responsible for the formation of the observed intricate hydrogen bonding scheme. From this structure it is clear that the symmetrical guanidinium–phosphate interaction is by no means so favored that it is formed under all circumstances; hydrogen bonding schemes other than the proposed symmetrical arrangement are consequently also worthy of consideration in the case of basic protein–DNA interactions.

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Molecular Conformation of the Thyroxine Analogue 3,5-Diiodo-L-thyronine *N*-Methylacetamide Complex (1:1)

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The crystal and molecular structure of the thyroxine analogue 3,5-diiodo-L-thyronine has been determined as a 1:1 complex with *N*-methylacetamide ($P2_1$; $Z=2$, $a=7{\cdot}988$, $b=22{\cdot}317$, $c=5{\cdot}995$ Å and $\beta=95{\cdot}54°$). The structural analysis shows the planes of the two phenyl rings of the thyronine molecule to be mutually perpendicular, as expected from stereochemical interaction studies. The amino acid backbone conformation, described by the rotation about the C^{α}–C^{β} bond, is 300°, showing a sterically preferred conformation. The complex is held together by a hydrogen bonding system where the amine nitrogen atom is hydrogen bonded to three oxygen atoms in a tetrahedral manner. There is also an unusually short iodine–carbonyl ($I\cdots O=C<$) contact distance of 3·03 Å.

Introduction

Extensive studies of the molecular conformations of many amino acids and polypeptides have been made in an effort to understand structural requirements for biological activity. One such investigation has centered upon efforts to establish structure-functional requirements for the activity of thyroid hormones. (Jorgensen, 1964; Money, Kumaoka & Rawson, 1962; Barker & Shimada, 1964; Selenkow & Asper, 1955; Jorgensen & Wright, 1970). Because little crystallographic work has been done on these hormones the crystal structure analysis of the thyroxine precursor, 3,5-diiodo-L-thyronine *N*-methylacetamide complex (1:1) shown in Fig. 1 was undertaken as the first structure in a series of thyroid hormones, hormone precursors and thyroxine analogues under investigation in this laboratory.

Experimental

Crystals of a 3,5-diiodo-L-thyronine *N*-methylacetamide (1:1) complex were grown in a temperature controlled chamber at 42 °C from a methanol solution of 3,5-diiodo-L-thyronine and *N*-methylacetamide. Preliminary diffraction analysis showed the crystals to have a monoclinic, primitive lattice with systematic absences occuring for $0k0$, $k=2n+1$ indicating the unique space group $P2_1$. There are two molecular units in the unit cell.

The cell dimensions were determined from a least-squares refinement of accurately measured values of 2θ for 30 high angle reflections. The crystal data are tabulated in Table 1.

Table 1. *Crystal data for the complex* 3,5-*diiodo*-L-*thyronine N-methylacetamide* (1:1)

Formula	$C_{15}H_{13}O_4NI_2.C_3H_7ON$
M.W.	598·0
Space group	$P2_1$
a	7·988 ± 0·003 Å,
b	22·317 ± 0·004,
c	5·995 ± 0·002,
β	95·54 ± 0·05°,
V	1063·0 Å^3,
D_c	1·86 g.cm^{-3},
Z	2,
μ	240·0 cm^{-1},
R	4·30 %,
wR	5·07 %.

A rectangularly shaped crystal (0·15 × 0·15 × 0·13 mm) with well defined faces was selected for data collection and mounted with the b axis parallel to the φ axis of a General Electric XRD-5 diffractometer. The intensities of all reflections (2079) with 2θ values less than 140° were measured by the stationary-crystal stationary-counter method with Cu $K\alpha$ 1·54015 Å) radiation monochromatized by balanced nickel and cobalt filters. All data in the copper hemisphere were measured; thus all unique reflections were measured twice. The equivalent reflections were averaged for greater accuracy. A reflection was considered observed if its intensity was greater than twice its estimated standard deviation. The shape anisotropy of the crystal measured at $\chi=90°$ indicated a less than 5 % variation in intensity over the θ range of data collection. The intensities were also corrected for Lorentz and polarization effects.

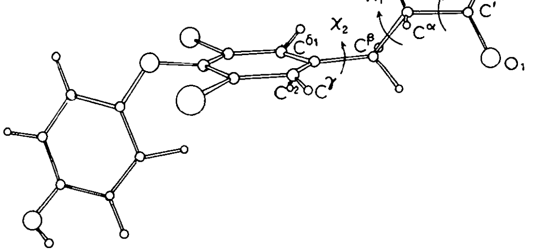

Fig. 1. 3,5-Diiodo-L-thyronine with conformational parameters defined.

Structure analysis

Positional parameters for the two iodine atoms were located in the Harker section of the Patterson function and the complete structure was then obtained through repeated application of a three-dimensional Fourier synthesis. After four cycles of isotropic diagonal least-squares refinement followed by seven cycles of anisotropic block-diagonal least-squares refinement, the R index ($R=\sum||F_o|-|F_c||/\sum F_o$) remained at 0·10. Inspection of the thermal parameters showed that several sub-determinants of the anisotropic thermal parameter matrix were negative and indicated possible absorption effects. An absorption correction (Coppens & Edmonds, 1970) was applied using the numerical Gaussian integration method with a grid size of 6 × 6 × 6, resulting in an absorption correction range of 0·05 to 0·21. Positional and thermal parameters were then refined with a full-matrix program (Coppens & Hamilton, 1970) which permitted variation of a parameter describing secondary extinction. This refinement process led to poor bond distances and angles for the *N*-methylacetamide even though Fourier difference maps revealed a molecule with good geometry. These parameters were eventually refined isotropically using only the high angle data ($\sin\theta/\lambda > 0{\cdot}30$).

A three-dimensional Fourier difference map, calculated without the hydrogen atom contributions to the structure factors, produced well defined electron densities for 17 of the 20 hydrogen atoms in the complex. However, six of these atoms were poorly placed and so they were put at their theoretically predicted positions. The hydrogen positional and thermal parameters were held constant throughout further refinement cycles with the thermal parameters fixed at 3·0 Å^2.

All scattering factors were taken from the *International Tables for X-ray Crystallography* (1962), and the real part of the anomalous dispersion correction applied. In order to determine the correct enantiomorph, all reflections (prior to averaging) were corrected for both the real and imaginary parts of the anomalous dispersion curve for iodine. The difference in the resulting R values (8·99 % and 8·51 % for plus and minus corrections respectively) was significant accord-

Table 2. *Positional and thermal parameters*

(*a*) Refined positional and thermal parameters of the 3,5-diiodo-L-thyronine molecule. Thermal parameters are defined by exp $\{-2\pi^2(U_{11}h^2a^{*2}+2U_{12}hka^*b^*+\ldots)\}$.

	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I(3)	0·1748 (1)	0·5001 (0)	0·4630 (1)	0·0539 (6)	0·0442 (5)	0·0699 (6)	−0·0032 (5)	0·0022 (4)	−0·0099 (5)
I(5)	0·8293 (1)	0·6376 (0)	0·5757 (1)	0·0380 (4)	0·0608 (6)	0·0527 (5)	−0·0004 (5)	0·0085 (3)	−0·0008 (4)
C(1)	0·3902 (14)	0·6323 (5)	0·9447 (18)	0·0382 (55)	0·0336 (56)	0·0326 (51)	0·0025 (53)	0·0037 (43)	−0·0021 (51)
C(2)	0·2902 (16)	0·5903 (5)	0·8304 (23)	0·0390 (67)	0·0284 (62)	0·0425 (70)	−0·0000 (50)	0·0073 (55)	−0·0002 (50)
C(3)	0·3394 (16)	0·5611 (5)	0·6418 (21)	0·0439 (66)	0·0253 (57)	0·0383 (62)	0·0010 (53)	−0·0010 (51)	−0·0009 (50)
C(4)	0·4984 (15)	0·5747 (5)	0·5715 (21)	0·0278 (54)	0·0232 (60)	0·0408 (69)	0·0059 (48)	0·0026 (53)	−0·0017 (55)
C(5)	0·5971 (15)	0·6149 (5)	0·6851 (19)	0·0409 (65)	0·0185 (57)	0·0325 (54)	0·0004 (47)	0·0050 (47)	0·0033 (43)
C(6)	0·5475 (15)	0·6449 (6)	0·8735 (20)	0·0421 (61)	0·0370 (66)	0·0430 (60)	0·0079 (59)	0·0052 (49)	0·0020 (58)
C(7)	0·3336 (17)	0·6661 (6)	1·1447 (20)	0·0446 (71)	0·0495 (73)	0·0231 (53)	0·0104 (64)	0·0052 (49)	0·0017 (52)
C(8)	0·1748 (15)	0·7018 (5)	1·0963 (20)	0·0322 (58)	0·0335 (61)	0·0295 (59)	−0·0004 (49)	0·0038 (46)	0·0014 (49)
N(8)	0·1889 (13)	0·7475 (5)	0·9176 (15)	0·0484 (61)	0·0433 (60)	0·0191 (42)	0·0022 (47)	0·0033 (40)	−0·0010 (38)
C(9)	0·1280 (14)	0·7335 (4)	1·3086 (19)	0·0293 (59)	0·0249 (51)	0·0329 (58)	0·0001 (45)	0·0056 (46)	−0·0002 (45)
O(9)	0·0699 (14)	0·7864 4)	1·2830 (15)	0·0647 (65)	0·0458 (58)	0·0335 (46)	0·0068 (51)	0·0070 (44)	−0·0011 (42)
O(10)	0·1476 (13)	0·7043 (4)	1·4847 (16)	0·0603 (63)	0·0485 (58)	0·0395 (49)	−0·0022 (50)	0·0111 (45)	0·0012 (43)
O(4)	0·5403 (12)	0·5503 (4)	0·3741 (14)	0·0548 (58)	0·0438 (53)	0·0292 (41)	0·0102 (46)	0·0040 (38)	−0·0001 (37)
C(1′)	0·6440 (14)	0·4994 (6)	0·3802 (17)	0·0341 (56)	0·0424 (61)	0·0239 (44)	−0·0033 (58)	0·0030 (40)	−0·0050 (54)
C(2′)	0·6632 (21)	0·4619 (6)	0·5614 (21)	0·0598 (95)	0·0404 (73)	0·0307 (58)	−0·0025 (65)	0·0082 (60)	−0·0044 (53)
C(3′)	0·7649 (17)	0·4111 (5)	0·5581 (20)	0·0500 (70)	0·0258 (61)	0·0348 (65)	0·0002 (55)	0·0108 (54)	−0·0009 (51)
C(4′)	0·8443 (15)	0·3989 (5)	0·3629 (20)	0·0330 (59)	0·0267 (56)	0·0339 (58)	−0·0015 (48)	0·0062 (47)	−0·0017 (46)
C(5′)	0·8224 (17)	0·4370 (6)	0·1843 (21)	0·0552 (80)	0·0385 (64)	0·0295 (60)	0·0024 (60)	0·0060 (55)	0·0004 (52)
C(6′)	0·7215 (18)	0·4878 (6)	0·1896 (20)	0·0554 (78)	0·0471 (85)	0·0308 (56)	−0·0008 (65)	0·0057 (53)	0·0039 (56)
O(4′)	0·9501 (12)	0·3504 (3)	0·3535 (14)	0·0584 (58)	0·0265 (43)	0·0410 (46)	0·0057 (41)	0·0131 (42)	0·0003 (36)

Table 2 (*cont.*)

(*b*) Positional and thermal parameters for the *N*-methylacetamide molecule and hydrogen positional parameters.

		x/a,	y/b,	z/c
A(O)	0·4874 (15)	0·8078 (5)	0·9733 (21)	4·89 (25)
A[C(1)]	0·7293 (31)	0·8839 (11)	0·9377 (41)	6·27 (45)
A[C(2)]	0·5548 (25)	0·7917 (9)	0·5812 (34)	5·04 (35)
A[C(3)]	0·5852 (28)	0·8187 (22)	0·8223 (40)	7·05 (42)
A(N)	0·7221 (39)	0·8535 (16)	0·8647 (53)	8·86 (60)
H(2)	0·169	0·579	0·888	
H(6)	0·629	0·677	0·961	
H[7(A)]	0·437	0·695	1·208	
H[7(B)]	0·332	0·649	1·302	
H(8)	0·073	0·671	1·043	
H[N(A)]	0·187	0·739	0·791	
H[N(B)]	0·301	0·759	0·932	
H[N(C)]	0·136	0·782	0·908	
H(2′)	0·599	0·471	0·707	
H(3′)	0·782	0·381	0·701	
H(5′)	0·884	0·427	0·036	
H(6′)	0·704	0·517	0·046	
H[C(1)A]	0·783	0·863	1·131	
H[C(1)B]	0·595	0·891	0·938	
H[C(1)C]	0·763	0·932	1·012	
H[C(2)A]	0·587	0·837	0·627	
H[C(2)B]	0·475	0·806	0·473	
H[C(2)C]	0·645	0·761	0·517	
H[A(N)]	0·834	0·839	0·793	
H[O(4′)]	0·937	0·336	0·458	

ing to the Hamilton (1965) test and verified that the molecule was the L-conformation.

The weighting scheme throughout the final cycles of refinement was $w^{-1}=\{1+[(|F_o|-55)/25]^2\}^{1/2}$ with weighting constants evaluated to make $\langle w\Delta^2\rangle$ invariant with changing $|F_o|$. Refinement terminated with $\sum w(|F_o|-|F_c|)^2/m-n$, the 'goodness of fit' at 1·96. The final R value is 4·3% (Table 1).

The final fractional coordinates and anisotropic thermal parameters for the thyronine molecule are given in Table 2(*a*) while the positional and isotropic thermal parameters for the *N*-methylacetamide group and the hydrogen atoms are listed in Table 2(*b*). The observed and calculated structure factor amplitudes for all observed data are listed in Table 3.

Molecular geometry

The bond lengths and angles calculated from the coordinates in Table 2 are given in Fig. 2. The estimated standard deviations for the bond lengths of the diiodothyronine molecule range from 0·012 to 0·020 Å with an average value of 0·016 Å while the e.s.d.'s for the corresponding bond angles range between 0·7 to 1·6°. The e.s.d.'s for the *N*-methylacetamide molecule range from 0·028 to 0·048 Å and 1·9 to 2·7°. The observed bond lengths and angles in the complex are within one standard deviation from their expected values. The only exceptions are two aromatic carbon–carbon bonds which are three standard deviations shorter than the expected aromatic distance of 1·397 Å.

The carbon–iodine distances of 2·112 and 2·089 Å in this structure are longer than the average value of 2·05 Å observed in other aromatic iodinated structures compiled in *Tables of Interatomic Distances* (1965) and are also longer than the 2·05 Å average distance reported in the structure of 3,5-diiodo-L-tyrosine dihydrate (Hamilton & Steinrauf, 1967).

Although the carbonyl–oxygen distances of 1·239 and 1·273 Å in the amino acid portion differ by two standard deviations, the location of tetrahedrally disposed hydrogen atoms on the amine nitrogen indicate that the molecule is in its zwitterion form. These values agree with those observed in other amino acids (Srinivasan, 1959; Hamilton *et al.*, 1967; Fries & Sundaralingam, 1971). The amine bond distance of 1·493 Å agrees well with the range of values found in other amino acids. Also the phenolic oxygen bond of 1·374 Å is typical of those found in tyrosine derivatives. There are no significant differences in the lengths of the ether linkages.

With the exception of the methyl–amide distance, the bonds and angles in the *N*-methylacetamide molecule are less than two standard deviations from their

Table 3. *Comparison of the observed structure amplitudes with those calculated from the refined atomic parameters*

H	K	L	FO	FC
0	0	2	1191	1293
0	0	3	469	502
0	0	4	177	135
0	0	5	106	127
0	0	6	146	195
0	0	7	126	119
0	1	1	597	597
0	1	2	396	367
0	1	3	666	650
0	1	4	306	330
0	1	5	150	137
0	1	7	74	83
0	2	0	1064	1033
0	2	2	659	681
0	2	3	446	434
0	2	4	273	263
0	2	5	241	199
0	2	6	200	243
0	2	7	172	173
0	3	1	858	834
0	3	2	881	917
0	3	3	861	779
0	3	4	666	691
0	3	5	413	440
0	3	6	177	161
0	3	7	103	72
0	4	1	391	357
0	4	2	417	390
0	4	3	534	501
0	4	4	444	478
0	4	5	312	328
0	4	6	161	181
0	4	7	151	153
0	5	1	1006	1013
0	5	2	912	967
0	5	3	1002	1034
0	5	4	591	625
0	5	5	388	391
0	5	6	205	196
0	5	7	133	125
0	6	0	1553	1458
0	6	1	1003	1002
0	6	2	810	820
0	6	3	508	533
0	6	4	165	171
0	6	5	192	196
0	6	6	171	169
0	6	7	212	194
0	7	1	291	206
0	7	2	226	213
0	7	3	415	416
0	7	6	97	81
0	8	0	1400	1349
0	8	1	1104	1105
0	8	2	759	775
0	8	3	332	344
0	8	4	148	157
0	8	5	172	178
0	8	6	242	237
0	9	1	357	340
0	9	2	455	461
0	9	3	576	577
0	9	4	379	386
0	9	5	298	295
0	9	6	158	148
0	10	0	602	533
0	10	1	457	433
0	10	2	440	433
0	10	3	355	363
0	10	4	374	409
0	10	5	209	251
0	10	6	194	215
0	11	1	547	519
0	11	2	543	535
0	11	3	706	747
0	11	4	479	512
0	11	5	389	396
0	11	6	192	168
0	12	0	784	698
0	12	1	475	472
0	12	2	393	408
0	12	3	356	362
0	12	4	148	175
0	12	5	129	196
0	12	6	147	165
0	13	1	234	255
0	13	2	446	464
0	13	3	448	465
0	13	4	347	360
0	13	5	183	204
0	13	6	109	119
0	14	0	1216	1205
0	14	1	973	1041
0	14	2	586	614
0	14	3	341	359
0	14	6	93	79
0	15	1	116	99
0	15	2	146	160
0	15	3	128	114
0	15	4	159	166
0	15	5	111	93
0	16	0	703	710
0	16	1	478	484
0	16	2	502	527
0	16	3	229	210
0	16	4	143	157
0	16	5	166	162
0	17	1	320	304
0	17	2	255	267
0	17	3	345	374
0	17	4	398	424
0	17	5	233	248
0	18	0	159	154
0	18	1	236	246
0	18	3	213	224
0	18	4	156	167
0	18	5	137	137
0	19	1	264	275
0	19	2	329	330
0	19	3	475	512
0	19	4	340	353
0	19	5	191	203
0	20	0	592	565
0	20	1	377	370
0	20	2	308	293
0	20	3	182	195
0	21	2	150	164
0	21	3	135	161
0	21	4	138	118
0	22	0	434	460
0	22	2	293	306
0	22	3	187	174
0	22	4	89	82
0	23	1	116	91
0	23	3	106	84
0	24	0	208	224
0	24	1	191	192
0	24	2	220	237
0	24	3	161	203
0	25	1	133	117
0	25	2	207	168
0	26	1	149	150
0	26	2	113	106
1	0	-7	112	107
1	0	-6	524	504
1	0	-5	470	470
1	0	-4	610	609
1	0	-3	599	605
1	0	-2	775	697
1	0	-1	444	429
1	0	0	368	339
1	0	1	1161	1357
1	0	2	1195	1277
1	0	3	937	963
1	0	4	777	839
1	0	5	498	525
1	0	6	297	315
1	1	-7	239	253
1	1	-6	308	321
1	1	-5	417	447
1	1	-4	358	318
1	1	-3	486	504
1	1	-2	695	666
1	1	-1	445	389
1	1	1	733	666
1	1	2	411	417
1	1	3	345	362
1	1	4	355	403
1	1	5	284	318
1	1	7	91	79
1	2	-7	107	103
1	2	-6	245	247
1	2	-5	442	396
1	2	-4	241	252
1	2	-3	393	377
1	2	-2	170	187
1	2	-1	420	363
1	2	1	663	712
1	2	2	1003	1021
1	2	3	859	917
1	2	4	495	501
1	2	5	279	290
1	2	6	196	221
1	2	7	125	124
1	3	-7	100	117
1	3	-6	142	138
1	3	-5	235	250
1	3	-4	544	542
1	3	-3	554	527
1	3	-2	1306	1286
1	3	-1	1571	1798
1	3	0	963	985
1	3	1	1154	1339
1	3	2	610	576
1	3	3	112	138
1	3	4	233	257
1	3	5	295	310
1	3	6	283	285
1	3	7	147	157
1	4	-7	120	97
1	4	-5	291	297
1	4	-4	430	417
1	4	-3	550	552
1	4	-2	215	159
1	4	0	709	696
1	4	1	648	642
1	4	2	514	487
1	4	3	273	286
1	4	4	155	137
1	4	5	298	315
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7	6	1	329	333
7	6	2	320	339
7	6	3	350	354
7	6	4	195	197
7	7	-5	124	152
7	7	-4	136	166
7	7	-2	278	272
7	7	-1	153	175
7	7	0	135	106
7	7	1	134	145
7	7	2	146	170
7	7	3	187	198
7	7	4	140	144
7	8	-5	258	288
7	8	-4	404	422
7	8	-3	398	403
7	8	-2	215	242
7	8	0	177	179
7	8	1	344	323
7	8	2	311	327
7	8	3	272	270
7	8	4	211	211
7	9	-3	226	224
7	9	-2	281	301
7	9	-1	327	347
7	9	0	416	422
7	9	1	246	259
7	9	2	183	205
7	9	3	141	156
7	10	-4	195	190
7	10	-3	238	247
7	10	-2	148	142
7	10	0	150	167
7	10	1	148	168
7	10	2	158	148
7	10	3	140	142
7	11	-4	101	97
7	11	-3	286	294
7	11	-2	450	446
7	11	-1	695	691
7	11	0	569	580
7	11	1	401	415
7	11	2	190	231
7	12	-4	194	216
7	12	-3	203	212
7	12	-2	141	143
7	12	1	120	112
7	13	-3	138	128
7	13	-2	283	277
7	13	-1	219	234
7	13	0	268	271
7	13	1	193	187
7	13	2	159	158
7	13	3	121	129
7	14	-3	219	214
7	14	-1	106	123
7	14	1	200	171
7	14	2	215	228
7	15	0	131	125
7	15	1	96	95
7	15	2	144	137
7	16	-3	220	239
7	16	-2	154	159
7	16	-1	121	103
7	16	0	110	100
7	16	1	206	204
7	16	2	219	221
7	17	-2	201	213
7	17	-1	312	308
7	17	0	288	291
7	17	1	233	237
7	18	-2	97	87
7	18	1	62	59
8	0	-4	138	149
8	0	-3	462	465
8	0	-2	506	554
8	0	-1	427	426
8	0	0	383	405
8	0	1	156	173
8	1	-4	214	203
8	1	-3	166	193
8	1	-2	124	112
8	1	0	134	138
8	1	1	197	203
8	1	2	139	166
8	1	3	126	129
8	2	-4	137	143
8	2	-3	305	337
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8	2	3	98	102
8	3	-4	295	321
8	3	-3	189	184
8	3	-1	272	270
8	3	0	304	318
8	3	1	420	438
8	3	2	300	325
8	3	3	182	187
8	4	-2	105	100
8	4	2	153	164
8	4	3	115	85
8	5	-4	290	276
8	5	-3	178	201
8	5	-2	115	128
8	5	-1	237	244
8	5	0	320	332
8	5	1	331	328
8	5	2	279	267
8	5	3	170	180
8	6	-4	199	238
8	6	-3	351	356
8	6	-2	386	437
8	6	-1	426	449
8	6	0	319	340
8	6	1	212	242
8	7	-4	215	234
8	7	-3	177	184
8	7	0	101	93
8	7	1	134	122
8	8	-4	231	260
8	8	-3	334	342
8	8	-2	464	484
8	8	-1	378	407
8	8	0	260	282
8	8	1	182	181
8	9	-3	134	120
8	9	-2	94	86
8	9	-1	124	132
8	9	0	185	203
8	9	1	233	234
8	9	2	178	180
8	10	-3	183	167
8	10	-2	204	189
8	10	-1	199	181
8	10	2	112	108
8	11	-3	124	125
8	11	-1	163	163
8	11	0	250	265
8	11	1	332	344
8	11	2	273	285
8	12	-3	139	159
8	12	-2	198	214
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8	14	-1	304	311
8	14	0	220	244
8	14	1	97	119
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9	0	-1	256	274
9	0	0	419	431
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9	0	2	290	301
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9	1	-2	195	227
9	1	-1	192	210
9	1	1	96	78
9	1	2	116	118
9	2	-1	210	222
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9	2	1	229	230
9	2	2	189	206
9	3	-3	280	329
9	3	-2	352	349
9	3	-1	336	340
9	3	2	102	102
9	4	-3	113	117
9	4	-1	97	110
9	4	0	101	111
9	5	-3	272	291
9	5	-2	262	273
9	5	-1	193	178
9	6	-2	133	141
9	6	-1	231	236
9	6	0	273	287
9	6	1	271	295
9	7	-2	97	99
9	8	-2	106	128
9	8	-1	289	274
9	8	0	317	313
9	8	1	289	296
9	9	-2	168	180
9	9	-1	147	155
9	10	-1	99	116
9	10	0	166	191

expected values as observed in similar acetamide structures (Katz & Post, 1960; Hamilton, 1965; Dubey, 1971; Koyama, Shimanouchi & Iitaka, 1971).

The observed carbon–hydrogen distances range from 0·73 to 1·18 Å with an average value of 1·02 Å while the nitrogen–hydrogen distances average 0·85 Å. The oxygen–hydrogen distance is 0·71 Å. The valency angles range in magnitude from 107 to 125° with an average value of 109°. The conformations of the hydrogen atoms are shown in Fig. 1 and the relative thermal motion of the 3,5-diiodo-L-thyronine is shown in Fig. 3.

Table 4, which lists the deviations from the best least-squares plane through each phenyl ring, shows that the iodine atoms and the hydroxyl and ether oxygen atoms lie in the plane of their respective phenyl rings.

Table 4. *Deviations from the least-squares plane through the two phenyl rings of* 3,5-*diiodo-*L-*thyronine*

Plane through first 6 atoms

Atom	Distance	Atom	Distance
C(1)	0·0072 Å	C(1′)	0·0033 Å
C(2)	−0·0087	C(2′)	−0·0052
C(3)	0·0036	C(3′)	0·0047
C(4)	0·0029	C(4′)	−0·0023
C(5)	−0·0044	C(5′)	0·0004
C(6)	−0·0006	C(6′)	−0·0008
C(7)	0·0529	O(4′)	0·0472
I(3)	0·0776	O(4)	−0·0337
I(5)	0·0645		
O(4)	0·1431		

Tyrosine conformation

The backbone conformation of the amino acid can be described in terms of the orientation of the carboxyl group with respect to the N–C^α–C′ plane (see Fig. 1). It turns out that the plane of the carboxyl group and the N–C^α–C′ plane nearly coincide. First, ψ_1 is the angle which the O_1–C′–C^α plane makes with the C′–C^α–N plane measured clockwise around the C′–C^α bond when viewed from C′ to C^α. Similarly, ψ_2 is the angle which the O_2–C′–C^α plane makes with the C′–C^α–N plane measured clockwise around the C′–C^α bond when viewed from C′ to C^α. An analysis of several amino acids (Lakshminarayanan, Sasisekharanan & Ramachandran, 1967) indicates that for amino acids with an aromatic side chain, the carboxyl group is tilted slightly counterclockwise from the N–C^α–C′ plane when viewed from C′ to C^α while for glycine-like amino acids the carboxyl group may tilt either way. This tilt is measured by the angle ψ, clockwise about the C′–C^α bond when viewed from C′ to C^α. The deviations of the carboxylate oxygens from the plane N–C^α–C′ of −0·33 and 0·29 Å agree with results found in other amino acids. Fig. 4 shows the torsional parameters ψ_1 and ψ_2 for 3,5-diiodo-L-thyronine and two tyrosine derivatives viewed down the C′–C^α bond from C′ to C^α.

Table 5 describes the amino acid backbone of a few thyroxine precursors and related tyrosine derivatives with conformational rotation parameters in terms of the convention suggested by Edsall *et al.* (1966). When comparing the conformation of the tyrosine portion of diiodothyronine to other tyrosine derivatives the greatest conformational difference is found in the rotation about the C^α–C′ bond. As already noted, the rotation of this bond is described by the parameters ψ_1 and ψ_2 which are the torsional angles N–C^α–C′–O_1 and N–C^α–C′–O_2 respectively. For most tyrosine derivatives ψ_2 is small and negative. In this structure the carboxyl group is tilted from the N–C^α–C′ plane in the opposite direction from that observed in other tyrosine structures.

The conformation about the C^α–C^β bond, described by the parameter $\chi_1(N\text{–}C^\alpha\text{–}C^\beta-C^\gamma)$, shows a preferred torsional angle about this bond of $\chi_1=300°$ which is sterically favored (Lakshminarayanan *et al.*, 1967), allowing the amino acid maximal contact area for potential hydrogen bonds or functional group interactions. Here χ_1 is the angle which the N–C^α–C^β plane makes with the C^α–C^β–C^γ plane measured clockwise around the C^α–C^β bond when viewed from C^α to C^β. While the torsional angle χ_1 is generally *anti* ($\chi_1 \simeq 180°$) for most tyrosine derivatives and *syn* ($\chi_1 \simeq 60°$) for several tyrosine–metal complexes, it appears that tyrosine nuclei with more than *para* substitution prefer a conformation of $\chi_1 \simeq 300°$. However, these parameters seem to be influenced by their molecular environment as well. A comparison of the three staggered positions

Table 5. *Conformational parameters for thyroid compounds and related amino acids*

Compound	ψ_1	ψ_2	χ_1	χ_{21}	χ_{22}	References
3,5-Diiodo-L-thyronine	195°	18°	300°	120°	305°	Cody, Duax & Norton (1971)
3,5-Diiodo-L-tyrosine ethyl ester (1)	154	328	305	92	275	Cody, *et al.* (1971)
3,5-Diiodo-L-tyrosine ethyl ester (2)	151	341	288	114	279	Cody *et al.* (1971)
3,5-Diiodo-L-tyrosine	108	302	180	90	267	Hamilton & Steinrauf (1971)
Tyrosine ethyl ester	141	319	180	71	252	Pieret *et al.* (1970)
L-Tyrosine HBr	155	322	187	65	250	Srinivasan (1959)
L-Phenylalanine HCl	178	358	62	84	262	Guskurya (1964)
L-Tyrosine-*O*-sulfate	164	342	72	80	277	Fries & Sundaralingam (1971).

about the C^{α}–C^{β} bond (χ_1) is shown in Fig. 4, a view of the projection of the amino acid looking down the C^{α}–C^{β} bond.

The parameters χ_{21} and χ_{22} describe the torsional angles between the least-squares plane of the phenyl ring and the plane C^{α}–C^{β}–C^{γ}. More precisely, χ_{21} is the angle which the C^{β}–C^{γ}–$C^{\delta 1}$ plane makes with the plane C^{α}–C^{β}–C^{γ} measured clockwise about the C^{β}–C^{γ} bond viewed from C^{β} to C^{γ}. Similarly χ_{22} is the angle between the planes C^{β}–C^{γ}–$C^{\delta 2}$ and $C^{\alpha}C^{\beta}$–C^{γ} respectively, measured in the same manner as χ_{21}. Although there is a wide range of values for χ_{21}, the value of 90° for χ_{21} appears to be compatible with each of the three most stable χ_1 values. If any trend is apparent, it is that χ_{21} tends to be greater than 90° when χ_1 is near 300° and less than 90° when χ_2 is near 180°.

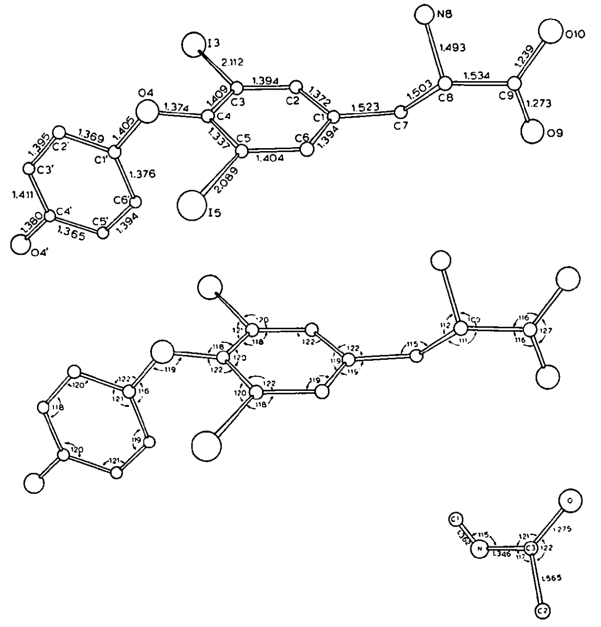

Fig. 2. Bond distances and bond angles for 3,5-diiodo-L-thyronine N-methylacetamide (1:1) complex.

Crystal packing and hydrogen bonding

The complex between diiodothyronine and *N*-methylacetamide is held together in the lattice by the network of hydrogen bonds shown in the packing diagram (Fig. 5). Each thyronine molecule is hydrogen bonded to six other thyronine molecules and to the *N*-methylacetamide molecule. The geometric details of the three N–H···O bonds and the O–H···O bond are presented in Table 6(*a*) and Fig. 6. Two of the hydrogen atoms of the amine nitrogen are directed toward carbonyl oxygen atoms forming strong hydrogen bonds while the third hydrogen atom is weakly hydrogen bonded to the hydroxyl oxygen atom. The hydroxyl hydrogen atom in turn establishes a strong hydrogen bond with a carboxylic oxygen. The angles formed by the hydrogen atoms are similar to those observed in other structures.

Because of the sp^2 hybridization of the carbonyl group, it is expected that the hydrogen bond donor will lie nearly in the plane defined by the carbon atom and its three ligands with each hydrogen atom nearly on the line joining its nearest neighbors and that the O···O=C and N···O=C angles will be close to 120°. While there are a number of examples where this is not the case (Donohue, 1969), in this structure [Table 6(*b*)] all the hydrogen atoms lie nearly in the plane of the carbonyl group with the O···O=C and N···O=C angles approximately 120°.

Inspection of the packing diagram (Fig. 5) shows the diiodothyronine molecules stacked over one another in both **a** and **c** directions and form chains hydrogen bonded head to tail along the **b** direction. The *N*-methylacetamide molecules are also stacked over one another in the **a** and **c** directions. The diagram also shows intermolecular contacts between molecules.

There are two iodine contacts of interest. The intermolecular contact between two iodine atoms of 4·22 Å is shorter than the normal van der Waals distance of 4·30 Å (Pauling, 1960) but longer than the 4·08 Å of Bondi (1964). The other contact is an iodine–oxygen (I···O=C<) distance of 3·03 Å which is significantly shorter than either Pauling or Bondi's values of 3·55 or 3·48 Å respectively. Another example where this type of iodine–oxygen contact was observed is the structure of 2,2'-diiododibenzoyl peroxide (Gougoutas & Clardy, 1970) in which an intramolecular contact of 3·25 Å was found. There are only three hydrogen–hydrogen contacts less than 2·60 Å.

Table 6. *Hydrogen bonding*

(*a*) Geometry involving the hydrogen bonds

X——H······Y	X–H	H···Y	X···Y	<X–H···Y	<H–X···Y
O(4')–H······O(9)	0·73 Å	1·93 Å	2·62 Å	168°	9°
N——H(A)···O(10)	0·94	1·99	2·76	160	13
N——H(B)···A(O)	0·78	1·83	2·73	167	9
N——H(C)···O(4')	0·89	2·24	2·96	139	29

Table 6 (*cont.*)

(*b*) The deviation of hydrogen atoms from the hydrogen bonding plane

Atom	Deviation	Bonds	Angles
H[N(A)]	−0·29 Å	A[C(3)]–A(0)–N	127°
H[N(B)]	−0·20	C(9)–O(9)–O(4')	117
H[N(C)]	−0·44	C(9)–O(10)–N	128
H[O(4')]	0·09	C(4')–O(4')–N	116

Diphenyl ether conformation

Although 3,5-diiodo-L-thyronine is not biologically active, its structure is closely related to the thyroid hormone thyroxine (3,3′,5,5′-tetraiodo-L-thyronine) and thus its main conformational features are probably similar to those of thyroxine.

From the measurements of dipole moments, three conformations have been considered for diphenyl ethers: planar, 'butterfly' and skewed as illustrated in Fig. 7. (Lehman & Jorgensen, 1965; Shimizu, Fujiwara & Morino, 1961; Higasi & Smyth, 1960; Smyth & Walls, 1932). In the planar conformation the two rings are coplanar with each other and with the plane of the two carbon–oxygen bonds. This conformation is expected to have the most steric repulsion as shown by molecular models making it an improbable conformation (Higasi *et al.*, 1960). The 'butterfly' conformation, on the other hand, is one in which the two rings are perpendicular to the plane of the two carbon–oxygen bonds and shows the least steric repulsion. Finally, the skewed conformation has one ring coplanar with and the other perpendicular to the plane of the two carbon–oxygen bonds and is also sterically possible. However, further results from nuclear magnetic resonance and infra-red spectral studies (Shimizu *et al.*, 1961; Lehman *et al.*, 1965) show the two phenyl rings to be non-equivalent indicating a preference for a skewed conformation.

Studies of molecular models of diiodothyronine derivatives show that the phenyl rings are so oriented that substituents in the 3- and 5-positions of the alanine-bearing ring approach closely those in the 2′- and 6′-positions of the phenolic ring as the rings rotate about the diphenyl ether bond. Minimal interaction between the bulky 3,5-iodine atoms and the 2′,6′-hydrogen atoms is maintained when the orientation of the two rings is skewed; *i.e.* one ring is coplanar with, and the other perpendicular to the plane of the two carbon–oxygen bonds (Jorgensen, Zenker & Greenberg, 1959; Lehman *et al.*, 1965) As seen in Fig. 1, the planes of the two phenyl rings are indeed skewed, being nearly mutually perpendicular while maintaining the 120° ether angle, which is similar to that found in other structures which contain diphenyl ether linkages

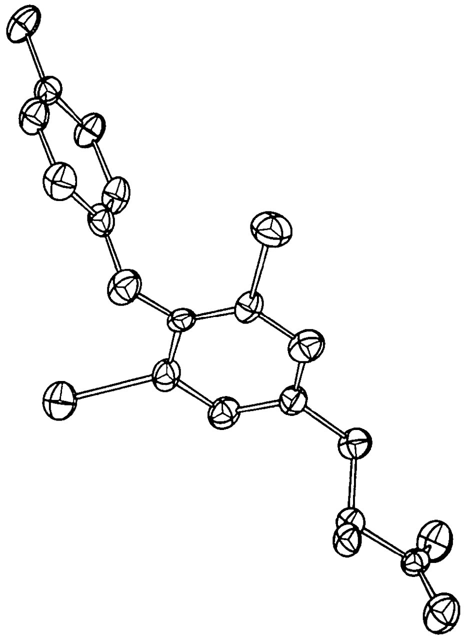

Fig. 3. 3,5-Diiodo-L-thyronine showing 50% probability thermal elipsoid plots.

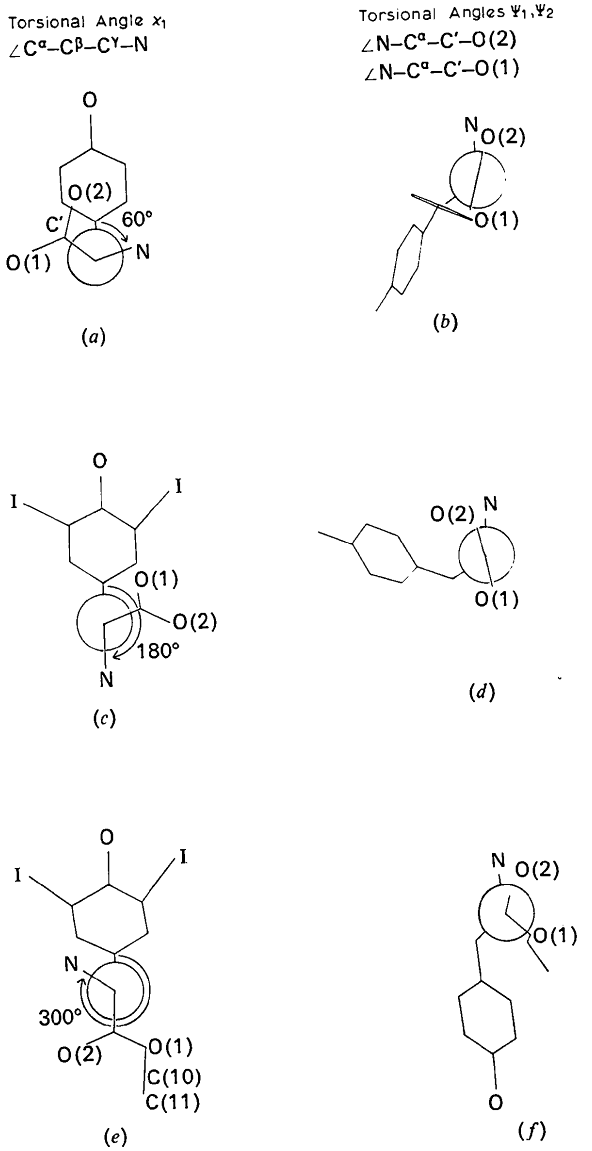

Fig. 4. Rotation parameters χ and ψ for various tyrosine containing molecules. χ is a projection from C^{α} to $C\beta$ and ψ is a projection from C' to C^{α}. (*a*) Potassium-L-tyrosine-*O*-sulfate. (*b*) 3,5-Diiodo-L-thyronine. (*c*) 3,5-Diiodo-L-tyrosine $2H_2O$. (*d*) Potassium-L-tyrosine-*O*-sulfate. (*e*) 3,5-Diiodo-L-tyrosine ethyl ester. (*f*) L-tyrosine ethyl ester.

(Toussaint, 1946; Maxwell, Hendricks & Mosley, 1935) The dihedral angle between the plane of the outer ring and the plane defined by the ether linkage is 19° and the angle made by the plane of the inner ring and the ether plane is 4° indicating that the outer phenyl ring is rotated such that C(6′) is proximal to I(5) (see Fig. 2).

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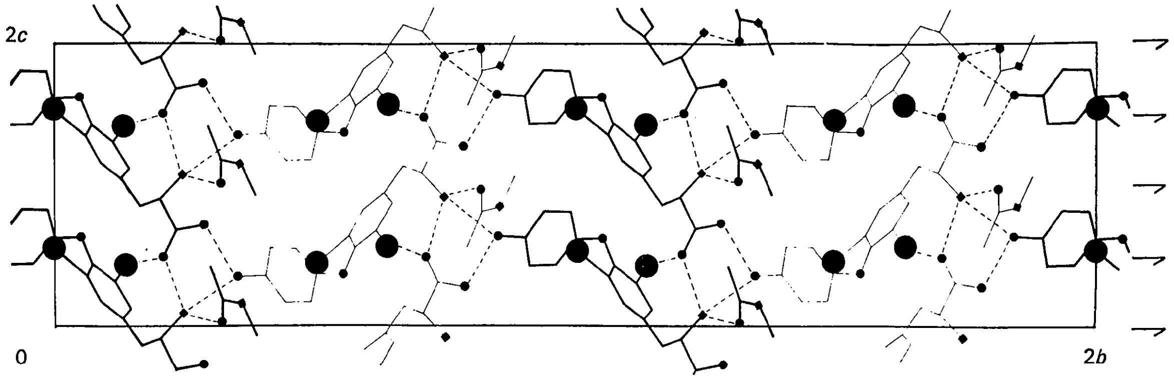


Fig. 5. Packing diagram for the (1:1) complex 3,5-diiodo-L-thyronine *N*-methylacetamide. The dark molecules are above the light ones.

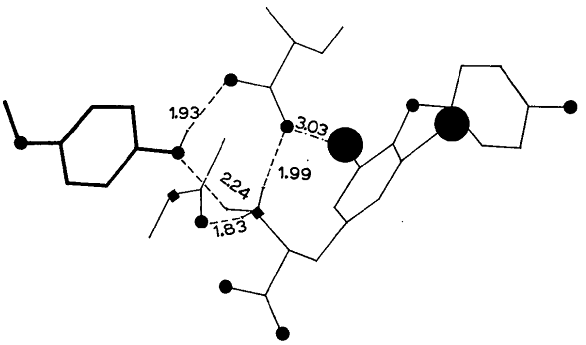
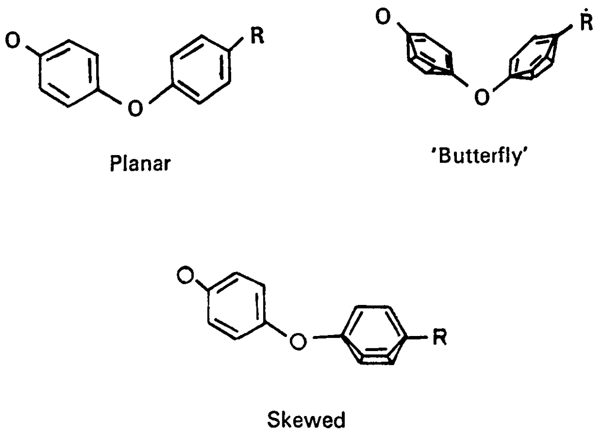


Fig. 6. Hydrogen bonding scheme for 3,5-diiodo-L-thyronine *N*-methylacetamide. The large circles are iodine, the squares are nitrogen, and the circles oxygen atoms. The dashed lines indicate hydrogen bonded distances from the hydrogen atom to the nitrogen or oxygen respectively. The dark molecules are above the light ones. Also shown is the iodine-oxygen contact distance.



Planar

'Butterfly'

Skewed

Fig. 7. Three conformations considered for diphenyl ethers: planar, 'butterfly' and skewed.

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The Crystal and Molecular Structure of Crocetindialdehyde

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Crystals of 2,6,11,15-tetramethylhexadeca-2,4,6,8,10,12,14-heptaen-1,16-dial (crocetindialdehyde) are triclinic, space group $P\bar{1}$, with $a=5\cdot136(2)$, $b=8\cdot369(2)$, $c=11\cdot146(3)$ Å, $\alpha=87\cdot30(5)$, $\beta=92\cdot63(5)$, $\gamma=112\cdot28(5)°$. Data were collected on an automated diffractometer using Cu $K\alpha$ radiation. The structure was solved by the symbolic addition procedure and refined by full-matrix least-squares methods to an R value of 0·047 based on 1142 observed reflexions. The molecules are all *trans* and nearly planar and are stacked in layers nearly parallel to the (577) plane. The packing of the molecules is probably determined by the aldehyde and methyl groups, as the shortest intermolecular distances involve such groups. The molecules show significant deviations from planarity, also within the double bond systems. Calculations of torsion angles show that the aplanarity decreases towards the middle of the chain. This is probably due to a higher degree of conjugation in this part of the chain, as the differences between single and double bond lengths also decrease towards the middle of the chain.

Introduction

Crocetin is a C_{20}-carotenoid and its digentiobiose ester, crocin, is the principal pigment of saffron (*Crocus sativus*) and has also been observed in several other flowers and in some fruits. Saffron has been used for artificial colouring of food since ancient times. Crocetindialdehyde can be synthesized as described by Isler, Gutman, Lindlar, Montavon, Rüegg, Ryser & Zeller (1956). Recently it has also been isolated from the leaves of *Jacquinia angustifolia* by Eugster, Hürlimann & Leuenberger (1969). Crocetindialdehyde is commonly used in syntheses of carotenoids according to the method of Wittig & Schöllkopf (1954).

It was shown by Karrer, Benz, Morf, Raudnitz, Stoll & Takahashi (1932) that crocetin is a dicarboxylic acid that has a polyene chain structure with seven double bonds and four side chain methyl groups. The numerous conjugated double bonds in the carotenoids are responsible for their colour and allow exceptional opportunities for *cis-trans*-isomerism as discussed by Zechmeister (1962).

The all-*trans* form is generally the more stable. It is found by ultraviolet spectroscopy that this form also dominates in solutions of crocetindialdehyde. One of the aims of this investigation was therefore to establish that the all-*trans* conformation is retained in the crystalline state. Furthermore I was interested in studying the packing and bonding effects of long-chain aldehydes.