Synthesis, structure and reactivity of a selenoxide derived from a bulky selenide: Bis(2,4,6-trimethylphenyl) selenoxide

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Bis(2,4,6-trimethylphenyl) selenoxide has been synthesized by oxidation of bis(2,4,6-trimethylphenyl) selenide with aqueous H$_2$O$_2$ and characterized by elemental analysis and NMR spectroscopy ($^1$H, $^{13}$C{$^1$H} and $^{77}$Se{$^1$H}). The single crystal X-ray diffraction analysis reveals that the selenium atom adopts a trigonal pyramidal configuration. The reactions of bis(2,4,6-trimethylphenyl) selenoxide with various thiols and other proton donor species in CDCl$_3$ have been studied by $^{77}$Se{$^1$H}; NMR spectroscopy that with thiols at room temperature regenerated the selenide. The data indicate that the selenoxide acts as a hydrogen bond acceptor to give Mes$_2$Se=O$^-$HX (Mes = 2,4,6-trimethylphenyl or mesityl) species.

Keywords: Coordination chemistry, Organometallic chemistry, Organoselenium compounds, Selenoxides, NMR spectroscopy, X-ray diffraction

Diorganoselenoxides, R$_2$SeO (R = alkyl or aryl) have been known for more than a century. They have been used as oxygen transfer reagents in organic$^1$ and organometallic$^2$ syntheses and as ligands in coordination chemistry$^3$. They have also been recognized as intermediates in biological antioxidant processes involving enzymes like glutathione peroxidase (GPx)$^4$. Ever since the GPx mimicking antioxidant activity of ebselen, a synthetic organoselenium compound$^5$, has been reported, different families including diorganoselenide, diorganodiselenide, N,Se-heterocycles, selenocysteine derivatives have been designed, synthesized and evaluated for their GPx mimicking action$^6,7$. Several mechanisms for GPx-like catalytic activity have been reported for different classes of organoselenium compounds$^4,7$. Depending on the nature of organoselenium compound, the reactive intermediate formed during the catalytic cycle are selenols (RSeH), selenoxides (R$_2$SeO), cyclic seleninate ester, selenenic acid (RSeOH) and spirodioxaselenourane.

The GPx mimicking activity shown by diorganoselenenides (R$_2$Se) is believed to proceed with the formation of the corresponding selenoxide by oxidation with H$_2$O$_2$ or organo peroxy compounds. The resulting selenoxide reacts with a thiol cofactor to yield presumably an unstable selenenylsulfide (I) which on further reaction with a second thiol molecule regenerates the parent selenide with concomitant formation of disulfide and water$^8$. The intermediate (I) has neither been isolated nor supported by any experimental evidences.

\[
\begin{align*}
R & \quad \text{OH} \\
\text{Se} & \quad \text{SR'}
\end{align*}
\]

With a view to gain further insight on this proposed intermediate (I), a selenoxide with bulky organic group (mesityl) was synthesized and its reactions with different protic ligands have been studied by $^{77}$Se{$^1$H} NMR spectroscopy. Results of this work are reported herein.

Materials and Methods

The commercially available 2,4,6-trimethylaniline and 2,4,6-trimethylbenzenethiol were purchased from Aldrich. Sodium borohydride and elemental selenium were purchased from Fluka. NMR spectra were recorded on a Bruker Avance-II 300 MHz spectrometer operating at 300.13 ($^1$H), 75.47 ($^{13}$C{$^1$H}) and 57.25 MHz ($^{77}$Se{$^1$H}). $^1$H and $^{13}$C{$^1$H} NMR chemical shifts are relative to internal chloroform peak ($\delta = 7.26$ ppm for $^1$H and $\delta = 77.0$ ppm for $^{13}$C{$^1$H}).
for $^{13}\text{C}^{1\text{H}}$ NMR). The $^{77}\text{Se}^{1\text{H}}$ NMR chemical shifts are relative to external diphenyl diselenide in CDCl$_3$ ($\delta$ 463.0 ppm relative to Me$_2$Se (0 ppm). Elemental analyses were carried out on Flash EA 1112 Series CHNS Analyzer. Melting points were determined in capillary tubes and are uncorrected.

Synthesis of bis(2,4,6-trimethylphenyl) selenide

Sodium selenide (Na$_2$Se) was prepared freshly according to literature method employing selenium powder (1.00 g, 12.66 mmol) and NaBH$_4$ (1.44 g, 37.90 mmol) in water under an argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature and then was allowed to warm up to 40 °C for 3 h. After the usual work-up, the crude product was recrystallized from hexane to give cream-colored prisms of the title compound (4.4 g, 50%).

Reactions of bis(2,4,6-trimethylphenyl) selenoxide with 2,4,6-trimethylaniline

In an NMR tube bis(2,4,6-trimethylphenyl) selenoxide (69.7 mg, 0.201 mmol) was dissolved in CDCl$_3$ (0.5 ml). To this solution 2,4,6-trimethylaniline (3.77 g, 27.86 mmol) at 0-5 °C was added, whereupon the pale yellow solution faded to colorless. The reaction mixture was stirred for another 2 h. The reaction was monitored for some time. A similar reaction was carried out with a reduced amount of 2,4,6-trimethylbenzenethiol (15.7 mg, 0.103 mmol). The formation of selenide (I) was observed ($\delta$ 234 ppm). The reaction was monitored for some time. A similar reaction was carried out with a reduced amount of 2,4,6-trimethylbenzenethiol (15.7 mg, 0.103 mmol). The formation of the selenide (I) was observed within 15 min together with a signal for (2). Similar results were obtained when (2) was treated with HSCH$_2$CH$_2$NMMe$_2$. Reactions with other proton donors in stoichiometric quantities were carried out in NMR tubes and were monitored by NMR spectroscopy.

X-ray crystallographic studies

Single crystal X-ray data for (2,4,6-Me$_3$C$_6$H$_2$)$_2$SeO (2) were collected at room temperature (298 ± 2 K) on a Rigaku AFC 7S diffractometer using graphite monochromated Mo-K$_\alpha$ ($\lambda = 0.71069$ Å) radiation so that $\theta_{\text{max}} = 16.4^\circ$. The unit cell parameters (Table 1) were determined from 25 reflections measured by a random search routine. The intensity data were corrected for Lorentz, polarization and absorption effects with an empirical procedure. The structure was solved by direct methods using SHELX-97 and refined by full-matrix least squares methods. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed in their calculated positions. The molecular structures were drawn by ORTEP.

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**Table 1 – Crystal structure refinement data for bis(2,4,6-trimethylphenyl) selenoxide (2)**

<table>
<thead>
<tr>
<th>Chemical formula</th>
<th>C$_6$H$_2$SeO</th>
</tr>
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<tbody>
<tr>
<td>Formula weight (Mr)</td>
<td>333.33</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.40 x 0.20 x 0.05</td>
</tr>
<tr>
<td>Crystal system / space group</td>
<td>Triclinic / P1</td>
</tr>
<tr>
<td>a (Å)</td>
<td>8.0287(11)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>8.3200(19)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>12.530(3)</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>98.020(18)</td>
</tr>
<tr>
<td>$\beta$</td>
<td>107.680(13)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>92.678(14)</td>
</tr>
<tr>
<td>V (Å$^3$)</td>
<td>786.1(3)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>$\mu$ (Mo-K$_\alpha$) mm$^{-1}$ / F (000)</td>
<td>2.382 / 344</td>
</tr>
<tr>
<td>$D_\text{g}$ (g/cm$^3$)</td>
<td>1.408</td>
</tr>
<tr>
<td>Limiting indices</td>
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</tr>
<tr>
<td>$\theta$ Range of data collection (°)</td>
<td>2.67-27.51$^\circ$</td>
</tr>
<tr>
<td>No. of reflections collected</td>
<td>3604</td>
</tr>
<tr>
<td>No. of independent reflections</td>
<td>1623</td>
</tr>
<tr>
<td>Data/Restraints/Parameters</td>
<td>3604/0/187</td>
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<tr>
<td>$R$ indices ($I &gt; 2 \sigma (I)$)</td>
<td>$R_1 = 0.0571$, wR$_2 = 11.37$</td>
</tr>
<tr>
<td>$R$ indices (all data)</td>
<td>$R_1 = 0.1956$, wR$_2 = 14.90$</td>
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<tr>
<td>Goodness-of-fit on $F^2$</td>
<td>0.949</td>
</tr>
<tr>
<td>($\Delta p$)$<em>{\text{max}}$: ($\Delta p$)$</em>{\text{min}}$ (Å$^{-3}$)</td>
<td>0.415; -0.686</td>
</tr>
</tbody>
</table>
Results and Discussion

Reaction of 4-amino-2,4,6-trimethylphenyl diazonium chloride with disodium selenide at 0-5 °C yielded bis(2,4,6-trimethylphenyl) selenide (1) as a cream colored crystalline solid. The oxidation of (1) with hydrogen peroxide yielded colorless compound which on recrystallization from dichloromethane-methanol afforded colorless crystals of the corresponding selenoxide, Mes₂SeO (2). The ¹H and ¹³C{¹H} NMR spectra of (1) and (2) displayed singlets for C-4(Me) and for C-2, 6 (Me) groups. The former resonance in the two compounds is little affected; however, the latter singlet is deshielded in (2) with respect to (1) but appeared at lower frequency in the ¹³C{¹H} NMR spectrum. The C-1 carbon resonance, on the other hand, is deshielded in (2) (δ 135.3 ppm) relative to (1) (δ 129.5 ppm). The ⁷⁷Se{¹H} NMR spectra showed single resonances which appeared in the expected regions.

The molecular structure of bis(2,4,6-trimethylphenyl) selenoxide (2) was established by single crystal X-ray diffraction analysis. The molecule adopts a trigonal pyramidal configuration (Fig. 1). Alternately, the geometry around selenium, considering VSEPR theory, can be considered distorted tetrahedral defined by two carbon atoms of mesityl groups, one oxygen atom and a stereochemically active lone pair of electrons. The average Se-C (1.966 Å) and Se-O (1.650(4) Å) distances are well within the range reported for several R₂SeO compounds (e.g. R = Me, C₆F₅, p-MeOC₆H₄)¹⁴-¹⁶. As a consequence of bulky mesityl groups, the C-Se-C (100.1(2)°) and C-Se-O (105.2(2), 109.5(2)°) angles are opened up as compared to those reported in other diorganoselenoxides, e.g. Me₂SeO (C-Se-C = 95.95(10)°, C-Se-O (average 102.9°)¹⁴ and (p-MeO)C₆H₄-SeO (C-Se-C = 97.21 (9)°; C-Se-O (average 102.68°)¹⁶.

Reactions of (2) with bulky (MesSH) and internally functionalized (Me₂NCH₂CH₂SH) thiols in CDCl₃ were monitored by ⁷⁷Se{¹H} NMR spectroscopy at room temperature. The reaction with an excess of mesitylthiol immediately regenerated (1) (Fig. 2). However, this reaction with one equivalent of mesitylthiol showed resonance for (1) together with unreacted (2). No other resonance for any other species was detected. The spectrum remained unchanged over a period of 1 h. A similar pattern was observed when reaction of (2) was carried out with

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Fig. 1—ORTEP diagram of bis(2,4,6-trimethylphenyl) selenoxide (2). [Selected interatomic parameters: Se(1)-(O)1, 1.650(4); C(1)-Se(1), 1.976(6); C(10)-Se(1), 1.956(6) Å. Bond angles (°): C(1)-Se(1)-C(10), 100.1(2); C(1)-Se(1)-O(1), 109.5(2); C(10)-Se(1)-O(1), 105.2(2); C(2)-C(1)-Se(1), 115.4(4); C(6)-C(1)-Se(1), 123.6(4); C(11)-C(10)-Se(1), 122.3(5); C(15)-C(10)-Se(1), 117.3(5)].

Fig. 2—⁷⁷Se{¹H} NMR spectra (in CDCl₃) of (a) bis(2,4,6-trimethylphenyl) selenide (1), and, (b) its redox interconversion with bis(2,4,6-trimethylphenyl) selenoxide (2).
one equivalent of Me₂NCH₂CH₂SH. These thiols were chosen to stabilize the proposed selenenyl sulfide either through steric crowding (as in the case of MesSH) or through intramolecular hydrogen bonding (as in HSCH₂CH₂NMe₂).

Theoretical calculations on diorganoselenoxide indicate that the selenium-oxygen bond is a highly polarized bond rather than a double bond. Due to this highly polarized nature of Se-O bond, diorganoselenoxides form hydrogen bond with hydrogen bond donor ligands (e.g. H₂O, Ph₃SiOH, Ph₃COH). The overall geometry of selenoxide on complexation with either proton donors or with metal atom does not change significantly except for lengthening of Se-O bond. In hydrogen bonded molecule a slight lengthening has been shown by IR spectroscopy and by X-ray crystallography (e.g. Ph₂SeO and Ph₃SeO₂H₂O; Se-O = 1.660 and 1.669 Å, respectively). In other cases ion pairs, such as [Ph₂SeOH][O₂Stol] are formed.

To assess the possibility of formation of hydrogen bonded species, reactions of (2) with various protic ligands were examined by ⁷⁷Se{¹H} NMR spectroscopy. Treatment of (2) with o-cresol in 1:1 ratio in CDCl₃ showed a ⁷⁷Se{¹H} NMR resonance at δ 900 ppm. Similarly reaction of (2) with benzoic acid showed shielding in ⁷⁷Se{¹H} NMR resonance (δ 896 ppm). In both the cases ⁷⁷Se{¹H} resonances are shielded (11 and 15 ppm) with respect to (2). The same reaction with picolinic acid under similar condition however gave (1). The formation of the latter is rapid in refluxing benzene and slower at RT as shown by the two ⁷⁷Se{¹H} resonances observed at δ 895.5 and 234 ppm. The ¹H NMR spectrum for the reaction at RT showed shielding of OH proton resonance with respect to free picolinic acid (δ OH: 8.90 (for the reaction) and 9.04 (for picolinic acid). In reaction with quinaldic acid, however two selenium containing species existed one showing resonance at δ 895 ppm and another due to (1). Interestingly no change in the ⁷⁷Se{¹H} chemical shift was noticed when (2) was refluxed with pyridine. From these results it can be inferred that with simple protic ligands, a hydrogen bonded species, R₂SeO---H-X (X = o-MeC₆H₄O, PhCOO) is formed but when the protic ligands contain an oxidizable group (e.g. heterocyclic nitrogen in picolinic or quinaldic acid), reduction of selenoxide (2) takes place and in the absence of any proton donor (e.g. pyridine) the selenoxide remains unchanged. It is likely that thiols also form hydrogen bonded species with selenoxide (Scheme 1) which on subsequent reaction with another molecule of thiol yields the parent selenide with concomitant formation of the corresponding disulfide and water.

Proposed mechanism of reduction of H₂O₂ with mesityl thiol

Scheme 1
Supplementary Data

Crystallographic data for the structural analysis of 
[bis(2,4,6-trimethylphenyl) selenoxide] (2) has been deposed with the Cambridge Crystallographic Data Centre, under CCDC No. 799124. Copy of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (int. code) +44 1223-336-033; Email: deposit@ccdc.cam.ac.uk; website: www: http://www.ccdc.cam.ac.uk].

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References