Crystal Structure and Conformation of the Thyroxine Analogue 3,5-Di-iodo-L-thyronine *N*-methylacetamide (1:1) Complex

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Summary The structure of 3,5-di-iodo-L-thyronine complexed with *N*-methylacetamide (1:1), an analogue of thyroxine, has been determined by *X*-ray analysis as the first in a series of thyroid hormone analogues which have the thyroxine nucleus.

IN recent years there has been an intensive study of thyroid hormones in order to establish the structural requirements for maximal thyroid activity. Numerous structural analogues[1] have been synthesized in an effort to determine the structural features and structural–functional relationships which cause stimulation or suppression of various physiological functions by thyroid hormones. Crystallographic investigations of a number of the most important thyroid hormones, hormone precursors, and hormone analogues are in progress in this laboratory in an attempt to delineate precisely the molecular conformations of these compounds. While there are a number of structural studies of compounds which contain the tyrosine nucleus,[2] no structure containing the thyroxine nucleus has been studied.

The crystal system of 3,5-di-iodo-L-thyronine-*N*-methylacetamide ($C_{15}H_{13}NO_4I_2 \cdot C_3H_7NO$) is monoclinic, $P2_1$, with dimensions $a = 7{\cdot}988(3)$, $b = 22{\cdot}317(4)$, $c = 5{\cdot}995(2)$ Å and $\beta = 95{\cdot}53(5)°$. Intensities for 1912 observed reflections with $2\theta < 140°$ were collected on a General Electric XRD-5 diffractometer using Cu-K_α radiation monochromatized by balanced nickel and cobalt filters. The data were corrected for absorption effects.

The iodine positions were located from Patterson functions and the complete molecule from repeated application of three-dimensional Fourier synthesis. After anisotropic block-diagonal least-squares refinement the reliability index *R* is 8%.

As predicted from steric interaction studies[3] the conformation of the two phenyl rings is nearly mutually perpendicular (see Figure). The dihedral angle between the planes of the rings is 95° and the C–O–C ether angle is 118°. The presence of bulky substituents in the 3′ and 5′ positions in thyroxine and tri-iodothyronine inhibits free rotation about the ether linkage and fixes the conformation. Although there is less hindrance to rotation in di-iodothyronine the observed conformation corresponds to that predicted for thyroxine and tri-iodothyronine.

The Table shows the amino-acid backbone of a few thyroxine precursors with conformational rotation parameters which follow the convention suggested by Edsall *et al.*[4] When comparing the conformation of the tyrosine portion of the di-iodothyronine to other tyrosine derivatives the greatest conformational difference is in the rotation about the C′–C^α bond. 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. Only in the complex of 3,5-di-iodothyronine with *N*-methylacetamide is the nitrogen rotated out of the plane in the opposite direction.

The conformation about the C^α–C^β bond described by the parameter χ_1 (N–C^α–C^β–C^γ) shows the preferred conformation of χ *ca.* 300° which is sterically favoured,[5] allowing the amino-acid maximal contact area for potential hydrogen bonds or functional group interactions. The parameters χ_{21} and χ_{22} describe the torsional angles between the phenyl ring and the plane $C^\alpha C^\beta C^\gamma$. The preferred conformation seems to be near 113° when χ_1 is *ca.* 300°.

The molecules of 3,5-di-iodo-L-thyronine are in the usual zwitterion form as indicated by the C–O bond lengths of 1·29(2) and 1·23(2) Å for the hydroxyl and carbonyl bonds, respectively. The molecules are held together in the lattice by a network of hydrogen bonds. The amine is hydrogen bonded to the carbonyl of the *N*-methylacetamide, and to the carboxylic oxygen of an adjacent molecule with contact distances of 2·84, and 2·72 Å, respectively. The phenyl hydroxyl is in turn hydrogen bonded to the other carboxylic oxygen and possibly to the nitrogen of the *N*-methylacetamide with contact distances of 2·64 and 3·07 Å, respectively.

Conformational parameters for thyroid compounds and related amino-acids

Compound	ψ_1	ψ_2	χ_1	χ_{21}	χ_{22}
3,5-Di-iodo-L-thyronine	196°	21°	300°	121°	301°
3,5-Di-iodo-L-tyrosine ethyl ester (1)[2a] ..	154	328	305	92	275
3,5-Di-iodo-L-tyrosine ethyl ester (2)[2a] ..	151	341	288	114	279
3,5-Di-iodo-L-tyrosine[2b]	108	302	180	90	267

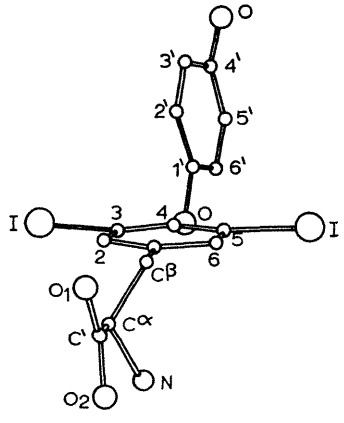

FIGURE. *End-on view of 3,5-di-iodo-L-thyronine.*

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