Cleavage of Sulfur-Sulfur Bonds with Sodium Hydrogen Selenide

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Sodium hydrogen selenide is shown to be an effective reagent for reduction of alkyl, aryl, aralkyl, and functionally substituted disulfides to thiols under mild conditions in protic solvents. Two-electron transfer from the hydrogen selenide anion, which promotes the cleavage of the S–S bond with concomitant production of elemental selenium, is found to occur only in a narrow pH range. Organic thiosulfates (Bunte salts) also give thiols through the intermediacy of the corresponding disulfide on reaction with sodium hydrogen selenide.

The nucleophilic cleavage of the sulfur-sulfur bond in both organic and inorganic compounds has been of considerable interest for many years and has been the subject of several reviews.¹⁻⁵ Studies of the reaction of organic thiosulfates with previously uninvestigated nucleophiles have recently been reported.^{6,7} In general, reactions of nucleophiles with organic disulfides result in production of the corresponding thiol and sulfenyl-substituted nucleophile, whereas, in reactions with organic thiosulfates, nucleophiles produce sulfenyl-substituted nucleophile and sulfite ion, which may react further under the reaction conditions.^{6,7} Among a myriad of reducing agents other than nucleophiles which have been used to cleave the S-S linkage are lithium aluminum hydride,⁸ sodium borohydride,⁹ and sodium borohydride-aluminum chloride.¹⁰ We report here a new reagent for the cleavage of sulfur-sulfur bonds, namely, sodium hydrogen selenide. Its reactions with representative organic disulfides and thiosulfates are described.

The study of reactions of the hydrogen selenide anion has been limited, partly because of the inconvenience of standard generation procedures for the anion and partly because of the facility of air oxidation of the anion to elemental selenium, rendering handling of solutions of the material difficult. We present here a study of nucleophilic behavior of this anion, the techniques involved in which are based on the new preparative procedure for sodium hydrogen selenide from elemental selenium and sodium borohydride devised by Klayman and Griffin.¹¹ This procedure allows the rapid and convenient preparation of aqueous or alcoholic solutions of sodium hydrogen selenide without the necessity of generating dangerously toxic hydrogen selenide gas.

Results and Discussion

Reaction of Sodium Hydrogen Selenide with Organic Disulfides. The reactions of sodium hydrogen selenide with organic disulfides in ethanol solution were studied as follows. After a solution of the reactants had been allowed to stand in an inert atmosphere, dilute hydrochloric acid was added, and elemental red selenium was noted to precipitate immediately from the reaction mixture. Examination of the organic products then allowed assessment of the efficiency of the reaction.

The reactions of dibenzyl disulfide (1), which was chosen as a model compound, with sodium hydrogen selenide, hydrogen selenide, and sodium diselenide are summarized in Table I. Dibenzyl disulfide (1) was shown to undergo reduction to α -toluenethiol (2) by hydrogen selenide anion (expt 1 and 2). A single molar quantity of sodium hydrogen selenide, however, only induced partial reduction of 1 (expt 1), whereas a 50% excess gave total conversion of 1 to 2 (expt 2). The reaction may be viewed as proceeding as illustrated in eq 1, involving a two-electron reduction of the di-

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sulfide linkage to produce 2 mol of thiol 2 and 1 g-atom of elemental selenium. The inefficiency of the molar quantity of NaHSe in promoting the reduction may be explained by the forward reaction of eq 2. As elemental selenium is produced as indicated in eq 1, it may interact with unreacted NaHSe to produce a di- or polyselenide anion. That such a process occurs, albeit inefficiently, at the natural pH of sodium hydrogen selenide is indicated by the development of the intense red-brown color (characteristic of polyselenide anions) which is noted shortly after the solutions are mixed. This process would apparently render the sodium hydrogen selenide less active in the reduction process. The selenium thus bound would then be regenerated on acidification (eq 2). Use of excess NaHSe in the reaction gives complete reduction of 1 to 2 and 1 g-atom of elemental selenium, indicating that the competing process may be offset by use of larger quantities of NaHSe. To determine if the diselenide anion was the reducing species in the reaction, sodium diselenide was generated and was combined with 1. As shown in Table I (expt 4 and 5), reduction does indeed take place but incompletely. Apparently the H₂Se produced on disproportionation of the diselenide anion may promote the cleavage, but the competing loss of H_2Se , purged from the solution, reduces its effectiveness as a reducing agent.

Hydrogen selenide gas, generated externally and bubbled through a solution of 1, had no reducing effect on 1 at its natural pH (expt 3); however, adjusting the hydrogen ion concentration of the hydrogen selenide saturated solution of 1 to pH 7 with aqueous sodium hydroxide caused precipitation of elemental selenium and complete reduction of 1 to 2. These experiments indicate that the reduction is pH dependent and that the pH range necessary to the reaction may be approached from either the high or low pH side.

The pH dependence of the reduction of the disulfide is not surprising in view of reports of variance of the potential E of thiol-disulfide couples. For example, the potential of the cystine-cyteine couple varies from +0.034 to -0.565 V over a pH range of 0-12 at 25°.¹² Similarly, the oxidation of negative selenium species varies with pH, as the potential for the hydrogen selenide-selenium couple has been calculated to be +0.36 V and that of the selenide (Se²⁻)-selenium couple to be +0.78 V.¹³ Comparison of these potential values to those of the system at hand may be only qualita-

Table I						
Treatment of Dibenzyl	Disulfide (1)	with	Selenide	Reagents		

 $C_{6}H_{5}CH_{2}SSCH_{2}C_{6}H_{5} + HSe^{-} \xrightarrow{H^{+}} 2C_{6}H_{5}CH_{2}SH + Se^{0}$

		1		2		
		Moles of reagent/	~Yi	elds of organic produ	cts, %	Gram-atoms ^a of Se ^o obtained after
Expt no.	Reagent	mol of 1	Absolute	Thiol (2)	Disulfide 1	acidification
1	HSe-	1.00	92	59	41	0.93
2	HSe-	1.50	99	100	0	1.00
3	H_2Se	5.00	94	0	100	b
4	$Se_{2}{}^{2}-$	1.00	94	88	12	2.00
5	\mathbf{Se}_{2}^{2} –	1.50	96	70	30	2.74

^a Gram-atoms of Se⁰ obtained per mole of starting 1. ^b Not applicable.

Table II							
Treatment of Disulfides	with	Excess	Sodium	Hydrogen	Selenide		

$\mathrm{RSSR}+2\mathrm{HSe}^{-}\stackrel{2\mathrm{H}^{-}}{\longrightarrow}2\mathrm{RSH}+\mathrm{Se}^{\scriptscriptstyle 0}+\mathrm{H}_{2}\mathrm{Se}^{\circ}$							
Expt no.	R	Starting disulfide, mmol	Thiol obtained, mmol	Thiol obtained, %	Se obtained, g-atoms ^a		
6	C_6H_5	7,39	14,1	96 ^{b,c}	0.99		
7	tert-C ₄ H ₉	11.2	O^d	0	0		
8	$HO_2CCH(NH_2)CH_2$	8.32%	16.1'	97^{g}	0.97		
9	$n-C_{10}H_{21}$	5.65	10.7	$95^{b,h}$	1.00		
10	$HN = C(NH_2)$ (HCl)	8.97	18.0^i	101^{b}	0,94		
11	$H_2NCH_2CH_2(HCl)$	10.00	19.2^{f}	97^{g}	0.93		

^a Gram-atom of Se^o obtained per mole of starting disulfide. ^b Yield determined by isolation of product. ^c Identity and thiol content verified by nmr analysis. ^d No product obtained even on refluxing the reaction mixture for 16 hr or allowing it to stand for 3 months. ^e Reaction conducted in water. ^f Product isolated as HCl salt. ^g Yield determined by titration of an aliquot with 1 N I₂ solution. Identity verified by ir and melting point. ^h Thiol content verified by titration with 1 N I₂ solution. ⁱ Thiour verified by ir and melting point.

tive, however, since the dissociation constants of the species involved would undoubtedly be different in the alcohol-water solvents used than in the aqueous systems on which the calculations were based. Nevertheless, interpolation of these values reported to the pH corresponding to the one obtained for precipitation of selenium, assuming that values for the cystine-cysteine couple would parallel those for the 1-2 couple, indicates that the oxidation-reduction process would take place. Of major interest and importance, moreover, is the extremely rapid rate observed for the redox process.

The generality of the reduction of disulfides by sodium hydrogen selenide was investigated, and the results are listed in Table II. Essentially quantitative conversion of disulfide to thiol was noted in the following reactions: diphenyl disulfide to benzenethiol (expt 6), cystine to cysteine (expt 8), didecyl disulfide to 1-decanethiol (expt 9), diformamidine disulfide to thiourea (expt 10), and bis(2-aminoethyl) disulfide to 2-mercaptoethylamine (expt 11). The guantities of selenium recovered on acidification corresponded very well to the theoretical values (see Table II). The sterically hindered di-tert-butyl disulfide (expt 7) shows negligible reduction to 2-methyl-2-propanethiol under the reaction conditions, even if the pH-adjusted solution of the reactants is heated under reflux for 16 hr or is allowed to stand for 3 months. Such a lack of lability of this compound to reduction is not surprising in view of the arrangement of the atoms of di-tert- butyl disulfide in the energetically favored anti conformation of the C-S-S-C bonds. A Fisher-Hirschfelder-Taylor model of the molecule indicates that there exists only a 1.9-Å opening to approach the S-S bond in the most favored conformation which has no eclipsing sulfur-methyl interactions. Even if this eclipsing is permitted, only a 3.0-Å opening exists. Since the hydrogen selenide anion is undoubtedly larger (unprotonated selenide anion has a diameter in crystals of 3.96 Å),¹⁴ the avenue of approach of the anion toward the S-S bond is severely restricted. Other potent reducing agents also have difficulty in cleaving the sulfur-sulfur bond of di-*tert*-butyl disulfide; indeed, even lithium aluminum hydride reduces this disulfide only slowly in boiling tetrahydrofuran.⁸

Thus sodium hydrogen selenide is useful for conversion of arvl, alkyl, aralkyl, and functionally substituted disulfides to the corresponding thiols under mild conditions. This method should find synthetic utility under conditions in which cleavage of S-S bonds, without disturbing other reducible functional groups, is desired. No contamination of the organic products by selenium-containing materials has been encountered with this method. The facile retrieval of the selenium utilized, which may be used to regenerate sodium hydrogen selenide, is an attractive feature of the reaction. Essentially sodium borohydride is the only material consumed, and synthetically the reaction sequence may be viewed as requiring selenium as a catalyst. In contrast, our experience is that sodium borohydride alone, in addition to reducing other functional groups present, requires higher temperatures and longer reaction times to cleave the S-S bond of disulfides than does sodium hydrogen selenide.

Reaction of Sodium Hydrogen Selenide with Organic Thiosulfates (Bunte Salts). The reaction of sodium benzyl thiosulfate (3) with sodium hydrogen selenide was found, after acidification, to give dibenzyl disulfide (1) and α -toluenethiol (2), the relative amounts of which were found to vary according to the sodium hydrogen selenide: Bunte salt ratio (Table III). Trends in Table III deserve comment. First, 0.5–1 mol of sodium hydrogen selenide converts 1 mol of the thiosulfate 3 entirely to disulfide 1 (expt 12 and 13), whereas at least 1.5 mol of the reagent are needed to give disulfide-free thiol 2 (expt 16, 18–20). SecExpt r

After

acidification

Table III Treatment of Sodium Benzyl Thiosulfate (3) with Sodium Hydrogen Selenide

	$C_{6}H_{3}CH_{2}SSO_{3}^{-} + HSe^{-} \xrightarrow{H^{-}} C_{6}H_{3}CH_{2}SH + C_{6}H_{5}CH_{2}SSCH_{2}C_{6}H_{5}$							
		3	2	1				
					Se obtained	l, g-atoms ^a -		
	Moles of HSe ^{-/}	Yie	lds of organic product	ts, %	Before	Af		
0.	mol of 3	Absolute	Thiol 2	Disulfide 1	acidification	acidifi		
	0 20	07		100				

15	2	0.50	97	0	100	0.47	0
1:	3	0.55	100	0	100	0.50	0
14	4	1.00	101	0	100	0.85	0.07
1	5	1,09	99	8	92	0.91	0.04
1	6	1.50	98	92	8	0.30	0.98
1'	7	1.50	96	0 ^b	100%	с	с
18	8	1.64	94	100	0	0.16	0.93
1	9	2.00	91	100	0	0.03	1.50
20	0	2.19	99	100	0	d	d

 a Gram-atoms of selenium obtained per mole of starting Bunte salt. b Acid work-up was not employed. At the point at which acid would have been added, the solvent was evaporated, and the organic product was obtained by leaching the residue with ether. ^c Not applicable, ^d Not determined.

ond, the quantity of selenium recovered from the alcoholinsoluble materials collected before acidification represents essentially complete recovery of all selenium used (expt 12-15) in the lower ratios. Finally, the amounts of selenium decrease as the sodium hydrogen selenide: thiosulfate ratio reaches higher values (expt 16, 18, and 19). The trends in product and selenium stoichiometry noted may be explained by eq 3 and 4 in Scheme I.

Scheme I

$$PhCH_2SSO_3^- + HSe^- \longrightarrow PhCH_2SSe^- + HSO_3^-$$
 (3)

$$\begin{array}{cccc} PhCH_{2}S & \overbrace{SO_{3}}^{-} & \longrightarrow & PhCH_{2}S & SO_{3}^{2} \\ \hline & & & & & & \\ PhCH_{2}S & \overbrace{Se}^{-} & & PhCH_{2}S & Se^{\theta} \end{array}$$
(4)

1

$$5H^+ + 3HSe^- + SO_3^{2^-} \longrightarrow H_2S + 3Se + 3H_2O$$
 (5)

The initiating reaction in the sequence involves thiophilic attack by hydrogen selenide anion on the sulfenyl sulfur atom of 3, forming the thioselenol anion 4 and bisulfite ion (eq 3). The intermediate 4 then interacts with unreacted 3, in a four-centered process analogous to that proposed for the reaction of Bunte salts with hydrodisulfides,⁷ to give dibenzyl disulfide, sulfite ion, and elemental selenium (eq 4). An alternative to eq 4, which may not be entirely ruled out, involves the extrusion of elemental selenium from the thioselenol anion 4 to give the anion of 2. The latter could subsequently attack 3 to give 1 and sulfite ion. The rate of such an extrusion process, however, might be expected to be slower than that observed for the reaction. In our view, this alternate mechanism is less attractive than that shown in eq 4.

In the presence of excess sodium hydrogen selenide, the previously discussed reaction depicted in eq 1 may take place. The disulfide 1 undergoes a two-electron reduction to give 2 mol of α -toluenethiol (2) and 1 g-atom of elemental selenium. That the proton participation as shown in eq 1 is necessary to the reduction was demonstrated by performing the reaction without adding acid and isolating only dibenzyl disulfide (1) (expt 17).

At higher sodium hydrogen selenide:thiosulfate ratios (i.e., above 0.5:1.0), the stoichiometry of the reaction becomes less clear. At first, larger quantities of elemental selenium are obtained before acidification, indicating that some process other than simple disulfide formation has

taken place. Such a process is illustrated in eq 5. Sulfite ion produced as in eq 3 and 4 may oxidize the negative selenium species to elemental selenium while itself being reduced to hydrogen sulfide. The oxidation of hydrogen selenide anion by sulfite accounts for the larger than theoretical quantities of selenium noted on acidification in expt 14 and 15. The production of hydrogen sulfide rather than hydrogen selenide on acidification as shown in eq 5 was verified in one experiment by scrubbing the purge gases through a saturated cadmium(II) chloride trap to produce mustard yellow cadmium(II) sulfide.

As the hydrogen selenide:Bunte salt ratio becomes greater than 1:1, decreasing quantities of selenium are produced before acidification (expt 16, 18, and 19). This observation may be explained if the equilibrium represented in eq 2 comes into play. The hydrogen selenide anion, present in these experiments at higher concentration, reacts with Se⁰ and thus causes the elemental selenium produced in eq 4 to dissolve to give a deeply colored solution of red-brown hydrogen diselenide anion. Apparently this process competes with oxidation of hydrogen selenide by sulfite. On acidification, the diselenide species then disproportionates, giving elemental selenium and hydrogen selenide as indicated in eq 2. That the acidic disproportionation occurs as shown was demonstrated by acidifying a solution of sodium diselenide¹¹ to cause the precipitation of elemental selenium and evolution of hydrogen selenide gas. The elemental selenium collected represented an essentially quantitative yield according to the stoichiometry represented in eq 2.

The pH dependence of the reaction (vide supra) was investigated as described below. The reaction of 7.61 mmol of sodium benzyl thiosulfate (3) with 11.4 mmol of sodium hydrogen selenide was performed as previously described. The procedure was followed as usual until the acidification stage, and at this point, the reaction mixture was titrated with standard hydrochloric acid. The change in the pH of the solution was monitored, and the results are given in Figure 1. The pH values, taken in a methanol-ethanolwater medium, are reported as apparent pH; however, since the electrode had been soaked in water for several months, the values are probably near the actual ones.¹⁵ An indication of the probable reliability of these values is provided by comparing the initial pH (8.2) of this alcoholic system to that obtained in a purely aqueous solution (pH 8.5).16

Adding acid to the initially buffered solution caused elemental selenium to precipitate at the point corresponding to the addition of sufficient acid to protonate the originally present 3. Because of the complicating influence of sulfite Cleavage of Sulfur-Sulfur Bonds



Figure 1. Apparent pH of an alcoholic solution of 7.61 mmol of sodium benzyl thiosulfate (3) treated with 11.4 mmol of solution hydrogen selenide as a function of added acid. (The shaded area indicates the point at which selenium precipitated from the solution.)

ion, the point of precipitation and the quantity of selenium may or may not have significance; however, the important fact to note is the extremely narrow pH range at which the reduction takes place. In contrast, it was noted by us that treatment of 3 with 2 mol of sodium hydrogen *sulfide* produced the disulfide 1 as the sole organic product.

To ascertain the utility of sodium hydrogen selenide in the reduction of Bunte salts to thiols, an investigation was conducted of the reaction of 2-aminoethanethiosulfuric acid (5) with the reagent. Attempts to reduce 5 to the corresponding thiol with sodium borohydride have been unsuccessful.¹⁶ Treatment of 5 with sodium hydrogen selenide in aqueous solution, however, gave a quantitative conversion to the thiol product 2-mercaptoethylamine (6) (eq

$$H_2NCH_2CH_2SSO_3H + HSe^- \longrightarrow 5$$

$$H_2NCH_2CH_2SH + Se + HSO_3^- (6)$$

$$6$$

6). The reduction, in contrast with the case of 3, required a 4 molar quantity of sodium hydrogen selenide because of the presence of the by-product, inorganic sulfite. The latter, being soluble in the aqueous medium, consumes some of the sodium hydrogen selenide necessary for cleavage of the intermediate disulfide (cystamine) and thus results in high recoveries of selenium. With only 2 mol of sodium hydrogen selenide per mole of thiosulfate, a maximum conversion to thiol of 28% was obtained, indicating that the sulfite oxidation of sodium hydrogen selenide is faster than is the cleavage of the intermediate disulfide by the latter. That the amine groups of 5 were not interfering with the stoichiometry of the reaction was shown by treating 1,6hexanediamine with 2 mol of sodium hydrogen selenide. No selenium was noted to precipitate on acidification of the reaction mixture.

These experiments demonstrate that sodium hydrogen selenide may be a useful reagent for conversion of Bunte salts to thiols under mild conditions.

Experimental Section

Infrared spectra were taken on a Beckman IR-5 spectrophotometer in KBr pellets, and nmr spectra were taken on a Varian Associates A-60 spectrometer in CDCl₃ solution. Chemical shifts are reported as δ (ppm) relative to the internal standard TMS. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Iodometric titrations were carried out using Fisher Scientific 1.0 N iodine. The pH measurements were determined with a Beckman Zeromatic meter. All of the reactions were conducted under an inert atmosphere to prevent air oxidation of the selenide species. The effluent gases from the reactions were scrubbed in two 5% lead(II) acetate traps.

Reactions of Dibenzyl Disulfide (1) with Sodium Hydrogen Selenide. Solutions of sodium hydrogen selenide¹¹ were generated as follows. To the desired number of gram-atoms of elemental selenium was added a 10 mol % excess of sodium borohydride. Ethanol (100 ml) was added, and the mixture was stirred until homogeneous. To the resulting clear solution was added a solution of 1.00 g (4.06 mmol) of 1 in 100 ml of ethanol. The mixture was stirred for 1 hr, and 15 ml of 1.2 N HCl was added. The mixture was stirred and purged for a minimum of 1 hr, and the precipitated selenium was collected, washed with methanol, ethanol, and ether, and dried (cf. Table I). The combined filtrate and washings were added to 350 ml of water, and the mixture was extracted with CHCl₃, dried (MgSO₄), and evaporated to give the organic product(s). In cases in which mixtures of benzyl mercaptan and dibenzyl disulfide were obtained, the relative amounts were determined by nmr utilizing multiple comparative integrations of the SH proton signal at δ 1.57 and the $-CH_2S$ - signals at δ 3.3-3.6. The results of these experiments are summarized in Table I.

Reactions of Dibenzyl Disulfide (1) with Sodium Diselenide. A solution of the desired quantity of sodium diselenide in 150 ml of ethanol was prepared from elemental selenium and sodium borohydride according to the recently described procedure.¹¹ After the excess H₂Se had been purged from the refluxing solution with argon, the reddish brown solution was cooled to room temperature, and 2.00 g (8.13 mmol) of 1 in 100 ml of degassed ethanol was added. The resulting solution was stirred for 45 min and 50 ml of 1.2 N HCl was added. Precipitation of selenium was immediate, and the mixture was stirred and purged with argon for 1 hr. The selenium was collected, and the filtrate was treated as above. The results of these experiments appear in Table I.

Treatment of Dibenzyl Disulfide (1) with Hydrogen Selenide. A. In a three-necked, round-bottomed flask, fitted with a pressure-equalizing dropping funnel, an argon purge tube, and a gas outlet tube, were allowed to interact with stirring 1.58 g (20 mg-atoms) of elemental selenium and 0.83 g (22 mmol) of sodium borohydride in 100 ml of ethanol. The gas outlet tube was directed into an ice bath cooled flask containing 1.00 g (4.06 mmol) of 1 in 100 ml of 10% water in ethanol. To the clear solution resulting from the reaction of selenium and borohydride was added dropwise, over a period of 1 hr, 100 ml of 1 N HCl. The H₂Se thus produced was bubbled through the solution of 1. The H₂Se saturated solution of 1 was stirred and purged with argon for 2 hr, after which the solvent was removed under reduced pressure to give 937 mg (94%) of recovered dibenzyl disulfide, identified by ir and nmr criteria.

B. The above experiment was repeated with 1.0 ml of concentrated HCl added to the ethanolic solution of 1. No change was noted in the solution when it was saturated with H₂Se. With the electrode of a pH meter inserted, 10% NaOH was added dropwise. As pH 7 was approached, precipitation of selenium, which subsequently redissolved at pH ~8, was noted. Addition of 10% NaOH was continued to pH 9.5, and the solution was allowed to stand for 5 min. To the resulting reddish brown solution was added 1 N HCl dropwise. At pH 7 precipitation of selenium was noted. The pH was further lowered to 5, and the precipitated selenium (311 mg, 3.94 mg-atoms, 97%) was collected and treated as above. The filtrate was added to 350 ml of water and extracted with CHCl₃. Evaporation of the dried CHCl₃ extract gave 0.994 g (8.02 mmol, 99%) of **2**, pure by nmr criteria.

Reactions of Other Disulfides with 2 Equiv of Sodium Hydrogen Selenide. Aqueous (or ethanolic) solutions containing 2 mol of sodium hydrogen selenide in 100 ml of solvent per mole of starting disulfide were prepared from elemental selenium and sodium borohydride as described above.¹¹ When the reaction of selenium with sodium borohydride was complete, the disulfide dissolved in 50 ml of argon-purged water (or ethanol) was added to the sodium hydrogen selenide solution with stirring. In all cases, with the exception of that of di-tert-butyl disulfide, the solution immediately turned deep red-brown. After the reaction mixture had been stirred for at least 1 hr, a volume of argon-purged ${\sim}1.2~N$ HCl sufficient to bring the pH to <2 was added. (Caution! Beware of toxic H₂Se evolution during acidification.) The solution was purged with argon for at least 1 hr and the precipitated elemental selenium (cf. Table II) was collected. The combined filtrate and washings were treated in one of the following ways. (a) In the cases beginning with diphenyl disulfide, di-tert-butyl disulfide, and di-

decyl disulfide (expt 6, 7, and 9, respectively), the filtrate was added to 350 ml of water, and the product (or unreacted starting material) was isolated by extraction with CHCl₃. The yields and thiol content of the products were determined as indicated in the summary of these experiments provided by Table II. (b) In the cases of cystine (expt 8) and of cystamine dihydrochloride (expt 11), an aliquot of the filtrate was titrated with 1 N I_2 to determine its thiol content. The remainder of the filtrate was evaporated to give a solid residue which was triturated with ethanol. Filtration and evaporation of the filtrate gave in each case colorless solids which were shown to be cysteine hydrochloride and 2-mercaptoethylamine hydrochloride, respectively, by the methods indicated in Table II. (c) In the case of diformamidine disulfide dihydrochloride (expt 10), the filtrate was evaporated under reduced pressure, and the residue was triturated with ethanol. After filtration, evaporation of the ethanol gave thiourea.

Reactions of Sodium Benzyl Thiosulfate (3) with Sodium Hydrogen Selenide. A. Solutions containing the desired quantities of sodium hydrogen selenide in 100 ml of ethanol were prepared from elemental selenium and sodium borohydride as described above for 1. When all of the selenium had dissolved, a solution of 1.72 g (7.61 mmol) of 3 in 50 ml of degassed methanol was added with stirring. After the mixture was stirred for at least 1 hr, the precipitated inorganic material was collected, washed with ethanol and ether, and was found to consist of a mixture of sodium sulfite and elemental selenium. The latter was guantitated by washing the precipitate with about 50 ml of water and collecting the residual selenium (cf. Table III).

The deep reddish brown filtrate from the above-described procedure was acidified with 15 ml of 1.2 N HCl and the mixture was purged with argon for a minimum of 1 hr. The effluent gases were passed through a 5% lead(II) acetate trap. The precipitated elemental red selenium was collected. The combined filtrate and washings were treated as described above for 1, and the yields and organic product ratios are given in Table III.

B. With pH Monitoring during Acidification. A solution of 1.72 g (7.61 mmol) of 3 in 50 ml of degassed methanol was added to a solution of sodium hydrogen selenide generated in 100 ml of ethanol from 902 mg (11.4 mg-atoms) of selenium and 976 mg (12.6 mmol) of sodium borohydride. The mixture was stirred for 1 hr, and the precipitated solid (834 mg) was collected and treated as described above to give 168 mg (2.13 mg-atoms) of elemental selenium. To the original filtrate and washings was added 1.00 N standard HCl, and the pH was monitored after the addition of each 1 ml of acid. The change in apparent pH vs. addition of acid is plotted in Figure 1. Precipitation of selenium was noted to occur during the addition of the eighth milliequivalent of HCl and between apparent pH 7.6 and 7.2. Selenium (564 mg, 7.14 mg-atoms) was collected after acidification.

Treatment of Sodium Benzyl Thiosulfate (3) with Sodium Hydrogen Sulfide. Into 75 ml of ethanol in which 0.21 g (9 mgatoms) of sodium metal had been dissolved was bubbled hydrogen sulfide gas until the solution was saturated. The solution was then purged with argon to remove excess H_2S , and 1.01 g (4.47 mmol) of 3 in 50 ml of degassed MeOH was added. The mixture was stirred for 1.5 hr and filtered to give 539 mg (85% based on 1 mol each of sodium sulfite and sodium thiosulfate produced) of colorless solid, identified by ir. To the filtrate was added 15 ml of 1.2 N HCl, and the solution was purged with argon until no further $\mathrm{H}_2\mathrm{S}$ evolution could be detected. The volume of the solution was reduced to 10 ml, and the residue was extracted with CHCl₃. The extracts were dried (MgSO₄) and evaporated to give 511 mg (93%) of dibenzyl disulfide with trace polysulfide contaminants, identified by nmr

Reactions of 2-Aminoethanethiosulfuric Acid (5) with Sodium Hydrogen Selenide. A. In Methanol-Ethanol. To a 100ml ethanolic solution of sodium hydrogen selenide generated as previously described from 1.42 g (18 mg-atoms) of elemental selenium and 0.748 g (19.8 mmol) of sodium borohydride was added a solution of 1.414 g (9.0 mmol) of 2-aminoethanethiosulfuric acid (5) and 0.580 g (10.3 mmol) of potassium hydroxide in 100 ml of MeOH. After the mixture was stirred for 3.25 hr, filtration gave 0.650 g of a colorless solid (a mixture of KNaSeSO₃ and KNaSO₃, by ir) which gave 61 mg of elemental selenium on acid hydrolysis (indicating 26% NaKSeSO₃). To the filtrate was added 25 ml of 1.2 N HCl. The precipitated elemental selenium (1.35 g, 17 mg-atom, 94% recovery) was collected, and the combined filtrate and washings were evaporated to a solid residue which was dried and dissolved in 100 ml of H_2O . Titration of an aliquot with 1.0 N I_2 indicated a maximum of 6% conversion to thiol. Evaporation of the remaining solution and recrystallization of the residue from 2.5 ml of EtOH gave tiny crystals, shown to be cystamine dihydrochloride: mp 213–216° (lit.¹⁷ mp 212–212.5°); ir (KBr) identical with that of authentic material.

B. In Water. Repeating the above experiment in aqueous solution and without the addition of potassium hydroxide gave a 100% recovery of elemental selenium on acidification. From titration of the filtrate with 1.0 N I_2 , the amount of conversion to thiol was calculated to be 28%. The effluent gases were scrubbed in a trap containing saturated CdCl₂, wherein there formed a precipitate of vellow CdS (CdSe is greenish brown or red), identified by the following experiment. A portion of the Cd salt (~10 mg) was suspended in 0.5 ml of H₂O and concentrated HCl was added dropwise until the mixture became homogeneous. To a few drops of the solution was added 5% H₂O₂; no precipitation of elemental selenium was noted. From the acidic solution could be detected, however, H_2S evolution by moistened $Pb(OAc)_2$ paper. In a control experiment, authentic H₂Se did produce elemental selenium under these conditions.

When the experiment was repeated with 4 equiv of sodium hydrogen selenide/mol of 5, a 92% recovery of elemental selenium was obtained on acidification. Titration of an aliquot of the filtrate with 1.0 N I_2 indicated a 100% conversion of 5 to the corresponding thiol. Evaporation of the remainder of the filtrate, followed by trituration with ethanol as described for cystamine, gave a crystalline solid which was identified as 2-mercaptoethylamine (6) hydrochloride by ir.

Generation and Acidification of Sodium Diselenide. A mixture of 3.00 g (38 mg-atoms) of elemental selenium and 1.00 g (27 mmol) of sodium borohydride was allowed to interact in 100 ml of ethanol under reflux with argon purging to produce sodium diselenide.¹¹ After reflux for 1 hr, 50 ml of degassed methanol and 30 ml of 1.2 N HCl were added to the cooled solution. The mixture was purged with argon until no further H₂Se evolution could be detected. The precipitated elemental selenium (984 mg, 12.5 mg-atoms) amounted to a 98% vield based on disproportionation.

Treatment of 1,6-Diaminohexane with Sodium Hydrogen Selenide. A solution of 1.00 g (8.61 mmol) of 1,6-diaminohexane in 50 ml of degassed ethanol was added to a solution of sodium hydrogen selenide generated as described above from 2.72 g (34.4 mg-atoms) of elemental selenium and 1.43 g (37.8 mmol) of sodium borohydride in 100 ml of ethanol. Acidification of the solution with 40 ml of 1.2 N HCl gave no precipitation of selenium, but rather copious evolution of hydrogen selenide.

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Registry No.-1, 150-60-7; 3, 6313-36-6; 5, 2937-53-3; sodium hydrogen selenide, 12195-50-3; sodium diselenide, 39775-40-0; hydrogen selenide, 7783-07-5; di-tert-butyl disulfide, 110-06-5; diphenyl disulfide, 882-33-7; didecyl disulfide, 10496-18-1; cystine, 56-89-3; cystamine dihydrochloride, 56-17-7; diformamidine disulfide dihydrochloride, 14807-75-1; 1,6-diaminohexane, 124-09-4.

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