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Polymorphism of DL-Norleucine

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The crystal structure of the α-form of DL-norleucine (DL-α-aminocaproic acid), with space group $P2_1/a$, has been analysed. The molecules are linked by hydrogen bonds into double-layer units, similar to those observed in the dimorphs of DL-methionine. The stacking of the units along the c axis is governed by the packing of the terminal CH_3–CH_2– groups of the aliphatic chains.

The probable existence of a second (or β-form) of DL-norleucine, with space group $I2/a$, corresponding to a packing of the CH_3–CH_2– groups which is slightly different from that in the α-form, is deduced from the occurrence of disorder observed in some crystals of this compound. The explanation of the existence of partially-ordered superlattice forms of DL-norleucine is based on the various sequential arrangements of these two packing formations.

Introduction

In a preliminary report on the aliphatic DL-α-amino acids, including DL-methionine, (Dawson & Mathieson, 1951) it was recorded that the unbranched compounds crystallized in either or both of the space groups $P2_1/a$ and $I2/a$. For convenience, the crystalline forms were termed α and β respectively. The detailed analyses of the dimorphs of DL-methionine (Mathieson, 1952) revealed that the molecules are bound in double-layer units by hydrogen bonds and that the free rotation of the –S–CH_2– bond permitted two stable orientations of the terminal CH_3–S– groups with respect to their neighbours. No disorder arising from the interleaving of the two types of double-layer units was observed in crystals of DL-methionine.

Although DL-norleucine was obtained in single crystals of the α-form, it was observed that most of the crystals exhibited partially-ordered superlattice structures, the c axis being four times that of the primitive form whilst a, b and β remained unchanged. This suggested that there must be a method of molecular packing alternative to that in α-DL-norleucine and corresponding to a second crystalline form of this compound. The probable planar configuration of the aliphatic chain precluded the explanation of dimorphism as being of the type displayed by DL-methionine.

The crystal structure of α-DL-norleucine has been analysed and used to deduce the structure of a second form, the β-type, with space group $I2/a$. An explanation of the existence of superlattice forms, based on an ordered sequence of the two packing arrangements is given.

Where no specific statement is made in the text reference is to the racemic form of norleucine.

Experimental

Crystals of DL-norleucine were grown as small thin plates from an alcohol–water solution by slow evaporation. The unit-cell dimensions (Table 1) were measured on rotation and zero-layer Weissenberg photographs. For comparison, the cell dimensions of the dimorphs of DL-methionine are appended.

The density, calculated for the given number of molecules, was 1·17 g.cm.$^{-3}$ and the measured value, by flotation in benzene–chloroform, 1·16 g.cm.$^{-3}$. The space-group data were obtained from equi-inclination Weissenberg photographs of zero-, first- and second-layers about the a and b axes. For α-norleucine, $h0l$ reflexions occur only for $h = 2n$ and $0k0$ reflexions for $k = 2n$. The space group is therefore $P2_1/a$. For the superlattice form, $h0l$ reflexions occur only for $h = 2n$ and $l = 4n$, the hkl reflexions with $h+k = 2n$ are sharp and occur only for $l = 4n$ but for $h+k = 2n+1$ the reflexions occur for all values of l and are linked by diffuse regions parallel to c^*. In Fig. 1, the first-layer moving film about the b axis for one such crystal is shown, the reflexions $01l$, $21l$ etc. illustrating their diffuse nature.

Intensity data for $h0l$ and $0kl$ reflexions of α-

Table 1. *Unit-cell dimensions*

	a (Å)	b (Å)	c (Å)	β (°)	Z	Space group
α-DL-norleucine	9·84	4·74	16·56	104·5	4	$P2_1/a$
β-DL-norleucine (deduced)	9·84	4·74	33·12	104·5	8	$I2/a$
s-DL-norleucine (superlattice)	9·84	4·74	66·24	104·5	16	—
α-DL-methionine	9·76	4·70	16·70	102·0	4	$P2_1/a$
β-DL-methionine	9·94	4·70	33·40	106·6	8	$I2/a$

Fig. 1. First-layer equi-inclination Weissenberg photograph, b-axis rotation.

norleucine were collected on multiple-film packs on a Weissenberg goniometer utilising filtered cobalt radiation. Measurement of the intensities was made by visual comparison with a standard set of reflexions. The observed structure amplitudes were placed on an absolute scale and the best temperature correction for the calculated values ($B = 3\cdot26\times10^{-16}$ cm.^{2}) determined by plotting log $\{\Sigma|F_c|/\Sigma|F_o|\}$ against $(\sin\theta/\lambda)^2$, the summations being over small ranges of $(\sin\theta/\lambda)^2$. The Fourier syntheses were calculated at intervals of 6° for the a and c axes and 12° for the b axis, using three-figure Beevers–Lipson strips. The electron-density distributions were contoured by interpolation of sections parallel to the two axes of the projection area.

Analysis and discussion of α-DL-norleucine

The similarity of chemical formulae and cell dimensions of norleucine $(CH_3.CH_2.CH_2.CH_2.CHNH_3^+.COO^-)$ and of methionine $(CH_3.S.CH_2.CH_2.CHNH_3^+.COO^-)$ indicated that the molecules of norleucine are also grouped in double-layer units stacked along the c axis. Moreover, the probable rigidity of the aliphatic chain in norleucine suggested a closer structural relationship with the molecular configuration exhibited by methionine in the β-form. Such a molecular model was therefore assumed for α-norleucine and positioned in the unit-cell so as to permit extensive hydrogen-bonding between the NH_3^+ and COO^- groups of the molecules of the double-layer (*vide* methionine). The initial agreement between the calculated and observed amplitudes of the $h0l$ reflexions was quite good and the refinement was carried out by successive Fourier syntheses. The final electron-density distribution for this projection is shown in Fig. 2 and the corresponding diagram of the crystal structure in Fig. 3(r). For the a-axis projection, the molecule was already located approximately by the system of hydrogen bonds, and

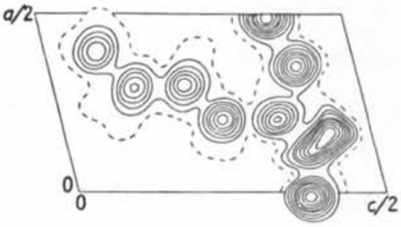

Fig. 2. Electron-density distribution for α-norleucine; projection down the b-axis.

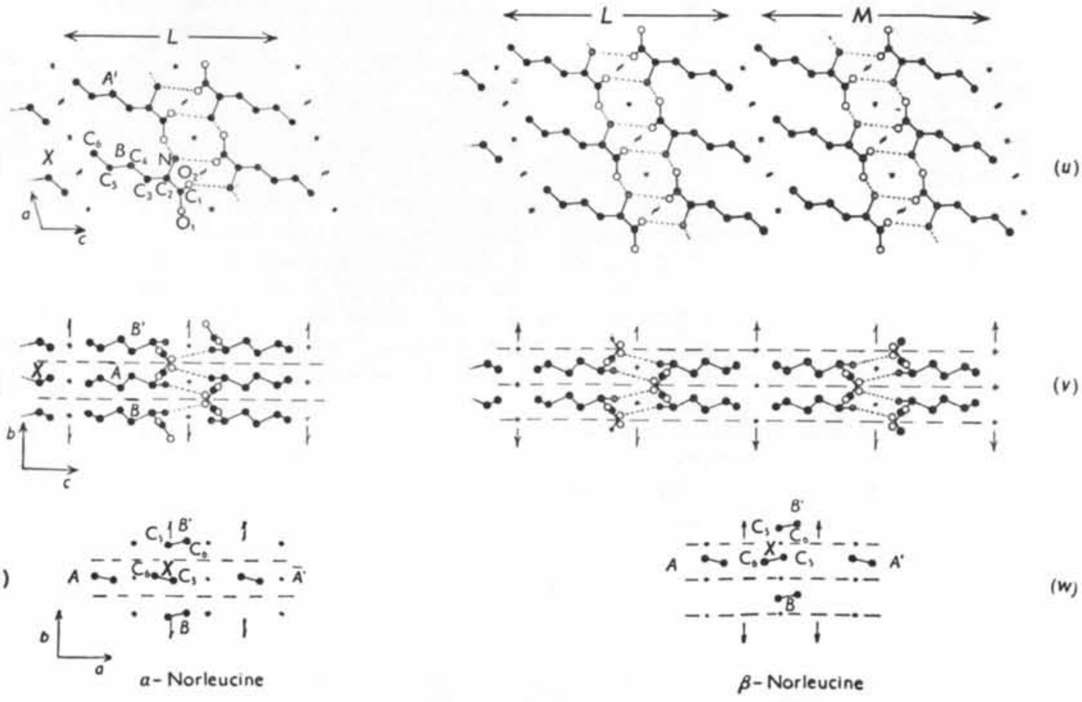

Fig. 3. Crystal structures of α- and β-DL-norleucine.

refinement of atomic parameters proceeded by the use of Fourier syntheses. The diagram of the crystal structure in this projection is given in Fig. 3(*s*), the actual electron-density distribution not being shown since it is similar to that of α-methionine (Mathieson, 1952).

Since the range of sin θ/λ was limited by the use of cobalt radiation in recording the intensity data, back-corrections for series termination were estimated from an $F_c(h0l)$ synthesis. It was not considered feasible to determine back-corrections for the *a*-axis projection owing to the large amount of overlap. The final discrepancy factors for the *h0l* and *0kl* sets of reflexions were 0·22 and 0·24 respectively. The atomic parameters are given in Table 2 and the interatomic distances and angles calculated from these values in Table 3, the probable errors being 0·04 Å and 5° respectively.

Table 2. *Atomic parameters for α-DL-norleucine*

	x	*y*	*z*
O_1	−0·012	−0·067	0·375
O_2	0·169	−0·317	0·432
N	0·356	0·050	0·404
C_1	0·118	−0·114	0·392
C_2	0·209	0·050	0·350
C_3	0·207	−0·069	0·261
C_4	0·301	0·089	0·217
C_5	0·288	−0·036	0·128
C_6	0·394	0·036	0·083

Table 3. *Interatomic distances and angles for α- and β-DL-norleucine*

C_6–C_5	1·48 Å	C_6–C_5–C_4	120°
C_5–C_4	1·57	C_5–C_4–C_3	110
C_4–C_3	1·51	C_4–C_3–C_2	114
C_3–C_2	1·58	C_3–C_2–C_1	112
C_2–C_1	1·49	C_3–C_2–N	110
C_2–N	1·50	C_1–C_2–N	109
C_1–O_1	1·26	C_2–C_1–O_1	120
C_1–O_2	1·20	C_2–C_1–O_2	118
		O_1–C_1–O_2	122
N(*A*)–O_1(*B*)	2·73 Å	C_2–N–O_1(*B*)	109°
N(*A*)–O_1(*B′*)	2·87	C_2–N–O_1(*B′*)	108
N(*A*)–O_2(*C*)	2·87	C_2–N–O_2(*C*)	105
		O_1(*B*)–N–O_1(*B′*)	116

Approach distance of C_6–C_5 groups

α-form		β-form	
C_6(*X*)–C_6(*A*)	3·84 Å	C_6(*X*)–C_6(*A*)	3·81 Å
C_6(*X*)–C_6(*B*)	4·16	C_5(*X*)–C_6(*B*)	4·23
C_6(*X*)–C_6(*B′*)	4·16	C_5(*X*)–C_6(*B′*)	4·23
C_5(*X*)–C_6(*B*)	4·04	C_6(*X*)–C_6(*B*)	3·98
C_5(*X*)–C_5(*B′*)	4·43	C_6(*X*)–C_6(*B′*)	4·37

As in the case of α- and β-DL-methionine, the discrepancy factors are rather greater than normally observed in structure analyses of compounds with a similar number of atoms in the unit cell. The high values can be ascribed to the shape of the crystals preventing accurate intensity measurement, omission of the hydrogen-atom contributions (this was evident in the comparison of the F_o and F_c syntheses) and in the use of a single temperature-correction factor for all atoms. It is evident from the fall of peak heights of atoms C_1 to C_6 in Fig. 2 that an increasing temperature-factor (possibly asymmetric) should be applied to the atoms in that order. Since the main aim of the investigation was to determine the packing arrangement of the CH_3–CH_2– groups, and since the introduction of the above factors would be unlikely to modify any signs of the Fourier terms, further improvement of the discrepancy factor was not attempted.

The bond lengths and angles of norleucine are in general close agreement with those observed in methionine. The asymmetry of the carboxyl group is again correlated with the distribution of the hydrogen bonds (Donohue, 1950). The carbon–carbon bond lengths display alternation, although the accuracy of the structure determination is not sufficient to place such an effect beyond doubt. The molecules are linked by hydrogen bonds between NH_3^+ and COO^- groups to yield double-layer units extending parallel to 001. The arrangement of bonds around the nitrogen atom is approximately tetrahedral, the mean distance N − − − O being 2·82 Å. The main interest lies in the mutual arrangement of the terminal groups of the aliphatic chains which determines the stacking of the layers. The method of packing of CH_3–CH_2– groups is best illustrated by the projection perpendicular to 001 in Fig. 3(*t*). The molecules, *A*, *A′* and *B*, *B′* are related by translations parallel to the *a* and *b* axes respectively, while molecule *X* is in the adjacent double-layer (see Fig. 3(*r*) and (*s*)). This grouping of molecules provides a type of distorted hexagonal packing akin to that observed in α-methionine. The approach distances are listed in Table 3.

Deduction of the crystal structure of β-DL-norleucine

In the diffraction data for the crystals displaying partially-ordered superlattice structures, the following features are of importance in deducing, first, the reason for disorder and, second, the possible creation of a superlattice. In such crystals, where $c_s = 4c_\alpha$ (c_α being the primitive translation of the α-form), the *h0l* reflexions occur only for $h = 2n$ and $l = 4n$, and the *hkl* reflexions, having $h+k = 2n$, for $l = 4n$. These reflexions are sharp, coincide with, and have exactly the same intensity distribution as, the corresponding reflexions of the α-form. The general reflexions with $h+k = 2n+1$ occur for all orders of *l*, are much less sharp and are linked by a diffuse region parallel to c^* (Fig. 1), the actual distribution varying from crystal to crystal.

If the occurrence of disorder is considered initially, then, since the crystal structure of norleucine is of a layer type, the diffuse spread of reflexions parallel to c^* can be correlated with some type of mistake in stacking of the layers (Wilson, 1949). The sharp spectra common to α-norleucine and the superlattice forms have the

Table 4. *Comparison of observed and calculated structure amplitudes*

hkl	F_o	F_c
001	55	-71
002	11	-2
003	20	25
004	72	-69
005	44	47
006	58	-51
007	7	-3
008	26	20
009	3	-3
0,0,10	< 2	3
0,0,11	< 2	0
0,0,12	< 2	-1
0,0,13	3	-1
0,0,14	5	6
0,0,15	4	4
0,0,16	< 1	0
0,0,17	4	-4
0,0,18	< 1	-1
2,0,$\overline{18}$	4	-4
2,0,$\overline{17}$	< 2	-1
2,0,$\overline{16}$	< 2	1
2,0,$\overline{15}$	11	-12
2,0,$\overline{14}$	6	-7
2,0,$\overline{13}$	8	12
2,0,$\overline{12}$	10	6
2,0,$\overline{11}$	4	-1
2,0,$\overline{10}$	10	12
20$\bar{9}$	10	-14
20$\bar{8}$	10	14
20$\bar{7}$	8	-9
20$\bar{6}$	< 2	1
20$\bar{5}$	12	13
20$\bar{4}$	28	-32
20$\bar{3}$	12	19
20$\bar{2}$	18	-22
20$\bar{1}$	9	-6
200	50	-45
201	< 1	-1
202	56	60
203	27	24
204	10	-4
205	2	-2
206	15	17
207	21	-23
208	< 2	-2
209	21	-23
2,0,10	10	5
2,0,11	13	16
2,0,12	13	-14
2,0,13	13	13
2,0,14	5	-4
2,0,15	< 2	0
2,0,16	1	4
4,0,$\overline{18}$	3	4
4,0,$\overline{17}$	2	-5
4,0,$\overline{16}$	7	9
4,0,$\overline{15}$	2	-4
4,0,$\overline{14}$	3	1
4,0,$\overline{13}$	6	-5
4,0,$\overline{12}$	34	-32
4,0,$\overline{11}$	28	28
4,0,$\overline{10}$	4	-7
40$\bar{9}$	< 2	3
40$\bar{8}$	22	23
40$\bar{7}$	15	-17
40$\bar{6}$	38	32
40$\bar{5}$	23	-19
40$\bar{4}$	17	-5
40$\bar{3}$	5	-6
40$\bar{2}$	2	2
40$\bar{1}$	2	-2
400	9	-3
401	21	15
402	42	-45
403	14	15
404	11	8
405	6	2
406	13	15
407	8	-7
408	7	13
409	7	6
4,0,10	14	-18
4,0,11	5	-8
4,0,12	5	2
4,0,13	3	-2
4,0,14	3	4
6,0,$\overline{16}$	< 2	3
6,0,$\overline{15}$	2	1
6,0,$\overline{14}$	< 2	-2
6,0,$\overline{13}$	6	7
6,0,$\overline{12}$	10	8
6,0,$\overline{11}$	15	-20
6,0,$\overline{10}$	10	-7
60$\bar{9}$	< 2	-4
60$\bar{8}$	2	1
60$\bar{7}$	8	8
60$\bar{6}$	14	-14
60$\bar{5}$	29	30
60$\bar{4}$	3	2
60$\bar{3}$	2	3
60$\bar{2}$	2	-3
60$\bar{1}$	21	-22
600	22	20
601	22	-21
602	11	9
603	4	4
604	14	-15
605	5	8
606	2	-2
607	2	3
608	2	1
609	2	2
6,0,10	< 2	4
6,0,11	7	8
6,0,12	4	-8
8,0,$\overline{15}$	2	4
8,0,$\overline{14}$	2	-3
8,0,$\overline{13}$	2	3
8,0,$\overline{12}$	< 2	-1
8,0,$\overline{11}$	3	0
8,0,$\overline{10}$	19	17
80$\bar{9}$	19	-20
80$\bar{8}$	2	1
80$\bar{7}$	4	1
80$\bar{6}$	17	-13
80$\bar{5}$	17	11
80$\bar{4}$	20	-16
80$\bar{3}$	6	10
80$\bar{2}$	22	22
80$\bar{1}$	13	-7
800	2	1
801	2	-1
802	7	-8
803	6	3
804	5	-7
805	< 2	-1
806	5	5
807	6	-5
808	4	6
10,0,$\overline{11}$	6	5
10,0,$\overline{10}$	5	-6
10,0,$\bar{9}$	< 2	3
10,0,$\bar{8}$	9	5
10,0,$\bar{7}$	10	-7
10,0,$\bar{6}$	4	2
10,0,$\bar{5}$	2	-4
10,0,$\bar{4}$	< 2	2
10,0,$\bar{3}$	< 2	-4
10,0,$\bar{2}$	6	-7
10,0,$\bar{1}$	< 2	1
10,0,0	8	9
10,0,1	< 2	4
10,0,2	7	-4
10,0,3	7	6
011	10	-16
012	34	33
013	31	-29
014	31	19
015	17	-9
016	24	9
017	8	9
018	25	-14
019	< 5	-2
0,1,10	< 5	0
0,1,11	< 5	4
0,1,12	< 5	-7
0,1,13	< 4	4
0,1,14	< 4	-3
0,1,15	11	9
0,1,16	< 3	-1
0,1,17	< 2	-6
020	58	52
021	5	2
022	14	-12
023	15	14
024	23	-28
025	8	2
026	6	-7
027	13	-17
028	20	24
029	8	-8
0,2,10	4	4
0,2,11	< 4	2
0,2,12	< 4	3
0,2,13	< 4	3
0,2,14	< 3	0
0,2,15	7	9
0,2,16	< 2	4
031	< 4	-2
032	5	5
033	< 4	2
034	8	-5
035	9	9
036	< 4	3
037	12	11
038	13	-12
039	13	-17
0,3,10	11	12
0,3,11	< 4	-7
0,3,12	< 4	0
0,3,13	< 3	1
0,3,14	< 2	-1
040	< 5	-1

Table 4 (*cont.*)

hkl	F_o	F_c
041	< 5	7
042	< 5	4
043	< 5	-1
044	< 5	-5
045	8	-9
046	< 5	2
047	< 4	2
048	< 4	-1
049	4	3
0,4,10	< 3	-3
051	< 4	2
052	6	-6
053	7	8
054	4	-2

same intensity distribution and hence the double-layer unit L in Fig. 3(r) is retained as a rigid unit in the formation of all types of norleucine crystals. That only reflexions with $h+k = 2n$ are sharp suggests that in stacking, this unit is occasionally shifted $\frac{1}{2}(a+b)$. Such a unit, translated $\frac{1}{2}(a+b)$ with respect to a unit L, will be designated as M.

When this displacement occurs, a new packing arrangement of the CH_3–CH_2– groups is achieved at the interface between L and M double-layer units. Inspection of such a grouping shows that the symmetry elements in the α-form, namely centres of symmetry and diad screw axes between double-layer units, L and L, are replaced by diad rotation axes and centres of symmetry between L and M. The molecules within any double-layer unit are still related by centres of symmetry and diad screw axes. The alternation of the sets of elements, centres and diad screw axes with diad rotation axes and centres, corresponds to the disposition of symmetry elements in the space group $I2/a$. Hence it can be deduced that norleucine could exist in such a crystalline form—termed β-norleucine. This deduction is consistent with the evidence of the previous investigation (Dawson & Mathieson, 1951) that unbranched aliphatic α-amino acids occur either with space group $P2_1/a$ or $I2/a$ and that methionine occurs in both. It appears probable that a very careful search among crystals of DL-norleucine would reveal some with this β-structure. No pure β-crystal was observed in the present investigation.

The crystal structure of β-norleucine is shown in Fig. 3(u) and (v), viewed down the b and a axes respectively. The c axis in this case is twice that of the primitive form, i.e. $c_\beta = 2c_\alpha$. The location of the double-layer units is determined by the relation of the symmetry elements at $\frac{1}{4}c_\beta$ and $\frac{3}{4}c_\beta$, and by the glide plane parallel to a. Since it is known that the configuration of the double-layer unit, and hence of the norleucine molecule, is invariant in the various crystalline forms of norleucine, the interatomic distances between the CH_3–CH_2– groups in β-norleucine can be calculated. The approach distances are listed in Table 3. The packing arrangement is illustrated in Fig. 3(w), the molecules being indicated by letter in a fashion similar to that in Fig. 3(t).

In Table 3, the approach distances have been grouped to show the essential similarity in the packing arrangements of the two forms. In the β-form the groups are arranged so that the $C_5(X)$ is equidistant from $C_6(B)$ and $C_6(B')$, whereas in the α-form it is $C_6(X)$ which is equidistant from these atoms. The two balanced arrangements of van der Waals bonds may be regarded as equally stable, and hence the probability of layer units stacking in either way is almost equal. The α-form may be designated by the arrangement of the double-layer units $L\ L\ L\ L$ etc. whereas the β-form is $L\ M\ L\ M$ etc. In the superlattice form illustrated in Fig. 1, longer-range order is evident. In this case, four units of L and M are grouped together to form a cell with $c_s = 4c_\alpha$. The diffuse spectra for $l = 4n+2$ are extremely weak, almost non-existent, and this suggests the sequence $L\ L\ M\ M$. If perfectly ordered in this sequence, only spectra for $l = 4n\pm1$ should appear, and it is noteworthy that the reflexions for $l = 4n$ are considerably weaker than the corresponding coincident spectra for the α-form. The stacking sequence is not perfect and hence $l = 4n$ reflexions occur with low intensity.

In another norleucine crystal, the diffuse distribution was different, being rather closer to the α-form, and the predominant sequence is probably $L\ L\ L\ M$ etc.

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