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X-Ray Crystal Structure of a Hindered 7-Cis Isomer of Vitamin A. 7-cis-8-Fluororetinal.

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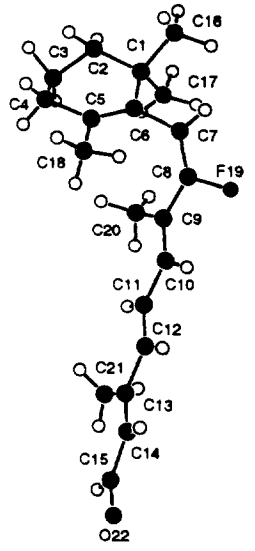
Abstract. The X-ray crystal structure of the title compound is the first for a hindered 7-cis isomer in the vitamin A series. The structural data show a simultaneous twisting of the 6,7-single bond that defines the ring-chain conformation (54°) and the adjacent 8,9-bond (30° for the 7,8-9,10 dihedral angle). The critical distance between the center of the cyclohexenyl ring and the carbonyl carbon is 11.1 Å, a value in between those of the binding isomers (11-cis and 9-cis) and the non-binding all-trans in interaction with the visual protein opsin. Copyright © 1996 Elsevier Science Ltd

Successful application of the method of selective triplet sensitization facilitated introduction of the hindered 7-cis geometry for compounds in the vitamin A series, which eventually led to the synthesis of all 16 possible stereoisomers of retinal.[1] The isomers in turn prompted a reexamination of binding stereoselectivity of the visual protein opsin.[2] Thus, several years ago we initiated a program to determine X-ray crystal structures of isomers of retinal.[3] However, none of the reported structures contained the sterically crowded 7-cis geometry (with the exception of a low resolution structure for methyl retinoate)[3a] because of difficulty in obtaining a crystalline sample of such an isomer. Meanwhile, some of the 7-cis isomers demonstrated interesting properties in their interaction with opsin.[4] Recently in our effort to prepare fluorinated retinals[5] for a F NMR study of fluorinated visual pigment analogs,[6] we successfully isolated 7-cis-8-fluororetinal in crystalline form. We now report its crystal structure and discuss its structural data in relation to some of the reported properties of 7-cis-retinal.

7-Cis-8-fluororetinal was isolated by HPLC from a mixture of isomers in a non-stereospecific synthesis of 8-fluororetinal.[5] The isomer was isolated by preparative HPLC and recrystallized from hexane (in the triclinic space group).[7] Its molecular structure is shown below. Some of the key structural features are the following.

The ring-chain conformation is twisted 6-S-cis with the 5,6-7,8 torsion angle found to be 54(1)°, which at first appears to be small when one compares it with the same values for the less crowded 7-trans isomers: $40.0 < |\Psi_{5,6\text{-}7,8}| < 76.0°$.[3c] However, a simultaneous twist of the adjacent 8,9-single bond ($|\Psi_{7,8\text{-}9,10}| = 30°$) apparently serves well to minimize ring-chain steric crowding while retaining partial conjugative interaction of all double bonds in the pentaenal chromophore. The remaining chromophore is nearly planar: $\Psi_{9,10\text{-}11,12} = -176(1)$, $\Psi_{11,12\text{-}13,14} = -177.2(9)$, $\Psi_{13,14\text{-}15,O22} = 178(1)°$. Bond distances and angles are listed below.[8] The calculated length of the chromophore, measured from the center of the cyclohexenyl ring to the carbonyl carbon, is 11.1 Å.

The latter distance is known to be critically important in formation of visual pigment analogs. An earlier analysis based on conformers of 11-cis-retinal led to the conclusion that the critical distance for optimum binding interaction is 9.6-10.9 Å.[3a] The 11.1 Å value for 7-cis-retinal, while much smaller than the corresponding value (12.4 Å) for the inactive all-trans isomer, is outside this range. (The negative result of the 13-cis isomer is believed to be due to a different reason.[2b]) This, we believe, accounts for the characteristic properties of 7-cis-retinal in interaction with opsin (i.e., a slower binding rate and a moderate 40-50% yield)[2a], necessitated by additional conformation adjustment (e.g., further twisting the 8,9 bond) before pigment formation.



It is also interesting to note that solution values of the ring-chain dihedral angles of 7-cis isomers as determined from an analysis of long-range coupling constants (developed by Karplus et al. for the 7-trans compounds)[9] between H_7 and H_4 or H_{Me5} (32-48°) are lower.[10] However, a similar trend was also observed for compounds with the 7-trans geometry.[3,9]

With other newly discovered biological activities associated with isomers and conformers of retinoids,[11] there will be a continued interest in acquiring accurate structural data for retinal isomers.[12]

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7. Cell dimensions: a = 7.378(3), b = 8.269(4), c = 15.155(7) Å, α = 85.22(4), β = 78.24(3), γ = 74.63(3)°, V = 872.4(7) $Å^3$, Z = 2, d_{expl} = 1.15 g cm^{-3}, μ = 0.8 cm^{-1}, F(000) = 328. X-ray diffraction data were collected at 160 K, λ(Mo, Kα) - 0.71073 Å, θ-2θ scan mode to $2\theta_{max}$ = 45°, crystal size = 0.48 x 0.48 x 0.16 mm. Of 2261 unique reflections collected, 1141 had I > 3.5σ(I). The structure was solved using the direct methods programs in Texasan and refined by full-matrix least-square procedures. Final values of the observed data are R = 0.083 and R_W = 0.079; S = 4.93.
8. Selected bond lengthes: 1,2 = 1.52(1), 2,3 = 1.42(1), 3,4 = 1.50 (1), 4,5 = 1.49(1), 5,6 = 1.32(1), 6,1 = 1.56(1), 6,7 = 1.48(1), 7,8 = 1.31(1), 8,9 = 1.45 (1), 8,F19 = 1.391(9), 9,10 = 1.34(1), 10,11 = 1.45(1), 11,12 = 1.36(1), 12,13 = 1.48(1), 13,14 = 1.35(1), 14,15 = 1.44(1) Å; bond angles: 1,6,5 = 122.6(8), 1,6,7 = 114.6(9), 5,6,7 = 122.8(8), 6,7,8 = 125.8(9), 7,8,9 = 133.4(9), 7,8,F19 = 116.0(8), 9,8,F19 = 110.6(8), 8,9,10 = 121.2(9), 9,10,11 = 127.4(9), 10,11,12 = 122.4(9), 12,13,14 = 115.9(9), 13,14,15 = 115.9(9), 14,15,O22 = 125(1)°.
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