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The Structures of 9-*cis*-Retinal and 19,19,19-Trifluoro-9-*cis*-retinal

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Abstract. 9-*cis*-Retinal (I): $C_{20}H_{28}O$, $M_r = 284\cdot4$, triclinic, $P\bar{1}$, $a = 5\cdot722$ (1), $b = 7\cdot279$ (2), $c = 23\cdot252$ (9) Å, $\alpha = 89\cdot70$ (3), $\beta = 92\cdot64$ (3), $\gamma = 108\cdot60$ (2)°, $V = 916\cdot9$ (5) Å^3, $Z = 2$, $D_x = 1\cdot030$ Mg m^{-3}, $F(000) = 312$, $T = 298$ K, μ_o(Cu $K\alpha$) $= 0\cdot44$ mm^{-1}. 19,19,19-Trifluoro-9-*cis*-retinal (II): $C_{20}H_{25}F_3O$, $M_r = 338\cdot4$, triclinic, $P\bar{1}$, $a = 5\cdot745$ (2), $b = 7\cdot239$ (5), $c = 23\cdot893$ (11) Å, $\alpha = 90\cdot56$ (5), $\beta = 93\cdot98$ (3), $\gamma = 106\cdot93$ (4)°, $V = 947\cdot9$ (9) Å^3, $Z = 2$, $D_x = 1\cdot186$ Mg m^{-3}, $F(000) = 360$, $T = 296$ K, μ_o(Mo $K\alpha$) $= 0\cdot09$ mm^{-1}. The crystal structures have been determined using counter methods and Cu $K\alpha$ radiation ($\lambda_{K\bar{\alpha}} = 1\cdot5418$ Å) for (I) and Mo $K\alpha$ radiation ($\lambda_{K\bar{\alpha}} = 0\cdot71069$ Å) for (II). The structures have been refined by full-matrix least-squares procedures using 2230 (2σ) and 1545 (2σ) unique and significant reflections to the final R values of 0·055 and 0·067 respectively. The structures of (I) and (II) are nearly isostructural. The structural data of 9-*cis*-retinal are consistent with those reported for NMR studies of (I) in solution.

Introduction. The 9-*cis* isomer of retinal has played an important role in the study of the binding-site specificity of the visual pigment rhodopsin. For example, more than 30 years ago, it was shown to form a pigment analogue when incubated with the apoprotein opsin (Hubbard & Wald, 1952/3; Wald, Brown, Hubbard & Oroshnik, 1955). More recent studies have shown that 9-*cis*-retinal is unique among the other non-naturally occurring retinal isomers, most of which have only been recently synthesized (Crouch, Purvin, Nakanishi & Ebrey, 1975; DeGrip, Liu, Ramamurthy & Asato, 1976; Kini, Matsumoto & Liu, 1979, 1980; Asato, Kini, Denny & Liu, 1983), in that its rate of combination with bovine opsin is an order or two greater in magnitude than the others, second only to the naturally occurring and structurally similar 11-*cis* isomer (Liu, Matsumoto, Kini, Asato, Denny, Kropf & DeGrip, 1984). Furthermore, both low-temperature steady-state spectroscopic studies (Yoshizawa & Wald, 1963) and room-temperature fast kinetic studies (Busch, Applebury, Lamola & Rentzepis, 1972) have shown that bathorhodopsin, the primary photoproduct of rhodopsin, can interconvert nearly equally well between rhodopsin and 9-*cis*-rhodopsin. This unique dynamic property plays an integral part in the recently formulated HT-*n* ('hula twist' at center *n*) model for the primary process of vision (Liu & Asato, 1985). In spite of the obvious biological importance of 9-*cis*-retinal, its crystal structure remained undetermined.

We wish to report the crystal structure of 9-*cis*-retinal and thereby add to the collection of structures of other retinal isomers, which include: all-*trans* (Hamanaka, Mitsui, Ashida & Kakudo, 1972), 11-*cis* (Gilardi, Karle & Karle, 1972; Drikos, Rüppel, Dietrich & Sperling, 1981), 13-*cis* (Simmons, Liu, Denny & Seff, 1981), and methyl-7,9-di*cis*-retinoate

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(the retinal is an oil; Matsumoto, Liu, Simmons & Seff, 1980). Also included is the crystal structure of 19,19,19-trifluoro-9-*cis*-retinal, an interesting compound used as a sensitive probe in our NMR studies of fluorine-labeled rhodopsin and bacteriorhodopsin (Liu, Matsumoto, Asato, Denny, Shichida, Yoshizawa & Dahlquist, 1981; Asato, Mead, Denny, Bopp & Liu, 1982; Mead, Loh, Asato & Liu, 1985). The unambiguous establishment of its structure is particularly important in light of the apparently erroneous configurational assignments recently made for 20,20,20-trifluoro-all-*trans*-retinal (Gärtner, Oesterhelt, Towner, Hopf & Ernst, 1981). The cumulative effects of the highly electronegative F atoms render the chemical shifts in the ^{1}H NMR spectra unreliable for the assignment of configurations (Asato *et al.*, 1982).

Experimental. The 9-*cis*-retinal (I) used for this study was generously supplied by Dr G. L. Olson of Hoffmann–La Roche Inc. The crude product was recrystallized from *n*-hexane. The procedure for the preparation of 19,19,19-trifluoro-9-*cis*-retinal (II) has previously been described (Asato *et al.*, 1982). The compound was purified by preparative HPLC (5 μm silica gel column), followed by recrystallization from *n*-hexane.

Single crystals of (I) and (II), 0·80 × 0·86 × 0·20 and 0·44 × 0·30 × 0·10 mm in size, were selected for X-ray diffraction studies. A Syntex $P\bar{1}$ four-circle computer-controlled diffractometer with graphite-monochromatized Cu $K\alpha$ radiation ($K\alpha_1 = 1·5406$; $K\alpha_2 = 1·5444$ Å) for (I) and Mo $K\alpha$ radiation ($K\alpha_1 = 0·70930$; $K\alpha_2 = 0·71359$ Å) for (II) were used for the measurements of all diffraction intensities. The unit-cell parameters and their standard deviations were determined by a least-squares treatment of the angular coordinates of 15 reflections with 2θ values up to 60·0° for (I) and 19·4° for (II). To avoid possible photodecomposition of the crystals, all intensities were measured in a darkened room. The θ–2θ scan mode was used with a constant scan rate (ω) of 3° min^{-1} for both crystals. The background time to scan time used was 1·0 for (I) and 0·5 for (II), and the scan range was from −1·0 to +1·0° (2θ) about the $K\alpha_1 - K\alpha_2$ angles for both. The intensities of three check reflections, measured after every 100 reflections, showed a decrease of *ca* 13% for (I) and no discernible decay for (II) during the course of data collection. An appropriate linear decay correction was subsequently applied to the intensity data of (I). Standard deviations were assigned according to the formula $\sigma(I) = \{[CT + (t_c/t_b)^2(B_1 + B_2)]\omega^2 + (pI)^2\}^{1/2}$, where CT is the total integrated count, t_c/t_b is the ratio of the total scan time to total background time, B_1 and B_2 are the background counts, $I = \omega[CT - (t_c/t_b)(B_1 + B_2)]$, and p (0·02) is a factor used to downweight intense reflections. Of the 2499 unique reflections measured ($4 < 2\theta < 115°$) for (I), 2230 had $I > 2\sigma(I)$, and of the 2499 unique reflections measured ($3 < 2\theta < 45°$) for (II), 1545 had $I > 2\sigma(I)$. The intensities were corrected for Lorentz and polarization effects but not for absorption. Range of *hkl:* (I) h 0→6, k −7→7, l −25→25; (II) h 0→6, k −7→7, l −25→23.

To solve the structure of 19,19,19-trifluoro-9-*cis* retinal, a ten-atom fragment from the structure of 13-*cis*-retinal (Simmons *et al.*, 1981) was used as input to the computer program *MULTAN* (Germain, Main & Woolfson, 1971). An overall isotropic thermal parameter, $B_{\rm iso} = 4·6$ Å^2, was calculated from the Debye curve, and normalized structure-factor amplitudes for the 300 reflections with $|E| > 1·52$ were used to generate a three-dimensional E function. This function, phased as indicated by the solution with the largest combined figure of merit, 2·59, revealed the positions of all 24 non-H atoms; the 25 H atoms were subsequently located by ΔF syntheses. Several cycles of full-matrix least-squares refinements (Gantzel, Sparks & Trueblood, 1976) with anisotropic thermal parameters for the non-H atoms and isotropic thermal parameters for the H atoms [two H atoms, H(16*A*) and H(17*A*), would not refine even with fixed B's, so their positions were taken from a final ΔF map] led to the final error indices: $R = 0·067$, $wR = 0·059$ and $S = 2·40$. The weights (w) of the 1545 observations used in the least-squares refinements of the 309 parameters were equal to $[\sigma(F_o)]^{-2}$. The function minimized in the refinements was $\sum w(|F_o| - |F_c|)$. The atomic scattering factors used (*International Tables for X-ray Crystallography*, 1974*a*) were corrected for anomalous dispersion (*International Tables for X-ray Crystallography*, 1974*b*). The largest shift in a non-H parameter in the final cycle of least-squares refinement was 88% of its corresponding e.s.d.

The structure of 9-*cis*-retinal was refined by full-matrix least-squares methods using the positional coordinates for (II) as starting coordinates. Anisotropic thermal parameters for all non-H atoms and isotropic thermal parameters for all H atoms led to the final error indices: $R = 0·055$, $wR = 0·074$ and $S = 4·92$. The weighting scheme, the function minimized, and the atomic scattering factors used in the least-squares refinements of (I) and (II) were the same. The largest shift in a non-H parameter in the final cycle of least-squares refinement was 25% of its corresponding e.s.d.

The final ΔF syntheses for (I) and (II) showed similar patterns of weak residual peaks. One peak [*ca* 0·11 for (I) and 0·24 e Å^{-3} for (II)] was located in the interior of each ring, about 1·7 Å from C(1), 1·3 Å from C(2), and 1·4 Å from C(3). In addition, a peak *ca* 0·19 e Å^{-3} was located 0·4 Å from C(16) and two peaks *ca* 0·18 and 0·17 e Å^{-3} were located 1·3 Å from C(17) in (II), while a peak *ca* 0·12 e Å^{-3} was located 1·1 Å from C(17) in (I). These residual peaks are indicative of a disorder involving two half-chair ring conformers. According to the ΔF syntheses, the disorder appears to be greater in (II) than in (I) (see *Discussion*).

Discussion. The final positional coordinates for 9-*cis*-retinal (I) and 19,19,19-trifluoro-9-*cis*-retinal (II) are given in Table 1, while bond lengths, bond angles, and torsion angles are given in Table 2.*

* Lists of structure factors, anisotropic thermal parameters and bond lengths and angles involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43109 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The crystal and molecular structures of (I) and (II) are shown in Figs. 1–3. The two structures are nearly isostructural. The molecules consist of trimethylcyclohexenyl rings attached to 9-*cis* polyene side chains which terminate in aldehydic groups. The C(5)—C(6)—C(7)—C(8) torsion angles, ψ_{5678}, which are characteristic of the attachment of the rings to the chains, are −76·0 (4) and −67·9 (7)° for (I) and (II) respectively. These are the largest values yet observed for 6-*s*-*cis* conformers of retinal and carotenoidal compounds (Simmons, Asato & Liu, 1986). Because the $|\psi_{5678}|$ torsion angle is 8·1° greater in (I) than in (II), the π character of its C(6)—C(7) bond should be smaller and the bond longer; accordingly, the corresponding bond lengths are 1·489 (3) and 1·439 (8) Å.

Table 1. *Fractional atomic coordinates* ($\times 10^4$, $\times 10^3$ *for* H) *with e.s.d.'s in parentheses*

The equivalent isotropic temperature factors, B_{eq} (Å^2), have been calculated by $B_{eq} = \frac{4}{3}(\beta_{11}a^2 + \cdots + \beta_{23}bc\cos\alpha)$; $\sigma(B_{eq}) = [\frac{8}{9}a^4\sigma^2(\beta_{11}) + \ldots + \frac{8}{9}b^2c^2\cos^2\alpha\sigma^2(\beta_{23})]^{1/2}$. This expression differs from that obtained from the usual propagation of error expression by a factor of $1/\sqrt{2}$ (Schomaker & Marsh, 1983).

9-*cis*-Retinal

	x	*y*	*z*	B_{eq},B_{iso}
C(1)	6109 (4)	12491 (3)	3954 (1)	5·5 (1)
C(2)	7195 (5)	13911 (4)	4453 (1)	6·8 (1)
C(3)	7608 (7)	15962 (4)	4283 (1)	7·5 (1)
C(4)	9460 (6)	16530 (4)	3818 (1)	7·6 (1)
C(5)	9061 (4)	15001 (3)	3351 (1)	5·9 (1)
C(6)	7519 (3)	13211 (3)	3406 (1)	4·97 (3)
C(7)	7109 (4)	11749 (3)	2935 (1)	5·9 (1)
C(8)	5769 (5)	11689 (4)	2458 (1)	5·9 (1)
C(9)	5254 (5)	10278 (3)	1992 (1)	6·3 (1)
C(10)	3775 (5)	10300 (4)	1532 (1)	6·9 (1)
C(11)	2478 (5)	11662 (4)	1403 (1)	6·9 (1)
C(12)	873 (5)	11485 (4)	945 (1)	7·2 (1)
C(13)	−535 (5)	12714 (4)	777 (1)	6·7 (1)
C(14)	−2056 (5)	12236 (4)	294 (1)	7·6 (1)
C(15)	−3593 (6)	13286 (5)	57 (1)	8·1 (1)
C(16)	6322 (6)	10527 (4)	4132 (1)	7·1 (1)
C(17)	3366 (5)	12233 (6)	3835 (2)	8·5 (1)
C(18)	10601 (8)	15683 (6)	2845 (2)	8·8 (1)
C(19)	6440 (7)	8698 (5)	2042 (2)	7·8 (1)
C(20)	−330 (8)	14458 (5)	1138 (1)	8·2 (1)
O(21)	−4875 (4)	12789 (3)	−385 (1)	9·8 (1)
H(2*A*)	599 (5)	1350 (3)	478 (1)	7·7 (6)
H(2*B*)	897 (5)	1367 (4)	459 (1)	9·2 (7)
H(3*A*)	824 (5)	1675 (4)	464 (1)	9·6 (8)
H(3*B*)	606 (6)	1611 (4)	411 (1)	9·6 (8)
H(4*A*)	1117 (8)	1689 (5)	398 (2)	13·1 (11)
H(4*B*)	947 (5)	1763 (4)	366 (1)	7·8 (7)
H(7)	784 (5)	1072 (4)	303 (1)	9·6 (8)
H(8)	512 (4)	1269 (3)	240 (1)	5·9 (5)
H(10)	356 (4)	928 (3)	126 (1)	6·4 (5)
H(11)	274 (4)	1275 (3)	163 (1)	6·4 (5)
H(12)	77 (5)	1061 (4)	70 (1)	7·3 (6)
H(14)	−211 (5)	1088 (4)	12 (1)	9·0 (7)
H(15)	−355 (4)	1454 (4)	29 (1)	7·5 (6)
H(16*A*)	824 (6)	1069 (4)	418 (1)	8·9 (7)
H(16*B*)	545 (5)	1000 (4)	455 (1)	9·8 (7)
H(16*C*)	571 (6)	963 (5)	381 (1)	10·0 (9)
H(17*A*)	334 (5)	1360 (5)	372 (1)	10·3 (9)
H(17*B*)	268 (5)	1112 (5)	351 (1)	10·1 (8)
H(17*C*)	232 (6)	1168 (4)	416 (1)	9·2 (8)
H(18*A*)	1086 (5)	1479 (5)	261 (1)	8·7 (9)
H(18*B*)	1236 (10)	1626 (7)	303 (2)	15·2 (14)
H(18*C*)	1037 (9)	1665 (7)	259 (2)	16·6 (16)
H(19*A*)	617 (6)	802 (4)	244 (1)	10·2 (8)
H(19*B*)	812 (7)	911 (4)	212 (1)	9·2 (9)
H(19*C*)	592 (5)	771 (4)	176 (1)	9·5 (8)
H(20*A*)	−45 (6)	1406 (5)	157 (2)	11·5 (9)
H(20*B*)	136 (6)	1527 (5)	121 (1)	10·1 (9)
H(20*C*)	−123 (7)	1533 (5)	98 (2)	12·1 (11)

19,19,19-Trifluoro-9-*cis*-retinal

	x	*y*	*z*	B_{eq},B_{iso}
C(1)	5963 (9)	12064 (8)	3961 (2)	5·1 (1)
C(2)	6905 (14)	13487 (8)	4467 (2)	8·2 (2)
C(3)	7391 (16)	15489 (12)	4337 (3)	7·8 (2)
C(4)	9216 (16)	16034 (12)	3905 (4)	7·1 (2)
C(5)	8955 (10)	14585 (9)	3440 (2)	4·8 (1)
C(6)	7434 (9)	12804 (8)	3452 (2)	4·3 (1)
C(7)	7130 (10)	11428 (9)	2994 (3)	5·2 (2)
C(8)	6102 (9)	11556 (9)	2483 (3)	5·2 (2)
C(9)	5722 (9)	10246 (8)	1993 (2)	4·9 (1)
C(10)	4404 (10)	10401 (9)	1526 (3)	5·6 (2)
C(11)	3075 (11)	11754 (10)	1409 (3)	5·4 (2)
C(12)	1503 (11)	11624 (10)	961 (3)	5·8 (2)
C(13)	−9 (10)	12850 (8)	819 (2)	5·3 (1)
C(14)	−1588 (11)	12321 (10)	363 (3)	6·5 (2)
C(15)	−3271 (12)	13322 (11)	147 (3)	7·3 (2)
C(16)	6394 (17)	10188 (14)	4153 (4)	8·0 (2)
C(17)	3268 (12)	11818 (14)	3802 (4)	9·3 (3)
C(18)	10602 (14)	15270 (13)	2970 (4)	7·3 (2)
C(19)	6801 (12)	8638 (10)	2031 (3)	6·1 (2)
C(20)	211 (15)	14557 (11)	1182 (3)	7·3 (2)
O(21)	−4632 (8)	12739 (7)	−279 (2)	9·8 (1)
H(2*A*)	555 (8)	1293 (6)	478 (2)	8·3 (12)
H(2*B*)	859 (13)	1338 (10)	466 (3)	17·1 (29)
H(3*A*)	784 (11)	1672 (10)	470 (3)	12·9 (20)
H(3*B*)	555 (12)	1540 (9)	410 (2)	8·1 (17)
H(4*A*)	1050 (9)	1621 (8)	403 (2)	5·8 (20)
H(4*B*)	924 (9)	1709 (8)	369 (2)	6·9 (19)
H(7)	756 (8)	1036 (6)	306 (2)	4·9 (14)
H(8)	572 (7)	1278 (6)	243 (2)	4·7 (12)
H(10)	421 (8)	947 (7)	124 (2)	5·6 (15)
H(11)	321 (7)	1276 (6)	163 (2)	3·9 (13)
H(12)	131 (9)	1055 (7)	71 (2)	7·4 (16)
H(14)	−193 (9)	1083 (8)	10 (2)	8·8 (16)
H(15)	−339 (10)	1452 (8)	33 (2)	7·9 (19)
H(16*A*)*	830	1030	410	
H(16*B*)	558 (8)	964 (7)	445 (2)	6·1 (14)
H(16*C*)	594 (10)	957 (8)	391 (2)	3·7 (17)
H(17*A*)*	350	1370	370	
H(17*B*)	274 (8)	1110 (6)	347 (2)	4·0 (13)
H(17*C*)	246 (10)	1110 (7)	407 (2)	6·2 (17)
H(18*A*)	1074 (10)	1421 (9)	268 (2)	9·1 (19)
H(18*B*)	1236 (13)	1619 (10)	315 (3)	12·1 (23)
H(18*C*)	1021 (12)	1629 (10)	281 (3)	12·2 (27)
F(19*A*)	5808 (6)	7346 (5)	2410 (2)	8·3 (1)
F(19*B*)	9193 (6)	9194 (5)	2198 (1)	7·3 (1)
F(19*C*)	6616 (6)	7614 (5)	1556 (2)	9·2 (1)
H(20*A*)	24 (15)	1455·(11)	162 (4)	17·4 (32)
H(20*B*)	217 (17)	1575 (12)	128 (3)	18·4 (30)
H(20*C*)	-47 (12)	1549 (9)	106 (3)	10·4 (23)

* Atoms H(16*A*) and H(17*A*) would not refine with fixed *B*'s; their atomic coordinates were taken from a final Fourier difference function and no corresponding e.s.d.'s are reported.

The side chains in (I) and (II) are almost structurally identical. One noteworthy difference, however, is that the C(9)—C(19) bond distance in (II), 1·470 (8) Å, is considerably shorter than in (I), 1·512 (4) Å, a result of the electronic effects of the highly electronegative F atoms. All conformations of C—C single bonds are *s-trans*. The methyl and trifluoromethyl groups have one H (or F) atom nearly eclipsing a double bond, thus showing the usual behavior of a methyl group attached to a double bond (Herschbach & Krisher, 1958).

Table 2. *Bond lengths* (Å), *bond angles* (°), *and torsion angles* (°) *involving non-*H *atoms with e.s.d.'s in parentheses*

The signs of the torsion angles follow the convention adopted by the IUPAC–IUB Commission on Biochemical Nomenclature (1970) and are appropriate for the enantiomers shown in Figs. 1 and 2. The e.s.d.'s are *ca* 0·3 and 0·8° for 9-*cis*-retinal and 19,19,19-trifluoro-9-*cis*-retinal respectively.

9-*cis*-Retinal		19,19,19-Trifluoro-9-*cis*-retinal	
C(1)–C(2)	1·529 (3)	C(1)–C(2)	1·541 (8)
C(1)–C(6)	1·539 (3)	C(1)–C(6)	1·540 (7)
C(1)–C(16)	1·526 (4)	C(1)–C(16)	1·519 (11)
C(1)–C(17)	1·532 (3)	C(1)–C(17)	1·526 (8)
C(2)–C(3)	1·489 (4)	C(2)–C(3)	1·435 (11)
C(3)–C(4)	1·511 (5)	C(3)–C(4)	1·496 (12)
C(4)–C(5)	1·516 (4)	C(4)–C(5)	1·490 (11)
C(5)–C(6)	1·330 (3)	C(5)–C(6)	1·332 (8)
C(5)–C(18)	1·489 (5)	C(5)–C(18)	1·512 (10)
C(6)–C(7)	1·489 (3)	C(6)–C(7)	1·439 (8)
C(7)–C(8)	1·312 (3)	C(7)–C(8)	1·335 (9)
C(8)–C(9)	1·451 (3)	C(8)–C(9)	1·463 (8)
C(9)–C(10)	1·336 (4)	C(9)–C(10)	1·329 (8)
C(9)–C(19)	1·512 (4)	C(9)–C(19)	1·470 (8)
C(10)–C(11)	1·439 (4)	C(10)–C(11)	1·425 (9)
C(11)–C(12)	1·353 (4)	C(11)–C(12)	1·336 (9)
C(12)–C(13)	1·424 (4)	C(12)–C(13)	1·439 (8)
C(13)–C(14)	1·364 (4)	C(13)–C(14)	1·345 (8)
C(13)–C(20)	1·496 (4)	C(13)–C(20)	1·472 (10)
C(14)–C(15)	1·429 (4)	C(14)–C(15)	1·440 (10)
C(15)–O(21)	1·221 (4)	C(15)–O(21)	1·231 (8)
		C(19)–F(19*A*)	1·341 (7)
		C(19)–F(19*B*)	1·345 (7)
		C(19)–F(19*C*)	1·330 (7)

C(2)–C(1)–C(6)	110·3 (2)	C(2)–C(1)–C(6)	110·2 (5)
C(2)–C(1)–C(16)	107·5 (2)	C(2)–C(1)–C(16)	104·8 (5)
C(2)–C(1)–C(17)	111·2 (2)	C(2)–C(1)–C(17)	110·9 (6)
C(6)–C(1)–C(16)	110·7 (2)	C(6)–C(1)–C(16)	110·1 (5)
C(6)–C(1)–C(17)	109·4 (2)	C(6)–C(1)–C(17)	109·0 (5)
C(16)–C(1)–C(17)	107·7 (2)	C(16)–C(1)–C(17)	111·9 (6)
C(1)–C(2)–C(3)	112·3 (2)	C(1)–C(2)–C(3)	114·9 (5)
C(2)–C(3)–C(4)	110·3 (3)	C(2)–C(3)–C(4)	111·0 (7)
C(3)–C(4)–C(5)	113·8 (2)	C(3)–C(4)–C(5)	116·0 (7)
C(4)–C(5)–C(6)	122·0 (2)	C(4)–C(5)–C(6)	121·9 (6)
C(4)–C(5)–C(18)	113·7 (2)	C(4)–C(5)–C(18)	115·0 (6)
C(6)–C(5)–C(18)	124·2 (2)	C(6)–C(5)–C(18)	123·1 (6)
C(1)–C(6)–C(5)	123·3 (2)	C(1)–C(6)–C(5)	122·5 (5)
C(1)–C(6)–C(7)	115·7 (2)	C(1)–C(6)–C(7)	115·8 (4)
C(5)–C(6)–C(7)	121·0 (2)	C(5)–C(6)–C(7)	121·7 (5)
C(6)–C(7)–C(8)	125·5 (2)	C(6)–C(7)–C(8)	125·3 (6)
C(7)–C(8)–C(9)	127·9 (2)	C(7)–C(8)–C(9)	129·3 (5)
C(8)–C(9)–C(10)	123·3 (2)	C(8)–C(9)–C(10)	123·6 (5)
C(8)–C(9)–C(19)	117·4 (2)	C(8)–C(9)–C(19)	117·7 (5)
C(10)–C(9)–C(19)	119·2 (3)	C(10)–C(9)–C(19)	118·7 (5)
C(9)–C(10)–C(11)	128·0 (2)	C(9)–C(10)–C(11)	128·5 (6)
C(10)–C(11)–C(12)	123·7 (3)	C(10)–C(11)–C(12)	124·2 (6)
C(11)–C(12)–C(13)	128·9 (3)	C(11)–C(12)–C(13)	128·5 (6)
C(12)–C(13)–C(14)	118·4 (2)	C(12)–C(13)–C(14)	116·9 (5)
C(12)–C(13)–C(20)	119·2 (2)	C(12)–C(13)–C(20)	118·9 (5)
C(14)–C(13)–C(20)	122·3 (3)	C(14)–C(13)–C(20)	124·2 (6)
C(13)–C(14)–C(15)	126·6 (3)	C(13)–C(14)–C(15)	126·3 (6)
C(14)–C(15)–O(21)	123·0 (3)	C(14)–C(15)–O(21)	121·7 (7)
		C(9)–C(19)–F(19*A*)	112·9 (5)
		C(9)–C(19)–F(19*B*)	113·6 (5)
		C(9)–C(19)–F(19*C*)	115·1 (5)
		F(19*A*)–C(19)–F(19*B*)	103·7 (5)
		F(19*A*)–C(19)–F(19*C*)	105·2 (5)
		F(19*B*)–C(19)–F(19*C*)	105·2 (5)

Table 2 (*cont.*)

9-*cis*-Retinal		19,19,19-Trifluoro-9-*cis*-retinal	
C(1)–C(2)–C(3)–C(4)	−62·3	C(1)–C(2)–C(3)–C(4)	−57·8
C(1)–C(6)–C(5)–C(4)	−3·3	C(1)–C(6)–C(5)–C(4)	−4·1
C(1)–C(6)–C(5)–C(18)	174·7	C(1)–C(6)–C(5)–C(18)	173·6
C(1)–C(6)–C(7)–C(8)	105·5	C(1)–C(6)–C(7)–C(8)	114·1
C(2)–C(1)–C(6)–C(5)	−13·8	C(2)–C(1)–C(6)–C(5)	−11·5
C(2)–C(1)–C(6)–C(7)	164·6	C(2)–C(1)–C(6)–C(7)	166·5
C(2)–C(3)–C(4)–C(5)	43·4	C(2)–C(3)–C(4)–C(5)	40·1
C(3)–C(2)–C(1)–C(6)	46·4	C(3)–C(2)–C(1)–C(6)	43·3
C(3)–C(2)–C(1)–C(16)	167·1	C(3)–C(2)–C(1)–C(16)	161·7
C(3)–C(2)–C(1)–C(17)	−75·1	C(3)–C(2)–C(1)–C(17)	−77·5
C(3)–C(4)–C(5)–C(6)	−11·6	C(3)–C(4)–C(5)–C(6)	−9·7
C(3)–C(4)–C(5)–C(18)	170·2	C(3)–C(4)–C(5)–C(18)	172·3
C(4)–C(5)–C(6)–C(7)	178·4	C(4)–C(5)–C(6)–C(7)	178·0
C(5)–C(6)–C(1)–C(16)	−132·7	C(5)–C(6)–C(1)–C(16)	−126·5
C(5)–C(6)–C(1)–C(17)	108·8	C(5)–C(6)–C(1)–C(17)	110·4
C(5)–C(6)–C(7)–C(8)	−76·0	C(5)–C(6)–C(7)–C(8)	−67·9
C(6)–C(7)–C(8)–C(9)	−178·3	C(6)–C(7)–C(8)–C(9)	179·7
C(7)–C(6)–C(1)–C(16)	45·7	C(7)–C(6)–C(1)–C(16)	51·4
C(7)–C(6)–C(1)–C(17)	−72·8	C(7)–C(6)–C(1)–C(17)	−71·6
C(7)–C(6)–C(5)–C(18)	−3·6	C(7)–C(6)–C(5)–C(18)	−4·3
C(7)–C(8)–C(9)–C(10)	177·2	C(7)–C(8)–C(9)–C(10)	171·4
C(7)–C(8)–C(9)–C(19)	−1·9	C(7)–C(8)–C(9)–C(19)	−6·6
C(8)–C(9)–C(10)–C(11)	0·9	C(8)–C(9)–C(10)–C(11)	−2·1
C(9)–C(10)–C(11)–C(12)	−175·0	C(9)–C(10)–C(11)–C(12)	−169·4
C(10)–C(11)–C(12)–C(13)	179·2	C(10)–C(11)–C(12)–C(13)	176·7
C(11)–C(10)–C(9)–C(19)	180·0	C(11)–C(10)–C(9)–C(19)	175·8
C(11)–C(12)–C(13)–C(14)	−179·8	C(11)–C(12)–C(13)–C(14)	−174·9
C(11)–C(12)–C(13)–C(20)	−0·7	C(11)–C(12)–C(13)–C(20)	3·6
C(12)–C(13)–C(14)–C(15)	−179·7	C(12)–C(13)–C(14)–C(15)	179·7
C(13)–C(14)–C(15)–O(21)	178·5	C(13)–C(14)–C(15)–O(21)	179·1
C(15)–C(14)–C(13)–C(20)	1·3	C(15)–C(14)–C(13)–C(20)	1·2
		C(8)–C(9)–C(19)–F(19*A*)	65·8
		C(8)–C(9)–C(19)–F(19*B*)	−52·0
		C(8)–C(9)–C(19)–F(19*C*)	−173·4
		C(10)–C(9)–C(19)–F(19*A*)	−112·3
		C(10)–C(9)–C(19)–F(19*B*)	129·9
		C(10)–C(9)–C(19)–F(19*C*)	8·6

The amount of in-plane bending in the side chains can be measured by the following equation: $\Delta = (a-b) + (c-d) + (e-f) + (g-h)$, where the angles a to h are the chain angles associated with atoms C(8) to C(15). The values for (I) and (II), 23·0 and 26·2°, indicate a greater strain in the chain of (II), attributable to the larger size of $-CF_3$ relative to $-CH_3$. Although these values are larger than those for all-*trans*-retinal (21·5°), all-*trans*-retinal$_2$ (22·5°), 11-*cis*-retinal (21·5°), methyl 7,9-di*cis*-retinoate (23°), and the 6-*s-cis* and 6-*s-trans* conformers of 13-*cis*-retinal (15·9 and 13·5°), they are smaller than that observed for the sterically strained C(9)-ethyl substituted analogue of all-*trans*-retinoic acid, 29·6°.

The short C(2)—C(3) bonds observed for (I) and (II), 1·489 (4) and 1·435 (11) Å, are most likely attributable to a conformational disorder of the trimethylcyclohexenyl rings (Simmons *et al.*, 1981). The conformation of the rings is half chair, with C(2) and C(3) on opposite sides of the plane through C(1), C(6), C(5) and C(4). Apparently, a fraction of the molecules have C(2) and C(3) switched to the other side of the plane, giving rise to alternative positions of the *gem*-methyl groups, C(16) and C(17). That the degree of disorder is greater in (II) than in (I) is evidenced not only by the shorter C(2)—C(3) bond length in the former, but also by the greater concentration of weak residual peaks found in the final ΔF map of (II) in the vicinity of C(2), C(3), C(16) and C(17) (see above).

It is interesting to compare the crystallographic results of 9-*cis*-retinal with the structural results obtained from studies of the same molecule in solution. Accordingly, [1]H NMR (Rowan & Sykes, 1975) and [13]C NMR (Rowan & Sykes, 1974) studies indicate that the conformations of all C—C single bonds throughout the polyene chain are *s-trans*, which agrees with the X-ray results reported herein. Such agreement, however, is not found for the sterically hindered 11-*cis* isomer. Its crystal structure (Gilardi *et al.*, 1972) reveals that the preferred conformation near the hindered geometry is twisted 12-*s-cis*, $\psi_{11,12,13,14} = 38\cdot7°$, while the results of various spectroscopic (Jurkowitz, 1959; Honig & Karplus, 1971), photochemical (Kropf & Hubbard, 1970; Honig & Karplus, 1971), and nuclear Overhauser NMR studies (Rowan, Warshel, Sykes & Karplus, 1974) in solution indicate a preference for the 12-*s-trans* conformation. In fact, recent resonance Raman studies of rhodopsin demonstrate that its most likely conformation in the pigment is 12-*s-trans* (Callender, Doukas, Crouch & Nakanishi, 1976). For sterically unhindered isomers, such as 9-*cis*-retinal, where the all-*s-trans* conformation is expected to be the most stable, crystallographic results seem to be consistent with the structural results obtained in solution. However, for those hindered isomers, such as 11-*cis*-retinal, where the *s-cis* and *s-trans* conformers are close in energy, any external forces, such as crystal-packing forces or protein–substrate non-bonding interactions, can affect the relative stability of the two conformers. In these circumstances, the use of X-ray results to interpret solution structural properties becomes less reliable.

Finally, we wish to indicate that the crystallographic results of 9-*cis*-retinal are consistent with the existence of a longitudinal distance in the binding-site cavity of opsin (Matsumoto & Yoshizawa, 1978; Matsumoto *et al.*, 1980). Our results are also in agreement with the recently postulated two-dimensional binding-site map of rhodopsin (Liu, Asato, Denny & Mead, 1984).

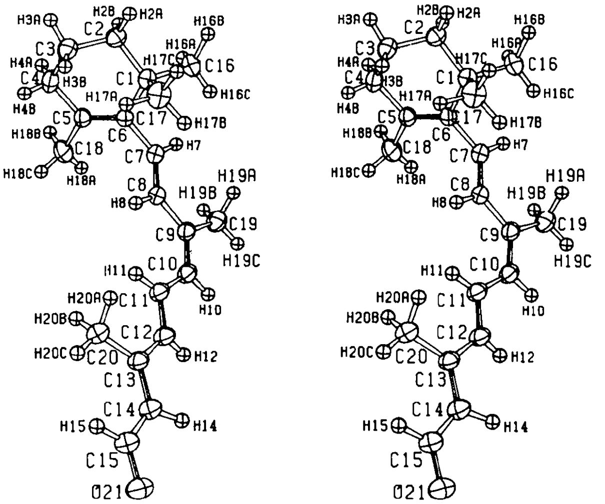

Fig. 1. Stereoview of 9-*cis*-retinal (I) shown with 25% probability ellipsoids; all H-atom B_{iso}'s have been fixed at 3·0 Å^2.

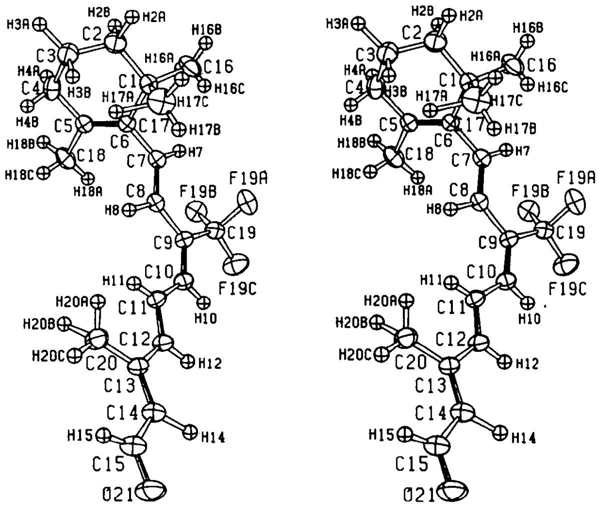

Fig. 2. Stereoview of 19,19,19-trifluoro-9-*cis*-retinal (II) shown with 25% probability ellipsoids; all H-atom B_{iso}'s have been fixed at 3·0 Å^2.

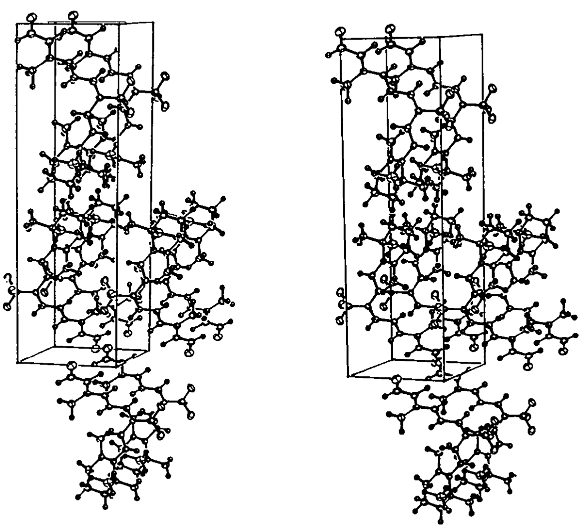

Fig. 3. Stereoview of the crystal structure of 19,19,19-trifluoro-9-*cis*-retinal using 15% probability ellipsoids; all H-atom B_{iso}'s have been fixed at 3·0 Å^2. The view is approximately into the +**a** direction, with +**b** extending horizontally to the right, and +**c** extending upwards in the plane of the page. The structures of 9-*cis*-retinal and 19,19,19-trifluoro-9-*cis*-retinal are nearly isostructural.

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Structure of Sulfisomidine Dihydrochloride Dihydrate

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Abstract. 4-Amino-*N*-(2,6-dimethyl-4-pyrimidinyl)-benzenesulfonamide dihydrochloride dihydrate, $C_{12}H_{16}N_4O_2S^{2+}.2Cl^-.2H_2O$, $M_r = 387{\cdot}3$, triclinic, $P\bar{1}$, $a = 13{\cdot}400$ (4), $b = 14{\cdot}474$ (3), $c = 5{\cdot}091$ (2) Å, $\alpha = 99{\cdot}73$ (2), $\beta = 94{\cdot}82$ (3), $\gamma = 111{\cdot}42$ (2)°, $V = 894{\cdot}5$ Å^3, $Z = 2$, $D_x = 1{\cdot}44$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 45{\cdot}153$ cm^{-1}, $F(000) = 404$, $T = 277$ (1) K, $R = 0{\cdot}040$, $wR = 0{\cdot}051$ for 1670 observed reflections. The conformation of the compound is similar to that observed in other sulfonamides. The

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