Molecular Conformation of Thyrotropin-releasing Hormone from the *X*-Ray Structural Analysis of its Tartrate

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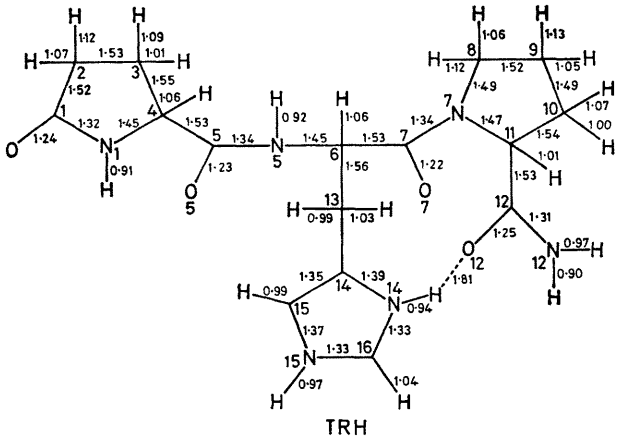
Summary An *X*-ray crystal study of thyrotropin-releasing hormone tartrate has revealed that its molecular structure, in contrast with predictions based on energy calculations and n m r spectroscopic studies, contains an extended peptide bond stabilized by a hydrogen bond between the π-NH unit of histidine and the carbonyl oxygen of the proline amide

THYROTROPIN-RELEASING hormone (TRH) is a tripeptide, pGlu-His-Pro-NH_2 that stimulates the release of thyrotropin and prolactin in animals, and is also important as a neurotransmitter or modulator Because of the biological and clinical significance of this releasing hormone, many semi-empirical energy calculations[1] and n m r determinations[2] have been carried out on its 3-dimensional structure. However, an *X*-ray analysis of TRH has not previously been reported owing to the difficulty in getting suitable crystals We now report the molecular structure of TRH in the solid state determined by *X*-ray analysis of TRH tartrate,[3] the monohydrate of which was obtained as colourless prisms from aqueous ethanol

Crystal data $C_{20}H_{28}N_6O_{10}\cdot H_2O$, monoclinic, space group $P2_1$, $a = 10{\cdot}522(2)$, $b = 16{\cdot}209(2)$, $c = 7{\cdot}472(2)$ Å, $\beta = 98{\cdot}88(5)°$, $Z = 2$ Using monochromated Mo-K_α radiation ($\lambda = 0\ 7107$ Å), 2495 independent reflexions up to $2\theta = 50°$ were measured with a Rigaku AFC-5 diffractometer A total of 2374 reflexions with $I > 3\sigma(I)$ were used for the calculation of the structure which was solved by direct



methods (MULTAN)[4] and refined by the least-squares method (XRAY)[5] to a residual R of 0·048.

The Figure shows a perspective view of the TRH molecule. The molecule is in an extended conformation stabilized by the intramolecular hydrogen bond between the imidazole π-NH of histidine and the carbamoyl oxygen of proline amide as shown by a dotted line in the Figure. The protonated TRH molecule, tartrate anion, and water of crystallization are connected with each other by 10 independent intermolecular hydrogen bonds in the crystal.

The six torsional angles which are usually adopted to describe the conformation of TRH are ψ_1 (146°), ϕ_2 (−70°), χ_1 (−163°), χ_2 (−71°), ψ_2 (137°), and ψ_3 (153°). Though some of these values are in accord with those predicted by energy calculations[1] or n.m.r. studies,[2] the overall conformation of TRH indicated by the present study is quite different. Its extended backbone conformation is rather similar to that of Phe[2]-TRH which has been determined by X-ray analysis of Phe[2]-TRH monohydrate.[6] The similar conformations in the crystalline state of TRH and of its Phe[2]-analogue indicate that the intramolecular hydrogen bond between the π-NH of histidine and the carboxamide of proline in TRH is unlikely to be important in stabilizing backbone conformation, since it is absent in the Phe[2]-analogue.

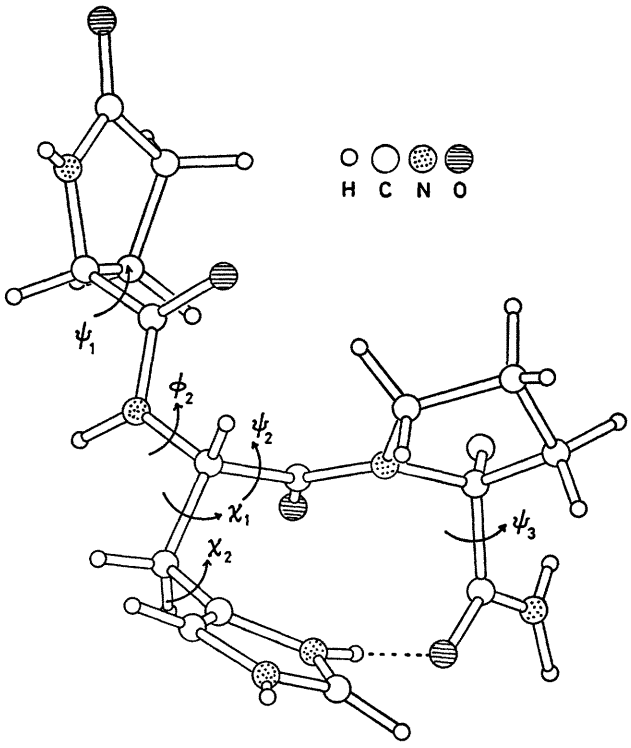


FIGURE. Perspective view of the TRH molecule showing the torsional angles and the intramolecular hydrogen bond.

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† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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