found in several anhydrous borates. In the present structure the pentaborate rings have two relatively short boron–oxygen edges, with boron–oxygen bond lengths of 1·336 Å [B(4)–O(4)] and 1·341 Å [B(2)–O(1)]. These bond lengths occur typically with threefold-coordinated borons, such as B(1) and B(4), bonded to one BO_4 tetrahedron and two BO_3 triangles. The opposite edges [B(3)–O(3)] and [B(5)–O(6)] of the pentaborate rings are longer (1·364 and 1·360 Å) due to the circumstance that the boron atoms B(3) and B(5) are each bonded to two BO_4 tetrahedra and only one BO_3 triangle. A similar asymmetry, though less pronounced, is seen for the triborate ring.

The intergroup bond angles [in the present case the boron–oxygen–boron bond angles for oxygens O(10) to O(16)] are distributed in the range 125·1 to 134·1°. This is a normal range for such bond angles. The boron–oxygen–boron in-ring bond angles are significantly smaller, however, ranging from 118·5 to 123·5°.

Only the potassium atom K(2) has a fairly well defined coordination shell, with 8 oxygen atoms in the range from 2·681 to 2·926 Å. (Table 3). No further oxygen atoms are found within a distance of 3·5 Å. The atoms K(3) (which occupies a special position at the origin) and K(1) do not have an obvious upper limit for the coordination number. K(1) has 7 neighbours in the range from 2·682 to 3·117 Å and K(3) has 6 neighbours in the range from 2·789 to 3·120 Å.

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Thyroid Hormone Stereochemistry. I. The Molecular Structures of 3,5,3′-Triiodo-L-Thyronine (T_3) and L-Thyroxine (T_4)

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The crystal and molecular structures of the two thyroid hormones, 3,5,3′-triiodo-L-thyronine (T_3) and L-thyroxine (T_4) have been determined by X-ray crystallography. Crystals of T_3 hydrochloride trihydrate are monoclinic with $a=29{\cdot}080$, $b=5{\cdot}236$, $c=17{\cdot}047$ Å, $\beta=115{\cdot}85°$, space group $C2$ with $Z=4$. T_4 hydrochloride monohydrate also crystallizes in space group $C2$ with $a=17{\cdot}23$, $b=5{\cdot}14$, $c=25{\cdot}15$ Å, $\beta=90{\cdot}47°$, $Z=4$. Both structures were solved by Patterson and Fourier techniques and refined by full-matrix anisotropic least-squares methods. Final *R values* are 0·07 for T_3 and 0·107 for T_4. In both T_3 and T_4 the two phenyl rings are not mutually perpendicular and mutually bisecting. Angles between the plane of the inter-ring ether linkage and the planes of the α- and β-phenyl ring planes are 90° and −13° respectively for T_3 and 101° and −34° respectively for T_4. The four iodine atoms of T_4 are at the apices of a rather distorted tetrahedron. The conformation of the alanine side chain is very similar in both compounds. The conformation of T_3 is such that the 3′-iodine atom is *proximal* to the diiodo ring rather than *distal;* this conformation is opposite to that inferred from chemical studies. Theoretical calculations indicate this *proximal* conformation to be energetically favored over the *distal* one.

Introduction

The thyroid hormones L-thyroxine (T_4) and 3,5,3′-triiodo-L-thyronine (T_3) appear to exert an effect on nearly every organ and tissue of the body. They are essential for normal growth and development and the control of oxidative metabolism, and have a profound effect on protein synthesis in many tissues. Although their biological importance is well established, the mechanisms of thyroid-hormone action remain largely obscure.

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Table 1. *Crystal data*

	L-Triiodothyronine	L-Thyroxine
Formula	$C_{15}H_{12}I_3NO_4.HCl.3H_2O$	$C_{15}H_{11}I_4NO_4.HCl.H_2O$
M.W.	741·53	831·39
Crystal system	Monoclinic	Monoclinic
a	29·080 ± 0·021 Å	17·234 ± 0·078 Å
b	5·236 ± 0·005	5·138 ± 0·025
c	17·047 ± 0·10	25·145 ± 0·100
β	115·85 ± 0·05°	90·47 ± 0·17°
D_x ($Z=4$)	2·11 g cm^{-3}	2·48 g cm^{-3}
$F(000)$	1392	1520
Space group	$C2$	$C2$
μ	334·2 (Cu $K\alpha$) cm^{-1}	58·6 (Mo $K\alpha$) cm^{-1}
Filter used	Ni	Nb
Crystal size (mm)	0·07 × 0·04 × 0·23	0·03 × 0·03 × 0·50
Intensities measured	1341	1700
Intensities $\geq 2\sigma_c$	1202	1019
Resolution	$2\theta = 100°$, $d = 1·006$ Å	$2\theta = 45°$, $d = 0·93$ Å

Table 2. *T_3 fractional atomic coordinates and anisotropic thermal parameters* ($\times 10^4$)

U_{ij} are coefficients in the expression $\exp[-2\pi^2(h^2U_{11}a^{*2}+\ldots+2klU_{23}b^*c^*)]$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I(3′)	0·3950	−0·6834	1·2292	1592	1866	840	250	571	539
I(5)	0·4315	−0·5337	0·8710	1065	1639	944	199	524	74
I(3)	0·2710	0·0000	0·9446	1358	566	591	−2	561	20
O(1)	0·4917	−0·3290	1·2946	1469	2411	444	283	15	−249
O(2)	0·3797	−0·1432	0·9463	1192	639	457	70	152	37
O(3)	0·1901	−0·2659	0·5487	1497	824	600	−4	458	−61
O(4)	0·1430	−0·4183	0·6079	1254	779	1275	311	651	241
N(1)	0·2499	−0·6860	0·5803	1330	772	371	319	328	182
C(1′)	0·4051	−0·1974	1·0331	1155	540	684	−188	500	−308
C(2′)	0·3884	−0·3826	1·0731	1089	826	511	321	230	144
C(3′)	0·4209	−0·3955	1·1674	901	1723	600	54	303	195
C(4′)	0·4635	−0·2887	1·2092	721	1387	756	564	−283	60
C(5′)	0·4814	−0·0810	1·1660	1464	1256	791	−650	432	−476
C(6′)	0·4499	−0·0504	1·0790	996	2114	1196	−501	575	−439
C(1)	0·2687	−0·6142	0·7666	1182	251	503	−96	278	116
C(2)	0·2521	−0·4189	0·8127	1418	326	630	26	541	38
C(3)	0·2921	−0·2594	0·8757	935	309	1076	193	532	631
C(4)	0·3428	−0·2923	0·8931	1185	570	254	−72	405	−82
C(5)	0·3550	−0·4804	0·8489	651	1169	725	106	275	682
C(6)	0·3182	−0·6637	0·7863	848	593	636	−205	254	26
C(7)	0·2273	−0·7857	0·7021	809	622	543	20	131	−10
C(8)	0·2055	−0·7062	0·6041	1189	1115	383	358	272	−33
C(9)	0·1795	−0·4433	0·5860	727	1508	442	112	243	333
Cl⁻(1)	0·3193	−0·1876	0·6267	1173	708	494	48	333	−9
O(W1)	0·0870	−0·0304	0·5376	1784	1207	1831	366	740	3
O(W2)	0·0839	−0·0497	0·3693	3187	1614	2331	312	1374	582
O(W3)	0·0794	0·4319	0·3785	1525	3669	1469	−599	653	−648

Approximate standard deviations of coordinates

I	0·0001	0·0010	0·0001	O(water)	0·0012	0·0096	0·0020
Cl	0·0003	0·0020	0·0004	C(best)	0·0010	0·0060	0·0017
O and N	0·0010	0·0060	0·0015	C(worst)	0·0017	0·0140	0·0030

Table 3. *T_4 fractional atomic coordinates and atomic thermal parameters* ($\times 10^4$)

U_{ij} are coefficients in the expression $\exp[-2\pi^2(h^2U_{11}a^{*2}+\ldots+2klU_{23}b^*c^*)]$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I(3′)	−0·0498	0·5000	0·0858	516	811	706	233	−116	−85
I(5′)	0·2213	−0·2127	0·0536	584	547	432	−32	64	13
I(5)	0·3674	0·5663	0·2075	654	545	453	67	15	14
I(3)	0·0728	0·0585	0·2810	496	1348	775	−86	73	1
Cl⁻(1)	0·1857	0·3997	0·4265	723	653	565	−4	−63	24

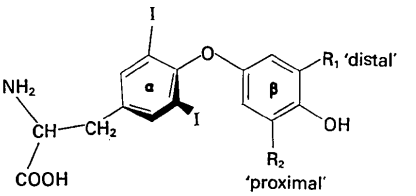
Table 3 (*cont.*)

	x	*y*	*z*	*U*
O(1)	0·0678	0·0530	0·0349	883
O(2)	0·1895	0·4342	0·2230	506
O(3)	0·3829	0·3495	0·4568	1291
O(4)	0·4831	0·1402	0·4094	689
N(1)	0·2872	−0·0840	0·4435	773
C(1′)	0·1665	0·3271	0·1757	288
C(2′)	0·0864	0·4251	0·1591	671
C(3′)	0·0586	0·3609	0·1115	360
C(4′)	0·0969	0·1310	0·0849	1627
C(5′)	0·1624	0·0170	0·0957	423
C(6′)	0·1973	0·1543	0·1442	531
C(1)	0·3235	−0·0397	0·3308	2562
C(6)	0·3593	0·1955	0·2953	2806
C(5)	0·3090	0·2985	0·2667	338
C(4)	0·2324	0·2691	0·2603	301
C(3)	0·1952	0·1603	0·2910	432
C(2)	0·2336	−0·0486	0·3189	714
C(7)	0·3638	−0·2046	0·3644	840
C(8)	0·3539	−0·0987	0·4164	888
C(9)	0·4042	0·1644	0·4320	388
O(*W*)	0·0483	0·0486	0·4385	1524

Approximate standard deviations of coordinates

I	0·0003	0·0020	0·0003
Cl	0·0014	0·0058	0·0010
O and N	0·0032	0·0154	0·0022
O (water)	0·0040	0·0388	0·0027
C (best)	0·0033	0·0103	0·0019
C (worst)	0·0063	0·0370	0·0044
C (average)	0·0044	0·0183	0·0028

There is much evidence however that stereochemical features of the hormones play a vital role in determining physiological activities. For example, (*a*) the D-isomers of T_4 and T_3 have only about 7% of the activity of the L forms; (*b*) T_4 and T_3 derivatives with alkyl groups in place of some of the iodines have hormonal activity (Bruce, Winzler & Kharasch, 1954; Jorgensen & Wright, 1970; Barker, Shimada & Makiuchi, 1965), indicating that the steric effect of the iodines or sterically similar groups must result in the molecular conformation and geometry necessary for interaction with the receptors; and (*c*) in most biological tests (*e.g.* minimal effective hormonal dose for treatment of myxedema) T_3 is about five times as active as T_4, indicating that the molecular asymmetry of the β ring of T_3 is important for hormonal activity. Jorgensen, Zenker & Greenberg (1960) and Jorgensen, Lehman, Greenberg & Zenker (1962) recognized that because of the approximately 120° bond angle at the ether oxygen the chemically identical 3′ and 5′ positions on the phenolic (β) ring of T_3 are not equivalent conformationally; they concluded from the synthesis and testing of 'conformationally fixed' analogs of T_3 that, in order for triiodothyronine to exhibit regulatory activity upon cellular oxygen consumption, the β ring must be oriented with its 3′-iodine distal to the diiodotyrosine (α) ring and that the 'free' (uniodinated) 5′ position must be proximal to the α ring.



Thyroxine was isolated and purified nearly 60 years ago and triiodothyronine was identified as a thyroid hormone some 35 years later. Since those times there has been widespread interest in the three-dimensional conformations of these vital hormones. However, despite the efforts of many research groups no X-ray crystallographic structure determination of either molecule has until recently been successfully accomplished (Camerman & Camerman, 1972*a*, *b*; Cody & Duax, 1973*b*). We report here the detailed crystal and molecular structures of 3,5,3′-triiodo-L-thyronine and L-thyroxine.

Experimental

Both T_3 and T_4 were separately crystallized from mixtures of methanol and hydrochloric acid by slow solvent evaporation. The crystals were later shown, from the respective structure determinations, to be the hydrochloride salts of the amino acids. In addition, T_3 crystallized as a trihydrate and T_4 as a monohydrate.

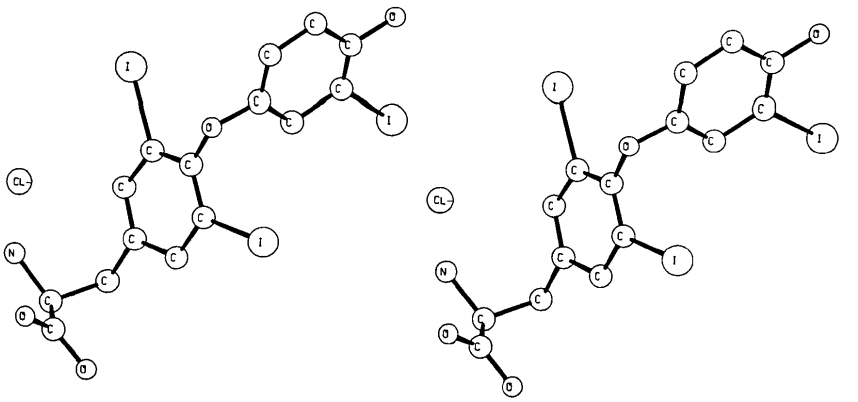
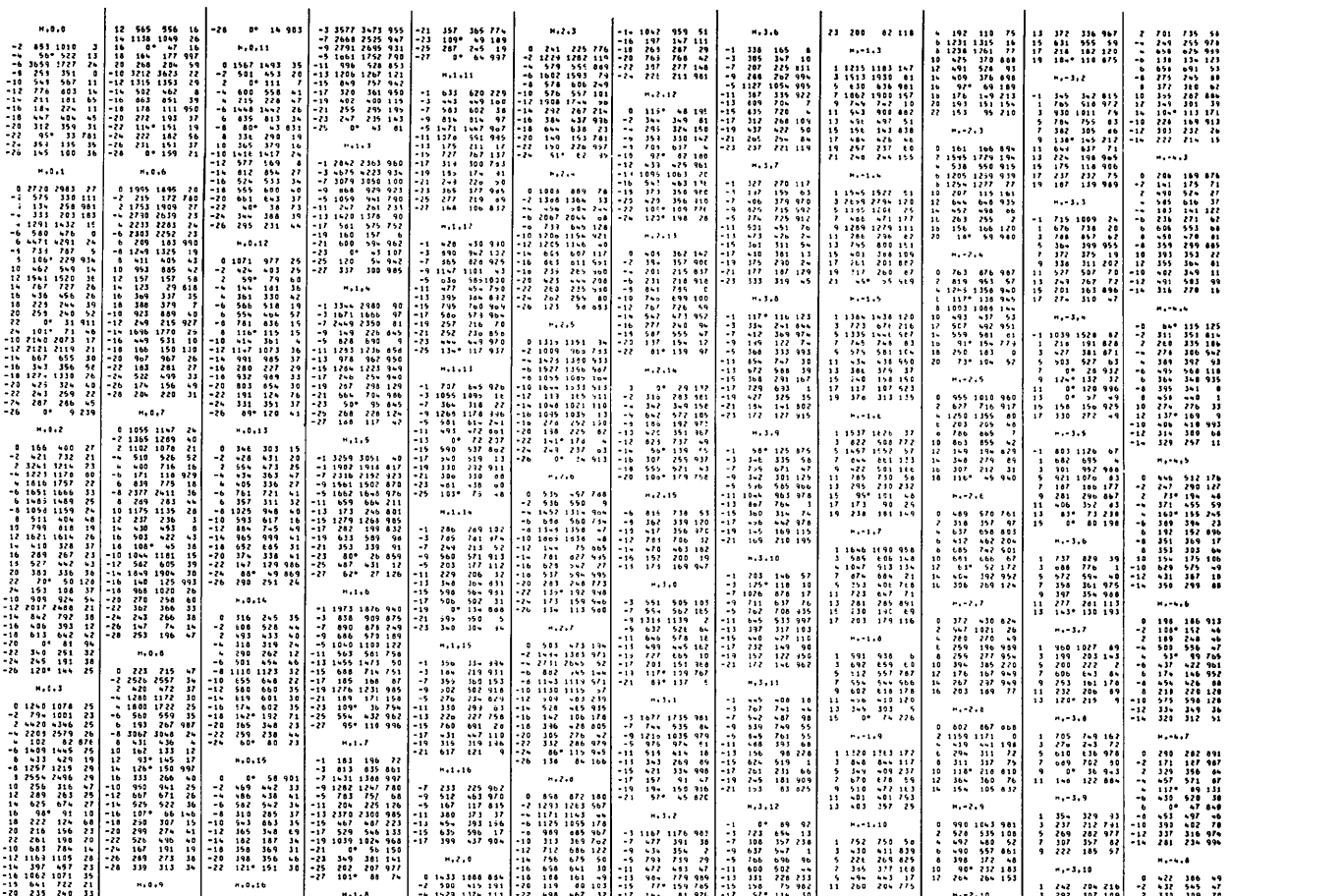


Fig. 1. Stereoscopic drawing of 3,5,3′-triiodo-L-thyronine hydrochloride illustrating the molecular conformation in the crystal.

Table 4. *Structure factor tables for triiodo-*L*-thyronine* .HCl.$3H_2O$

The data are listed in groups of constant k and l. The four columns within each group are h, $10|F_o|$, $10|F_c|$ and phase (millicycles). Reflections whose measured intensities were less than $2\sigma_c$ are indicated with an asterisk and were not used in the refinement procedure.



Unit-cell dimensions and crystal and intensity data are listed in Table 1. X-ray intensities were measured on an automated four-circle diffractometer using the moving crystal moving-counter scan technique (2θ scan) with stationary counts for background radiation on both sides of each reflection. Reflections used in structure refinement were those with intensity greater than $2\sigma_c$, where $\sigma_c^2=(N_{B1}+N_{PK}+N_{B2})+[0{\cdot}01(N_{PK}-N_{B1}-N_{B2})]^2$; N_{B1} and N_{B2} are the background counts and N_{PK} is the scan count. For both compounds, X-ray intensities

Table 5. *Structure factor tables for* L-*thyroxine*. HCl. H_2O

The data are listed in groups of constant k and l. The four columns within each group are h, $10|F_o|$, $10|F_c|$ and phase (millicycles). Reflections whose measured intensities were less than $2\sigma_c$ are indicated with an asterisk and were not used in the refinement procedure.

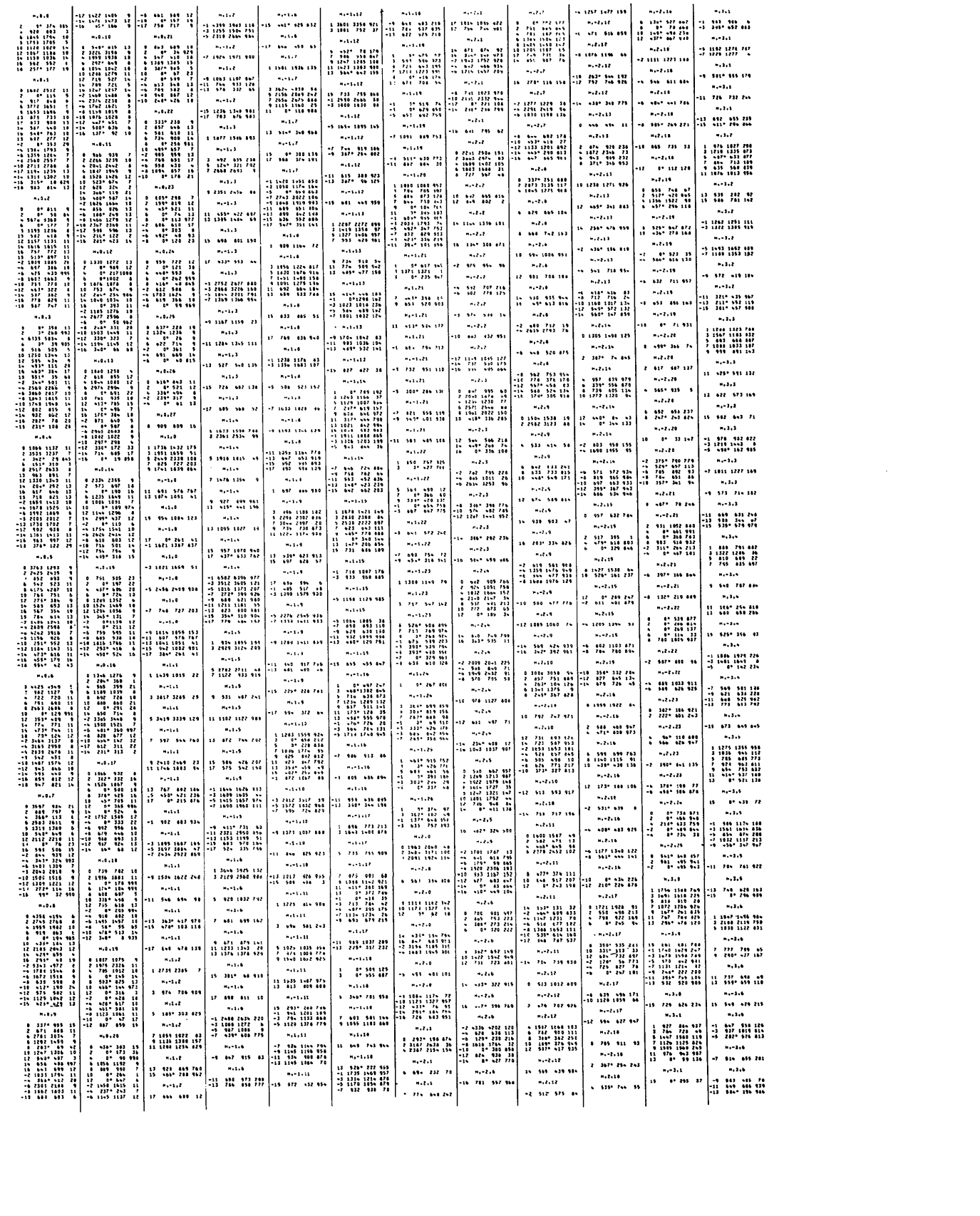
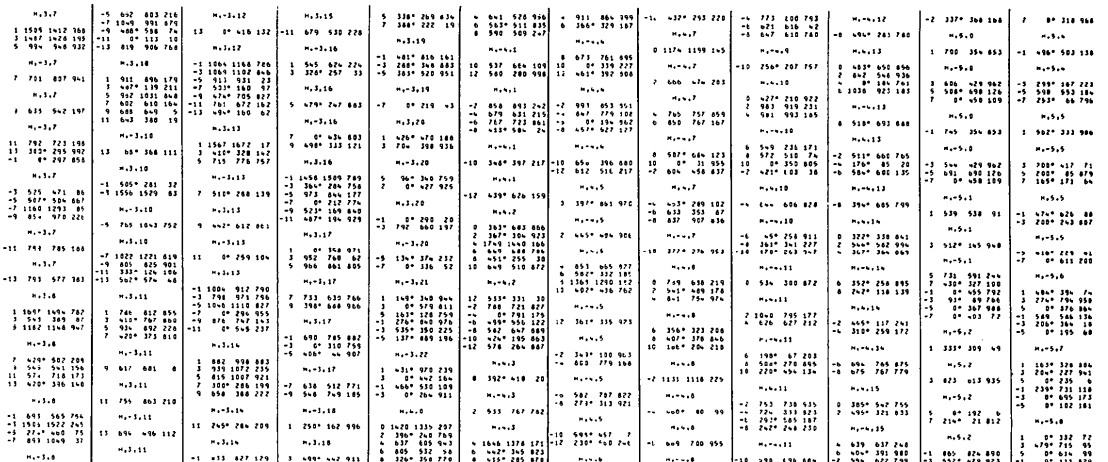


Table 5 (*cont.*)



used as monitors fell appreciably during data collection and the crystals turned from colorless to slightly yellow, indicating decomposition due to X-ray exposure and probable liberation of iodine. Linear scale factors were applied to the data sets to correct for this fall-off of intensity with time. In addition, the T_3 data were further corrected for X-ray absorption with a modified version of the method of de Meulenaer & Tompa (1965). Structure amplitudes were obtained from the intensities in the usual fashion.

Structure determination and refinement

The T_3 and T_4 molecular structures were solved by determination of iodine atom positions from origin-removed, sharpened three-dimensional Patterson functions and subsequent location of the other atom positions from three dimensional Fourier and difference Fourier maps.

Refinement of atomic positions and anisotropic thermal parameters was by full-matrix least-squares calculations. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with initially the weights $w = 1/\sigma_F^2$. During the refinement procedures we noticed that the non-iodine atom coordinates tended to oscillate in successive least-squares cycles and that bond lengths in the two molecules were erratic. We decided to change the weighting scheme and adopt unit weights for all X-ray data. The X-ray data for these crystals, particularly thyroxine, are not as accurate as is usual in crystal structure investigations because of the poor quality crystals we were forced to use; the errors in the measured X-ray intensities are large and not of a random nature. After refinement with unit weights the bond lengths and angles, though still somewhat erratic, were much improved. Refinements ended with discrepancy indices $R = \sum||F_o| - |F_c||/\sum|F_o|$, of 0·07 for T_3 and 0·107 for T_4 (for reflections with intensities greater than $2\sigma_c$). Almost all of the anisotropic thermal parameters for the non-halogen atoms of T_4 proved to be non-positive-definite so that an additional cycle of refinement was performed for this molecule with isotropic thermal parameters assigned to the non-halogen atoms. The final R is 0·118. No attempt was made to locate hydrogen atoms in either case. Atomic fractional coordinates and thermal parameters for T_3 are given in Table 2 and for T_4 in Table 3. Atomic scattering factors used were as follows, I: Thomas & Umeda (1957); Cl^-, O, N and C: Berghuis, Haanappel, Potters, Loopstra, MacGillavry & Veenendaal (1955). Final observed and calculated structure factors are listed in Tables 4 and 5.

Discussion

The three-dimensional molecular conformations of triiodo-L-thyronine and L-thyroxine hydrochlorides are illustrated by stereoscopic drawings in Figs. 1 and 2 respectively.

It has been widely assumed that in triiodothyronine and thyroxine the two phenyl rings are mutually perpendicular and bisect one another. This is not quite the case in the two crystal structures. The orientation of the rings can best be described by the angle that the normal to the plane through each ring makes with the

normal to the plane through the three atoms of the ether linkage: atoms O(2), C(4) and C(1′). If the α and β ring planes were mutually perpendicular and bisected one another these angles would be 90° and 0° respectively. For T_3 the angle between the normal to the plane of the α ring and the normal to the plane of the ether linkage is 90° while between the β ring and the ether linkage plane the angle is −13°. In thyroxine these angles are 101° and −34° respectively; hence in T_4 the α and β rings are more appreciably rotated away from being respectively perpendicular to, and parallel with, the C–O–C plane than is the case in T_3. Because of this rotation the four iodines in T_4 form the apices of a rather distorted tetrahedron with I···I distances of 5·8–7·8 Å and apical angles of the tetrahedral faces of 47–83° (*vs.* 60° in a regular tetrahedron). Iodine–iodine distances in T_3 and T_4 are listed and compared with corresponding distances in triiodothyropropionic acid (Camerman & Camerman, 1974*b*) in Table 6.

Table 6. *Iodine–iodine distances* (Å)

	Thyroxine	Triiodothyronine	Triiodothyropropionic acid
I(3)–I(5)	6·0	6·0	6·0
I(3)–I(3′)	5·8	5·8	6·1
I(5)–I(3′)	7·8	6·7	6·5
I(3′)–I(5′)	6·4		
I(3)–I(5′)	6·0		
I(5)–I(5′)	6·1		

The bond lengths and angles in thyroxine are somewhat erratic and have high standard deviations, as is obvious from the high standard deviations of the non-iodine atom fractional coordinates (Table 3). This lack of precision is caused by two factors: crystal quality limitations on the accuracy of the X-ray data and domination of X-ray scattering by the four iodine atoms. Because the scattering power of an atom for X-rays is proportional to the square of the number of electrons it possesses, the percentage scattering due to the non-halogen atoms in T_4 is only 7·8%. In T_3, it is 10·8%. Hence, the agreement between observed and calculated structure factors is not sensitive to small shifts in the coordinates of the carbon, nitrogen and oxygen atoms with the consequence that these atoms

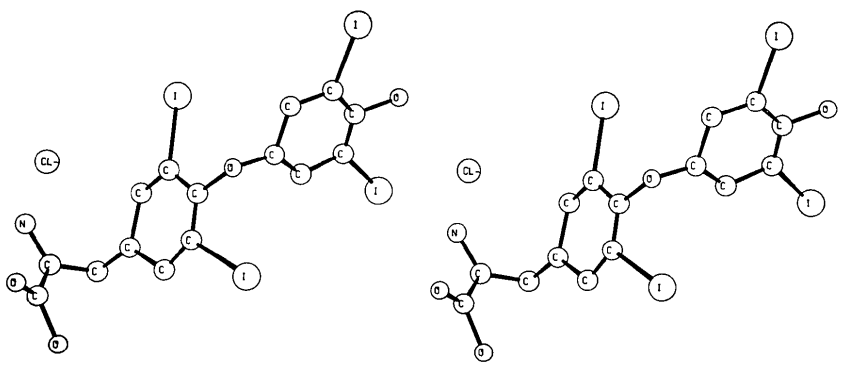


Fig. 2. Stereoscopic drawing illustrating the three-dimensional molecular conformation of L-thyroxine hydrochloride in the crystal

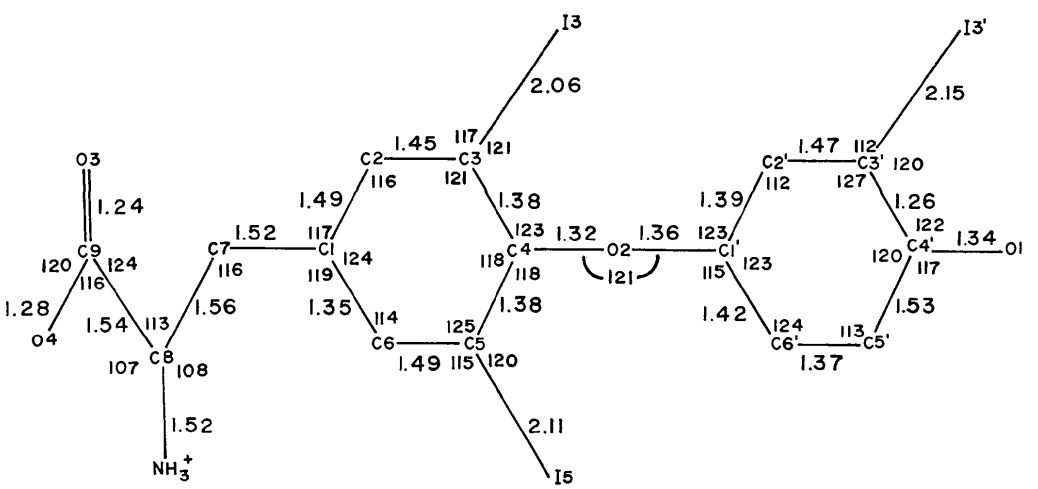


Fig. 3 Bond lengths (Å) and angles (°) in 3,5,3′-triiodo-L-thyronine.

are not as precisely located as they would be if fewer or no iodine atoms were present. When the far more serious limitation arising from the unavoidable use of a split crystal for T_4 data collection is also taken into account, then the higher standard deviations of coordinates and more erratic bond lengths and angles in T_4 are understandable. When equivalent bonds are averaged, however, we find that these averages are respectable: average I–C bond lengths in T_4 and (T_3) are: 2·11 Å (2·11 Å); phenyl C–C, 1·40 Å (1·41 Å); phenyl C–O, 1·41 Å (1·34 Å); average phenyl ring bond angle is 119·4° (119·1°). The C–O–C inter-ring ether linkage angle in T_4 is $118 \pm 3°$, similar to the value of $121 \pm 3°$ found in T_3 and to values found in other diphenyl ether compounds. Individual bond lengths and angles for T_3, as well as the numbering scheme used for both compounds, are shown in Fig. 3.

The three water molecules of crystallization in T_3 take part in a hydrogen-bond network that also includes carboxyl and phenolic oxygen atoms. The chloride ion makes close contacts with three symmetry-related nitrogen atoms and with one of the water oxygens. In addition, there is a short intermolecular iodine–iodine distance of 3·73 Å (*vs.* normal van der Waals separation of 4·30 Å) between symmetry-related I(3)'s, which indicates a degree of charge-transfer bonding between these atoms in the crystal. All T_3 short intermolecular contacts are listed in Table 7.

Table 7. *T_3 short intermolecular distances*

O(4)·····O(*W*1)	2·55 Å
O(*W*1)···O(*W*2)	2·83
O(*W*2)···O(*W*3)	2·53
Cl^-(1)···N(1)	3·18
Cl^-(1)···N(1^{i})	3·19
Cl^-(1)···N(1^{ii})	3·20
O(*W*3)···O(*W*2^{i})	2·73
O(*W*3)···Cl^-(1^{ii})	3·05
O(1)·····O(*W*2^{iii})	2·68
O(1)·····O(*W*3^{iii})	2·69
I(3)·····I(3^{iv})	3·73

Symmetry code

Superscript None	x	y	z
i	x	$1+y$	z
ii	$\frac{1}{2}-x$	$\frac{1}{2}+y$	$1-z$
iii	$\frac{1}{2}+x$	$-\frac{1}{2}+y$	$1+z$
iv	$\frac{1}{2}-x$	$\frac{1}{2}+y$	$2-z$

In the T_4 crystal structure the water molecule is hydrogen bonded to a carboxyl oxygen and to the chloride ion. The chloride also forms short contacts with the nitrogen atoms in three symmetry-related molecules. In addition there are short intermolecular I···I contacts in the crystal which may indicate some charge-transfer bonding between these atoms. All short intermolecular contacts are listed in Table 8.

Table 8. *T_4 short intermolecular distances*

Cl^-(1)···N(1)	3·07 Å
Cl^-(1)···O(*W*)	2·99
Cl^-(1)···N(1^{i})	3·20
Cl^-(1)···N(1^{ii})	3·30
O(4)·····O(*W*^{iv})	2·49
I(3)·····I(5^{iv})	3·98
I(5′)·····I(5′^{v})	3·86

Symmetry code

Superscript None	x	y	z
i	x	$1+y$	z
ii	$\frac{1}{2}-x$	$\frac{1}{2}+y$	$1-z$
iii	$\frac{1}{2}+x$	$\frac{1}{2}+y$	z
iv	$\frac{1}{2}-x$	$\frac{1}{2}+y$	$-z$

The conformations of the alanine parts of T_3 and T_4 can be observed in the stereoscopic drawings (Figs. 1 and 2); they can be numerically described by the values of the torsion or dihedral angles between pairs of bonded atoms. Following the rules adopted by the IUPAC-IUB Commission on Biochemical Nomenclature (1971) torsion angles describing rotation about C^{α}–C are denoted by ψ, torsion angles in the side-chain are denoted by χ, and each angle is measured in the range from $-180°$ to 180°. For T_3, torsion angles are ψ_1: $+8°$; ψ_2: $-175°$; χ_{11}: $+56°$; χ_{21}: $+98°$; χ_{22}: $-89°$. In T_4 similar values are found: ψ_1, and ψ_2, are $-9°$ and $+172°$ respectively, differing by only 17° and 13° from those found for T_3. Torsion angles in the side chain are: χ_{11}: $+66°$; χ_{21}: $+98°$; χ_{22}: $-84°$. These angles are more fully described and compared with corresponding values for diiodothyronine, thyronine and tyrosine in paper II of this series (Camerman & Camerman, 1974*a*).

The elucidation of the crystal structures of triiodo-L-thyronine and of L-thyroxine has shown that the conformations of T_4 and T_3, aside from the absence of one iodine, are on the whole remarkably similar. The major change accompanying deiodination of the 5′ position in going from T_4 to T_3 seems to be a 20° rotation of the β ring with respect to the plane of the ether linkage and consequent change in the I(3′)–I(5) distance. There is little difference in alanine chain conformations between the two molecules.

The most surprising feature of the crystal structure of T_3 is that the orientation of the outer or β ring is such that the 3′-iodine is situated proximal to the α ring and the uniodinated 5′ position distal, rather than the opposite orientation which was suggested by the chemistry-activity studies. This unexpected result poses questions concerning the conclusiveness of the chemical results, the effects of environment (crystal *vs.* solution *vs.* physiological), and influence of receptor on hormone conformation.

In order to test whether this conformation is due to crystal environment – that is, if it is favored because of strong intermolecular interactions existing when the molecules pack in the crystal with the 3′-iodine in this proximal orientation – we examined intermolecular

distances between the atoms of one molecule and those of all its nearest neighbors. All distances involving I(3′) correspond to normal van der Waals separations; thus, no attractions of the charge-transfer I···O type, such as have been elsewhere noted (Hassel & Rømming, 1962; Camerman & Trotter, 1964) are observed to be a factor in stabilizing the 3′-iodine proximal orientation.

To further remove the effects of crystal environment from the issue of proximal *vs.* distal conformation of the 3′-iodine we have performed extended Hückel molecular orbital (EHMO) calculations to calculate the total energy of each conformation. The calculations were performed on the basis of isolated molecules, completely free of crystal environment, using an uncharged T_3 molecule and omitting the chloride ion and waters of crystallization. Details of the EHMO program and orbital parameters employed are given in a previous paper (Camerman & Camerman, 1972*a*). The total energy for the T_3 molecule with the 3′-iodine proximal to the α ring (the conformation in the crystal) is significantly lower than that calculated for the 3′ iodine distal. Because EHMO methods tend to overestimate energy differences only qualitative significance can be attributed to this type of calculation; nevertheless, the results are independent confirmation of the stability of the observed crystal structure conformation.

Notes have recently appeared (Cody & Duax, 1973*a*, *b*), describing the crystal structure of a 3,5,3′-triiodothyroacetic acid *N*-diethanolamine (1:1) complex and of a triiodothyronine crystal, in which the 3′-iodines were found to be oriented distal to the α ring. The authors also refer to unpublished data for another structure having distal orientation for 3′-iodine. We have recently elucidated the crystal structures of two thyromimetic compounds, 3,5,3′-triiodothyropropionic acid (Camerman & Camerman, 1972*c*, 1974*b*) and 3′-isopropyl-3,5-diiodo-L-thyronine (Fawcett, Camerman & Camerman, 1973) the most potent known thyromimetic agent. In the former compound the 3′-iodine is proximal to the α ring as in T_3, and in the latter the 3′-isopropyl group is again proximal to the α ring. Our crystals were prepared from acidic alcohol solutions while the other authors appear to have had large excesses of organic reagents present in their crystallization media. These results indicate that crystallization conditions may play a significant role in influencing the conformation of these asymmetric thyronine derivatives, and they will undoubtly provoke much interesting work on structural and biological aspects of thyroid hormones and analogs under different environmental conditions.

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