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Crystal and Molecular Structure of the Orthorhombic Form of Prostaglandin A_1[1]

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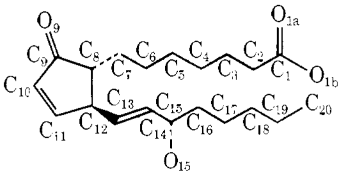
Abstract: The crystal and molecular structure of the orthorhombic polymorph of the renal antihypertensive prostaglandin A_1 [15(*S*)-hydroxy-10,13-dien-9-ketoprostanoic acid, structure A], $C_{20}H_{32}O_4$, has been determined by X-ray diffraction techniques. The compound crystallizes in the orthorhombic space group $P2_12_12_1$, with cell constants $a = 18.106$ (3), $b = 21.091$ (4), and $c = 5.420$ (1) Å; $Z = 4$, $d_{\text{calcd}} = 1.086$ g cm^{-3}. The structure was solved by direct methods employing calculated values for the cosines of the seminvariant Σ_2 triples. The refinement by F^2-based full-matrix least squares led to final agreement factors of $R(F) = 0.098$ [$R_w = 0.109$; $S = 1.14$, $\Sigma w(F_o - sF_c) = 1312$] for 1002 intensities measured on a G.E. XRD-5 single-crystal orienter using the stationary counter–stationary crystal technique. The molecular structure is characterized by extensions of the two side chains in the same direction away from the cyclopentenone ring. The crystal structure is stabilized by an infinite helical hydrogen-bonding network paralleling *c*, which does not involve the cyclopentenone moiety.

The prostaglandins are a ubiquitous class of compounds commonly found in mammals at levels approximating 1 ng/ml of plasma. They are implicated in a wide range of bodily functions, ranging from maintenance of normal tension to participation in the inflammation response and secretion of gastric acid. Current interest in prostaglandins as drugs is based upon their ability to maintain menstrual regulation, induce abortion at midtrimester, and induce labor at term. Their potential use in the treatment of asthma, hypertension, and duodenal ulcers is also under investigation. The chemical differences among the natural prostaglandins result in many of these intense biofunctional variations.[3,4]



A

The availability of a good single crystal of orthorhombic prostaglandin A_1 [PGA_1(o)][5] permitted a study of the molecular conformation of an unsubstituted prostaglandin and a comparison with the molecular structure of the prostaglandin $F_{1\beta}$ tribromobenzoate ($PGF_{1\beta}$) previously reported.[6] Although the structure of $PGF_{1\beta}$ confirmed the relative configuration of the prostaglandins, there remained some doubt concerning the influence of the bromobenzoate substituents upon the basic prostaglandin molecular conformation as observed in the crystal structure. To resolve this question, and to increase the molecular data base for further comparative studies, we have undertaken the crystal structure analysis of a series of prostaglandins beginning with PGA_1.

Experimental Section

Crystal Data. A clear columnar crystal extended along *c* was selected from a sample as received and analyzed under a polarizing microscope. The crystal, with dimensions 0.2 × 0.2 × 0.4 mm, was mounted with the *c* axis along the diffractometer ϕ axis, and the reciprocal cell orientation was determined by the stereographic projection method. The assigned cell was checked for errors by doubling all cell lengths and scanning low-angle reciprocal space for missed reflections. Centering 40 reflections in the range $55° \leq 2\theta \leq 65°$ with Cu Kα_1 radiation ($\lambda = 1.54051$ Å) and fitting these *via* least squares yielded these final cell dimensions: $a = 18.106$ (3), $b = 21.091$ (4), and $c = 5.420$ (1) Å. Systematic absences for $h00$, $h = 2n + 1$, $0k0$, $k = 2n + 1$, and $00l$, $l = 2n + 1$, imply space group $P2_12_12_1$. Scarcity of sample precluded a density measurement. The calculated density for $Z = 4$ (four molecules per unit cell) is 1.086 g cm^{-3}.

Intensity Measurement. The intensity data were collected on a General Electric XRD-5 manual diffractometer operated in the stationary crystal–stationary counter mode. Cu Kα_1 radiation was used with a 10-sec count for each reflection. A 0.0004 in. nickel foil was used as a filter, positioned in the shutter in front of the detector aperture. Background was collected for 10 sec at the same

Table II. Final Positional Parameters ($\times 10^4$) and Their Estimated Standard Deviations in Parentheses

Atom	X (σx)	Y (σy)	Z (σz)
C_1	−1377 (10)	0619 (6)	8462 (26)
C_2	−1048 (8)	1058 (7)	6523 (33)
C_3	−1588 (7)	1445 (6)	5029 (27)
C_4	−1182 (9)	1922 (7)	3337 (30)
C_5	−1689 (10)	2340 (7)	1852 (28)
C_6	−1270 (8)	2815 (6)	0313 (26)
C_7	−1791 (9)	3244 (7)	−1264 (28)
C_8	−1376 (8)	3743 (7)	−2845 (25)
C_9	−1904 (9)	4099 (8)	−4489 (31)
C_{10}	−1752 (9)	4775 (8)	−4246 (36)
C_{11}	−1252 (11)	4878 (8)	−2443 (35)
C_{12}	−0966 (7)	4245 (8)	−1271 (27)
C_{13}	−0127 (9)	4202 (7)	−1367 (30)
C_{14}	0290 (9)	4212 (7)	0583 (27)
C_{15}	1132 (7)	4105 (7)	0460 (26)
C_{16}	1297 (8)	3480 (9)	1753 (49)
C_{17}	1102 (10)	2909 (10)	0622 (56)
C_{18}	1115 (9)	2324 (12)	2238 (48)
C_{19}	0917 (10)	1712 (14)	0891 (61)
C_{20}	0889 (13)	1153 (11)	2580 (53)
O_{1a}	−2033 (6)	0584 (5)	8782 (21)
O_{1b}	−0899 (5)	0322 (5)	9834 (21)
O_9	−2369 (6)	3879 (5)	−5823 (21)
O_{15}	1472 (5)	4613 (5)	1778 (24)

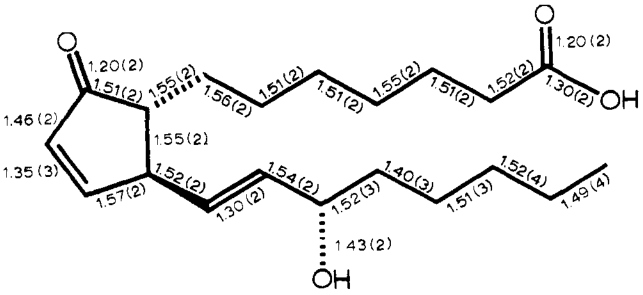


Figure 1. Uncorrected bond distances for orthorhombic prostaglandin A_1.

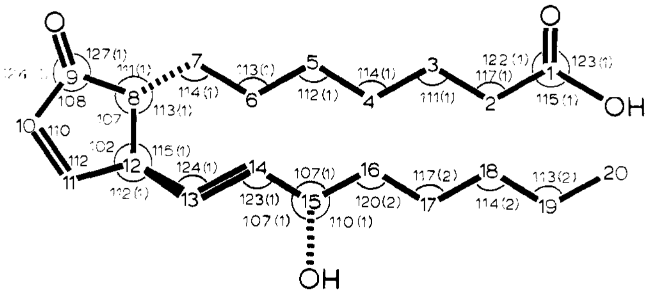


Figure 2. Uncorrected bond angles for orthorhombic prostaglandin A_1.

angle settings, with a 0.0004 in. cobalt filter replacing the nickel filter. Data were measured out to $2\theta = 105°$, but beyond $2\theta = 90°$ no reliable intensities could be measured due to the effects of thermal motion [$PGA_1(o)$ melts at $\simeq 40°$]. Five standard intensities were collected once every day, and no significant decrease of intensity with time was observed during the course of data collection. A total of 1428 unique reflections was measured, 757 of which were considered to be observed.[7] Absorption corrections were applied based upon an experimental curve of intensity *vs.* ϕ setting obtained by measuring two intense reflections at $\chi = 90°$. The range of the normalized multiplicative correction was 1.00–1.86.

Structure Determination. The structure was solved using known direct method techniques for phasing in the space group $P2_12_12_1$.[8] The values of the calculated cosines for the seminvariant Σ_2 triples were used to restrict the choice of hand phased vectors to those of high reliability.[9] Thirty-three two-dimensional vectors phased by hand were permitted to build up to a total of 160 vectors by the SUMA procedure,[10] and these were then refined by the tangent procedure.[11] An E map revealed the positions of 13 of the 24 independent atoms, which were then used to determine the remainder of the structure by Fourier techniques.

The 24 nonhydrogen atoms were refined by block-diagonal least squares based upon F for the observed data only. Convergence was reached at an agreement index (*vide infra*) $R = 0.15$, using a weighting scheme in which $w = 1/\sigma^2(F)$, and $\sigma^2(F)$ was approximated to be $[1 + [(F_o - 12)/20]^2]^{1/2}$. A difference Fourier map (with data restricted to $\sin \theta/\lambda \leq 0.35$) revealed well-resolved positions for 7 and poorly resolved positions for 11 other hydrogens. Continued refinement by F^2-based full-matrix least squares using all data agreeing to within $7\sigma(F)$, with the same weighting scheme as above converted to F^2 measure [*i.e.*, $\sigma(F^2) \simeq 2F\sigma(F)$], and anisotropic heavy atoms and isotropic hydrogens indicated the data were inadequate to support freedom of refinement of the hydrogen positional coordinates. Theoretical positions were then calculated for 30 hydrogens (excluding those involved in the hydrogen bonding) based upon the best heavy atom parameters and assuming tet-

Table III. Final Thermal Parameters ($U^{ij} \times 10^3$) for Nonhydrogen Atoms and Their Estimated Standard Deviations in the Last Significant Figure in Parentheses[a]

Atom	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C_1	88 (13)	67 (9)	57 (9)	0 (10)	5 (11)	1 (8)
C_2	79 (10)	76 (9)	94 (11)	12 (9)	8 (10)	−8 (11)
C_3	66 (10)	86 (10)	55 (9)	16 (8)	14 (9)	11 (10)
C_4	97 (10)	73 (9)	70 (10)	4 (9)	−1 (11)	−14 (10)
C_5	115 (13)	73 (9)	61 (9)	2 (10)	9 (11)	21 (9)
C_6	69 (9)	76 (9)	67 (9)	6 (8)	−3 (9)	−18 (9)
C_7	101 (10)	77 (10)	70 (9)	−5 (9)	0 (10)	5 (9)
C_8	87 (10)	68 (8)	65 (8)	8 (8)	−16 (9)	−13 (9)
C_9	56 (11)	94 (12)	76 (11)	18 (10)	−10 (10)	8 (11)
C_{10}	83 (11)	92 (13)	114 (14)	−1 (9)	−13 (12)	18 (12)
C_{11}	120 (15)	82 (12)	96 (13)	−9 (11)	16 (13)	6 (11)
C_{12}	59 (10)	111 (13)	63 (8)	3 (9)	16 (8)	15 (10)
C_{13}	81 (13)	104 (11)	54 (11)	−23 (10)	0 (11)	−17 (10)
C_{14}	67 (12)	84 (11)	74 (9)	−20 (9)	23 (9)	−29 (9)
C_{15}	56 (8)	83 (11)	61 (10)	−7 (8)	18 (8)	−17 (10)
C_{16}	45 (9)	121 (12)	194 (23)	−12 (9)	22 (14)	−11 (16)
C_{17}	69 (12)	106 (13)	292 (31)	−24 (11)	−13 (18)	5 (20)
C_{18}	65 (11)	120 (17)	245 (27)	11 (12)	0 (15)	−28 (20)
C_{19}	63 (12)	185 (24)	272 (33)	11 (15)	23 (18)	−51 (25)
C_{20}	103 (18)	156 (18)	247 (27)	17 (14)	18 (20)	−13 (19)
O_{1a}	48 (5)	101 (8)	103 (9)	5 (6)	14 (7)	24 (7)
O_{1b}	63 (6)	108 (8)	106 (8)	26 (5)	−12 (7)	38 (8)
O_9	82 (8)	126 (9)	91 (9)	−2 (7)	−36 (7)	3 (8)
O_{15}	57 (6)	112 (8)	159 (10)	−9 (6)	3 (7)	−77 (9)

[a] The temperature factor is of the form $\exp[-2\pi^2\Sigma_{ij}a_i^*a_j^*h_ih_jU^{ij}]$.

Table IV. Molecular Least-Squares Planes[a]

Atom	D, Å	Atom	D, Å
Plane 1	$-0.0476x + 0.6745y + 0.7367z = 4.247$		
C_1*	0.15	C_7*	0.02
C_2*	−0.06	C_8*	0.07
C_3*	−0.05	C_9	−0.05
C_4*	−0.04	C_{12}	1.40
C_5*	−0.08	O_{1a}	0.26
C_6*	−0.00	O_{1b}	0.19
Plane 2	$-0.6993x + 0.0340y + 0.7141z = 0.971$		
C_8*	−0.08	C_{12}*	0.06
C_9*	−0.01	O_9*	0.06
C_{10}*	−0.06	C_7	1.05
C_{11}*	0.02	C_{13}	−1.05
Plane 3	$0.1155x + 0.9877y - 0.1050z = 8.772$		
C_{12}*	−0.02	C_8	−1.09
C_{13}*	0.02	C_{11}	1.28
C_{14}*	0.02	C_{16}	−1.34
C_{15}*	−0.02	O_{15}	1.05
Plane 4	$0.9506x - 0.1284y - 0.2827z = 0.937$		
C_{15}*	−0.18	C_{19}*	0.05
C_{16}*	0.10	C_{20}*	−0.14
C_{17}*	0.11	C_{14}	−1.68
C_{18}*	0.05	O_{15}	0.07

[a] Atoms defining the least squares plane are indicated by an asterisk.

rahedral or planar carbon atoms where appropriate. These were included in the refinement with fixed positional parameters but variable isotropic thermal parameters. Refinement was continued by full-matrix least-squares fit of the heavy atom parameters. When new heavy atom positions resulted in unusual geometry with the fixed hydrogens, new hydrogen positional parameters were calculated but the current isotropic thermal parameters were retained. This procedure converged at $R(F) = 0.114$ and $R_w(F) = 0.126$ for 951 reflections passing the $7\sigma(F)$ acceptance criteria. Measures of the reliability of the weighting scheme are S, the standard deviation of a reflection of unit variance, $[S_{\text{theo}} = 1.0]$, and the sum of the weighted differentials $\Sigma w(F_o - sF_c)^2$ which should equal the number of data included in the refinement. The values at this stage of refinement were 1.71 and 2104, respectively.

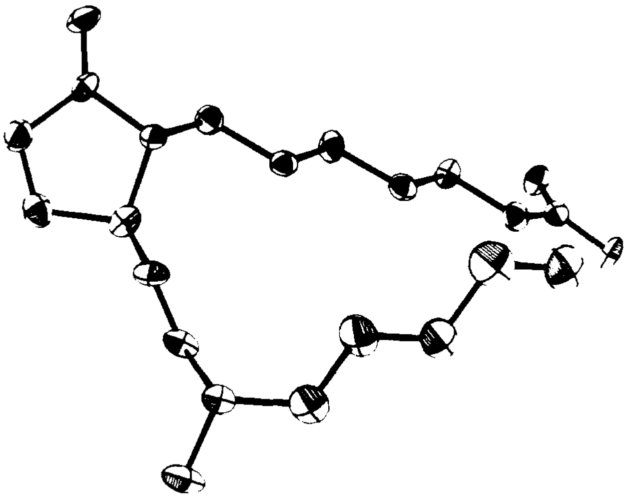


Figure 3. Orthorhombic prostaglandin A_1 viewed from above the cyclopentenone ring. Thermal motion represented by 15% probability ellipsoids.

An analysis of variance was then performed on the data in an attempt to devise an acceptable weighting scheme which would yield constant variance with increasing F^2_{obsd} and sin θ/λ. The final weighting scheme, where the weight $w = 1/\sigma^2(F^2)$, was chosen to be $F^2 \leq 20.5$, $\sigma(F^2) = 9$, 208 reflections; $20.5 < F^2 \leq 300$, $\sigma(F^2) = 2.15{*}(F^2)^{1/2}$, 588 reflections; $300 < F^2$, $\sigma(F^2) = 0.124{*}F^2$, 206 reflections. The minimum F^2_{obsd} was 20.5. This scheme approximates one where $\sigma(F^2) \approx 0.10F^2$ for all $F^2 > 20.5$, with the exception that the actual analysis implied that $\sigma(F^2) = 0.28{*}F^2$ if $F^2 \geq 2850$ (25 reflections). It was felt that although this apparent increase of $\sigma(F^2)$ with F^2 indicated the difficulties encountered during the course of data collection, it was a totally unrealistic approximation for the σ's necessary for the least-squares weighting function and, therefore, ignored. Final agreement factors for the converged full-matrix least squares using the weighting scheme above and based upon 1002 reflections passing the acceptance criteria[12] are

Table V. Molecular Torsion Angles[a] in Degrees

	PGA_1(o)	$PGF_{1\beta}$		PGA_1(o)	$PGF_{1\beta}$
		Chain[b]			
O_{1a}–C_1–C_2–C_3	0	−24	C_{13}–C_{14}–C_{15}–O_{15}	129	132
O_{1b}–C_1–C_2–C_3	−176	169	C_{13}–C_{14}–C_{15}–C_{16}	−113	−111
C_1–C_2–C_3–C_4	174	173	C_{14}–C_{15}–C_{16}–C_{17}	72	69
C_2–C_3–C_4–C_5	−178	178	O_{15}–C_{15}–C_{16}–C_{17}	−172	−173
C_3–C_4–C_5–C_6	178	173	C_{15}–C_{16}–C_{17}–C_{18}	−166	180
C_4–C_5–C_6–C_7	179	173	C_{16}–C_{17}–C_{18}–C_{19}	−179	−175
C_5–C_6–C_7–C_8	179	170	C_{17}–C_{18}–C_{19}–C_{20}	−176	−180
C_{12}–C_{13}–C_{14}–C_{15}	174	−175			
		Ring–Chain[c]			
C_6–C_7–C_8–C_9	175	145	C_8–C_{12}–C_{13}–C_{14}	−132	−133
C_6–C_7–C_8–C_{12}	−65	−99	C_{11}–C_{12}–C_{13}–C_{14}	113	116
		Ring–Function[d]			
C_7–C_8–C_9–C_{10}	132	163	O_{11}–C_{11}–C_{10}–C_9		−130
C_7–C_8–C_9–O_9	−49	−74	O_{11}–C_{11}–C_{12}–C_8		154
C_7–C_8–C_{12}–C_{11}	−129	−175	O_{11}–C_{11}–C_{12}–C_{13}		−85
C_7–C_8–C_{12}–C_{13}	111	72	C_{13}–C_{12}–C_8–C_9	−127	−161
O_9–C_9–C_{10}–C_{11}	174	−132	C_{13}–C_{12}–C_{11}–C_{10}	125	162
O_9–C_9–C_8–C_{12}	−173	160			
		Ring[e]			
C_8–C_9–C_{10}–C_{11}	−7	−12	C_{11}–C_{12}–C_8–C_9	−6	−47
C_9–C_{10}–C_{11}–C_{12}	3	−19	C_{12}–C_8–C_9–C_{10}	8	37
C_{10}–C_{11}–C_{12}–C_8	3	41			

[a] Torsional angle defined as the angle of twist about bond B–D in the ordered set A–B–D–E. Viewing along the B–D bond, with A nearer the observer, a *positive* angle is defined here as the *clockwise* rotation necessary to bring the projection of A–B into coincidence with the projection of D–E. This is in agreement with the definition of Cahn, Ingold, and Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966). [b] All atoms in fatty acid chain. [c] Two atoms in chain, two in ring. [d] Three atoms in ring, one external, or two atoms external separated by two in the ring. [e] Four atoms in ring.

Table VI. Hydrogen Bonding

	D, Å		Angle, deg
O_{15}–O_{1b}[a]	2.59	C_{15}–O_{15}–O_{1b}	128.1
		O_{15}–O_{1b}–C_1	114.7
O_{15}–O_{1a}[b]	2.76	C_{15}–O_{15}–O_{1a}	104.8
		O_{15}–O_{1a}–C_1	164.5

[a] Position: $-x$, $^1/_2 + y$, $1^1/_2 - z$. [b] Position: $^1/_2 + x$, $^1/_2 - y$, $1 - z$.

$$R(F) = \Sigma|F_o - sF_c|/\Sigma|F_o| = 0.098$$

$$R_w(F) = \Sigma w|F_o - sF_c|^2/\Sigma w|F_o|^2 = 0.109$$

with

$$S = (\Sigma w|F_o - sF_c|^2)^{1/2}/(N_o - N_v) = 1.14$$

and

$$\Sigma w(F_o - sF_c)^2 = 1312$$

where s is the scale factor, N_o = number of observations, 1002, and N_v = number of parameters fit, 239. Final observed and calculated structure factors are given in Table I (see paragraph at end of paper regarding supplementary material). Tables II and III give the final positional and thermal motion parameters for the nonhydrogen atoms, respectively. The theoretical hydrogen atoms are not included in Tables II and III, as their positions are artificial (*vide supra*). The range of the hydrogen isotropic thermal motion parameters is $0.6 < B < 11.6$. As there is neither a completely adquate means for correcting fatty acid bond distances and angles for thermal motion, nor does it appear that additional significance could be gained by applying known corrections to the model based upon this data set, the uncorrected values with the estimated standard deviations have been indicated in Figures 1 and 2. The thermal motion, represented by 15% probability ellipsoids, is shown in Figure 3. Spherical atomic scattering factors were used for H, C, and O.[13]

Computer Programs. A CDC 6400 was used for direct methods (programs by C. M. Weeks, S. Pokrywiecki, and J. W. Edmonds), Fourier maps, least squares, and molecular illustration. The remaining procedures were performed on an IBM 1130.

Discussion

The final parameters for the extended chains of PGA_1(o) indicate the decreases in bond lengths and increases in bond angles expected as a consequence of thermal motion.[14,15] The cyclopentenone distances and angles show the expected shortening of the C_9–C_{10} aliphatic bond as observed with other α,β-unsaturated ketones.[16]

The uncorrected C_{16}–C_{17} bond distance of 1.40 (3) Å is within 3σ of both the isolated double bond, C_{13}–C_{14}, and the shortest single bonds. The bond angles about C_{16} and C_{17} are, however, smaller than those about C_{13} and C_{14}. As the synthetic route to this compound assures its stated integrity, it appears that the foreshortened bond distance is due to the effects of large thermal motion in the C_{15}–C_{20} chain rather than to the presence of a second exocyclic unsaturation.

The molecule is made up of four distinct planar groups, which greatly increased the difficulty in adequately establishing the enantiomorph during structure solution. The least-squares plane parameters for the four groups are presented in Table IV. The carboxylic fatty acid chain appears to exhibit a helical twist similar to the one observed for the 1,3-diglyceride of 11-bromoundecanoic acid.[15] The pitch along the C_1–C_8 chain is calculated as 158° and can be observed in Figure 4.

The side chains in both PGA_1(o) and $PGF_{1\beta}$ are extended in the same direction away from the cyclopentenone ring. The similarity in torsional angles about C_{15} for both structures implies that the C_{11} and C_{15} bromobenzoate substituents in $PGF_{1\beta}$ have apparently not affected the conformation of the C_{12}–C_{20} chain. That a chemical change within the ring during oxidation of $PGF_{1\beta}$ to PGA_1(o) will grossly affect the intrachain conformation is apparent from models and inspection of the ring torsional angles in Table V. Assuming no alteration of the torsional angles about C_7–C_8 or C_{12}–C_{13}, flattening the ring in going from $PGF_{1\beta}$ to PGA_1(o) will thrust the C_1–C_8 chain out and away from the C_{12}–C_{20} chain. The two chains are restored to the observed PGA_1(o) proximal interaction by an acute alteration of the torsional angles about C_7–C_8 (see Table V). Inspection of the crystal packing reveals the efficacy of this rotation in stabilizing the crystal structure by the observed hydrogen bonding scheme (*vide infra*). The crystal is not significantly stabilized by attractive fatty acid and chain-chain interactions as no intra- or intermolecular chain contacts are shorter than 4.0 Å, *i.e.*, twice the methylene van der Waals radii. The differences between the PGA_1(o) and $PGF_{1\beta}$ conformations indicate the flexibility of the fatty acid fragments, and it is not entirely certain that the observed conformation would be favored in biological actions *in vivo*. The spread of conformational alternatives may therefore be considered quite broad until additional data demonstrate otherwise.

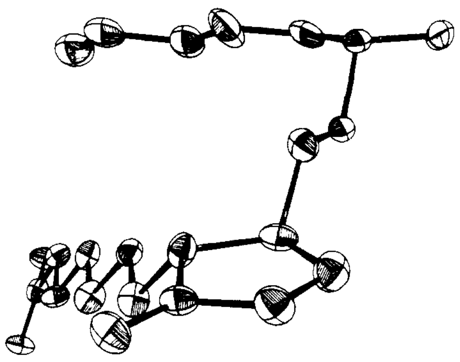


Figure 4. Orthorhombic prostaglandin A_1 viewed nearly along the O_9–O_{1a} vector. The pitch of the nearly planar C_1–C_8 chain is approximately 158°.

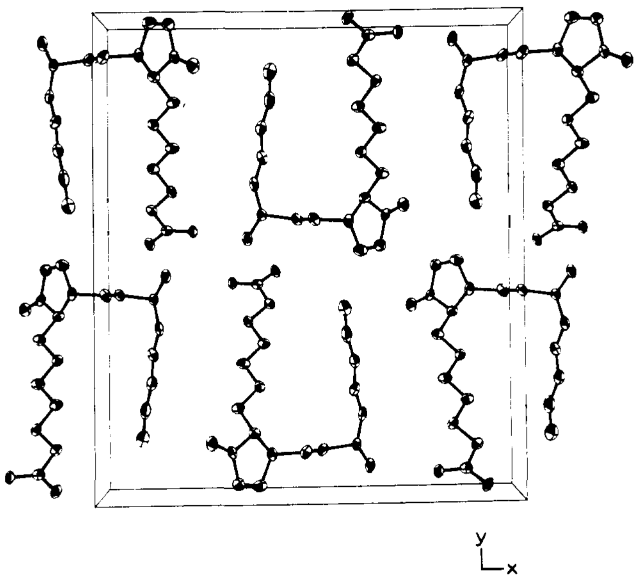


Figure 5. Molecular packing of orthorhombic prostaglandin A_1 viewed down the 2_1 axis paralleling c.

The crystal packing and hydrogen bonding are illustrated in Figures 5 and 6. The distances and angles for the hydrogen bonds are tabulated in Table VI. The hydrogen bonding

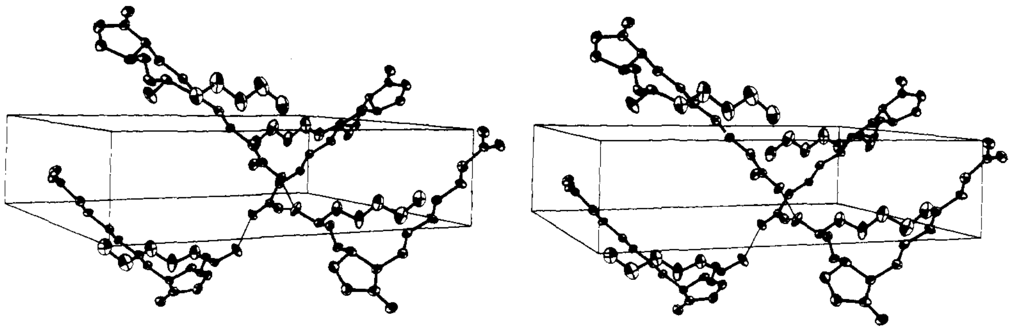


Figure 6. Stereo representation of the molecular packing and helical hydrogen bonding along the *c* direction. The unit cell is represented with *a* toward the viewer, *b* in the plane of the diagram, and *c* vertical.

scheme is unusual in that the cyclopentenone moiety does not participate and lattice stabilization is left to an infinite helical chain of carboxylic acid–alcohol hydrogen bonds along *c* in which the C_{15} hydroxyl acts both as an acceptor and a donor. Difference maps do not permit accurate determination of the placement of the two oxygenic hydrogens, but based upon data for various types of oxygen–oxygen hydrogen bonds, the hydrogens most likely lie along the oxygen–oxygen vectors such that the ∠HOO is close to 0°.

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Supplementary Material Available. Table I, a listing of structure factor amplitudes, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-75-413.

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