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Neighboring Group Participation in the Oxidation of Hydroxy Sulfides. Control of the Reaction Courses and Products

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Oxidation of the hydroxy sulfides [$PhS(CH_2)_nCH(OH)R$] with hexabutyldistannoxane (HBD)–bromine system was studied in order to clarify neighboring group participation during the course of reaction. The oxidation products were found to be highly dependent on the positions of the two functional groups [sulfide and hydroxyl group]. Thus hydroxy sulfoxides [$PhSO(CH_2)_nCH(OH)R$] were obtained as the main product when $n=1$ or 2, bromo sulfones [$PhSO_2(CH_2)_nCHBrR$] being predominant when $n=3$ or 4. Keto sulfoxide [$PhSO(CH_2)_nCOR$] was exclusively formed when $n=6$. The results are discussed in terms of the different intramolecular interactions depending on the positions of the two functional groups.

Neighboring group participation is an important factor controlling reactions. For example, neighboring group participation in biological systems operates to fix and activate the substrates in an unequivocal manner particularly in enzymatic reactions.[1]

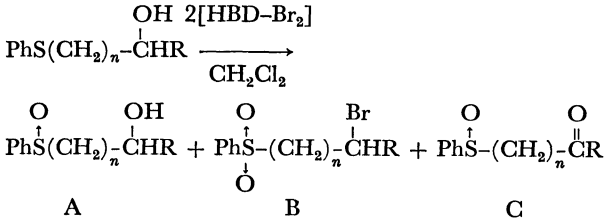
Studies have been carried out to explore the neighboring group participation or intramolecular interactions in static state by means of spectroscopic methods such as IR, UV, Fluorescence, NMR, or ESR spectroscopy.[2] However, no study seems to have been carried out on these subjects during the course of reaction.

In order to investigate neighboring group participation as a function controlling the reaction courses and products, it is important to choose suitable model compounds having two functional groups. We chose hydroxy sulfides, in which both hydroxyl and sulfide groups are isolated systematically by different methylene-chain lengths ($n=1$—6). It was shown that a hexabutyldistannoxane (HBD)–bromine system is an effective oxidant for alcohols[3] or sulfides.[4] Especially this oxidant has one advantage over the existing ones, since sulfides are oxidized selectively to the corresponding sulfoxides without overoxidation to sulfones even in the presence of excess HBD–Br_2. These observations enable us to investigate the oxidation of these two functional groups existing in the same molecule with HBD–Br_2.

Results and Discussion

The hydroxy sulfides were prepared by the usual methods (see Experimental). Oxidation was carried out in dichloromethane at room temperature. Bromine solution (2.4 equiv.) was added to a solution of HBD (2.4 equiv.) and hydroxy sulfides (1 equiv.). The results of oxidation are given in Table 1.

The products were hydroxy sulfoxides (Type A), bromo sulfones (Type B), and Keto sulfoxides (Type C). In some cases, one of the three was formed exclusively.



Distribution of the products depends on the methylene-chain length, Type A being predominant when the two functional groups are located in relatively closer positions ($n=1$ or 2), and Type B when $n=3$ or 4. Keto sulfoxide was formed exclusively when $n=6$. The differences in product distribution should arise from the different neighboring group participations during the course of reaction depending on the distance between the two functional groups. This is discussed in terms of the most fovorable cyclic intermediate in each substrate.

Hydrogen Bonding between Hydroxyl and Sulfoxide Group. Hydroxy sulfoxides (Type A) exibited in their IR spectra an ultimate shift to lower wave numbers of both νO–H (3320—3380 cm^{-1}) and νS–O (990—1020 cm^{-1}) streching frequencies, indicating a strong hydrogen bonding between OH and SO groups. The figures in parentheses indicate isolated yields of hydroxy sulfoxides. The hydrogen bondings seem to prevent the hydroxyl group from further oxidation to the corresponding carbonyl group.

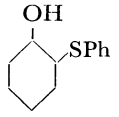
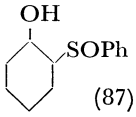
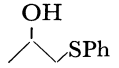
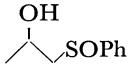
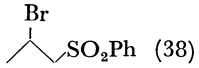
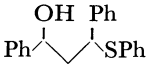
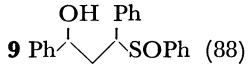
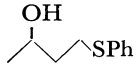
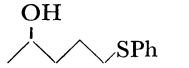
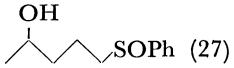
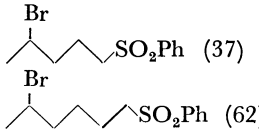
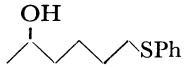
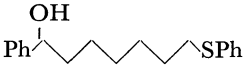
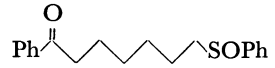
The hydrogen bondings are composed of six-, seven- or eight-membered (less effective) ring systems. Larger ring systems should be extremely unfavorable, since no hydroxy sulfoxides were obtained from **4** and **5**, which should undergo cyclization to nine- and eleven-membered ring, respectively, for the sake of intramolecular hydrogen bonding.

A bulky substituent such as the phenyl group in compound **9** might contribute to the more rigid hydrogen bonding formation by the restriction of the free rotation of the molecule, resulting in a higher yield of hydroxy sulfoxides.

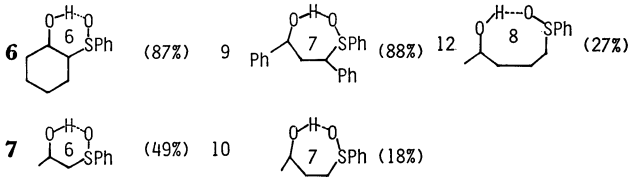
Intramolecular Oxygen Transfer via *Cyclic Alkoxysulfoxonium Ions.* Bromo sulfones (Type B) were obtained unexpectedly, since HBD–Br_2 gave no sulfones. Since both oxidation and work-up were carried out under anhydrous conditions, it is unlikely that the one oxygen atom of the sulfones is derived from the external sources such as water. The formation of bromo sulfones may be best explained by the intramolecular oxygen atom transfer mechanism (Scheme 1).

The detailed mechanism for the formation of the alkoxysulfoxonium bromide (**17**) is not clear. However, a possible scheme is the intramolecular cyclization by the attack of hydroxyl group towards stannyloxysulfonium ion (**16**).[5] This cyclic alkoxysulfoxonium bromide

Table 1. Oxidation of hydroxy sulfides

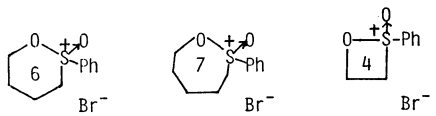
Hydroxy sulfide	Products (%)		
	Hydroxy sulfoxide	Bromo sulfone	Keto sulfoxide
1a 	**6**  (87)		
1b 	**7**  (49)	**8**  (38)	
2a 	**9**  (88)		
2b 	**10**  (18)	t[a]	**11**  (24)
3 	**12**  (27)	**14**  (37) (62)	t[a]
4 			
5 			**15**  (97)

a) Formation of a trace amount of the corresponding products was observed.



(**17**)[6] may be a key intermediate, which undergoes cleavage to a bromo sulfone by the attack of bromide ion. This is supported by the fact that the yield of bromo sulfone (**13**) increases (37%→66%), when lithium bromide is added as an additive.

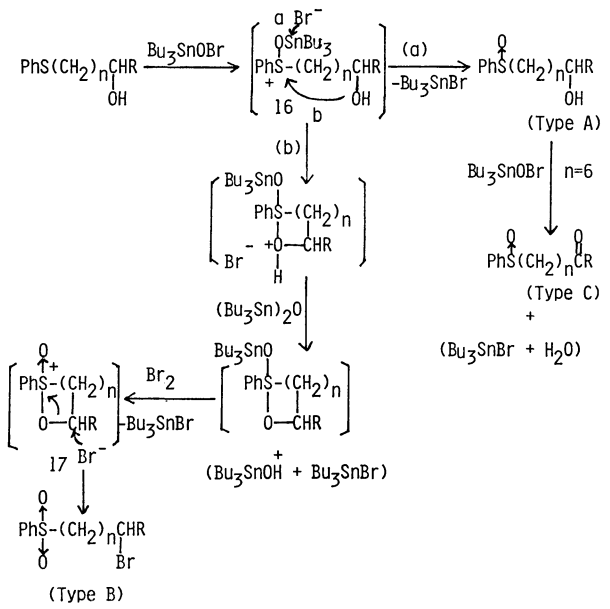
The alkoxysulfoxonium ions again fall into mainly six- and seven-membered rings except one four-membered intermediate.



Keto Sulfoxide Formation. When the hydroxyl and sulfide groups were isolated by six methylene-chains (compound **5**), oxidation proceeded to give keto sulfoxide almost quantitatively. This indicates no appreciable interaction, either hydrogen bonding (eleven-membered ring) or cyclic alkoxysulfoxonium ion formation (nine-membered ring) during the course of reaction, *viz.*, no possible cyclic intermediates more than eight-membered rings opperate, two functional groups behaving independently.

A plausible reaction scheme for the formation of the Type A, B and C products is shown in Scheme 1. Oxidation is assumed to proceed by consumption of twice the molar amount of HBD and bromine except for the formation of Type A product.

In conclusion, mainly more favorable six- and seven-membered cyclic intermediates determine the reaction courses and the products.



Scheme 1.

Experimental

General. Infrared spectra were taken in a film for liquids and KBr pellets for solids using a Hitachi EPI-S2 IR

spectrometer. All NMR spectra were measured with a TMS internal standard using a Varian EM-360 or JEOL JNM-C 100.

Materials. Hydroxy sulfides were prepared by the usual process by means of sodium borohydride reduction of the corresponding keto sulfides in methanol. *trans*-2-Phenylthiocyclohexanol (**1a**) was prepared by the reaction of sodium benzenethiolate with cyclohexene oxide.[7]

*1-Phenylthio-2-propanol (**1b**).* This was obtained in 71% yield from 1-phenylthio-2-propanone; bp 100—120 °C/2 mmHg (1 mmHg=133.322 Pa); NMR (CCl_4) δ=1.20 (d,3, J=6 Hz, CH_3), 2.87 (d, 2, J=6 Hz, SCH_2), 3.43 (s, 1, OH), 3.53—4.07 (m, 1, OCH), and 7.00—7.50 (m, 5, C_6H_5).

*3-Phenylthio-1,3-diphenyl-1-propanol (**2a**).* This was similarly obtained in 96% yield as an oil from 3-phenylthio-1,3-diphenyl-1-propanone: NMR (CCl_4) δ=2.10 (m, 2, CH_2), 2.93 (s, 1, OH), 4.26 (m, 1, OCH), 4.67 (t, 1, J=6 Hz, SCH), and 6.83—7.37 (m, 15, C_6H_5). Found: C, 78.88; H, 6.23%. Calcd for $C_{22}H_{20}OS$: C, 78.70; H, 6.30%.

*4-Phenylthio-2-butanol (**2b**).* This was similarly obtained in 62% yield: bp 105—106 °C/2 mmHg; NMR (CCl_4) δ=1.17 (d, 3, J=6 Hz, CH_3), 1.70 (q, 2, J=6 Hz, CH_2), 2.93—2.97 (m, 3, SCH_2 and OH), 3.87 (m, 1, OCH), and 7.07—7.40 (m, 5, C_6H_5). Found: C, 66.22; H, 8.18; S, 17.45%. Calcd for $C_{10}H_{14}OS$: C, 65.91; H, 7.74; S, 17.56%.

*5-Phenylthio-2-pentanol (**3**).* To a solution of pyridinium chlorochromate (14.7 g, 68 mmol) in dichloromethane (90 ml) was added a solution of 4-phenylthiobutanol (6.2 g, 34 mmol) in the same solvent (15 ml) at room temperature. After being stirred for 2 h, dry ether was added to the mixture, the organic layer being decanted three times. The combined etheral solution was washed with saturated aqueous sodium hydrogencarbonate and aqueous sodium chloride. 4-(Phenylthio)butanal was obtained as a colorless oil after the usual work-up in 43% yield: bp 113—115 °C/1 mmHg; IR 1720 cm^{-1} (νC=O). NMR (CCl_4) δ=1.80 (q, 2, J=6 Hz, CH_2), 2.56 (t, 2, J=6 Hz, CH_2CO), 2.93 (t, 2, J=6 Hz, CH_2S), 7.13—7.17 (m, 5, C_6H_5), and 9.53 (t, 1, J=1.2 Hz, CHO), 2,4-dinitrophenylhydrazone; mp 103—105 °C. Found: C, 53.39; H, 4.40; N, 15.73; S, 8.92%. Calcd for $C_{16}H_{16}N_4O_4S$: C, 53.32; H, 4.48; N, 15.55; S, 8.90%.

To a solution of methylmagnesium iodide prepared from methyl iodide (27 mmol) and magnesium (27 mg atom) in dry ether was added a solution of 4-(phenylthio)butanal (1.14 g, 8 mmol) in dry ether (15 ml). After being stirred at room temperature for 3 h, the mixture was treated with water (30 ml) and 0.5 mol/l sulfuric acid for 1 h. After the usual work-up, 5-phenylthio-2-pentanol (**3**) was obtained by distillation in 93% yield as a colorless oil: bp 120—125 °C/2 mmHg; NMR (CCl_4) δ=1.06 (d, 3, J=6 Hz, CH_3), 1.56 (m, 4, CH_2CH_2), 2.83 (t, 2, J=6 Hz, SCH_2), 3.26 (broad s, 1, OH), 3.63 (m, 1, OCH), and 6.96—7.33 (m, 5, C_6H_5). Found: C, 67.30; H, 8.37%. Calcd for $C_{11}H_{16}OS$: C, 67.31; H, 8.23%.

*6-Phenylthio-2-hexanol (**4**).* 5-Acetoxyhexyl phenyl sulfide was prepared by the reaction of sodium benzenethiolate and 5-acetoxy-1-bromohexane[8] in 76% yield as an oil. This was treated with 30% aqueous potassium hydroxide (40 ml) and dioxane (40 ml) under reflux for 5 h. The usual work-up gave 6-phenylthio-2-hexanol (**4**) in 95% yield as a colorless oil: bp 135—138 °C/2 mmHg; NMR (CCl_4) δ=1.25 (d, 3, J=7 Hz, CH_3), 1.37—1.86 (m, 6, $(CH_2)_3$), 2.70—3.26 (m, 3, SCH_2 and OH), 3.33—3.37 (m, 1, OCH), and 7.03—7.53 (m, 5, C_6H_5). Found: C, 68.61; H. 8.52%. Calcd for $C_{12}H_{18}OS$: C, 68.51; H, 8.64%.

*7-Phenylthio-1-phenyl-1-heptanol (**5**).* 1-Bromo-6-(Phenylthio)hexane (2.28 g, 8 mmol) was treated with magnesium (0.20 g, 8 mg atom) in the presence of a catalytic amount of iodine in dry ether for 70 min under argon atmosphere. Benzaldehyde (0.85 g, 8 mmol) was added dropwise to the mixture. The resulting mixture was refluxed for 1 h. The usual work-up gave 7-phenylthio-1-phenyl-1-heptanol (**5**) in 13% yield: mp 50.5—51.5 °C (pentane); NMR (CCl_4) δ=1.1—2.0 (m, 10), 1.7 (m, 1), 2.9 (t, 2, J=6 Hz), 4.6 (t, 1, J=6 Hz), and 7.2 (m, 10). Found: C, 76.16; H, 7.97%. Calcd for $C_{19}H_{24}OS$: C, 75.97; H, 8.05%.

Oxidation of Hydroxy Sulfides. General Procedure: To a mixture of hydroxy sulfide (6 mmol) and hexabutyldistannoxane (HBD, 13 mmol) in dichloromethane (15 ml) was added dropwise a solution of bromine (13 mmol) in dichloromethane (10 ml). The red color of bromine was immediately discharged and the reaction mixture was stirred at room temperature for 2—3 h. The solvent was removed under reduced pressure and the residue was separated by chromatography on silica gel. Tributyltin bromide was isolated by elution with hexane. Type B and C products were then obtained by elution with chloroform, the type A product being finally eluted with chloroform–ethanol (2 : 1).

*2-(Phenylsulfinyl)cyclohexanol (**6**).* After evaporation of dichloromethane the residue was treated with a small amount of pentane with cooling (Dry Ice–acetone bath) to give white solid **6** in 87% yield: mp 154—155 °C (benzene); IR 1008, 990 cm^{-1} (νS–O), 3320 cm^{-1} (νOH), Found: C, 63.80; H, 7.42, S, 14.01%. Calcd for $C_{12}H_{16}O_2S$: C, 64.25, H, 7.19: S, 14.29%. 2-(Phenylsulfinyl)cyclohexanol **6** obtained seems to be trans isomer, since its melting point is close to that reported (mp 156.0—156.6 °C[7]). When the same reaction was carried out in methanol or tetrahydrofuran in place of dichloromethane, hydroxy sulfoxide **6** was obtained in 57 or 60% yield, respectively.

*2-Bromopropyl Phenyl Sulfone (**8**).* This was obtained in 38% yield as an oil: IR 1300, 1150 cm^{-1} (νSO_2). NMR ($CDCl_3$), δ=1.88 (d, 3, J=6.9 Hz, CH_3), 3.53—3.70 (m, 2, SO_2CH_2), 4.13—4.67 (m, 1, BrCH), and 7.40—8.10 (m, 5, C_6H_5). This compound is too unstable to be satisfactorily purified for elemental analysis. Found: C, 42.07: H, 4.65; S, 12.45%. Calcd for $C_9H_{11}BrO_2S$: C, 41.07; 4.22; S, 12.18%.

*3-Phenylsulfinyl-2-propanol (**7**).*[9] This was obtained as an oil in 49% yield. IR: 3330 cm^{-1} (νOH), 1014, 990 cm^{-1} (νS–O). NMR ($CDCl_3$) δ=1.29, 1.35 (each d, 3, J=6 Hz, CH_3), 2.58—3.25 (m, 2, CH_2), 4.00—4.63 (m, 1, CH), 4.73—5.08 (broad s, 1, OH), and 7.30—7.85 (m, 5, C_6H_5). Found: C, 58.28; H, 6.25%. Calcd for $C_9H_{12}O_2S$: C, 58.69; H, 6.57%.

*3-Phenylsulfinyl-1,3-diphenyl-1-propanol (**9**).* This was isolated as a white solid in 88% yield in a similar way as that for compound **6**: mp 148—150 °C (CH_2Cl_2–hexane); IR 3380 (νOH), 1010, 990 cm^{-1} (νS–O). NMR (DMSO-d_6) δ=2.28 (m, 2, CH_2), 3.84 (t, 1, J=3.4 Hz, SOCH), 4.68 (broad s, 1, OH), 5.60 (m, 1, OCH), and 6.76—7.47 (m, 15, C_6H_5). Found: C, 74.62, H, 6.01; S, 10.01%. Calcd for $C_{21}H_{20}O_2S$: C, 74.96; H, 6.00; S, 9.53%.

*4-Phenylsulfinyl-2-butanol (**10**).* This was obtained as an oil in 18% yield. IR 3360 cm^{-1} (νOH), 1020 cm^{-1} (νS–O). NMR ($CDCl_3$) δ=1.17 (d, 3, J=6 Hz, CH_3), 1.50—1.98 (m, 2, CH_2), 2.97 (t, 2, J=8 Hz, $SOCH_2$), 3.37—4.10 (m, 2, OH and O–CH), and 7.33—7.73 (m, 5, C_6H_5). Found: C, 60.34; H, 7.23%. Calcd for $C_{10}H_{14}O_2S$: C, 60.59; H, 7.12%.

*4-Phenylsulfinyl-2-butanone (**11**).* This was isolated as oil in 24% yield. IR 1720 cm^{-1} (νC=O), 1010 cm^{-1} (νS–O). NMR (CCl_4) δ=2.00 (s, 3, CH_3), 2.40—2.73 (m, 2, CH_2), 2.83—3.17 (m, 2, $SOCH_2$), and 7.00—7.04 (m, 5, C_6H_5), Found: C, 60.86; H, 6.23%. Calcd for $C_{10}H_{12}O_2S$: C, 61.19;

H, 6.17%.

5-Phenylsulfinyl-2-pentanol (12). An oil, 27%. IR 3380 cm^{-1} (νOH), 1010 cm^{-1} (νS–O). NMR ($CDCl_3$) δ=1.15 (d, 3, J=6 Hz, CH_3), 1.32—2.15 (m, 4, CH_2CH_2), 2.62—3.12 (m, 2, $SOCH_2$), 3.45—4.15 (m, 2, OH and OCH), and 7.32—7.82 (m, 5, C_6H_5). The procuct **12** was identified by comparison with the authentic sample prepared by sodium periodate oxidation of hydroxy sulfide **3**.

5-Bromopentyl Phenyl Sulfone (13). This was obtained as an oil in 37% yield. IR 1310, 1150 cm^{-1} (νSO_2). NMR ($CDCl_3$)=δ 1.72 (d, 3, J=4 Hz), 1.96 (m, 4, CH_2CH_2), 3.20 (m, 2, SO_2CH_2), 4.10 (m, 1, BrCH), and 7.60—7.78 (m, 5, C_6H_5). Found: C, 45.51; H, 5.31; S, 11.65%. Calcd for $C_{11}H_{15}BrO_2S$: C, 45.36; H, 5.15; S, 11.00%.

5-Bromohexyl Phenyl Sulfone (14). This was obtained as an oil in 62% yield. IR 1300, 1140 cm^{-1} (νSO_2). NMR ($CDCl_3$)=δ 0.87—2.37 (m, 9, $(CH_2)_3$ and CH_3), 2.92—3.37 (m, 1, BrCH), 3.53 (t, 2, J=7 Hz, SO_2CH_2), and 7.47—8.30 (m, 5, C_6H_5). Found: C, 47.48; H, 5.54%. Calcd for $C_{12}H_{17}BrO_2S$: C, 47.21; H, 5.62%.

1-Phenyl-7-phenylsulfinyl-1-heptanone (15). The oxidation of **5** was carried out at −75 °C. After evaporation of methylene chloride, the residue was treated with ether (50 ml) and aqueous ammonium fluoride (4 g/50 ml) with stirring. The resulting solid was filtered and the filtrate was washed with water and dried over magnesium sulfate. Evaporation of ether followed by cooling with a small amount of hexane gave white solids **15** (97%): mp 62—63 °C (hexane). IR 1675 cm^{-1} (νC=O), 1030 cm^{-1} (νS–O). NMR (CCl_4) δ= 1.1—2.0 (m, 8), 2.6—3.0 (m, 4), 7.2—7.7 (m, 8), and 7.8—8.0 (m, 2). Found: 72.36: H, 7.14; S; 10.40%. Calcd for $C_{19}H_{22}O_2S$: C, 72.57; H, 7.05; S, 10.18%. When the same reaction was carried out at room temperature, keto sulfoxide (**15**) was obtained in 99% yield.

Oxidation in the Presence of Lithium Bromide. To a mixture of hydroxy sulfide **3** (0.35 g, 1.8 mmol), HBD (2.3 ml, 4.5 mmol), and lithium bromide (0.16 g, 1.8 mmol) in chloroform (10 ml) was added dropwise a solution of bromine (3.96 mmol) in chloroform (10 ml) at −70 °C. Stirring was continued at −70 °C for 30 min and then at room temperature for 1 h. The usual work-up gave bromo sulfone **13** in 66% yield.

References

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