The Crystal Structure of CG 4305, a Biologically Active Prostacyclin Analogue with Exceptional Chemical and Metabolic Stability

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The *X*-ray structure determination of CG 4305 dihydrate presents the first crystallographically established conformational data for a biologically active prostacyclin analogue.

CG 4305 is a totally synthetic prostacyclin analogue that displays biological activity similar to that of the natural product[1] but possesses considerably enhanced stability towards chemical and metabolic degradation. Comparison of the chemical structures of CG 4305 and prostacyclin, PGI_2, make it obvious that the synthetic analogue has considerably less conformational freedom than the natural product. Consequently, we felt that a crystal structure determination of CG 4305 would be particularly appropriate for gaining insight into the conformational properties of PGI_2.

Crystals of racemic CG 4305 dihydrate were grown by slow evaporation of an aqueous methanol solution. *Crystal data:* $C_{25}H_{32}O_4 \cdot 2H_2O$, space group $P2_1/c$, a = 13.338(4), b = 5.378(2), c = 34.975(8) Å, β = 105.99(2)° for a crystal at *ca.* 120 K, Z = 4, D_c = 1.19 g cm^{-3}. *X*-Ray diffraction data were measured with monochromatized Mo-K_α radiation with a Syntex $P\bar{1}$ autodiffractometer operating in an ω-scan mode. 5423 Unique reflections were measured, $(\sin\theta/\lambda)_{max}$ = 0.704 Å^{-1}; 2777 with $I \geq 3\sigma(I)$ were classified as observed.

The initial structural model was determined by direct methods[2] and refined[3] by variable block–block diagonal least-squares methods. Positional disorder was found in the cyclohexane ring, the 15-hydroxy group, and in one hydrate molecule. Most of the hydrogen atoms could be found in difference electron density maps, but where possible those used in the model were obtained by calculation. Fractional atomic co-ordinates and anisotropic temperature factors were refined for C and O atoms; hydrogen atom parameters were not refined. Disordered atoms were assigned population parameters of 0.5, which resulted in refined temperature factors of comparable size for related atoms. A total of 4287 reflections were used in the refinement of 320 variables to give R 0.097 and R_w 0.123.

The observed conformation of CG 4305, Figure 1, has a number of features worthy of mention. The *m*-carboxyphenyl moiety is essentially planar (σ <0.01 Å for non-hydrogen atoms). Intramolecular steric repulsion prevents extension of planarity to include the exocyclic double bond; the torsion angle C(3)–C(4)–C(5)–C(6) is 27.5°, which still allows *ca.* 90% π-orbital overlap. The bond distances C(1)–C(2) 1.491(6) and C(4)–C(5) 1.469(6) Å are also indicative of conjugation between the exocyclic double bond and the aromatic ring. The ω-chain displays disorder in the tail [O(15) and the cyclohexane ring]. The disorder is reproduced in Figure 1 with one conformation with the ring as an exaggerated chair

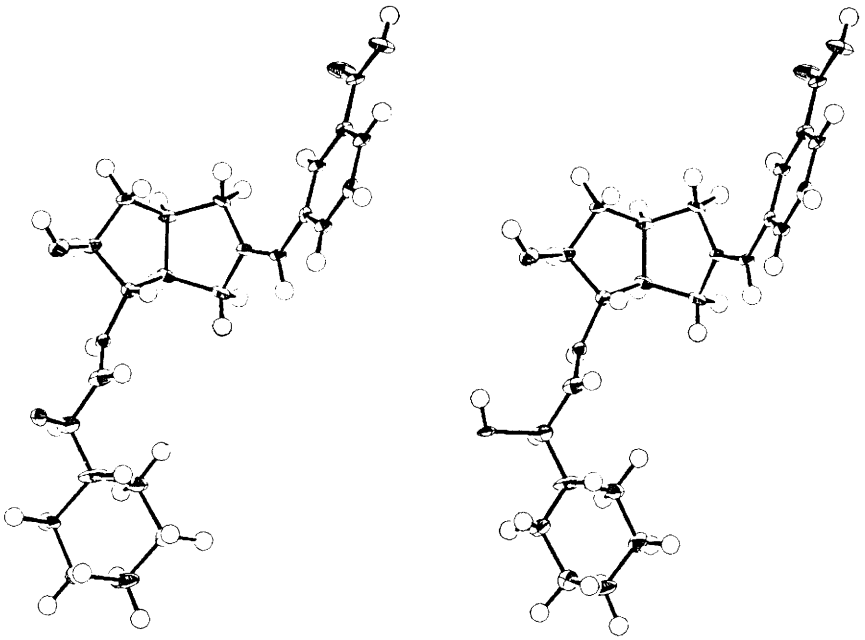

Figure 1. A stereoscopic projection (ref. 4) of the molecular conformation of CG 4305. The disorder in the ω-chain is depicted with one conformation in the left image and the other in the right. Presentation in this manner will normally result in 'blinking' of the disordered atoms when the figure is viewed in stereo.

(average endocyclic torsion angle 69.5°) on the left and another conformation, with an intermediate ring conformation between a chair and twist form (average torsion angle 29.7°) shown on the right.

Flohé *et al.*[1] have found that, for the *m*-carboxyphenyl modified prostacyclin family, the most active compounds were those with a cyclohexyl residue rather than those with the open chain n-pentyl residue of the natural product. This observation suggests that the receptor bound conformation of prostacyclin does not have an extended ω-chain. Steric considerations preclude an identical conformation to that of, *e.g.* CG 4305, however, a conformation with atoms C(16)—C(19) in nearly the same conformation is possible.

Because of the disorder in the crystal, a complete description of the hydrogen bonding interactions is beyond the scope of this report. There is one intermolecular hydrogen bond between the 11-hydroxy group (donor) and the carboxylate (receptor) of a symmetry related molecule. The remaining hydrogen bonds involve interactions with water molecules and will be described in detail in a future full paper.

We acknowledge the technical assistance of P. Kollat and partial financial support from the Verband der Chemischen Industrie, e.V.

Received, 22nd July 1983; Com. 984

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