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Reactivity of Nucleophiles toward and the Site of Nucleophilic Attack on Bis(alkylthio) Selenides[1]

John L. Kice* and Henryka Slebocka-Tilk

Contribution from the Department of Chemistry, Texas Tech University, Lubbock, Texas 79409.
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Abstract: Bis(alkylthio) selenides, RSSeSR (**1**), a class of compounds that occupy a key role as intermediates in the incorporation of inorganic selenium into biological systems, react quite readily with nucleophilic reagents. In principle, such reactions could take place at either sulfur (eq 3a) or at selenium (eq 3b). In the present work the reaction of a series of **1** having R groups of varying steric dimensions (*n*-Bu, *i*-Pr, *t*-Bu) with a group of common nucleophiles (thiolate, cyanide, and sulfite ions, phenyllithium, piperidine) has been examined. The results show that when R = *t*-Bu, reaction with the nucleophile at selenium occurs considerably faster than reaction at sulfur, but that when R is an *n*-alkyl group (*n*-Bu), reaction at sulfur is considerably faster than reaction at selenium. With R = *i*-Pr, the rates of reaction at the two sites are comparable. For reaction at sulfur, the retardation in rate accompanying a change in R from *n*-Bu to *i*-Pr to *t*-Bu parallels closely the decrease in rate with the same change in R that has been observed in other nucleophilic substitutions at dicoordinate sulfur. As might be expected, an increase in the steric dimensions of R has a considerably smaller effect on the rate of reaction at selenium. Comparison of the rate of reaction of *n*-BuS$^-$ with *n*-BuSSeSBu-*n* and *n*-BuSSBu-*n* shows that bis(*n*-alkylthio) selenides can be expected generally to be more than several orders of magnitude more reactive toward nucleophiles than the corresponding disulfide.

The reaction of the thiol groups in biologically important molecules like cysteine residues, glutathione, or coenzyme A with selenite to form bis(alkylthio) selenides RSSeSR (also sometimes[2] called "selenotrisulfides") is believed[2,3] to be one of the principal pathways by which inorganic selenium is initially incorporated into living systems. Once formed, these selenotrisulfides are then consumed by various further reactions, although the exact nature of all of these is not fully understood at this time. From this it is obvious that bis(alkylthio) selenides occupy a key position in the chemistry of the physiological incorporation of selenium and that it is important that we know as much about their chemical behavior as possible.

Unfortunately at present only a very limited amount is known about the chemistry and reactivity of bis(alkylthio) selenides. What little is known is the following. Ganther[2b] has shown that selenotrisulfides can react with thiols in the fashion shown in eq 1. The product **2** in eq 1 (which Ganther[2b] terms a "selenopersulfide") can either break down to give selenium and a thiol (eq 2a), or, in the presence of a suitable alkylating agent, be converted to a selenenyl sulfide (eq 2b). Reduction of RSSeSR to RSSeH can also be brought about enzymatically by glutathione reductase.[2b] Bis(alkylthio) selenides have been reported[4] to undergo alkaline hydrolysis easily, and the stoichiometry 2RSSeSR + 6OH$^-$ → 4RS$^-$ + Se + SeO$_3^{2-}$ + 3H$_2$O has been suggested[4] for this reaction.

$$\mathrm{RSH} + \underset{\mathbf{1}}{\mathrm{RSSeSR}} \rightarrow \mathrm{RSSR} + \underset{\mathbf{2}}{\mathrm{RSSeH}} \qquad (1)$$

$$\underset{\mathbf{2}}{\mathrm{RSSeH}} \rightarrow \mathrm{RSH} + \mathrm{Se} \qquad (2a)$$

$$\xrightarrow{\mathrm{R'X}} \mathrm{RSSeR'} \qquad (2b)$$

Given their structure, much of the chemistry of bis(alkylthio) selenides is likely to involve reaction of **1** with nucleophiles. Reaction of a nucleophile with **1** could occur either at sulfur (eq 3a) or at selenium (eq 3b). Besides direct displacement, the possibility of reaction of some nucleophiles with **1** via an electron-transfer mechanism, i.e., Nu$^-$ + RSSeSR → [Nu· + RSSeSR^{-}·] → products, also has to be considered, especially given the recent demonstration by Ashby and co-workers[5] of the importance of electron-transfer mechanisms in reactions of certain nucleophiles and organic substrates. In the present work, we have attempted to achieve a better general insight into the reactions of nucleophiles with bis(alkylthio) selenides by examining the reactions of several common nucleophiles with a series of bis(alkylthio) selenides RSSeSR where the R groups are of varying steric dimensions. We have been particularly interested in the following points: (a) How reactive are RSSeSR toward nucleophiles, and how is that reactivity affected by changes in the steric bulk of R? (b) Does a nucleophile react with a given RSSeSR primarily at sulfur, or at selenium? (c) Are there any indications that some reactions of **1** with nucleophiles may proceed by a mechanism other than a simple nucleophilic displacement? (d) How does the reactivity of **1** toward nucleophiles compare with that of such related compunds as di- or trisulfides?

$$\mathrm{RSSeSR} + \mathrm{Nu}^- \xrightarrow{\text{reaction at S}} \mathrm{RSNu} + \mathrm{RSSe}^- \qquad (3a)$$

$$\mathrm{RSSeSR} + \mathrm{Nu}^- \xrightarrow{\text{reaction at Se}} \mathrm{RSSeNu} + \mathrm{RS}^- \qquad (3b)$$

Results

Rate of Disappearance of Bis(alkylthio) Selenides in the Presence of Thiols. As noted earlier, Ganther[2b] has shown that a bis(alkylthio) selenide (RSSeSR) reacts with the corresponding alkanethiol (RSH) in the manner shown in eq 1. To obtain accurate kinetic data on eq 1 spectrophotometrically, it is necessary (as discussed in detail in the Experimental Section) to select conditions where the rate of eq 1 is either much faster or much slower than the rate of subsequent decomposition of RSSeH. For the particular set of bis(alkylthio) selenides used in the present work—*n*-BuSSeSBu-*n* (**1a**), *i*-PrSSeSPr-*i* (**1b**), and *t*-BuSSeSBu-*t* (**1c**)— it turns out that the best way to do this is to study the reaction kinetically in either 1:1 or 2:1 RS$^-$–RSH buffers with the thiol present in sizable stoichiometric excess over RSSeSR. The experimental first-order rate constants (k_{exptl}) for the reactions of the three bis(alkylthio) selenides with the corresponding thiol under such conditions are collected in Table I. The rate data for **1a** and **1b** were obtained by stopped-flow spectrophotometry,

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[1] This research supported by the National Science Foudation, Grant CHE-79-18877.

[2] (a) Ganther, H. E. *Biochemistry* **1968**, *7*, 2898. (b) *Ibid.* **1971**, *10*, 4089. (c) Ganther, H. E.; Corcoran, C. *Ibid.* **1969**, *8*, 2257.

[3] (a) Martin, J. L. In "Organic Selenium Compounds: Their Chemistry and Biology"; Klayman, D. L., Gunther, W. H. H., Eds.; Wiley: New York, 1973; pp 675–686. (b) Shrift, A., ref 3a, pp 781–790.

[4] Jenkins, K. L. *Can. J. Biochem.* **1968**, *46*, 1417.

[5] (a) Ashby, E. C.; Goel, A. B.; DePriest, R. N. *J. Am. Chem. Soc.* **1980**, *102*, 7779; **1981**, *103*, 973. (b) Ashby, E. C.; Goel, A. B.; DePriest, R. N. *Tetrahedron Lett.* **1981**, 1879, 1963. (c) Ashby, E. C.; Goel, A. B.; Park, W. S. *Ibid.* **1981**, 4209.

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Table I. Rates of Disappearance of Bis(alkylthio) Selenides in the Presence of Thiols in 60% Dioxane

R	$[\mathrm{RSSeSR}]_0$, M	temp, °C	$[\mathrm{RS}^-]_0 \times 10^2$, M	$[\mathrm{RSH}]_0 \times 10^2$, M	k_{exptl}, s^{-1}	$k_{\mathrm{RS}}{}^{\mathrm{S}} = k_{\mathrm{exptl}}/[\mathrm{RS}^-]_{\mathrm{av}}$,[a] $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$
n-Bu	3×10^{-4}	25.0	0.40	0.40	4.6	1.2×10^3
			0.80	0.40	10.9	1.4×10^3
			0.80	0.80	10.9	1.4×10^3
			0.80	0.80 (RSSR)[b]	10.9	1.4×10^3
			1.2	1.2	16.5	1.4×10^3
	6×10^{-4}	25.0	1.2	1.2	16.1	1.4×10^3
			0.80	0.80	9.8	1.3×10^3
i-Pr	3×10^{-4}	16.6	0.80	0.40	0.50	62
		25.0	0.40	0.40	0.35	88
			0.80	0.40	0.80	1.0×10^2
			0.80	0.80	0.76	95
		29.8	0.40	0.40	0.42	1.1×10^2
			0.80	0.80	0.89	1.1×10^2
		34.3	0.40	0.40	0.53	1.3×10^2
			0.80	0.80	0.99	1.2×10^2
t-Bu	5×10^{-4}	20.0	2.0	2.0	0.000 138	0.006 9
		25.0	1.0	1.0	0.000 113	0.011
			2.0	2.0	0.000 225	0.011
		28.0	2.0	2.0	0.000 28	0.014
		40.0	2.0	2.0	0.000 79	0.039

[a] $[\mathrm{RS}^-]_{\mathrm{av}}$ is average $[\mathrm{RS}^-]$ during run = $([\mathrm{RS}^-]_0 + [\mathrm{RS}^-]_\infty)/2$. [b] Disulfide (RSSR), 1×10^{-3} M added initially.

those for the much more slowly reacting **1c** by conventional spectrophotometry. All reactions were carried out in 60% dioxane as solvent.

From Table I, it is evident that k_{exptl} is linearly dependent on $[\mathrm{RS}^-]$ but independent of [RSH], showing, not unexpectedly, that it is the thiolate (RS^-) rather than the undissociated thiol (RSH) that attacks the bis(alkylthio) selenide. Added disulfide (RSSR) is seen to have no effect on k_{exptl}. The last column in the table gives the second-order rate constants ($k_{\mathrm{RS}}{}^{\mathrm{S}} = k_{\mathrm{exptl}}/[\mathrm{RS}^-]$) for the reaction of each thiolate RS^- with the corresponding bis(alkylthio) selenide (eq 4) under the various reaction conditions.

$$\mathrm{RS}^- + \mathrm{RSSeSR} \xrightarrow{k_{\mathrm{RS}}{}^{\mathrm{S}}} \mathrm{RSSR} + \mathrm{RSSe}^- \tag{4}$$

One sees that $k_{\mathrm{RS}}{}^{\mathrm{S}}$ shows a very large dependence on the nature of the alkyl group, $k_{\mathrm{R}}/k_{n\text{-Bu}}$ being *n*-Bu, 1.0; *i*-Pr, 0.07; *t*-Bu, 8×10^{-6}.

The variation of $k_{\mathrm{RS}}{}^{\mathrm{S}}$ with temperature was examined for the isopropyl and *tert*-butyl compounds. The thermodynamic activation parameters are $E_a = 8.6 \pm 1.4$ kcal/mol and $\Delta S^{\ddagger} = -23 \pm 4$ eu for the isopropyl system and $E_a = 15.4 \pm 1$ kcal/mol and $\Delta S^{\ddagger} = -18.0 \pm 3.0$ eu for the *tert*-butyl system.

Rate of Exchange of Labeled Thiols with Bis(alkylthio) Selenides. Attack of a thiol on the selenium atom of the corresponding bis(alkylthio) selenide (eq 5) does not, of course, lead to any chemical change. However, if the thiol is labeled with ^{35}S, the

$$\mathrm{R^*SH} + \mathrm{RSSeSR} \rightarrow \mathrm{R^*SSeR} + \mathrm{RSH} \tag{5}$$

occurrence of eq 5 will result in an exchange of the labeled sulfur between the thiol and the bis(alkylthio) selenide, and determination of the rate of this exchange under appropriate conditions will provide a measurement of the rate constant for eq 5 and its dependence on various reaction variables. Of course, if the usual straightforward treatment[6] of the kinetics of isotopic exchange (which assumes that there is no significant consumption of the species undergoing exchange by other reactions during the time required for the exchange to proceed to near equilibrium) is to be applicable, the rate of eq 5 will have to be considerably faster than eq 1. That condition, however, is easily met in the case of the **1c**–*t*-Bu*SH system.

The exchange of ^{35}S-labeled 2-methyl-2-propanethiol (*t*-Bu*SH) with *t*-BuSSeSBu-*t* (**1c**) in 60% dioxane can be followed by monitoring the change in the activity of the thiol (isolated by precipitation as its silver salt from neutralized reaction solutions). Control experiments showed that in either neutral or acid solution exchange was extremely slow. On the other hand, in solutions in which a significant fraction of the thiol was present as *t*-BuS⁻, exchange was quite rapid. Since there are two *t*-BuS groups in each molecule of **1c**, the pertinent exchange equilibrium is

Table II. Kinetics of the Exchange of ^{35}S-Labeled 2-Methyl-2-propanethiol with Bis(*tert*-butylthio) Selenide (**1c**) in 60% Dioxane

temp, °C	[**1c**] × 10^3, M	$C_{\mathrm{RSH}} \times 10^3$, M	α[a]	$k_{\mathrm{exch}} \times 10^4$, s^{-1}	$k_{\mathrm{RS}}{}^{\mathrm{Se}} = \dfrac{2k_{\mathrm{exch}}}{\alpha(C_{\mathrm{RSH}} + 2[\mathbf{1c}])}$, $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$
25.0	2.0	2.9	0.05	0.525	0.30
			0.10	1.13	0.32
			0.20	2.10	0.31
			0.50	5.23	0.30
	4.0	2.9	0.10	1.70	0.31
	1.0	2.9	0.10	0.72	0.29
10.5	2.0	2.9	0.10	0.238	0.069
			0.20	0.42	0.061
			0.50	1.02	0.059
0.0	2.0	2.9	0.10	0.057	0.016
			0.20	0.108	0.016
			0.50	0.28	0.016

[a] α is the fraction of the total thiol present as the thiolate (RS^-).

$$2t\text{-}\mathrm{Bu^*SH} + t\text{-}\mathrm{BuSSeSBu}\text{-}t \rightleftarrows t\text{-}\mathrm{Bu^*SSe^*SBu}\text{-}t + 2t\text{-}\mathrm{BuSH}$$

and the kinetic expression relating the fraction of exchange (*F*) and the time (*t*) is that shown in eq 6,[6] where *R* is the gross rate

$$-\ln(1-F) = R\left[\frac{C_{\mathrm{RSH}} + 2C_{1}}{2C_{\mathrm{RSH}}C_{1}}\right]t \tag{6}$$

of exchange, C_1 is the concentration of **1c**, and C_{RSH} is the concentration of thiol. If the process responsible for exchange is the reaction of the thiolate ion with **1c** shown in eq 7, then $R = k_{\mathrm{RS}}{}^{\mathrm{Se}}\alpha C_{\mathrm{RSH}}C_1$, where α is the fraction of the thiol present as the thiolate ion in the reaction solution. The measured experimental first-order rate constant (k_{exch}) obtained from the slope of a plot of $-\ln(1 - F)$ vs. *t* should therefore be given by eq 8a, and one should find (eq 8b) for the various runs at a given temperature, that $2k_{\mathrm{exch}}/\alpha(C_{\mathrm{RSH}} + C_1)$ should be a constant whose value will be equal to the second-order rate constant ($k_{\mathrm{RS}}{}^{\mathrm{Se}}$) for the reaction shown in eq 7.

$$t\text{-}\mathrm{Bu^*S}^- + t\text{-}\mathrm{BuSSeSBu}\text{-}t \xrightarrow{k_{\mathrm{RS}}{}^{\mathrm{Se}}} t\text{-}\mathrm{Bu^*SSeSBu}\text{-}t + t\text{-}\mathrm{BuS}^- \tag{7}$$

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[6] Frost, A. A.; Pearson, R. G. "Kinetics and Mechanism", 2nd ed.; Wiley: New York, 1961; pp 192–193.

$$k_{\mathrm{exch}} = (k_{\mathrm{RS}}{}^{\mathrm{Se}}\alpha(C_{\mathrm{RSH}} + 2C_1))/2 \qquad (8a)$$

$$k_{\mathrm{RS}}{}^{\mathrm{Se}} = 2k_{\mathrm{exch}}/(\alpha(C_{\mathrm{RSH}} + 2C_1)) \qquad (8b)$$

The exchange of *t*-Bu*SH with **1c** was studied kinetically at three temperatures in the range 0–25 °C. The results are shown in Table II. One sees that the variation of k_{exch} with α, C_{RSH}, and C_1 is that predicted by eq 8a.

At 25 °C, the rate constant $k_{\mathrm{RS}}{}^{\mathrm{Se}}$ for the reaction of *t*-BuS⁻ at the selenium atom of **1c** (eq 7) is 0.3 $\mathrm{M^{-1}\,s^{-1}}$, which is approximately 30 times larger than the rate constant $k_{\mathrm{RS}}{}^{\mathrm{S}}$ for its reaction at the sulfur of the same substrate (eq 4, R = *t*-Bu). Studies with several other nucleophiles to be outlined subsequently indicate that these species also react with **1c** at selenium considerably faster than they react at sulfur. The variation of $k_{\mathrm{RS}}{}^{\mathrm{Se}}$ with temperature gives E_a = 18.6 kcal/mol and ΔS^{*} = −0.7 eu for reaction 7.

While the kinetic behavior of the exchange of *t*-Bu*SH with **1c** is consistent in all aspects with that expected for the exchange occurring via eq 7 and is therefore thought to provide a reliable measurement of $k_{\mathrm{RS}}{}^{\mathrm{Se}}$, the same was not true for the exchange of *i*-Pr*SH with *i*-PrSSeSPr-*i* (**1b**), which we also attempted to investigate. The behavior of the reactions of **1b** with several other nucleophiles (vide infra) indicates that with **1b** reaction at sulfur and selenium occurs at roughly comparable rates. One would therefore expect that the rate of exchange of *i*-Pr*SH with **1b** would be comparable to the rate at which the thiol reacts with **1b** via eq 1. However, in actual fact, in 60% dioxane in a bicarbonate buffer,[7] the rate of exchange of *i*-Pr*SH with **1b** was too fast to measure accurately ($k_{\mathrm{exch}} \gtrsim 0.015\ \mathrm{s^{-1}}$) even though the pseudo-first-order rate constant for the reaction of **1b** with the thiol according to eq 1 under the same conditions is only $8.3 \times 10^{-5}\ \mathrm{s^{-1}}$. The possible origin of this rapid exchange process, which we do *not* believe can reasonably be ascribed to a process equivalent to eq 7, will be considered under Discussion. It was shown, however, that it is not due to any exchange between thiol and **1b** occurring during the isolation of the silver salt of the thiol from the acidified reaction solution since solutions of *i*-Pr*SH and **1b** in 60% dioxane containing 0.001 M $\mathrm{HClO_4}$ did not undergo exchange at a significant rate.

Reaction of Phenyllithium with Bis(alkylthio) Selenides. Reaction of phenyllithium with RSSeSR at sulfur might be expected to give the alkyl phenyl sulfide RSPh, while reaction at selenium should result in the formation of the alkyl phenyl selenenylsulfide RSSePh. Examination of the reaction products and determination of the product ratio PhSeSR/PhSR resulting from the reaction of the various bis(alkylthio) selenides with an equimolar amount of phenyllithium should therefore hopefully provide a reliable measure of the relative importance of reaction at selenium vs. reaction at sulfur as a function of bis(alkylthio) selenide structure in reaction with this nucleophilic reagent.

Each of the three bis(alkylthio) selenides, **1a**, **1b**, **1c**, was reacted in cyclohexane–ether solution with slightly less than an equimolar amount of phenyllithium, and the reaction products were analyzed by gas chromatography In the case of the *tert*-butyl compound (**1c**), the only products found were *t*-BuSSePh and *t*-BuSPh, and these were formed in a molar ratio of *t*-BuSSePh/*t*-BuSPh = 11. With the isopropyl compound (**1b**), the molar ratio of *i*-PrSSePh/*i*-PrSPh in the products was much smaller, 1.1; with the *n*-butyl compound (**1a**), no *n*-BuSSePh could be detected in the products, so that for **1a** the ratio *n*-BuSSePh/*n*-BuSPh ≅ 0.0.

In both the isopropyl (**1b**) and *n*-butyl (**1a**) reactions, but not in the one with the *tert*-butyl (**1c**) compound, significant amounts of the disulfide RSSR were also formed, and the amount of disulfide was considerably larger for the reaction involving **1a** than for that of **1b**. Although we are not completely certain of the origin of this product, the fact that it is absent in the *tert*-butyl case suggests that it arises from a competition of eq 4 with the reactions of PhLi with **1** (eqs 9a and 9b), and that the thiolate needed for

$$\mathrm{PhLi + RSSeSR \xrightarrow[\text{Se}]{\text{reaction at}} PhSeSR + RS^-} \qquad (9a)$$

$$\mathrm{\xrightarrow[\text{S}]{\text{reaction at}} PhSR + RSSe^-} \qquad (9b)$$

eq 4 arises not only from eq 9a but also via a facile reaction of $\mathrm{RSSe^-}$ with PhLi (eq 10).

$$\mathrm{RSSe^- + PhLi \rightarrow RS^- + PhSeLi} \qquad (10)$$

Table III. Kinetics of the Reaction of Bis(alkylthio) Selenides with Cyanide Ion in 60% Dioxane at 25 °C

R	$[\mathrm{RSSeSR}]_0 \times 10^4$, M	$\mathrm{CN^-/HCN}$ buffer ratio	$[\mathrm{CN^-}] \times 10^2$, M	$[\mathrm{HCN}] \times 10^2$, M	$k_1 \times 10^2$, $\mathrm{s^{-1}}$	k_{CN}, $\mathrm{M^{-1}\,s^{-1}}$ [a]
t-Bu	5.0	2:1	1.0	0.50	0.00118	
			2.0	1.0	0.0023	0.00115
			3.0	1.5	0.0034	
i-Pr	5.0	2:1	0.25	0.125	0.062	
			0.50	0.25	0.125	
			1.0	0.50	0.25	0.24
			1.5	0.75	0.35	
			2.0	1.0	0.48	
n-Bu	5.0	2:1	0.25	0.125	0.31	
			0.50	0.25	0.52	
			1.0	0.50	1.03	0.93
			1.5	0.75	1.45	
			2.0	1.0	1.94	
		3:1	0.25	0.083	0.65	
			0.50	0.16	0.93	
			1.0	0.33	1.51	1.02
			1.5	0.50	2.0	
			2.0	0.66	2.4	

[a] k_{CN} is the slope of a plot of k_1 vs. $[\mathrm{CN^-}]$.

Kinetics of Reaction of Cyanide Ion with Bis(alkylthio) Selenides. Treatment of a bis(alkylthio) selenide with excess cyanide ion in a HCN–CN⁻ buffer in 60% dioxane leads to the disappearance of the bis(alkylthio) selenide in a process that is easily followed spectrophotometrically. The disappearance of **1** under such conditions follows good first-order kinetics, and the experimental first-order rate constants (k_1) for the various runs are shown in Table III. The second-order rate constants (k_{CN}) obtained from the slope of a plot of k_1 vs. [CN⁻] for each **1**–CN⁻ system are also given in Table III. Since reaction of CN⁻ with **1** at both sulfur (eq 11a) and selenium (eq 11b) results in the

$$\mathrm{CN^- + RSSeSR \xrightarrow{k_{CN}{}^{S}} RSCN + RSSe^-} \qquad (11a)$$

$$\mathrm{\xrightarrow{k_{CN}{}^{Se}} RSSeCN + RS^-} \qquad (11b)$$

disappearance of **1**, the values of k_{CN} in Table III are equal to the sum of the rate constants for eq 11a and 11b for a particular RSSeSR, i.e., $k_{\mathrm{CN}} = k_{\mathrm{CN}}{}^{\mathrm{S}} + k_{\mathrm{CN}}{}^{\mathrm{Se}}$. The dependence of k_{CN} on the nature of the alkyl group R in RSSeSR, expressed as *k*(R)/*k*(*n*-Bu), is *n*-Bu, 1.0; *i*-Pr, 0.24; *t*-Bu, 0.0012. One sees that this is a much less pronounced dependence on the nature of R than was found for eq 4.

Other Reactions. The behavior of bis(alkylthio) selenides toward two other nucleophiles was also examined briefly.

Sulfite ion frequently shows a nucleophilic reactivity toward dicoordinate sulfur comparable to that of cyanide ion.[8] In accord with this, the first-order rate constant (k_1) for the disappearance of **1a** in a 1:1 $\mathrm{SO_3{}^{2-}}$–$\mathrm{HSO_3{}^-}$ buffer in 60% dioxane at 25 °C was found to be linearly dependent on $[\mathrm{SO_3{}^{2-}}]$ with $k_1/[\mathrm{SO_3{}^{2-}}]$ having

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[7] The magnitude of $k_{\mathrm{RS}}{}^{\mathrm{S}}$ for **1b** reacting with *i*-PrS⁻ via eq 4 (95 $\mathrm{M^{-1}\,s^{-1}}$ at 25 °C) dictates that one can only hope to study the exchange in a buffer in which a very small fraction of the thiol is present as *i*-PrS⁻. The buffer must also be one that after acidification will not yield species that will interfere with the straightforward precipitation of the silver salt of the thiol upon addition of silver nitrate. Of the various buffers examined, only bicarbonate seemed to meet both of these requirements satisfactorily.

[8] (a) Chau, M. M. Kice, J. L. *J. Org. Chem.* **1978**, *43*, 914. (b) Kice, J. L.; Liu, A. C.-C. *Ibid.* **1979**, *44*, 1918.

Table IV. Effect of Alkyl Group Structure on the Rate of Reaction of **1** with Thiolate Ions and Related Reactions

reaction	k_2 for R = n-Bu, $M^{-1}\ s^{-1}$	$k/k_{R=n\text{-Bu}}$		
		n-Bu	i-Pr	t-Bu
$RS^- + RSSeSR \xrightarrow[60\%\ diox]{25\ °C} RSSR + RSSe^-$	1.4×10^3	(1.0)	0.067	8×10^{-6}
$R{*}S^- + RSSR \xrightarrow[MeOH]{25\ °C} R{*}SSR + RS^{-\,a}$	0.26	(1.0)		0.4×10^{-6}
${*}SO_3^{2-} + RSSO_3^- \xrightarrow[H_2O]{25\ °C} RS{*}SO_3^- + SO_3^{2-\,b}$	0.10^c	$(1.0)^c$	0.0014	12×10^{-6}

[a] Data are from ref 9a. [b] Data are from ref 9b. [c] R = Et rather than n-Bu, but rate constant for R = Et should be very similar to that for R = n-Bu.

a value of 0.9 $M^{-1}\ s^{-1}$, which is essentially the same as the second-order rate constant for the reaction of cyanide with **1a** under the same conditions.

Amine groups are ubiquitous in biological systems. It therefore seemed of interest to ascertain whether or not bis(alkylthio) selendies are significantly reactive toward amines. Piperidine was used as a representative amine since it normally exhibits quite high nucleophilic reactivity, and the first-order rate constants for the disappearance of **1a** in 4:1 and 2:1 piperidine–piperidine H^+ buffers in 60% dioxane at 25 °C were determined. While **1a** disappears quite rapidly under such conditions, the rate is independent of piperidine concentration and dependent only upon the buffer ratio, being 0.0064 s^{-1} in the 2:1 buffers and 0.013 s^{-1} in the 4:1 buffers. It is clear that the relatively rapid rate of disappearance of **1a** under such conditions is not due to any reaction between **1a** and the amine but rather to the reaction of hydroxide ion with the bis(alkylthio) selenide.

Discussion

The kinetic data in Table I show that attack of the thiolate ion on the bis(alkylthio) selenide RSSeSR (**1**) (eq 4) is the rate-controlling step for the reaction[2b] of a thiol with **1** (eq 1). In Table IV the variation in the rate of eq 4 with variation in the nature of R in **1** is compared with the effect of the same changes in R on the rates of two previously studied nucleophilic substitutions at dicoordinate sulfur—(a) the exchange of ^{35}S-labeled thiolate with the disulfide RSSR[9a] and (b) the exchange of labeled sulfite ion with the alkyl Bunte salts $RSSO_3^-$.[9b] One sees that the retardation observed upon increasing the steric bulk of R is generally quite similar for all three reactions, the main difference being that the magnitude of the retardation for R = t-Bu is somewhat greater for the thiolate–disulfide exchange than in the other two cases. In our opinion, the variation in the rate of eq 4 with variation in the steric bulk of R in **1** is sufficiently comparable to that observed in the other two substitutions at dicoordinate sulfur as to be entirely compatible with eq 4 taking place via attack of the thiolate ion on one of the dicoordinate sulfur atoms in **1** with displacement of the ion $RSSe^-$.

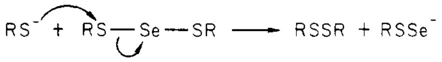
From Table IV one also sees that the rate of reaction of **1a** with n-BuS^- in eq 4 ($k_2 = 1.4 \times 10^3\ M^{-1}\ s^{-1}$) is about 5000 times faster than the rate of reaction of the same thioate with n-BuSSBu-n ($k_2 = 0.26\ M^{-1}\ s^{-1}$). The difference in the two reactions is that in eq 4 the group being displaced is n-$BuSSe^-$ while in the reaction involving the disulfide it is n-BuS^-. In the reaction of $(Et_2N)_3P$ with benzyl di- and trisulfides, Harpp and co-workers[10] have found that the rate constant for the reaction of the phosphine with the trisulfide (eq 12a) is about 17 000 times larger than the rate constant for its reaction with the disulfide (eq 12b), and they have attributed this large rate difference to the fact the that $PhCH_2SS^-$, being the anion of a significantly stronger acid, represents a considerably better leaving group than $PhCH_2S^-$. Since one might expect that $RSSe^-$, like RSS^-, should be a much better leaving group than RS^-, the large difference between the rates of reaction of n-BuS^- with **1a** and n-BuSSBu-n in not only understandable but of a magnitude that seems reasonable given the findings of Harpp and co-workers.[10]

$$(Et_2N)_3P + PhCH_2SSSCH_2Ph \rightarrow (Et_2N)_3P^+\text{-}SCH_2Ph + PhCH_2SS^- \quad (12a)$$

$$(Et_2N)_3P + PhCH_2SSCH_2Ph \rightarrow (Et_2N)_3P^+\text{-}SCH_2Ph + PhCH_2S^- \quad (12b)$$

For eq 4, the activation energy for the reaction when R = t-Bu (15.4 kcal/mol) is about 7 kcal/mol larger than when R = i-Pr (8.6 kcal/mol). The situation is thus quite closely analogous to the behavior of the thiolate–disulfide exchange reaction. There, Fava and co-workers[9a] found that the activation energy when R = t-Bu (21.8 kcal/mol) was about 7.5 kcal larger than for R = n-Bu.

It would thus appear that all aspects of the reactivity of thiolate ions with **1** in eq 4 are in accord with this reaction being a process (eq 13) in which the thiolate ion performs a nucleophilic displacement of $RSSe^-$ from a dicoordinate sulfur atom of **1**.



$$RS^- + RS\text{—}Se\text{—}SR \longrightarrow RSSR + RSSe^- \quad (13)$$

Reaction of a reagent-like phenyllithium with **1** at selenium would be expected to result in the formation of the selenenyl sulfide RSSePh (eq 9a), while reaction at sulfur would result in the formation of the sulfide RSPh (eq 9b). One might therefore hope that measurement of the product ratio RSSePh/RSPh in the reaction products resulting from the reaction of RSSeSR with an equimolar amount of added phenyllithium would provide at least a semiquantitative indication of the ratio of reaction at selenium to reaction at sulfur that might typically be expected for the reaction of nucleophiles with RSSeSR. With the *tert*-butyl compound (**1c**), one finds RSSePh/RSPh ≅ 11, indicating that reaction at Se is strongly favored over reaction at sulfur. With the isopropyl compound (**1b**), one finds RSSePh/RSPh ≅ 1.0, indicating that in this case reaction at selenium and reaction at sulfur are closely competitive in rate. With the n-butyl compound (**1a**), one finds no detectable amount of RSSePh in the reaction products, suggesting that reaction at sulfur is strongly favored over reaction at selenium in this case.[11]

The behavior of **1c** in its reaction with phenyllithium suggests that there is a strong preference for nucleophiles to react with this particular bis(alkylthio) selenide at selenium rather than at sulfur. One might therefore expect that in the presence of ^{35}S-labeled 2-methyl-2-propanethiol, the exchange reaction shown in eq 5 would occur considerably more rapidly than the other reaction with the thiol shown in eq 1 and that by determining the kinetics associated with the exchange, one could ascertain accurately for t-BuS^- as the nucleophile not only exactly how much faster re-

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[9] (a) Fava, A.; Iliceto, A.; Camera, E. *J. Am. Chem. Soc.* **1957**, *79*, 833. (b) Fava, A.; Iliceto, A. *Ibid.* **1958**, *80*, 3478.

[10] Harpp, D. N.; Ash, D. K.; Smith, R. A. *J. Org. Chem.* **1980**, *45*, 5155.

[11] Consumption of RSSePh by further reaction with PhLi (RSSePh + PhLi → RSPh + PhSeLi) is a potential problem, especially when the R group is one like n-Bu where attack on sulfur is unhindered. While one would hope to minimize this by carrying out the reaction by addition of PhLi to **1** (rather than the inverse order of addition), it may still play some role in the reaction involving **1a**, and may be the reason that no significant amount of PhSeSBu-n was found in the products.

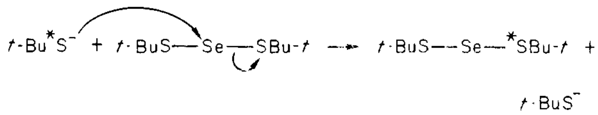
Table V. Effect of Alkyl Group Structure on the Rate of Reaction of **1** with Cyanide Ion

R in RSSeSR	k_{CN}, M^{-1} s^{-1}	$k_{\mathrm{R}=n\text{-Bu}}$
n-Bu	1.0	(1.0)
i-Pr	0.24	0.24
t-Bu	0.00115	0.00115

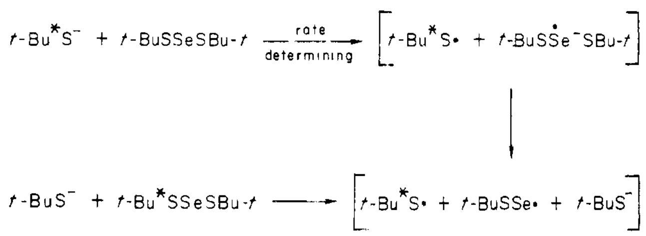
action at the Se atom of **1c** is than reaction at sulfur but also the thermodynamic activation parameters associated with the exchange reaction at Se and how these differ from those for the reaction of the same nucleophile at sulfur.

The data in Table II show that the exchange of *t*-Bu*SH with *t*-BuSSeSBu-*t* does indeed occur considerably more rapidly under a given set of reaction conditions than eq 1 and that the exchange occurs by the reaction of the thiolate ion with **1c** at selenium (eq 7). At 25 °C, the rate constant for this reaction is 0.3 M^{-1} s^{-1}, which is 27 times larger than the rate constant for the other reaction of *t*-BuS$^-$ with **1c** shown in eq 4. When the statistical factor that there are two equivalent sulfur atoms but only one selenium atom in **1c** is taken into account, this indicates that reaction of *t*-BuS$^-$ with **1c** at selenium is about 60 times faster than reaction at sulfur. Such a result seems quite reasonable, given that the ratio of PhSeSBu-*t*/PhSBu-*t* in the products from the reaction of phenyllithium with **1c** would appear to indicate that PhLi reacts about 25 times faster with **1c** at selenium than at sulfur.

The activation parameters for eq 7 are somewhat unexpected, however, for one finds that E_a for eq 7 is about 3 kcal/mol *larger* than E_a for eq 4 for R = *t*-Bu, while $\Delta S^{\ddagger}$ is approximately 17 eu *less negative*. The very small negative $\Delta S^{\ddagger}$ (−0.7 eu) that we find for eq 7 is certainly not typical of what one usually finds for S$_N$2-type nucleophilic substitutions involving an anion and a neutral molecule in a polar protic solvent; such reactions customarily have a $\Delta S^{\ddagger}$ in the range from −6 to −20 eu. It is, of course, conceivable that our measurements of k_{exch} as a function of temperature are subject to some systematic error that results in a spurious estimate of E_a and therefore also an incorrect $\Delta S^{\ddagger}$. However, since there is no obvious reason to believe this should be the case, we feel that it is more reasonable at this stage to assume that E_a for eq 7 as measured is accurate and that $\Delta S^{\ddagger}$ for eq 7 is in fact only ∼−1.0 eu. Two explanations for this $\Delta S^{\ddagger}$ seem possible: (1) that eq 7 does take place by a direct S$_N$2-type displacement (eq 14), but that reactions of this type at dicoordinate selenium for some reason have considerably less negative entropies of activation than those occurring at such electrophilic centers as sp^3 carbon or dicoordinate sulfur; (2) that eq 7 actually takes place *not* by a simple S$_N$2-type displacement but rather by an electron-transfer mechanism (eq 15), analogous to the process shown recently by Ashby and co-workers[5c] to be involved in the formation of Ph$_3$CSBu-*n* from the reaction of trityl halides with *n*-BuSLi in tetrahydrofuran. That **1** may undergo electron-transfer reactions with some nucleophiles is suggested by certain observations regarding the reaction of **1** with the anion of 9-cyanofluorene that are outlined in a footnote.[12]



$$t\text{-Bu}^{*}\text{S}^- + t\text{-BuS—Se—SBu-}t \longrightarrow t\text{-BuS—Se—}^{*}\text{SBu-}t + t\text{-BuS}^- \quad (14)$$



$$t\text{-Bu}^{*}\text{S}^- + t\text{-BuSSeSBu-}t \xrightarrow[\text{determining}]{\text{rate}} \left[t\text{-Bu}^{*}\text{S}\cdot + t\text{-BuS}\dot{\text{S}}\text{e}^-\text{SBu-}t\right]$$
$$t\text{-BuS}^- + t\text{-Bu}^{*}\text{SSeSBu-}t \longrightarrow \left[t\text{-Bu}^{*}\text{S}\cdot + t\text{-BuSSe}\cdot + t\text{-BuS}^-\right] \quad (15)$$

The *i*-PrSSePh/*i*-PrSPh ratio from the reaction of **1b** with PhLi suggests that nucleophiles are likely to react at the sulfur and selenium of this bis(alkylthio) selenide at comparable rates. The behavior of the reaction of cyanide ion with **1b** (to be discussed later) points to a similar conclusion. We therefore expected that under a given set of conditions the exchange of *i*-Pr*SH with **1b** (eq 5, R = *i*-Pr) should occur at a rate comparable to the rate at which the thiol reacts with **1b** in the manner shown in eq 1. We were therefore most surprised to find that in a bicarbonate buffer in 60% dioxane, the exchange of *i*-Pr*SH with **1b** was at least 200 times faster than the rate of reaction to give disulfide and *i*-PrSSeH (eq 1). Since neither the reaction of PhLi or of cyanide ion with **1b** suggest that reaction of **1b** with nucleophiles is likely to occur much faster at selenium than sulfur we consider that this unexpectedly fast exchange of *i*-Pr*SH with **1b** should *not* be attributed to the reaction *i*-Pr*S$^-$ + *i*-PrSSePr-*i* → *i*-Pr*SSePr-*i* + *i*-PrS$^-$ being much more rapid than eq 4. Rather we feel the rapid exchange must arise as a result of an entirely different reaction sequence.

In considering what this reaction sequence might be, the following points are pertinent. Whatever the reaction sequence is, it must be one that while important for the *i*-Pr*SH–**1b** system under the conditions used is not kinetically important compared to eq 7 for the *t*-Bu*SH–**1c** system, since the exchange of *t*-Bu*SH with **1c** behaves "normally" and occurs at a rate entirely consistent with the expected relative rates for eq 7 vs. eq 4 on the basis of the rates of reaction at selenium vs. sulfur for other nucleophiles (PhLi, CN$^-$) reacting with **1c**. Second, one apparently needs to have some reaction between *i*-PrS$^-$ and **1b** according to eq 4 in order to initiate the rapid exchange process, since under conditions where eq 4 does not occur at a measurable rate (weakly acid solution), the rapid exchange does not occur. One reaction scheme that is consistent with the above requirements and that would seem to be capable of accounting for the rapid exchange of *i*-Pr*SH with **1b** under the conditions used is shown in eq 16a–c (R = *i*-Pr),

$$\text{RS}^- + \text{RSSeSR} \xrightarrow[\text{(eq 4)}]{k_{\mathrm{RS}}{}^{\mathrm{S}}} \text{RSSR} + \text{RSSe} \qquad \text{(initiation)} \quad (16a)$$

$$\begin{array}{ccccccc} \text{RSSe}^- & + & \text{R}^{*}\text{S}^- & \longrightarrow & \text{R}^{*}\text{SSe}^- & + & \text{RS} \\ \text{or} & & \text{or} & & \text{or} & & \text{or} \\ \text{RSSeH} & & \text{R}^{*}\text{SH} & \rightarrow & \text{R}^{*}\text{SSeH} & & \text{RSH} \end{array} \quad (16b)$$

$$\text{R}^{*}\text{SSe}^- + \text{RSSeSR} \rightarrow \text{R}^{*}\text{SSeSR} + \text{RSSe}^- \quad (16c)$$

with the rate of exchange being controlled by the rate of eq 16c With the *t*-Bu*SH–**1c** system, where $k_{\mathrm{RS}}{}^{\mathrm{Se}}$ (eq 7) ≫ $k_{\mathrm{RS}}{}^{\mathrm{S}}$ (eq 4), the amount of RSSe$^-$ present during the time that the exchange is proceeding to equilibrium will be much lower relative to the

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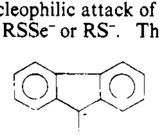
(12) The behavior of the reaction of **1** with the anion (**3**) of 9-cyanofluorene shows that this particular nucleophile certainly does not react with **1** via nucleophilic attack of **3** on either sulfur or selenuim and displacement of either RSSe$^-$ or RS$^-$. Thus when solutions of **3** in degassed methanol were



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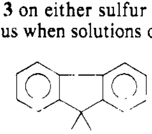

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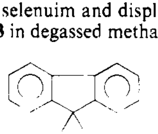

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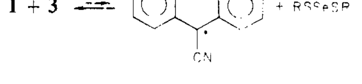
treated with a large excess of **1**, there was an *increase* in the optical density of the solution at longer wavelengths, rather than the fading of the color that should have been observed if one had a simple displacement to form either **4** or **5**. The kinetics associated with the process were also not compatible with a simple substitution reaction between **3** and **1**. Thus the rate showed a higher than first-order dependence on [**1**], and although the observed increase in optical density followed first-order kinetics, the first-order rate constant was dependent on the initial concentration of **3**. Although the system was not examined in sufficient detail to permit an unequivocal assignment of what was going on, it seemed possible that the various unusual features being observed could quite likely be ascribed to an initial equilibrium electron transfer (eq i) between **1** and **3**, followed by further reactions of the two radicals so produced with the various species present in the solution.



(i)

concentration of RS$^-$ than in the case of the *i*-Pr*SH–**1b** system. Furthermore, the studies with **1b** were done (in an attempt to keep the rates measurable) in a bicarbonate buffer where less than 0.1% of the thiol was present as RS$^-$ while most of the considerably more acidic selenopersulfide RSSeH was presumably still dissociated to RSSe$^-$. In contrast, the studies with **1c** were carried out at pH where from 5 to 50% of the total thiol was present as RS$^-$. This pH difference by itself will mean that the ratio [RSSe$^-$]/[RS$^-$] during the exchange will be *much* larger for the *i*-Pr*SH–**1b** system than during the exchange involving **1c**. Finally, there is the fact that the markedly greater steric hindrance to attack on sulfur in **1c** as compared to **1b** should cause the rate constant for eq 16c to be approximately 10^4 slower for R = *t*-Bu than for R = *i*-Pr, so that any exchange via eq 16b,c will, at the same concentration of RSSe$^-$, occur at a much slower rate than for **1b**. These three factors collectively could easily combine to produce a situation where for *i*-Pr*SH–**1b** in the bicarbonate buffer, exchange via eq 16a–c is much faster than exchange via eq 7, whereas with *t*-Bu*SH–**1c** in solutions containing significant concentrations of *t*-BuS$^-$, exchange via eq 7 is much faster than exchange via the reaction sequence in eq 16a–c.

The particular mechanism for exchange shown in eq 16a–c predicts that the rate of exchange should increase with time, since the concentration of RSSe$^-$ (which is produced in eq 16a) will increase with time. Unfortunately, in the bicarbonate buffer the exchange of *i*-Pr*SH and **1b** was too fast to allow one to obtain enough data points before equilibrium was reached to be able to ascertain with certainty whether such an acceleration is observed, and experimental difficulties that prevented satisfactory isolation of uncontaminated RSAg samples for counting upon acidification of other buffers (phosphate, acetate) of lower pH (where the rate of eq 16a should be correspondingly slower due to lower [RS$^-$]) did not allow us to study the process under conditions where the exchange would be expected to be slower. Therefore this aspect of the proposed mechanism for the unexpectedly rapid exchange of *i*-Pr*SH with **1b** remains unproven. Until it is, one must therefore obviously regard the proposed mechanism as tentative. It is, however, one that seems much better able to account for the fact that the unexpectedly rapid exchange is observed with **1b**, but not with **1c**, than any of the alternative explanations we have examined. The mechanism in eq 16a–c also requires that the exchange shown in eq 16b be a facile process. This does not seem unreasonable, however, particularly given the evidence that the reaction in eq 10 apparently occurs readily during the reaction of phenyllithium with **1**.

The reaction of cyanide ion with bis(alkyltho) selenides in HCN–CN$^-$ buffers is easily followed kinetically and shows simple and straightforward kinetic behavior indicating that the rate-determining step is the reaction of CN$^-$ with **1**. Since reaction of CN$^-$ with **1** will lead to a chemical change whether the reaction occurs at sulfur (eq 11a) or at selenium (eq 11b), the measured second-order rate constants (k_{CN}) are the sum of the rate constants for the rate of reaction at sulfur ($k_{CN}{}^{S}$) and at selenium ($k_{CN}{}^{Se}$).[13] The variation in k_{CN} with variation in the nature of the alkyl group in **1** (Table V) is most interesting, particularly when compared with the variation in the rate of eq 4 (Table IV) with the same variation in R group. One sees that k_{CN}(*t*-Bu)/k_{CN}(*n*-Bu) (1×10^{-3}) is 150 times larger than $k_{RS}{}^{S}$(*t*-Bu)/$k_{RS}{}^{S}$(*n*-Bu) for eq 4 (8×10^{-6}). One also notes that the value for k_{CN}(*t*-Bu)/k_{CN}(*n*-Bu) is of the same order of magnitude as $k_{RS}{}^{Se}$(*t*-Bu)/$k_{RS}{}^{S}$(*n*-Bu). Both these results are understandable if the reaction of **1c** with CN$^-$ takes place at selenium, so that for **1c**, k_{CN} measures the rate of eq 11b ($k_{CN}{}^{Se}$, R = *t*-Bu), while the reaction of CN$^-$ with **1a** (where attack of the nucleophile on sulfur is not sterically hindered) takes place at sulfur, and k_{CN} for **1a** measures the rate of eq 11a ($k_{CN}{}^{S}$, R = *n*-Bu). In addition, the fact that k_{CN}(*i*-Pr)/k_{CN}(*n*-Bu) is about 3.5 times greater than $k_{RS}{}^{S}$(*i*-Pr)/$k_{RS}{}^{S}$(*n*-Bu) for eq 4 is compatible with the idea (suggested by the results of the reaction of **1b** with phenyllithium) that with **1b** the reactions of a nucleophile at sulfur and selenium are competitive in rate and that both $k_{CN}{}^{S}$ and $k_{CN}{}^{Se}$ make a significant contribution to k_{CN} for **1b**.

With **1a**, where the reaction with cyanide is thought to take place at sulfur, $k_{CN}/k_{RS}{}^{S} = 7 \times 10^{-4}$. Such a value for the relative reactivity of cyanide vs. *n*-BuS$^-$ as nucleophiles is quite similar to the values ($\sim 4 \times 10^{-4}$) of $k_{CN}/k_{n\text{-BuS}}$ found for the relative reactivity of these two nucleophiles in substitutions at the dicoordinate sulfur atom of aryl thiolsulfonates (ArSSO$_2$Ar).[8a,14]

Since reaction of CN$^-$ with **1c** is thought to occur at selenium, the ratio of k_{CN} for **1c** to $k_{RS}{}^{Se}$ for eq 7 should provide a measure of the relative reactivity of the two nucleophiles CN$^-$ and *t*-BuS$^-$ in a reaction at the selenium atom of a bis(alkylthio) selenide. The magnitude of $k_{CN}/k_{RS}{}^{Se}$ (3.3×10^{-3}) is seen not to be greatly different from $k_{CN}/k_{RS}{}^{S}$ for **1a** (0.7×10^{-3}).

The lack of reactivity of piperidine toward **1a** suggests that in biological systems the reaction of amino groups with bis(alkylthio) selenides is not likely to be important, compared to reactions with other nucleophiles, as a route for the disappearance of these compounds.

Conclusions. Bis(alkylthio) selenides RSSeSR (**1**) can react with nucleophilic reagents at either sulfur (eq 3a) or selenium (eq 3b). The ion RSSe$^-$ is, of course, a considerably better leaving group than RS$^-$; on that basis reaction at sulfur should be strongly favored. On the other hand, data[15] of the relative reactivity of arene selenosulfonates (PhSeSO$_2$Ar) vs. thiolsulfonates (PhSSO$_2$Ar) toward cyanide ion indicate that nucleophilic substitution at dicoordinate selenium is much faster than substitution at an equivalent dicoordinate sulfur. The results of the present work suggest that for substitutions of bis(alkylthio) selenides these two factors approximately cancel each other out, allowing a factor like the steric bulk of the R group in RSSeSR, which exerts a greater retarding effect on the rate for reaction at sulfur than at selenium, to determine which reaction path will be preferred by a particular bis(alkylthio) selenide. Thus for **1c**, where R is *tert*-butyl, reaction at selenium occurs considerably faster than rection at sulfur. On the other hand, for **1a**, where R is an *n*-butyl group, reaction at sulfur is enough faster than reaction at selenium so that the only reaction pathway of importance is eq 3a. In the intermediate situation where R is a secondary alkyl group (**1b**, R = *i*-Pr), the rates of reaction at the two sites are approximately equal.

Comparison of the rates of reaction of *n*-BuS$^-$ with *n*-BuSSeSBu-*n* and *n*-BuSSBu-*n* indicates that bis(alkylthio) selenides (like alkyl trisulfides[10]) can be expected generally to be several orders of magnitude more reactive toward nucleophiles than the corresponding disulfide.

Finally, the somewhat unexpected entropy of activation for eq 7 raises the possibility that reactions of nucleophiles with **1** at selenium, even though they lead to the substitution products expected for eq 3b, may take place by something other than the usual simple S$_N$2-type displacement, such as, for example, the electron-transfer mechanism shown in eq 15.

Experimental Section

Preparation and Purification of Bis(alkylthio) Selenides. The various bis(alkylthio) selenides (**1**) were all conveniently prepared by the general procedure described by Kice, Lee, and Pan[16] in which 50 mmol of the appropriate thiol is allowed to react with 10 mmol of selenium dioxide at room temperature in 60% dioxane (50 mL) as solvent. The different **1** were then isolated and purified as follows.

Bis(*n*-butylthio) Selenide (1a). The mixture of **1a** and *n*-butyl disulfide obtained[16] from chromatography of the crude reaction product on silica gel was fractionally distilled twice under high vacuum, with the fraction boiling at 85–87 °C (0.4 torr) being collected in each case. The ^{1}H NMR spectrum of this material showed that it contained less than

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(13) At the outset we had thought that reversibility of eq 11b might be a significant problem and lead to kinetic complications. However, the straightforward kinetic behavior exhibited even by those systems (**1c**) that other evidence indicates react almost entirely at selenium shows that this is not a problem after all.

(14) Kice, J. L.; Rogers, T. E.; Warheit, A. C. *J. Am. Chem. Soc.* **1974**, *96*, 8020.

(15) Gancarz, R. A.; Kice, J. L. *J. Org. Chem.* **1981**, *46*, 4899.

(16) Kice, J. L.; Lee, T. W. S.; Pan, S.-T *J. Am. Chem. Soc.* **1980**, *102*, 4448.

2% of *n*-butyl disulfide on the basis of the relative intensities of the CH_2S triplet of the disulfide (δ 2.62–2.80) to the CH_2S triplet of **1a** (δ 2.90–3.05).

Bis(isopropylthio) Selenide (1b). The crude reaction product was first fractionally distilled under high vacuum (0.5 torr), and the main fraction (bp 50–60 °C) was then subjected to flash chromatography on silica gel with methylene chloride as eluent. A second fractional distillation then gave 0.35 g (15%) of very pure **1b**: bp 56 °C (0.5 torr); ^{1}H NMR ($CDCl_3$) δ 3.23 (septet 2 H), 1.38 (d, 12 H); mass spectrum, *m/e* 230 (M^+, ^{80}Se) 228 (M^+, ^{78}Se).

Bis(*tert*-butylthio) Selenide (1c). The crude product was purified by chromatography in the manner previously outlined,[16] followed by vacuum distillation bp 59 °C (0.3 torr).

Preparation of ^{35}S-Labeled Thiols. ^{35}S-Labeled 2-methyl-2-propanethiol (*t*-Bu*SH) was prepared from ^{35}S-labeled thiourea (New England Nuclear) by using the procedure for the preparation of 2-methyl-2-propanethiol from *tert*-butyl alcohol, thiourea, and 48% aqueous hydrobromic acid developed by Lee, Saville, and Trego.[17] The resulting thiouronium salt was converted to the thiol by treatment with aqueous sodium hydroxide. Final distillation gave *t*-Bu*SH, bp 63–64 °C, in 75% overall yield.

To prepare ^{35}S-labeled 2-propanethiol (*i*-Pr*SH), we allowed isopropyl bromide to react with ^{35}S-labeled thiourea following the procedure described by Backer and Dijkstra,[18] and the resulting thiouronium salt was decomposed by treatment with aqueous sodium hydroxide. The thiol was separated from the reaction mixture by extraction with toluene, the toluene dried ($MgSO_4$), and the labeled thiol then fractionally distilled (bp 58–60 °C) from the toluene solution. The overall yield of *i*-Pr*SH was 40%.

The labeled thiols were stored under either nitrogen or argon until used.

Other Reagents. Commercial samples (Aldrich Chemical) of the unlabeled thiols used (*n*-BuSH, *i*-PrSH, and *t*-BuSH) were further purified by fractional distillation and stored under nitrogen. Dioxane was purified by the procedure described by Fieser and Fieser,[19] fractionally distilled, and then frozen and stored at −20 °C to prevent the formation of peroxides prior to use. All distilled water used in rate studies was refluxed with a small amount of potassium permanganate before being doubly distilled from glass. Piperidine was purified as previously described.[20] All other reagents (KCN, $HClO_4$, $LiClO_4$, $AgNO_3$, and Na_2SO_3) were of the highest purity commercially available.

Reaction of Bis(alkylthio) Selenides with Phenyllithium. To 1.0 mL of a 1 M solution of **1** in cyclohexane was added 0.48 mL of a 1.9 M solution of phenyllithium in cyclohexane–diethyl ether (70:30) (Aldrich Chemical). In each instance a rapid reaction appeared to occur as evidenced by the reaction solution becoming colored (reddish for **1a** and **1b**, yellow with **1c**). The reaction mixture was then warmed gently for ~0.5 h. Additional cyclohexane was then added, and the organic phase was washed several times with water (the materials responsible for the color of the reaction solution went into the aqueous phase), dried ($MgSO_4$), and the solvent carefully removed under reduced pressure. The residue was then analyzed by gas chromatography[21] to determine its composition. For comparison purposes, authentic samples of the various selenenyl sulfides (RSSePh) were prepared by the procedure described by Kice and Lee,[22] and samples of the various sulfides (RSPh) were synthesized by literature procedures.[23] The hydrocarbon diphenylmethane was used as an internal standard for the analysis of the various runs.

Gas chromatography of the residue from the reaction of **1c** with phenyllithium showed only two products, *t*-BuSSePh and *t*-BuSPh, in a molar ratio of 11 to 1. In the case of the reaction of **1b** with PhLi, three products were found. These and their relative amounts were *i*-PrSPh (1.0), *i*-PrSSePh (1.14), and *i*-PrSSPr-*i* (1.2). Gas chromatography of the product mixture from the phenyllithium–**1a** reaction did not show the presence of any significant amount of *n*-BuSSePh. The only products seen were *n*-BuSPh and *n*-BuSSBu-*n*, in the molar ratio 1:2.5. There was also another peak having a retention time corresponding to that of **1a**, indicating that some of the **1a** was recovered unreacted.

Kinetic Study of the Reaction of Thiolate Ions with 1. In RS^-–RSH buffers, the reactions of both *n*-BuS^- with **1a** and of *i*-PrS^- with **1b** show biphasic behavior. There is an initial rapid change in absorbance due to the occurrence of eq 4, which is then followed by a much slower, and at most wavelengths considerably larger, change in absorbance. In the case of the reaction involving **1b**, this second stage shows an isosbestic point at 295 nm, but in the case of **1a** there is no wavelength where this is true. While the rate of the first stage is much faster than the second in media where $[RS^-]$ is reasonably high (>0.001 M), this is not true in lower pH media, such as HPO_4^{2-}–$H_2PO_4^-$ buffers, where the fraction of the total thiol present as thiolate is very small, and under such conditions one cannot obtain useful kinetic data on the first stage of the thiol–**1a** reaction. It was for this reason that all of the kinetic studies of the **1a**–*n*-BuSH reaction were carried out in *n*-BuSH–*n*-BuS^- buffers containing at least 0.004 M *n*-BuS^-. Under such conditions the rate of eq 4 for **1a** could be easily determined accurately without any complications.

Because of the rapidity of the reaction of **1a** and **1b** with their respective thiolate ions when $[RS^-] \geq 1 \times 10^{-3}$ M, the reactions were followed by stopped-flow spectrophotometry. A solution of the bis(alkylthio) selenide (**1a** or **1b**) in 60% dioxane was placed in one of the reservoir syringes of a Durrum-Gibson Model D-110 stopped-flow spectrophotometer, and a solution of the thiol and thiolate (prepared by adding the proper amount of standard sodium hydroxide to a solution of the thiol in 60% dioxane) was placed in the other reservoir syringe. After mixing, the course of the reaction was followed by monitoring the change in absorbance with time on the storage oscilloscope by using a wavelength of 295 nm for the runs with **1b** and either 275 or 370 nm (both gave the same rate) for the runs with **1a**.

For the much slower reaction of *t*-BuS^- with **1c**, conventional spectrophotometry was used. A measured volume (3.5 mL) of a solution containing the desired amounts of *t*-BuS^- and *t*-BuSH in 60% dioxane was placed in a 1-cm spectrophotometer cell in the thermostated cell compartment of a Cary Model 17 UV–visible spectrophotometer, and the reaction was initiated by the injection of 35 μL of a 0.05 M solution of **1c** in dioxane. The change in the optical density of the solution with time at 275 nm was then followed.

Exchange of ^{35}S-Labeled Thiols with 1. The procedure used to study the exchange of *t*-Bu*SH with **1c** was as follows. A solution of *t*-Bu*SH in 60% dioxane was prepared immediately prior to use, and 30 mL of this solution was placed in a thermostated reaction vessel of a type previously described[24] that allows carefully measured aliquots of the reaction solution to be withdrawn under nitrogen without disturbing the remainder of the solution. To the solution in the reaction flask was then added the proper amount of standard sodium hydroxide to give the desired concentration of thiolate ion, and the exchange reaction was then initiated by the addition and thorough mixing of 30 μL of a concentrated (0.1–0.4 M) stock solution of **1c** in anhydrous dioxane. Aliquots (2 mL) of the reaction solution were withdrawn at zero time and appropriate times thereafter (total of 10–12 aliquot samples per run) and were immediately neutralized by the addition of a small amount (3–30 μL) of 0.1 N aqueous perchloric acid in order to stop any further exchange. (A control experiment had shown that in neutral or weakly acid solution the rate of exchange of *t*-Bu*SH with **1c** is negligible.)

Separation of the thiol from the other reagents was then achieved by precipitation of the thiol as its silver salt via the addition of slightly more than an equimolar amount of aqueous silver nitrate (0.4 mL of 0.01 N $AgNO_3$). (Again control experiments had shown that the thiol is cleanly separated from **1c** by this procedure, provided a large excess of silver nitrate is avoided.) The precipitate of the silver mercaptide was centrifuged and washed with alcohol. Acetonitrile (0.5 mL) was then added to the precipitate, the mixture of silver mercaptide plus acetonitrile was transfered to a glass counting vial, and the level of radioactivity was counted with a Beckmann LS 7000 Scintillation Counter using a complete liquid scintillation cocktail for organic samples (Scint, -0).

Rate constants for exchange were determined from plots of log $(I - I_\infty)$ vs. time, where I is the counting rate for the sample removed at time t and I_∞ is the counting rate for a sample removed after the exchange has reached equilibrium. Because the incursion of reaction 4 at long reaction times makes an accurate experimental determination of I_∞ impractical, I_∞ was calculated in the present work from the relationship $I_\infty = I_0(a/(a + 2b))$, where I_0 represents the counting rate for the sample removed at $t = 0$ and a and b represent the initial concentrations of *t*-Bu*SH and **1c**, respectively.

The study of the exchange of *i*-Pr*SH with **1b** was carried out in the same general way. The labeled thiol was dissolved in 30 mL of 60% dioxane containing 0.01 M sodium bicarbonate, and the exchange reac-

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(21) The gas chromatography was carried out on a 2 ft × $^1/_8$ in. column of 5% SE-30 on Chromosorb P. The carrier gas was hydrogen at a flow rate of 30 mL/min. The column temperature was programmed to rise from 90 °C at the start of each analysis to 170 °C at the end, in order that one might have reasonable retention times for the selenenyl sulfides, PhSeSR.

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tion was then initiated by adding **1b**. Aliquots were removed and immediately made weakly acid by the addition of an appropriate amount of 0.1 N aqueous perchloric acid. (A control experiment had shown that in weakly acid solution the rate of exchange of *i*-Pr*SH with **1b** is negligible.) The isolation of the thiol as its silver salt and the determination of its level of activity was done in the same manner as described for 2-methyl-2-propanethiol.

Kinetic Study of Other Reactions of 1. Unlike some of the reactions of thiolate ions with **1**, none of the reactions of **1** with cyanide ion showed biphasic behavior when studied in HCN–CN⁻ buffers containing a large stoichiometric excess of cyanide ion over **1**. The reactions were also slow enough that they could be followed by conventional spectrophotometry. A measured volume (3.5 mL) of a 60% dioxane solution containing the desired concentrations of CN⁻ and HCN was placed in a 1-cm spectrophotometer cell in the thermostated cell compartment of a spectrophotometer. The reaction was then initiated by adding 35 μL of a 0.05 M solution of **1** in pure dioxane and followed by monitoring the decrease in absorbance at an appropriate wavelength (275 nm for **1a** and **1b**, 280 nm for **1c**). The reaction of sulfite ion with **1a** was followed in a similar manner with a 1:1 Na_2SO_3–$NaHSO_3$ buffer.

The disappearance of **1a** in piperidine buffers was followed at 250 nm. It exhibited biphasic behavior, an initial rather rapid increase in absorbance, followed by a much slower decrease. The rates of the two processes were sufficiently different that one could easily determine accurately the absorbance at the end of the first stage of the reaction.

Registry No. 1a, 75272-64-9; **1b**, 83511-37-9; **1c**, 75272-63-8; **3**, 12564-43-1; *n*-BuS^-, 20733-16-8; *i*-PrS^-, 20733-15-7; *t*-BuS^-, 20733-19-1; SO_3^{2-}, 14265-45-3; Na_2SO_3, 7757-83-7; KCN, 151-50-8; *i*-$Pr^{35}SH$, 83511-39-1; *t*-$Bu^{35}SH$, 58204-98-1; CN^-, 57-12-5; ^{35}S-thiourea, 5022-67-3; *tert*-butyl alcohol, 75-65-0; hydrobromic acid, 10035-10-6; isopropyl bromide, 75-26-3; phenyllithium, 591-51-5; piperidine, 110-89-4; ^{35}S-*tert*-butylthiourea hydrobromide, 58204-97-0; ^{35}S-isopropylthiourea hydrobromide, 83511-38-0.

Activation of Reducing Agents. Sodium Hydride Containing Complex Reducing Agents. 18.[1] Study of the Nature of Complex Reducing Agents Prepared from Nickel and Zinc Salts

Jean-Jacques Brunet,[2a] Denis Besozzi,[2a] Alain Courtois,[2b] and Paul Caubere*[2a]

Contribution from the Laboratoire de Chimie Organique I, Universitê de Nancy I, Facultê des Sciences, B.P. 239, 54506 Vandoeuvre les Nancy, France. *Received April 1, 1982*

Abstract: Complex reducing agents "NaH–RONa–MX_n" (referred to as MCRA) are new versatile reagents that have already found many applications in organic synthesis. In the present study, the composition and structure of NiCRA and ZnCRA (CRA prepared from a nickel salt and a zinc salt, respectively) have been investigated. It has been found that, in both reagents, the metal (Ni or Zn) is formally in a zero-valent oxidation state. The active part of NiCRA is constituted of new species (formed from Ni^0 (1 equiv), RONa (R = *t*-Bu) (2 equiv), NaH (2 equiv), and maybe some AcONa) in which each constituent has lost its own characteristics. A picture of the structure of these new species is proposed. The composition of the active part of ZnCRA is less clear. Indeed, associations between RONa (R = *t*-Am) and Zn^0 have been evidenced, but these species do not exhibit the reducing properties of ZnCRA, e.g., toward carbonyl compounds. In fact, control experiments have shown that no ketone reduction occurred in the absence of NaH. These observations led us to propose that the active part of ZnCRA should be constituted of associations of the type $[(t\text{-AmO})_yH_zZnNa_{y+z}]_n$, which may be formed, in low concentration, from NaH and the inactive species $[(t\text{-AmO})_xZnNa_x]_n$.

Over the past few years, we have been interested in a new kind of reducing system, the complex reducing agents[3] (abbreviated CRA[4]). These reagents, formulated as "NaH–RONa–MX_n", are very easily prepared from sodium hydride, a metal salt,[4] and an alcohol (generally a tertiary alcohol). They resulted from the concept of activation by alkoxides, which was reported earlier from this laboratory concerning complex bases "$NaNH_2$–RONa".[5]

Until now, we have essentially explored the possible synthetic applications of CRA. It has been shown that they are very useful reagents in the field of chemical reductions[6] and that they allow many highly selective reductions.[6c,7] They also constitute a new source of heterogeneous, very active and selective hydrogenation catalysts such as Nic.[8] Their preparation concept has been applied to the development of new coupling reagents[9] and to the development of reaction media,[10] allowing unprecedented cobalt- and iron-catalyzed carbonylations of organic halides under atmospheric carbon monoxide pressure.[11,12] Finally, from intensive work now in progress in this laboratory, it can be affirmed that other applications of CRA are still very promising.

The usefulness of CRA having been proved, it was decided to undertake a study with the object of obtaining better knowledge about the nature of the active species involved in these surprising reagents. However, it is a very hard task to determine the constitution and reaction pathways of CRA—heterogeneous

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