Characterization of Monomeric Thiopivaldehyde

Edwin Vedejs,* David A. Perry, and Richard G. Wilde

Contribution from the S. M. McElvain Laboratory of Organic Chemistry, Chemistry Department, University of Wisconsin, Madison, Wisconsin 53706. *Received August 13, 1985*

Abstract: The title compound is the first aliphatic thioaldehyde to be observed under ordinary laboratory conditions. Its spectral data and chemical characterization are described, including 2 + 3 cycloadditions with nitronate ester **6**, 2 + 4 cycloaddition with reactive dienes, thiophilic addition with phenyllithium, carbophilic addition with butyllithium, conversion to episulfide **15** by the Wittig reagent, and oxidation to sulfine **17** with MCPBA. Independent generation of thiopivaldehyde from *tert*-butyllithium + ethyl thionoformate followed by heating **9** in xylene or by cycloreversion of 2-*tert*-butyl-1,2-dithiolane with butyllithium are also described.

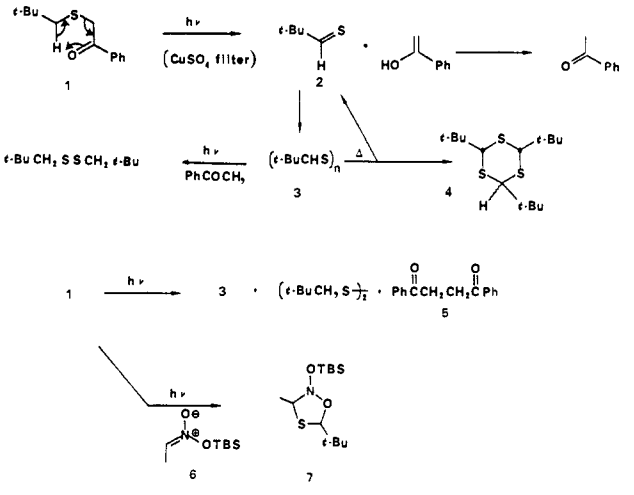
Thioaldehydes first appeared in the literature during the evolution of structural organic chemistry.[1] Their instability had been recognized by the end of the 19th century, and molecular weight determinations established that trimers or oligomers were formed in those cases where products of the correct empirical formula had been isolated. In this way, "Laurent's thioaldehyde"[2] was shown to consist of oligomeric thiobenzaldehyde by Baumann and Fromm,[3] who also established the structure of the two diastereomeric trimers which are formed under acidic conditions. In 1937, Wood and Bost presented reasonable (but not conclusive) evidence for a long-lived thioaldehyde (2-ethoxynaphthalene-1-thiocarboxaldehyde) in the distillate from thermolysis of the polymer.[4] The same group also mentioned observation of the transient blue color characteristic of thiobenzaldehyde from PhCHO + H_2S/H^+.

More recently, a variety of vinylogous thioformates or vinylogous thioformamides have been referred to as thioaldehydes,[5] and the very stable 2,4,6-tri-*tert*-butylthiobenzaldehyde has been isolated.[6] However, prior to our preliminary report,[7] there were no examples of simple aliphatic thioaldehydes which could be observed under ordinary laboratory conditions. Attempts to prepare them gave various decomposition products, trimers, or oligomers.[1]

A substantial number of methods had appeared, however, for the generation of transient thioaldehydes which could be intercepted by suitable reactants.[8-10] Our experience with one of these methods, the Norrish type II cleavage of phenacyl sulfides,[9,10] suggested that aliphatic thials might be more stable than implied in the literature. Trimers were not formed in these reactions if pure starting materials were used, suggesting that self-condensation might be a catalyzed process which could be avoided under neutral, nonpolar conditions. It seemed possible that a sterically protected molecule such as thiopivaldehyde (2,2-dimethylpropanethial) might have a significant lifetime, but we did not expect that solutions of this substance would be stable for hours at room temperature which has now been demonstrated.

Simple heating of the solid polymer **3**, obtained by sun lamp irradiation of phenacyl sulfide **1**, with a small Bunsen flame results in rapid depolymerization. The volatile products are easily con-

Scheme I



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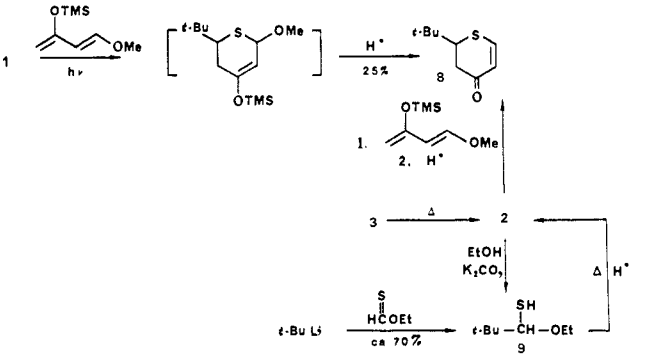
densed in a liquid nitrogen trap as a magneta-colored solid. Upon warming with inert solvents such as ether, chloroform, etc., a pink solution is obtained which contains **2** and lesser amounts of the previously reported trimers **4**.[11] The yield of thiopivaldehyde is in the 40–50% range on an ca. 10-mg scale, but it drops to 25% on an 80-mg scale, as estimated by titration with the reactive nitronate ester **6**[12] in a 2 + 3 cycloaddition to give **7** (1 isomer, stereochemistry not known). In base-washed glassware, the pink color of **2** survives for 16–20 h at 20 °C while solid polymer slowly precipitates. Decomposition is accelerated by sunlight or by impurities, but the thioaldehyde can be easily handled with no special precautions other than adequate ventilation. Decomposition affords varying ratios of polymer and trimers, depending on the quality of glassware and solvents, as well as small amounts of uncharacterized material which appears to consist of soluble oligomers. However, we have been unable to obtain any conclusive evidence for dimer formation which has been reported as a decomposition pathway for thermally generated thioacetaldehyde.[13]

Typical thiocarbonyl spectral data[1,5] confirm the presence of monomeric **2** in solution: visible λ_{max} = 508 nm (ϵ ca. 16 by titration vs. nitronate **6** to estimate concentration); C=S stretching, 1085 cm^{-1}; deshielded ^1H NMR signal at 11.67 ppm (C*H*=S). The ^{13}C spectrum is more difficult to obtain due to polymer precipitation during data acquisition. The thioaldehyde carbon can be assigned with reasonable certainty at 255.6 ppm ($CDCl_3$; signal to noise, ca. 2:1 for *C*H=S) and the *tert*-butyl methyl carbons are observed at 26.8 ppm. However, the assignment for *tert*-butyl quaternary carbon remains uncertain due to interfering trimer and oligomer signals. Overall, the NMR spectra underscore the deshielding nature of C=S relative to C=O, as is also observed for conjugated thioformyl compounds.[5,6]

Initial studies of thiopivaldehyde chemistry were hampered by the low (<20%) yield of solid polymer produced by sunlamp photolysis of **1**. However, isolation of consistently high yields of acetophenone suggested that the 6-center fragmentation proposed by earlier workers is very efficient.[9] If photolysis is conducted in the presence of excess 2,3-dimethylbutadiene, the yield of polymer increases to 50–60%. A similar improvement is obtained by filtering the sunlamp radiation through an aqueous $CuSO_4$ bath to cut off wavelengths below 320 nm. Exposure of the isolated polymer to sunlamp photolysis does not cause significant decomposition, but when this experiment is repeated in the presence of acetophenone, then substantial loss of polymer and formation of dineopentyl disulfide can be demonstrated. Direct photolysis of **1** also forms dineopentyl disulfide (ca. 40%) together with diketone **5** (5%) and complex nonvolatile byproducts, but we can find no dimers and at most traces of trimers **4**. We conclude that acetophenone acts as a sensitizer to induce secondary photochemical reactions which destroy the polymer or its precursors. This problem is minimized by adding 2,3-dimethylbutadiene to quench acetophenone triplets or by filtering out higher energy UV frequencies with the $CuSO_4$ bath.

With suitable precautions, a mass balance of ca. 90% for sulfur-containing products can be obtained (50–60% polymer **3**; 30–40% dineopentyl disulfide), and the evidence is strong that conversion of **1** to **2** is a high-yield process. Thus, photolysis with nitronate ester **6** present in situ affords 78% of the 2 + 3 cycloadduct **7**. With less reactive trapping agents, the yield of cycloadducts drops, and the yield and complexity of secondary photoproducts increases. The Danishefsky diene in situ traps only 25% of the thioaldehyde as the Diels–Alder adduct **8**[10b] (after acid-induced elimination), and the less reactive 2-(*tert*-butyldimethylsiloxy)-1,3-butadiene in situ gives 4.5% of the 2 + 4 adduct, but 2,3-dimethylbutadiene is too unreactive to intercept the hindered thioaldehyde. Using a solution of thermally generated **2**, cycloaddition with the Danishefsky diene is complete within ca. 5 min at room temperature, but thioaldehyde self-condensation

Scheme II



is also accelerated and the yield of adduct is not much improved over the in situ trapping experiment from phenacyl sulfide **1**.

Similar observations have been made with many other thioaldehydes generated by the photochemical method. If the trapping agent is photostable and sufficiently reactive, then good yields of 2 + 4 adducts are obtained.[10a,b,d,14] Otherwise, secondary photochemical reactions or thioaldehyde self-condensation can become dominant. Every example of $PhCOCH_2SCH_2R$ photolysis studied in our laboratory produces the thial in situ and affords characteristic products in the presence of sufficiently reactive trapping agents. Although a number of interesting methods have been reported recently for thioaldehyde generation,[15] we believe that the Norrish cleavage of phenacyl sulfides remains the most versatile. However, in no case have we observed that monomeric thioaldehydes accumulate under the *photolytic* conditions. Thermolysis remains the only procedure which has been shown to produce long-lived monomeric alkanethials.[16]

The 2 + 3 and 2 + 4 cycloadditions described above are general for thioaldehydes and are described elsewhere in detail.[14,17] Here, we will focus on other characteristic thioaldehyde reactions using long-lived solutions of **2** in inert solvents. As mentioned before, **2** survives for many hours in ether, chloroform, etc. However, in hydroxylic solvents such as ethanol, the color is discharged within an hour and trimers **4** are formed together with some polymer. If protic or Lewis acid catalysts are added, decomposition is instantaneous in all solvents. This observation accounts for the failure of previous workers to detect monomeric aliphatic thials from acid-catalyzed aldehyde thiation experiments.[1-4] Thioaldehyde decomposition in ethanol is also accelerated by K_2CO_3 catalysis. Under these conditions, decomposition gives a small amount of the hemithioacetal **9** as well as the trimers **4**. The same hemithioacetal is more conveniently obtained from *tert*-butyllithium and ethyl thionoformate. It can be distilled unchanged, but upon heating in boiling xylene + TsOH, **9** decomposes to give a pink distillate containing **2** and ethanol. This solution can also be used for thioaldehyde trapping experiments where ethanol does not interfere.

Thiopivaldehyde is reactive in a variety of nucleophilic addition reactions. Simple borohydride reduction affords neopentylmercaptan while alkyllithium reagents form adducts or reduction products. Our initial report described the thiophilic addition of PhLi to give neopentyl phenyl sulfide (**10**) (30%). In contrast, *n*-butyllithium reacts in much better yield and forms products of

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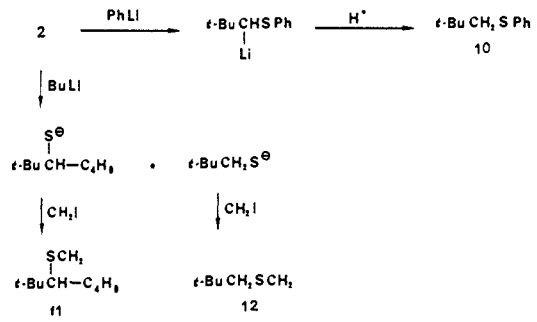
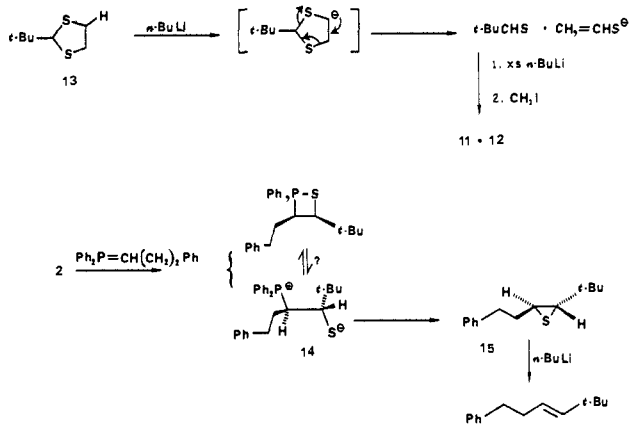
(16) To date, we have been unable to prepare solutions of *enolizable* thials by polymer thermolysis. Other tertiary thioaldehydes, however, can be made by this method. For example, heating polymeric 2-methyl-2-phenylpropanethial in diphenyl ether affords a pink solution containing the thioaldehyde which survives upon rapid cooling to room temperature.
(17) Vedejs, E.; Wilde, R. G., submitted for publication.

Scheme III



Scheme IV



addition at carbon as shown by methyl iodide quenching to give the sulfide **11** (70%) together with reduction product **12** (17%), presumably derived by β-hydride transfer from the butyllithium. Wilson et al. have previously reported similar results when thioaldehydes are generated in situ by butyllithium-induced cycloreversion of 2-alkyl-1,3-dithiolanes.[8d] We have compared Wilson's method with the reaction of distilled **2**. Thus, 2-*tert*-butyl-1,3-dithiolane (**13**) reacts with *n*-butyllithium to give the same two products **11** (39%) and **12** (32%) as obtained from **28** although in a somewhat different ratio. Since the two reactions occur in the presence of different byproducts (trimer **4** in the case of **2**; CH_2=CHSLi in the case of **13**), this difference in product ratio is no reason to doubt that the same thioaldehyde **2** is involved in both experiments. Attempts to induce dithiolane cycloreversion under similar conditions with phenyllithium afford only traces of product **10** together with recovered starting material.

We have also observed that **2** reacts with 3-phenylpropylidenetriphenylphosphorane to give an episulfide **15**.[18] Similar reactions have been reported for nonenolizable thioketones. Only one isomer of the episulfide can be detected, and trans stereochemistry is established by butyllithium-induced conversion into the corresponding *trans*-alkene.[19] Assuming that Ph_3P is displaced with *inversion* by intramolecular attack of mercaptide, the precursor betaine must have stereochemistry as shown in structure **14**. The initial condensation step between thioaldehyde and phosphorus ylide therefore occurs in the same stereochemical sense as does the reaction of ylide and pivaldehyde. In the latter case, a *cis*-dialkyloxaphosphetane is formed at low temperature and decomposes with *retention* to the *cis*-alkene.[20]

Several other reaction categories have been surveyed with limited success. In contrast to thiobenzaldehyde[21] or analogues containing π-acceptor substituents,[17] **2** is unreactive as the 2π-component for ene insertion with β-pinene due to competing self-condensation. It does not readily participate in 2 + 2 cycloadditions with carbon–carbon double bonds and gives no adducts with 1,1-diphenylallene or with methylketene. In the case of diphenylketene, a mixture of 2:1 adducts tentatively assigned structure **16** is formed in modest yield, but we cannot detect a 1:1 adduct which might be a precursor of the 2:1 products. In general, reactions with electrophilic π-acceptors or with other electrophiles give no reaction or accelerated trimer and oligomer formation in the case of alkylating agents. However, simple oxidation of **2** with MCPBA is possible and gives the previously described sulfine **17**[22] at low temperatures.

In summary, the chemical properties of thiopivaldehyde are, as expected, enhanced in rate but otherwise similar to those of nonenolizable thioketones. The thioaldehyde is more sensitive to self-condensation, but its stability in solution and ease of handling are surprising in view of the extensive unsuccessful attempts made by early workers to prepare monomeric alkanethials. The synthetic potential of thioaldehydes is under investigation and will be described in due course.

Experimental Section

Dry reaction solvents were obtained as follows: diethyl ether and tetrahydrofuran (THF) distilled from sodium–benzophenone; chlorocarbons and benzene distilled from P_2O_5; toluene distilled from CaH_2. Hexane and workup solvents were flash distilled from bulk sources. Amines were distilled from CaH_2 or BaO.

Chromatography was performed in five media: analytical thin layer was performed on precoated Merck EM silica gel 60F-254 plates; column chromatography was done with Davisil 62 60–200 mesh silica gel (gel/sample about 40:1 by weight), and elution solvents was identical with those used in the analytical TLC unless otherwise stated; flash chromatography[24] was performed on Merck EM silica gel 60 230–400 mesh; preparative TLC (PTLC) was done on Merck EM silica gel 60 PF-254 plates, 2-mm thick; and high-performance liquid chromatography (HPLC) was performed with an LDC constametric II pump, Whatman Partisil M9 10/50 column, and Waters Associates differential refractometer detector.

Synthesis of Neopentyl Phenacyl Sulfide (1). Neopentylmercaptan was prepared by the reaction of neopentylmagnesium chloride with sulfur (82%) and exhibited properties identical with those reported previously.[23] The thiol (3.27 g, 31.4 mmol) was stirred in 50 mL of THF under N_2, and 10 mL of a THF solution of α-chloroacetophenone (Aldrich, 4.85 g, 31.4 mmol) and triethylamine (5.00 mL, 35.9 mmol) was added dropwise with stirring over 10 min. After an additional 2 h of stirring, the mixture was poured into 50 mL of H_2O and extracted with 2 × 20 mL portions of CH_2Cl_2. The extracts were combined, dried over $MgSO_4$, and evaporated to afford sulfide **1** (4.72 g, 21.3 mmol, 68%) after chromatography.

1: oil, separated on silica gel 60 F254, 10% ether–hexane, R_f = 0.32; *m/e*, base = 105 amu; exact mass for $C_{13}H_{18}OS$ 222.1074, found 222.1079; error = 2.3 ppm; IR ($CDCl_3$, 1/cm) (C=O) 1670, ((*t*-Bu) 1470, (*t*-Bu) 1440; 200 MHz NMR ($CDCl_3$, ppm) 7.98–7.4 (5 H, m), 3.75 (2 H, s), 2.51 (2 H, s), 0.94 (9 H, s).

Photolysis of Sulfide 1. Sulfide **1** (2.92 g, 13.2 mmol) was dissolved in 100 mL of benzene with 2 mL of 2,3-dimethyl-1,3-butadiene (Aldrich), and the mixture was distributed to four 50-mL round-bottom flasks. The flasks were immersed in a water-cooled (≤28 °C) Pyrex bath containing 6% aqueous $CuSO_4$ solution placed above a 275-W sunlamp, and the apparatus was surrounded with aluminum foil. The samples were irradiated and magnetically stirred for 4 h, when a large amount of gelatinous white precipitate had formed. The samples were combined, and polymer **3** was isolated by, first, centrifugation from the reaction mixture and then repeated centrifugation from hexane followed by drying with a gentle N_2 flow (0.80 g, 7.8 mmol, 59%). The supernatant was evaporated and analyzed by flash chromatography[24] (10% ethylacetate–hexane) to afford 468 mg of impure dineopentyl disulfide (≤34%) and 3.4 mg (1%) of recovered **1**.

In a separate experiment, **3** (13.3 mg, 0.13 mmol) was triturated with benzene-d_6 and delivered in two equal aliquots to two flasks, one containing 15 μL of acetophenone. Each flask was then irradiated as above for 4 h. Centrifugation afforded 6.6 mg (99%) of **3** recovered from the sample without acetophenone and 4.7 mg (71%) from the one with acetophenone present. The supernatant for each sample was then analyzed directly by NMR. The spectrum of the sample without aceto-

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phenone was featureless. The other contained dineopentyl disulfide (by comparison with an authentic sample prepared by I_2 oxidation of thiol).

Also, photolysis of **1** (240 mg, 1.08 mmol) in benzene in a distilled H_2O bath without dimethylbutadiene present for 3 h afforded 10.1 mg of **3** (9%). Evaporation of solvent and flash chromatography (10% ether-hexane) afforded (in order of elution) 43.9 mg (40%) of dineopentyl disulfide, 53.4 mg of total unidentified products, 19.8 mg (8%) of recovered **1**, 74.7 mg of acetophenone, and 6.7 mg (5%) of biphenacyl **5**.

Generation of Monomeric Thiopivaldehyde 2 and Trapping with Silyl Nitronate 6 and Danishefsky's Diene. All glassware was base-washed prior to the experiment. Polymer **3** (82.6 mg, 0.81 mmol) was placed in a jointed tube, and a plug of glass wool was placed on top of the polymer in the tube. The tube was then joined to a simple vacuum line apparatus, having a trap tube (or flask) in liquid N_2 and a solvent (CH_2Cl_2, here) reservoir with needle valve. The solvent was degassed by freeze–thaw cycles and then inntroduced into the trap tube to form a frozen coating. Next, **3** was heated by a small Bunsen flame (~250 °C) until the collection of red condensate in the trap was complete. The tube was then coated with solvent again, flooded with N_2 or Ar, and allowed to come to room temperature. The solution was delivered to three flasks in equal aliquots.

One sample was stirred overnight until colorless (16 h). Centrifugation then afforded 10.5 mg of **3**. The supernatant was evaporated and eluted on flash silica gel (15% CH_2Cl_2–hexane) to afford two trimers **4a** (1.2 mg) and **4b** (0.2 mg) in order of elution.

4a: solid, mp 128–130 °C (crystallized from hexane–ethyl acetate); *m/e*, base = 147 amu; exact mass for $C_{15}H_{30}S_3$ 306.1503, found 306.1508; error = 1.6 ppm; IR (KBr, 1/cm) (*t*-Bu) 1370; 200 MHz NMR ($CDCl_3$, ppm) 4.39 (1 H, s), 4.22 (2 H, s), 1.16 (9 H, s), 1.1 (18 H, s).

4b: solid, mp 104–108 °C (crystallized from hexane–ethyl acetate); *m/e*, exact mass for $C_{15}H_{3S3}$ 306.1503, found 306.1508; error = 1.6 ppm; IR (KBr, 1/cm) (*t*-Bu) 1362; 200 MHz NMR ($CDCl_3$, ppm) 3.89 (3 H, s), 1.17 (27 H, s).

The second aliquot was titrated to colorless endpoint with 192 μL of a 0.348 M solution of nitronate **6** in benzene. A small excess of **6** was then added, and the oxathiazolidine adduct **7** was isolated by PTLC (17.5 mg).

7: oil, separated on silica gel 60 F254, 10% ether–hexane, R_f 0.70; *m/e*, base = 75 amu; exact mass for $C_{13}H_{29}O_2NS$: 291.1681, found 291.1633; error = 16.5 ppm; IR (neat, 1/cm) (*t*-Bu) 1360; 200 MHz NMR ($CDCl_3$, ppm) 5.54 (1 H, s), 4.68 (1 H, q, J = 6.5 Hz), 1.44 (3 H, d, J = 6.5 Hz), 0.97 (9 H, s), 0.92 (9 H, s), 0.17 (3 H, s), 0.13 (3 H, s).

The third aliquot was treated with excess (50 mg) 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Aldrich). The pink color faded to colorless after 5 min. The solvent was evaporated, the 5 mL of THF and 0.3 mL of 25% concentrated aqueous HCl was added. After 5 min, the solution was poured into H_2O and extracted with 3 × 10 mL portions of CH_2Cl_2. The extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The resulting enone **8** was then isolated by flash chromatography (5.6 mg).

8: Solid, mp 57–58 °C (crystallized from hexane); *m/e* exact mass for $C_9H_{14}OS$ 170.0762, found 170.0766; error = 2.3 ppm; IR ($CHCl_3$, 1/cm) (C=O) 1660, (*t*-Bu) 1370; 200 MHz NMR (CDCl3, ppm) 7.51 (1 H, dd, J = 10.1, 0.5 Hz), 6.18 (1 H, dd, J = 10.1, 0.7 Hz), 3.38 (1 H, ddd, J = 14.2, 3, 0.5 Hz), 2.78 (1 H, ddd, J = 15.8, 3, 7 Hz), 2.58 (1 H, dd, J = 15.8, 14.2 Hz), 1.06 (9 H, s).

Preparation of Hemithioacetal 9. (a) From Ethyl Thionoformate. Freshly distilled ethyl thionoformate (3.37 g, 37.5 mmol) in 50 mL of ether was cooled to −78 °C under N_2 and 23 mL of a 1.8 M solution of *tert*-butyllithium in pentane (Alfa) was added slowly. After being warmed to 20 °C, the solution was poured into saturated brine and extracted with three equal volumes of pentane. The remaining aqueous layer was acidified with dilute aqueous H_2SO_4 and reextracted with pentane and CH_2Cl_2. Both extracts contained product (by TLC), so they were dried over Na_2SO_4, combined, and evaporated. The resulting oil was purified by distillation to afford 3.84 g of hemithioacetal **9** (70%).

9: liquid, bp 45–50 °C at 25 mm, bulb-to-bulb; *m/e*, exact mass for $C_7H_{16}OS$ 148.0918, found 148.0918; error = 0 ppm; IR ($CDCl_3$, 1/cm) (SH) 2590, (COC) 1130; 200 MHz NMR ($CDCl_3$, ppm) 4.31 (1 H, d, J = 7.8 Hz), 3.88 (1 H, dq, J = 9.3, 6.9 Hz), 3.34 (1 H, dq, J = 9.3, 6.9 Hz), 1.61 (1 H, d, J = 7.8 Hz), 1.19 (3 H, t, J = 6.9 Hz), 1 (9 H, s).

(b) From Thiopivaldehyde. An ether solution of **2** (prepared from 21 mg of **3** as above) was kept below 0 °C, absolute ethanol (500 μL, 8.5 mmol) and potassium carbonate (10 mg, 0.02 mmol) were added, and the solution was allowed to stir and warm to 20 °C. Disappearance of the pink color was noted after about 1 h. Evaporation of solvent, filtration, and NMR analysis then showed signals identical with those corresponding to **9** above, as well as signals for trimers **4** (**9**:**4** ≤ 1:10).

Thiopivaldehyde by Cracking of 9. Hemithioacetal **9** (186 mg, 1.26 mmol) was quickly added to 25 mL of refluxing xylene (containing a single crystal of *p*-toluenesulfonic acid monohydrate) under N_2 under a short-path still head. The solution rapidly became dark pink, and pink liquid began distilling into a collection flask containing Danishefsky's diene (516 mg, 3 mmol). Distillation was discontinued after the pot lost all pink color and went to a yellowish shade. Analysis of this solution by NMR showed trimers **4**. The solution in the collection flask was stirred for 2.5 h, and the solvent was distilled off. The residue was treated as for **8** above, and flash chromatography (50% ether–hexane) afforded 66.2 mg (31%) of pure enone **8**.

Reaction of 2 with Phenyllithium. A solution of **2** (3 mL, prepared from 26.4 mg of **3** as above) in ether was cooled to 0 °C under N_2, and 0.10 mL of a 1.8 M solution of phenyllithium in 70:30 cyclohexane–ether (Aldrich) was added via syringe. After being stirred for 0.5 h, the mixture was allowed to warm to 20 °C for 0.5 h. It was poured into an equal volume of saturated aqueous NH_4Cl and extracted with 3 × 20 mL portions of CH_2Cl_2. The extracts were combined, dried over $MgSO_4$, filtered, and evaporated to afford 44 mg of residue. NMR analysis showed a 2:1 mixture of trimers **4** and neopentyl phenyl sulfide **10** (9.7 mg, 0.054 mmol, 30%) isolated by flash chromatography (15% CH_2Cl_2–hexane).

10: oil, separated on silica gel 60 F254, 15% CH_2Cl_2–hexane, R_f = 0.42; *m/e*, exact mass for $C_{11}H_{16}S$ 180.0969, found 180.0973; error = 2.3 ppm; 200 MHz NMR ($CDCl_3$, ppm) 7.6–7.1 (5 H, m), 2.9 (2 H, s), 1.04 (9 H, s).

Reaction of 2 with *n*-Butyllithium. Five milliliters of an ether solution of **2** (generated as above from 47.6 mg of **3**) was cooled to 0 °C, and 0.30 mL of a 1.55 M solution of *n*-butyllithium in hexane was added dropwise via syringe. The pink color disappeared immediately. After the mixture was warmed to 20 °C, 35 μL (0.56 mmol) methyl iodide was added, and the solution was allowed to stir an additional 0.5 h. It was poured into an equal volume of saturated aqueous NH_4Cl, extracted with 3 × 20 mL of CH_2Cl_2, dried over $MgSO_4$j, filtered, and evaporated to afford 62.6 mg of an oil. Yields of **11** (70%, 28 mg) and neopentyl methyl sulfide **12** (17%, 4 mg) were estimated by NMR analysis. The oil was eluted on flash silica gel (5% ethyl acetate–hexane) to afford 11 mg of pure **11** and 21 mg of unresolved **11** + **12** as a mixture.

11: oil, separated on silica gel 60 F254, 5% ethyl acetate–hexane, R_f = 0.66; *m/e*, exact mass for $C_{10}H_{22}S$ 174.1437, found 174.1432; error = 2.9 ppm; 200 MHz NMR ($CDCl_3$, ppm) 2.61 (1 H, t, J = 7 Hz), 2.02 (3 H, s), 1.4–1.15 (6 H, m), 0.89 (9 H, s), 0.83 (3 H, t, J = 7 Hz).

12: oil, separated on silica gel 60 F254, 5% ethyl acetate–hexane, R_f 0.52; *m/e*, exact mass for $C_6H_{14}S$ 118.0813, found 118.0819; error = 5.1 ppm; 200 MHz NMR ($CDCl_3$, ppm) 2.42 (2 H, s), 2.11 (3 H, s), 0.97 (9 H, s).

Reaction of 2-*tert*-Butyl-1,3-dithiolane (13) with *n*-Butyllithium. The procedure of Wilson et al.[8d] was followed, so that 5 mL of an ether solution of **13**[25] (129.5 mg, 0.80 mmol) under N_2 was treated with 2.00 mL of a 1.55 M hexane solution of *n*-BuLi with stirring for 4 h at 20 °C. The reaction was quenched by addition of methyl iodide (200 μL, 3.21 mmol). The mixture was poured into saturated aqueous NH_4Cl and extracted with 3 × 20 mL portions of CH_2Cl_2. The extracts were combined, dried over $MgSO_4$, filtered, and evaporated. Yields of sulfides **11** (39%) and **12** (32%) were determined by NMR analysis of the crude mixture and confirmed by isolation of the two materials by HPLC (5% ethyl acetate–hexane).

Reaction of 2 with (3-Phenylpropylidene)triphenylphosporane. (3-Phenylpropyl)triphenylphosphonium bromide (prepared from the bromide and triphenylphosphine) (128 mg, 0.278 mmol) was suspended in 0.7 mL of THF under N_2, and 0.56 mL of a 0.45 M solution of potassium *tert*-butoxide in THF was added directly via syringe. The resulting orange solution was stirred for 1.5 h and then cooled to −78 °C. Three milliliters of a THF solution of **2** (prepared from 58.7 mg of polymer **3** as above) was cooled to −78 °C. The solution was allowed to warm to 20 °C, excess H_2O was added after 1 h, and all remaining color disappeared. The mixture was extracted with pentane (3 × 3 mL), and the extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The resulting residue was eluted with pentane through a short silica gel plug, and the pentane was evaporated to afford 91.2 mg of material. Nearly pure episulfide **15** was separated from triphenylphosphine by HPLC (2% ether–hexane, 21.1 mg, 0.096 mmol).

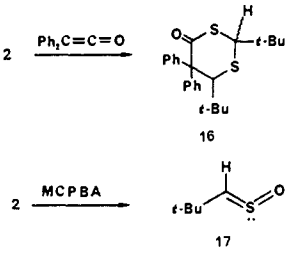
15: oil, separated on silica gel 60 F254, 2% ethyl acetate–hexane, R_f = 0.42; *m/e*, base 91 amu; exact mass for $C_{14}H_{20}S$ 220.1281, found 220.1285; error = 1.7 ppm; IR ($CDCl_3$, 1/cm) (*t*-Bu) 1370; 270 MHz NMR ($CDCl_3$, ppm) 7.34–7.17 (5 H, m), 2.83–2.73 (2 H, m), 2.73–2.64 (2 H, m), 2.17–2.01 (1 H, m), 1.87–1.69 (1 H, m), 0.95 (9 H, s).

Proof of Episulfide Stereochemistry. Episulfide **15** (17.1 mg, 0.0776 mmol) was dissolved in 2 mL of THF and cooled to −78 °C under N_2.

Then, 0.10 mL of a 1.72 M hexane solution of *n*-butyllithium was added via syringe, and the mixture was stirred for 1 h. It was warmed to room temperature overnight and quenched with H_2O. The aqueous layer was extracted with pentane, and the organic portions were combined, dried over $MgSO_4$, filtered, and evaporated. The resulting brown oil was eluted through a short silica gel plug with pentane to afford 11.0 mg (75%) of (*E*)-2,2-dimethyl-6-phenyl-3-hexene: oil, separated on silica gel 60 F254, 2% ether–hexane, R_f = 0.58; *m/e*, exact mass for $C_{14}H_{20}$ 188.156, found 188.1565; error = 2.6 ppm; IR (neat, 1/cm) (*t*-Bu) 1380, (C=C) 1670; 270 MHz NMR ($CDCl_3$, ppm) 7.3–7.13 (5 H, m), 5.44 (1 H, dd, *J* = 15.6 Hz), 5.34 (1 H, dt, *J* = 15.6, 5.8 Hz), 2.65 (2 H, dd, *J* = 7.3, 9.6 Hz), 2.28–2.24 (2 H, m), 0.97 (9 H, s).

Oxidation of 2 with mCPBA. A solution of **2** in 1 mL of $CDCl_3$ (+repared as above from 5.6 mg of polymer **3**) was cooled to −78 °C under N_2, and 182 μL of a 100 mg/mL $CDCl_3$ solution of *m*-chloroperbenzoic acid (Aldrich, 80–85%, 55 μmol) was titrated via syringe to a colorless endpoint. Direct NMR analysis of the reaction medium showed signals corresponding to *m*-chlorobenzoic acid, a trace of trimers **4** and sulfine **17** (identified as the *E* isomer by comparison with literature spectra[22]) in the molar ratio 9.5:1:8.

Reaction of 2 with Diphenylketene. Two milliliters of a $CDCl_3$ solution of **2** (generated as above from 12 mg of **3**) were treated under N_2 with 0.15 mL of a 0.50 M solution of diphenylketene[26] in benzene. After the pink color had diminished (1 h), solvent was evaporatd and the resulting residue was eluted on a PTLC plate (20% ether–hexane). The R_f 0.59 band was isolated as a 3:1 inseparable mixture of diasteriomers of **16** (11.2 mg, 0.0282 mmol).



16: oil, separated on silica gel 60 F254, 20% ether–hexane, R_f 0.59; *m/e*, base = 105 amu; exact mass for $C_{24}H_{30}OS_2$ 398.1731, found 398.1739; error = 2 ppm; IR ($CDCl_3$, 1/cm) (C=O) 1670; 200 MHz NMR ($CDCl_3$, ppm) 7.75–7.28 (10 H, m), 4.8 (1 H, s), 4.43 (1 H, s) 1.19 (9 H, s), 0.76 (9 H, s). Isomer: 200 MHz NMR ($CDCl_3$, ppm) 7.75–7.28 (10 H, m), 4.51 (1 H, s), 4.32 (1 H, s) 1.15 (9 H, s), 0.73 (9 H, s).

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Host–Guest Complexation. 38. Cryptahemispherands and Their Complexes[1]

Donald J. Cram,* Siew Peng Ho, Carolyn B. Knobler, Emily Maverick, and Kenneth N. Trueblood

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024. *Received October 15, 1985*

Abstract: Syntheses and crystal structures are reported for a new class of hosts, their complexes, and their precursors. The cryptahemispherands **5–8** are composed of molecular modules that are half spherand **1** and half cryptand **3**. They were synthesized by the reactions of diacid chloride **20** with cyclic diamines **21–23** to produce diamides **13–16**, reduction of which gave the desired hosts **5–8**. These diamines were best purified, stored, and handled through their respective hydroborane complexes, **9–12**. Hosts **6** and **7** are diastereomeric, as are diamides **14** and **15** and hydroborane complexes **10** and **11**. Diamines **6** and **7** equilibrate rapidly at 25 °C probably by ring inversion of the methoxyl groups to give a 5:1 ratio of **6** over **7**. Diamides **14** and **15** equilibrate readily at 90 °C to give only **14** in detectable amounts. Hydroborane complexes **10** and **11** do not equilibrate at 90 °C. Cryptahemispherands **5**, **6**, and **8** formed a variety of complexes with the alkali metal cations, diamides **14** and **16** exhibited a low level of binding power, and hydroborane complexes **10** and **12** had no detectable affinity for the alkali metal cations. Hemispherand **17** was synthesized for comparison purposes. Crystal structures were determined for the isomeric diamides **14** and **15**, for hydroborane complex **9**, and for alkali cation complexes **5**·$NaB(Ph)_4$, **6**·KSCN, **8**·NaSCN, **8**·KSCN, and **8**·$CsClO_4$. The trisanisyl modules of all eight compounds possess the same preorganized conformation, with the unshared electron pairs of the three methoxyl groups turned inward and the methyl groups outward. The potential cavities of **9**, **14**, and **15** are filled with inward-turned hydrogens of the ethylene bridges. In the alkali metal ion complexes, the unshared electron pairs of the heteroatoms are all turned inward toward the guest metal ion. The use of CPK molecular models in predicting the structures of complexes is evaluated.

Structures **1–4** portray a prototypical spherand, a hemispherand, a cryptand, and a chorand, respectively. In prior studies, we compared the binding abilities of these types of hosts toward the alkali metal ions in $CDCl_3$ at 25 °C. We concluded that the spherands > cryptands > hemispherands > chorands > podands > solvents in their binding power toward complementary alkali metal ions. The same order applies to their states of organization for binding and being unsolvated prior to complexation. Extensive examinations of the relationships between structure and binding provided the corollary that the highest specificities in alkali metal ion binding were associated with the most highly preorganized systems.[2,3]

The anisyl groups of the hemispherands are self-organizing, whereas the bridging ethyleneoxy groups can turn their unshared electron pairs and methylene groups either inward or outward, depending on the demands of solvent or guests.[4] Because of this

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