Selenium, the Element of Moon in Life on Earth

Selene: Greek Goddess of the Moon

www.flickr.com
Selenium discovered by Swedish scientist J. J. Berzelius (1817)

Red deposit – remains after the roasting of copper pyrites during $\text{H}_2\text{SO}_4$ manufacturing

Named after Greek mythological Goddess (in Greek, Selene = Moon)
Natural Resources of Se and its stable Isotopes Abundance

Se

Atomic Mass – 79.9165

<table>
<thead>
<tr>
<th>Mass</th>
<th>Natural Abundance</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>0.88</td>
</tr>
<tr>
<td>76</td>
<td>8.95</td>
</tr>
<tr>
<td>77</td>
<td>7.65 (I = ½)</td>
</tr>
<tr>
<td>78</td>
<td>23.51</td>
</tr>
<tr>
<td>80</td>
<td>49.62</td>
</tr>
<tr>
<td>82</td>
<td>9.39</td>
</tr>
</tbody>
</table>

- Minerals containing selenium are very uncommon
- 70th in abundance of the 88 that are present naturally in the earth crust
- Most selenium is recovered as a by-product of processing copper ores (Copper Pyrites)
- $^{77}$Se is NMR active

Allotropes of Selenium

- Grey (trigonal) selenium ($\text{Se}_n$ helical chain polymers)
- Grey (rhombohedral) selenium ($\text{Se}_6$ molecules)
- Three deep-red (monoclinic) forms ($\alpha$, $\beta$, and $\gamma$-selenium containing $\text{Se}_8$ molecules)
- Amorphous red selenium
- Black vitreous selenium
- Most thermodynamically stable and the densest form: gray (trigonal)

http://www.chemistryexplained.com/A-Ar/Allotropes.html
Selenium chemistry

- Large, soft atom, much softer than sulfur

- Big, squishy atom; its electron clouds large, diffuse and easily distorted

- Nucleus exerts little effect on what happens at the periphery

- Means Se can spread its electron over many neighbors

- Dual nature; ability to donate electrons (metallic) and take electrons (nonmetallic) metalloid
### Dissociation Energies (kcal/mol)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dissociation Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}_2\text{O}$</td>
<td>119</td>
</tr>
<tr>
<td>$\text{H}_2\text{S}$</td>
<td>93</td>
</tr>
<tr>
<td>$\text{H}_2\text{Se}$</td>
<td>75</td>
</tr>
<tr>
<td>$\text{H}_2\text{Te}$</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{RS}^-$</td>
<td>8.5</td>
</tr>
<tr>
<td>$\text{RSe}^-$</td>
<td>5.2</td>
</tr>
</tbody>
</table>

~ Physiological pKa

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Cysteine (Cys)

\[
\text{H}_2\text{N} \quad \text{SH} \\
\quad \text{COOH}
\]

Selenocysteine (Sec)

\[
\text{H}_2\text{N} \quad \text{SeH} \\
\quad \text{COOH}
\]
Importance of Selenium and its Derivatives

Materials Chemistry

✓ Se
✓ Metal chalcogenides (CdSe) - Semiconductors

Ligands in catalysis
Selenium in Biology

Selenium Toxicity

- **Selenosis**
  - High blood levels of selenium (greater than 100 μg/dL)
  - Symptoms - Gastrointestinal upsets, hair loss, white blotchy nails, garlic breath odor, fatigue, irritability, and mild nerve damage

- **Blind Staggers**
  - Acute selenium poisoning in cows and sheep caused by ingestion of plants with high selenium content

- **Alkali Disease**
  - Acute selenium poisoning in Cattle (Moxon, 1937)

Marco Polo (1254–1324) writes for Kublai Khan in his travelogue into China about poisonous plants that animals ate and shed their hooves
Selenium deficiency (1930, China)

- Keshan disease, which results in an enlarged and poor heart function
- Hypothyroidism (worsens iodine deficiency)
- Weakens immune system
Selenium Supplements

Boost Your Immune System with Selenium

Maximum doses: 400 μg per day

- Serving Size: 2 Droppers (2 mL) daily in water or juice as maintenance
- Servings Per Container: 120

http://www.mineralifeonline.com/pd-selenium-8oz.cfm
ROS Generating and Scavenging Systems

- ONOO$^-$
- HOCl
- $\text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{O}$
- $\text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{O}$
- MPO - Myeloperoxidase

Oxidative Stress

- Catalase
- GPx
- SOD
- lactoferrin
- Fe$^{2+}$
- Fe$^{3+}$
- *OH
- oxidation
- nitration
- nitrosation
- lipid peroxidation

Antioxidant enzymes

H$_2$O $\rightarrow$ O$_2$ $\rightarrow$ O$_2^-$ $\rightarrow$ H$_2$O$_2$ $\rightarrow$ *OH $\rightarrow$ ONOO$^-$
Reactive Oxygen Species (ROS)

- Damage of cell membranes
- DNA cleavage
- Guanine Oxidation
- Neurodegenerative diseases like Alzheimer, Parkinson’s
- Ageing
- Inflammation
- Certain Cancers
The defense system

- **Cellular thiols (Glutathione, thioredoxine)** - Redox Buffers

- **Antioxidants**
  - Ascorbic acid
  - Vitamin E and other Phenolic compounds

- **Antioxidant enzymes**
  - **Catalase** is a hemeprotein
    - Catalyzes the disproportion of $H_2O_2$
  - **Superoxide dismutase**: Cu-Zn-SOD, Fe-SOD, Mn-SOD
    - Catalyzes the disproportionation of $HO_2$
  - **Sulfiredoxine** is a cysteine containing enzyme
    - Reduction of $H_2O_2$
  - **Glutathione peroxidase** is a selenocysteine containing enzyme
    - Reduction of $H_2O_2$
Selenoenzymes (14 discovered)

- Selenium Biochemistry Emerged in 1973, after the discovery two bacterial enzymes

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formate dehydrogenases</td>
<td>HCOOH $\rightarrow$ CO$_2$ + 2H$^+$ 2e$^-$</td>
</tr>
<tr>
<td>Glysine reductase</td>
<td>Gly + 2e$^-$ + 4H$^+$ + ADP + P$_i$ $\rightarrow$ Acetate + NH$_4^+$ + ATP</td>
</tr>
<tr>
<td>Glutathione peroxidases (GPx)</td>
<td>H$_2$O$_2$ + 2GSH $\rightarrow$ 2H$_2$O + GSSG</td>
</tr>
<tr>
<td>Phospholipide-hydroperoxide-GPx</td>
<td>ROOH + 2GSH $\rightarrow$ ROH + H$_2$O + GSSG</td>
</tr>
<tr>
<td>Type-I iodothyronine deiodinase</td>
<td>L-Thyroxine + 2e$^-$ + H$^+$ $\rightarrow$ 3,5,3'-iodothyronine + I$^-$</td>
</tr>
<tr>
<td>Thioredoxin reductase</td>
<td>NADPH + Trx$<em>{ox}$ $\rightarrow$ NADP+ Trx$</em>{red}$</td>
</tr>
<tr>
<td>Selenophosphate synthetase</td>
<td>HSe$^-$ + ATP $\rightarrow$ HSe-PO$_3$H$_2$ + AMP + P$_i$</td>
</tr>
<tr>
<td>Selenoprotein P</td>
<td>Antioxidant?</td>
</tr>
</tbody>
</table>

- GSH - Reduced glutathione
- ROOH - Lipid hydroperoxide
- Trx - Thioredoxin
The thyroid is one of the largest endocrine glands in the body.

This gland is found in the neck inferior (below) to the thyroid cartilage (also known as the Adam's apple in men) and at approximately the same level as the cricoid cartilage.

The thyroid controls how quickly the body uses energy, makes proteins, and controls how sensitive the body should be to other hormones.

Ratio of $\text{T4}/\text{T3}$ released in blood = 20/1
Catalytic Cycle of Iodothironine Deiodinase


➤ Thiol cofactor
   Is not yet identified
Glutathione Peroxidase (GPx)

- Cytosolic GPx (cGPx) - uses GSH as co-substrate
- Reduction of hydrogen peroxides and organic peroxides

\[
\text{ROOH} + 2\text{GSH} \xrightarrow{\text{GPx}} \text{ROH} + \text{GSSG} + \text{H}_2\text{O}
\]

- Tetramer of four identical subunits; each subunit contains a selenocysteine residue
- Catalytic triad - SeCys, Gln, Trp - Selenolate is highly stabilized

\[
\gamma\text{-Glu-Cys-Gly} \quad \text{(GSH)}
\]
Structure of Glutathione Peroxidase

Tetramer of four identical subunits; each subunit (M.W. 21,000 Dalton) contains a selenocysteine residue at the active site


Catalytic Activity

- **UV Method using Benzenethiol as GSH Alternative**

- **Initial reduction rates of hydrogen peroxides**

- **UV absorption increases at 305 nm due to the formation of PhSSPh**

\[ C = (\varepsilon_1 C_0 - 2a)/(\varepsilon_1 - 2\varepsilon_2) \]

\[ C = \text{conc. of PhSH}, \; C_0 = \text{Initial conc. of PhSH}, \; a = \text{absorption} \]

\[ \varepsilon_1 = \text{Molar extinction coefficient of PhSSPh} = 1.24 \times 10^3 \; M^{-1}cm^{-1} \]

\[ \varepsilon_2 = \text{Molar extinction coefficient of PhSH} = 9 \; M^{-1}cm^{-1} \]

Since \( \varepsilon_1 \gg \varepsilon_2 \), \[ C = C_0 - 2a/\varepsilon_1 \]

* Initial reduction rates \( 1/v \) vs \( 1/C \) plots - Lineweaver-Burk plots

* Comparison of \( v_0 \) at PhSH 1 mM level
Catalytic Activity

- Lineweaver-Burk plots obtained for 0.01 mM of 18. The initial $H_2O_2$ concentration was fixed to 3.75 mM. The initial PhSH concentration ($C_0$) was 1 mM

- **Best Fit** : $Y = 4.73111X + (-3.04687)$

- **Initial Reduction Rate** ($v_0$) = 593.74 $\mu$m min$^{-1}$. This $v_0$ was obtained by substituting $X = 1$ mM in the above linear equation.
**GPx-Like Activity of Chiral Ferrocenyl Selenium Derivatives**

- Initial Reduction Rates ($v_0$) of $H_2O_2$ (3.75 mM) with PhSH (1 mM) in methanol in the presence of various selenium catalysts (0.01 mM)

<table>
<thead>
<tr>
<th>Catalysts</th>
<th>$v_0$ $\mu$M min$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0.55 (0.18)</td>
<td></td>
</tr>
<tr>
<td>3.39 (0.37)</td>
<td></td>
</tr>
<tr>
<td>3.16 (0.52)</td>
<td></td>
</tr>
<tr>
<td>3.83 (0.32)</td>
<td></td>
</tr>
<tr>
<td>5.78 (0.79)</td>
<td></td>
</tr>
<tr>
<td>28.38 (3.88)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Catalysts</th>
<th>$v_0$ $\mu$M min$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>36.10 (0.12)</td>
<td></td>
</tr>
<tr>
<td>574.01 (23.98)</td>
<td></td>
</tr>
<tr>
<td>466.49 (28.26)</td>
<td></td>
</tr>
</tbody>
</table>

Inactive Catalysts

- [R, S; R, S] (+)
- [S, R; S, R] (-)
Intermediates and Catalytic Cycle

✓ Nucleophilic attack by thiol at sulfur and not at selenium
Intramolecular Interaction and Thiol Exchange

- **Strong Se⋯N interaction**
  - Does not favor selenol formation
  - Thiol exchange occurs

- **Weak Se⋯N interaction**
  - Favors selenol formation
  - No thiol exchange

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Glutathione Peroxidase-like Antioxidant Activity of Diaryl Diselenides: A Mechanistic Study

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Introduction

Glutathione peroxidase (GPx) is a well-known selenoenzyme that functions as an antioxidant. This selenoprotein catalyzes the reduction of harmful peroxides by glutathione and protects the lipid membranes and other cellular components against oxidative damage. The enzyme catalytic site includes a selenocysteine residue in which the selenium undergoes a redox cycle involving the selenol (ESeH) as the active form that reduces hydrogen peroxides and organic peroxides. The selenol is oxidized to selenenic acid (ESeOH), which reacts with reduced glutathione (GSH) to form selenenyl sulfide adduct (ESeSG). A second glutathione then regenerates the active form of the enzyme by attacking the ESeSG to form the oxidized glutathione (GSGG) (Scheme 1). Thus, in the overall process as a selenol, the selenium was found to exist as a seleninic acid [E-SeO-H] in the crystals of human plasma GPx. This suggests

![Scheme 1. Proposed Catalytic Mechanism of Glutathione Peroxidase](image-url)
Acknowledgements

- Prof. Ray J. Butcher
- Prof. N. S. Punekar

- DST, CSIR, BRNS
- Department of Chemistry
- SAIF and IRCC
- IIT Bombay
UGA - Codon

- Uracil-Guanine-Adenine (UGA)

- This codon is generally a stop codon

- The UGA codon is made to encode selenocysteine by the presence of a SECIS element (SelenoCysteine Insertion Sequence) in the mRNA
The cover picture shows the Earth rising above the Moon’s horizon taken in June 1969 from the Apollo 11 spacecraft. As Selene is the goddess of the moon in Greek mythology, some very recent news on selenium chemistry is shown on the Post-It and much more is contained in the Microreview entitled Recent Advances in Organoselenium Chemistry by T. Wirth et al. on p. 1649ff. The X-ray structures of a selenium-containing macrocycle (left structure, Kamigata et al.\textsuperscript{13}) and a selenirenium ion (right structure, Poleschner et al.\textsuperscript{67b}) shown in the foreground are taken from the literature references.
Application of Organoselenium Compounds in Organic Synthesis

Diphenyl Diselenide

CAS Number: 1666-13-3
Commercial

In-Situ $^{77}$Se NMR Studies/Oxazoline Derivatives

Thiol exchange