Chemistry of the Thyroid Gland: Thyroid Hormones and Antithyroid Drugs

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Thyroid Hormone Synthesis

Tyrosine → TPO → Tyrosine Hydroxylase → Dihydroxytyrosine → TPO → Iodination → Iodothyronine → Thyroid Hormone

Iodine Recommended Daily Intake

Hyperthyroidism - anti-thyroid drugs

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Selenenyl Iodide – Non-existent Compound?

For a long time, uncharged covalent selenium iodides have been regarded as non-existent.

W. E. Dasent, Nonexistent compounds, Marcel Dekker, New York (1965).

\[
\begin{align*}
\text{Isodesmic Equation} & \\
\text{Se-Se} + \text{I-I} & \rightleftharpoons 2 \text{Se-I} \\
172 + 150 & = 322 \text{ kJ/mol} \\
2 \times 150 & = 300 \text{ kJ/mol}
\end{align*}
\]


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Anti-thyroid Drugs – Treatment for Hyperthyroidism

- Inhibition of thyroid peroxidase (TPO) by coordination to iron
- Donor-acceptor complexes with molecular iodine
- PTU and MTU – Block T4 \( \rightarrow \) T3 conversion (ID-I)

Interactions of Antithyroid Drugs with Iodine


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Se-MMI – Tautomeric Structures

\[ \begin{align*}
(1a) & \quad E = S \\
(2a) & \quad E = Se
\end{align*} \]

\[ \begin{align*}
(1b) & \quad E = S \\
(2b) & \quad E = Se
\end{align*} \]

E = O, does not exist; E = Te, very unstable

13-C NMR: \( ^1J_{se-c} = 220 \text{ Hz} \)

C-Se single bond, \( ^1J_{se-c} \approx 110-140 \text{ Hz} \); C=Se double bond, \( ^1J_{se-c} \approx 220-240 \text{ Hz} \)


Interactions of Antithyroid Drugs with Iodine

Hydrolysis by Metallo-β-Lactamases

Cephalothin

Cefamandole

Cefazolin

Moxalactam

Moxalactam

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Tautomeric Forms of MTT and MDT

Thyroid Gland

Anti-thyroid drugs

Tyrosine

Thyroxine (T4)


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Inhibition of LPO-catalyzed Iodination


<table>
<thead>
<tr>
<th>No</th>
<th>Compound</th>
<th>Structure</th>
<th>IC$_{50}$ values (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MMI</td>
<td><img src="image1" alt="Structure of MMI" /></td>
<td>4.09 ± 0.56</td>
</tr>
<tr>
<td>2</td>
<td>MTT</td>
<td><img src="image2" alt="Structure of MTT" /></td>
<td>7.29 ± 0.77</td>
</tr>
<tr>
<td>3</td>
<td>MDT</td>
<td><img src="image3" alt="Structure of MDT" /></td>
<td>3.04 ± 0.65</td>
</tr>
</tbody>
</table>

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Tamilselvi, A.; Mugesh, G.


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Sulfur-Iodine Interactions

Thione-Iodine complexes (a) DMETT.I$_2$, (b) MMI.I$_2$, (c) MDT.I$_2$, (d) PTU-I$_2$, (e) MTDT-I$_2$, (f) free iodine

Tamilselvi, A.; Mugesh, G.  
Thyroid hormone binding in Transthyretin (TTR)

- Halogen binding sites P1, P2, P3 and their symmetry related pairs P1', P2', P3' in thyroid hormone transport protein Transthyretin.
- $T_4$ (ball and stick - red) binding is greatly influenced by charged residues Lys15 and Glu54 in P1 pocket.
Hydrogen bonding with Lys15 and Glu54

4-phenolic hydroxyl group forms water mediated hydrogen bond to Ser117.


Halogen bonding in human TTR-T4 complex

- 5'-I atom of phenolic ring interacts with Leu110 backbone N atom in P3 pocket (I…..N, 3.5 Å)
- 3'-I atom interacts with the carbonyl oxygen of Ala109 in P2 pocket formed by other monomer of the protein (I…..O, 2.8 - 3.3 Å)
Binding of T3 with TTR

3'-I interacts directly with Ser117 side chain hydroxyl (I….O, 2.86 Å) although a series of contacts with 108-110 and 117-119 residues are possible with distances between 2.86 Å & 3.72 Å.

Superimposed structure of T4 (thick line) and T3 (light line) bound to human TTR. Amino acids are represented by single letter codes.

*J. Biol. Chem. 1992, 267, 1, 353-357.*
The binding affinity decreases upon removal of iodines.

*J. Biol. Chem. 1992, 267, 1, 353-357.*
The entire body metabolism depends on the amount of thyroid hormones produced. INACTIVATION produces the active thyroid hormone. INACTIVATION protects tissues from an excess of thyroid hormone.


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Iodothyronine Deiodinase Mimics


- Enol-keto tautomerism is required
- Outer ring iodines are more reactive than the inner-ring ones
Iodothyronine Deiodinase Mimics

- Physiologically relevant conditions
- Highly specific to inner-ring deiodination
- Quantitative conversion of T4 to rT3 in 30 h

The rate of deiodination is highly pH dependent.

A thiol adjacent to selenol is important for the deiodination.

Replacing -SeH with -SH reduces the activity.
Positive charge on inner–ring iodine decreases upon deiodination of T4.

Halogen bonding may play an important role in the inner-ring deiodination.
Iodothyronine Deiodinase Mimics

Does an increase in reactivity change the selectivity??

Manna and Mugesh, Unpublished results.

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An increase in the reactivity does not change the selectivity, but it leads to further deiodination.

rT3 undergoes a further deiodination to form T2.

Manna and Mugesh, Unpublished results.
Iodothyronine Deiodinase Mimics

Manna and Mugesh, Unpublished results.

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Effect of Se…N interactions on $^{77}$Se NMR
### DFT Calculations

![Chemical Structure](image)

#### Table 1: Calculated Bond lengths and angles for different compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>$r_{\text{Se1-Se2}}$ (Å)</th>
<th>$r_{\text{Se2-N}}$ (Å)</th>
<th>$\angle \text{Se1-Se2-N}$ (°)</th>
<th>$q_{\text{Se1}}$</th>
<th>$q_{\text{Se2}}$</th>
<th>$E$ (kcal.mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.467</td>
<td>2.337</td>
<td>167.14</td>
<td>0.133</td>
<td>0.450</td>
<td>21.16</td>
</tr>
<tr>
<td>2</td>
<td>2.472</td>
<td>2.327</td>
<td>167.14</td>
<td>0.129</td>
<td>0.452</td>
<td>37.16</td>
</tr>
<tr>
<td>3</td>
<td>2.471</td>
<td>2.337</td>
<td>167.00</td>
<td>0.130</td>
<td>0.448</td>
<td>37.75</td>
</tr>
<tr>
<td>4</td>
<td>2.495</td>
<td>2.250</td>
<td>167.34</td>
<td>0.104</td>
<td>0.477</td>
<td>47.51</td>
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<tr>
<td>5</td>
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<td>2.629</td>
<td>164.65</td>
<td>0.172</td>
<td>0.294</td>
<td>14.79</td>
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<tr>
<td>6</td>
<td>2.431</td>
<td>2.593</td>
<td>165.08</td>
<td>0.165</td>
<td>0.294</td>
<td>16.61</td>
</tr>
<tr>
<td>7</td>
<td>2.432</td>
<td>2.586</td>
<td>165.46</td>
<td>0.164</td>
<td>0.290</td>
<td>16.91</td>
</tr>
<tr>
<td>8</td>
<td>2.434</td>
<td>2.583</td>
<td>164.71</td>
<td>0.162</td>
<td>0.289</td>
<td>17.37</td>
</tr>
</tbody>
</table>

Geometry optimization: B3LYP/6-31+G**; NBO analyses: B3LYP/6-311++G**

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### DFT Calculations

<table>
<thead>
<tr>
<th>Compound</th>
<th>$r_{\text{Se-S}}$ (Å)</th>
<th>$r_{\text{S-N}}$ (Å)</th>
<th>$&lt;\text{Se-S-N}$ (°)</th>
<th>$q_{\text{Se}}$</th>
<th>$q_{\text{S}}$</th>
<th>$E$ (kcal.mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>2.924</td>
<td>2.549</td>
<td>172.15</td>
<td>0.268</td>
<td>0.252</td>
<td>12.77</td>
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<tr>
<td>10</td>
<td>2.293</td>
<td>2.557</td>
<td>172.13</td>
<td>0.268</td>
<td>0.251</td>
<td>12.44</td>
</tr>
<tr>
<td>11</td>
<td>2.294</td>
<td>2.552</td>
<td>172.13</td>
<td>0.268</td>
<td>0.2578</td>
<td>12.67</td>
</tr>
<tr>
<td>12</td>
<td>2.301</td>
<td>2.518</td>
<td>172.11</td>
<td>0.258</td>
<td>0.253</td>
<td>13.97</td>
</tr>
<tr>
<td>13</td>
<td>2.284</td>
<td>2.734</td>
<td>168.2</td>
<td>0.271</td>
<td>0.165</td>
<td>7.75</td>
</tr>
<tr>
<td>14</td>
<td>2.289</td>
<td>2.688</td>
<td>168.94</td>
<td>0.264</td>
<td>0.164</td>
<td>9.23</td>
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<tr>
<td>15</td>
<td>2.293</td>
<td>2.659</td>
<td>169.38</td>
<td>0.260</td>
<td>0.161</td>
<td>10.10</td>
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<tr>
<td>16</td>
<td>2.287</td>
<td>2.719</td>
<td>168.15</td>
<td>0.267</td>
<td>0.162</td>
<td>8.68</td>
</tr>
</tbody>
</table>

Geometry optimization: B3LYP/6-31+G**; NBO analyses: B3LYP/6-311++G**
## DFT Calculations

**Compound** | $r_{S-Se}$ (Å) | $r_{Se-N}$ (Å) | $<$S-Se-N ($^\circ$) | $q_S$ | $q_{Se}$ | E (kcal.mol$^{-1}$) | $n_N \rightarrow \sigma^{*}\text{S-Se}$
---|---|---|---|---|---|---|---
17 | 2.372 | 2.284 | 165.94 | 0.017 | 0.518 | 41.70 |
18 | 2.377 | 2.273 | 165.95 | 0.012 | 0.522 | 43.70 |
19 | 2.376 | 2.283 | 166.00 | 0.012 | 0.519 | 40.85 |
20 | 2.394 | 2.229 | 166.11 | 0.003 | 0.537 | 49.94 |
21 | 2.318 | 2.582 | 164.54 | 0.054 | 0.357 | 16.72 |
22 | 2.322 | 2.557 | 164.74 | 0.049 | 0.357 | 18.96 |
23 | 2.322 | 2.556 | 164.97 | 0.050 | 0.355 | 18.20 |
24 | 2.324 | 2.549 | 164.28 | 0.047 | 0.351 | 18.78 |

**Geometry optimization**: B3LYP/6-31+G**; **NBO analyses**: B3LYP/6-311++G**

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Thank You

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Interactions of Antithyroid Drugs with Iodine

Far-IR spectra

141: $\nu$(I-I) stretching vibration mode.

Di-iodine vapor gives a strong band at 216, which appears at 180 in the solid state.

This band shifts to lower wavenumbers upon coordination to a donor atom, reflecting a reduction in the I-I bond order.


FT-Raman spectra

$\Gamma^{-}$ can exist as a real $\Gamma^{-}$ entity or an $\Gamma^{-}\cdot I_{2}$ adduct.

110: normally attributed to the symmetric stretching of $\Gamma^{-}$ – symmetric ion – one Raman active band.

143: the anti-symmetric stretching may become Raman active.