Table 6. *Mean S—S distances* (Å) *and torsion angles* (°) *in compounds having bridging polysulphide chains*

Bridge	S—S	R—S—S—R	References
Two-S	2·084 (2)	72·5 (2)	This work
Four-S	2·074 (2)	108·0 (1)	This work
	2·061 (2)	98·2 (2)	
Four-S	2·066 (2)	86·9 (1)	Ricci & Bernal (1971)
Three-S	2·064 (2)	92·4 (2)	This work
	2·053 (2)	89·8 (2)	
Three-S	2·054 (1)	81·0 (1)	Lemmer *et al.* (1973)
S₄(NH)₂	2·051 (6)	99·7 (2)	van de Grampel & Vos (1969)
PhHCN—S₄—NCHPh	2·083 (4)	106·5 (2)	Barrick *et al.* (1973)

mation is the most stable, we may predict that the [2.2] derivatives (V) (Fig. 6) will exhibit the *anti* conformation.

As far as point (iv) is concerned, we have already observed that there is an increase in the mean of the torsion angles around the S—S bonds with an increase in the length of the polysulphide chain. Furthermore, the geometrical parameters of different kinds of $R-S-S-R'$ chains seem to be qualitatively in agreement with the relationship found by Hordvik (1966), who observed that the shortest S—S bond length (d) corresponds to a dihedral angle φ of about 90°, while smaller dihedral angles correspond to longer bonds. From Table 6, where d and φ values are reported for ours and other bridging chains, we suggest that, in addition to this statement, it may be assumed that dihedral angles larger than 90° also correspond to longer bonds.

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Prostadienoic Acids PGE₂ and PGF₂β: Crystallographic Studies of Conformational Transmission and Receptor Recognition

BY GEORGE T. DETITTA,* DAVID A. LANGS, JAMES W. EDMONDS† AND WILLIAM L. DUAX

Molecular Biophysics Department, Medical Foundation of Buffalo, Inc., 73 High Street, Buffalo, New York 14203, *USA*

Abstract

The conformations of the prostadienoic acids PGE₂ and PGF₂β have been determined by X-ray diffraction techniques. While both molecules are 'hairpin' shaped, *i.e.* their side chains are ~5 Å apart at their ends and are approximately parallel, subtle yet significant variations in conformation distinguish the two prostaglandins. The variations in conformation have been traced to a short (2·81 Å) C(6)···O(9) contact which precludes PGE₂ from attaining the C(8) ring/

* To whom correspondence may be addressed.
† Present address: Dow Chemical USA, Midland, MI 48640, USA.

chain junction geometry of $PGF_{2\beta}$, and are transmitted throughout the PGE_2 skeletal structure by the dispersion-force energy of attraction inherent in the hairpin shape. Relative to a common nine-atom molecular moiety [atoms C(7) through C(16)] the ends of the PGE_2 side chains are displaced more than 4 Å with respect to the ends of the $PGF_{2\beta}$ side chains. The variations on the hairpin theme exemplified by PGE_2 and $PGF_{2\beta}$ throw light on the stereostructural requirements for receptor recognition of prostaglandins. Crystals of both compounds are triclinic, space group $P1$. Unit-cell constants for PGE_2 are $a = 9.7111$ (4), $b = 10.5190$ (8), $c = 5.1600$ (2) Å, $\alpha = 86.835$ (7), $\beta = 93.266$ (6), $\gamma = 91.455$ (6)°; unit-cell constants for $PGF_{2\beta}$ are $a = 9.2517$ (5), $b = 10.5002$ (8), $c = 5.5717$ (5) Å, $\alpha = 103.995$ (8), $\beta = 91.596$ (8), $\gamma = 89.393$ (6)°. The structural parameters for PGE_2 were refined to residuals $R = 0.087$ and $R_w = 0.105$; corresponding values for $PGF_{2\beta}$ are $R = 0.041$ and $R_w = 0.060$. (PGE_2 has the formula $C_{20}H_{32}O_5$ and $PGF_{2\beta}$ the formula $C_{20}H_{34}O_5$.)

The concept of a preferred, aligned conformation for prostaglandins,* the 'hairpin hypothesis', is traced to the pioneering diffraction study of a heavy-atom derivative of $PGF_{1\beta}$ methyl ester by Abrahamsson (1963). In that study the proposed connectivity of the PG skeleton (Bergström, Dressler, Krabisch, Ryhage & Sjovall, 1962; Bergström, Ryhage, Samuelsson & Sjovall, 1962) was confirmed, the relative chirality of its asymmetric carbons established, and the basic hairpin shape revealed. Subsequent diffraction studies of unsubstituted, natural prostaglandins dispelled suggestions that the overall conformation of $PGF_{1\beta}$ observed by Abrahamsson was due to the influence of three bulky p-bromobenzoate groups at oxygens O(9), O(11), and O(15). Confirmatory spectral (Andersen, Mackay & Moore, 1976) and theoretical (Murakami & Akahori, 1974) evidence suggests that the aligned conformation persists in solution and is an inherently stable conformation. With the notable exception of PGB_1 (DeTitta, Langs & Edmonds, 1979) every prostaglandin studied to date by diffraction techniques can be characterized as hairpin shaped.

If the hairpin conformation is indeed a hallmark of the prostaglandin skeleton, then the hairpin shape *per se* is insufficient to explain the varied and specific biological activities of prostaglandins. Prostaglandins PGE_2 (I) and $PGF_{2\beta}$ (II) are members of the

prostadienoic (PG_2) family of PG's. PGE_2, with a keto oxygen at C(9), is a highly active, natural prostaglandin; $PGE_{2\beta}$, with β-hydroxyl oxygen at C(9), is a generally less active (Hamosh & Da Silva, 1975; Koss, 1976), synthetic prostaglandin. $PGF_{2\beta}$ is a side-product of the sodium borohydride reduction of PGE_2 to $PGF_{2\alpha}$. The diffraction studies detailed herein reveal both PGE_2 and $PGF_{2\beta}$ to be hairpin shaped. The subtle differences in conformation which these prostaglandins display probably account for their differing biological profiles. The genesis of these differences appears to be the position of the O(9) oxygen *vis à vis* the α chain. The results suggest a long-range conformational transmission effect at work, the driving force of which is probably the preservation of the hairpin conformation. A short communication outlining some of the results of the PGE_2 investigation (Edmonds & Duax, 1974a) has appeared previously.

(I)

(II)
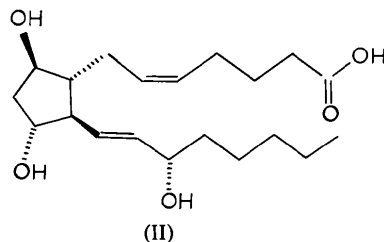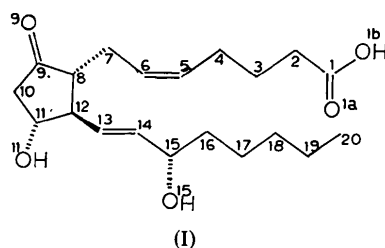
Experimental

A single crystal of PGE_2 suitable for diffraction studies was selected from the original vial supplied by The Upjohn Co. Crystals of $PGF_{2\beta}$ were grown by slow evaporation of an acetonitrile/water mixture. Intensity data for PGE_2 were measured on a GE XRD-5 diffractometer, as previously described (Edmonds & Duax, 1975). Refined cell constants for PGE_2 were provided by Dr D. Duchamp of The Upjohn Co. Intensity data for $PGF_{2\beta}$ were measured on a CAD-4 diffractometer in the $\theta:2\theta$ scanning mode. A variable scan width of $0.85° + (0.15 \tan \theta)°$ was employed. Both data sets were measured with Cu $K\alpha$ radiation, corrected for Lorentz and polarization effects, and in the case of PGE_2 corrected for absorption. For PGE_2, 1565 independent reflections were measured ($\sin \theta_{max}/\lambda = 0.56$ Å^{-1}), of which 1005 were considered observable, $I \geq 2\sigma_I$. For $PGF_{2\beta}$, 2154 independent reflections were measured ($\sin \theta_{max}/\lambda = 0.63$ Å^{-1}), of which

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* Abbreviations employed: PG, prostaglandin; PGE_2, (5Z,11α,13E,15S)-11,15-dihydroxy-9-oxoprosta-5,13-dien-1-oic acid; $PGF_{2\beta}$, (5Z,9β,11α,13E,15S)-9,11,15-trihydroxyprosta-5,13-dien-1-oic acid; α chain, atoms C(1) to C(7); ω chain, atoms C(13) to C(20); $\pm sc$, $\pm$synclinal, a torsion angle ranging from ±30 to $\pm90°$; $\pm ac$, $\pm$anticlinal, a torsion angle ranging from ±90 to $\pm150°$; ap, antiperiplanar, a torsion angle ranging from $+150$ to $+210°$; e.s.d., estimated standard deviation.

1553 were considered observable, $I \geq 2\sigma_I$. The crystallographic data are given in Table 1.

Structure determination and refinement

The structures of PGE$_2$ and PGF$_{2\beta}$ were determined by direct methods. In the case of PGE$_2$ the phase problem was overcome by a combination of hand-phasing techniques and tangent-formula refinement described elsewhere (Edmonds & Duax, 1974b). In the case of PGF$_{2\beta}$ the structure was determined employing $QTAN$

Table 1. Crystallographic data for PGE$_2$ and PGF$_{2\beta}$

Cell constants for PGE$_2$ were measured at 295 K.

Space group	PGE$_2$ $P1$	PGF$_{2\beta}$ $P1$
a (Å)	9·7111 (4)	9·2517 (5)
b (Å)	10·5190 (8)	10·5002 (8)
c (Å)	5·1600 (2)	5·5717 (5)
α (°)	86·835 (7)	103·995 (8)
β (°)	93·266 (6)	91·596 (8)
γ (°)	91·455 (6)	89·393 (6)
V (Å^3)	525·3	525·0
Formula	C$_{20}$H$_{32}$O$_5$	C$_{20}$H$_{34}$O$_5$
M_r	352·47	354·48
D_c (Mg m^{-3})	1·114	1·118
Z	1	1
μ_{Cu} (mm^{-1})	0·64	0·64
Crystal dimensions (mm)	0·16 × 0·20 × 0·40	0·08 × 0·20 × 0·40

(Langs & DeTitta, 1975), a global tangent refinement procedure written by one of us (DAL), which actively employs the four phase structure invariants $\varphi_h + \varphi_k + \varphi_l + \varphi_{-h-k-l} \approx \pi$ as a figure of merit (DeTitta, Edmonds, Langs & Hauptman, 1975). In both cases the structure determinations were not straightforward; that is, complete structures were not developed ab $initio$ from the phasing techniques. In the determination of PGF$_{2\beta}$ initial $QTAN$ runs over 128 ambiguities produced a phase set which yielded a four-atom fragment identifiable as a portion of an all-$trans$ planar zigzag chain. Such a fragment is centrosymmetric; it was therefore translated so that the molecular inversion center was placed at the origin of the unit cell. Structure factors, with real phases, were then calculated for the largest E values and a number of phases were set to their calculated values in order to specify an origin-fixing basis set for further direct phasing attempts. A number of additional ambiguities were introduced into the basis set and $QTAN$ was permitted to produce a small number of phase sets with acceptable figures of merit. A map calculated from the most promising of these [NQEST = −0·37, RESID = 0·29, average cos($\varphi_h + \varphi_k + \varphi_{-h-k}$) = 0·59] yielded essentially the complete structure, but in examining the map it was clear that the four atoms which had generated phases to specify the origin had shifted away from that origin.

The two structures were refined by full-matrix least-squares techniques; in both cases atomic positional and anisotropic thermal parameters for nonhydro-

Table 2. Atomic positional parameters and estimated standard deviations for prostaglandin PGE$_2$ ($\times 10^3$) and PGF$_{2\beta}$ ($\times 10^4$)

	PGE$_2$			PGF$_{2\beta}$		
	x	y	z	x	y	z
C(1)	−579 (2)	−686 (1)	−67 (2)	1482 (4)	5482 (3)	2851 (6)
C(2)	−552 (2)	−575 (1)	−248 (3)	1230 (4)	6488 (4)	6192 (7)
C(3)	−408 (2)	−515 (2)	−233 (3)	−136 (5)	7294 (4)	6154 (7)
C(4)	−392 (2)	−396 (1)	−412 (3)	−485 (6)	8177 (5)	8594 (9)
C(5)	−245 (2)	−347 (1)	−389 (4)	−1882 (5)	8899 (4)	8559 (7)
C(6)	−200 (1)	−250 (1)	−244 (3)	−2356 (4)	9877 (4)	10281 (7)
C(7)	−267 (1)	−175 (1)	−73 (3)	−1625 (4)	10477 (3)	12712 (6)
C(8)	−253 (1)	−34 (1)	−129 (1)	−1740 (3)	11973 (3)	13567 (5)
C(9)	−111 (1)	23 (1)	−117 (2)	−3302 (3)	12520 (3)	13632 (5)
C(10)	−92 (2)	127 (1)	−313 (3)	−3347 (3)	13721 (4)	15815 (6)
C(11)	−235 (1)	153 (1)	−432 (3)	−1815 (3)	13885 (3)	16959 (5)
C(12)	−316 (1)	20 (1)	−398 (2)	−1149 (4)	12503 (4)	16221 (5)
C(13)	−464 (1)	21 (1)	−429 (3)	475 (3)	12523 (3)	16395 (5)
C(14)	−548 (1)	−25 (1)	−604 (2)	1301 (3)	12027 (3)	17905 (5)
C(15)	−697 (2)	−9 (1)	−607 (3)	2923 (3)	12111 (3)	17958 (5)
C(16)	−782 (1)	−136 (1)	−543 (3)	3663 (3)	10764 (3)	17334 (6)
C(17)	−758 (2)	−239 (1)	−723 (3)	3364 (4)	9964 (4)	14734 (6)
C(18)	−863 (2)	−355 (1)	−663 (3)	4332 (4)	8745 (4)	14050 (7)
C(19)	−853 (2)	−461 (2)	−823 (4)	4005 (6)	7868 (4)	11520 (9)
C(20)	−956 (3)	−575 (2)	−746 (5)	5006 (8)	6699 (5)	10857 (12)
O(1A)	−494 (1)	−714 (1)	102 (2)	674 (3)	5258 (4)	2097 (6)
O(1B)	−691 (1)	−745 (1)	−113 (2)	2681 (3)	4831 (3)	3930 (5)
O(9)	−19 (1)	−19 (1)	37 (2)	−3756 (2)	12804 (2)	11345 (4)
O(11)	−236 (1)	202 (1)	−691 (2)	−1905 (2)	14399 (2)	19592 (4)
O(15)	−743 (1)	37 (1)	−866 (2)	3352 (2)	12795 (3)	20458 (5)

Table 3. *Bond distances* (Å), *bond angles* (°) *and torsion angles* (°) *for* PGE_2 *and* $PGF_{2\beta}$

	PGE₂	PGF₂β		PGE₂	PGF₂β		PGE₂	PGF₂β
O(1A)—C(1)	1·196	1·192	C(8)—C(9)	1·489	1·548	C(13)—C(14)	1·288	1·316
O(1B)—C(1)	1·256	1·302	C(8)—C(12)	1·568	1·536	C(14)—C(15)	1·460	1·503
C(1)—C(2)	1·482	1·489	O(9)—C(9)	1·235	1·428	O(15)—C(15)	1·446	1·451
C(2)—C(3)	1·519	1·516	C(9)—C(10)	1·464	1·527	C(15)—C(16)	1·582	1·531
C(3)—C(4)	1·524	1·490	C(10)—C(11)	1·511	1·532	C(16)—C(17)	1·496	1·508
C(4)—C(5)	1·506	1·494	O(11)—C(11)	1·405	1·440	C(17)—C(18)	1·599	1·531
C(5)—C(6)	1·348	1·306	C(11)—C(12)	1·594	1·537	C(18)—C(19)	1·432	1·510
C(6)—C(7)	1·412	1·495	C(12)—C(13)	1·437	1·503	C(19)—C(20)	1·590	1·509
C(7)—C(8)	1·500	1·531						
			C(9)—C(8)—C(12)	103·2	104·0	C(11)—C(12)—C(13)	117·5	112·5
O(1A)—C(1)—O(1B)	125·8	122·6	O(9)—C(9)—C(8)	122·1	112·6	C(12)—C(13)—C(14)	131·1	126·7
O(1A)—C(1)—C(2)	119·1	124·8	C(8)—C(9)—C(10)	113·1	106·7	C(13)—C(14)—C(15)	122·7	122·7
O(1B)—C(1)—C(2)	115·1	112·6	O(9)—C(9)—C(10)	124·7	112·9	O(15)—C(15)—C(14)	107·8	106·5
C(1)—C(2)—C(3)	117·3	114·3	C(9)—C(10)—C(11)	105·1	106·4	C(14)—C(15)—C(16)	114·3	113·1
C(2)—C(3)—C(4)	113·8	114·1	C(10)—C(11)—C(12)	104·3	104·4	O(15)—C(15)—C(16)	107·1	108·8
C(3)—C(4)—C(5)	109·5	113·4	O(11)—C(11)—C(10)	113·6	109·0	C(15)—C(16)—C(17)	113·2	114·5
C(4)—C(5)—C(6)	124·9	127·0	O(11)—C(11)—C(12)	113·4	113·7	C(16)—C(17)—C(18)	108·6	112·5
C(5)—C(6)—C(7)	132·2	126·8	C(8)—C(12)—C(11)	101·8	102·9	C(17)—C(18)—C(19)	115·0	114·3
C(6)—C(7)—C(8)	114·9	115·4	C(8)—C(12)—C(13)	116·4	113·0	C(18)—C(19)—C(20)	112·4	113·2
C(7)—C(8)—C(9)	117·3	114·6						
C(7)—C(8)—C(12)	116·8	112·5	C(12)—C(8)—C(9)—O(9)	−163·2	146·7	O(11)—C(11)—C(12)—C(13)	−72·0	−80·9
			C(7)—C(8)—C(12)—C(11)	−159·5	−161·9	C(8)—C(12)—C(13)—C(14)	−126·1	−128·6
O(1A)—C(1)—C(2)—C(3)	9·0	−3·3	C(7)—C(8)—C(12)—C(13)	71·5	76·4	C(11)—C(12)—C(13)—C(14)	112·8	115·3
O(1B)—C(1)—C(2)—C(3)	−169·1	178·4	C(9)—C(8)—C(12)—C(11)	−29·3	−37·3	C(12)—C(13)—C(14)—C(15)	−177·3	−180·0
C(1)—C(2)—C(3)—C(4)	−175·9	172·5	C(9)—C(8)—C(12)—C(13)	−158·4	−158·9	C(13)—C(14)—C(15)—C(16)	−111·1	−119·2
C(2)—C(3)—C(4)—C(5)	−178·1	−176·3	C(8)—C(9)—C(10)—C(11)	9·1	1·4	C(13)—C(14)—C(15)—O(15)	130·1	121·4
C(3)—C(4)—C(5)—C(6)	−99·4	−168·6	O(9)—C(9)—C(10)—C(11)	−174·1	−122·8	C(14)—C(15)—C(16)—C(17)	−57·4	64·5
C(4)—C(5)—C(6)—C(7)	3·7	−1·6	C(9)—C(10)—C(11)—C(12)	−27·7	−24·7	O(15)—C(15)—C(16)—C(17)	61·8	−177·4
C(5)—C(6)—C(7)—C(8)	−126·7	140·8	C(9)—C(10)—C(11)—O(11)	−151·6	−146·5	C(15)—C(16)—C(17)—C(18)	−172·8	169·7
C(6)—C(7)—C(8)—C(9)	−60·8	53·7	C(10)—C(11)—C(12)—C(8)	35·5	38·5	C(16)—C(17)—C(18)—C(19)	180·0	176·3
C(6)—C(7)—C(8)—C(12)	62·4	172·2	C(10)—C(11)—C(12)—C(13)	163·9	160·4	C(17)—C(18)—C(19)—C(20)	177·8	178·1
C(7)—C(8)—C(9)—C(10)	143·6	145·6	O(11)—C(11)—C(12)—C(8)	159·6	157·2			
C(7)—C(8)—C(9)—O(9)	−33·3	−90·0						
C(12)—C(8)—C(9)—C(10)	13·7	22·4						

gen atoms were varied. H atomic positions could be ascertained by inspection of difference Fourier maps for $PGF_{2\beta}$, but they could not be determined for PGE_2. Those H atoms fixed by the geometry of the C atoms to which they are bonded were located at their calculated positions throughout the final stages of refinement.

For the PGE_2 refinement reflections passing the tests $|(F_o^2 - F_c^2)/\sigma| \leq 4\cdot0$, $F_o^2/F_c^2 \leq 0\cdot5$ and $F_c^2/F_o^2 \leq 0\cdot5$ were employed regardless of whether or not they passed the $2\sigma_I$ criterion for observability. A total of 1079 reflections passed these tests. The estimate σ was given by $\sigma = (F_o^2 + 0\cdot012F_o^4)^{1/2}$ for $F_o^2 \geq 4\cdot0$ and $\sigma = 2\cdot05$ for $F_o^2 \leq 4\cdot0$. The function minimized was $\sum w(F_o^2 - F_c^2)^2$ where $w = 1/\sigma^2$. For the $PGF_{2\beta}$ refinement the 1553 reflections passing the $2\sigma_I$ criterion for observability were employed during the refinement. The function minimized was $\sum w(F_o^2 - F_c^2)^2$ where $w = 1/\sigma^2$; in this case σ is given by equation (H14) of Stout & Jensen (1968) except that the factor $0\cdot01N_{pk}$ is replaced by $0\cdot06N_{pk}$. For PGE_2 the final residuals are $R = 0\cdot081$ and $R_w = 0\cdot105$, and S, the estimated standard deviation of an observation of unit weight, is $1\cdot04$; for $PGF_{2\beta}$ the corresponding values are: $R = 0\cdot041$, $R_w = 0\cdot060$, $S = 1\cdot26$. Values for atomic form factors employed throughout the refinement processes are those given by Cromer & Waber (1974) for C and O, and those given by Stewart, Davidson & Simpson (1965) for H. Final positional parameters for PGE_2 and $PGF_{2\beta}$ are given in Table 2. Bond distances, bond angles and torsion angles are presented in Table 3.

Unless stated otherwise the estimated standard deviations and associated variances of derived results for PGE_2 are: bond distance $0\cdot022$ (4) Å, bond angle $1\cdot01$ (1)°, torsion angle $1\cdot5$ (4)°. Corresponding values for $PGF_{2\beta}$ are $0\cdot005$ (2) Å, $0\cdot34$ (7)°, and $0\cdot45$ (13)°. There were no individual e.s.d.'s which exceeded the average e.s.d. by more than a factor of two for any of the derived quantities in either structure.*

Results

The conformations of $PGF_{2\beta}$ and PGE_2 are shown in Fig. 1. Both molecules are hairpin shaped. The α and ω chains are in close proximity at their ends; $C(1)\cdots C(20)$ intramolecular separations for PGE_2 and $PGF_{2\beta}$ are $5\cdot02$ and $4\cdot96$ Å respectively. These values should be contrasted with $16\cdot82$ Å observed for PGB_1, which is L shaped, and ~21 Å for a hypothetical, fully extended conformation. In Fig. 2 the two molecules have been superimposed by a least-squares technique similar to that described by Nyburg (1974). Atomic positions for $C(7)$ through $C(16)$ of the two molecules are fit together; the average separation of correspond-
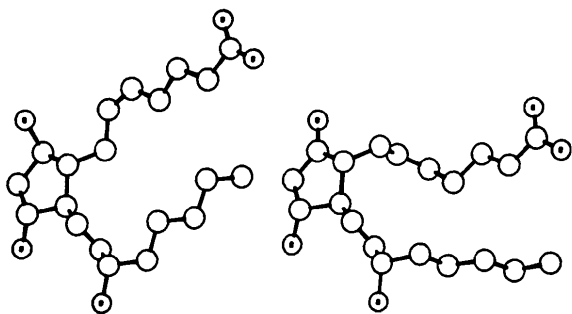
Fig. 1. Molecular conformations of PGF$_{2\beta}$ (left) and PGE$_2$ (right). The views are consistent: The vector through the midpoints of the lines C(8)—C(12) and C(9)$\cdots$C(11) first defines the horizontal axis while the line C(8)—C(12) defines the vertical plane. Thereafter the view is rotated 40° in the vertical. O atoms are denoted by dots at their centers.
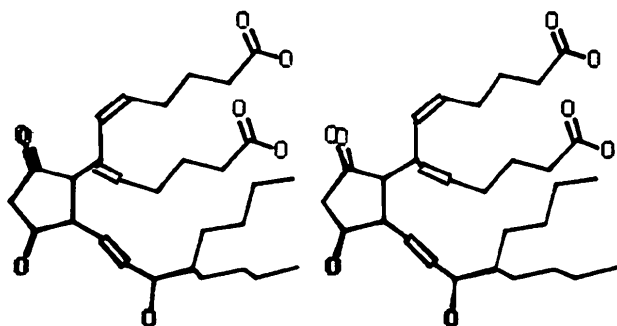

Fig. 2. Stereoview of PGE$_2$ and PGF$_{2\beta}$ superimposed on their C(7)-through-C(16) moieties (see text). The α chain of PGF$_{2\beta}$ is towards the top of the page, followed in descending order by the α chain of PGE$_2$, the ω chain of PGF$_{2\beta}$, and finally the ω chain of PGE$_2$.

ing atoms is 0·07 (3) Å. Relative to this common moiety, C(1) moves 4·3 Å in going from PGF$_{2\beta}$ to PGE$_2$; likewise C(20) moves 4·0 Å in going from PGF$_{2\beta}$ to PGE$_2$.

The locus of chemical variability distinguishing these two molecules is C(9). Changes there might be expected to influence primarily ring conformation and α-chain/ring junction geometry. The ring conformation (Table 4) of PGE$_2$ is best described as a C(9) half-chair; *i.e.* there is an approximate diad axis along the O(9)=C(9) carbonyl bond. The ring conformation of PGF$_{2\beta}$ is best described as a C(12) envelope with C(12) below* the plane of C(8)—C(11). It is interesting to note that PGF$_{2\beta}$, with ring substituents nominally tailor-made for a molecular diad axis (Beddell & Goodford, 1977; DeTitta, Erman, Fortier, Fronckowiak & Langs, 1977) through C(10) and the

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* The term specifically refers to the view in Fig. 1; below the cyclopentane ring corresponds to its α face; above the ring corresponds to its β face.

Table 4. *Ring asymmetry parameters for PGE$_2$ and PGF$_{2\beta}$*

The asymmetry parameters (Duax, Weeks & Rohrer, 1976) give a measure of the deviation from ideal half-chair (ΔC_2) and ideal envelope (ΔC_s) symmetry at each potential site on the cyclopentane ring. Small values, such as $\Delta C_s = 1\cdot 8°$ at C(12) for PGF$_{2\beta}$, indicate small departures from ideal symmetry. The minimum values for PGE$_2$ and PGF$_{2\beta}$ are underlined.

ΔC_2	PGE$_2$	PGF$_{2\beta}$	ΔC_s	PGE$_2$	PGF$_{2\beta}$
C(8)	35·5°	49·7°	C(8)	33·6°	30·1°
C(9)	<u>3·3</u>	17·3	C(9)	43·1	47·0
C(10)	30·3	21·7	C(10)	37·2	46·1
C(11)	52·3	52·4	C(11)	15·2	27·2
C(12)	54·3	63·1	C(12)	10·9	<u>1·8</u>

midpoint of the C(8)—C(12) bond, is devoid of such symmetry.

A critical distinction in conformation between PGF$_{2\beta}$ and PGE$_2$ is made at the C(8) ring/chain junction. In PGE$_2$ the junction geometry is ±synclinal; the torsion angles C(6)—C(7)—C(8)—C(9) and C(6)—C(7)—C(8)—C(12) are −60·8 and +62·4° respectively. In contrast, the PGF$_{2\beta}$ junction geometry is +synclinal/antiperiplanar; corresponding torsion angles are +53·7 and +172·2° respectively. The ±*sc* geometry of PGE$_2$ positions the *cis* unsaturation below the cyclopentanone ring; the +*sc/ap* geometry of PGF$_{2\beta}$ positions the *cis* unsaturation within the plane of the cyclopentanol ring. The +*sc/ap* junction geometry of PGF$_{2\beta}$ has been observed in two crystallographically independent molecules of the C(9) epimer PGF$_{2\alpha}$(Langs, Erman & DeTitta, 1977) and in two crystallographically independent molecules of (15R)-15-methyl-PGF$_{2\alpha}$ p-iodophenacyl ester (Chidester & Duchamp, 1974). Five independent observations of the +*sc/ap* junction geometry suggest that it is a preferred conformation. To understand why PGE$_2$ might adopt an atypical junction conformation a modeling experiment was performed. The molecular structure of PGE$_2$ was computer generated from the crystallographic coordinates (Table 2) and the α chain was rotated about the C(7)—C(8) bond until the junction geometry of PGF$_{2\beta}$ [torsion angle C(6)—C(7)—C(8)—C(9) = 53·7°] was achieved. The resulting structure is shown in Fig. 3. Calculation of non-bonded intramolecular distances revealed that, if PGE$_2$ were to adopt the more common +*sc/ap* junction geometry, a 2·81 Å contact between O(9) and C(6) would result. The 2·81 Å value should be compared with the 3·31 Å value which is the observed C(6)$\cdots$O(9) separation in PGE$_2$, and with $\sim$3·32 Å which is the sum of the van der Waals radii (Pauling, 1960). Therefore PGE$_2$ is precluded from the preferred +*sc/ap* junction geometry. It should be noted, however, that the reverse is not true; PGF$_{2\beta}$ is not excluded on grounds of C(6)$\cdots$O(9) steric interaction from the ±*sc* junction geometry of PGE$_2$.

Fig. 3. PGE$_2$ with the +sc/ap C(8) junction geometry of PGF$_{2\beta}$ and the resulting C(6)···O(9) contact. Note further the serious disruption of the hairpin shape in this conformation.

The conformational consequences of the ±sc geometry of PGE$_2$ appear to extend along the distal ω chain as well as along the proximal α chain. The C(8)–C(7)–C(6)–C(5) and C(6)–C(5)–C(4)–C(3) torsion angles for PGE$_2$ are −126·7 and −99·4° respectively; in PGF$_{2\beta}$ these angles are +140·8 and −168·6° respectively. In both molecules the moiety C(5) through O(1B) of the α chain is fully extended. The C(12) ring/chain junction geometries of the two molecules are very similar; they are ±anticlinal (±ac) with torsion angles C(8)–C(12)–C(13)–C(14) and C(11)–C(12)–C(13)–C(14) of −126·1 and +112·8° for PGE$_2$, −128·6 and +115·3° for PGF$_{2\beta}$, respectively. In both molecules the ω chains turn in towards the α chains at C(15); the torsion angles C(13)–C(14)–C(15)–C(16) are −111·1 and −119·2° for PGE$_2$ and PGF$_{2\beta}$ respectively. But the +sc/ap twist about the C(15)–C(16) bond in PGF$_{2\beta}$ [torsion angles C(14)–C(15)–C(16)–C(17) = 64·5°; O(15)–C(15)–C(16)–C(17) = −177·4°] is ±sc for PGE$_2$ (torsion angles −57·4 and +61·8°). Modeling experiments again show that if PGE$_2$ adopted the more typical +sc/ap C(15)–C(16) geometry the ω chain would run into the α chain; i.e. a C(2)···C(19) separation of ~3·5 Å would result.

The crystal structures of PGE$_2$ and PGF$_{2\beta}$ are illustrated in Figs. 4 and 5 which are projections down the crystallographic c and a axes respectively. The hydrogen-bonding patterns of the two molecules are very similar; in fact, in the c projections the packings appear to be indistinguishable. The a projection shows the additional O(9)–H···O(11)' hydrogen bond in PGF$_{2\beta}$ and the differing chain orientations of the molecules. A common feature of the hydrogen bonding is the simultaneous interaction of the O(11) and O(15) hydroxyl groups of a single PG with a carboxylic acid group of a neighboring PG to form a 12-atom hydrogen-bond ring. Starting at O(11) there is an O(11)–H···O(1A)=C(1)–O(1B)–H···O(15) hydrogen bond followed by an O(15)–H···O(9)' hydrogen bond [and then an O(9)'–H···O(11)'' hydrogen bond

Fig. 4. Crystal structures of (a) PGE$_2$ and (b) PGF$_{2\beta}$ viewed down the crystallographic c axes. Note the hydrogen-bond ring formed by the oxygens O(11) and O(15) of one molecule and the carboxylic acid group of a neighboring molecule.

Fig. 5. Crystal structures of (a) PGE$_2$ and (b) PGF$_{2\beta}$ viewed down the crystallographic a axes. Note the additional hydrogen bond (length 2·76 Å) in the PGF$_{2\beta}$ structure between O(9) of one molecule and O(11) of a second molecule one cell removed in the a direction.

in PGF$_{2\beta}$]. The hydrogen bonding in PGE$_2$ links molecules into sheets; the additional hydrogen bond in PGF$_{2\beta}$ links the sheets into a three-dimensional network.

Discussion

From an inspection of Dreiding-type models, prostaglandins may appear to be 'floppy' molecules. They

have 12 to 13 single bonds in their side chains, and cyclopentane rings capable of restricted flexion. Murakami & Akahori (1974, 1977) describe calculations, based primarily on nonbonded and electrostatic interactions, which suggest that as many as 315 distinct conformers are possible for PGF$_{1\beta}$, and yet, with the notable exception of PGB$_1$, every prostaglandin studied to date by diffraction techniques can be characterized as hairpin shaped.

The inherent stability of the hairpin or aligned conformation for prostaglandins has been traced in part to the dispersion-force energy of attraction between the α and ω side chains (Rabinowitz, Ramwell & Davison, 1971; Hoyland & Kier, 1972). Model studies on PGE$_1$ suggest dispersion terms in the total-energy equation of the order of 20–30 kJ mol^{-1}. The disruption of the hairpin shape would be energetically unfavorable and therefore its preservation may be considered a driving force which determines the ultimate conformation of a prostaglandin. Variations within the hairpin motif may be accommodated by the large number of σ bonds (capable of rotation) and the cyclopentane ring (capable of pseudorotation) without seriously disturbing the alignment of the side chains.

The conformation of the prostaglandin skeleton of PGF$_{2\beta}$ is quite similar to that observed for PGF$_{2\alpha}$ (Langs, Erman & DeTitta, 1977) and the p-iodophenacyl ester of 15-methyl-PGF$_{2\alpha}$ (Chidester & Duchamp, 1974) and for the purposes of this discussion is taken as the reference conformation. Attention should be focused on the C(9)—O(9) bond, the nature of which distinguishes PGE$_2$ from PGF$_{2\beta}$. Upon oxidation of the β-hydroxyl bond of PGF$_{2\beta}$ the oxygen atom O(9) moves approximately* 1·0 Å towards the cyclopentane ring plane. An O(9)$\cdots$C(6) contact of 2·81 Å results, destabilizing the $+sc/ap$ C(8) junction geometry. For PG$_1$ compounds the $+sc/ap$ junction geometry with C(6) antiperiplanar to either C(9) or C(12) is calculated to be a minimum-energy conformation (Hoyland & Kier, 1972). The junction geometry with C(6) antiperiplanar to C(9) would alleviate the short C(6)$\cdots$O(9) contact inherent in the arrangement C(6) antiperiplanar to C(12), but produces a short C(6)$\cdots$C(13) contact (3·1 Å) in the case of 5-cis-unsaturated PGE$_2$. Denied both PG$_1$ minimum-energy $+sc/ap$ junction arrangements, a $\pm sc$ junction geometry is assumed. Once a commitment is made to a C(8) junction geometry which has the serious potential to disrupt the hairpin shape, dispersion forces step in to correct the situation. The bonds flanking the cis unsaturation and the C(15)—C(16) bond twist to maintain the proximity of the chains.

The resulting PGE$_2$ conformation is visually distinct (Fig. 2) from that of PGF$_{2\beta}$, although the hairpin shape
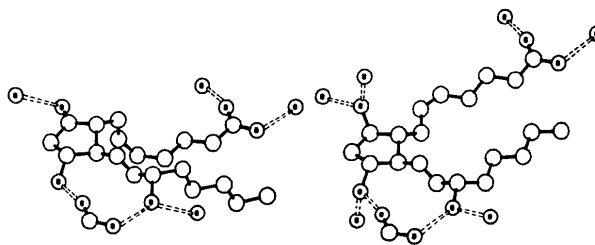
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* The value is calculated relative to the least-squares fit of atoms C(7) through C(16) described in the text.

Fig. 6. The hydrogen-bond neighborhood of PGE$_2$ (left) and PGF$_{2\beta}$ (right). The C(7)—C(16) moieties (see text) of the two molecules are oriented in a similar arbitrary view. Note the hydrogen-bond ring formed by the carboxylic acid group with O(11) and O(15).

has been conserved. A group such as the carboxylic acid function shifts more than 4 Å relative to a fixed C(7)-through-C(16) moiety, O(9) not only changes its chemical character but also moves 1·0 Å relative to the fixed moiety, and yet the hairpin shape is not seriously disturbed. In the process a significantly less-planar prostaglandin results. Calculation of the least-squares plane fit to all 25 nonhydrogen atomic positions for PGF$_{2\beta}$ yields a root-mean-square (r.m.s.) displacement of 0·32 Å and a maximum displacement of 0·86 Å from that plane; for PGE$_2$ similar calculations yield a r.m.s. displacement of 0·66 Å and a maximum displacement of 1·44 Å from the plane.

It is likely that some part of the recognition and/or interaction process between prostaglandins and their receptors involves hydrogen bonding between the various amino acid side groups of the receptor and the oxygenic functions of the prostaglandin molecule. In Fig. 6, PGE$_2$ and PGF$_{2\beta}$ are shown with the oxygenic functions which constitute their immediate hydrogen-bond neighborhoods in their respective crystal structures. In both molecules a neighboring carboxylic acid group, such as might be found on a proximal glutamic or aspartic acid residue, is found to bind both O(11) and O(15) of a single prostaglandin into a hydrogen-bonded ring. In this light it is interesting to note that a hydroxyl group such as might be found on a proximal tyrosine or serine residue can also serve as a 'reverse bidentate' hydrogen-bond ligand, at least for PGE$_1$ as seen by Spek (1977). Inspection of Fig. 6 further suggests that if PGE$_2$ and PGF$_{2\beta}$ were bound by a fixed carboxylic group on the receptor, the O(9) and carboxylic acid oxygens O(1A) and O(1B) of the two molecules could not bind the same constellation of hydrogen-bond donors and acceptors.

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The Structure of Deuterated Cytosine Monohydrate at 82 K by Neutron Diffraction

BY H. P. WEBER AND B. M. CRAVEN

Department of Crystallography, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA

AND R. K. MCMULLAN

Chemistry Department, Brookhaven National Laboratory, Upton, Long Island, New York 11973, USA

Abstract

At 82 K, deuterated cytosine monohydrate ($C_4H_2D_3$-$N_3O.D_2O$) is monoclinic, space group $P2_1/c$, with four molecules per unit cell and lattice parameters $a = 7.713$ (1), $b = 9.830$ (4), $c = 7.505$ (4) Å and $\beta = 100.52$ (2)°. A structure refinement to $R_w(F^2) = 0.049$ has been carried out using neutron intensities for 1993 reflections measured at wavelength $\lambda = 0.9094$ (1) Å and 270 at $\lambda = 1.0441$ (1) Å. At the shorter wavelength there appeared to be double Bragg reflection of 2λ neutrons from the Be monochromator. All atoms, particularly H(D), are more accurately located than in previous X-ray determinations at 298 K, to give