Acta Cryst. (1980). B**36**, 1099–1103

The Structure of Thromboxane B_2

BY SUZANNE FORTIER, MARY G. ERMAN, DAVID A. LANGS AND GEORGE T. DETITTA

Medical Foundation of Buffalo, Inc., 73 High Street, Buffalo, NY 14203, USA

(*Received* 3 *July* 1979; *accepted* 22 *January* 1980)

Abstract

Thromboxane B_2, $C_{20}H_{34}O_6$, crystallizes in space group $P2_1$ with cell constants $a = 9{\cdot}971$ (3), $b = 40{\cdot}45$ (2), $c = 5{\cdot}510$ (2) Å, $\beta = 102{\cdot}5$ (1)°, $Z = 4$. The intensity data were limited; only 1227 reflections were observed out of a total of 2272 measured within a Bragg angle of 50°. The structure was determined by Fourier and direct methods and refined by full-matrix least squares to a final residual of 0·145. Both thromboxane molecules were found to be similar in conformation except for the orientation of the carboxylic acid chains which are bent in opposite directions.

Introduction

Thromboxanes, prostaglandins and prostacyclin are hormones formed in cells from polyunsaturated fatty acids which are cleaved from the cell membrane and transformed into a common highly reactive endocyclic peroxide precursor. Many of these hormones exhibit opposing physiological activities in spite of similar chemical and even conformational characteristics. For example, thromboxane A_2 (TXA_2) is a potent blood-platelet aggregator (Hamberg, Svensson & Samuelsson, 1975) while prostacyclin is an equally potent disaggregator (Moncada, Gryglewski, Bunting & Vane, 1976). Thromboxane B_2 (TXB_2) is a stable hydrolysis product (Hamberg & Samuelsson, 1974) of TXA_2; it possesses none of the aggregator properties of TXA_2 and is a moderately active bronchodilator (Wasserman & Griffin, 1977) in its own right. The chemical line formulae and atomic numbering convention for TXA_2 and TXB_2 are indicated in Fig. 1.

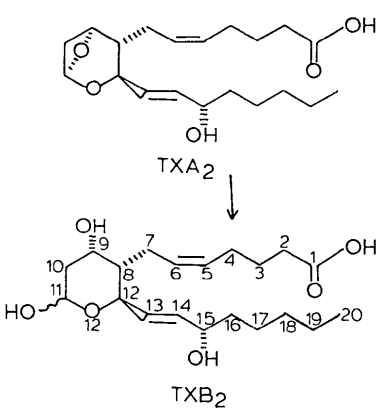

Fig. 1. Chemical line formulae and atomic numbering convention for TXA_2 and TXB_2.

Experimental

Crystals of TXB_2 suitable for diffraction were grown from ethyl acetate by slow evaporation at 292 ± 1 K. Outside this temperature range the crystals were either very small or twinned. The crystals are colorless monoclinic laths. At slightly higher temperatures clusters of fine needles and even very thin plates were observed. The diffraction data did not extend far beyond a Bragg angle of 50°. Lattice constants were determined on a CAD-4 diffractometer by means of a least-squares fit of 25 chosen reflections whose diffraction maxima were measured with Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å) in the 2θ range of 17 to 48°. The cell constants are $a = 9{\cdot}971$ (3), $b = 40{\cdot}45$ (2), $c = 5{\cdot}510$ (2) Å, $\beta = 102{\cdot}5$ (1)°, $Z = 4$, $d_{calc} = 1{\cdot}137$, d_{obs} (flotation) = 1·141 Mg m^{-3}. The space group is $P2_1$ with two molecules of TXB_2 in the asymmetric unit.

A single crystal of dimensions 0·12 × 0·12 × 0·40 mm was used for the intensity measurements which were recorded with a CAD-4 diffractometer, with Cu $K\alpha$ radiation and Ni filters. The scan width for the individual reflections was adjusted as $\Delta\theta = 0{\cdot}8° + 0{\cdot}14° \tan\theta$. A total of 2272 independent reflections were recorded to a Bragg angle of 50°; 1227 of these were regarded as observable ($I > 2\sigma I$). The intensity data were reduced to structure factors without an absorption correction ($\mu = 0{\cdot}680$ mm^{-1}). The average decrease in the intensities of four reference standards approached 15% during the period of the data collection.

Structure determination and refinement

Direct-methods procedures were used to determine the crystal structure. Normalized $|E|$ amplitudes were

0567-7408/80/051099-05$01.00

scaled with the aid of a Debye group scattering factor (Debye, 1915) which represented the thromboxane molecule as a small number of conformationally invariant fragments. The initial attempts to obtain a phase solution were unsuccessful in that tangent refinement produced no phase sets for which the NQEST figure of merit (DeTitta, Edmonds, Langs & Hauptman, 1975) was greater than 20% of its expected value (−0·25). These phasing difficulties were thought to arise from an overabundance of inconsistent π-quadruple relations among the triple-phase invariants (Viterbo & Woolfson, 1973) as it was noted that many of the largest E values had common h and l indices with k being both even and odd. The largest 2000 structure products were examined for imbedded π-quadruple relationships and 420 triples found entering into such relationships were discarded from the convergence mapping procedure. Tangent refinement now produced one solution for which NQEST was −0·11. The resultant E map revealed a fragment centered on the pyranose ring of one of the two independent molecules. Although there were at least six interpretations as to how the hydroxyl functions and aliphatic side chains fit to the ring, one such interpretation fitted the contiguous 14-atom portion of the molecule from C(7) to C(16). It was erroneously assumed that O(9) was equatorial to the pyranose ring rather than axial as expected. Attempts to elucidate the entire structure by tangent recycling procedures (Karle, 1968) were unsuccessful and led us to the conclusion that the molecular fragment was misplaced in the unit cell. Alternative positions of the fragment suggested by correlating translation functions (Langs, 1975) with suitably weighted NQEST maps (Fortier, 1979) were unsuccessful. It appeared that the original position of the fragment was considerably more likely than any of the alternative positions tested. The turning point in the structure determination came when the F map computed from the original 14-atom fragment was closely examined to disclose a chemically tenable fragment of seven atoms for the second molecule which permitted the eventual completion of the structure by straight Fourier methods.

The early stages of full-matrix least-squares refinement required sufficiently large shifts in the temperature factors and overall scale such that the weighting scheme based on counting statistics could not bring about convergence with the observed data. Unit weights were initially used to refine the structure and even then it was necessary to dampen the computed shifts by half. The nonhydrogen atoms of the structure were refined to isotropic convergence at which point the H atoms bonded to C were incorporated into the structure factor calculations at positional values computed from the geometry of the molecules. The temperature factors of the H atoms were set approxi-

Table 1. *Fractional coordinates and thermal parameters for the TXB_2 β-tail (molecule 1) and α-tail (molecule 2) scorpion conformers*

	β-Tail conformer				α-Tail conformer			
	x	*y*	*z*	*B* (Å²)	*x*	*y*	*z*	*B* (Å²)
C(1)	0·332 (3)	1·322 (1)	0·399 (5)	5·9 (6)	0·852 (3)	0·775 (1)	0·195 (6)	8·0 (8)
C(2)	0·424 (3)	1·338 (1)	0·611 (5)	5·8 (6)	0·942 (3)	0·760 (1)	0·402 (6)	7·9 (8)
C(3)	0·337 (3)	1·363 (1)	0·725 (5)	6·7 (7)	0·861 (4)	0·735 (1)	0·534 (7)	9·0 (9)
C(4)	0·430 (3)	1·382 (1)	0·939 (5)	6·7 (7)	0·966 (4)	0·717 (1)	0·748 (7)	10·0 (10)
C(5)	0·353 (3)	1·407 (1)	1·067 (3)	6·0 (6)	0·898 (3)	0·696 (1)	0·898 (6)	6·9 (7)
C(6)	0·385 (3)	1·435 (1)	1·152 (5)	6·0 (6)	0·944 (3)	0·668 (1)	0·999 (5)	6·3 (7)
C(7)	0·516 (2)	1·450 (1)	1·146 (4)	3·5 (5)	1·064 (3)	0·647 (1)	0·945 (6)	7·1 (7)
C(8)	0·517 (2)	1·472 (1)	0·908 (4)	4·0 (5)	1·052 (2)	0·610 (1)	0·969 (4)	4·0 (5)
C(9)	0·396 (2)	1·494 (1)	0·838 (4)	3·0 (4)	0·927 (2)	0·596 (1)	0·807 (4)	4·8 (5)
C(10)	0·400 (2)	1·517 (1)	0·612 (4)	4·4 (5)	0·923 (3)	0·561 (1)	0·816 (5)	5·6 (6)
C(11)	0·545 (2)	1·531 (1)	0·642 (4)	3·5 (5)	1·059 (3)	0·545 (1)	0·785 (5)	6·7 (7)
C(12)	0·644 (2)	1·490 (1)	0·929 (4)	4·2 (5)	1·185 (2)	0·591 (1)	0·925 (4)	4·0 (5)
C(13)	0·775 (2)	1·472 (1)	0·981 (4)	3·1 (4)	1·308 (2)	0·602 (1)	1·113 (4)	4·1 (5)
C(14)	0·874 (2)	1·475 (1)	1·182 (5)	5·1 (6)	1·423 (2)	0·615 (1)	1·061 (1)	5·1 (6)
C(15)	1·010 (3)	1·458 (1)	1·252 (5)	5·4 (6)	1·546 (3)	0·625 (1)	1·267 (6)	7·7 (8)
C(16)	1·027 (3)	1·436 (1)	1·485 (6)	7·5 (8)	1·592 (4)	0·657 (1)	1·203 (8)	11·5 (11)
C(17)	0·933 (4)	1·411 (1)	1·489 (9)	11·9 (12)	1·493 (6)	0·685 (1)	1·18 (1)	16·0 (18)
C(18)	0·904 (6)	1·387 (1)	1·33 (1)	15·6 (17)	1·455 (7)	0·697 (2)	1·37 (1)	17·7 (19)
C(19)	0·813 (6)	1·355 (2)	1·39 (1)	17·1 (18)	1·360 (8)	0·729 (2)	1·34 (2)	22·8 (28)
C(20)	0·785 (5)	1·335 (1)	1·20 (1)	14·9 (16)	1·33 (1)	0·754 (3)	1·22 (2)	19·4 (31)
O(1*A*)	0·215 (2)	1·326 (0)	0·306 (4)	7·9 (5)	0·734 (2)	0·774 (1)	0·130 (4)	9·0 (6)
O(1*B*)	0·411 (2)	1·302 (1)	0·268 (4)	9·0 (6)	0·928 (3)	0·797 (1)	0·095 (5)	10·3 (7)
O(9)	0·390 (2)	1·516 (0)	1·036 (3)	4·9 (3)	0.930 (2)	0·606 (1)	0·534 (3)	6·8 (4)
O(11*A*)					1·051 (5)	0·541 (1)	0·573 (9)	6·2 (12)
O(11*B*)	0·555 (2)	1·547 (0)	0·413 (3)	5·3 (4)	1·066 (3)	0·510 (1)	0·760 (5)	5·9 (6)
O(12)	0·644 (1)	1·507 (0)	0·693 (3)	3·9 (3)	1·167 (2)	0·559 (0)	0·948 (3)	4·7 (3)
O(15)	1·112 (2)	1·482 (1)	1·288 (4)	7·5 (5)	1·655 (2)	0·603 (1)	1·267 (4)	7·5 (5)

mately equal to those of the atoms to which they were attached. The H coordinates and temperature factors were adjusted from time to time as refinement progressed. Refinement with unit weights converged with $R = 0{\cdot}151$. Refinement with statistical weights now proved stable and converged with $R = 0{\cdot}172$ and $R_w = 0{\cdot}123$ for the observed data. It was noted, however, that the geometry which had been reasonable at the end of the aliphatic chains of the two molecules deteriorated as a number of atoms were shifted by more than 0·5 Å. A simple pivot-point weighting scheme was tested which proved adequate ($w = F_{obs}/A$ if $F_{obs} < A$; $w = A/F_{obs}$ if $F_{obs} > A$; where an A value of 20 was found to minimize $\langle W\Delta F^2 \rangle$ for the median reflection group based on $\sin\theta/\lambda$). Isotropic refinement converged* with $R = 0{\cdot}145$ and $R_w = 0{\cdot}165$ for 212 parameters. Additional refinement in which the nonhydrogen atoms with isotropic temperature factors less than 10 Å^2 were allowed to refine anisotropically converged to $R = 0{\cdot}105$ and $R_w = 0{\cdot}114$ for 431 parameters. Although Hamilton's (1965) significance test strongly supports the vibrational anisotropy of this latter refinement ($\mathscr{R}_{219,796,0{\cdot}005} = 1{\cdot}151$), it must be remarked that the geometrical improvement of the model appears dubious. The mean and standard deviations of the 34 chemically equivalent C–C single bonds for the isotropic (1·485 ± 0·093 Å) and anisotropic (1·479 ± 0·105 Å) refinement do not correlate with the expected reduction in the errors in the atomic coordinates commensurate with a 30% reduction in the residual (Booth, 1945; Luzzati, 1952). The R-factor ratio test might not be justified in view of the low overdeterminacy in the latter refinement, *i.e.* 2·8 *vs* 5·8 for the isotropic refinement, and the rather high residual value at which anisotropic refinement was attempted. We shall therefore only consider the results of the isotropic refinement. The final positional and thermal parameters for the nonhydrogen atoms of the structure are summarized in Table 1; the positions of the hydroxyl protons were not determined. The bond distances and angles are shown in Fig. 2 and the torsion angles are given in Table 2.

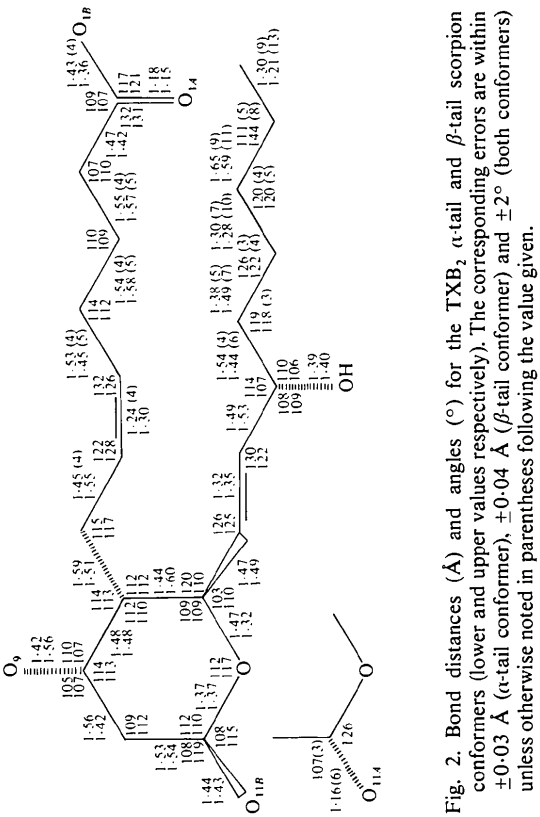

Fig. 2. Bond distances (Å) and angles (°) for the TXB_2 α-tail and β-tail scorpion conformers (lower and upper values respectively). The corresponding errors are within ±0·03 Å (α-tail conformer), ±0·04 Å (β-tail conformer) and ±2° (both conformers) unless otherwise noted in parentheses following the value given.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34943 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Torsion angles* (°) *for* TXB_2

Torsion angles are given to the nearest whole degree. Estimated standard errors in these values range from 2·5 to 7·0° at the C(20) chain ends. The α-tail values appear first followed by the β-tail values in parentheses.

O(1A)	C(1)	C(2)	C(3)	3(8)	O(1B)	C(1)	C(2)	C(3)	172(178)
C(1)	C(2)	C(3)	C(4)	-177(176)	C(2)	C(3)	C(4)	C(5)	-179(174)
C(3)	C(4)	C(5)	C(6)	-142(145)	C(4)	C(5)	C(6)	C(7)	-1(-13)
C(5)	C(6)	C(7)	C(8)	92(-148)	C(6)	C(7)	C(8)	C(9)	44(58)
C(6)	C(7)	C(8)	C(12)	172(-177)	C(7)	C(8)	C(9)	O(9)	60(57)
C(7)	C(8)	C(9)	C(10)	177(175)	C(7)	C(8)	C(12)	C(13)	55(60)
C(7)	C(8)	C(12)	O(12)	174(180)	C(8)	C(9)	C(10)	C(11)	-43(-48)
C(8)	C(12)	C(13)	C(14)	-116(-125)	C(8)	C(12)	O(12)	C(11)	65(61)
C(9)	C(10)	C(11)	O(11B)	169(-172)	C(9)	C(10)	C(11)	O(11A)	(-89)
C(9)	C(10)	C(11)	O(12)	50(51)	C(9)	C(8)	C(12)	C(13)	-176(-172)
C(9)	C(8)	C(12)	O(12)	-57(-52)	O(9)	C(9)	C(10)	C(11)	77(69)
O(9)	C(9)	C(8)	C(12)	-68(-70)	C(10)	C(9)	C(8)	C(12)	49(48)
C(10)	C(11)	O(12)	C(12)	-62(-61)	C(11)	O(12)	C(12)	C(13)	-166(-179)
O(11B)	C(11)	O(12)	C(12)	178(161)	O(11A)	C(11)	O(12)	C(12)	(78)
C(12)	C(13)	C(14)	C(15)	180(-179)	O(12)	C(12)	C(13)	C(14)	122(117)
C(13)	C(14)	C(15)	C(16)	-116(-135)	C(13)	C(14)	C(15)	O(15)	121(110)
C(14)	C(15)	C(16)	C(17)	57(61)	C(15)	C(16)	C(17)	C(18)	57(69)
O(15)	C(15)	C(16)	C(17)	178(178)	C(16)	C(17)	C(18)	C(19)	166(174)
C(17)	C(18)	C(19)	C(20)	175(-29)							

Molecular anomerization

In the course of the structure refinement it was noted that the temperature factor of O(11) in the second molecule remained anomalously high. Difference syntheses examined at this time revealed that the O(11) hydroxyl group was disordered with both axial and equatorial orientations. This observation was reasonable since TXB_2 is an anomeric sugar that permits such an equilibrium. The occupancies of the two sites were adjusted during the refinement to equalize the two temperature factors. The β or equatorial anomer remained predominant with an occupancy of 0·65, the α or axial anomer being 0·35. This coincidentally corresponds to the 2:1 ratio noted for the unspecified methoxy TXB_2 epimers reported earlier (Hamberg, Svensson & Samuelsson, 1975). No anomeric disorder was detectable for the first molecule which retained an 11β-hydroxy configuration.

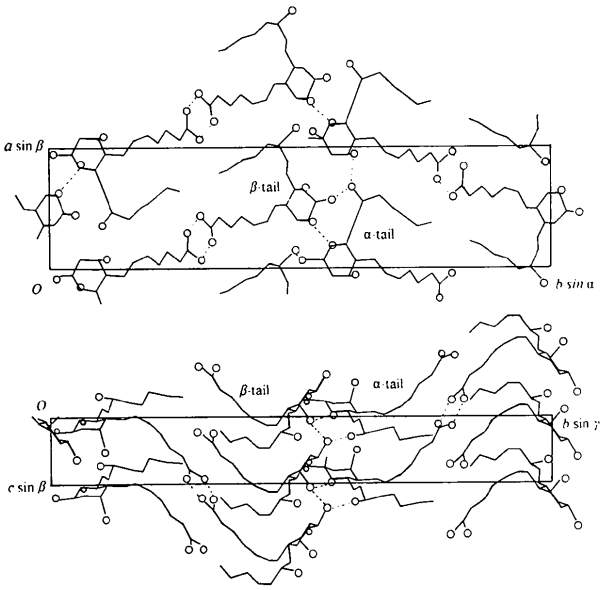

Fig. 3. Projections of the TXB_2 structure down the *c* axis (top) and *a* axis (bottom); α- and β-tail conformers are indicated.

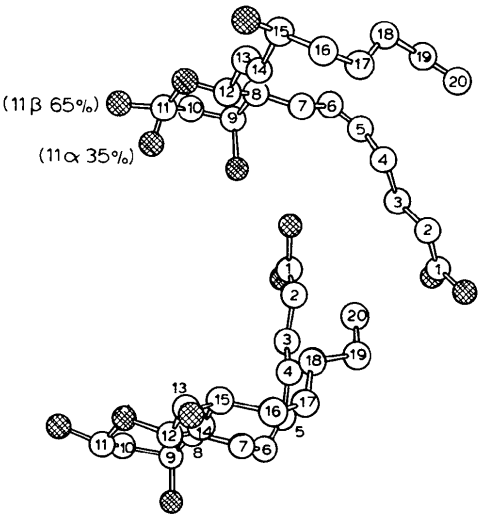

Fig. 4. Perspective illustrations for the α-tail (top) and β-tail (bottom) scorpion conformers.

The thromboxane molecules associate as carboxylic acid dimers in the crystal structure, as can be seen in Fig. 3. Apart from this the structure is largely held together by head-to-head interactions of the hydroxylic pyranose ends of the molecules as shown. This latter region defines a two-dimensional hydrogen-bonding network in the *ac* plane.

Molecular conformation

The molecular conformations of the two TXB_2 hormone molecules are shown in the perspective illustration of Fig. 4. It may be noted from Table 2 that all but three of the 35 torsion angles of the two conformers agree to within an average angular discrepancy of only 7°. The torsion angles flanking the *cis*-C(5)=C(6) bond differ between the two conformers and turn the ends of the carboxyl chains in opposite directions approximately normal to the mean plane of the pyranose ring of the molecules. The arching of the carboxyl side chain for both conformers is reminiscent of the 'scorpion' configuration described for tyrosine ethyl ester (Pieret, Durant, Griffe, Germain & Debaerdemaeker, 1970). It may be useful to refer to these two forms as the α-tail and β-tail scorpion conformers which would denote the facial side of the molecule toward which the carboxylic acid side chain turns (see Fig. 4 for clarification of the stereochemical convention). Although the overall conformations of the aliphatic or ω side chains are remarkably similar from C(12) to C(19), the observed conformations are unusual in that the C(15)—C(16)—C(17)—C(18) torsion angles are (+)-synclinal rather than *trans*-planar as had been anticipated from structural comparisons with related prostaglandin compounds. All known structures of biologically active prostaglandin hormones adopt what is described as a 'hairpin' conformation (Andersen, Ramwell, Loevey & Johnson, 1976) requiring parallel side-chain alignment of approximately equal length. The thromboxane conformers cannot be so described. This fundamental distinction between prostaglandin and thromboxane conformation may be important in understanding the pattern of variation of physiological activities induced by a number of thromboxane analogs (Falardeau, Hamberg & Samuelsson, 1976; Needleman, Minkes & Raz, 1976; Langs, Fortier, Erman & DeTitta, 1979).

Discussion

An examination of physiological data measured for different TXA analogs suggests a number of probable structure–activity relationships with the assumption that the side-chain conformations of TXA compounds are similar to those of their corresponding TXB hydrolysis products. Direct conformational investigation of the TXA structure is unlikely in view of the extremely short half lives ($\simeq$ 30 s) of these hormones (Hamberg, Svensson & Samuelsson, 1975). Although the chemistry and binding preferences of the pyranoside head groups of TXA and TXB compounds are sufficiently different to insure the differentiation of these hormones at the molecular level, the ring-junction geometries of the side chains to the head groups are constrained so as to suggest that the side-chain conformations of related TXA and TXB compounds are similar.

An examination of the biological properties of four thromboxane compounds (Needleman, Minkes & Raz, 1976) revealed that TXA_2 and TXA_3 possessed vasoconstrictive activity while TXA_2 and nor-2-TXA_2 caused blood-platelet aggregation. TXA_1 was found to be inactive in both tests, to suggest that the presence of a *cis*-C(5)=C(6) bond in the carboxyl chain was critical for encoding activity for both processes. The *cis*-Δ^5 unsaturation may be important insofar as it permits the bending of the carboxylic acid side chain to form α-tail and β-tail conformers. Given that nor-2-TXA_2 may be naturally disposed to form an intramolecular hydrogen bond between O(9) and the carboxylate group at C(3) in an α-tail conformation, one might question whether α-tail scorpion conformers are required for vasoconstrictive activity. It may be noted, however, that the presence of a *cis*-Δ^{17} unsaturation in the aliphatic or ω chain of TXA_3 does not noticeably alter the side-chain van der Waals contacts of one scorpion conformer relative to the other to suggest a predictable shift in the conformational equilibrium in one direction or the other. The hypothesis that there is a simple α-tail *vs* β-tail conformational preference to encode blood-platelet aggregation and arterial vasoconstriction respectively requires further testing, both by biological-activity studies and conformational analysis.

Apart from their physiological activities, thromboxanes are many times more resistant to biodegradation by 15-hydroxy prostaglandin dehydrogenase (PGDH) than are the biologically active prostaglandins (Kindahl, 1977; Roberts, Sweetman, Morgan, Payne & Oates, 1977). The observation that even prostacyclin compounds are metabolized by PGDH (Sakai, 1979) has suggested that the enzyme is rather non-specific with regard to recognition of the hormones and minimally requires an intact ω chain and head group to establish α and β faces for the enzyme substrate. It was proposed in a structural study of PGB_1 (DeTitta, 1976) that β-facial abstraction of H(15) by NAD^+ is a necessary geometrical requirement for prostaglandin oxidation in the hairpin conformation. The crystal structure of lactate dehydrogenase (Eventoff, Rossmann, Taylor, Torff, Meyer, Keil & Kiltz, 1977) supports the conjecture that NAD^+ must lie above the β face of the bound substrate molecule in PGDH. Thus although prostacyclin is not a hairpin conformer, it must possess an ω-chain conformation permitting β-facial abstraction of H(15). It is now apparently clear that the (+)-*gauche* twist in the ω chains of TXB_2 scorpion conformers would sterically hinder the approach of the nicotinamide group of NAD^+ to abstract H(15) from the β face of the molecule, as the end of the ω chain would be extending in that general direction. The observation that TXB_2 is unfavorably oxidized to the 15-keto metabolite compared to other PGDH substrates (Dawson, Boot, Cockerill, Mallen & Osborne, 1976) indeed admits that TXB_2 can be induced to adopt a hairpin conformation similar to substrate prostaglandins but that the TXB_2 scorpion conformers are far more stable *vis à vis* the hairpin conformations than might have been imagined.

We wish to express our thanks to Drs G. M. Bundy and J. E. Pike of The Upjohn Company for offering the TXB_2 used in this study. Dr S. Hannessian made useful suggestions regarding the crystallization procedure and Dr D. C. Rohrer was instrumental in supervising the diffractometry and insuring the optimal precautions with regard to the data collection. This work was supported by Grant No. HL-15378 awarded by the National Heart, Lung and Blood Institute, DHEW.

References

ANDERSEN, N. H., RAMWELL, P. W., LOEVEY, E. M. & JOHNSON, M. (1976). *Advances in Prostaglandin and Thromboxane Research*. Vol. 1, edited by B. SAMUELSSON & R. PAOLETTI, pp. 271–289. New York: Raven.

BOOTH, A. D. (1945). *Philos. Mag.* **36**, 609–615.

DAWSON, W., BOOT, J. R., COCKERILL, A. F., MALLEN, D. N. B. & OSBORNE, D. J. (1976). *Nature (London)*, **262**, 699–702.

DEBYE, P. (1915). *Ann. Phys. (Leipzig)*, **46**, 809–823.

DETITTA, G. T. (1976). *Science*, **191**, 1271–1272.

DETITTA, G. T., EDMONDS, J. W., LANGS, D. A. & HAUPTMAN, H. (1975). *Acta Cryst.* A**31**, 472–479.

EVENTOFF, W., ROSSMANN, M. G., TAYLOR, S. S., TORFF, H.-J., MEYER, H., KEIL, W. & KILTZ, N.-H. (1977). *Proc. Natl Acad. Sci. USA*, **74**, 2677–2681.

FALARDEAU, P., HAMBERG, M. & SAMUELSSON, B. (1976). *Biochim. Biophys. Acta*, **441**, 193–200.

FORTIER, S. (1979). Unpublished results.

HAMBERG, M. & SAMUELSSON, B. (1974). *Proc. Natl Acad. Sci. USA*, **71**, 3400–3404.

HAMBERG, M., SVENSSON, J. & SAMUELSSON, B. (1975). *Proc. Natl Acad. Sci. USA*, **72**, 2994–2998.

HAMILTON, W. C. (1965). *Acta Cryst.* **18**, 502–510.

KARLE, J. (1968). *Acta Cryst.* B**24**, 182–186.

KINDAHL, H. (1977). *Prostaglandins*, **13**, 619–629.

LANGS, D. A. (1975). *Acta Cryst.* A**31**, 543–550.

LANGS, D. A., FORTIER, S., ERMAN, M. G. & DETITTA, G. T. (1979). *Nature (London)*, **231**, 237–238.

LUZZATI, V. (1952). *Acta Cryst.* **5**, 802–810.

MONCADA, S., GRYGLEWSKI, R. J., BUNTING, S. & VANE, J. R. (1976). *Nature (London)*, **263**, 663–665.

NEEDLEMAN, P., MINKES, M. & RAZ, A. (1976). *Science*, **193**, 163–165.

PIERET, A. F., DURANT, F., GRIFFE, M., GERMAIN, G. & DEBAERDEMAEKER, T. (1970). *Acta Cryst.* B**26**, 2117–2124.

ROBERTS, L. J., SWEETMAN, B. J., MORGAN, J. L., PAYNE, N. A. & OATES, J. A. (1977). *Prostaglandins*, **13**, 631–648.

SAKAI, K. (1979). ACS/CSJ Chemical Congress, Medicinal Chemistry Section, Abstract No. 1.

VITERBO, D. & WOOLFSON, M. M. (1973). *Acta Cryst.* A**29**, 205–208.

WASSERMAN, M. A. & GRIFFIN, R. L. (1977). *Eur. J. Pharmacol.* **46**, 303–313.