Synthesis and Structure of Functionalized Derivatives of the Cleft-Shaped Molecule Dithiosalicylide

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Introduction

Conformationally rigid molecules whose structures define cavities and clefts have potential uses as receptors, catalysts, and as molecular building blocks in the construction of new materials. Dithiosalicyclides are a class of conformationally well-defined, dect-shaped molecules. NMR and X-ray crystallographic studies have shown that dithiosalicylide (1) adopts a boat conformation where the aromatic rings form a shallow “V-shaped” pocket in which the dihedral angle between the aromatic rings is approximately 65°.8 Although dithiosalicyclides are not conformationally locked, as is the case for the structurally related Kagan’s ether1,2 and Troeger’s base3 compounds, the inversion barrier between the enantiomeric boat conformations is quite high (∼25 kcal/mol).7

As part of investigations9-11 into the chemistry of 3H-1,2-benzodithiole-3-ones, we recently developed a simple preparation of dithiosalicylides (1),12,13 Treatment of 2 with triphenylphosphine provides good yields of 1, presumably via dimerization of a benzothetan-2-one (3) or ketene (4) intermediate (Scheme 1).14 We describe here the application of this protocol to the preparation of dithiosalicylides that present larger cavities than the parent compound and to several analogs that may be amenable to further functionalization. In addition, we present the crystal structures of two dithiosalicylides that show that the compounds form discrete, self-included dimers and that interactions between the dimers give rise to interesting supramolecular structures.

Results and Discussion

The 3H-1,2-benzodithiole-3-ones (5) used in these studies were prepared by conversion of the appropriately substituted anthranilic acid derivatives (6) to the corresponding thiosalicylic acid analogs (7), followed by cyclization using thiocarboxylic acid in sulfuric acid (Scheme 2).16 In each case, treatment of 5 with triphenylphosphine in methylene chloride at room temperature affords good yields of the corresponding dithiosalicylide analogs (8) (Scheme 2). Consistent with the notion (Scheme 1) of negative charge developing on sulfur in the transition state of the triphenylphosphine-mediated dimerization reaction, we observe that 5b reacts more rapidly than either 5a or 2.

With the aim of preparing functionalizable dithiosalicylides, we sought to brominate the methyl positions of 8a. Accordingly, treatment of 8a with N-bromosuccinimide (NBS) in carbon tetrachloride yields a mixture of brominated analogs that are separable by careful silica gel column chromatography and recrystallization. With careful control of conditions, it is possible to obtain the monobrominated cleft (9) and the dibrominated cleft (10) in 30% and 27% recovered yields respectively (Scheme 3).

Because the dithiosalicylide-forming reaction described here (Scheme 1) involves dimerization of triphenylphosphine-activated 3H-1,2-benzodithiole-3-ones, it is possible to prepare asymmetrical functionalized clefts by this method. For example, treatment of a 1:1 mixture of 5b and 5c with triphenylphosphine in methylene chloride at 24 °C affords 11, 8b, and 8c in approximately equal yields. These products are separable by careful column chromatography. Using this approach, the asymmetric clefts 11-14 were prepared.

Crystals of dithiosalicylides 8c and 11 suitable for X-ray analysis were obtained by dissolving each compound in a mixed solvent system (ethyl acetate:hexane for 11 and chloroform:methanol for 8c) and allowing slow evaporation to dryness. As shown in Figure 1, each molecule contains a self-included dimer with dihedral angles between the planes of their aromatic units of 56.6° (8c) and 62.2° (11), similar to the parent dibenzo derivative 1.8 Notably, elaboration of 1 has increased the size of each cleft such that the entrance to each pocket approaches nanometer dimensions as demonstrated by “upper rim” H-H (8.29 Å) and H-Br (8.16 Å) separations for 8c and 11, respectively, which are greater than those H-Br separations (6.43 and 6.69 Å) of 1.

Views depicting the crystal structures of 8c and 11 are shown in Figure 1cd. Both molecules assemble such that they form self-included dimers held together by offset face-to-face (plane-to-plane distances: 3.36 (8c), 3.43 Å (11)) and tilted T-edge-to-face π-π interactions (ring center–ring center distances: 5.37 (8c), 5.37 Å (11)).17 The self-inclusion exhibited by the unsymmetrical cleft 11

displays selectivity, with the naphthyl, rather than the bromo, substituent residing within the cleft. Neighboring dimers in both structures interact via offset face-to-face \( \pi \) interactions [plane-to-plane distances: 3.48 and 3.60 Å (8c), 3.62 and 3.67 Å (11)], which give rise to infinite supramolecular layered arrays.

**Experimental Section**

Chemicals were purchased from the following suppliers: absolute ethanol, McCormick Distilling Co.; NaOH, NaHCO₃, Na₂SO₄, H₂SO₄, HCl, Fisher Chemical Company; 3-amino-2-naphthoic acid, Fluka Chemical Co. All other chemicals were purchased from Aldrich Chemical Co. Thin-layer chromatography was performed on silica gel plates, 0.25 mm, with F₂₅₄ fluorophore (Aldrich), and visualization of compounds was achieved with UV light at 254 or 360 nm. Column chromatography was performed using 230–400 mesh silica gel (Merck) with technical-grade solvents that were distilled prior to use. High resolution mass spectrometry was performed at the Midwest Centre for Mass Spectrometry (University of Nebraska—Lincoln), and elemental analysis was performed at M-H-W Laboratories (Phoenix, AZ). Intensity data for crystallographic studies were collected on Enraf-Nonius CAD-4 diffractometers at 298 K. All crystallographic calculations were conducted using the NRCVAX program package¹⁸ locally implemented on an IBM-compatible pentium-based PC. Packing diagrams were constructed with the aid of RES2INS.¹⁹

**General Procedure for the Synthesis of Substituted 3H,1,2-Benzodithiol-3-ones (5).** To a stirred suspension of the appropriate anthranilic acid derivative (165 mmol) in water (85 mL) and conc HCl (33 mL) at 5 °C was added dropwise a solution of NaNO₂ (11.4 g, 165 mmol) in water (45 mL) and the solution maintained at 5 °C. Crushed ice was added to the reaction mixture periodically during addition to keep the temperature below 5 °C. Meanwhile, Na₂S·9H₂O (43.7 g, 182 mmol) and sublimed sulfur (5.8 g, 181 mmol) were dissolved in water (48 mL) by heating and made alkaline by addition of 10 M NaOH (17 mL), and the resulting alkaline disulfide solution was cooled to 5 °C in an ice bath. The cold diazo solution was added to the alkaline disulfide solution dropwise with crushed ice added periodically to maintain the temperature below 5 °C. Following addition of the diazo solution, the mixture was stirred at 24 °C until evolution of N₂ gas stopped. Concentrated HCl was added to the solution until precipitation of the crude product as a yellow solid was complete. The precipitate was collected and boiled in a saturated solution of NaHCO₃ (400 mL). After being boiled for 15 min, the mixture was filtered to remove the insoluble material, and conc HCl was added to the filtrate until the precipitate was complete. Excess conc HCl was added to the mixture until precipitation was complete, and the precipitate was isolated by filtration. This material was boiled in absolute EtOH (150 mL) for 15 min and filtered and the filtrate concentrated under reduced pressure to yield the 2,2′-dithiosalicylic acid derivative (approximately 90% pure).

The 2,2′-dithiosalicylic acid derivative was mixed with Zn dust (10 g) in glacial CH₃COOH (150 mL) and refluxed for 48 h. The mixture was then cooled and filtered. The solid collected in this manner was boiled in 5 M NaOH (300 mL). After being boiled for 30 min, the undissolved solid was removed by filtration and the filtrate acidified with conc HCl until the crude product precipitated out as a yellow solid. Concentrated HCl was added to the mixture until the precipitation was complete. The precipitate was collected and boiled in EtOH (125 mL) and

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¹⁹ Barbour, L. J. University of Missouri—Columbia, unpublished program.
stirred in CH₂Cl₂ (30 mL) under N₂ at 24 °C. When TLC indicated that the reaction was nearly complete (∼160 h), the turbid yellow mixture was evaporated to dryness under reduced pressure to obtain the crude product. Reaction times can be decreased with use of excess triphenylphosphine. Because the triphenylphosphine sulfide byproduct of this reaction migrates close to the dithiosalicylic acid product on silica gel, it was desirable to convert the triphenylphosphine sulfide to the more polar triphenylphosphine oxide prior to column chromatography. Accordingly, glycidol (2.6 mL, 38.6 mmol) and CF₃COOH (3.0 mL, 39 mmol) were added to a solution of the crude product in benzene (25 mL), and the mixture was heated at 55 °C until all triphenylphosphine sulfide was converted to triphenylphosphine oxide as indicated by TLC. This workup procedure does not affect the yield of the desired product. The solution was then cooled, diluted with EtOAc (30 mL), and extracted with saturated NaHCO₃ (2 × 50 mL) and water (2 × 50 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure to yield a thick oil that was subsequently purified by column chromatography.

Flash chromatography on silica gel eluted with hexane–EtOAc (8:1) provided 8a as a white solid (74%). This material was recrystallized from CH₂Cl₂–hexane to give white crystals: mp 174–176 °C (lit.¹⁰ mp 175–176 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.35 (m, 4H), 7.25 (m, 4H); ¹³C NMR (500 MHz, CDCl₃) δ 197.3, 142.5, 135.6, 131.2, 130.0, 126.5, 125.2 (corresponds with literature data)¹¹.

**2,9-Dimethyl-6,12-dibromo[b,f][1,5]dithiocin-6,12-dione (8b).** Compound 8b was prepared as described above, except that the reaction was complete at ∼140 h. Flash chromatography on silica gel eluted with hexane–EtOAc (8:1) provided 8b as a white solid (72%). This material was recrystallized from EtOAc–hexane to give colorless cubic crystals: mp 224–225 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.23 (s, 1H), 7.26 (s, 1H), 3.79–3.97 (m, 4H); ¹³C NMR (500 MHz, CDCl₃) δ 123.9, 126.2, 129.7, 134.5, 136.8, 139.6, 178.3; HRMS (EI) m/z calculated for C₁₃H₆O₂S₃ 427.8176, found 427.8171.

**Dinaphtho[2,3-c:2′,3′-g][1,5]dithiocin-7,15-dione (8c).** Flash chromatography on silica gel eluted with EtOAc provided 8c as a white solid (48%). This material was recrystallized from EtOH–CHCl₃–hexane to give colorless cubic crystals: mp 324–325 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.48 (m, 4H), 7.77 (m, 2H), 7.80 (s, 2H), 7.88 (s, 2H); ¹³C NMR (500 MHz, CDCl₃) δ 120.9, 127.4, 128.1, 128.5, 128.6, 132.3, 133.1, 136.8, 139.8, 179.7; HRMS (EI) m/z calculated for C₂₂H₁₂O₂S₃Br₂ 427.0279, found 427.0267. Anal. Calcd for C₂₂H₁₂O₂S₃Br₂: C, 60.06; H, 2.77. Found: C, 59.96; H, 2.76.

**General Procedure for the Synthesis of Dithiocalyci-roles 1 and 8.** The appropriate 3H-1,2-benzodithiol-3-one (3.84 mmol) and triphenylphosphine (1.01 g, 3.84 mmol) were mixed with a 10:1:100 mL) and water (2 × 100 mL). The mixture was stirred for 4 h. The dark mixture was then poured over crushed ice and allowed to stand at 24 °C for 30 min. The precipitate so obtained was triturated with boiling CHCl₃ (2 × 100 mL), the resulting CHCl₃ solution filtered, and the filtrate extracted with saturated NaHCO₃ (2 × 100 mL) and water (2 × 100 mL). The organic layer was dried over Na₂SO₄ and the solvent removed under reduced pressure to yield the crude product (5), which was subsequently purified by column chromatography.

5-Methyl-3H-1,2-benzodithiol-3-one (5a). The yellow solid was purified by flash chromatography on silica gel with hexane–EtOAc (6:1) to yield 5a as a yellow solid (64% yield from 5-methylanthranilic acid). This material was recrystallized from EtOAc–hexane to form fine yellow needles: mp 78 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.46 (s, 3H), 7.52–7.67 (m, 2H), 7.75 (s, 1H), 1.34, 135.9, 145.4, 193.6 IR (CHCl₃) 3032, 1675, 1221 cm⁻¹; HRMS (EI) m/z calculated for C₇H₃O₂S₂Br₂ 245.8808, found 245.8813.

5-Bromo-3H-1,2-benzodithiol-3-one (5b). The yellow solid was purified by flash chromatography on silica gel with hexane–EtOAc (8:1) to yield 5b as a yellow solid (38% yield from 5-bromomethylanthranilic acid). This material was recrystallized from EtOAc–hexane to form fine light yellow needles: mp 111–115 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.50 (d, J = 8.6 Hz, 1H), 7.73 (dd, J = 1.9 Hz, 8.6 Hz, 1H), 8.08 (d, J = 1.9 Hz, 1H), 134.9, 135.9, 145.4, 193.6; IR (CHCl₃) 3032, 1675, 1221 cm⁻¹; HRMS (EI) m/z calculated for C₇H₃O₂S₂Br₂ 245.8808, found 245.8813. Anal. Calcd for C₇H₃O₂S₂Br₂: C, 52.90; H, 3.49.

3H-1,2-Naphthodithiolan-3-one (5c). The reddish yellow powder (prepared as described above except stirred for only 45 min in the thiosalicylic acid reaction) was purified by flash chromatography on silica gel with hexane–EtOAc (6:1) to yield 5c as a reddish yellow solid (48% yield from 3-amino-2-naphthoic acid). This material was recrystallized from EtOAc–hexane to form reddish yellow crystals: mp 149–150 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.47 (m, 1H), 7.48 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 8.54 (s, 1H), 134.9, 135.9, 145.4, 193.6; IR (CHCl₃) 3032, 1675, 1221 cm⁻¹; HRMS (EI) m/z calculated for C₁₃H₄O₂S₃Br₂ 425.8813, found 425.8812. Anal. Calcd for C₁₃H₄O₂S₃Br₂: C, 52.90; H, 1.32.

Figure 1.

Notes


[(21) The author has deposited atomic coordinates for 8c and 11 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.]
mg, 1.8 mmol) were stirred in CH₂Cl₂ (20 mL) under N₂ at 24 °C. When starting material was consumed as indicated by TLC, the turbid yellow mixture was evaporated to dryness under reduced pressure to yield the crude product. Glycidol (550 µL, 8.3 mmol) and CF₃COOH (639 µL, 8.3 mmol) were added to a solution of the crude reaction product in benzene (10 mL), and the mixture was heated at 55 °C until all triphenyl phosphine sulfide was converted to triphenylphosphine oxide as indicated by TLC. The solution was cooled, diluted with EtOAc (25 mL), and extracted with saturated NaHCO₃ (2 × 25 mL) and water (2 × 25 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure to yield a thick oil that was subsequently purified by column chromatography.

2-Bromo-6H,12H-dibenzo[b,f][1,5]dithiocin-6,12-dione (12). Flash chromatography on silica gel eluted with hexane–EtOAc (10:1) provided 12 as a yellow-white solid (28%). Compounds 8a and 1 were obtained in 24% and 26% yields, respectively. This material was recrystallized from EtOAc–hexane to give white crystals: mp 139–140 °C; 'H NMR (500 MHz, CDCl₃) δ 2.27 (s, 3H), 7.03 (m, 2H), 7.20 (d, J = 7.6 Hz, 1H), 7.25 (m, 2H), 7.35 (m, 2H); 'C NMR (500 MHz, CDCl₃) δ 21.2, 122.0, 125.4, 126.6, 127.2, 131.0, 131.2, 131.8, 135.6, 135.7, 142.1, 142.4, 142.8, 197.7, 198.0; HRMS (EI) m/z calcld for C₁₅H₉O₂S₂Br: m/z = 286.0122, found 286.0121. Anal. Calcd for C₁₅H₁₀O₂S₂: C, 49.46; H, 2.49. Found: C, 49.66; H, 2.32.

2-Bromo-6H,12H-dibenzo[b,f][1,5]dithiocin-6,12-dione (13). Flash chromatography on silica gel eluted with hexane–EtOAc (10:1) provided 13 as a white solid (35%). Compounds 8b and 12 were obtained in 27% and 25% yields, respectively. This material was recrystallized from EtOH–hexane to give white crystals: mp 198–199 °C; 'H NMR (500 MHz, CDCl₃) δ 7.2 (d, J = 7.6 Hz, 1H), 7.25 (m, 1H), 7.32 (m, 1H), 7.37–7.42 (m, 4H); 'C NMR (500 MHz, CDCl₃) δ 124.3, 124.8, 125.6, 126.6, 129.4, 131.4, 131.5, 134.0, 135.8, 136.8, 142.3, 143.7, 195.6, 196.3; HRMS (EI) m/z calcld for C₁₅H₁₀O₂S₂Br: m/z = 286.0127, found 286.0129. Anal. Calcd for C₁₅H₁₀O₂S₂Br: C, 48.01; H, 2.02. Found: C, 48.20; H, 2.18.

Supporting Information Available: Complete X-ray data and methods for 8c and 11 (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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