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# Competing Ene-Reactions in the *p*-Oxidation and *o*-Phenylselenylation of Phenol with Benzeneseleninic Acid

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**Abstract:** Reaction of phenol with benzeneseleninic acid gives 2-(phenylseleno)- and 2,6-bis(phenylseleno)-1,4-benzoquinone *via* the corresponding 2- and 2,6-selenylated phenols; initiating ene-reactions are suggested for both the *o*-selenylation and the *p*-oxidation sequence.

The spectacular *o*-oxidation of phenols[1,2,3] has initiated an extensive research into the application of benzeneseleninic acid (**1**) and its anhydride (**2**) as specific oxidants.[4]

$Ph\text{-}SeO_2H$ (**1**) $\qquad$ $(Ph\text{-}SeO)_2O$ (**2**)

However, the reactions of phenolic substrates with **1** and **2** appear to form a complex pattern. Allthough subsequent papers by the Barton group[5,6] have provided a considerable amount of insight into this pattern a number of questions still remain unanswered: It was observed that **2** gives mainly *o*-oxidation while the application of **1** changes the pattern to predominant *p*-oxidation. It has been convincingly argued that the *o*-oxidation with **2** involve the formation and subsequent [2,3]-shift of an aryl benzeneseleninate. The route to *p*-oxidation seems less clearly elucidated. As well *p*-seleninylation with Pummerer rearrangement as *o*-seleninylation with [2,3]-shift have been suggested as possible pathways. A solvent influence on the regioselectivity of the oxidations has been demonstrated, *e.g.* tetrahydrofurane (THF) favors the *o*-oxidation while the *p*-oxidation is favored in dichloromethane. Simultaneous phenylselenation has been observed with both reagents. The occurrence of phenylselenylated products has been ascribed to the action of some Se(II) electrophile formed by an equilibrium reaction, *e.g.* (1), between **1** or **2** and their reduction product, diphenyl

$$PhSeO_2H\ (\mathbf{1}) + PhSeSePh\ (\mathbf{3}) = PhSeOH + (PhSe)_2O \qquad (1)$$

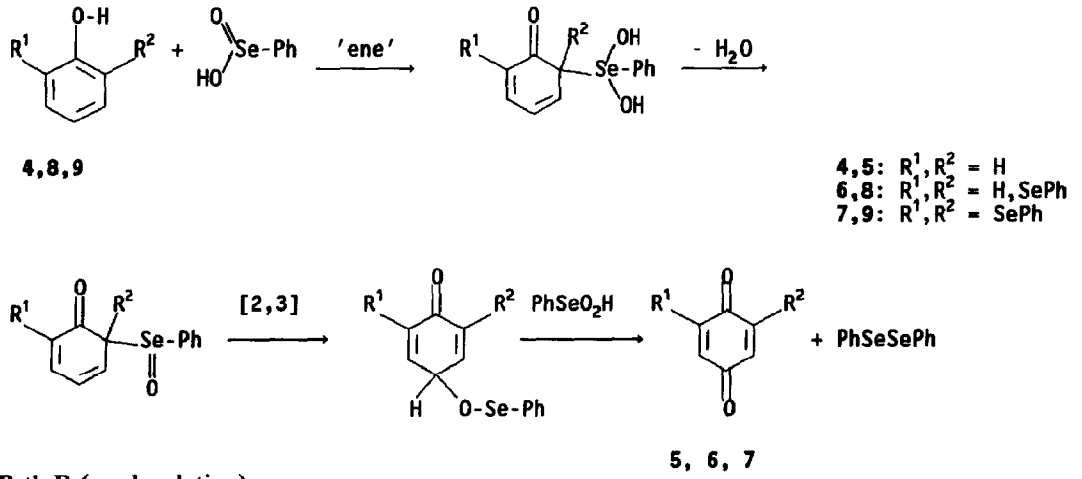
diselenide (**3**), but the fact that only *o*-selenylated products are isolated while phenylselenylation with (phenylseleno)dimethylsulfonium ion as the electrophile proceeds with high *p*-selectivity[7] is left unexplained. The present communication on the reaction between phenol (**4**) and **1** may add some of the missing pieces to this puzzle.

The treatment of **4** (3 mmol) with **1** (6 mmol) in dichloromethane (10 ml, 24°C, 24 h) gave, beside **3**, a mixture of 1,4-benzoquinone (**5**), 2-(phenylseleno)-1,4-benzoquinone (**6**)[8] [red crystals, $\lambda_{max}$ (log $\epsilon$) 455 nm (3.42); m.p. 113-114°C] and 2,6-bis(phenylseleno)-1,4-benzoquinone (**7**) [purple crystals, $\lambda_{max}$ (log $\epsilon$) 413 nm (3.69), 511 nm (3.50); m.p.219-220°C] in the approximate molar ratio **5**:**6**:**7** = 3:4:3. The initial addition of **3** (0.5 mmol) to the reaction mixture changed this ratio to 2:5:4, *i.e.* in favor of selenylated products in support of the concept of a selenylating agent formed according to eq. (1). The products **3**, **5**, **6** and **7** accounted for more than 80% of the selenium and about 50% of the phenol inserted and no other defined products were present in amounts exceeding 2%; the remaining phenol seems lost to oxidative polymerization. If 1,2-benzoquinone is formed in these mixtures it is destroyed at a rate that prevents its accumulation.

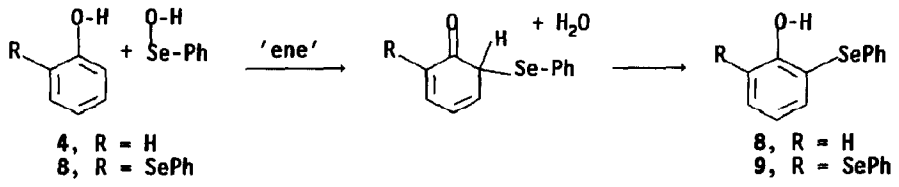
From the reaction performed with the molar ratio **4**:**1**:**3** = 3:2:1 were isolated three additional products, 2-(phenylseleno)phenol (**8**) [oil; lit.[7]: oil] (40%), 2,6-bis(phenylseleno)phenol (**9**) [m.p. 59-61°C] and 4-(phenylseleno)phenol (**10**) [m.p.50-51°C; lit.[7]: 52-53°C]( 2%, each). When resubjected to the original reaction conditions **8** gave a mixture of **6**, **7** and **9** while **9** yielded only **7** indicating that these selenylated phenols are the precursors of the selenylated quinones. The product mixture from **10** was qualitatively identical to that observed from **4**; apparently a phenylselenyl group can be lost during *p*-oxidation as previously reported[5] for the *o*-oxidation.

**Scheme 1.**

Path A (*p*-oxidation)




Path B (*o*-selenylation).



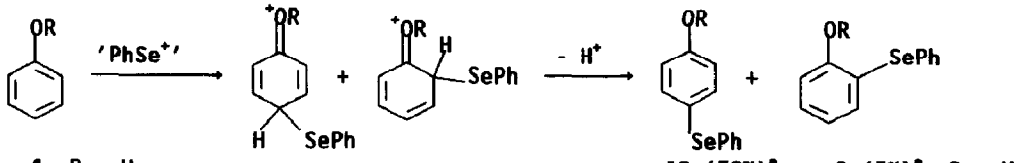
Although a proper kinetic treatment is precluded by the complexity af the reaction system an estimate of the over-all rate of conversion of **1** can be obtained by determining the amount of **1** remaining at a given point of the reaction. A rather precise (±2%) analysis for **1** consists of the extraction from the reaction mixture with aqueous sodium hydrogencarbonate, the reduction with hydrazine in hydrochloric acid and the determination of the amount of **3** formed by the reduction. By this technique the reaction (24°C) of **1** (2 mmol), **3** (0.5 mmol) and **4** (3 mmol) was studied in a series of solvent systems (10 ml each): i) dichloromethane (DCM); ii) DCM-20% AcOH; iii) DCM-20% AcOEt; iv) DCM-20% THF; v) DCM-20% MeOH and vi) DCM-20% DMSO. The results (% residual **1**, time) were: i) 26%, 6 h; ii) 69%, 6 h; iii) 28%, 120 h; iv) 49%, 120 h; v) 34%, 136 h; vi) 69%, 136 h. Although reaction i) proceeds from a suspension of **1** while reactions ii) and iv)-vi) are homogeneous alle five co-solvents strongly suppres the over-all reaction rate. However the ratio of **5** to selenylated products, **6-9**, remained almost constant through the series. These results imply a non-polar rate determining transition state for both the *p*-oxidation and the *o*-selenylation reaction. Moreover the retarding effect appears to reflect the capacity of the co-solvent as a hydrogen bond acceptor, *i.e.* AcOH < AcOEt < MeOH ~ THF < DMSO, and thus indicates the participation of an acidic hydrogen atom.

These observations are in accord with a rate determining ene-reaction in the *p*-oxidation as well as the *o*-selenylation sequence as outlined in Scheme 1. The *p*-quinones, **5**, **6** and **7**, could arise from phenols **4**, **8** and **9**, respectively, by an ene-reaction followed by dehydration to selenoxide, [2,3]-shift and elimination of benzeneselenol (Path A). A similar, but dissociative, ene-reaction of phenols **4** and **8** with benzeneselenenic acid (or a derived Se(II) species) gives the dienone tautomers of **8** and **9**, respectively (Path B).

Additional support for the ene-route to *o*-phenylselenylation is found in the following observations: Anisole (**11**) lacking the proton necessary for the ene-reaction is inert to the mixture of **1** and **3**. Addition of *p*-toluenesulfonic acid (one molar equivalent) to this mixture provides a more efficient phenylselenylating reagent which gives **8** and **10** from phenol as well as 4- and 2-(phenylseleno)anisole (**12**) and (**13**), respectively, from anisole but in both cases with high *p*-selectivity (Scheme 2). These product distributions are similar to the results obtained with (phenylseleno)dimethylsulfonium ion[7] and suggest an unaided electrophilic substitution.

**Scheme 2.**

$$PhSe(OH)_2^+ + PhSeSePh = PhSe^+ + 2\ PhSeOH$$




**4** R = H
**11** R = Me

**10** (72%)[a] **8** (5%)[a] R = H
**12** (85%)[b,c] **13** (2%)[b] R = Me

[a]Isolated yields. [b]Determined by $^{77}Se$ NMR. [c]Isolated (62%) by cryst. from pentane; m.p. 40-42°C (lit.[7]: oil).

Also the above mentioned study of solvent effects indicates the existence of two different selenylation paths. While **10** is observed in all solvents the ratio **10**: **8** increases from 0.05 in pure dichloromethane to 1,0 with THF, to 1,5 with methanol and to 5 with DMSO added. This trend agrees with the expectation that increased solvation, in addition to impeding the non-polar *o*-substitution, facilitates the dipolar *p*-substitution route.

The present results appear to hold a key to the rationalization of several literature observations on phenolic oxidations with **1** and **2**. First the phenylselenylation *o*- to the original hydroxy group is in accord with the ene-mechanism for selenylation. Secondly the ene-mechanism could explain the unique efficiency of indol as a scavenger for selenenic species;[6] this molecule contains a donor-activated carbon atom and a labile N-proton in the correct relation for the ene-reaction. Thirdly the superiority of THF as a solvent for the *o*-oxidation with **2** may be rationalized: This solvent is non-hydroxylic and non-polar and thus should not interfer with the formation of an aryl benzeneseleninate nor with its subsequent [2,3]-shift . On the other hand the first reaction step produces **1** and the second **3** and water as by-products. Consequently hydrolysis[9] followed by *o*-phenylselenylation as well as *p*-oxidation are *enforced competitors* to the *o*-oxidation with **2**, even with complete initial formation of an aryl benzeneseleninate. As shown by the present results the rates of the ene-reactions initiating both of the latter reaction routes are markedly lowered by the presence of THF.

In conclusion the occurrence of ene-routes to *o*-phenylselenylation and *p*-oxidation should be taken into account in the reactions of phenolic substrates with benzeneseleninic derivatives. However, an extrapolation of the present results to other phenolic systems should be carried out with caution. The trade mark of organoselenium chemistry, the high polarizability of the selenium atom, allows the occurrence of simultaneous low-energy reaction paths the balance of which may be determined by minor structural changes.

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*References and notes.*

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8. Compounds **6-10** and **12** were satisfactorily characterized by elemental analysis (C,H), mass spectra, $^{1}H$, $^{13}C$ and $^{77}Se$ NMR spectra.
9. Exchanges among seleninic derivatives are rapid reactions; a $^{77}Se$ NMR experiment showed that the equilibrium concentration of methyl benzeneseleninate was reached in < 10 min after the mixing of **1** and methanol (30°C).

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