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Crystal Structure and Conformation of the Cyclic Dipeptide Cyclo-L-prolyl-D-phenylalanyl*

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The structure of cyclo-L-prolyl-D-phenylalanyl has been refined to a final R of 0·030 for 1439 observed reflexions. The space group is $P2_1$, with $a=8{\cdot}107$, $b=6{\cdot}638$, $c=12{\cdot}083$ Å, $\beta=96{\cdot}43°$, $Z=2$. The molecular packing coefficient is about 0·72, with pairs of molecules held together by an N–H···O hydrogen bond between the peptide N and O (2·855 Å). The molecule is in the folded conformation ($\chi_2^1=75{\cdot}0°$) with the aromatic side chain facing the diketopiperazine ring. The latter assumes a boat conformation with the α-carbon atoms deviating about 0·2 Å from the plane through the two peptide bonds. The pyrrolidine ring assumes a half-chair conformation with approximate C_2 symmetry.

Introduction

As part of our investigations on the structures of some biologically interesting molecules, we have undertaken crystal structure studies of some cyclic dipeptides which feature the 2,5-diketopiperazine (DKP) ring. The latter is present in a number of molecules with important biological activity; cycloserine, for example, is found to be effective against mycobacterium tuberculosis (Michalsky, Ctvrtnik, Horakova & Bydzovsky, 1962). Some non-ionic water-soluble DKP's exhibit a strong denaturant action on globular proteins such as ribonuclease (Crescenzi, Cesaro & Russo, 1973). DKP's containing an arylmethyl side chain seem to prefer a folded conformation with the aromatic ring face-to-face with the DKP ring, and the attractive forces between the two rings may play an important role (Kopple & Marr, 1967; Gawne, Kanner, Rogerts, Sheppard & Titlestad, 1968). The present study of cyclo-L-prolyl-D-phenylalanyl (cyclo-L-pro-D-phe) was undertaken for a further understanding of the conformational flexibilities of cyclic dipeptides having various side chains. Among other results, we find that the phenylalanyl side chain is indeed folded back so as to face the DKP ring.

Experimental

Preliminary Weissenberg photographs showed Laue symmetry $2/m$; systematic absences $0k0$ with k odd together with the presumed optical activity of the material indicated space group $P2_1$. Cell dimensions were obtained by a least-squares fit to $\sin^2\theta/\lambda^2$ values for 52 $h0l$ and 42 $hk0$ reflexions, measured on Weissenberg photographs prepared in a special camera which holds the film in the asymmetric position. The density was measured by the neutral buoyancy technique. Crystal data are collected in Table 1.

Table 1. *Crystal data*

Cyclo-L-prolyl-D-phenylalanyl
Monoclinic
Space group $P2_1$
$a=$ 8·107 (1) Å
$b=$ 6·638 (1)
$c=$ 12·083 (2)
$\beta=$ 96·43 (2)°
λ(Cu $K\alpha$) = 1·5418 Å

$C_{14}H_{16}N_2O_2$
F. W. 244·3
$Z=2$
$F(000)=260$
$V=646{\cdot}1$ Å^3
$D_m=1{\cdot}236$ g cm^{-3}
$D_x=1{\cdot}256$
μ(Cu $K\alpha$) = 7·0 cm^{-1}

The crystal used for intensity measurements was an irregularly truncated prism, with cross-section 0·22 × 0·37 mm and maximum length 0·68 mm. It was mounted on a Datex-automated General Electric quarter-circle diffractometer with its long dimension, the b axis, inclined by about 0·6° to the φ axis. Intensities were collected by θ–2θ scans at a speed of 1° (in 2θ) min^{-1}, the scan range varying from 2·4° at $2\theta=4°$ to 3·6° at $2\theta=150°$; backgrounds were collected for 40 s at each extreme. A check reflexion (313) was monitored every 25 reflexions; it showed a slow, steady drop in intensity which reached 3% at the end of the week of data collection.

Initially, the quadrant $\pm h,k,l$ was surveyed out to $2\theta=150°$ (Cu $K\alpha$ radiation). The 157 reflexions with $2\theta<52°$ were then recollected at a reduced tube current and a scan speed of 2° min^{-1}; even under these conditions the intensities of four reflexions ($\bar{1}03$, 101,

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011, $\bar{1}12$) overflowed the capacity of the counter (10^6 counts), and were surveyed by hand. Finally, 221 reflexions with $120° < 2\theta < 135°$ were surveyed as the equivalent form $\mp h,k,-l$ as a check on the quality of the crystal and the reproducibility of the results. The agreement with the first set of measurements was slightly poorer than would have been predicted by counting errors alone, but slightly better than would be predicted from the assigned variances $\sigma^2(I)$ [which included an additional 'lack-of-confidence' factor $(0{\cdot}02S)^2$, where S is the scan count]. After averaging the equivalent measurements, and summing their weights, the resulting list of intensities totalled 1439; of these, eight were negative and another 40 were less than 3σ above background. Absorption was neglected ($\mu t_{\max} \simeq 0{\cdot}28$).

Solution and refinement of the structure

An approximate scale factor and the four coefficients of a general anisotropic temperature factor were obtained from a least-squares adaptation (Levy, Thiessen & Brown, 1970) of Wilson's (1942) method, and E values (Karle & Hauptman, 1956) were calculated. Initial attempts to solve the phase problem by application of the tangent formula (Karle & Hauptman, 1956) to many starting sets of phases determined by the symbolic addition procedure (Karle & Karle, 1966) were unsuccessful, mainly because of the appearance of a majority of centric phases and hence a spurious mirror plane perpendicular to **b**. However, use of *MULTAN* for 300 reflexions with $|E| > 1{\cdot}22$ (Germain, Main & Woolfson, 1971) led to a satisfactory starting set of reflexions and 16 ways of assigning phases were obtained. The set with the highest combined figure-of-merit was used for an initial E map and a molecular plot was obtained by the peak search procedure (Declerq, Germain, Main & Woolfson, 1973). The structure was refined, first by block-diagonal least-squares calculations (Shiono, 1968), until R was reduced to 0·083. The H atoms were then placed at stereochemically reasonable positions, and their coordinates and isotropic temperature coefficients added to the parameter list.

In the final refinement cycles, which were carried out on an IBM 370/155 computer with the CRYM system of programs, the 227 parameters were divided into two matrices; the first contained the coordinates of the 18 heavier atoms (53 parameters, the y coordinate of N(1) being held fixed to establish the origin), the second the coordinates and isotropic temperature parameters of the H atoms, the anisotropic temperature coefficients of the heavy atoms, the scale factor and an isotropic extinction parameter (Larson, 1967;

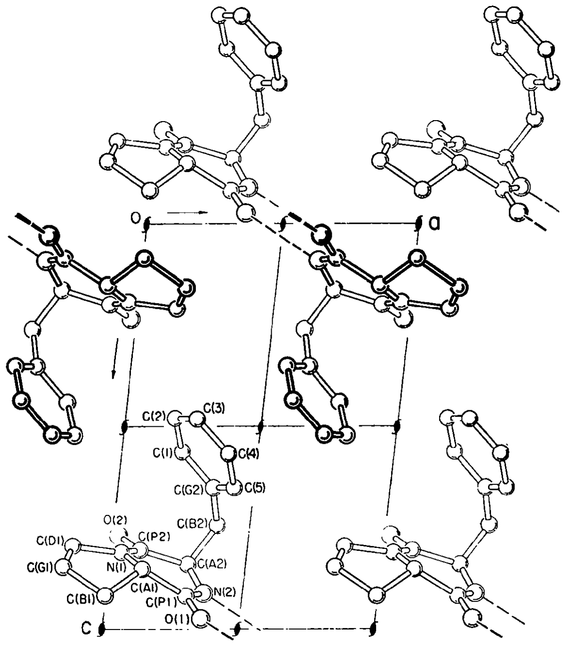

Fig. 1. The crystal structure of cyclo-L-pro-D-phe, viewed down **b**.

Table 2. *Atomic coordinates* ($\times 10^5$) *and anisotropic temperature parameters* ($\times 10^4$)

The temperature factor expression has the form $\exp[-2\pi^2(U_{11}h^2a^{*2}\cdots+2U_{23}klb^*c^*)]$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(*P*1)	29040 (20)	70204 (35)	91440 (13)	582 (8)	513 (11)	484 (8)	−103 (8)	−119 (6)	−3 (7)
O(1)	35818 (20)	84068 (35)	97055 (14)	823 (9)	701 (11)	858 (10)	−174 (9)	−300 (8)	−172 (9)
C(*A*1)	12391 (19)	73943 (31)	84876 (11)	564 (8)	385 (8)	421 (7)	−58 (7)	−23 (6)	16 (6)
N(1)	3755 (15)	55607 (0)	80953 (10)	455 (6)	442 (8)	479 (6)	−49 (6)	−27 (5)	−69 (5)
C(*B*1)	−362 (24)	84098 (35)	91396 (13)	789 (11)	434 (10)	526 (8)	0 (9)	77 (7)	−40 (7)
C(*G*1)	−16787 (24)	79459 (42)	84365 (18)	632 (10)	696 (15)	777 (12)	103 (10)	92 (9)	−89 (11)
C(*D*1)	−14235 (20)	58998 (42)	79103 (17)	467 (8)	670 (13)	778 (12)	20 (8)	−57 (8)	−138 (10)
C(*P*2)	10357 (19)	37353 (31)	80249 (11)	568 (8)	409 (8)	379 (6)	−42 (7)	−1 (5)	12 (6)
O(2)	2324 (16)	22671 (27)	76718 (10)	752 (8)	429 (7)	627 (7)	−125 (6)	−19 (6)	−52 (6)
C(*A*2)	28774 (20)	35155 (33)	84017 (12)	612 (9)	441 (9)	465 (7)	42 (7)	−69 (6)	83 (7)
N(2)	35600 (16)	51932 (32)	90789 (10)	528 (7)	602 (10)	478 (7)	2 (7)	−162 (6)	46 (7)
C(*B*2)	38317 (23)	31277 (39)	73889 (15)	609 (9)	617 (12)	640 (10)	177 (9)	25 (8)	13 (9)
C(*G*2)	34634 (19)	46486 (38)	64730 (12)	472 (7)	684 (11)	501 (7)	101 (8)	96 (6)	21 (8)
C(1)	22282 (23)	42471 (51)	56023 (15)	637 (10)	1099 (22)	512 (8)	2 (13)	23 (7)	11 (11)
C(2)	18269 (31)	56423 (72)	47824 (17)	803 (14)	1804 (40)	555 (11)	191 (20)	17 (10)	247 (18)
C(3)	26402 (38)	74416 (68)	47944 (21)	1124 (21)	1464 (35)	718 (14)	374 (23)	230 (14)	479 (20)
C(4)	38634 (38)	78732 (55)	56363 (25)	1070 (19)	890 (21)	1037 (19)	104 (16)	549 (17)	270 (16)
C(5)	42816 (23)	64752 (45)	64800 (16)	578 (9)	819 (15)	689 (11)	28 (10)	183 (8)	33 (11)

equation 3). During the last cycle, the maximum shift in a parameter was 1·0σ and the average shift 0·15σ. The final R was 0·030 for the 1431 reflexions with positive net intensity and the goodness-of-fit, based on all 1439 reflexions, was 3·54. We see no apparent trend in $\sqrt{w}(F_o^2-F_c^2)$, which appears to be normally distributed; without doubt, the somewhat high goodness-of-fit value represents abnormally small observational variances, and hence high weights, owing to the large size of the diffracting crystal and the relatively slow scanning rate. Thus, the discrepancies $||F_o|-|F_c||$, which show an average value of only 0·14e, are due primarily to small residual errors in the model rather than to inaccuracies in the measurements.

Table 3. *Coordinates* ($\times 10^3$) *and isotropic temperature parameters of the* H *atoms*

H atom on	x	y	z	B
C(*A*1)	145 (2)	832 (4)	786 (2)	4·3 (0·4)
C(*B*1)	12 (3)	782 (4)	987 (2)	5·2 (0·5)
C(*B*1)	20 (3)	972 (6)	922 (2)	7·1 (0·7)
C(*G*1)	−261 (4)	779 (5)	891 (3)	8·1 (0·8)
C(*G*1)	−195 (3)	897 (5)	784 (2)	5·9 (0·6)
C(*D*1)	−203 (4)	488 (6)	833 (3)	8·4 (0·8)
C(*D*1)	−177 (3)	589 (4)	711 (2)	5·7 (0·5)
C(*A*2)	300 (3)	249 (4)	888 (2)	4·6 (0·4)
N(2)	454 (3)	501 (4)	947 (2)	5·7 (0·5)
C(*B*2)	504 (3)	319 (4)	766 (2)	5·4 (0·5)
C(*B*2)	347 (3)	174 (4)	705 (2)	5·1 (0·5)
C(1)	157 (4)	283 (5)	559 (2)	7·5 (0·7)
C(2)	94 (3)	532 (6)	416 (3)	8·3 (0·8)
C(3)	231 (4)	834 (6)	413 (3)	8·4 (0·8)
C(4)	449 (4)	930 (6)	572 (3)	8·7 (0·8)
C(5)	506 (3)	674 (4)	707 (2)	4·9 (0·5)

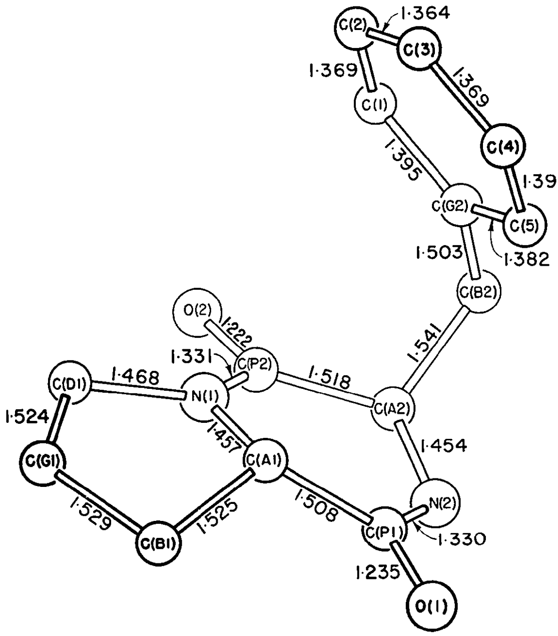

Fig. 2. Bond distances. E.s.d.'s are in the range 0·002–0·004 Å except for the bond C(2)–C(3), which has an e.s.d. of 0·006 Å.

Atomic form factors for C, N, and O were taken from *International Tables for X-ray Crystallography* (1962) and for H from Stewart, Davidson & Simpson (1965). We did not correct them for the effects of anomalous dispersion, and hence made no attempt to confirm the absolute configuration of the molecule.

Results and discussion

Atomic coordinates and thermal parameters are shown in Tables 2 and 3.* A view of the structure is shown in Fig. 1. Hydrogen bonds N(2)–H...O(1), with N...O = 2·848 Å and H–N...O = 17°, are arranged along one screw axis to join the molecules into a chain parallel to **b**. Packing about the other three structurally distinct screw axes involves a typical herring-bone pattern of the hydrophobic benzene and pyrrolidine rings. The packing of these rings is fairly loose, with no C...C distance below 3·40 Å and a packing coefficient (Bondi, 1968) of 0·72.

Bond distances involving the heavier atoms are shown in Fig. 2; bond angles are given in Table 4. Dimensions of the diketopiperazine ring lie within the range of values found in other cyclic dipeptides, *e.g.* cyclo-L-prolylglycyl (Von Dreele, 1975), cyclo-L-prolyl-L-leucyl (Karle, 1972), cyclo-L-prolyl-L-prolyl (Benedetti, Goodman, Marsh, Rapoport & Musich, 1976), cyclo-L-tyrosylglycyl (Morris, Geddes & Sheldrick, 1974), cyclo-L-alanyl-D-alanyl (Sletten, 1970; Benedetti, Corradini & Pedone, 1969*a*), cyclo-L-alanyl-L-analyl (Sletten, 1970; Benedetti, Corradini & Pedone, 1969*b*), cyclo-L-tyrosylglycyl (Lin & Webb, 1973), cyclo-L-tyrosyl-L-seryl (Lin & Webb, 1973), and cycloglycylglycyl (diketopiperazine) (Degeilh & Marsh, 1959; Corey, 1938).

The difference in length of the two C–O bonds presumably reflects the effects of hydrogen bonding (Ramani & Venkatesan, 1973): the longer, C(*P*1)–

Table 4. *Bond angles* (°)

E.s.d.'s range from 0·015° to 0·030°.

C(*A*1)–C(*P*1)–N(2)	117·3	C(*P*2)–N(1)—C(*D*1)	122·0
C(*A*1)–C(*P*1)–O(1)	118·9	C(*A*1)–N(1)—C(*D*1)	110·8
N(2)—C(*P*1)–O(1)	123·8	C(*A*1)–C(*B*1)–C(*G*1)	102·9
C(*A*2)–C(*P*2)–N(1)	117·2	C(*B*1)–C(*G*1)–C(*D*1)	105·1
C(*A*2)–C(*P*2)–O(2)	119·7	C(*G*1)–C(*D*1)–N(1)	104·6
N(1)—C(*P*2)–O(2)	123·1	C(*A*2)–C(*B*2)–C(*G*2)	113·4
C(*P*1)–C(*A*1)–N(1)	113·8	C(*B*2)–C(*G*2)–C(1)	119·6
C(*P*1)–C(*A*1)–C(*B*1)	114·8	C(*B*2)–C(*G*2)–C(5)	122·0
N(1)—C(*A*1)–C(*B*1)	102·0	C(1)—C(*G*2)–C(5)	118·4
C(*P*2)–C(*A*2)–N(2)	113·2	C(*G*2)–C(1)—C(2)	120·6
C(*P*2)–C(*A*2)–C(*B*2)	110·0	C(1)—C(2)—C(3)	120·6
N(2)—C(*A*2)–C(*B*2)	112·4	C(2)—C(3)—C(4)	120·0
C(*P*1)–N(2)—C(*A*2)	127·0	C(3)—C(4)—C(5)	120·1
C(*P*2)–N(1)—C(*A*1)	126·8	C(4)—C(5)—C(*G*2)	120·2

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31359 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

O(1), involves the O atom that accepts the only hydrogen bond in the structure. A similar effect is seen in crystals of cyclo-L-pro-L-leu (Karle, 1972), where the C–O distances are 1·243 (6) to the O atom involved in hydrogen bonding and 1·229 (6) Å to the other. The situation with regard to cyclo-L-pro-gly (Von Dreele, 1975) is somewhat more complicated; when refinement was carried out on all 1234 observed intensities the two C–O distances were appreciably different, 1·237 (3) to the O atom involved in hydrogen bonding* and 1·227 (3) Å to the other, but when the refinement was limited to the 967 reflexions with $\sin\theta/\lambda \geq 0{\cdot}40$, the two C–O distances became equal at the intermediate value 1·233 (2) Å. We found no such effect in the present study; when the final parameters were submitted to full-matrix least-squares refinement based on the 1047 reflexions with $\sin\theta/\lambda \geq 0{\cdot}40$, neither C–O distance changed by as much as 0·001 Å. The 15 C–H lengths range from 0·89 to 1·08 Å, with an average of 0·99 Å and an r.m.s. deviation of 0·06 Å; the N–H distance is 0·89 (3) Å. Angles involving H atoms show an r.m.s. deviation of 3·4° from the expected values of 109·5 or 120°.

Molecular conformation

A stereoscopic view of the molecule is shown in Fig. 3. The phenyl ring is folded back over the DKP ring, a conformation that is apparently characteristic of cyclic dipeptides containing tyrosyl or phenylalanyl residues, as it has also been found in crystals of cyclo-L-tyr-gly and cyclo-L-tyr-L-ser monohydrate (Lin & Webb, 1973). Kopple & Marr (1967) and Gawne *et al.* (1968) conclude, from n.m.r. studies in solution, that this folded conformation is characteristic of cyclic dipeptides containing *any* aromatic side chain. Indeed the minimum energy conformation predicted for these types of molecules by MO methods (Caillet, Pullman & Maigret, 1971) and by semi-empirical methods (Chandrasekaran, Lakshminarayanan, Mohanakrishnan & Ramachandran, 1973) are in agreement with the experimental observations. However, Morris, Geddes & Sheldrick (1974) find an extended conformation of the tryptophan side chain in crystals of cyclo-L-try-gly.

The DKP ring is in a rather shallow boat conformation, the two α-carbon atoms C(*A*1) and C(*A*2) lying approximately 0·2 Å above the plane of N(1), N(2), C(*P*1), and C(*P*2) (Table 5); the phenylalanyl side chain occupies an axial, or 'flag-pole', position on the boat. The two O atoms, as well as the H atom on N(2), are displaced below the plane of the boat, to the side opposite from the phenylalanyl side chain. Other planes of interest are described in Table 5.

The angles ω_1 and ω_2 are 2·8 and 0·7° (Table 6). Such angles have been found to be as large as 8° in a cyclic dipeptide (Sletten, 1970) and as large as 11° in a linear peptide (Vasantha Pattabhi, Venkatesan & Hall, 1973, 1974). Some recent quantum mechanical studies (Ramachandran, Lakshminarayanan & Kolaskar, 1973), based on *N*-methylacetamide as a model, have suggested that the non-planar amide grouping is the energetically favoured configuration; however, it is not yet clear whether the non-planarity that is expressed by non-zero values of the angle ω is due to an actual rotation about this C′–N bond or whether it results from a pyramidal configuration of the bonding about the N atom. Whereas the three bonds to the carbonyl C(*P*) of a peptide grouping have almost invariably been found to be closely coplanar (see, for example, Table 5), bonding to a peptide N atom may be appreciably nonplanar; in the present case, for example, N(1) lies 0·054 Å from the plane through C(*A*1), C(*P*2), and C(*D*1). As the bonding orbitals about the N atom become pyramidal, suggesting ap-

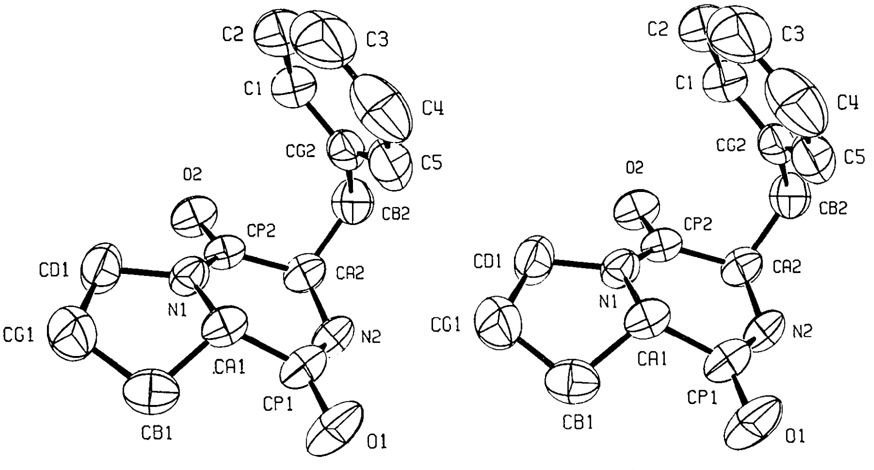

Fig. 3. A stereoscopic view of the molecule. The atoms are represented by thermal ellipsoids drawn at the 50% probability level (Johnson, 1970).

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* Von Dreele (1975) reports that 'there are no hydrogen bonds' in cyclo-L-pro-gly; however, the published coordinates (his Table 2) lead to $N_2\cdots O_2' = 2{\cdot}829$ and $H(N_2)\cdots O_2' = 1{\cdot}89$ Å and $N_2–H(N_2)\cdots O_2' = 173{\cdot}1°$, where O_2' is at $x-\frac{1}{2}, \frac{1}{2}-y, 1-z$.

preciable sp^3 hybridization, it becomes more difficult to define an ideal value for the torsion angle ω and to discuss the energetics of rotation about the N–C(*P*) bond. This problem warrants additional study.

The conformation of the pyrrolidine ring is somewhat unusual. Its usual conformation is that of an envelope, with C$^\gamma$ as the flap in most linear peptides (Marsh & Donohue, 1967) and C$^\beta$ as the flap in cyclic dipeptides (Table 6). In the present compound, however, there is no planar grouping of four atoms; the simplest description is based on the plane through N(1), C(*D*1), and C(*G*1), with C(*A*1) displaced by 0·27 to one side and C(*B*1) by 0·34 Å to the opposite side.

It is relatively and, perhaps, deceptively simple to understand the various forces that work to establish the overall conformation of the molecule. First the bond angle constraints of the pyrrolidine ring force the β-carbon atom C(*B*1) into a quasi-equatorial position with respect to C(*A*1), requiring a puckering of the DKP ring; for the amide groups to remain approximately planar, this puckering must lead to a boat conformation. Ideal conformational angles for such a cyclo-L-prolyl grouping appear to be $\varphi \sim -40^\circ$, $\psi \sim 35^\circ$, and $\chi^4 \sim 0^\circ$ [columns (*b*), (*c*), and (*d*), Table 6], the pyrrolidine ring having an envelope conformation with C$^\beta$ as the 'flap'. The puckering of the DKP ring forces the D-phenylalanyl residue into an axial position, and the phenyl group folds back so as to lie on top of the DKP ring. However, the amount of this folding is limited by close contacts between the phenyl and DKP rings [which include C(1)...C(*P*2), 3·20 and C(5)...N(2), 3·37 Å], in turn limiting the amount of puckering of the DKP ring. As a result, the DKP ring is appreciably more planar than in other cyclo-L-pro compounds, the conformational angles being reduced to $\varphi \sim -18^\circ$ and $\chi \sim 16^\circ$ (Table 6). Finally, the decreased puckering of the DKP ring forces the pyrrolidine ring to adopt a somewhat unusual conformation.

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Table 5. *Least-squares planes for various groups of atoms*

Coefficients *A*, *B*, and *C* are direction cosines relative to the orthogonal axes *a*, *b*, and *c**; *D* is the origin-to-plane distance.

		Deviation			Deviation
Plane 1	N(1)	−0·002 Å	Plane 2	C(*G*2)	0·003 Å
	C(*P*1)	0·002		C(1)	0·004
A=0·441	N(2)	−0·002	*A*=0·745	C(2)	−0·003
B=0·255	C(*P*2)	0·002	*B*=−0·401	C(3)	0·001
C=−0·861	C(*A*1)	0·188*	*C*=−0·533	C(4)	0·001
D=−9·465 Å	C(*A*2)	0·210*	*D*=−1·277 Å	C(5)	0·000
	O(1)	−0·135*		C(*B*2)	−0·054*
	O(2)	−0·147*			
Plane 3	N(1)	0·001	Plane 4	N(2)	0·000
	C(*P*2)	−0·002		C(*P*1)	−0·001
A=0·313	C(*A*2)	0·000	*A*=0·547	C(*A*1)	0·000
B=0·207	O(2)	0·001	*B*=0·294	O(1)	0·000
C=−0·927	C(*A*1)	0·019*	*C*=−0·784	C(*A*2)	0·058*
D=−9·868 Å	C(*D*1)	−0·196*	*D*=−8·575 Å	H(N2)	0·00*

* Omitted from calculation of mean plane.

Table 6. *Torsion angles in cyclo*-L-*prolyl compounds*

Dihedral angle	Atoms involved	(*a*)	(*b*)	(*c*)	(*d*)
φ_1	C(*P*1)–C(*A*1)–N(1)—C(*P*2)	−17·1°	−41·5°	−37°*	−44·0°
ψ_1	N(2)—C(*P*1)–C(*A*1)–N(1)	14·9	33·7	36*	38·5
ω_1	C(*A*2)–N(2)—C(*P*1)–C(*A*1)	2·8	6·3	0*	0·4
φ_2	C(*P*2)–C(*A*2)–N(2)—C(*P*1)	−19·0	−41·5		−37·3
ψ_2	N(1)—C(*P*2)–C(*A*2)–N(2)	16·6	33·8		32·7
ω_2	C(*A*1)–N(1)—C(*P*2)–C(*A*2)	0·7	6·2		7·4
χ_1^1	N(1)—C(*A*1)–C(*B*1)–C(*G*1)	−37·9	−31·5	−32*	−32·7
χ_1^2	C(*A*1)–C(*B*1)–C(*G*1)–C(*D*1)	31·9	36·0	36*	35·6
χ_1^3	C(*B*1)–C(*G*1)–C(*D*1)–N(1)	−13·5	−25·1	−24*	−24·0
χ_1^4	C(*G*1)–C(*D*1)–N(1) —C(*A*1)	−11·3	4·5	3*	3·2
χ_2^1	N(2)—C(*A*2)–C(*B*2)–C(*G*2)	−75·0	−72·3		

* Average of two independent, but nearly equal, values.

(*a*) Cyclo-L-pro-D-phe (this investigation). (*b*) Cyclo-L-pro-L-leu (Karle, 1972). (*c*) Cyclo-L-pro-L-pro (Benedetti *et al.*, 1975). (*d*) Cyclo-L-pro-gly (Von Dreele, 1975).

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The Crystal and Molecular Structure of Biurea

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The structure of biurea, $(NH_2CONH)_2$, has been determined by Patterson methods and refined by full-matrix least-squares calculations to a final conventional R of 0·058 for the 528 observed reflexions. The data were collected on a Hilger and Watts four-circle diffractometer. The unit cell is monoclinic, $C2/c$, with $a=15\cdot780$ (2), $b=4\cdot637$ (1), $c=9\cdot331$ (1) Å, $\beta=133\cdot84$ (1)° and $Z=4$. The molecules are held together by extensive hydrogen bonding, so that every H atom is bonded to an O atom in a neighbouring molecule. The N–N bond, 1·391 (4) Å, is one of the shortest reported for a N–N single bond.

Introduction

Biurea is used industrially as a high-temperature blowing agent for expanding plastics such as polypropylene. The thermal decomposition of biurea is currently being studied and the crystal structure has been determined in order to provide evidence to explain the mechanism of the solid-state decomposition.

Experimental

Crystals were grown from aqueous solution in the form of hexagonal platelets. Many of the crystals were twinned but after considerable searching a crystal suitable for X-ray examination was found.

Table 1. *Distribution statistics of normalized structure factors*

	Centric	Acentric	Experimental
$\langle\lvert E\rvert\rangle$	0·798	0·886	0·809
$\langle\lvert E^2\rvert\rangle$	1·000	1·000	1·000
$\langle\lvert E^2-1\rvert\rangle$	0·968	0·736	0·975
$\lvert E\rvert>3\cdot0$	0·27 %	0·01 %	0·37 %
$\lvert E\rvert>2\cdot0$	4·55	1·83	4·82
$\lvert E\rvert>1\cdot0$	31·73	36·79	30·75