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(R)-(+)-2-(4-Chlorophenoxy)propionic acid

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Abstract

The crystal structure of optically active 2-(4-chlorophenoxy)propionic acid ($C_9H_9ClO_3$) has been determined. The carboxylic acid group is in an antiplanar conformation and hydrogen bonds along the twofold screw axis link the carboxylic acid groups to form a catemer motif, in contrast to the hydrogen-bonded cyclic dimers observed in the equivalent racemic compound. Also, the weaker intermolecular interactions display significant differences.

Comment

Crystallization of a racemic mixture of the two enantiomers of a chiral compound will most frequently lead to the formation of a racemic compound, *i.e.* crystals with a well defined structure composed of the two enantiomers in equal amounts. More rarely, a spontaneous resolution occurs which leads to a conglomerate of crystals containing the pure enantiomers. In a description of the crystallization habits of racemates, Jacques *et al.* (1981) estimated that racemic compounds were formed in *ca* 90% of cases. The racemic compound can have either a higher or a lower melting point than the pure enantiomer. A recent survey of 1114 racemic and enantiomer pairs indicates that the average melting point of racemates, T_r, is 402 K, only slightly higher than that of the enantiomers, T_a, which is 399 K. Moreover, the average difference, $T_r - T_a$, is a symmetrical bell-shaped distribution with an s.u. of ± 20 K (Collet, 1998).

The difference in melting point and melting enthalpy between the enantiomer and the equivalent racemic compound is closely linked to differences in their crystal structures. Comparative studies of enantiomers and racemic compounds for a series of related compounds, *e.g.* monofluoro mandelic acids and halogen-substituted 3-hydroxy-3-phenylpropionic acids (Larsen & Marthi, 1997), containing identical functional groups, showed a significant degree of diversity in their hydrogen-bond patterns. From the structural comparisons, it became obvious that weaker interactions, such as C—H···O hydrogen bonds and halogen–hydrogen interactions, should be taken into account to explain the variation in melting behaviour from the structural differences. However, in most of these systems the enantiomer melts at a higher temperature than the racemic compound; therefore, we looked for systems where the racemic compound is the higher melting one. The 2-phenoxypropionic acids were selected, since some of the cases with the largest differences in melting point and melting enthalpy between the racemic compound and the enantiomer are found in these compounds (Gabard & Collet, 1986). In addition, they contain only one functional group that could be expected to take part in the hydrogen bonding, which reduces the number of possible hydrogen-bond patterns. This paper describes the work with (R)-(+)-2-(4-chlorophenoxy)-propanoic acid, (I).

(I)
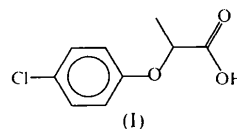
Two independent structure determinations have been conducted previously for racemic 2-(4-chlorophenoxy)-propionic acid (Kennard *et al.*, 1982; Raghunathan *et al.*, 1982) at room temperature, with a reported melting point of 386 K (Gabard & Collet, 1986). The structure determination for the equivalent enantiomeric compound, with a melting point of 359 K (Gabard & Collet, 1986), should enable us to relate these differences in thermodynamic behaviour to differences between the two crystal structures. The *ORTEP*II (Johnson, 1976) drawing in Fig. 1 shows 2-(4-chlorophenoxy)propionic acid as found in crystals of the pure enantiomer. The bond lengths and angles listed in Table 1 are virtually identical to those found in the racemic compound (Kennard *et al.*, 1982). All of them agree within 2 s.u., apart from the O7—C8—C9 angle, which displays the largest difference of 4 s.u. The *exo* angles around C1 show the same difference of *ca* 10° that was observed in the racemic compound.
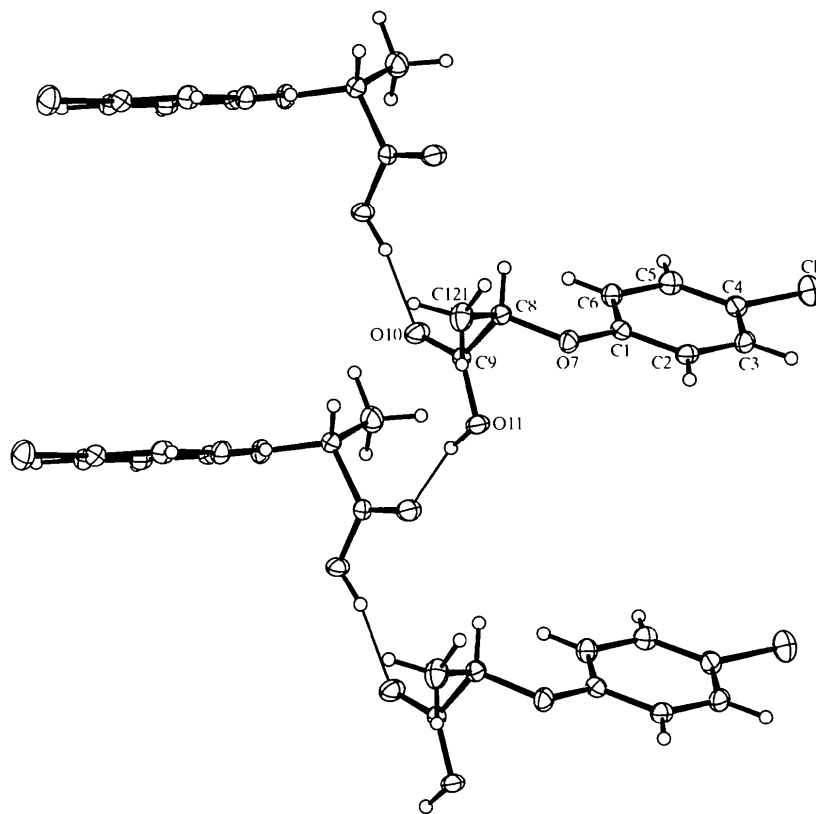
Fig. 1. *ORTEP*II (Johnson, 1976) drawing of the title compound, showing the molecular structure and chain formation. Displacement ellipsoids are drawn at 50% probability and H atoms are shown as spheres of an arbitrary radius.

The overall conformation of (I) can be described by the three torsion angles C2—C1—O7—C8, C1—O7—C8—C9 and O7—C8—C9—O10. These angles were reported to be 171.1, 73.8 and −27.7°, respectively, in the crystal structure of the racemic compound, which reveals that the acid adopts similar conformations in the two crystal structures, apart from the orientation of the carboxylic acid group. In the present structure, the carbonyl group is in an antiplanar conformation relative to the ether O atom, in contrast to the synplanar conformation found in the equivalent racemic compound. A synplanar conformation was also observed in the corresponding unsubstituted racemic 2-phenoxypropionic acid (Kennard *et al.*, 1982).

Racemic 2-(4-chlorophenoxy)propionic acid and racemic 2-phenoxypropionic acid have identical hydrogen-bond patterns, where the carboxylic acid groups form cyclic hydrogen-bonded dimers over crystallographic inversion centres. However, the chiral compound, (I), cannot be connected by this type of hydrogen-bond interaction, so it is likely that it is this difference in hydrogen-bond interactions that leads to the difference in the orientation of the carboxylic acid group. The hydrogen bonds that connect the carboxylic acid groups in the present structure form the so-called catemer motif, connecting molecules related by the twofold screw

axis into infinite chains of hydrogen-bonded molecules parallel to the *b* axis. If the conformation of O7—C8—C9—O10 in the optically active compound were to be synplanar as in the racemic compound, an antiplanar conformation of the carboxylic acid (O10—C9—O11—H11) would be required in order to maintain the catemer hydrogen-bonding motif. This antiplanar conformation is energetically unfavourable compared to the synplanar conformation and is not normally found in compounds containing intermolecular hydrogen bonds (Leiserowitz, 1976).

The O11—H11···O10 hydrogen bonds in the catemer motif found in (I) are slightly shorter [2.616 (2) Å] than those forming the cyclic dimers in the racemic compounds [2.657 (7) Å]. In addition to these strong intermolecular interactions, weaker intermolecular interactions are observed in both the racemic compound and the enantiomer. Stacks of the hydrogen-bonded dimers found in the racemic compound are connected by C121—H121···O10 hydrogen bonds, with an H121···O10 distance of 2.57 Å. In the optically active compound, C8—H81···O10 hydrogen bonds are observed, with H81···O10 2.61 (2) Å. These connect acids already linked by hydrogen bonds, serving as an additional stabilization of the catemer motif. Intermolecular H···Cl interactions are observed in both the racemic and

the optically active compound, with a phenyl-C atom as the hydrogen-bond donor. Two different types of H···Cl interactions are observed in the racemic compound and one of these (H3···Cl 2.92 Å and C3—H3···Cl 175°) is across a crystallographic inversion centre, leading to the formation of cyclic dimers. The other, between H2 and Cl, appears to be slightly weaker (H2···Cl 2.99 Å and C2—H2···Cl 122°). There are also two intermolecular H···Cl interactions in the present structure, but they also appear to be weak, with H2···Cl 3.09 (2) Å and C2—H2···Cl 130 (2)°, and H121···Cl 3.08 (2) Å and C121—H121···Cl 158 (2)°.

The known structure of the racemic compound at room temperature has a density of 1.41 g cm^{-3}, whereas the present structure is known at 122 K, with a corresponding density of 1.472 g cm^{-3}. This hampers a comparison of the packing efficiency. The unit cell of the racemic compound can be assumed to shrink on cooling, but it is not likely that this will lead to a density significantly higher than the one for the pure enantiomer, indicating that the two crystal structures do not differ much in their packing efficiency.

The comparison of the present structure with the racemic counterpart has revealed some distinct differences with respect to the conformation of the acid and the intermolecular interactions, although the latter are comparable in number and type. However, the relation between these differences and the difference in the thermodynamic properties is not immediately transparent and requires further analysis.

Experimental

The title compound was synthesized using the procedure described by Gabard & Collet (1986) and was recrystallized from petroleum ether (338–353 K).

Crystal data

$C_9H_9ClO_3$
$M_r = 200.61$
Monoclinic
$P2_1$
$a = 6.377 (2)$ Å
$b = 6.972 (3)$ Å
$c = 10.514 (16)$ Å
$\beta = 104.45°$
$V = 452.7 (7)$ Å^3
$Z = 2$
$D_x = 1.472$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54184$ Å
Cell parameters from 20 reflections
$\theta = 40.29–43.62°$
$\mu = 3.520$ mm^{-1}
$T = 122.0 (2)$ K
Prism
$0.41 \times 0.36 \times 0.07$ mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction:
  Gaussian by integration method (DeTitta, 1985)
  $T_{min} = 0.392$, $T_{max} = 0.782$
3805 measured reflections
1005 independent reflections (plus 849 Friedel-related reflections)

1854 reflections with $I > 2\sigma(I)$
$R_{int} = 0.024$
$\theta_{max} = 74.92°$
$h = -7 \rightarrow 7$
$k = -8 \rightarrow 8$
$l = -13 \rightarrow 13$
5 standard reflections
  frequency: 167 min
  intensity decay: 3.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.022$
$wR(F^2) = 0.062$
$S = 1.048$
1854 reflections
154 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0432P)^2 + 0.0899P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$

$\Delta\rho_{max} = 0.214$ e Å^{-3}
$\Delta\rho_{min} = -0.199$ e Å^{-3}
Extinction correction:
  SHELXL97 (Sheldrick, 1997)
Extinction coefficient:
  0.0105 (12)
Scattering factors from International Tables for Crystallography (Vol. C)
Absolute structure:
  Flack (1983)
Flack parameter = $-0.003 (11)$

Table 1. *Selected geometric parameters (Å, °)*

Cl—C4	1.7455 (18)	O11—C9	1.3085 (17)
O7—Cl	1.3747 (18)	C121—C8	1.5248 (18)
O7—C8	1.423 (2)	C8—C9	1.5204 (19)
O10—C9	1.222 (2)		
Cl—O7—C8	118.09 (11)	O7—C8—C121	106.11 (11)
O7—Cl—C6	125.32 (13)	C9—C8—C121	109.15 (12)
O7—Cl—C2	114.58 (13)	O10—C9—O11	123.04 (12)
C3—C4—Cl	119.00 (12)	O10—C9—C8	122.70 (12)
O7—C8—C9	112.27 (12)	O11—C9—C8	114.19 (12)
C2—Cl—O7—C8	176.2 (1)	O7—C8—C9—O10	−151.8 (1)
O7—Cl—C6—C5	176.0 (1)	C121—C8—C9—O10	90.9 (2)
Cl—O7—C8—C9	76.5 (1)	O7—C8—C9—O11	31.4 (2)
Cl—O7—C8—C121	−164.3 (1)	C121—C8—C9—O11	−86.0 (2)

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
O11—H11···O10^i	0.89 (2)	1.74 (2)	2.6161 (19)	168 (2)
C8—H81···O10^{ii}	0.953 (19)	2.611 (19)	3.452 (2)	147.3 (14)
C2—H2···Cl^{iii}	0.93 (2)	3.094 (19)	3.760 (3)	130.1 (16)
C121—H121···Cl^{iv}	0.98 (2)	3.08 (2)	4.002 (6)	157.9 (17)

Symmetry codes: (i) $1 - x, y - \frac{1}{2}, -1 - z$; (ii) $-x, \frac{1}{2} + y, -1 - z$; (iii) $x - 1, y, z$; (iv) $x - 1, y, z - 1$.

All H atoms, apart from H11, were refined freely with geometric and isotropic displacement parameters. The isotropic displacement parameter of H11 was constrained to $1.5U_{eq}$(O11).

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994). Cell refinement: *CAD-4 EXPRESS*. Data reduction: *DREADD* (Blessing, 1987). Program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Molecular graphics: *ORTEPII* (Johnson, 1976). Software used to prepare material for publication: *SHELXL97*.

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(S)-2-Amino-3-methyl-1-butanol (2S,3S)-hydrogen tartrate monohydrate†

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Abstract

In the title compound, $C_5H_{14}NO^+ \cdot C_4H_5O_6^- \cdot H_2O$, the hydrogen-bond system created by the chains of head-to-tail linked hydrogen tartrate ions and water molecules forms a V-shaped layer that is effective in discriminating between the two enantiomers of protonated 2-amino-3-methyl-1-butanol. The cation adopts a conformation that isolates its hydrophilic and hydrophobic parts, which is

† Alternative name: (S)-1-hydroxy-3-methylbut-2-ylammonium hydrogen (2S,3S)-tartrate monohydrate.

common for other cations containing the same N—C—C—O fragment.

Comment

Optically active tartaric acid is widely used as a resolving agent for racemic amines. The naturally occurring (2R,3R) enantiomer is most frequently used for the resolutions performed with the acid and base in equimolar amounts. It is a characteristic feature of the resulting diastereomeric salts that the crystal structures contain infinite chains of hydrogen tartrate ions. The carboxylic acid group from one anion is connected by a short hydrogen bond to the carboxylate group from another anion related by a translational period between 7 and 8 Å. Another property of the diastereomeric hydrogen tartrate salts is that they often form hydrates. A survey of hydrogen tartrate salts with chiral cations (Ryttersgaard & Larsen, 1999) showed that about half of the salts are solvated. The water molecules are well integrated into the hydrogen-bond system functioning as links between different chains of hydrogen-bonded hydrogen tartrate ions leading to the formation of V-shaped layers of hydrogen tartrate ions. The chiral environment created by these layers seems to be well suited to discriminate between the two enantiomers of a protonated amine which, by hydrogen bonds, can form links to the hydrogen tartrate layers. The survey also showed that smaller cations seem to fit best between the layers explaining the suitability of tartaric acid for such systems (Ryttersgaard & Larsen, 1999). To evaluate these results we undertook a structure determination of the diastereomeric salt, (I), formed between (S)-2-amino-3-methyl-1-butanol and (2S,3S)-tartaric acid to investigate how well it would conform with these observations.

(I)
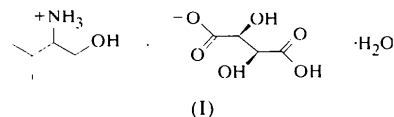
The structure determination verified that the diastereomeric salt is hydrated – it contains one water molecule per ion pair. Fig. 1 illustrates the cation and anion found in the asymmetric unit. The bond lengths and angles for the hydrogen tartrate ion listed in Table 1 conform well with the geometry of hydrogen tartrate ions found in other crystal structures and it also adopts the conformation that is common for hydrogen tartrate salts (Ryttersgaard & Larsen, 1999). The torsion angles listed for the cation in Table 1 show that it has an extended conformation – the angle O7—C21—C22—N9, −61.70 (13)°, shows that the two hydrophilic groups are close. Fig. 1 illustrates how the cation can be considered composed of a hydrophilic moiety N9, C22, C21, O7 and a hydrophobic fragment comprised of the isopropyl group. A search in the Cambridge Structural