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Structures of Racemic Halogen-Substituted 3-Hydroxy-3-phenylpropionic Acids; Relations Between Spontaneously Resolved and Racemic Compounds

By Sine Larsen and Katalin Marthi

Centre for Crystallographic Studies, Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark*

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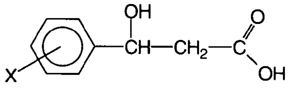
Abstract

Low-temperature [122.0(5) K] X-ray diffraction data [$\lambda(\mathrm{Cu}\,K\alpha) = 1.54184$ Å] showed that racemic 3-hydroxy-3-(3′-chlorophenyl)propionic acid and its bromo-substituted analogue are isostructural. 3-Hydroxy-3-(3′-chlorophenyl)propionic acid: $C_9H_9ClO_3$, $M_r = 200.61$, monoclinic, $P2_1/c$, $a = 15.301$ (2), $b = 5.7117$ (8), $c = 11.2462$ (13) Å, $\beta = 110.873$ (10)°, $V = 918.4$ (2) Å^3, $Z = 4$, $D_x = 1.451$ g cm^{-3}, $\mu = 35.15$ cm^{-1}, $F(000) = 416$, $wR_2 = 0.0775$ for 1880 contributing reflections [$R = 0.0274$ for $F > 4\sigma(F)$], m.p. 342.7 (5) K. 3-Hydroxy-3-(3′-bromophenyl)propionic acid: $C_9H_9BrO_3$, $M_r = 245.07$, monoclinic, $P2_1/c$, $a = 15.498$ (3), $b = 5.7513$ (12), $c = 11.298$ (2) Å, $\beta = 111.280$ (14)°, $V = 938.4$ (3) Å^3, $Z = 4$, $D_x = 1.735$ g cm^{-3}, $\mu = 58.07$ cm^{-1}, $F(000) = 488$, $wR_2 = 0.0769$ for 1926 contributing reflections [$R = 0.0284$ for $F > 4\sigma(F)$], m.p. 348.7 (5) K. The results from these structure determinations were combined with results from crystal structure determinations of other halogen-substituted 3-hydroxy-3-phenylpropionic acids in an analysis performed to obtain insight into their conglomerate *versus* racemic compound formation. In all the structures studied, the O—H···O hydrogen bonds are formed between identical donor and acceptor atoms leading to two distinct motifs. The crystallization of the racemates as either racemic compounds or mechanical mixtures of enantiomers can only be rationalized if weaker intermolecular interactions are taken into account.

Introduction

Chiral compounds are often found to react differently than the corresponding racemate. The increasing demand for chiral compounds to be used as drugs and in nonlinear optics has increased interest in understanding the structural and physico-chemical background for the interactions between chiral molecules. Studies of crystals obtained from the crystallization of racemates may provide insight into the interactions between chiral molecules. Most frequently a *racemic compound* precipitates from a racmic mixture, *i.e.* the crystals formed contain both enantiomers, thus in a racemic compound there can be interactions between molecules of the same chirality (homochiral) and/or of opposite chirality (heterochiral). A spontaneous resolution of the racemate into its enantiomers may also occur by crystallization. In this case a mechanical mixture of crystals is formed, each containing only one enantiomer. In this mixture, which is classified as a *conglomerate*, there are only homochiral interactions in the crystals. In this context it should also be mentioned that there are few examples of crystals isolated from a racemic mixture which form a *solid solution*, *i.e.* the crystals may contain the enantiomers in all ratios with only minor changes of the crystal packing (Jacques, Collet & Wilen, 1981; Roozeboom, 1899).

One may wonder what structural differences lead to the formation of either a racemic compound or a conglomerate. We have tried to elucidate this by studying the structure of 3-hydroxy-3-phenylpropionic acid and some of its halogen substituted analogues.



X = H, F, Cl, Br

The racemic unsubstituted acid has been shown by thermal analysis and X-ray diffraction to form a conglomerate (Collet & Jacques, 1972; Cesario & Guilhem, 1974*a*). The *para*-fluoro acid forms a racemic compound and the crystal structures are known of both the pure enantiomer and the racemic compound (Cesario & Guilhem, 1974*b*,*c*). The *para*-chloro and -bromo-substituted acids form conglomerates with known crystal structures (Cesario & Guilhem, 1974*d*,*e*), whereas the equivalent *meta*-chloro- and -bromo-substituted acids have been reported to crystallize as racemic compounds (Collet & Jacques, 1972).

To attain insight into structural differences between the conglomerate and racemic compounds formed by closely related compounds we have performed crystal structure determinations for the racemic *meta*-bromo-

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and -chloro-3-hydroxy-3-phenylpropionic acids and have analysed the known crystal structures of the unsubstituted and *para*-halogen-substituted 3-hydroxy-3-phenylpropionic acids.

Experimental

The preparations of 3-hydroxy-3-(3′-chlorophenyl)propionic acid and 3-hydroxy-3-(3′-bromophenyl)propionic acid were based on the method described by Collet & Jacques (1972).

3-*Hydroxy*-3-(3′-*chlorophenyl*)*propionic acid*

A mixture of 25.00 g (177.8 mmol) of 3-chlorobenzaldehyde, 29.70 g (177.8 mmol) of ethyl bromoacetate and 11.63 g (177.8 mmol) of Zn and one spatula of $HgCl_2$ was made in 107 ml of toluene. The mixture was refluxed for 1 h and thereafter cooled to room temperature. After adding a solution of 19.0 g (355.6 mmol) of NH_4Cl in 100 ml of water, the mixture was thoroughly stirred for 10 min and extracted five times with 100 ml portions of ether. The ether extracts were combined and evaporated to dryness to give 35.73 g (156.2 mmol, 88%) of crude hydroxyester. The hydroxyester was dissolved in 125 ml of ethanol and hydrolysed by reflux for 1 h with 313 ml of 1 M NaOH. The reaction mixture was shaken with ether. The aqueous phase was cooled by adding ice, acidified with 10% H_2SO_4 solution until pH ~2–3, followed by extraction four times with 200 ml portions of ether. The combined ether extracts were dried over $MgSO_4$, and evaporated to dryness to give 23.89 g (119.1 mmol, yield: 67%) of crude acid. The acid was dissolved in 100 ml of benzene and filtered after addition of charcoal. The solvent was removed by evaporation and the crystalline mass suspended in 50 ml of benzene; 13.71 g (68.3 mmol, 38%) of pure acid was removed by filtration as first fraction, and a further 3.07 g (15.3 mmol, 9%) of acid was obtained after evaporation of the solvent.

Found: C 53.92, H 4.50, Cl 17.71; calc.: C 53.88, H 4.52, Cl 17.67. The ^1H and ^{13}C NMR spectra measured in $CDCl_3$ verified the identity of the compound. Crystals suitable for X-ray diffraction were grown from a 1:1 ether/*n*-hexane mixture.

3-*Hydroxy*-3-(3′-*bromophenyl*)*propionic acid*

This compound was prepared from 25.00 g (135.1 mmol) of 3-bromobenzaldehyde. The reactants were used in the same molar ratio as described above for the preparation of 3-hydroxy-3-(3′-chlorophenyl)propionic acid. The crude acid obtained was dissolved in 100 ml of CCl_4, and filtered after the addition of charcoal. The solution was left at room temperature. After 2 d the crystalline precipitate was removed by filtration to give 7.20 g (29.4 mmol, 22%) of pure acid as the first fraction, and a further 4.25 g (17.3 mmol, 13%) as the solvent evaporated.

Found: C 44.00, H 3.67, Br 32.65, calc.: C 44.11, H 3.70, Br 32.60. The ^1H and ^{13}C NMR spectra in $CDCl_3$ were as expected for 3-hydroxy-3-(3′-bromophenyl)propionic acid. The crystals obtained in this manner could be used for the single-crystal X-ray diffraction study without further purification.

Thermodynamic measurements

Melting points and heats of fusion were measured by differential scanning calorimetry 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^{-1} was used. The mass of the samples varied betwen 3.12 and 3.16 mg, measured with a precision of 0.001 mg. The samples showed sharp, reproducible melting, proving that the compounds were pure. The associated melting enthalpies were determined with a reproducibility of 5%. Thermogravimetric measurements on the samples showed that no decomposition occurs in the temperature range investigated.

Structure determinations

The structure deteminations were conducted almost identically for both compounds. 3-Hydroxy-3-(3′-bromophenyl)propionic acid was characterized by room-temperature Weissenberg photographs. Its space group was determined uniquely from the systematically absent reflections.

The data collections were performed with a CAD-4 diffractometer. Cu $K\alpha$ ($\lambda = 1.54184$ Å) radiation, obtained from a graphite monochromator, was used. The crystals were cooled with an Enraf–Nonius gas-flow low-temperature device. The temperature, 122 K, was monitored with a thermocouple placed a few cm above the crystal in the exhaust pipe. It remained constant within 1 K during the experiments. An analysis of reflection profiles provided the basis for the selection of scan mode and scan interval for the data collection. 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 every 10 000 s. The orientation of the crystals was checked every 300 reflections. The reflections used for the intensity control showed a systematic decay for both compounds. 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. Averaging was performed for the reflections related by the symmetry of the crystal class.

Table 1. *Summary of the data collection and structure refinement results*

	rac. *m*-Cl	rac. *m*-Br
Crystal dimensions (mm)	(1,0,$\bar{1}$):0.02, ($\bar{1}$,0,1):0.02 (2,0,1):0.07, ($\bar{2}$,0,$\bar{1}$):0.07 (0,1,0):0.22, (0,$\bar{1}$,0):0.22	(1,0,$\bar{1}$):0.075, ($\bar{1}$,0,1):0.075 (1,0,0):0.10, ($\bar{1}$,0,0):0.10 (0,1,0):0.00, (3,$\bar{1}$,$\bar{1}$):0.28
No. of reflections used in determination of cell parameters	18	18
θ range (°)	32.64–47.15	32.40–47.03
Scan type	ω–2θ	ω–2θ
Standard reflections	300, 020, 112 90$\bar{6}$, 0$\bar{2}$6	200, 0$\bar{2}$0, 004 12,0,$\bar{6}$, 026
Max. variation of intensity control reflections (%)	3.4	4.2
θ range for data collection (°)	3.09–74.99	3.06–74.92
h range	0→19	−19→19
k range	−7→7	−7→7
l range	−14→13	−14→13
R_{int}	0.0181	0.0272
Transmission factor range	0.462–0.868	0.244–0.536
Number of measured reflections (including standard reflections)	3834	5338
Number of independent reflections	1880	1927
Number of contributing reflections [$I > -3\sigma(I)$]	1880	1926
Number of observed reflections [$I > 2\sigma(I)$]	1734	1907
$w^{-1}[P = (F_o^2 + 2F_c^2)/3]$	$\sigma^2(F_o^2) + (0.0461P)^2 + 0.2309P$	$\sigma^2(F_o^2) + (0.0429P)^2 + 1.0931P$
Number of variable	146	146
R for $F > 4\sigma(F)$	0.0274	0.0284
wR_2 for all F^2 data	0.0775	0.0779
S for all F^2 data	1.062	1.142
Isotropic extinction coefficient (Å^{-3})	0.0087 (7)	0.0090 (4)
Max. shift/e.s.d.	0.001	−0.001
Max. and min. $\Delta\rho$ (eÅ^{-3})	0.305 and −0.233	0.892 and −0.536

The structures were solved by direct methods using *SHELXS*86 (Sheldrick, 1990), and refined by full-matrix least-squares with *SHELXL*93 (Sheldrick, 1993), minimizing $\Sigma w(F_o^2 - F_c^2)^2$. The scattering factors were taken from *International Tables for Crystallography* (1992, Vol. C) and used as contained in the program. After anisotropic displacement parameters were 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 using isotropic displacement parameters (U_{eq}) of the parent C or O atom multiplied by 1.2 and 1.5, respectively. Extinction corrections were applied for both data sets. The final fractional coordinates for both structures are listed in Table 2.* The final residual electron-density maps were featureless with maximum density adjacent to the Br and Cl atoms. The program *PLATON* (Spek, 1990) was used in the analysis of the structures.

Table 2. *Atomic coordinates and equivalent isotropic displacement parameters* (Å) *for racemic 3-hydroxy-3-(3-halophenyl)propionic acids*

$$U_{\text{eq}} = (1/3)\textstyle\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j .$$

	x	y	z	U_{eq}
Racemic 3-hydroxy-3-(3′-chlorophenyl)propionic acid				
Cl	0.17578 (2)	0.17637 (6)	0.27073 (3)	0.03005 (13)
O1	0.44044 (6)	1.0500 (2)	0.83527 (8)	0.0200 (2)
O2	0.52637 (6)	0.7306 (2)	0.90535 (8)	0.0210 (2)
O3	0.40394 (6)	0.7993 (2)	0.56501 (8)	0.0176 (2)
C1	0.45324 (8)	0.8210 (2)	0.83874 (11)	0.0170 (3)
C2	0.36885 (9)	0.6915 (2)	0.75170 (11)	0.0191 (3)
C3	0.33208 (8)	0.8058 (2)	0.61935 (11)	0.0172 (3)
C4	0.24499 (8)	0.6857 (2)	0.53154 (11)	0.0182 (3)
C5	0.25072 (8)	0.5008 (2)	0.45402 (11)	0.0193 (3)
C6	0.16846 (9)	0.4007 (2)	0.37242 (11)	0.0217 (3)
C7	0.08140 (9)	0.4762 (3)	0.36710 (13)	0.0256 (3)
C8	0.07647 (10)	0.6589 (3)	0.44625 (13)	0.0272 (3)
C9	0.15768 (9)	0.7637 (3)	0.52770 (12)	0.0235 (3)
Racemic 3-hydroxy-3-(3′-bromophenyl)propionic acid				
Br	0.17731 (2)	0.16715 (4)	0.26313 (2)	0.02541 (14)
O1	0.44258 (11)	1.0554 (3)	0.8346 (2)	0.0200 (3)
O2	0.52752 (11)	0.7388 (3)	0.90642 (14)	0.0210 (3)
O3	0.40434 (11)	0.8066 (3)	0.5644 (2)	0.0179 (3)
C1	0.4554 (2)	0.8285 (4)	0.8388 (2)	0.0172 (4)
C2	0.3721 (2)	0.6995 (4)	0.7516 (2)	0.0188 (4)
C3	0.3340 (2)	0.8128 (4)	0.6191 (2)	0.0177 (4)
C4	0.2478 (2)	0.6921 (4)	0.5331 (2)	0.0181 (4)
C5	0.2526 (2)	0.5094 (4)	0.4552 (2)	0.0184 (4)
C6	0.1710 (2)	0.4087 (4)	0.3753 (2)	0.0205 (4)
C7	0.0847 (2)	0.4821 (4)	0.3713 (2)	0.0247 (5)
C8	0.0809 (2)	0.6625 (4)	0.4510 (2)	0.0263 (5)
C9	0.1615 (2)	0.7679 (4)	0.5308 (2)	0.0228 (5)

Theoretical calculations

Mopac 6.0 PM3 calculations were performed using the InsightII program package (InsightII, 1994) implemented on a Silicon Graphics Personal Iris computer to obtain estimates of the atomic charges. The geometries used were those obtained by the present structure determinations or extracted from the Cambridge Structural Database [CSD (Allen *et al.*, 1979)]

Description of the racemic *meta*-chloro- and -bromo-3-hydroxy-3-phenylpropionic acids

Thermodynamic properties

The DSC traces between room temperature and the sharp melting points showed no signs of phase transitions, indicating that the samples are thermodynamically stable compounds. From the DSC measurements the melting points and enthalpies of fusion were determined for the racemic *meta*-chloro- and -bromo-substituted 3-hydroxy-3-phenylpropionic acids. The results are listed in Table 3. The thermodynamic properties of the unsubstituted and halogen-substituted 3-hydroxy-3-phenylpropionic acids have previously been described by Collet & Jacques (1972). Within experimental error, our results for the *meta*-bromo-substituted acid agree with those reported earlier (Collet & Jacques, 1972), but there are some discrepancies for the *meta*-

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* Lists of structure factors, anisotropic displacement parameters and H-atom parameters have been deposited with the IUCr (Reference: AB0332). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Thermochemical data*

	3-Hydroxy-3-(3′-chloro-phenyl)propionic acid	3-Hydroxy-3-(3′-bromo-phenyl)propionic acid
Melting point (K)	342.7 (5)	348.7 (5)
$\Delta H^{\ominus}_{fus}$ (kJ mol^{-1})	25 (1)	25 (1)
$\Delta S^{\ominus}_{fus}$ (J mol^{-1} K^{-1})	73 (2)	72 (2)

chloro-substituted acid that merit closer examination. Collet & Jacques (1972) determined the melting point of 3-hydroxy-3-(3′-chlorophenyl)propionic acid to be 340 K, and stated that it was highly probable that this acid transforms into a conglomerate (calculated m.p. 342 K) on melting. However, they did not provide evidence to support this statement. The melting point 342.7(5) K determined by us for 3-hydroxy-3-(3′-chlorophenyl)propionic acid is, within experimental error, identical to the value Collet & Jaques (1972) calculated for the conglomerate (342 K). Our DSC trace for this compound does not provide any support to the proposed racemate–conglomerate transformation (Collet & Jacques, 1972), which should imply an unlikely separation of enantiomers. The enthalpies of fusion listed in Table 3 for the two *meta*-substituted acids are in accordance with the observation that the two acids are isostructural and have identical intermolecular interactions (*vide infra*).

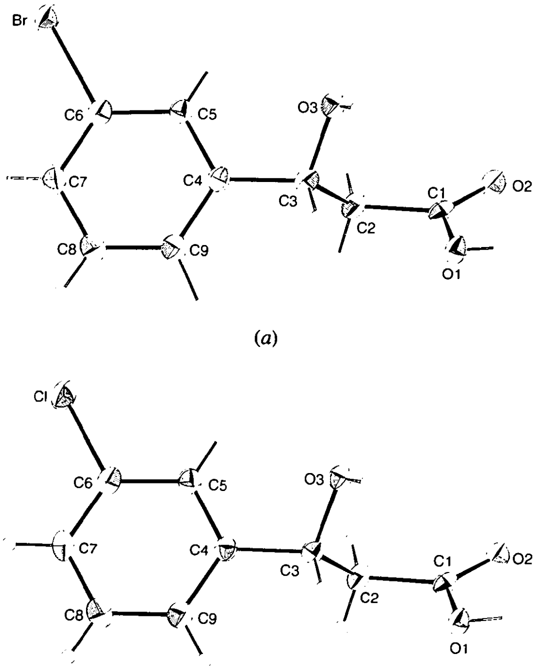
Molecular structures

The cell dimensions and atomic coordinates (Table 2) show that 3-hydroxy-3-(3′-chlorophenyl)propionic acid and its bromo-substituted analogue are isostructural. As a consequence, the two acids have identical molecular geometries with the expected exception of the C6–halogen bond length. The molecular geometry and the numbering scheme of the molecule is shown in Fig. 1. The bond lengths and angles are listed in Table 4, and some selected torsion angles in Table 5. The halogen substitution in these 3-hydroxy-3-(3′-halophenyl)propionic acids occurs on the same side of the phenyl ring compared with the position of the hydroxy group, as observed for racemic *meta*-fluoromandelic acid (Larsen & Marthi, 1994). The bond angles in the phenyl groups deviate significantly from the idealized value of 120°. This is the effect of the two substituents. Domenicano & Murray-Rust (1979) have, among others, shown that the angular deformations of phenyl groups can be described as a sum of the effects of the different substituents.

In a recent study of racemic monofluoro-substituted mandelic acids (Larsen & Marthi, 1994), we found that the angular deviations of the bond angles could be reproduced as the sum of the substituent effects of F and the CHOHCOOH group, assuming that the effect of the latter group was similar to the effect of a methyl ketone group. Assuming the effect of the $CH(OH)CH_2COOH$ group to be also similar to a methyl ketone group, the angular distortions listed by Domenicano (1992) were

Table 4. *Bond distances* (Å) *and angles* (°) *for racemic 3-hydroxy-3-(3′-halophenyl)propionic acids*

X	Cl	Br
X—C6	1.7474 (13)	1.906 (2)
O1—C1	1.321 (2)	1.319 (3)
O2—C1	1.218 (2)	1.216 (3)
O3—C3	1.4363 (14)	1.436 (3)
C1—C2	1.507 (2)	1.505 (3)
C2—C3	1.537 (2)	1.540 (3)
C3—C4	1.511 (2)	1.507 (3)
C4—C5	1.392 (2)	1.390 (3)
C4—C9	1.394 (2)	1.398 (3)
C5—C6	1.389 (2)	1.386 (3)
C6—C7	1.381 (2)	1.389 (3)
C7—C8	1.391 (2)	1.389 (3)
C8—C9	1.390 (2)	1.387 (3)
O1—C1—O2	122.15 (11)	122.3 (2)
O1—C1—C2	112.53 (11)	112.4 (2)
O2—C1—C2	125.31 (12)	125.2 (2)
C1—C2—C3	110.72 (10)	111.3 (2)
O3—C3—C2	109.25 (10)	109.0 (2)
O3—C3—C4	109.93 (9)	110.2 (2)
C2—C3—C4	111.94 (10)	111.7 (2)
C3—C4—C5	121.06 (11)	121.2 (2)
C3—C4—C9	119.16 (11)	119.1 (2)
C5—C4—C9	119.78 (11)	119.7 (2)
C4—C5—C6	118.78 (11)	118.8 (2)
C5—C6—C7	122.21 (12)	122.3 (2)
C5—C6—*X*	118.67 (10)	118.9 (2)
C7—C6—*X*	119.10 (10)	118.8 (2)
C6—C7—C8	118.56 (12)	118.3 (2)
C7—C8—C9	120.36 (13)	120.5 (2)
C4—C9—C8	120.30 (12)	120.4 (2)



(*a*)

(*b*)

Fig. 1. *ORTEP*II (Johnson, 1976) drawings showing the molecular geometry of the 3-hydroxy-3-(3′-halophenyl)propionic acid: (*a*) Br and (*b*) Cl. The thermal ellipsoids are scaled to include 50% probability, H atoms are drawn as spheres with a fixed radius.

Table 5. *Comparison of the crystal structures of* 3-*hydroxy*-3-*phenylpropionic acids**

	rac. *m*-Br	rac. *m*-Cl	*p*-Br		*p*-Cl		rac. *p*-F	o.a. *p*-F	H
a (Å)	15.498 (3)	15.301 (2)	9.710 (5)		9.67 (3)		19.25 (3)	5.963 (5)	6.02 (2)
b (Å)	5.7513 (12)	5.7117 (8)	5.768 (3)		5.69 (1)		5.95 (1)	7.411 (6)	7.33 (1)
c (Å)	11.298 (2)	11.2462 (13)	17.054 (7)		16.91 (2)		7.66 (1)	10.019 (9)	10.03 (1)
β (°)	111.280 (14)	110.873 (10)	101.9 (1)		102.4 (1)		90.0	102.9 (1)	103.5 (2)
D_x (g cm^{-3})	1.735	1.451	1.742		1.466		1.394	1.417	1.282
Space group	$P2_1/c$	$P2_1/c$	$P2_1$		$P2_1$		$Pna2_1$	$P2_1$	$P2_1$
Molecules/ asymmetric unit	1	1	2		2		1	1	1
Molecular geometry (Å/°)									
C(6,7)—*X*	1.906 (2)	1.7474 (13)	1.92	1.91	1.73	1.75	1.36	1.36	1.08
O2—C1—C2—C3	−133.2 (2)	−132.00 (12)	134	138	−134	−136	−154	−149	−137
C1—C2—C3—C4	−177.2 (2)	−177.61 (10)	−175	−175	175	176	−167	−166	−169
C1—C2—C3—O3	60.9 (2)	60.40 (13)	−55	−54	53	56	71	71	66
C2—C3—C4—C5	−91.1 (2)	−90.61 (13)	79	78	−79	−78	−73	−82	−85
C2—C3—C4—C9	89.8 (2)	89.99 (14)	−101	−98	99	98	100	94	93
Intermolecular interactions (Å/°)									
O1···O3	2.656 (2)	2.655 (1)	2.64	2.66	2.68	2.64	2.62	2.63	2.65
O1—H1···O3	167 (3)	167 (2)	180	180	167	137	141	179	177
H1···O3	1.91 (4)	1.81 (2)	1.56	1.59	1.72	1.75	1.79	1.56	1.61
O3···O2	2.674 (2)	2.658 (1)	2.76	2.70	2.73	2.70	2.72	2.73	2.77
O3—H30···O2	172 (4)	173 (2)	179	160	150	139	161	179	179
H30···O2	2.05 (4)	1.85 (2)	1.67	1.53	1.87	1.87	1.85	1.64	1.67
N_1	$C(6)C(6)$	$C(6)C(6)$	$C(6)C(6)$	$C(6)C(6)$	$C(6)C(6)$	$C(6)C(6)$	$C(6)C(6)$	$C(6)C(6)$	$C(6)C(6)$
N_2	$C_2^2(6)[R_2^2(12)]$	$C_2^2(6)[R_2^2(12)]$	$C_2^2(6)[R_2^2(12)]$	$C_2^2(6)[R_2^2(12)]$	$C_2^2(6)[R_2^2(12)]$	$C_2^2(6)[R_2^2(12)]$	$C_2^2(6)[R_4^4(18)]$	$C_2^2(6)[R_4^4(18)]$	$C_2^2(6)[R_4^4(18)]$
C1···O3	3.031 (3)	2.981 (1)							
C5···O2			3.36	3.40	3.39	3.41	3.41	3.36	3.40
C5—H5···O2			169	163	171	170	168	154	154
H5···O2			2.37	2.45	2.40	2.43	2.41	2.36	2.42
N_2†			$R_2^2(9)$	$R_2^2(9)$	$R_2^2(9)$	$R_2^2(9)$	$R_2^2(9)$	$R_2^1(7)$	$R_2^1(7)$
C8···O3							3.52	3.53	3.57
C8—H8···O3							149	159	155
H8···O3							2.62	2.51	2.56
N_1‡							$C(6)$	$C(6)$	$C(6)$
C2···F1							3.27		
C—H2···F							127		
H2···F							2.56		
N_1‡							C(8)		
Packing									
Phenyl 6 Å axis (°)	41.04 (8)	40.91 (5)	29	29	29	29	28	28	28
Carboxylic 6 Å axis (°)	3.96 (10)	4.25	1	2	1	3	5	8	1

* Prefixes: rac.: racemic compound, o.a.: optically active none: optically active since conglomerate *p*: *para, m*: *meta,* the number of digits reflect the accuracy of the data extracted from CSD.

† The ring with the lowest possible degree given by C5—H5···O2 and one of the O—H···O hydrogen bonds.

‡ The motif given by the C—H···O hydrogen bond only.

used to predict angles in the phenyl ring for 3-hydroxy-3-(3′-chlorophenyl)propionic acid. Within experimental error, they were identical to those determined experimentally. As the angles are identical for the bromo-substituted acid, we would expect that Cl and Br have very similar effects.

The carbon chain adopts an antiperiplanar conformation. The two planar fragments of the molecule, the phenyl ring and the carboxylic acid group, form an interplanar angle of 41.90 (7)° for the chloro- and 43.07 (13)° for the bromo-substituted acids. The C3—O3 bond makes angles of 29.52 (8) and 28.9 (2)° with the phenyl ring and 64.40 (8) and 65.3 (2)° with the carboxylic acid groups, respectively, for racemic *meta*-chloro- and -bromo-3-hydroxy-3-phenylpropionic acid.

Crystal packing

The intermolecular interactions in *meta*-bromo- and -chloro-substituted 3-hydroxy-3-phenylpropionic acids are dominated by hydrogen bonds. The overall packing is illustrated by the stereopair in Fig. 2. The acids have two potential hydrogen-bond donors (from the OH and COOH groups) and three potential hydrogen-bond acceptors (O1, O2 and O3). In the resulting hydrogen-bonding scheme, the carboxylic acid group donates its proton to O3 of the hydroxy group which in turn donates its proton to O2 of the carboxylic acid group. The two O—O distances are rather short (less than 2.7 Å), and very similar for the two types of hydrogen bonds. A molecule donates its two protons to another molecule related by the symmetry of a twofold screw axis, giving rise to columns of hydrogen-bonded molecules. Using the graph theoretical method devised by Etter, MacDonald & Bernstein (1990), and further developed by Bernstein, Davis, Shimoni & Chang (1995) to describe this hydrogen-bonding scheme, we obtain the first level network N_1 to be $C(6)C(6)$ (the H atom of the carboxylic acid group has the highest priority). The second level network is $N_2 = C_2^2(6)[R_2^2(12)]$. The six-membered chain that involves both types of hydrogen bonds defines the translational symmetry of the column, and the ring defines the interactions between two molecules related by a twofold screw axis. This network of hydrogen bonds connects molecules of the same chirality into columns parallel to the *b*-axis, as shown in Fig. 3. Analysing the packing for interactions between the columns, it is found that the distance between C1 of the carboxylic acid group and O3 from a hydroxyl group related by the glide plane are 0.189 (3) (Br) and 0.239 (1) Å (Cl) shorter than the sum of the van der Waals radii (Bondi, 1964) of C and O. PM3 calculations showed that C1 in the carboxylic acid group is the atom with the highest positive charge, and O3 from the hydroxy group is the atom with the second most negative charge. Therefore, we assume that these short C1—O3 distances correspond to attractive electrostatic interactions. This distance as well as the O3—H3···O2 hydrogen bond is shorter in the chloro than in the bromo compound. This could imply that the intermolecular interactions are slightly stronger in this acid. However, as described above, the two compounds have virtually identical melting enthalpies.

Comparison of the crystal structures of 3-hydroxy-3-phenylpropionic acids

A summary of the structural results is presented in Table for the unsubstituted acid (H), and the *para*-fluoro-substituted (racemic compound: rac. *p*-F and enantiomer: o.a. *p*-F) compounds, along with the data for the racemic *para*-chloro- and -bromo-substituted acids (*p*-Cl and *p*-Br), which form conglomerates. Data for the racemic compounds of the *meta*-chloro and -bromo acids (rac. *m*-Cl and rac. *m*-Br) are also included in Table 5. Results from the structure determinations for H, rac. *p*-F, o.a. *p*-F, *p*-Br and *p*-Cl were extracted from the Cambridge Structural Database (CSD; Allen *et al.*, 1979) and from the original papers. It should be noted that the *R*-values associated with these structure determinations are rather high (0.074–0.094), which reflects the accuracy of the values reported. However, coordinates have been

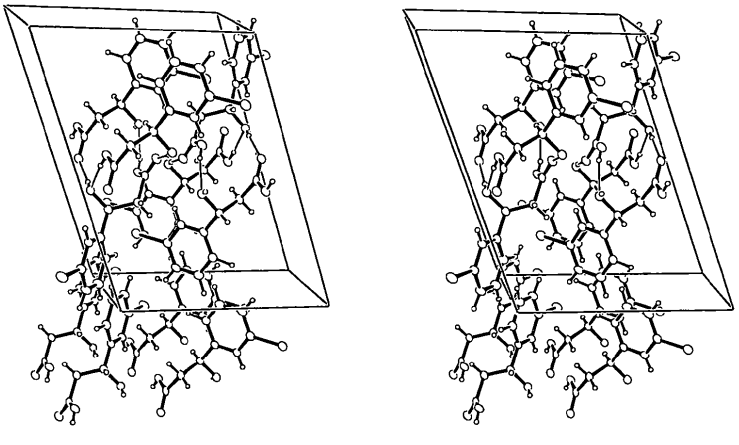
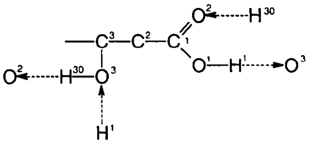


Fig. 2. The packing of the isostructural 3-hydroxy-3-(3′-chlorophenyl)propionic acid and 3-hydroxy-3-(3′-bromophenyl)propionic acid is illustrated by the stereopair (Johnson, 1976) of the latter, as seen along the *b*-axis. The O—H···O hydrogen bonds are shown as thin lines.

reported for all the H atoms. To ease the comparison, the numbering scheme in Fig. 1 is used for all the compounds. An account of conglomerate *versus* racemic compound formation based solely on O—H···O hydrogen bonds have previously been given by Cesario, Guilhem, Pascard, Collet & Jacques (1978) for some aromatic hydroxy acids.

A comparison of the cell dimensions listed in Table 5 also shows that *p*-Cl and *p*-Br are isostructural, and that the unsubstituted acid (H) is isostructural with the optically active form of the *para*-fluoro-substituted acid (o.a. *p*-F). These similarities are in agreement with those observed earlier by Kálmán, Párkányi & Argay (1993) for halogen substitution.

The acids have identical functional groups with identical possibilities for hydrogen-bond formation, and indeed the same donor and acceptor atoms make the hydrogen-bond interactions, as illustrated below.



The geometries of the O1—H1···O3 and O3—H30···O2 hydrogen bonds as they are found in the structures are listed in Table 5. Both hydrogen bonds are of the linear two-centre type. It is noteworthy that the O1···O3 distances are almost of the same magnitude (2.62–2.68 Å). Slightly larger variations are observed for the O···O2 hydrogen bond (2.66–2.77 Å).

Despite this apparent similarity in the hydrogen-bond systems, they lead to two different hydrogen-bonding patterns. In all the Cl and Br substituted acids we find the columns illustrated in Fig. 3 and described in the crystal packing of rac. *m*-Cl and rac. *m*-Br. The *para*-chloro- and -bromo-substituted acids crystallize with two molecules per asymmetric unit, and separate hydrogen-bonded columns are formed of each of the crystallographically independent molecules. Also in the *p*-Cl and *p*-Br structures the second level graph set assigned separately for each independent chain can be used to classify this hydrogen bond packing mode as $N_2 = C_2^2(6)[R_4^4(12)]$. The columns of homochiral molecules are parallel to a twofold screw axis, with a translational period in the range 5.7–5.8 Å.

The hydrogen-bonding pattern found in the remaining three structures is illustrated in Fig. 4. The molecules are linked by the hydrogen bonds in a sheet-like arrangement. In contrast to the column arrangement where one molecule donates the two protons to one molecule related by a twofold screw axis, the molecules in the sheet-like structure donate protons to two different molecules. The sheets have the same first level O—H···O hydrogen-bonding network [$N_1 = C(6)C(6)$] as the columns, and even the chain running parallel to the *ca* 6 Å axis in the second level network is the same. However, in contrast to the column arrangement, the *ca* 6 Å axis is not parallel to a twofold screw axis and the ring formed is different. The second level graph set is $N_2 = C_2^2(6)[R_4^4(18)]$.

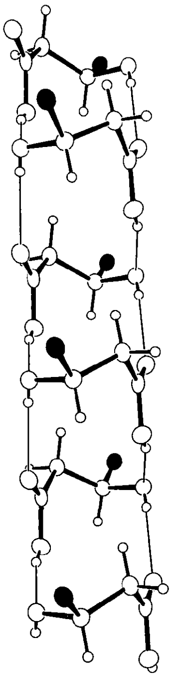


Fig. 3. Schematic drawing (Johnson, 1976) illustrating the columns of O—H···O hydrogen-bonded molecules of racemic 3-hydroxy-3-(3′-bromophenyl)propionic acid. The phenyl group is replaced by C4 (drawn black) for clarity. The O—H···O hydrogen bonds are shown as thin lines.

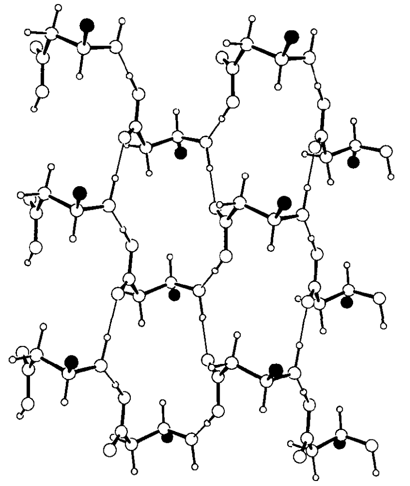


Fig. 4. Schematic drawing (Johnson, 1976) illustrating the sheet-like O—H···O hydrogen bonding network for 3-hydroxy-3-phenylpropionic acid. The phenyl group is replaced by C4 (drawn black) for clarity. All atoms are drawn as spheres with a fixed radius. The O—H···O hydrogen bonds are shown as thin lines.

In the o.a. *p*-F and H structures the two hydrogen bonds link molecules related by the symmetry of a twofold screw axis. This direction of the sheet corresponds to a translational period in the range 7.3–7.4 Å. If the symmetry of the twofold screw axis is replaced with a glide plane parallel to the plane of the sheet and with a translation symmetry in the same direction and length as the twofold screw axis, one obtains the packing arrangement of rac. *p*-F. Only heterochiral O—H···O hydrogen-bond interactions exist in rac. *p*-F. The infinite hydrogen-bonded chains are parallel in rac. *p*-F, whereas they are antiparallel in H and o.a. *p*-F. This is a consequence of the symmetry of a glide plane *versus* twofold screw axis.

With these apparent similarities in mind, some pertinent questions emerge. What makes the structures of the conglomerate forming *p*-Cl and *p*-Br different from the equivalent rac. *m*-Cl and *m*-Br, and why does H, which is isostructural with o.a. *p*-F, crystallize as a conglomerate?

In rac. *m*-Cl and rac. *m*-Br we found an attractive electrostatic interaction between Cl and O3 from different hydrogen-bonded columns related by the symmetry of a glide plane as described above. A similar interaction is not found in the *p*-Cl and *p*-Br acids. This could explain the small difference between the *m*- and *p*-Cl and -Br substituted acids in their Cl—C2—C3—O3 angles, 60.5 (2) and 55 (2)°, respectively. However, it does not lead to a significant variation in the angle that the carboxylic acid groups make with the *ca* 5.7 Å axis. The crystal structures were examined for other intermolecular interactions. We looked for interatomic distances shorter than the sum of the van der Waals radii (Spek, 1990), that are not a consequence of the O—H···O hydrogen bonds. In *p*-Cl and *p*-Br this revealed the existence of a C5—H5···O2 hydrogen bond between the molecules related by the twofold screw axis and already linked by hydrogen bonds, leading to an additional stabilization of the homochiral columns. The steric effect from the *meta*-substituents in rac. *m*-Cl and rac. *m*-Br would prevent the formation of a C5—H5···O2 hydrogen bond. This C5—H5···O2 hydrogen bond explains the variation in the orientation of the phenyl ring: In *p*-Cl and *p*-Br the torsion angle [C2—C3—C4—C5(C9)] is more asymmetric [79 (2) and 99 (2)°] than we found in the equivalent racemic *meta*-substituted acids. It is also reflected in the difference in the angle that the phenyl group makes with the twofold screw axis.

The hydrogen-bonded columns pack differently in the *m*- and *p*-Cl and -Br substituted acids, although one might expect that the second molecule in the asymmetric unit in the *para*-acids would take the role of the mirror image molecule. However, this is not the case. Both columns run parallel to the twofold screw axis in *p*-Cl and *p*-Br, their hydrogen-bonded networks being approximately perpendicular. In rac. *m*-Cl and rac. *m*-Br the equivalent networks are parallel. Therefore, it is not surprising that the *para*- and *meta*-substituted acids have different *a*- and *c*-axes.

In the chloro- and bromo-substituted acids the packing of the columns is also influenced by interactions between phenyl groups. Intercolumn electrostatic interactions between Cl and O3 are not found in the *para*-substituted acids. This cannot be attributed to the *para*-halogen substitution, since the charges on the two atoms involved are slightly higher in the *para*-substituted acids according to the Mopac PM3 calculations. However, it can be rationalized if one considers that the interaction in rac. *m*-Cl and rac. *m*-Br propionic acids was observed between molecules of opposite chirality, and *p*-Cl and *p*-Br are built from one enantiomer. If one visualized the packing of *m*-Br and *m*-Cl, as shown in Fig. 2, with *para*-substituted phenyl groups instead, it would be apparent that the *para*-substitution leads to unfavourable contacts. This could indicate why a racemic compound with this crystal structure is not formed by crystallization of the racemic *para*-substituted acids.

Comparing the structures of the rac. *p*-F, o.a. *p*-F and H, similar differences are found in the weaker (C—H···O) interactions. In all three structures a C5—H5···O2 hydrogen bond links molecules already interacting by the O—H···O hydrogen bonds. The difference in the second level graph set between rac. *p*-F and the o.a. *p*-F and H acids reflects the difference in the hetero- and homochiral interactions that exist in these structures. This difference may also account for the difference in the C2—C3—C4—C5(9) torsion angles. In all three structures, C8—H8···O3 hydrogen bonds connect the sheets related by the symmetry of a twofold screw axis. Looking for differences between the interatomic interactions in the rac. *p*-F and o.a. *p*-F structures, we find that an additional C2—H2···F hydrogen bond links the sheets in the rac. *p*-F structure. A similar but slightly longer interaction is found in o.a. *p*-F. As this interaction cannot exist in the unsubstituted acid, it can carry some of the explanation to the crystallization of this acid as a conglomerate.

This analysis of crystal structures of 3-hydroxy-3-phenylpropionic acids with different halogen substituents has shown that there are great similarities in their O—H···O hydrogen-bonding systems. The crystallization of the racemates of the acids as conglomerates or racemic compounds can only be rationalized if other weaker interactions like C—H···O hydrogen bonds are taken into consideration.

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The Trifluoroacetato ($CF_3COO—$) and Trifluoroacetate (CF_3COO^-) Groups, their Conformation from a Database Survey of Crystal Structures and *Ab Initio* MO Calculations

By J. T. Gleghorn and R. W. H. Small

Chemistry Department, University of Lancaster, Lancaster LA1 4YA, England

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Abstract

Data for structures involving either of these groups have been drawn from the Cambridge Structural Database and divided into bidentate and monodentate categories. Statistical distributions of bond distances, selected bond and torsion angles from 414 groups contained in 194 structures yield the following mean values (with e.s.d.'s): C—F = 1.29 (6), C—C = 1.53 (4), C—O (bidentate) = 1.24 (5), C—O— (monodentate) = 1.25 (4), C=O (monodentate) = 1.21 (4) Å. Angles in the CF group vary widely from the expected threefold symmetry (e.s.d. of distribution 8.8°). Torsion angles F—C—C—O for the bidentate groups range fairly evenly over all possible values, suggesting free internal rotation. Among monodentate groups all values of the torsional angles are possible but with a marked preference for a C—F to eclipse the carbonyl C=O bond. These observations show good agreement with the results of *ab initio* calculations using *GAUSSIAN*90. The calculated barrier to rotation for the bidentate (ion) form of the group is only 310 J mol^{-1} and for the monodentate form (as in the acid) 2.55 kJ mol^{-1}.

Introduction

Examination of the Cambridge Structural Database (CSD) at 1.9.92 revealed references to 186 structures involving trifluoroacetato groups and 42 references to trifluoroacetate groups. For the purpose of this investigation these 228 structures were treated together and the abbreviation TFA implies both types of group. Coordinate data is available for 194 of these references and the work is based on these, containing a total of 414 TFA groups. A list of the CSD reference codes of these is given in Table 3.*

The TFA group was selected for detailed study because it had been noticed that there was exceptionally wide disparity in the molecular parameters from different reported structures. Problems frequently occur in the location of F atoms, at the worst they may not be found at all. Torsion angles relating the CF_3 and carboxyl groups are often not explicitly reported, but when calculated

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* A full list of references with compound names and CSD codes has been deposited with the IUCr (Reference: LI0176). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.