# Chiral Molecular Alloys: Patterson-Search Structure Determination of L-Carvone and DL-Carvone from X-ray Powder Diffraction Data at 218 K

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## Abstract

The crystal structures of pure L-carvone [(*R*)-(−)-2-methyl-5-(1-methylethenyl)-2-cyclohexen-1-one, $C_{10}$-$H_{14}O$] and the equimolar mixture DL-carvone (*RS*) have been determined by Patterson-search methods at low resolution from laboratory X-ray powder diffraction data (218 K). Crystal data: (L) $a = 6.8576$ (3), $b = 6.8831$ (5), $c = 19.988$ (2) Å, $P2_12_12_1$ space group, $Z = 4$; (DL) $a = 6.9744$ (3), $b = 6.8094$ (6), $c = 20.038$ (7) Å, $Pcmn$ space group, $Z = 4$. The L-carvone structure has been refined by the Rietveld method as a rigid body, allowing the rotation of the isopropenyl group ($R_p = 0.030$ and $R_{wp} = 0.043$). Although the structure of DL-carvone could be unambiguously established, the Rietveld refinement was not possible due to the existence of preferred orientation in the sample and the difficulty in modelling the disorder. The molecular packing is essentialy the same for both compounds and can be explained as a stacking of two different molecular layers in the [001] direction. In each layer the molecules are placed with their long axis perpendicular to the layer plane, in a head-to-tail manner. The great similarity between the molecular shapes of L and D enantiomers favours the positional disorder in DL-carvone. This result confirms the mixed crystal formation for the chiral carvone system as proposed in recent thermodynamic studies. The DL-carvone crystal must be considered as a pseudo-racemate, since both enantiomers are randomly distributed over all the lattice sites.

## 1. Introduction

The molecular alloys constitute an active research field because of the potential interest of their physical properties in many areas of science and industry. As in metallic alloys, molecular compounds also form solid solutions, but with two or more different molecules as structural units. In the case of binary systems $A_{1-x}B_x$, their existence is related to the similarity between molecules rather than to the nature of the atomic species. The main structural features of these materials are: (*a*) great variety in size, molecular shape and intermolecular interactions: *A—A*, *B—B* or *A—B* in van der Waals, directed bonds,

hydrogen bonds *etc.*; (*b*) the possibility of several molecular orientations and/or conformations on a given crystallographic site; (*c*) the trend towards the most compact space filling (Cuevas-Diarte, Chanh & Haget, 1987; Haget, 1993). One of the practical applications of molecular alloys is thermal protection and energy storage by latent heat (Mondieig *et al.*, 1991; Labrador *et al.*, 1991). The operating temperature of the classic materials used for these purposes is determined by their melting point. In the molecular alloys, however, the possibility of optimizing the efficiency by adjusting their composition according to the desired temperature exists. Another field where the study of molecular alloys between optically active substances has increasing importance is the biomedical sciences. Here the interest is related to the fact that the active centre of many drugs is composed of chiral molecules and that, very often, the biological activity is different for both enantiomers. Therefore, the crystallographic and thermodynamic characterization of chiral molecular alloys supplies valuable information for optimizing the process of drug production.

In general, when cooling an equimolar liquid mixture of two enantiomers some cases are possible. The most usual case is the formation of the 1:1 compound (racemate). Other possibilities, less frequently found, are the formation of a mixture of two species or a solid solution (pseudo-racemate). These two cases differ in their phase diagrams (Calvet & Oonk, 1995). The solid–liquid phase diagram for the carvone system proposed by Gallis, Bougrioua, Oonk, van Ekeren & van Miltenburg (1996) has a minimum which indicates solid solution formation (see Fig. 1). In order to confirm these thermodynamic results and to better understand this binary system, crystal structure determinations from X-ray powder diffraction data of the pure L and equimolar DL mixture have been carried out. The diffraction patterns studied were measured at 218 K and the structures solved by Patterson-search methods.

## 2. Experimental

The D- and L-carvone isomers were purchased from Fluka Chemica and their purities, tested by gas

chromatography, were >99%. The optical rotatory power confirmed the presence of only D and L isomers, respectively. The DL mixture was prepared by combining the same proportions of the liquid components at room temperature.

For indexing purposes two patterns, one of L-carvone and one of the DL mixture (L$_I$ and DL$_I$, respectively), were measured on a Siemens D-500 diffractometer in Bragg–Brentano geometry using Cu $K\alpha$ radiation. The data were collected at 218 K using a low-temperature camera Anton PAAR TTK. The samples, liquid at room temperature, were mixed with amorphous SiO$_2$ gel to minimize the preferred orientation and covered with a curved cellophane to reduce sublimation. The samples were first cooled to 193 K and then heated to 218 K at 0.02 K s$^{-1}$. The patterns were scanned in steps of 0.02° (2$\theta$) with fixed counting time (6 s). The Cu $K\alpha_2$ contribution was analytically subtracted. Two additional patterns of both substances (L$_{II}$ and DL$_{II}$) were measured for structure determination and refinement purposes at the same temperature as in Debye–Scherrer geometry with an Inel position-sensitive detector (CPS-120). To produce monochromatic Cu $K\alpha_1$ an incident-beam curved quartz monochromator with asymmetric focusing (short focal distance 130 mm, long focal distance 510 mm) was used. The samples were introduced in a 0.3 mm diameter Lindemann glass capillary and were rotated around the $\theta$ axis during the experiments to ensure proper averaging of crystallites. The patterns were collected over 18 h. The detector consisted of 4096 channels and the angular step was ~0.03° (2$\theta$). Deviation from angular linearity in PSD was corrected according to Evain, Deniard, Jouaneaux & Brec (1993) with the *INEL.PRO* program (Guirado, 1995) using the external standard Na$_2$Ca$_3$Al$_2$F$_{14}$ purchased from Laboratoire des Fluorures, Université du Maine. Strong preferred orientation effects were observed in the DL$_{II}$ pattern. Unfortunately, all attempts to reduce them were unsuccessful.

## 3. Structure solution

### 3.1. L-Carvone

The L$_I$ data set was indexed assuming a tetragonal unit cell with the *DICVOL91* program (Boultif & Louër, 1991). The refinement of profile parameters and the intensity extraction were performed on the L$_{II}$ data set with the whole profile fitting program *AJUST* (Rius et al., 1996) and converged to $R_{wp}$ = 0.092 with $a$ = 6.855 (1), $c$ = 19.960 (1) Å, $V_{cell}$ = 937.9 (2) Å$^3$ and $Z$ = 4 (2$\theta$ range 7–47°). The only space group compatible with the systematic absences and with the crystal density was $P4_2$. However, this space group was rejected because, according to the geometry of the molecules and the unit-cell dimensions, the application of the 4$_2$ screw-axis of symmetry would produce molecular overlap. Consequently, an orthorhombic unit cell was assumed and a new whole profile fitting refinement was performed on L$_{II}$, starting from the tetragonal unit cell. The $R_{wp}$ value decreased to 0.058, with $a$ = 6.8576 (3), $b$ = 6.8831 (5), $c$ = 19.988 (2) Å and $V_{cell}$ = 943.5 (1) Å$^3$. According to the systematic absences the space group $P2_12_12_1$ was assumed for the structure solution.

Overlapping of Bragg reflections is inherent to powder diffraction methods and, consequently, only a limited set of integrated intensities can be extracted from the diffraction pattern. This problem is especially severe in most organic compounds because of their low symmetry and the lack of diffracted intensities at high angles. From the L$_{II}$ data set only 34 resolved integrated intensities could be extracted by whole profile fitting. Due to the paucity of intensity data and the absence of heavy scatterers in the molecule, structure solution by direct methods was not possible. The structure was solved by Patterson-search methods using the coordinates of L-carvoxime (Kroon, van Gurp, Oonk, Baert & Fouret, 1976) to build the search model. Although the present case is not trivial, the program *ROTSEARCH* (Rius & Miravitlles, 1987) could determine unambiguously the position of the molecule in the unit cell.

The subsequent Rietveld refinement was performed with the *RIBOLS* program (Rius, 1989) using a Pearson-VII profile function. The molecule was refined as a rigid body, allowing for the rotation of the isopropenyl group. Without any preferred orientation correction the $R_{wp}$ converged to 0.083. Posterior analysis of the L$_I$ and L$_{II}$ data sets showed a slight preference of the crystallites to orientate with the $b$ axis of the unit cell parallel to the $\theta$ axis of the diffractometer. Inclusion of the preferred orientation correction caused the $R_{wp}$ value to fall to 0.043 (see Fig. 2).
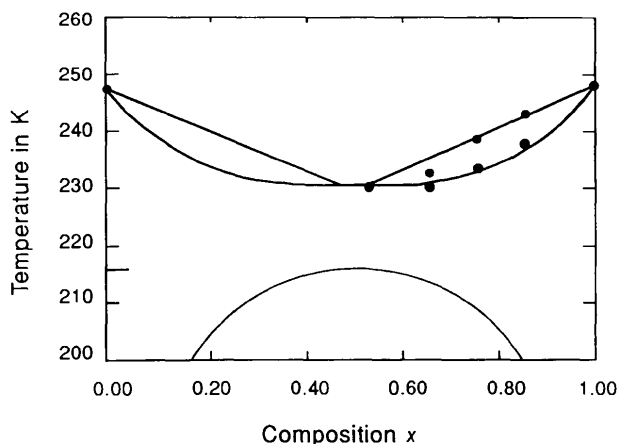


Fig. 1. Solid–liquid phase diagram of the carvone system (Gallis, Bougrioua, Oonk, van Ekeren & van Miltenburg, 1996). Dots, experimental points; $x$, concentration of L-carvone; 1 − $x$, concentration of D-carvone.

## Table 1. *Experimental details*

| | $L_I$ data set | $DL_I$ data set |
|---|---|---|
| **Crystal data** | | |
| Chemical formula | $C_{10}H_{14}O$ | $C_{10}H_{14}O$ |
| Chemical formula weight | 150.01 | 150.01 |
| Cell setting | Orthorhombic | Orthorhombic |
| Space group | $P2_12_12_1$ | $Pcmn$ |
| $a$ (Å) | 6.8576 (3) | 6.9744 (3) |
| $b$ (Å) | 6.8831 (5) | 6.8094 (6) |
| $c$ (Å) | 19.988 (2) | 20.038 (7) |
| $V$ (Å$^3$) | 943.5 (1) | 951.6 (4) |
| $Z$ | 4 | 4 |
| $D_x$ (Mg m$^{-3}$) | 1.049 | 1.040 |
| Radiation type | Cu $K\alpha_1$ | Cu $K\alpha$ |
| Wavelength (Å) | 1.54051 | 1.5418 |
| No. of reflections for cell parameters | 96 | 79 |
| $\theta$ range ($^\circ$) | 3.5–23.5 | 3–23 |
| $\mu$ (mm$^{-1}$) | 0.51 | 0.51 |
| Temperature (K) | 218 K | 218 K |
| | | |
| **Data collection** | | |
| Detector | Incl CPS120 | Scintillation counter |
| Instrument geometry | Debye–Scherrer | Bragg–Brentano |
| Sample holder | 0.3 mm glass capillary | Plate covered with cellophane |
| $2\theta$ step ($^\circ$) | – | 0.02 |
| Collection time | 18 h (total) | 6 s (step) |
| | | |
| | Rietveld refinement | Whole profile fitting |
| Background | Visually subtracted | Visually subtracted |
| No. of refined parameters | 9 | 7 |
| Zero shift in $2\theta$ ($^\circ$) | −0.003 (1) | −0.0531 (6) |
| No. of reflections | 96 | 79 |
| Scale factor | 0.064 | 0.990 |
| Profile function | Pearson-VII | Pseudo-Voigt |
| Thermal parameters (Å$^2$) | $B_{C,O}$ = 7.1 (5) | – |
| | $B_H$ = 10.1 (5) | |
| S.u.'s (Å)* of the coordinates defining the molecule centre | $\sigma(x)$ = 0.013 | – |
| | $\sigma(y)$ = 0.026 | – |
| | $\sigma(z)$ = 0.012 | – |
| S.u.'s ($^\circ$)* of the Euler angles defining the molecule orientation | $\sigma(\varphi)$ = 0.54 | – |
| | $\sigma(\psi)$ = 0.48 | – |
| | $\sigma(\phi)$ = 0.66 | – |
| $R_p$† | 0.030 | – |
| $R_{wp}$‡ | 0.043 | 0.069 |
| $R_B$§ | 0.079 | – |
| $R_F$¶ | 0.085 | – |

* S.u. = standard uncertainties.  † $R_p = \Sigma_i|y_o(i) - y_c(i)|/\Sigma_i y_o(i)$.  ‡ $R_{wp} = \{\Sigma_i w(i)[y_o(i) - y_c(i)]^2/\Sigma_i w(i)y_o(i)^2\}^{1/2}$; $w(i) = 1/y_o(i)$.
§ $R_B = \Sigma^{nref}_j|I_o(j) - I_c(j)|/\Sigma^{nref}_j I_o(j)$.  ¶ $R_F = \Sigma^{nref}_j|[I_o(j)]^{1/2} - [I_c(j)]^{1/2}|/\Sigma^{nref}_j[I_o(j)]^{1/2}$.

## Table 2. *Fractional atomic coordinates for L-carvone*

| | $x$ | $y$ | $z$ |
|---|---|---|---|
| C1 | 0.026 (2) | 0.508 (4) | 0.0396 (6) |
| C2 | 0.032 (2) | 0.688 (4) | 0.0009 (7) |
| C3 | 0.000 (2) | 0.678 (4) | −0.074 (1) |
| C4 | 0.092 (2) | 0.489 (4) | −0.102 (1) |
| C5 | 0.001 (2) | 0.314 (4) | −0.066 (1) |
| C6 | 0.009 (2) | 0.339 (4) | 0.0087 (6) |
| C7 | 0.033 (2) | 0.523 (4) | 0.1157 (9) |
| C8 | 0.071 (2) | 0.470 (4) | −0.177 (2) |
| C9 | 0.226 (3) | 0.426 (4) | −0.214 (3) |
| C10 | −0.120 (2) | 0.487 (4) | −0.205 (2) |
| O1 | 0.054 (2) | 0.849 (5) | 0.0331 (6) |

In the structure refinement constraints and restraints are normally used when the ratio of observations to refined parameters is too small. This is the case for most organic structures where the number of resolved intensities is usually small. While constraints allow the expression of several least-squares variables in terms of a reduced number (*i.e.* rigid groups or atoms placed in special positions), restraints introduce additional information in the form of observational equations. Since for L-carvone the full molecular model was available, the rigid-body refinement was preferred. In related compounds such as carvoxime and perillartine the isopropenyl group exhibits several conformations as a function of the molecular packing (Kroon, van Gurp, Oonk, Baert & Fouret, 1976; Oonk & Kroon, 1976; Hooft, van der Sluis, Kanters & Kroon, 1990). Consequently, in L-carvone the isopropenyl conformation was determined by rotating the group around the C4—C8 axis in 10° steps and performing, for each step, a Rietveld rigid-body refinement. The result of this procedure is shown in Fig. 3, where the $R$ values are plotted as a function of the orientation. Due to the isopropenyl geometry the $R$ plots display two minima. The orientation with the lowest $R_{wp}$, $R_B$ and $R_F$

values was assumed to be the correct one (see Figs. 4 and 5). This conformation was confirmed by one referee by calculating the non-bonded energy profiles for both the isolated molecule and the molecule in the crystal.

### 3.2. DL-Carvone

The DL$_I$ data set was indexed as orthorhombic with the *DICVOL91* program (Boultif & Louër, 1991). The refinement of profile parameters and the intensity extraction was performed with the whole profile fitting program *AJUST* (Rius *et al.*, 1996) using the *Pcmn* systematic absences (2$\theta$ range 6–46°). The good fit reached (see Fig. 6) converged $R_{wp}$ to 0.069 with $a$ = 6.9744 (3), $b$ = 6.8094 (6), $c$ = 20.038 (7) Å and $V_{cell}$ = 951.6 (4) Å$^3$. From the 44 available integrated intensities, a Patterson search was performed with the *ROTSEARCH* program (Rius & Miravitlles, 1987). The



Fig. 2. Rietveld rigid-body refinement of L-carvone at 218 K: experimental diffraction pattern L$_{II}$ (above) and difference profile (below).

best solution* showed the same molecular packing as for the L-carvone, but with the enantiomers disordered, so that, from the X-ray diffraction point of view, the structural unit can be regarded as an average molecule of both enantiomers. This unit possesses a mirror plane which is perpendicular to the six-membered ring and parallel to the long molecular axis. Unfortunately, the preferred orientation observed in DL$_I$ and the difficulty in modelling the disorder renders the Rietveld refinement impossible. However, the proposed structure for DL-carvone is very reasonable. The unit-cell parameters of L and DL-carvone are very close and the relative peak heights of L$_{II}$ and DL$_I$ are similar (see Figs. 2 and 6).

## 4. Discussion

The pure L-carvone material displays complex polymorphic behaviour. When heating a supercooled sample a glass transition at 171 K occurs, followed by (i) crystallization to a metastable phase II, (ii) recrystallization to a stable phase I between 202 and 225 K and (iii) melting at 247.5 K. In addition, a previously crystallized sample shows a reversible phase transition I$\beta$ to I$\alpha$ between 190 and 215 K (van Miltenburg, van der Eerden, Oonk & Gallis, 1995). The structure determination of phase I$\alpha$ is reported. The structure can be described as a stacking of two different molecular layers in the [001] direction with the molecules placed with the long axis parallel to this direction. There are two layers in the unit cell and, in each one, the molecules are arranged in a head-to-tail manner with respect to their longest
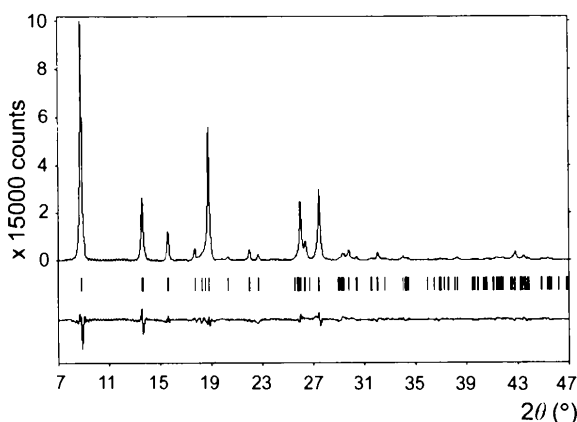
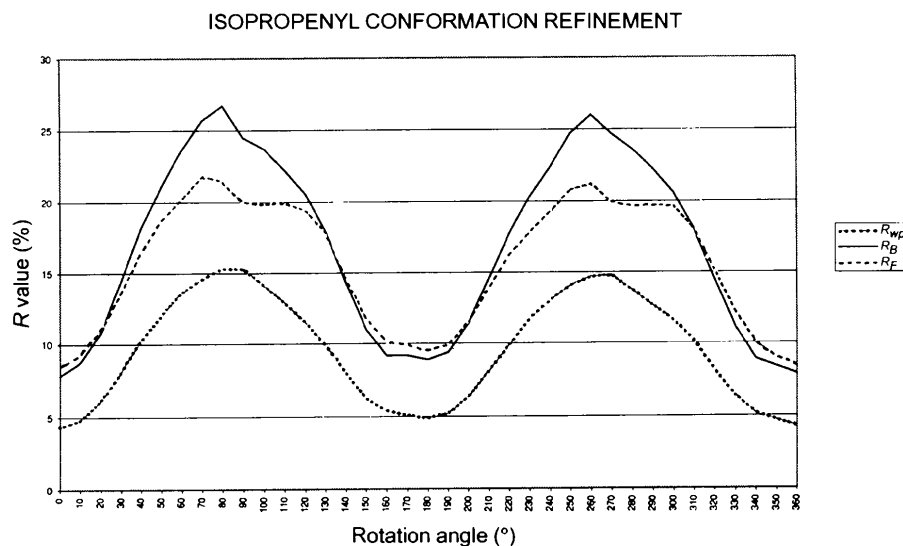### ISOPROPENYL CONFORMATION REFINEMENT



Fig. 3. $R$ values of the Rietveld refinement for L-carvone as a function of the rotation of the isopropenyl group around the C4—C8 bond. The correct orientation corresponds to a rotation angle of 0°.
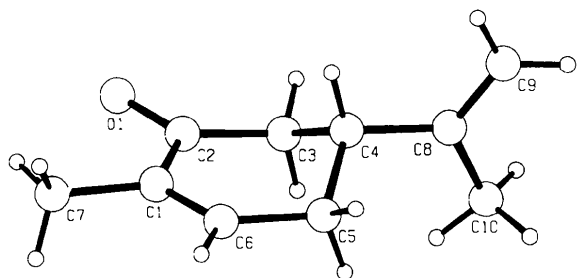
Fig. 4. L-Carvone molecule, showing the atom numbering. The conformation of isopropenyl was determined by Rietveld methods.
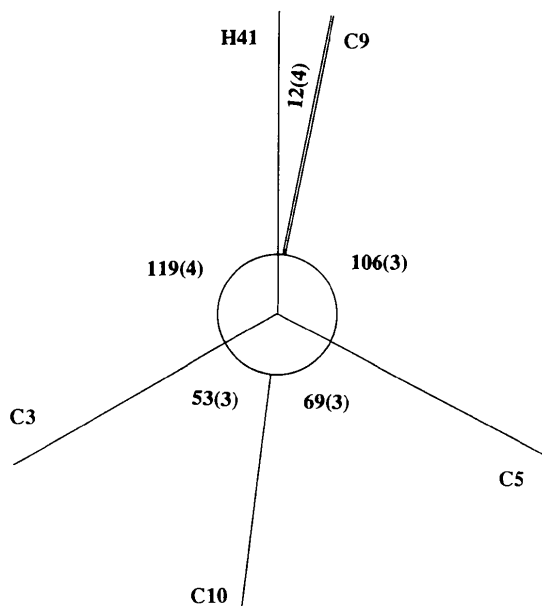
axis (Figs. 7 and 8). The isopropenyl group displays an eclipsed conformation with respect to the H41 atom, as shown in the Neuman projection (Fig. 5). In contrast to similar compounds, e.g. L-carvoxime (Kroon, van Gurp, Oonk, Baert & Fouret, 1976), all molecules in the unit cell show the same conformation. The shortest intermolecular contact is 3.17(2) Å for $O(1)^i \cdots C(3)^{ii}$ [(i) x, y, z; (ii) $\frac{1}{2} + x$, $\frac{3}{2} - y$, $-z$].

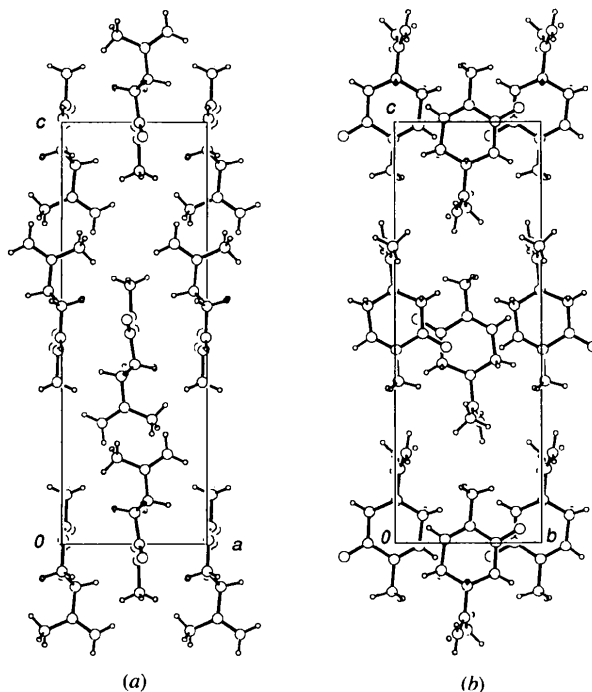When starting from a supercooled DL-carvone equimolar mixture, even at a slow crystallization rate, a



Fig. 5. Angles of the projection of C3, C5, C9, C10 and H41 in the direction of the C4—C8 bond for the L-carvone molecule.



Fig. 7. L-Carvone crystal structure at 218 K: (a) projection along the b axis; (b) projection along the a axis.



Fig. 6. Whole profile fitting refinement of DL-carvone at 218 K for data set DL$_1$: experimental and calculated diffraction patterns (above) and difference profile (below).



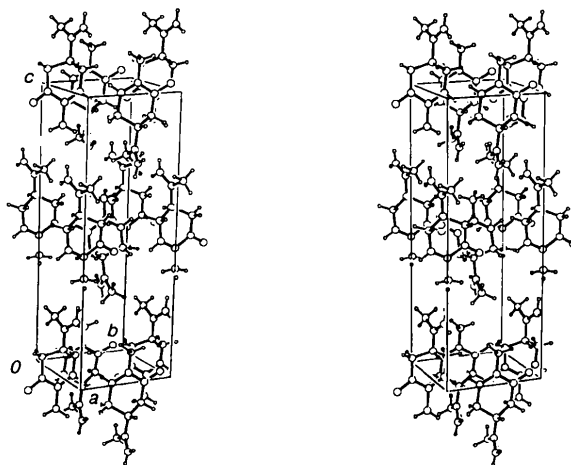Fig. 8. Stereoplot of the crystal structure of L-carvone at 218 K.

metastable material is formed and the melting occurs at 231 K. A complete recrystallization to the stable form is observed when keeping the partially melted sample under adiabatic conditions for 5 d. The stable form does not show any phase transition and its melting occurs at 241 K (Gallis & van Miltenburg, 1996). As reported in this paper, the metastable form is a disordered structure which exhibits a similar molecular packing as the L-carvone. The great similarity between the molecular shapes of both enantiomers favours the positional disorder. This result confirms the mixed crystal formation indicated by the solid–liquid phase diagram of the carvone system (Fig. 1). Although the carvoxime metastable series also forms mixed crystals, the behaviour of both systems is different. Effectively, opposite the DL-carvone, the racemic form DL-carvoxime is an ordered crystal ($P2_1/c$, $Z = 4$), where the D and L enantiomers are related by space-group symmetry. However, if the amount of D or L component is increased, the molecules become randomly replaced by their chiral opposites, resulting in a disordered mixed crystal (Oonk & Kroon, 1976). From the crystallographic point of view the DL-carvone crystal must be considered as a pseudo-racemate, since both enantiomers are randomly distributed over all the lattice sites.

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