the calcualted values of the heat of mixing respect to the case of $W \neq 1$ (1).

Four parameters afforded the best correlation of the data at T = 288.35 and 313.15 K, whereas three parameters were sufficient at T = 298.15 K and the same number of parameters was chosen for the mixture at T = 298.65 K for which only four experimental data were available.

Conclusions

From Table I and Figure 1 we note the following:

The sign of ΔH_m is changed as a function of the temperature, the mixture being athermic near T = 298 K, whereas exothermal and endothermal effects are measured below and above this temperature.

The molar enthalpies of mixing ΔH_m of the system 1,3-dioxolane–chlorobenzene are small, with a maximum value of about 40 J mol^{-1} in the temperature range 288.15–313.15 K. For comparison, the corresponding maximun value of ΔH_m for the system 1,3-dioxolane–water at T = 318 K is about 900 J mol^{-1}. However, these low values of ΔH_m are coupled with liquid-phase activity coefficients up to 1.9 and 1.5 for 1,3-dioxolane and chlorobenzene, as evaluated by VLE measurements in the previous work (1).

Thus, we must think in terms of a balance between interaction and free volume contribution to ΔH_m rather than feeble interactions between molecules in a nearly ideal solution.

Registry No. PhCl, 108-90-7; 1,3-dioxolane, 646-06-0.

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NEW COMPOUNDS

Organic Disulfides and Related Substances. 45. Synthesis and Properties of Some Disulfide Sulfinate Salts Containing No Nitrogen

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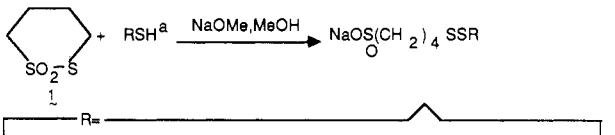
Disulfide sulfinates of the structure $RSS(CH_2)_4SO_2Na$ were synthesized by reaction of 1,2-dithiane 1,1-dioxide (1), thiols, and sodium methoxide in methanol. Disproportionation was minimized by precipitating and reprecipitating the products with ether as quickly as possible; where R = aryl, protection from light is advisable. The groups R typify large lipophilic ones (*n*-decyl, 1-adamantyl), small hydrophilic ones (2-carboxyethyl, 2,3-dihydroxypropyl), disulfide sulfinates $[(CH_2)_nSS(CH_2)_4SO_2Na]$, and aryl groups substituted by electron-donating or electron-withdrawing groups. The products usually were quite hygroscopic and were isolated as hydrates. They disproportionated with varying ease in aqueous solution either to 1 or to the two symmetrical disulfides, RSSR and $NaO_2S(CH_2)_4SS(CH_2)_4SO_2Na$.

Introduction

Several disulfide sulfinate salts of the general structure $RSS(CH_2)_4SO_2Na$ afford promising mammalian protection against ionizing radiation (1–6). This paper reports new types of disulfide sulfinates obtained by reaction of 1,2-dithiane 1,1-dioxide (1) with heretofore unexplored types of thiols, in a search for radioprotective agents that lack the nitrogen functions believed to cause adverse effects (Scheme I); once optimum thiols are known, the model dioxide **1** can be replaced by other dioxides. Stability of **2–11** in solution was examined, since this property is clearly important in biological administration, is probably so in biological activity (cf. ref 6), and is chemically significant for clarification of factors involved in disproportionation to symmetrical disulfides.

Scheme I



2, n-Decyl
3, 1-Adamantyl
4, $(CH_2)_2CO_2H$
5, $CH_2CH(OH)CH_2OH$
6[a], $(CH_2)_4SS(CH_2)_4SO_2Na$
7[a], $(CH_2)_2SS(CH_2)_4SO_2Na$
8, p-MeOPh
9, p-ClPh
10, 3,4-Cl_2Ph
11, 2,6-Cl_2Ph

[a] For 6, R of RSH=$HS(CH_2)_4$. For 7, R of RSH=$HS(CH_2)_2$. For other thiols, R of RSH has the same structure R shown for the product.

Results and Discussion

Apparent advantages of high lipophilicity for antiradiation activity (7) made the *n*-decyl and 1-adamantyl groups attractive (Scheme I, **2** and **3**). To assess the effect of small hydrophilic groups, **4** and **5** were synthesized; only 1 equiv of base was used for **4** (cf. ref 4), since the carboxylate ion first engenders

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sufficient thiolate ion, after which the stronger sulfinic acid (cf. ref *8*) ends as the salt. The bisdisulfides **6** and **7** were obtained by using two molar proportions of the dioxide **1** and the base with 1,4-butane- or 1,2-ethanedithiol. the *p*-tolyl analogue of **8–11** (R = *p*-$CH_3C_6H_4$) was reported some years ago (*9*); its promising radioprotective activity led to the synthesis of the variants **8** and **9**. In efforts to obtain the further variants **10** and **11**, the appropriate thiols at −65 °C with **1** (50% excess) and the base gave **10** and **11** in 71–73% yield, but disproportionation occurred within a few minutes and good analyses could not be obtained.

Disproportionation, which can present major problems in the preparation of most of the group **2–11**, was minimized during preparations and purifications by precipitating the salts without delay. The dioxide **1** frequently was used in excess to assure complete reaction of the thiolate, since it is readily removed in the precipitations. The dry products showed no significant change after at least a year at 0 °C (as indicated by turbidity on dissolution in water).

Confirmation that the reactions occur as formulated in Scheme I is afforded by the kinds of evidence adduced earlier (viz. items 1, 2, and 4 of ref *5*). Moreover, NMR spectra and elemental analyses agreed with expectation; since the salts were reprecipitated from methanol with ether, had significant disproportionation occurred differing solubilities of the products would distort the elemental analyses (thus satisfactory analyses could not be obtained for **10** and **11**).

In order to asssess the stability of **2–11** in water, solutions were extracted at regular intervals with chloroform. Extraction of the dioxide **1** occurred with **4** and **6**, in contrast to **8–11** where extraction gave only the symmetrical disulfide (RSSR of Scheme I; cf. also ref *3*).

Disproportionation of **2** and **3** could not be evaluated because the solutions were too soapy. The 2-carboxyethyl disulfide (**4**) resisted disproportionation to a much greater extent than the aryl counterparts **8–11**. Extraction removed no material after 24 h with **5** or **7**. The disulfides **6** and **8–11** disproportionated rapidly either to **1** (*6*) or to RSSR (**8–11**; cf. Scheme I) with little difference.

The order of resistance of a group of related disulfides, $XAr(CH_2)_2NH_3^+$, was inverted by photolytically induced vis-ā-vis thermally induced disproportionation, evidently because of a change to a homolytic from a heterolytic reaction (*10*). To examine the possibility that the rapid disproportionation of **8–11** might have a homolytic component, solutions of **4** and **6–9** were irradiated with UV for 25 min at ca. 28 °C under the previous conditions (*10*). Although the aryl disulfides differed little (48% from **8** and 53% from **9**), isolation of about the same amount of symmetrical disulfide (RSSR) from them in about half the time required without irradiation indicates that homolysis probably plays a role in the disproportionation of **8** and **9** (and no doubt of **10** and **11** as well), and that protection from light would be wise. The alkyl compounds **4**, **6**, and **7** showed little effect in irradiation (no turbidity, 17% of dioxide **1**, and no turbidity, respectively).

Experimental Section

Melting points were determined by using a Thomas-Hoover stirred-liquid apparatus and are corrected. NMR spectra, reported in parts per million (δ), were obtained with a JEOL Model JNM-MH-100 spectrometer (^1H) with Me_4Si as an internal standard or in D_2O with DSS, $Me_3Si(CH_2)_3SO_3Na$. IR spectra were obtained by using KBr pellets with a Perkin-Elmer Model 727 spectrometer. Elemental analyses were performed by Galbraith Laboratories. Moist extracts were dried by using $MgSO_4$, and solvent was removed by using a rotary-flask evaporator. TLC was performed on Eastman Chromatogram Catalog No. 13181 with visualization by UV or I_2 vapor. 1,2-Dithiane dioxide (**1**) was prepared by using H_2O_2 as reported (*11*). 1-Adamantanethiol, synthesized according to Khullar and Bauer (*12*), was kindly provided by J. A. Waites. All other materials were commercial unless otherwise stated.

General. Procedures for the preparation of the disulfide sulfinate salts **2–11** can be exemplified by the preparation below of sodium 4-(*n*-decyldithio)butanesulfinate (**2**). Significant variations from this procedure are reported under individual disulfide sulfinate salts.

With the notable exception of **7**, drying to constant weight by the analyst still left a hydrate. Calculated values for analyses ("anal. as ...") therefore were based on the residue stated of 0.50, 0.75, or 4.0 H_2O. the loss of water on drying was used to estimate the hydration of the product as originally isolated ("isol. as ..."). For example, "Isolated as **5**·1.15H_2O; anal. as **5**·0.75H_2O" means that **5** as isolated had 1.15H_2O and that when dried it lost the appropriate amount of H_2O (±0.4%) and gave **5**·0.75H_2O, for which C, H, and S analyses were satisfactory; satisfactory analytical data for **2–9** were submitted for review. Since the degree of initial hydration probably is variable, however, all percent yields are based on the presumption that the initial products were anhydrous.

Reaction of Thiols with 1,2-Dithiane 1,1-Dioxide (1). For the preparation of **2**, a solution of sodium (230 mg, 10.0 mg atoms) in 10 mL of MeOH was added dropwise during ca. 30 min to a mixture of **1** (1.52 g, 10.0 mmol) and 1-decanethiol (1.74 g, 10.0 mmol) in MeOH (50 mL) with constant stirring at 0–5 °C. After addition was complete (15 min; the reaction of the thiol was complete by TLC), dry Et_2O (500 mL) was added to the reaction mixture until no more precipitate formed. Solvent was decanted, and the white precipitate was redissolved in a minimum amount of MeOH (ca. 10 mL). Anhydrous Et_2O again was added until a slight turbidity resulted (ca. 50 mL). This mixture was centrifuged, and the clear solution so obtained was removed and diluted with sufficient Et_2O (ca. 400 mL) to precipitate the sodium salt of the disulfide sulfinate **2**. Decantation and drying at 2.0 torr for 24 h gave 2.70 g (77% yield) of the product **2**: NMR (D_2O) δ 3.04–2.68 (m), 2.40 (t), 1.96–1.56 (m), 1.50 (s, br), minor upfield peaks; IR (KBr) 2900, 2850, 1460, 1340, 1210, 980, 960, 700 cm^{-1}. TLC showed one spot (R_f 0.60; 1:1 MeOH–Me_2CO). Isol. as **2**·H_2O; anal. as **2**·0.5H_2O.

Sodium 4-(1-Adamantyldithio)butanesulfinate (3). Prepared from 3.04 g (20.0 mmol) of **1**, 3.36 g (20.0 mmol) of 1-adamantanethiol, and 460 mg of sodium (20.0 mg atom) in 10 mL of MeOH; yield, 6.1 g (89%); TLC showed one spot (R_f 0.61; 1:1 MeOH–Me_2CO); NMR (CD_3OD) δ 2.76 (m, 2 H), 2.48–1.60 (m, 21 H); IR (KBr) 3300, 2900, 2850, 2650, 1640, 1500, 1440, 1330, 990, 940, and 700 cm^{-1}. Anal. as **3**·1.25H_2O.

Sodium 4-(2-Carboxyethyldithio)butanesulfinate (4). The dioxide **1** (3.04 g, 20 mmol) when cleaved with 3-mercaptopropionic acid (2.12 g, 20.0 mmol) and sodium (460 mg, 20 mg atom) in MeOH (20 mL) afforded 4.30 g (77%) of **4**: mp 188–190 °C (dec.) (other samples with different degrees of hydration have shown mp 142–143 °C dec); NMR (D_2O) δ 3.12–2.72 (m, 6 H), 2.44 (t, 2 H), 2.08–1.48 (m, 4 H); IR (KBr) 2950, 2600–2200, 1710, 1405, 1260, 1200, 1040, 1000, 940, 900, 760, 720 cm^{-1}. TLC showed only one spot (R_f 0.51; 1:1 MeOH–Me_2CO). Anal. as **4**·0.75H_2O.

Sodium 3-(4-Sulfinobutyldithio)-1,2-propanediol (5). Prepared from 2.28 g (15.0 mmol) of **1**, 1.08 g (10.0 mmol) of 3-mercapto-1,2-propanediol, and 230 mg (10.0 mg atoms) of Na in 10 mL of MeOH; yield, 2.59 g (92%): TLC showed one spot (R_f 0.58; 1:1 MeOH–Me_2CO); IR (KBr) 3500–3200 (br), 2950, 1660, 1460, 1410, 1340, 1300, 1225, 1180, 1140, 1095, 1020–960, 880, 860, and 800 cm^{-1}; NMR (D_2O) δ 4.20–3.90 (m), 3.70 (m), 3.20–2.72 (m), 2.60–2.20 (m), 2.08–1.44 (m).

Isol. as 5·1.15H_2O; anal. as 5·0.75H_2O.

Disodium (1,4-Butylenedithio)bis(4-butanesulfinate) (6). Sodium (230 mg, 10 mg atoms) dissolved in MeOH (15 mL) was added dropwise to a mixture of dioxide **1** (1.52 g, 10 mmol) and 1,4-butanedithiol (0.61 g, 5.0 mmol) in MeOH. Isolation as usual afforded 2.0 g (74% based on 6·4H_2O) of white **6**. TLC showed one spot (R_f 0.54; 1:1 MeOH–Me_2CO). Additional TLC spots appeared in 5 min or less after dissolution of **6** in H_2O, the solution became turbid, and the NMR spectrum (D_2O) changed. IR (KBr): 3400, 2950, 1660, 1440, 1220, 1000 (br), 980, 800, and 720 cm^{-1}; NMR (D_2O) δ 3.40–2.64 (m, 8 H), 2.60–2.20 (m, 4 H), 2.04–1.40 (m, 12 H). Anal. as 6·4H_2O.

Disodium (1,2-Ethylenedithio)bis(4-butanesulfinate) (7). For the preparation of **7**, sodium (230 mg, 10 mg atoms) dissolved in MeOH (10 mL) was added to a mixture of dioxide **1** (2.28 g, 15 mmol) and 1,2-ethanedithiol (0.47 g, 5.0 mmol) in MeOH (20 mL) with stirring at 0–5 °C. By the general procedure, 1.80 g (81%) of the **7** was isolated. TLC showed one spot (R_f 0.67; 1:1 MeOH–Me_2CO). IR (KBr) 3400, 2950, 2860, 1640, 1460, 1420, 1240, 1200, 1120, 1000 (br), 900, and 780 cm^{-1}; NMR (D_2O) δ 3.12 (s, 2 H), 3.00–2.72 (m, 2 H), 2.60–2.20 (q, 2 H), 2.08–1.40 (m, 4 H). Isol. as 7·1.25H_2O; anal. as anhydrous **7**.

Sodium 4-(p-Methoxyphenyldithio)butanesulfinate (8). Compound **8** was obtained in a yield of 2.50 g (80%) by use of sodium (230 mg, 10 mg atoms), dioxide **1** (2.28 g, 15.0 mmol), and 4-methoxythiophenol (1.40 g, 10.0 mmol). TLC gave a single spot (R_f 0.31; 1:1 MeOH–Me_2CO); IR (KBr) 3500–3200 (br), 2950, 1600, 1500, 1480, 1400, 1290, 1240, 1180, 1000 (doub), and 820 cm^{-1}; NMR (CD_3OD) δ 7.60–6.80 (m, 4 H), 3.80 (s, 3 H), 2.72 (t, 2 H), 2.20 (t, 2 H), 1.92–1.48 (m, 4 H). Isol. as 8·0.9H_2O; anal. as 8·0.5H_2O.

Sodium 4-(p-Chlorophenyldithio)butanesulfinate (9). The cleavage of dioxide **1** (2.28 g, 15.0 mmol) with 4-chlorothiophenol (1.44 g, 10 mmol) and sodium (230 mg, 10 mg atoms) in MeOH was carried out at −65 °C. Thus 2.60 g of **9** (82%) was isolated. TLC showed one spot (R_f 0.44; 1:1 MeOH–Me_2CO). Additional spots appeared a few minutes after dissolution of **8** in H_2O, and the solution became turbid. IR (KBr) 3400, 2950, 2850, 1570, 1460, 1420, 1220, 1100, 1010 (br), 820, and 780 cm^{-1}; NMR (CD_3OD) δ 7.64–7.28 (m, 4 H), 2.80 (t, 2 H), 2.40–2.12 (m, 2 H), 1.92–1.48 (m, 4 H). Isol. as 9·2H_2O; anal. as 9·0.75H_2O.

Disproportionation of 4, 6, 8, and 9–11. Solutions of 10 mmol of **4**, **6**, **8**, and **9–11** in 50 mL of H_2O under the ambient conditions of interest in practial use at ca. 25 °C were well stirred and extracted periodically with $CHCl_3$ (4–5 × 20 mL). Drying ($MgSO_4$) and evaporation of the extract, then drying to constant weight, gave the dithiane dioxide **1** with **4** and **6**; **8–11** gave the corresponding sparingly soluble symmetrical disulfides RSSR (cf. Scheme I). The dioxide **1** was identified by melting point and usually mixture melting point. The disulfides RSSR from **8** to **11** were characterized by mixture melting point and IR; an authentic sample of each was prepared by oxidation of the thiol with I_2 in an aqueous solution of KI. The cumulative % yields of the dioxide (**1**) from **4** and **6**, or of the symmetrical disulfide (RSSR) from **8–11**, were as follows at 1, 4, 8, and 16 h, respectively. Compd **4**: 14, 22, 27, and 30%. Compd. **6**: 42, 54, 62, and 66%. Compd. **8**: 41, 52, 60, and 65%. Compd. **9**: 45, 53, 64, and 69%. Compd. **10**: 47, 54, 63, and 68%. Compd. **11**: 39, 48, 59, and 62%.

Registry No. **1**, 18321-15-8; **2**, 101009-93-2; **3**, 101009-94-3; **4**, 101009-95-4; **5**, 101009-96-5; **6**, 101009-97-6; **7**, 101009-98-7; **8**, 101009-99-8; **9**, 101010-00-8; **10**, 101010-01-9; **11**, 101010-02-0; $H_3C(CH_2)_9SH$, 143-10-2; $HO_2C(CH_2)_2SH$, 107-96-0; $HOCH_2CH(OH)CH_2SH$, 96-27-5; $HS(CH_2)_4SH$, 1191-08-8; $HS(CH_2)_2SH$, 540-63-6; *p*-$H_3COC_6H_4SH$, 696-63-9; *p*-ClC_6H_4SH, 106-54-7; 3,4-$Cl_2C_6H_3SH$, 5858-17-3; 2,6-$Cl_2C_6H_3SH$, 24966-39-0; *p*-$H_3COC_6H_4S_2C_6H_4OCH_3$-*p*, 5335-87-5; *p*-$ClC_6H_4S_2C_6H_4Cl$-*p*, 1142-19-4; 3,4-$Cl_2C_6H_3S_2C_6H_3Cl_2$-3,4, 4235-78-3; 2,6-$Cl_2C_6H_3S_2C_6H_3Cl_2$-2,6, 4184-39-8; 1-adamantanethiol, 34301-54-7.

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