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The Crystal Structures of Complexes of Cyclodisarcosyl with Metal Salts. I. The 2:1 Complex of Cyclodisarcosyl with Lithium Perchlorate

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The crystal structure of the 2:1 complex of cyclodisarcosyl with lithium perchlorate, $Li(C_6N_2O_2H_{10})_2ClO_4$, has been determined. The compound is obtained by mixing in stoichiometric ratio the ethyl acetate solution of cyclodisarcosyl with that of lithium perchlorate. The space group is $P\bar{1}$, with $a = 11{\cdot}575$ (4), $b = 8{\cdot}107$ (2), $c = 11{\cdot}561$ (3) Å, $\alpha = 110{\cdot}95$ (1), $\beta = 89{\cdot}97$ (1), $\gamma = 116{\cdot}63$ (2)°, and $Z = 2$. The final R is 0·085. There are four crystallographically independent cyclodisarcosyl molecules in the crystal. Each is planar and lies on a centre of symmetry at $y = 0$. The cyclodisarcosyl molecules are linked together by coordination of the carbonyl groups to the Li ion, and make an infinite two-dimensional network parallel to the *ac* plane. The Li ion is located at each knot in the network, and the arrangement of the O atoms around the Li ion is almost tetrahedral. The perchlorate ion, whose orientation is disordered, is at the centre of each vacancy in the network.

Introduction

The interaction between cyclic peptides and metal cations is closely related to the activities of cyclic peptide antibiotics and to the transportation mechanism of alkali-metal cations through a biological membrane by complexation. Cyclodisarcosyl (*N*,*N*′-dimethyldiketopiperazine) is known to form crystalline complexes with metal salts (such as copper perchlorate, lithium perchlorate, barium perchlorate, silver perchlorate and silver nitrate) and with boron trifluoride (Sugihara, Imanishi & Higashimura, 1973). It has been shown by infrared absorption spectra that the carbonyl O atoms of the peptide coordinate to the metal cations in these metal complexes. Since the linear analogue of the peptide forms no insoluble complex with the metal salts, the conformation of cyclodisarcosyl seems to play an important role in the complex formation.

As the first of a series of investigations concerning the interaction between cyclodisarcosyl and metal cations in crystals, the structure of the 2:1 complex of cyclodisarcosyl with lithium perchlorate was studied.

Experimental

Li(cyclodisarcosyl)$_2$ClO$_4$ was obtained as a precipitate by mixing in stoichiometric ratio an ethyl acetate solution of cyclodisarcosyl with that of lithium perchlorate. Colourless plate-like crystals were obtained by slow evaporation of an ethanol solution. The crystals were almost invariably twinned in section, parallel to the *ac* plane. A specimen with one component negligibly small was used for the intensity measurements.

The crystal is triclinic with cell dimensions: $a = 11{\cdot}575(4)$, $b = 8{\cdot}107(2)$, $c = 11{\cdot}561(3)$ Å, $\alpha = 110{\cdot}95$ (1), $\beta = 89{\cdot}97$ (1), $\gamma = 116{\cdot}63$ (2)°. The observed density of the crystal, 1·412 g cm^{-3}, suggested that the number of chemical units in a cell was two, the calculated density being 1·424 g cm^{-3}. The intensity measurements were made on an AFC-III (Rigaku Denki automatic four-circle diffractometer). The ω–2θ scan method and Ni-filtered Cu $K\alpha$ radiation were used. The background intensities were measured on either side of the scan. 2552 reflexions within a limit of $2\theta = 120°$ were collected. The Lp corrections were made as usual; no absorption correction was made. The size of the crystal used in the experiment was 0·3 × 0·2 × 0·1 mm. Since the statistics of the normalized structure factors suggested a space group with a centre of symmetry, $P\bar{1}$ was adopted. The systematic weak intensities of the reflexions with $(h + l)$ odd suggested a pseudo base-centred lattice.

Structure determination

The structure was solved by the direct method with the symbolic addition procedure and weighted multisolution tangent formula refinement of the phases (Main, Germain & Woolfson, 1971). An *E* map showed clearly the positions of the Cl atom and four independent cyclodisarcosyl molecules. However, the position of the perchlorate O atoms could not be determined because eight broad peaks arranged with an approximate symmetry of $4/m$ appeared around the Cl atom. In several attempts to locate the perchlorate ion, it behaved anomalously, and a disordered model had to be taken into account.

All the eight peaks surrounding the Cl atom were considered to be O atoms with a statistical weight of one-half. During the least-squares refinement these weights were retained. The refinement proceeded smoothly and the *R* value converged at 0·112 for non-zero reflexions.

The difference electron density map, which was calculated after several cycles of least-squares refinement, showed all the H and Li atoms. These atoms were also included in the subsequent refinements. In this process the block-diagonal least-squares program *HBLS* V (Ashida, 1973) was used. The weighting scheme at the final stage of the refinement was: for $|F_o| > 0$, $w = [\sigma^2(|F_o|) - 0{\cdot}645|F_o| + 0{\cdot}035|F_o|^2]^{-1}$, and for $|F_o| = 0$, $w = 0{\cdot}923$, where $\sigma(|F_o|)$ is from the counting statistics of the intensity measurements. The atomic scattering factors for Li^+, Cl, O, N, C and H were taken from *International Tables for X-ray Crystallography* (1974). The final *R* value was 0·065 for non-zero reflexions, and 0·085 for all reflexions. The final atomic parameters are listed in Tables 1 and 2.* All the computations were carried out on a FACOM 230-60 computer of this University. The numbering of the atoms is shown in Fig. 1.

Discussion

The cyclodisarcosyl molecule

There are four crystallographically independent cyclodisarcosyl molecules in the crystal, each lying on

Table 1. *The atomic parameters* ($\times 10^4$) *and their e.s.d.'s in parentheses*

	x	*y*	*z*
C(1)	7521 (1)	28 (1)	2478 (1)
O(1)	3074 (2)	−1524 (3)	3091 (2)
N(1)	5641 (2)	2011 (3)	5731 (2)
C(11)	6026 (3)	849 (4)	6018 (2)
C(12)	4611 (3)	1288 (4)	4718 (3)
C(13)	6222 (3)	4120 (5)	6471 (3)
O(2)	1943 (2)	1545 (3)	3871 (2)
N(2)	680 (2)	2014 (4)	5320 (2)
C(21)	1057 (3)	900 (4)	4424 (3)
C(22)	−360 (3)	1288 (5)	5971 (3)
C(23)	1320 (4)	4153 (5)	5723 (4)
O(3)	1085 (2)	−1530 (3)	1110 (2)
N(3)	367 (2)	2008 (3)	399 (2)
C(31)	−552 (3)	863 (4)	−574 (2)
C(32)	1019 (3)	1291 (4)	1039 (3)
C(33)	839 (4)	4136 (5)	893 (4)
O(4)	3949 (2)	1571 (3)	1898 (2)
N(4)	5440 (2)	2021 (4)	640 (2)
C(41)	4463 (3)	896 (4)	1023 (3)
C(42)	6054 (3)	1275 (5)	−375 (3)
C(43)	5929 (4)	4157 (5)	1215 (4)
Li	2515 (5)	38 (7)	2511 (4)
O(11)	7635 (10)	1151 (13)	3732 (6)
O(12)	6216 (6)	−1307 (11)	2111 (8)
O(13)	7903 (8)	1323 (10)	1858 (7)
O(14)	8245 (8)	−1008 (13)	2189 (9)
O(21)	6717 (7)	885 (13)	2857 (8)
O(22)	7193 (8)	−1154 (12)	1190 (5)
O(23)	8792 (6)	1471 (11)	2874 (8)
O(24)	7449 (9)	−1221 (11)	3081 (7)

Table 2. *The positional* ($\times 10^3$) *parameters of the hydrogen atoms*

	Bonded to	*x*	*y*	*z*
H(11)	C(12)	478	194	411
H(12)	C(12)	390	170	502
H(13)	C(13)	604	421	734
H(14)	C(13)	607	473	607
H(15)	C(13)	684	442	664
H(21)	C(22)	−93	174	598
H(22)	C(22)	−8	197	693
H(23)	C(23)	219	435	570
H(24)	C(23)	100	498	617
H(25)	C(23)	151	442	500
H(31)	C(32)	99	180	195
H(32)	C(32)	194	171	114
H(33)	C(33)	39	387	139
H(34)	C(33)	64	471	50
H(35)	C(33)	157	496	152
H(41)	C(42)	707	163	−33
H(42)	C(42)	607	181	−95
H(43)	C(43)	649	425	154
H(44)	C(43)	555	496	193
H(45)	C(43)	632	491	71

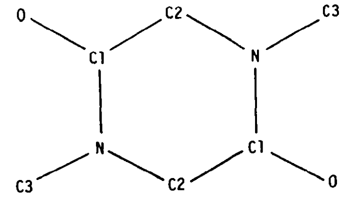

Fig. 1. Atomic numbering of the cyclodisarcosyl molecule.

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32421 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *Bond distances* (Å) *and angles* (°) *in cyclodisarcosyl molecules*

Estimated standard deviations are in parentheses.

	c(-Gly$_2$-)$^{(a)}$	*c*(-Sar$_2$-)$^{(b)}$	*A**	*B*†	I	II	III	IV
C(1)–C(2)	1·499 (7)	1·506 (4)	1·453 (4)	1·459 (4)	1·440 (5)	1·465 (5)	1·456 (5)	1·461 (5)
C(1)–N	1·325 (7)	1·348 (3)	1·334 (3)	1·291 (3)	1·340 (4)	1·327 (5)	1·289 (4)	1·292 (5)
C(1)–O	1·239 (7)	1·234 (3)	1·231 (3)	1·258 (3)	1·240 (4)	1·221 (4)	1·264 (4)	1·252 (4)
C(2)–N	1·449 (7)	1·455 (3)	1·426 (4)	1·455 (4)	1·423 (5)	1·428 (5)	1·453 (5)	1·457 (5)
C(3)–N	—	1·475 (3)	1·428 (4)	1·436 (3)	1·426 (5)	1·430 (5)	1·437 (4)	1·435 (5)
O–C(1)–N	122·6 (3)	123·6 (2)	124·1 (2)	123·3 (2)	123·0 (3)	125·2 (3)	123·0 (3)	123·6 (3)
N–C(1)–C(2)	118·9 (3)	118·1 (2)	119·6 (2)	116·9 (2)	120·3 (3)	118·9 (3)	117·1 (3)	116·7 (3)
O–C(1)–C(2)	118·5 (3)	118·3 (2)	116·3 (2)	119·7 (2)	116·7 (3)	115·8 (3)	119·7 (3)	119·6 (3)
N–C(2)–C(1)	115·1 (3)	117·0 (2)	115·1 (2)	118·5 (2)	115·2 (3)	114·9 (3)	118·4 (3)	118·5 (3)
C(1)–N–C(2)	126·0 (3)	124·6 (2)	125·3 (2)	124·6 (2)	124·5 (3)	126·1 (3)	124·4 (3)	124·7 (3)
C(1)–N–C(3)	—	119·7 (2)	121·2 (2)	118·1 (2)	121·4 (3)	120·9 (3)	118·1 (3)	118·1 (3)
C(2)–N–C(3)	—	115·5 (2)	113·5 (2)	117·3 (2)	114·0 (3)	113·0 (3)	117·5 (3)	117·1 (3)

(*a*) Degeilh & Marsh (1959). (*b*) Groth (1969).

* Mean values of molecules I and II.
† Mean values of molecules III and IV.

the centre of symmetry at $y = 0$. They are (I)–(IV) in Fig. 2, and are classified, according to the bond distances and angles, into two groups; group *A* contains (I) and (II), and group *B* contains (III) and (IV). This is not explained satisfactorily at present. In Table 3 a comparison of bond distances and angles in the two groups is given.

If the Li–O distance is shorter, C(1)–O is longer and C(1)–N shorter, the mean Li–O distances being 1·945 Å in group *A* and 1·899 Å in *B*. This seems to show that as the coordination bond of Li–O becomes strong, the double-bond character of the C(1)–N bond increases. There is, however, no quantitative correlation between the shifts of the stretching frequencies (Sugihara *et al.*, 1973) and the bond distances of the C(1)–O and C(1)–N bonds.

In Table 3 the distances and angles of diketopiperazine (Degeilh & Marsh, 1959) and cyclodisarcosyl (Groth, 1969) are also listed. The C(1)–C(2) and C(3)–N bonds are significantly shorter in the present crystal. This may also be a result of the complex formation.

The previous investigations of the diketopiperazine ring conformation have shown that there are two possible conformations, boat or planar (extremely flattened chair), according to the kind of substituents on the C$^{\alpha}$ atoms (Karle, 1972). A boat conformation has been found in *cyclo*(-L-Ala-L-Ala-) (Sletten, 1970; Benedetti, Corradini & Pedone, 1969*a*), *cyclo*(-L-Pro-L-Leu-) (Karle, 1972), *cyclo*(-Gly-L-Tyr-) and *cyclo*(-L-Ser-L-Tyr-) (Lin & Webb, 1973), *cyclo*(-L-Pro-Gly-) (Von Dreele, 1975), *cyclo*(-Sar-L-Val-) (Timmins, 1975), and *cyclo*(-L-Thr-L-His-) (Cotrait, Ptak, Busetta & Heitz, 1976).

Table 4. *The best planes for cyclodisarcosyl molecules and the displacements* (Å) *of atoms from these planes*

Molecule I
$$0{\cdot}6671X + 0{\cdot}4134Y - 0{\cdot}6088Z + 0{\cdot}2524 = 0$$
Molecule II
$$-0{\cdot}6900X + 0{\cdot}2107Y - 0{\cdot}6925Z + 4{\cdot}1656 = 0$$
Molecule III
$$-0{\cdot}7127X - 0{\cdot}3551Y + 0{\cdot}6050Z = 0$$
Molecule IV
$$-0{\cdot}7096X + 0{\cdot}2474Y - 0{\cdot}6597Z + 4{\cdot}1068 = 0$$

$X = ax + by \cos\gamma + cz \cos\beta$, $Y = by \sin\gamma - cz \cos\alpha^* \sin\beta$, $Z = cz \sin\alpha^* \sin\beta$ in A.

	I	II	III	IV	Cyclodisarcosyl†
N(1)	–0·000	0·002	0·004	0·001	0·031
O(1)	0·002	0·012	0·006	0·002	0·024
C(1)	0·000	–0·002	–0·004	–0·001	–0·007
C(2)	0·000	–0·002	–0·004	–0·001	–0·051
C(3)	0·049	0·019	0·032	0·065	0·008

† Groth (1969).

On the other hand, a planar conformation has been found in the compounds in which C$^{\alpha}$ atoms have no side groups, *e.g.* DKP (Degeilh & Marsh, 1959), and *cyclo*(-Sar-Sar-) (Groth, 1969; this work), or in which the absolute configurations of the two C$^{\alpha}$ atoms are different, as in the case of *cyclo*(-D-Ala-L-Ala-) (Sletten, 1970; Benedetti, Corradini & Pedone, 1969*b*).

All molecules which can themselves have centres of symmetry occupy centres of symmetry in the crystal lattices. Consequently they have planar, as in the present case, instead of boat conformations.

The equations of the present molecular planes and the shifts of atoms from the planes are listed in Table 4.

The planarity of the DKP rings is usually excellent; the maximum deviation is found in cyclodisarcosyl, 0·05 Å (Groth, 1969).

The perchlorate ion

The Cl atom lies close to a 'special' position ($x = \frac{3}{4}, y = 0, z = \frac{1}{4}$). As previously stated, and shown in Fig. 2, the perchlorate ions are disordered, and two equilibrium orientations seem to be possible. The models shown by solid and broken lines are distributed with equal probabilities. A $\bar{4}$ axis of each model is almost perpendicular to the *ac* plane. In addition to this orientational disorder, the perchlorate ion undergoes exceptionally large thermal vibrations; this suggests a librational motion of the perchlorate ion around its $\bar{4}$ axis.

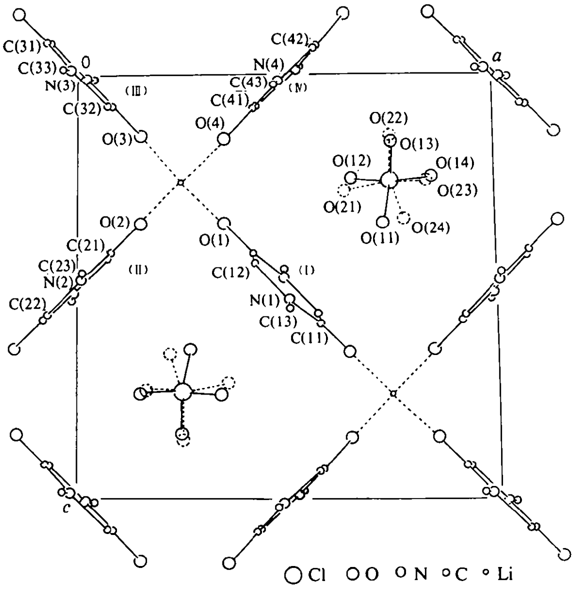

Fig. 2. A representation of the unit cell viewed on the *ac* plane, showing the one-layer network structure near $y = 0$. Both the Li ions and the Cl atoms lie almost at $y = 0$, and the cyclodisarcosyl molecules are at the centres of symmetry.

In Table 5 are presented the bond distances and angles. The apparent shortening of the Cl—O distances, 1·35 ~ 1·40 Å, in the present crystal is due to the disorder and the large thermal vibrations. The mean value of the normal Cl—O distances is reported as 1·44 Å (*International Tables for X-ray Crystallography*, 1968, p. 273).

The coordination of cyclodisarcosyl molecules to the lithium ion

The Li ion also lies at a 'special' position ($x = \frac{1}{4}, y = 0, z = \frac{1}{4}$). The ion is surrounded almost tetrahedrally by the four carbonyl O atoms, each from four independent cyclodisarcosyl molecules (Fig. 3).

In Table 6 are presented the distances and angles of the coordination bonds. The Li—O distances vary from 1·892 to 1·952 Å (mean 1·922 Å). This distance is significantly shorter than the value of 1·98 Å given as the average for the Li—O distances for four coordination (*International Tables for X-ray Crystallography*, 1968, p. 258). The O—Li—O angles are from 104·7 to 116·2°. Thus the tetrahedron of the ligands around the Li ion in the present crystal is much more regular than those around the Li ions in other organic crystals. The Li—O—C(1) angles are from 126·3 to 128·2° (mean

Table 5. *Bond distances* (Å) *and angles* (°) *in the perchlorate group*

Estimated standard deviations are in parentheses.

C(1)–O(11)	1·38 (1)	O(11)–C(1)–O(12)	103·2 (6)
O(1)–O(12)	1·36 (1)	O(11)–C(1)–O(13)	107·6 (6)
C(1)–O(13)	1·39 (1)	O(11)–C(1)–O(14)	117·3 (6)
C(1)–O((14)	1·40 (1)	O(12)–C(1)–O(13)	111·5 (6)
C(1)–O(21)	1·38 (1)	O(12)–C(1)–O(14)	109·5 (6)
C(1)–O(22)	1·39 (1)	O(13)–C(1)–O(14)	107·8 (6)
C(1)–O(23)	1·35 (1)	O(21)–C(1)–O(22)	112·2 (6)
C(1)–O(24)	1·40 (1)	O(21)–C(1)–O(23)	109·6 (6)
		O(21)–C(1)–O(24)	112·2 (6)
		O(22)–C(1)–O(23)	113·8 (6)
		O(22)–C(1)–O(24)	106·3 (6)
		O(23)–C(1)–O(24)	102·3 (6)

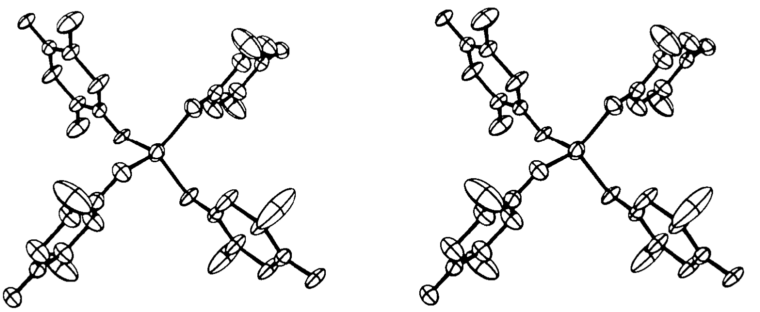

Fig. 3. Stereoscopic view of the coordination of the Li ion to carbonyl O atoms of four cyclodisarcosyl molecules.

Table 6. *Interatomic distances* (Å) *and angles* (°) *involving the lithium ion*

Estimated standard deviations are in parentheses.

Li–O(1)	1·952 (6)	Li–O(4)–C(41)	126·4 (3)
Li–O(2)	1·937 (6)	O(1)–Li–O(2)	109·0 (3)
Li–O(3)	1·906 (6)	O(1)–Li–O(3)	114·6 (3)
Li–O(4)	1·892 (6)	O(1)–Li–O(4)	105·9 (3)
Li–O(1)–C(11)	126·6 (3)	O(2)–Li–O(3)	106·6 (3)
Li–O(2)–C(21)	128·2 (3)	O(2)–Li–O(4)	116·2 (3)
Li–O(3)–C(31)	126·3 (3)	O(3)–Li–O(4)	104·7 (3)

126·9°). Each Li–O vector is almost coplanar with the cyclodisarcosyl molecule to which the O atom belongs. These facts indicate that a lone pair of electrons of the O atom is pointing to the Li ion.

The other carbonyl O atom of each cyclodisarcosyl molecule coordinates to another Li ion. No N atoms are in the vicinity of the Li ion.

Molecular packing

The crystal structure of Li(cyclodisarcosyl)$_2$ClO$_4$ viewed on the *ac* plane is illustrated in Fig. 2, where all the cyclodisarcosyl molecules, and the ions whose centres are close to the plane of $y = 0$, are shown. Each cyclodisarcosyl molecular plane is almost normal to the *ac* plane. These molecular planes are almost perpendicular to each other. Thus, the cyclodisarcosyl molecules linked by coordination of the carbonyl groups to the Li ion make an infinite two-dimensional network parallel to the *ac* plane, the Li ion being at each knot in the network. Such a network structure may have something to do with the insolubility of this compound in organic solvents.

The perchlorate ion is at the centre of each vacancy of the network. The nearest neighbours of the ion in this layer structure are the N atoms with fractional positive charge. Thus, the electrostatic forces also play an important part in the crystal structure.

The crystal is composed of the parallel stackings of these layer structures (networks) along **b**. The interactions between the networks are mainly due to van der Waals forces. A methyl group of the cyclodisarcosyl molecule whose centre is at ($x = \frac{1}{2}$, $y = 1$, $z = 1$) approaches the perchlorate ion at ($x = \frac{1}{4}$, $y = 0$, $z = \frac{3}{4}$), the closest $CH_3 \cdots O$(perchlorate) contact being 3·24 Å. Thus the perchlorate ion is completely enclosed by the cyclodisarcosyl molecules.

Fig. 2 also shows clearly a pseudo base-centred lattice. The twinning, which occurs across the *ac* plane in almost every specimen, is easily understandable in view of such a packing scheme.

In order to make clear the relationship between the metal ion and cyclodisarcosyl, further studies on the complexes (*e.g.* between Ag, Cu, and Ba ions and cyclodisarcosyl) seem to be necessary.

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References

ASHIDA, T. (1973). *The Universal Crystallographic Computing System – Osaka*, p. 55. The Computation Center, Osaka Univ.

BENEDETTI, E., CORRADINI, P. & PEDONE, C. (1969*a*). *Biopolymers*, **7**, 751–764.

BENEDETTI, E., CORRADINI, P. & PEDONE, C. (1969*b*). *J. Phys. Chem.* **73**, 2891–2895.

COTRAIT, M., PTAK, M., BUSETTA, B. & HEITZ, A. (1976). *J. Amer. Chem. Soc.* **98**, 1073–1076.

DEGEILH, R. & MARSH, R. E. (1959). *Acta Cryst.* **12**, 1007–1014.

GROTH, P. (1969). *Acta Chem. Scand.* **23**, 3155–3162.

International Tables for X-ray Crystallography (1968). Vol. III, 2nd ed. Birmingham: Kynoch Press.

International Tables for X-ray Crystallography (1974). Vol. IV, pp. 72–75. Birmingham: Kynoch Press.

KARLE, I. L. (1972). *J. Amer. Chem. Soc.* **94**, 81–84.

LIN, C.-F. & WEBB, L. E. (1973). *J. Amer. Chem. Soc.* **95**, 6803–6811.

MAIN, P., GERMAIN, G. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

SLETTEN, E. (1970). *J. Amer. Chem. Soc.* **92**, 172–177.

SUGIHARA, T., IMANISHI, Y. & HIGASHIMURA, T. (1973). *Biopolymers*, **12**, 2823–2830.

TIMMINS, P. A. (1975). *Acta Cryst.* B**31**, 2561–2565.

VON DREELE, R. B. (1975). *Acta Cryst.* B**31**, 966–970.