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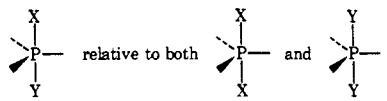


The same is true for the equatorial subset. It appears that the contribution of a ligand to the total chemical binding energy of the phosphorane is less in the "heterosystem" than the mean of the contribution of the same ligand in the "homosystem". LSS affects also the $^{31}P$ NMR chemical shift resulting from a given set of ligands; a molecule with LSS gives resonance at a higher magnetic field than another without it, even though they may have the same number of ligands of the same electronegativity (ref 2, 5, 7, 21, 22).
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# Thyroid Hormone Stereochemistry. IV.[1] Molecular Conformation of 3′-Isopropyl-3,5-diiodo-L-thyronine in the Crystal and in Solution

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**Abstract:** The three-dimensional structure of 3′-isopropyl-3,5-diiodo-L-thyronine (ip-$T_2$), the most potent known thyromimetic agent, has been determined by a single-crystal x-ray diffraction study of ip-$T_2$ hydrochloride trihydrate. The unit cell dimensions are $a = 30.408$, $b = 5.308$, $c = 17.176$ Å; $\beta = 117.93°$; space group $C2$, with four molecules per cell. The structure was solved by Patterson methods and refined to $R = 0.051$. The planes of the $\alpha$- and $\beta$-phenyl rings make dihedral angles of 97 and −26°, respectively, with the plane of the inter-ring linkage, and the $\beta$-ring orientation is such that the 3′-isopropyl group is positioned proximal to the $\alpha$ ring. High-resolution NMR studies of ip-$T_2$ in methanol and methanol–acid indicate that the 3′-substituent proximal conformation is favored in acidic media and that the 3′-distal conformation predominates in alcohol.

3′-Isopropyl-3,5-diiodo-L-thyronine (ip-$T_2$) is chemically very similar to 3,5,3′-triiodo-L-thyronine ($T_3$), the most potent naturally occurring thyroid hormone; the two molecules differ in chemical structure only in the replacement of the iodine at the 3′ position of the $\beta$ ring of $T_3$ by an isopropyl group in ip-$T_2$. The hormonal activity of ip-$T_2$ is 50–100% greater than that of $T_3$, making it the most potent thyromimetic agent known.[3,4]

The conformational characteristics of $T_3$ and its analogues have been the subject of much interest. The presence of iodines at the 3 and 5 positions of the $\alpha$ ring, ortho to the phenolic $\beta$ ring, favors a roughly mutually perpendicular arrangement of the two aromatic rings, and the question of whether the $\beta$ ring is then oriented with its 3′-substituent proximal or distal (the 120° angle at the inter-ring ether link makes these positions conformationally nonequivalent) to the $\alpha$ ring has been extensively investigated. On the basis of studies utilizing fixed-conformation analogues, the 3′-iodine distal arrangement for $T_3$ was concluded to be the biologically active conformation.[3,5] However, structure determinations of $T_3$ hydrochloride[6] and ethyl 3,5,3′-triiodothypropionate[7] ($T_3P$) revealed that both of these molecules adopt conformations having the 3′-iodine proximal to the $\alpha$ ring in the crystalline state. The great hormonal potency of ip-$T_2$, its close structural resemblance to $T_3$, and its possession of an isopropyl group instead of iodine at the 3′ position, thereby eliminating any possibility of intermolecular electrostatic effects involving that substituent stabilizing a particular conformation, combine to make a three-dimensional molecular structure determination of ip-$T_2$ highly desirable.[8]

Recently crystal structures have also been reported[9] in which $T_3$ and analogues exist in the 3′-iodine distal conformation. These crystals were obtained from alcoholic solutions, in some cases containing excesses of urea or salicylic acid, while the crystals in which the 3′-substituent proximal conformation is found were prepared from alcohol–HCl solutions. Thus solution conditions appear to exert a profound influence on conformational stability in these thyromimetics, and an NMR investigation of the structure of 3,5,3′-triiodothyropropionic acid in differing media has indicated that acidic solutions stabilize the 3′-substituent proximal conformation.[10] A similar NMR investigation of acidic and neutral solutions of ip-$T_2$ is of great interest in determining

Table I. Data Collection Details for the Three Intensity Crystals

| | Crystal A | Crystal B | Crystal C |
|---|---|---|---|
| Crystal size, mm | 0.1 × 0.15 × 0.7 | 0.07 × 0.15 × 0.7 | 0.07 × 0.15 × 0.7 |
| Fall-off in net intensity of standards during data collection, % | 21 | 17 | 21 |
| Scan rate, deg/min | 1.0 | 1.0 | 2.0 |
| Background time, sec | 20 | 20 | 10 |
| Region of reciprocal space measured, deg | $0 < 2\theta \leq 30$ | $30 \leq 2\theta \leq 40$ | $0 < 2\theta \leq 40$ |

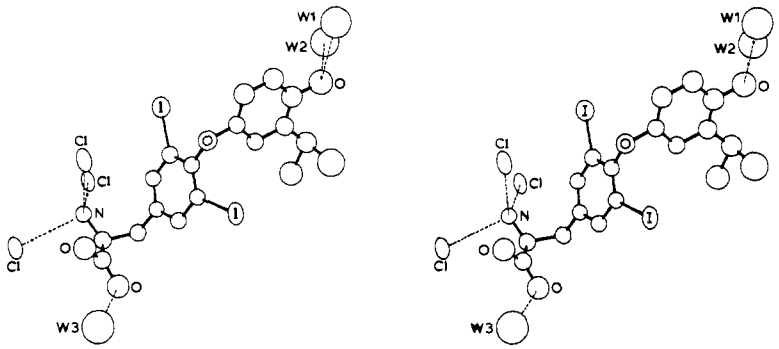


Figure 1. Stereoscopic drawing of the molecular conformation of 3′-isopropyl-3,5-diiodo-L-thyronine hydrochloride hydrate.

the generality of the solution phenomena and establishing whether the 3′-iodine atom is directly involved.

We now present the detailed three-dimensional structure of ip-$T_2$ in the solid state and the NMR spectra with their implications for the structure in acidic and neutral solutions.

## Experimental Section

**A. Crystallographic Studies.** 3′-Isopropyl-3,5-diiodo-L-thyronine (ip-$T_2$) was dissolved by warming in 1 *M* HCl and slow solvent evaporation gave small needles, elongated along *b*, of ip-$T_2$·HCl with about three water molecules of crystallization per molecule of ip-$T_2$. The unit cell parameters were obtained by diffractometer measurement of various axial reflections on all three intensity crystals. The crystals decomposed, with accompanying small changes in cell parameters, on exposure to x rays. The unit cell parameters are averages of measurements taken before, during, and after data collection, the estimated standard deviations being root mean square deviations from the averages.

**Crystal data** ($\lambda_{Mo\ K\alpha}$ = 0.71069 Å) for 3′-isopropyl-3,5-diiodo-L-thyronine hydrochloride trihydrate: $C_{18}H_{19}O_4NI_2$·HCl·3$H_2O$, molar mass 657.7 g; monoclinic, $a$ = 30.408 (19), $b$ = 5.308 (2), $c$ = 17.176 (10) Å; $\beta$ = 117.93 (5)° (errors are $2\sigma$); $U$ = 2449 (5) Å$^3$; $d_x$ = 1.78 g cm$^{-3}$, $Z$ = 4; absorption coefficient for Mo K$\alpha$ x rays, $\mu$ = 27.4 cm$^{-1}$; absent spectra, $hkl$ when $h + k$ odd, space group $C2$ (confirmed by structure analysis).

The intensities of all reflections having $2\theta_{Mo\ K\alpha} \leq 40°$ (corresponding to a minimum interplanar spacing $d$ = 1.04 Å) were measured on an automated four-circle diffractometer with zirconium-filtered Mo K$\alpha$ radiation using the $2\theta$–$\theta$ scan technique. Because the crystals deteriorated rather quickly on exposure to x rays, three crysals were used for data collection. Table I gives crystal characteristics, method of data collection, and region of reciprocal space measured for each of the three crystals. A set of 12 reflections, ranging in intensity from medium-weak to very strong, was used to place all three sets of data on a common scale. Because the faster scan rate used for crystal C resulted in poorer estimates of the many weak reflections, combined data from crystals A and B were used for structure refinement. The intensities were corrected for background and linearly corrected for fall-off in intensity, the two sets scaled together, and Lorentz and polarization factors applied. No absorption corrections were made. A total of 1314 unique reflections were measured of which 1145 (87%) had $I > 2\sigma(I)$ and were considered to be observed.

**Structure Determination.** The positions of the iodine and chlorine atoms were determined from analysis of the three-dimensional Patterson function. These positions are closely related to those of the corresponding atoms in 3,5,3′-triiodo-L-thyronine hydrochloride,[11] as the similarity in the cell dimensions had led us to expect. Using initially phases based on the halogen atoms, two cycles of weighted[12] Fourier summations revealed positions for the oxygen, nitrogen, and carbon atoms of the ip-$T_2$ molecule as well as the three major sites for water molecules. Three cycles of isotropic refinement gave $R$ = 11.7%. A difference Fourier map, after two cycles with the halogen atoms anisotropic ($R$ = 6.5%), revealed 12 hydrogen atoms of the ip-$T_2$ molecule and three partially occupied water sites near the twofold axis. A further four cycles of full-matrix least squares, refining the halogen atoms anisotropically, the ip-$T_2$ oxygen, nitrogen, and carbon atoms isotropically, and the site-occupancy factors of the water molecules ($B$ = 16.0 Å$^2$) with the 12 hydrogen atoms contributing to the structure factors, gave a final conventional $R$ = 5.1% for the 1145 observed reflections. Throughout the refinement reflections measured from crystal A were given a different scale from those measured from crystal B. The final values of these scale factors [where $F$(absolute) = $kF$(measured)], $k_A$ = 2.829 and $k_B$ = 2.857, indicate that the experimentally determined scale factor relating sets A and B was accurate to 1%. Unit weights were used throughout the refinement as statistical weights gave higher $R$ factors and significantly worse agreement among chemically similar bonds. The final $\Sigma w\Delta^2/(m - n)$ = 1.66. Scattering factors for I, Cl$^-$, O, N, and C were those of Cromer and Mann[13] and for the hydrogen atoms those of Stewart, Davidson, and Simpson.[14] Table II lists the atomic fractional coordinates and thermal parameters; the observed and calculated structure factors may be found in the microfilm edition of this journal.[15]

**B. NMR Studies.** The NMR spectra of the aromatic ring hydrogen atoms of ip-$T_2$ in methanol and methanol–HCl solutions were recorded at room temperature on a 220-MHz spectrometer, with tetramethylsilane as an internal reference. The molar concentration of ip-$T_2$ used in each case was the maximum that could be obtained under the given conditions: ~0.03 *M* in methanol and ~0.08 *M* in methanol–1 *M* HCl (2:1 v/v).

## Discussion

A stereoscopic drawing of 3′-isopropyl-3,5-diiodothyronine hydrochloride projected along the *b* axis is given in Figure 1. As expected from the similarity of cell dimensions, its conformation is similar to that of 3,5,3′-triiodo-L-thyronine hydrochloride;[11] the isopropyl group is proximal to the $\alpha$ ring. This demonstrates that the possibility for the 3′-sub-

**Table II.** Atomic Coordinates and Thermal Parameters[a]

$T = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$

| | $x$ | $y$ | $z$ | $\beta_{11}$ | $\beta_{22}$ | $\beta_{33}$ | $\beta_{12}$ | $\beta_{13}$ | $\beta_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| I(3) | 0.2255 (1) | 0.5000 | 0.0528 (1) | 0.00273 (3) | 0.0427 (7) | 0.00441 (8) | 0.0002 (2) | 0.00174 (4) | −0.0001 (3) |
| I(5) | 0.0687 (1) | 0.0555 (7) | 0.1298 (1) | 0.00249 (4) | 0.1204 (20) | 0.00673 (10) | −0.0010 (3) | 0.00192 (5) | 0.0009 (4) |
| $Cl^-$(1) | 0.1815 (2) | 0.3403 (14) | 0.3759 (3) | 0.00281 (13) | 0.0504 (31) | 0.00381 (28) | −0.0018 (6) | 0.00111 (16) | −0.0011 (8) |

| | $x$ | $y$ | $z$ | $B$, Å$^2$ | | $x$ | $y$ | $z$ | Site occupancy |
|---|---|---|---|---|---|---|---|---|---|
| O(1) | −0.0046 (7) | 0.286 (5) | −0.2983 (13) | 10.3 (6) | O(W3) | 0.414 | 0.409 | 0.469 | 0.99 (3) |
| O(2) | 0.1233 (6) | 0.419 (3) | 0.0561 (9) | 6.1 (4) | O(W2) | 0.411 | 0.502 | 0.621 | 0.80 (3) |
| O(3) | 0.3065 (7) | 0.232 (4) | 0.4443 (12) | 8.3 (5) | O(W1) | 0.414 | 0.018 | 0.633 | 0.84 (3) |
| O(4) | 0.3507 (6) | 0.049 (5) | 0.3895 (10) | 8.5 (5) | O(W4A) | 0.496 | 0.680 | 0.465 | 0.25 (3) |
| N(1) | 0.2486 (6) | −0.167 (4) | 0.4190 (10) | 4.7 (4) | O(W4B) | 0.498 | 0.005 | 0.520 | 0.13 (3) |
| C(1) | 0.2234 (7) | −0.096 (4) | 0.2245 (12) | 4.3 (5) | O(W4C) | 0.499 | 0.227 | 0.470 | 0.21 (4) |
| C(2) | 0.2390 (7) | 0.079 (4) | 0.1823 (12) | 4.6 (5) | | | | | |
| C(3) | 0.2031 (7) | 0.247 (4) | 0.1208 (12) | 4.3 (5) | | | | | $B$, Å$^2$ |
| C(4) | 0.1565 (7) | 0.238 (5) | 0.1078 (13) | 4.5 (5) | HC(2) | 0.272 | 0.080 | 0.196 | 5.0 |
| C(5) | 0.1402 (7) | 0.058 (5) | 0.1473 (13) | 5.1 (5) | HC(6) | 0.162 | −0.195 | 0.235 | 6.0 |
| C(6) | 0.1755 (8) | −0.109 (4) | 0.2060 (13) | 4.7 (5) | H1C(7) | 0.253 | −0.420 | 0.274 | 6.5 |
| C(7) | 0.2608 (8) | −0.267 (5) | 0.2898 (14) | 5.2 (5) | H2C(7) | 0.287 | −0.310 | 0.273 | 5.0 |
| C(8) | 0.2835 (8) | −0.178 (5) | 0.3912 (15) | 5.4 (5) | HC(8) | 0.306 | −0.250 | 0.388 | 5.5 |
| C(9) | 0.3165 (8) | 0.060 (5) | 0.4094 (13) | 5.3 (5) | H1N(1) | 0.219 | −0.030 | 0.383 | 6.5 |
| C(1') | 0.0898 (8) | 0.366 (5) | −0.0341 (14) | 5.0 (5) | H2N(1) | 0.254 | −0.255 | 0.475 | 6.5 |
| C(2') | 0.1023 (8) | 0.191 (5) | −0.0791 (13) | 5.0 (5) | H3N(1) | 0.222 | −0.360 | 0.373 | 6.5 |
| C(3') | 0.0683 (9) | 0.162 (5) | −0.1734 (15) | 6.3 (6) | HC(2') | 0.134 | 0.055 | −0.057 | 5.5 |
| C(4') | 0.0277 (10) | 0.303 (6) | −0.2065 (18) | 7.8 (7) | HC(5') | −0.025 | 0.585 | −0.177 | 8.5 |
| C(5') | 0.0151 (9) | 0.464 (7) | −0.1599 (16) | 7.4 (6) | HC(6') | 0.046 | 0.655 | −0.040 | 7.5 |
| C(6') | 0.0488 (8) | 0.507 (8) | −0.0687 (14) | 7.2 (6) | HC(7') | 0.047 | −0.170 | −0.280 | 8.5 |
| C(7') | 0.0801 (9) | 0.008 (9) | −0.2302 (15) | 7.9 (6) | | | | | |
| C(8') | 0.1258 (12) | −0.199 (8) | −0.1769 (21) | 10.6 (1.0) | | | | | |
| C(9') | 0.1115 (14) | 0.160 (9) | −0.2629 (25) | 13.5 (1.2) | | | | | |

[a] Standard deviations are given in parentheses.

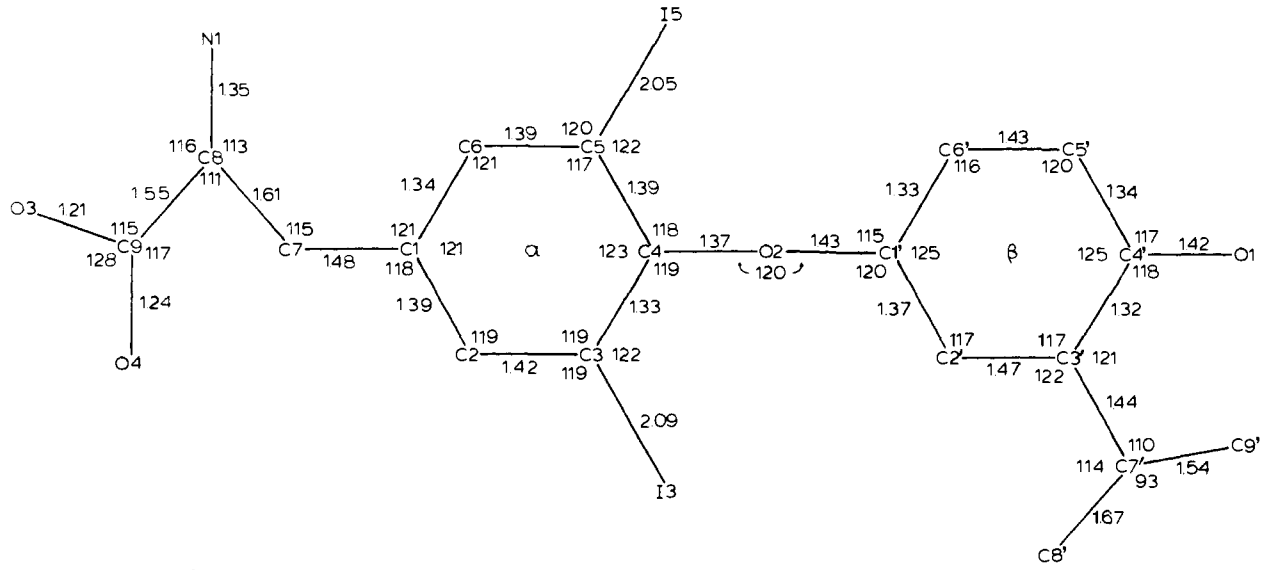


Figure 2. Bond lengths (Å) and valency angles (degrees) in 3′-isopropyl-3,5-diiodo-L-thyronine hydrochloride hydrate.

stituent to take part in attractive intermolecular interactions is not a requirement for the adoption of the proximal conformation. The planes of the phenyl rings are skewed with respect to one another and approach mutual perpendicularity, the angles between the $\alpha$ and $\beta$ rings and the plane of the inter-ring ether linkage (see ref 1 for the definition of the sense of these angles) being 97 and −26°, respectively (vs. 91 and −13° in $T_3$,[11] 88 and −10° in $T_3P$,[1] and 86 and 19° in the 3,5-diiodo-L-thyronine-*N*-methylacetamide complex).[16] The conformation angles for the amino acid portion of the molecule, defined in accordance with IUPAC-IUB rules,[17] are given in Table III. A comparison of these values with other thyroid hormone analogues having the alanine side chain shows a constancy of the conformation of the side chain in those strucutres crystallized from acid solution.[18]

Figure 2 shows the bond lengths and angles for ip-$T_2$. Because the iodine atoms dominate the x-ray scattering and because of the fall-off in intensity during data collection, the estimated standard deviations of the light atom bond lengths and valency angles are rather large, 0.02-0.05 Å and 1.5-3.0°, respectively. All values are normal within $3\sigma$. The angle at the ether oxygen is 120°, in agreement with other diphenyl ether compounds. Bond distances and angles involving hydrogen atoms are omitted from Figure 2; the inaccuracies in their values are too large to warrant their inclusion.

The aromatic rings and the carboxyl group are planar; atomic deviations from the planes are given in Table IV.

Table V gives the short intermolecular contacts. The hydrogen bonding network involves the phenolic hydroxyl, carboxyl, and amino groups of the ip-$T_2$ moiety and the chloride and three major water sites and is identical with that found for $T_3$·HCl·$3H_2O$.[11] Each chloride ion is surrounded by three amino groups and one water molecule in a distorted tetrahedral arrangement. There is one short contact between I(3) atoms on two different molecules of 3.883 (4) Å (3.73 Å in $T_3$·HCl). This distance is significantly shorter than the normal van der Waals separation of 4.30 Å given by Pauling[19] and the value of 4.08 Å given by Bondi[20] and indicates that some degree of interaction between the iodines of different molecules may be stabilizing the crystal structure.

ip-$T_2$ is the most potent thyromimetic substance known and the conformation of ip-$T_2$·HCl in the crystal structure is very similar in all respects to that for $T_3$·HCl. This similarity adds support to the inference which may be drawn from the biological tests, namely that any interaction between the 3′-substituent and the biological receptors must be of a steric and/or hydrophobic nature.

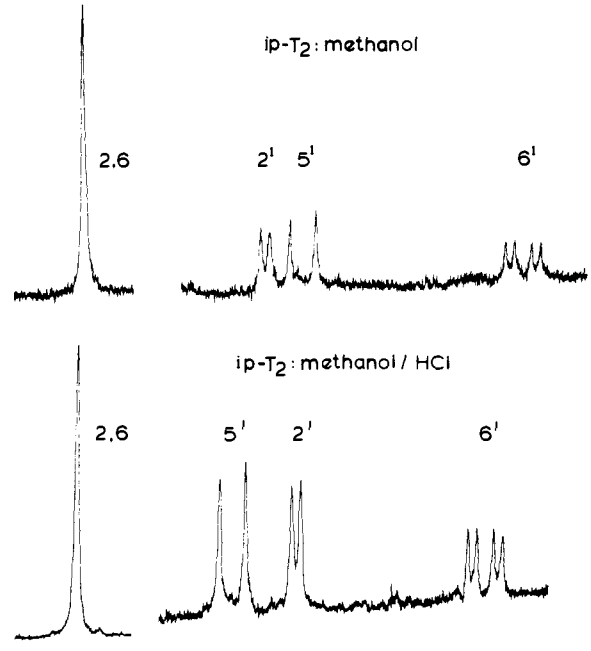


Figure 3. NMR spectra of the aromatic-ring protons of 3′-isopropyl-3,5-diiodo-L-thyronine in methanol and in methanol–HCl solutions. The field increases to the right.

Table III. Conformational Angles for ip-$T_2$

| Torsion angle | Defining atoms | Value, deg |
|---|---|---|
| $\psi_1$ | N(1)–C(8)–C(9)–O(3) | −2 |
| $\psi_2$ | N(1)–C(8)–C(9)–O(4) | 176 |
| $\chi_{11}$ | C(1)–C(7)–C(8)–N(1) | 63 |
| $\chi_{21}$ | C(2)–C(1)–C(7)–C(8) | 96 |
| $\chi_{22}$ | C(6)–C(1)–C(7)–C(8) | −84 |
| | C(3)–C(4)–O(2)–C(1′) | 98 |
| | C(5)–C(4)–O(2)–C(1′) | −84 |
| | C(2′)–C(1′)–O(2)–C(4) | −26 |
| | C(6′)–C(1′)–O(2)–C(4) | 157 |

Figure 3 shows the NMR spectra of the aromatic ring protons of ip-$T_2$ in methanol and in methanol-HCl. Peak

Table IV. Deviations of Atoms from Least-Squares Planes

| Plane 1 | | Plane 2 | | Plane 3 | |
|---|---|---|---|---|---|
| Atom | Δ, Å | Atom | Δ, Å | Atom | Δ, Å |
| C(1) | −0.02 | C(1') | 0.01 | C(8) | 0.00 |
| C(2) | 0.00 | C(2') | −0.02 | C(9) | 0.01 |
| C(3) | 0.02 | C(3') | 0.01 | O(3) | 0.00 |
| C(4) | −0.02 | C(4') | 0.02 | O(4) | 0.00 |
| C(5) | 0.01 | C(5') | −0.03 | C(7)[a] | 1.19 |
| C(6) | 0.01 | C(6') | 0.02 | N(1)[a] | −0.07 |
| C(7)[a] | −0.07 | O(2)[a] | 0.09 | | |
| I(3)[a] | 0.13 | C(7')[a] | 0.15 | | |
| O(2)[a] | −0.16 | O(1)[a] | 0.10 | | |
| I(5)[a] | −0.13 | | | | |

[a] These atoms not used in calculating the plane.

Table V. Short Intermolecular Contacts

| Atom (molecule 1) to atom 2 | Distance, Å | Symmetry relation for atom 2 |
|---|---|---|
| I(3)–I(3) | 3.88 | $\frac{1}{2}-x,\frac{1}{2}+y,-z$ |
| N(1)–Cl⁻(1) | 3.25 | $x,y,z$ |
| N(1)–Cl⁻(1) | 3.18 | $x,1+y,z$ |
| N(1)–Cl⁻(1) | 3.15 | $\frac{1}{2}-x,-\frac{1}{2}+y,1-z$ |
| O(1)–O(W1) | 2.51 | $-\frac{1}{2}+x,\frac{1}{2}+y,-1+z$ |
| O(1)–O(W2) | 2.73 | $-\frac{1}{2}+x,-\frac{1}{2}+y,-1+z$ |
| O(4)–O(W3) | 2.60 | $x,y,z$ |
| Cl⁻(1)–O(W1) | 2.99 | $\frac{1}{2}-x,\frac{1}{2}+y,1-z$ |
| O(W1)–O(W2) | 2.58 | $x,y,z$ |
| O(W1)–O(W2) | 2.74 | $x,1+y,z$ |
| O(W2)–O(W3) | 2.70 | $x,y,z$ |

Table VI. Chemical Shifts (Parts per Million) of Aromatic Ring Hydrogen Atoms in ip-$T_2$ Proton Magnetic Resonance Spectra

| | Protons | | | |
|---|---|---|---|---|
| Solvent | $H_6'$ | $H_5'$ | $H_2'$ | $H_{2,6}$ |
| $CH_3OH$ | 6.274 | 6.614 | 6.672 | 7.885 |
| $CH_3OH$–HCl | 6.361 | 6.746 | 6.648 | 7.918 |

assignments are labeled on Figure 3 and chemical shifts are given in Table VI. It is clear from Figure 3 that in going from methanol to the acidic solution there is an upfield shift of the 2′ doublet and a downfield movement of the 5′ doublet (and to a lesser extent the 6′ quadruplet). Qualitatively, these observations are consistent with a greater shielding effect of the α ring on the 2′ proton and thus a predominance of the 3′-isopropyl proximal conformer in acidic solution. In methanol the 5′ proton is shifted upfield, consistent with an interpretation of the greater presence of the 3′-isopropyl distal conformer in neutral solution. This result is similar to that found in our previous NMR studies of 3,5,3′-triiodothyropropionic acid[10] (although in that case two sets of peaks were observed which could be interpreted as indicating the presence of both conformations in the acid medium). For ip-$T_2$ in acidic solution, therefore, both crystallographic and NMR studies concur that the 3′-isopropyl proximal conformation is preferred. Quantitatively, the changes in chemical shifts are far too complex to be explained by simple consideration of α-ring shielding effects. (For example the change in chemical shift of the 5′ proton in going to acidic solution is greater than the changes in the 2′ and 6′ proton chemical shifts, even though the 5′ proton is farthest from the α ring.)

How, why, and to what extent high hydrogen ion concentration serves to stabilize a particular arrangement of the aromatic rings are perplexing questions; one suggestion[21] is that protonation of the ether oxygen occurs in mild acid and results in stabilization of the 3′-substituent proximal configuration. No evidence of ether protonation exists in the solid-state crystallographic results so far obtained, and further elucidation of this and other possible mechanisms must await systematic NMR experiments, varying the solvent systems and pH. Such studies are presently underway in our laboratories.

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**Supplementary Material Available:** final observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal (9 pages). Ordering information is given on any current masthead page.

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