585, and 400 cm^{-1}. The nmr spectrum in CCl_4 solution showed singlets at τ 2.74 and 2.54 and a broad resonance at τ −1.7, with relative intensities 5:1:1, attributed to the phenyl, vinyl, and hydroxyl protons, respectively. Assignment of the structure as the *cis* isomer follows from the position of the vinyl proton resonance.

Anal. Calcd for $C_9H_7ClO_2$: C, 59.19; H, 3.87; Cl, 19.42; O (diff), 17.52. Found: C, 59.11; H, 3.38; Cl, 19.17; O (diff), 17.89.

Phenylpropiolic Acid (15a) by Hydrolysis of 10a. About 0.2 g of **10a** was left standing in contact with 3 ml of H_2O for 4 days. During this time, needle-like crystals formed in the pool of water. The water was drawn off, and the solid was recrystallized from cyclohexane, then sublimed at 120° (5 Torr) to give 0.05 g of a white solid. The melting point (133–135°) and infrared spectrum (COOH absorption at 2900 (vb); C≡C at 2230 (s) and 2200 (s); C=O at 1680 (s); lower frequency bands at 1500 (m), 1450 (m), 1430 (s), 1310 (s), 1210 (s), 1180 (m), 1040 (w), 930 (m), 770 (s), and 690 (m) cm^{-1} were identical with those of authentic phenylpropiolic acid.

***p*-Fluorophenylpropiolic Acid (15b) by Hydrolysis of 10b.** Hydrolysis of **10b**, according to the procedure above, gave *p*-fluorophenylpropiolic acid as a white solid, mp 148–152°. The infrared spectrum in the region 4000–625 cm^{-1} showed absorption bands at 2860 (w, br), 2530 (w, br), 2230 (sh), 2200 (s), 1700 (s), 1600 (s), 1510 (m), 1385 (vs), 1340 (w), 1305 (m), 1290 (m), 1225 (vs), 1165 (s), 1100 (vs), 925 (w), 840 (s), 815 (w), and 745 (w) cm^{-1}.

Anal. Calcd for $C_9H_5FO_2$: C, 65.85; H, 3.05. Found: C, 65.41; H, 3.03.

Reaction with 1-Phenyl-2,3,3-trichlorocyclopropene with KO-*t*-Bu. The reaction of 1-phenyl-2,3,3-trichlorocyclopropene (**2a**) with KO-*t*-Bu to give phenylhydroxycyclopropenone was carried out according to the method of Farnum, Chickos, and Thurston.[10] The product was obtained in yields of 1–12% as fluffy light yellow needles, mp 244–246° (crystallized from acetonitrile). The ultraviolet spectrum exhibited an absorption maximum at 248 mμ in strong acid (5% HCl) and at 256 mμ in strong base (5% NaOH). The infrared spectrum (Nujol mull) showed broad, rounded absorption maxima at 1610, 1350, and 1080 cm^{-1}, along with strong peaks at 770 and 690 cm^{-1}. All of the above properties are consistent with those reported for phenylhydroxycyclopropenone.[9,10]

Reaction of 1-*p*-Fluorophenyl-2,3,3-trichlorocyclopropene with CF_3COOAg. Eleven grams of CF_3COOAg (50 mmol) was added to 300 ml of anhydrous ether in a 2-necked, 500-ml round-bottomed flask, equipped with a stirrer and immersed in an ice–water bath. Compound **2b** dissolved in 10 ml of ether, was added dropwise to the ethereal mixture with vigorous stirring. The mixture immediately turned milky due to the precipitation of AgCl. The ice–water bath was removed and stirring was continued for 2 hr. The AgCl was filtered from the solution by the use of a Büchner funnel with filter cell; 4.3 g (30 mmol) was collected. The ethereal solution was washed with 3 50-ml portions of water, dried over $CaCl_2$, filtered, and concentrated by rotary evaporation, leaving an off-white pasty solid. Hot cyclohexane was added and the solution filtered while hot. In this manner, 3.0 g of unreacted CF_3COOAg (14 mmol) was collected on the filter. Upon cooling the filtrate, a white solid crystallized. This was filtered to give 1.58 g (7.9 mmol; 49%) of **14b**, mp 144–145°, infrared spectrum identical with that of **14b** prepared as described above.

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Conformation of Cyclic Dipeptides. The Crystal and Molecular Structures of Cyclo-D-alanyl-L-alanyl and Cyclo-L-alanyl-L-alanyl (3,6-Dimethylpiperazine-2,5-dione)[1a,b]

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Abstract: The structures of cyclo-D-alanyl-L-alanyl and cyclo-L-alanyl-L-alanyl have been determined by single crystal X-ray analysis. The crystals of the DL form are monoclinic, space group $P2_1/n$, a = 6.3497 Å, b = 6.2203 Å, c = 9.0438 Å, β = 95.814°, and Z = 2. The crystals of the LL isomer are triclinic, space group P1, a = 5.1552 Å, b = 8.0596 Å, c = 4.6698 Å, α = 103.155°, β = 103.680°, γ = 97.578°, and Z = 1. Diffractometer data were collected using niobium-filtered Mo Kα radiation and the structures were refined to R values of 0.037 for the DL compound and 0.030 for the LL compound. The DL molecule is nearly planar, while the LL molecule is appreciably puckered adopting a skewed boat conformation with the methyl substituents quasi-equatorial. This difference in conformation might account for the difference in hydrolysis rate between DL and LL isomers.

The present structure investigations were undertaken to see if any conformational aspects could explain the observed differences in hydrolysis rate between DL and LL isomers of cyclic dipeptides. In acid solution cyclo-L-alanyl-L-alanyl, *e.g.*, hydrolyses 2.5 times more rapidly than does the DL isomer.[2] The relevance of crystal structure analysis in predicting the conformation of a molecule in solution may be questionable since the quantitative effect of packing forces in the crystal is still an unknown factor in most structure determinations. These forces are often invoked by chemists to explain unexpected features found in a crystal structure. Several theoretical approaches have been made to obtain reliable functions for nonbonded interactions in the solid state, but thus far no general solution to the problem has been found.

The diketopiperazine ring system, later referred to as DKP, is present in a number of molecules with important biological activities; cycloserine, *e.g.*, is found to be effective against *Mycobacterium tuberculosis*.[3] DKP rings may also be present in protein molecules, though

(1) (a) Paper presented at Annual Meeting of the American Crystallographic Association, Seattle, Wash., 1969. (b) The same two compounds have also just been investigated by E. Benedetti, P. Corradini, M. Goodman, and C. Pedone. Paper presented at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 14–18, 1969. (c) Address correspondence to the author at the Chemical Institute, University of Bergen, 5000 Bergen, Norway.

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Table I. Positional and Thermal Parameters for Cyclo-D-alanyl-L-alanyl and Cyclo-L-alanyl-L-alanyl[a]

Atom	x/a	y/b	z/c	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
				DL Compound					
N	0.13743 (15)	0.02459 (14)	−0.10520 (9)	2.91 (3)	2.32 (3)	2.38 (3)	−0.22 (2)	1.63 (3)	−0.22 (2)
O	−0.07988 (15)	0.31170 (13)	0.19096 (9)	4.92 (4)	2.78 (3)	3.97 (3)	−0.25 (3)	2.58 (3)	−1.22 (3)
C(1)	−0.04487 (15)	0.16573 (14)	0.10403 (10)	2.58 (4)	2.10 (3)	2.16 (3)	0.24 (3)	1.05 (3)	−0.05 (3)
C(2)	0.11382 (15)	0.20538 (15)	−0.00638 (10)	2.73 (4)	1.75 (3)	2.26 (4)	−0.08 (3)	1.11 (3)	0.02 (3)
C(3)	0.32757 (22)	0.26520 (34)	0.07545 (19)	3.30 (5)	5.44 (8)	4.46 (6)	−1.53 (5)	1.14 (5)	−1.59 (6)
H(1)	0.2214 (24)	0.0403 (19)	−0.1764 (18)	3.8 (8)	1.6 (6)	5.7 (6)	−0.9 (5)	0.9 (6)	−1.1 (5)
H(2)	0.0606 (24)	0.3336 (20)	−0.0704 (14)	5.2 (7)	2.9 (5)	2.4 (8)	1.1 (5)	1.9 (6)	0.3 (5)
H(3)	0.3720 (32)	0.1486 (29)	0.1393 (27)	5.1 (11)	3.2 (9)	10.7 (14)	−1.3 (7)	1.2 (10)	0.5 (10)
H(4)	0.4379 (28)	0.2833 (28)	0.0018 (20)	4.7 (9)	6.9 (10)	6.3 (9)	−3.5 (8)	2.2 (8)	−2.4 (8)
H(5)	0.3176 (32)	0.3774 (31)	0.1403 (21)	7.2 (11)	7.7 (12)	8.0 (10)	−5.3 (10)	3.1 (9)	−6.7 (10)
				LL Compound					
O(1)	0.7500	0.2500	0.7500	3.22 (6)	4.17 (7)	5.10 (6)	0.34 (5)	1.48 (5)	2.11 (5)
O(2)	0.2800 (4)	0.6344 (2)	0.0730 (4)	2.58 (6)	4.28 (7)	3.47 (6)	0.32 (5)	0.51 (5)	1.86 (5)
N(1)	0.7439 (3)	0.5092 (2)	0.6453 (4)	1.91 (5)	3.48 (6)	3.11 (5)	0.24 (4)	0.80 (4)	0.87 (4)
N(2)	0.2507 (3)	0.3903 (2)	0.2313 (3)	2.03 (5)	3.63 (6)	2.58 (5)	0.24 (4)	0.59 (4)	1.11 (5)
C(1)	0.6276 (3)	0.3484 (2)	0.6270 (4)	2.26 (4)	3.69 (6)	2.56 (5)	0.51 (4)	0.43 (4)	0.96 (4)
C(2)	0.3311 (4)	0.2877 (2)	0.4442 (4)	2.05 (5)	3.68 (6)	2.66 (5)	0.19 (4)	0.26 (4)	1.19 (5)
C(3)	0.2716 (7)	0.0978 (3)	0.2694 (9)	4.80 (11)	3.40 (10)	6.03 (14)	0.00 (8)	1.97 (11)	1.13 (9)
C(4)	0.3651 (3)	0.5533 (2)	0.2596 (4)	1.76 (4)	3.56 (6)	2.31 (5)	0.70 (4)	0.04 (4)	0.81 (4)
C(5)	0.6044 (3)	0.6394 (2)	0.5387 (4)	2.12 (4)	3.21 (6)	2.17 (5)	0.62 (4)	0.10 (4)	0.46 (4)
C(6)	0.8056 (4)	0.7724 (3)	0.4764 (6)	2.82 (6)	3.78 (8)	4.17 (9)	−0.13 (6)	0.26 (7)	1.28 (7)
H(1)	0.922 (7)	0.538 (3)	0.769 (7)	5.4 (15)	1.9 (9)	6.2 (15)	0.7 (10)	2.3 (13)	1.8 (9)
H(2)	0.091 (5)	0.334 (3)	0.081 (5)	2.6 (11)	4.4 (11)	2.2 (9)	0.7 (9)	1.0 (8)	1.2 (8)
H(21)	0.221 (5)	0.301 (4)	0.586 (6)	2.4 (11)	10.3 (20)	4.2 (12)	2.2 (11)	0.3 (9)	4.5 (13)
H(31)	0.411 (8)	0.093 (4)	0.142 (7)	6.1 (17)	4.5 (15)	3.8 (14)	−0.2 (13)	1.4 (13)	1.2 (11)
H(32)	0.313 (8)	0.034 (4)	0.385 (11)	6.7 (21)	3.2 (15)	11.1 (29)	1.5 (15)	2.6 (20)	0.6 (18)
H(33)	0.075 (8)	0.059 (4)	0.151 (10)	8.5 (25)	5.0 (18)	9.0 (23)	2.1 (20)	3.3 (21)	0.9 (16)
H(51)	0.527 (4)	0.695 (3)	0.699 (5)	2.6 (9)	3.7 (9)	3.5 (9)	1.5 (8)	0.3 (8)	2.8 (8)
H(61)	0.879 (7)	0.714 (3)	0.308 (6)	7.9 (18)	4.0 (12)	4.6 (14)	1.4 (11)	3.7 (13)	1.0 (10)
H(62)	0.731 (7)	0.871 (4)	0.437 (7)	6.3 (16)	5.2 (15)	7.9 (19)	−0.6 (13)	0.3 (14)	5.5 (14)
H(63)	0.962 (7)	0.812 (3)	0.653 (7)	6.0 (16)	3.7 (14)	6.0 (16)	−1.7 (12)	0.8 (14)	2.0 (12)

[a] The B_{ij}'s are the thermal parameters in the expression $T_i = \exp[-1/4(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$. Estimated standard deviations are given in parentheses; the numbers refer to the last decimal places.

the evidence for this is not conclusive since rapid cyclization of amino acids may take place during sequence analysis.

A theoretical analysis of nonbonded interaction minima in unsubstituted DKP (cyclic glycine) indicated that the planar conformation is the most stable,[4] in agreement with the results from X-ray analysis.[5] Kopple and coworkers have carried out nmr studies on cyclic dipeptides in solutions of trifluoroacetic acid, dimethyl sulfoxide-d_6, and deuterium oxide. In their first paper[6] they concluded that the diketopiperazine ring probably is planar in solution and, furthermore, that aromatic side chains tend to be folded over the DKP ring. However, recent nmr studies in the same laboratory[7] indicate that the DKP ring is nonplanar in DMSO solvent while planar in trifluoroacetic acid. A twist boat model is proposed for the nonplanar conformation.

Experimental Section

Cyclo-D-alanyl-L-alanyl and cyclo-L-alanyl-L-alanyl, later referred to as DL and LL, crystallize from methanol as irregular, pyramidal lumps and long needles, respectively. The DL crystals could easily be cut to shape while the LL crystals had to be cut with a solvent saw to prevent splitting into multiple thin needles. Preliminary Weissenberg and precession photographs gave the space groups as $P2_1/n$ for DL and P1 for LL. The cell dimensions were determined from a least-squares treatment of 2θ measurements on a manually operated four-circle diffractometer using Mo Kα radiation (λ = 0.71069 A). The standard deviations quoted for the cell parameters are those obtained from the least-squares matrix. Densities were determined by flotation in a xylene–bromobenzene mixture.

Integrated intensities were measured by the moving crystal–moving counter technique using Nb-filtered Mo Kα radiation. The scan ranges were calculated according to the equation $\Delta 2\theta = A + B \tan \theta$.[8] The constant A depends on the mosaic spread of the crystal and is determined by measuring the scan range sufficient for strong low-order reflections. For the DL crystals, which has a fairly low mosaic spread, A was found to be 1.5°, and for the LL crystal an A value of 1.8° was found. The constant B was set equal to 1.0°, a value which has been found to be satisfactory for Mo radiation. For reflections with peak scan less than 30,000 dekacounts, the Mo tube was operated at 14 mA and 50 kV. For stronger reflections, the tube current was reduced to 3 mA keeping the potential constant at 50 kV. This procedure is found to be more satisfactory than the use of attenuators. At low 2θ, where the Nb Kα absorption edge is close to the Mo Kα peak, the background at the low 2θ side appears only as a small "shoulder" and the starting point of the 2θ scans has to be adjusted accordingly.

Both sets of data were measured within a sphere limited at $\sin\theta/\lambda = 0.70$. The uncertainty in net count due to counting statistics is $\sigma_c = (N_{B_1} + N_{Pk} + N_{B_2})^{1/2}$ where N_{Pk} is the number of counts in a scan and N_{B_1} and N_{B_2} are the background counts on each side of the peak. Three standard reflections were measured every 4 hr during data collection to check the electronic stability of the instrument and any deterioration of the crystal. The fluctuation in the intensities of the standard reflections was less than 1%. Both sets of data were corrected for Lorentz and polarization effects in the usual way. Correction for coincidence loss was carried out according to a procedure outlined elsewhere.[9] The standard deviations in the intensities were estimated at $\sigma_I = [\sigma_c^2 + (0.02)^2\sigma_c^4]^{1/2}$

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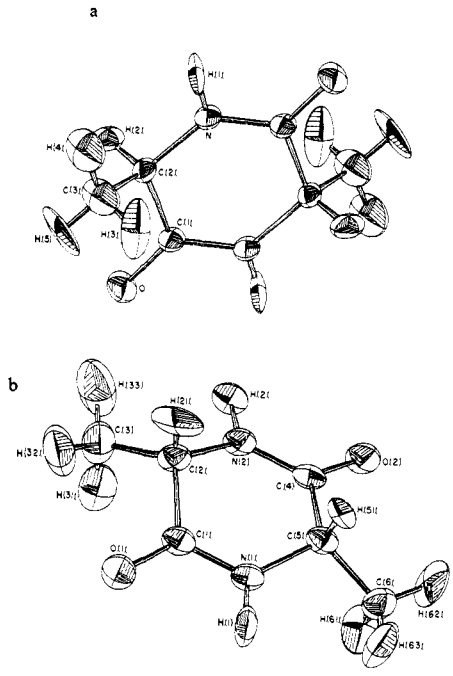

Figure 1. Thermal ellipsoids plotted at 40% probability: a, cyclo-D-alanyl-L-alanyl; b, cyclo-L-alanyl-L-alanyl.

and the corresponding standard deviation in structure factors, $\sigma_F = [F^2 + \sigma_I(\mathrm{Lp})^{-1}]^{1/2} - F$ (Lp = Lorenz polarization).

Crystal Data. Cyclo-D-alanyl-L-alanyl exhibited the following characteristics: $C_6H_{10}N_2O_2$, formula weight = 142.16; space group $P2_1/n$, $Z = 2$, $a = 6.3497\ (3)$ Å, $b = 6.2203\ (4)$ Å, $c = 9.0438\ (5)$ Å, $\beta = 95.814\ (9)°$, $V = 355.37$ Å^3; d_x (calcd density) = 1.329 g cm^{-3}, d_m (measured density) = 1.334 g cm^{-3}; crystal dimension 0.62 mm × 0.61 mm × 0.36 mm. Of the 1040 reflections measured, 948 were significantly greater than their background count.

Cyclo-L-alanyl-L-alanyl exhibited the following characteristics: space group P1, $Z = 1$, $a = 5.1552\ (4)$ Å, $b = 8.0596\ (5)$ Å, $c = 4.6698\ (2)$ Å, $\alpha = 103.155\ (4)°$, $\beta = 103.680\ (5)°$, $\gamma = 97.587\ (4)°$, $V = 180.00$ Å^3; $d_x = 1.312$ g cm^{-3}, $d_m = 1.310$ g cm^{-3}; dimensions of the crystal 0.67 mm × 0.22 mm × 0.10 mm. Of the 1061 reflections measured, 1010 were significantly greater than their background count.

Structure Determinations. The structure of DL was derived by a symbolic addition procedure and refined by full-matrix least squares to an agreement factor of 0.040 ($R = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$) using anisotropic thermal parameters for nonhydrogen atoms. Two more least-squares cycles, where the five hydrogen atoms were also refined anisotropically, lowered the R factor to 0.037. Before the last cycle, an empirical correction for secondary extinction was applied.

The structure of the LL form was solved by an origin removed, sharpened Patterson synthesis. The vector row O–C···C–O was located and the corresponding atoms were used in the initial structure factor calculation. The succeeding Fourier map at $R = 0.41$ gave the positions of the remaining carbon and nitrogen atoms. After two cycles of isotropic refinement, the ten hydrogen atoms were located by difference synthesis. Further least-squares refinement with anisotropic temperature factors for the ten nonhydrogen atoms gave an R of 0.031. At this stage, the hydrogen atoms were also assigned anisotropic thermal parameters, and after two cycles the refinement converged with shifts in parameters less than 0.6σ and $R = 0.030$. The quadratic form of the temperature-factor exponents of the hydrogen atoms all remained positive definite. The improvement in R from 0.031 to 0.030 is not significant according to Hamiltons R test.[10]

Final coordinates and thermal parameters for both structures are listed in Table I. The average C–H distances obtained from these coordinates are 0.98 and 0.97 Å for DL and LL, respectively. The corresponding N–H distances are 0.88 and 0.93 Å. A correction for riding motion[11] increased the average of the C–H bond lengths to 1.02 Å in DL and to 1.00 Å in LL with rms deviations of 0.02 and 0.05 Å, respectively. No significant change in N–H distances were obtained by riding motion correction.

The coordinates from the least-squares refinement refer to the centroid of electron density rather than the nuclear positions. For hydrogen atoms the two sets of coordinates are significantly different, and this ought to be taken into account, especially in conformational studies. Table II gives the nuclear positions of hydrogen atoms obtained by moving the hydrogen out along the X–H vector to a predetermined distance (C–H = 1.09 Å, N–H = 1.00 Å). These coordinates are used in calculating nonbonded internuclear contacts. The details of the anisotropic refinement of the hydrogen atoms are discussed elsewhere.[12] All the above calculations were carried out using computer programs from the X-ray 67 system.[13] The scattering curves for C, N, and O were those given by Berghuis, *et al.*[14] For hydrogen, the scattering curve published by Stewart, *et al.*,[15] was used.

Table II. Nuclear Positions for Hydrogen Atoms in Cyclo-D-alanyl-L-alanyl and Cyclo-L-alanyl-L-alanyl[a]

Atom	x/a	y/b	z/c
	DL Compound		
H(1)	0.233	0.042	−0.186
H(2)	0.057	0.342	−0.075
H(3)	0.378	0.132	0.149
H(4)	0.445	0.285	−0.003
H(5)	0.316	0.398	0.152
	LL Compound		
H(1)	0.936	0.540	0.779
H(2)	0.078	0.330	0.070
H(21)	0.207	0.303	0.604
H(31)	0.419	0.092	0.135
H(32)	0.325	0.014	0.419
H(33)	0.058	0.055	0.141
H(51)	0.518	0.701	0.717
H(61)	0.885	0.709	0.293
H(62)	0.721	0.884	0.432
H(63)	0.979	0.817	0.671

[a] These positions are obtained from the coordinates of the least-squares refinement by moving the hydrogen atom out along the X–H vector to a predetermined distance (C–H = 1.09 Å, N–H = 1.00 Å).

Thermal Analysis. The thermal vibration of the diketopiperazine ring may be described as rigid body motion, while the methyl substituents and the hydrogen atoms have additional torsional and riding motion. The RBM approximation[16] gave an excellent fit to the observed thermal parameters. In DL the estimated standard deviation between observed and calculated U_{ij}'s are 0.0008 Å^2 and in LL 0.0010 Å^2.

The thermal ellipsoids of the atoms in DL and LL are plotted at 40% probability in Figures 1a and b. The torsional motion of the methyl groups in DL is apparent. The ellipsoids of hydrogen atoms attached to nitrogens do not look physically meaningful. These atoms participate in hydrogen bonding and the elongation of the ellipsoids more or less in the bond direction may reflect the presence of double minima for the hydrogen position[17] or polarization of the bonding electrons of the nitrogen atom due to hydrogen bonding.

Results

Intramolecular bond lengths and angles not involving hydrogen atoms are compiled in Table III together with corresponding values for DKP.[5] The torsional angles

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Table III. Bond Distances, Bond Angles, and Torsional Angles[a]

Bonds (angles)	DL	LL		DKP[b]	Open peptide[c]
C^{α}–C^{β}	1.525 (2)	1.514 (3)	1.517 (3)		
	[1.551]	[1.545]	[1.532]		
C^{α}–C′	1.509 (1)	1.516 (3)	1.518 (2)	1.499 (7)	1.53
	[1.519]	[1.521]	[1.523]	[1.509]	
C^{α}–N	1.454 (1)	1.461 (3)	1.454 (3)	1.449 (7)	1.47
	[1.460]	[1.465]	[1.457]	[1.452]	
C′–N	1.322 (1)	1.329 (3)	1.330 (2)	1.325 (7)	1.32
	[1.329]	[1.334]	[1.336]	[1.334]	
C′–O	1.236 (1)	1.235 (2)	1.239 (3)	1.239 (7)	1.24
	[1.241]	[1.238]	[1.241]	[1.243]	
(N–C′–C^{α})	118.61 (8)	116.84 (19)	116.89 (19)	118.9 (3)	118
(C′–C^{α}–N)	113.44 (8)	111.97 (16)	110.53 (14)	115.1 (3)	
(C^{α}–N–C′)	127.89 (9)	125.87 (16)	126.16 (14)	126.0 (3)	126
(N–C′–O)	122.96 (10)	122.99 (18)	122.53 (17)	122.6 (3)	123
(C^{α}–C′–O)	118.43 (9)	120.17 (17)	120.56 (17)	118.5 (3)	119
($\psi_{C^{\alpha}-C'}$)	182.8	200.6	206.9	181.2	
($\omega_{N-C^{\alpha}}$)	176.9	147.6	154.3	178.7	
($\phi_{C'-N}$)	183.2	188.1	180.7	181.3	

[a] Standard deviations are given in parentheses and the numbers refer to the last decimal place. Bond lengths corrected for thermal motion are given in brackets. The C^{α}–C^{β} bonds are corrected for riding motion.[11] The other bonds are corrected for rigid body motion. [b] See ref 5. [c] See ref 4.

Table IV

DL[a]		LL[b]			
		a. Intramolecular Contacts			
C(2)···C(2)(i)	2.944	C(2)···C(5)	2.881		
O···C(3)	2.901	O(1)···C(3)	2.820	O(2)···C(6)	2.822
O···H(1)	2.41	O(1)···H(1)	2.37	O(2)···H(2)	2.53
O···H(2)	2.64	O(1)···H(21)	2.83	O(2)···H(51)	2.86
O···H(5)	2.63	O(1)···H(32)	2.60	O(2)···H(62)	2.74
C(3)···H(1)	2.75	C(3)···H(2)	2.49	C(6)···H(1)	2.65
N···H(4)	2.63	N(1)···H(63)	2.57	N(2)···H(33)	2.65
H(1)···H(2)	2.44	H(1)···H(51)	2.65	H(2)···H(21)	2.49
H(1)···H(4)	2.52	H(1)···H(63)	2.39	H(2)···H(33)	2.31
H(2)···H(4)	2.51	H(21)···H(32)	2.50	H(51)···H(62)	2.49
H(2)···H(5)	2.52	H(21)···H(33)	2.47	H(51)···H(63)	2.51
		b. Intermolecular Contacts			
O···C(3)(i)	3.617	O(2)···C(3)(ii)	3.646	O(2)(i)···C(6)	3.565
O···H(3)(ii)	2.71	O(2)···H(32)(ii)	3.07	O(2)(i)···H(61)	2.57
O···H(4)(i)	2.82	O(1)···H(33)(iv)	2.98	O(1)(ii)···H(62)	2.95
O···H(2)(iii)	2.41	O(1)···H(21)(i)	2.61	O(2)(iii)···H(51)	2.40
		H(33)(v)···H(63)	2.48	H(62)···H(63)(ii)	2.41
		H(21)···H(2)(iii)	2.39		
		c. Hydrogen Bonds			
O···N(i)	2.886	O(1)···N(2)(iv)	2.885	O(2)(iv)···N(1)	2.895
O···H(1)(i)	1.94	O(1)···H(2)(iv)	1.89	O(2)(iv)···H(1)	1.91

[a] (i) $x - 1/2, 1/2 - y, 1/2 + z$; (ii) $1/2 - x, y + 1/2, 1/2 - z$; (iii) $-x, 1 - y, -z$. [b] (i) $1 + x, y, z$; (ii) $x, 1 + y, z$; (iii) $x, y, 1 + z$; (iv) $1 + x, y, 1 + z$; (v) $1 + x, 1 + y, 1 + z$.

usually quoted for peptide structures are also listed. The DL molecule has a small but significant deviation from planarity, adopting a chair form with the methyl groups in axial position. The LL molecule is appreciably puckered and might be described as a twist boat with methyl substituents quasi-equatorial. One of the amide groups are essentially planar ($\omega_{N(2)-C(4)}$ = 180.7°) while the other group (N(91)–C(11)) has a torsional angle ω = 188.1°. The torsion about the C–C and C–N single bonds are also quite asymmetric (Table III). In both molecules each methyl group is staggered relative to the α-hydrogen. In LL, where the methyl substituents and the carbonyl groups are nearly eclipsed, the $C_{Me}\cdots O$ contacts (2.820 and 2.822 Å) are shorter by approximately 0.1 Å compared to the distance in DL. However, the distances between the carbonyl oxygen and the closest methyl hydrogen are not significantly different from the corresponding distance in DL. The puckering of the LL molecule causes the distances between carbonyl oxygens and α-hydrogens to increase from 2.64 Å in DL to 2.83 and 2.86 Å in LL. Pertinent intramolecular contacts in the two molecules are compiled in Table IVa.

Molecular packing is shown in stereo Figures 2a and b. Hydrogen bonds and intermolecular contacts are listed in Table IVb, c. In both structures N–H···O hydrogen bonds of approximately the same length are formed, though differently arranged. The DL molecules related by screw axis are linked together by hydrogen bonds in an infinite two-dimensional network parallel to (101). The LL molecules are hydrogen bonded in ribbons which run along the *ac* diagonal parallel to (10$\bar{1}$). In both structures the only short intermolecular contacts other than hydrogen bonds appear between an

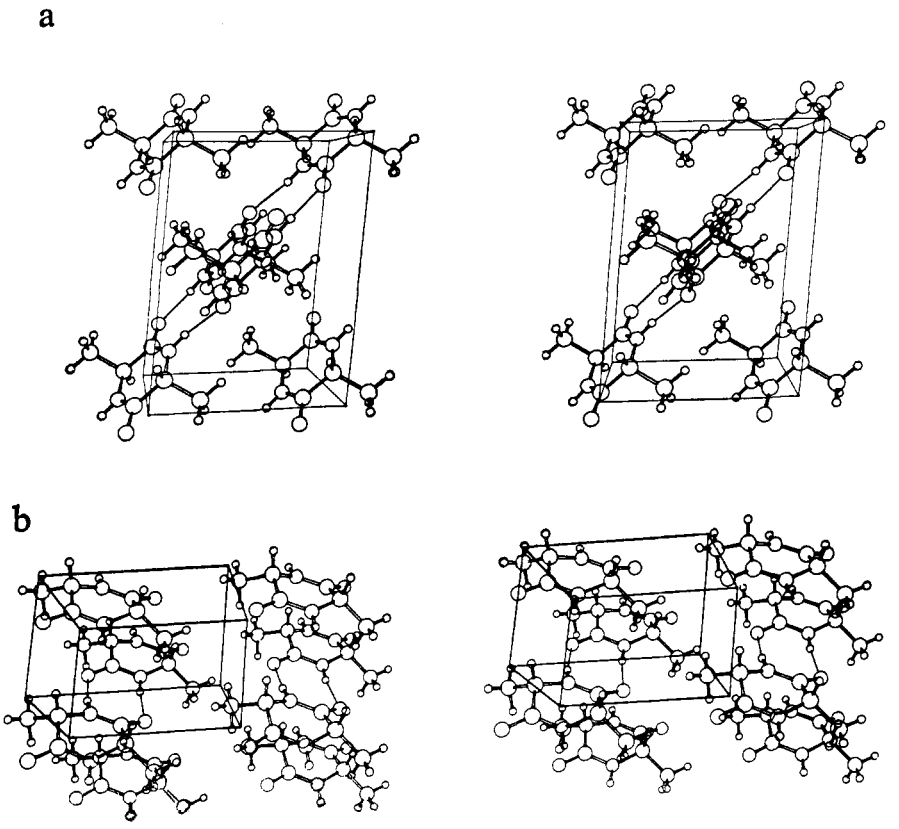

Figure 2. a, stereopicture of the molecular packing in cyclo-D-alanyl-L-alanyl viewed along the *b* axis; b, stereopicture of the molecular packing in cyclo-L-alanyl-L-alanyl viewed approximately normal to the *ab* plane.

α-hydrogen in one molecule and a carbonyl oxygen in the molecule translated one unit along the shortest axis. In DL the internuclear distance H(2)(iii)···O is 2.41 Å and in LL the distance H(51)···O(2)(iii) is 2.40 Å.

Discussion

The most interesting feature observed in this analysis in the puckering of the LL molecule, and the main questions to be discussed, are (1) why does the diketopiperazine ring in LL deviate appreciably from planarity, and (2) will the conformation in the crystalline state be retained in solution. The deviation from planarity does not seem to relieve any critical intramolecular strain in the molecule and a planar DKP ring would not lead to any short contacts between the methyl substituents. In the extended conformation of the LL molecule the methyl groups eclipse the carbonyl groups. Contrary to what one might expect, such arrangement is preferred in most aliphatic aldehydes, esters, and amides. In propionaldehyde, *e.g.*, the *cis*-methyl-carbonyl conformation is more stable by about 900 cal than the *gauche* form, where the α-hydrogen and carbonyl eclipse.[18] The energy required to twist the amide bond in LL 8.1° is by comparison only about 400 cal. This value is arrived at by using Ramachandran's formula for torsional barrier in an amide bond[4] $\Delta V_\omega(\Delta\omega)^2 = 20(\Delta\omega)^2$ kcal/mole.

A useful discussion of the observed differences in bond lengths and angles depends to a certain degree on the validity of the applied thermal correction. Without corrections for thermal motion there exist significant differences between chemically equivalent bond lengths in DL and LL. These differences disappear when the corrections are applied. The C^α–C′ and C^α–N bonds in DL and LL are systematically, though not significantly, longer than the corresponding bonds in DKP; while the internal angles at C^α are consistently smaller. A comparison between related dimensions in 2,5-dimethyl-*p*-benzoquinone[19] and *p*-benzoquinone[20] reveals a similar trend. Hirshfeld[19] suggests that this may be due to change in hybridization on C^α when hydrogen is replaced by a methyl group, diverting more of its 2s orbital into a C–C bond than into a C–H bond. The importance of making proper correction for thermal motion is clearly demonstrated by considering the nature of the exocyclic C^α–C^β bond in DL, LL, and 2,5-dimethyl-*p*-benzoquinone. In the latter, the methyl groups were treated as part of the rigid body model in the thermal analysis, and the $C_{sp^2{}^\alpha}$–$C_{sp^3{}^\beta}$ bond was found to be equal to the cyclic $C_{sp^2{}^\alpha}$–$C_{sp^2{}'}$ bond. The explanation offered is that "the tetrahedral C^β carbon is able to use as much of its 2s orbital in its bond to C^α, in competition with three C–H bonds, as does the trigonal C′, whose bond to C^α must compete with another C–C and a C=O bond."[19] The C^α–C^β and C^α–C′ bonds in DL and LL are also found to be equal if the whole molecule is treated as a rigid body. However, since it is reasonable to assume that the methyl groups have additional riding motion,[11] this was taken into account in the thermal corrections. Even though the corrections for riding motion is rather crude, the corrected distances for the three C^α–C^β bonds in DL and LL are close to the expected C_{sp^3}–C_{sp^3} single bond value.

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The significant asymmetry in torsional angles between chemically equivalent parts of the LL molecule is probably caused by packing forces, though it is difficult to ascribe this to any specific short intermolecular contacts. Since the LL molecules are laced together by fairly strong N–H···O hydrogen bonds, the energy of each bond amounting to several kilocalories per mole, one might expect major conformational adjustments to accommodate these bonds. However, the hydrogen bonds established in LL do not result in any short intermolecular contacts that might be responsible for the observed distortion. Chemically equivalent parts of the molecule have slightly different environments in the crystal. Especially the methyl group C(3) has a much "looser" packing than the equivalent group C(6), as reflected in the thermal ellipsoids (Figure 1). The methyl group C(6) is fairly tightly surrounded by neighboring molecules, and the interaction between C(6) and, *e.g.*, O(2)(i), though not critical, may be sufficient to cause the observed asymmetry in the ring. If that is the case, the normal conformation of a LL molecule in solution would be a regular twist boat. However, this assumption has to be tested by structure analysis of other substituted diketopiperazines. As to the difference in hydrolysis rate between the DL and LL isomers, it might be ascribed to the slight twist of the amide bonds in the LL molecule.[21]

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(21) NOTE ADDED IN PROOF. The complete reports on the parallel, independent structure determinations of the DL and LL compounds have just appeared (E. Benedetti, P. Corradini, and C. Pedone, *J. Phys. Chem.*, **73**, 2891 (1969); *Biopolymers*, **7**, 751 (1969)). A comparison with the present investigation revealed some quite significant differences in molecular dimensions obtained. The largest discrepancies appear in the bond length C—C′ of the DL structure where the value 1.470 ± 0.005 Å is quoted as compared to 1.509 ± 0.001 Å in the present determination. The difference of 0.04 Å is highly significant (8σ), and a comparison with the chemically equivalent bond length in the LL compound strongly indicate that the value 1.470 Å is in error.

The Circular Dichroism of 3-Methylpyrrolidin-2-one[1]

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Abstract: (+)-(*R*)-3-methylpyrrolidin-2-one has been prepared, and its circular dichroism spectra studied in various solvents. The compound shows a positive ellipticity band at 210–220 nm, which is red shifted upon going from water to solvents with lower polarity, which probably arises from an $n \rightarrow \pi^*$ transition. The sign of this transition, however, does not obey the simple quadrant rule for the sign of the $n \rightarrow \pi^*$ transition of amides proposed by Litman and Schellman. A second negative ellipticity band is centered at 189–196 nm and may be due to the $\pi \rightarrow \pi^*$ transition. However, the circular dichroism spectra of the compound cannot be resolved by only two Gaussian bands, so the assignment of this lower band is not absolute. The compound associates in *n*-hexane to produce an additional band at 202 nm, which is lost upon dilution.

In the past few years there have been extensive theoretical studies on the optical properties of polypeptides in ordered conformations.[3–14] This work has concerned itself with the interactions among transitions of the amide chromophores of peptides aligned in regular arrays. Unfortunately, there are relatively few studies on simple, rigid, optically active amide monomers, which are suitable reference compounds for the elucidation of the optically active transitions of the peptide bond.

In 1964, Litman and Schellman[15] studied the ORD[16] of 3-aminopyrrolidin-2-one. They reported a positive Cotton effect centered near 220 nm which red shifted upon changing the solvent from water to acetonitrile and dioxane. They assigned this band to an $n \rightarrow \pi^*$ transition of the amide. The ultraviolet absorption spectra indicated the beginning of a transition centered at a lower wavelength which blue shifted under the same conditions. They assigned this to the $\pi \rightarrow \pi^*$ transition of the amide. Litman and Schellman[15] postulated that the sign of the $n \rightarrow \pi^*$ transition was controlled by a quadrant rule which depended upon the charge on the nearest atom perturbing the peptide bond. However, the quadrant rule for peptides refers only to a

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(16) Abbreviations used in this paper: ORD, optical rotatory dispersion; CD, circular dichroism.