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RESEARCH ARTICLE

Derivatization of dicubyl disulfide

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Our recent preparation of dicubyl disulfide (**1**) revealed some unusual properties concerning the S-S as well as the C-S bonds. In our continuing examination of this novel compound, we investigated its oxidation as well as sulfur insertion reactions. The oxidation process delivers all four possible derivatives, whereas the insertion reactions only provided mixed polysulfides.

Keywords: Dicubyl disulfide; Oxidation; Sulfur insertion

1. Introduction

Since the initial synthesis of cubane in 1964 [1], a wide variety of its derivatives have been prepared. Many of these have exhibited some remarkable properties. Octonitrocubane has been classified as the most powerful non-nuclear explosive [2] and cubylamine has been reported to exhibit antiviral activity [3]. Certain cubane derivatives have been reported to undergo cage opening; cubanol has been shown to spontaneously open to form vinylcyclobutenylketene [4, 5]. This phenomenon has also been reported with cubane thiols[4b] as well as cubylamines [6, 7].

In contrast, dicubyl disulfide (**1**) has been shown to be a very stable molecule. Remarkably, it contains the shortest reported C–S bond length of 1.77Å where the carbon is sp^3 hybridized (average 1.86Å); while having a lower than average torsional barrier of 5.2 kcal/mol opposed to the average of 9 kcal/mol [8]. The latter of these properties have been hypothesized to be due to $LP_s \rightarrow \sigma^*$(C–C) bonding–antibonding interactions [8]. These unanticipated results led us to examine derivatives of dicubyl disulfide, in particular its oxidized forms as well as sulfur chain elongation.

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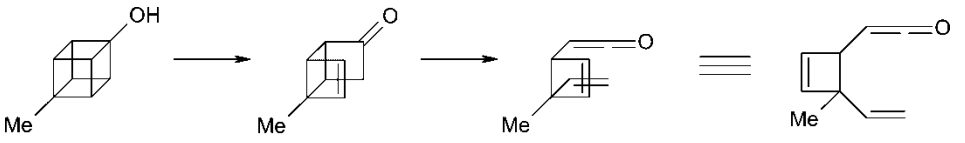


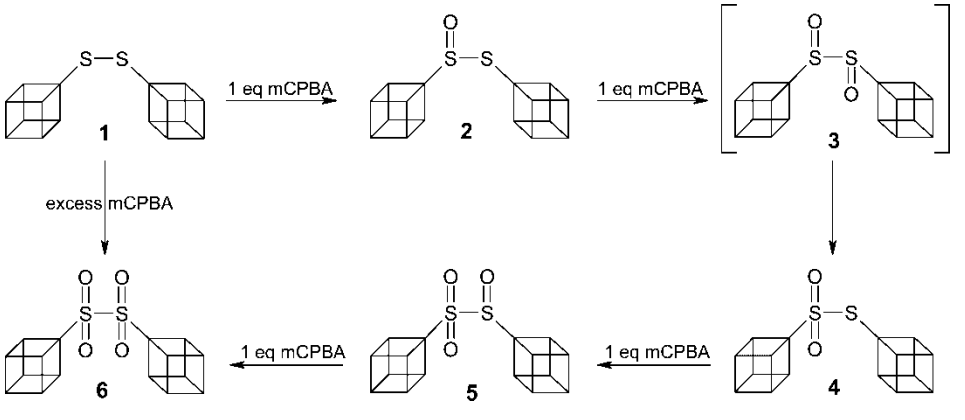
SCHEME 1. Proposed rearrangement of cubanol to vinylcyclobutenylketene [4, 5].

2. Results and discussion

The oxidation of disulfides with various reagents have been well-documented. Two commonly employed reagents are *m*CPBA [9–12] and H_2O_2 [13–16]; we focused on the former for our work (scheme 1). By careful addition of stoichiometric amounts of *m*CPBA to **1,** it was possible to obtain dicubyl thiosulfinate (**2**) in >90% yield, with only moderate amounts of over oxidized products. Similarly, addition of a further equivalent of *m*CPBA to the purified dicubyl thiosulfinate (**2**) yielded the dioxide product, **4**, in 85% yield. As is the norm with the oxidation of disulfides, *vic*-disulfoxide that may initially form, rapidly undergo an intramolecular rearrangement to form thiosulfonates [10, 12–14, 17]. Unfortunately, *vic*-disulfoxide **3** was not detected during the reaction. Stepwise oxidation to the cubylsulfinyl cubylsulfone (**5**) and ultimately to dicubyl *vic*-disulfone (**6**) was successful, as was direct oxidation of dicubyl disulfide (**1**).

Appropriate crystals for X-ray analysis were not obtained of any of oxidized products; however, ^{1}H-NMR did reveal interesting data. The protons on the adjacent carbon (C2) of the starting dicubyl disulfide (**1**), more commonly referred to as the 'ortho' protons, appear at 3.95 ppm; this is a typical chemical shift for cubane and its derivatives [18, 19]. As more oxygen atoms were added, the 'ortho' protons shift further downfield. Upon synthesis of the dicubyl *vic*-disulfone (**6**), the ^{1}H-NMR signal for the 'ortho' protons was at 4.68 ppm. This is the lowest field position for any mono-substituted cubane derivative reported to date. As a comparison, the corresponding proton on nitrocubane (with a much stronger electron withdrawing group) gives a resonance of 4.63 ppm [19].

We theorized that an intramolecular C-H···O hydrogen bond could exist that might rationalize this shift. Using hybrid density functional theory (DFT) at the BLYP level (Accelrys Software Inc., Burlington, Massachusetts, USA) in vacuum, as well as using a dielectric of 4.806 (chloroform), did indeed reveal possible five-membered ring arrangements



SCHEME 2. Synthesis of oxidized derivatives of dicubyl disulfide (**1**).

with a H···O bond lengths of 2.9–3.0 Å, well within the required H-bonding length of <3.2 Å [20]; as well as a C···O bond lengths of 2.9–3.1 Å, again within the required 4.0 Å limit [20].

In addition, six-membered ring systems were also observed with H···O bond lengths of 3.0–3.2 Å, and C···O bond lengths of 3.4–3.8 Å using the DFT calculations. These pseudo-rings had C-H···O bond angles of an average of 82.2° and 102.5° for the five-membered and six-membered rings, respectively. Recently, Tian reported justification for this claim by examining the blue-shifting intramolecular hydrogen bonds of 15 nitrocubane derivatives [21]. This could explain the downfield shift of the 'ortho' protons observed in ^{1}H-NMR *via* an increased acidity. With **6** the additional possible six-membered ring system could explain the even larger downfield shift compared to all other mono-substituted cubane derivatives (figure 1).

Another derivatization of dicubyl disulfide that was undertaken was the formation of dicubyl polysulfides. Earlier work in our laboratory determined that 1–3 sulfur units could be transferred to various disulfides using triphenylmethylsulfenyl chloride compounds [22–24]. The use of sulfenyl chloride **7** delivers one sulfur atom into the disulfide bond, triphenylmethylthiosulfenyl chloride (**8**) delivers two, and the dithio derivative **9** afforded three (figure 2). Using this methodology, it was hoped that the dicubyl tri- to pentasulfides could be obtained.

While the reaction did not afford any detectable amounts of the symmetric polysulfides, we were able to isolate the corresponding mixed sulfides. The final step in the formation of the polysulfide is believed to involve the attack of the sulfur attached to the triphenylmethyl group on the sulfur bearing the chlorine atom (scheme 2). The obvious bulk of **1** and **8** provides a rationale as to why the reaction did not proceed to completion. The steric effect is further complicated by the fact that the carbon-sulfur bond of cubylsulfenyl chloride would most likely be shorter than normal, as is observed with the dicubyl disulfide [8].

We thus focused on synthesizing the series of mixed cubyltriphenylmethyl polysulfides. The tri- and tetrasulfides (**10** and **11**) were successfully prepared (figure 3); however the cubyltriphenylmethyl disulfide was not obtained. Steric considerations are likely to blame whereby the initial attack on the sulfur connected to the triphenylmethyl group was blocked.

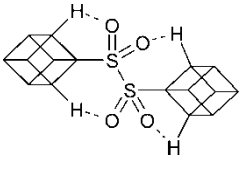


Figure 1. Possible intramolecular H-bonding of dicubyl *vic*-disulfone (**6**) forming 5 and 6-membered arrangements.

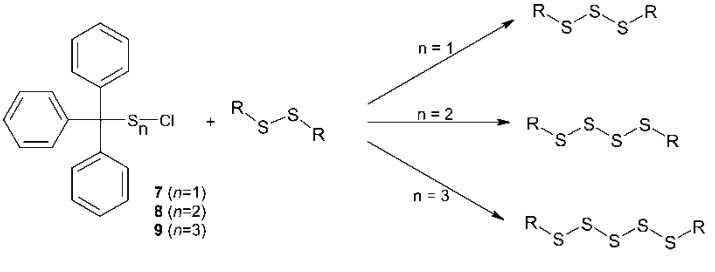
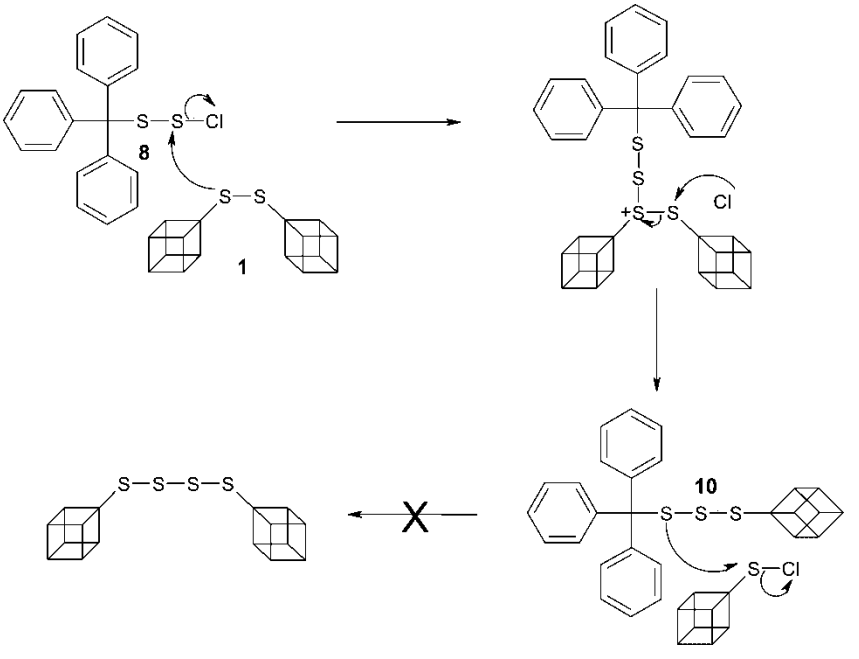


Figure 2. Method for formation of polysulfides from disulfides.



SCHEME 3. Proposed mechanism for the formation of dicubyl tetrasulfide.

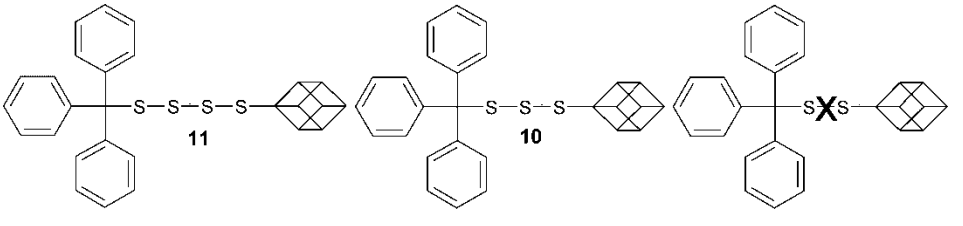


Figure 3. Series of target cubyltriphenylmethyl polysulfides.

3. Experiment

All commercial reagents were obtained from Aldrich Chemical Company and tested by ^{1}H NMR for purity. Solid reagents were recrystallized when needed and distillations were performed on liquid reagents when required. THF and benzene were distilled over sodium and benzophenone; CH_2Cl_2 and Et_3N over calcium hydride. Compound **1** was synthesized as previously described [8].

Thin Layer Chromatography were performed on 0.25 mm Silicycle silica gel plates with aluminum backing and visualized using UV light, iodine absorbed onto silica gel, followed by a 10% aqueous sulfuric acid solution of ammonium molybdate–cerium sulfate developing dip. Column chromatography was carried out on Silicycle (230–400 mesh) using flash chromatography conditions. Melting points were obtained using open end capillaries on Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR were recorded on Varian 400 MHz. Chemical shifts are reported in parts per million (ppm) and referenced to TMS.

3.1 *Dicubyl thiosulfinate (2) from dicubyl disulfide (1)*

To a solution of dicubyl disulfide (0.12 g, 0.45 mmol) dissolved in dry CH_2Cl_2 (50 mL) under N_2, at 0°C, *m*CPBA (0.090 g, 0.45 mmol) was added in one portion. After 10 min the solution was warmed to room temperature and allowed to stir for 4 h. The reaction was quenched with the addition of H_2O (25 mL) and the layers were separated. The organic layer was washed with H_2O (2 X 25 mL) and brine (25 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure to dryness. Column chromatography [$CHCl_3$] afforded dicubyl thiosulfinate (**2**, 0.12 g, 91%) as a white solid; mp 128–130°C. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 4.04$ (m, 1H), 4.08 (m, 7H), 4.24 (m, 3H), 4.44 (m, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): $\delta = 45.04$, 45.40, 48.34, 48.46, 49.87, 54.06, 58.75, 69.97. Elemental anal.: calcd $C_{16}H_{14}S_2O$: C 67.10, H 4.93; found C 67.06, H 4.88.

3.2 *Dicubyl dicubyl thiosulfonate (4) from dicubyl thiosulfinate (2)*

To a solution of dicubyl thiosulfinate (0.10 g, 0.35 mmol) dissolved in dry CH_2Cl_2 (50 mL) under N_2, at 0°C, *m*CPBA (0.071 g, 0.36 mmol) was added in one portion. After 10 min the solution was warmed to room temperature and allowed to stir for 3h. The reaction was quenched with the addition of H_2O (25 mL) and the layers were separated. The organic layer was washed with H_2O (2 X 25 mL) and brine (25 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure to dryness. Column chromatography [$CHCl_3$] afforded dicubyl thiosulfonate (**4**, 0.091g, 85%) as a white solid; mp 68–70°C. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 4.07$ (m, 8H), 4.16 (m, 3H), 4.49 (m, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): $\delta = 44.31$, 45.57, 48.04, 48.29, 50.36, 54.77, 60.21, 71.74. Elemental anal.: calcd $C_{16}H_{14}S_2O_2$: C 63.55, H 4.67; found C 63.67, H 4.51.

3.3 *Cubylsulfinyl cubylsulfone (5) from dicubyl thiosulfonate (4)*

To a solution of dicubyl thiosulfonate (0.070 g, 0.24 mmol) dissolved in dry CH_2Cl_2 (30 mL) under N_2, at 0°C, *m*CPBA (0.050 g, 0.26 mmol) was added in one portion. After 10 min the solution was warmed to room temperature and allowed to stir for 7 h. The reaction was quenched with the addition of H_2O (25 mL) and the layers were separated. The organic layer was washed with H_2O (2 X 25 mL) and brine (25 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure to dryness. Column chromatography [$CHCl_3$] afforded cubylsulfinyl cubylsulfone (**5**, 0.061 g, 78%) as a white solid; mp 79–80°C. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 4.07$ (m, 5H), 4.18 (m, 3H), 4.58 (m, 3H), 4.63 (m, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): $\delta = 45.33$, 46.20, 47.86, 48.09, 51.62, 53.81, 69.17, 70.26. Elemental anal.: calcd $C_{16}H_{14}S_2O_3$: C 60.35, H 4.43; found C 60.07, H 4.41.

3.4 *Dicubyl vic-disulfone (6) from cubylsulfinyl cubylsulfone (5)*

To a solution of cubylsulfinyl cubylsulfone (0.051 g, 0.16 mmol) dissolved in dry CH_2Cl_2 (30 mL) under N_2, at 0°C, *m*CPBA (0.030 g, 0.17 mmol) was added in one portion. After 10 min the solution was warmed to room temperature and allowed to stir for 6 h. The reaction was quenched with the addition of H_2O (25 mL) and the layers were separated. The organic layer was washed with H_2O (2 X 25 mL) and brine (25 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure to dryness. Column chromatography [$CHCl_3$] afforded dicubyl *vic*-disulfone (**6**, 0.050 g, 93%) as a white solid; mp 150–153°C. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 4.00$ (m, 2H), 4.17 (m, 6H), 4.68 (m, 6H). ^{13}C-NMR (100.6 MHz, $CDCl_3$):

δ = 46.36, 47.76, 51.37, 68.88. Elemental anal.: calcd $C_{16}H_{14}S_2O_4$: C 57.47, H 4.22; found C 57.46, H 4.16.

3.5 *Dicubyl vic-disulfone (6) from dicubyl disulfide (1)*

To a solution of dicubyl disulfide (0.110 g, 0.390 mmol) dissolved in dry CH_2Cl_2 (50 mL) under N_2, at 0°C, *m*CPBA (0.380 g, 1.96 mmol) was added in one portion. After 10 min the solution was warmed to room temperature and allowed to stir overnight. The reaction was quenched with the addition of H_2O (25 mL) and the layers were separated. The organic layer was washed with H_2O (2 X 25 mL) and brine (25 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure to dryness. Column chromatography [$CHCl_3$] afforded dicubyl *vic*-disulfone (**6**, 0.12 g, 94%) as a white solid; mp 151–153°C.

3.6 *Cubyltriphenylmethyl trisulfide (10) from dicubyl disulfide (1)*

To a solution of dicubyl disulfide (0.050 g, 0.19 mmol) dissolved in dry CH_2Cl_2 (3 mL) under N_2, at 0°C, triphenylmethylthiosulfenyl chloride (0.070 g, 0.20 mmol) dissolved in dry CH_2Cl_2 (3 mL) under N_2 was cannulated in. After 10 min the solution was warmed to room temperature and allowed to stir for 2 h, then evaporated to dryness. Column chromatography [hexanes] afforded cubyltriphenylmethyl trisulfide (**10**, 0.030 g, 45%) as an off-white solid; mp 84–86°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.96 (m, 3H), 4.02 (m, 1H), 4.07 (m, 3H), 7.25–7.36 (m, 15H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 44.67, 48.83, 52.61, 62.69, 73.31, 126.96, 127.78, 130.24, 143.34. Elemental anal.: calcd $C_{27}H_{22}S_3$: C 73.26, H 5.01; found C 72.98, H 5.14.

3.7 *Cubyltriphenylmethyl tetrasulfide (11) from dicubyl disulfide (1)*

To a solution of dicubyl disulfide (0.050 g, 0.19 mmol) dissolved in dry CH_2Cl_2 (3 mL) under N_2, at 0°C, triphenylmethyldithiosulfenyl chloride (0.070 g, 0.19 mmol) dissolved in dry CH_2Cl_2 (3 mL) under N_2 was cannulated in. After 10 min the solution was warmed to room temperature and allowed to stir for 2h, then evaporated to dryness. Column chromatography [hexanes] afforded cubyltriphenylmethyl tetrasulfide (**11**, 0.041 g, 43%) as an off-white solid; mp 89–91°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.95 (m, 3H), 4.02 (m, 1H), 4.06 (m, 3H), 7.26–7.38 (m, 15H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 44.61, 48.56, 52.79, 61.99, 73.48, 127.14, 127.83, 130.10, 142.87. Elemental anal.: calcd $C_{27}H_{22}S_4$: C 68.61, H 4.67; found C 68.55, H 4.61.

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