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Disorder in 13-*cis*-Retinoic Acid

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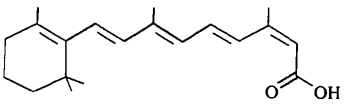
Abstract

13-*cis*-Retinoic acid [(2*Z*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)-2,4,6,8-nonatetraenoic acid, $C_{20}H_{28}O_2$] was found to adopt the 6-*s*-*trans* conformation, with the ring double bond and all the C atoms of the polyene chain coplanar. The plane of the double-bond system is coincident with a crystallographic mirror plane. The crystal displays crystallographic symmetry arising from disorder, indeed the cyclohexene ring, in a half-chair conformation, is present in two equally occupied conformations related to one another by the mirror plane. The carboxylic acid group is also disordered, lying on opposite sides of the plane of the double-bond system. In the crystal, the molecules form dimers connected by hydrogen bonds involving the carboxylic acid groups, and the dimers pack in parallel layers.

Comment

It has been well established that, of the naturally occurring isomeric vitamin A acids (Zechmeister, 1962), 13-*cis*-retinoic acid (isotretinoin) is of relevant practical importance due to its outstanding pharmacological activities (Bollag, 1981). The material is synthetically available by regioselective isomerization of the 11-double bond of 11,13-di-*cis*-retinoic acid obtained in a C-15 + C-5 Wittig condensation (Pattenden & Weedon, 1968), using either Pd^0 chemistry (US Patent 4 556 518) or photochemical methods (Mag Laboratories, 1997). A major drawback of 13-*cis*-retinoic acid is its apparent intrinsic instability and its remarkable aptitude to react with oxygen of the air. Although numerous related compounds have been characterized by X-ray diffraction, until now there has been no structural information in the literature for isotretinoin, (I). The X-ray analysis of this compound has been undertaken and its molecular conformation and crystal structure are reported here.



(I)

The perspective view of 13-*cis*-retinoic acid is shown in Fig. 1. The molecule is found to have a 6-*s*-*trans* conformation, so that the double-bond system from C5 to C14 has an all-*trans* conformation and is perfectly planar, its plane being coincident with a crystallographic mirror plane. The ring adopts an almost half-chair conformation; atoms C1 and C2 are located at distances of 0.22 (2) and 0.537 (5) Å, respectively, from the double-bond plane and C3 on the other side of the plane is located at a distance of 0.36 (7) Å. The molecule shows disorder both of the cyclohexene ring and of the carboxylic O atoms. The most interesting feature of the disorder is that the atoms involved, *i.e.* C1, C2, C3, C16 and C17, O1, O2, flip over two symmetrical and equally occupied positions on opposite sides of the plane of the double-bond system. As a result, the disorder allows the two alternative half-chair conformers of the cyclohexene ring to co-exist in the crystal structure as a 1:1 mixture; in accordance, the methyl groups (C16 and C17) also assume alternative positions (Fig. 2).

Conformational disorder of the cyclohexene ring was found or supposed to exist in crystal structures of a number of vitamin A retinal-related compounds and carotenoids. The evidence for this is as follows: (i) the unusually short C2—C3 bond length as found in the triclinic modification of the vitamin A acid (Stam, 1972), in the 6-*s*-*cis* conformer of 13-*cis*-retinal (Simmons, Liu, Denny & Seff, 1981), in a 9-*cis*-retinal derivative (Simmons, Asato, Denny & Liu, 1986) and in all-*trans* retinal (Hamanaka, Mitsui, Ashida & Kakudo, 1972); (ii) the unexpected planarity of the cyclohexene ring, as found in 2,6-di-*cis*-4-hydroxy-retinoic acid γ-lactone (Thackeray & Gafner, 1974); (iii) the presence of residual peaks in the final $\Delta\rho$ map in the vicinity of C_{sp^3} ring atoms and the presence of very large displacement parameters for these atoms, as commonly observed in the above-mentioned class of compounds. The disorder has been interpreted either as static and ascribed to the co-existence of the two alternative half-chair conformers in a variable reciprocal ratio, or as dynamic and attributed to high thermal motion of some of the ring atoms. In isotretinoin, the attribution of the two equally occupied conformations to the cyclohexene ring allows good ring geometry (see Table 2) and is also consistent with the molecular packing. The distance between the two half-occupied

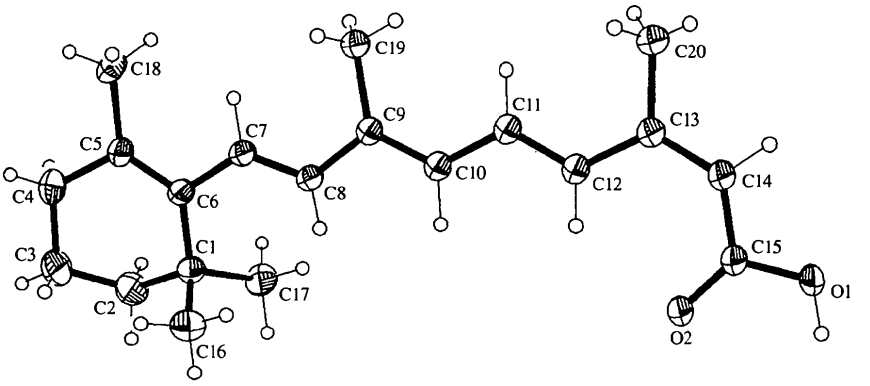


Fig. 1. Perspective view of the title molecule showing the atom-labelling scheme. Displacement ellipsoids are plotted at the 25% probability level, while the H atoms are represented by spheres of arbitrary size. Only one of the two possible positions of each of the disordered atoms is shown.

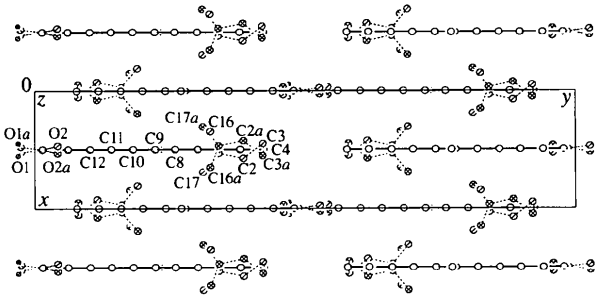


Fig. 2. Packing arrangement of the molecules on the (001) plane, showing the cyclohexene rings and the carboxylic acid groups disordered over two positions related by a mirror plane parallel to the *xy* plane. For clarity, not all atoms are labelled (H atoms have been omitted).

positions of each disordered atom (maximum value of 1.07 Å for atom C4) seems to be in favour of static disorder, however, the asymmetric vibrations of the double-positioned atoms are consistent with the hypothesis of dynamic disorder. The disordered atoms are elongated along the **x** direction with respect to the molecular plane.

In the crystal, the molecules form centrosymmetric dimers through hydrogen bonds between carboxylic acid groups, with a O1—H···O2($-x$, $1-y$, $-z$) distance of 1.64 (3) Å and an angle of 163 (3)°. The dimers form sheets parallel to the *yz* plane at $x = 0$ and $x = 0.5$. Fig. 2 shows how the interlayers pack together. From the diagram of the packing arrangement on the (001) plane, it may be seen that the two half-chair ring conformers have the same environment, allowing the same statistical occurrence. The attachment of the ring to the chain in this class of compounds seems to depend on the method of crystallization (Liu & Asato, 1984); in any case, there is a predictable correlation between the C5—C6—C7—C8 torsion angle and the C6—C7—C8 bond angle. In the 6-*s*-*trans* structures, the steric energy arising from a short intramolecular contact (C17—H172···H8) is decreased by the opening of the C6—C7—C8 bond angle to about 131°, compared with the mean value of 127° for the 6-*s*-*cis* form; at the same time, in the 6-*s*-*trans* compounds, the C5—C6—C7 bond angle decreases to a mean value of 118°, while in the 6-*s*-*cis* form, it is about 122°. In the present compound, the intramolecular contact distance C17—H172···H8 is 1.80 Å and the C6—C7—C8 and the C5—C6—C7 bond angles are in agreement with the typical geometry of 6-*s*-*trans* structures already observed in the monoclinic modification of vitamin A (Stam, 1972), in the 6-*s*-*trans* conformer of 13-*cis*-retinal (Simmons *et al.*, 1981) and in a carotenoidal compound (Braun, Hornstra & Leenhouts, 1971).

The structure shows some extra strain caused by the repulsion between the methyl groups and the H7, H10 and H13 atoms. Owing to steric interaction, the C8—C9—C10 bond angle, opposite to the C19 methyl group, is compressed to 119.2 (2)° (the mean value for an unhindered conjugate chain is 125°) and a slight in-plane bending of the chain is observed. In contrast to the all-*trans* isomers of the other related structures, the bond angle opposite the C20 methyl group does not decrease quite so significantly because of the short contact (H12···O2) present in the 13-*cis* conformer. Accordingly, the C20—C13—C14 bond angle appears more compressed than in the all-*trans* isomers, where a mean value of 123.7° is observed. This effect is also found in the 13-*cis*-retinal (Simmons *et al.*, 1981), where the C8—C9—C10, C12—C13—C14 and C20—C13—C14 bond angles are 117.6, 123.5 and 118.7°, respectively. As a result of the repulsion effects, the shape of the chain of the 13-*cis* isomer is straighter compared with the sabre-like appearance of the all-*trans* isomer. The bond distances along the chain show the typical alternation of shorter and longer bonds of the conjugate systems and are within the expected values. The methyl groups at C19 and C20 have one H atom

eclipsing a chain double bond, a feature commonly observed in a methyl group attached to a double bond.

The carboxyl hydrogen bond is in a *trans* conformation with respect to the C14—C15 double bond, the C13—C14—C15—O1 torsion angle being 171.6 (10)°. The carboxylic acid group plane is rotated by 10.9 (9)° with respect to the chain plane.

Experimental

The crystals of (I) were provided by Mag Laboratories and the synthesis will be described elsewhere (Malpezzi, Boschetti, Fuganti, Grasselli, Magnone & Pellegatta, 1997). Crystallization from ethyl acetate yielded orange single crystals suitable for the X-ray analysis. To avoid possible oxidation of the compound on exposure to air, the crystal used for data collection was freshly prepared and sealed in a capillary tube.

Crystal data

$C_{20}H_{28}O_2$
M_r = 300.42
Orthorhombic
Cmca
a = 7.170 (1) Å
b = 30.766 (1) Å
c = 16.910 (1) Å
V = 3730.2 (6) Å^3
Z = 8
D_x = 1.070 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 40 reflections
θ = 18–38°
μ = 0.520 mm^{-1}
T = 293 (2) K
Irregular
0.5 × 0.4 × 0.3 mm
Orange

Data collection

Siemens $P4$ diffractometer
$\theta/2\theta$ scans
Absorption correction: none
2963 measured reflections
1367 independent reflections
1139 reflections with $I > 2\sigma(I)$
R_{int} = 0.0307

θ_{max} = 56.73°
$h = -7 \rightarrow 7$
$k = -33 \rightarrow 9$
$l = -18 \rightarrow 1$
3 standard reflections
every 100 reflections
intensity decay: <0.5%

Refinement

Refinement on F^2
$R(F)$ = 0.0449
$wR(F^2)$ = 0.1330
S = 1.043
1365 reflections
167 parameters
$w = 1/[\sigma^2(F_o^2) + (0.077P)^2 + 0.9186P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.080

$\Delta\rho_{max}$ = 0.144 e Å^{-3}
$\Delta\rho_{min}$ = −0.196 e Å^{-3}
Extinction correction: *SHELXL93*
Extinction coefficient: 0.0049 (4)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\sum_i\sum_j U^{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
O1†	−0.025 (3)	0.52660 (6)	0.09332 (12)	0.097 (3)
O2†	0.032 (2)	0.45848 (6)	0.05958 (11)	0.082 (3)
C1†	−0.031 (3)	0.16009 (11)	0.0555 (2)	0.074 (4)
C16†	0.1523 (16)	0.1760 (3)	0.0188 (6)	0.104 (3)
C17†	−0.1927 (17)	0.1896 (3)	0.0287 (6)	0.090 (2)
C2†	−0.0749 (7)	0.11510 (12)	0.0225 (2)	0.115 (2)
C3†	0.0502 (16)	0.08002 (13)	0.0569 (2)	0.119 (5)
C4	0	0.07737 (8)	0.1451 (2)	0.0911 (9)
C5	0	0.12094 (7)	0.18474 (14)	0.0631 (6)
C18	0	0.11788 (8)	0.27425 (14)	0.0775 (8)
C6	0	0.15917 (7)	0.14531 (13)	0.0620 (6)
C7	0	0.19922 (7)	0.19080 (12)	0.0591 (6)
C8	0	0.24081 (7)	0.16857 (13)	0.0585 (6)
C9	0	0.27811 (6)	0.22047 (12)	0.0550 (6)
C10	0	0.31845 (7)	0.18868 (13)	0.0596 (6)
C11	0	0.35904 (7)	0.22948 (13)	0.0602 (6)
C12	0	0.39791 (7)	0.19357 (13)	0.0611 (6)
C13	0	0.43948 (7)	0.23327 (12)	0.0617 (6)
C14	0	0.47803 (7)	0.19530 (13)	0.0683 (7)
C15	0	0.48583 (7)	0.11086 (14)	0.0690 (7)
C19	0	0.27061 (7)	0.30828 (13)	0.0651 (7)
C20	0	0.43958 (8)	0.32245 (13)	0.0753 (8)

† Site occupancy = 0.50.

Table 2. *Selected geometric parameters (Å, °)*

O1—C15	1.301 (4)	C7—C8	1.334 (3)
O2—C15	1.229 (4)	C8—C9	1.445 (3)
C1—C2	1.525 (6)	C9—C10	1.353 (3)
C1—C6	1.535 (5)	C10—C11	1.427 (3)
C2—C3	1.519 (8)	C11—C12	1.341 (3)
C3—C4	1.537 (6)	C12—C13	1.445 (3)
C4—C5	1.498 (3)	C13—C14	1.349 (3)
C5—C6	1.352 (3)	C14—C15	1.448 (3)
C6—C7	1.453 (3)		
C2—C1—C6	112.0 (3)	C8—C9—C19	118.6 (2)
C3—C2—C1	112.5 (6)	C9—C10—C11	127.7 (2)
C2—C3—C4	105.7 (5)	C12—C11—C10	124.2 (2)
C5—C4—C3	112.7 (2)	C11—C12—C13	125.4 (2)
C6—C5—C4	123.9 (2)	C14—C13—C12	123.9 (2)
C5—C6—C7	118.5 (2)	C14—C13—C20	118.3 (2)
C5—C6—C1	120.3 (2)	C12—C13—C20	117.8 (2)
C7—C6—C1	120.5 (2)	C13—C14—C15	128.0 (2)
C8—C7—C6	131.7 (2)	O2—C15—O1	121.6 (2)
C7—C8—C9	126.2 (2)	O2—C15—C14	125.6 (2)
C10—C9—C8	119.2 (2)	O1—C15—C14	112.6 (2)
C10—C9—C19	122.2 (2)		
C6—C5—C4—C3	14.7 (4)	C5—C6—C1—C2	4.6 (14)
C5—C4—C3—C2	−50.1 (6)	C1—C6—C7—C8	−9.7 (8)
C4—C3—C2—C1	65.9 (8)	C13—C14—C15—O1	171.6 (10)
C3—C2—C1—C6	−43.5 (13)		

Using the diffractometer software package, automatic Bravais lattice determination and a systematic search for weak reflections supported an orthorhombic lattice and Laue group *mmm*. Systematic absences were consistent with space group *Cmca* and 16 units per cell. According to these findings, the resulting value of the calculated density was unacceptable; on the other hand, the molecule inherently lacked any element of symmetry and could not be placed on a special position. As a result, the number of formula units per cell cannot be reduced unless some crystallographic disorder is present. The reflections can also be indexed with a monoclinic cell and the corresponding systematic absences indicate, in this case, space group $P2_1/c$. The monoclinic cell was: a = 7.172 (1), b = 16.917 (1), c = 15.795 (2) Å, β = 103.11 (1)°, V = 1866 (3) Å^3, Z = 4. The two solutions are related to each other since the monoclinic cell transforms into the orthorhombic one with the following matrix: (100, $\bar{1}0\bar{2}$, 010). The title structure shows disorder and in order to resolve it the C_{sp^3} cyclohexene atoms and the carboxylic acid group were assumed to be doubled, the occupation factor being refined together with the other atomic parameters. Any attempt to clarify the molecular geometry along these lines on the basis of the monoclinic cell was not

satisfactory because of the high value of R (0.087) and the presence in the final $\Delta\rho$ map of considerable residual electron density around the ring C atoms and the tail O atoms. A disorder model was assumed, involving the two alternative half-chair ring conformations and the carboxylic acid group flipping over two symmetrical positions obtained by reflection through the plane of the chain, with site-occupancy factors of 0.5 for all double-positioned atoms. The final accepted solution of the phase problem, with the highest symmetry and the highest figure of merit, *i.e.* in the orthorhombic *Cmca* space group, appeared to be consistent with the proposed disordered structure and was accepted as the correct one. The H atoms of the methyl groups were placed in calculated positions using the $\Delta\rho$ map as a guide. During the following refinement, the methyl groups were treated as rigid bodies with free rotation around the methyl C—C bonds (*SHELXL*93; Sheldrick, 1993). The H atoms bonded to the C2, C3 and C4 atoms were added at calculated positions and refined using a riding model. The carboxyl hydrogen was placed in a calculated position to form the best hydrogen bond and then freely refined. To further verify the validity of the structural model adopted, the coordinates and anisotropic displacement parameters, refined in the orthorhombic lattice, were transformed again to the monoclinic system and refined. As expected, no significant change was found and the residual error index R converged to 0.0495 for 330 parameters refined with 1989 unique reflections. Only the results of the refinement in orthorhombic space group *Cmca* are reported and deposited.

Data collection: *XSCANS* (Siemens, 1992). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Molecular graphics: *SHELXTL/PC* (Sheldrick, 1990). Software used to prepare material for publication: *SHELXL*93.

Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: NA1267). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Absolute Structure of (Thian-5-one 1,1-dioxide)-3-spiro-3′-(5′-*O*-*tert*-butyldimethylsilyl-3′-deoxy-1′,2′-*O*-isopropylidene-α-D-*xylo*-pentofuranose), a Novel Type of Spirosugar

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Abstract

The absolute structure of the title compound, $C_{18}H_{32}O_7SSi$, has been determined. The thianone ring adopts a chair conformation whereas the furanose ring exists in an envelope conformation. No short interatomic distance was observed in the molecular packing.

Comment

The discovery of the powerful anti-HIV-1 activity of the TSAO derivatives (Ingate, Camarasa, De Clercq & Balzarini, 1995) has renewed interest in spironucleosides. The title compound, (I), has been prepared (Tronchet, Kovacs & Bernardinelli, 1996) as a synthetic building block to be used for the synthesis of a novel type of spironucleoside. The two electron-withdrawing groups of the thianone *S,S*-dioxide ring afford a large flexibility for the further functionalization of the ring in such a way as to design hopefully, biologically active derivatives. The stereospecific spiro insertion of the thianone ring has been carried out *via* the nucleophilic attack of the conjugate base of dimethylsulfone upon the *Z* diasteroisomer of the corresponding 3-deoxy-3-methoxycarbonylmethylidenefuranose derivative. An