Metallodrug Mechanosynthesis

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Mechanosynthesis of the Metallodrug Bismuth Subsalicylate from Bi_2O_3 and Structure of Bismuth Salicylate without Auxiliary Organic Ligands**

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Mechanochemical reactions are versatile for the synthesis of new pharmaceutical forms,[1] particularly cocrystals, salts and, since very recently, coordination complexes.[2] Mechanochemistry can be very efficient for the synthesis of metal–organic frameworks (MOFs)[3] and magnesium-based pharmaceuticals[4] directly from inexpensive and otherwise inert materials, such as metal oxides or carbonates. In addition to short reaction times and the lack of bulk solvents, oxide-based mechanosynthesis also has the advantage of generating water as the sole byproduct.[5] We now demonstrate how ion- and liquid-assisted grinding (ILAG), previously utilized for the mechanosynthesis of large-pore MOFs and zeolitic imidazolate frameworks[5,6] based on zinc, can be extended to the pharmaceutical chemistry of bismuth oxide. We demonstrate the rapid and efficient conversion of Bi_2O_3 into a variety of bismuth salicylate complexes, including the commercial active pharmaceutical ingredient (API) bismuth subsalicylate (**1**), marketed under the trade name Pepto-Bismol.[7]

The pharmaceutical value of bismuth complexes with salicylic acid (H_2sal) has been established over a century ago and still remains an area of active research.[7–12] At least three different forms of bismuth salicylate, which differ in the stoichiometric ratio of bismuth and H_2sal, have been reported. These are the API bismuth subsalicylate BiO(Hsal), the disalicylate (**2**) with assigned formula $Bi_2O(Hsal)_4$,[8] and the trisalicylate (**3**) involving bismuth and salicylic acid in the 1:3 stoichiometric ratio. Until now, the structure for any of these materials has remained unknown. Models for **1** and its biological activity were initially devised by Thurston et al.[9] who used auxiliary chelating ligands to trap discrete oligonuclear clusters of Bi^{3+} and salicylate anions ($Hsal^-$), and by Burford et al. who explored complexation of Bi^{3+} with thiosalicylic acid.[10] The potential of mechanochemistry to generate bismuth carboxylates was revealed by Andrews and co-workers,[11,12] who investigated combined mechano- and thermochemical routes involving carboxylic acids and triphenylbismuth. With H_2sal this approach provides different organobismuth salicylates unless the ratio of Bi to acid is 1:3, in which case it leads to the tricarboxylate **3** (Figure 1a). Recrystallization of **3** from acetone yielded metal–organic clusters containing coordinated solvent that are currently the best models for the structure of **1** (Figure 1b).[12] Unfortunately, this synthetic pathway is of limited use due to regulatory aspects of organobismuth precursor and the formation of aromatic hydrocarbon byproducts.[13]

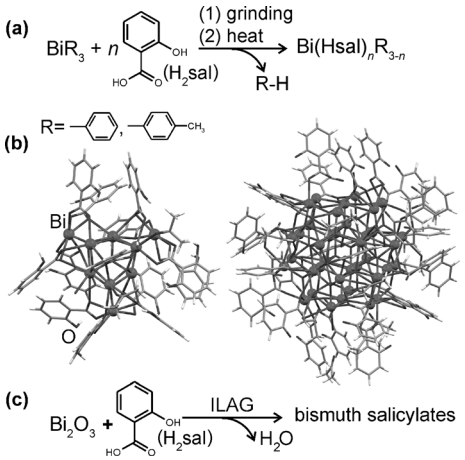

Figure 1. a) Reported mechanochemical synthesis of bismuth salicylates from organobismuth precursors, b) two types of bismuth salicylate clusters obtained by recrystallization of bismuth trisalicylate from acetone, and c) proposed ILAG mechanosynthesis of bismuth salicylates from Bi_2O_3.

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We recognized the synthesis of **1** from Bi_2O_3 (Figure 1c) as a challenge which could lead to practical applications of oxide-based ILAG beyond the MOF arena. We expected that oxide-based reactivity would be energy- and environmentally advantageous to previous methodologies and could even provide a selective route to **1**, **2**, or **3**. The expected selectivity is based on recent reports on the self-assembly of coordination polymers[14a,b] and cocrystals.[14c,d] However, such stoichiometric control has not yet been demonstrated in an oxide-based mechanochemical reaction, which couples[5] acid–base neutralization with coordination-driven self-assembly. Attempts to achieve a reaction between Bi_2O_3 and salicylic acid by neat grinding in a 1:6, 1:4 or 1:2 respective stoichiometric ratios (corresponding to Bi:H_2sal ratios of 1:3, 1:2, and 1:1, respectively) were not successful, as evidenced by the powder X-ray diffraction (PXRD) pattern of the ground material (Figure 2a–c).

Mechanochemical reactivity can be tremendously improved by small amounts of a liquid (liquid-assisted grinding, LAG, technique).[15] Consequently, we conducted the grinding of Bi_2O_3 and H_2sal in a 1:6 ratio in the presence of water. As evidenced by PXRD, 30 min LAG led to partial conversion of Bi_2O_3 and H_2sal into a new material. The comparison of the PXRD pattern of this product with the reported patterns for solution-synthesized **1** and **2** indicated that the mechanochemical product is a mixture of **2** and another crystalline substance (Figure 2d,e). In the case of the 1:4 ratio of Bi_2O_3 and H_2sal, grinding yielded variable mixtures of **2**, **1**, and an unknown substance. Finally, LAG using 1:2 ratio of Bi_2O_3 and H_2sal yielded mixtures of **2** and unreacted Bi_2O_3 (Figure 2d,e). Attempts to conduct LAG reactions using organic solvents or ionic liquids were unsuccessful, each time providing only a mixture of reactants.

Following the promising results of LAG in activating Bi_2O_3 and H_2sal, we attempted ILAG synthesis by conducting reactions in the presence of 5% by weight of simple ionic salts, as well as water. A variety of ionic additives were explored (see Supplementary Information, Scheme S1–S3) and NH_4NO_3 and KNO_3 were found to be among the most efficient. As evidenced by PXRD, 60 min ILAG of Bi_2O_3 and H_2sal in a 1:2 stoichiometric ratio produced a phase identified by PXRD as the API bismuth subsalicylate **1** (Figure 2f,g). Although ILAG of mixtures of Bi_2O_3 and H_2sal in the stoichiometric ratio 1:4 did not yield a single product, the results were reproducible and consistently gave a mixture of **1** and **2**. Subsequently, we found out that **2** is quantitatively obtained in 30 min if ILAG is conducted in grinding jars pre-heated to 80°C (Figure 2h).[14a,16]

Similarly, 30 min ILAG with NH_4NO_3 led to complete conversion of the 1:6 stoichiometric mixture of Bi_2O_3 and H_2sal into a new material, tentatively formulated as the trisalicylate **3**. The PXRD pattern (Figure 2i) indicated **3** is the unknown substance accompanying **2** as a product of LAG (Figure 2e).

Identification of the ILAG product as **1** was confirmed by thermogravimetric analysis (TGA), as well as FTIR attenuated total reflection (FTIR-ATR) spectroscopy which also allowed **1**, **2**, and **3** to be mutually distinguished (Figure 2j) through differences in the spectral region associated with O–H stretching vibrations. The O–H stretching bands are not noticeable for **1**, but appear in the spectra of **2** and **3**.

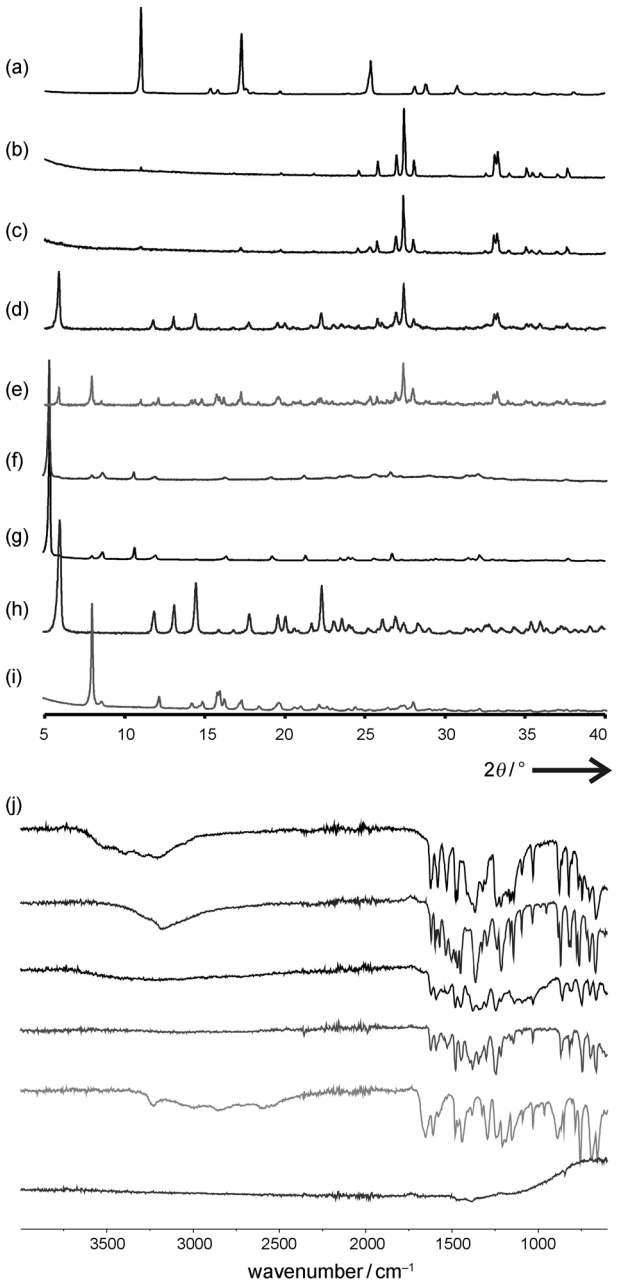

Figure 2. PXRD patterns for selected reactants and products of mechanochemical reactions with indicated ratio of Bi_2O_3 and H_2sal: a) H_2sal, b) Bi_2O_3, c) neat grinding 1:2, d) LAG 1:2, e) LAG 1:6, f) **1** obtained by 1:2 ILAG with KNO_3, g) commercial bismuth subsalicylate, h) **2** obtained by 1:4 ILAG with KNO_3 in pre-heated jars, and i) **3** obtained by 1:6 ILAG with NH_4NO_3. j) FTIR-ATR spectra of (top to bottom): **3**, **2**, **1**, commercial bismuth subsalicylate, H_2sal, and Bi_2O_3.

While the mechanistic details behind ILAG are not clear, the ^{15}N direct polarization solid-state (SS) NMR of **1**, **2**, and **3** prepared with the aid of ^{15}N-labeled KNO_3 revealed a spectrum identical to that of pure $K^{15}NO_3$. This suggests that chemical decomposition of the salt or its inclusion[6] in the product are not likely. We also explored whether LAG can be

replaced with a longer slurry-based[17] process: overnight slurrying of mixtures of Bi_2O_3 and H_2sal in a suitable stoichiometric ratio in water readily produced **1** or **2**. Attempts to synthesize **3** from a slurry yielded only mixtures of **1** and **2**, and slurrying mechanochemically prepared **3** in water produced a mixture of **1** and **2**.[18]

Recrystallization of **1** was not successful due to its low solubility. However, **2** and **3** were soluble in a number of organic solvents upon heating, including *N*,*N*-dimethylformamide (DMF). Recrystallization of **2** from DMF after 24 h yielded rectangular crystals (**4**) isostructural with the cluster structure obtained by Andrews et al. from wet acetone.[12] Structure determination revealed an almost identical cuboctahedral Bi_{38} cluster with coordinated acetone replaced by DMF (Figure 3a). The Bi···O separations involving DMF were found to be approximately 0.1–0.2 Å shorter than analogous distances with acetone.

The formation of the identical bismuth core from a different solvent is indicative of its robustness and supports its relevance for the activity of bismuth subsalicylate.[12] In order to find out whether the Bi_{38} core is also a structural feature of its precursors **2** or **3**, we decided on crystal-structure determination of **2** using powder X-ray diffraction data.[18] Data suitable for structural characterization were obtained using the high-resolution powder diffraction beamline ID31 at the ESRF operating at 40 keV ($\lambda = 0.30659$ Å). Structure solution in the space group $P2_1/c$ revealed a two-dimensional coordination polymer (Figure 3b) held by Bi–O linkages (range of Bi–O distances: 2.18–2.70 Å) and O-H···O hydrogen bonds (O···O distances 2.54 Å and 2.71 Å). The asymmetric unit of **2** contains one bismuth atom, one salicylate monoanion and one salicylate dianion. The monoanionic salicylate coordinates to a single Bi^{3+} ion through its carboxylate group only, whereas the dianionic salicylate additionally employs the phenoxide oxygen atom as a bridging ligand to form four-membered Bi_2O_2 rings (Figure 3c).. An additional oxygen atom is bonded to bismuth in the form of a water molecule (Figure 3d), as indicated by TGA and Rietveld refinement. This modifies the structure previously proposed on the basis of FTIR spectra,[8,19] involving monoanionic salicylates and a bridging oxide.

Structure of **2** was verified through CP-MAS ^{13}C SS NMR (Figure 3d) which revealed two sets of signals for carboxylate groups. The signals differ in chemical shift and width, the latter being attributable to unresolved coupling of ^{13}C to one, or to three, quadrupolar bismuth nuclei (^{209}Bi is a spin-9/2 nucleus).[20] The structure of **2** complements existing models based on discrete oligonuclear clusters involving auxiliary organic ligands, and confirms the tendency of bismuth salicylate to adopt extended structures in the absence of organic auxiliaries. The structure also demonstrates that **2** does not contain basic hydroxide or oxide.

In conclusion, we have demonstrated new mechanochemical pathways that allow the quantitative and selective conversion of bismuth oxide into different forms of bismuth salicylate, including the pharmaceutical ingredient bismuth subsalicylate. We also provide the first crystal structure of a bismuth salicylate without organic auxiliaries. The extended structure demonstrates that bismuth disalicylate hydrate is a two-dimensional inorganic-organic hybrid material and that, although Bi oxo-clusters could resemble the active form of bismuth subsalicylate, they are not necessarily inherent to the crystal structure of its precursor. In that way, bismuth salicylate resembles the recently studied bismuth complexes with substituted benzoic acids.[21]

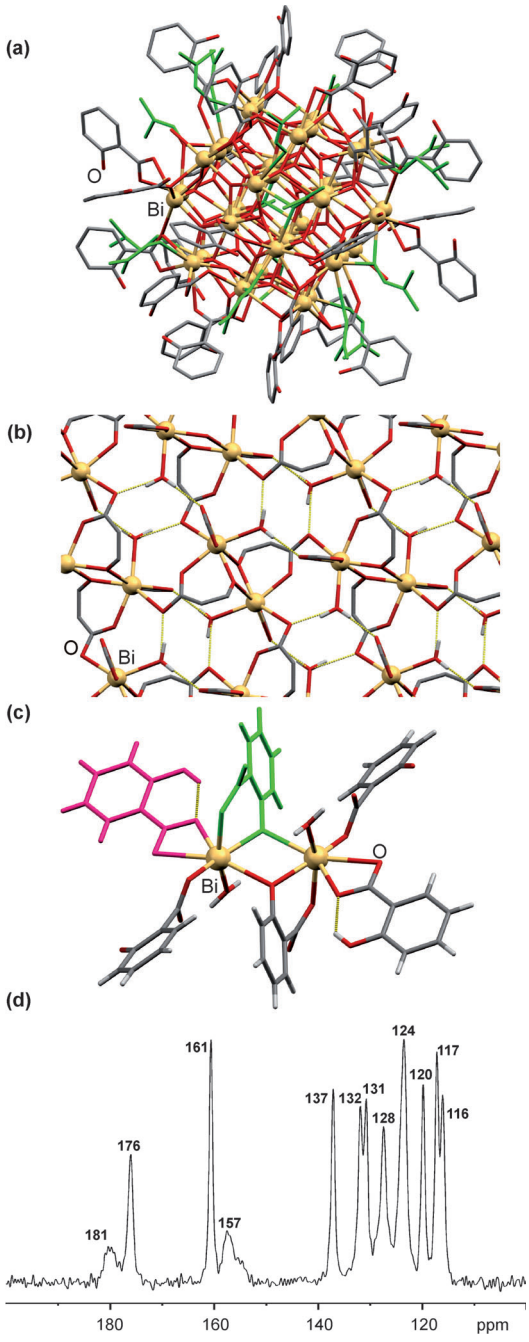

Figure 3. a) A single $Bi_{38}O_{44}(Hsal)_{26}(H_2O)_4(DMF)_{18}$ cluster in **4**, with coordinated DMF shown in green; b) a polymeric sheet of **2** viewed along the crystallographic *a* axis, displaying only the sections of $Hsal^-$ and sal^{2-} ligands directly involved in coordination and hydrogen (shown in yellow) bonding; c) a fragment of a sheet of **2** highlighting different bonding modes of sal^{2-} (green) and $Hsal^-$ (purple) anions; and d) ^{13}C CP-MAS SS NMR spectrum of **2**.

Experimental Section

Mechanochemical experiments: 200 mg of a solid reactant mixture (Bi_2O_3 and H_2sal in appropriate stoichiometric ratio) was placed in a stainless steel grinding jar, along with two stainless steel balls of 7 mm diameter. The mixture was ground, typically between 10 and 60 min, in a Retsch MM200 mill at a frequency of 30 Hz. In a typical 30 min experiment the temperature of the jar increased by ca 4 °C. For LAG experiments, 50 μL of a liquid was added to the reaction mixture. For ILAG, 50 μL of a liquid and 10 mg of a salt were added.

Crystallographic data: **2**: $C_{14}H_{11}BiO_7$, $M_r = 500.2$, monoclinic, $P2_1/c$, $a = 15.0475(2)$, $b = 8.5569(1)$, $c = 11.2134(1)$ Å, $\beta = 91.455(1)°$, $V = 1443.36(3)$ Å^3, $Z = 4$, $\lambda = 0.30659$ Å, $R_p = 5.06$, $R_{wp} = 6.57$, structure solution and refinement were conducted using Topas;[22] **4**: $C_{254}H_{298}Bi_{38}N_{24}O_{150}$, $M_r = 14028.4$, orthorhombic, $Pbca$, $a = 31.0543(1)$, $b = 32.6249(2)$, $c = 32.7838(2)$ Å, $V = 33214.69(3)$ Å^3, $Z = 4$, $\lambda = 0.71073$ Å ($Mo_{K\alpha}$), $R = 0.051$, w$R = 0.126$ for 23162 reflections (out of 30406 independent reflections) with $I \geq 2\sigma(I)$ and 2083 parameters. Structure solution and refinement were conducted using SHELX-97 within the WinGX package.[23] CCDC 823766 and 823767 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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