Thyroxine

Thyroxine is a four times iodized amino acid derivative which is formed by the thyroid gland as a hormone, regulating the metabolism.

It is also named 3,3',5,5'-tetraiodothyronine (T4) or, more exactly, β-[(4-hydroxy-35-diiodphenoxy)-3,5-diiodphenyl]-a-alanine.

Next to T4, there's a three times iodized amino acid derivative, formed in lower concentration. It is called 3,5,3’triiodothyronine (T3).

Physical characterization:

- molecular formula: \( \text{C}_{15}\text{H}_{11}\text{I}_{4}\text{NO}_{4} \)
- molar mass: 776,87 g/mol
- crystallized, non coulored needles
- melting point between 231°C and 233°C
- specific polarisation in a solvation of NaOH and EtOH (1:2 \( [\alpha]_D = -5.00^1 \))
- pKa-data: carboxyl-group: pKa = 2.4
  phenol-group: pKa = 6.87
  amino-group: pKa = 10.1

Safety informations:

- Xn: -R20/21/22: harmful on inhalation, in contact with skin and if swallowed
  -S24: avoid contact with skin
  -S25: avoid contact with eyes

History:

1856: Schiff recognizes, that removing the thyroid gland during animal researches causes heavy damage of the nervous system and spasmodic states.

1915: Thyroxine is synthesized by Kendall for the first time.

1927: Bager & Harington are able to prove the constitution by synthesis. (Constitution and Synthesis of Desjodo-Thyroxine (1926)/ Isolation of Thyroxine from the Thyroid Glad (1926))

\(^1\) Just valid for this product: L-Thyroxin, 99%; available at ACROS Organics No.: 215600010

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Group H Thyroxine
The human body:

In living beings, thyroxine is formed from coupling two 3,5-diiodotyrosine by the thyroid gland.

\[
\text{Oxidative coupling with loss of three carbon unit (1 bis 6)}
\]

You get the T3 molecule by splitting off an iodine molecule from the 5'-position. It can also be formed intrathyreoidal in smaller quantities by coupling of 3-monoiodotyrosine with 3,5-diiodotyrosine.

The thyroid glands hormones are at first bound to thyreoglobulin and can be donated to the periphery on demand.

A healthy person's everyday secretion of T4 is about approximately 100µg. Of T3 it's just about 10µg.

Transporting thyroxine in the human body runs by connecting it to transport proteins just like globulin, albumin or préambulin.

Generally T4 has a biological half-life of seven days and T3 one of 20 hours.

A metabolic active are just the hormones, not connected to proteins. However, the fraction of free thyroxine in the blood amounts less than 0.1%.

Indeed, the amount of the bound hormones depends directly on the amount of connecting proteins. Therefore, a decrease of those proteins leads directly to a reduced thyroxine concentration, as well. The thyroid glands hormone synthesis is at first regulated by the so called 'Hypothalamus'. It controls the secretion of a thyreoida-stimulating hormone (TSH) by producing thyreotropin-realising-hormones. TSH docks at specific receptors in the cell membrane, which causes a release of thyroxine.
Generally, TSH causes a constancy in volume, weight, secretory activity of the thyroid gland and the stimulated release of thyroxine.

T4/T3 secretion and the TSH-secretion are connected to each other by a regulating equilibrium. That means, if the concentration of thyroid glands hormones lowers, the TSH-secretion is forced to increase. According to that, higher thyroid gland hormone concentration induces less TSH-secretion.

The thyroid glands hormones have got a regulating effect on the bodies' metabolism. They effect a raise of the oxygen usage, an increased warming of the body and, as a result, the basal metabolism increases, as well.

In the carbohydrate metabolism thyroid glands hormones lead for example to more Glycogen formed and a highered glucose resorption.

An increased level of thyroid gland hormones also highers the lipolysis, which causes a degradation of the fatty tissue, because the formed fatty acids are used within the increased metabolism.

Human beings might have two forms of incidents of the thyroid glands activity. These are hypothyroidism and hyperthyroidism.

<table>
<thead>
<tr>
<th>hypothyroidism (not enough T3/T4 formed)</th>
<th>hyperthyroidism (too much T3/T4 formed)</th>
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<tbody>
<tr>
<td>• saggy musculature</td>
<td>• lowered growth</td>
</tr>
<tr>
<td>• imbecility, restricted mental skills</td>
<td>• restlessness and insomnia</td>
</tr>
<tr>
<td>• costiveness</td>
<td>• diarrhea</td>
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<tr>
<td>• dry skin</td>
<td>• increased blood pressure</td>
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<tr>
<td>• lowered blood pressure</td>
<td>• sensitivity towards heat</td>
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<tr>
<td>• sensitivity towards cold</td>
<td>• Loss of weight</td>
</tr>
<tr>
<td>• overweight</td>
<td>• raised body temperature</td>
</tr>
<tr>
<td>• lowered body temperature</td>
<td>• protruding eyes (Basedows disease)</td>
</tr>
<tr>
<td>• goiter</td>
<td>• goiter</td>
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</tbody>
</table>

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Group H Thyroxine
Reasons for hypothyroidism: incident of the thyroid gland during embryonic development; deficit of iodine; absence of released psychotropic hormones (TSH); damage of the thyroid glands tissue;

Reasons for hyperthyroidism: tumor-like growth of the thyroid gland; growth of the thyroid gland because of an autoimmunity reaction (Basedows disease); too much TSH;

Reasons for a goiter:

- **hypofunction**: The thyroid gland increases its volume to be able to absorb more iodine, the number of iodine receptors escalates.

- **hyperfunction**: There's too much TSH which can't be used completely by the Thyroid gland. Thereby the Thyroid increases in order to enable the forming of Thyroxine according to the amount of TSH.

In case of hypothyroidism, the patient gets thyroxine in the form of tablets. For this reason, we will take a look at the industrial synthesis of thyroxine during the following part.

**Synthesis**

Now we will discuss several ways of synthesizing T4.

The Chalmers-synthesis, whose starting compound is the amino acid L-tyrosine, will be discussed in detail because of its quite simple chemistry. The reactions yield is about 25%.

The first step's a nitration ($S_{E}Ar$) of the L-tyrosine in both ortho positions (in relation to the OH-group):

Now we've got an electron-poor, aromatic ring which is able now to act in a nucleophilic aromatic substitution ($S_{N}Ar$).

During the second step we first have to add a protective group to the amino-group before we can remove the OH-group (by reacting with TsCl for to get a good leaving group).
In the third step we have to add another protective group for the carboxylic acid group, as well:

The fourth step is forming the leaving group and afterwards a nucleophilic substitution. 4-methoxyphenol is the nucleophilic in this substitution and it is already deprotonated by adding pyridine to the reaction:

During the fifth step the nitro-groups are going to be converted into amino-groups by hydrogenation, followed by a reaction with HONO in which we get two diazo-groups instead of the formerly built amino-groups:

In the sixth step, the methoxy-group gets converted into a OH-group by reacting with HI. When adding AcOH as a compound we get back the amino-group:
The seventh step depends on the OH-group bonded to the left-sided ring, becoming activated by deprotonation during the reaction with Et₂NH:

**Synthesis according to Harington & Barger:**

1. 3,5-Dinitrobenzen, K₂CO₃, methylketone
2. AcOH, SnCl₂ and dry HCl

**Synthesis via DIHPPA:**

1. Acyl nitrite, AcOH, HCl, ECN, water
2. SnCl₂, dry HCl, CHCl₃

**Deiodizing thyroxine / Synthesis of T3**

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Sources:

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- Sicherheitsdatenblatt : L-Thyroxine von Sigma-Aldrich

- Chemistry of Thyroxine; Isolation of Thyroxine from the thyroid gland by Charles Robert Harington

- Chemistry of Thyroxine; Constitution and synthesis of desioso-thyroxine by Charles Robert Harington