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 BO₄ tetrahedron and two BO₃ 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 BO₄ tetrahedra and only one BO₃ 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 $\tilde{K}(2)$ 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 (T₃) and L-Thyroxine (T₄)

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The crystal and molecular structures of the two thyroid hormones, 3,5,3'-triiodo-L-thyronine (T₃) and L-thyroxine (T₄) have been determined by X-ray crystallography. Crystals of T₃ hydrochloride trihydrate are monoclinic with a=29.080, b=5.236, c=17.047 Å, $\beta=115.85^{\circ}$, space group C2 with Z=4. T₄ hydrochloride monohydrate also crystallizes in space group C2 with a=17.23, b=5.14, c=25.15 Å, $\beta=90.47^{\circ}$, 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 T₃ and 0.107 for T₄. In both T₃ and T₄ 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 T₃ and 101° and -34° respectively for T₄. The four iodine atoms of T₄ 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 T₃ 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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	L-Triiodothyronine	L-Thyroxine
Formula	$C_{15}H_{12}I_{3}NO_{4}.HCl.3H_{2}O$	$C_{15}H_{11}I_4NO_4.HCl.H_2O$
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
С	17.047 ± 0.10	25·145 ± 0·100
β	115·85 ± 0·05°	$90.47 \pm 0.17^{\circ}$
$D_x (Z=4)$	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 Ka) cm ⁻¹
Filter used	Ni	Nb
Crystal size (mm)	$0.07 \times 0.04 \times 0.23$	$0.03 \times 0.03 \times 0.50$
Intensities measured	1341	1700
Intensities $\geq 2\sigma_c$	1202	1019
Resolution {	$2\theta = 100^{\circ}$ $d = 1.006 \text{ Å}$ {	$2\theta = 45^{\circ}$ d = 0.93 Å

Table 1. Crystal data

Table 2. T_3 fractional atomic coordinates and anisotropic thermal parameters (×10⁴)

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

	x	v	Z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
1(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
1(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(2)	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
$\tilde{\mathbf{C}}(1)$	0.2687	-0.6142	0.7666	1182	251	503	-96	278	116
$\tilde{C}(2)$	0.2521	-0.4189	0.8127	1418	326	630	26	541	38
$\tilde{C}(\bar{3})$	0.2921	-0.2594	0.8757	935	309	1076	193	532	631
C(4)	0.3428	-0.2923	0.8931	1185	570	254	-7 2	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
Approxima	ate standard	deviations o	f coordinates						
T	0.0001	0.0010	0.0001	O(water)	0.0012	0.0096	0.0	020
- Cl	0.0003	0.0020	0.0004	C	best)	0.0010	0.0060	0.0	017
O and N	0.0010	0.0060	0.0015	C	worst)	0.0017	0.0140	0.0	030

Table 3. T_4 fractional atomic coordinates and atomic thermal parameters (×10⁴)

	U_{ij} are	coefficients in	the expressior	$\sup_{U_{11}} \left[-2\pi^2\right]$	$(h^2 U_{11}a^{*2} + U_{22})$	$\dots + 2klU$ U_{33}	$U_{23}b^*c^*)].$ U_{12}	<i>U</i> ₁₃	U23
I(3')	$ \begin{array}{r} -0.0498 \\ 0.2213 \\ 0.3674 \\ 0.0728 \\ 0.1857 \end{array} $	0.5000	0.0858	516	811	706	233	-116	-85
I(5')		0.2127	0.0536	584	547	432	- 32	64	13
I(5)		0.5663	0.2075	654	545	453	67	15	14
I(3)		0.0585	0.2810	496	1348	775	- 86	73	1
C17(1)		0.3997	0.4265	723	653	565	- 4	-63	24

Table 3 (cont.)

	x	У	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	0.1201	671
C(3')	0.0286	0.3609	0.1115	360
C(4')	0.0969	0.1310	0.0849	16 2 7
C(5')	0.1624	0.0170	0.0957	423
C(6')	0.1973	0.1243	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· 2 985	0· 2 667	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	- 0.09 87	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

Ι	0.0003	0.0020	0.0003
Cl	0.0014	0.0028	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 T₃ 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 T₃ are not equivalent conformationally; they concluded from the synthesis and testing of 'conformationally fixed' analogs of T₃ 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, 1972a, b; Cody & Duax, 1973b). 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.3H₂O

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 $\sigma_c^2 = (N_{B1} + N_{PK} + N_{B2}) + [0.01(N_{PK} - N_{B1} - N_{B2})]^2$; 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. H₂O

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.

-, 1.1 2 1- 37- 385	-17 1422 1485 1	-4 441 349 12 -19 756 317 19	H.1.7 -1 -399 3943 114 -	*.*1.6 15 -41* 925 932				-12-17 	1257 1+77 159 m,-2,12	n2.10 . 230- 527 007 . 0- 70 000	3.1 -1 943 946 6 -3 395* 957 863
- 920 803 3 6 1845 1794 10 3 1753 1705 5 10 1120 1020 14 12 1067 1186 10 14 1138 1036 15	#.0.10 0 5-0* 015 13 2 3221 3150 0 5 1059 1336 10	H. 4, 21	-3 1255 1564 751 -> 2318 2664 984 	H.L.6 17 646 450 65 H.L.7	H-1-12 H-1-12 7 332* 78 179	13 622 525 215 n1.19 1 31 625 52	n.2.1 1: 421 425 423	- 741 147 715 - 1149 150- 171 4 149 150- 171 4 149 150 1-7 10 1705 1107 15 17 7-9 711 76	-1. 171 816 859 -1.2.12 -8 1876 1196 66	12 137 27 238 m.2.11	**************************************
16 562 552 t 16 257- 177 19 H.D.1	• 292* 6+9 8 • 105+ 10+2 18 10 1248 1279 11 12 719 527 14 14 789 721 5	6 1349 1345 15 8 347- 945 5 10 4- 67 23 -2 8- 599 7 -4 813 548 13	H.1.2 -9 1063 1107 967 -11 766 933 128	1 1541 1916 195 H-1.7	• 12-7 1245 144 11 1-23 1343 490 13 564* 6-7 155 m1.12	3 541 546 373 4 721 643 145 7 1214 1223 141 4 6* 48 124 1: 671 708 54				H2.18	
* 1642 2512 11 2 0* 115 5 417 454 5 5 3772 1651 1	10 1247 1257 14 -2 1460 1488 6 -6 2376 2230 8 -6 1762 1621 5	-6 741 542 4 -8 148 847 12 -10 244 426 18	-13 576 332 65 m1.7 -15 1236 1348 961	3 362 838 54 5 2156 2089 2-2 7 2656 2673 888 9 1115 1160 25 11 0- 116 988	15 733 755 868 -1 2510 2685 58 -3 1800 1830 84	*-1.19 -1 1* 519 75	-8 741 1023 970 10 2151 2532 944 17 8* 221 108 14 238* 238 799	#.2.7 -7 1277 1279 14 -5 2291 2519 96	++2+12 -1+ +34+ 348 775	2.18 -6 48-7 4-1 786	-11 726 732 744
13 479 733 10 17 833 908 13 14 547 660 18 15 548 763 18	-10 1076 1028 8 -12 4074 451 7 -14 500 636 6 -16 137 92 10	4 333- 238 4 2 457 646 13 5 781 610 11	-17 703 676 983 -1.1.3 1 1477 1546 893	H.1.7 13 51-* 348 968	*-1-12 -5 165- 1895 165 #1-12	-5 651 642 759 H,-1+19 -7 1091 869 751	-12-1 18 6-1 745 62	-6 1030 1198 136 H,-2,7 -8 6-4 682 178	#2.13 0 000 010 11 #.2.13	-8 985* 269 225 H12,58	-13 692 655 235 -15 613* 786 866 -1.1,7
-2 174- 1793 20 -4 1359 126- 7 -4 1359 126- 7 -4 2540 2557 7	N.0.11 0 945 939 7 2 2265 3239 10	4 4 254 181 10 495 657 7 -2 985 959 13 -4 769 651 17	mu=1.3 3 492 635 234 6 1744 121 292	***1.7 15 ** 100 119 17 *** 37* 191		-,1,19 -11 211- 530 773	***** * 22:1 250* 151 2 3**3 247* *3 * 1699 1*02 105	-10 +53* 418 27 -12 1133 1201 492 -14 +65* 290 413 -16 +67 645 961	2 874 929 234 - 1472 2345 73 - 5-3 959 232 - 371+ 345 953	-18 665 735 33 H2,18	1 876 1827 784 3 1218 1335 873 5 487* 633 877 7 455 713 189
-17 114, 1235 13 -1, 1311 1302 10 -1, 315, 14 424 -1, 943 41, 13	6 1847 1969 9 6 1524 1626 12 10 523 674 7 11 628 325 2	-8 1095 857 16 -10 0* 176 21 -10	7 2668 2693 9 Hala	H.1.7 -1 1.20 1991 490 -3 1050 117- 160	-11 615 148 923 -13 367+ 96 125	H.+1.20 1 1000 1000 452	6 1803 1846 - 11 8 727 - 567 - 46 H2.2	H.2.0 0 337- 251 680 7 2073 3135 117 1 445 1271 944	*.*2.13 10 1238 1271 926	•12 0* 112 120 •.2.19 • 050 740 07	4 435 568 439 11 1876 1813 484 m3.2
*.1.2 *****	16 600° 587 16 -7 1626 1654 10 -8 856 826 13 -6 188° 269 13	0 005- 208 7 2 159- 819 12 4 -55- 521 11 6 - 05 75 13	H1-1-3	-7 27+3 3022 106 -9 18+6 1919 993 11 689 651 305 13 899 6+2 198	-15 681 469 959	6 480 873 124 7 500 710 4-3 9 0* 100 761 11 3* 345 103	10 4.2 445 415 12 4.4 442 2 4.2.2	m,-2,8 6 829 865 184	H-2-13 12 405* 301 843 H-2-13	2 512* 570 865 5 1356 1522 98 6 557- 296 118	13 535 282 62 15 546 761 162 1.3.2
5 1195 1236 4 15 562 518 4 12 1157 1131 11	-10 2367 2369 11 -12 2367 2369 11 -12 298 596 13 -16 241* 122 2 -16 241* 423 14	-2 446 610 17 -5 67 303 6 -6 472 60 13 -8 07 120 23	H.1.3	17 5474 351 141 Hala	1 2297 2272 499 3 1419 1356 97 5 1327 1466 457 7 353 424 161	-3 2034 1743 34 -5 6424 367 753 -7 632 624 513 -1 6214 336 214	14 1104 1330 101 m2.2	H.2.8 8 568 742 553 54-74	14 256* 476 959 H.2.13	1 33- 97 172 1	-1 1262 1251 111 -3 1372 1365 116
16 757 772 11 15 515* 497 11 -2 1009 1045 71 -4 617 146 10	H.0.12 0 1330 1272 13 7 0 040 12	8.4.25 133,727,127	H1.3 17 433- 553 44		*.1.13 * 73* 918 5- 11 77* 509 5-2	m1.21	4.2.7 +2 975 954 96	10 59+ 1006 951 H.Z.&	-2 +36* 136 818 2-13 5+1 718 85+	-2 0* 523 15 566* 616 130	-5 1493 1452 489 -7 1149 1353 192 +.3.2
-10 751 1463 4 -10 751 770 10 -12 461 322 4 -14 597 362 3	6 8-1002 8 5 14/6 1878 8 10 753 674 9 12 2454 255 986	-2 412 544 4	-1 2752 2627 840 -3 2864 3226 168 -3 1844 2281 791	7 1-51 1-80 154 4 1091 1275 196 11 892 865 185 11 659 533 744	*1.13	1 0-235 1u7 H.L.21 7	H1-212 -4 592 707 216 -6 502 778 125	12 801 708 184 n2,8 14 930 935 944	n.2.13 73 717 718 82	-6 632 713 457	-4 572 419 184 H3.2 -11 3214 435 967
-11 607 907 11 *-11-3	16 0* 393 11 -2 1105 1276 19 -4 2677 2596 0 -6 0* 50 962	-4 6- 59 969	*, *1, 3 *, *1, 3	H,1.8 15 833 885 51	-3 1023 1018 236 -3 564 089 192 -7 1001 1032 124	9 653 520 903 He-1.21	**************************************	ie	-10 1160 1017 134 -12 549- 572 132 -14 560- 147 659	-8 653 886 160 4,-2,19	-13 211 252 115 -15 301 - 557 500 3,3
2 3* 260 493 4135 583~ 8 5 3* 39 905 5 516 505 5	-10 1503 1649 11 -12 330+ 323 7 -14 1194 1145 12 -16 3-0+ 66 6	2 1324 1236 4 07 76 9 4 422 714 9 -2 07 361 5	m.1.3 -11 1284 1345 111	17 769 036 9+0 17 769 036 9+0	-9 170+ 18+2 43 -11 983 1036 10+ -13 +49+ 532 1+1	**1.21 -1 at. 79* 213	-10 +03 +32 +51 H.2.2	-1 2615 2743 76 H,-2,4	0 1305 1+94 125 #2.1+	m2.28 8 -999 366 76	1 1746 1173 748 3 1567 1163 532 5 463 466 587 7 1088 1833 187 9 469 491 163
10 1250 1344 13 12 595 434 4 14 493* 111 24 16 463* 364 17 13 551* 35 66	H.0.13 0 1440 1250 2 2 610 655 12	-6 691 669 15 -6 89 60 815 -6 89 60 815	H,-1,3 -13 527 5+0 135 H,1,3	1 1230 1171 43 8,-1,4	#++1+13 +1> 027 422 38	*.+1.21 -1 732 951 110	-17 11-9 1845 127 -14 737 530 175 -16 736 445 084		2 347* 7* 8*5	H+2,20 2 617 607 137 H-2,26	*3.3 11 +75* 591 132
-2 344 501 11 -4 2569 2266 9 -6 3060 2617 10 -8 1043 1415 11 -10 1748 1948 14	4 10-4 1040 12 6 2974 2094 9 8 2* 691 22 10 741 935 10 12 411* 785 15	0 616* 843 11 2 6* 521 12 4 336* 496 6 -2 239* 317 9 -4 0* 61 13	-15 728 682 130 Mg=1,3	-5 386 523 152 1,8	H1,14 1 0* 709 192 3 1243 1164 37 5 1179 1007 934	-5 300* 206 130 Hu-1.23	0 ev7 995 60 2 7040 147e 49 1210 1230 77	-12 567* 458 83 -14 548 524 134 -18 374* 305 918	139- 556 870 1739 605 115 10 1777 1120 9.	* 565* 935 5 n.2.24	H.3.3 13 622 573 169
-12 802 815 9 -14 932 862 17 -16 2820 78 20 -13 2310 108 28	16 176+ 38+ 1 16 176+ 38+ 18 -2 871 640 5 -4 2965 2643	H.0,27 8 909 809 15	-17 685 568 52 M.1.4 3 1623 1598 784	-7 1633 1828 96	7 217 619 157 9 624 645 972 11 317 446 798 13 1021 442 994 14 10-4 492 943	-7 821 555 119 -9 5637 601 918 1.21	\$ 1961 2022 150 10 -18* 136 285 2.3	0 150- 1538 19 2 2582 3123 40		6 652 654 237 8 2474 248 624 8,-2,20	15 582 643 71 m.3,3
#.8.4 8 1046 1132 11 2 3535 1237 7 4 342* 29 445	-8 10+2 1022 9 -10 297* 298 6 -12 330* 172 33 -16 716 645 37 -16 6* 19 850	H,1,0 1 1736 1432 175 3 1951 1659 51 5 2449 2338 108	\$ 2361 2534 99 Ma-1.4 \$ 1918 1415 49	H.1.8 •11 1359 1164 778 •13 947 053 919	-1 1911 1968 865 -3 1326 1203 199 -5 9-1 444 16 	-11 583 485 188 H,1,22	12 5ec 566 218 1	* 533 *1* 58 #.2.9	-2 803 150 155 1690 1155 95	10 0* 33 1+7 ×+2.20	-1 478 482 422 -3 1219 1443 8 -5 410* 167 985
6 151* 310 3 8 2517 2633 4 13 963 891 7 12 1330 13+3 11 15 20+* 252 13	H.C.14 0 2334 2355 0 2 573 697 1	7 825 727 203 9 1741 1439 464 8,-1,0	7 1076 1350 9	-15 952 995 893 -17 893 594 139 -4,1,8	-7 8-8 724 884 -9 754 762 69 -11 563 452 836 -13 144* 423 239	1 150 757 761 3 3+ 427 761 84-1-22	-2 742 795 228 -4 845 1011 26 -6 2614 1253 96	6 6-2 133 741 6 633 733 635 10 4-6 64 171	-6 571 572 934 -8 819 965 964 -10 697 663 933	-1 529* 657 113 -6 785 682 11 -8 765 682 11 -1 765 681 88	-7 1811 1227 169 H. 313
16 617 646 13 15 718 821 13 -2 1659 1413 10 -4 1678 1525 14 -6 1992 1469 6	6 1235 1669 11 6 1235 1669 11 8 1006 1091 7 10 6* 189 974 12 1146 1296 4	11 691 576 767 13 1974 1051 41 4.1.0	9 927 699 961 11 4154 441 146	1 697 886 980 M1.9 3 996 1108 182	-15 6+2 662 203 #1.15 1 1678 1+21 1+9	5 561 690 12 7 5 366 40 9 334- 470 131 -1 0* 656 756 -3 467 647 775	H,-2,3 -4 346* 396 776 -10 574 482 745	12 674 565 614	-10 616 636 646 m.2.15	#12121 # 147* 78 216	-9 573 71+ 162 n,-3,3
-3 2003 2012 7 -13 1730 1702 7 -12 902 938 4 -14 1381 1413 11 -16 981 997 12	14 299* 437 12 -2 8* 110 4 -4 1754 1541 10 -6 2626 2*14 11	19 95% 100% 123 H1.8 17 0* 261 %1	H,1.4 13 1095 1027 14 H,-1.4	5 2296 2302 836 7 30-4 2997 20 9 735 730 873 11 122- 117- 930	3 2610 2308 84 5 2530 2222 897 7 623 643 111 9 455 778 888 11 8 340 144	H.1.22 -3 6.1 672 2.0	-12 1247 1441 952 #.2.3 -14 346* 242 236	14 939 903 47 H2.9	n2.15 2 517 355 1	2 931 1052 840 4 93 641 991 6 0. 368 763	-13 335- 575 974 -13.
-11 374+ 122 29 +,1,5	-10 716 501 1 -12 756 756 1 -16 489* 518 1	-1 1621 1367 437 H,1,0 -3 1021 1659 51	15 957 1070 940 17 4374 633 767	H.1.4 13 539* 421 913 15 697 628 57	13 1-7* 205 454 15 733 686 189 7.1.15	-7 690 754 72 -9 -5-* 314 141	H2,3 -16 584* 499 466	-2 019 561 94	6 0+ 329 646	-2 311- 24- 213 -2 9- 47 141 #.2.21	1 838 791 867 3 1322 1286 86 5 810 649 22 7 755 835 697
2 2425 2415 4 452 493 9 4 542 523 11 8 4175 4247 10 10 241 751 4	0 751 505 21 2 0+ 197 24 5 57- 605 21	H1-2,8 -5 2456 2429 108	-1 6582 6396 977 -3 3512 3605 121 -5 1016 1373 207 -7 272* 399 926		-1 716 1007 176 -3 933 960 645 H1-15	H1.23 1 1308 11+9 79 H.1.23	4.2.4 0 042 905 765 2 924 1051 756 4 1832 1664 153	-6 1359 1676 969 -6 366 677 936 -8 1688 1976 129 2.9	10 526- 161 237 w2.15	-6 397+ 166 804	H3.4 9 542 787 834
12 275* 38% 9 1* 585 653 13 16 367 35* 19 15 78* 61* 13	8 1249 1352 10 152% 1669 1 12 1286 1056 16 345* 131	Hulu0 -7 746 727 203	-9 688 621 980 -11 1211 1181 55 -13 623 800 981 -15 354* 110 904	N.1.9	-5 1158 1128 945 N.1.15	3 717 547 142	0 21-0 21-7 34 0 517 441 211 10 772 873 65 12 0* 105 34	-10 500 477 776	-2 611 601 879 -2 715		11 100° 250 410
-+ 2409 2594 4 -+ 6262 3916 7 -5 1156 926 1 -10 251* 552 13	-6 0* 211 1 -6 759 595 1 -8 685 538 1 -10 1616 1766 1	-9 1414 1855 153 -11 607 576 767 -13 1041 1051 41	#+1+5 1 93% 1855 193 1 2929 312% 293	#1-219 -9 1289 1-11 839	-7 030 033 110 -9 629 630 130 -11 932 1099 996 -13 400* 129 761	5 526* 508 895 7 711 769 976 9 2* 265 905 -1 675 739 203 -1 392* 539 795	1. 8.0 7.9 791 1. 3.3- 535 1	-12 1085 1060 74 m2.9 -14 569 424 935	1205 134- 53 m2.15 802 1103 871	* ** 269 117 * 0* 114 31 * 740 1014 417	15 525* 356 43
-14 473 616 11 -16 455 179 16 -18 954 42 43	-14 450+ 524 11 H.0.16	-17 344 261 41 Hilis	m1.5	H.1.4 -11 540 917 756 -13 681 680 68	H1.15 -15 635 455 447 H1.16	-3 393* 430 354 -7 0* 329 561 -3 635 610 128	-2 2009 20-1 22 545 8-9 7 545 8-9 7	+16 342+ 392 965 #42+10 0 3006 3050 54	-5 766 760 894 m.2.19 -18 354* 332 294	-2 \$67* 498 90 m2.72	-1 1886 1979 226 -3 1981 1699 8 -5 6* 192 239
2 4425 4549 1 7 942 1127 1 7 722 720 11	2 244 * 360 4 565 359 2 6 1389 1039 8 692 726 1	H1.1 3 3417 3245 25	H+1+5 9 531 487 241	+,-1,9 -15 225* 228 701	1 0* 007 2×7 3 008*1302 8×5 5 710 038 873 7 1235 1269 132	1 0* 267 454	-8 570 795 51 H,-2,4 -10 978 1127 80	2 457 751 447 6 261+ 10+ 12 6 13+1 1375 8 2-5* 367 42	-12 877 645 13- -14 679 726 45 -1.2.16	-+ 649 1033 911 -6 549 626 929 	-7 549 581 138 -9 621 635 228 -11 648 525 962
10 0° 129 991 12 353° 409 14 774 771 1	12 0 291 2 14 450 714 -2 3345 3448 -4 1500 1521	H-1+1 5 3+19 3339 129	M1.5	-17 59- 372	9 617 511 1-1 11 173* 128 35 13 +54* 555 978 -1 -76* 776 20	3 364* 699 859 + 305* 819 156 7 282* 668 98 -1 3* 69 110 -1 332* 426 176	4,2,4 -12 631 497 7	10 792 7-7 97 H-2-10	* 1459 1922 ** #2.15 2 548 465 947	5 342* 186 92 2 222* 601 2* 12.23	-11 773 613 742 h:3.4
14 72* 12% 1 -2 3%6* 1137 -4 3165 2950 -5 2838 2676 1	-4 420 477 1 -10 454- 147 1 -17 612 111 7 -16 211- 113	7 597 544 760 7 197 544 760	13 672 7mm 202 Hu-1.5	1 1243 1559 924 3 0* 454 212 5 3* 228 434 7 1645 177- 55 9 425 442 413	-5 1710 1740 945 W.L.16	-3 649 642 654 -7 269- 356 964 H1.25	-1+ 23+* 408 1 -1+ 10+3 1037 90	12 73(643 12) 16 723 547 45 -2 1653 1653 10 -4 524 657 44	71. 808 973 	5 565 110 40 5 566 625 15	n,3.5 1 1275 1355 958 3 1836 946 112
-10 1407 1574 11 -12 143 446 1 -14 593 446 1 -14 651 412 1	4.6.17 0 1046 932 2 342- 332 1	*,-1,1	15 586 426 207 17 575 542 190 H.1.5	11 423 847 792 13 354 454 49 16 4070 855 454 -1 472 1657 45	-1 005 486 894	1 465* 915 757 5 483 461 56 -1 7* 393 186 -1 303* 244 29	H.2.5 0 520 662 95 2 1269 1213 98 - 1922 1979 16	-6 505 496 1 -8 626 771 21 -10 373+ 327 41 -10 -10 -10	6 11-0 1115 01 10 -39* -30 130 	-2 390° 6+1 13 H2.23	7 924 963 611 9 954 753 612 11 414- 137 149 13 8- 521 136
.0.7 • 3597 915 2	6 0° 540 1 576° 525 1 10 55° 705 1 12 0° 365 1	1 13 767 802 146 5 450 421 236 1 17 0° 215 876	-1 1646 1626 113 -3 1609 1605 4- -5 1415 1657 974 -7 1690 1460 111	-,1,10 -3 2812 3517 39 -5 1572 1832 968 -7 392 725 429	-11 559 536 635 -11 540- 144 635		+ 161+ 1727 3 5 12-7 1321 1+ 10 1401 1752 + 12 746 9-8 8 1- 0 +11 13	-12 513 593 91 #22.10	-2 531* 639		h,-3,5 15 8* 439 72
366* 113 6 2583 2611 5 1311 1360 10 543* 649	-2 1752 1345 1 -4 992 956 1 -4 992 956 1	-1 902 403 934 M-1,1	H1.5 -9 611* /31 63 -11 2321 2550 356 -13 1153 1199 51	4,-1,17 -9 1373 1057 888	1 496 773 213 3 1643 1400 876	3 367 107 C4 -1 137 648 354 -3 635 757 393	H,-2,5 10 402° 326 30	-10 71 717 10 5.7.11 0 1600 1507 5	H2-16		-1 506 117- 148 -3 1561 161- 616 -5 65- 67- 206
14 595 506 1 -2 499 939 1 -3 391 129 939	-12 417 424 1 -14 664 68 1	3 -3 1895 1887 185 2 -5 3697 3886 47 -7 2434 2522 869	-17 52. 135 746 -17 52. 135 746	+.1.10 -11 440 425 923 -1.18	1.17 5 733 755 909 +1.17	0 1943 2040 48 2 3484 3171 100 1 2041 1924 114	2-5 -2 3701 1767 1 -6 6-1 616 79 -6 179* 59 56	3 6 2379 2452 10 5 w2,11		*2.28	·
-1 2040 2010 -10 1505 1516 -12 1309 1221 1 -11 272 114 1	0 739 782 1 2 1956 1861 1 0 176 9	0 1 -9 1574 1622 248 9 -1.1	1 3646 3925 132 3 2129 2564 966 	-13 1213 926 955 -15 588 +94 3	2 975 991 68 9 1398 11-2 921 11 -11* 300 169	6 561 334 424	-+ 1920 2306 11 +10 953 1167 15 -12 +27 +63 + -14 + 0* 65 44	3 2 3 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	1 7 -10 -17 210 ⁺ + 34 220 ⁺ 226 4 -17 210 ⁺ 226 47	N,3,1	-13 746 F01 142
-16 44- 32 34 -16 44- 32 34 -18 4194	10 336 494 12 735 616 1 -2 6 265 6 -9 910 402	-11 546 694 98 H-111	5 928 1832 792 Hydrb	1 1225 41+ 900	-1 0 -14 15 -3 713 744 42 -4 487+ 395 175 -7 111- 1234 20	1 1111 1142 1-2 10 1171 1127 14 12 3* 42 14	-1,2,6 0 705 901 96 7 405 753 2	**2.11 1* 151* 131 3 7 -2 **** 609 63 3 -4 1147 1231 7	*.2.17 2 0 1721 1928 9 3 2 550 496 21 0 798 922 16	3 1001 1010 22 5 414 610 2 7 1072 1706 92 8 157* 261 6 1 157* 261 6	-15 0° 246 484
1955 1962 1 6 919 163 1 919 163		5 -15 +74+ 103 114 5 -1.5 +74+ 103 114	H1.6 9 671 879 141	3 096 561 2-3	-11 969 1037 269	H2.0 14 4334 134 754 16 447 643 911	- 146* 273 21 - 0* 320 21 	-6 518 177 18 -8 1348 1653 11 -10 530* 614 18 -17 548 767 53	2 6 6° 2«5 9 1 . m2.17 7 8 350° 535 24	- 13 246* 578 13 	5 3 2160 2119 790 5 1030 1127 031 m,-3,6
12 2145 2443 1 14 4244 455 16 245* 40 1 -2 5343 4972 -4 1704 1544	1 1417 1075 1 1417 1075 2 1975 2326 1 7 1975 1012	• K-1-72	13 1376 1378 525 m.1.6	7 4/1 1004 776 9 10-0 1002 925 	1.18 1 01 509 12	1443 19-5 301 H.7.0	1 342* 657 11 10 1427 1542 4 12 731 723 4	4 H2.11 4 -1. 70. 738 83 H.2.12	10 331° 513 3 12 605 732 49 -2 120° 56 77 -5 725 627 7 -6 0° 257 10	1 -1 1/40 1029 24 7 -3 1078 1558 74 1 -5 170 442 4 4 -7 1131 1214 1 -9 244* 222 2	7 777 744 65 4 240* -27 167
-8 1672 1518 -8 635 598 -10 612* 190 2 -12 575 582 1 -16 1125 1862 1	8 503 425 1 10 414 144 97 1 12 0* 316 2 -7 0* 428 1	3 ×1,2 3 3 974 706 909	17 810 811 10	11 1935 1487 975 13 413 809 404 #1.11	H.1.18		1	5 0 513 1012 41 m2.12	-4 639 696 17 -10 1120 1859 6	-13 532 523 5	11 554- 554 att n1.4
-15 969-469 1 H.8.9 B 3374 995 1	-6 +61* 581 -8 1123 1061 -10 0* 47 5 -12 887 859	M:1.2 5 185* 303 825 15 M:-1.2	-1 2468 2634 220 -3 1068 1272 6	15 293* 200 7 40 -1 941 1201 10 -3 794 1133 844 -5 1129 1378 779	H1.18 7 603 541 144 9 1055 1180 441	-12 -11 - 74 - 91 -12 -291 - 145 -74 -16 -724 - 643 -951 -16 -724 - 643 -951	167+ 396 70 -2 +336 +207 1	4 2 .74 202 4: Hit.12 10 4 1507 1268 1	*2.17 -12 594 627 94	-15 729 626 2 Hi3il 1 927 844 9	n,3.6 17 -1 647 536 126
2 871 888 1 6 2781 3034 6 1292 1459 8 283* 69 4 19 1247 1306 1	7 H, 8, 25 8 434-343 2 0-173	7 1059 1077 03 9 11116 1300 157 11 1200 1216 029	-7 -1.4	*,1,11 -7 926 1166 796 -9 1165 1196 954	H,1,10 11 649 743 944 H,41-18	2 292+ 198 474 2 3147 2434 36 4 2347 2154 154	-+ 628 636 1 -6 129 230 2 -6 1016 1764 -10 0 340 8 -17 824 938	13 6 742 100 1 16 8 308* 342 2 12 10 149* 376 9 14 12 507* 417 9 14	H,2.18 H,2.18 H,2.18 H,-2.18	3 74- 728 1 5 1+47 1548 1 7 112- 1125 8 9 1585 1548 2 11 976 943 9	-3 737 1017 614 -5 282* 526 813 -6 -3.6
17 960* 687 16 656 688 99 16 661 699 1 -2 1835 1796 1 -6 366* 652 4	7 6 1056 1192 2 8 889 950 1 10 8 266 1 12 8 647	13 121 441 741	-11 650 173 200	-13 1145 1064 70 m.+1.11	13 526* 222 55 -L 1735 1669 95 -S 1316 1216 67	H1-2-1 6 69- 232 70 H-7-1	-14 8+ 427 7 -14 781 557 9	10 N2.12 14 565 439 5 14 7.2.12	14 2 3674 254 24 H,2,18	.3 13 8* 59 1 .3	16 -7 816 655 281 1,2,6 17 -9 843 485 28
-6 2301 2188 -8 1862 1803 1 -13 683 603	• -2 1458 1615 -4 237* 243 • -6 1145 1137	11 #1,-1,2 12 17 11 11 11	-13 786 858 777	-15 572 532 854	-7 932 939 7	· 774 648 243		-2 512 575	a 535° 744 1	*	-11 52. 18 12

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H.3.7	-5 652 803 216	H3.12	H. 3.15	5 336 269 434	- 6-1 526 956	- 911 86- 799	-1. +32* 293 220	773 200 793	H4.12	-2 337+ 368 188	7 84 318 968
1 1505 1412 368	-9 +08* 558 74	13 0* 416 132	-11 679 530 228		\$ 590 509 2.7	0 300- 324 387	H.4.7	-6 647 610 740	-0 4944 243 240	×.5.0	
5 994 948 932	-13 819 906 768	m.3.12	H3.16	P.3.19	N1.1	*. *	0 1174 1199 145	P9	H. S. 13	1 700 354 453	-1
H3.7	H.3.16	-1 1064 1168 786	1 545 624 224	-1 -3 268* 348 683	10 537 644 109	8 673 761 695 10 0* 339 227	H	-10 254+ 207 757			
7 701 807 941	1 911 496 179	-3 1069 1102 846	3 326" 257 33	-5 383* 520 951	12 560 280 998	12 +61* 397 508			2 8+2 5+6 936		*>
	3 407* 119 211	-7 533- 160 97	H, 3, 16	+3.19	H.4,1	*	/ 666 6/4 283	*.*.10	E 1036 923 145	5 508* 698 126	-5 598 553 184
	7 602 610 164	-11 /61 672 162	5 4795 247 665	-7 0* 219 +3	-2 858 893 242	-2 991 653 551	4.5.7	2 983 919 231	m	7 0* +50 109	-7 253* 66 796
1 633 947 14/	11 6-3 340 19	-13 4944 160 62	H3.16	H.3.24	-6 267 223 861	** 6*7 779 102	- 765 757 859 0 850 767 167	· 501 993 185		H.5.0	H.5.5
4,-3,7	H-3-10	n.3.13	7		-8 +53* 584 24	-8 457 627 127		P 10		-1 745 254 453	1 902* 333 980
11 792 723 195		1 1567 1672 17	9 498* 333 121	3 70+ 398 936	#*.1	H		6 5-9 231 171	P.4.15	a5.0	#5.5
-1 4. 297 858		5 715 776 757	H.J.16	H3.20	-10 3+6+ 397 217	-10 650 396 880	8 587* 644 123 10 0* 31 955	10 0* 350 805	-2 511* 661 765	-3 544 429 967	3 2000 412 21
H. 1.7	*.3.10	w3.13	-1 1.58 1509 789	5 96- 340 759	P.9.3	-12 612 516 217	-7 604 458 637	-2 +21* (03 36	-6 58+* 600 135	-5 691 690 126	> 200 45 479
-3 525 471 86	-1 505* 281 32	7 510* 268 139	-3 364* 284 758	2 0* +27 925		H.4.5	H. 4.7	····10	H4,13		
-5 507* 504 667	B-1.10		-7 0* 212 774	H.3.20		3 397* 861 970	249 102	606 828	-8 394+ 685 799	*>.1	H.3.3
-9 85. 970 220			-11 487* 194 929	-1 0* 290 20	P.4.2	*. **. 5	-8 633 353 67	P 10	P.9.19	1 539 538 91	-1 474* 626 88
H3.7			H+3.17	-3 /42 660 197	2 367 304 923	2	····.7	-6 -5- 258 911	0 322* 330 643	H.5.1	81.5
-11 747 785 188	H.3.10	m3.13	1 0* 15# 971	H 3.20	- 17-9 14-0 166	P 6	-10 1774 276 161	-4 361* 341 227	2 544* 562 994	3 912* 145 948	
H.3.7	-7 1022 1221 619	11 0* 259 104	3 952 768 62	-5 134 374 232	6 +51* 255 30 10 549 510 472	* #51 855 877			N1.1.	m5.1	-7 0* 611 200
-13 795 577 383	-11 333- 124 106	******	Ha+3,17	8.01.21		6 582* 332 185				5 731 591 244	H3.6
8.1.4	w. t. tt	-1 100+ 912 790				13 402* 436 762	7 5-1- 489 178		8 242* 118 139	-1 0* 455 792	1 4849 394 /4
		-5 10+6 1110 827	9 398* 668 966	3 0* 579 411	-2 768 721 427	*. **.5		P.4.11		-3 93* 89 766	3 2740 794 950
3 5+3 349 47	3 410- 767 800	-9 876 747 143	H. 3.17	-1 276* 8+0 976	-6 -99 556 122	12 361* 335 975	H8	2 10-0 795 177	-2 445- 117 241	-7 003 72	-1 549 546 136
9 1182 1148 447	7 +20+ 375 810	-11 0- 5-5 237	-1 690 745 442	-3 535* 350 225	-8 542 647 689	P. 1. 5	6 356* 323 208		-4 310* 259 172	H,-5,2	-5 0* 195 60
H3.6	81.11	8.3.14	-1 6* 310 755		-12 578 264 887		10 106* 204 218		H4.34	1 333* 309 49	H5.7
7 429* 502 209		1 862 994 683			A.A.3	853 779 168	H 8	5 504* 270 A95	-6 696 765 875	H.5.2	1 163* 328 884
11 574 718 173		5 415 1007 921		3 0* 4+2 16+	0 392* 410 20	H 5	-2 1133 1118 225	10 2200 494 134	-8 675 767 779	3 023 013 935	5 0* 235 6
		9 656 368 222	-9 546 749 185	-3 0* 26+ 911	NN.3			*. 4.11	*. *. 15	n5.2	-1 239* 731 118
	11 755 863 210	R3.14	a1.18	H.L.0	2 533 767 742	-8 279* 313 921		-2 753 738 935	0 385* 5+2 755	5 AP 197 5	-5 0* 102 181
-1 693 565 754	#,-3.11	11 2450 246 209	1 250* 162 996	0 1520 1335 297	P	P.V.5		-t 292* 585 187		7 2140 21 412	H5.8
-3 27. 460 75	13 696 496 112	8.3.15		2 196* 240 769		-10 5950 657 7				n.5.2	1 0* 132 72
H 1. 4	H.J.11			6 805 532 58	6 ++2* 3+5 \$23				6 .0.* 391 980	-1 065 024 890	5 0* 614 99
-3 641 648 768	-1 708 681 222	-3 0* 121 142	5 525* 351 4-1	10 +13+ 57+ 112	10		*****	-10 >90 (96 664		-3 552* 429 923	-1 0* 111 629 -3 0* 531 163
11 553 624 103	-5 526 . 495 9	-7 0* 448 64	H3.18	H4.0	H4.3	2 693 729 122	-10 2/9* 630 459	*****	-6 702 568 988	H5.2	-5 0* 208 167
H.3.6	-9 1027 929 792	-9 646 598 128	7 01 450 219	12 .52* .34 471	12 0. 375 226	• 347* 245 992 • 435* 424 771	A. 4.9	0 1025 526 762	m4.16	-5 369* +52 951	H,-5,9
11 762 715 533	-13 664 710 102	*,-3,1*	9 503* 745 19	-2 -2 2-3 767	-2 337* 6+3 1+2	8 481° 629 173 10 174° 48 777	0 747 790 174	* 3 2	2 299* 225 40		1
H.J.9	H.3.12	-11 57- 3-3 787	H. 3.18		-0 +30* 605 856			2 62* 601 2	\$ 379* 127 96		-1 359 457 171
1 554 -47 491		n. 3. 15	-1 770 645 183		N.N.3			1 313 307 377	-2 578 847 858	3 -10- 21 200	-5 264 295 20
80. 81. 207	1 0 75	1 715 650 843	-5 -577 20	-6 339- 52 30	-0 6-+ 7et 183	-2 525 413 214	2 -24- 370 850	*.*.12	-6 609 359 936	5 304* 788 134	H5.10
7 1661 1623 231		5 577 1063 81	-/ //1 /35 140	H	-10 774 860 228	P.4.6	9	6 521* 358 163	Pares 17	-1 542* 546 79	1
7 647 751 456	H.+ 3.12	m3.15	H3.16	-8 367* 404 755	H4.3	963 955 183	- 800 673 1-6 b 605 510 837	*****12	0 01 367 19	-5 550 616 71	3 39- 210 107
H3.9	7 508 252 914	7 -000 -0 210	-9 +18* 699 124	0	-12 0* 151 166	-6 1063 1219 186	1 +33* +51 433		2 0 237 40		-3 .57. 563 2.5
11 461* 594 12 13 0* 260 67	H,3,12	9 741 632 793	H, 3, 19	-18 633 574 112	**.*	*	*9	M 12	-2 570 639 925		*5.11
8.1.9	9 685 791 992	-1 -01* 264 157	1 358* 110 136		0 523 743 747	-5 316* 449 733	10 579 519 241	-7 155 362 125	>00- >44 462	1 447 346 996	1 30
		-5 224 512	H3.19		·	····	H 9	-6 0* 389 893	H18	M5.4	-1 0* 307 488
-1 60/* 611 187		-9 307- 461 826	3 707 777 229	2 931 - 123 402	2 1109 909 221	-13 62- 52-1060	-7 913 895 167	ł	2 478 762 826	3 707 643 193 5 514 399 204	1

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 originremoved, 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 T₃ are given in Table 2 and for T₄ 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 T₄ 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, 1974b) in Table 6.

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-

Table 6. Iodine-iodine distances (Å)

	Thyroxine	Triiodo- thyronine	Triiodothyropro- pionic 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		

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 T₄ is only 7.8%. In T₃, 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 fillustrating 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 T₄ data collection is also taken into account, then the higher standard deviations of coordinates and more erratic bond lengths and angles in T₄ 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 T₄ is $118 \pm 3^\circ$, similar to the value of $121 \pm 3^\circ$ found in T₃ 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.

	Tal	ble	7.	T_3	short	intermol	lecul	'ar a	listances
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$O(4) \cdot \cdot \cdot O(W1)$	2·55 Å
$O(W1) \cdots O(W2)$	2.83
$O(W2) \cdots O(W3)$	2.53
$Cl^{-}(1) \cdots N(1)$	3.18
$Cl^{-}(1) \cdots N(1^{i})$	3.19
$Cl^{-}(1) \cdots N(1^{11})$	3.20
$O(\hat{W3}) \cdots O(\hat{W2}^{i})$	2.73
$O(W3) \cdots Cl^{-}(1^{ii})$	3.05
$O(1) \cdots O(W2^{i11})$	2.68
$O(1) \cdots O(W3^{III})$	2.69
$I(3) \cdots I(3^{i_v})$	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 $\frac{1}{2} - x + y$	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 $I \cdots I$ contacts in the crystal which may indicate some charge-transfer bonding between these atoms. All short intermolecular contacts are listed in Table 8.

Tal	ble	8.	T_4	short	intermol	ecul	lar a	listances
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Cl ⁻ (1) Cl ⁻ (1) Cl ⁻ (1) Cl ⁻ (1) O(4) I(3) I(5')	N(1) N(1) N(1) N(1) O(1) I(5)) V) ¹) ¹¹) V ¹ v) V) V)	3.07 Å 2.99 3.20 3.30 2.49 3.98 3.86
Symmetry co	ode		
Superscrip	t		
None	x	У	Ζ
i	х	1+y	Ζ
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 T₃, torsion angles are ψ_1 : +8°; ψ_2 : -175°; χ_{11} : +56°; χ_{21} : +98°; χ_{22} : -89°. In T₄ similar values are found: ψ_1 , and ψ_2 , are -9° and $+172^{\circ}$ respectively, differing by only 17° and 13° from those found for T₃. 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, 1974a).

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 $I \cdots O$ 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, 1972a). 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, 1973a, 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, 1972c, 1974b) 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 T₃, 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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