

## Structural and Thermodynamic Relationships Between Optically Active and Racemic Compounds. The Crystal Structures of Optically Active Chloro- and Bromo-Substituted 3-Hydroxy-3-phenylpropionic Acids

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### Abstract

The crystal structures of the isostructural optically active *R*-(+)-*meta*-chloro- and *meta*-bromo-substituted 3-hydroxy-3-phenylpropionic acids have been determined from low-temperature [122.0 (5) K] X-ray [ $\lambda(\text{Cu } K\alpha) = 1.54184 \text{ \AA}$ ] diffraction data. (*R*)-(+)-3-Hydroxy-3-(3'-chlorophenyl)propionic acid ( $\text{C}_9\text{H}_9\text{ClO}_3$ ,  $M_r = 200.61$ ), orthorhombic,  $P2_12_12_1$ ,  $a = 5.6938 (7)$ ,  $b = 5.7913 (7)$ ,  $c = 27.052 (4) \text{ \AA}$ ,  $Z = 4$ , m.p. = 365.8 (5) K. 3-Hydroxy-3-(3'-bromophenyl)propionic acid ( $\text{C}_9\text{H}_9\text{BrO}_3$ ,  $M_r = 245.07$ ), orthorhombic,  $P2_12_12_1$ ,  $a = 5.8020 (8)$ ,  $b = 5.8638 (8)$ ,  $c = 27.345 (4) \text{ \AA}$ ,  $Z = 4$ , m.p. = 350.3 (5) K. The O—H...O hydrogen-bond pattern found in these acids is identical to those found in the equivalent racemic compounds with hydrogen-bonded chains parallel to the  $a$  axis. The enantiomeric and racemic crystals differ only in the orientation of these chains. Short contact distances are found between the halogen atoms and one of the H atoms of the phenyl group. Statistical data show that these interactions are of repulsive character. The structural results are related to the thermodynamic measurements, which show that the conglomerate and racemic compound are in equilibrium for the chloro-substituted acid. The formation of a racemic compound for the bromo-substituted acid appears to be favoured by repulsive H...Br interactions in the enantiomeric crystals, giving the latter a higher enthalpy.

### 1. Introduction

Interactions between chiral molecules play an important role in biological processes and it happens frequently that one enantiomer reacts differently from its mirror image. In these complex systems it is rarely possible to obtain a detailed picture of the type of interactions that are responsible for the different reactivity of the enantiomers. Therefore, we have chosen to study the simplest systems that exhibit a discrimination between enantiomers, namely the structures of the crystals that can precipitate from a racemic mixture.

In most cases a *racemic compound* is formed. This can be higher or lower melting than the pure enantiomer. More rarely a spontaneous resolution occurs, *i.e.* a *conglomerate* of crystals containing the pure enantiomers is formed by crystallization, and most rarely is a *pseudo-racemate (solid solution)* of the two enantiomers obtained. The halogen-substituted 3-hydroxy-3-phenylpropionic acids are well suited as a model system to elucidate the factors that are important for the crystallization of racemates in terms of structure, energy and entropy. These compounds form conglomerates and racemic compounds with the same frequency. In the cases where they do form a racemic compound, it has a melting point that is similar or lower than the melting point of the pure enantiomer. The relative stability of a racemic compound is reflected in its melting point, which has to be higher than the melting point of the eutectic,  $T_e$ , formed by the two enantiomers. A hypothetical racemic compound with a melting point  $T_R < T_e$  would undergo a phase transition to a conglomerate instead of melting under thermodynamic equilibrium.

In a previous paper which included the structure determinations of the racemic *meta*-chloro- and *meta*-bromo-substituted 3-hydroxy-3-phenylpropionic acids a structural comparison was made of all known structures of unsubstituted and halogen-substituted 3-hydroxy-3-phenylpropionic acids (Larsen & Marthi, 1995). The chloro- and bromo-substituted acids are isostructural in all these systems. Therefore, it was surprising that when the *meta*-bromo-substituted acid forms a racemic compound, the corresponding chloro-substituted acid was reported to form both a racemic compound and a conglomerate with a phase transition taking place upon melting (Collet & Jacques, 1972). The measured melting point of the racemic chloro-substituted acid was identical to the calculated melting point of the eutectic formed by the two enantiomers. However, in our investigation of the racemic acids we did not observe any phase transition upon heating of the racemic *meta*-chloro-3-hydroxy-3-phenylpropionic acid.

In this paper we describe the crystal structures of optically active *meta*-chloro- and *meta*-bromo-substituted 3-hydroxy-3-phenylpropionic acids. The structures are

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related to the thermochemical properties of the crystals of other chloro- and bromo-substituted 3-hydroxy-3-phenylpropionic acids to achieve a better understanding of the factors that play a role in the crystallization mode of racemates.

## 2. Experimental

The optically active *meta*-chloro- and *meta*-bromo-substituted 3-hydroxy-3-phenylpropionic acids were prepared from the corresponding racemic compounds obtained as reported by Larsen & Marthi (1995). The optical resolutions were performed with brucine in ethanol based on the recipes given by Collet & Jacques (1972).

### 2.1. 3-Hydroxy-3-(3'-chlorophenyl)propionic acid

Racemic 3-hydroxy-3-(3'-chlorophenyl)propionic acid (2.00 g, 10.0 mmol) was resolved with 3.85 g (9.8 mmol) of brucine to give 2.14 g (3.6 mmol, 72% for one enantiomer) of the less-soluble diastereomeric salt. This precipitate was dissolved in a minimum amount of water and eluted through a strong cation ion-exchange column [Lewatit Ionenaustauscher Merck, S1080G1, 0.1–0.2 mm (70–150 mesh ASTM)]. After evaporation of the solvent the isolated acid (0.475 g, 2.4 mmol) was recrystallized from benzene to give the optically pure compound as a white crystalline powder (0.217 g, 1.1 mmol). Crystals suitable for single-crystal diffraction studies were obtained by recrystallization in microtubes from a 2:1 ether:*n*-hexane mixture.

### 2.2. 3-Hydroxy-3-(3'-bromophenyl)propionic acid

Racemic 3-hydroxy-3-(3'-bromophenyl)propionic acid (2.00 g, 8.2 mmol) was resolved with 3.00 g (7.6 mmol) of brucine to give 2.51 g (3.9 mmol, 96% for one enantiomer) of the less-soluble diastereomeric salt. The white salt was recrystallized from ethanol to yield 1.68 g (2.6 mmol, 63%) of white crystalline powder. This salt (1.28 g, 2.0 mmol) was dissolved in 5 ml of water and 0.5 ml of 5 M aqueous HCl solution was added. The solution was kept at 278 K overnight. The white precipitate isolated from the solution was dissolved in water and extracted with ether. A white powder (0.35 g, 1.4 mmol, 70%) was isolated from the ether phase. This was recrystallized from CCl<sub>4</sub> and CHCl<sub>3</sub> to give 0.18 g (0.7 mmol, 35%) of a white microcrystalline material. Crystals suitable for single-crystal diffraction studies were obtained by recrystallization in microtubes from a 2:1 chloroform:*n*-hexane mixture.

### 2.3. Thermochemical measurements

Melting points and heats of fusion of the optically active and racemic acids were measured by Differential Scanning Calorimetry (DSC) using a PL-DSC instrument

calibrated with indium and tin. The measurements were carried out under a nitrogen atmosphere in open crucibles. Sampling was made every 1.25 s and a heating rate of 5 K min<sup>-1</sup> was used. The mass of each sample was between 3.4 and 3.6 mg. They were measured with a precision of 0.001 mg. The samples of the optically pure compounds showed sharp reproducible melting, proving that the compounds were pure. The associated melting enthalpies were determined with a reproducibility of 5%, so the accuracy can be estimated to be <10%.

### 2.4. X-ray crystallography

2.4.1. *X-ray powder diffraction patterns.* A Stoe Stadi P powder diffractometer was used to record the diagrams of optically active and racemic *meta*-chloro- and *meta*-bromo-substituted 3-hydroxy-3-phenylpropionic acids using Cu K $\alpha_1$  radiation selected by a curved germanium monochromator. The diffraction patterns from the samples recorded in a transmission mode were measured with a position sensitive detector covering 7° in 2 $\theta$ . The diffraction patterns were compared with the expected patterns calculated from the single-crystal X-ray diffraction studies. The software *Visual X<sup>POW</sup>* provided with the instrument was used for this analysis.

2.4.2. *Structure determinations.* Optically active 3-hydroxy-3-(3'-bromophenyl)propionic acid was characterized by room-temperature Weissenberg photographs and its space group assigned from the systematically absent reflections. A CAD-4 diffractometer equipped with graphite monochromated Cu K $\alpha$  ( $\lambda = 1.54184 \text{ \AA}$ ) radiation was used for the two data collections for the bromo- and chloro-substituted acids. The crystals were cooled with Enraf–Nonius gas-flow low-temperature devices. The temperature, 122 K, was monitored with a thermocouple placed a few centimetres above the crystal in the exhaust pipe. It remained constant within 1 K during both data collections. In both cases an analysis of reflection profiles provided the basis for the selection of scan mode and scan interval. The different experimental conditions with information on the data reduction and refinement results are summarized in Table 1. The intensities of five standard reflections were measured after every 10 000 s. The orientation of the crystals was checked after every 300 reflections. The reflections used for the intensity control showed a systematic decay for both crystals. Corrections were made for these variations, using a polynomial fit up to third order. The data reduction, performed with the *DREADD* data reduction package (Blessing, 1987), also included corrections for Lorentz, polarization, background and absorption effects. The latter correction was performed using a Gaussian integration procedure. Averaging was performed for the reflections related by the symmetry of the crystal class.

The crystal structure of 3-hydroxy-3-(3'-chlorophenyl)propionic acid was solved by direct methods, *SHELXS86* (Sheldrick, 1990). Since the cell dimensions

Table 1. *Experimental details*

	<i>m</i> -Cl	<i>m</i> -Br
Crystal data		
Chemical formula	C <sub>10</sub> H <sub>9</sub> CH(OH)CH <sub>2</sub> COOH	BrC <sub>6</sub> H <sub>4</sub> CH(OH)CH <sub>2</sub> COOH
Chemical formula weight	200.61	245.07
Cell setting	Orthorhombic	Orthorhombic
Space group	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
<i>a</i> (Å)	5.6938 (7)	5.8020 (8)
<i>b</i> (Å)	5.7913 (7)	5.8638 (8)
<i>c</i> (Å)	27.052 (4)	27.345 (4)
<i>V</i> (Å <sup>3</sup> )	892.0 (2)	930.3 (2)
<i>Z</i>	4	4
<i>D<sub>x</sub></i> (Mg m <sup>-3</sup> )	1.494	1.750
Radiation type	Cu <i>K</i> α	Cu <i>K</i> α
Wavelength (Å)	1.54184	1.54184
No. of reflections for cell parameters	25	20
$\theta$ range (°)	38.79–42.60	38.29–41.64
$\mu$ (mm <sup>-1</sup> )	3.619	5.857
Temperature (K)	122.0 (5)	122.0 (5)
Crystal form	Plate	Needle
Crystal size (mm)	0.44 × 0.16 × 0.13	0.27 × 0.14 × 0.05
Crystal colour	White	White
Data collection		
Diffractometer	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4
Data collection method	$\omega$ -2 $\theta$ scans	$\omega$ -2 $\theta$ scans
Absorption correction	Integration	Integration
<i>T</i> <sub>min</sub>	0.417	0.379
<i>T</i> <sub>max</sub>	0.743	0.756
No. of measured reflections	5221	2230
No. of independent reflections	1827	1777
No. of observed reflections	1806	1730
Criterion for observed reflections	<i>I</i> > 2 $\sigma$ ( <i>I</i> )	<i>I</i> > 2 $\sigma$ ( <i>I</i> )
<i>R</i> <sub>int</sub>	0.0238	0.0205
$\theta$ <sub>max</sub> (°)	74.89	74.91
Range of <i>h</i> , <i>k</i> , <i>l</i>	-7 → <i>h</i> → 3 -7 → <i>k</i> → 7 -33 → <i>l</i> → 33	0 → <i>h</i> → 6 -3 → <i>k</i> → 7 -33 → <i>l</i> → 34
No. of standard reflections	5	5
Frequency of standard reflections (min)	166.7	166.7
Intensity decay (%)	8.0	4.0
Refinement		
Refinement on	<i>F</i> <sup>2</sup>	<i>F</i> <sup>2</sup>
<i>R</i> [ <i>F</i> <sup>2</sup> > 2 $\sigma$ ( <i>F</i> <sup>2</sup> )]	0.0200	0.0322
<i>wR</i> ( <i>F</i> <sup>2</sup> )	0.0531	0.0974
<i>S</i>	1.066	1.085
No. of reflections used in refinement	1827	1774
No. of parameters used	146	145
H-atom treatment	Only coordinates of H atoms refined	Only coordinates of H atoms refined
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0288P)^2 + 0.2283P]$ , where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0288P)^2 + 0.2283P]$ , where $P = (F_o^2 + 2F_c^2)/3$
$\Delta/\sigma$ <sub>max</sub>	0.001	-0.001
$\Delta\rho$ <sub>max</sub> (e Å <sup>-3</sup> )	0.204	0.588
$\Delta\rho$ <sub>min</sub> (e Å <sup>-3</sup> )	-0.248	-0.850
Extinction method	<i>SHELXL93</i> (Sheldrick, 1993)	None
Extinction coefficient	0.0122 (6)	—
Source of atomic scattering factors	<i>International Tables for Crystallography</i> (1992, Vol. C)	<i>International Tables for Crystallography</i> (1992, Vol. C)
Absolute configuration	Flack (1983)	Flack (1983)
Absolute structure parameter	0.019 (11)	0.02 (3)

and symmetry of the two compounds are similar, the structure of the *meta*-chloro-substituted 3-hydroxy-3-phenylpropionic acid could be used as a starting model in the refinement of the *meta*-bromo-substituted acid.

Both structures were refined by full-matrix least-squares with *SHELXL93* (Sheldrick, 1997), minimizing  $\Sigma w(F_o^2 - F_c^2)^2$ . The scattering factors were taken from *International Tables for Crystallography* (1992, Vol. C)

Table 2. Fractional atomic coordinates and equivalent isotropic displacement parameters ( $\text{\AA}^2$ )
$$U_{\text{eq}} = (1/3)\Sigma_i \Sigma_j U^{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{eq}}$
<i>(R)</i> -(+)-3-Hydroxy-3-(3'-chlorophenyl)propionic acid				
Cl	0.43045 (6)	0.16108 (7)	0.843290 (12)	0.02787 (11)
O1	1.3834 (2)	0.9582 (2)	0.97014 (3)	0.0172 (2)
O2	1.0648 (2)	1.0520 (2)	1.01341 (3)	0.0182 (2)
O3	1.1288 (2)	0.4894 (2)	0.94663 (3)	0.0147 (2)
C1	1.1531 (2)	0.9748 (2)	0.97592 (5)	0.0135 (2)
C2	1.0173 (2)	0.8892 (2)	0.93199 (5)	0.0154 (3)
C3	1.1197 (2)	0.6670 (2)	0.90965 (5)	0.0139 (2)
C4	0.9669 (2)	0.5895 (2)	0.86683 (4)	0.0149 (2)
C5	0.7884 (2)	0.4290 (2)	0.87392 (5)	0.0158 (2)
C6	0.6483 (2)	0.3679 (2)	0.83410 (5)	0.0168 (3)
C7	0.6764 (2)	0.4644 (2)	0.78761 (5)	0.0205 (3)
C8	0.8543 (3)	0.6255 (3)	0.78105 (5)	0.0235 (3)
C9	1.0002 (2)	0.6860 (2)	0.82001 (5)	0.0210 (3)
<i>(R)</i> -(+)-3-Hydroxy-3-(3'-bromophenyl)propionic acid				
Br	0.41798 (8)	0.14455 (8)	0.844601 (14)	0.0367 (2)
O1	1.3560 (4)	0.9584 (4)	0.97113 (9)	0.0203 (5)
O2	1.0416 (4)	1.0506 (4)	1.01388 (9)	0.0212 (5)
O3	1.1087 (5)	0.4921 (4)	0.94847 (9)	0.0181 (5)
C1	1.1301 (6)	0.9736 (5)	0.97705 (12)	0.0181 (7)
C2	0.9984 (7)	0.8862 (5)	0.93359 (10)	0.0188 (7)
C3	1.1012 (7)	0.6678 (5)	0.91188 (11)	0.0176 (6)
C4	0.9579 (6)	0.5878 (5)	0.86888 (12)	0.0194 (7)
C5	0.7820 (6)	0.4314 (5)	0.87518 (12)	0.0187 (7)
C6	0.6503 (6)	0.3671 (6)	0.83514 (12)	0.0218 (7)
C7	0.6845 (8)	0.4569 (7)	0.78893 (14)	0.0258 (8)
C8	0.8597 (8)	0.6137 (7)	0.78285 (14)	0.0331 (9)
C9	0.9976 (8)	0.6781 (7)	0.82217 (14)	0.0309 (9)

and used as contained in the program. After anisotropic displacement parameters had been introduced for the non-H atoms, the calculated difference-Fourier maps showed the positions for all the H atoms. Their positional parameters were included in the refinements and given isotropic displacement parameters equal to  $U_{\text{eq}}$  of the parent C or O atom multiplied by 1.2 and 1.5, respectively. The absolute configuration was established by refinement of the absolute structure parameter (Flack, 1983).

An extinction correction was employed to the data of optically active 3-hydroxy-3-(3'-chlorophenyl)propionic acid. The final fractional coordinates for both structures are listed in Table 2.† The peaks in the final residual electron density maps were found close to the Br and Cl atoms.

### 3. Results and discussion

Throughout this section we will refer to the various substituted 3-hydroxy-3-phenylpropionic acids by a two word combination. The word *rac.* refers to the racemic

† Lists of atomic coordinates, anisotropic displacement parameters and structure factors have been deposited with the IUCr (Reference: AB0374). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. Selected geometric parameters

	Cl	Br
X—C6	1.7420 (13)	1.894 (4)
O1—C1	1.324 (2)	1.323 (4)
O2—C1	1.217 (2)	1.217 (4)
O3—C3	1.4361 (14)	1.437 (4)
C1—C2	1.502 (2)	1.503 (5)
C2—C3	1.536 (2)	1.533 (4)
C3—C4	1.517 (2)	1.514 (5)
C4—C5	1.390 (2)	1.384 (5)
C4—C9	1.397 (2)	1.402 (5)
C5—C6	1.386 (2)	1.387 (5)
C6—C7	1.386 (2)	1.383 (5)
C7—C8	1.389 (2)	1.380 (6)
C8—C9	1.387 (2)	1.393 (6)
O2—C1—O1	122.28 (12)	122.9 (3)
O2—C1—C2	124.60 (11)	124.5 (3)
O1—C1—C2	113.12 (11)	112.6 (3)
C1—C2—C3	113.09 (10)	113.1 (3)
O3—C3—C4	109.90 (10)	109.6 (3)
O3—C3—C2	109.84 (9)	109.9 (3)
C4—C3—C2	109.31 (10)	110.2 (3)
C5—C4—C9	119.44 (11)	119.0 (3)
C5—C4—C3	120.79 (11)	120.9 (3)
C9—C4—C3	119.73 (11)	120.0 (3)
C6—C5—C4	118.95 (11)	119.2 (3)
C7—C6—C5	122.40 (12)	122.6 (3)
C7—C6—C1	119.28 (10)	119.3 (3)
C5—C6—C1	118.32 (10)	118.1 (3)
C6—C7—C8	118.11 (12)	118.0 (4)
C9—C8—C7	120.63 (13)	120.7 (4)
C8—C9—C4	120.44 (12)	120.4 (3)
O2—C1—C2—C3	−138.78 (12)	−139.0 (3)
C1—C2—C3—C4	178.05 (10)	179.1 (3)
C1—C2—C3—O3	57.38 (13)	58.2 (4)
C2—C3—C4—C5	−94.14 (13)	−92.9 (4)
C2—C3—C4—C9	83.63 (14)	84.9 (4)

compound, o.a. to optically active. The lack of these two words indicates that the compound forms a conglomerate and has only crystals built from the same enantiomers. The second word gives the position and type of substituent, *i.e.* *para*-chloro is *p*-Cl, *para*-bromo is *p*-Br, *meta*-chloro is *m*-Cl and *meta*-bromo is *m*-Br.

#### 3.1. Molecular structures

The crystal structures of o.a. *m*-Cl and o.a. *m*-Br are isostructural, as revealed by their similar cell dimensions and atomic coordinates. The displacement parameters in o.a. *m*-Br are considerably higher than in the o.a. *m*-Cl. Inspection of the bond lengths, angles and torsion angles in Table 3 and the molecular drawings in Fig. 1 reveals that the conformations adopted in the crystal structures of the pure enantiomers are virtually identical to those reported earlier for the equivalent racemic compounds (Larsen & Marthi, 1995). However, small, but significant, differences are observed in the conformations of the different bromo- and chloro-substituted 3-hydroxy-3-phenylpropionic acids with known crystal structures (o.a. *m*-Cl, o.a. *m*-Br, *rac.* *m*-Cl, *rac.* *m*-Br, *p*-Cl and *p*-Br).

The relative orientation of the carboxylic acid group is defined by the torsion angle O2—C1—C2—C3. This is *ca* 6° larger in the o.a. *m*-Cl and o.a. *m*-Br than in the equivalent racemic structures [−138.9 (3)° compared with −132.6 (6)°] and resembles those found in the *p*-Cl and *p*-Br. Variations of the same order of magnitude are observed with respect to the orientation of the phenyl group described by the two torsion angles C2—C3—C4—C5 and C2—C3—C4—C9. These torsion angles in the o.a. *m*-Cl and o.a. *m*-Br acids take values that are between those found in the equivalent racemic *meta*-substituted acids and in the optically active *para*-substituted acids. As described later these small differences can all be attributed to small differences in the intermolecular interactions. It is somewhat surprising that the phenyl groups are oriented in the same way in all *meta*-chloro- and *meta*-bromo-substituted structures with the halogen substitution on the same side as O3. In the monofluoro-substituted mandelic acids the F atom was found both on the same side and the opposite side relative to the hydroxy group (Larsen & Marthi, 1994, 1997).

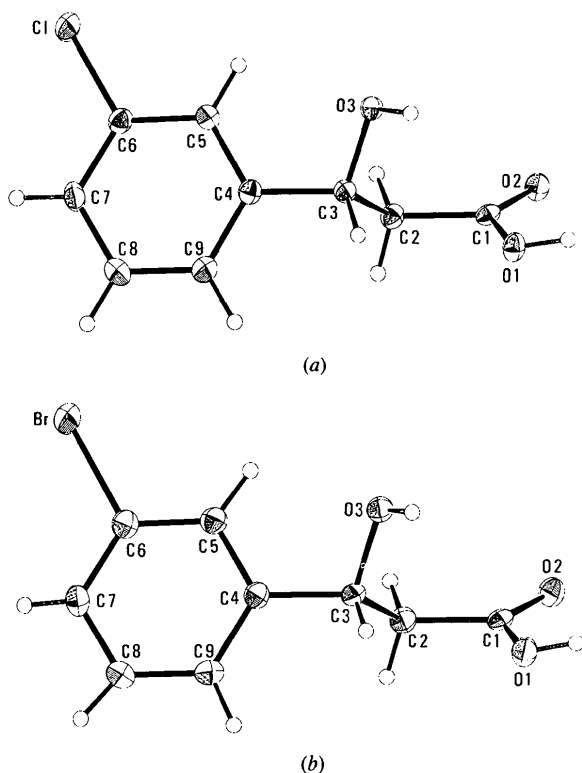


Fig. 1. ORTEP (Johnson, 1976) drawings showing the molecular geometry of the optically active *meta*-chloro- (a) and *meta*-bromo-substituted (b) 3-hydroxy-3-phenylpropionic acids in the crystals of the pure enantiomers. The thermal ellipsoids are scaled to include 50% probability. The H atoms are drawn as spheres with a fixed radius.

Table 4. Intra- and intermolecular interactions in the optically active *meta*-chloro- and *meta*-bromo-3-hydroxy-3-phenylpropionic acids

D—H...A	D...A (Å)	D—H...A (°)	H...A (Å)
<i>(R)</i> -(+)-3-Hydroxy-3-(3'-chlorophenyl)propionic acid			
O1—H1...O3 <sup>i</sup>	2.667 (1)	167 (2)	1.82 (2)
O3—H3...O2 <sup>i</sup>	2.718 (1)	176 (2)	1.85 (2)
C5—H5...O2 <sup>ii</sup>	3.305 (2)	142.5 (13)	2.49 (2)
C5—H5...O3	2.783 (2)	98.5 (11)	2.47 (2)
C9—H9...C <sup>iii</sup>	3.738 (1)	155.4 (13)	2.83 (2)
C1...O3 <sup>iv</sup>	3.087 (2)		
<i>(R)</i> -(+)-3-Hydroxy-3-(3'-bromophenyl)propionic acid			
O1—H1...O3 <sup>i</sup>	2.658 (4)	166 (5)	1.86 (5)
O3—H3...O2 <sup>i</sup>	2.726 (4)	180 (4)	1.96 (5)
C5—H5...O2 <sup>ii</sup>	3.340 (4)	150 (3)	2.48 (4)
C5—H5...O3	2.782 (4)	102 (3)	2.42 (4)
C9—H9...Br <sup>iii</sup>	3.715 (4)	147 (4)	2.87 (5)
C1...O3 <sup>iv</sup>	3.142 (4)		

### 3.2. Crystal packing

The intra- and intermolecular interactions observed in o.a. *m*-Cl and *m*-Br are listed in Table 4. The crystal packing in o.a. *m*-Cl is shown in Fig. 2. The strongest intermolecular interactions in the o.a. *m*-Cl and *m*-Br are the O—H...O hydrogen bonds. The O—H...O hydrogen-bond pattern found in the present structures is identical to that observed in other chloro- and bromo-substituted 3-hydroxy-3-phenylpropionic acids (Cesario & Guilhem 1974*a,b*; Larsen & Marthi 1995). The carboxylic acid group and the hydroxy group of one molecule donate their protons to the hydroxy group and

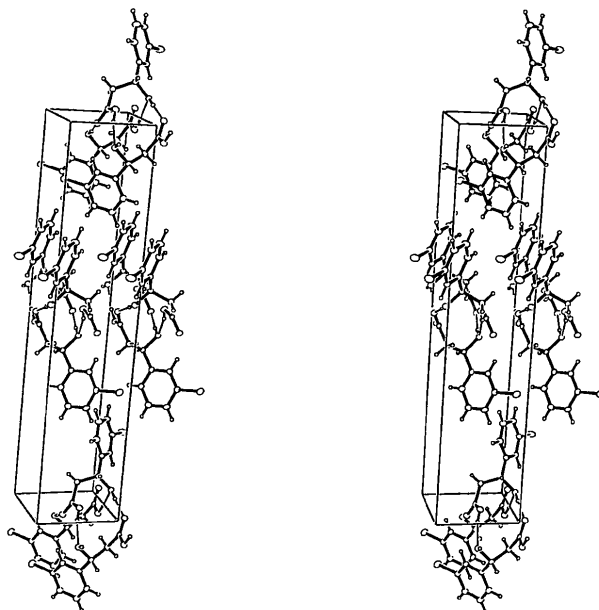
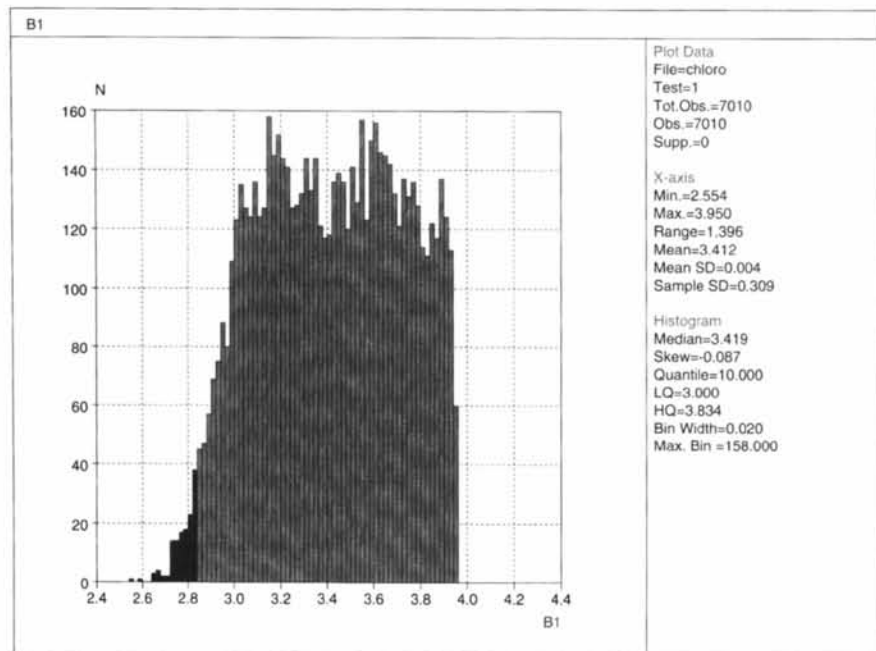


Fig. 2. Stereopair (Johnson, 1976) illustrating the packing in optically active 3-hydroxy-3-(3'-chlorophenyl)propionic acid as seen along the *a* axis with the *b* axis horizontal and the *c* axis vertical. The O—H...O hydrogen bonds are shown as thin lines.

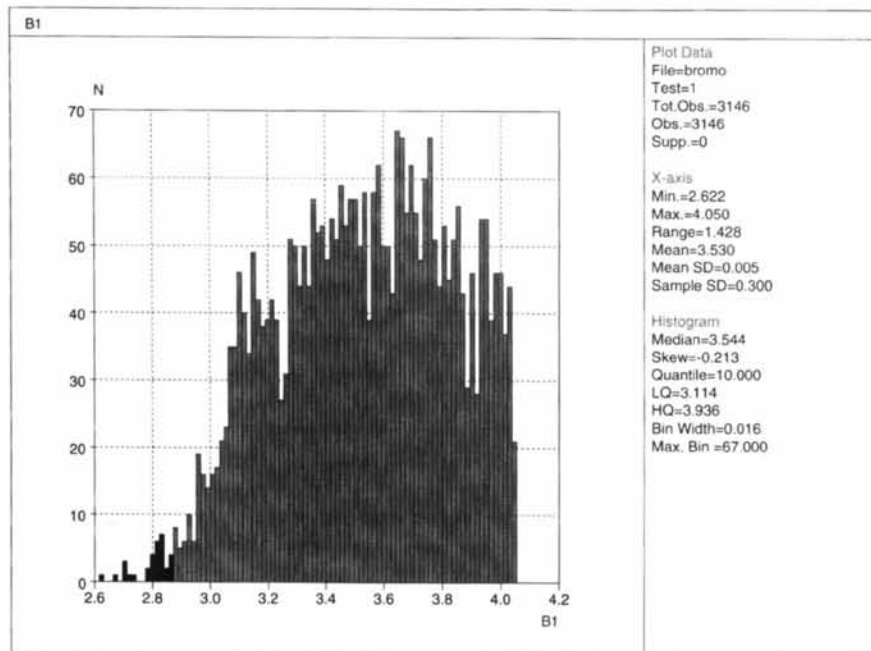
the carboxyl group of another molecule related by a twofold screw axis, which has a corresponding translational period of *ca* 5.7 Å. In the present crystal structures the hydrogen-bonded chains are parallel to the *a* axis, as shown in Fig. 2.

A C5—H5...O2 hydrogen bond that further stabilizes the hydrogen-bonded chains was observed in the *para*-substituted acids. The lack of this interaction in the

racemic *meta*-chloro- and *bromo*-substituted acids was earlier attributed to steric hindrance (Larsen & Marthi, 1995). It was therefore unexpected that this interaction was observed in the hydrogen-bonded chains of o.a. *m*-Cl and o.a. *m*-Br. This intermolecular interaction tends to fix the conformation and could explain why the optically active *meta*- and *para*-substituted acids have similar orientations of the phenyl group.



(a)



(b)

Fig. 3. Distribution of the C(phenyl)—H...X distances. The area indicated in black has H...X distances smaller than those observed in o.a. *m*-Cl and o.a. *m*-Br. (a) X = Cl; (b) X = Br.

Table 5. Thermochemical data for chloro- and bromo-substituted 3-hydroxy-3-phenylpropionic acids with known crystal structures

Remeasurements of the heat of fusion for the racemic acids showed that the e.s.d.'s of the values reported previously (Larsen & Marthi, 1995) were underestimated.

	$T_A$ (K)	$T_R$ (K)	$\Delta_f H_A$ (kJ mol <sup>-1</sup> )	$\Delta_f H_R$ (kJ mol <sup>-1</sup> )	$\Delta_f S_A$ (J mol <sup>-1</sup> K <sup>-1</sup> )	$\Delta_f S_R$ (J mol <sup>-1</sup> K <sup>-1</sup> )
<i>m</i> -Cl	365.8 (5)	341.9 (5)	29 (2)	30 (2)	79 (5)	88 (5)
<i>m</i> -Br	350.3 (5)	349.0 (5)	25 (2)	29 (2)	71 (5)	83 (5)

Apart from the small variations of the hydrogen-bond interactions within the hydrogen-bonded columns, the main differences between the crystal packing in the o.a. and rac. bromo- and chloro-substituted acids is found in the packing of these columns. The C1...O3 electrostatic interaction observed in rac. *m*-Br and *m*-Cl takes place between molecules related by a glide plane. A similar interaction is also found in the optically active crystals, but in these structures the glide plane is replaced by pure translation. These interactions between the individual hydrogen-bonded chains have been shown to influence the C1—C2—C3—O3 torsion angle (Larsen & Marthi, 1995).

Analysis of the other intermolecular interactions revealed short interatomic contacts between the halogen atoms and one of the H atoms of the phenyl group. The fact that the C9...halogen distance in the bromo-substituted acid was even shorter [3.715 (4) Å] than in the equivalent chloro compound [3.738 (1) Å] made us examine this interaction more closely. Searches were made in the Cambridge Structural Database (CSD Version 5.11; Allen *et al.*, 1979) for contact distances between Cl and Br atoms and a H atom bonded to a phenyl group that were within 3.95 and 4.05 Å, respectively. These numbers correspond to the sum of the van der Waals radii plus 1 Å. The results from two searches are depicted in the histograms shown in Fig. 3. The searches revealed that examples of hydrogen...halogen distances shorter than those found in the present structures were very rare. They were only encountered 128 times in the chloro- and 32 times in the bromo-containing structures, which shows that in particular the short H...Br distance does not correspond to an interaction with minimum energy.

Although statistical analysis of structural parameters cannot lead to quantitative energy relationships (Bürgi & Dunitz, 1988), the short H...halogen distances from Table 4 and their position in the diagrams in Fig. 3 is a clear indication of the repulsive character of these interactions, which is most strongly pronounced for the bromo-substituted acid. Inspection of the crystal packing diagram in Fig. 2 reveals that this interaction is a consequence of the O—H...O hydrogen bonding and the C1...O3 interaction.

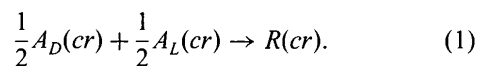
The other twofold screw axis makes the O—H...O hydrogen-bonded chains run antiparallel. The interchain interaction is mimicked by the two independent mole-

cules in the structures of the equivalent *para*-substituted acids which form conglomerates.

### 3.3. Relations to thermodynamic properties

The aim of this study is to relate differences in the crystal structures to differences in the thermochemical behaviour of the compounds. Virtually identical O—H...O hydrogen-bond patterns were found in the bromo- and chloro-substituted 3-hydroxy-3-phenylpropionic acids and the only structural differences can be attributed to differences in weaker interactions. We will attempt to relate these structural differences to differences in Gibbs free energy.

The existence of a thermodynamically stable racemic compound, symbolized by *R*, implies a negative  $\Delta G^\ominus$  for its formation from the pure enantiomers, designated  $A_D$  and  $A_L$



This reaction can only take place at temperatures lower than the melting point of the lowest melting compound, whether this is the pure enantiomer ( $A_L$  or  $A_D$ ) or the racemic compound (*R*). It is assumed in the following that the system resembles those we are investigating here with the melting point of the racemic compound ( $T_R$ ) lower than the melting point of the pure enantiomer ( $T_A$ ).

As shown in the *Appendix* an estimate of  $\Delta G^\ominus$  for the reaction at  $T < T_R$  can be calculated from the measured heats of fusion at their normal melting points for the racemic compound,  $\Delta_f H_R(T_R)$ , and the pure enantiomer  $\Delta_f H_A(T_A)$ :  $\Delta G^\ominus(T) \simeq \Delta_f H_A(T_A) - \Delta_f H_R(T_R) - T[\Delta_f H_A(T_A)/T_A - \Delta_f H_R(T_R)/T_R + R \ln 2]$ . The first term represents an enthalpy difference  $\Delta \Delta_f H = \Delta_f H_A(T_A) - \Delta_f H_R(T_R)$  and the second an entropy difference, thus  $\Delta G^\ominus(T) = \Delta \Delta_f H - T(\Delta \Delta_f S + R \ln 2)$ . The heats of fusion for the bromo- and chloro-substituted 3-hydroxy-3-phenylpropionic acids are listed in Table 5.

For the *meta*-chloro-substituted acid  $\Delta \Delta_f H = -1$  kJ mol<sup>-1</sup> and  $\Delta \Delta_f S + R \ln 2 = -3$  J K<sup>-1</sup> mol<sup>-1</sup>. These differences are well within the experimental accuracy and therefore we conclude that the associated  $\Delta G^\ominus$  is 0, in agreement with the value reported earlier by Jacques, Collet & Wilen (1981). This shows that the conglomerate and the racemic compound must be in equilibrium at a temperature  $T < T_R$ .

In our previous description of rac. *m*-Cl, based on DSC measurements and single-crystal X-ray diffraction data, we did not observe any phase transition to a conglomerate. As part of the comparison of o.a. *m*-Cl and rac. *m*-Cl we measured the powder diffraction diagrams of the racemic acids. To our surprise we found that the microcrystalline batch of rac. *m*-Cl that we used for DSC measurements in 1994 (Larsen & Marthi, 1995), now 2 years after its preparation, had a powder diffraction pattern that was identical to the pattern recorded for the microcrystalline batch of o.a. *m*-Cl and to the calculated powder diffraction pattern calculated based on the crystal structure determination for o.a. *m*-Cl. The powder diffraction pattern of the small batch of rac. *m*-Cl that contained the crystals suitable for single-crystal X-ray diffraction studies was also recorded and found to contain a mixture of the optically active and racemic compound crystals.

Melting of the crystals requires a disruption of all the intermolecular interactions in the crystals. For the halogen-substituted 3-hydroxy-3-phenylpropionic acids that have very similar melting points, melting corresponds to breaking a common hydrogen-bonding pattern and some weaker secondary interactions. In line with this we find that within experimental precision three of the *meta*-bromo- and *meta*-chloro-substituted acids have almost the same heat of fusion, 29–30 kJ mol<sup>-1</sup>. O.a. *m*-Br has a slightly lower melting enthalpy  $\Delta_f H_A = 25$  kJ mol<sup>-1</sup>. The analysis of the crystal packing revealed short C9—H9...Br contacts that were interpreted as repulsive contributions to the lattice energy. The decrease in heat of fusion relative to the other equivalent acids confirms this interpretation. The larger displacement parameters of o.a. *m*-Br relative to rac. *m*-Br indicate larger vibrations, therefore o.a. *m*-Br could intuitively be expected to have higher entropy. This is in accordance with the observed entropy difference of  $\Delta \Delta_f S + R \ln 2 = -6$  J K<sup>-1</sup> mol<sup>-1</sup>. This entropy difference would tend to favour the formation of a conglomerate of the *meta*-bromo-substituted acid, but the entropy contribution to the free energy  $\sim +2$  kJ mol<sup>-1</sup> cannot compensate for the difference in the enthalpies ( $\Delta \Delta_f H = -4$  kJ mol<sup>-1</sup>). This has led us to conclude that it is the lower enthalpy of the racemic compound due to the repulsive interactions in the optically active form that accounts for the formation of a racemic compound.

This above analysis has shown that whether a racemic compound or a conglomerate is formed seems to be related to very small differences in enthalpy and entropy, which are barely detectable experimentally. In systems such as that investigated here, where racemic compounds are lower melting than the pure enantiomers, we found that although small differences in the hydrogen-bond interactions may be of significance, the weaker secondary interactions also contribute to the small difference in relative stability between the conglomerate and the racemic compound.

## APPENDIX

We want to use the experimental melting points and heats of fusion of the pure enantiomer and the racemic compound to estimate  $\Delta G^\ominus$  for reaction (1) at  $T_R$

$$\Delta G^\ominus(T_R) = \Delta H^\ominus(T_R) - T_R \Delta S^\ominus(T_R) \quad (2)$$

where

$$\begin{aligned} \Delta H^\ominus(T_R) &= H_R^{\text{cr}}(T_R) - H_A^{\text{cr}}(T_R) \\ &= H_R^{\text{cr}}(T_R) - H_R^{\text{l}}(T_R) + H_R^{\text{l}}(T_R) - H_A^{\text{cr}}(T_R) \\ &= -\Delta_f H_R(T_R) + \Delta_f H_A(T_R). \end{aligned} \quad (3)$$

$\Delta_f H_R(T_R)$  is the melting enthalpy at its normal melting point for the racemic compound. The melting enthalpy for the pure enantiomer at  $T_R$  can be calculated from  $\Delta_f H_A(T_R) = \Delta_f H_A(T_A) - \int_{T_R}^{T_A} (C^{\text{l}} - C^{\text{s}}) dT$ , where  $C^{\text{l}}$  is the heat capacity for the liquid (melt) and  $C^{\text{s}}$  a common heat capacity at  $T_R$  for the pure enantiomer and the racemic compound, as they are expected to be very alike. Both heat capacities  $C^{\text{l}}$  and  $C^{\text{s}}$  are assumed to be constant in the investigated temperature range. Therefore, we obtain

$$\begin{aligned} \Delta H^\ominus(T_R) &= \Delta_f H_R(T_R) + \Delta_f H_A(T_A) \\ &\quad - (C^{\text{l}} - C^{\text{s}})(T_A - T_R). \end{aligned} \quad (4)$$

The  $\Delta S^\ominus$  term in (2) designates the difference in entropy at  $T_R$  between the crystals of the racemic compound and the pure enantiomer

$$\Delta S^\ominus(T_R) = S_R^{\text{cr}}(T_R) - S_R^{\text{cr}}(T_R). \quad (5)$$

Assuming ideal behaviour of the liquid phase, *e.g.* mixing entropy of  $R \ln 2$  for a mixture of racemic composition, and using the usual thermodynamic relations we obtain for (5)

$$\begin{aligned} \Delta S^\ominus(T_R) &= S_R^{\text{cr}}(T_R) - S_R^{\text{l}}(T_R) + S_R^{\text{l}}(T_R) - S_A^{\text{cr}}(T_R) \\ &= -\Delta_f S_R(T_R) + S_A^{\text{l}}(T_R) + R \ln 2 - S_R^{\text{cr}}(T_R) \\ &= -\Delta_f S_R(T_R) + R \ln 2 + \Delta_f S_A(T_R) \\ &= -\Delta_f S_R(T_R) + R \ln 2 + \Delta_f S_A(T_A) \\ &\quad - (C^{\text{l}} - C^{\text{s}}) \ln T_A/T_R. \end{aligned} \quad (6)$$

In (6)  $\Delta_f S_R(T_R)$  is the melting entropy for the racemic compound at the normal melting point,  $\Delta_f S_R(T_R) = \Delta_f H_R(T_R)/T_R$ , similarly we can calculate  $\Delta_f S_A(T_A)$  from the melting enthalpy of the pure enantiomer  $\Delta_f S_A(T_A) = \Delta_f H_A(T_A)/T_A$ .

Inserting the expressions from (4) and (6) into (2) gives

$$\begin{aligned} \Delta G^\ominus(T_R) &= -\Delta_f H_R(T_R) + \Delta_f H_A(T_A) \\ &\quad - (C^{\text{l}} - C^{\text{s}})(T_A - T_R) \\ &\quad - T_R [\Delta_f S_A(T_A) - \Delta_f S_R(T_R) + R \ln 2] \\ &\quad - (C^{\text{l}} - C^{\text{s}}) \ln(T_A/T_R). \end{aligned} \quad (7)$$



Numerical calculations for systems where the measurements of heat capacities have been performed (Jacques, Collet & Wilen, 1981) show that the two terms  $-(C^l - C^s)(T_A - T_R)$  and  $+T_R(C^l - C_s)\ln T_A/T_R$  are small,  $\sim 1-2 \text{ kJ mol}^{-1}$ , and tend to cancel each other. This allows us to simplify the expression to

$$\Delta G^\ominus(T_R) \simeq \Delta_f H_A(T_A) - \Delta_f H_R(T_R) - T_R[\Delta_f H_A(T_A)/T_A - \Delta_f H_R(T_R)/T_R + R\ln 2]. \quad (8)$$

Expressions (4) and (6) were derived explicitly for  $T = T_R$ , but are also valid at other temperatures if it can be assumed that crystalline  $R$  and  $A$  have very similar heat capacities, therefore,  $\Delta C_p = 0$  for reaction (1). For  $T < T_R$  we can express  $\Delta G^\ominus$  for (1) as

$$\Delta G^\ominus(T) \simeq \Delta_f H_A(T_A) - \Delta_f H_R(T_R) - T[\Delta_f H_A(T_A)/T_A - \Delta_f H_R(T_R)/T_R + R\ln 2]. \quad (9)$$

The two parts of (9) represent differences in enthalpy and entropy. They can be estimated from the experimentally determined melting points and heats of fusion for the pure enantiomers and the racemic compound.

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