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Towards a molecular model for bismuth(III) subsalicylate. Synthesis and solid-state structure of $[Bi(Hsal)_3(bipy)(C_7H_8]_2$ and $[Bi(Hsal)(sal)(1,10\text{-phenanthroline})(C_7H_8]_2$

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The synthesis and characterization of the first bismuth salicylate complexes, stabilized by chelating amine ligands, offers the possibility for detailed investigation of molecular precursors of the biologically significant compound bismuth subsalicylate (BSS).

Salicylate and other hydroxycarboxylic acid complexes of bismuth, most often in their hydrolyzed form as colloidal suspensions, have been shown to possess an extensive biological chemistry.[1,2] Bismuth subsalicylate—'BiO(Hsal)' (BSS)—is used to treat disorders of the upper and lower digestive tract including gastral mucosal lesions, gastric ulcers and diarrhea[2] and is effective against infections of *H. pylori*, *E. coli*, *S. aureus*, *K. pneumonia* and eterococci,[3–5] which often occur in conjunction with the previously mentioned conditions. Reports have appeared showing that coadministration of colloidal bismuth compounds with platinum anticancer drugs significantly reduces renal and nephrotoxicity from the chemotherapeutic agents.[6,7]

The development of the carboxylate chemistry of bismuth is hindered by the Lewis acidity of the metal center and its ability to easily expand its coordination sphere.[8] This, coupled with the lability of the ligands often results in difficult to control hydrolysis of molecular complexes and the formation of the 'BiO^+' cation,[9] or in the formation of coordination oligomers or polymers, which are difficult to characterize. The sensitivity of bismuth carboxylate complexes to water has been attenuated in several ways including the incorporation of N, O or S donor atoms into coordinating ligands, which may mimic sites bound by bismuth in biologically active environments.[8,10–14] From these, several thiocarboxylate complexes,[9,15,16] including thiosalicylate[17] or methylthiosalicylate ligands,[18] have emerged as potential platforms for the study of biologically active bismuth-based complexes. However there have been no studies reported of the chemistry and structure of bismuth salicylate complexes that might serve as a molecular model for biologically active BSS. Consequently, the mechanism by which these compounds function in the body is still largely speculative.

We have explored the reactivity of bismuth salicylate and have previously reported that a pale-yellow complex analyzing as bismuth salicylate, $[Bi(Hsal)_3]_n$ (Hsal = $O_2CC_6H_4$-2-OH) (**1**), can be generated from the reaction of triphenyl bismuth with a stoichiometric amount of salicylic acid in refluxing toluene in practically quantitative yield.[19] The salicylate complex is stable in the solid-state, but will slowly hydrolyze—presumably to BSS—when exposed to moist air in solution. We have found that the molecular complex '$Bi(Hsal)_3$' can be successfully trapped and characterized through reaction with 2,2′-bipyridine (bipy) or with 1,10-phenanthroline (phen) in a 1:1 ratio in methanol. These two ligands were selected due to their exceptionally high affinity for and ability to form stable adducts with bismuth(III).[8] We have found that reactions using other amine ligands such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), pyridine, and ethylenediamine, or other coordinating ligands such as THF or dimethylsulfide have all failed so far to produce tractable products by this method.

The structures of the bismuth salicylate complexes are found to be dependant upon the stabilizing amine ligand that is employed in the synthesis. The reaction of $\{Bi(Hsal)_3\}_n$ with bipyridine resulted in the formation of $[Bi(Hsal)_3(bipy)\cdot C_7H_8]_2$ (**2**) (Fig. 1).† This complex consists of three salicylate ligands coordinated through the carboxylate group to form a four-membered chelate ring (Fig. 3-I).‡ One of the salicylate ligands bridges between two metal centers, bringing the coordination number of the bismuth to nine and assembling the dimer that is observed in the solid-state (Fig. 3-II). In contrast, the use of phenanthroline in the synthesis resulted instead in the elimination of a molecule of salicylic acid and isolation of $[Bi(Hsal)(sal)(phen)\cdot C_7H_8]_2$ (**3**) (Fig. 2). In this case, the compound contains one salicylate ligand which is coordinated to the metal center through the carboxylate group in a fashion similar to that observed in **2** and another salicylate ligand coordinated through both phenolic and carboxylic oxygen atoms to form a five-membered chelate ring (Fig. 3-III). The carboxylate group of the doubly deprotonated salicylate ligand bridges between two metal centers, bringing the coorination number of the metal to seven and completing the dimeric structure that is obseved in the solid state.

The differences in reactivity of the two amine ligands with the bismuth center is suprising. However, the observations from the solid-state structures of these two molecules are consistent with previous reports which suggest that 1:1 adducts of bismuth and 1,10-phenanthroline, when stable, require lower coordination numbers than do 1:1 adducts of bismuth and 2,2′-bipyridine.[20] This appears to result in the ligand elimination reactions that form the novel salicylate coordination mode (Fig. 3-III) observed in **3**.

The bismuth–carboxylate oxygen and bismuth–nitrogen bond lengths in **2** and **3** range from 2.233(4) to 2.906(6) Å and from 2.383(4) to 2.609(4) Å, respectively, and fall within the

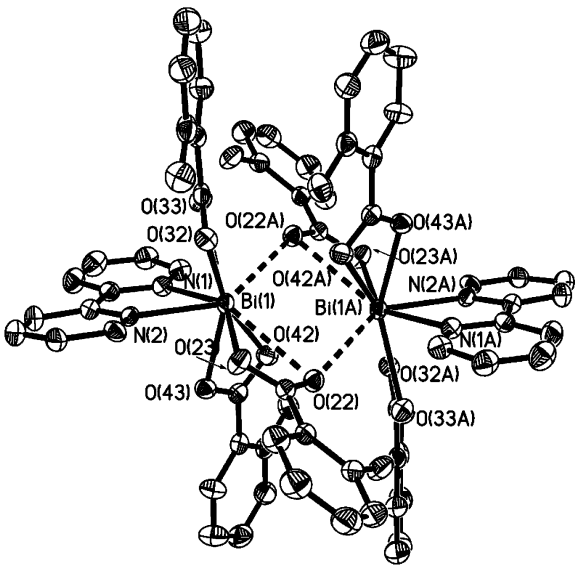

Fig. 1 ORTEP representation of **2**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity. Bridging interactions are represented by broken lines.

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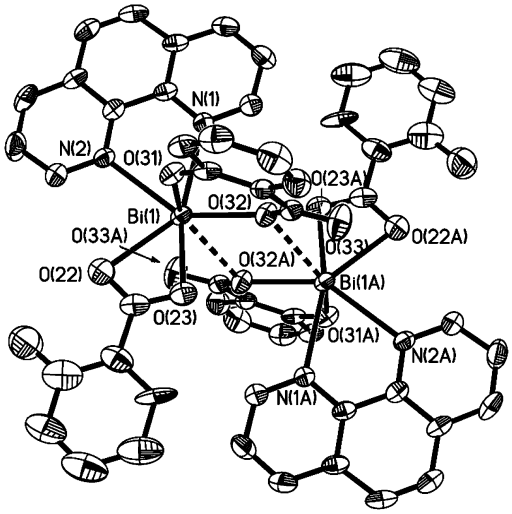

Fig. 2 Coordination modes of salicylic acid between one and two metal centers observed in **2** and **3**.

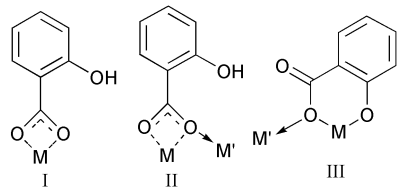

Fig. 3 ORTEP representation of **3**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity. Bridging interactions are represented by broken lines.

distances accepted for similar conplexes.[8,20,21] The phenolic oxygen–bismuth bond distance in **3** is 2.117(4) Å and agrees well with that reported for other bismuth(III) phenoxide complexes.[21] As expected, the bridging metal–oxygen bond distances are longer than the distances of the terminal ligands. The metal–oxygen interactions within a single terminal salicylate ligand are generally asymmetric with one metal–oxygen bond being significantly longer than the other.

The compounds developed in this work display unique structural characteristics and remarkable stability, making them a viable platform for the study of biologically active bismuth(III) coordination complexes. In addition, the procedures developed in this work present an accessible, high yield route to the synthesis and isolation of potentially biologically significant bismuth carboxylate compounds.

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Notes and references

† The synthesis of the complexes discussed in this work is similar, so only a general procedure is outlined here. A methanolic solution of **1** was carefully layered with a methanolic solution of 2,2′-bipyridine. The colorless solution was allowed to stand undisturbed at room temperature for 24 h, during which time large colorless crystals deposited in the reaction flask. The solid was collected by filtration, washed with diethyl ether and dried briefly under reduced pressure to give **2**·$2C_7H_8$ in 96% yield. Elemental analysis (%). Calc. for $C_{31}H_{26}N_2O_9Bi·0.4C_7H_8$: C 49.73, H 3.60, N 3.43. Found for **2**: C 49.46, H 3.33, N 3.44. ^{1}H NMR (d^6-DMSO): δ 6.81 (s, 6H, sal), 7.36 (s, 3H, sal), 7.48 (m, 2H, bipy), 7.71 (s, 3H, sal), 7.95 (td, 2H, bipy, J^1_{HH} 7.52, J^2_{HH} 1.80 Hz), 8.40 (dt, 2H, bipy, J^1_{HH} 7.96, J^2_{HH} 0.98 Hz), 8.72 (d, 2H, bipy, J_{HH} 4.67 Hz). ^{13}C{^{1}H} NMR (d^6-DMSO): δ 117.36 (sal), 118.33 (sal), 120.78 (bipy), 124.48 (bipy), 130.66 (sal), 134.03 (sal), 137.68 (bipy), 149.36 (bipy), 155.05 (bipy), 160.79 (COH), 174.21 (COO); mp 165–168 °C. **3**·$2C_7H_8$, 85% yield. Elemental analysis (%). Calc. for $C_{26}H_{20}N_2O_6Bi·0.1C_7H_8$: C 47.77, H 2.67, N 4.17. Found for **3**: C 47.62, H 2.71, N 3.97. ^{1}H NMR (d^6-DMSO): δ 6.72 (s, 4H, sal), 7.34 (s, 2H, sal), 7.65 (s, 2H, sal), 8.06 (dd, 2H, phen, J^1_{HH} 7.7, J^2_{HH} 3.2 Hz), 8.11 (s, 2H, phen), 8.75 (d, 2H, phen, J_{HH} 7.9 Hz), 9.46 (s, 2H, phen). ^{13}C{^{1}H} NMR (d^6-DMSO) δ 117.61 (sal), 118.88 (sal), 125.32 (phen), 128.01 (phen), 130.25 (phen), 131.62 (sal), 134.44 (sal), 139.09 (phen), 145.15 (phen), 150.95 (phen), 161.56 (COH), 174.92 (COO); mp 304–307 °C.

‡ Crystal structure determinations of **2** and **3**: $C_{62}H_{46}N_4O_{18}Bi_2·2C_7H_8$ (**2**), M = 1737.26, colorless plate, 0.3 × 0.27 × 0.15 mm, triclinic, $P\bar{1}$ (no. 2), a = 10.830(2), b = 12.489(3), c = 14.319(3) Å, α = 87.22(3), β = 81.65(3), γ = 64.33(3)°, V = 1727.0(6) Å^3, Z = 1, D_c = 1.670 g cm^{-3}, 7438 measured reflections, 4920 unique reflections (R_{int} = 0.0294). $C_{52}H_{34}N_4O_{12}Bi_2·2C_7H_8$ (**3**), M = 1507.04, colorless plate, 0.32 × 0.25 × 0.11 mm^3, monoclinic, $P2_1/n$ (no. 14), a = 10.022(2), b = 24.530(5), c = 12.195(3) Å, β = 107.167(4)°, V = 2864.3(10) Å^3, Z = 2, D_c = 1.747 g cm^{-3}, 12698 measured reflections, 4113 unique reflections (R_{int} = 0.0464). Intensities were measured on Bruker SMART 1000 diffractometer using a CCD area detector. Mo-Kα radiation (λ = 0.71073Å) was used in the experiments. Empirical absorption correction using the program SADABS was applied to the data (μ = 51.64 cm^{-1} (**2**), 62.04 cm^{-1} (**3**)).[22] The structures were solved using direct methods and refined against F^2 with the SHELXTL software package.[23] All non-hydrogen atoms in the complexes were refined anisotropically. Hydrogen atoms were included in calculated positions and allowed to ride on the adjacent carbon during refinement. Final refinement values for **2** are R ($I > 2\sigma(I)$): $R1$ = 0.0272, wR_2 = 0.0623. R (all data): $R1$ = 0.0328, wR_2 = 0.0644, S = 0.987. Residual electron density is between −0.753 and 0.800 e$^-$ Å^{-3}. Final refinement values for **3** are R ($I > 2\sigma(I)$): $R1$ = 0.0281, wR_2 = 0.0616. R (all data): $R1$ = 0.0422, wR_2 = 0.0652, S = 0.973. Residual electron density is between −0.395 and 0.601 e$^-$ Å^{-3}. Figures presented in this publication were created with the programs in the SHELXTL software package.[23] CCDC 194668 and 194669. See http://www.rsc.org/suppdata/cc/b2/b209188g/ for crystallographic files in CIF or other electronic format.

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