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Skeletal Reorganization of Mercaptoacetaldehyde Dialkyl Acetal in Acid: Formation of Disulphide, 1,2-Bis(mercapto)ethylene and 1,1,2-Tris(mercapto)ethane Derivatives

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The reaction of mercaptoacetaldehyde dialkyl acetals **1a-c** in the presence of sulfuric acid, polyphosphoric acid and zinc chloride is described. Other than the disulfide reported previously, new compounds 1,2-bis-(mercapto)ethylene, 1,2,3-tris-(mercapto)ethane and 1,2-bis-(mercapto)methane have been isolated for the first time.

INTRODUCTION

Mercaptoacetaldehyde dialkyl acetal derivatives have been prepared from the nucleophilic addition of the corresponding sulfide salts to bromo- or chloroacetaldehyde dialkyl acetal.[1] It has been reported that acidic reagents readily cause fission of the sulfur carbon bond in mercaptoacetaldehyde dialkyl acetal, and this gives rise to the corresponding disulfide and tar.[2] Thus, sulfuric acid was found to promote the formation of di-2-napthyl sulfide as the principle product from mercaptoacetaldehyde dimethyl acetal. Recently, Clark[3] reported the formation of diphenyl disulphide from the reaction of phenylmercaptoacetaldehyde diethyl acetal over zinc chloride-promoted montmorillonite clay together with benzothiophene. Benzothiophene can also be obtained when mercaptoacetaldehyde dialkyl acetals were treated with an excess of polyphosphoric acid and the product vacuum distilled directly from the reaction mixture.

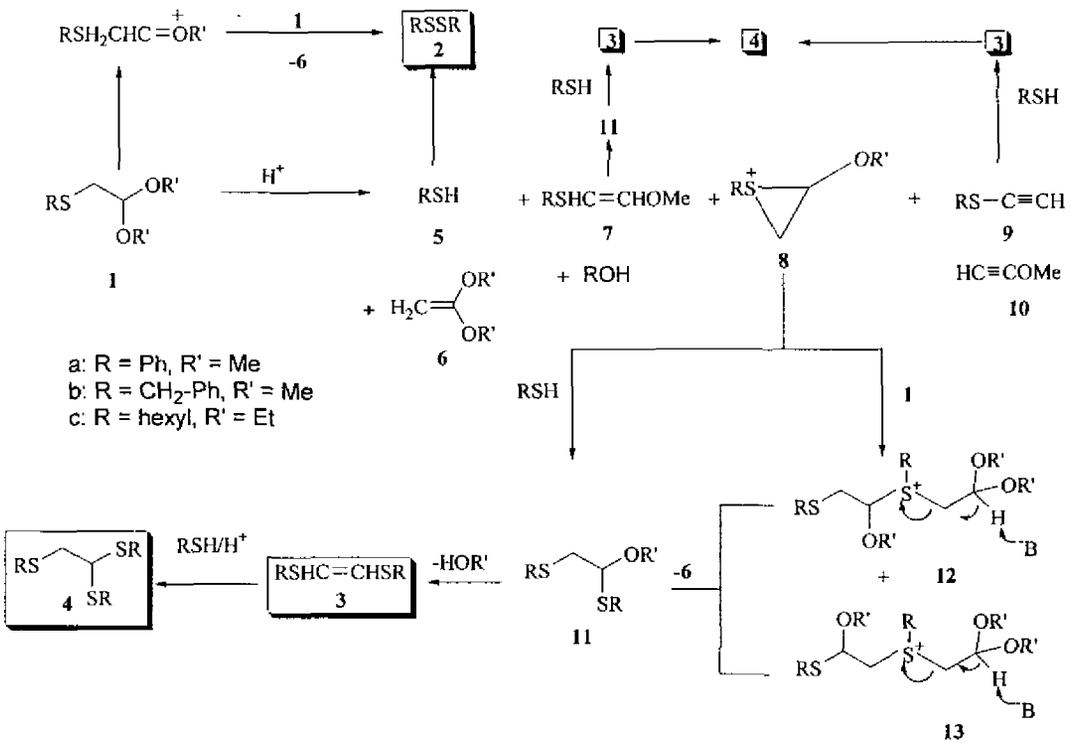
It was known in our laboratory that 2,3-dimercapto-1-propanol under acidic conditions rearranges to dialkyl sulfide, dialkyl disulfide and 1,2,3-tris-(alkylthio)propane through the release of free alkylmercaptan during the reaction.[4] The reaction of mercaptoacetaldehyde dialkyl acetal with acid is in close parallel to our studies in the acid catalyzed rearrangement of 2,3-dimercapto-1-propanol and should give rise to a wide array of products other than the disulfide which has been reported. This led us to carry out a more detailed investigation on the products that arise from the acid catalysis of mercaptoacetaldehyde dialkyl acetal.

RESULTS AND DISCUSSION

The phenylmercaptoacetaldehyde dimethylacetal **1a**, benzylmercaptoacetaldehyde **1b** and hexylmercaptoacetaldehyde **1c** were readily prepared from bromo- or chloroacetaldehyde dimethyl acetal with the corresponding mercaptan in the presence of sodium hydride.[1] We began our investigation by reaction of compound **1a** in the presence of concentrated sulfuric acid under various conditions, and this was worked up after the disappearance of the starting material. Thus **1a** was found to give diphenyl disulfide **2a** as the principle product at 0 °C in accordance with previous reports.[2,3] The reaction of **1a** at room temperature gave three principle products; diphenyl disulfide **2a**, 1,2-bis-(phenylmercapto)ethylene **3a** and 1,1,2-tris-(phenylmercapto)ethane **4a** in equal amounts. Somewhat interestingly, the reaction in refluxing toluene gave 1,1,2-tris-(phenylmercapto)ethane **4a** as the major product. This is the first report for the formation of **3a** and **4a** during the reaction.

Compound **1a** can be protonated at either the sulfur or oxygen atom by acid. Protonation at the sulfur atom may lead to the elimination of phenylmecaptan **5** together with the formation of 1,1-dimethoxyethylene **6**. In the case of protonation at the oxygen atom, this may lead to the following reaction: (i) the elimination of a methanol to give 1-methoxy-2-phenylmercaptoethylene **7**; (ii) the formation of a thiarinium intermediate **8**; and (iii) the further elimination of methanol from **7** to give phenylmercaptoacetylene **9** or the elimination of phenylmercaptan **5** to give methoxyacetylene **10**. The possible existence of thiarinium intermediate has been previously pointed out.[5] The formation of **3a** and **4a** can be explained by the addition of the phenylmercaptan **5** or the sulfur atom of another **1a** as proposed by Clark[3] to either the thiarinium intermediate **8**, phenylmercaptoethylene **7**, or mercapto-acetylene **9** in the bulk solution (Scheme I). The reaction of 1-methoxy-2-phenylmercaptoethylene **7** and thiarinium intermediate **8** with phenylmercaptan give rise to 1-methoxy-1,2-bis-(phenylmercapto)ethane **11** which then eliminates a molecule of methanol to give

Scheme I Proposed pathways leading to the formation of **2**, **3**, **4**



1,2-bis-(phenylmercapto)ethylene **3a**. Also, the reaction of thiarinium **8** with another molecule of **1a** give rise to intermediate **12** and/or **13** which further undergo the elimination of 1,1-dimethoxyethylene to give **11** and finally **3a**. One closest parallel mechanism is the reported reaction of chloroacetaldehyde dimethyl acetal with n-butyl mercaptan which gave 1,2-bis-(n-butylmercapto)ethylene and 11,2-tris-(n-butylmercapto)ethane.[6] Likewise, the phenylmercaptoacetylene by the elimination of two methanol molecules from **1a**, can also react with phenylmercaptan to give **3a**. *It has been reported that 1,2-bis-(phenylmercapto)ethylene* **3a** can be synthesized directly from the reaction of phenylmercaptoacetylene with phenylmercaptan.[7] The attack of **3a** by another molecule of phenylmercaptan led to the formation of 1,1,2-tris-(mercaptophenyl)ethane **4a**, and this is favored under refluxing toluene. The formation of diphenyl disulfide **2a** should arise from the oxidative dimerisation of phenylmercaptan in the solution.[8] This can thus account for all the products formed in Scheme I.

The reactions of benzylmercaptoacetaldehyde dimethyl acetal **1b** and hexylmercaptoacetyldehyde diethyl acetal **1c** were also studied and similar trends were observed. The results are summarized in Table 1. Treatment of **1b** with sulfuric acid at 0 °C also gave dibenzyl disulfide **2b**; at room temperature gave dibenzyl disulfide **2b** and 1,2-bis-(benzylmercapto)ethylene **3b**; and in refluxing toluene gave 1,1,2-tris-(benzylmercapto)ethane **4b** as the major product. The reaction of **1c** is more interesting, whereby reaction at 0 °C gave dihexyl disulfide **2c** and a trace amount of 1,2-bis-(hexylmercapto)ethylene **3c**, 1,1,2-tris-(hexylmercapto)ethane **4c** together with a new product, bis-(hexylmercapto)methane **14**. Similar products were obtained for the reaction of **1c** at room temperature and under refluxing toluene. It was thought that the bis-(hexylmercapto)methane **14** might arise from 1,1,2-tri-(hexylmercapto)ethane **4c**. This was proven by refluxing **4c** with sulfuric acid to give bis-(hexylmercapto)methane **14** and dihexyl disulfide **2c**. In all these reactions, side reactions leading to polymeric products occur to a significant degree.

We were curious as to whether the reaction by other acid catalysis can give the same results. We turned our attention to polyphosphoric acid.[1,9] No appreciable reaction was observed at 0 °C and room temperature. The results for the reaction of **1a**; **b**, **c** with polyphosphoric acid in refluxing xylene are summarized in Table 2. The reaction in refluxing toluene was found to give a lower yield of **7a-c**. Thus somewhat disappointingly, PPA promotes the elimination of alkanol from **1a-c** to give 1-alkoxy-2-mercaptoethylene **7a-c** as the major product. This might be due to the more favorable coordination of the alkoxy oxygen to the phosphorus site in polyphosphoric acid, leading to the selective elimination of methanol. Formation of benzothiophene

Table 1. Products from Thioacetals Reacted in Conc. H_2SO_4/toulene

S.M.	T(°C)	Time(d)[a]	$2(RS)_2$ (%)	$3(RSCH)_2$[b] (%)	$4RSCH_2CH(RS)_2$ (%)	$14(RS)_2CH_2$ (%)
1a	reflux	3	*	0	12	
	r.t.	12	2	4	*	
	0 °C	14	2	0	0	
1b	reflux	3	6	0	60	
	r.t.	5	4	2	0	
	0 °C	16	2	0	0	
1c	reflux	2	16	0	12	4
	r.t.	4	10	*	2	2
	0 °C	15	2	*	*	*

[a] Reaction was worked up after disappearance of starting material.
[b] **3b**: *cis*:*trans* = 1.7:1, **3c**: *cis*:*trans* = 5.6:1. * Minute amount.

Table 2. Products from Thioacetals Reacted in PPA/o-xylene

S.M.	Time(hr)[a]	2RSSR(%)	7RSCHCHOR'[b](%)
1a	12	2	10
1b	5	*	50
1c	48	10	17

[a] Reaction was worked up after disappearance of starting material.
[b] **12a**: *cis*:*trans* = 1:3.1, **12b**: *cis*:*trans* = 1:2.5, **12c**: *cis*:*trans* = 1:1. * Minute amount.

from **1a** under this condition was not observed.

The above results led us to re-examine the reaction of **1a-c** with zinc chloride as the catalyst in dichloromethane following the report of Clark,[3] but in the absence of montmorrillonite clay. The results are shown in Table 3. At 0 °C, no reaction was observed for **1a-c**. The reaction at room temperature gave the disulfides **2a, b, c** as the principle products. When **1a, b** were refluxed, disulfides **2a, b** were again formed as the principle products. This was similar to that reported by Clark[5] when **1a** was treated with a small ratio of montmorillonite K 10-$ZnCl_2$ catalyst (0.1 ratio) giving diphenyl disulfide **2a** as the principle product. As proposed by Clark,[3] the zinc chloride would be expected to coordinate with the oxygen atom and intermolecular attack by sulfur of another molecule led to the formation of disulfide selectively. Furthermore, the phenyl ring serves as a bonus for the coordination. Surprisingly, **1c** under refluxing condition was found to give the disulfide **2c**, together with a substantial amount of bis(mercapto)methane **14**. This can be envisaged to arise from the weaker interaction of **1c** with zinc chloride, whereby a mechanism similar to that of sulphuric acid can take place.

CONCLUSION

These results suggest that mercaptoacetaldehyde dial-

Table 3. Products from Thioacetals Reacted in $ZnCl_2/CH_2Cl_2$

S.M.	T(°C)	Time(d)[a]	$2(R^1S)_2$ (%)	$3(R^1SCH)_2$ (%)	$4R^1SCH_2CH(R^1S)_2$ (%)	$14(RS)_1CH_2$ (%)
1a	reflux	4	2	0	0	
	r.t.	7	8	0	1	
	0 °C	14	0	0	0	
1b	reflux	14	2	0	0	
	r.t.	14	6	0	0	
	0 °C	14	0	0	0	
1c	reflux	8	24	*	*	16
	r.t.	9	30	0	*	*
	0 °C	11	0	0	0	0

[a] Reaction was worked up after disappearance of starting material.
* Minute amount.

kyl acetal derivatives can undergo a wide array of reactions to give disulfide, 1,2-bis(mercapto)ethylene, 1,1,2-tris-(mercapto)ethane and bis(mercapto)methane. Overall, the type of principle product(s) obtained is dependent on the acid used.

EXPERIMENTAL SECTION

All the ^{1}H NMR spectra were recorded at 300 MHz in chloroform-d solution. All column chromatography operations were conducted using Kieselgel 60 (70-230 mesh).

General Method For Preparing Mercaptoacetaldehyde Dialkyl Acetal

To a solution of mercaptan (1 eq.) in dried THF was added sodium hydride (1.5 eq.). The mixture was left to reflux for 2 h under nitrogen and then cooled to room temperature. After this period, the bromo- or chloroacetaldehyde dimethyl acetal (1 eq.) reagent was added and the mixture refluxed for 2 days. The solvent was removed on a rotary evaporator and ice water added, followed by extraction with CH_2Cl_2.

Phenylmercaptoacetaldehyde Dimethyl Acetal 1a

This was prepared using reported methods.[10,11] Yield, 83% (Oil) ^{1}H NMR δ 3.11 (d, J = 5.5 Hz, 2H), 3.34 (s, 6H), 4.53 (t, J = 5.5 Hz, 1H), 7.21-7.42 (m, 5H); *m/z* (EI) 198 (M^+), 167, 135, 109, 75.

Benzylmercaptoacetaldehyde Dimethyl Acetal 1b

This was prepared using reported methods.[12,13] Yield, 98% (Oil) ^{1}H NMR δ 2.59 (d, J = 5.5 Hz, 2H), 3.33 (s, 6H), 3.77 (s, 2H), 4.40 (t, J = 5.5 Hz, 1H), 7.21-7.33 (m, 5H); *m/z* (EI) 212 (M^+). [Found (EI) M^+ 212.0871. $C_{11}H_{16}O_2S$ requires 212.0863].

Hexylmercaptoacetaldehyde Diethyl Acetal 1c

This was prepared using bromoacetaldehyde diethoxy acetal.[14] Yield, 99% (Oil) ^{1}H NMR δ 0.89 (t, J = 6.6 Hz, 3H), 1.20-1.58 (m, 8H), 2.59 (t, J = 7.5 Hz, 2H), 2.70 (d, J = 5.4 Hz, 2H), 3.53-3.71 (m, 10H), 4.61 (t, J = 5.4 Hz, 1H); *m/z* (EI) 234 (M^+). [Found (EI) M^+ 234.1653. $C_{12}H_{26O2}S$ requires 234.1637].

Rearrangements by H_2SO_4 and PPA

To the mercaptoacetaldehyde dialkyl acetal in dried solvent was added a catalytical amount of the acids. This was either kept at 0 °C, room temperature or under reflux. The progress was checked with TLC until no more new spots appeared and most of the starting material was consumed. The solvent was removed on a rotary evaporator and NaOH(aq) added, followed by extraction with CH_2Cl_2. The results are shown in Tables 1 and 2.

Rearrangement by Zinc Chloride

The mercaptoacetaldehyde dialkyl acetal in dried CH_2Cl_2 was added with anhydrous $ZnCl_2$ (5 molar ratio) and then worked up as above and the results are shown in Table 3.

1,2-Bis-(phenylmercapto)ethylene 3a

This was prepared using reported methods.[7,15] (Oil) ^{1}H NMR δ 6.52 (d, J = 2.2 Hz, 2H), 7.26-7.52 (m, 10H); *m/z* (EI) 244 (M^+). [Found (EI) M^+ 244.0380. $C_{14}H_{12}S_2$ requires 244.0378]. Found: C, 68.62; H, 4.98. $C_{14}H_{12}S_2$ requires C, 68.84; H, 4.96.

1,2-Bis-(benzylmercapto)ethylene 3b

This was prepared using reported methods.[16,17] (Oil) ^{1}H NMR δ 3.91 (s, 4H), 6.01 (s, 2H), 7.26-7.30 (m, 10H); *m/z* (EI) 272 (M^+). [Found (EI) M^+ 272.0693. $C_{16}H_{16}S_2$ requires 272.0698]. Found: C, 70.16; H, 5.88. $C_{16}H_{16}S_2$ requires C, 70.57; H, 5.93.

1,2-Bis-(hexylmercapto)ethylene 3c

(Oil) ^{1}H NMR (*cis* form) δ 0.89 (t, J = 6.7 Hz, 6H), 1.26-1.42 (m, 12H), 1.57-1.67 (m, 4H), 2.72 (t, J = 7.5 Hz, 4H), 6.06 (s, 2H); (*trans* form) δ 0.89 (t, J = 6.7 Hz, 6H), 1.26-1.42 (m, 12H), 1.57-1.67 (m, 4H), 2.72 (t, J = 7.5 Hz, 4H), 6.12 (s, 2H); *m/z* (EI) 260 (M^+). [Found (EI) M^+ 260.1611. $C_{14}H_{28}S_2$ requires 260.1632].

1,1,2-Tris-(phenylmercapto)ethane 4a

This was prepared using reported methods.[18] (Oil) ^{1}H NMR δ 3.26 (d, J = 7.2 Hz, 2H), 4.38 (t, J = 7.2 Hz, 1H), 7.20-7.46 (m, 15H); *m/z* (EI) 354 (M^+). [Found (EI) M^+ 354.0554. $C_{20}H_{18}S_3$ requires 354.0570]. Found: C, 68.02; H, 5.07. $C_{20}H_{18}S_3$ requires C, 67.75; H, 5.12.

1,1,2-Tris-(benzylmercapto)ethane 4b

This was prepared using reported methods.[16,19] (Oil) ^{1}H NMR δ 2.79 (d, J = 6.9 Hz, 2H), 3.59 (t, J = 6.9 Hz, 1H), 3.60 (s, 2H), 3.76 (s, 4H), 7.17-7.33 (m, 15H); *m/z* (EI) 396 (M^+). [Found (EI) M^+ 396.1042. $C_{23}H_{24}S_3$ requires 396.1040].

1,1,2-Tris-(hexylmercapto)ethane 4c

(Oil) ^{1}H NMR δ 0.88 (t, J = 6.6 Hz, 9H), 1.27-1.60 (m, 24H), 2.56-2.72 (m, 6H), 2.94 (d, J = 7.2 Hz, 2H), 3.90 (t, J

= 7.2 Hz, 1H); *m/z* (EI) 378 (M^+). [Found (EI) M^+ 378.2449. $C_{20}H_{42}S_3$ requires 378.2444]. Found: C, 63.36; H, 11.20. $C_{20}H_{42}S_3$ requires C, 63.45; H, 11.19.

Bis-(hexylmercapto)methane 14

It was prepared using reported methods.[19,20] (Oil) ^{1}H NMR δ 0.89 (t, *J*= 6.7 Hz, 6H), 1.26-1.60 (m, 16H), 2.63 (t, *J* = 7.5 Hz, 4H), 3.66 (s, 2H); *m/z* (EI) 248 (M^+). [Found (EI) M^+ 248.1635. $C_{13}H_{28}S_2$ requires 248.1632].

1-Methoxy-2-phenylmercaptoethylene 7a

It was prepared using reported methods.[27] (Oil) ^{1}H NMR (*trans* form) δ 3.71 (s, 3H), 5.44 (d, *J* = 12.3 Hz, 1H), 6.92 (d, *J* = 12.3 Hz, 1H), 7.00-7.45 (m, 5H); (*cis* form) δ 3.75 (s, 3H), 5.19 (d, *J* = 5.1 Hz, 1H), 6.41 (d, *J* = 5.1 Hz, 1H), 7.00-7.45 (m, 5H); *m/z* (EI) 166 (M^+).

1-Methoxy-2-benzylmercaptoethylene 7b

(Oil) ^{1}H NMR (*trans* form) δ 3.52 (s, 3H), 3.67 (s, 2H), 5.18 (d, *J* = 12.1 Hz, 1H), 6.61 (d, *J* = 12.1 Hz, 1H), 7.21-7 33 (m, 5H); (*cis* form) δ 3.64 (s, 3H), 3.82 (s, 2H), 4.81 (d, *J* = 5.4 Hz, 1H), 6.13 (d, *J* = 5.4 Hz, 1H), 7.21-7.31 (m, 5H) (*cis*); *m/z* (EI) 180 (M^+). [Found (EI) M^+ 180.0625. $C_{10}H_{12}O_1S_1$ requires 180.0609].

1-Ethoxy-2-benzylmercaptoethylene 7c

(Oil) ^{1}H NMR (*trans* form) δ 0.89 (t, *J* = 6.7 Hz, 3H), 1.24-1.32 (m, 8H), 1.50-1.68 (m, 6H), 2.47 (t, *J* = 7.1 Hz, 3H), 3.75-3.86 (q, *J* = 7.1 Hz, 2H), 5.29 (d, *J* = 12.3 Hz, 1H), 6.69 (d, *J* = 12.3 Hz, 1H); (*cis* form) δ 0.89 (t, *J* = 6.7 Hz, 3H), 1.24-1.32 (m, 8H), 1.50-1.68 (m, 6H), 2.63 (t, *J* = 7.1 Hz, 3H), 3.84-3.94 (q, *J* = 7.1 Hz, 2H), 4.86 (d, *J* = 5.5 Hz, 1H), 6.23 (d, *J* = 5.5 Hz, 1H); *m/z* (EI) 188 (M^+).

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