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Bismuth(III) Saccharinate and Thiosaccharinate Complexes and the Effect of Ligand Substitution on Their Activity against *Helicobacter pylori*

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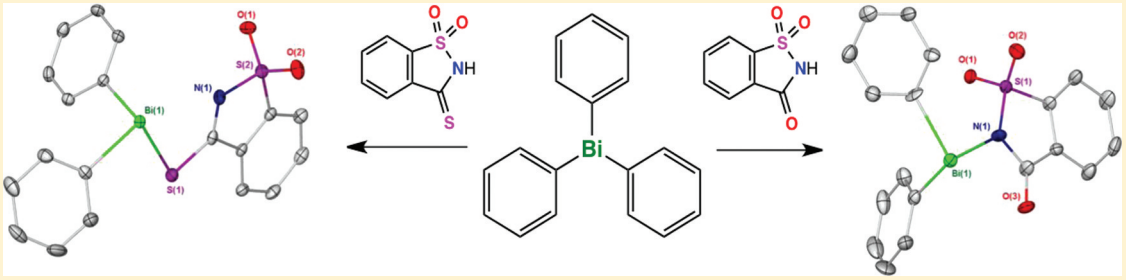

ABSTRACT: Five bismuth(III) saccharinate and thiosaccharinate complexes, $[Ph_2Bi(sac)]_\infty$ **1**, $[Bi(sac)_3]_n$ **2**, $[Ph_2Bi(tsac)]_\infty$ **4**, $[PhBi(tsac)_2]_n$ **5**, $[Bi(tsac)_3]_n$ **6** (sacH = saccharin, tsacH = thiosaccharin), have been synthesized and fully characterized. The tendency for ligand redistribution in $[Ph_2Bi(sac)]_\infty$ has been investigated in solution by NMR spectroscopy. The structures of $[Ph_2Bi(sac)]_\infty$ **1** and $[Ph_2Bi(tsac)]_\infty$ **4** have been confirmed by X-ray crystallography. In $Ph_2Bi(sac)$ the sac ligand is bound to a four-coordinate bismuth center via its imino nitrogen atom with an accompanying long-range Bi−O interaction. However, in the structure of $[Ph_2Bi(tsac)]_\infty$ the ligand is σ-bound through the exocyclic sulfur atom, giving a thiolate complex, confirming the more thiophilic nature of bismuth(III). Both complexes consist of polymeric chain structures with formally four-coordinated bismuth atoms. The complexes were assessed for their activity against *H. pylori*. The activity is both ligand dependent and sensitive to the degree of ligand substitution. The saccharinate complexes, **1** and **2**, show activity comparable with standard tris-carboxylato bismuth(III) compounds, 6.25 μg/mL, while the activity of the thiolato complexes, **4**−**6**, increases dramatically on increasing the number of thiolate groups from one to three (range 50−6.25 μg/mL). Saccharin, thiosaccharin, and $BiPh_3$ were found to be inactive.

INTRODUCTION

That bismuth is considered to be relatively benign and of low systemic toxicity in humans means that the metal and its compounds are currently attracting considerable attention in materials, environmental, and sustainable chemistry, and though not as dramatic, there has also been some resurgence of interest in its biological and medicinal chemistry.[1−3] The predominant use of bismuth compounds (bismuth subsalicylate, colloidal bismuth citrate) is in treating and eradicating *Helicobacter pylori*, the bacterium responsible for gastritis, peptic and duodenal ulcers, and gastric cancers.[4−8] The role of bismuth in this arena is becoming more important as resistance rates toward triple therapies, combining a proton pump inhibitor (e.g., omeprazole) with a combination of regular antibiotics, including clarithromycin, increases.[9,10] There has been no evidence of resistance toward the bismuth compounds, and they have the advantage of not requiring a neutral stomach pH to be effective.

In addition, evidence is accumulating that metal−organic and organometallic bismuth compounds generally show good *in vivo* and *in vitro* antimicrobial and antitumor activity.[1,11−16]

To be able to fully exploit the potential bismuth compounds have in protective and therapeutic applications, we need to understand more about the coordination chemistry of the compounds, their structure, solubility, and stability, and their activity and behavior in a biological environment. Currently, our knowledge, when compared to related metals and their complexes, is poorly developed.

Over the past few years we have been successful in developing and describing reproducible and high-yielding solvent-free and solvent-mediated methods to obtain a range of homoleptic and heteroleptic bismuth(III) thiolates,[17] carboxylates,[18−21] sulfonates,[19,22] and alkoxides.[23] The pure

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tris-substituted bismuth carboxylates (including NSAID derivatives) and sulfonate complexes generally display a greater activity against *Helicobacter pylori* (minimum inhibitory concentration (MIC) 6.25 μg/mL) than commercial compounds—BSS (12.5 μg/mL), RBC (8 μg/mL), CBS (12.5 μg/mL)—even in the case where only one sulfonate ligand is present, e.g., $[Ph_2Bi(O_3S\text{-Tolyl})]_\infty$.[22]

While sulfonic acids provide ligands that show little or no toxic effects, it is still desirable to search for ligands that are known to be regarded as safe for use in humans. Combining this with a desire to explore a new class of bismuth coordination compounds, we turned our attention to saccharin and thiosaccharin. Saccharin (*o*-sulfobenzimide), Figure 1, is

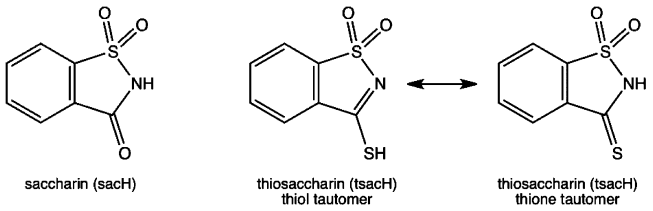

Figure 1. Structures of saccharin and thiosaccharin.

one of the most widely used artificial sweetening agents.[24] Though known for over 100 years, it fell out of favor as studies in rats seemed to suggest a link to some stomach cancers. This was later shown to be species-specific, and saccharin regained the status of being nonharmful for humans.[25−27] More generally it has been suggested as having potential in chelation therapy,[28] as an antidote for metal poisoning,[29] and because of its weak acidity may be useful as a salt former in enhancing the solubility of certain drugs.[30]

Many transition metal complexes of saccharin and thiosaccharin have been reported, though complexes with p-block metals remain limited to Pb, Sn, and Tl.[31] Interestingly, the Zn, Cu, Ce, and Pb complexes of saccharin have all shown an inhibitory effect, *in vitro*, over carbonic anhydrase.[32,33] The biological chemistry of thiosaccharin and its derivatives is less developed, though in one study it is claimed that they exhibit powerful antifungal activity.[34] While the coordination chemistry of saccharin and thiosaccharin has been the subject of ongoing study, the bioinorganic chemistry remains poorly developed and is an area that deserves greater attention in terms of antimicrobial and therapeutic potential.

The saccharinate and thiosaccarinate anions have heteroatoms that are able to form ionic, covalent, or dative bonds with metals and can thus act as polyfunctional complexing agents. The M−N interaction is most common in transition metal complexes, while M−O or M−S bonds dominate for alkali, alkaline-earth, and inner-transition metals. For p-block metal complexes these ligands show monodentate (through S or O atoms), bidentate (S/O and N), or bridging (through N and O/S) bonding modes.[31]

In this paper we describe the synthesis of five new bismuth(III) compounds containing saccharinate and thiosaccharinate ligands, $[Ph_2Bi(sac)]_\infty$ **1**, $[Bi(sac)_3]_n$ **2**, $[Ph_2Bi(tsac)]_\infty$ **4**, $[PhBi(tsac)_2]_n$ **5**, and $[Bi(tsac)_3]_n$ **6**, formed through solvent-mediated and solvent-free methods. We also describe their composition in the solid and solution states, a tendency for ligand rearrangement in solution, and a ligand-based sensitivity in their activity toward the bacterium *H. pylori*.

RESULTS AND DISCUSSION

Saccharin. Saccharinate complexes of bismuth(III) were synthesized by solvent-mediated and solvent-free reactions. The solvent-mediated reactions were conducted in ethanol at reflux temperature for a period of 8−12 h. The solvent-free reactions involved heating a mixture of the reactants, which had been ground together, to a temperature of 200 °C for 2 h.

The solvent-mediated reaction of saccharin (sacH) with triphenylbismuth always produced the mono-substituted complex, $[Ph_2Bi(sac)]_\infty$ **1**, irrespective of the ratio of the reactants used or the reaction temperature (Scheme 1). In

Scheme 1. Treatment of Saccharin (n = 1−3) with $BiPh_3$ in Ethanol under Reflux[a]

$$n\ sacH + BiPh_3 \longrightarrow \underset{\mathbf{1}}{Ph_2Bi(sac)} + (n\text{-}1)\ sacH + PhH$$

[a] t = 8−12 h.

contrast, complex **1** could also be produced through the solvent-free reaction of sacH with $BiPh_3$ in a 1:1 ratio, while the tris-substituted saccharinate product, $[Bi(sac)_3]_n$ **2**, was obtained when the reaction was conducted solvent-free using a 3:1 ratio (Scheme 2).

Scheme 2. Reaction of Saccharin with $BiPh_3$ in a 3:1 Ratio under Solvent-Free Conditions[a]

$$3\ sacH + BiPh_3 \longrightarrow \underset{\mathbf{2}}{Bi(sac)_3} + 3\ PhH$$

[a] T = 200 °C, t = 2 h.

Neither the solvent-mediated nor the solvent-free reactions produced the expected bis-substituted saccharinate product, $[PhBi(sac)_2]_n$ **3**, from a 2:1 (sacH:$BiPh_3$) reaction stoichiometry. Therefore, the reaction was attempted using a simple metathesis route involving the treatment of $PhBiCl_2$ with two equivalents of sodium saccharinate (sacNa). However, the reaction in toluene did not produce **3** as expected; instead a mixture of $[Bi(sac)_3]_n$ and $BiPh_3$ was obtained in 2:1 ratio. Since sacNa is soluble only in water and $PhBiCl_2$ decomposes in water, the metathesis reaction has to be conducted under heterogeneous conditions. Using toluene as the solvent, in which $PhBiCl_2$ is insoluble, means any metathesis reaction is slow, and hence the ultimate formation of $[Bi(sac)_3]_n$ and $BiPh_3$ can be rationalized as resulting either from the rearrangement of $PhBiCl_2$ into $BiCl_3$ and $BiPh_3$ and then subsequent reaction with sacNa or from ligand rearrangement of $PhBi(sac)_2$. Most likely both these processes occur concurrently.

To examine further the lability of the sac ligands in the heteroleptic complexes, a sample of **1** was dissolved in d_6-DMSO, and NMR spectra were recorded at different time intervals: immediately and after several hours, days, or months. The rearrangement is illustrated in Scheme 3. The spectra, shown in Figure 2 (t = 0 and 24 h), show clearly the formation of **3** (*o*-Ph resonance at δ 8.75) and $BiPh_3$ (*p*-Ph resonance at δ 7.30) from **1**. The amount of **3** formed increased on standing and reached equilibrium after approximately 13 days. Using integration of the various *o*-Ph and *p*-Ph resonances, the equilibrium constant for the formation of **3** and $BiPh_3$ from **1** is calculated to be 0.25, reflecting the expected stoichiometric ratios (Scheme 3).

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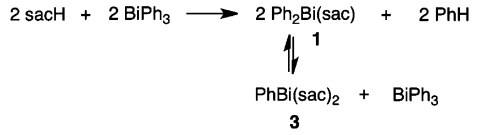
Scheme 3. Ligand Redistribution of 1 in d_6-DMSO to 3 and $BiPh_3$



Attempts were made using a variety of solvents and solvent mixtures (including ethanol, acetone, DMSO, and DMF) to obtain crystals of **3** through cocrystallization with **1** and/or $BiPh_3$. Unfortunately, this proved unsuccessful in all solvents tried due to the preferential precipitation of **1** and, we believe, a consequent shift in the equilibrium away from **3**.

Thiosaccharin. The 1:1 and 2:1 reactions of thiosaccharin with $BiPh_3$ under reflux in ethanol produced the expected products, $[Ph_2Bi(tsac)]_\infty$ **4** and $[PhBi(tsac)_2]_n$ **5**, respectively, as depicted in Scheme 4.

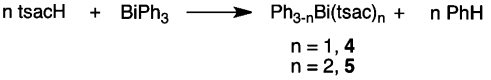
In contrast, the 3:1 reaction did not give the expected product, $[Bi(tsac)_3]_n$ **6**, but instead produced a mixture of **4** and **5**. As such, an alternative synthetic approach using the stronger base $Bi(^tOBu)_3$ was employed (Scheme 5). A THF solution of thiosaccharin was added to a THF solution of $Bi(^tOBu)_3$, under dry nitrogen and already cooled to −80 °C. The reaction mixture was allowed to warm slowly to room temperature, giving the tris-substituted thiosaccharinate product **6** as a pale orange solid in high yield.

^1H and ^{13}C NMR spectra were obtained on **4**–**6** in d_6-DMSO. The spectra showed all the expected chemical shifts relating to the Ph and tsac ligands with no evidence of the facile ligand rearrangement processes observed with the analogous sac complexes, highlighting the greater kinetic stability of the Bi–S bond.

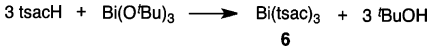
Table 1. ^1H NMR Shifts, in ppm, of Ph Protons in 1, 3, and $BiPh_3$

compound	*o*-H	*m*-H	*p*-H
$BiPh_3$	7.75	7.42	7.30
$[Ph_2Bi(sac)]_\infty$ **1**	8.29	7.74	7.40
$[PhBi(sac)_2]_n$ **3**	8.75	8.05	7.40

Scheme 4. Treatment of Thiosaccharin (n = 1, 2) with $BiPh_3$ in Ethanol under Reflux (t = 8–12 h), Giving Compounds 4 and 5



Scheme 5. Reaction of Thiosaccharin with Bismuth *tert*-Butoxide in a 3:1 Ratio in THF, N_2[a]



[a] T = −80 °C to RT, t = 12 h.

Infrared Spectroscopy. The absorption bands corresponding to N–H bond stretching and bending in saccharin (2681 and 1591 cm^{-1}) and in thiosaccharin (3341 and 1318 cm^{-1}) are absent in the IR spectra of the corresponding bismuth complexes, indicating deprotonation of the acid from N–H. A summary of the main absorption bands for each complex and their assignments is given in Table 2.

Both bismuth saccharinate complexes show a shift in the carbonyl stretching vibration from 1717 cm^{-1} in the free acid to

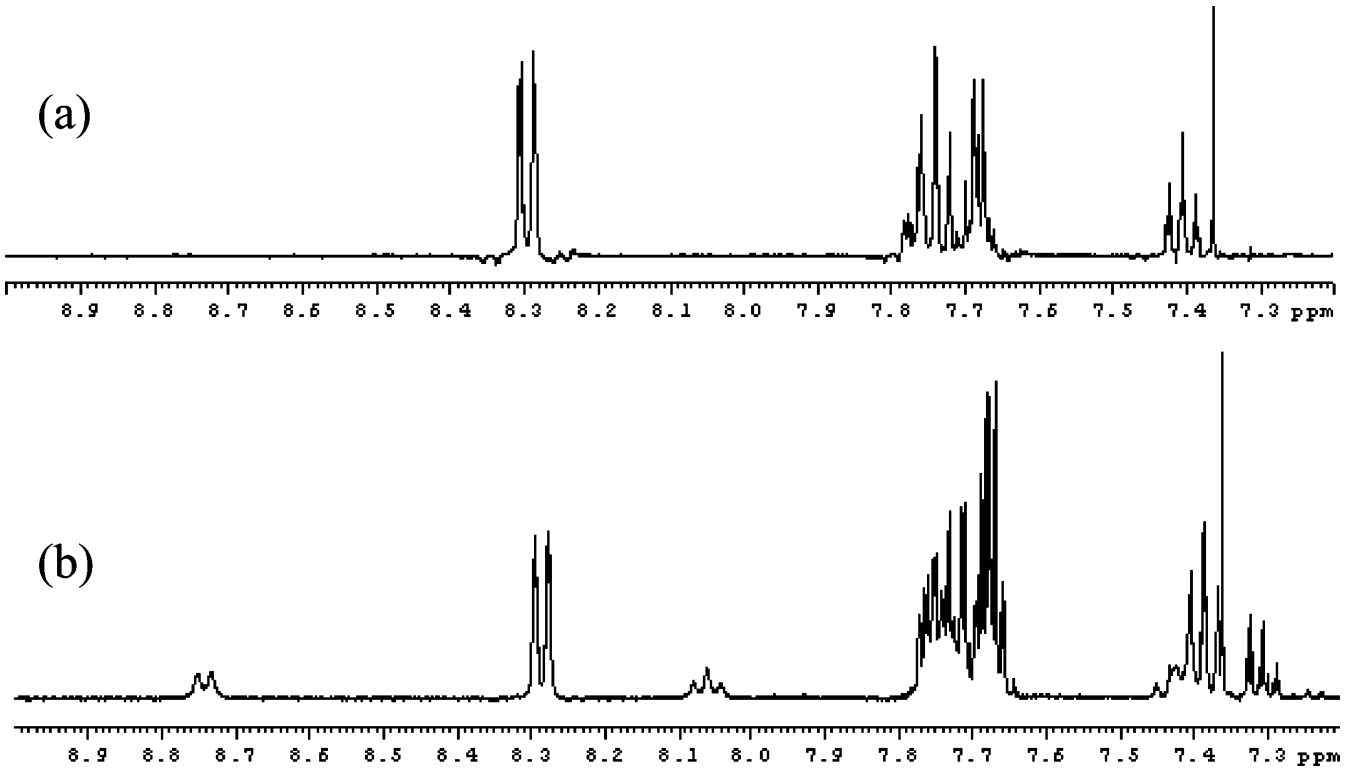


Figure 2. ^1H NMR spectra showing gradual rearrangement of $Ph_2Bi(sac)$ **1** into $PhBi(sac)_2$ **3** in d_6-DMSO: (a) 0 h, (b) 24 h. Chemical shift assignments are given in Table 1.

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Table 2. Summary of IR Bands (cm^{-1}) and Assignments

	saccharin	1	2	thiosaccharin	4	5	6
ν(NH)	2681 s			3341 s			
ν(C═O)	1716 s	1689 m	1606 s				
$\nu_{as}(SO_2)$	1335 m	1270 m	1257 m	1376 m	1324 m	1324 m	1325 m
δ(NH)	1591 s			1318 s			
ν(CN)	1296 m	1337 m	1337 m	1247 m	1420 m	1420 m	1419 m
$\nu_{s}(SO_2)$	1177 m	1143 m	1146 m	1156 m	1156 m	1156 m	1156 m
ν(CS)				1039 m	1005 m	1003 m	1001 m
ν(NS)	900 w	783 w	772 w	817 w	805 w	805 w	805 w

1689 cm^{-1} in $[Ph_2Bi(sac)]_\infty$ and 1606 cm^{-1} in $[Bi(sac)_3]_n$. The relatively small bathochromic shift for $[Ph_2Bi(sac)]_\infty$ suggests that delocalization and subsequent interaction with the Bi(III) center is not substantial, subsequently supported by X-ray crystallography (see below). A stronger chelate is certainly suggested for the tris-substituted complex, $[Bi(sac)_3]_n$, although the higher frequency shift (Δ 41 cm^{-1}) for the C−N bond is identical for both complexes.

When compared with free thiosaccharin,[35] the stretching mode assigned to C═S shifts to lower frequency in the three bismuth complexes by an average of 36 cm^{-1}, the shift gradually increasing as substitution by thiosaccharinate ligands increases. Conversely, the C−N stretching mode shifts to higher wavenumbers by ca. 27 cm^{-1}, indicating an increase in the bond order. Taken together, these observations support the thiolate nature of the ligand in its bonding with Bi(III).

The stretching vibrations of the SO_2 groups are expected to appear at lower wavenumbers in both bismuth saccharinate and thiosaccharinate complexes due to increased S−O bond lengths as a result of the interaction of this group with the bismuth(III) center. This expectation can be seen clearly in the asymmetric SO_2 stretching modes. Bismuth complexes of saccharin showed a shift from 1335 cm^{-1} to 1270 cm^{-1} (in **1**) and 1257 cm^{-1} (in **3**), whereas bismuth complexes of thiosaccharin showed a shift of 1376 cm^{-1} to 1324/1325 cm^{-1}, indicating a stronger (S═)O−Bi interaction in bismuth saccharinate complexes than in bismuth thiosaccharinate complexes.

Crystallography. Crystallization of $[Ph_2Bi(sac)]_\infty$ **1** from ethanol produces well-formed, colorless crystals. Unfortunately obtaining good-quality diffraction data proved challenging. Several data sets were collected on crystals from a number of different batches using a standard CCD diffractometer, but all showed evidence of twinning. The final data presented here were collected on a single, but very small, crystal using the high-intensity radiation available at the Australian Synchrotron.

The complex represents the first crystallographically characterized bismuth(III) acid-amide derivative, and the structure is shown in Figures 3 and 4 with selected bond distances and angles in Table 3. The complex crystallizes in an orthorhombic crystal system with space group $Pna2_1$. The saccharinate ligand is attached to the bismuth(III) center primarily through its imino N^- atom. In gross structural terms the complex forms a polymer through alternate bonding of the central bismuth atom to the imino N^- and to a single O of the SO_2 moiety of a second ligand, providing for an overall (κ^2-*N,O*) zigzag conformation. A similar bonding pattern is seen in the heteroleptic Sn complex $[Ph_3Sn(sac)]_\infty$.[36]

The overall coordination number around the bismuth center is formally four, but is raised to five when long-range intramolecular Bi−O(═C) interactions of 3.22 Å are included. The Bi−N bond distance of 2.353(4) Å is only slightly longer

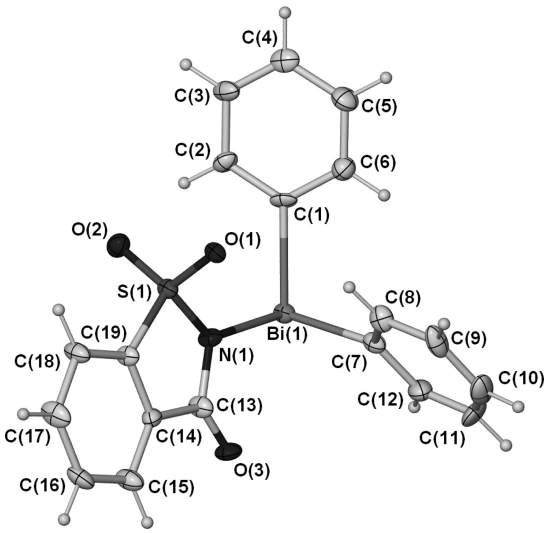

Figure 3. Molecular structure of $[Ph_2Bi(sac)]_\infty$ **1** with non-hydrogen atoms represented by 50% thermal ellipsoids and hydrogen atoms as spheres of arbitrary size. Only the crystallographically unique component is shown.

than those typically observed in homoleptic bismuth(III) amides, e.g., 2.20(2) Å (av) in $[Bi(NPh_2)_3]$,[37] and compensates for the relatively weak C═O···Bi interaction, which while long is still comparable with similar neutral chelating bonds observed in bismuth(III) carboxylates.[18,19,38]

The Pb(II) complex $[Pb(sac)_2]\cdot H_2O$[39] has Pb^{2+} in an eight-coordinate environment, contrasting with the low coordination number for Bi^{3+} in **1**, and shows definite N and O(═C) coordination to the metal, demonstrated by the more central location of the Pb ion between the chelating atoms: in **1**, the C(13)−N(1)−Bi(1) angle of 114.6(3)° (cf. C−N−Pb 87.64° in $[Pb(sac)_2]\cdot H_2O$) indicates that rather than a formal chelate the proximity of the O(═C) within a recognized Bi−O bonding distance may be simply a result of ligand geometry.

The sulfonyl (S═)O−Bi bond distance is 2.605(4) Å and is located *trans* to that formed with the imino N^- atom, providing an almost linear N(1)−Bi(1)−O(1) bond angle of 170.2(2)°. The short distance no doubt reflects the low coordination environment of the bismuth(III) center. Only three other structures allow for a comparison of this interaction; the most similar is in the organometallic complex $[(PhSO_2{}^tBu)Bi(Tol)Cl]$,[40] which shows a (S═)O−Bi distance of 2.592(5) Å and in which Bi(III) is also four-coordinate, while longer bonds are found in the analogous complex $[(PhSO_2{}^tBu)_2Bi(Tol)]$,[40] 2.914(6) Å, and in (3-sulfanilamido-6-methoxypyridazine)-bismuth(III) trichloride, 3.09(2) Å.[41]

Crystallization of $[Ph_2Bi(tsac)]_\infty$ **4** from ethanol gave orange cubic crystals, which proved suitable for single-crystal X-ray

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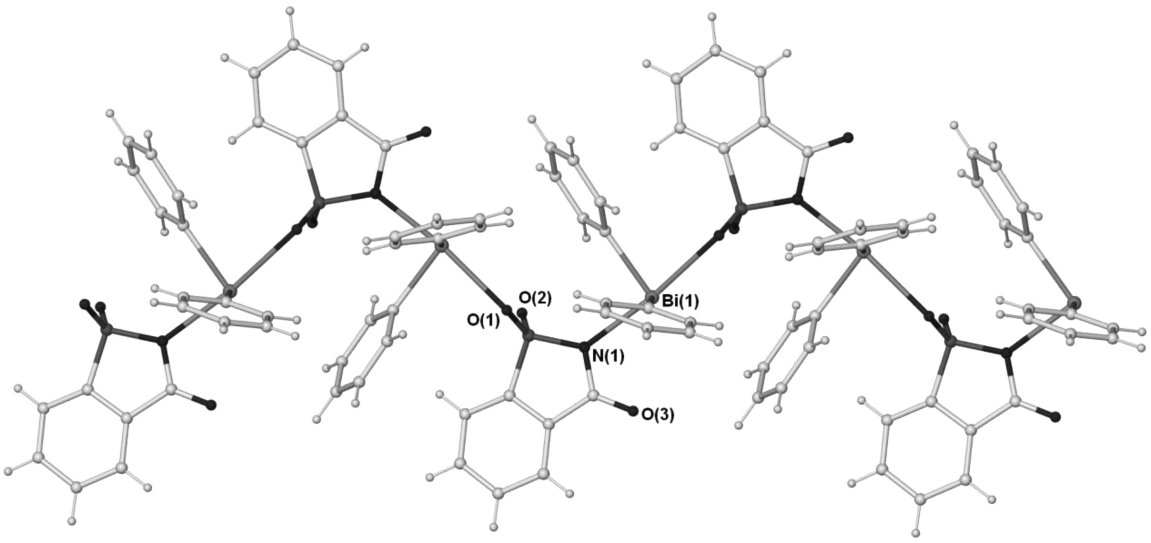

Figure 4. Polymeric structure of $[Ph_2Bi(sac)]_\infty$ **1**.

Table 3. Selected Bond Distances (Å) and Angles (deg) for Compounds 1 and 4

	$[Ph_2Bi(sac)]_\infty$ **1**	$[Ph_2Bi(tsac)]_\infty$ **4**
Bi(1)−C(1)	2.256(4)	2.233(3)
Bi(1)−C(7)	2.245(9)	2.243(3)
Bi(1)−N(1)/S(1)	2.353(4)	2.6399(7)
Bi(1)−O(1)	2.605(4)	2.890(2)
C(1)−Bi(1)−C(7)	96.6(3)	94.1(1)
C(1)−Bi(1)−N(1)/S(1)	90.8(2)	90.09(7)
C(1)−Bi(1)−O(1)	83.3(2)	82.01(8)
C(7)−Bi(1)−N(1)/S(1)	89.2(2)	90.34(7)
C(7)−Bi(1)−O(1)	83.8(2)	93.72(8)
N(1)/S(1)−Bi(1)−O(1)	170.2(2)	171.35(5)

diffraction studies. The complex crystallizes in the monoclinic crystal system and in space group $P2_1/n$. The asymmetric unit is shown in Figure 5, and the polymeric chain in Figure 6, with

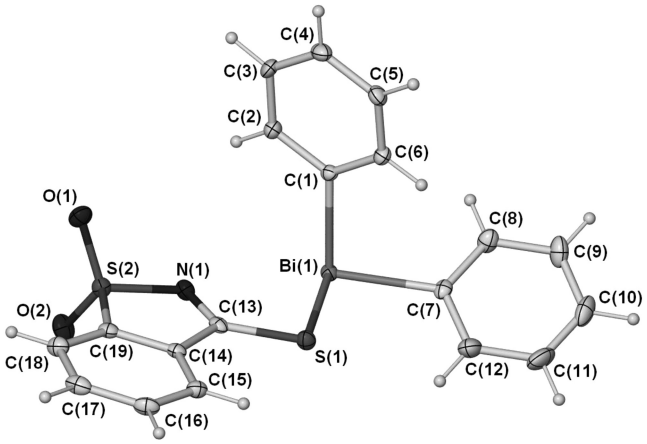

Figure 5. Molecular structure of $[Ph_2Bi(tsac)]_\infty$ **4** with non-hydrogen atoms represented by 50% thermal ellipsoids and hydrogen atoms as spheres of arbitrary size. Only the crystallographically unique component is shown.

selected bond distances and angles listed in Table 2. The complex comprises a zigzag polymeric chain with the Bi(III) centers bridging thiosaccharinate ligands, (κ^2-*S,O*), forming alternating bonds with the thiolate S^- and one of the sulfonyl O atoms. The S(1)−Bi(1)−O(1) angle is almost linear at 171.35(5)°.

In contrast to **1**, where bismuth bonds to the saccharinate ligand through the imino N^-, the replacement of the carbonyl O with S leads to **2** being classed as a bismuth thiolate, with formal attachment to the ligand being through the Bi−S_{exo} σ-bond. This is not surprising given the thiophilic nature of bismuth and earlier evidence from structural reports on a series complexes with Pb(II).[39,42] The Bi(1)−S(1) bond distance of 2.6399(7) Å is typical for bismuth thiolates,[43−46] while the sulfonyl O(1)−Bi(1) distance of 2.890(2) Å is significantly longer than in **1** and is comparable with that observed in $[(PhSO_2{}^tBu)_2Bi(Tol)]$, 2.914(6) Å.[40] The imine double bond in **2**, N(1)−C(13), is 1.303(3) Å, while C(13)−S(2) is 1.719(3) Å and displays single-bond character. These can be compared with the analogous bonds in $[Pb_2(tsac)_4(py)_4]$,[42] which show similar bond distances of 1.321(17) and 1.699(14) Å, respectively, and can be contrasted with those in the crystal thione form of thiosaccharin, which are 1.384(4) and 1.622(6) Å, respectively.[47]

More contentious is the long-range interaction of 3.143(2) Å from Bi(1) to N(1). Comparison with compounds with similar bonds indicates this to be, if real, one of the longest. Normally C═N···Bi bond lengths are found in the range 2.5−2.7 Å; for example in $[Bi(SC(Me)N^iPr)_3]$ the longest interaction is 2.738(5) Å.[48] However, the geometry would seem to suggest a genuine if weak interaction: the C(13)−S(1)−Bi(1) angle is 96.50(9)°.

Biological Testing. The *in vitro* antibacterial activity of compounds **1**, **2**, **4**−**6**, saccharin (sacH), thiosaccharin (tsacH), and $BiPh_3$ was assessed against three standard laboratory strains of *H. pylori*: B128, 251, and 26695. The MIC of each compound was established using the agar dilution method (described in the Experimental Section). The homo- and heteroleptic composition of the compounds allows an evaluation to be made on the effect of the degree and variance of substitution at the Bi(III) center and also the structural impact on changing from saccharin to thiosaccharin. The results are summarized in Table 4.

Our previous studies on heteroleptic organometallic bismuth sulfonates of composition $[Ph_2Bi(O_3SR)]_\infty$ showed that

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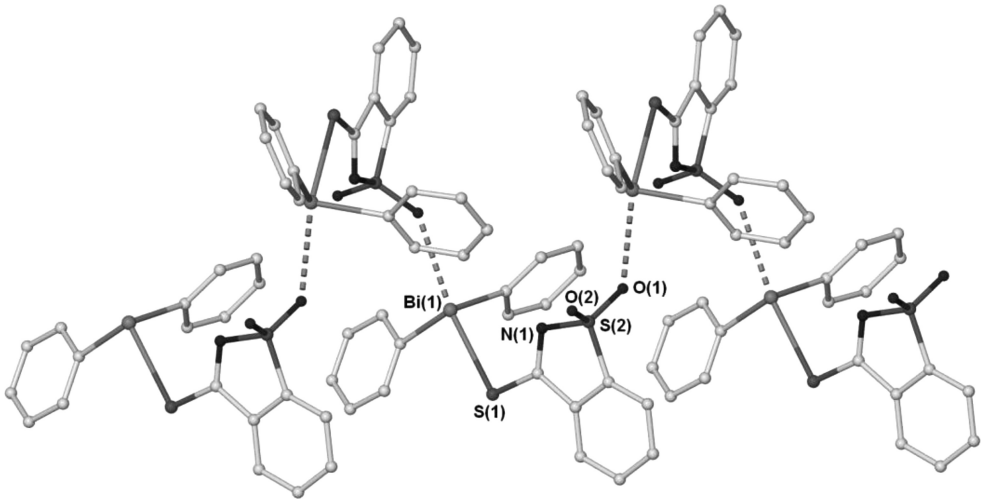

Figure 6. Polymeric structure of $[Ph_2Bi(tsac)]_\infty$ **4** with hydrogen atoms omitted for clarity.

Table 4. Minimum Inhibitory Concentrations (MIC) for Complexes, 1, 2, 4–6, $BiPh_3$, sacH, and tsacH in Their Activity against *H. pylori*

	MIC, mg/mL		
compound	(26695)	(B128)	(251)
$[Ph_2Bi(sac)]_\infty$ **1**	6.25	6.25	6.25
$[Bi(sac)_3]_n$ **2**	6.25	6.25	6.25
$[Ph_2Bi(tsac)]_\infty$ **4**	50.0	50.0	50.0
$[PhBi(tsac)_2]_n$ **5**	12.5	12.5	12.5
$[Bi(tsac)_3]_n$ **6**	6.25	6.25	6.25
sacH	inactive	inactive	inactive
tsacH	inactive	inactive	inactive
$BiPh_3$	>64	>64	>64

replacement of one Ph group with one sulfonate moiety increased the activity toward *H. pylori* significantly with the sulfonate compounds giving MICs of 6.25 μg/mL relative to $BiPh_3$ (>64 μg/mL) and the sulfonic acids, which were essentially inactive.

The activity of the two saccharinate complexes also seems insensitive to the degree of substitution, with the MIC of both $[Ph_2Bi(sac)]_\infty$ **1** and $[Bi(sac)_3]_n$ **2** found to be 6.25 μg/mL, which is also comparable with the majority of bismuth carboxylates.[19] In contrast, the thiosaccharinate complexes showed activity that is highly sensitive to the degree of substitution: $[Ph_2Bi(tsac)]_\infty$ gave an MIC of 50 μg/mL, $[PhBi(tsac)_2]_n$ 12.5 μg/mL, and $[Bi(tsac)_3]_n$ 6.25 μg/mL. Saccharin and thiosaccharin were found to be inactive within the concentrations 100–3.125 μg/mL.

These data support two previous studies indicating good activity of bismuth thiolates against *H. pylori* and also the dependency of the scale of the activity on the nature of the ligands, degree of substitution, and their binding mode(s) to the Bi(III) center. An MIC_{50} value of 3.13 μg/mL was observed for a series of three bismuth(III) thiolate complexes derived from 2-mercaptoethanol,[44] while the effect of varying the actual thiolato ligand was exemplified by a series of metallocyclic homo- and heteroleptic bismuth thiolates, which gave MIC values in the range 0.5–5.0 μg/mL.[49] These studies taken with evidence from compounds **4–6** indicate that increasing the number of Bi–S bonds improves the bactericidal activity. The more kinetically stable Bi–C bonds inhibit activity, but only in the presence of thermodynamically stable Bi–S bonds. Our evidence from the MIC values obtained for **1** and **2**, and for the series of organobismuth sulfonates $[Ph_2Bi(O_3SR)]_\infty$ studied previously,[22] indicates that more labile carboxylates and sulfonates are less sensitive to the degree of substitution and presence of more kinetically stable ligands.

CONCLUSIONS

Five new homo- and heteroleptic bismuth(III) compounds derived from saccharin and thiosaccharin have been synthesized through solvent-free and solvent-mediated methods. The compounds have been fully characterized, two by single-crystal X-ray diffraction. The mono-substituted complexes $[Ph_2Bi(sac)]_\infty$ **1** and $[Ph_2Bi(tsac)]_\infty$ **4** were generated through treatment of saccharin or thiosaccharin with $BiPh_3$ in a 1:1 ratio in ethanol at reflux. The 2:1 reaction of thiosaccharin and $BiPh_3$ at reflux in ethanol produced the bis-substituted compound $[PhBi(tsac)_2]_n$ **5**. The fully substituted complex $[Bi(sac)_3]_n$ **2** was obtained from the solvent-free combination of saccharin and $BiPh_3$ in a 3:1 ratio and heating to 200 °C. The fully substituted thiosaccharinate complex $[Bi(tsac)_3]_n$ **6** could not be synthesized from $BiPh_3$ cleanly by either solvent-free or solvent-mediated methods, and so $Bi(O^tBu)_3$ was employed as the base, producing the target compound cleanly and in high yield from the required 3:1 reaction stoichiometry. It was not possible to synthesize the "missing" complex $[PhBi(sac)_2]_n$ **3** from reactions employing the required 2:1 stoichiometry of reactants either by a solvent-free or solvent-mediated approach. NMR studies though showed that $Ph_2Bi(sac)$ **1** slowly undergoes ligand rearrangement in solution to give $PhBi(sac)_2$ **3** and $BiPh_3$; however it was not possible to obtain a pure sample of **3**. The solid-state structures of $[Ph_2Bi(sac)]_\infty$ **1** and $[Ph_2Bi(tsac)]_\infty$ **4** were determined by X-ray crystallography. Both complexes are polymers, adopting zigzag conformations with the ligands bridging Bi(III) centers through the anionic imino N and sufonyl O atoms for **1** (with a possible long-range interaction with the carbonyl O) and the exocyclic thiolato S and sulfonyl O atoms for **2**. The different coordination modes reflect the high thiophilicity of bismuth.

Both saccharin and thiosaccharin show no inhibitory activity against *H. pylori*; however their bismuth(III) compounds do. The saccharin complexes, $[Ph_2Bi(sac)]_\infty$ **1** and $[Bi(sac)_3]_n$ **2**, show an MIC of 6.25 μg/mL, indicating that the activity is not

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particularly sensitive to the degree of substitution. This is in contrast to the thiosaccharin complexes, for which the inhibitory activity is highly ligand- and substitution-dependent. The MIC values of 50 μg/mL for $[Ph_2Bi(tsac)]_\infty$ **4**, 12.5 μg/mL for $[PhBi(tsac)_2]_n$ **5**, and 6.25 μg/mL for $[Bi(tsac)_3]_n$ **6** indicate the high activity of homoleptic bismuth thiolates and also illustrates the rapid increase in activity on increasing the number of Bi−S bonds and reducing the number of kinetically stable Bi−C bonds.

EXPERIMENTAL SECTION

Triphenylbismuth was synthesized through a standard Grignard metathesis reaction from the treatment of $BiCl_3$ with PhMgBr in dried diethyl ether at 0 °C and subsequently recrystallized from ethanol. Bismuth *tert*-butoxide, $Bi(O^tBu)_3$, was synthesized according to a literature procedure.[50] Saccharin was purchased from Sigma-Aldrich Co. Thiosaccharin was synthesized according to a literature procedure.[51] NMR spectra were recorded on a Bruker DRX 400 spectrometer. All spectra were internally referenced using the deuterated solvent signal. Electrospray ionization spectra (ESI) were generated on a Micromass Platform II QMS spectrometer. Infrared spectra, as KBr disks or Nujol mulls, were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Elemental microanalyses were performed by the Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, Dunedin, New Zealand. Melting points were measured on a Stuart Scientific SMP3 melting point apparatus.

Bacterial Strains and Culture Conditions. *H. pylori* strains 251, B128, and 26695 were routinely cultured on horse blood agar (HBA) or in brain heart infusion broth (BHI), supplemented with either 7.5% (v/v) fresh horse blood or 10% (v/v) FCS, respectively. Culture media were further supplemented with 155 mg/L polymyxin B, 6.25 mg/L vancomycin, 3.125 mg/L trimethoprim, and 1.25 mg/L amphotericin B.[52]

Determination of the Minimum Inhibitory Concentration. The MICs of bismuth complexes **1**, **2**, **4**, **5**, and **6** were determined by the agar dilution technique. All bismuth complexes were dissolved in DMSO to give clear, colorless solutions of known concentration. *H. pylori* cultures were incubated in BHI for 18 h, shaking at 140 rpm at 37 °C under micro aerobic conditions. Bacteria were pelleted, washed in phosphate-buffered saline, then resuspended in BHI.[53] Each suspension was adjusted to give an approximate density of 10^6 bacteria/mL. Aliquots (10 mL) of these suspensions were then streaked onto HBA plates containing doubling dilutions of the different concentrations of bismuth compounds, ranging in concentration from 6.25 to 25 mg/mL. Each compound was tested alongside $BiPh_3$ and the free acids in comparable concentrations. The MICs of the different compounds were determined by examination of the plates after incubation for 3−5 days at 37 °C.

Synthesis of $[Ph_2Bi(sac)]_\infty$, 1. A mixture of $BiPh_3$ (0.22 g, 0.50 mmol) and saccharin (0.092 g, 0.50 mmol) was refluxed in ethanol overnight to produce a cloudy solution. Filtration removed a small amount of insoluble residue (later identified as $Bi(sac)_3$), leaving a clear, colorless solution. Volatiles were removed under vacuum, and the remaining solid was washed with toluene to remove any unreacted $BiPh_3$. The solid was recrystallized from ethanol and identified as $[Ph_2Bi(sac)]_\infty$. Yield: 0.13 g, 47%. Mp (dec): >215 °C. FT-IR (cm^{-1}): 1689 w, 1270 w, 1110 w, 972 w, 726 w, 693 w, 601 w. Anal. ($C_{19}H_{14}BiNO_3S$) Calcd (Found): C 41.84 (42.71), H 2.59 (2.73), N 2.57 (2.59). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.29 (dd, 4H, *o*-Ph), 7.74 (t, 4H, *m*-Ph), 7.68 (m, Ar-H-sac), 7.40 (t, 2H, *p*-Ph). ^{13}C NMR (100 MHz, d_6-DMSO): δ 166.9 (C═O), 144.1 (*C*-SO_2), 137.2 (*C*-CO), 136.5 (CH_{sac}), 132.2 (CH_{sac}), 131.9 (CH_{sac}), 130.2 (*C*-Ph), 128.2 (*o*-Ph), 127.2 (*m*-Ph), 122.9 (*p*-Ph), 119.5 (CH_{sac}). Mass spectrum, ES^+: 363.1 (53%, $[Ph_2Bi]^+$), 441.2 (100%, $[Ph_2Bi(DMSO)]^+$), 568.1 (20%, $Ph_2BiLNa]^+$).

Synthesis of $[Bi(sac)_3]_n$, 2. $BiPh_3$ (0.22 g, 0.50 mmol) and saccharin (0.28 g, 1.50 mmol) were ground together using a mortar and pestle. This mixture was heated to 200 °C in a glass tube in a Kugelrohr oven for 2 h. Elimination of benzene was indicated by condensation at the top of the tube. The solid obtained was washed with toluene and ethanol to remove any unreacted $BiPh_3$ and saccharin. The remaining white solid was identified to be $Bi(sac)_3$. Yield: 0.3 g, 81%. Mp: 220 °C. FT-IR (cm^{-1}): 1606 m, 1257 m, 1117 w, 946 w, 757 w, 678 w. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.69 (t, 1H), 7.62 (m, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 169.5 (C═O), 144.4 (*C*-SO_2), 137.5 (*C*-CO), 136.3 (CH_{sac}), 132.5 (CH_{sac}), 131.3 (CH_{sac}), 130.8(CH_{sac}), 119.8 (CH_{sac}). Mass spectrum, ES^-: 790.8 (50%, $[Bi(sac)_3Cl]^-$), 182 (75%, $[L]^-$).

Synthesis of $[PhBi(sac)_2]_n$, 3. Compound **3** formed as a ligand redistribution product of $Ph_2Bi(sac)$. The complex could not be obtained in a pure form, and therefore complete analysis was not possible. However ^{1}H NMR resonances were observed as a part of the mixture. ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.75 (dd, 2H, *o*-Ph), 8.05 (t, 2H, *m*-Ph), 7.68 (m, Ar-H), 7.40 (t, 1H, *p*-Ph).

Synthesis of $[Ph_2Bi(tsac)]_\infty$, 4. A mixture of $BiPh_3$ (0.22 g, 0.50 mmol) and thiosaccharin (0.10 g, 0.50 mmol) was refluxed in ethanol for 30 min. All volatiles were removed under vacuum, and the remaining solid product was washed with toluene. The yellow solid was recrystallized from ethanol and identified as $[Ph_2Bi(tsac)]_\infty$. Yield: 0.14 g, 50%. Mp (dec): >200 °C. FT-IR (cm^{-1}): 1324 w, 1243 w, 1167 m, 1117 w, 1003 m, 805 m, 768 w, 724 w, 693 w, 626 w. Anal. ($C_{19}H_{14}BiNO_2S_2$) Calcd (Found): C 40.64 (39.82), H 2.49 (2.25), N 2.49 (2.99). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.33 (d, 4H, *o*-Ph), 7.93 (t, 1H, ArH_{tsac}), 7.85 (t, 1H, ArH_{tsac}), 7.76 (m, 2H, ArH_{tsac}), 7.61 (t, 4H, *m*-Ph), 7.36 (t, 2H, *p*-Ph). ^{13}C NMR (100 MHz, d_6-DMSO): δ 218.1 (C═S), 137.8 (*C*-SO_2), 134.9 (*C*-CS), 132.1 (CH_{tsac}), 132.6 (CH_{tsac}), 131.7 (CH_{tsac}), 129.7 (*C*-Ph), 128.5 (*o*-Ph), 125.3 (*m*-Ph), 123.8 (*p*-Ph), 119.7 (CH_{tsac}). Mass spectrum, ES^+: 363 (100%, $[Ph_2Bi]^+$), 483.9 (25%, $[PhBi(tsac)]^+$), 584 (5% $[Ph_2Bi(tsac)Na]^+$).

Synthesis of $[PhBi(tsac)_2]_n$, 5. A mixture of $BiPh_3$ (0.22 g, 0.50 mmol) and thiosaccharin (0.20 g, 1.0 mmol) was refluxed in ethanol for 1 h. All volatiles were removed under vacuum, and the residual solid was washed with toluene. The yellow solid product was identified as $PhBi(tsac)_2$. Yield: 0.25 g, 73.0%. Mp (dec): >210 °C. FT-IR (cm^{-1}): 1324 w, 1244 w, 1167 m, 1119 w, 1005 m, 805 m, 768 w, 728 w, 695 w, 626 w. Anal. ($C_{20}H_{13}BiN_2O_4S_4$) Calcd (Found): C 35.19 (35.53), H 1.91 (2.10), N 4.10 (4.04). ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.86 (d, 2H, *o*-Ph), 8.01 (t, 2H, *m*-Ph), 7.91 (t, 2H, ArH_{tsac}), 7.80 (t, 2H, ArH_{tsac}), 7.70 (q, 4H, ArH_{tsac}), 7.45 (t, 1H, *p*-Ph). ^{13}C NMR (100 MHz, d_6-DMSO): δ 219.1 (*C*═S), 137.8 (*C*-SO_2), 134.9 (*C*-CS), 133.1 (CH_{tsac}), 132.5 (CH_{tsac}), 131.6 (CH_{tsac}), 129.9 (*C*-Ph), 128.8 (*o*-Ph), 125.0 (*m*-Ph), 123.8 (*p*-Ph), 119.5 (CH_{tsac}). Mass spectrum, ES^+: 484.0 (20%, $[PhBi(tsac)]^+$), 561.9 (5%, $[PhBi(tsac)DMSO]^+$).

Synthesis of $[Bi(tsac)_3]_n$, 6. All the manipulations were carried out under nitrogen atmosphere with predried solvents. Thiosaccharin (0.23 g, 1.50 mmol) was added to a solution of bismuth *tert*-butoxide (0.21 g, 0.50 mmol) in THF (20 mL) at −80 °C and stirred overnight. Removal of volatiles under vacuum left a light orange solid, which was washed with ethanol to remove any unreacted acid and/or bismuth butoxide. This solid product was identified as $Bi(tsac)_3$. Yield: 0.30 g, 75.0%. Mp (dec): >160 °C. FT-IR (cm^{-1}): 1325 w, 1241 w, 1167 m, 1001 w, 794 w, 694 w, 626 w. Anal. ($C_{21}H_{12}BiN_3O_6S_6$) Calcd (Found): C 31.38 (32.11), H 1.49 (1.76), N 5.23 (4.92). ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.91 (t, 1H, ArH_{tsac}), 7.74 (t, 1H, ArH_{tsac}), 7.66 (t, 2H, ArH_{tsac}). ^{13}C NMR (100 MHz, d_6-DMSO): δ 191.3 (C═S), 137.7 (C-SO_2), 136.5 (C-CS), 132.2 (CH_{tsac}), 131.2 (CH_{tsac}), 125.3 (CH_{tsac}), 119.1 (CH_{tsac}). Mass spectrum, ES^+: 604.7 (100%, $[Bi(tsac)_2]^+$), 825.5 (5%, $[Bi(tsac)_3Na]^+$); ES- 198.0 (100%, $tsac^-$), 1005.5 (5%, $[Bi(tsac)_4]^-$).

Crystallography. Crystals of **1** were examined using the MX1 beamline at the Australian Synchrotron, Victoria Australia. A very small crystal was mounted on a cryo-loop and then flash cooled to 100 K. Data were collected using a single wavelength (λ = 0.710698 Å). The MX1 end station comprised a phi goniostat and ADSC Quantum 210r 210 × 210 mm large-area detector. Due to hardware constraints (fixed detector angle, minimum detector distance), the maximum

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available data resolution on MX1 was limited to approximately 0.80 Å at the detector edges. Data were collected using the Blu Ice[54] GUI and processed with the XDS[55] software packages.

Crystals of **4** were examined using an Oxford Gemini Ultra CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å). A representative yellow prismatic crystal of dimensions 0.25 × 0.10 × 0.10 mm was mounted on a cryoloop and then flash cooled to 123 K. Data were collected and processed using the Chrysalis^{PRO} software package.[56]

Summary of Crystallographic Data. [$Ph_2Bi(sac)$], **1**: $C_{19}H_{14}BiNO_3S$, M = 545.35 orthorhombic, space group $Pna2_1$. a = 11.762(2) Å, b = 16.999(3) Å, c = 8.823(2) Å, V = 1764.1(6) Å^3, Z = 4, D_c = 2.053 g cm^{-3}, μ= 10.130 mm^{-1}, F_{000} = 1032, T = 100(2) K, $2\theta_{max}$ = 53.8°, 11 595 reflections collected, 3321 unique (R_{int} = 0.088). R_1 = 0.039, wR_2 = 0.096 for 3287 data with $I > 2\sigma I$; R_1 = 0.039, wR_2 = 0.096 for all data. GoF = 1.141, Flack x_{abs} = 0.038(8).

[$Ph_2Bi(tsac)$], **4**: $C_{19}H_{14}BiNO_2S_2$, M = 561.43, 0.25 × 0.10 × 0.10 mm, orthorhombic, space group $P2_1/n$. a = 13.1449(2) Å, b = 9.2362(1) Å, c = 15.1477(2) Å, V = 1820.92(4) Å^3, Z = 4, D_c = 2.048 g cm^{-3}, μ = 9.924 mm^{-1}, F_{000} = 1064, T = 123 K, $2\theta_{max}$ = 62.98°, 6059 reflections collected, 5536 unique (R_{int} = 0.028). R_1 = 0.022, wR_2 = 0.038 for 4272 data with $I > 2\sigma I$; R_1 = 0.035, wR_2 = 0.042 for all data. GoF = 1.039.

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