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Note added in proof: In a recent paper (Gourdon, Launay, Bujoli-Doeuff, Heisel, Miehé, Amongal & Boillot, 1993), the structure of DMABN, determined at room temperature, is interpreted differently than in this paper.

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Structures of Racemic Monofluoro-Substituted Mandelic Acids, Their Relation to the Thermochemical Properties and an Analysis of Short Intermolecular Fluorine–Carbon Contacts

By Sine Larsen and Katalin Marthi*

Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

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Abstract

The structures of the three monofluoro-substituted mandelic acids ($C_8H_7FO_3$, $M_r = 170.14$) have been determined from low-temperature [122 (1) K] X-ray diffraction data [$\lambda(\mathrm{Cu}\ K\alpha) = 1.54184$ Å]. *o*-Fluoromandelic acid, monoclinic, $P2_1/c$, $a = 8.4238\ (12)$, $b = 5.4766\ (7)$, $c = 15.959\ (2)$ Å, $\beta = 95.962\ (11)°$, $V = 732.3\ (3)$ Å^3, $Z = 4$, $D_x = 1.543$ g cm^{-3}, $\mu = 11.25$ cm^{-1}, $F(000) = 352$, $R = 0.040$ for 1357 contributing reflections, m.p. 388.3 (5) K. *m*-Fluoromandelic acid (metastable modification), monoclinic, $P2_1/a$, $a = 10.8657\ (14)$, $b = 9.2663\ (10)$, $c = 15.722\ (2)$ Å, $\beta = 107.474\ (10)°$,

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* On leave from Technical University of Budapest, Hungary.

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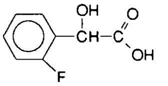
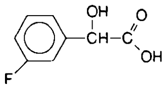
$V = 1509.9\ (6)$ Å^3, $Z = 8$, $D_x = 1.497$ g cm^{-3}, $\mu = 10.92$ cm^{-1}, $F(000) = 704$, $R = 0.048$ for 2977 contributing reflections, m.p. 368.4 (5) K. *p*-Fluoromandelic acid, orthorhombic, *Pbca*, $a = 9.4685\ (9)$, $b = 16.497\ (2)$, $c = 9.7677\ (8)$ Å, $V = 1525.7\ (5)$ Å^3, $Z = 8$, $D_x = 1.481$ g cm^{-3}, $\mu = 10.80$ cm^{-1}, $F(000) = 704$, $R = 0.042$ for 1489 contributing reflections, m.p. 408.9 (5) K. The results obtained from the structure determination are related to their physico-chemical properties examined by differential scanning calorimetry (DSC). The DSC measurements showed that *m*-fluoromandelic acid is prepared as a metastable modification. The distortions of the angles of the benzene rings observed in the three acids are identical, within experimental error, to those predicted from the sum of the substitutent effects. Hydrogen bonds are important for the crystal packing in all these structures, and in addition very short distances are observed in the *ortho*- and *para*-substituted acids between the F atom and the C atom of the carboxylic acid group. Semi-empirical calculations indicated that these short distances correspond to attractive electrostatic interactions. The carbon–fluorine interactions were also elucidated by a search in the Cambridge Structural Database. *m*-Fluoromandelic acid has the lowest melting enthalpy and entropy. This is consistent with the lack of C···F interactions and the presence of two molecules per asymmetric unit in this compound. The *ortho* and *para* acids which have similar intermolecular interactions have similar melting enthalpies and entropies, which are higher than those observed in *m*-fluoromandelic acid.

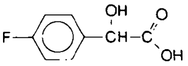
Introduction

The increasing demand for chiral compounds to be used as drugs and in non-linear optics has led to an increase in the desire to understand the nature of the intermolecular interactions between chiral molecules. Chiral compounds are often found to behave differently to the corresponding racemate and several preconceptions exist on the relationship between the physico-chemical properties of an enantiomer and its racemate. Wallach's rule is one example, it states that the racemate is more dense than the enantiomer. This was examined recently by Brock, Schweizer & Dunitz (1991). They found that although Wallach's rule is not valid for racemates in general, it represents a statistically significant trend. A similar relation exists between the melting points of a racemate and the pure enantiomer. In the systems Jacques, Collet & Wilen (1981) have investigated, the racemate is the higher melting in *ca* two thirds of the cases. This difference in melting point must be related to differences in the intermolecular actions in the crystals. In the racemate they can be homochiral, *i.e.* between molecules of the same chirality or heterochiral between molecules of opposite handedness, whereas only the former type of interaction can occur in the crystals of the enantiomer.

The closely related monofluoro-substituted mandelic acids display many unusual differences that merit further investigations. Only *o*-fluoromandelic acid is 'normal' in the sense that its racemate is higher melting than the pure enantiomer. The reverse is the case for the *meta*- and *para*-substituted acids (Jacques, Collet & Wilen, 1981).







Another interesting aspect of these closely related acids is the large variation in their physico-chemical properties. The melting points vary about 40 K and the melting enthalpies and entropies display similarly large variations. We assume that these differences are due to differences between the intermolecular interactions in the crystalline state. Therefore, we have undertaken investigations of the crystal structures and thermochemical properties of the three racemic monofluoro-substituted mandelic acids. The results from these studies are reported here, and the relations between the crystal structures and the physico-chemical properties are discussed.

Experimental

The preparation of the three monofluoro-substituted mandelic acids was based on the method described by Collet & Jacques (1973).

o-Fluoromandelic acid

10.00 g (0.081 mol) of *o*-fluorobenzaldehyde and 10.54 g (0.162 mol) of potassium cyanide were dissolved in 40 ml of ethanol and cooled on an ice bath while stirring. 40 ml of 10% sulfuric acid solution was added dropwise to ensure that the temperature was kept below 281 K. The mixture was filtered and the solid was washed with ether. The solution was extracted five times with 30 ml portions of ether. The ether extracts were combined and washed with 60 ml of water and dried over magnesium sulfate, filtered evaporated to obtain 10.75 g (0.071 mol, 88%) of crude cyanohydrin.

This material was hydrolysed at room temperature with 50 ml of concentrated hydrochloric acid for 19 h without stirring. The resulting crude acid was suspended in 80 ml of water. After steam distillation the acid was retrieved by extracting with 40 ml portions of ether five times. The ether extracts were dried over magnesium sulfate, filtered and evaporated to obtain 11.77 g (0.069 mol, 85%) of crude *o*-fluoromandelic acid, which was recrystallized from chloroform (250 ml). The solution was left to cool slowly to room temperature. Filtering after 12 h gave 7.08 g (0.042 mol, 52%) of the pure acid. The colourless needle-like crystals obtained were of a suitably quality for single-crystal X-ray diffraction work. (Found: C, 56.43; H, 4.14. Calculated: C, 56.48; H, 4.15.)

m- and p-Fluoromandelic acids

These were prepared following the same method as described above. For *m*-fluoromandelic acid the starting materials were in the same quantities as for the *ortho* compound. The yield of the crude *m*-fluoromandelic acid was 12.10 g (0.071 mol, 88%). Crystals (silky needles) suitable for the X-ray diffraction study could not be obtained from chloroform but by recrystallization from a 3:1 chloroform–*n*-heptane mixture. (Found: C, 56.50; H, 4.13. Calculated: C, 56.48; H, 4.15.) *p*-Fluoromandelic acid was obtained from a reaction of 7.10 g (0.057 mol) of *p*-fluorobenzaldehyde and 7.89 g (0.121 mol) of potassium cyanide. The yield of the crude acid was 6.37 g (0.037 mol, 65%). Like the *meta*-substituted acid, *p*-fluoromandelic acid had to be recrystallized in microtubes from a 3:1 chloroform–*n*-heptane mixture in order to obtain colourless crystal needles of a sufficient quality for the diffraction study. (Found: C, 56.60; H, 4.16. Calculated: C, 56.48; H, 4.15.)

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 heating rates of 0.5, 2, 5 and 10 K min^{-1} were used. The mass of the samples was between 0.700 and 5.200 mg, measured with a precision of 0.001 mg. The error of the melting-point determination is ±0.5 K. The heat of fusion could be determined with a reproducibility of 5%. Thermogravimetric measurements on the samples showed that they do not decompose in the temperature range investigated.

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

Formula		$C_8H_7FO_3$	
M_r		170.14	
Radiation		Cu $K\alpha$ (λ = 1.54184 Å)	
Temperature (K)		122 (1)	
	ortho	*meta*	*para*
Space group	$P2_1/c$	$P2_1/a$	$Pbca$
a (Å)	8.4238 (12)	10.8657 (14)	9.4685 (9)
b (Å)	5.4766 (7)	9.2663 (10)	16.497 (2)
c (Å)	15.959 (2)	15.722 (2)	9.7677 (8)
β (°)	95.962 (11)	107.474 (10)	—
V (Å^3)	732.3 (3)	1509.9 (6)	1525.7 (5)
Z	4	8	8
$F(000)$	352	704	704
Crystal size (mm)	0.05 × 0.17 × 0.40	0.15 × 0.15 × 0.40	0.12 × 0.45 × 0.25
D_x (g cm^{-3})	1.543	1.497	1.481
μ (cm^{-1})	11.25	10.92	10.80
Reflections used in determination of cell parameters	13	18	18
θ range (°)	33–46	36–46	38–43
Scan type	ω–2θ	ω–2θ	ω–2θ
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.626	0.626	0.626
Standard reflections	(200) (004) (020)	(210) (202) (020)	(210) (10$\bar{2}$) (020)
Max. variation of intensity control reflections (%)	20	10	15
Range of h	−10–4	0–13	0–11
Range of k	−6–6	0–11	0–20
Range of l	−19–19	−18–18	−12–12
R_{int}	0.034	0.026	0.034
No. of measured reflections including standard reflections	4724	5961	3513
No. of unique reflections	1511	3106	1563
No. of contributing reflections $[\|F\|^2 > 3\sigma(\|F\|^2)]$	1357	2977	1489
No. of variables	130	259	130
w^{-1}	$\sigma^2_{cs}(F)$ $+ 0.00625F^2$	$\sigma^2_{cs}(F)$ $+ 0.004F^2$	$\sigma^2_{cs}(F)$ $+ 0.004F^2$
$S = [\sum w\Delta F^2/(n-m)]^{1/2}$	2.20	3.85	3.38
Max. shift/e.s.d.	0.02	0.00	0.00
Max. and min. $\Delta\rho$ (e Å^{-3})	0.36, −0.31	0.26, −0.53	0.29, −0.34
R	0.040	0.048	0.042
wR	0.063	0.084	0.074

NMR spectroscopy

The ^{13}C NMR spectra were recorded at 298 K using a Varian Unity 400 spectrometer. The concentration of the solutions was in all cases 100 mg in 500 µl of dimethyl sulfoxide. The line broadening was 3.0 Hz. The signals of the C atoms in the phenyl rings appear as doublets because of coupling with fluorine. The ^{13}C NMR spectra of all three compounds can be assigned using the chemical shifts and the coupling constants of CH_2OH and F substituents. The labelling of the atoms refers to Fig. 2. It was not possible to assign the signals arising from C6 and C8 in *o*-fluoromandelic acid and from C4 and C6 in the *m*-fluoromandelic acid unambiguously.

o-Fluoromandelic acid. 66.446 (C2); 115.155, 115.368 (C5); 124.364, 124.395 (C7); 127.558, 127.702 (C3); 128.848, 128.878 and 129.735, 129.819 (C6 and C8); 158.395, 160.837 (C4); 173.293 (C1).

m-Fluoromandelic acid. 71.794 (C2); 113.152, 113.372 and 114.313, 114.526 (C4 and C6); 122.665, 122.688 (C8); 130.077, 130.160 (C7); 143.064, 143.132 (C3); 160.814, 163.234 (C5); 173.581 (C1).

p-Fluoromandelic acid. 71.711 (C2); 114.844, 115.057 (C5 and C7); 128.612, 128.688 (C4 and C8); 136.509, 136.532 (C3); 160.458, 162.878 (C6); 173.983 (C1).

X-ray crystallography

Powder diffraction diagrams were recorded at ambient temperature for *m*-fluoromandelic acid with a Guinier Hägg type camera using graphite-monochromated Cu $K\alpha$ radiation and Si as an internal standard. The program *LAZY-PULVERIX* (Yvon, Jeitschko & Parthé, 1977) was used to predict the powder diffraction diagrams based on results from the single-crystal studies.

Structure determinations

The structure determinations for the three compounds were conducted in an almost identical way. The compounds were characterized by room temperature Weissenberg and precession photographs. The space groups were determined from 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 centimetres above the crystal in the exhaust pipe. It remained constant within 1 K during the experiments. The different experimental conditions with a summary information of the data reduction and refinement results are presented in Table 1. An analysis of reflection profiles provided the basis for the selection of scan mode and scan interval for the data collection. The intensities of three 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 systematic variations for all three compounds. In the data reduction performed with the *DREADD* data-reduction package (Blessing, 1987), corrections were only made for these variations, Lorentz, polarization and background effects, as the effect of absorption was considered to be marginal. Reflections related by the symmetry of the crystal class were averaged.

The structures were solved by direct methods *SHELXS*86 (Sheldrick, 1990) and refined by full-matrix least squares, minimizing $\sum w(|F_o| - |F_c|)^2$ using the *SDP* program system (Enraf–Nonius, 1985). Scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV) and used as contained in the program. After anisotropic displacement parameters were introduced for the non-H atoms, the difference Fourier map showed the positions for all the H atoms in the three structures. Their positional parameters were included in the refinements using a fixed isotropic displacement parameter of 3.0 Å^2. The final fractional coordinates are listed in Tables 2–4.* The final residual electron-density maps were featureless. Inspection of the structure-factor listings showed that no correction for extinction was required.

Theoretical calculations

Mopac 6.0 PM3 calculations were performed for molecules of the three monofluoro-substituted mandelic acids using the *Insight*II program package (Biosym Technologies, 1992) implemented on a Silicon Graphics Personal Iris computer. The geometries used were those from the structure determination for the non-H atoms. The positions for the H atoms were generated. Calculations were carried out for both conformations of the *m*-fluoromandelic acid observed in the crystal.

Results and discussion

Thermodynamic properties of racemic o-, m- and p-fluoromandelic acids

The thermodynamic properties of the three monofluoro-substituted mandelic acids have been described by Collet & Jacques (1973) and by Compere (1968). The results from our measurements are listed in Table 5. According to Collet & Jacques (1973), *o*-fluoromandelic acid exists as two (or more) polymorphic modifications, the more stable having a melting point of 390 K and a heat of fusion of 30.1 kJ mol^{-1}. Our preparation of *o*-fluoromandelic acid gave a homogenous sample. The melting point, 388.3 (5) K and the heat of fusion, 31 (2) kJ mol^{-1}, listed in Table 5 are within experimental error, in agreement with the values reported by Collet & Jacques (1973) and Compere (1968), but it should be stressed that we have only found one modification.

m-Fluoromandelic acid has also been reported to exist in different polymorphic modifications. According to Collet & Jacques (1973), the most stable modification should melt at 370 K with a corresponding heat of fusion of 24.7 kJ mol^{-1}. We have examined the thermal behaviour of *m*-fluoromandelic acid and a summary of our results is illustrated by the DSC curves shown in Fig. 1. Heating of the crystalline sample obtained from the reaction at moderately fast heating rates (5, 10 and 20 K min^{-1}) produces the middle curve (2) of the figure. It shows that the compound undergoes a phase transition between 369 and 371 K, melting, followed by recrys-

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* Lists of structure factors, anisotropic displacement parameters and H-atom parameters have been deposited at the British Library Document Supply Centre as Supplementary Publication No. SUP 71749 (72 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AB0316]

Table 2. *Positional parameters and equivalent isotropic displacement parameters, U_{eq}, for o-fluoromandelic acid*

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

	x	y	z	U_{eq} (Å^2)
F	0.77191 (9)	0.1993 (1)	0.44286 (5)	0.0338 (2)
O1	0.6111 (1)	0.7263 (2)	0.49464 (5)	0.0231 (2)
O2	0.46202 (9)	0.9425 (2)	0.39646 (5)	0.0229 (3)
O3	0.5256 (1)	0.6516 (2)	0.27486 (5)	0.0263 (3)
C1	0.5485 (1)	0.7691 (2)	0.41776 (7)	0.0195 (3)
C2	0.5945 (1)	0.5791 (2)	0.35511 (7)	0.0214 (3)
C3	0.7751 (1)	0.5571 (2)	0.36052 (7)	0.0206 (3)
C4	0.8567 (1)	0.3681 (2)	0.40395 (7)	0.0222 (3)
C5	1.0202 (2)	0.3443 (3)	0.41058 (8)	0.0265 (3)
C6	1.1076 (1)	0.5215 (3)	0.37231 (8)	0.0277 (3)
C7	1.0307 (2)	0.7134 (3)	0.32885 (8)	0.0284 (3)
C8	0.8653 (2)	0.7306 (2)	0.32302 (8)	0.0256 (3)

Table 3. *Positional parameters and equivalent isotropic displacement parameters, U_{eq}, for m-fluoromandelic acid*

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

	x	y	z	U_{eq} (Å^2)
F1*A*	0.2240 (1)	0.5784 (1)	0.06222 (6)	0.0502 (3)
O1*A*	0.41198 (9)	0.9553 (1)	0.39624 (6)	0.0262 (3)
O2*A*	0.29823 (8)	0.7695 (1)	0.42509 (5)	0.0220 (3)
O3*A*	0.45870 (8)	0.57949 (9)	0.39100 (6)	0.0213 (3)
C1*A*	0.3841 (1)	0.8163 (1)	0.39872 (7)	0.0174 (3)
C2*A*	0.4725 (1)	0.7222 (1)	0.36334 (7)	0.0172 (3)
C3*A*	0.4377 (1)	0.7371 (1)	0.26265 (7)	0.0187 (3)
C4*A*	0.3434 (1)	0.6477 (1)	0.20689 (8)	0.0244 (3)
C5*A*	0.3146 (1)	0.6668 (2)	0.11616 (8)	0.0295 (3)
C6*A*	0.3726 (1)	0.7687 (2)	0.07745 (8)	0.0336 (4)
C7*A*	0.4652 (2)	0.8564 (2)	0.13321 (9)	0.0374 (4)
C8*A*	0.4988 (1)	0.8404 (2)	0.22573 (8)	0.0293 (3)
F1*B*	0.86614 (9)	1.0066 (1)	0.89938 (5)	0.0512 (3)
O1*B*	0.75464 (8)	0.55604 (9)	0.62301 (6)	0.0242 (3)
O2*B*	0.62561 (8)	0.74651 (9)	0.57163 (6)	0.0223 (3)
O3*B*	0.82613 (8)	0.91534 (9)	0.57319 (5)	0.0199 (2)
C1*B*	0.7317 (1)	0.6931 (1)	0.60112 (7)	0.0171 (3)
C2*B*	0.8561 (1)	0.7792 (1)	0.61834 (7)	0.0167 (3)
C3*B*	0.9165 (1)	0.8039 (1)	0.71707 (7)	0.0184 (3)
C4*B*	0.8627 (1)	0.9009 (1)	0.76328 (8)	0.0239 (3)
C5*B*	0.9195 (1)	0.9141 (2)	0.85408 (8)	0.0280 (3)
C6*B*	1.0266 (1)	0.8365 (2)	0.90101 (8)	0.0315 (4)
C7*B*	1.0790 (2)	0.7407 (2)	0.85366 (9)	0.0342 (4)
C8*B*	1.0251 (1)	0.7245 (2)	0.76237 (8)	0.0271 (3)

Table 4. *Positional parameters and equivalent isotropic displacement parameters, U_{eq}, for p-fluoromandelic acid*

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

	x	y	z	U_{eq} (Å^2)
F	0.36237 (9)	0.89758 (4)	0.6521 (1)	0.0262 (3)
O1	0.14121 (8)	0.54982 (5)	0.44023 (7)	0.0237 (2)
O2	0.34652 (8)	0.48198 (5)	0.43553 (8)	0.0261 (2)
O3	0.39993 (9)	0.52051 (5)	0.70147 (8)	0.0234 (2)
C1	0.2622 (1)	0.52604 (6)	0.4932 (1)	0.0198 (3)
C2	0.2849 (1)	0.55995 (6)	0.63577 (9)	0.0200 (3)
C3	0.3031 (1)	0.65139 (6)	0.6331 (1)	0.0212 (3)
C4	0.2193 (1)	0.69865 (7)	0.7182 (1)	0.0296 (3)
C5	0.2373 (2)	0.78243 (7)	0.7243 (1)	0.0344 (3)
C6	0.3408 (1)	0.81616 (7)	0.6429 (1)	0.0285 (3)
C7	0.4245 (1)	0.77189 (7)	0.5553 (1)	0.0289 (3)
C8	0.4049 (1)	0.68797 (7)	0.5510 (1)	0.0267 (3)

Table 5. *Thermodynamic data for the o-, m- and p-fluoromandelic acid determined from DSC measurements*

	ortho	*meta*		*para*
		(I)	(II)	
Melting point, T_f (K)	388.3 (5)	368.4 (5)	376.8 (5)	408.9 (5)
$\Delta H_{\mathrm{fus}}(T_f)$ (kJ mol^{-1})	31 (2)	21 (2)	23 (2)	30 (2)
$\Delta S_{\mathrm{fus}}(T_f)$ (J K^{-1} mol^{-1})	79 (2)	57 (2)	60 (2)	73 (2)

Notes: The heating rate was 5 K min^{-1}, the sample mass varied between 4.372 and 4.876 mg, it was 0.586 mg for the lower melting modification of *m*-fluoromandelic acid.

tallization, before the real melting takes place. This can also be detected by direct inspection of the crystals in a microscope with a hot stage. With lower heating rates (0.5 K min^{-1}) the DSC curve is smooth in this temperature range showing a gradual phase transition. The original sample was also examined by powder diffraction, the diagram obtained was in agreement with that calculated from the single crystal data (Yvon, Jeitschko & Parthé, 1974). It appears that our preparation results in a homogeneous *m*-fluoromandelic acid sample consisting of one modification (I).

The modification stable at high temperature (II) has been obtained by heating the sample to 371 K. The powder-diffraction pattern of this material is different from that obtained from the starting material. The DSC curve (3) of this material shows that it has a melting point of 376.8 (5) K, with a heat of fusion of 23 (2) kJ mol^{-1}. This modification stable at high temperature (II) has been obtained by heating the sample to 371 K. The powder-diffraction pattern of this material is different from that obtained from the starting material. The DSC curve (3) of this material shows that it has a melting point of 376.8 (5) K with a heat of fusion of 23 (2) kJ mol^{-1}. This modification can also be obtained at room temperature from a chloroform solution of *m*-fluoromandelic acid by seeding with a small amount of the high-temperature modification. Unfortunately, we were unable to obtain crystals of the high-temperature modification of a suitable quality for a crystal structure determination.

By rapid cooling of the melt a powdered material was obtained. The DSC curve for this sample is shown as curve 1 in Fig. 1. It is obviously different from the trace (curve 3) of the high-temperature modification (II). It has a powder-diffraction diagram that is identical to that of the original sample, which indicates that it is the material studied by single-crystal diffraction. From these results we conclude that the modification of *m*-fluoromandelic acid obtained by the preparation has a melting point of 368.4 (5) K and $\Delta H^{\ominus}_{\mathrm{fus}} = 21$ (2) kJ mol^{-1}.

Based on these observations we conclude that the lower melting modification (I) is a form of *m*-

fluoromandelic acid that is metastable in the temperature range 163–368 K. In support of this is not only its lower melting point, but the fact that it crystallizes from the melt [the 'law of successive reactions' by Ostwald] (Findlay, 1951) and that no phase transitions are observed at low heating rates between 163 and 368 K.

From the present results we are not able to decide whether the phase transformation is monotropic or enantiotropic (Burger, 1982; Jacques, Collet & Wilen, 1981). However, if the latter is the case, the transition temperature is likely to be below 163 K.

Both the powder-diffraction diagram and the DSC curve indicate that only one modification is obtained for *p*-fluoromandelic acid; it has a melting point of 408.9 (5) K. This value falls between the melting points 411.2–412.7 and 403 K reported for this acid by Compere (1968) and Collet & Jacques (1973). The heat of fusion of 29.3 kJ mol^{-1} reported in the latter paper agrees with the 30 (2) kJ mol^{-1} we find for *p*-fluoromandelic acid.

Comparison of o-, m- and p-fluoromandelic acids

Two crystallographically independent molecules are found in *m*-fluoromandelic acid. As illustrated in Fig. 2 and by the bond lengths, bond and torsion angles listed in Tables 6 and 7, the two independent molecules differ only in the orientation of the phenyl groups: the C1—C2—C3—C4 torsion angle is −87.96 (13) and −72.69 (14)° in the two molecules. The two crystallographically independent molecules are arranged in the crystal so that their phenyl rings are almost coplanar, with an interplanar angle of 9.5 (2)°.

The CO—COO fragment is virtually planar in the *ortho*-substituted acid; the largest deviations from planarity are found in the two *m*-fluoromandelic acids. The O2—C1—C2—O3 torsion angles have values that are in the same range as was found in mandelate salts (Larsen & Lopez de Diego, 1993). As shown in Fig. 2, the fluorine substitution in the *ortho* and *meta* acids occurs at opposite sides of the phenyl group compared with the position of the OH group. The bond angles of the phenyl groups deviate significantly from the idealized value of 120° in all three monofluoro-substituted mandelic acids. These deviations should be due to two substituents, F and CH(OH)COOH. Domenicano & Murray-Rust (1979), amongst others, have shown that the angular deformations of phenyl groups can be described as a sum of the effects of the different substituents. We have investigated if the angles in the phenyl groups can be rationalized along these lines. With the assumption that the CH(OH)COOH moiety has a substituent effect similar to that of a methyl ketone group, the angular deformations given by Domenicano (1992) have been used to calculate the angles in the phenyl rings. The values estimated in this way are identical within experimental error to those found in the three structures.

Comparison of the crystal packing

The crystal structures are strongly influenced by the different intermolecular interactions, which are listed in Table 8 and shown in the stereopairs in Fig. 3. Besides the hydrogen bonds, some very short C···F distances are found which will be discussed later. All possible donor atoms are involved in hydrogen bonds. The three structures, however, display significant differences in their hydrogen-bonding patterns. In *o*-fluoromandelic acid, hydrogen bonds connect the carboxylic acid groups related by inversion symmetry leading to the formation of carboxylic acid dimers with an O1—H···O2 distance

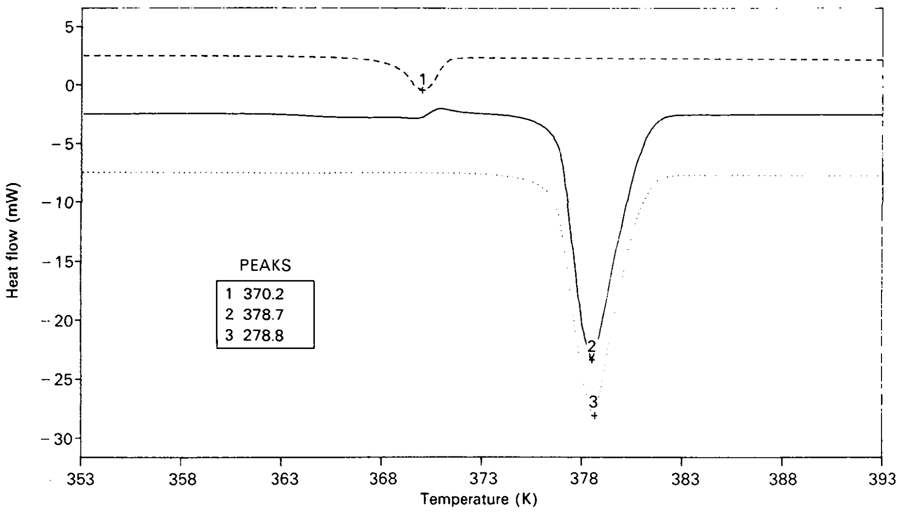
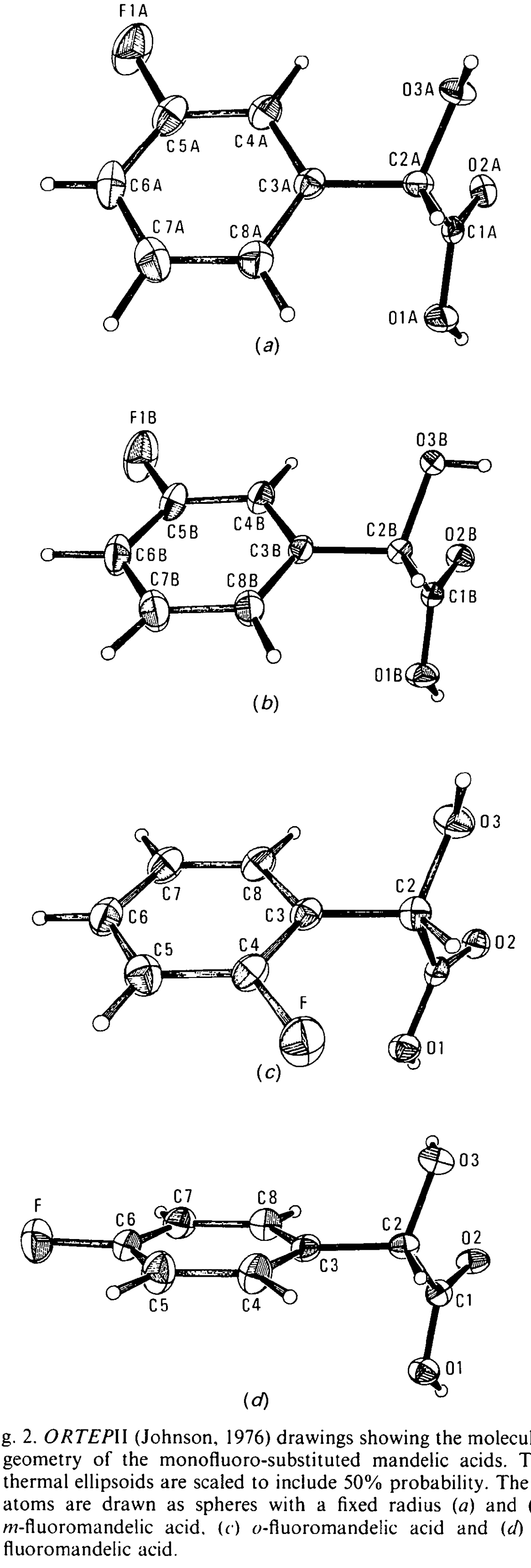


Fig. 1. DSC curves of different samples of *m*-fluoromandelic acid with a heating rate of 5 K min^{-1} in nitrogen gas; sample size: 0.59, 4.89 and 4.90 mg. The continuous curve (2) is of the original sample, the dotted curve (3) is of a sample that has been kept at 371 K for some time and the dashed curve (1) is of a sample that has undergone rapid cooling after melting at 378 K.



(*a*)

(*b*)

(*c*)

(*d*)

Fig. 2. *ORTEP*II (Johnson, 1976) drawings showing the molecular geometry of the monofluoro-substituted mandelic acids. The thermal ellipsoids are scaled to include 50% probability. The H atoms are drawn as spheres with a fixed radius (*a*) and (*b*) *m*-fluoromandelic acid, (*c*) *o*-fluoromandelic acid and (*d*) *p*-fluoromandelic acid.

Table 6. *Bond distances for o-, m- and p-fluoromandelic acid*

		ortho (Å)	*meta A* (Å)	*meta B* (Å)	*para* (Å)
O1	C1	1.3052 (10)	1.3263 (8)	1.3203 (7)	1.3163 (8)
O2	C1	1.2234 (10)	1.2096 (8)	1.2113 (8)	1.2179 (8)
O3	C2	1.4073 (10)	1.4138 (7)	1.4358 (7)	1.4220 (7)
C1	C2	1.5209 (12)	1.5207 (9)	1.5221 (8)	1.5165 (8)
C2	C3	1.5192 (11)	1.5194 (9)	1.5102 (8)	1.5186 (8)
C3	C4	1.3877 (12)	1.4018 (9)	1.3904 (9)	1.3885 (9)
C3	C8	1.3907 (12)	1.3873 (9)	1.3917 (9)	1.3917 (9)
C4	C5	1.3764 (13)	1.3770 (10)	1.3801 (9)	1.3939 (9)
C5	C6	1.3962 (13)	1.3741 (12)	1.3785 (12)	1.3795 (10)
C6	C7	1.3827 (14)	1.3824 (12)	1.3862 (11)	1.3760 (11)
C7	C8	1.3898 (13)	1.3972 (10)	1.3860 (10)	1.3974 (10)
F	C(4,5,6)	1.3573 (10)	1.3633 (9)	1.3512 (8)	1.3614 (8)

Table 7. *Bond and torsion angles for o-, m- and p-fluoromandelic acid*

			ortho (°)	*meta A* (°)	*meta B* (°)	*para* (°)
O1	C1	O2	124.83 (8)	124.36 (6)	125.18 (6)	124.55 (5)
O1	C1	C2	112.93 (7)	111.79 (6)	111.71 (5)	111.97 (5)
O2	C1	C2	122.25 (7)	123.85 (6)	123.11 (6)	123.48 (6)
O3	C2	C1	107.22 (7)	106.65 (5)	108.36 (5)	110.76 (5)
O3	C2	C3	112.94 (7)	112.91 (5)	109.82 (5)	112.03 (5)
C1	C2	C3	109.81 (7)	110.01 (5)	110.55 (5)	111.52 (5)
C2	C3	C4	121.93 (7)	120.29 (6)	120.92 (6)	118.85 (6)
C3	C4	C5	123.29 (8)	117.88 (7)	118.02 (7)	120.84 (6)
C4	C5	C6	118.00 (8)	123.75 (7)	123.45 (7)	117.53 (6)
C5	C6	C7	120.45 (9)	117.77 (7)	117.62 (7)	123.60 (7)
C6	C7	C8	119.96 (9)	120.71 (7)	120.76 (7)	117.92 (6)
C7	C8	C3	120.90 (8)	120.04 (7)	120.16 (7)	120.27 (6)
C8	C3	C4	117.39 (8)	119.84 (6)	119.98 (6)	119.82 (6)
F	C(4,5,6)	C(3,4,5)	118.64 (8)	117.63 (7)	118.15 (7)	117.82 (6)
F	C(4,5,6)	C(5,6,7)	118.07 (8)	118.61 (7)	118.39 (6)	118.57 (6)

				ortho (°)	*meta A* (°)	*meta B* (°)	*para* (°)
O2	C1	C2	O3	2.3 (2)	− 16.18 (14)	− 14.89 (14)	− 12.11 (14)
C1	C2	C3	C4	100.81 (13)	− 87.96 (13)	− 72.69 (14)	127.75 (10)

of 2.6291 (9) Å. The OH group donates its proton to another OH group related by the symmetry of a twofold screw axes.

In *p*-fluoromandelic acid, the carboxylic acid group donates its proton to an OH group, which in turn donates its H atom to another COOH group. This leads to a hydrogen-bonding system that connects the molecules in a three-dimensional zigzag pattern. Compared with the hydrogen bonds observed in the *ortho*-substituted acid, the O1—H1···O3 hydrogen bond is comparable in length to the O1—H1···O2 bond and O3—H3···O2 is significantly shorter than the O1—H3···O3 distance.

A very complicated hydrogen-bonding pattern is found in *m*-fluoromandelic acid. One of the independent molecules (*B*) is involved in hydrogen bonds that resemble those found in the related *para* compound; however, the O1*B*—H1*B*···O3*A* distance is much shorter and the O3*B*—H3*B*···O2*A* distance longer than those found in the *para* compound. The H1*A* atom is involved in bifurcated hydrogen bonds to O2*B* and O3*B* from the same molecule. Although there are interactions between two carboxylic acid groups, they do not lead to the formation of the

Table 8. *Intermolecular interactions* (Å, °) *in o-, m- and p-fluoromandelic acid*

ortho			
D—H···*A*	*D*—*A*	*D*—H—*A*	H—*A*
O1—H1···O2^{i}	2.6291 (9)	168.8 (14)	1.87 (2)
O3—H3···O3^{ii}	2.8711 (4)	149.6 (11)	2.096 (14)
F—C1^{iii}	3.0163 (10)		
meta			
D—H···*A*	*D*—*A*	*D*—H—*A*	H—*A*
O1*A*—H1*A*···O2*B*^{i}	2.8606 (7)	126.9 (9)	2.290 (11)
O1*A*—H1*A*···O3*B*^{i}	3.0182 (7)	150.8 (9)	2.274 (11)
O3*A*—H3*A*···O3*B*^{iv}	2.7030 (7)	173.2 (11)	1.934 (11)
O1*B*—H1*B*···O3*A*^{v}	2.5871 (7)	173.1 (10)	1.720 (11)
O3*B*—H3*B*···O2*A*^{vi}	2.8324 (7)	144.4 (10)	2.149 (10)
para			
D—H···*A*	*D*—*A*	*D*—H—*A*	H—*A*
O1—H1···O3^{vii}	2.6338 (6)	175.1 (10)	1.739 (11)
O3—H3···O2^{v}	2.7488 (7)	164.0 (10)	1.994 (11)
F—C1^{viii}	2.8794 (7)		

Symmetry codes: (i) $1-x, 2-y, 1-z$; (ii) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$; (iii) $x, y-1, z$; (iv) $1.5-x, y-\frac{1}{2}, 1-z$; (v) $1-x, 1-y, 1-z$; (vi) $x+\frac{1}{2}, \frac{3}{2}-y, z$; (vii) $\frac{1}{2}-x, 1-y, z-\frac{1}{2}$; (viii) $\frac{1}{2}-x, \frac{1}{2}+y, z$.

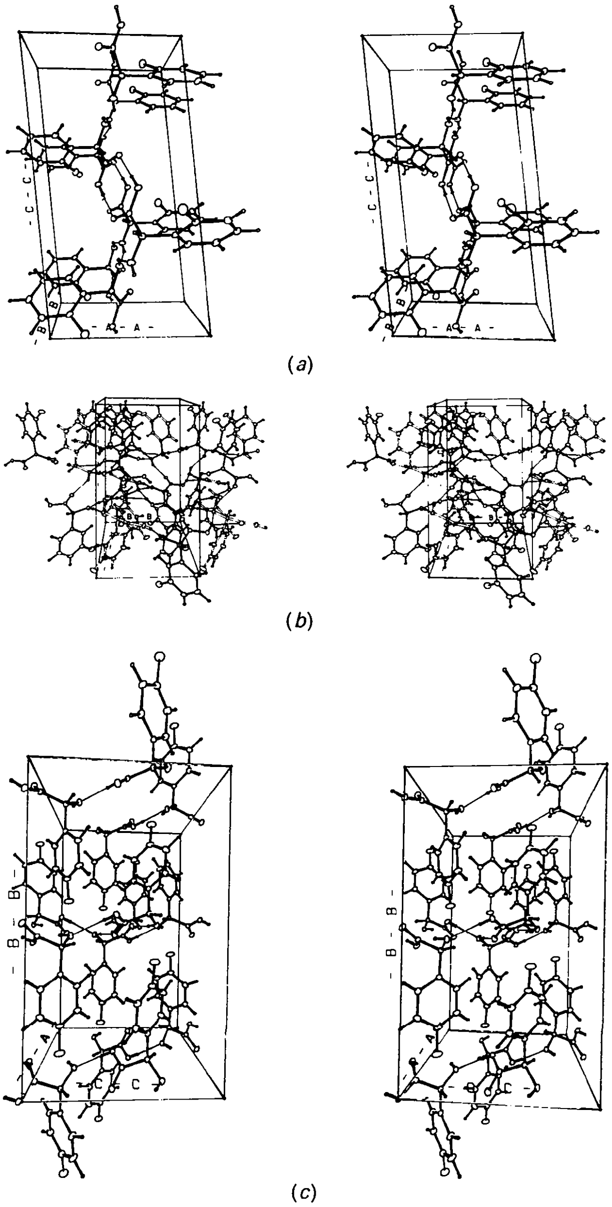
usual carboxylic acid dimer, which was observed in *o*-substituted acid. The hydrogen bonds that connect the OH groups of molecule *A* and *B* are significantly shorter than the equivalents in *o*-fluoromandelic acid. All the hydrogen bonds link the two crystallographically independent molecules. The hydrogen-bond pattern in *m*-fluoromandelic acid contains elements of the hydrogen-bond patterns found in the *ortho* and *para* acids.

Besides the hydrogen bonds, very short C1···F distances are observed in the *ortho*- and *para*-fluorosubstituted mandelic acids. From simple chemical arguments it could be predicted that this C atom has a small positive charge. Thus, these short distances could reflect electrostatic interactions between the electronegative F and the C atom in the COOH group.

An investigation of the carbon–fluorine interactions

The analysis of the crystal packing showed the existence of very short C···F distances, which we interpret as attractive electrostatic interactions between two oppositely charged atoms. To investigate this further, semi-empirical calculations were performed for the four independent molecules. For the *meta*-substituted acid, computations were undertaken for both independent molecules and for the assembly of atoms. For all the systems investigated these calculations estimated the effective charge of fluorine to be −0.10. The C atom of the carboxylic group was in all cases the atom with the largest positive charge, its charge varying from 0.34 in the *ortho*-substituted acid to 0.38 in *p*-fluoromandelic acid. These changes compare well with the values Kubota & Ohba (1992) found in their investigation of the charge distribution in *p*-fluorobenzoic acid, and also support the interpretation of the short C···F distances as a result of an attractive electrostatic interaction.

The difference between the C1···F distance in the *o*- and *p*-fluoromandelic acid is in accordance with the different charges on the C1 atom. Based on the charges on F and C1, one should expect that very



(*a*)

(*b*)

(*c*)

Fig. 3. Stereo pairs illustrating the packing in *o*-, *m*- and *p*-fluoromandelic acids seen along the (*a*) *b*, (*b*) *a* and (*c*) *a* axes, respectively. The hydrogen bonds are shown as thin lines. In *m*-fluoromandelic acid the molecules labelled *B* are drawn with open bonds.

short Cl···F interactions could also occur in *m*-fluoromandelic acid, but they were not observed in the crystal structure. To investigate this further, a search in the CSD (Version 5.04; Allen, Kennard & Taylor, 1983) was made on all the *ortho*-, *meta*- and *para*-monofluoro-substituted phenyl rings. Selecting structures where the intermolecular C···F distances are smaller than 3.1 Å, which is 0.1 Å less than the sum of the van der Waals radii (Bondi, 1964) for C and F, only one compound, tri-*p*-tolylbis(2-fluorophenyl)bismuth (Schmuck, Pyykkö & Seppelt, 1990) was found for the *ortho*-fluoro-substituted phenyl groups. In this structure a distance of 2.97 Å was found between fluorine and a carbon. For the *meta*-fluoro-substituted phenyl rings only one entry with a carbon–fluorine distance of less than 3.1 Å was found. In *N*-(3-fluorophenyl)succinimide (Taira, Takayama & Terada, 1988), F has a distance of 3.07 Å to a C atom in the succinimide ring.

The search on *para*-fluoro-substituted phenyl groups resulted in 23 hits. Omitting disordered structures we found C···F distances less than 3.0 Å in three of the structures. In one of these structures, (4-fluorobenzoyloxymethyl)trifluorosilane (Zel'bst *et al.*, 1981), F has a short intermolecular distance of 2.906 Å to the acetal C atom, which could be expected to have a positive charge. This interaction resembles that observed in *p*-fluoromandelic acid. These results show that although the atomic charges could lead to attractive C···F interactions they are not abundant, and that these interactions appear to be more favourable in *para*-fluoro-substituted phenyl groups.

Relation between thermochemical properties and the crystal stuctures

The crystal structure determinations revealed some significant differences between intermolecular interactions in the three monofluoro-substituted mandelic acids. The thermochemical properties listed in Table 5 show that the *ortho*- and *para*-substituted fluoromandelic acid have similar melting enthalpies and entropies.

These two compounds are also very similar with respect to intermolecular interactions in the crystals. We attribute the slightly higher values for *o*-fluoromandelic acid to the existence of carboxylic acid dimers in this structure.

Both forms of *m*-fluoromandelic acid have very similar but significantly lower melting enthalpies and entropies than the other two compounds. This could indicate that similar intermolecular interactions are found in the two polymorphic modifications. The presence of two molecules in the asymmetric unit and the lack of C···F interactions in *m*-fluoromandelic acid is consistent with its lower melting entropy and enthalpy.

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