

## The dimensions of the ester unit\*

C RAMAKRISHNAN AND JAYATI MITRA

Molecular Biophysics Unit, Indian Institute of Science, Bangalore 560 012

MS received 31 May 1977; revised 10 December 1977

**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

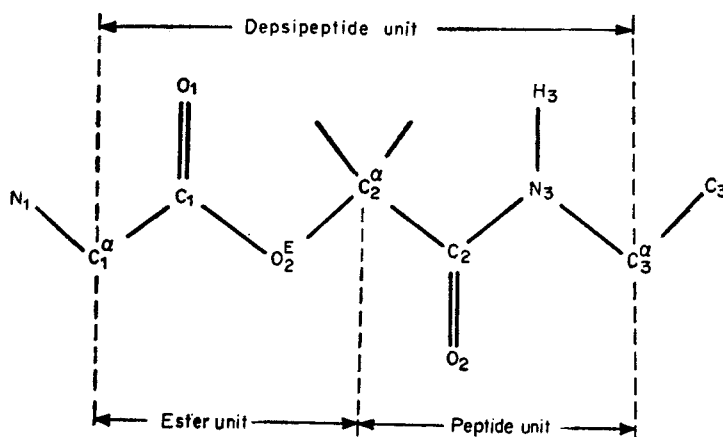


Figure 1. The atoms in the backbone of a depsipeptide unit. The ester and the peptide units are also indicated.

\*Contribution No. 108 from the Molecular Biophysics Unit, Indian Institute of Science, Bangalore.

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  $\omega$  ( $C^{\alpha}-C-O^E-C^{\alpha}$ )  $\simeq 180^{\circ}$ .\* 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)  $C^{\alpha}-C$  ( $b_1$ ), (ii)  $C=O$  ( $b_2$ ), (iii)  $C-O^E$  ( $b_3$ ) and (iv)  $O^E-C^{\alpha}$  ( $b_4$ ), four bond angles, namely, (i)  $C^{\alpha}-C=O$  ( $\tau_1$ ), (ii)  $O=C-O^E$  ( $\tau_2$ ), (iii)  $C^{\alpha}-C-O^E$  ( $\tau_3$ ) and (iv)  $C-O^E-C^{\alpha}$  ( $\tau_4$ )

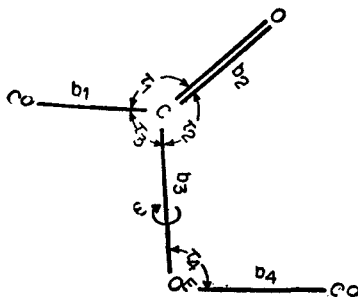


Figure 2. The bond lengths, bond angles and torsion angle associated with the ester unit.

\*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 <sup>†</sup>	C <sup>α</sup> -C(b <sub>1</sub> )	C=O(b <sub>2</sub> )	C-O <sup>E</sup> (b <sub>3</sub> )	O <sup>E</sup> -C <sup>α</sup> (b <sub>4</sub> )
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	1.33	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  $\alpha$ -Fluro ... acetate monohydrate (Terzis and Theophanides 1975)  
(6) Pyrrolizidine alkaloid mono ester (Wodak 1975)  
(7) 3, 20-D-*o*-acetoxypregnane (Karle 1975)  
(8) 6-chloro-*hydroxy*-pregnadiene (Chandross and Bordner 1975)  
(9) 2 $\alpha$ -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) 11 $\beta$ , 12 $\beta$ ... methyl ester (Gopalakrishna *et al* 1969)  
(16) CBO-L-Leu-*p*-nitrophenyl ester (Coiro *et al* 1974)  
(17) 15, 17 $\alpha$ ... bromobenzoate (Thierry and Weiss 1972)  
(18) (+)  $\alpha$ -(1-Naphthyl...) bromobenzoate (Nyburg *et al* 1972)  
(19) Ethyl-*p*-azoxy-benzoate (Krigbaum and Barbar 1971)  
(20) 6 $\alpha$ , 7 $\alpha$ ... *p*-bromobenzoate (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 iodoacetate (Coetzer *et al* 1971)  
(25) Trans... benzoate (Barnett and Davis 1970)  
(26) Dithienyl glycolic 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 <sup>†</sup>	C <sup>α</sup> -C=O (τ <sub>1</sub> )	O=C-O <sup>E</sup> (τ <sub>2</sub> )	C <sup>α</sup> -C-O <sup>E</sup> (τ <sub>3</sub> )	C-O <sup>E</sup> -C <sup>α</sup> (τ <sub>4</sub> )	C <sup>α</sup> -C-O <sup>E</sup> -C <sup>α</sup> (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)
<i>Lengths (Å)</i>				
C <sup>α</sup> -C	1.49	1.49 (±0.016)	1.53	1.52
C=O	1.21	1.20 (±0.015)	1.22	1.24
C-O <sup>E</sup>	1.33	1.33 (±0.014)	1.34	1.35
O <sup>E</sup> -C <sup>α</sup>	1.46	1.45 (±0.015)	1.44	1.45
<i>Angles (°)</i>				
C <sup>α</sup> -C-O <sup>E</sup>	111	111 (±1.0)	114	118
C <sup>α</sup> -C=O	125	125 (±1.2)	121	119
O=C-O <sup>E</sup>	124	124 (±1.1)	125	123
C-O <sup>E</sup> -C <sup>α</sup>	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  $C^{\alpha}-C-O^E-C^{\alpha}$  ( $\omega$ ). 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 ( $\delta$ ) of the parameter from the average value is obtained.

(c) The average value of the deviation ( $\delta_{av}$ ) and the standard deviation ( $\delta_s$ ) are calculated according to the formula

$$\delta_s = 1.25 \delta_{av}$$

(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

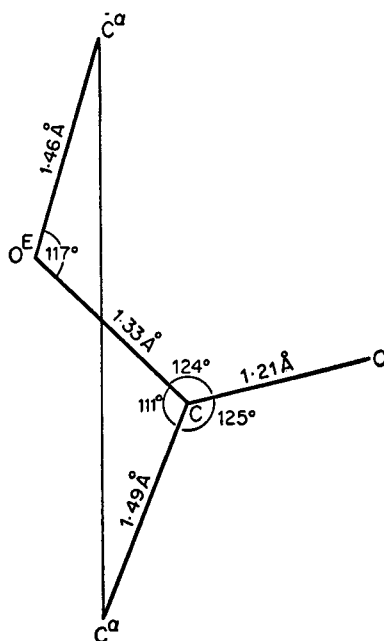


Figure 3. The dimensions of the ester unit.

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

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

where,  $p_i$  is the parameter involved,  $\sigma_i$  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 parentheses. 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  $\omega$  ( $C^a-C-O^E-C^b$ ) for each structure and is given in column 6 of table 1b. The values are found to be evenly distributed around  $180^\circ$  in that the arithmetic mean of the deviation is only  $0.3^\circ$ . The mean of the modulus of the deviation is  $3.98^\circ$ . However, a deviation of about  $8-10^\circ$  from  $180^\circ$  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  $0.02\text{\AA}$  for the bond lengths and  $2^\circ$  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.

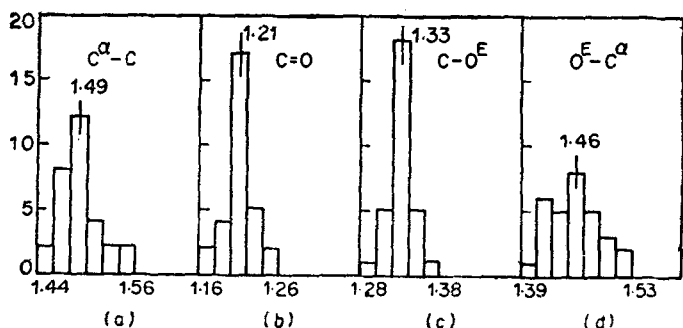


Figure 4. Histograms showing the distribution of bond lengths of the ester unit; (a)  $C^a-C$  ( $b_1$ ), (b)  $C=O$  ( $b_2$ ), (c)  $C-O^E$  ( $b_3$ ), and (d)  $O^E-C^a$  ( $b_4$ ).

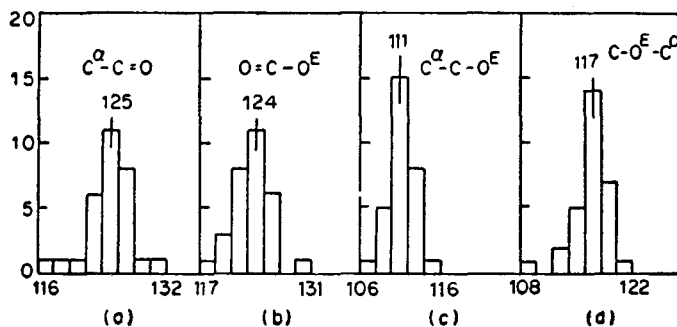


Figure 5. Histograms showing the distribution of bond angles of the ester unit; (a)  $C^\alpha-C=O$  ( $\tau_1$ ), (b)  $O=C-O^E$  ( $\tau_2$ ), (c)  $C^\alpha-C-O^E$  ( $\tau_3$ ) and (d)  $C-O^E-C^\alpha$  ( $\tau_4$ ).

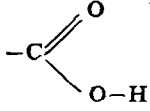
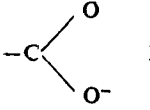
Table 3a. Distribution of the observed bond lengths in the ester unit.

$C^\alpha-C$ ( $b_1$ )		$C=O$ ( $b_2$ )		$C-O^E$ ( $b_3$ )		$O^E-C^\alpha$ ( $b_4$ )	
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

$C^\alpha-C=O$ ( $\tau_1$ )	$O=C-O^E$ ( $\tau_2$ )	$C-C-O^E$ ( $\tau_3$ )	$C-O^E-C$ ( $\tau_4$ )
Range (deg.)	Range (deg.)	Range (deg.)	Range (deg.)
116-118	117-119	106-108	108-110
118-120	119-121	108-110	110-112
120-122	121-123	110-112	112-114
122-124	123-125	112-114	114-116
124-126	125-127	114-116	116-118
126-128	127-129		118-120
128-130	129-131		120-122
130-132			
Total			

**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 <sup>α</sup> -C	C=O	C-O <sup>E</sup> (N)	O-C <sup>α</sup> (H)	C <sup>α</sup> -C=O	C <sup>α</sup> -C-O <sup>E</sup> (N)	O=C-O <sup>E</sup> (N)	C-O <sup>E</sup> -C <sup>α</sup> (H)
 (Ester)	1·51 (1·49)	1·22 (1·21)	1·31 (1·33)	0·98 (1·46)	123 (125)	112 (111)	125 (124)	111 (117)
 (Peptide)	1·54 (1·53)	1·24 (1·24)	1·25 (1·32)	— —	117·5 (121)	116 (114)	126 (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<sup>-</sup> 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<sup>-</sup> 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 polydepsi-peptide 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<sup>α</sup>-C length and C-O<sup>E</sup>-C<sup>α</sup> 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 depsi-peptides or ester units. Stereochemical studies on depsi-peptides and cyclic depsi-peptides are in progress by using the dimensions obtained for the ester unit. The results are reserved for later publications.

### Acknowledgements

The authors would like to thank Profs K Venkatesan and V Sasisekharan for their valuable comments. One of us (J M) would like to thank the Council of Scientific and Industrial Research (India) for the award of Junior Research Fellowship. The work was partly supported by a grant from the Department of Science and Technology, India, to whom our thanks are due.



## References

- Barnett B L and Davis R E 1970 *Acta Cryst.* **B26** 326  
Brant D A, Tonelli A E and Flory P J 1969 *Macromolecules* **2** 228  
Chandross R J and Bordner J 1975 *Acta Cryst.* **B31** 928  
Christensen A T 1970 *Acta Cryst.* **B26** 1519  
Coetzer J, Baxter W J and Gafner G 1971 *Acta Cryst.* **B27** 1434  
Coiro V M, Mazza F and Mignucci G 1974 *Acta Cryst.* **B30** 2607  
Corey R B and Pauling L 1953 *Proc. R. Soc. London* **B141** 10  
Curl R F Jr 1959 *J. Chem. Phys.* **30** 1529  
Gopalakrishna E M, Cooper A and Norton D A 1969 *Acta Cryst.* **B25** 1601  
Hanson A W 1975 *Acta Cryst.* **B31** 831  
Huisgen R and Ott H 1959 *Tetrahedron* **6** 253  
Ingwall R T and Goodman M 1974 *Macromolecules* **7** 598  
Karle I 1975 *Acta Cryst.* **B31** 1519  
Kashino S, Ashida T and Kakudo M 1974 *Acta Cryst.* **B30** 2074  
Kinashi H *et al* 1975 *Acta Cryst.* **B 31** 2411  
Knox J R and Prout C K 1969 *Acta Cryst.* **B25** 1952  
Koch M H J, German G, Declercq J P and Dusansoy Y 1975 *Acta Cryst.* **B31** 2547  
Krigbaum W R and Barbar P G 1971 *Acta Cryst.* **B27** 1884  
Mallikarjunan M, Thyagaraja Rao S and Venkatesan K 1969 *Acta Cryst.* **B25** 220  
Meyerhoffer A 1970 *Acta Cryst.* **B26** 341  
Miyazawa T 1961 *Bull. Chem. Soc. Jpn.* **34** 691  
Morikawa K, Torii K, Iitaka Y and Masamichi T 1975 *Acta Cryst.* **B31** 1004  
Nyburg S C, Brook A G, Pascol J D and Szymanski J T 1972 *Acta Cryst.* **B28** 1785  
O'Gorman J M, Shand W Jr. and Schomaker V 1950 *J. Am. Chem. Soc.* **72** 4222  
Pieret A F, Durant F and Griffe M 1970 *Acta Cryst.* **B26** 2117  
Popov E M and Pletnev V Z 1971 *Biofizika* **16** 407  
Ramachandran G N, Kolaskar A S, Ramakrishnan C and Sasisekharan V 1974 *Biochim. Biophys. Acta* **359** 298  
Ramachandran G N, Lakshminarayanan A V and Kolaskar A S 1973 *Biochim. Biophys. Acta* **303** 8  
Riveros J M and Wilson E B Jr 1967 *J. Chem. Phys.* **46** 4605  
Terzis A and Theophanides T 1975 *Acta Cryst.* **B31** 796  
Thierry J C and Weiss R 1972 *Acta Cryst.* **B28** 3241  
Timmins P A 1975 *Acta Cryst.* **B31** 2240  
Ueki T *et al* 1969 *Acta Cryst.* **B25** 1840  
Ukaji T 1959 *Bull. Chem. Soc. Jpn.* **32** 1266, 1270, 1275  
Vijayalakshmi B K and Srinivasan R 1975a *Acta Cryst.* **B31** 999  
Vijayalakshmi B K and Srinivasan R 1975b *Acta Cryst.* **B31** 993  
Weeks C M, Duax W L and Osawa Y 1975 *Acta Cryst.* **B31** 1502  
Wodak S 1975 *Acta Cryst.* **B31** 569  
Winkler F K and Dunitz J D 1971 *J. Mol. Biol.* **59** 169