁻¹, 2 θ_{max} = 55.0°, 172 443 reflections collected, 34 804 unique (*R*_{int} = 0.108). Final GOF = 1.010, *R*₁ = 0.0490, *wR*₂ = 0.0871, *R* indices based on 21 680 reflections with *I* > 2 σ (*I*) (refinement on *F*²) *R*₁ = 0.107, *wR*₂ = 0.106 (all data). Crystal data for **2**: C₂₂₁H₂₀₇Bi₁₈O₁₀₇, *M*_r = 8336.51, 0.20 × 0.15 × 0.15 mm, triclinic, space group *P* $\bar{1}$ (No. 2), *a* = 16.485(3), *b* = 28.643(6), *c* = 28.853(6) Å, α = 68.99(3), β = 79.27(3), γ = 75.78(3)°, *V* = 12 256(4) Å³, *Z* = 2, ρ_{calcd} = 2.259 g cm⁻³, *F*₀₀₀ = 7766, μ = 12.966 mm⁻¹, 2 θ_{max} = 56.5°, 178 890 reflections collected, 57 507 unique (*R*_{int} = 0.2130). Final GOF = 0.941, *R*₁ = 0.0891, *wR*₂ = 0.1440, *R* indices based on 24 017 reflections with *I* > 2 σ (*I*) (refinement on *F*²), 1536 parameters, 0 restraints. CCDC-289350 for compound **1** and CCDC-289351 for compound **2** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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