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# Mechanism of a Redox Coupling of Seleninic Acid with Thiol

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Supporting Information

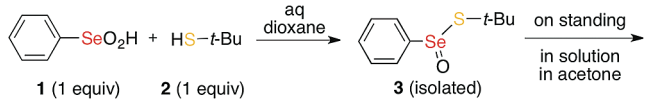
**ABSTRACT:** Equimolar quantities of 2-ethoxyethaneseleninic acid and *p*-thiocresol react rapidly in dichloromethane solution to give the selenosulfide along with disulfide, diselenide, and two products oxidized at sulfur, the thiosulfonate and the selenosulfonate. The latter two are new for this sort of coupling; their formation may be the result of an early thioseleninate to selenosulfinate isomerization. A radical chain mechanism is proposed to account for all five products, as well as their relative amounts.

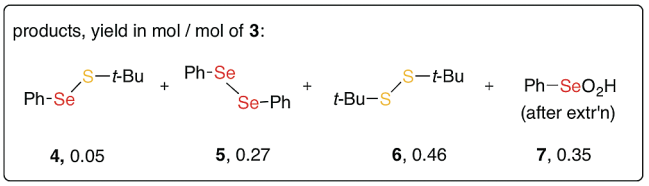
## INTRODUCTION

Coupling reactions that occur rapidly and efficiently under mild conditions, sometimes called "click reactions," have applications not available to other transformations.[1,2] For example, the redox coupling of seleninic acid and thiol to give the selenosulfide succeeds with a variety of coupling partners and in a wide range of solvents.[3] Applications to the efficient coupling of biomolecular components or biomimetics resembling amino acids, peptides, nucleosides, phosphatidic acids, and carbohydrates can be envisioned.[4] Indeed, a tyrosine-derived seleninic acid, as a substrate mimic, couples with a cysteine thiol residue in the active site of protein tyrosine phosphatase to effectively deactivate the enzyme by covalent modification.[5]

Two authoritative papers by Kice and co-workers established the coupling reaction of benzeneseleninic acid **1** with *t*-butanethiol **2** to proceed by initial formation of the thioseleninate intermediate **3** (Scheme 1).[3,6] When two additional equivalents of **2** are present, **3** is reduced efficiently to the selenosulfide product **4**. However, with equimolar amounts of **1** and **2**, the reaction stops at **3**, which can then with care be isolated and characterized, and its decomposition studied separately. In concentrated acetone solution, **3** is rapidly converted to a mixture of selenosulfide **4**, diselenide **5**, and disulfide **6**. As for certain other transformations of Se=O species,[7−9] the fate of the oxygen atoms remained mysterious[3] until Kice and Purkiss, who described the extraction of crude product with aqueous sodium carbonate, were able to isolate an oxidized product, the seleninic acid **7** (=**1**).[6] Yields based on moles of **3** are shown in Scheme 1 and together account for 94% of the Se, 97% of the S, and 52% of the O atoms, assuming that the latter arose by hydrolysis upon extraction of benzeneseleninic anhydride, PhSe(=O)OSe(=O)Ph. A radical chain mechanism featuring a mixed selenenic−seleninic anhydride intermediate was advanced to account for the formation of products **4**−**7**.[6]

**Scheme 1. Coupling Reaction of *t*-Butanethiol and Benzeneseleninic Acid Described by Kice et al.**




In this paper, we analyze the results of a seemingly analogous seleninic acid/thiol coupling reaction that takes an entirely different course and suggest a mechanism that accounts for the differences.

## RESULTS AND DISCUSSION

We find that 2-ethoxyethaneseleninic acid[10] (**8**, Scheme 2) couples with 3 equiv of thiocresol (**9**, added last) in dichloromethane solution to give the selenosulfide **10** along with bis-(2-ethoxyethyl) diselenide (**11**)[10,11] and di-*p*-tolyl disulfide (**12**). No particular efforts were made to exclude oxygen, water, or light other than capping the reaction vessel. The reaction solution immediately becomes foggy, presumably with the water of reaction, and is over in less than a minute, judging from TLC analysis. No gas evolution is observed, nor are other nonvolatile products detected, according to $^{1}$H, $^{13}$C, and $^{77}$Se NMR spectroscopic examination of the concentrated crude reaction mixture. Reversing the order of addition, or changing the rate of addition, or conducting the reaction at 0 °C did not change the results appreciably. Careful chromatography enabled the isolation of **10**−**12** in the yields shown (yields shown are based on the respective chalcogen-containing precursor), which together account for 98% of the Se (i.e., 81% + 17%) and 96% of the S (i.e., one-third of 81%, plus 69%)

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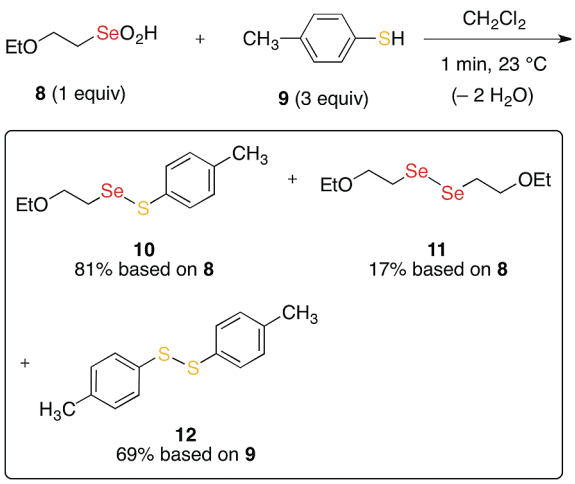
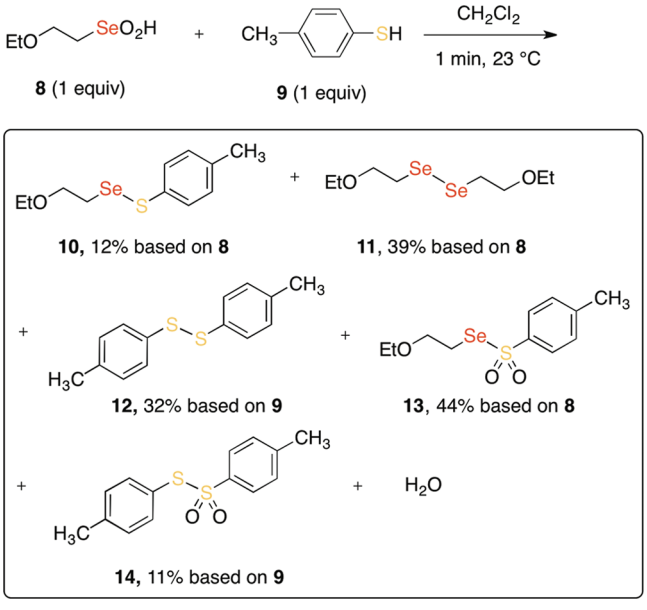
**Scheme 2. Redox Coupling Reaction of 2-Ethoxyethaneseleninic Acid and Thiocresol**




atoms. Selenosulfide **10**, although stable to isolation and characterization, does slowly disproportionate in solution to give a mixture of **10**, **11**, and **12**. Analogous chalcogen scrambling behavior has been seen with other selenosulfides.[3,12−14]

In comparison to the reaction of Scheme 2, the coupling reaction of *equimolar equivalents* of **8** and **9** under otherwise identical conditions (0.111 mmol/mL in dichloromethane solution) gave the previously observed products **10**−**12**, as well as two new *S*-oxidized products, the selenosulfonate **13** and the thiosulfonate **14** (Scheme 3). The products were isolated by

**Scheme 3. Stoichiometric Coupling Reaction of 2-Ethoxyethaneseleninic Acid and Thiocresol, and Isolation of Two New *S*-Oxidized Products**

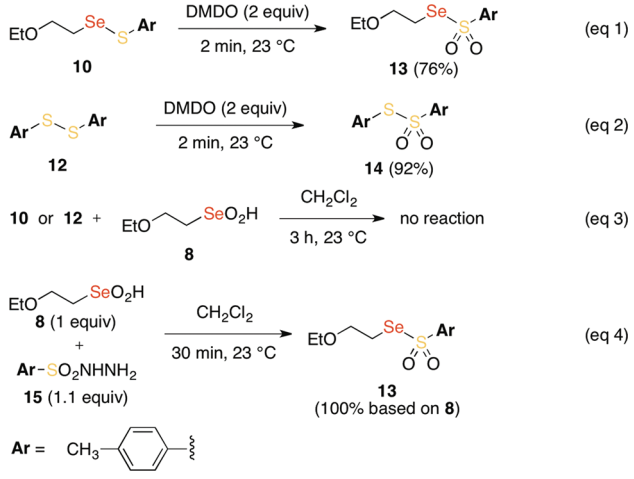



column chromatography on silica (eluent 9:1 hexanes/ethyl acetate; order of elution: **12**, **10**, **11**, **14**, and finally **13**) and were characterized by mass spectrometry; $^{1}$H, $^{13}$C, and $^{77}$Se NMR spectroscopy; and by comparison to authentic samples. Taken together, the isolated yields (each based on the respective chalcogen precursor) account for 95% of the Se (12% + 39% + 44%) and 99% of the S (12% + 32% + 44% + 11%) atoms; **13** and **14** together account for 99% [respectively, 88% (two O's per 44% S) plus 11% (one O per 11% S)] of the expected oxygen atoms from **8**, exclusive of the water of reaction of coupling. No other products are apparent in the crude concentrated reaction mixture, according to TLC and $^{1}$H, $^{13}$C, and $^{77}$Se NMR analysis. As far as we are aware, *S*-oxidized products have not been previously isolated from a seleninic acid/thiol coupling reaction.

The reaction of Scheme 3 was scaled up to 1.5 mmol (0.75 mmol/mL) in order to quantitate the water produced. Extraction of the dichloromethane solution with $D_2O$ and then analysis of the $^{1}$H NMR spectrum with integration relative to *N*-acetylglycine as an internal standard allowed assessment[15] of the approximate amount of water produced: 1.1 equiv based on 1 equiv of **8**. Details of this analysis as well as the accompanying calibration of the method are given in the Experimental Section. A trace (about 1%) of a 2-ethoxyethaneseleninic product ($\delta$ 4.01, t, $J$ = 6.5 Hz), distinct from **8** ($\delta$ 3.90, t, $J$ = 6.5 Hz) and possibly the anhydride, was also detected in the aqueous layer. Examination of the $^{1}$H, $^{13}$C, and $^{77}$Se NMR spectra of the concentrated crude dichloromethane soluble reaction mixture showed the exclusive formation of the previous five products, and integration of the proton signals (the well-resolved tolyl methyl singlets at 2.2−2.5 ppm and the distinct methylene quartet of **11** at 3.53 ppm) allowed assignment of the relative yields (based on 100%), which are virtually identical to the isolated yields of Scheme 3 (**10**−**14**, respectively: 14, 40, 32, 44, and 10%). Because of this agreement, the isolated yields may be taken as quite accurately reflective of the relative amounts of products formed.

Several control reactions (Scheme 4) were undertaken to support the product assignments and the transformations

**Scheme 4. Control Reactions Confirming the Identity of Products and the Susceptibility of 10 and 12 toward *S*-Oxidation**




implied by Scheme 3. Independent oxidation of selenosulfide **10** to selenosulfonate **13** was carried out by treating **10** with dimethyldioxirane (DMDO, eq 1). Analogous oxidation of disulfide **12** gave the thiosulfonate **14** (eq 2). The products were spectroscopically and chromatographically identical to those produced earlier from the coupling of **8** and **9** (Scheme 3). Both **10** and **12** were shown to be unreactive toward 2-ethoxyethaneseleninic acid **8** (eq 3). The structure of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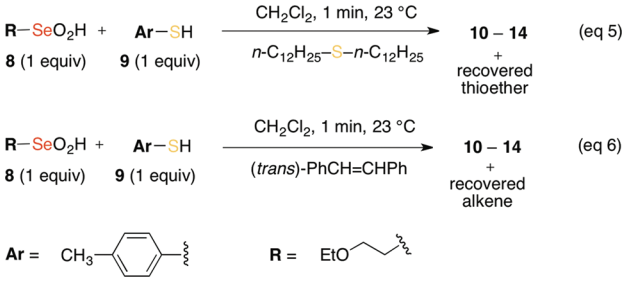
selenosulfonate **13** was confirmed by independent synthesis: redox coupling[16,17] of **8** with *p*-toluenesulfonylhydrazide (**15**) gave **13** quantitatively (eq 4).

The equimolar condensation of **8** and **9** was repeated as in Scheme 3, but with the respective prior addition of 1 equiv of dodecyl sulfide (eq 5, Scheme 5) and *trans*-stilbene (eq 6,

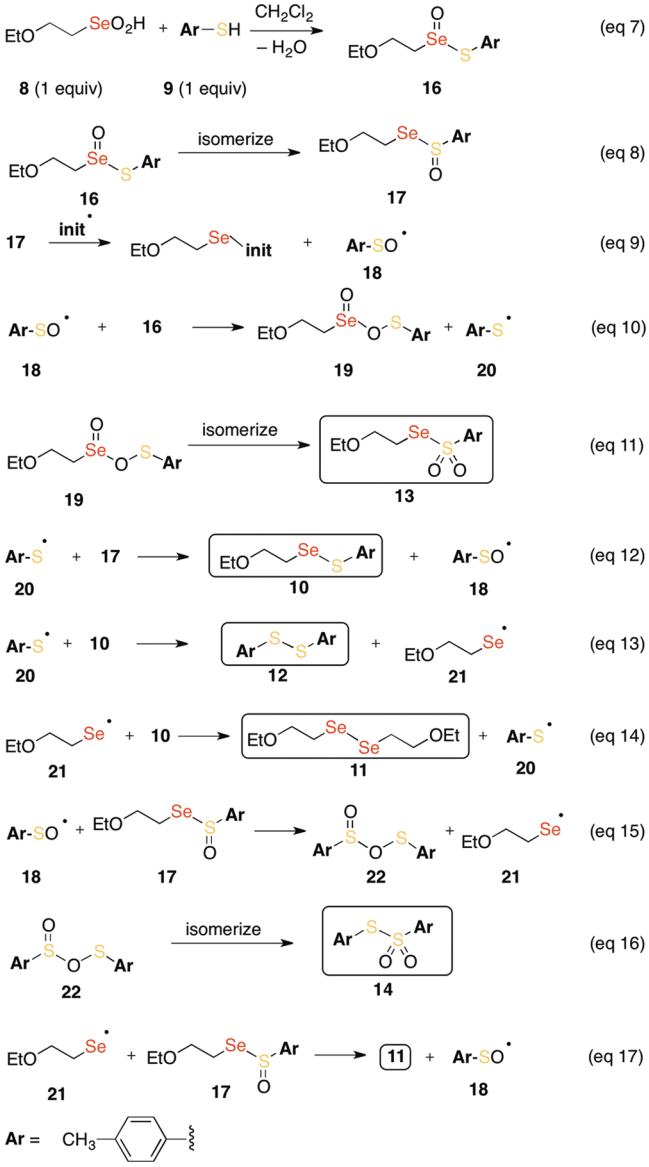
**Scheme 5. Attempted Trapping of Reactive Intermediates with Dodecyl Sulfide and *trans*-Stilbene**




Scheme 5). Neither additive reacts with **8** under these conditions. For both reactions, analysis of the crude reaction mixtures by $^1$H NMR spectroscopy indicated the same five products (**10**–**14**) in approximately the same ratio. Furthermore, no dodecyl sulfoxide was formed (eq 5), and no C=C trapped product was detected (eq 6). Thus, it may be concluded that any oxidizing, electrophilic, or radical intermediates reacted faster with species present anyway in the course of the reaction rather than with the traps, even though the latter are present in relative excess. Sulfides have been oxidized to the sulfoxide by seleninic acids,[18] and a selenoxide,[10] but only in the presence of strong acid. Seleninic acid **8** is a weak acid, p$K_a$ ~ 5,[19] as is $ArSO_2H$. Traces of $ArSO_3H$ might be formed here, although its salt with **8** would likely precipitate from dichloromethane solution.[20] Electron-rich alkenes can add selenenic acids RSeOH if the latter survive contact with other reducing species in the reaction mixture.[9]

A mechanism for the formation of coupled products **10**–**14** is proposed in Scheme 6 (isolated products are shown in the boxes). The initial condensation of seleninic acid **8** and thiocresol **9** to give the thioseleninate **16** and water (eq 7) is suggested to proceed rapidly and completely, consistent with the observations of Kice and co-workers.[3,6] A new isomerization, the conversion of thioseleninate **16** into selenosulfinate **17** (eq 8), can account for the appearance of *S*-oxidized products, as will be seen. This isomerization is analogous to the apparent scrambling of aryl groups in the thermal rearrangement of *S*-aryl arenethiosulfinates,[21] although this one would occur at a lower temperature. Caged radical recombination processes[21] may be involved, and the mixed selenenic–sulfenic anhydride ($EtOCH_2CH_2Se$-O-SAr), although not expected to be stable itself,[6] is a likely intermediate. Initiation of the radical chain occurs with selenenyl abstraction from **17** (eq 9). The resulting arenethioxyl radical **18** can combine with thioselenenate **16** to give the seleninic–sulfenic anhydride **19** (eq 10), or equivalently, the α-selenoxide-sulfoxide ($EtOCH_2CH_2Se(=O)$-S(=O)Ar), either of which should rearrange rapidly to the selenosulfonate **13** (eq 11). This rearrangement finds precedent in the analogous behavior of α-disulfoxides, which rearrange to thiosulfonates so fast at −20 °C as to be undetectable.[22,23] The same intermediates (**16**, **17**, and the α-selenoxide-sulfoxide) could also be involved in the rapid DMDO oxidation of selenosulfide **10** to selenosulfonate **13**

**Scheme 6. Proposed Radical Chain Reaction for Redox Coupling of 8 and 9**[a]




[a]Products are shown in the boxes.

(Scheme 4, eq 1), assuming that kinetic oxidation of **10** occurs on Se. The arenethiyl radical **20** produced in eq 10 can react with selenosulfinate **17** (eq 12) to give the selenosulfide **10** and arenethioxyl radical **18**, which continues the chain. The mixed chalcogen coupled products **10** and **13** are accounted for by eqs 9–12, while a separate, parallel radical chain sequence is necessary to explain the formation of the same-chalcogenide products **11**, **12**, and **14**.

Selenosulfide **10** can be further transformed, in part, by reaction with arenethiyl radical **20** to produce the product disulfide **12** and a selenyl radical **21** (eq 13). Further reaction of **21** with more of **10** leads to the product diselenide **11** and regenerates **20** to continue the chain (eq 14). Chalcogen scrambling of selenosulfides in the presence of radicals is well-precedented.[3,24] The fifth product **14** can be formed by reaction (eq 15) of arenethioxyl radical **18** with selenosulfinate **17**, the proposed source of S=O groups in both sulfonate products **13** and **14**. The resulting sulfenic–sulfinic anhydride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**22** (or equivalently, the $\alpha$-disulfoxide) would be expected[22,23] to rapidly rearrange to thiosulfonate **14** (eq 16). The remaining selenosulfinate **17** is converted (eq 17) to additional diselenide **11** and enough arenethioxyl radical **18** to continue the chain by reentry at eq 15.

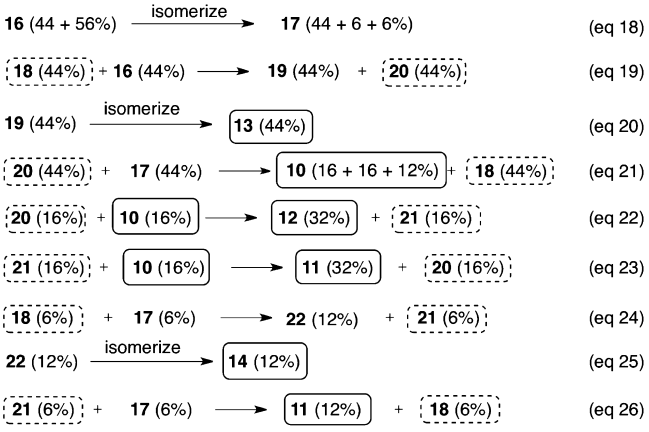
Is the proposed mechanism of Scheme 6 consistent with the trapping experiments of Scheme 5? No strong oxidizing species (stronger than seleninic acid **8**, that is) is proposed as an intermediate, so the noninvolvement of dodecyl sulfide is understandable. Direct transfer of [O] from thioseleninate **16** as an oxidant might be possible, but ought to require strong acid catalysis (to protonate Se=O).[10] Whether ArSeO• can serve as an oxidant is not known at this time, but it would have to be selective for **10** and **12** in the presence of thioether. We propose that the respective precursors of selenosulfonate **13** and thiosulfonate **14** are probably not the corresponding dichalcogenides, **10** and **12**, each of which is stable to **8**, if not DMDO. The selenenic acid $EtOCH_2CH_2SeOH$, which might react with *trans*-stilbene as an electrophile,[9] is not invoked as an intermediate. Seleninic acids are also known to combine with sulfinates to produce selenosulfonates (compare **13**) as well as sulfonic acid,[20] but the latter is not found here among the products.

Selenosulfonates, such as **13**, can also react with alkenes by photoactivated formation and addition of $ArSO_2$•,[20] but no such adducts are seen, and $ArSO_2$• is not a required intermediate in Scheme 6. Indeed, *trans*-stilbene and dodecyl sulfide are found to coexist with **13** in solution under the conditions of the reaction. The radical chain carriers ArS• (**20**), ArSO• (**18**), and $EtOCH_2CH_2Se$• (**21**) might be expected to add to an alkene, but the addition could be reversible, and other radicalophiles, including **16** and **17**, are present and can react rapidly by rupture of their weak chalcogen−chalcogen bonds. Of course, it cannot be assumed that a radical trap more reactive than *trans*-stilbene might not have intercepted, say, arenethioxyl radical **18**. Under certain conditions, ArS• (but perhaps not RSe•[25]) can trap dissolved molecular oxygen,[26] but no product attributable to such a reaction was found.

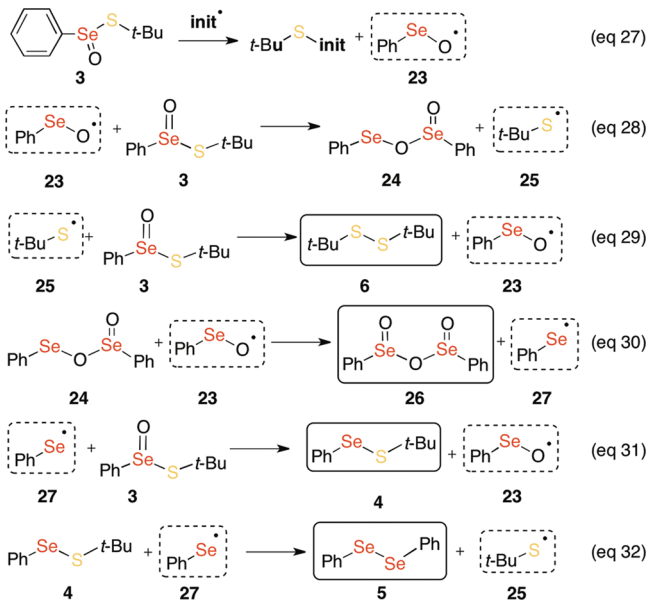
The mechanism proposed in Scheme 6 also formally accounts for the *relative yields* of the five products **10**−**14**. Scheme 7 delineates the consequences of the mechanism of Scheme 6 if one assumes a 44/56 partitioning of intermediates thioseleninate **16** and selenosulfinate **17** (eq 18). This is a logical choice given that the 44% isolated yield of product **13** (the selenosulfonate) comes only from **16** (eqs 19 and 20). Products are shown in solid boxes, and chain carriers [ArS• (**20**), ArSO• (**18**), and $EtOCH_2CH_2Se$• (**21**)] are shown in dashed boxes. Note that the yields shown are based on the respective S and Se starting materials **8** and **9**, as in Scheme 3. A 44% portion of **17** gives rise to a 44% initial yield of selenosulfide **10**, as shown (eq 21), but the latter is partitioned into 16% (which leads to disulfide **12**, eq 22), an additional 16% (which leads to diselenide **11**, eq 23), and the remaining 12%, which is isolated. The remaining selenosulfinate **17** (12%) goes in equal parts, at least formally, to the formation of thiosulfonate **14** (eqs 24 and 25) and also additional diselenide **11** (eq 26). The amounts of carrier species ArS• (**20**), ArSO• (**18**), and $EtOCH_2CH_2Se$• (**21**) and other intermediates balance on both sides of the arrows. The product yields predicted by Scheme 7 (given the **16**/**17** partitioning) for **10**−**14** are 12, 44, 32, 44, and 12%, respectively, whereas the corresponding isolated yields are 12, 39, 32, 44, and 11%, a very close match. Not all the predicted diselenide **11** was isolated (39% vs 44% predicted), possibly because some was lost to the aqueous layer as the seleninic anhydride (also a Kice product; see Scheme 1). This accounting lends credence to the proposed mechanism of Scheme 6, in that the chalcogen atoms and oxidation states are properly conserved.

An analogous radical chain mechanism (Scheme 8) can be drawn for the formation of the Kice coupling products (shown in Scheme 1) that allows a comparison between the two reactions. In this case, no rearrangement of the thioseleninate (here, **3**) to a selenosulfinate occurs. Instead, **3** initiates the radical chain by forming benzeneselenoxyl radical **23** (eq 27), which can combine with more **3** to produce a mixed selenenic−seleninic anhydride **24** as well as *t*-butanethiyl radical **25** (eq 28). The latter abstracts the *t*-butylthio group from **3** to give di-*t*-butyl disulfide **6** and regenerate the radical carrier species **23**

**Scheme 7. Formal Partitioning of Scheme 6 Intermediates, Radical Carrier Species (in Dashed Boxes), and Coupled Products (in Solid Boxes)**




**Scheme 8. Proposed Radical Mechanism for the Kice Decomposition of *S*-*tert*-Butyl Benzenethioseleninate**[a]




[a]Products are shown in solid boxes, and radical carrier species in dashed boxes.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(eq 29). Combination of **23** with **24** leads to benzeneseleninic anhydride **26**, and benzeneselenyl radical **27** (eq 30), and **27**, in turn, produces the other two products (selenosulfide **4** and diphenyl diselenide **5**, eqs 31 and 32) by radical exchange. Further chalcogen scrambling of **4**, isolated as a minor product, can be expected to occur under the radical conditions, leading to the formation of additional amounts of disulfide **6** and diselenide **5**. Hydrolysis of benzeneseleninic anhydride **26** upon aqueous base workup accounts for the isolation of benzeneseleninic acid **7**. Kice proposed a mechanism[6] similar to Scheme 8 for radical decomposition of **3**.

The Kice reaction[6] produces no *S*-oxidized products, possibly because (a) steric hindrance at *tert*-butyl-S suppresses the thioseleninate-to-selenosulfinate rearrangement (eq 8, Scheme 6), and/or (b) the chalcogen−chalcogen bond of **3** (eq 27, Scheme 8) is stronger than that of **16** (eq 7, Scheme 6). Because the early coupled products differ, the radical chain carriers in the two reactions are different: ArSO• in the case of Scheme 6, and PhSeO• in the reaction of Scheme 8. In an earlier investigation of the same reaction, Kice and Lee[3] combined benzeneseleninic acid **1** and *t*-butanethiol **2** in equimolar amounts and observed that the thioseleninate intermediate **3** decomposed rapidly in concentrated acetone solution to give three products only: **4**, **5**, and **6**. No oxygen-containing products were found, and preliminary speculation[3] that the other product is molecular oxygen ($O_2$) was withdrawn in the later investigation,[6] where the formation of benzeneseleninic acid **7** as the oxygen-containing product from separate decomposition of **3** was reported. In our earlier studies of alkaneseleninic acids,[4] we have also found that the seleninic acid oxygens sometimes "disappear" during coupling reactions with thiols, even though all the chalcogen atoms are accounted for in the products. At present, we have no general explanation for this phenomenon, but would note that possible conversion of the carrier species RSeO• to RSe• can theoretically account for the absence of oxygen-containing coupled products. A somewhat analogous process has been proposed for oxygen insertion from dimethyldioxirane into R−H.[27] The missing oxygen atom could well be incorporated into solvent or other nonchalcogen species.

The radical chain mechanism of Scheme 6 might not operate effectively in dilute solution, nor in the active site of an enzyme,[5] since bimolecular encounters and radical initiation events would be infrequent. In these cases, an alternative reducing agent might be serving to transform the putative thioseleninate intermediate to products. However, attempts to improve the efficiency of such equimolar seleninic acid/thiol redox couplings by intentionally adding an in situ reducing agent have thus far been unsuccessful.

## CONCLUSION

The remarkably fast equimolar redox coupling reaction of 2-ethoxyethaneseleninic acid and *p*-thiocresol (Scheme 3) is shown to take a new course explainable by isomerization of the initial coupled product, a thioseleninate (**16**), to a selenosulfinate (**17**). A radical chain mechanism (Scheme 6) is proposed to rationalize the formation of the five products **10**−**14**, with intermediate **17** suggested as the source of the novel *S*-oxidized products **13** and **14**. The water of reaction is quantified for the first time.

## EXPERIMENTAL SECTION

***S*-*p*-Tolyl 2-Ethoxyethaneselenenylthioate (10), Bis-(2-ethoxyethyl)diselenide (11),[10,11] and Di-*p*-tolyl Disulfide (12).**[28,29] A solution of 2-ethoxyethaneseleninic acid **8** (11.1 mg, 0.060 mmol) in dichloromethane (0.5 mL) was treated, over about 5 s, with a solution of *p*-thiocresol **9** (22.4 mg, 0.180 mmol) in dichloromethane (0.5 mL). After 1 min of stirring at room temperature, TLC analysis indicated the consumption of starting materials. The reaction mixture was concentrated and chromatographed on silica with 9:1 hexanes/ethyl acetate as the eluant to give 13.4 mg (81%) of selenosulfide **10** as a colorless oil, 1.5 mg (17%) of diselenide **11** as a yellow oil, and 15.3 mg (69%) of disulfide **12** as a colorless oil.

*Selenosulfide **10**:* $R_f$ 0.47 (9:1 hexanes/ethyl acetate); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.44 (d, 2H, $J$ = 8.4 Hz), 7.08 (d, 2H, $J$ = 8.4 Hz), 3.71 (t, 2H, $J$ = 6.8 Hz), 3.46 (q, 2H, $J$ = 7.2 Hz), 3.09 (t, 2H, $J$ = 6.8 Hz), 2.32 (s, 3H), 1.17 (t, 3H, $J$ = 7.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 137.6, 133.8, 130.5, 129.9, 69.4, 66.5, 31.8, 21.2, 15.4; $^{77}$Se NMR (76 MHz, $CDCl_3$) $\delta$ 437.4 [vs PhSeSePh at 460.0 ppm as an external standard]; HRMS (ESI) Calcd for $C_{11}H_{16}ONaSSe$ ($MNa^+$) 298.9985, found 298.9970.

*Diselenide **11**:* $R_f$ 0.32 (9:1 hexanes/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.71 (t, 2H, $J$ = 6.8 Hz), 3.53 (q, 2H, $J$ = 7.2 Hz), 3.11 (t, 2H, $J$ = 6.8 Hz), 1.21 (t, 3H, $J$ = 7.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 70.7, 66.5, 29.6, 15.4; $^{77}$Se NMR (76 MHz, $CDCl_3$) $\delta$ 295.4 [vs PhSeSePh at 460.0 ppm as an external standard]; ESI-MS $m/z$ 329 $MNa^+$, molecular ion cluster: two Se.

*Disulfide **12**:* $R_f$ 0.64 (9:1 hexanes/ethyl acetate); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.40 (d, 4H, $J$ = 8.0 Hz), 7.12 (d, 4H, $J$ = 7.5 Hz), 2.33 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 137.7, 134.2, 130.0, 128.8, 21.3; ESI-MS $m/z$ 269 $MNa^+$.

**Equimolar Redox Coupling of 2-Ethoxyethaneseleninic acid (8) and *p*-Thiocresol (9).** A solution of seleninic acid **8** (20.6 mg, 0.111 mmol) in dichloromethane (1 mL) was treated with *p*-thiocresol **9** (13.8 mg, 0.111 mmol) in one aliquot. After 1 min of stirring at room temperature, TLC analysis indicated the consumption of starting materials. The reaction mixture was concentrated and chromatographed on silica with 9:1 hexanes/ethyl acetate as the eluant to give in order of elution: 4.3 mg (32%) of disulfide **12** as a colorless oil, 3.7 mg (12%) of selenosulfide **10** as a colorless oil, 6.6 mg (39%) of diselenide **11** as a yellow oil, 1.7 mg (11%) of thiosulfonate **14** as a white solid, and 14.9 mg (44%) of selenosulfonate **13** as a colorless oil.

*Se-(2-Ethoxyethyl)-p-toluenesulfonylselenylate (**13**):* $R_f$ 0.13 (9:1 hexanes/ethyl acetate); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.77 (d, 2H, $J$ = 8.5 Hz), 7.33 (d, 2H, $J$ = 8.5 Hz), 3.76 (t, 2H, $J$ = 6.5 Hz), 3.46 (q, 2H, $J$ = 7.0 Hz), 3.38 (t, 2H, $J$ = 6.5 Hz), 2.45 (s, 3H), 1.15 (t, 3H, $J$ = 7.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 144.8, 144.7, 130.0, 126.7, 69.1, 66.8, 33.3, 21.9, 15.2; $^{77}$Se NMR (76 MHz, $CDCl_3$) $\delta$ 857.2 [vs PhSeSePh at 460.0 ppm as an external standard]; HRMS (ESI) Calcd for $C_{11}H_{16}O_3NaSSe$ ($MNa^+$) 330.9883, found 330.9875.

*S-p-Tolyl-p-toluenesulfonylthioate (**14**).*[30] $R_f$ 0.27 (9:1 hexanes/ethyl acetate); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.47 (d, 2H, $J$ = 8.0 Hz), 7.25 (d, 2H, $J$ = 8.5 Hz), 7.22 (d, 2H, $J$ = 8.0 Hz), 7.15 (d, 2H, $J$ = 8.0 Hz), 2.43 (s, 3H), 2.38 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 144.8, 142.3, 140.7, 136.7, 130.4, 129.6, 127.8, 124.9, 21.9, 21.7; ESI-MS $m/z$ 301 $MNa^+$.

**Oxidation of Selenosulfide 10 to Selenosulfonate 13.** Dimethyldioxirane (total ~196 $\mu$L of a 0.30 M titrated solution of dimethyldioxirane (DMDO) in chloroform[31] (~2.0 equiv) was added to a stirred solution of selenosulfide **10** (8.1 mg, 0.029 mmol) in moist dichloromethane (1 mL). After 2 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 4:1 hexanes/ethyl acetate as the eluant to give 6.8 mg (76%) of selenosulfonate **13** as a white solid.

**Oxidation of Disulfide 12 to Thiosulfonate 14:** DMDO (total ~366 $\mu$L of a 0.30 M titrated solution in chloroform, ~2.0 equiv) was added to a stirred solution of disulfide **12** (13.5 mg, 0.0549 mmol) in moist dichloromethane (1 mL). After 2 min of stirring at room temperature, the reaction mixture was concentrated and chromato-


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graphed on silica with 9:1 hexanes/ethyl acetate as the eluant to give 14.1 mg (92%) of thiosulfonate **14** as a white solid.

**Independent Synthesis of Selenosulfonate 13 by the Redox Coupling of 8 with *p*-Toluenesulfonylhydrazide.** Seleninic acid **8** (8.4 mg, 0.045 mmol) in dichloromethane (1 mL) was added dropwise to a solution of *p*-toluenesulfonylhydrazide (9.3 mg, 0.050 mmol) in dichloromethane (1 mL). After 30 min of stirring at room temperature, the reaction mixture was concentrated and chromatographed on silica with 4:1 hexanes/ethyl acetate as the eluant to give 13.9 mg (~100%) of selenosulfonate **13** as a white solid.

**Water of Reaction Produced by the Equimolar Coupling of 8 and 9.** A solution of seleninic acid **8** (277 mg, 1.50 mmol) in dichloromethane (2 mL) was treated with thiocresol **9** (186 mg, 1.50 mmol) in one aliquot. After 1 min of stirring at room temperature (the solution became slightly foggy), 2.0 mL of deuterium oxide was added. The organic layer was concentrated in vacuo; examination of the $^{1}$H, $^{13}$C, and $^{77}$Se NMR spectra of the crude product showed the exclusive formation of compounds **10**–**14** with relative spectroscopic yields of 14, 40, 32, 44, and 10%, respectively (based on the integration of proton signals of the tolyl methyls and the methylenes of **11**). The aqueous layer was separated, and 0.75 mL was combined with *N*-acetylglycine (5.9 mg, 0.050 mmol) as an internal NMR integration standard. The resulting aqueous solution was transferred to an NMR tube, and the $^{1}$H NMR spectrum was examined. The integration value of the HOD signal relative to the methylene of *N*-acetylglycine was 7.86 to 2.21, corresponding to 1.1 equiv of water produced (based on 1.0 equiv of **8**), after background correction. The control experiments as well as the calibration of the method (i.e., quantitation of known added amounts of water) are summarized in Table 1 in the Supporting Information.

**Equimolar Condensation of 8 and 9 in the Presence of Dodecyl Sulfide.** A solution of seleninic acid **8** (5.0 mg, 0.027 mmol) and dodecyl sulfide (10.0 mg, 0.027 mmol) in dichloromethane (0.5 mL) was treated in one aliquot with a solution of *p*-thiocresol **9** (3.4 mg, 0.027 mmol) in dichloromethane (0.5 mL). After 1 min of stirring at room temperature, TLC analysis indicated the consumption of starting material. The reaction mixture was concentrated, and the crude $^{1}$H NMR spectrum (Supporting Information) showed the exclusive formation of compounds **10**–**14** in addition to unchanged didodecyl sulfide.

**Equimolar Condensation of 8 and 9 in the Presence of *trans*-Stilbene.** A solution of seleninic acid **8** (11.7 mg, 0.063 mmol) and *trans*-stilbene (11.4 mg, 0.063 mmol) in dichloromethane (0.5 mL) was stirred at room temperature for 30 min. No reaction between seleninic acid **8** and *trans*-stilbene was observed. The reaction solution was then treated in one aliquot with a solution of *p*-thiocresol **9** (7.9 mg, 0.063 mmol) in dichloromethane (0.5 mL). After 1 min of stirring at room temperature, TLC analysis indicated the consumption of starting material. The reaction mixture was concentrated, and the crude $^{1}$H NMR spectrum (Supporting Information) showed the exclusive formation of compounds **10**–**14** in addition to unchanged *trans*-stilbene.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^{1}$H, $^{13}$C, and $^{77}$Se NMR spectra of reaction products **10**–**14**, and details of the controls and calibration of the water detection method. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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