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The dimensions of the ester unit*

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Abstract. The dimensions of the ester unit, which is a component of the depsipeptide unit has been obtained by analysing the data on crystal structures of compounds having the ester unit. The dimensions indicate that this unit is slightly different from the peptide unit both as far as the bond length and bond angles are concerned.

Keywords. Ester unit; dimension-ester unit; depsipeptides; parameters-ester unit; standard values-ester unit.

1. Introduction

Cyclic depsipeptides are biologically important compounds in that they are capable of forming active metal complexes. In addition to the ion-transportation property, cyclic depsipeptides show a wide spectrum of antimicrobial activity. Structurally, depsipeptides consist of an amino acid and a hydroxy acid residue. Just as the peptide unit can be treated as a conformationally repeating unit in the case of polypeptides, proteins and cyclic peptides, a combination of peptide and ester unit can be considered as a repeating unit for conformational studies on depsipeptides.

In order to study the conformation of a cyclic depsipeptide, the geometry of the

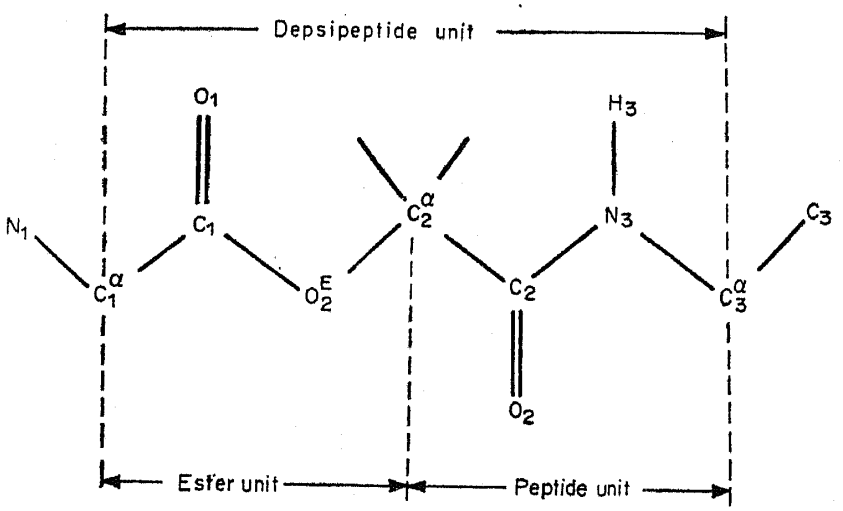

Figure 1. The atoms in the backbone of a depsipeptide unit. The ester and the peptide units are also indicated.

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depsipeptide unit must first be obtained. The depsipeptide repeating unit consists of a set of peptide and ester units as shown in figure 1. The geometry of the peptide unit is now well established and the standard dimensions have been given by Pauling and his group (Corey and Pauling 1953). The atoms of the peptide unit are generally taken to be coplanar and rotation about the peptide bond is highly restricted. A slight modification in the dimension of the peptide unit has been reported (Ramachandran *et al* 1974) and it is also found that any rotation about the C—N bond is in general accompanied by a deviation of the coplanarity of the three bonds meeting at the nitrogen atom (Ramachandran *et al* 1973; Winkler and Dunitz 1971). The dimensions of the ester unit, however, has not been established to the same extent as the peptide unit. Microwave spectroscopic analysis of methyl formate (O'Gorman *et al* 1950) and electron diffraction studies of methyl formate and methyl acetate (Curl 1959) provide some structural data for the ester group. Further microwave studies on ethyl formate (Riveros and Wilson 1967) confirm the above results. Electron diffraction studies on methyl acrylate and methyl methacrylate (Ukaji 1959) also corroborate these results.

In this paper the mean geometry of the ester unit has been obtained using available data on crystal structures of organic compounds containing the ester group. In all the cases, it is observed that the ester unit exists in the *trans* conformation, i.e. the torsion angle ω (C^{α}—C—O^{E}—C^{α}) $\simeq 180°$.* The occurrence of the *cis* ester unit is very rare. They are found only in strained lactones with less than 11 members in the ring (Huisgen and Ott 1959). The exclusion of the possibility of *cis* conformation for the ester unit has also been indicated by the infrared spectral study of methyl formate and methyl acetate (Miyazawa 1961).

2. Dimensions of ester unit

Parametrically, the ester unit consists of four bond lengths, namely, (i) C^{α}—C(b_1), (ii) C=O (b_2), (iii) C—O^{E} (b_3) and (iv) O^{E}—C^{α} (b_4), four bond angles, namely, (i) C^{α}—C=O(τ_1), (ii) O=C—O^{E} (τ_2), (iii) C^{α}—C—O^{E} (τ_3) and (iv) C—O^{E}—C^{α} (τ_4)

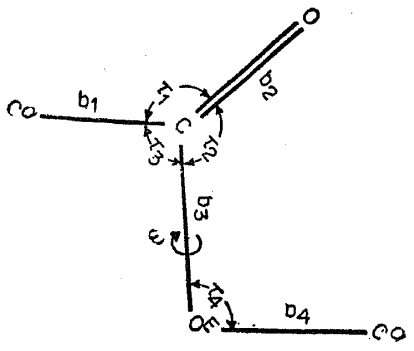


Figure 2. The bond lengths, bond angles and torsion angle associated with the ester unit.

*The ester oxygen in the main chain of the ester group is denoted by O^{E} and the carbonyl oxygen by O.

Table 1a. Bond lengths in Å observed in the crystal structures of different compounds containing the ester unit.

Compound†	$C^{\alpha}-C(b_1)$	$C=O(b_2)$	$C-O^{E}(b_3)$	$O^{E}-C^{\alpha}(b_4)$
1	1·50	1·20	1·36*	1·46
2	1·50	1·17*	1·31	1·47
2	1·49	1·19	1·31	1·53*
3	1·34*	1·19	1·34	1·47
4	1·50	1·25*	1·33	1·44
5	1·49	1·20	13·3	1·43
6	1·53*	1·20	1·33	1·45
7	1·46	1·23	1·36*	1·43
8	1·46	1·20	1·37*	1·46
9	1·49	1·20	1·33	1·44
9	1·47	1·20	1·33	1·43
10	1·48	1·20	1·34	1·45
11	1·51	1·20	1·31	1·48
12	1·55*	1·23	1·29*	1·50*
12	1·50	1·21	1·34	1·45
13	1·52	1·18*	1·33	1·48
14	1·49	1·20	1·32	1·41*
15	1·53*	1·23	1·35	1·52*
16	1·52	1·21	1·34	1·39*
17	1·46	1·20	1·32	1·48
18	1·46	1·20	1·35	1·46
19	1·50	1·20	1·32	1·48
19	1·50	1·19	1·32	1·47
20	1·45*	1·21	1·35	1·43
21	1·47	1·23	1·31	1·50*
22	1·47	1·23	1·32	1·50*
23	1·49	1·21	1·34	1·47
24	1·45*	1·26*	1·31	1·43
25	1·51	1·20	1·32	1·49
26	1·56*	1·19	1·33	1·46

*See text.

†(1) Salinomycin-*p*-iodophenacyl *ester* (Kinashi *et al* 1975)
(2) Bz-DL-Leu-Gly-ethyl *ester* (Timmins 1975)
(3) P-Br-*CBO*-Gly-Pro-Leu-Gly (Ueki *et al* 1969)
(4) (+) 5-*p*-Hydroxyphenyl ... ethyl *acetate* (Koch *et al* 1975)
(5) 9 α-Fluro ... *acetate* monohydrate (Terzis and Theophanides 1975)
(6) Pyrolizidine alkaloid mono *ester* (Wodak 1975)
(7) 3, 20-D-*o-acetoxy* pregnane (Karle 1975)
(8) 6-chloro-*hydroxy*-pregnadiene (Chandross and Bordner 1975)
(9) 2α-hydroxy estosterone *diacetate* (Weeks *et al* 1975)
(10) 2, 4-hexadixylenedi *benzoate* (Hanson 1975)
(11) DL-Trp-ethyl *ester* HCl (Vijayalakshmi and Srinivasan 1975a)
(12) L-Cys-dimethyl *ester* 2HCl (Vijayalakshmi and Srinivasan 1975b)
(13) Uridine-5-oxyacetic acid methyl *ester* (Morikawa *et al* 1975)
(14) N-T-BOC-S-Benzyl-Cys-Gly-methyl *ester* (Kashino *et al* 1974)
(15) 11β, 12β... methyl *ester* (Gopalakrishna *et al* 1969)
(16) CBO-L-Leu-*p*-nitrophenyl *ester* (Coiro *et al* 1974)
(17) 15, 17α... bromo*benzoate* (Thierry and Weiss 1972)
(18) (+) α-(1-Naphthyl...) bromo*benzoate* (Nyburg *et al* 1972)
(19) Ethyl-*p*-azoxy-*benzoate* (Krigbaum and Barbar 1971)
(20) 6α, 7α... *p*-bromo*benzoate* (Christensen 1970)
(21) Tyr-ethyl *ester* (Pieret *et al* 1970)
(22) Nitrogeno-MO-Carbene chelate (Knox and Prout 1969)
(23) L-Thr-L-Phe-*p*-nitrobenzyl *ester* (Mallikarjunan *et al* 1969)
(24) Phragmalin iodo*acetate* (Coetzer *et al* 1971)
(25) Trans... *benzoate* (Barnett and Davis 1970)
(26) Dithienyl glycollic *ester* (Meyerhoffer 1970)

Table 1b. Bond angles and torsion angles (in degrees) observed in the crystal structures of different compounds containing the ester unit.

Compound†	$C^{\alpha}-C=O$ (τ_1)	$O=C-O^{E}$ (τ_2)	$C^{\alpha}-C-O^{E}$ (τ_3)	$C-O^{E}-C^{\alpha}$ (τ_4)	$C^{\alpha}-C-O^{E}-C^{\alpha}$ (ω)	Deviation from planarity
1	124·6	122·8	112·5	114·9	171·6	−8·4
2	126·4	123·6	110·0	117·4	−178·6	1·4
2	126·1	123·2	110·8	113·4*	−177·9	2·1
3	126·9	122·5	110·6	116·9	−171·3	8·7
4	121·8*	126·3*	111·5	109·0*	−176·6	3·4
5	125·7	123·1	111·2	116·4	−179·5	0·5
6	124·5	124·2	111·2	118·5	−175·8	4·2
7	129·6*	119·4*	110·9	120·6*	176·7	−3·3
8	126·7	126·7*	110·5	117·5	−174·9	5·1
9	126·1	121·9	112·0	118·4	−179·5	0·5
9	127·6	119·4*	113·0	118·7*	−179·7	0·3
10	125·5	122·1	112·4	114·9	176·8	3·2
11	123·9*	123·1	113·0	117·1	178·9	−1·1
12	127·4	122·6	110·0	116·6	170·8	−2·9
12	119·0*	129·4*	111·5	115·5	175·0	−5·0
13	125·9	125·8	108·2*	116·8	175·4	−4·6
14	125·5	124·3	110·3	116·2	176·4	−3·6
15	132·0*	119·8*	107·4*	118·8*	−179·4	0·6
16	125·8	124·7	109·5*	120·0*	−175·0	5·0
17	124·3*	122·9	112·8	118·7*	−173·0	7·0
18	124·8	122·5	112·6	118·7*	174·9	−5·1
19	123·1*	124·3	112·5	116·5	177·6	−2·4
19	122·7*	125·3	111·9	115·7	−174·6	5·4
20	125·1	123·1	111·8	116·5	−179·4	0·6
21	118·0*	124·6	111·4	115·9	−175·5	4·5
22	122·2*	122·1	115·7*	112·3*	179·5	−0·5
23	127·9	118·8*	113·2*	117·7	171·6	−8·4
24	124·5	123·6	109·1*	117·5	170·4	−9·6
25	122·0	126·8*	111·1	117·5	−179·2	0·8
26	123·7*	125·1	111·3	116·6	−179·4	0·3

*See text.
†For compounds and references, see table 1a.

Table 2. Dimension of the ester unit

Parameters	Present paper*	Weighted Mean value†	Ingwall and Goodman (1974)	Popov and Pletnev (1971)
Lengths (Å)				
$C^{\alpha}-C$	1·49	1·49 (±·016)	1·53	1·52
$C=O$	1·21	1·20 (±·015)	1·22	1·24
$C-O^{E}$	1·33	1·33 (±·014)	1·34	1·35
$O^{E}-C^{\alpha}$	1·46	1·45 (±·015)	1·44	1·45
Angles (°)				
$C^{\alpha}-C-O^{E}$	111	111 (±1·0)	114	118
$C^{\alpha}-C=O$	125	125 (±1·2)	121	119
$O=C-O^{E}$	124	124 (±1·1)	125	123
$C-O^{E}-C^{\alpha}$	117	117 (±1·0)	113	114·5

*For procedure used see text.
† The values given in bracket are the standard deviation of the mean

and one dihedral angle C^{α}—C—O^{E}—C^{α} (ω). These are shown in figure 2. For the present study, recent crystal structure data of organic compounds containing the ester group have been collected. Data from 26 crystal structure reports are gathered and these are given in tables 1a and 1b. All the above mentioned parameters have been analysed and the standard dimensions of the ester unit thus obtained are given in column 2 of table 2. While arriving at the standard dimensions some of the data have been omitted and the procedure followed for each parameter is given below.

(a) The arithmetic mean value of the parameter is obtained taking into account all the observed values.

(b) In each case the deviation (δ) of the parameter from the average value is obtained.

(c) The average value of the deviation (δ_{av}) and the standard deviation (δ_s) are calculated according to the formula

$$\delta_s = 1{\cdot}25\ \delta_{av}$$

(d) Those deviations which are greater than the standard deviation are omitted for further calculation (They are marked by * in tables 1a and 1b).

The steps (a) to (d) are repeated iteratively till all the deviations are found to be less than the standard deviation. The values which are not crossed out in the above procedure are finally used for computing the average. The procedure adopted thus makes the average more realistic than the simple arithmetic mean.

In the procedure described above, all the observations had been treated alike and the elimination of some of the values, for the calculation of the average, were made if they differ too much from the initial average value. However, it will be more appropriate if weightage is given using a factor which depends upon the standard deviation of the observed parameter. For this purpose, the estimated standard deviation of the

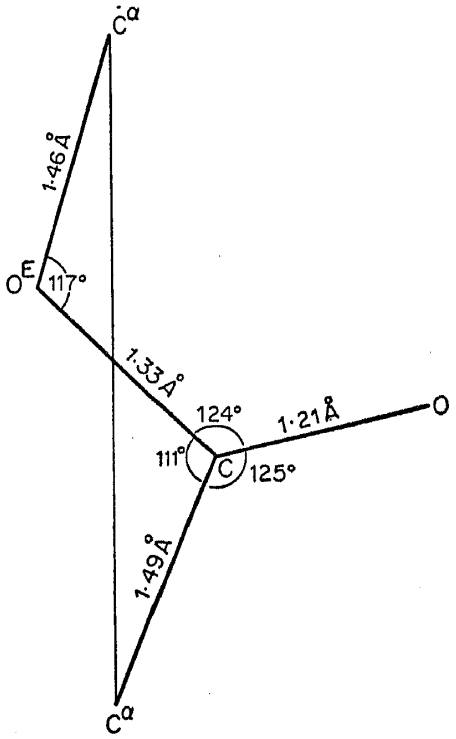


Figure 3. The dimensions of the ester unit.

coordinates, as reported in the literature are used and from these, the standard deviations of the bond lengths and bond angles associated with the ester unit are calculated. The weighted mean values for these parameters are calculated from the following expression

$$\text{Weighted mean} = \sum_{i=1}^{N} \frac{p_i}{\sigma_i^2} \Big/ \sum_{i=1}^{N} \frac{1}{\sigma_i^2}$$

where, p_i is the parameter involved, σ_i the associated standard deviation and N is the total number of examples. These weighted mean values are given in column 3 of table 2, in which the standard deviation of the weighted mean is also given in parantheses. It can be observed on comparing columns 2 and 3 of table 2, that the values obtained by the two procedures are almost the same, thus establishing the standardness of the values of the parameters.

The dimensions of the ester unit, thus obtained is shown in figure 3. The planarity of the ester unit is checked by calculating the dihedral angle ω (C^{α}—C—O^{E}—C^{α}) for each structure and is given in column 6 of table 1b. The values are found to be evenly distributed around 180° in that the arithmetic mean of the deviation is only 0·3°. The mean of the modulus of the deviation is 3·98°. However, a deviation of about 8-10° from 180° is also observed in some cases (table 1b). In view of the even distribution of the deviation, the ester unit can be taken to be almost planar.

3. Analysis and discussion of results

The above results are also analysed through histograms. The distributions of the bond lengths and bond angles are given in tables 3a and 3b. The chosen intervals are 0·02Å for the bond lengths and 2° for the bond angles. The histograms are shown in figures 4 (a to d) and 5 (a to d). It is interesting to note that the middle of the range in which the maximum in the histogram occurs agrees exactly with the average dimensions obtained by the above procedure. This is the case with every parameter.

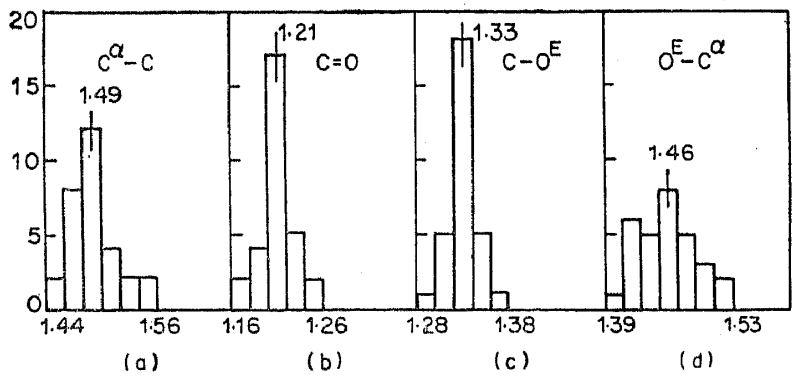


Figure 4. Histograms showing the distribution of bond lengths of the ester unit; (a) C^{α}—C(b_1), (b) C=O(b_2), (c) C—O^{E}(b_3), and (d) O^{E}—C^{α}(b_4).

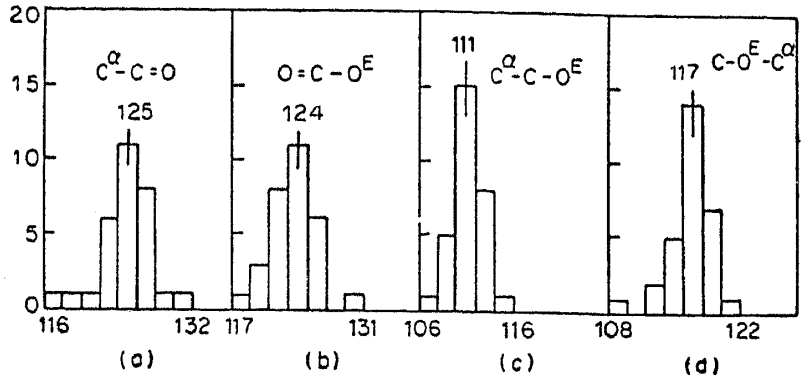


Figure 5. Histograms showing the distribution of bond angles of the ester unit; (a) $C^{\alpha}-C=O$ (τ_1), (b) $O=C-O^{E}$ (τ_2), (c) $C^{\alpha}-C-O^{E}$ (τ_3) and (d) $C-O^{E}-C^{\alpha}$ (τ_4).

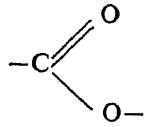
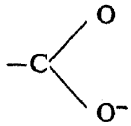
Table 3a. Distribution of the observed bond lengths in the ester unit.

$C^{\alpha}-C$ (b_1)		$C=O$ (b_2)		$C-O^{E}$ (b_3)		$O^{E}-C^{\alpha}$ (b_4)	
Range Å	No.	Range Å	No.	Range Å	No.	Range Å	No.
1·44–1·46	2	1·16–1·18	2	1·28–1·30	1	1·39–1·41	1
1·46–1·48	8	1·18–1·20	4	1·30–1·32	5	1·41–1·43	6
1·48–1·50	12	1·20–1·22	17	1·32–1·34	18	1·43–1·45	5
1·50–1·52	4	1·22–1·24	5	1·34–1·36	5	1·45–1·47	8
1·52–1·54	2	1·24–1·26	2	1·36–1·38	1	1·47–1·49	5
1·54–1·56	2					1·49–1·51	3
						1·51–1·53	2
Total	30		30		30		30

Table 3b. Distribution of the observed bond angles in the ester unit

$C^{\alpha}-C=O$	(τ_1)	$O=C-O^{E}$	(τ_2)	$C-C-O^{E}$	(τ_3)	$C-O^{E}-C$	(τ_4)
Range (deg.)	No.	Range (deg.)	No.	Range (deg.)	No.	Range (deg.)	No.
116-118	1	117-119	1	106-108	1	108-110	1
118-120	1	119-121	3	108-110	5	110-112	0
120-122	1	121-123	8	110-112	15	112-114	2
122-124	6	123-125	11	112-114	8	114-116	5
124-126	11	125-127	6	114-116	1	116-118	14
126-128	8	127-129	0			118-120	7
128-130	1	129-131	1			120-122	1
130-132	1						
Total	30		30		30		30

Table 4. Average bond lengths in Å and bond angles in degrees observed at the C-terminal end of amino acids and peptides. The standard bond lengths and angles for the ester and peptide units are given within parentheses in rows 2 and 4.

Type	$C^{\alpha}-C$	C=O	$C-O^{E}$ (N)	$O-C^{\alpha}$ (H)	$C^{\alpha}-C=O$	$C^{\alpha}-C-O^{E}$ (N)	$O=C-O^{E}$ (N)	$C-O^{E}-C^{\alpha}$ (H)
	1·51	1·22	1·31	0·98	123	112	125	111
(Ester)	(1·49)	(1·21)	(1·33)	(1·46)	(125)	(111)	(124)	(117)
	1·54	1·24	1·25	—	117·5	116	126	—
(Peptide)	(1·53)	(1·24)	(1·32)	—	(121)	(114)	(125)	(123)

Another possible verification can be obtained by considering the crystal structures of amino acids and peptides. The C-terminal end of an amino acid can be either COOH group or COO^{-} group. The ester group can be taken to be similar to C—COOH except that the terminal H is replaced by another carbon atom C. The two types of amino acids are classified and the parameters at the C-terminal end are studied by finding the average values. The results are given in table 4. On comparing the averages in the two cases with that of the peptide dimensions (given in bracket below each parameter) it is found that the averages for the —COOH group parameters are closer to those of the ester group than to those of the peptide. However, the parameters in those cases where the C-terminal end is COO^{-} group, resemble the peptide dimensions very closely. This indicates that the dimensions of the ester unit are slightly different from that of the peptide unit.

In the calculation of the conformation of randomly coiled and ordered polydepsipeptide chains, Ingwall and Goodman (1974) adopted the dimensions of the ester unit given by Brant *et al* (1969). Their dimensions differed slightly from that obtained above, especially the C^{α}—C length and $C—O^{E}—C^{\alpha}$ angle. The values are given in column 3 of table 2. The ester unit dimensions used by Popov and Pletnev (1971) are given in column 4 of table 2. There are minor differences in the values of the parameters. In view of the different conformations mentioned in this paper, the dimensions of the ester unit obtained by us can be safely used for any conformational calculations involving depsipeptides or ester units. Stereochemical studies on depsipeptides and cyclic depsipeptides are in progress by using the dimensions obtained for the ester unit. The results are reserved for later publications.

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