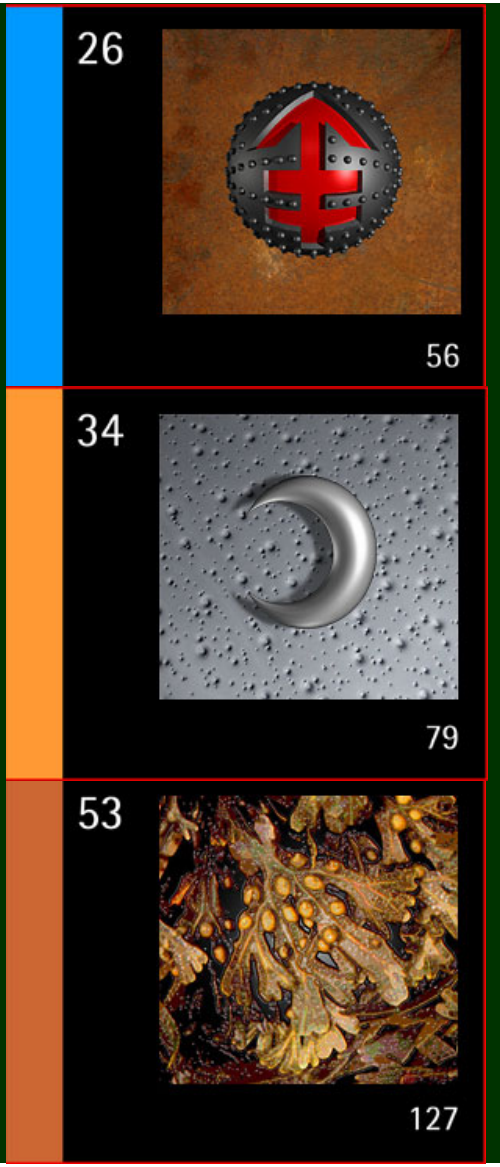
Chemistry of the Thyroid Gland: Thyroid Hormones and Antithyroid Drugs



G. Mugesh
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Hormones and Thyroid Gland

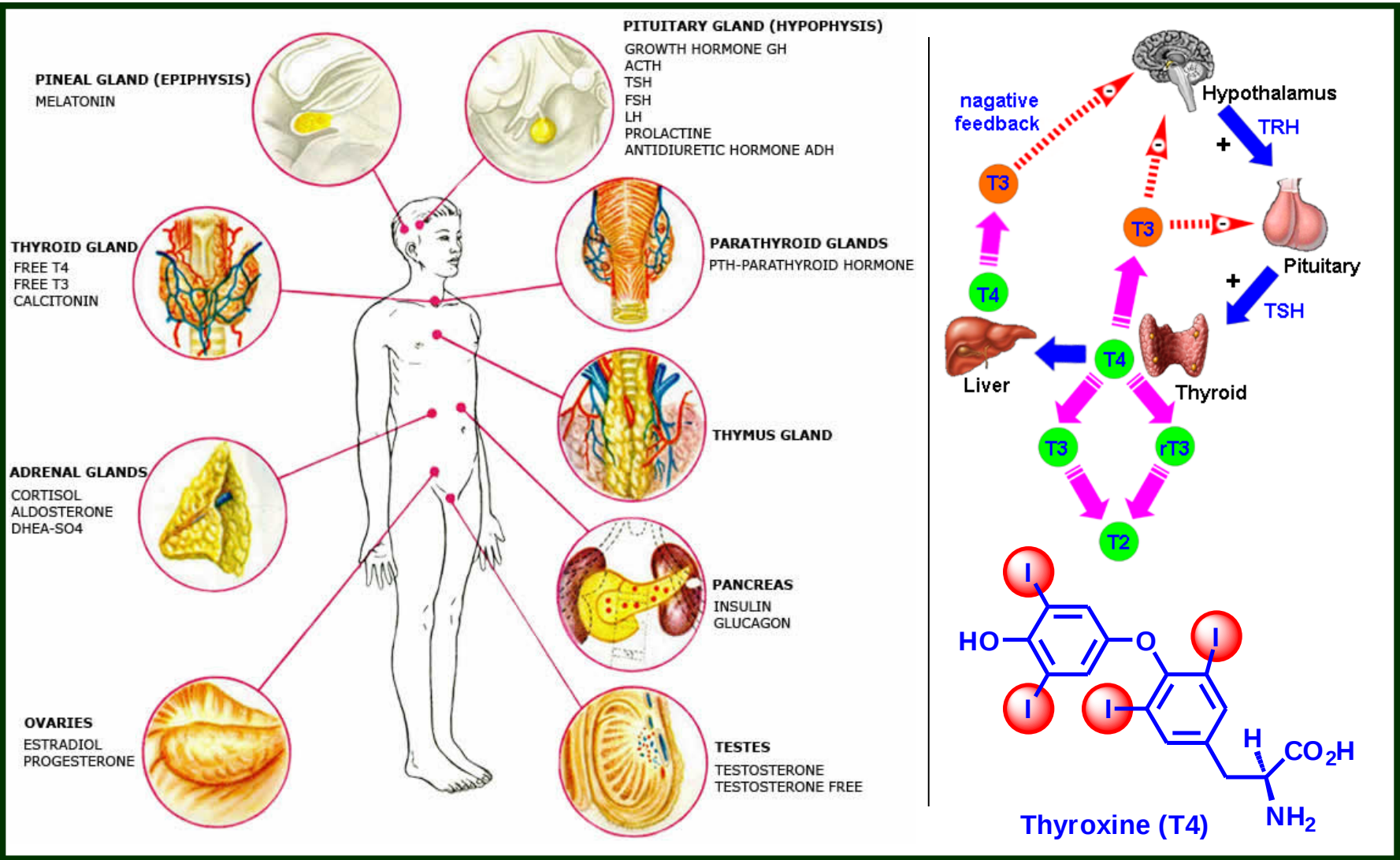
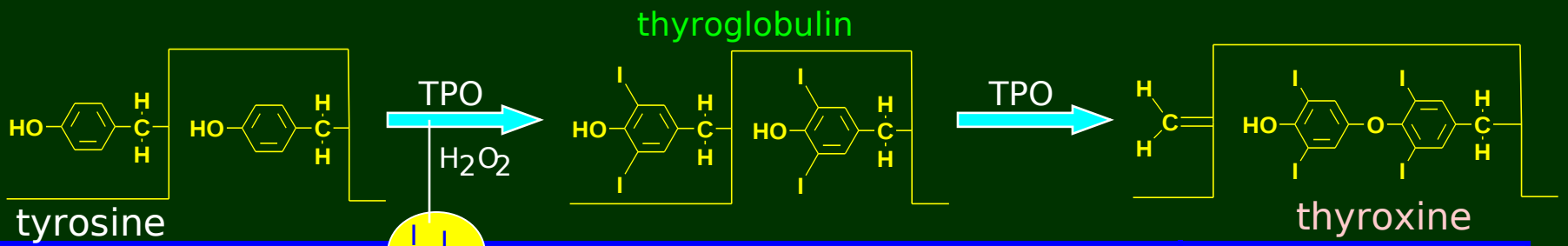
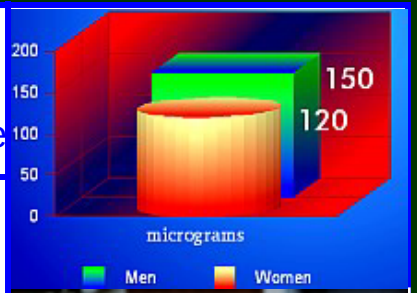


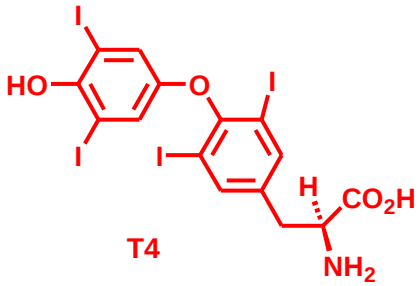
Image taken from: http://www.biodiagnostiki.com

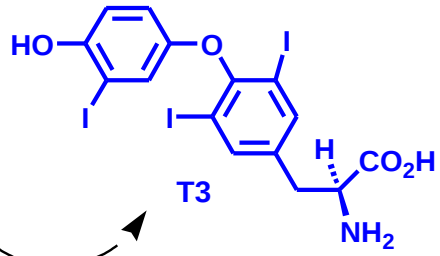
Thyroid Hormone Synthesis



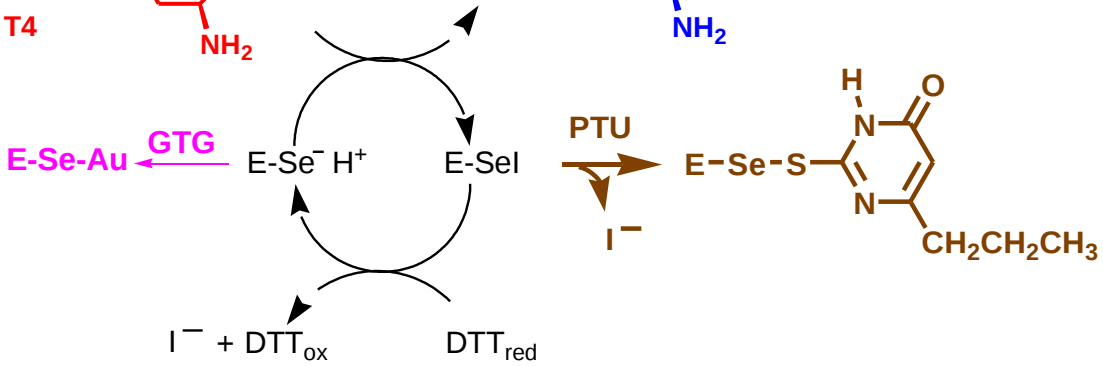
IODINE
Recommended Daily Intake







Thyroid



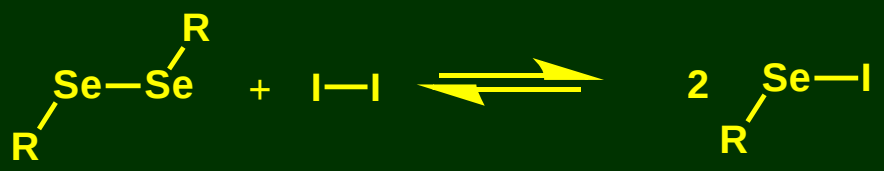
Hyperthyroidism – anti-thyroid drugs

Selenenyl Iodide – Non-existent Compound?

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

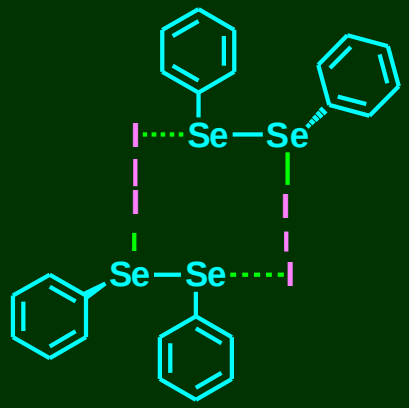
W. E. Dasent, Nonexistent compounds, Marcel Dekker, New York (1965) .

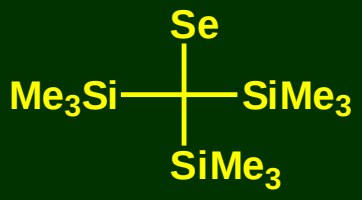
Isodesmic Equation



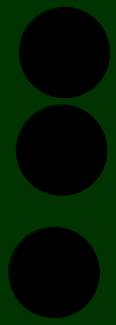
172 + 150 = 322 kJ/mol

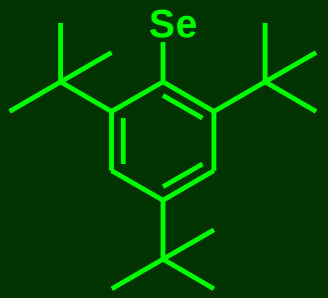
2 x 150 = 300 kJ/mol



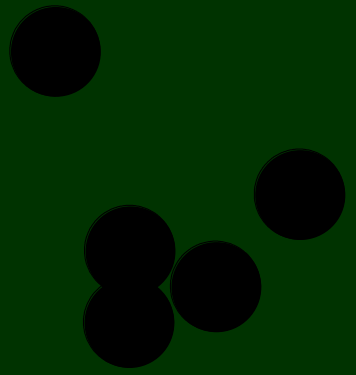


trisyl





supermesityl

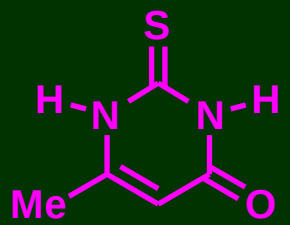


du Mont, et al. *Angew. Chem. Int. Ed.* 1987, 26, 780.

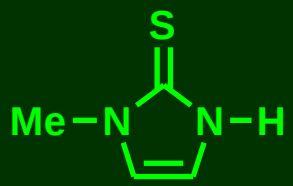
Anti-thyroid Drugs – Treatment for Hyperthyroidism

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

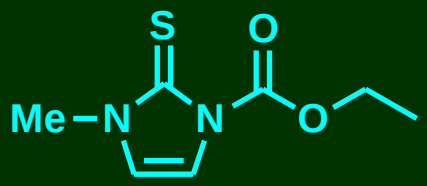
PTU



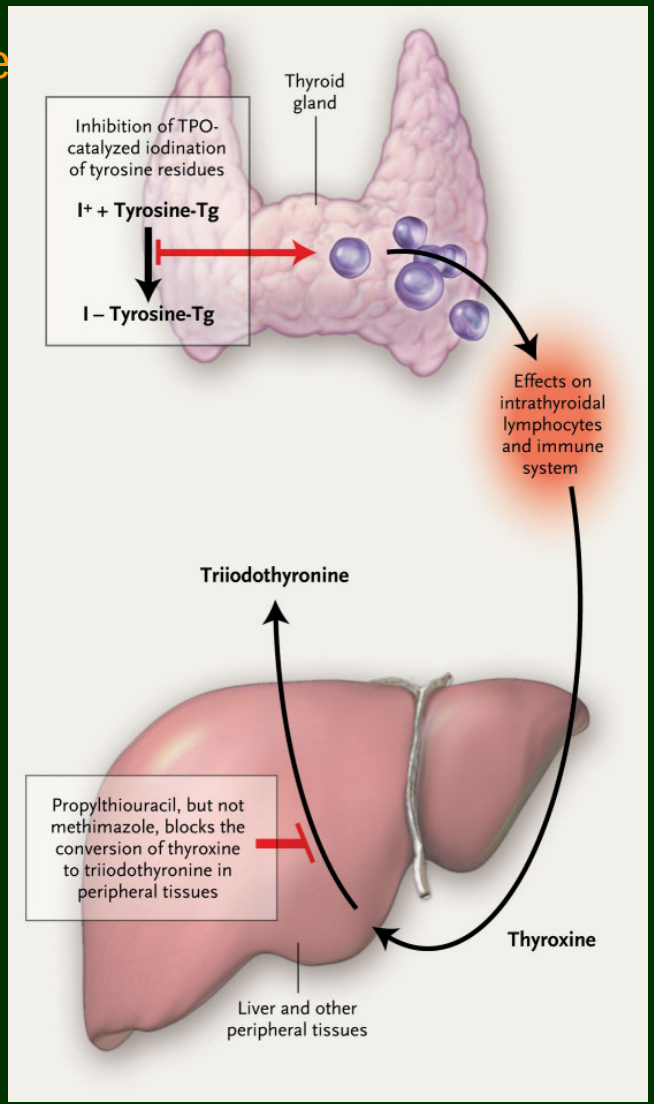
MTU



MMI

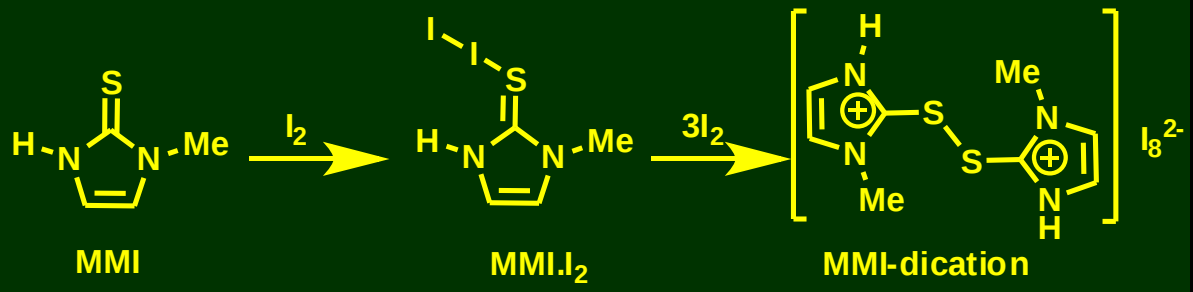


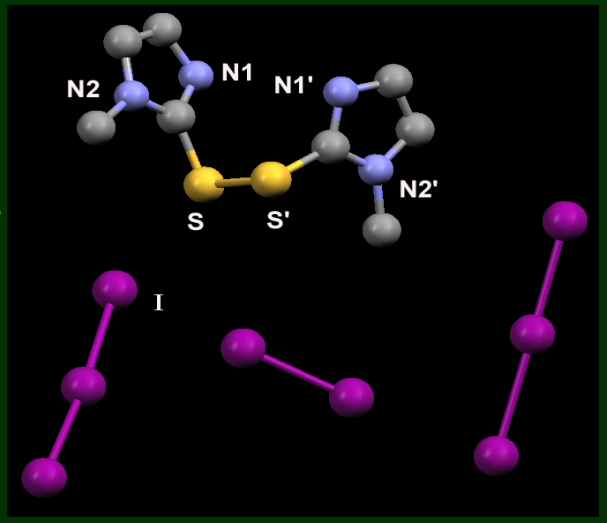
CBZ



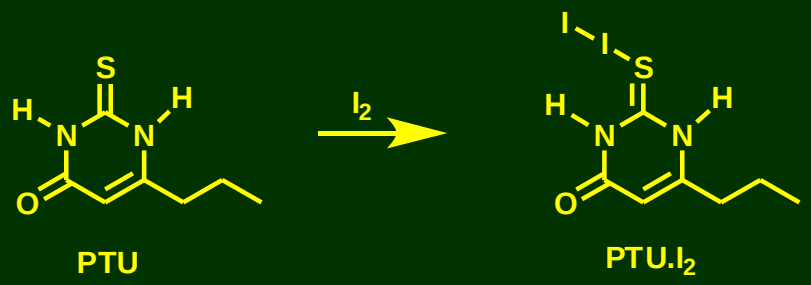
Cooper, D. S. *N. Engl. J. Med. 2005, 352, 905.*

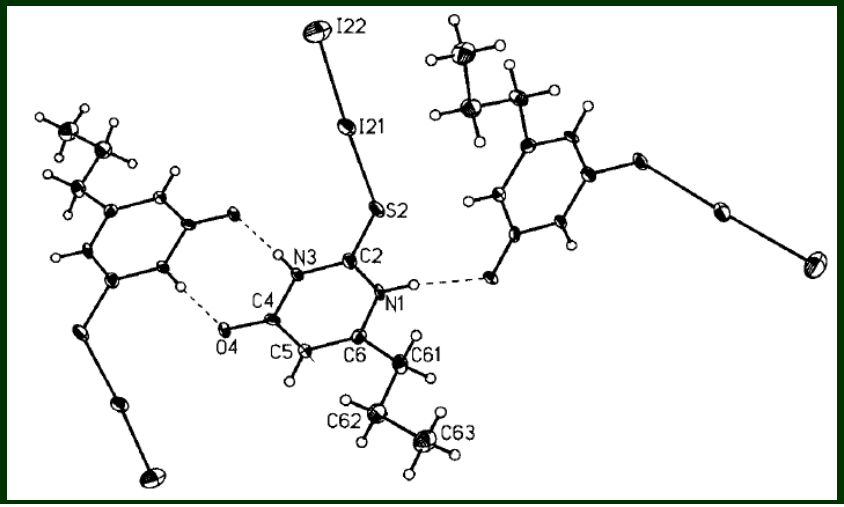
Interactions of Antithyroid Drugs with Iodine





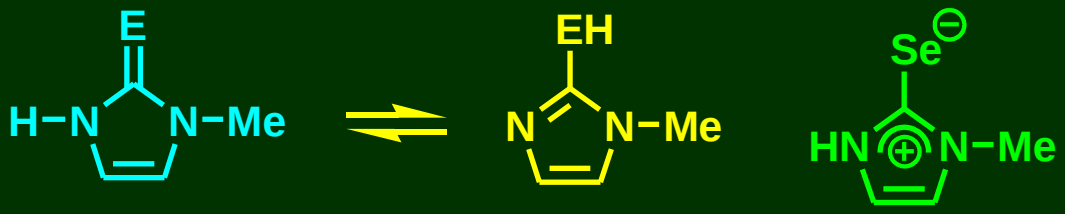
Isaia *et al.* *J. Am. Chem. Soc.* 2002, *124*, 4538.
J. Med. Chem. 2008, 51, 4050.





Hadjiliadis *et al.* *Eur. J. Inorg. Chem.* 2003, 1635.

Se-MMI – Tautomeric Structures

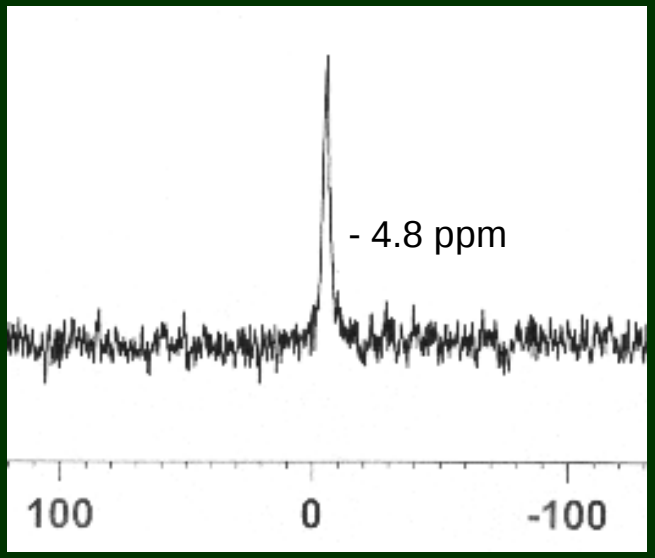


(1a) E = S **(1b) E = S**

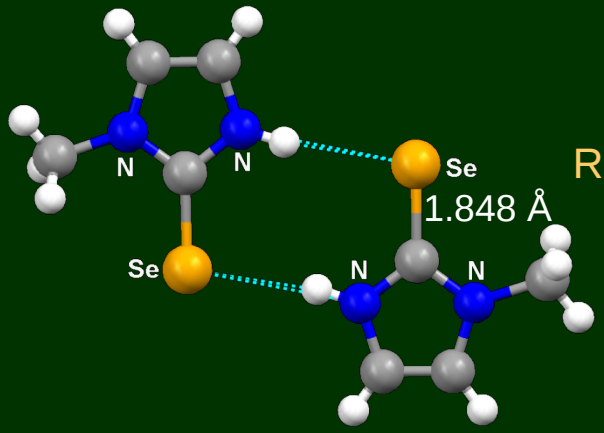
(2a) E = Se **(2b) E = Se**

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

13-C NMR: $^{1}J_{Se\text{-}C}$ = 220 Hz



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

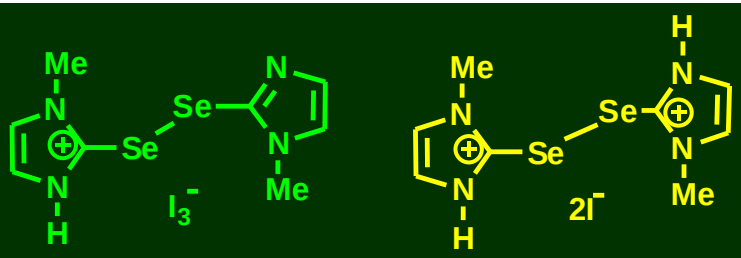


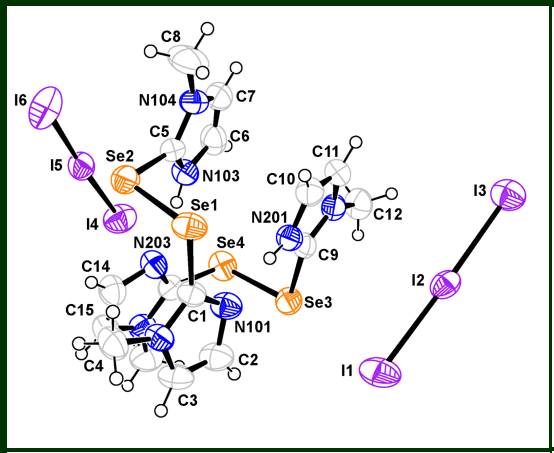
Roy, Nethaji & Mugesh, *J. Am. Chem. Soc.* 2004, *126*, 2712.

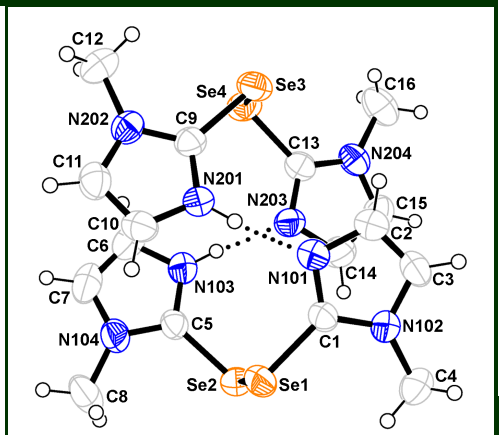
Roy & Mugesh, *J. Am. Chem. Soc.* 2005, *127*, 15207.

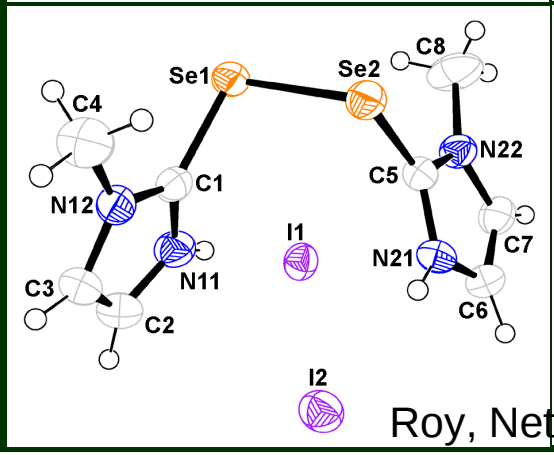
Roy, Das & Mugesh, *Inorg. Chim. Acta.* 2007, *360*, 303.

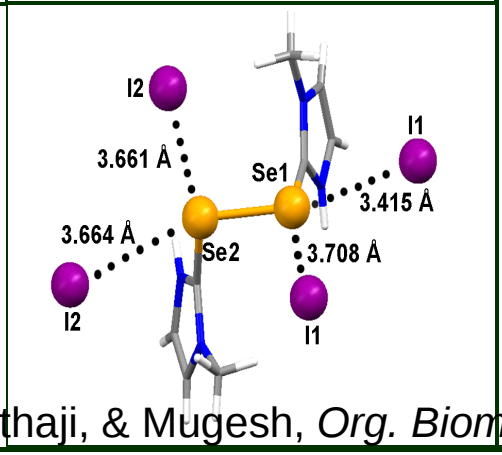
Interactions of Antithyroid Drugs with Iodine

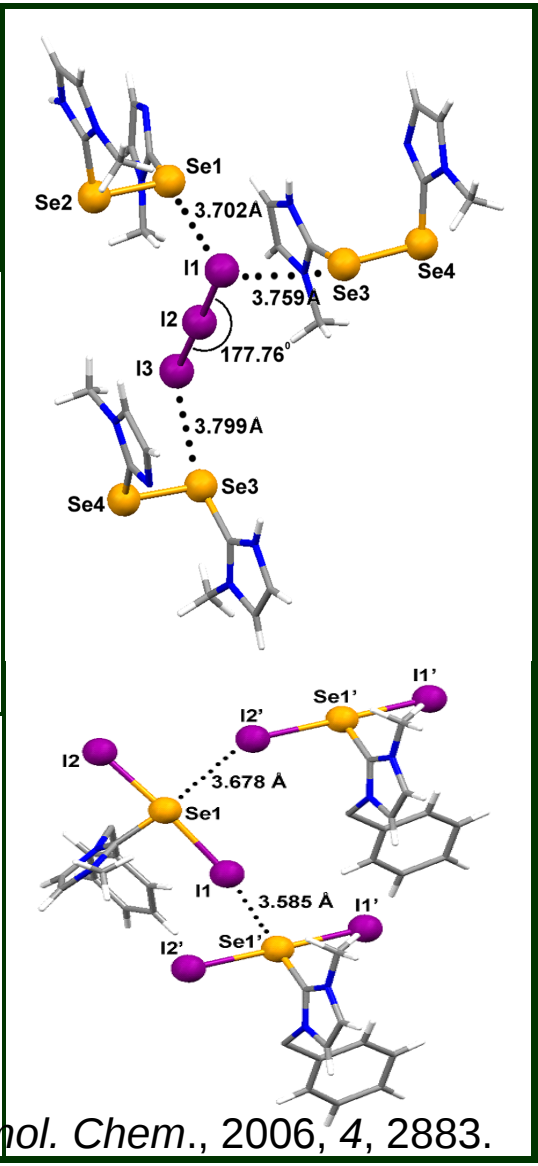






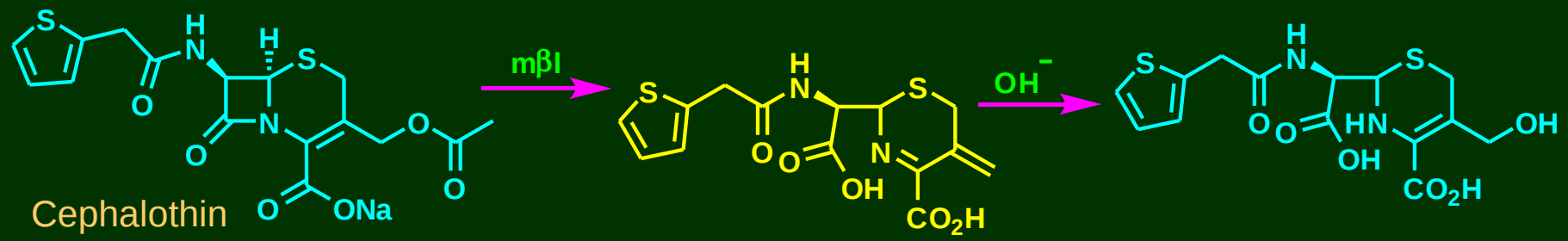


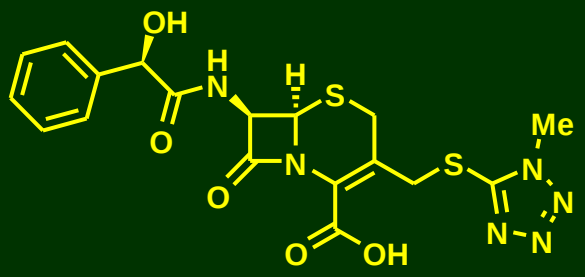


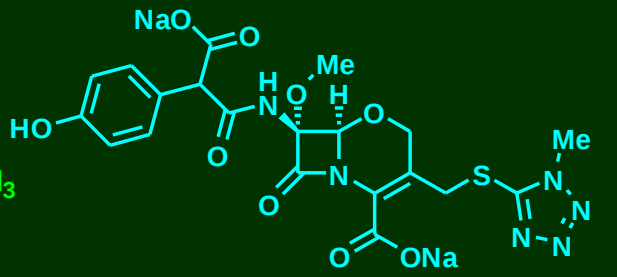


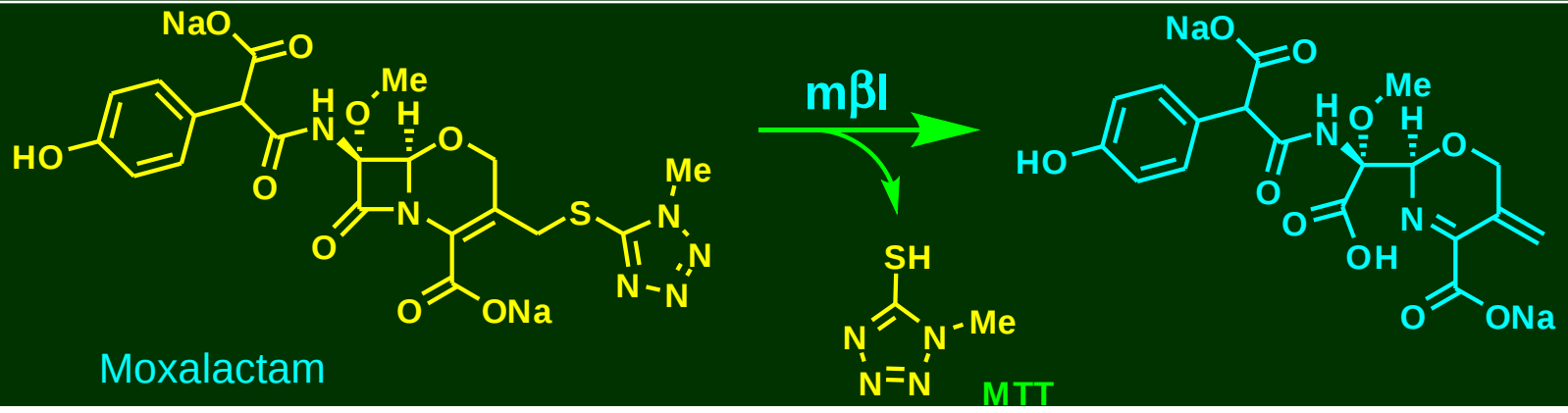
Roy, Nethaji, & Mugesh, *Org. Biomol. Chem.*, 2006, *4*, 2883.

Hydrolysis by Metallo-β-Lactamases

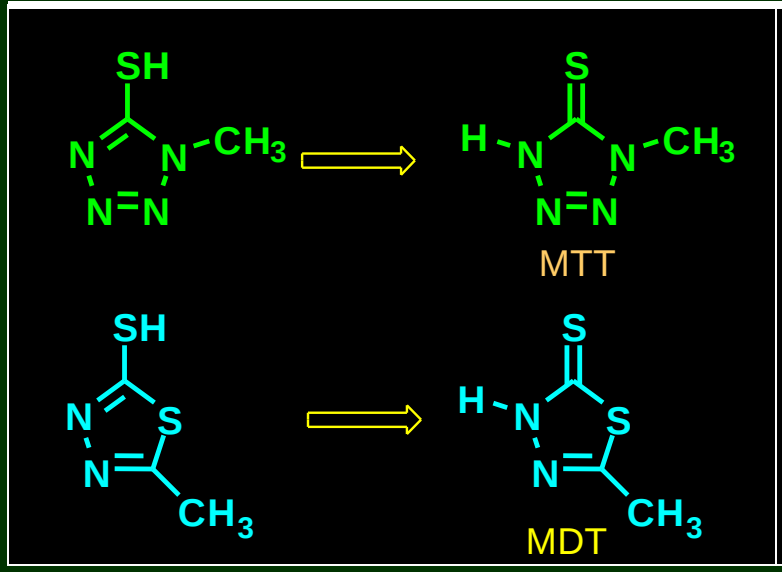


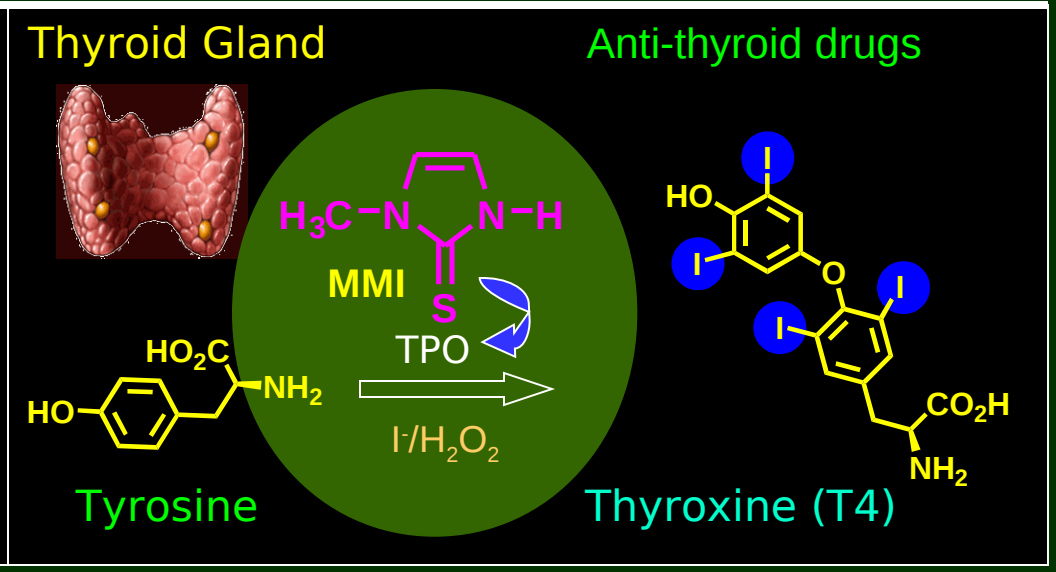


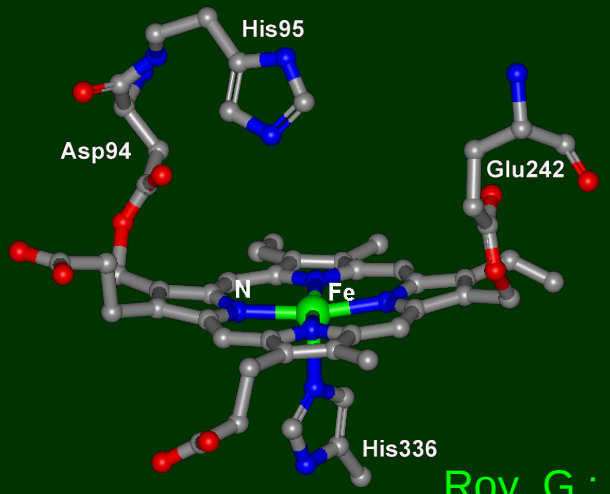


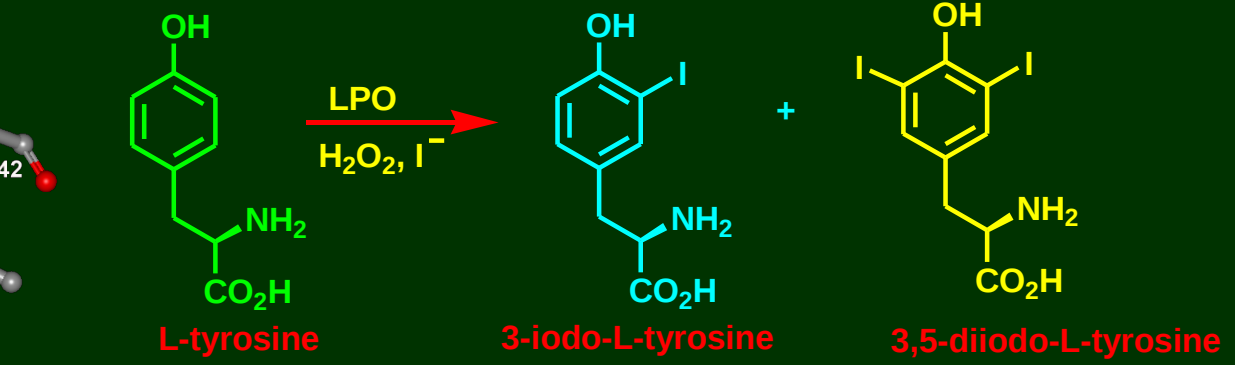


Tautomeric Forms of MTT and MDT







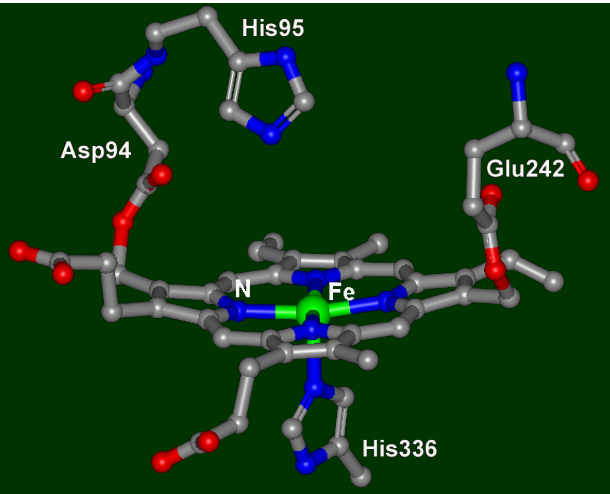


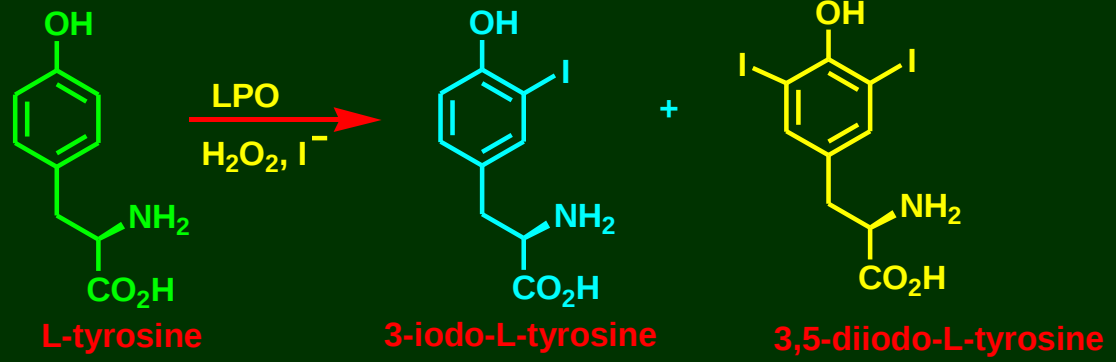
Roy, G.; Mugesh. G. *J. Am. Chem. Soc.* 2005, *127*, 15207.

Roy, G.; Nethaji, M.; Mugesh, G. *J. Am. Chem. Soc.* 2004, *126*, 2712.

Bhuyan, B. J.; Mugesh, G. *Inorg. Chem.* 2008, *47*, 6569.

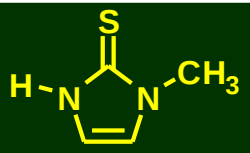
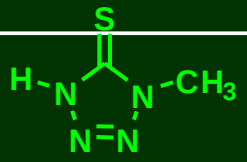
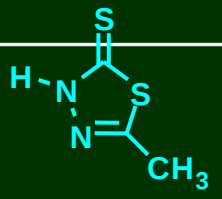
Inhibition of LPO-catalyzed Iodination

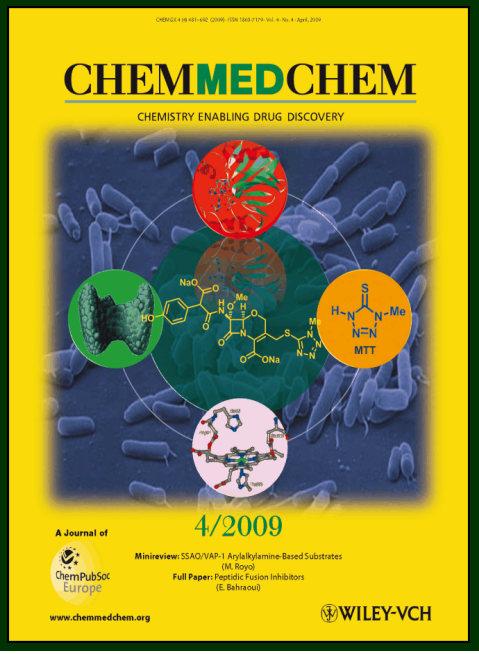




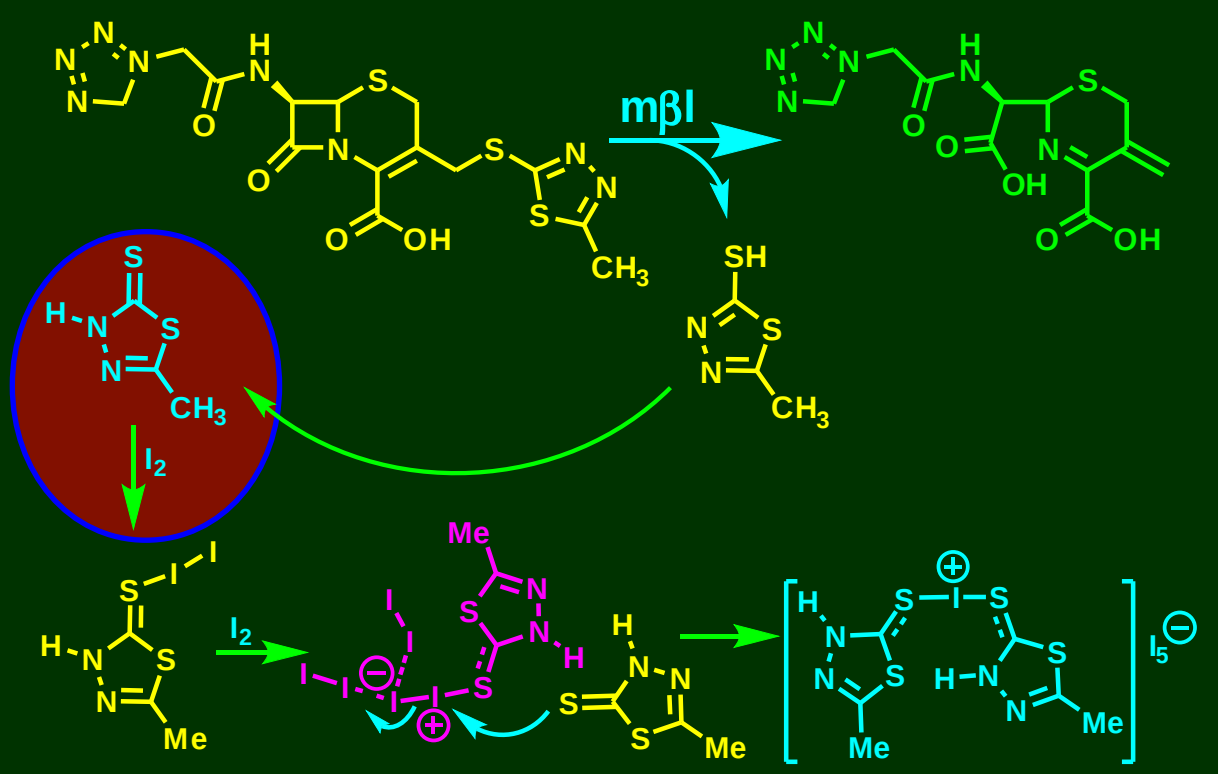
L-tyrosine — 3-iodo-L-tyrosine — 3,5-diiodo-L-tyrosine

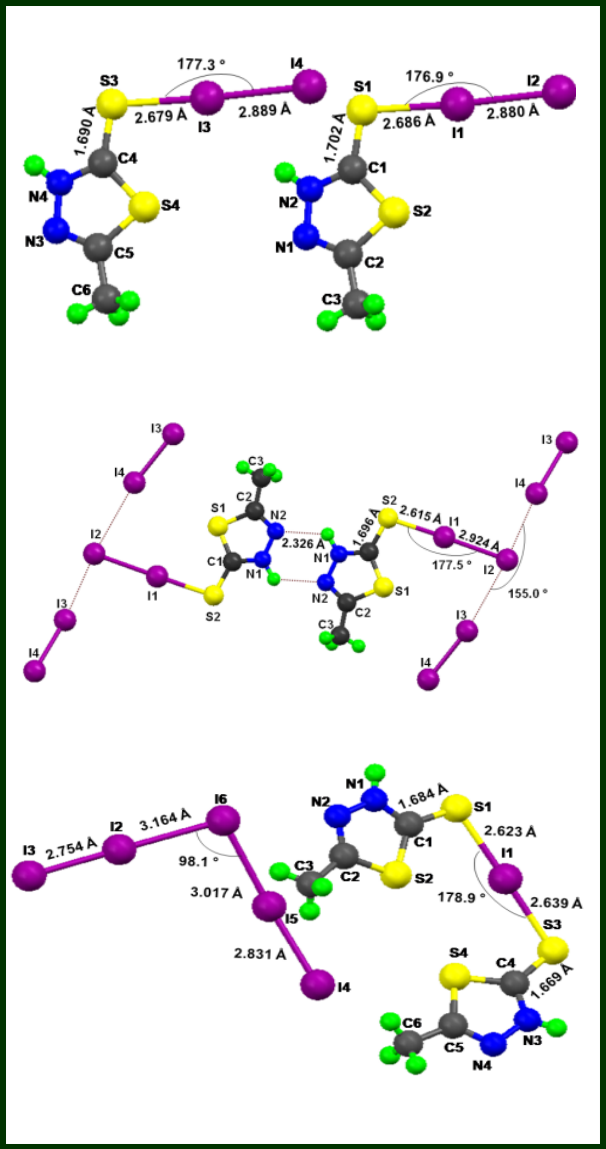
Tamilselvi & Mugesh, *ChemMedChem*, 2009, *4*, 512.

No	Compound	Structure	IC_{50} values (μM)
1	MMI		4.09 ± 0.56
2	MTT		7.29 ± 0.77
3	MDT		3.04 ± 0.65



Sulfur-Iodine Interactions

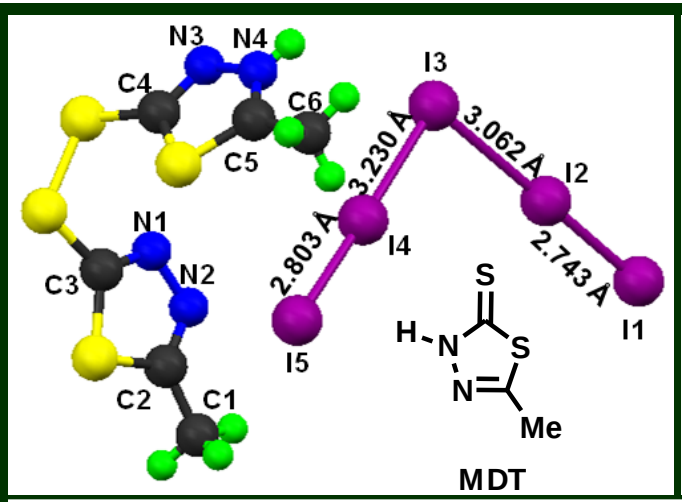


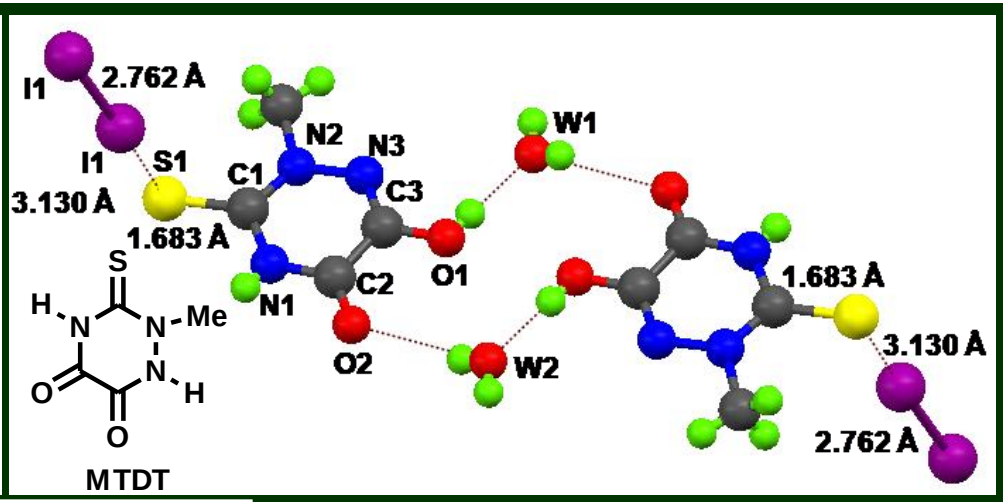


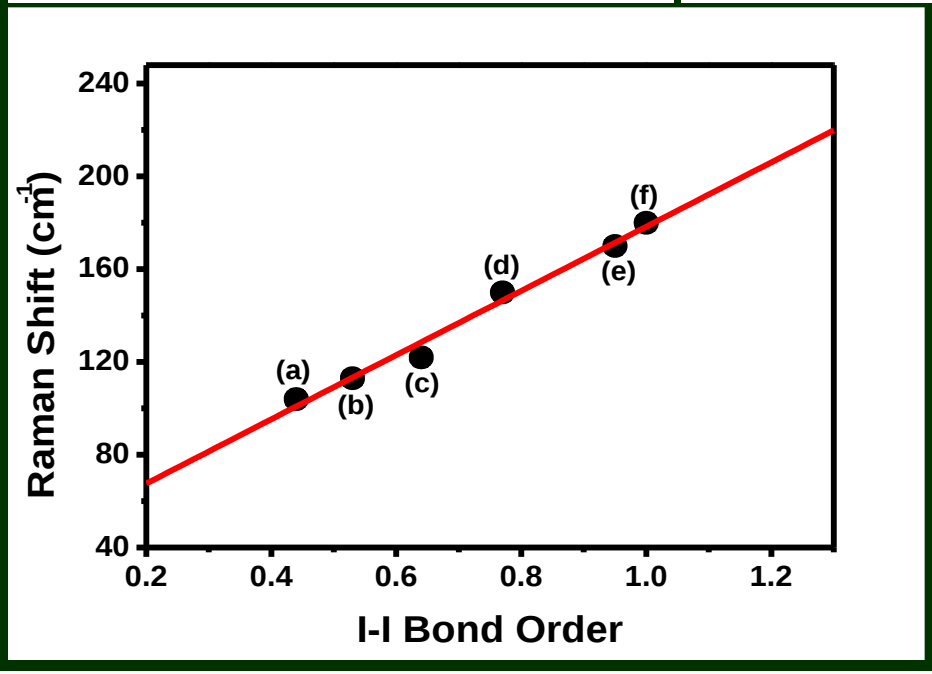
Tamilselvi, A.; Mugesh, G.

Bioorg. Med. Chem. Lett. 2010, 20, 3692.

Sulfur-Iodine Interactions





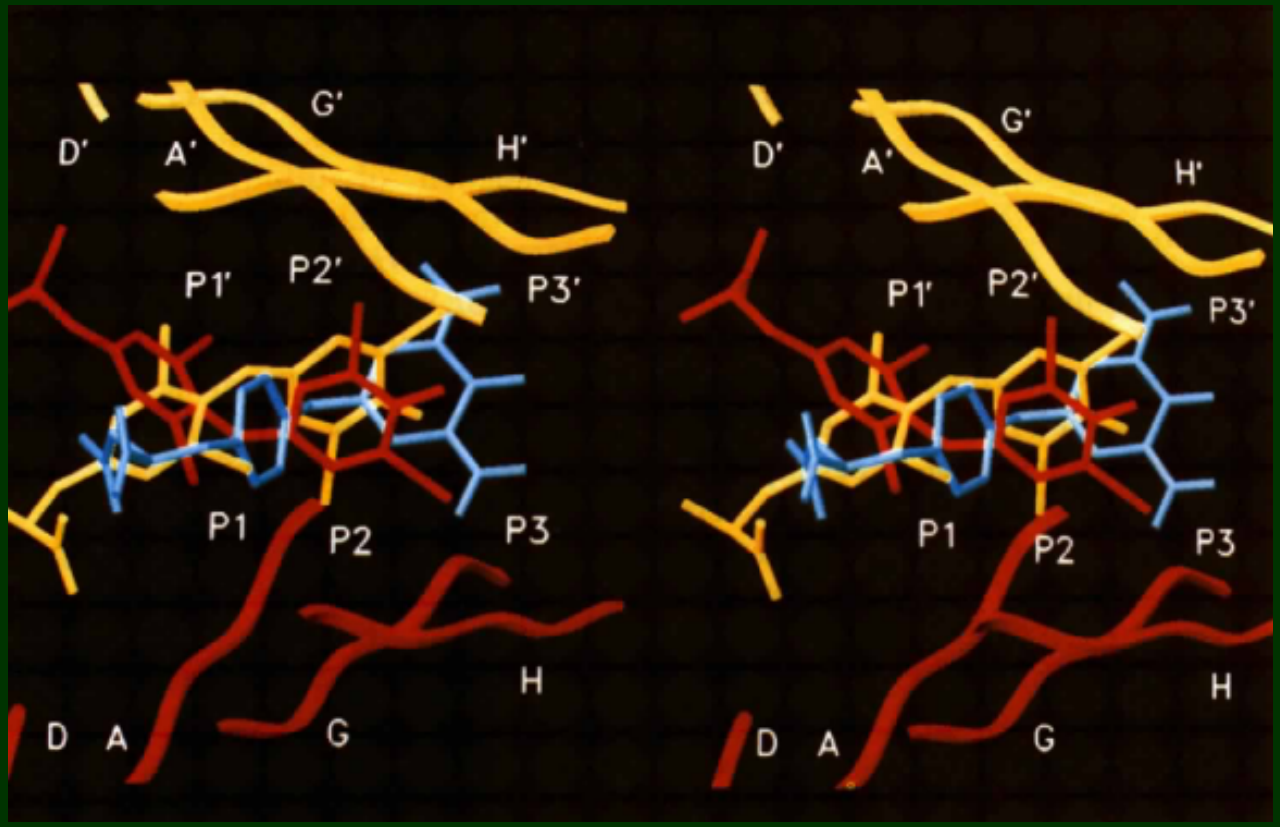


Thione-Iodine complexes (a) DMETT.I_2 (b) MMI.I_2, (c) MDT.I_2, (d) PTU-I_2 (e) MTDT-I_2, (f) free iodine

Tamilselvi, A.; Mugesh, G.

Bioorg. Med. Chem. Lett. 2010, 20, 3692.

Thyroid hormone binding in Transthyretin (TTR)

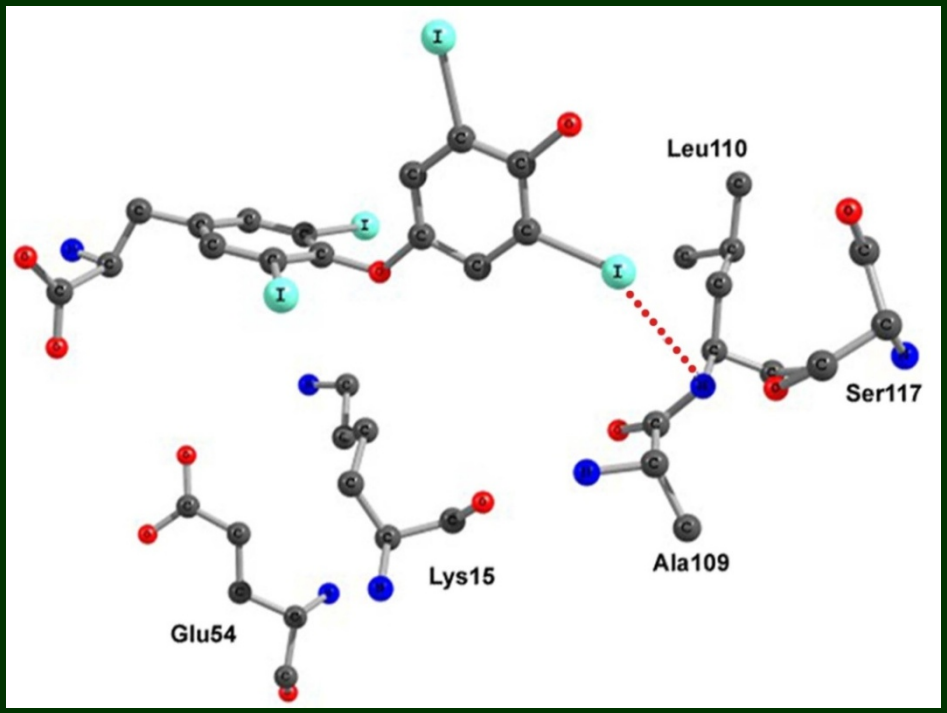


- Halogen binding sites P1, P2, P3 and their symmetry related pairs P1', P2', P3' in thyroid hormone transport protein Transthyretin.
- T_4 (ball and stick - red) binding is greatly influenced by charged residues Lys15 and Glu54 in P1 pocket.

Halogen bonding in human TTR-T4 complex

- Hydrogen bonding with Lys15 and Glu54
- 4-phenolic hydroxyl group forms water mediated hydrogen bond to Ser117.

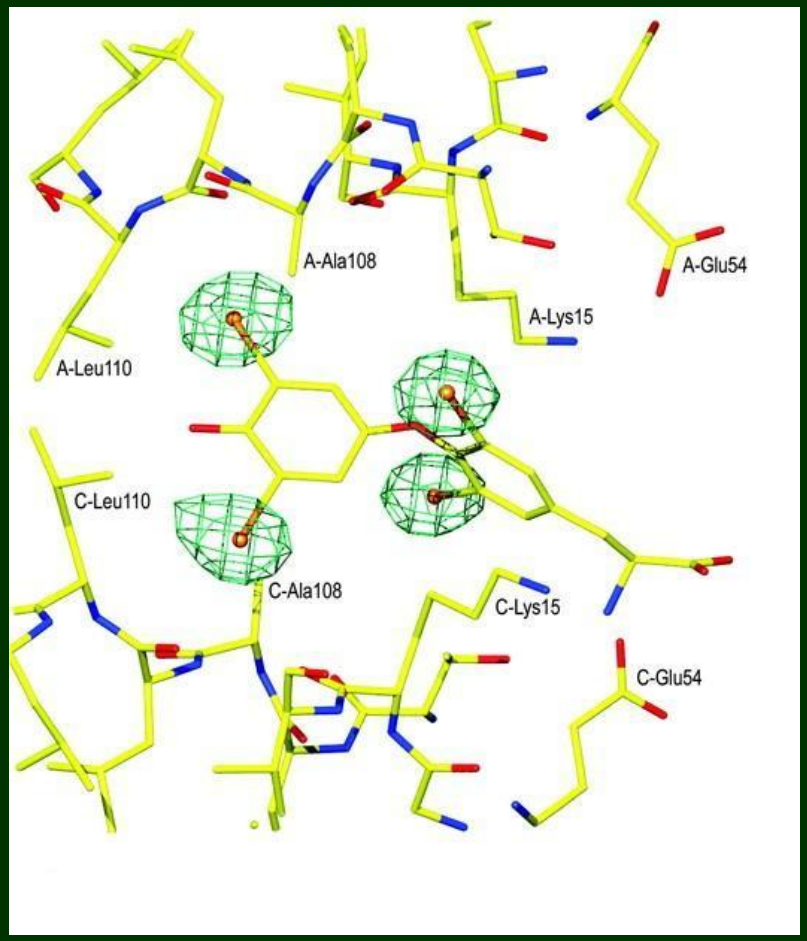
Acta Cryst. 1996, D52, 758-765.

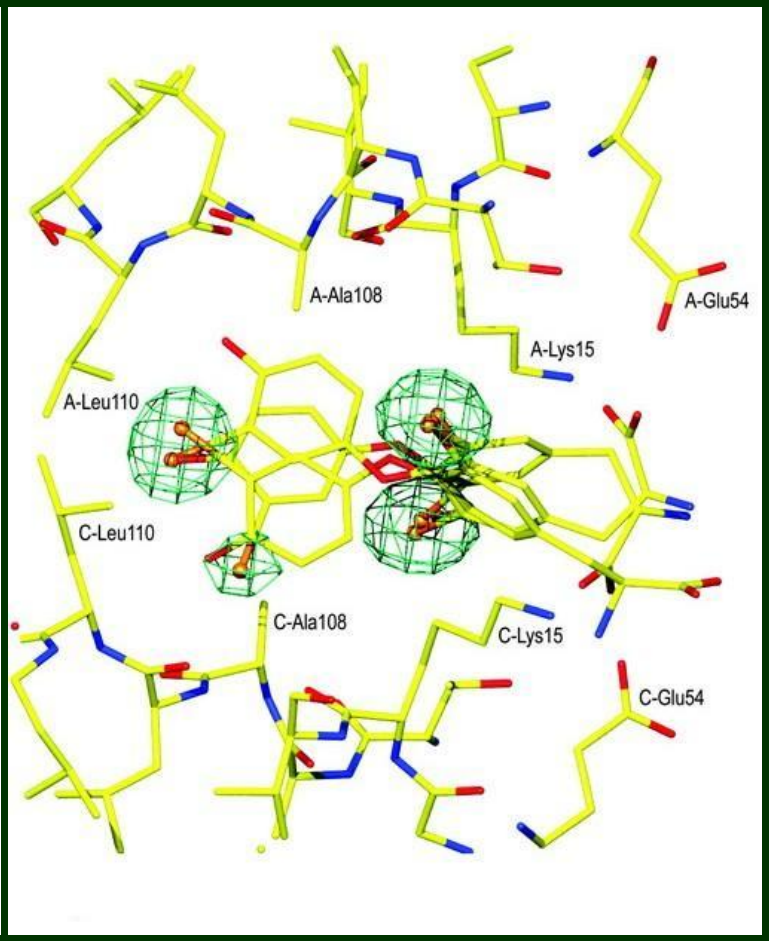


Halogen Bonding

- 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)

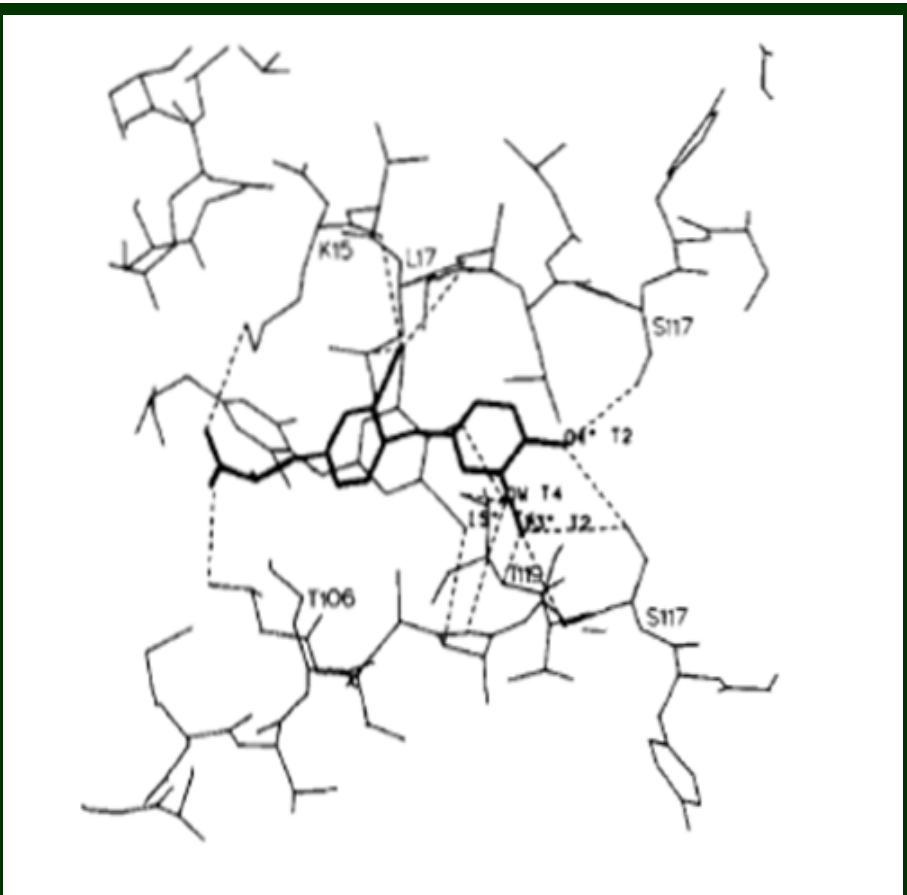
Binding of T3 with TTR





J. Biol. Chem. 2004, 279, 25, 26411 - 26416.

Binding of 3,3'-T2 with human TTR

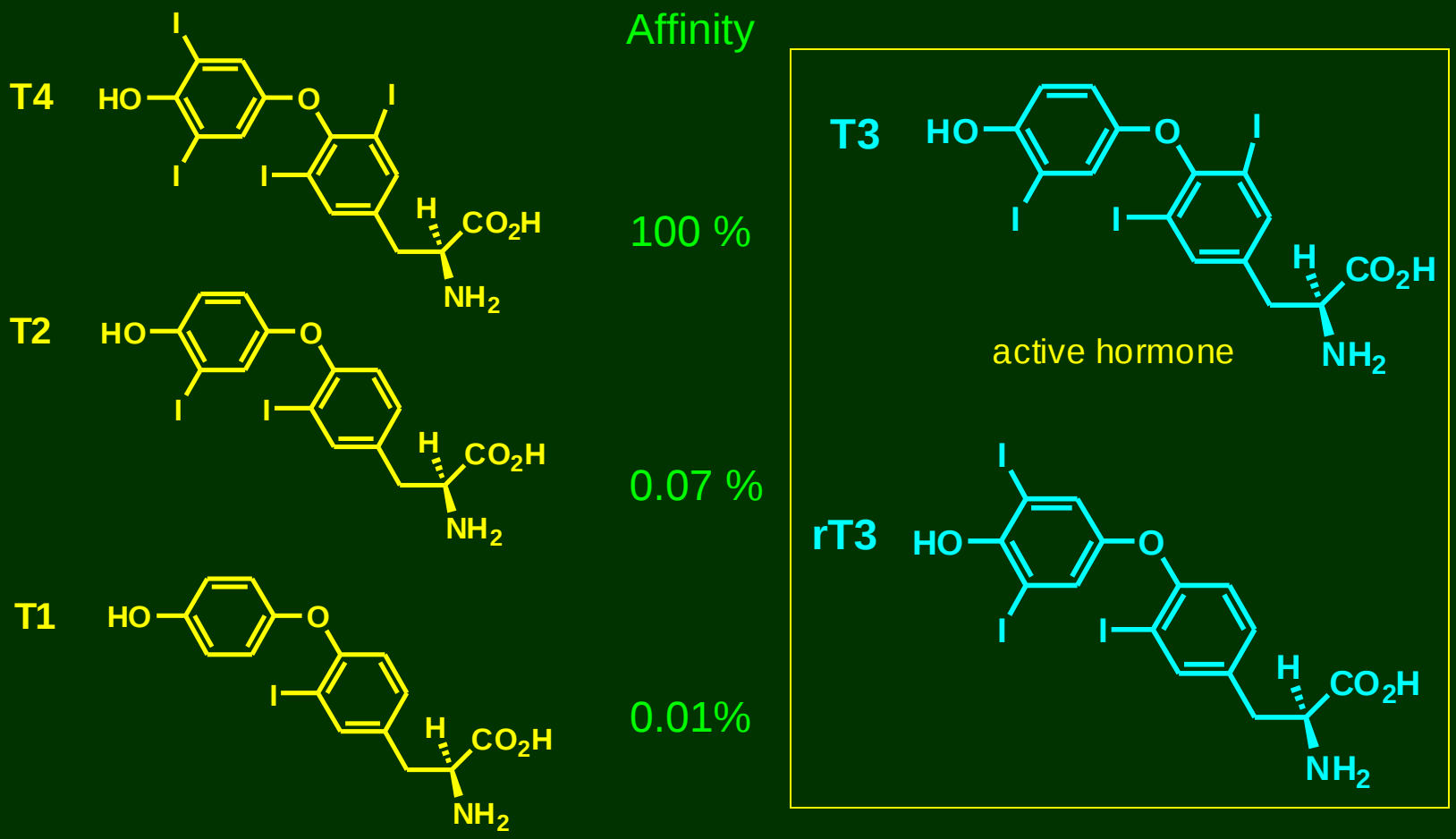


Superimposed structure of T4 (thick line) and T3 (light line) bound to human TTR. Amino acids are represented by single letter codes.

J. Biol. Chem. 1992, 267, 1, 353-357.

- 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)

Binding of Thyroid Hormones to TTR

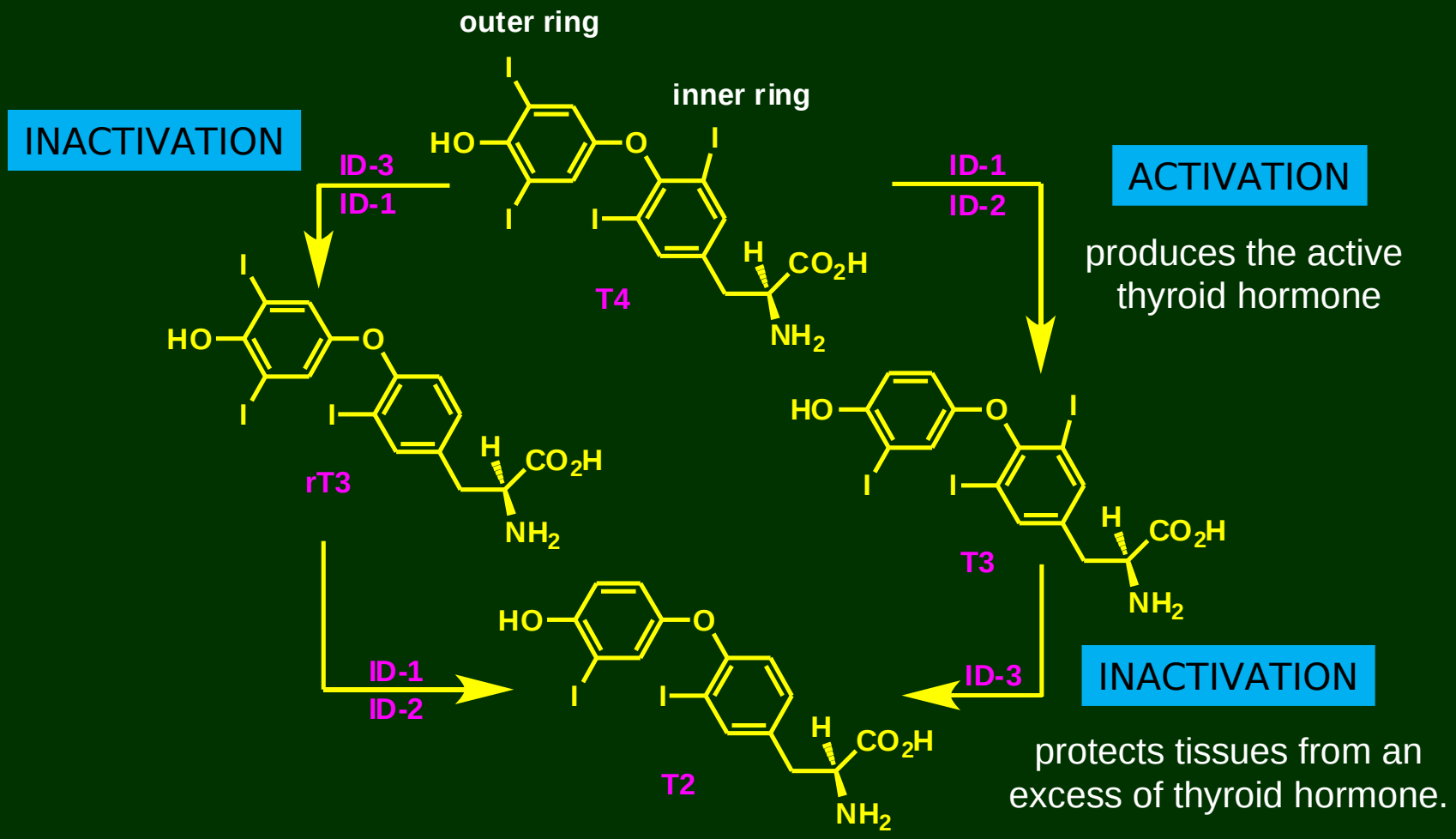


The binding affinity decreases upon removal of iodines.

J. Biol. Chem. 1992, 267, 1, 353-357.

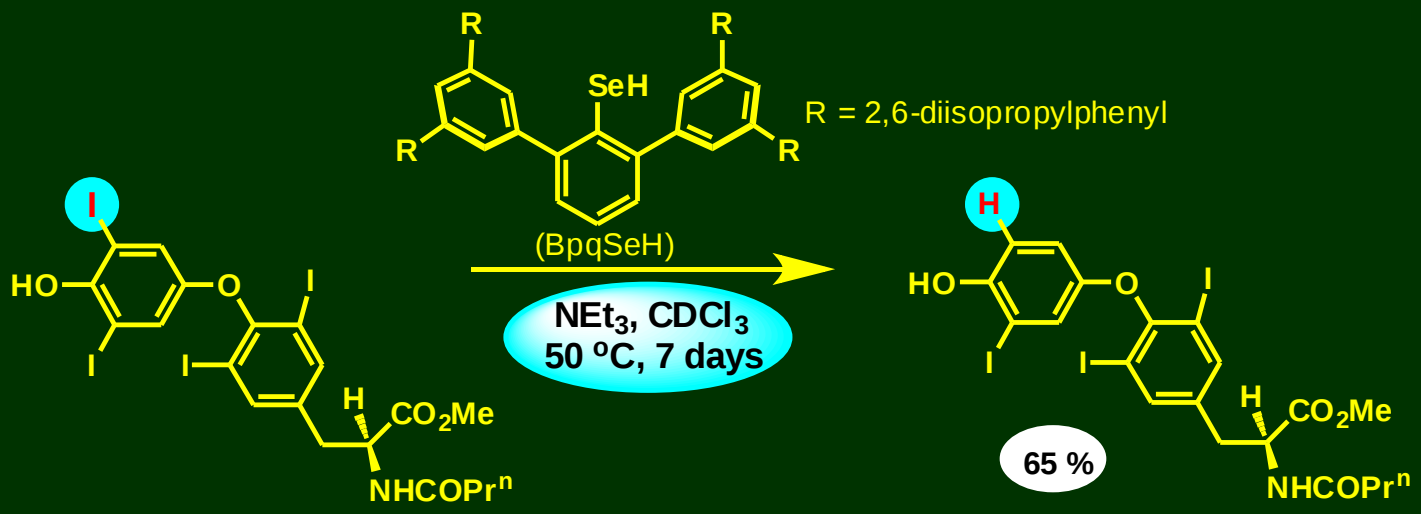
Iodothyronine Deiodinases

The entire body metabolism depends on the amount of thyroid hormones produced.

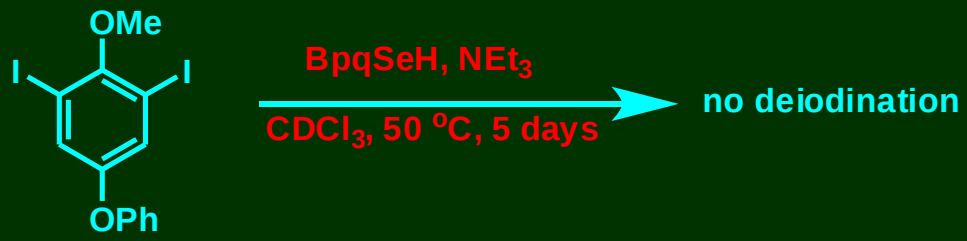


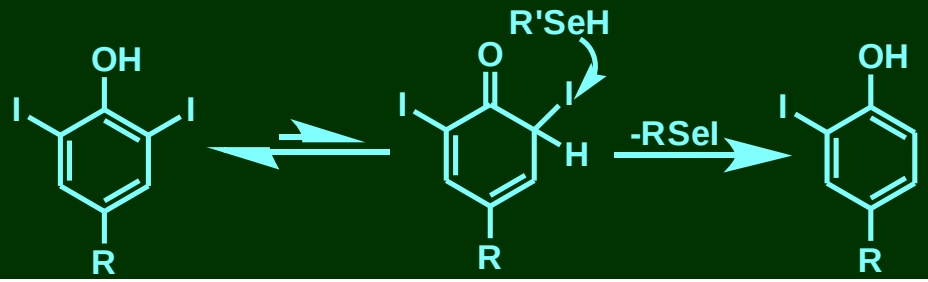
Behne et al. *BBRC,* 1990, *173*, 1143; Berry et al. *Nature* 1991, *349*, 438.

Iodothyronine Deiodinase Mimics



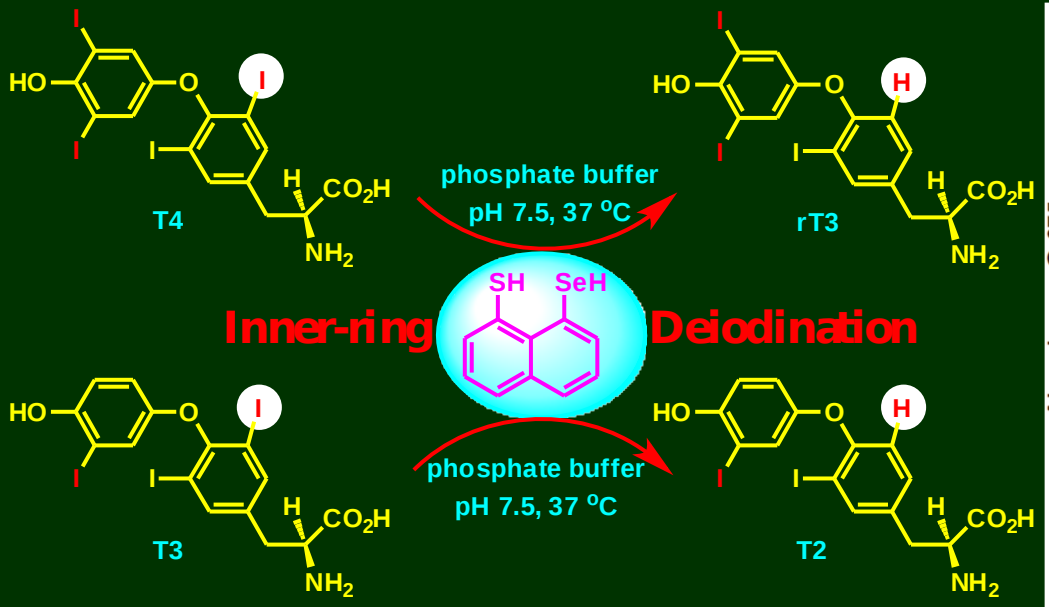
Goto et al. *Angew. Chem. Int. Ed.* 2010, 49, 545.

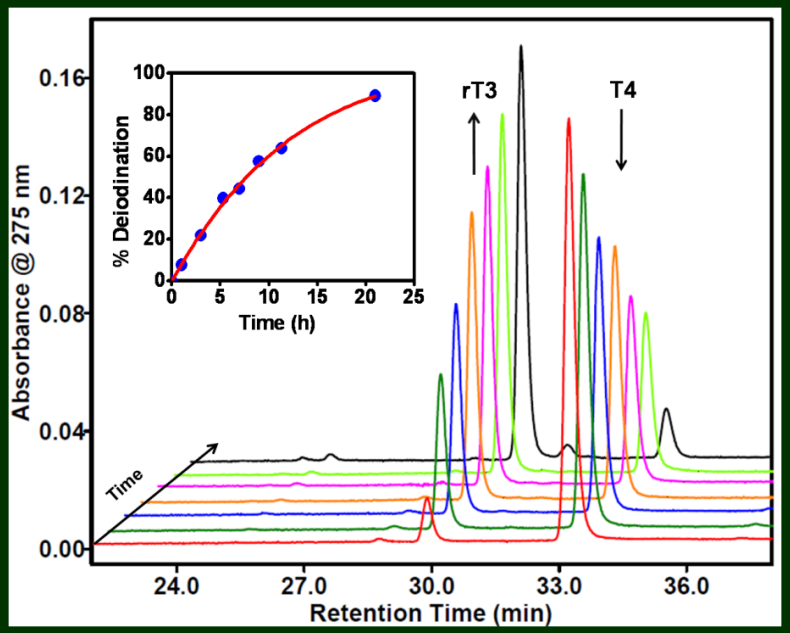




- Enol-keto tautomerism is required
- Outer ring iodines are more reactive than the inner-ring ones

Iodothyronine Deiodinase Mimics

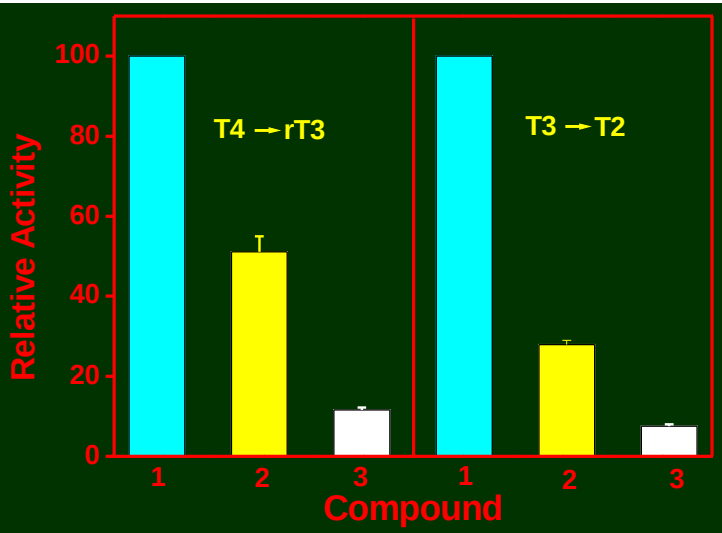


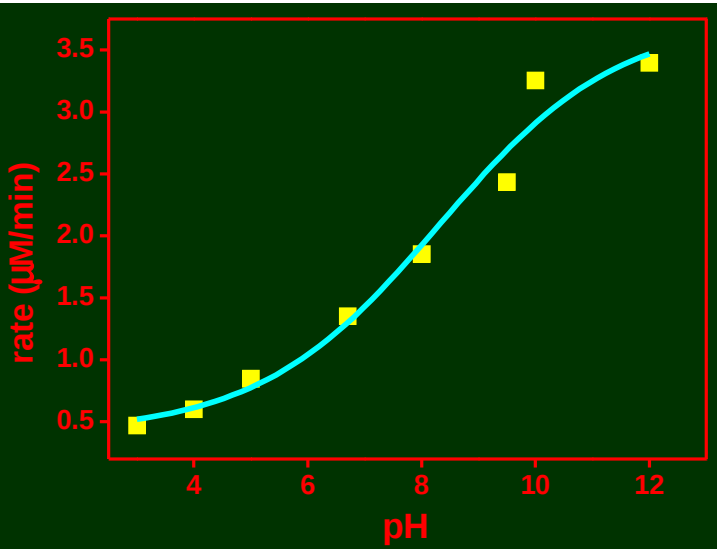


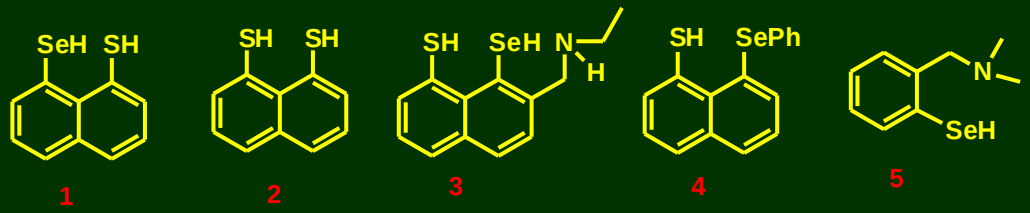
- Physiologically relevant conditions
- Highly specific to inner-ring deiodination
- Quantitative conversion of T4 to rT3 in 30 h

Manna and Mugesh, *Angew. Chem. Int. Ed.* 2010, 49, 9246 - 9249.

Iodothyronine Deiodinase Mimics





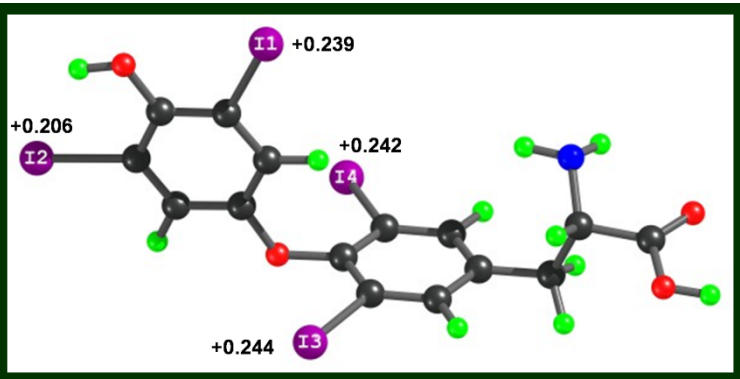


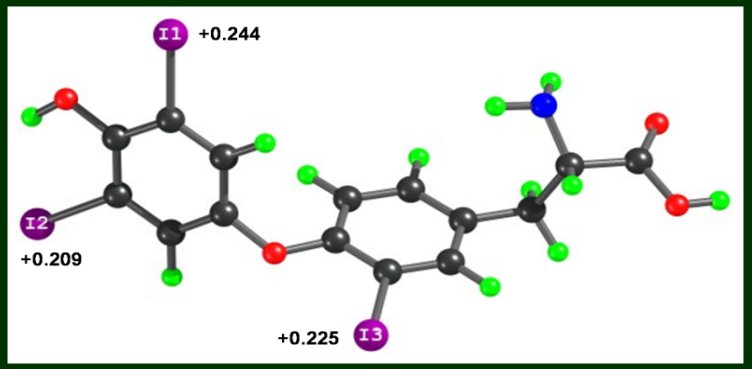
1 2 3 4 5

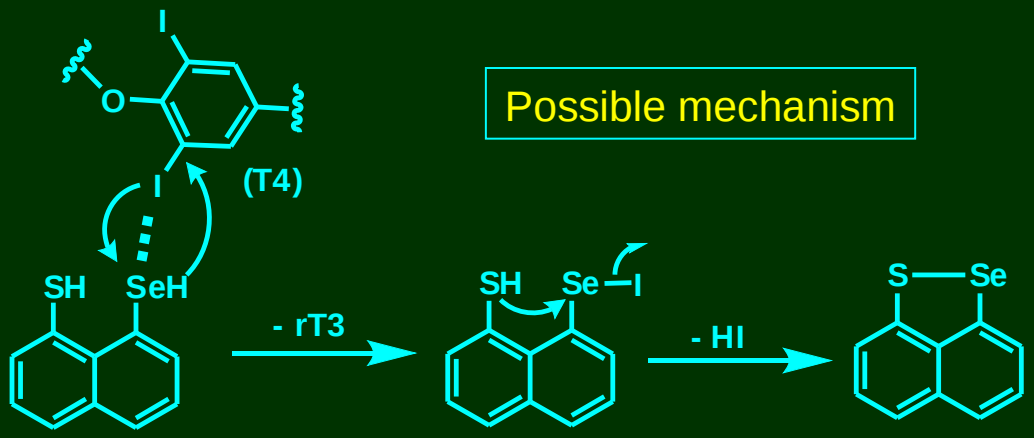
- The rate of deiodination is highly pH dependent.
- A thiol adjacent to selenol is important for the deiodination.
- Replacing -SeH with -SH reduces the activity.

Possible Mechanism

```
HumanD3    :  RPLVLNFGSCT*PPF
RatD3      :  RPLVLNFGSCT*PPF
ChickenD3  :  RPLILNFGSCT*PPF
XenopusD3  :  RPLVVNFGSCT*PPF
RanaD3     :  RPLVLNFGSCT*PPF
TilapiaD3  :  RPLILNFGSCS*PPF
Consensus     RPLvlNFGSCt*PPF
```



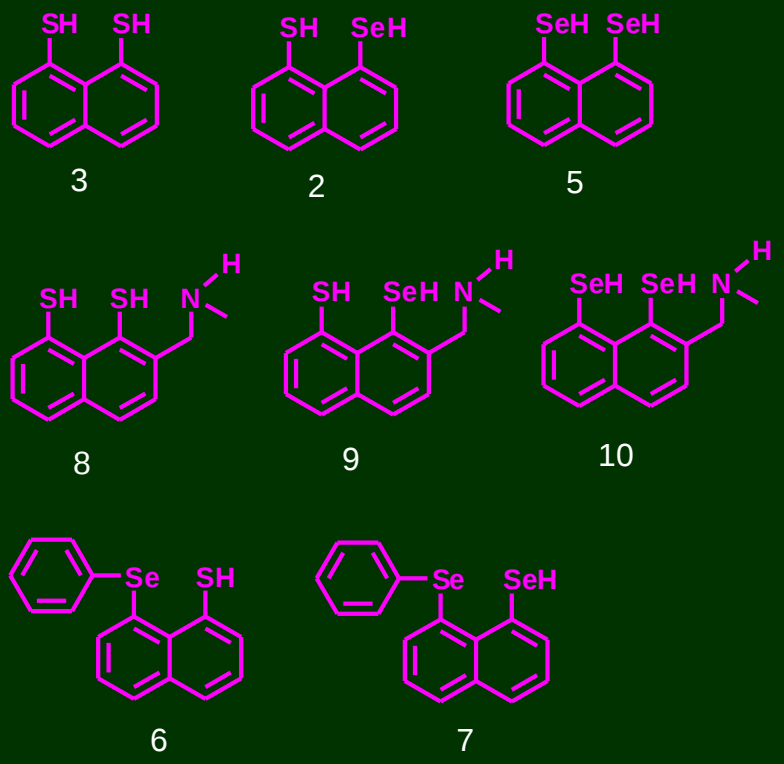


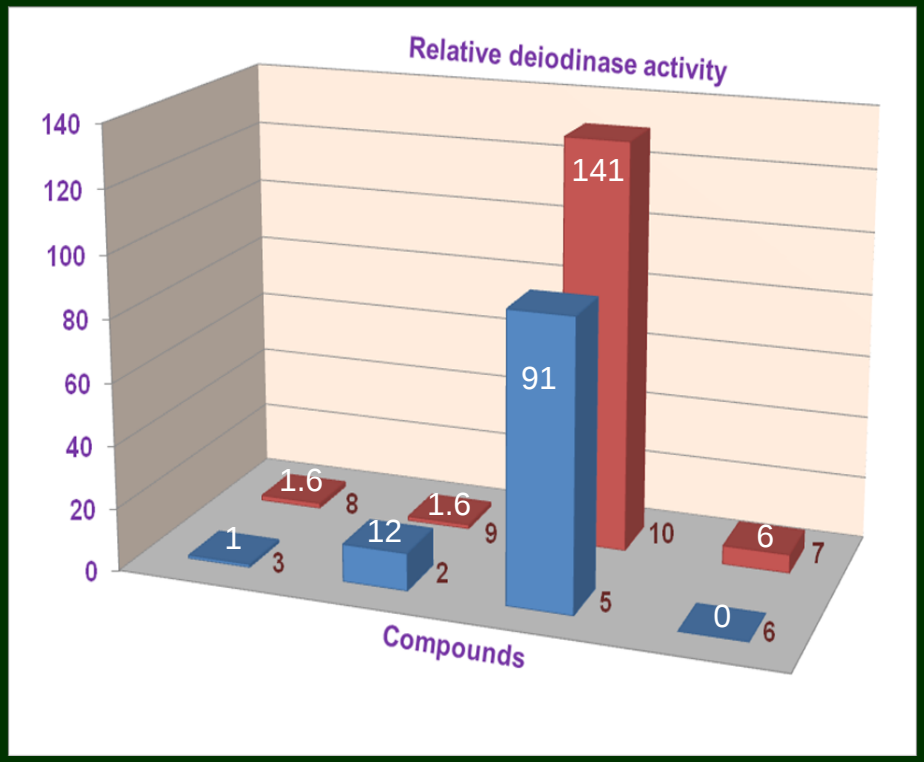


Possible mechanism

- 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

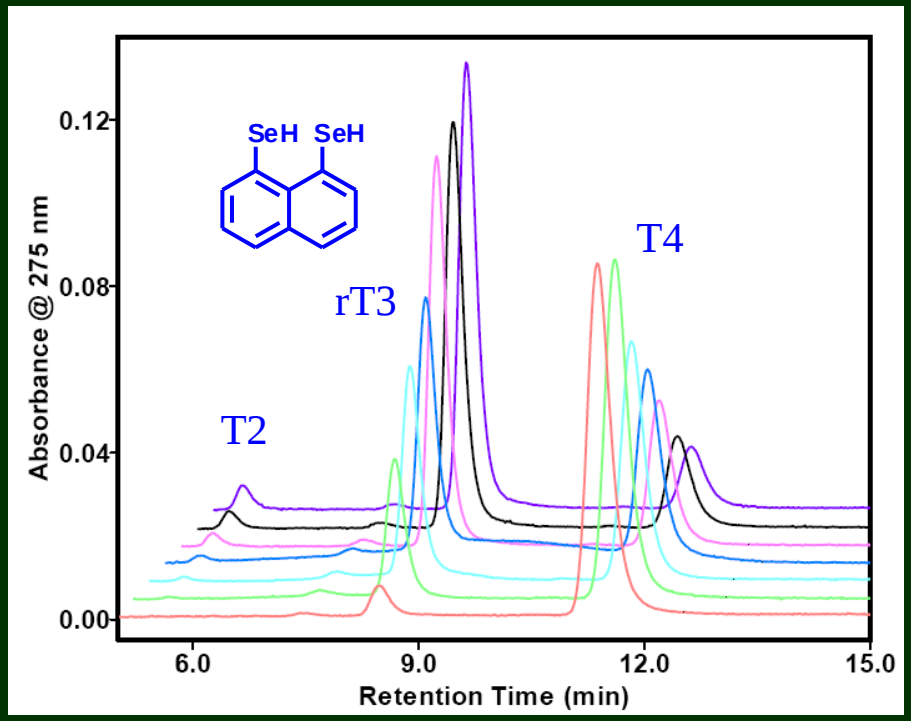


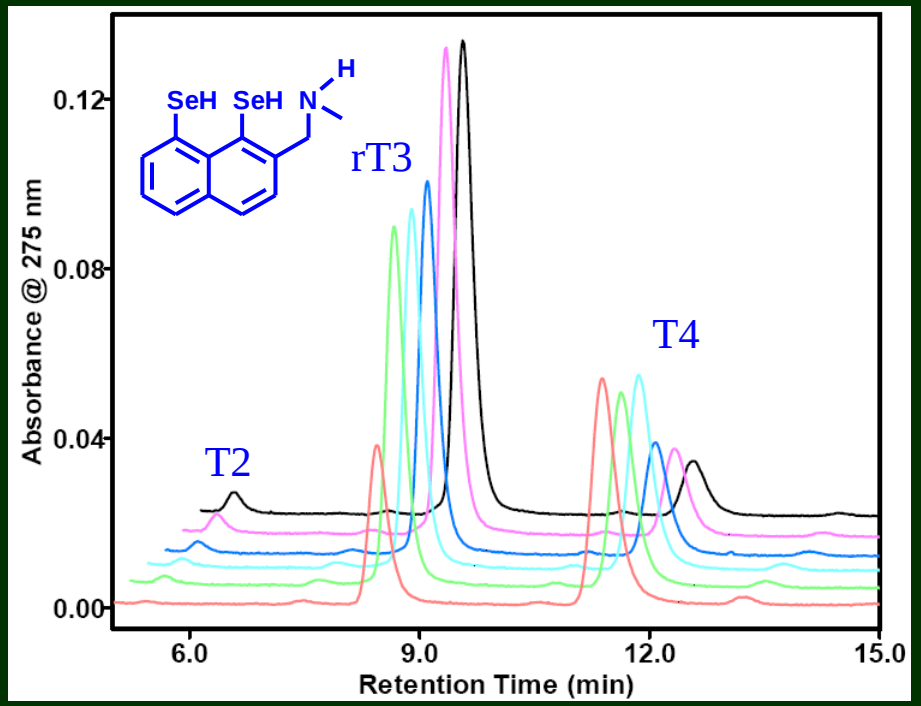


Does an increase in reactivity change the selectivity??

Manna and Mugesh, Unpublished results.

Iodothyronine Deiodinase Mimics

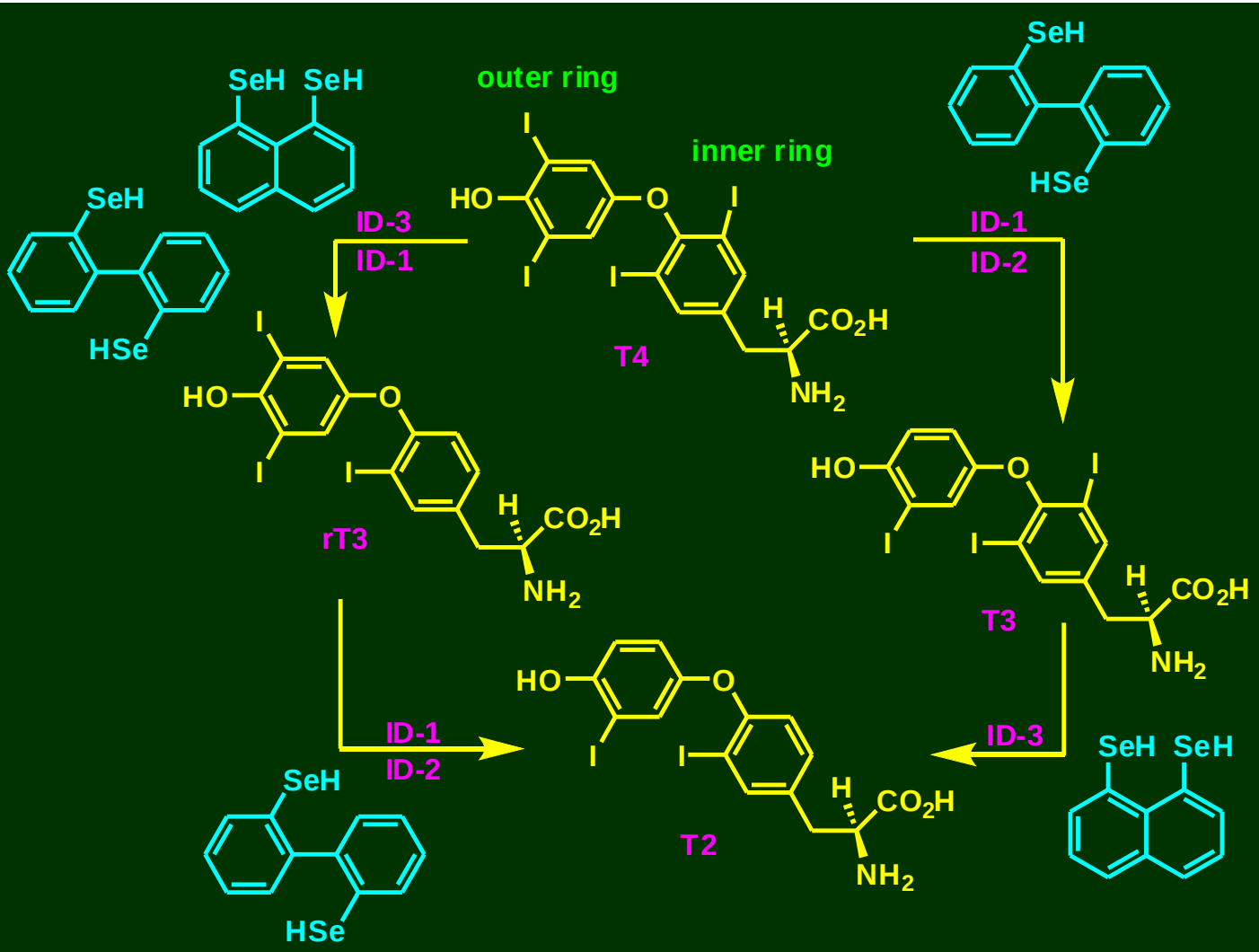




- An increase in the reactivity does not change the selectivity, but it leads to further deiodination.
- rT3 undergoes a further deiodination to form T2.

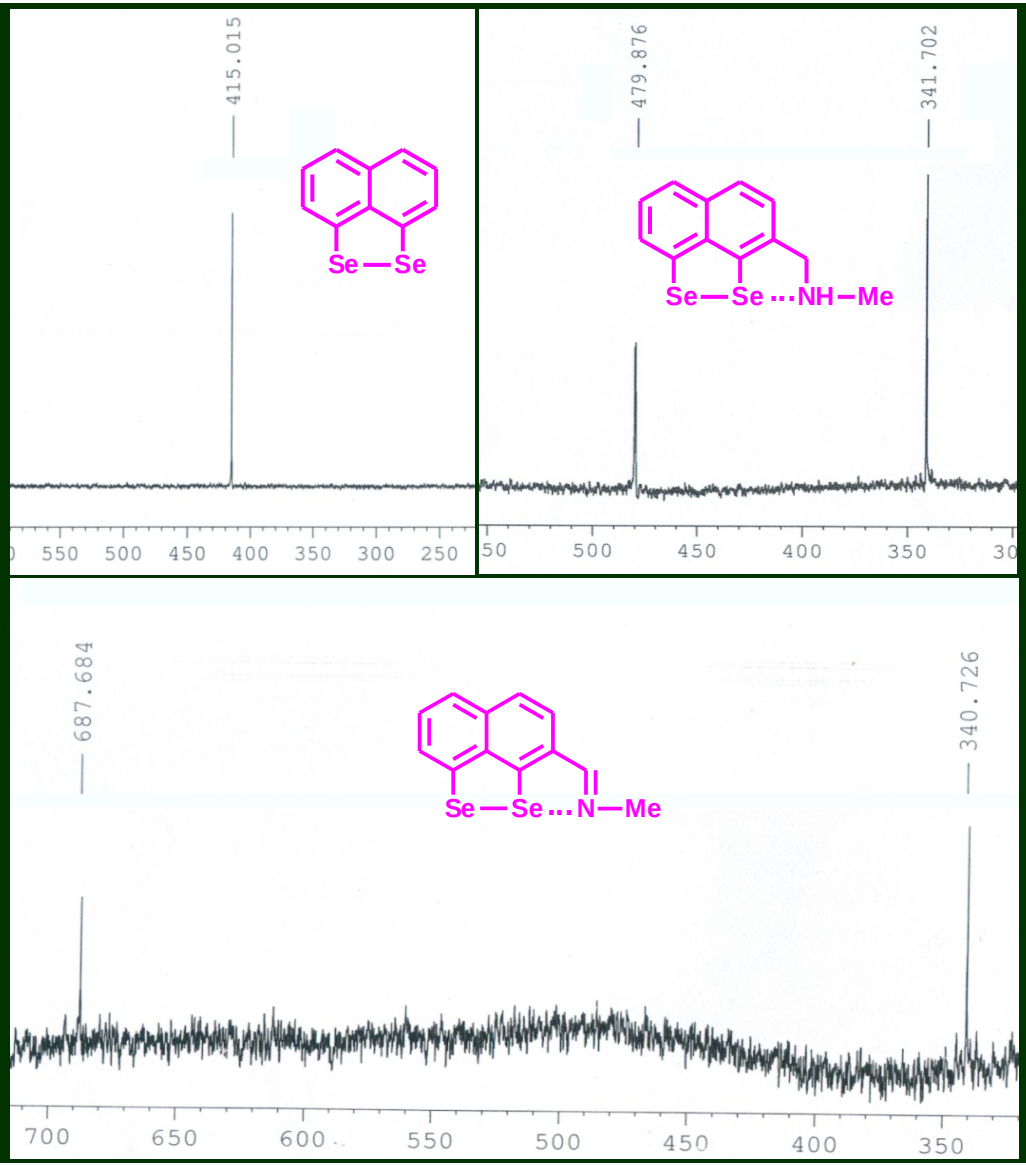
Manna and Mugesh, Unpublished results.

Iodothyronine Deiodinase Mimics



Manna and Mugesh, Unpublished results.

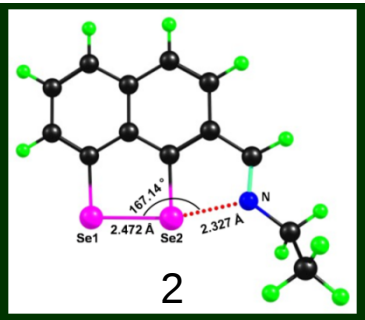
Effect of Se…N interactions on ^{77}Se NMR



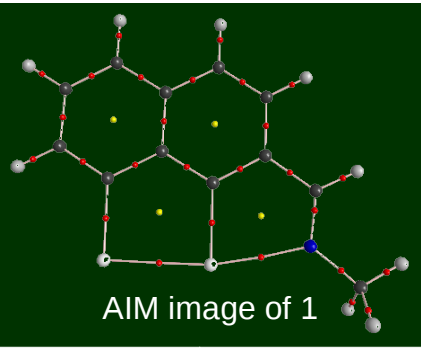
DFT Calculations

1, R = Me
2, R = Et
3, R = *n*Pr
4, R = *i*Pr

5, R = Me
6, R = Et
7, R = *n*Pr
8, R = *i*Pr



2



AIM image of 1

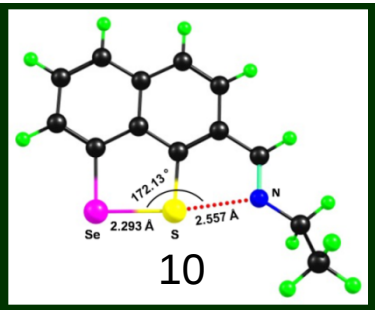
Compound	$r_{Se1\cdot\cdot Se2/}$ (Å)	$r_{Se2\cdot\cdot N/}$ (Å)	<Se1-Se2-N (º)	q_{Se1}	q_{Se2}	E (kcal.mol^{-1}) $n_N \rightarrow \sigma^*_{Se—Se}$
1	2.467	2.337	167.14	0.133	0.450	21.16
2	2.472	2.327	167.14	0.129	0.452	37.16
3	2.471	2.337	167.00	0.130	0.448	37.75
4	2.495	2.250	167.34	0.104	0.477	47.51
5	2.426	2.629	164.65	0.172	0.294	14.79
6	2.431	2.593	165.08	0.165	0.294	16.61
7	2.432	2.586	165.46	0.164	0.290	16.91
8	2.434	2.583	164.71	0.162	0.289	17.37

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

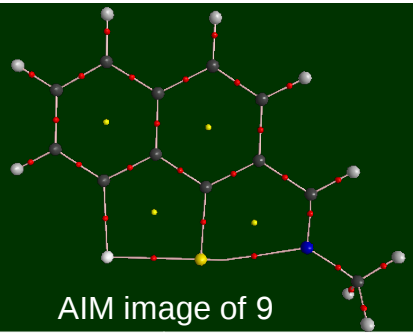
DFT Calculations

9, R = Me
10, R = Et
11, R = *n*Pr
12, R = *i*Pr

13, R = Me
14, R = Et
15, R = *n*Pr
16, R = *i*Pr



10



AIM image of 9

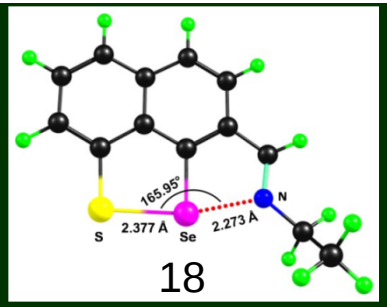
Compound	$r_{Se\cdot\cdot S/}$ (Å)	$r_{S\cdot\cdot N/}$ (Å)	<Se-S-N (º)	q_{Se}	q_S	E (kcal.mol^{-1}) $n_N \rightarrow \sigma^*_{Se—S}$
9	2.924	2.549	172.15	0.268	0.252	12.77
10	2.293	2.557	172.13	0.268	0.251	12.44
11	2.294	2.552	172.13	0.268	0.2578	12.67
12	2.301	2.518	172.11	0.258	0.253	13.97
13	2.284	2.734	168.2	0.271	0.165	7.75
14	2.289	2.688	168.94	0.264	0.164	9.23
15	2.293	2.659	169.38	0.260	0.161	10.10
16	2.287	2.719	168.15	0.267	0.162	8.68

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

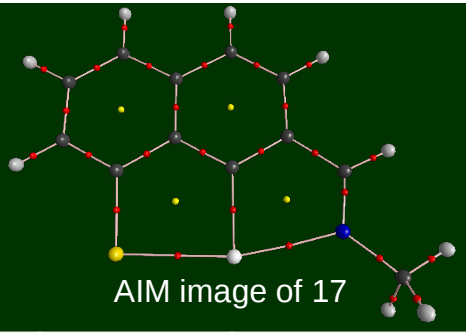
DFT Calculations

17, R = Me
18, R = Et
19, R = *n*Pr
20, R = *i*Pr

21, R = Me
22, R = Et
23, R = *n*Pr
24, R = *i*Pr



18



AIM image of 17

Compound	$r_{S\cdot\cdot Se/}$ (Å)	$r_{Se\cdot\cdot N/}$ (Å)	<S-Se-N (º)	q_S	q_{Se}	E (kcal.mol^{-1}) $n_N \rightarrow \sigma^*_{S—Se}$
17	2.372	2.284	165.94	0.017	0.518	41.70
18	2.3 77	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**

Acknowledgement

Department of Science and Technology (DST), New Delhi

Alexander von Humboldt Foundation, Germany

Gouriprasanna Roy

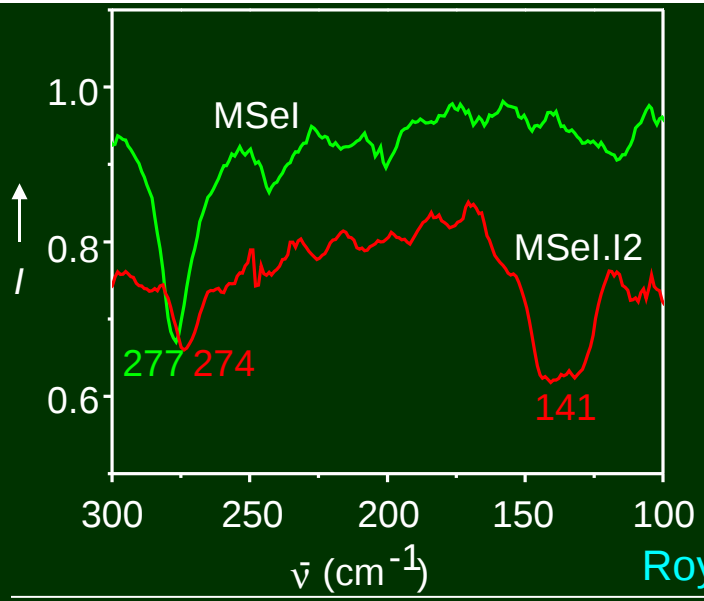
Debasis Das

A. Tamilselvi

Debasish Manna

Thank You

Interactions of Antithyroid Drugs with Iodine



Far-IR spectra

141: ν(I-I) stretching vibration mode.

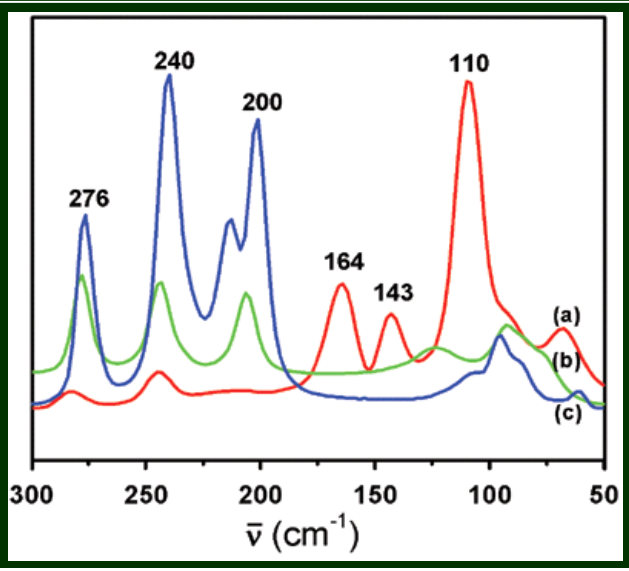
Di-iodine vapor gives a strong band at 216, which appears at 180 in the solid state.

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

Roy, Nethaji, & Mugesh, *Org. Biomol. Chem.*, 2006, *4*, 2883.

FT-Raman spectra

✓ I_3^- can exist as a real I_3^- entity or an $I^- \cdot I_2$ adduct.

110 : normally attributed to the symmetric stretching of I_3^- – symmetric ion – one Raman active band.

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