

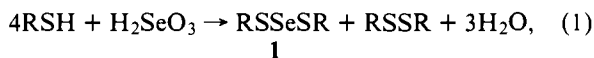
Mechanism of the Reaction of Thiols with Selenite¹

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Abstract: The mechanism of the biochemically important reaction of alkanethiols (RSH) with selenite to form bis(alkylthio)selenides (RSSeSR) has been investigated in acidic buffers of varying pH in aqueous dioxane as solvent. The reaction is kinetically biphasic with the rate of the first stage normally being much faster than the rate of the second. The first stage is shown to be a reversible reaction of the thiol with selenious acid that leads to the formation of an alkylthioseleninic acid RSSeO₂H. There are strong indications that formation of RSSeO₂H occurs by addition of the thiol to a small amount of selenium dioxide present in equilibrium with H₂SeO₃, rather than by direct reaction of the thiol with H₂SeO₃ itself. In the second stage RSSeO₂H reacts with a second thiol in a reaction that exhibits a pH-rate profile which shows that at pH ≤ 2 the kinetically important process is reaction of RSH with RSSeO₂H₂⁺; from pH 2 to 4 it is reaction of RSH with RSSeO₂H; above pH 4 it is reaction of RS⁻ with RSSeO₂H. The modest dependence of rate on the steric requirements of the R group shows that these processes do not involve attack of the thiol on the sulfur atom of RSSeO₂H. Other considerations suggest that these reactions involve attack on the selenium and the formation of the intermediate RSSe(O)SR. The path by which RSSe(O)SR is converted to RSSeSR is not yet established with certainty, but the formation of a considerable amount of the thiolsulfonate *t*-BuSO₂SBu-*t* when the reacting thiol is *t*-BuSH suggests that pathways leading from RSSe(O)SR plus thiol to RSSeSR and the sulfenic acid RSOH may well be involved.

The reaction of selenite with the thiol groups in molecules like cysteine, glutathione, or coenzyme A to form bis(alkylthio)selenides RSSeSR is believed²⁻⁴ to be one of the principal pathways by which inorganic selenium is initially incorporated into living systems. From examination of the process Ganther^{2a} concluded that the usual combining ratio of thiol to selenite is 4:1 and that the normal stoichiometry is



While the bis(alkylthio)selenides (**1**) formed in eq 1 break down rather rapidly at higher pHs, they were found by Ganther^{2a,b} to be relatively stable in acid solution.

In view of the considerable current interest in the physiological chemistry of selenium,⁵⁻⁷ and the importance of eq 1 as a means for the initial incorporation of inorganic selenium into living systems, a detailed knowledge of the mechanism of the reaction between selenite and thiols would certainly seem to be highly desirable.

The present paper describes a study of the mechanism of the reaction of selenious acid with two simple alkanethiols (*n*-BuSH and *t*-BuSH) in aqueous dioxane over acidities ranging from 0.6 N HClO₄ to a 1:5 acetic acid-acetate buffer. As is not surprising, given the stoichiometry shown in eq 1, the reaction is a relatively complex one, exhibiting biphasic kinetics and a number of other complicating features. Although the present study has not elucidated every detail of mechanism for each of the several stages of the reaction, it has provided sufficient insight, especially regarding the initial stages of the reaction, that we feel one can now present a reasonably comprehensive picture of the probable mechanism by which thiols react with selenite to give **1**. While our data and conclusions of course pertain to the reaction of simple thiols with selenite in a nonenzymatic system, we would hope that they would still be of value in developing an understanding of how the reaction might be expected to proceed under physiological conditions.

Results

Stoichiometry of the Reaction. The stoichiometry for the reaction of selenite with thiols proposed by Ganther^{2a} is shown in eq 1. In accord with this we find that the bis(alkylthio)selenide RSSeSR (R = *n*-Bu or *t*-Bu) is the only isolable, selenium-containing product of the reaction of simple alkanethiols (RSH = *n*-BuSH or *t*-BuSH) with selenite in acid solution in

aqueous dioxane, and that the amount of **1** isolated on workup (0.8 mol/mol of H₂SeO₃ taken) is in reasonable accord with a stoichiometry where 1 mol of RSSeSR is formed for each mole of selenite reacting. However, in the reaction involving 2-methyl-2-propanethiol (*t*-BuSH) significantly less *tert*-butyl disulfide is formed than required by eq 1, and there is produced in its stead a considerable amount of *tert*-butyl 2-methyl-2-propanethiolsulfonate, *t*-BuSO₂SBu-*t* (0.3 mol/mol of *t*-BuSSeSBu-*t* formed). In the reaction of 1-butanethiol (*n*-BuSH) with selenite some *n*-butyl 1-butanethiolsulfonate is also formed, but the amount is much less (0.03 mol/mol of H₂SeO₃ reacting), and the yield of the disulfide, *n*-BuSSBu-*n*, is much larger per mol of H₂SeO₃ than in the reaction involving the tertiary thiol.

The stoichiometry of the thiol-selenite reaction is thus apparently not always as simple as in eq 1, and, in particular, some of the corresponding thiolsulfonate RSO₂SR can be formed along with the disulfide RSSR. The formation of the thiolsulfonate is especially noticeable when the thiol is a tertiary one, such as *t*-BuSH.

Kinetics of the Thiol-Selenite Reaction. General Considerations. The kinetics of the reactions of both thiols with selenite (0.5–2.0 × 10⁻⁴ M) were studied at 25 °C in 60% dioxane (v/v) under conditions where the thiols were present in large stoichiometric excess over selenite. A pH range from 0.22 (0.6 N HClO₄) to 8.1 (a 5:1 AcO⁻-AcOH buffer) was used. At all pHs with *t*-BuSH, and at all pHs below 8 with *n*-BuSH, biphasic kinetics are observed, with the rate of the first stage of the reaction being enough faster than the rate of the second that the kinetics of the two stages are easily studied independently.

Figure 1 shows the changes in the absorbance of the solution that occur during the reaction of 1-butanethiol with selenite in a 3:1 HCOO⁻-HCOOH buffer in 60% dioxane (pH 6.6). The rapid first stage of the reaction is associated with a marked increase in absorbance in the region 245–285 nm and the formation of an intermediate having a maximum at 262 nm. During this stage there is little increase in absorbance beyond 300 nm. During the much slower second stage the absorbance in the region 255–280 nm decreases, and there is a significant increase in the absorbance at wavelengths from 300 to 350 nm. The second stage has an isosbestic point at 248 nm. The final spectrum of the solution is similar to those reported by Ganther^{2a,b} for other selenotrisulfides. At somewhat more acidic pHs, due to a change in the ionization state of the intermediate produced in the first stage (vide infra), one does not see the

development of a well-defined maximum at 262 nm during the first stage of the reaction, although there is still a marked increase in absorbance in the region 245–285 nm, and little increase in absorbance beyond 300 nm. The changes in absorbance that accompany the reaction of 2-methyl-2-propanethiol with selenite are generally similar to those just described for *n*-BuSH.

The kinetics of the first stage of the reaction with *n*-BuSH were monitored at either 248 or 262 nm, while the kinetics of the slower second stage were followed at 310 nm. Similar wavelengths were used to follow the two stages of the reaction of *t*-BuSH and selenite.

Kinetics of the First Stage of the Thiol–Selenite Reaction.

At any given pH, under conditions where the thiol is present in large stoichiometric excess over selenite, a plot of $\log(A_{\infty}^i - A)$ vs. time (where A_{∞}^i is the absorbance at the end of the first stage at the wavelength used to follow the reaction) is nicely linear. Its slope gives k_i , the experimental first-order rate constant for the first stage.

Values of k_i for the reaction of 1-butanethiol with selenite as a function of pH and thiol concentration may be found in Table I.⁸ At any given pH k_i varies linearly with $[n\text{-BuSH}]$, as would be expected if the first stage of the *n*-BuSH–selenite reaction is first order in thiol, as well as first order in selenite. Rate constants k_a ($k_a = k_i/[n\text{-BuSH}]$), although independent of pH in the more acidic solutions, decrease rapidly with increasing pH once the pH exceeds 4.5. This pH–rate profile will be considered shortly.

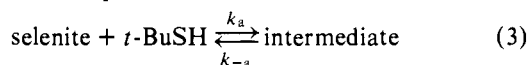
Values of k_i for the reaction of 2-methyl-2-propanethiol with selenite are found in Table II.⁸ In this case the dependence of k_i on thiol concentration is given by

$$k_i = k_{-a} + k_a[t\text{-BuSH}] \quad (2)$$

One also finds, in contrast to the behavior of the *n*-BuSH reaction, where $A_{\infty}^i - A_0$ for the first stage of the reaction is effectively independent of $[n\text{-BuSH}]$ for thiol concentrations in excess of 0.001 M, that $A_{\infty}^i - A_0$ for the first stage of the *t*-BuSH reaction increases with increasing $[t\text{-BuSH}]$ up to $[t\text{-BuSH}] \approx 0.02$ M, with the dependence of $A_{\infty}^i - A_0$ on thiol concentration following a relationship of the form

$$A_{\infty}^i - A_0 = C_{\text{selenite}} \left[\frac{K[t\text{-BuSH}]}{[t\text{-BuSH}] + K'} \right]$$

Both this dependence of $A_{\infty}^i - A_0$ for the first stage of the reaction on $[t\text{-BuSH}]$ and the dependence of k_i on $[t\text{-BuSH}]$ shown in eq 2 suggest that the first stage of the *t*-BuSH–selenite reaction is an equilibrium:



The experimental first-order rate constant for the attainment of equilibrium in such a system would be given by eq 2.⁹ The value of $K_{\text{eq}} = k_a/k_{-a}$ calculated from the slope and intercept of a plot of k_i vs. $[t\text{-BuSH}]$ according to eq 2 agrees quite well with K_{eq} as estimated from the variation of $(A_{\infty}^i - A_0)$ with $[t\text{-BuSH}]$ at the same pH. Values of k_a and k_{-a} estimated from plots of k_i vs. $[t\text{-BuSH}]$ at different pHs indicate that K_{eq} varies somewhat with pH, having a value of approximately 600 at pHs below 5, but one of approximately 300 at pHs above 5.5. One also finds that k_a varies with pH in exactly the same fashion as does k_a for the *n*-BuSH–selenite reaction.

The reversible nature of the first stage of the *t*-BuSH–selenite reaction is readily apparent from both the dependence of k_i on $[t\text{-BuSH}]$ shown in eq 2 and from the dependence of $(A_{\infty}^i - A_0)$ on thiol concentration. We think that the first stage of the *n*-BuSH–selenite reaction is probably also reversible. However, in this case the equilibrium constant K_{eq} is enough larger than in the *t*-BuSH case so that $k_{-a} \ll k_a[n\text{-BuSH}]$ for $[n\text{-BuSH}] \geq 1 \times 10^{-3}$ M. As a result there is (a) no significant

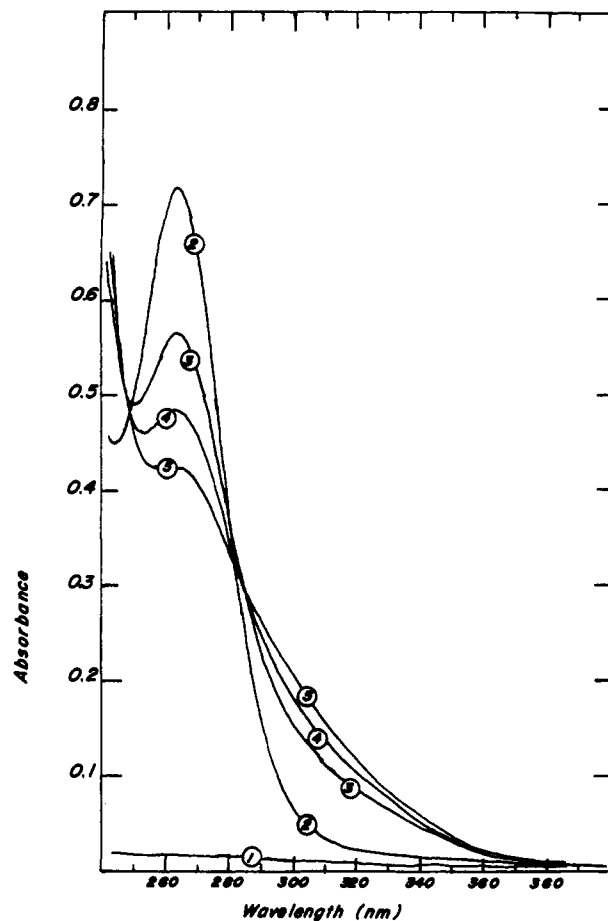


Figure 1. Change in absorbance with time for reaction of selenite (1×10^{-4} M) with 1-butanethiol (4×10^{-3} M) in a formate buffer (pH 6.5) in 60% dioxane: ①, selenite, 10^{-4} M; ②, 3 min after adding 1-butanethiol; ③, 13 min after adding thiol; ④, 23 min after adding thiol; ⑤, 33 min after adding thiol.

contribution of k_{-a} to k_i under the conditions of our kinetic runs and (b) no variation of $(A_{\infty}^i - A_0)$ with $[n\text{-BuSH}]$ at the thiol concentrations used.

pH–Rate Profile for the First Stage of the Thiol–Selenite Reaction. Figure 2 shows the pH–rate profile for k_a for reaction of *n*-BuSH and *t*-BuSH with selenite. Although k_a for *t*-BuSH at any given pH is about eight times smaller than k_a for *n*-BuSH, the pH–rate profiles for the two thiols are of identical shape. The pHs of the various carboxylate buffers in 60% dioxane were derived, as outlined in an earlier paper,¹⁰ from the measured pHs of each buffer in water and a knowledge of ΔpK_a for each carboxylic acid for its transfer from water to 60% dioxane as solvent.

The solid lines in Figure 2 show that the pH–rate profiles for k_a for the two thiols are fitted by an equation of the form

$$k_a = k_0 \left[\frac{a_{\text{H}^+}}{a_{\text{H}^+} + K_1} \right] \quad (4)$$

where K_1 has a value of 1.0×10^{-5} M, and where k_0 for *n*-BuSH is taken to be $4 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, while k_0 for *t*-BuSH is taken to be $50 \text{ M}^{-1} \text{ s}^{-1}$; K_1 is considered to be the acid dissociation constant for the first ionization of selenious acid, i.e., $\text{H}_2\text{SeO}_3 \rightleftharpoons \text{HSeO}_3^- + \text{H}^+$. Given its value in water ($K_1 = 3 \times 10^{-3}$ M) and the values of ΔpK_a for transfer of an acid of the type $\text{HA} \rightleftharpoons \text{A}^- + \text{H}^+$ from water to 60% dioxane typically observed, a value of 1.0×10^{-5} M for K_1 for H_2SeO_3 in 60% dioxane is entirely reasonable.

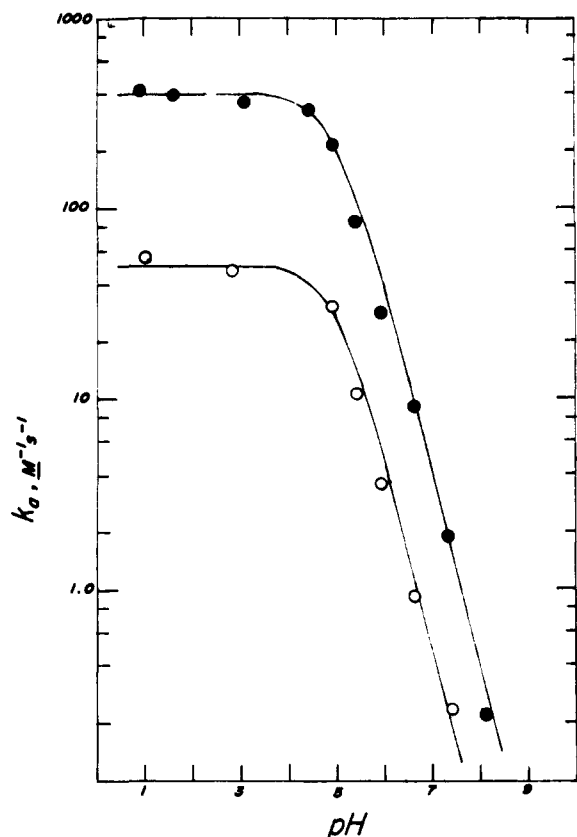


Figure 2. pH-rate profile for first stage of the reaction between thiols and selenite in 60% dioxane at 25 °C: ●, rate constants, k_a , for *n*-BuSH; ○, rate constants, k_a , for *t*-BuSH. Solid curves calculated from eq 4, using K_1 for $\text{H}_2\text{SeO}_3 = 1 \times 10^{-5}$ M, and $k_0 = 400$ for *n*-BuSH, 50 for *t*-BuSH.

The form of eq 4 indicates that for the first stage the only reaction of importance kinetically in the pH range 0.2–8.0 is that between undissociated thiol (RSH) and undissociated selenious acid, H_2SeO_3 .

Kinetics of the Second Stage of the Thiol–Selenite Reaction.

The kinetics of the second stage of the *t*-BuSH–selenite reaction were examined using thiol concentrations ($[\textit{t}\text{-BuSH}] = 0.02\text{--}0.08$ M) large enough to ensure that the equilibrium in eq 3 would be displaced completely to the right at the end of the first stage of the reaction. As noted earlier, the equilibrium constant for the first stage of the *n*-BuSH–selenite reaction is enough larger so that the analogous equilibrium for *n*-BuSH and selenite will be displaced completely to the right at much lower thiol concentrations ($\sim 10^{-3}$ M); accordingly, thiol concentrations of 0.002–0.008 M were employed in the runs used to study the kinetics of the second stage of the *n*-BuSH–selenite reaction.

Plots of $\log(A_\infty^{ii} - A)$ vs. time at 310 nm for the second stage of the reaction of either thiol with selenite were nicely linear, indicating that the disappearance of the intermediate formed in the first stage of the reaction follows first-order kinetics. The slope of such a plot is equal to k_{ii} , the experimental first-order rate constant for the second stage of the reaction. Values of k_{ii} for the reactions of both *n*-BuSH and *t*-BuSH with selenite at different pHs may be found in Table III.⁸

For both thiols k_{ii} varies linearly with [thiol]. The second stage of the reaction is thus first order in thiol, and $k_{ii} = k_b[\text{RSH}]$.

pH–Rate Profile for the Second Stage of the Thiol–Selenite Reaction. Figure 3 shows the pH–rate profile for k_b . The solid curves in Figure 3 are calculated using the expression for k_b shown in eq 5, and the following values of k , k' , and k'' :

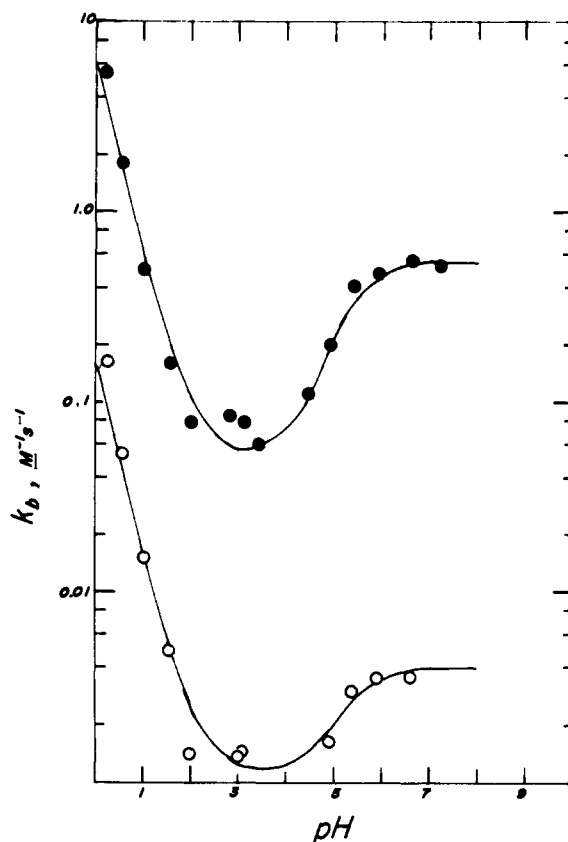


Figure 3. pH-rate profile for second stage of the reaction between thiols and selenite in 60% dioxane at 25 °C: ●, rate constants, k_b , for *n*-BuSH; ○, k_b for *t*-BuSH. Solid curves are calculated from eq 5 using $K_a = 5 \times 10^{-6}$ M and the following values of k , k' , and k'' : *n*-BuSH, $k = 6 \text{ M}^{-2} \text{ s}^{-1}$, $k' = 0.05 \text{ M}^{-1} \text{ s}^{-1}$, and $k'' = 2.7 \times 10^{-6} \text{ s}^{-1}$; *t*-BuSH, $k = 0.15 \text{ M}^{-2} \text{ s}^{-1}$, $k' = 0.0011 \text{ M}^{-1} \text{ s}^{-1}$, $k'' = 2.0 \times 10^{-8} \text{ s}^{-1}$.

$$k_b = \frac{[ka_{\text{H}^+} + k'a_{\text{H}^+} + k'']}{K_a + a_{\text{H}^+}} \quad (5)$$

	k	k'	k''
for <i>n</i> -BuSH	$6 \text{ M}^{-2} \text{ s}^{-1}$	$0.05 \text{ M}^{-1} \text{ s}^{-1}$	$2.7 \times 10^{-6} \text{ s}^{-1}$
for <i>t</i> -BuSH	$0.15 \text{ M}^{-2} \text{ s}^{-1}$	$0.0011 \text{ M}^{-1} \text{ s}^{-1}$	$2.0 \times 10^{-8} \text{ s}^{-1}$

A value of $K_a = 5 \times 10^{-6}$ M is used for both reactions. These values of k , k' , k'' , and K_a give a good fit of k_b to the experimental data.

The intermediate (InH) formed in eq 3 apparently possesses an ionizable proton, and K_a is the acid dissociation constant for the equilibrium $\text{InH} \rightleftharpoons \text{In}^- + \text{H}^+$ in 60% dioxane. The magnitude of K_a is the same whether the intermediate is formed from *n*-BuSH or *t*-BuSH.

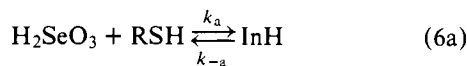
The variation of k_b with a_{H^+} shown in eq 5 has the same form as the dependence of rate constant on pH found¹⁰ in the first stage of the reaction of PhSeO_2H with thiols.

Attempted Isolation of an Intermediate from the End of the Second Stage of the *t*-BuSH–Selenite Reaction. In the reaction of benzeneseleninic acid with *t*-BuSH¹⁰ it was possible to isolate an intermediate formed during that reaction and to establish its structure, $\text{PhSe(O)SBU-}t$, with reasonable certainty. We had hoped that by using a similar experimental approach, i.e., by allowing the reaction of *t*-BuSH and selenite to proceed until the second stage of the reaction was complete and then removing the solvent and excess thiol by lyophilization at low temperature, we might be able to obtain whatever intermediate(s) was produced as a product of the second stage, and then to ascertain its structure by spectroscopic techniques. However, when this experiment was carried out, the NMR

spectrum of the lyophilization residue (taken at $-20\text{ }^{\circ}\text{C}$ to preclude any possible decomposition of the intermediate on warming to room temperature) was identical with that of a mixture of the final reaction products. Any intermediate formed in the slow second stage (step k_b) of the reaction apparently reacts sufficiently rapidly in a subsequent step that its concentration never builds up to a significant level during the reaction.

Discussion

The reaction of selenite with alkanethiols ($n\text{-BuSH}$ or $t\text{-BuSH}$) exhibits biphasic kinetics. The general form of the two kinetic stages of the reaction is

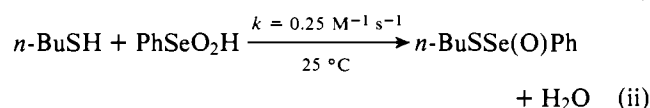
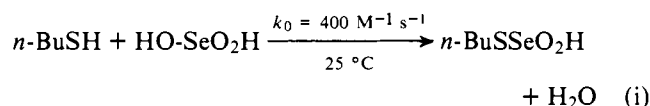


In the first stage (eq 6a) selenious acid reacts *reversibly* with a molecule of thiol to give an intermediate (InH). The pH-rate profile for eq 6b indicates that this intermediate possesses an ionizable proton with a pK_a similar to the first ionization constant (pK_1) for selenious acid. The equilibrium constant, k_a/k_{-a} , for eq 6a is noticeably dependent on thiol structure. When $R = t\text{-Bu}$, the equilibrium constant is small enough that a thiol concentration of 0.02 M is required in order for the formation of InH from selenite (10^{-4} M) to be complete at equilibrium. When $R = n\text{-Bu}$, k_a/k_{-a} is enough larger that a considerably lower ($\sim 10^{-3}\text{ M}$) thiol concentration is sufficient to displace the equilibrium completely to the right.

In the second kinetic stage (eq 6b) InH reacts with another thiol molecule to form a second intermediate, II. Further reactions starting from II, at least some of which, from the overall stoichiometry of the reaction, must clearly involve additional thiol, lead on to the final products. These consist of the bis(alkylthio)selenide, RSSeSR , the disulfide, RSSR , and, in the case where $R = t\text{-Bu}$, a considerable amount of the thiol-sulfonate, RSO_2SR . This thiol-sulfonate is formed at the expense of the disulfide. None of the reactions leading from II to the final products is accessible to kinetic study under our reaction conditions.

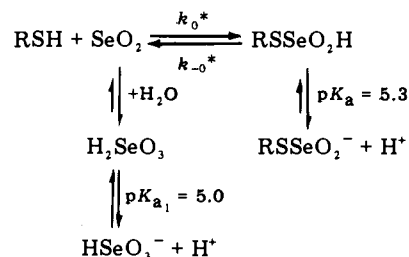
First Stage of the Thiol-Selenite Reaction. The most reasonable structure for InH, given that it is formed from one molecule each of selenious acid and thiol and has a pK_a similar to pK_1 for selenious acid, would seem to be RSSeO_2H . Such an alkylthioseleninic acid could certainly have a pK_a close to pK_1 for H_2SeO_3 .

In 60% dioxane over the pH range from 1.0 to 8.0 the only reaction of kinetic importance for the formation of RSSeO_2H is that between undissociated thiol and undissociated selenious acid (eq i). Its rate constant (k_0) is over 10^3 larger than the rate constant for the otherwise closely related reaction of the same thiol with undissociated benzeneseleninic acid (eq ii):¹⁰



Later we will see that the reaction of undissociated $n\text{-BuSH}$ with undissociated $n\text{-BuSSeO}_2\text{H}$ (a process that is believed to lead to $n\text{-BuSSe(O)SBu-}n$) has a rate constant, $0.05\text{ M}^{-1}\text{ s}^{-1}$, not greatly different from the rate constant for eq ii. Thus the much faster rate of reaction of HOSeO_2H with RSH , as compared with the rate of reaction of PhSeO_2H with the same thiol, can hardly be ascribed to any inductive effect associated

Scheme 1. Mechanism of the First Stage of the Reaction of Thiols with Selenite in 60% Dioxane



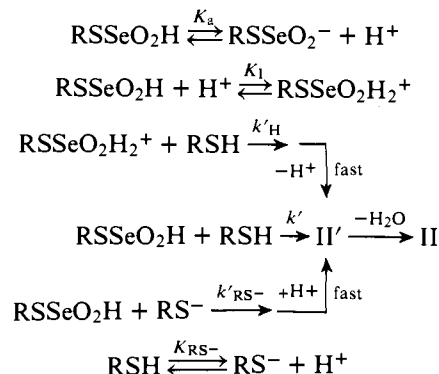
with the replacement of Ph by OH; yet, clearly, something allows HOSeO_2H to react much faster with a thiol than does PhSeO_2H (or RSSeO_2H).

We suggest that HOSeO_2H reacts much faster than PhSeO_2H (or RSSeO_2H) because, unlike these other two species, it can lose water to give a small amount of its dehydration product (SeO_2) in equilibrium with it. This small amount of selenium dioxide present in equilibrium with H_2SeO_3 is many orders of magnitude more reactive toward the thiol than HOSeO_2H , PhSeO_2H , or RSSeO_2H , and is the species that actually reacts with the thiol in the first stage of the thiol-selenite reaction. We suggest, therefore, that the proper complete description of the mechanism of the first stage of the thiol-selenite reaction is as shown in Scheme 1.

It is certainly reasonable to expect SeO_2 to be orders of magnitude more reactive toward the thiol than H_2SeO_3 . It also seems reasonable that there could be a small but significant amount of SeO_2 present in equilibrium with H_2SeO_3 in these aqueous dioxane solutions. In water the equilibrium $\text{H}_2\text{SO}_3 \rightleftharpoons \text{SO}_2 + \text{H}_2\text{O}$ is known^{11,12} to lie far over to the right. While the corresponding equilibrium for the selenium acid, i.e., $\text{H}_2\text{SeO}_3 \rightleftharpoons \text{SeO}_2 + \text{H}_2\text{O}$, has been shown¹³ under the same conditions to lie well to the left, the position of the equilibrium for the S(IV) acid certainly suggests that there is likely to be at least a few percent of SeO_2 present at equilibrium in the Se(IV) case.

The variation of k_0^* with thiol structure, $k_0^*(n\text{-BuSH})/k_0^*(t\text{-BuSH}) = 8$, is modest and similar to the $n\text{-BuSH}/t\text{-BuSH}$ rate ratio for the reaction of the two thiols with PhSeO_2H .¹⁰ The fact that pK_a for RSSeO_2H differs from pK_1 for H_2SeO_3 by only 0.3 pK unit is the reason why the apparent equilibrium constant for eq 6a, k_a/k_{-a} , varies by only a factor of 2 on changing from pHs where both RSSeO_2H and H_2SeO_3 are present almost entirely as their conjugate bases (RSSeO_2^- and HSeO_3^-) to more acidic pHs where both are not significantly ionized.

Second Stage of the Thiol-Selenite Reaction. The pH-rate profile for the second stage of the reaction of either thiol with selenite (Figure 3 and eq 5) is of the same type as that found¹⁰ for the reaction of thiols with PhSeO_2H . This similarity in the pH-rate profiles for the two reactions indicates that the mechanism for the second stage of the thiol-selenite reaction presumably has the kinetic form:

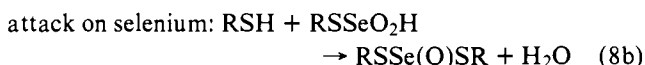
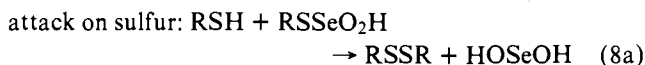


Such a scheme will give the dependence of rate on pH for k_b

$$k_b = \frac{k_H'K_1a_{H^+}^2 + k'a_{H^+} + k'_{RS}K_{RSH}}{a_{H^+} + K_a} \quad (7)$$

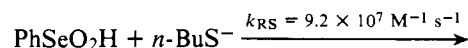
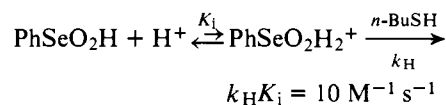
one that is, of course, of exactly the same form as eq 5. At pH ≤ 2 the dominant path for the formation of II is reaction of thiol with $RSSeO_2H_2^+$ (present at low concentration in equilibrium with $RSSeO_2H$ in these acidic solutions); in this pH range $a_{H^+} \gg K_a$, and therefore $k_b = k_H'K_1a_{H^+}$. Above pH ≈ 2 the rate of the reaction involving $RSSeO_2H_2^+$ and RSH has become slow enough that reaction of thiol with $RSSeO_2H$ becomes kinetically the dominant reaction. This reaction, whose rate is independent of pH as long as $a_{H^+} > K_a$, is the dominant process only over a narrow pH range ($\sim 2-4$), because above pH ≈ 4 the fraction of RSH present as RS^- , although still extremely small, becomes large enough so that reaction of RS^- with $RSSeO_2H$ (step k'_{RS}) becomes the important route kinetically for the formation of II. At pHs ≥ 4.5 where the k'_{RS} -term is the major contributor to k_b , k_b will be given by $k_b = k'_{RS}K_{RSH}/(K_a + a_{H^+})$. In this region k_b will increase with increasing pH up to the point where $K_a > a_{H^+}$. At that point k_b will become independent of pH with a value equal to $k'_{RS}K_{RSH}/K_a$.

A priori there would seem to be three ways that RSH might attack $RSSeO_2H_2^+$ or $RSSeO_2H$ (or RS^- attack $RSSeO_2H$). These are shown in eq 8a-c using the reaction of the thiol with $RSSeO_2H$ for the illustrative example:



Reactions involving nucleophilic attack on the sulfur of a t -BuS group are known¹⁴ to be *much* slower than the rate of attack on the sulfur of an n -BuS group in the same reaction. Rate differences of k_{n-BuS}/k_{t-BuS} of $10^{4.5}-10^6$ have been observed.^{10,14} The fact that k_{n-BuS}/k_{t-BuS} for the reaction of RSH with $RSSeO_2H$ is only 40 seems to be much too small to be consistent with a mechanism (eq 8a) where attack of the thiol on $RSSeO_2H$ occurs at sulfur, and would appear to allow us to rule out attack on sulfur as the mode of attack of thiol on $RSSeO_2H$.

This leaves us to decide between attack on selenium (eq 8b) and attack on oxygen (eq 8c). Two features of the kinetic results suggest that attack on selenium is what is involved. First, from eq 7, the values of k , k' , k'' , and K_a required to fit eq 5 to the experimental data, and a previous estimate¹⁵ of K_{RSH} for n -BuSH in 60% dioxane, one calculates values of $k_H'K_1$ ($6 \text{ M}^{-2} \text{ s}^{-1}$), k' ($0.05 \text{ M}^{-1} \text{ s}^{-1}$), and k'_{RS} ($9.6 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$) for the n -BuSH- n -BuSSeO₂H system. One can compare these with the rate constants for the various reactions of the n -BuSH-PhSeO₂H system:



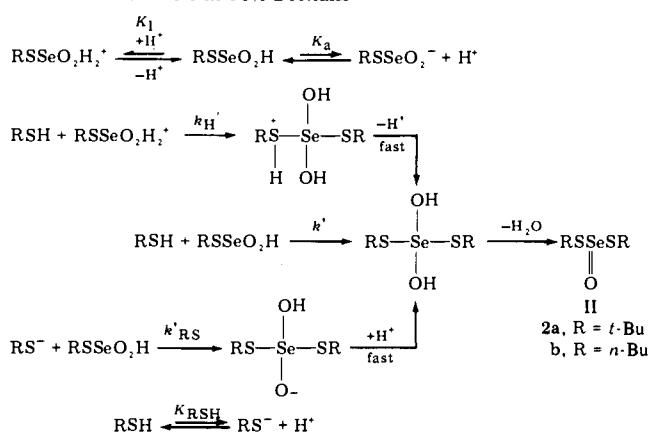
These reactions are known¹⁰ to involve attack of the thiol on the selenium atom of the seleninic acid. The considerable similarity of k'_{RS} -vs. k_{RS} -, k' -vs. k -, and $k_H'K_1$ -vs. $k_H K_1$ is easy

to understand if attack of thiol on n -BuSSeO₂H also is occurring at selenium, since in reactions in which both are being attacked by the same reagent in the same fashion n -BuSSeO₂H and PhSeO₂H would probably be expected to exhibit quite similar reactivity. On the other hand, if attack on n -BuSSeO₂H were taking place at oxygen, it seems doubtful that one would get the degree of similarity between the rate constants for the two different systems that is observed. Second, the rate ratio (k_{n-BuSH}/k_{t-BuSH}) for $k_H'K_1$, k' , and k'_{RS} - is from 40 to 50, considerably larger than for the reactions involving the thiols and PhSeO₂H ($k_H K_1$, k , and k_{RS} -) where the rate ratio (k_{n-BuSH}/k_{t-BuSH}) is from 2 to 5. In the reactions involving PhSeO₂H the group attached to the selenium remains the same as the thiol is changed from n -BuSH to t -BuSH, but in the present system involving $RSSeO_2H$ it changes from n -BuS to t -BuS when the reacting thiol is changed from n -BuSH to t -BuSH. Given the greater steric bulk of t -BuS relative to n -BuS, one can understand how this could exert some retarding effect on the rate of attack of thiol on the selenium atom of t -BuS-SeO₂H and lead to a larger k_{n-BuSH}/k_{t-BuSH} rate ratio than for the attack of the two thiols on the selenium atom of PhSeO₂H. On the other hand, if attack of RSH on $RSSeO_2H$ were on oxygen, there would be no reason to expect that k_{n-BuSH}/k_{t-BuSH} would be larger than for the attack of RSH on the selenium of PhSeO₂H, since the oxygen atoms of $RSSeO_2H$ are far enough away from the RS group that the steric size of R should have little if any effect on the rate of eq 8c.

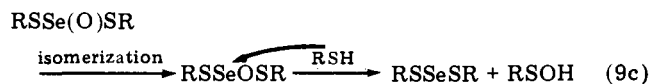
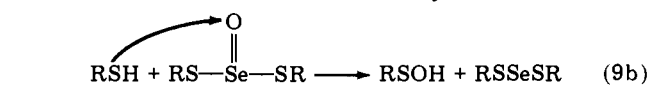
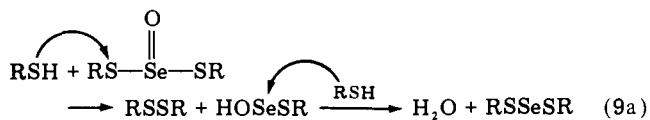
For these reasons we believe that the attack of thiol (or thiolate) on $RSSeO_2H$ (or $RSSeO_2H_2^+$) in the second stage of the thiol-selenite reaction takes place at selenium. The attack of RSH (or RS^-) on the selenium atom of PhSeO₂H (or PhSeO₂H₂⁺) has been shown to lead to the formation of the thiol-seleninate PhSe(O)SR. The similarity in the rates of reaction of n -BuSH with PhSeO₂H and n -BuSSeO₂H discussed above makes it reasonable to propose that the mechanism for the reaction involving $RSSeO_2H$ and thiol should be exactly analogous to that established¹⁰ for the PhSeO₂H reaction. We suggest, therefore, that the mechanism of the second stage of the thiol-selenite reaction is as shown in Scheme II and that the intermediate previously designated in eq 6b as II has the structure $RSSe(O)SR$.

Subsequent Stages of the Thiol-Selenite Reaction. Given that intermediate II apparently has the structure $RSSe(O)SR$ (2), how is it converted to the final reaction products? Since the kinetics of the stages of the reaction leading on from 2 to the final products are not accessible to study under our reaction conditions, any proposals regarding the mechanism of this portion of the reaction will, of necessity, be less precise than those for the first two stages of the reaction.

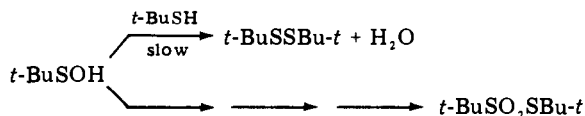
Scheme II. Mechanism of the Second Stage of the Reaction of Thiols with Selenite in 60% Dioxane



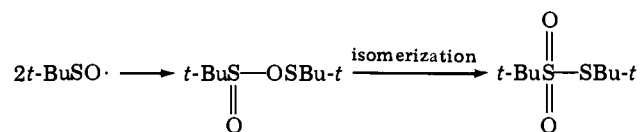
One can write three reasonable paths that would transform **2** into RSSeSR , which, as we know from investigation of the products of the reaction, is apparently the only final selenium-containing product of the reaction. These are shown as eq 9a-c.



Consider first the situation when $\text{R} = t\text{-Bu}$. In the reaction of $t\text{-BuSH}$ with selenite the amount of *tert*-butyl disulfide produced is much less than required by the stoichiometry of eq 1, and there is formed in its place a considerable amount of the thiolsulfonate $t\text{-BuSO}_2\text{SBu-}t$. The formation of so much thiolsulfonate cannot be accounted for in any simple manner if the reaction of $t\text{-BuSSe(O)SBu-}t$ (**2a**) with thiol takes the course shown in eq 9a, but it can be explained if $t\text{-BuSOH}$ is being formed as an intermediate (eq 9b or 9c). Because of the hindrance to nucleophilic attack on sulfur provided by the *tert*-butyl group in $t\text{-BuSOH}$, reaction of this sulfenic acid with thiol to give *tert*-butyl disulfide should be quite slow, thereby allowing time for much of the sulfenic acid to undergo a sequence of reactions that results in the formation of the thiolsulfonate:

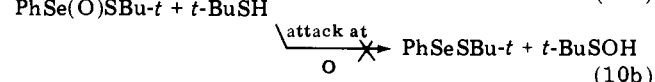
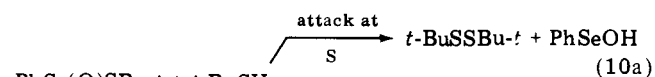


Although we do not know the exact path by which $t\text{-BuSOH}$ is converted to $t\text{-BuSO}_2\text{SBu-}t$, any route that leads to the formation of $t\text{-BuSO}\cdot$ radicals from the sulfenic acid can account for the thiolsulfonate, since interaction of two $t\text{-BuSO}\cdot$ radicals is known¹⁶ to lead to the formation of the thiolsulfonate $t\text{-BuSO}_2\text{SBu-}t$, presumably by the path



(Speculation on how $t\text{-BuSO}\cdot$ might be formed from $t\text{-BuSOH}$ in the present system, and other possible ways that $t\text{-BuSO}_2\text{SBu-}t$ could be formed from $t\text{-BuSOH}$, will be presented later.) We believe, therefore, that the formation of a large amount of $t\text{-BuSO}_2\text{SBu-}t$ as one of the products of the reaction of $t\text{-BuSH}$ with selenite strongly suggests that **2a** disappears by either eq 9b or 9c.

The manner of reaction of **2a** (either eq 9b or 9c) contrasts with that of the related compound $\text{PhSe(O)SBu-}t$. Earlier work¹⁰ suggested that the reaction of $\text{PhSe(O)SBu-}t$ with $t\text{-BuSH}$ involves attack by the thiol on the sulfur atom of the thiolseleninate (eq 10a). To confirm this we have carefully

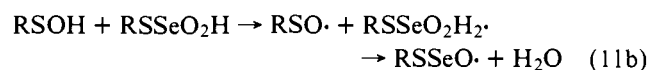


reexamined the products of the reaction and have been able to show that *no* $t\text{-BuSO}_2\text{SBu-}t$ is formed. Were attack of thiol

on the oxygen of $\text{PhSe(O)SBu-}t$ (eq 10b) involved to any extent one would presumably have expected to find some $t\text{-BuSO}_2\text{SBu-}t$ formed as a result of further reactions of the $t\text{-BuSOH}$ liberated by eq 10b. That **2a** and $\text{PhSe(O)SBu-}t$ would behave differently in their reaction with thiol, while not expected in advance, does not seem unreasonable after the fact. Some speculative suggestions for the possible origin of the difference in behavior are given in a note.¹⁷

Does the corresponding intermediate $n\text{-BuSSe(O)SBu-}n$ (**2b**) formed in the $n\text{-BuSH}$ -selenite reaction also disappear by the same path (eq 9b or 9c) as **2a**, or does the lack of steric hindrance to nucleophilic attack on sulfur in **2b** as compared to **2a** mean that the rate of eq 9a when $\text{R} = n\text{-Bu}$ will be faster than the rate of either eq 9b or 9c? The fact that a small amount of $n\text{-BuSO}_2\text{SBu-}n$ is isolated from the $n\text{-BuSH}$ reaction suggests that some sulfenic acid is being formed. One also needs to recognize that, because of the lack of steric hindrance to nucleophilic attack on sulfur in $n\text{-BuSOH}$, conversion of any sulfenic acid formed to disulfide via the reaction $n\text{-BuSOH} + n\text{-BuSH} \rightarrow n\text{-BuSSBu-}n + \text{H}_2\text{O}$ should compete more effectively with the pathway that converts $n\text{-BuSOH}$ to thiolsulfonate than is the case in the *tert*-butyl system, so that the small yield of thiolsulfonate cannot be construed as evidence that only a small fraction of **2b** reacts by eq 9b or 9c. In fact the results are perfectly compatible with a mechanism in which **2b** disappears entirely by eq 9b or 9c, with almost all of the $n\text{-BuSOH}$ so produced then reacting with thiol to produce $n\text{-BuSSBu-}n$, and only a small amount being converted to thiolsulfonate. At the same time, the amount of thiolsulfonate is small enough that one can probably also defend the alternative position that it arises in the $n\text{-Bu}$ case from some not-understood minor side reaction having nothing to do with the decomposition of **2b** and that the important route for the disappearance of **2b** is that shown in eq 9a.

We will close with some speculation as to how a sulfenic acid RSOH might be converted to thiolsulfonate RSO_2SR in these systems. We have already noted that any process that converted RSOH to $\text{RSO}\cdot$ could account for the formation of the thiolsulfonate since combination of two $\text{RSO}\cdot$ is known¹⁶ to lead to this product. Sulfenic acids have been shown¹⁸ to undergo hydrogen-atom transfer to free radicals, i.e., $\text{RSOH} + \text{R}'\cdot \rightarrow \text{RSO}\cdot + \text{R}'\text{H}$, extremely readily. Conceivably they might also readily transfer a hydrogen atom to one of the selenium intermediates as, for example, in eq 11a or 11b. Once



produced the $\text{RSSeO}\cdot$ radical could then abstract a hydrogen atom from another sulfenic acid (eq 12), giving a second $\text{RSO}\cdot$ and RSSeOH ; the latter species could then react with a thiol molecule to give RSSeSR and water. An alternative way to achieve the same overall result would be for RSOH to react with either **2** or RSSeO_2H in a nonhomolytic reaction to give the mixed anhydride RSSe(O)OSR , and for this species to then undergo very rapid homolysis to an $\text{RSO}\cdot$ plus an $\text{RSSeO}\cdot$ radical, with the latter radical then reacting as in eq 12.



Since the disproportionation of a sulfinic acid (RSO_2H) leads to the formation of the thiolsulfonate RSO_2SR ,¹⁹ it is also possible that RSOH is first oxidized by one of the selenium intermediates to RSO_2H , with the sulfinic acid then undergoing disproportionation to the thiolsulfonate. While disproportionation of sulfinic acids is normally quite slow in aqueous solution at room temperature, it might be markedly catalyzed

in the present system by one or more of the selenium species that are present.

There are then at least several plausible possible routes by which the thiosulfonate could be formed from the sulfenic acid in the present system.

Experimental Section

Purification of Materials. 1-Butanethiol (Aldrich) and 2-methyl-2-propanethiol (Aldrich) were purified by fractional distillation and stored under nitrogen. Dioxane was purified by the procedure described by Fieser and Fieser,²⁰ with the freshly fractionally distilled solvent then being frozen and stored at -20°C to prevent the formation of peroxides prior to use. All water used in the kinetic studies was doubly distilled from glass. Selenium dioxide (Alfa) and sodium selenite (Alfa) were of the highest purity commercially available and were used as received. The carboxylic acids used in the preparation of the various buffers were all of the highest degree of purity commercially available.

Products of Reaction of 2-Methyl-2-propanethiol with Selenite. 2-Methyl-2-propanethiol (4.5 g, 50 mmol) was added dropwise to a well-stirred solution of 1.1 g (10 mmol) of selenium dioxide in 50 mL of 60% dioxane. After the addition was complete the mixture was allowed to stand for 2 h at room temperature. At that point most of the dioxane and some of the water were removed under reduced pressure at room temperature. The residue was mixed with 150 mL of water and extracted with two 50-mL portions of methylene chloride. The combined methylene chloride extracts were washed with water and dried over anhydrous magnesium sulfate, and the methylene chloride was then removed under reduced pressure. The residue was then treated in different ways in different experiments.

In the first experiment the residue was distilled in vacuo (bp 59°C , 0.3 mm). The distillate (1.7 g) was then chromatographed on silica gel using hexane, hexane-ether (3:1, 1:1, and 1:2), and finally ether as eluents. Elution with hexane gave 1.47 g of bis(*tert*-butylthio)selenide, *t*-BuSSeS*Bu-t*, having the following characteristics: IR (neat) 2960, 1460, 1365, and 1160 cm^{-1} ; NMR (CDCl_3) δ 1.42 (s). The mass spectrum showed a molecular ion at m/e 258 (M^+ for ^{80}Se) and satellite molecular ion peaks at m/e 254, 255, 256, and 260 due to the other isotopes of selenium (^{76}Se , ^{77}Se , ^{78}Se , and ^{82}Se) that provide a characteristic fingerprint establishing the presence of a selenium atom in the molecule.

Elution with ether gave 0.23 g of a compound whose infrared, NMR (both ^1H and ^{13}C), and mass spectrum were identical with those of a known sample of *tert*-butyl 2-methyl-2-propanethiosulfonate prepared by the oxidation of *tert*-butyl 2-methyl-2-propanethiosulfinate (vide infra).

In a second experiment the residue after removal of the methylene chloride was chromatographed directly on silica gel without the initial vacuum distillation. The NMR spectrum of the fraction eluted with hexane now showed a weak singlet at δ 1.32 as well as a much stronger singlet at δ 1.42 due to *t*-BuSSeS*Bu-t*. The singlet at δ 1.32 is due to the presence of *tert*-butyl disulfide. From the total weight of the fraction and the relative intensity of the singlet at δ 1.42 the yield of *t*-BuSSeS*Bu-t* was found to be 2.0 g (7.8 mmol). Elution with ether again gave *tert*-butyl 2-methyl-2-propanethiosulfonate, 0.34 g (1.62 mmol).

In a third experiment the NMR spectrum of the residue was taken in CDCl_3 immediately after the removal of the methylene chloride. It consisted of four singlets: δ 1.32 (*t*-BuSS*Bu-t*), 1.42 (*t*-BuSSeS*Bu-t*), and 1.46 and 1.62 (*t*-BuSO₂S*Bu-t*). One can determine accurately the integrated intensity of each of the singlets at δ 1.32 and 1.62 and the combined integrated intensity of the two singlets at δ 1.42 and 1.46. One can then use relationships between the integrated intensities to determine the molar ratio of (a) *t*-BuSO₂S*Bu-t* to *t*-BuSSeS*Bu-t* and (b) *t*-BuSS*Bu-t* to *t*-BuSSeS*Bu-t* in the product mixture. Thus $t\text{-BuSO}_2\text{S}i\text{Bu-t} : t\text{-BuSSeS}i\text{Bu-t} = 2 \times \delta_{1.62} / (\delta_{1.46} + 1.42 - \delta_{1.62})$, and $t\text{-BuSS}i\text{Bu-t} : t\text{-BuSSeS}i\text{Bu-t} = \delta_{1.32} / (\delta_{1.46} + 1.42 - \delta_{1.62})$. These molar product ratios were found to be $t\text{-BuSO}_2\text{S}i\text{Bu-t} : t\text{-BuSSeS}i\text{Bu-t} = 0.28$ and $t\text{-BuSS}i\text{Bu-t} : t\text{-BuSSeS}i\text{Bu-t} = 0.23$. An experiment in which a known amount of additional *tert*-butyl disulfide was added to the final reaction mixture before workup indicated that some of the disulfide is lost during workup, presumably owing to its greater volatility as compared to *t*-BuSSeS*Bu-t* and the thiosulfonate. Thus the molar ratio of *t*-BuSS*Bu-t* : *t*-BuSSeS*Bu-t* of 0.23 is a minimum value for the ratio in which disulfide is produced in the actual reaction

and the true value is almost certainly somewhat higher, probably about 0.3 mol/mol selenotrisulfide.

***tert*-Butyl 2-Methyl-2-propanethiosulfonate.** *tert*-Butyl 2-methyl-2-propanethiosulfinate^{21,22} (7.67 g) was dissolved in 16 mL of glacial acetic acid and 4.5 mL of 30% hydrogen peroxide was then added. The reaction mixture was stirred overnight at room temperature. It was then extracted with chloroform. The chloroform extracts were washed with saturated sodium bicarbonate until the washings remained faintly alkaline. The chloroform extracts were then dried over anhydrous magnesium sulfate and the chloroform was removed under reduced pressure. The NMR spectrum of the residue showed sharp singlets at δ 1.42, 1.46, 1.50, and 1.62, indicating that the crude product was a mixture.²³

Chromatography of a portion of the residue on silica gel using benzene as eluent permitted its separation into two main fractions. The one which was eluted first had the following spectral properties: IR 2960, 1460, 1395, 1365, 1300 ($>\text{SO}_2$), 1155 and 1100 ($>\text{SO}_2$), and 1020 cm^{-1} ; NMR (CDCl_3) δ 1.42 (s, 9 H), 1.50 (s, 9 H); mass spectrum m/e 242 (M^+). The compound appears to be identical with the compound 2-methyl-2-propanesulfenic 2-methyl-2-propanesulfonic thioanhydride, *t*-BuSO₂SS*Bu-t*, reported by Block and O'Connor.²⁴

The second main fraction eluted, which weighed about half as much as the first, consisted of *tert*-butyl 2-methyl-2-propanethiosulfonate, *t*-BuSO₂S*Bu-t*. This thiosulfonate has an infrared spectrum (2960, 1460, 1395, 1365, 1300 ($>\text{SO}_2$), 1155, 1100 ($>\text{SO}_2$) cm^{-1}) essentially identical with that of *t*-BuSO₂SS*Bu-t*. Its ^1H NMR (CDCl_3), δ 1.46 (s, 9 H), 1.62 (s, 9 H), is, however, quite different from that of *t*-BuSO₂SS*Bu-t* as is also its mass spectrum: m/e 210 (M^+ , 1.1%), 146 ($\text{M}^+ - \text{SO}_2$, 39%), 91 (37%), 90 (45%), 89 (41%), 88 (40%), 76 (43%), 75 (41%), 64 (60%), 58 (40%), 57 (100%), 56 (74%). Anal. Calcd for $\text{C}_8\text{H}_{18}\text{O}_2\text{S}_2$: C, 45.70; H, 8.63; S, 30.45. Found: C, 45.96; H, 8.69; S, 30.70. The proton-decoupled ^{13}C NMR spectrum of the thiosulfonate in CDCl_3 shows peaks at 23.74, 31.52, 56.29, and 68.02 ppm, with the signals at 23.74 and 31.52 ppm being of greater intensity than the other two. The resonance at 68.02 ppm is considered to be associated with the carbon bonded to the sulfonyl group, that at 56.3 ppm with the carbon bonded to the other sulfur.

Products of Reaction of 1-Butanethiol with Selenite. 1-Butanethiol (4.5 g, 50 mmol) was added dropwise to a well-stirred solution of 1.1 g (10 mmol) of selenium dioxide in 50 mL of 60% dioxane. After the addition was complete the mixture was allowed to stand for an additional 20 min at room temperature. It was then worked up in the same way as for the reaction of *t*-BuSH with selenite.

Two fractions were obtained upon chromatography of the residue on silica gel using hexane and ether as eluents. The first fraction (2.7 g), which was by far the larger, had an NMR spectrum that indicated that it was a mixture of *n*-butyl disulfide and bis(*n*-butylthio)selenide. There was a distorted triplet at δ 0.82–1.06 (CH_3 groups of both *n*-BuSS*Bu-n* and *n*-BuSSeS*Bu-n*), a multiplet between δ 1.22 and 1.88 (all methylene groups in both compounds except those attached to sulfur), a triplet at δ 2.62–2.80 (CH_2S protons of the disulfide), and a triplet at δ 2.90–3.05 (CH_2S protons of *n*-BuSSeS*Bu-n*). The assignment of the triplet at δ 2.62–2.80 to the disulfide followed from the NMR spectrum of a known sample of the disulfide. From the ratio of the integrated intensities of the two triplets one can make a rough estimate of the amounts of disulfide and bis(alkylthio)selenide in the fraction. This indicated that there were 7.8 mmol of *n*-BuSSeS*Bu-n* and 4.0 mmol of *n*-BuSS*Bu-n* present. However, since other experiments revealed that owing to its greater volatility a sizable amount of disulfide is lost during the workup and the removal of the last traces of solvent from the chromatographic fractions, the actual amount of disulfide produced in the reaction is undoubtedly significantly larger than this.

The second fraction consisted of only 0.07 g. It had the following spectral properties: IR (neat) 2960, 1460, 1415, 1390, 1330 ($>\text{SO}_2$), 1230, 1130, 1100 ($>\text{SO}_2$), and 910 cm^{-1} ; NMR (CDCl_3) δ 0.84–1.1 (pair of overlapping triplets, 6 H), 1.26–2.08 (multiplet, 8 H), 3.06–3.42 (pair of overlapping triplets, 4 H); mass spectrum m/e 210 (M^+). These properties indicated that the compound was *n*-butyl 1-butanethiosulfonate, *n*-BuSO₂S*Bu-n*, and indeed the compound was identical with a sample of this thiosulfonate synthesized by oxidation of *n*-butyl disulfide with 2 equiv of hydrogen peroxide in acetic acid as solvent.

Procedure for Kinetic Runs Using Conventional Spectrophotometry. A stock solution of selenenic acid was prepared by dissolving a care-

fully weighed amount of reagent-grade selenium dioxide in water. Stock solutions of the two thiols were prepared immediately prior to use by dissolving a weighed amount of the thiol in purified dioxane. A measured volume (3.5 mL) of a 60% dioxane solution containing the proper amount of either perchloric acid or buffer was placed in a 1-cm stoppered cell in the thermostated cell compartment of a Cary Model 17 spectrophotometer. The desired amount of selenious acid stock solution (10–50 μL) was then added by a microsyringe. The reaction was then initiated by adding the proper amount (10–50 μL) of the stock solution of the thiol.

To follow the first stage of the reaction the increase in the absorbance of the solution with time at an appropriate wavelength (248 or 262 nm for *n*-BuSH, 253 or 262 nm for *t*-BuSH) was then monitored. At whatever wavelength was used the absorbance of the end of the first stage (A_{∞}^i) remained stable for a long enough period of time compared to the half-life for the first stage so that accurate values for A_{∞}^i could be obtained with no difficulty. The rate constant for the first stage of the reaction was then determined from a plot of $\log(A_{\infty}^i - A)$ vs. time.

To follow the slower second stage of the reaction the change in absorbance with time was followed at 310 nm, a wavelength at which there is little change in absorbance during the first stage of the reaction but a significant increase during the second stage. The final absorbance at this wavelength (A_{∞}^{ii}) was stable. The rate constant for the second stage of the reaction was evaluated from a plot of $\log(A_{\infty}^{ii} - A)$ vs. time. Under the conditions of the present work the rate of the second stage of the reaction is enough slower than the rate of the first that it can be treated kinetically as an independent reaction.

Procedure for Kinetic Runs Using Stopped-Flow Spectrophotometry. Many of the first-stage rates were too rapid to follow using conventional spectrophotometry, and in these cases stopped-flow spectrophotometry was used instead. For the stopped-flow runs a solution of the thiol (*n*-BuSH or *t*-BuSH) in 60% dioxane containing the proper amount of either buffer or perchloric acid was prepared and placed in one of the reservoir syringes of a Durrum-Gibson Model D-110 stopped-flow spectrophotometer. A solution of selenious acid ($1.0\text{--}2.0 \times 10^{-4}$ M) in 60% dioxane was placed in the other syringe. The reaction was then initiated by mixing the two solutions using the stopped-flow device and the change in absorbance with time at a suitable wavelength recorded on the oscilloscope.

Attempted Isolation of an Intermediate from the End of the Second Stage of the *t*-BuSH-Selenite Reaction. 2-Methyl-2-propanethiol (72.2 mg, 0.8 mmol) was dissolved in 2 mL of dioxane. This solution was then added dropwise with stirring to a solution containing 33.3 mg (0.3 mmol) of selenium dioxide dissolved in 8 mL of 60% dioxane. The solution was allowed to stand for 8 h at room temperature. It was then frozen in dry ice, and the solvent and any other adequately volatile material were removed by lyophilization. To prevent any possible thermal decomposition of the intermediate the lyophilization flask was cooled externally at -20°C throughout the latter stages of the lyophilization. The residue remaining at the end of the lyophilization was dissolved in acetone- d_6 at -20°C and its NMR spectrum determined. The only signals observed were a singlet at δ 1.41 (*t*-BuS-SeSBu-*t*) and two much weaker singlets of equal intensity at δ 1.43 and 1.59 (*t*-BuSO₂SBu-*t*). Warming the acetone- d_6 solution to room temperature and allowing it to stand at that temperature for 1 h produced no change in the spectrum.

Search for *tert*-Butyl 2-Methyl-2-propanethiolsulfonate as a Product of the Reaction of Benzeneseleninic Acid with 2-Methyl-2-

propanethiol. The reaction of 1.8 g (20 mmol) of 2-methyl-2-propanethiol with benzeneseleninic acid (0.76 g, 4.0 mmol) in 60% dioxane was carried out exactly as described in an earlier paper,¹⁰ and the final products were carefully examined by thin layer chromatography on silica gel to see if any *t*-BuSO₂SBu-*t*, which had not been reported as a product in the earlier work,¹⁰ was in fact formed. None was observed, and an experiment in which a small amount of the thiolsulfonate was added to the final products before TLC showed that, if present, it would have easily been detected.

Supplementary Material Available: Tabulation of results of individual kinetic runs (Tables I–III) (4 pages). Ordering information is given on any current masthead page.

References and Notes

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- (7) See, for example, articles in *Chem. Eng. News* **1976**, *54* (May 3), 24–36; **1977**, *55* (Jan 17), 35–36.
- (8) See paragraph at end of paper regarding supplementary material.
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- (17) One possible explanation is that in YSe(O)SR the substitution of RS for Ph as Y causes the equilibrium constant for the isomerization $\text{YSe(O)SR} \rightleftharpoons \text{YSeOSR}$ to become much more favorable, to the point that reaction of thiol with YSeOSR by attack on selenium (eq 9c) becomes the most rapid path by which YSe(O)SR can be converted to products. A second is that the presence of the second RS group attached to the seleninyl function in RSSe(O)SR in some way significantly enhances the rate of attack of the thiol on oxygen (eq 9b) as compared to its rate of attack on sulfur (eq 9a).
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- (23) A previous report²¹ that *tert*-butyl 2-methyl-2-propanethiolsulfonate is produced in a pure state by this oxidation is obviously in error. The oxidation actually gives a mixture of *t*-BuSO₂SSBu-*t* and *t*-BuSO₂SBu-*t*, with the former strongly predominating. Since the two compounds have virtually identical infrared spectra they cannot be distinguished by infrared, which was the only method used by Asakawa et al.²¹ to attempt to establish the nature of their product.
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