Prostaglandins PGA_1 and PGB_1. Crystallographic Studies of the Conformational Requirements for 15-Hydroxyprostaglandin Dehydrogenase Activity†

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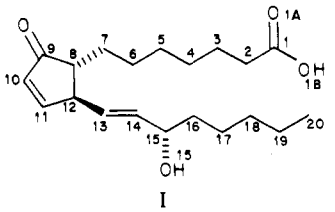
ABSTRACT: Prostaglandins PGA_1 and PGB_1 are double-bond isomers with radically differing conformations and biological activity profiles. Single-crystal X-ray diffraction studies of the two prostaglandins reveal that PGA_1 assumes a "hairpin" conformation, i.e., one in which the carboxylic acid (α) and pentyl (ω) side chains are approximately parallel and in close proximity at their ends, while PGB_1 assumes an atypical "L-shape" conformation, i.e., one in which the α and ω side chains are approximately perpendicular. The unusual L shape of PGB_1 is a consequence of the all-trans dienone system O(9)=C(9)–C(8)=C(12)–C(13)=C(14)–C(15) and cis orientation of the O(15) hydroxyl with respect to the exocyclic unsaturation. The L shape of PGB_1 has been shown to persist in solution, indicating that prostaglandin-specific enzymes very likely interact with an L-shaped PGB_1. (15*S*)-15-Hydroxyprostaglandin dehydrogenase, the primary metabolizing enzyme for the prostaglandins, oxidizes the C(15)–O(15) bond of PGA_1 to form 15-keto-PGA_1, but PGB_1 is resistant to metabolism. Two possible explanations for the inability of the dehydrogenase to metabolize PGB_1 are suggested by the observed prostaglandin conformations: either the more open L-shape prevents PGB_1 from attaining the prostaglandin site on the enzyme or, attaining the site, the disposition of the C(15) hydrogen with respect to the nicotinamide ring of NAD^+, an obligatory coenzyme for prostaglandin dehydrogenase, prevents hydrogen abstraction. The conformational studies, in conjunction with binding and activity data, suggest that prostaglandin dehydrogenase metabolizes hairpin-shaped prostaglandins. Crystals of PGA_1 are monoclinic, space group $P2_1$, with a = 13.637 (2) Å, b = 7.567 (1) Å, c = 10.576 (2) Å, and β = 107.37 (3)°; crystals of PGB_1 are orthorhombic, space group $P2_12_12_1$, with a = 18.744 (2), b = 23.017 (1), and c = 4.6935 (4) Å.

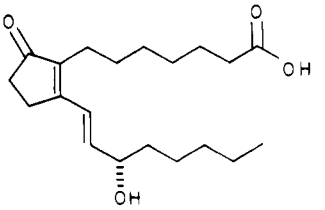
The prostaglandins[1] are a family of C(20) fatty acids with a variety of putative biological roles. Pharmacological doses of prostaglandins, i.e., those which can trigger a discernible response, can be as low as 10 ng/mL (Jones, 1977). Clearly, the body must have a reliable mechanism for the inactivation of these potent compounds. Most classical prostaglandins are metabolized by the enzyme (15*S*)-15-hydroxyprostaglandin dehydrogenase which oxidizes the C(15) hydroxyl of the PG skeleton to a 15-keto group (Marrazzi & Andersen, 1974). In general, 15-keto metabolites of prostaglandins have much lower biological profiles than their corresponding (15*S*)-hydroxy precursors. While prostaglandin A_1 is a substrate for PGDH, prostaglandin B_1 is not (Nakano et al., 1969). The conformations of PGA_1 (I) and PGB_1 (II) were studied by



I

single-crystal diffraction techniques in order to investigate the possibility that the differing biological profiles of the two chemically similar prostaglandins might be explained by substantially differing shapes.

Earlier studies of an orthorhombic polymorph of PGA_1 (Edmonds & Duax, 1975) revealed that unsubstituted natural



II

prostaglandins could adopt a conformation very similar to that observed by Abrahamsson (1963) in his study of a tri-*p*-bromobenzoate-substituted methyl ester of prostaglandin $PGF_{1\beta}$. This shape has been called (Andersen & Ramwell, 1974) the "hairpin shape" and is characterized by the approximately parallel arrangement of the alkyl portions of the α and ω side chains[2] of the prostaglandin skeleton. Subsequent studies of other prostaglandins such as PGE_2 (Edmonds & Duax, 1975), PGE_1 (Spek, 1977), $PGF_{2\alpha}$ (Langs et al., 1977), and $PGF_{2\beta}$ (G. T. DeTitta, D. A. Langs, J. W. Edmonds, and W. L. Duax, unpublished experiments) revealed that the hairpin shape is a distinctive characteristic of these prostaglandins. All of these prostaglandins are metabolized by PGDH. The diffraction studies of PGA_1 and PGB_1 reveal striking dissimilarities in the conformations of these two compounds. Analysis of these dissimilarities can explain the differing biological profiles of PGA_1 and PGB_1 to PGDH. The studies also indirectly support the hypothesis that the hairpin

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[1] Abbreviations used: PG, prostaglandin; PGA_1, prostaglandin A_1, (13*E*,15*S*)-15-hydroxy-9-oxoprosta-10,13-dien-1-oic acid; PGB_1, prostaglandin B_1, (13*E*,15*S*)-15-hydroxy-9-oxoprosta-8(12),13-dien-1-oic acid; PGDH, (15*S*)-15-hydroxyprostaglandin dehydrogenase (EC 1.1.1.141).

[2] The α side chain is considered to be atoms C(1)–C(7), and the ω side chain is considered to be atoms C(13)–C(20); the alkyl portion of the ω chain is considered to be C(16)–C(20).

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Table I: Crystallographic Data for PGA_1 and PGB_1

	PGA_1	PGB_1
space group	$P2_1$	$P2_12_12_1$
a (Å)	13.637 (2)	18.744 (2)
b (Å)	7.567 (1)	23.017 (1)
c (Å)	10.576 (2)	4.6935 (4)
β (deg)	107.37 (3)	90
formula	$C_{20}H_{32}O_4$	$C_{20}H_{32}O_4$
M_r	336.48	336.48
d_c (g cm^{-3})	1.073	1.104
Z	2	4
μ_{Cu} (cm^{-1})	5.9	6.1

conformations of prostaglandins observed by diffraction techniques are biologically relevant molecular conformations. Short notes (DeTitta et al., 1975a; DeTitta, 1976) outlining the preliminary results of these studies have appeared elsewhere; here we detail fully the results of these studies.

Experimental

Crystals of PGA_1 and PGB_1 were grown by very slow evaporation from saturated hexane–ethyl acetate and acetonitrile solutions, respectively. Crystal quality and space group assignments were in both cases checked by Weissenberg photography. Observed densities were not measured due to a scarcity of crystals. Intensity measurements were collected on a κ-geometry diffractometer. Data were scanned in the θ–2θ mode by using Cu K$\bar{\alpha}$ radiation and a variable scan width of $1.0° + (0.1 \tan \theta)°$ for PGA_1 and $1.2° + (0.2 \tan \theta)°$ for PGB_1. These were corrected in both cases for Lorentz and polarization effects; in addition, absorption corrections were applied to the PGA_1 data. Cell constants were obtained by least-squares refinement of initial values obtained from X-ray photography; 14 reflections in the range $16° \leq \theta \leq 27°$ and 31 reflections in the range $23° \leq \theta \leq 32°$ were measured on the κ-geometry diffractometer and employed in the fitting procedures for PGA_1 and PGB_1, respectively. Intensity data were considered as observable if the intensity $I \geq 3\sigma_I$ for PGA_1 and $I \geq 2\sigma_I$ for PGB_1. Of 2320 unique reflections measured for PGA_1, 1857 passed the 3σ criterion; corresponding values for PGB_1 are 2447 and 1252. A résumé of pertinent crystallographic data is given in Table I (also see paragraph at end of paper regarding supplementary material).

Structure Determination and Refinement. In both cases the crystal structures were determined by multisolution tangent refinement techniques (Germain et al., 1971) combined with a figure of merit based on four-phase structure invariants estimated to be negative, i.e., $\phi_h + \phi_k + \phi_l + \phi_m \simeq \pi$ (DeTitta et al., 1975b). Refinement of the structural models was by least-squares techniques in both cases. Hydrogen atomic positions not fixed by geometry were located in difference Fourier maps. Positional and isotropic thermal parameters for the 24 nonhydrogen atoms were refined by full matrix least-squares techniques in both cases; in neither case were hydrogen atomic positions refined. The following are the final residuals: for PGA_1, $R = 0.075$ and $R_w = 0.095$; for PGB_1, $R = 0.076$ and $R_w = 0.088$. Estimated standard deviations for observations of unit weight are 1.49 for PGA_1 and 1.70 for PGB_1. The average estimated standard deviations in derived parameters for PGA_1 are as follows: bond distances, 0.008 Å; bond angles, 0.5°; torsion angles, 0.8°. Corresponding values for PGB_1 are 0.009 Å, 0.5°, and 0.9°, respectively. Values for atomic form factors employed throughout the refinement process are those given by Cromer & Waber (1974) for carbon and oxygen and those given by Stewart et al. (1965) for hydrogen. Final atomic positional parameters for PGA_1 and PGB_1 are listed in Table II. Bond distances, bond angles, and torsion angles are given in Table III.

Results

Prostaglandins PGA_1 and PGB_1 have visibly different conformations (Figure 1). PGA_1 is hairpin-shaped; i.e., its side chains are approximately parallel throughout their alkyl regions and the C(1)···C(20) intramolecular distance, a measure of the proximity of the α and ω chains, is 5.52 Å. In contrast, PGB_1 is L-shaped, i.e., its side chains are approximately perpendicular throughout their alkyl regions and the C(1)···C(20) distance is 16.84 Å.

Of all the prostaglandins studied to date by diffraction techniques only PGB_1 defies characterization as hairpin-shaped. PGA_1 is representative of other members of the PG_1

Table II: Positional Parameters and Standard Deviations for PGA_1 and PGB_1

	PGA_1			PGB_1		
atom	x	y	z	x	y	z
C(1)	−0.2586 (4)	0.192 (1)	−0.0106 (6)	0.6888 (4)	0.3607 (3)	0.382 (2)
C(2)	−0.1499 (4)	0.227 (1)	−0.0084 (7)	0.6823 (3)	0.4162 (2)	0.534 (2)
C(3)	−0.0696 (4)	0.175 (1)	0.1112 (6)	0.6510 (3)	0.4657 (2)	0.364 (2)
C(4)	0.0379 (4)	0.220 (1)	0.1088 (6)	0.6337 (3)	0.5188 (2)	0.543 (2)
C(5)	0.1240 (4)	0.162 (1)	0.2290 (5)	0.6099 (3)	0.5706 (2)	0.369 (1)
C(6)	0.2286 (4)	0.222 (1)	0.2184 (6)	0.5835 (3)	0.6204 (2)	0.543 (2)
C(7)	0.3155 (4)	0.177 (1)	0.3378 (5)	0.5645 (3)	0.6739 (2)	0.361 (1)
C(8)	0.4173 (4)	0.253 (1)	0.3282 (4)	0.5269 (3)	0.7183 (2)	0.540 (1)
C(9)	0.5014 (5)	0.253 (1)	0.4581 (4)	0.4485 (3)	0.7187 (2)	0.574 (1)
C(10)	0.5978 (5)	0.218 (1)	0.4305 (5)	0.4289 (3)	0.7659 (2)	0.771 (2)
C(11)	0.5796 (4)	0.169 (1)	0.3058 (5)	0.4965 (3)	0.7964 (2)	0.853 (1)
C(12)	0.4666 (3)	0.158 (1)	0.2318 (4)	0.5552 (3)	0.7618 (2)	0.699 (1)
C(13)	0.4386 (3)	0.233 (1)	0.0943 (4)	0.6301 (3)	0.7740 (2)	0.723 (1)
C(14)	0.4128 (3)	0.138 (1)	−0.0144 (4)	0.6578 (3)	0.8119 (2)	0.901 (1)
C(15)	0.3908 (3)	0.216 (1)	−0.1505 (3)	0.7360 (3)	0.8247 (2)	0.943 (2)
C(16)	0.2952 (4)	0.143 (1)	−0.2512 (4)	0.7530 (3)	0.8880 (2)	0.883 (2)
C(17)	0.1974 (5)	0.201 (1)	−0.2267 (6)	0.8265 (3)	0.9078 (2)	0.991 (2)
C(18)	0.1011 (6)	0.143 (2)	−0.3375 (7)	0.8438 (3)	0.9695 (2)	0.921 (2)
C(19)	0.0037 (7)	0.203 (2)	−0.323 (1)	0.9156 (3)	0.9892 (3)	1.018 (2)
C(20)	−0.0903 (8)	0.151 (3)	−0.424 (1)	0.9355 (4)	1.0492 (3)	0.944 (3)
O(1A)	−0.2845 (4)	0.151 (1)	0.0812 (5)	0.6451 (3)	0.3484 (2)	0.195 (1)
O(1B)	−0.3221 (3)	0.217 (1)	−0.1288 (5)	0.7348 (2)	0.3240 (2)	0.464 (2)
O(9)	0.4903 (4)	0.278 (1)	0.5668 (4)	0.4084 (2)	0.6858 (2)	0.445 (1)
O(15)	0.4787 (3)	0.168 (1)	−0.1941 (8)	0.7751 (3)	0.7868 (1)	0.753 (1)

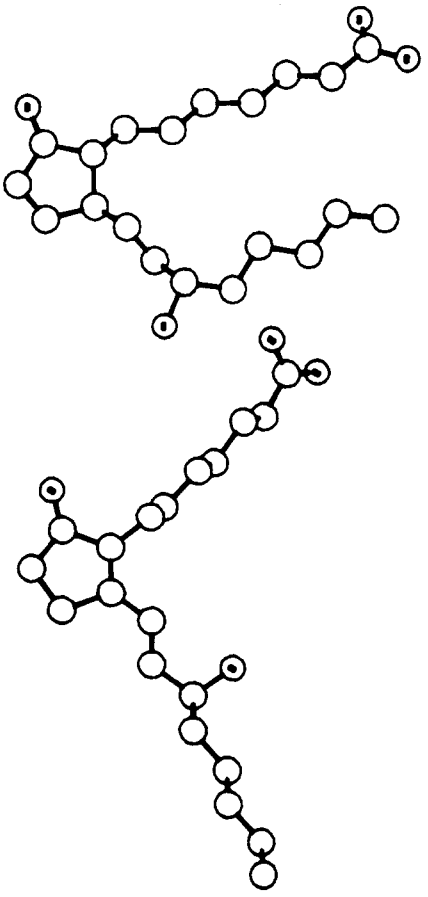

FIGURE 1: The hairpin conformation of PGA_1 (top) and the L-shape conformation of PGB_1 (bottom). The molecules are identically oriented so that the line joining the midpoints of the C(9) → C(11) and C(8) → C(12) vectors defines the horizontal axis while the C(8)–C(12) bond lies in the vertical plane.

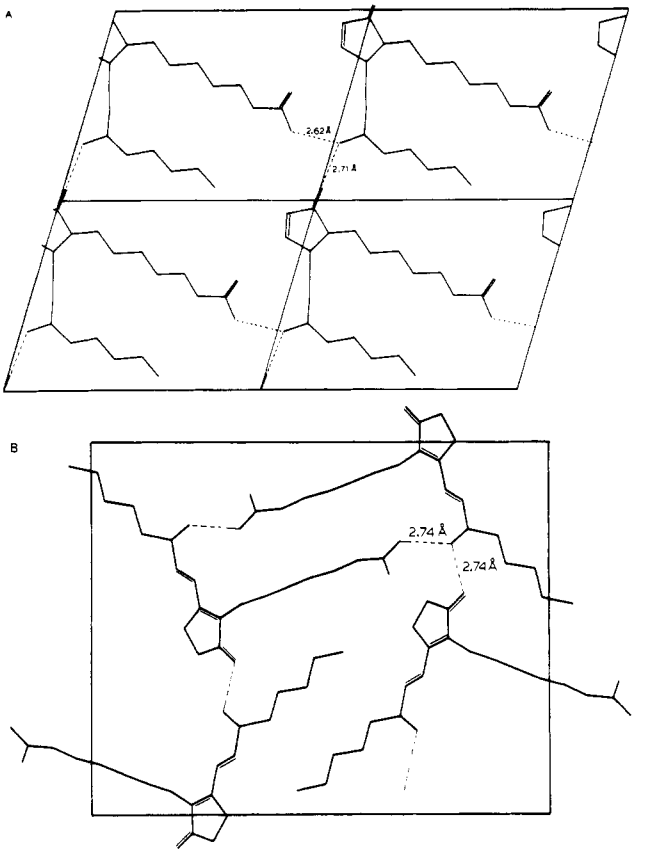

FIGURE 2: The crystal packing of PGA_1 (top) and PGB_1 (bottom). The projections are down the *b* and *c* axes, respectively. Hydrogen bonds are indicated by broken lines. It should be noted that for PGA_1 only the molecular layer at $y \simeq {}^1/_4$ is shown; the screw-related layer at $y \simeq {}^3/_4$ is omitted for clarity.

series.[3] Its α chain is fully extended in the all-trans zigzag conformation typical of fatty acids. The C(8) ring junction geometry is –synclinal/antiperiplanar, while the C(12) ring junction geometry is ±anticlinal. The ω chain turns at C(15), positioning O(15) antiperiplanar to the alkyl portion of the ω chain and away from the centroid of the molecule. The alkyl portion of the ω chain is fully extended. PGB_1 is a very distinct PG_1 conformer. While it displays the fully extended geometry of the alkyl regions of its α and ω chains as do other PG_1 compounds studied, its ring junction geometries and twisting at C(15) are of an entirely different nature. Its C(8) junction geometry is perpendicular in nature while its C(12) junction geometry is synclinal/antiperiplanar. The coplanarity of the C(8)=C(12) and C(13)=C(14) double-bond regions, the shortening of the C(9)–C(8) and C(12)–C(13) formal single bonds, and the observation of a strong ultraviolet absorption at a wavelength of 278 nm in ethanol (Shaw & Ramwell, 1969) are consistent with the formation of a conjugated dienone system reaching from O(9) to C(15) through the C(8)=C(12) bond. The dienone is of the all-trans variety.

The disposition of the O(15)-hydroxyl oxygen of PGB_1 is unexpected. It is synperiplanar to the double bond and –synclinal to the ω-alkyl chain. In PGA_1 it is +anticlinal to the double bond and antiperiplanar to the ω-alkyl chain. The cis coplanarity of O(15) and the C(13)=C(14) double bond directs the ω-alkyl region away from the α chain and an L shape results.

The ring conformations of PGA_1 and PGB_1 differ considerably. The ring of PGB_1 is quite flat while the ring of PGA_1 is puckered, adopting a C(8) envelope conformation. The ring of PGA_1 in its orthorhombic modification (Edmonds & Duax, 1975) is considerably more planar than that observed for the monoclinic form. Internal torsion angles for orthorhombic PGA_1 range from 2.5° about the C(11)–C(12) bond to 8.4° about the C(8)–C(9) bond. Modeling indicates that if C(8) is above the endocyclic double-bond plane as in monoclinic PGA_1 [0.29 Å above C(9)–C(10)=C(11)–C(12) when viewed as in Figure 1], then the O(9) oxygen must be below the plane in order to maintain the planarity of the keto function. O(9) is 0.18 Å below the C(9)–C(12) plane in monoclinic PGA_1. It is possible that opposing forces determined the conformation of the ring of PGA_1. If the ring is completely flat, then the stability afforded by the conjugation of the α,β-unsaturation is maximized. On the other hand, the eclipsing of substituents around the ring, e.g., C(7) and H(12) and C(13) and H(8), is also maximized. With the adoption of a C(8) envelope conformation, the eclipsing is reduced but the conjugation is also reduced.

The crystal packing (Figure 2) of the two prostaglandins reveals a similarity of hydrogen-bonding pattern. In each case there is a sequence of O(1B)–H···O(15)–H···O(9) hydrogen bonds. In PGA_1 these hydrogen bonds link up translationally related molecules into layers perpendicular to the crystallographic *b* axis. There are no hydrogen bonds linking molecules

[3] The PG_1 series of prostaglandins, e.g., PGA_1, PGB_1, PGE_1, and $PGF_{1\alpha}$, is characterized by a common (13*E*,15*S*)-15-hydroxyprost-13-en-1-oic acid skeletal structure but is distinguished by ring substitution and the degree of saturation. The PG_2 series of prostaglandins is characterized by a common (5*Z*,13*E*,15*S*)-15-hydroxyprosta-5,13-dien-1-oic acid skeletal structure.

Table III: Bond Distances (Å), Bond Angles (deg), and Torsion Angles (deg) for Prostaglandin A_1 (PGA_1) and Prostaglandin B_1 (PGB_1)

distance (Å)			angle (deg)			torsion angle (deg)		
	PGA_1	PGB_1		PGA_1	PGB_1		PGA_1	PGB_1
O(1A)-C(1)	1.163	1.176	O(1A)-C(1)-O(1B)	123.6	125.3	O(1A)-C(1)-C(2)-C(3)	11.6	−37.6
O(1B)-C(1)	1.308	1.336	O(1A)-C(1)-C(2)	124.9	120.9	O(1B)-C(1)-C(2)-C(3)	−169.6	154.1
C(1)-C(2)	1.499	1.518	O(1B)-C(1)-C(2)	111.6	112.7	C(1)-C(2)-C(3)-C(4)	−178.2	170.4
C(2)-C(3)	1.464	1.514	C(1)-C(2)-C(3)	117.0	111.6	C(2)-C(3)-C(4)-C(5)	−178.0	176.4
C(3)-C(4)	1.510	1.534	C(2)-C(3)-C(4)	114.4	110.5	C(3)-C(4)-C(5)-C(6)	−177.1	173.5
C(4)-C(5)	1.519	1.559	C(3)-C(4)-C(5)	116.2	110.3	C(4)-C(5)-C(6)-C(7)	177.1	177.3
C(5)-C(6)	1.532	1.541	C(4)-C(5)-C(6)	111.5	110.3	C(5)-C(6)-C(7)-C(8)	−175.0	170.6
C(6)-C(7)	1.496	1.544	C(5)-C(6)-C(7)	113.4	108.3	C(6)-C(7)-C(8)-C(9)	164.9	−91.9
C(7)-C(8)	1.535	1.511	C(6)-C(7)-C(8)	111.6	108.9	C(6)-C(7)-C(8)-C(12)	−74.8	84.5
C(8)-C(9)	1.508	1.467	C(7)-C(8)-C(9)	113.9	122.1	C(7)-C(8)-C(9)-C(10)	144.5	173.8
C(8)-C(12)	1.546	1.361	C(7)-C(8)-C(12)	116.1	130.5	C(7)-C(8)-C(9)-O(9)	−35.5	−6.2
O(9)-C(9)	1.213	1.247	C(9)-C(8)-C(12)	103.6	107.3	C(12)-C(8)-C(9)-C(10)	17.4	−3.4
C(9)-C(10)	1.450	1.469	O(9)-C(9)-C(8)	125.9	121.7	C(12)-C(7)-C(9)-O(9)	−162.6	176.6
C(10)-C(11)	1.319	1.542	C(8)-C(9)-C(10)	108.3	111.1	C(7)-C(8)-C(12)-C(11)	−142.8	−177.0
C(11)-C(12)	1.513	1.509	O(9)-C(9)-C(10)	125.8	127.2	C(7)-C(8)-C(12)-C(13)	92.7	1.6
C(12)-C(13)	1.498	1.449	C(9)-C(10)-C(11)	109.3	104.6	C(9)-C(8)-C(12)-C(11)	−17.1	0.0
C(13)-C(14)	1.313	1.319	C(10)-C(11)-C(12)	113.4	103.9	C(9)-C(8)-C(12)-C(13)	−141.6	178.5
C(14)-C(15)	1.499	1.498	C(8)-C(12)-C(11)	102.1	112.8	C(8)-C(9)-C(10)-C(11)	−10.5	5.3
O(15)-C(15)	1.448	1.439	C(8)-C(12)-C(13)	114.9	124.7	O(9)-C(9)-C(10)-C(11)	169.5	−174.7
C(15)-C(16)	1.525	1.558	C(11)-C(12)-C(13)	114.5	122.4	C(9)-C(10)-C(11)-C(12)	−1.5	−5.0
C(16)-C(17)	1.495	1.562	C(12)-C(13)-C(14)	124.2	125.7	C(10)-C(11)-C(12)-C(8)	12.3	3.4
C(17)-C(18)	1.548	1.521	C(13)-C(14)-C(15)	122.9	126.2	C(10)-C(11)-C(12)-C(13)	137.1	−175.3
C(18)-C(19)	1.456	1.550	O(15)-C(15)-C(14)	104.4	108.6	C(8)-C(12)-C(13)-C(14)	−135.3	−173.5
C(19)-C(20)	1.464	1.561	C(14)-C(15)-C(16)	114.6	109.5	C(11)-C(12)-C(13)-C(14)	107.0	5.0
			O(15-C(15)-C(16)	108.0	110.7	C(12)-C(13)-C(14)-C(15)	−176.5	176.9
			C(15)-C(16)-C(17)	113.6	111.6	C(13)-C(14)-C(15)-C(16)	−134.8	123.3
			C(16)-C(17)-C(18)	113.0	108.5	C(13)-C(14)-C(15)-O(15)	107.3	2.3
			C(17)-C(18)-C(19)	115.4	108.1	C(14)-C(15)-C(16)-C(17)	70.8	166.7
			C(18)-C(19)-C(20)	118.1	111.1	O(15)-C(15)-C(16)-C(17)	−173.3	−73.6
						C(15)-C(16)-C(17)-C(18)	174.1	180.0
						C(16)-C(17)-C(18)-C(19)	−176.8	−175.2
						C(17)-C(18)-C(19)-C(20)	−180.0	177.6

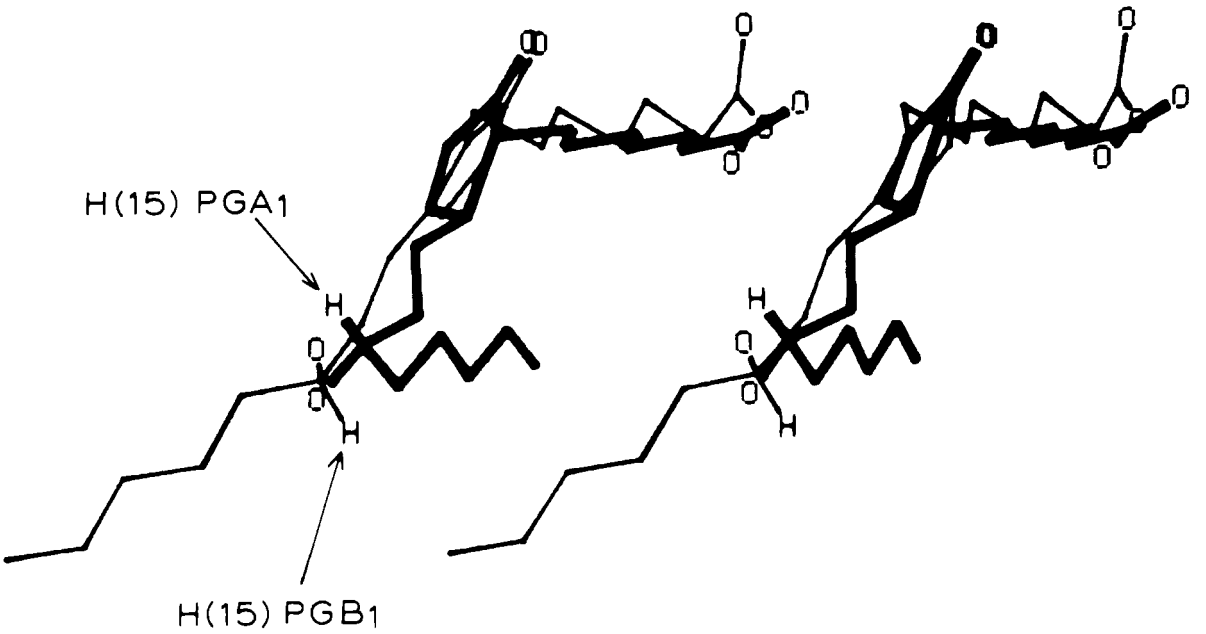

FIGURE 3: Stereoview of prostaglandins PGA_1 (bold line) and PGB_1 (light line) fit by a procedure which minimizes $\sum_i d_i^2$, the sum of squares of distances separating C(2), C(4), C(6), and C(8)–C(12) of the PGB_1 molecule to the PGA_1 molecule. The H(15) hydrogen abstracted by PGDH is indicated.

along the polar axis. In PGB_1, while the same series of hydrogen bonds is observed, a three-dimensional pattern of bonding is produced. In neither PGA_1 nor PGB_1 is the carboxylic O(1A) oxygen involved in the hydrogen-bond network.

Discussion

The primary metabolic fate of prostaglandins is the oxidation of the C(15)-hydroxyl group of the PG skeleton by the NAD^+ (or in rarer instances $NADP^+$) dependent cytosol enzyme (15*S*)-15-hydroxyprostaglandin dehydrogenase. PGDH is specific for prostaglandins, exhibiting no capacity to metabolize sterols, alcohols, etc. (Änggård & Samuelsson, 1966). By analogy to other NAD^+-dependent alcohol dehydrogenases, PGDH probably abstracts the hydrogen at C(15) stereospecifically, transfers it directly to the nicotinamide ring of NAD^+ to form NADH, and releases the O(15) hydrogen to the medium as a proton to balance the reaction.

It is possible that hydrogen-bond formation involving the O(15)-hydroxyl group and the enzyme or coenzyme might constitute the formation of an enzyme–substrate complex prior to or concomitant with hydride abstraction by NAD^+.

Binding and kinetic studies (Sun et al., 1976) show that PGDH is exquisitely sensitive to substrate modification of the PG skeleton in the vicinity of C(15) but is only moderately sensitive to substrate modification of the ring or α-chain substituents. Prostaglandin A_1 is a substrate for PGDH but PGB_1 is not. Two reasonable explanations of why this may be so are suggested by the observed conformations of PGA_1 and PGB_1. The simplest explanation is that the L shape of PGB_1 physically prevents PGB_1 from binding the PG site on PGDH. A more complicated explanation is that PGB_1 binds the PG site but is not metabolized. If PGB_1 binds the PG site, the kinetic and binding studies suggest that its α chain and ring will be recognized in a manner similar to prostaglandins which are substrates. In Figure 3 the observed conformers of PGA_1 and PGB_1 have been superimposed by a fitting procedure similar to one described by Nyburg (1974). The rings and α chains have been fit together. If attention is focused on the C(15)–H bonds of the two PG's, it is clear that they are oriented *in opposite* directions. If the nicotinamide ring of NAD^+ normally occupies a position over the C(15)–H bond of PGA_1, it is clear that it cannot be in a position to accept the C(15) hydrogen of PGB_1 also.

It is interesting to note that the conformations of prostaglandins observed in the crystalline state are probably preserved in solution. This is inferred from the lanthanide-induced shift nuclear magnetic resonance studies of Andersen and coworkers (Leovey & Andersen, 1975; Andersen et al., 1976). Relying on the specificity of the praesodymium ion for the carboxylate group of fatty acids, Andersen et al. correlate the relative chemical shift of proton resonances for each proton-bearing carbon of the PG skeleton with its distance from C(1). They note that for $PGF_{2\alpha}$, which is hairpin-shaped (Langs et al., 1977), the relative shift decreases steadily as a function of chain position, minimizes at C(11), and increases a small but significant amount as one proceeds along the ω chain. The relative shift of the terminal methyl group is 3.8% of that of the α-methylene group, a value which they conclude, based on calibration experiments with small fatty acids, is inconsistent with either an L shape or an extended conformation. In contrast, the relative shifts for PGB_1 decrease nearly monotonically with position along the chains, the shift of C(20) being 1.8% of that of C(2). While the LIS-NMR results cannot directly infer a solution conformation, in conjunction with diffraction results they strongly suggest that the hairpin conformation of $PGF_{2\alpha}$ and L shape of PGB_1 are retained in solution.

In summary, the conformations of two chemically similar prostaglandins are visibly dissimilar. Analysis of the structures in light of kinetic and binding data for PGDH suggests two possible explanations for the inactivity of PGDH to PGB_1. Both explanations implicitly assume that PGDH must interact with an L-shaped PGB_1. Confirmatory evidence for the persistence of the L shape of PGB_1 in solution has been discussed. We believe that these considerations are strong, albeit inferential, arguments for the contention that the conformations of prostaglandins revealed by diffraction studies are biologically relevant ones.

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Supplementary Material Available

Observed and calculated structure factors for both PGA_1 and PGB_1 and atomic thermal and hydrogen positional parameters (31 pages). Ordering information is given on any current masthead page.

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