The Conformation and Crystal Structure of the Cyclotetradepsipeptide ⌐D-HyIv-L-MeIleu-D-HyIv-L-MeLeu⌐

John Konnert[1] and Isabella L. Karle

Contribution from the Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D. C., 20390.

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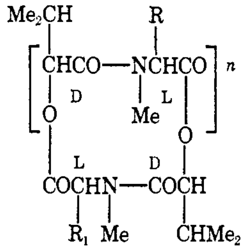
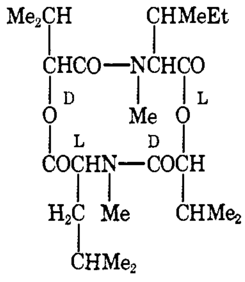
Abstract: The DLDL-cyclotetradepsipeptide ring consists of two α-hydroxy acid units in the *trans* conformation and two peptide units in the *cis* conformation. All the carbonyl groups extend in the same direction, roughly perpendicular to the average plane of the ring, while the hydrocarbon side chains extend in the opposite direction. All the side chains are in the fully extended form. The nitrogen atoms in the peptide groups are methyl substituted precluding any hydrogen bond formation. The material crystallizes in the orthorhombic space group $P2_12_12_1$ with cell parameters $a = 23.442 \pm 0.006$, $b = 10.021 \pm 0.003$, and $c = 11.524 \pm 0.003$ Å. The X-ray intensity data were collected with an automatic diffractometer. The crystal structure was solved by the symbolic addition procedure for phase determination as applied to noncentrosymmetric crystals.

One group of naturally occurring cyclodepsipeptides has the general formula



The antibiotics enniatin A and enniatin B have been shown to be cyclohexadepsipeptides with $n = 2$ and $R = R_1 = \text{CHMeEt}$ for enniatin A and CHMe_2 for enniatin B.[2-4] Originally it was thought that the enniatins were cyclotetradepsipeptides[5] with $n = 1$. However, the synthesis of cyclotetradepsipeptides by Shemyakin and Ovchinnikov[6] has shown that they do not possess any antibiotic properties, in contrast to the high antibiotic activity of the cyclohexadepsipeptides. A knowledge of the conformations of the cyclodepsipeptides should prove useful in understanding the differences in their biological activities. The crystal structure and conformation of



as determined by an X-ray diffraction analysis is reported here. The material was prepared by the method of Shemyakin, Ovchinnikov, Ivanov, and Kiryushkin.[7]

Experimental Section

The X-ray intensity data were collected from one crystal on a four-circle automatic diffractometer using the θ–2θ technique with a $1.8° + 2\theta(\alpha_2) - 2\theta(\alpha_1)$ scan over 2θ. The diffracted intensities decreased very rapidly in magnitude at d spacings near 1.0 Å. At d spacings less than 1.0 Å, only those reflections were retained for which $|F_o|$ was determined to be >10.0. The intensities were corrected for Lorentz and polarization factors and normalized structure factors $|E|$ were derived. Some of the physical constants for the crystal are listed in Table I.

Table I. Physical Constants

Molecular formula	$C_{24}H_{42}O_6N_2$
Molecular weight	454.6
Melting point	164–165°
Habit	Prismatic
Crystal size	0.4 × 0.4 × 0.6 mm (a, b, c directions)
Space group	$P2_12_12_1$
a	23.442 ± 0.006 Å
b	10.021 ± 0.003 Å
c	11.524 ± 0.003 Å
V	2707.1 Å^3
δ_{calcd}	1.115 g/cc
Radiation	Mo Kα 0.7107 Å
No. of independent reflections	1753
Molecules per unit cell	4

Phase Determination and Refinement. The initial phases for the structure factors were determined by the symbolic addition procedure for noncentrosymmetric crystals.[8] Phase determination was begun with the relationship in eq 1 for reflections with large $|E|$.

$$\phi_{\bar{h}} \approx \langle \phi_{\bar{k}} + \phi_{\bar{h}-\bar{k}} \rangle_{\bar{k}} \tag{1}$$

To implement (1), four phases were assigned appropriate values to specify the origin and the enantiomorph.[9] The phases of three additional reflections were denoted with symbols, Table II.

Seventy phases with $|E| > 1.7$ were obtained as functions of a, b, c, 0, π, and $\pm\pi/2$. During the course of the phase determination

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[1] National Academy of Sciences–National Research Council Postdoctoral Resident Research Associate.

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[3] P. Quitt, R. O. Studer, and K. Vogler, *ibid.*, **46**, 1715 (1963).

[4] M. M. Shemyakin, Yu. A. Ovchinnikov, A. A. Kiryushkin, and V. T. Ivanov, *Tetrahedron Letters*, 885 (1963); *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **579**, 1148 (1963).

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[7] M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, and A. A. Kiryushkin, *Tetrahedron*, **19**, 581 (1963).

[8] I. L. Karle and J. Karle, *Acta Cryst.*, **17**, 835 (1964); J. Karle and I. L. Karle, *ibid.*, **20**, 555 (1966).

[9] H. Hauptman and J. Karle, *ibid.*, **9**, 45 (1956).

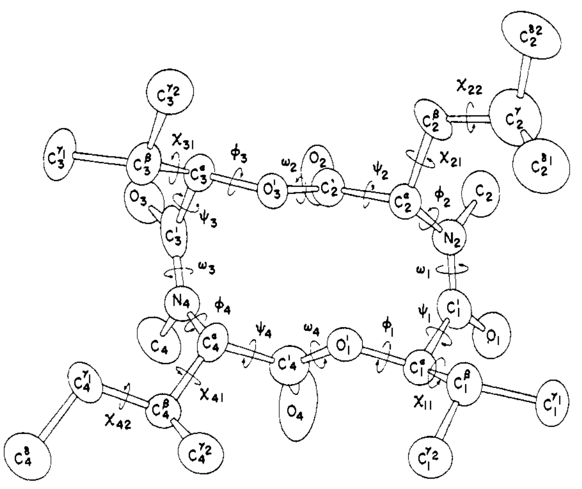

Figure 1. The configuration of D-HyIv-L-MeIleu-D-HyIv-L-MeLeu. The figure was drawn by a computer from a program by C. K. Johnson (ORTEP, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965).

there were many indications that $b = c = 0$ and several indications that $a = +\pi/2$. These indications proved to be correct.

The initial set of 70 phases was refined and phases for additional reflections were obtained with the tangent formula[10]

$$\tan \phi_{\vec{h}} = \frac{\sum |E_{\vec{k}} E_{\vec{h}-\vec{k}}| \sin (\phi_{\vec{k}} + \phi_{\vec{h}-\vec{k}})}{\sum |E_{\vec{k}} E_{\vec{h}-\vec{k}}| \cos (\phi_{\vec{k}} + \phi_{\vec{h}-\vec{k}})} \qquad (2)$$

A total of 620 phases for reflections with $|E| > 1.1$ were used to compute a three-dimensional E map. Fourteen of the largest peaks in the E map corresponded to reasonable atom positions which included 11 of the 12 ring atoms. These 14 atoms were used as a partial structure to calculate initial phases for reflections with $|E| > 1.5$ for another tangent formula expansion.[11] The new E map revealed 29 of the 32 carbon, nitrogen, and oxygen atoms present. A difference Fourier map revealed the remaining three atoms as all carbon atoms in terminal methyl groups with extremely large thermal factors.

Table II. Phase Assignments for Specifying the Origin and Enantiomorph and Implementing Eq 1

$\vec{h}$	$\phi_{\vec{h}}$	$\lvert E_{\vec{h}}\rvert$
1 0 2	0	2.41
1 3 0	$+\pi/2$	3.06
11 0 9	$+\pi/2$	2.88
0 1 1	$+\pi/2$	2.27
4 0 1	a	2.67
20 4 0	b	3.03
6 0 4	c	2.82

The data used in the least-squares refinement were all reflections with an interplanar spacing greater than or equal to 1.0 Å and those reflections with an interplanar spacing less than 1.0 Å with $|F_o| > 10$. These groups were composed of 1624 and 129 reflections, respectively. Refinement on the atomic positions and anisotropic thermal parameters reduced the conventional R value to 12.3%. The full-matrix least-squares refinement was carried out on the function $\Sigma w(|F_o| - |F_c|)^2$ where $w = 0.5$ for $F_o = 0$, $w = 1.0$ for $|F_o| < 15$, and $w = 15/[F_o]$ for $|F_o| > 15$. The atomic scattering factors used were those listed in the International Tables for X-Ray Crystallography. Table III lists the fractional coordinates and thermal parameters.

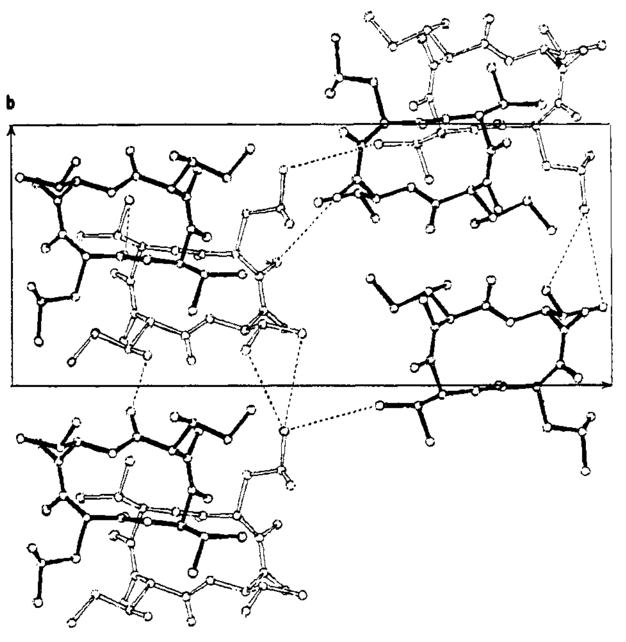

Figure 2. The molecular packing viewed down the c axis. Some of the nearest approaches between molecules are indicated by the dotted lines.

Discussion

The configuration of the molecule and the molecular packing in the crystal are illustrated in Figures 1 and 2, respectively. Atoms are labeled according to the convention proposed by Edsall, *et al.*[12] This convention has been extended to include the condensed α-hydroxy acids. Tables IV and V list the bond distances and bond angles while Table VI lists the standard polypeptide conformational parameters. The conformation with the C_{j-1}'–O_j' or C_{j-1}'–N_j *trans* to the C_j^{α}–C_j' bond is defined as $\phi_j = 0$.

Inspection of the thermal parameters in Table III shows that the values are quite large. For the 12 atoms in the ring the B values range from 5 to 7 Å^2. For atoms bonded to the ring they increase to 7 to 10 Å^2 and are even larger for some of the terminal atoms of the side chains. The large thermal parameters were expected since the diffraction data extended only to d spacings of 1.0 Å. Since there is no hydrogen bonding and since the molecule is rather large and unwieldy, the large thermal factors probably indicate positional disorder from cell to cell. The standard deviations for the bond lengths based solely on the least-squares fit is ~0.03 A for the ring bonds and up to ~0.06 Å for some of the side chains. Atoms $C_2^{\delta_1}$ and O_4 have B values of ~15 Å^2 corresponding to rms amplitudes of vibration of 0.44 Å. The electron density for these atoms can be described as "banana" shaped. Since these atoms could not be located with any precision, especially $C_2^{\delta_1}$, bond distances and angles involving $C_2^{\delta_1}$ are quite unreliable. They are enclosed in brackets in Tables IV and V. All the other bond distances are similar within experimental error to those found in other peptides.[13]

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(10) J. Karle and H. Hauptman, *Acta Cryst.*, **9**, 635 (1956).

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(12) J. T. Edsall, P. J. Flory, J. C. Kendrew, A. M. Liquori, G. Nemetny, G. N. Ramachandran, and H. A. Scheraga, *J. Mol. Biol.*, **15**, 399 (1966).

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Table III. Fractional Coordinates and Thermal Parameters[a] with Standard Deviations

	x	y	z	B^b	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
O_1'	0.3316	0.2578	0.4826	5.2	27	127	108	−3	−2	−7
	(4)	(9)	(7)	(0.2)	(2)	(10)	(8)	(4)	(3)	(8)
C_1^{α}	0.3908	0.2144	0.4712	6.6	26	159	173	6	4	27
	(6)	(15)	(14)	(0.4)	(3)	(18)	(16)	(6)	(6)	(15)
C_1'	0.4215	0.2880	0.3651	7.1	27	194	149	−10	3	−21
	(6)	(18)	(13)	(0.5)	(3)	(26)	(15)	(8)	(6)	(18)
O_1	0.4557	0.2194	0.3108	9.4	36	271	229	17	25	−65
	(5)	(13)	(11)	(0.4)	(3)	(20)	(15)	(7)	(6)	(16)
C_1^{β}	0.4193	0.2356	0.5923	7.5	32	236	167	−7	−21	−3
	(7)	(19)	(16)	(0.5)	(4)	(25)	(21)	(9)	(8)	(23)
$C_1^{\gamma_1}$	0.4860	0.2009	0.5810	10.3	30	380	219	−12	−21	104
	(7)	(23)	(19)	(0.7)	(4)	(40)	(26)	(11)	(9)	(30)
$C_1^{\gamma_2}$	0.3917	0.1397	0.6827	9.7	39	257	208	−11	−14	69
	(7)	(20)	(17)	(0.6)	(4)	(28)	(21)	(10)	(9)	(24)
N_2	0.4144	0.4201	0.3496	5.8	26	173	122	5	3	19
	(5)	(13)	(10)	(0.3)	(3)	(16)	(12)	(6)	(5)	(13)
C_2^{α}	0.3757	0.5044	0.4158	5.1	24	172	94	−6	−3	−12
	(6)	(15)	(12)	(0.4)	(3)	(20)	(12)	(7)	(5)	(15)
C_2'	0.3185	0.5047	0.3466	5.6	25	185	85	−3	0	−8
	(5)	(13)	(10)	(0.4)	(3)	(16)	(10)	(6)	(5)	(12)
O_2	0.3120	0.4996	0.2460	8.5	29	500	88	−6	6	−61
	(4)	(15)	(8)	(0.4)	(2)	(27)	(8)	(8)	(4)	(14)
C_2	0.4437	0.4718	0.2405	7.3	34	309	123	3	18	−1
	(7)	(22)	(14)	(0.5)	(4)	(36)	(16)	(10)	(7)	(23)
C_2^{β}	0.3931	0.6585	0.4293	7.8	35	230	156	−48	−20	24
	(7)	(19)	(16)	(0.5)	(4)	(28)	(20)	(10)	(8)	(22)
C_2^{γ}	0.4508	0.6773	0.4797	10.8	60	358	191	−31	−43	−1
	(12)	(33)	(21)	(0.8)	(8)	(54)	(27)	(17)	(13)	(35)
$C_2^{\delta_1}$	0.4656	0.6201	0.5718	15.5	84	337	379	−50	−110	61
	(13)	(35)	(32)	(1.1)	(9)	(65)	(54)	(20)	(20)	(53)
$C_2^{\delta_2}$	0.4559	0.8278	0.5144	13.4	76	237	327	−50	−32	18
	(11)	(22)	(27)	(1.0)	(8)	(31)	(47)	(13)	(17)	(34)
O_3'	0.2742	0.5186	0.4206	5.0	23	145	94	−3	4	−14
	(3)	(8)	(7)	(0.2)	(2)	(10)	(7)	(4)	(3)	(8)
C_3^{α}	0.2177	0.5328	0.3692	5.7	24	199	116	7	−7	14
	(5)	(15)	(13)	(0.4)	(3)	(22)	(13)	(7)	(6)	(15)
C_3'	0.1989	0.4007	0.3035	7.0	19	371	103	−17	3	−62
	(6)	(23)	(14)	(0.5)	(3)	(36)	(14)	(10)	(6)	(22)
O_3	0.1727	0.4310	0.2111	9.1	43	336	132	−26	−26	5
	(5)	(15)	(11)	(0.4)	(3)	(25)	(13)	(8)	(6)	(16)
C_3^{β}	0.1778	0.5757	0.4689	6.6	28	241	116	20	14	−12
	(6)	(18)	(13)	(0.4)	(3)	(26)	(14)	(8)	(6)	(18)
$C_3^{\gamma_1}$	0.1141	0.5752	0.4225	8.6	23	361	197	29	6	62
	(7)	(22)	(17)	(0.6)	(4)	(37)	(21)	(11)	(8)	(28)
$C_3^{\gamma_2}$	0.1974	0.7129	0.5123	8.1	49	201	171	5	17	−71
	(8)	(18)	(16)	(0.6)	(5)	(26)	(21)	(10)	(10)	(22)
N_4	0.2064	0.2765	0.3447	6.8	29	173	197	−3	3	−5
	(6)	(15)	(14)	(0.4)	(3)	(20)	(17)	(7)	(6)	(17)
C_4^{α}	0.2317	0.2462	0.4567	5.6	23	208	118	15	−8	−6
	(6)	(17)	(13)	(0.4)	(3)	(21)	(14)	(8)	(6)	(17)
C_4'	0.2912	0.1945	0.4301	7.1	39	155	227	8	−6	−79
	(8)	(17)	(19)	(0.5)	(5)	(22)	(25)	(9)	(9)	(21)
O_4	0.3004	0.0992	0.3716	15.0	38	522	541	20	−26	−368
	(6)	(20)	(19)	(0.7)	(4)	(42)	(40)	(11)	(10)	(37)
C_4	0.1873	0.1717	0.2601	9.8	52	261	242	−50	−12	−121
	(9)	(21)	(19)	(0.7)	(6)	(34)	(28)	(12)	(11)	(27)
C_4^{β}	0.1965	0.1418	0.5226	7.3	28	182	213	−6	1	60
	(7)	(19)	(17)	(0.5)	(4)	(24)	(21)	(9)	(8)	(21)
$C_4^{\gamma_1}$	0.1392	0.2036	0.5532	9.3	28	276	269	−14	12	112
	(7)	(21)	(21)	(0.6)	(4)	(33)	(34)	(10)	(10)	(31)
$C_4^{\gamma_2}$	0.2273	0.1176	0.6389	11.5	46	343	270	−18	−16	166
	(9)	(23)	(22)	(0.8)	(6)	(41)	(33)	(13)	(13)	(34)
C_4^{δ}	0.0997	0.0913	0.6119	12.7	42	341	312	−19	−1	125
	(9)	(26)	(24)	(0.9)	(6)	(47)	(37)	(14)	(13)	(40)

[a] The thermal parameters are expressed in the form $T = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)(\times 10^4)]$. [b] Thermal factors from last isotropic refinement.

There is an approximate twofold axis in the molecule. Deviations from a twofold symmetry are caused by different R and R_1 groups, CHMeEt and CH_2CHMe_2, and probably by the packing environment. The shape of

Table IV. Bond Angles in Degrees. The Standard Deviations Range from 1.5° for Ring Angles to 3.0° for Some Side Chain Angles

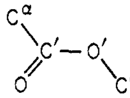
Angle	j = 1	j = 2	j = 3	j = 4
$C'NC^\alpha$		125.4		124.1
$C'O'C^\alpha$	120.6		116.9	
$NC^\alpha C'$		105.6		105.6
$O'C^\alpha C'$	111.1		111.3	
$C^\alpha C'O$	115.2	128.2	109.6	123.7
$C^\alpha C'N$	119.9		124.6	
$C^\alpha C'O'$		109.8		114.4
$OC'N$	124.4		125.7	
$OC'O'$		122.0		121.8
$C'NC$		112.8		112.3
CNC^α		121.1		123.5
$NC^\alpha C^\beta$		116.8		111.3
$O'C^\alpha C^\beta$	106.6		106.0	
$C^\beta C^\alpha C'$	115.2	105.4	114.9	111.2
$C^\alpha C^\beta C^{\gamma_1}$	108.4	113.1	108.6	108.2
$C^\alpha C^\beta C^{\gamma_2}$	109.6		108.2	106.7
$C^\beta C^\gamma C^{\delta_1}$		[121.7]		108.8
$C^\beta C^\gamma C^{\delta_2}$		107.0		
$C^{\delta_1}C^\beta C^{\gamma_2}$	109.0		113.2	106.0
$C^{\delta_1}C^\gamma C^{\delta_2}$		[101.7]		

Table V. Bond Lengths in Ångström Units[a]

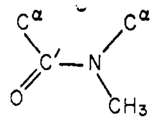
Bond	j = 1	j = 2	j = 3	j = 4
NC^α		1.45		1.45
$O'C^\alpha$	1.46		1.46	
$C_{j-1}'N_j$		1.35		1.34
$C_{j-1}'O_j'$	1.29		1.35	
$C^\alpha C'$	1.60	1.56	1.59	1.52
$C'O$	1.23	1.17	1.27	1.19
NC		1.52		1.50
$C^\alpha C^\beta$	1.56	1.60	1.54	1.53
$C^\beta C^{\gamma_1}$	1.61	1.48	1.59	1.52
$C^\beta C^{\gamma_2}$	1.56		1.53	1.54
$C^\gamma C^{\delta_1}$		[1.26]		1.61
$C^\gamma C^{\delta_2}$		1.56		

[a] The standard deviations range from 0.03 Å for ring bonds to 0.06 Å for some side-chain bonds.

the ring is determined by two α-hydroxy acid units



which are in the *trans* conformation and nearly planar (within ±0.04 Å) and by two N-methyl peptide units



which are also nearly planar (within ±0.06 Å) but have the *cis* conformation. The *cis* conformation is unusual for a peptide unit. In cyclohexaglycyl,[14] the only other cyclic peptide whose crystal structure has been determined, there are four *different* conformations of the ring for the four molecules in the asymmetric unit of the unit cell. However, each of the 24 different peptide units has the *trans* conformation. In the cyclotetradepsipeptide, the dihedral angles between adjacent planes of the peptide and α-hydroxy acid units range from 95 to 114°. These values can be compared with 90–116° found for the dihedral angles between adjacent peptide units in the cyclohexaglycyl molecules.

Angles about the C═O group differ in the peptide and α-hydroxy acid units, Figure 3. The large difference between ∠$C^\alpha C'N$, 123°, and ∠$C^\alpha C'O'$, 112°, appears to be due to the configuration of the ring. Near the peptide unit the intramolecular distances between $C_4^\alpha \cdots O_3'$ and $C_2^\alpha \cdots O_1'$ are only 2.8–2.9 Å. Accordingly the $C^\alpha C'N$ and $C'NC^\alpha$ angles assume minimal values.

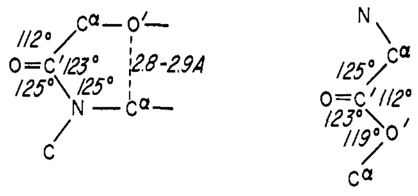


Figure 3. Angles about the C═O groups. The values shown are the averages for the two peptide units and the two α-hydroxy acid units in the molecule.

It is interesting to note that for this molecule (LDLD), all the C═O groups are on one side of the ring and all the hydrocarbon side chains are on the other. This arrangement is relevant to the chemical and biological behavior of the molecule. Shemyakin and Ovchinnikov[6] found that for the eight stereoisomeric linear tetradepsipeptides, *i.e.*, LDLD, LDDD, etc., cyclization and high yield occurred most easily with the LDLD isomer and with low yield and considerable difficulty for the DDDD isomer. The ease of cyclization was correlated with the assumed bent configuration of the linear LDLD isomer compared with the completely extended configuration of the linear DDDD isomer. It would be interesting to determine the crystal structure of the linear LDLD tetradepsipeptide to see whether the two peptide chains are already in the *cis* conformation or whether a conformational change occurs upon cyclization.

The hydrocarbon side chains tend to be fully extended in the *trans* conformation. The angles χ_{j1} and χ_{j2}, in Table VI, which are a measure of the deviation from a planar zig-zag chain, are within 9° of −180 or −60°. Hydrogen atoms were not located from this experiment. Their placement in the molecule was quite unambiguous except for the -CH$_3$ groups. In those cases, the -CH$_3$ group was rotated so as to have the maximum intramolecular distance between atoms, about 2.2–2.3 Å for H···H and H···O. A stereodiagram of the molecule with the assumed H positions is shown in Figure 4.

Table VI. Standard Conformational Parameters

j	ϕ_j	ψ_j	ω_j	χ_{j1}	χ_{j2}
1	−88.7	−143.7	−177.5	−175.2	
2	77.9	−33.7	−2.6	−55.5	−50.9
3	−114.1	−141.2	−173.5	−172.9	
4	72.4	−59.2	0.3	−66.5	174.9

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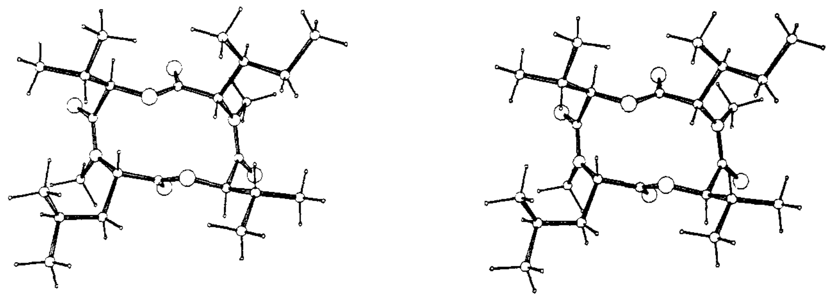

Figure 4. A stereodiagram of the molecule based on experimentally determined heavy atom positions and assumed hydrogen atom positions.

Packing of the molecules in the unit cell is shown in Figure 2. Dotted lines indicate the closest approaches between molecules. The smallest intermolecular distances are 3.4 Å between C=O···Me and 3.8 Å between Me···Me, normal van der Waals separations.

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A Spectroscopic Study of the Polarized Luminescence of Indoles[1]

Pill-Soon Song[1] and William E. Kurtin[2]

Contribution from the Department of Chemistry, Texas Technological University, Lubbock, Texas 79409. Received February 24, 1969

Abstract: The method of photoselection has been used to determine the polarized fluorescence excitation and emission spectra of indole and several of its derivatives. The results are compared with theoretical predictions from the P-P-P SCF MO-CI method. The first and second (π,π^*) states were assigned as ^1L_b and ^1L_a, respectively, in all cases studied. Emission from both ^1L_a and ^1L_b 0–0 states has been confirmed in most of the indoles studied on the basis of sharp changes in the degree of polarization of the fluorescence bands with the possible exception of indole-N-acetic acid. The dual emission seems to occur in both glycerol–methanol (9:1, 263 °K) and in an EPA rigid glass (77 °K). The polarized phosphorescence spectra and mean lifetimes have also been obtained at 77 °K in EPA glass. The triplet–singlet emission in seven indole derivatives has been shown to originate from $^3(\pi,\pi^*)$ states of ^3L_a type. The 0–0 phosphorescence emission bands were found to be negatively polarized, indicating predominant out-of-plane polarizations. Significant vibronic activity along the phosphorescence bands has been revealed, and in particular the degree of polarization increases considerably beyond the 0–0 bands of the carboxyl and formyl indoles. The possible contributions of various states (out-of-plane n,π^*, σ,π^*, or π,σ^*, and in-plane π,π^*) to the triplet–singlet transition probability *via* (a) direct spin–orbit, (b) spin vibronic (first order), and (c) vibronic spin–orbit (second order) couplings have been discussed qualitatively.

The study of the electronic structure in the excited states of biomolecules has increased markedly in the past decade, primarily because of an increased interest in their photochemical and photobiological reactivities.[3–6] Many biomolecules, because of their complex structure, often present unusually interesting spectroscopic and photochemical problems. Flavins and indoles are two of these types of molecules. We have previously reported on the nature of the excited singlet and triplet states of flavins using both theoretical and experimental methods.[7–11] Theoretically and spectroscopically, indole and its derivatives are of considerable interest. Platt[12] suggested a spectroscopic correlation based on the positions and intensities of the electronic bands, and placed indole between indene and naphthalene (isoelectronic with indole). Several workers have noted some peculiarities in the indole luminescence. Schutt and Zimmermann[13] observed an unusual dual fluorescence emission from both L_a and L_b states of indole. This result has not been re-

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(1) To whom reprint requests should be sent.

(2) Part III of the series, "Photochemistry of the Model Phototropic System Involving Flavins and Indoles." Supported by the Robert A. Welch Foundation (Grant No. D-182) and National Science Foundation (Grant No. GB-8055). W. E. K. is a predoctoral fellow of the Robert A. Welch Foundation.

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