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Structures of the Configurational Isomers of 2,2′-Bis(3-chlorophenyl)-[3,3′-bi-1,3-thiazolidine]-4,4′-dione

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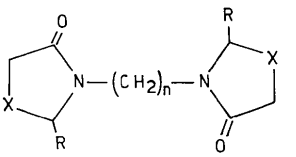
Abstract. *PA*, $C_{18}H_{14}Cl_2N_2O_2S_2$, $M_r = 425{\cdot}36$, triclinic, $P\bar{1}$ (after structure determination), $a = 11{\cdot}232\ (2)$, $b = 10{\cdot}465\ (2)$, $c = 8{\cdot}386\ (2)$ Å, $\alpha = 107{\cdot}07\ (3)$, $\beta = 83{\cdot}63\ (4)$, $\gamma = 98{\cdot}90\ (3)°$, $V = 928{\cdot}7\ (4)$ Å^3, $Z = 2$, $D_x = 1{\cdot}521$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 5{\cdot}27$ cm^{-1}, $F(000) = 436$, room temperature. Final conventional R value is 0·033 (wR = 0·041) for 2716 diffractometer-measured intensities with $I \geq 3\sigma(I)$. The molecular structure is characterized by the different conformations of the two thiazolidine rings, one of which is an envelope, and by opposite chirality of the two asymmetric C atoms. In the crystal structure both the enantiomers 2*S*,2′*R* and 2*R*,2′*S* are present. *PB*, $C_{18}H_{14}Cl_2N_2O_2S_2$, $M_r = 425{\cdot}36$, orthorhombic, *Pbcn*, $a = 7{\cdot}759\ (2)$, $b = 19{\cdot}625\ (4)$, $c = 12{\cdot}504\ (3)$ Å, $V = 1904{\cdot}0\ (6)$ Å^3, $Z = 4$, $D_x = 1{\cdot}483$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 5{\cdot}14$ cm^{-1}, $F(000) = 872$, room temperature. Final conventional R value is 0·049 (wR = 0·067) for 1334 diffractometer-measured intensities with $I \geq 3\sigma(I)$. Because the molecular structure has exact C_2 symmetry, the two phenyl rings are strictly parallel and the conformations (half chair) of the two thiazolidine rings are the same as well as the chirality of the two asymmetric C atoms. Nevertheless both enantiomers 2*R*,2′*R* and 2*S*,2′*S* are in the crystal.

Introduction. As part of our investigations on the anti-inflammatory, analgesic, antipyretic and antihistamine properties of some derivatives of the 3,3′-bi[1,3-thiazolidine]-4,4′-dione system, we performed (Previtera, Basile, Vigorita, Fenech, Occhiuto, Circosta & Costa De Pasquale, 1986; Vigorita, Previtera, Basile, Fenech, Costa De Pasquale, Occhiuto & Circosta, 1984; Bruno, Bombieri, Del Pra, Previtera, Vigorita & Basile, 1984) the synthesis, the physico-chemical and pharmacological characterization of bisthiazolidinones with general formula:



(I)

where $n = 0$ or 2; $X = S$ or SO_2 and R is an aryl residue.

According to Shen (1967) and Scherrer (1974), on the basis of their structural, electronic and pharmacological features, the examined derivatives of the 3,3′-bi[1,3-thiazolidine]-4,4′-dione system can be broadly defined as classical non-steroidal anti-inflammatory agents. A common property, reported for many of these classical agents, is the ability to inhibit prostaglandin synthetase (Scherrer, 1974). Several years ago, on the basis of observed structure–activity relationships for indomethacin analogues, an anti-inflammatory receptor site was hypothesized to consist of two non-coplanar hydrophobic regions and a cationic centre; in addition a related hypothetical receptor site was proposed from the shape of some anti-inflammatory benzoic acid derivatives (Gund & Shen, 1977, and references therein).

While crystal structure analysis of the purified enzyme (*i.e.* receptor) will no doubt give in due time the most definitive picture of the active site for the anti-inflammatory agents derived from the 3,3′-bi-[1,3-thiazolidine]-4,4′-dione system, we nevertheless expect that the knowledge of their geometry and conformation will prove useful in unifying and organizing results to date, in guiding further studies of the enzymes and in designing novel, specifically acting, anti-inflammatory drugs.

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We report here on the solid-state conformations of the configurational isomers of 2,2′-bis(3-chlorophenyl)-3,3′-bi[1,3-thiazolidine]-4,4′-dione as obtained from an accurate single-crystal X-ray analysis of two products (hereinafter *PA* and *PB*, respectively). These isomers differ in their pharmacological behaviour: *PA* displays acute anti-inflammatory analgesic and antipyretic activities whereas *PB* is not active (Vigorita *et al.*, 1984).

Experimental. *PA*: Crystals from methanol, crystal size 0·62 × 0·44 × 0·12 mm. Data collection with Philips PW1100 automated diffractometer with monochromated Mo $K\alpha$ radiation, 2θ-scan technique; 25 reflections with $10 < \theta < 13°$ used for refinement of cell dimensions; index ranges $-13 \le h \le 13$, $-11 \le k \le 11$, $0 \le l \le 9$, two reflections (121 and $3\bar{2}2$) measured after every 180 min of X-ray exposure time. Scan width 1·20°, scan speed 0·30° s^{-1}, total background measuring time 20 s; 2θ range 4–50°, total number of reflections measured 3522, 2716 reflections having $I \ge 3\sigma(I)$ used in the analysis, corrections for Lorentz and polarization effects. Structure solved by direct methods (Hull, Viterbo, Woolfson & Zhang, 1981) and refinement on F by a full-matrix least-squares procedure, with anisotropic thermal parameters for all non-H atoms, H atoms located by difference Fourier maps, refined isotropically. Refinement converged to $R = 0{\cdot}033$, $wR = 0{\cdot}041$, $S = 1{\cdot}38$, $w = 1/[\sigma^2(F_o) + 0{\cdot}001044(F_o)^2]$, $\Delta/\sigma < 0{\cdot}01$, residual electron density $\pm 0{\cdot}3$ e $Å^{-3}$.

PB: white transparent crystals from ethanol; diffractometer measurements and structure determination as for *PA* except: crystal size 0·24 × 0·28 × 0·52 mm; cell dimensions from 25 reflections in the range 8–16°; 1959 reflections measured, 1334 considered observed with $I \ge 3\sigma(I)$; index ranges $0 \le h \le 9$, $0 \le k \le 23$, $0 \le l \le 10$; two reflections (531 and 152) measured after every 180 min of X-ray exposure time. Refinement converged to $R = 0{\cdot}049$, $wR = 0{\cdot}067$, $S = 1{\cdot}39$, $w = 1/[\sigma^2(F_o) + 0{\cdot}003668(F_o)^2]$, $\Delta/\sigma < 0{\cdot}01$, residual electron density $\pm 0{\cdot}4$ e $Å^{-3}$. Scattering factors used in all structure-factor calculations were taken from *SHELX*76. Data processing and computation were carried out using *SHELX*76 program package (Sheldrick, 1976) and molecular illustrations were drawn with *ORTEP* (Johnson, 1976).

Discussion. The final positional parameters are given in Table 1* and the interatomic distances and interbond angles, with the e.s.d.'s calculated from the full variance–covariance matrix, are listed in Table 2. Perspective views of the molecular structures, with the atom-numbering schemes, are in Figs. 1 and 2 for *PA* and *PB*, respectively.

Table 1. *Atomic coordinates* ($\times 10^4$) *for non-*H *atoms and* U_{eq} ($\times 10^4$) *with e.s.d.'s in parentheses*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}(Å^2)
Compound *PA*				
Cl(1)	−725·3 (6)	549·6 (7)	2916 (1)	629 (3)
Cl(2)	−854·7 (6)	4117·9 (7)	6749 (1)	643 (3)
S(1)	4795·0 (6)	3263·7 (6)	3499·4 (7)	472 (2)
S(2)	2378·7 (6)	2988·1 (7)	10777·1 (7)	517 (2)
N(1)	4064 (1)	2829 (2)	6377 (2)	345 (6)
N(2)	3352 (2)	2560 (2)	7729 (2)	340 (6)
O(1)	5781 (2)	3116 (2)	7700 (2)	563 (7)
O(2)	3865 (2)	421 (2)	7107 (2)	519 (7)
C(1)	5290 (2)	3048 (2)	6455 (3)	399 (8)
C(2)	5915 (2)	3135 (3)	4817 (3)	523 (11)
C(3)	3501 (2)	2863 (2)	4903 (2)	329 (7)
C(4)	3460 (2)	1375 (2)	8090 (3)	387 (8)
C(5)	3015 (3)	1437 (3)	9864 (3)	469 (9)
C(6)	3118 (2)	3737 (2)	9148 (2)	367 (7)
C(7)	2705 (2)	1582 (2)	4117 (2)	325 (7)
C(8)	3165 (2)	351 (2)	3518 (3)	406 (8)
C(9)	2434 (2)	−792 (2)	2731 (3)	475 (9)
C(10)	1243 (2)	−733 (2)	2509 (3)	490 (9)
C(11)	787 (2)	482 (2)	3125 (3)	406 (8)
C(12)	1507 (2)	1647 (2)	3929 (2)	348 (8)
C(13)	2316 (2)	4609 (2)	8719 (2)	338 (7)
C(14)	1224 (2)	4038 (2)	8034 (3)	384 (8)
C(15)	510 (2)	4846 (2)	7629 (3)	399 (8)
C(16)	853 (2)	6200 (2)	7885 (3)	470 (9)
C(17)	1945 (2)	6767 (2)	8574 (3)	495 (9)
C(18)	2677 (2)	5973 (2)	8992 (3)	421 (8)
Compound *PB*				
Cl	3891 (2)	6065·1 (5)	4253 (1)	883 (5)
S	1665 (1)	3374·1 (5)	4091·8 (8)	596 (4)
N	4476 (3)	3340 (1)	2955 (2)	358 (7)
O	5951 (3)	2432 (1)	3625 (2)	550 (8)
C(1)	2723 (4)	3617 (2)	2830 (3)	426 (9)
C(2)	3242 (6)	2740 (2)	4421 (3)	562 (14)
C(3)	4704 (4)	2801 (2)	3640 (2)	414 (9)
C(4)	2652 (4)	4376 (2)	2656 (2)	419 (10)
C(5)	3257 (4)	4821 (2)	3435 (3)	463 (10)
C(6)	3121 (5)	5510 (2)	3272 (4)	567 (12)
C(7)	2404 (6)	5777 (2)	2342 (4)	690 (15)
C(8)	1817 (6)	5333 (3)	1575 (4)	732 (15)
C(9)	1934 (4)	4628 (2)	1716 (3)	568 (12)

The present analysis demonstrates that, in the solid state, the four possible configurational isomers of *PA* and *PB*, *i.e.* *RR*, *SS*, *RS* and *SR* of 2,2′-(3-chlorophenyl)-3,3′-bi[1,3-thiazolidine]-4,4′-dione are all present. Two asymmetric C atoms of *PA*, *i.e.* C(3) and C(6), exhibit opposite chirality. In the solid state both enantiomers 2*S*,2′*R* and 2*R*,2′*S* are present, and *PB* exhibits exact C_2 molecular symmetry through the mid-point of the N—N′ bond and coincident with the crystallographic twofold axis along **b**. Therefore the chirality of the two asymmetric C atoms C(1) and C(1′) must be the same. Nevertheless, both isomers 2*R*,2′*R* and 2*S*,2′*S* are in the crystal.

In both structures the observed C(sp^2)—Cl distances are equal within experimental error and the mean 1·743 (4) Å, which is only slightly longer than the expected C(aryl)—Cl = 1·73 Å value, falls in the range (1·72–1·76 Å) of those usually found by X-ray

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52769 (19 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Selected bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

Compound *PA*

Cl(1)—C(11)	1·741 (2)	Cl(2)—C(15)	1·741 (2)
S(1)—C(2)	1·808 (3)	S(1)—C(3)	1·843 (2)
S(2)—C(5)	1·800 (3)	S(2)—C(6)	1·829 (3)
N(1)—N(2)	1·385 (2)	N(1)—C(1)	1·366 (3)
N(1)—C(3)	1·461 (3)	N(2)—C(4)	1·386 (3)
N(2)—C(6)	1·474 (3)	O(1)—C(1)	1·213 (3)
O(2)—C(4)	1·208 (3)	C(1)—C(2)	1·492 (4)
C(3)—C(7)	1·507 (3)	C(4)—C(5)	1·502 (3)
C(6)—C(13)	1·515 (4)	C(7)—C(8)	1·396 (3)
C(7)—C(12)	1·386 (3)	C(8)—C(9)	1·376 (3)
C(9)—C(10)	1·384 (4)	C(10)—C(11)	1·380 (3)
C(11)—C(12)	1·389 (3)	C(13)—C(14)	1·386 (3)
C(13)—C(18)	1·379 (3)	C(14)—C(15)	1·383 (4)
C(15)—C(16)	1·369 (3)	C(16)—C(17)	1·386 (4)
C(17)—C(18)	1·392 (4)		

C(2)—S(1)—C(3)	94·3 (1)	C(5)—S(2)—C(6)	92·9 (1)
C(1)—N(1)—C(3)	121·3 (2)	N(2)—N(1)—C(3)	120·0 (2)
N(2)—N(1)—C(1)	118·6 (2)	N(1)—N(2)—C(6)	116·3 (2)
N(1)—N(2)—C(4)	117·0 (2)	C(4)—N(2)—C(6)	117·4 (2)
N(1)—C(1)—O(1)	122·9 (2)	O(1)—C(1)—C(2)	125·8 (3)
N(1)—C(1)—C(2)	111·3 (2)	S(1)—C(2)—C(1)	108·1 (2)
N(1)—C(3)—C(7)	114·0 (2)	S(1)—C(3)—C(7)	113·3 (1)
N(2)—C(4)—O(2)	124·3 (2)	O(2)—C(4)—C(5)	124·5 (2)
N(2)—C(4)—C(5)	111·2 (2)	S(2)—C(5)—C(4)	108·3 (2)
S(2)—C(6)—N(2)	103·6 (2)	N(2)—C(6)—C(13)	112·2 (2)
S(2)—C(6)—C(13)	111·2 (2)	C(3)—C(7)—C(12)	119·0 (2)
C(3)—C(7)—C(8)	121·2 (2)	C(8)—C(7)—C(12)	119·8 (2)
C(7)—C(8)—C(9)	120·1 (3)	C(8)—C(9)—C(10)	120·6 (3)
C(9)—C(10)—C(11)	119·1 (3)	Cl(1)—C(11)—C(10)	119·3 (2)
C(10)—C(11)—C(12)	121·3 (3)	Cl(1)—C(11)—C(12)	119·5 (2)
C(7)—C(12)—C(11)	119·2 (2)	C(6)—C(13)—C(18)	120·1 (2)
C(6)—C(13)—C(14)	120·1 (2)	C(14)—C(13)—C(18)	119·8 (2)
C(13)—C(14)—C(15)	119·4 (2)	Cl(2)—C(15)—C(14)	119·1 (2)
C(14)—C(15)—C(16)	121·7 (3)	Cl(2)—C(15)—C(16)	119·1 (2)
C(15)—C(16)—C(17)	118·7 (3)	C(16)—C(17)—C(18)	120·6 (3)
C(13)—C(18)—C(17)	119·8 (3)		

Compound *PB*

Cl—C(6)	1·746 (4)	S—C(1)	1·841 (3)
S—C(2)	1·793 (4)	N—C(1)	1·473 (4)
N—C(3)	1·373 (4)	O—C(3)	1·209 (4)
C(1)—C(4)	1·506 (5)	C(2)—C(3)	1·501 (5)
C(4)—C(5)	1·390 (5)	C(4)—C(9)	1·392 (5)
C(5)—C(6)	1·372 (5)	C(6)—C(7)	1·392 (6)
C(7)—C(8)	1·374 (7)	C(8)—C(9)	1·398 (6)

C(1)—S—C(2)	94·1 (2)	C(1)—N—C(3)	118·0 (3)
S—C(1)—N	103·0 (2)	N—C(1)—C(4)	114·4 (2)
S—C(1)—C(4)	111·3 (2)	S—C(2)—C(3)	108·1 (3)
O—C(3)—C(2)	124·6 (3)	N—C(3)—C(2)	111·7 (3)
N—C(3)—O	123·7 (3)	C(1)—C(4)—C(9)	119·2 (3)
C(1)—C(4)—C(5)	120·5 (3)	C(5)—C(4)—C(9)	120·2 (3)
C(4)—C(5)—C(6)	119·3 (3)	Cl—C(6)—C(5)	119·0 (3)
C(5)—C(6)—C(7)	121·8 (4)	Cl—C(6)—C(7)	119·2 (3)
C(6)—C(7)—C(8)	118·4 (4)	C(7)—C(8)—C(9)	121·3 (4)
C(4)—C(9)—C(8)	119·0 (4)		

diffraction in analysis of standard accuracy (Herbstein, 1979).

In the phenyl rings bond lengths and valence angles range from 1·369 (7) to 1·398 (7) Å and from 118·4 (4) to 121·7 (4)°, respectively. Whereas the mean planes through the two C_6 rings of *PA* make an angle of about 26° with each other, those of *PB*, owing to C_2 molecular symmetry, are strictly parallel. Three contact distances of about 3·5 Å between the phenyl rings of *PB* are observed [C(6)···C(6′) 3·490 (6), C(4)···C(5′) 3·563 (4) and C(5)···C(5)′ 3·575 (5) Å]. These data, along with the partial overlap of the two phenyl rings, indicate an intramolecular interaction between the phenyl groups, which could be responsible for the overall conformation of this molecule.

In the molecule of *PA* there are two independent thiazolidine rings: N(1)C(1)C(2)S(1)C(3) and N(2)-C(4)C(5)S(2)C(6) (herein after rings *A* and *A′* respectively). The puckering amplitude *Q* (Cremer & Pople, 1975) is 0·125 (3) and 0·277 (3) Å for rings *A* and *A′*, respectively. Within ring *A*, there is a pseudo-mirror plane through C(2) and the mid-point of the N(1)—C(3) bond. Fig. 3(*a*) and the asymmetry parameter of Duax, Weeks & Rohrer (1976), $\Delta C_s[C(2)] = 0{\cdot}9\ (4)°$, indicate that ring *A* assumes an envelope conformation. In addition C(2) is 0·20 (1) Å out of the mean plane through S(1)C(3)N(1)C(1) on the side opposite the substituent groups. From Fig.

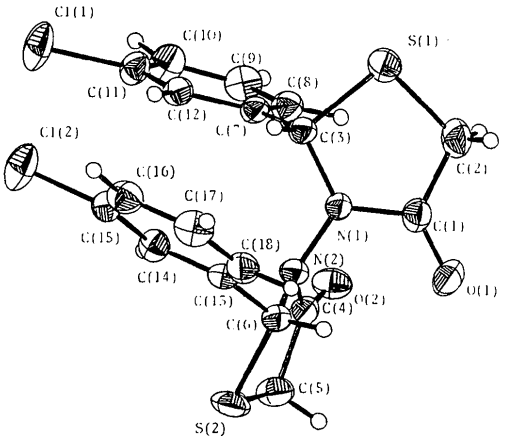

Fig. 1. A perspective view of the *PA* molecule, with the atom-numbering scheme.

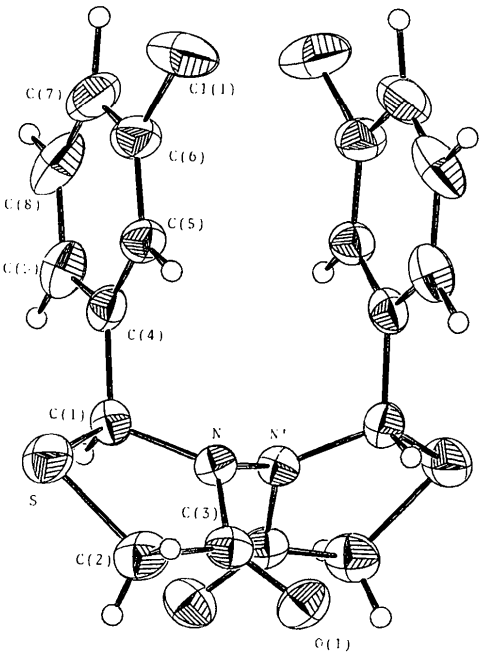

Fig. 2. A perspective view of the *PB* molecule, with the atom-numbering scheme.

3(*a*) it seems that the conformation of ring *A'* does not fit with any of the three most symmetric conformations observed for five-membered rings, *i.e.* planar (*P*), envelope (*E*) and half-chair (*HC*) (Duax *et al.* 1976). It has been pointed out by Cremer & Pople (1975) that the two forms *E* and *HC* are easily interconverted by pseudorotation. Because the barrier to such motion is often low the ring will pass to intermediate conformations with no symmetry (point-group C_1) corresponding to linear combinations of *E* and *HC*. It is noteworthy that the pentaatomic ring of the 2,2'-bidioxolane molecule in the crystal (Furberg & Hassel, 1950) exhibits the same ring puckering coordinates as *A'* ($Q = 0{\cdot}270$ Å, $\varphi = 130°$) and it has been emphasized that this structure may well be modified by intermolecular interactions (Cremer & Pople, 1975).

The two thiazolidine rings (hereinafter *B* rings) of *PB*, owing to C_2 molecular symmetry, must present the same conformation and the puckering amplitude *Q* is 0·223 (3) Å. There is a pseudo twofold axis through C(2) and the midpoint of the N(1)—C(1) bond (Fig. 3*b*). The asymmetry parameter ΔC_2[C(2)] (Duax *et al.*, 1976) of 3·7 (4)° indicates that the conformation of ring *B* is half chair. The chlorophenyl group is on the side opposite the O atom with respect to the mean plane through the ring.

Although the *A*, *A'*, *B* ring conformations are different, the corresponding bond distances and angles are similar. The molecular dimensions of all three five-membered rings fall within the ranges of the observed distances and angles in accurate studies on thiazolidine rings (Parthasarathy, Paul & Korytnyk, 1976; Hickel, Leger, Carpy, Vigorita, Chimirri & Grasso, 1983; Bruno *et al.*, 1984).

The geometry of the bonds about the three N atoms is significantly different. Whereas N(1) of *PA* is strictly planar, N(2) of *PA* and N of *PB* tend to be tetrahedral, the N atoms being about 0·26 (1) and 0·25 (2) Å respectively out of the plane through the three bonded atoms. These data appear to be unusual, because the N atoms are equivalent from the chemical point of view.

The observed N—N distances [of 1·385 (3) and 1·398 (3) Å for *PA* and *PB* respectively] are very close to those found in related compounds, 2,2'-bis-(4-chlorophenyl)-5,5'-dimethyl-[3,3'-bi-1,3-thiazolidine]-4,4'-dione (Bruno *et al.*, 1984) and diacetylhydrazine (Shintani, 1960), and fall within the range of distances observed for this bond in analogous systems (Jensen & Lingafelter, 1961; Karle & Karle, 1965).

In both crystal structures the packing is due mainly to van der Waals interactions and all intermolecular contacts agree with those predicted from radii-sum rules.

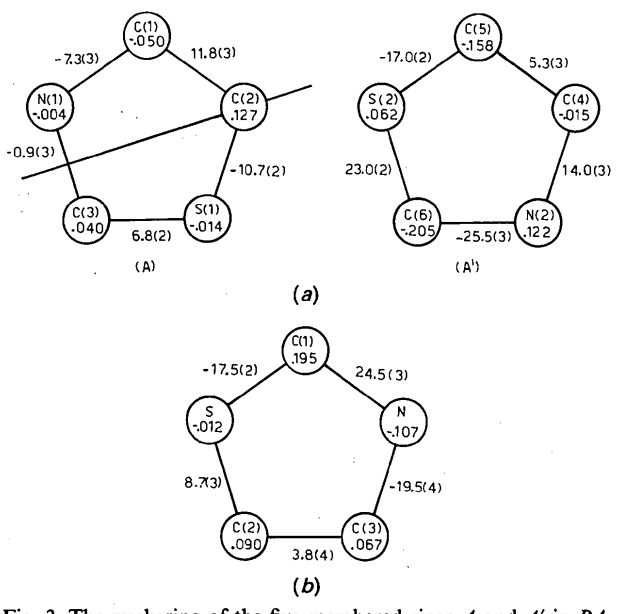

Fig. 3. The puckering of the five-membered rings *A* and *A'* in *PA* and of ring *B* in *PB*. In the circles the numerical values are the perpendicular displacements (Å) (average e.s.d. 3×10^{-3} Å) of the corresponding atoms of the mean plane through the ring (torsion angles in degrees).

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