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Crystal Structure and Conformation of the Cyclic Dipeptide *cyclo*-(L-Histidyl-L-aspartyl) Trihydrate^{1a}

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Abstract: The crystal structure of *cyclo*-(L-histidyl-L-aspartyl) trihydrate has been determined by x-ray diffraction techniques, and refined to a final *R* index of 0.056 for 1601 reflections. The molecule is in a folded conformation, with the imidazole ring facing the diketopiperazine ring. However, since the diketopiperazine ring is essentially planar, the interaction between the two rings is not as intimate as in those cyclic dipeptides in which the diketopiperazine ring is in a boat conformation with the side chain occupying an axial, or flagpole, site. Planarity of the diketopiperazine ring may be dictated by steric interactions between the imidazole ring and the aspartyl side chain. The molecule is a zwitterion, a proton having been transferred from the carboxyl group of the aspartyl side chain to the imidazole ring.

Introduction

X-ray diffraction studies on a number of cyclic dipeptides indicate that the six-membered diketopiperazine (hereafter, DKP) ring usually adopts either a planar or a boat conformation. In the absence of steric effects due to the amino acid side chains the preferred conformation is apparently planar, as observed for *cyclo*-(L-alanyl-D-alanyl)² and for diketopiperazine itself, *cyclo*-(glycylglycyl).³ Predictably, a prolyl residue, which results in a fusion between the DKP ring and the five-membered pyrrolidine ring, requires a quasi-equatorial site for the β -carbon atom and forces the DKP ring into a nonplanar conformation.⁴ The favored nonplanar conformation is a boat, which permits the torsion angles about the peptide bonds C'-N to remain close to 0°.

A particularly interesting observation, first noted by Kopple and co-workers from NMR studies,⁵ is that cyclic dipeptides containing an aromatic sidechain, such as phenylalanyl, tyrosyl, tryptophyl, or histidyl, tend to adopt a folded conformation with the aromatic ring facing the DKP ring. The folded conformation has been confirmed by x-ray diffraction studies on crystals of *cyclo*-(glycyl-L-tyrosyl),⁶ *cyclo*-(L-seryl-L-tyrosyl),⁶ and *cyclo*-(L-prolyl-D-phenylalanyl),^{4a} and in the

N-methylated derivatives of *cyclo*-(L-phenylalanyl-L-phenylalanyl) and *cyclo*-(L-phenylalanyl-D-phenylalanyl).⁷ On the other hand, in crystals of *cyclo*-(glycyl-L-tryptophyl)⁸ and *cyclo*-(L-threonyl-L-histidyl) dihydrate⁹ the aromatic side chains have been found to adopt an extended conformation with no intramolecular interaction with the DKP rings.

We report here the results of a crystal-structure investigation of *cyclo*-(L-histidyl-L-aspartyl) trihydrate. Unlike the structure of *cyclo*-(L-threonyl-L-histidyl) dihydrate, the imidazole ring, which is protonated in this zwitterionic molecule, is folded back over the DKP ring.

Experimental Section

Crystals were supplied by Professor K. D. Kopple of the Department of Chemistry, Illinois Institute of Technology. The one chosen for data collection was of irregular shape, approximately 0.3 mm in maximum dimension. X-ray data were collected using a Datex-automated General Electric diffractometer equipped with a scintillation detector and pulse-height discriminator; the radiation was Ni-filtered Cu K α .

Crystal data are collected in Table I. Intensities for all reflections within the *hkl* octant of reciprocal space were measured using θ - 2θ scans at a scan speed of 1° (in 2θ) per minute, to a limiting 2θ value

Table I. Crystal Data for *cyclo*-(L-his-L-asp)

$C_{10}N_4O_4H_{12} \cdot 3H_2O$	Mol wt 306.3
Orthorhombic	$P2_12_12_1$
$a = 16.771 (2) \text{ \AA}$	$Z = 4$
$b = 13.792 (1)$	$F(000) = 648 e$
$c = 6.143 (1)$	$D_x = 1.432 \text{ g cm}^{-3}$
$\lambda(\text{Cu K}\alpha) = 1.5418 \text{ \AA}$	$\mu = 10.3 \text{ cm}^{-1}$

of 146° . Of the 1704 independent reflections that were surveyed, 94 showed negative net intensities. Three reflections were rejected because of unrealistic scan or background counts; the remaining 1701 averaged intensities were assigned variances $\sigma^2(I)$ based on counting statistics plus an empirical term $(0.02S)^2$, where S is the scan count.

For many of the reflections with large values of χ and 2θ , the incident radiation impinged directly upon the brass mounting pin, leading to high background counts and relatively large variances. These low-weight reflections tended to have large values of I .

Use of MULTAN¹⁰ for 300 reflections with $|E| \geq 1.23$ led to a satisfactory set of starting reflections and 64 combinations of starting phases. After phase expansion, the E map¹¹ calculated for the solution with the largest absolute figure of merit, 0.961, and the third largest combined figure of merit, 2.309, contained peaks at stereochemically reasonable positions for all of the atoms of the cyclic dipeptide. Least-squares refinement of the coordinates and isotropic temperature parameters led to an R index of 0.31, at which time three additional peaks on the E map were identified, from packing and hydrogen-bonding considerations, as probable water molecules of crystallization. Hydrogen atoms were introduced at stereochemically reasonable sites, and refinement was continued.

During the final least-squares cycles, 263 parameters were partitioned among two matrices, the coordinate of the C, N, and O atoms in one and their anisotropic temperature parameters, a scale factor, a secondary extinction coefficient, and the coordinates and isotropic temperature parameters of the H atoms in the second. The quantity minimized was $\sum w(F_o^2 - F_c^2)^2$, with weights w equal to $\sigma^{-2}(F_o^2)$.

The final R index was 0.056 and the goodness of fit, $(\sum w(F_o^2 - F_c^2)^2 / (n - p))^{1/2}$, was 1.59 for $n = 1701$ reflections and $p = 263$ parameters. No account was taken of anomalous dispersion, and hence the absolute configuration of the molecule was not confirmed.

Final coordinates and temperature parameters are listed in Tables II and III. Since the reflections having large values of l tend to have lower than average weights (see above), the esd's in the z coordinates and in the $U(33)$ terms of the anisotropic temperature factors tend to be larger than those of the other parameters.

Results and Discussion

The molecule is a zwitterion, the proton of the carboxyl

Table III. Coordinates ($\times 10^3$) and Isotropic Thermal Parameters of the Hydrogen Atoms

Atom	x	y	z	B
H(N1)	146 (2)	584 (2)	489 (5)	4.8 (0.8)
H(N2)	154 (1)	451 (1)	1183 (4)	1.6 (0.5)
H(ND1)	-61 (2)	659 (2)	1116 (6)	5.8 (0.9)
H(NE1)	-142 (2)	454 (2)	736 (7)	8.5 (1.1)
H(CA1)	177 (1)	669 (1)	815 (4)	2.0 (0.5)
H(CA2)	217 (1)	374 (2)	885 (5)	2.9 (0.6)
H(CB1)	55 (1)	727 (2)	902 (5)	2.6 (0.6)
H'(CB1)	61 (2)	706 (2)	638 (6)	4.9 (0.8)
H(CB2)	48 (2)	356 (2)	879 (5)	3.1 (0.6)
H'(CB2)	113 (2)	292 (2)	747 (6)	5.1 (0.8)
H(CD1)	-23 (2)	523 (2)	567 (5)	3.9 (0.8)
H(CE1)	-164 (2)	535 (3)	1069 (7)	8.5 (1.2)
H(W1)	249 (2)	837 (2)	786 (6)	5.0 (0.7)
H'(W1)	219 (2)	857 (2)	976 (6)	3.9 (1.0)
H(W2)	176 (2)	742 (3)	1250 (8)	9.2 (1.2)
H'(W2)	241 (2)	800 (3)	1390 (7)	7.8 (1.2)
H(W3)	98 (3)	849 (3)	1270 (10)	15.0 (1.7)
H'(W3)	12 (3)	839 (3)	1226 (9)	11.4 (1.3)

group of the aspartyl residue having been transferred to the imidazole ring of the histidyl residue.

The packing of the molecules in the unit cell is shown in Figure 1. There are ten protons available for hydrogen bonding, and all of them are involved in intermolecular hydrogen bonds. Details are given in Table IV. A feature of the packing motif is the ribbon of translationally equivalent DKP rings, hydrogen bonded to one another along the direction of the c axis. The repeat distance along this direction, 6.14 \AA , lies in the middle of the range of values 6.08–6.19 \AA found in the other cyclic dipeptides *cyclo*-(gly-gly),³ *cyclo*-(L-ala-L-ala),^{2a,12} *cyclo*-(gly-L-tyr),⁶ *cyclo*-(L-ser-L-tyr),⁶ *cyclo*-(gly-L-try),⁸ and *cyclo*-(L-val-D-val),¹³ whose crystal structures show this same ribbon of repeating DKP rings. The hydrogen-bond lengths $N \cdots O$ in these compounds range from 2.84 \AA to 2.93 \AA .

The ribbons of hydrogen-bonded DKP molecules are oriented approximately parallel to the (100) planes, and pairs of ribbons lie face to face across a 2_1 screw axis such that the DKP ring of one ribbon is opposite the $N-H \cdots O$ bonds of the ribbon facing it, at a distance of about 3.40 \AA . Similar face-to-face pairing of ribbons across twofold screw axes are found in crystals of *cyclo*-(gly-gly),³ *cyclo*-(gly-L-tyr),⁶ *cyclo*-(L-ser-L-try),⁶ and *cyclo*-(gly-L-try).⁸

Table II. Coordinates ($\times 10^5$) and Anisotropic Temperature Parameters ($\times 10^4$) of the Nonhydrogen Atoms^a

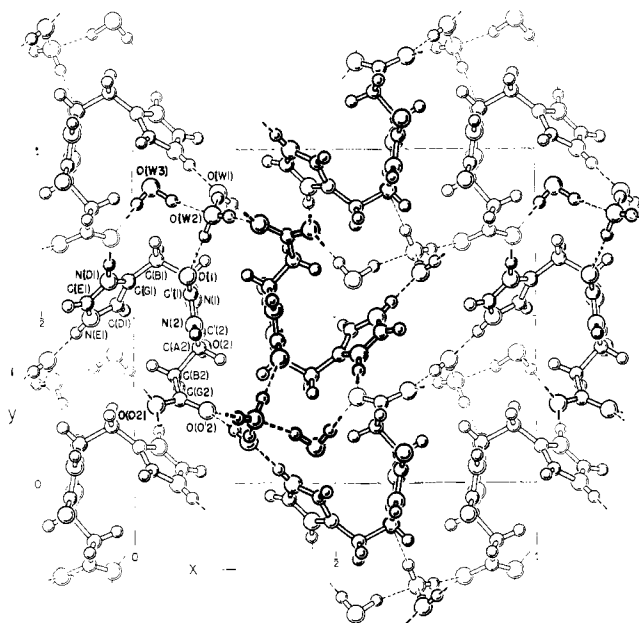
Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	148 49 (12)	552 73 (13)	639 03 (36)	427 (12)	330 (10)	155 (15)	55 (10)	37 (14)	41 (10)
N(2)	151 30 (13)	475 84 (13)	105 021 (35)	459 (13)	338 (11)	136 (14)	26 (10)	3 (14)	35 (11)
N(D1)	-6125 (13)	610 50 (15)	997 99 (43)	442 (13)	454 (13)	373 (18)	47 (11)	73 (16)	-63 (14)
N(E1)	-106 35(14)	499 31 (16)	785 82 (51)	436 (15)	558 (15)	611 (24)	-15 (12)	-105 (17)	-143 (17)
C'(1)	141 88 (14)	570 70 (16)	103 850 (46)	304 (13)	352 (12)	204 (18)	-11 (10)	-6 (15)	20 (13)
C'(2)	161 13 (13)	457 19 (15)	649 02 (46)	281 (11)	351 (12)	189 (17)	4 (10)	-23 (14)	12 (13)
C(A1)	137 45 (14)	619 25 (14)	821 06 (46)	364 (13)	287 (11)	203 (17)	-18 (11)	11 (16)	27 (14)
C(A2)	162 88 (14)	409 00 (15)	868 69 (44)	329 (12)	302 (12)	230 (19)	4 (10)	4 (15)	4 (12)
C(B1)	5746 (15)	673 94 (15)	794 96 (50)	445 (15)	329 (12)	262 (18)	50 (12)	-15 (18)	2 (14)
C(B2)	101 38 (15)	327 13 (17)	875 69 (49)	465 (17)	391 (14)	253 (21)	-83 (13)	-28 (18)	62 (15)
C(G1)	-1272 (15)	608 75 (16)	818 58 (52)	385 (13)	369 (13)	304 (19)	109 (11)	-27 (17)	-10 (15)
C(G2)	114 72 (16)	256 51 (16)	106 325 (51)	482 (15)	304 (12)	342 (21)	-39 (12)	39 (17)	15 (14)
C(D1)	-4150 (16)	538 85 (19)	686 69 (58)	409 (16)	565 (18)	410 (24)	40 (14)	-33 (19)	-115 (20)
C(E1)	-117 51 (17)	543 40 (21)	975 10 (63)	429 (17)	603 (18)	641 (29)	0 (15)	91 (22)	-75 (22)
O(1)	135 68 (11)	622 04 (11)	120 432 (31)	594 (13)	390 (9)	191 (12)	47 (9)	0 (12)	-30 (10)
O(2)	172 14 (12)	407 82 (11)	485 70 (31)	675 (14)	383 (10)	187 (12)	69 (9)	24 (12)	-11 (10)
O(D2)	5616 (12)	237 92 (12)	117 972 (38)	585 (13)	511 (11)	417 (14)	-5 (10)	141 (14)	141 (12)
O(D'2)	182 64 (12)	221 15 (14)	108 308 (37)	574 (13)	647 (13)	458 (16)	200 (11)	126 (14)	211 (12)
O(W1)	215 10 (12)	869 61 (16)	855 91 (39)	634 (16)	900 (19)	451 (20)	370 (14)	72 (18)	84 (18)
O(W2)	199 77 (14)	805 83 (13)	128 015 (41)	792 (18)	556 (14)	604 (20)	-27 (13)	-273 (17)	53 (14)
O(W3)	4631 (15)	888 70 (16)	119 596 (54)	919 (21)	782 (18)	1044 (28)	-32 (18)	39 (25)	316 (20)

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

Table IV. Details of the Hydrogen Bonds, D-H...A

D	H	A	D...A, Å $\sigma \sim 0.003 \text{ \AA}$	H...A, Å $\sigma \sim 0.04 \text{ \AA}$	$\angle(\text{D-H}\cdots\text{A})$, deg $\sigma \sim 2^\circ$	$\angle(\text{H-D}\cdots\text{A})$, deg $\sigma \sim 2^\circ$
N(1)	H(N1)	O(1) ^a	2.844	1.84	172	5
N(2)	H(N2)	O(2) ^b	2.856	1.98	172	6
N(D1)	H(ND1)	O(D2) ^c	2.649	1.67	177	2
N(E1)	H(NE1)	O(W1) ^d	2.699	1.78	177	2
O(W1)	H(W1)	O(D'2) ^e	2.705	1.87	169	8
O(W1)	H'(W1)	O(W2)	2.762	2.02	165	11
O(W2)	H(W2)	O(1)	2.793	1.81	178	2
O(W2)	H'(W2)	O(D'2) ^f	2.737	1.77	175	3
O(W3)	H(W3)	O(D2) ^c	2.804	1.90	174	4
O(W3)	H'(W3)	O(W2)	2.863	1.80	155	16

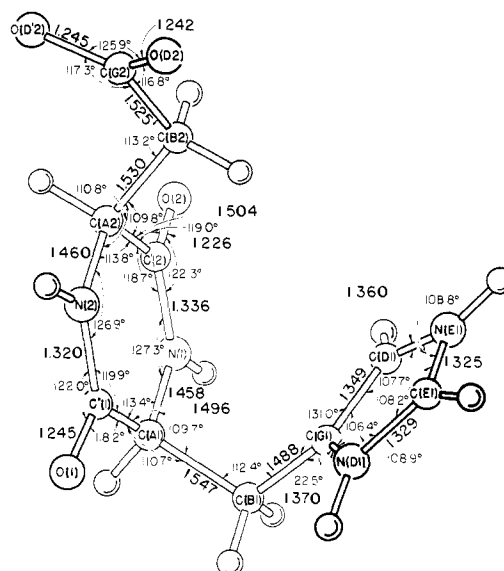
^aAt $x, y, z - 1$. ^bAt $x, y, z + 1$. ^cAt $-x, y + \frac{1}{2}, -z + \frac{1}{2}$. ^dAt $-x, y - \frac{1}{2}, -z + \frac{3}{2}$. ^eAt $-x + \frac{1}{2}, -y + 1, z - \frac{1}{2}$. ^fAt $-x + \frac{1}{2}, -y + 1, z + \frac{1}{2}$.

**Figure 1.** The crystal structure of *cyclo-(L-histidyl-L-aspartyl) trihydrate*, as viewed along the c axis. Dashed lines indicate hydrogen bonds.

Bond distances and angles involving the C, N, and O atoms are shown in Figure 2. Differences in dimensions of the two halves of the DKP ring are significant, and reflect the different hydrogen bonding environments. Oxygen atom O(1) accepts two hydrogen bonds compared to one for O(2), and as a result the carbonyl bond C'(1)-O(1) is appreciably longer than C'(2)-O(2) while the neighboring bonds C'(1)-N(2) and C'(1)-C(A1) are shorter, by lesser amounts, than the corresponding bonds C'(2)-N(1) and C'(2)-C(A2).

The dimensions of the imidazole ring are in satisfactory agreement with values found in other compounds in which the ring is similarly protonated, including DL-histidine hydrochloride dihydrate,¹⁴ L-histidine hydrochloride monohydrate,¹⁵ and L-N-acetylhistidine monohydrate;¹⁶ however, they differ significantly from values found for compounds containing an unprotonated ring, including L-histidine,¹⁷ DL-histidine,¹⁸ and *cyclo-(L-threonyl-L-histidyl) dihydrate*.⁹ Average values for protonated and unprotonated rings are given in Table V. As noted by Madden et al.,¹⁷ differences between the two forms can be attributed to increased aromaticity upon protonation, leading to shorter bond lengths, by about 0.01 Å, and more equal bond angles. Perhaps surprisingly, differences in the distances and angles involving the nitrogen atom ND which accepts the additional proton are no larger than those involving other atoms.

The large difference between the two external bond angles

**Figure 2.** Bond distances and angles involving the C, N, and O atoms. Standard deviations are approximately 0.004 Å and 0.2°.**Table V.** Comparison of Bond Lengths (Å) and Angles (deg) in Neutral and Protonated Forms of the Imidazole Rings^a

	Neutral ring ^b	Present study	Protonated ring ^b
Distance			
C(B)-C(G)	1.505	1.488	1.493
C(G)-C(D)	1.364	1.349	1.352
C(G)-C(D)	1.380	1.370	1.375
C(D)-N(E)	1.374	1.360	1.365
N(D)-C(E)	1.326	1.325	1.325
C(E)-N(E)	1.342	1.329	1.321
Angle			
C(B)-C(G)-C(D)	129.5	131.0	130.8
C(B)-C(G)-N(D)	120.8	122.5	122.8
N(D)-C(G)-C(D)	109.7	106.4	106.4
C(G)-C(D)-N(E)	106.1	107.7	107.3
C(D)-N(E)-C(E)	107.1	108.8	109.0
N(E)-C(E)-N(D)	112.0	108.2	108.4
C(E)-N(D)-C(G)	105.1	108.9	108.8

^a Standard deviations in the average values, as calculated from the esd's of the various investigations, are about 0.003 Å and 0.2°. In all cases the individual values are in adequate agreement, within their esd's, with the average values. ^b Weighted average of values from monoclinic L-histidine^{17b} ($\sigma = 0.012 \text{ \AA}$), orthorhombic L-histidine^{17a} ($\sigma = 0.003 \text{ \AA}$), DL-histidine¹⁸ ($\sigma = 0.006 \text{ \AA}$), and *cyclo-(L-threonyl-L-histidyl)·2H₂O*⁹ ($\sigma = 0.006 \text{ \AA}$). ^c Weighted average of values from DL-histidine·HCl·2H₂O¹⁴ ($\sigma = 0.01 \text{ \AA}$), L-histidine·HCl·H₂O¹⁵ ($\sigma = 0.01 \text{ \AA}$), L-N-acetylhistidine·H₂O¹⁶ ($\sigma = 0.004 \text{ \AA}$), and this investigation ($\sigma = 0.004 \text{ \AA}$).

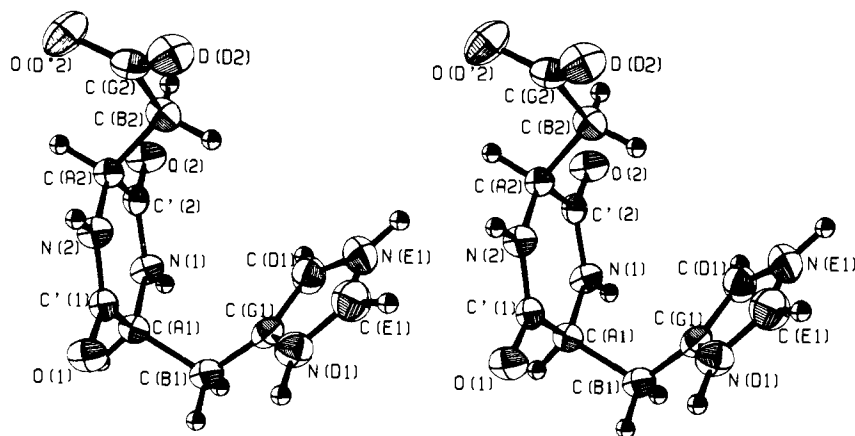


Figure 3. A stereoscopic drawing²¹ of the molecule. Temperature ellipsoids for the C, N, and O atoms are drawn at the 50% probability level; the hydrogen atoms are represented as small spheres of arbitrary diameter.

Table VI. Torsion Angles in *cyclo*-(L-histidyl-L-aspartyl)

Torsion angle	Notation ^a	Value, deg
C'(2)-N(1)-C(A1)-C'(1)	ϕ_1	0.4
N(1)-C(A1)-C'(1)-N(2)	ψ_1	-2.9
C(A1)-C'(1)-N(2)-C(A2)	ω_1	3.8
C'(1)-N(2)-C(A2)-C'(2)	ϕ_2	-1.8
N(2)-C(A2)-C'(2)-N(1)	ψ_2	-0.9
C(A2)-C'(2)-N(1)-C(A1)	ω_2	1.5
N(1)-C(A1)-C(B1)-C(G1)	χ_1^1	67.5
C'(1)-C(A1)-C(B1)-C(G1)		-58.4
C(A1)-C(B1)-C(G1)-N(D1)	χ_1^2	107.6
C(A1)-C(B1)-C(G1)-C(D1)		-71.1
N(2)-C(A2)-C(B2)-C(G2)	χ_2^1	-70.0
C'(2)-C(A2)-C(B2)-C(G2)		163.5
C(A2)-C(B2)-C(G2)-O(D2)	χ_2^2	-51.8
C(A2)-C(B2)-C(G2)-O(D'2)		129.7

^a See ref 20.

at the imidazole ring, C(B1)-C(G1)-C(D1) and C(B1)-C(G1)-N(D1), has been noted previously.¹⁴ It is not greatly influenced by protonation of the imidazole ring.

Molecular Conformation

A stereoscopic view of the molecule is shown in Figure 3, and selected torsion angles are given in Table VI. The imidazole ring is folded back over the DKP ring, with the trace of the C(B1)-C(G1) bond approximately bisecting the C'(1)-C(A1)-N(1) bond angle (note the nearly equal but opposite values of the torsion angles N(1)-C(A1)-C(B1)-C(G1) and C'(1)-C(A1)-C(B1)-C(G1), Table VI). Thus it is the positively charged imidazole ring, rather than the negatively charged carboxylate group, that chooses to interact with the DKP ring.

As noted earlier, the aromatic side groups in crystals of *cyclo*-(glycyl-L-tyrosyl),⁶ *cyclo*-(L-seryl-L-tyrosyl),⁶ and *cyclo*-(L-prolyl-D-phenylalanyl)^{4a} also fold back so as to stack on top of the DKP ring. On the other hand, the histidyl side chain of *cyclo*-(L-threonyl-L-histidyl) dihydrate⁹ and the tryptophan side chain of *cyclo*-(glycyl-L-tryptophyl)⁸ adopt an extended conformation. In both of these latter cases, unusual intermolecular interaction can be invoked to explain the nonfolded conformation. In crystals of *cyclo*-(L-threonyl-L-histidyl) dihydrate one of the water molecules of crystallization forms hydrogen bonds with both the threonyl and the histidyl side chains of a single molecule, and hence presumably dictates the molecular conformation; NMR studies suggest that this particular molecule shows the same extended conformation in aqueous solution.¹⁰ In crystals of *cyclo*-(glycyl-L-tryptophyl), hydrogen-bonded chains of DKP rings pack closely on

top of one another to form continuous stacks in one region of the structure while the tryptophan rings of different molecules pack together in a characteristic herringbone fashion in another region; in solution, where intramolecular forces dominate, the folded conformation is preferred.^{5b}

As noted by Lin and Webb,⁶ the torsion angles χ_1^2 must be close to 90° to prevent interference between the imidazole ring and the DKP ring—that is, the dihedral angle between the plane of the imidazole ring and the plane of atoms C(A1), C(B1), and C(G1) must be near 90°. This dihedral angle in *cyclo*-(L-histidyl-L-aspartyl) trihydrate is 72°, compared with 71° in *cyclo*-(L-seryl-L-tyrosyl),⁶ 69° in *cyclo*-(glycyl-L-tyrosyl),⁶ 85° in *cyclo*-(L-prolyl-D-phenylalanyl)^{4a} and 81° in *cyclo*-(L-threonyl-L-histidyl) dihydrate.⁹

The DKP ring is approximately planar, none of the six ring atoms lying more than 0.020 Å from their best plane. The two oxygen atoms are displaced from this plane by approximately 0.06 Å, in a direction opposite to that of the side chains. The imidazole ring and the carboxylate group are planar within 0.01 Å; they make dihedral angles of 60.2 and 67.4°, respectively, with the DKP ring and are themselves nearly perpendicular, at 84.5°.

The planarity of the DKP ring prevents the histidine side chain from adopting a truly axial, or "flagpole", site and hence the imidazole ring is not in intimate contact with the DKP ring. It seems apparent that it is the presence of the methylene group of the aspartyl side chain that prevents further folding of the molecule; the distance from this carbon atom, C(B2), to N(E1) of the imidazole ring is 4.25 Å and to C(D1), only 3.95 Å. The corresponding H(CB2)⋯N(E1) and H(CB2)⋯C(D1) distances are 3.30 and 3.16 Å. A similar situation obtains in crystals of *cyclo*-(L-seryl-L-tyrosyl),⁶ where interaction between the seryl side chain and the hydroxyphenyl group again results in an approximately planar DKP ring. In contrast, in crystals of *cyclo*-(glycyl-L-tyrosyl)⁶ and *cyclo*-(L-prolyl-D-phenylalanyl),^{4a} where the aromatic side chain has only a cross-ring hydrogen atom to contend with, the DKP ring is buckled into a boat conformation, thus allowing the aromatic group in the flagpole position to fold more intimately back on the DKP ring.

From an analysis of crystallographic data on saturated and unsaturated carboxylic acids, Dunitz and Strickler²² observed that the C=O bond tends to be syn-planar with respect to the C α -C β bond—that is, that the torsion angle C(A2)-C(B2)-C(G2)-O(D'2) tends to be approximately 0°. In an aspartyl grouping, this conformation places the carbonyl oxygen atom within 3.0 Å of the nitrogen atom. Indeed, in crystals of DL-aspartic acid²³ the torsion angle is 3.1° and the oxygen atom, at 2.09 Å from the nitrogen atom, probably

participates in an intramolecular hydrogen bond. However, in L-aspartic acid²⁴ as well as in the present compound nitrogen atom N(2) participates only in intermolecular hydrogen bonding, and repulsion between the carboxyl group and the hydrogen-bond acceptor prevents the syn-planar conformation; the C-C-C O torsion angle is about -52° in both compounds.

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References and Notes

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Synthesis, Reactions, and Crystal and Molecular Structure of a Sulfurane with Two Apical Nitrogen-Centered Ligands: a Spirodiazasulfurane¹

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Abstract: Oxidation of bis[2-(*N*-isopropylcarbamoyl)phenyl] sulfide (**6**) with *tert*-butyl hypochlorite gives monocyclic chloroazasulfurane **7**. Treatment of **7** with potassium hydride affords spirodiaryldiamidosulfurane **4**, the first example of a sulfurane with two apical nitrogen ligands. The crystal structure of **4** reveals slightly distorted trigonal bipyramidal geometry about sulfur. The C-S-C angle is $104.8(2)^\circ$. The S-N bond lengths, 1.899 (3) and 1.897 (3) Å, are 0.16 Å longer than the sum of the covalent radii and are among the longest reported S-N bond lengths. The calculated bond order is 0.55. The sums of the bond angles around the nitrogen atoms are 352.8 and 354.0° with the nitrogens being 0.24 and 0.22 Å out of their S-C-C planes. The crystals of **4** are monoclinic, the space group is $P2_1/c$, and there are four molecules in a unit cell of dimensions $a = 13.980(3)$, $b = 16.091(6)$, $c = 9.009(3)$ Å, $\beta = 112.00(2)^\circ$. The structure was refined to an *R* factor of 0.059 for 2212 non-zero reflections. Comparisons of **4** with closely related structures emphasize S-N bond lengths and the geometry of nitrogen bonded to sulfur. A chloroform solution of diazasulfurane **4** hydrolyzes in seconds to sulfoxide diamide **8** upon the addition of water. Sulfurane **4** reacts with hydrogen chloride to form chloroazasulfurane **7**. Attempted oxidation of **4** with ozone or ruthenium tetroxide to form spirodiaryldiazasulfurane oxide **18** fails. We discuss the relevance of this work to earlier work on the mechanism of the facile cleavage of secondary amides in reactions with dialkoxysulfuranes.

Introduction

Sulfuranes with two apical oxygen ligands have been reported.² These compounds, which can be viewed as ketal analogues of sulfoxides, vary widely in their reactivities. For example, spirobicyclic sulfurane **1** is found to be inert toward acid or base hydrolysis.^{2b} In contrast, acyclic sulfurane **2** reacts instantly with water to form diphenyl sulfoxide and hexafluoroocumyl alcohol.^{2c} Sulfurane **3** is hydrolyzed with difficulty.^{2d}

