DISTAL CONFORMATION OF THYROID HORMONES. THE CRYSTAL STRUCTURE OF 3,5,3'-TRIIODOTHYROACETIC ACID *N*-DIETHANOLAMINE (1:1) COMPLEX

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SUMMARY. In the crystal structure of a complex of the hypocholesteremic thyromimetic agent, 3,5,3'-triiodothyroacetic acid and *N*-diethanolamine (1:1), the 3'-iodine is observed for the first time in the *distal* position, away from the α-ring of the diphenyl ether portion of a thyroactive analogue of thyroxine. This result was anticipated from stereochemical and biological activity studies. However, previous observations of structures in which the 3'-iodine was *proximal* had cast some doubt on the stability of the 3'-*distal* conformation. The present evidence now suggests that the relative energies of the two conformers are similar and that both conformers are readily accessible in solution.

Introduction

Recently there has been an intensive study of thyroid hormones in order to establish the structural requirements for maximal thyroid activity, particularly of the hormone triiodothyronine (T_3), which, because of the single iodine on the outer (β) ring imparts a degree of asymmetry not shared by thyroxine (T_4). This asymmetry results in two distinct conformers, one with the 3'-iodine oriented *distally*, or away from the inner (α) alanine bearing ring, and the other oriented *proximally* toward the inner ring. This makes the question of the conformational preference of T_3 in its active form very pertinent.

From the results of stereochemical and biological activity studies of a number of structural analogues of thyroxine[1], it appears that hormonal activity is restricted to the *distal* orientation of the 3'-iodine. The requirement of a *distal* 3'-substituent for activity was further substantiated by Schussler[2] in the binding study of T_3 to thyroxine binding globulin (TBG) using the thyroxine analogues 3,5-diiodo-2',3'-dimethylthyronine and 3,5-diiodo-2',5'-dimethylthyronine as test examples where either the *proximal* or *distal* conformation is locked by steric hindrance of the 2'-substituent. This investigation showed the *distal* analogue to have an almost two-fold greater binding affinity for TBG than the *proximal* form.

However, previous observations by Camerman and Camerman[3,4] of crystal structures of triiodothyronine HCℓ and the ethyl ester of triiodothyropropionic acid, which showed the 3'-iodine in the *proximal* conformation, had cast some doubt on the stability of the 3'-*distal* conformation. Here we report the first crystallographic observation of a compound with the 3'-iodine in the *distal* conformation, as anticipated from stereochemical and biological activity data.

Methods

Crystals of a 3,5,3'-triiodothyroacetic acid *N*-diethanolamine (1:1) complex were grown at room temperature from a methanol solution containing a ten-fold molar excess of urea. The crystal system is monoclinic C2/c, $Z = 8$ with dimensions $a = 29.21(2)$, $b = 8.038(3)$, $c = 20.48(2)$Å and $\beta = 107.13(9)°$. Intensities for 4060 (3360 observed) reflections with $2\theta<50°$ were collected on a General Electric XRD-5 diffractometer using Mo-Kα radiation monochromatized by balanced zirconium and yttrium filters. The intensities of the standard reflections fell 10% in a linear manner during the course of data collection concurrent with crystal decoloration. A decay factor as a linear function of time was applied to the data.

The iodine atoms were located from Patterson functions and the complete molecule from three-dimensional Fourier synthesis. After block diagonal least-squares refinements of all data the reliability index is 0.10. This structure comes closest to the ideal geometry of two mutually perpendicular, bisecting phenyl rings with the α-ring making

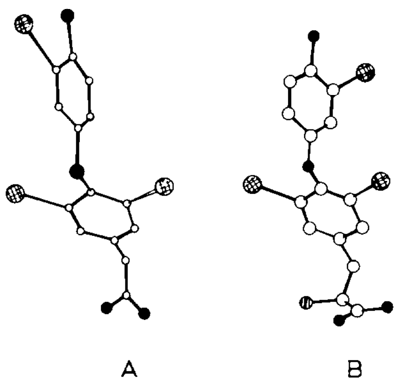

Figure 1.

a) The *distal* conformation of 3,5,3'-triiodothyroacetic acid.

b) The *proximal* conformation of 3,5,3'-triiodothyronine HCℓ[3].

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an angle of 4° with the C-O-C plane and the β-ring making an angle of 93° with the C-O-C plane. The C-O-C ether angle is 122° in agreement with that observed in other thyronine structures.

Discussion

The observation of a *distal* 3'-iodine observed here (Figure 1) in the crystal structure of the hypocholesteremic thyromimetic agent[5,6], 3,5,3'-triiodothyroacetic acid complexed with *N*-diethanolamine (1:1) as well as in the crystal structures of 3,5,3'-triiodo-L-thyronine and 3,5,3'-triiodo-L-thyronine methyl ester[7], indicates that the *distal* conformer is stable, that both the *distal* and *proximal* conformers are readily available in solution, and the relative energies of the two conformers is similar.

On the basis of molecular orbital energy calculations on trihalothyronines, Kier and Hovland[8] suggest a perpendicular arrangement of the phenyl rings that is "locked in" by a considerable barrier to internal rotation. However, their calculations do not show any significant preference for either conformer.

These results are not in agreement with the observations of

Cammerman and Cammerman[3] who find that the total energy of the *proximal* form is lower than that of the *distal* form. Thus, from their results Camerman and Camerman[3] put forth two alternative explanations for their observation that the *proximal* conformer is the energetically favored one, (1) that the biological data are inconclusive, (2) that if the *distal* conformation is necessary for hormonal activity, then the total energy of a T_3-receptor complex is favorable enough "to easily effect rotation of the β-ring". However, the present observation of a stable *distal* form supports the evidence of biological activity studies and makes unnecessary the assumption of a T_3-receptor complex to provide the energy to swing the β-ring to the active *distal* form.

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