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A Study of Two Polymorphic Modifications of (*S*)-1-Phenylethylammonium (*S*)-Mandelate and the Structural Features of Diastereomeric Mandelate Salts

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Abstract

A low-temperature modification of (*S*)-1-phenylethylammonium (*S*)-mandelate has been investigated: $C_8H_{12}N^+.C_8H_7O_3^-$, $M_r = 273.33$, monoclinic, $P2_1$, $a = 8.322$ (4), $b = 6.801$ (2), $c = 12.885$ (3) Å, $\beta = 91.74$ (3)°, $V = 728.9$ (8) Å^3, $Z = 2$, $D_x = 1.245$ g cm^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 6.60$ cm^{-1}, $F(000) = 292$, $T = 122.0$ (5) K, $R = 0.044$ for 1571 observed reflections. In this polymorph both the stereochemistry of the ions and their hydrogen bonding are identical to the orthorhombic modification obtained at 298 K. An analysis of 23 different mandelate stuctures showed the existence of a preferred conformation of the mandelate ion with an almost planar arrangement of the carboxy and the hydroxy groups. The hydrogen bonding in the mandelates is described by graph theory. This shows that, although a single common motif is not observed in all the mandelate structures, chains of hydrogen bonds are found in all the mandelates of primary and secondary amines.

Introduction

A very common method of separating a racemic mixture into its enantiomers is through the formation of diastereomeric compounds by reaction with an optically active compound. If the difference in their solubilities is sufficiently large, a separation of the enantiomers may be achieved. For an understanding of the differences between the physicochemical properties of the diastereomeric salts, knowledge of their crystal structure is of great significance. As for other compounds, different polymorphic modifications may exist for the diastereomeric salts. Interactions between chiral molecules should be common in polymorphic structures and it seems plausible that the structural differences between polymorphic modifications are related to differences in the interactions between chiral entities.

Mandelic acid is widely used as a resolving agent for the resolution of racemic amines and has been used to resolve 1-phenylethylamine (Larsen & Lopez de Diego, 1992). In our investigations of the dia-

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stereomeric salts formed between 1-phenylethylamine and mandelic acid, we isolated a salt which appeared to be a polymorphic modification of the less soluble diasteromeric salt (*S*)-1-phenylethylammonium (*S*)-mandelate. This salt has previously been structurally characterized by Brianso, Leclercq & Jacques (1979). They found that (*S*)-1-phenylethylammonium (*S*)-mandelate crystallizes in the orthorhombic space group $P2_12_12_1$. The modification we obtained by crystallization at 278 K crystallizes in the monoclinic space group $P2_1$. A crystal structure determination was made for the latter polymorph in order to be able to compare the two modifications. The difference in thermochemical stability between polymorphs or diastereomeric salts containing chemically identical entities could be caused by differences in conformational energy of the entities forming the crystal, differences in the intermolecular interactions or a combination of both of these factors.

The present paper includes a study of the structural features of diasteromeric mandelate salts. Some of the interactions between the chiral ions are through hydrogen bonds. In hydrogen tartrate salts the stereochemistry of the hydrogen tartrate ion is virtually invariant and common features are observed in the patterns of hydrogen bonds (Larsen, Andersen & Dam, 1990). To determine if the diastereomeric mandelate structures exhibit similar features, an analysis was made of the hydrogen-bond patterns in mandelate structures. The graph-set analysis of the hydrogen-bond patterns described recently by Etter, MacDonald & Bernstein (1990) was found to be suitable and therefore employed for the comparative study of hydrogen bonding in mandelates. In order to compare the conformation of the mandelate ions in the salts, the torsion angles involving the carboxylate and hydroxy groups are examined and related to variations in energy found by force-field calculations.

Experimental

Crystals of (*S*)-1-phenylethylammonium (*S*)-mandelate were precipitated at 278 K from an aqueous solution which contained equivalent molar amounts of (*S*)-1-phenylethylamine and (*S*)-mandelic acid. A few very large colourless prismatic crystals were formed after slow evaporation. They were recrystallized from water at 278 K and removed from the solvent when they had reached a size suitable for X-ray diffraction. If the crystals were recrystallized from water at room temperature their Weissenberg photographs showed that they belonged to the orthorhombic space group $P2_12_12_1$ and had cell dimensions identical to those reported by Brianso, Leclercq & Jacques (1979). Similar recrystallizations from ethanol gave the monoclinic crystals at 278 K and the orthorhombic modification at room temperature.

The crystal used for the diffractometer measurements had dimensions $0.1 \times 0.1 \times 0.4$ mm^3. The data collection was performed at 122 K using an Enraf–Nonius CAD-4 diffractometer with graphite-monochromatized Cu $K\alpha$ radiation, $\lambda = 1.5418$ Å. An Enraf–Nonius gas-flow low-temperature device was used to cool the crystal. The temperature was monitored with a thermocouple in the exhaust pipe; it was constant to within 0.5 K. Intensities were measured using the ω–2θ scan mode, $\Delta\omega = 1.5° + (0.15\tan\theta)°$; the maximum scan time was 120 s. Unit-cell dimensions were determined from a least-squares refinement of 18 reflections with $33 < \theta < 45°$. The orientation of the crystal was checked after every 300 reflections. Remeasurement of the reflections 112, 200 and 001 every 10 000 s showed no significant decrease in intensity. The reflections were measured in the range $0 < h < 10$, $0 < k < 8$, $-16 < l < 16$; the maximum $(\sin\theta)/\lambda$ was 0.626 Å^{-1}. Data reduction included corrections for Lorentz, polarization and background effects, as no correction for absorption or decay was necessary. The symmetry-equivalent reflections were averaged corresponding to the crystal class, $R_{\text{int}} = 0.032$. Of the 1638 unique reflections, 1571 were considered observed $(|F^2| > 3\sigma|F^2|)$. The structure was solved by direct methods using the program *SHELXS86* (Sheldrick, 1990) and refined using the full-matrix least-squares method minimizing $\sum w(|F_o| - |F_c|)^2$, $w^{-1} = \sigma^2_{\text{cs}}(F) + 0.0004F^2$. The absolute configuration was chosen to be in agreement with the known absolute configuration for (*S*)-mandelic acid. After the introduction of anisotropic displacement parameters into the refinement, a $\Delta\rho$ map showed the positions of all the hydrogen atoms in the structure. The positional parameters for the hydrogen atoms were refined but their isotropic temperature factors were fixed at 2.5 Å^2. The final residuals are $R = 0.044$ and $wR = 0.053$ for 237 parameters, $S = 2.49$ and $(\Delta/\sigma)_{\max} = 0.01$. The final difference Fourier had $(\Delta\rho)_{\max} = 0.322$ and $(\Delta\rho)_{\min} = -0.326$ e Å^{-3}. The fractional coordinates for non-H atoms are listed in Table 1.

All calculations except the structure determination were performed using the Enraf–Nonius structure determination package (*SDP*) program system (Enraf–Nonius, 1985). Scattering factors, including the contributions from anomalous dispersion, were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV).*

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* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55498 (14 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AB0285]

Table 1. *Final fractional coordinates and equivalent isotropic thermal parameters*

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

	x	y	z	U_{eq} (Å^2)
Mandelate ion				
O(1)	0.6668 (2)	0.7134 (2)	0.4740 (1)	0.0241 (3)
O(2)	0.7907 (2)	1.000	0.50337 (9)	0.0229 (3)
C(1)	0.7824 (2)	0.8282 (3)	0.4655 (1)	0.0199 (4)
C(2)	0.9293 (2)	0.7649 (3)	0.4041 (1)	0.0208 (4)
O(3)	0.9240 (2)	0.5588 (2)	0.3832 (1)	0.0267 (3)
C(3)	0.9377 (2)	0.8835 (3)	0.3043 (1)	0.0219 (4)
C(4)	1.0259 (2)	1.0566 (4)	0.3018 (1)	0.0280 (4)
C(5)	1.0355 (3)	1.1641 (4)	0.2099 (2)	0.0353 (5)
C(6)	0.9564 (3)	1.0967 (4)	0.1202 (2)	0.0363 (5)
C(7)	0.8670 (3)	0.9250 (4)	0.1226 (2)	0.0350 (5)
C(8)	0.8582 (2)	0.8177 (3)	0.2144 (1)	0.0275 (4)
1-Phenylethylammonium ion				
N	0.6104 (2)	0.3151 (3)	0.4165 (1)	0.0206 (3)
C(9)	0.5046 (2)	0.0661 (3)	0.2930 (1)	0.0262 (4)
C(10)	0.5974 (2)	0.2587 (3)	0.3037 (1)	0.0206 (4)
C(11)	0.5179 (2)	0.4170 (3)	0.2385 (1)	0.0204 (4)
C(12)	0.5714 (2)	0.4486 (3)	0.1381 (1)	0.0266 (4)
C(13)	0.4919 (3)	0.5803 (4)	0.0718 (1)	0.0313 (5)
C(14)	0.3588 (3)	0.6813 (3)	0.1045 (1)	0.0282 (4)
C(15)	0.3049 (2)	0.6516 (3)	0.2047 (2)	0.0265 (4)
C(16)	0.3840 (2)	0.5203 (3)	0.2708 (1)	0.0247 (4)

Table 2. *Bond lengths* (Å) *and angles* (°) *in the monoclinic modification*

Anion		Cation	
O(1)—C(1)	1.247 (2)	N—C(10)	1.504 (1)
O(2)—C(1)	1.267 (2)	C(9)—C(10)	1.525 (2)
C(1)—C(2)	1.538 (2)	C(10)—C(11)	1.507 (2)
C(2)—O(3)	1.428 (2)	C(11)—C(12)	1.397 (2)
C(2)—C(3)	1.523 (2)	C(11)—C(16)	1.392 (2)
C(3)—C(4)	1.388 (2)	C(12)—C(13)	1.392 (2)
C(3)—C(8)	1.390 (2)	C(13)—C(14)	1.380 (2)
C(4)—C(5)	1.395 (2)	C(14)—C(15)	1.394 (2)
C(5)—C(6)	1.391 (2)	C(15)—C(16)	1.387 (2)
C(6)—C(7)	1.386 (3)		
C(7)—C(8)	1.394 (2)		
O(1)—C(1)—O(2)	125.2 (1)	N—C(10)—C(9)	109.2 (1)
O(1)—C(1)—C(2)	119.9 (1)	N—C(10)—C(11)	112.0 (1)
O(2)—C(1)—C(2)	115.0 (1)	C(9)—C(10)—C(11)	110.5 (1)
C(1)—C(2)—O(3)	110.6 (1)	C(10)—C(11)—C(12)	118.7 (1)
C(1)—C(2)—C(3)	110.1 (1)	C(10)—C(11)—C(16)	122.4 (1)
O(3)—C(2)—C(3)	111.2 (1)	C(12)—C(11)—C(16)	118.7 (1)
C(2)—C(3)—C(4)	120.5 (1)	C(11)—C(12)—C(13)	120.6 (1)
C(2)—C(3)—C(8)	120.0 (1)	C(12)—C(13)—C(14)	120.2 (1)
C(4)—C(3)—C(8)	119.5 (1)	C(13)—C(14)—C(15)	119.7 (1)
C(3)—C(4)—C(5)	120.5 (1)	C(14)—C(15)—C(16)	120.1 (1)
C(4)—C(5)—C(6)	119.6 (2)	C(11)—C(16)—C(15)	120.7 (1)
C(5)—C(6)—C(7)	120.0 (1)		
C(6)—C(7)—C(8)	120.2 (1)		
C(3)—C(8)—C(7)	120.2 (1)		

Table 3. *Comparison of cell parameters and torsion angles in the two polymorphic modifications of* (*S*)-1-*phenylethylammonium* (*S*)-*mandelate*

	Monoclinic	Orthorhombic
Temperature (K)	122	298
Space group	$P2_1$	$P2_12_12_1$
Z	2	4
a (Å)	8.322 (4)	25.602 (7)
b (Å)	6.801 (2)	6.874 (2)
c (Å)	12.885 (3)	8.401 (3)
wR	0.053	0.049
Torsion angles (°)		
O(1)—C(1)—C(2)—O(3)	− 12.4 (2)	− 11.5
O(1)—C(1)—C(2)—C(3)	110.9 (2)	112.4
C(1)—C(2)—C(3)—C(4)	92.1 (2)	92.2
O(3)—C(2)—C(3)—C(4)	− 144.9 (2)	− 144.4
N—C(10)—C(11)—C(12)	144.2 (2)	145.4
C(9)—C(10)—C(11)—C(12)	− 93.8 (2)	− 92.5

Table 4. *Hydrogen-bond geometry for the two modifications* (Å, °)

D—H···A	D—A	H—A	∠DHA
Monoclinic			
N—H(N1)—O(1)	2.844 (2)	1.96 (2)	160 (2)
N—H(N2)—O(1$^{\rm i}$)	2.825 (2)	1.94 (2)	158 (2)
N—H(N3)—O(2$^{\rm ii}$)	2.828 (2)	1.96 (2)	164 (2)
O(3)—H(O3)—O(2$^{\rm iii}$)	2.7790 (14)	2.00 (2)	160 (2)

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

D—H···A	D—A	H—A	∠DHA
Orthorhombic*			
N—H(N1)—O(1)	2.868	1.99	
N—H(N2)—O(1$^{\rm iv}$)	2.833	1.87	
N—H(N3)—O(2$^{\rm v}$)	2.842	1.88	
O3—H(O3)—O(2$^{\rm vi}$)	2.842		

Symmetry code: (iv) $-x$, $\frac{1}{2} + y$, $\frac{1}{2} - z$; (v) x, $1 + y$, z; (vi) $1 - x$, $\frac{1}{2} + y$, $\frac{1}{2} - z$.

* The hydrogen atom of the hydroxy group [H(O3)] was not located in the orthorhombic modification and the coordinates quoted for one of the hydrogen atoms [H(N3)] attached to the ammonium group corresponds to an unrealistic position. This atom was introduced in an idealized position corresponding to an sp^3 hybridization of the N atom.

Results and discussion

Description of the monoclinic modification

The *ORTEP*II (Johnson, 1971) drawings presented in Fig. 1 illustrate the conformation of the two ions and their atomic labelling. The bond lengths and angles in Table 2 agree well with those found in other compounds containing these ions. Some selected torsion angles are given in Table 3. The cation and anion have virtually identical orientations of the phenyl group relative to the other substituents of the asymmetric carbon atom. The small torsion angle O(1)—C(1)—C(2)—O(3) of −12.4° is in accordance with the values found in other mandelate structures (*vide infra*). The packing in the unit cell is illustrated by the stereo drawing in Fig. 2. The hydrogen bonds are described in Table 4. As expected, the two C—O bonds of the carboxylate group are nearly equal. Both O atoms accept protons from the 1-phenylethylammonium ion. The hydrogen bonds between the ions lead to a network parallel to the *ac* plane with the aromatic groups pointing out on both sides of the plane. Hydrogen bonds connect mandelate ions related by the symmetry of the 2_1 axis.

Comparison of the monoclinic and orthorhombic modifications

The crystal structure of the orthorhombic modification at room temperature has been reported by Brianso *et al.* (1979). The torsion angles in Table 3 demonstrate that, within the experimental accuracy, the two polymorphic modifications contain superimposable cations and anions. The oblique angle β is so close to 90° in the monoclinic form that this unit cell deviates only slightly from an orthogonal cell. The cell parameters for the two forms, listed in Table 3, reveal that the unit cells are related in the following way: $a_{\text{ortho}} \simeq 2c_{\text{mono}}$; $b_{\text{ortho}} \simeq b_{\text{mono}}$; $c_{\text{ortho}} \simeq a_{\text{mono}}$. The stereo pairs in Figs. 3 and 4 illustrate the packing in the two polymorphs with the unit cells oriented to display this relation. The two polymorphs have similar hydrogen-bond interactions, as shown in Table 4. The ions are linked through hydrogen bonds in planes perpendicular to the longest axis. The presence of a common hydrogen-bond pattern in the two structures could indicate that similar interactions occur in solution and that crystal nucleation occurs through this common hydrogen-bond pattern. An inspection of the packing diagrams reveals that the ionic arrangement in the centre of the orthorhombic unit cell is identical to the ionic arrangement in the monoclinic cell. The only difference between the crystal packing in the two polymorphs is found in the interactions between the phenyl groups. In the orthorhombic structure a twofold screw axis parallel to the a_{ortho} axis generates the next hydrogen-bonded layer, in the monoclinic cell the hydrogen-bonded layers are generated by the translational symmetry of the c_{mono} axis. A comparison of the arrangements of interacting phenyl groups show that they differ by a 180° rotation. The a_{ortho} axis is significantly shorter than

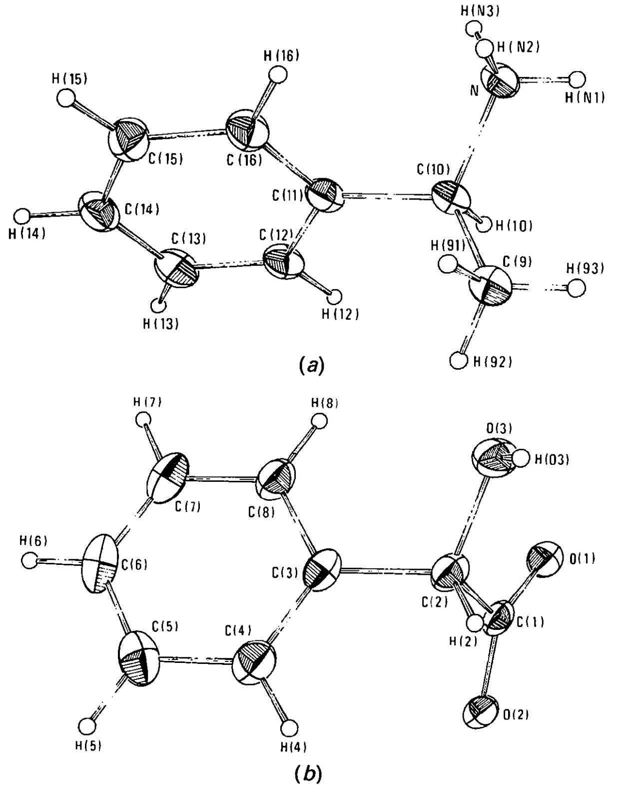

Fig. 1. *ORTEP* (Johnson, 1971) drawings of (*a*) the (*S*)-1-phenylethylammonium and (*b*) the mandelate ions illustrating the atomic numbering scheme. The thermal ellipsoids enclose 50% probability and the H atoms are drawn as spheres with a fixed radius.

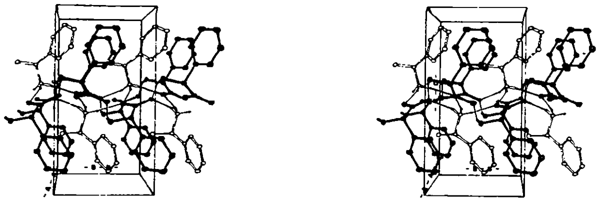

Fig. 2. Stereo drawing of the packing in monoclinic (*S*)-1-phenylethylammonium (*S*)-mandelate seen in the direction of the crystallographic *a* axis. The hydrogen bonds are drawn as thin lines.

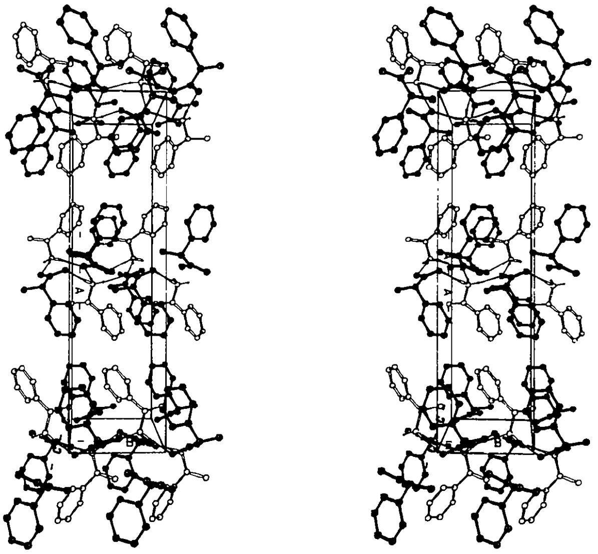

Fig. 3. Stereo drawing of the packing in orthorhombic (*S*)-1-phenylethylammonium (*S*)-mandelate seen in the direction of the crystallographic *c* axis. The hydrogen bonds are drawn as thin lines.

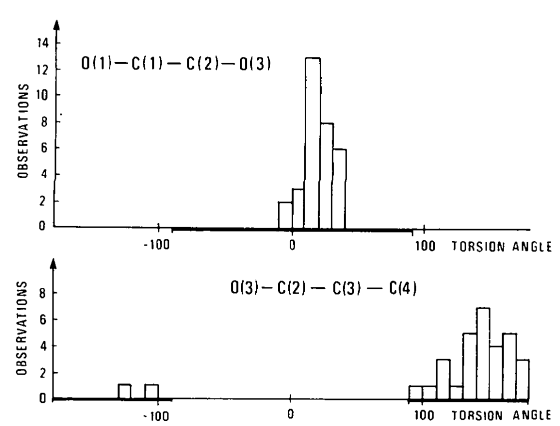

Fig. 4. Histograms showing the distributions of torsion angles in mandelates.

Table 5. *The mandelates examined and the occurrence of graph sets in the hydrogen-bond-patterns; the graph sets for (S)- and racemic mandelic acid are included for comparison*

Refcodes are as in the Cambridge Structural Database (1991).

N type	No.	Mandelate	Refcode/reference	N_1
Tertiary	1	(1*R*,4a*S*,5*R*,9b*S*)-(+)-1-Methyl-5-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine (*R*)-mandelate	FEMLUE	$[D]_2R^2_2(10)$
	2	(1*S*,3*S*)-4-[3-(3,4-Dichlorophenyl)-1-indanyl]-1-methylpiperazinium (*R*)-mandelate	Larsen (1990)	$DC(5)$
	3	(*S*)-Biperidenium (*S*)-mandelate	FAYBOW	$DDS(5)$
	4	1-[(*S*)-1-Cyclohexyl-1-hydroxy-phenylbutyl]piperidinium (*R*)-mandelate	KAMMOA	$DDS(5)$
	5	(−)-(4a*R*,10a*R*)-*trans*-1,2,3,4,4a,5,-10,10a-Octahydro-6-hydroxy-1-*n*-propylbenz[*g*]quinolinium (*R*)-mandelate	SAYPOX	$DDS(5)$
	6	Cinchonine (*S*)-mandelate	Larsen, Lopez de Diego & Kozma (1993)	$DDC(5)$
	7	Cinchonine (*R*)-mandelate	Larsen, Lopez de Diego & Kozma (1993)	$[D]_2C(7)[S(5)]_2$
(+H_2O)	8	(+)-(4a*R*,8a*R*)-2-Methyl-4aβ-(3-methoxyphenyl)-1,2,3,4,4a,5,6-7,8,8aα-decahydroisoquinoline (*R*)-mandelate dihydrate	FUPBUN	$DR^1_2(4)C^2_2(6)S(5)$
Secondary	9	*trans*-(2*R*,5*R*)-2,5-Dimethylpyrrolidinium (*S*)-mandelate	DMPYRM	$C^2_2(6)S(5)$
	10	(+)-(1*S*,2*S*)-*trans*-2-Pyrrolidinyl-*N*-methylcyclohexylammonium (*R*)-mandelate	FOYZUO	$C^3_4(10)DD[S(5)]_2$
	11	*cis*-2-(1-Hydroxy-1-methylethyl)-5-methylpyrrolidinium (*S*)-mandelate	Dahlén, Hjalmarsson, Norin, Csöregh & Ertan (1991)	$C^2_2(6)R^4_4(8)[S(5)]_2$
	12	(1*S*,2*R*)-(+)-Ephedrinium (*S*)-mandelate	DINKUG01	$C^1_2(4)DR^2_2(10)$
	13	(1*S*,2*R*)-(+)-Ephedrinium (*R*)-mandelate	DINLAN	$C^1_2(4)DC(5)$
	14	(1*R*,2*R*)-(−)-Pseudoephedrinium (*R*)-mandelate	GAJPIQ	$C^2_2(6)DS(5)$
	15	(1*S*,2*S*)-(+)-Pseudoephedrinium (*R*)-mandelate	GAJPOW	$C^1_2(4)DS(5)$
	16	(−)-(3*R*,4*R*)-3-(Propylamino)-6-methoxy-1-benzopyran-4-ol (*S*)-mandelate	KECTOB	$C^2_2(6)DC(5)$
Primary	17	(*S*)-1-Phenylethylammonium (*S*)-mandelate ($P2_1$)	Present investigation	$C^1_2(4)C^2_2(6)[R^3_4(10)]C(5)$
	18	(*S*)-1-Phenylethylammonium (*S*)-mandelate ($P2_12_12_1$)	PEAMAN	$C^1_2(4)C^2_2(6)[R^3_4(10)]C(5)$
	19	2-Hydroxy-2-phenylethylammonium (*R*)-mandelate	Acs, Kozma & Larsen (1992*a*)	$[C^1_2(4)]_2[C^2_2(6)]_4[D]_4[D]_2[S(5)]_2$
	20	(*S*)-2-Hydroxy-1-phenylethylammonium (*R*)-mandelate	Acs, Kozma & Larsen (1992*b*)	$C^1_2(4)[R^2_2(12)]_2D[D]_2[D]_3[D]_4S(5)$
(+$2H_2O$)	21	(*S*)-2-Hydroxy-1-phenylethylammonium (*S*)-mandelate.H_2O	Acs, Kozma & Larsen (1992*b*)	$C^2_2(6)C^3_3(6)DD$
Amidinium	22	(*R*)-*O*-Bromomandelamidinium (*R*)-mandelate	BERVUP	$C^2_2(6)C^2_2(6)DD$
	23	(*S*)-*O*-Bromomandelamidinium (*R*)-mandelate	BERWAW	$C^2_2(6)[R^2_2(8)]C(5)DS(5)$
		(*S*)-Mandelic acid	FEGHAA	$C(5)C(5)$
		Racemic mandelic acid	DLMAND01	$C(5)R^2_2(10)$

the 2 × c_{mono} axis that is measured at low temperature. This could indicate that energetically more favourable interactions between the phenyl groups exist in the orthorhombic modification.

Structural features of mandelates

The following analysis was based on the 23 mandelate structures listed in Table 5. A search in the Cambridge Structural Database (1991) provided information on 15 salts of mandelic acid; Dahlén, Hjalmarsson, Norin, Csöregh & Ertan (1991) have recently published the structure of a mandelate; and seven mandelate structures including the one reported here have been determined by the authors. The atomic numbering scheme of the mandelates corresponds to the one used in Fig. 1(*b*), *e.g.* O(1) is the oxygen atom of the carboxy group with the shortest distance to the hydroxy group and C(4) in the phenyl group is *anti* to O(3). Nine of the mandelate structures were (*S*)-mandelates. They were inverted to make all of the 23 structures salts of the (*R*)-mandelic acid in order to compare the stereochemistry.

Conformation of the mandelate ion

The torsion angles O(1)—C(1)—C(2)—O(3) and O(3)—C(2)—C(3)—C(4) are suitable to use to describe the stereochemistry of the mandelate ions in the salts. The two histograms in Fig. 4 illustrate the relative frequency of these torsion angles at intervals of 10°. The diagrams show that the torsion angle O(1)—C(1)—C(2)—O(3) is observed in the interval from -10 to 40° with preferred conformation between 10 and 20°. This small positive value of the O(1)—C(1)—C(2)—O(3) torsion angle for the (*R*)-mandelate ion gives the related torsion angle O(1)—C(1)—C(2)—C(3) values in the range -80 to 30°, corresponding to an anticlinal conformation. An intramolecular hydrogen bond is often found in mandelates. Inspection of the mandelate structures revealed an intramolecular hydrogen bond in 13 of the salts. The torsion angle O(1)—C(1)—C(2)—O(3) is between 3 and 23° in these systems, except in two cases where the intramolecular hydrogen bond is part of a bifurcated hydrogen bond. As expected the intramolecular hydrogen bond tends to stabilize an almost planar arrangement of the O(1)—C(1)—C(2)—O(3) moiety, but it should be emphasized that in mandelate structures without intramolecular hydrogen bonds the torsion angle O(1)—C(1)—C(2)—O(3) is also small.

The torsion angle O(3)—C(2)—C(3)—C(4), which describes the relative orientation of the phenyl group, displays a much larger variation. In the (*R*)-mandelate ions values are observed between 90 and 180°. The most abundant conformation has the torsion angle O(3)—C(2)—C(3)—C(4) around 150°.

Based on the distribution of the different torsion angles of (*R*)-mandelates one would predict that the preferred (*i.e.* lowest energy) conformation of the (*R*)-mandelate ion has torsion angles O(1)—C(1)—C(2)—O(3) and O(3)—C(1)—C(2)—C(3) of 20 and 150° respectively. The frequency and range of the torsion angles suggest that the value corresponding to the minimum energy of the O(1)—C(1)—C(2)—O(3) angles is better defined than the minimum energy for the O(3)—C(2)—C(3)—C(4) angle. As pointed out by Bürgi & Dunitz (1988), one should not attempt to obtain quantitative energy relationships from a statistical analysis of structural data. To obtain information from another source, empirical force-field calculations were performed for (*R*)-mandelic acid with the program *DISCOVER* (Biosym Technologies Inc., 1990). The calculations showed that (*R*)-mandelic acid has minimum energy when the torsion angles O(1)—C(1)—C(2)—O(3) and O(3)—C(1)—C(2)—C(3) are 40 and 130°, respectively. The torsion angle O(1)—C(1)—C(2)—O(3) is significantly larger than 20°, the size most frequently observed. It is likely that this discrepancy is caused by the fact that the program does not take the intramolecular hydrogen bonding into account. Apart from this, the results from force-field calculations support the conclusions reached from statistical analysis.

Comparison of hydrogen-bond patterns in mandelates

The method based on graph theory described by Etter *et al.* (1990) is very convenient for the comparison of hydrogen-bond patterns. The hydrogen bonds in the structure are firstly classified in types characterized by the donor and acceptor atoms and the chemical functionality of these atoms. For each type a motif is formed by the hydrogen bonds and the covalent bonds linking these in chains and rings in the structure. The motif is described by graph sets $B^a_d(l)$, where B is one of the following letters: C (infinite chain), R (ring), D (definite chain) or S (intramolecular ring), d and a are the numbers of proton donors and acceptors involved and l is the

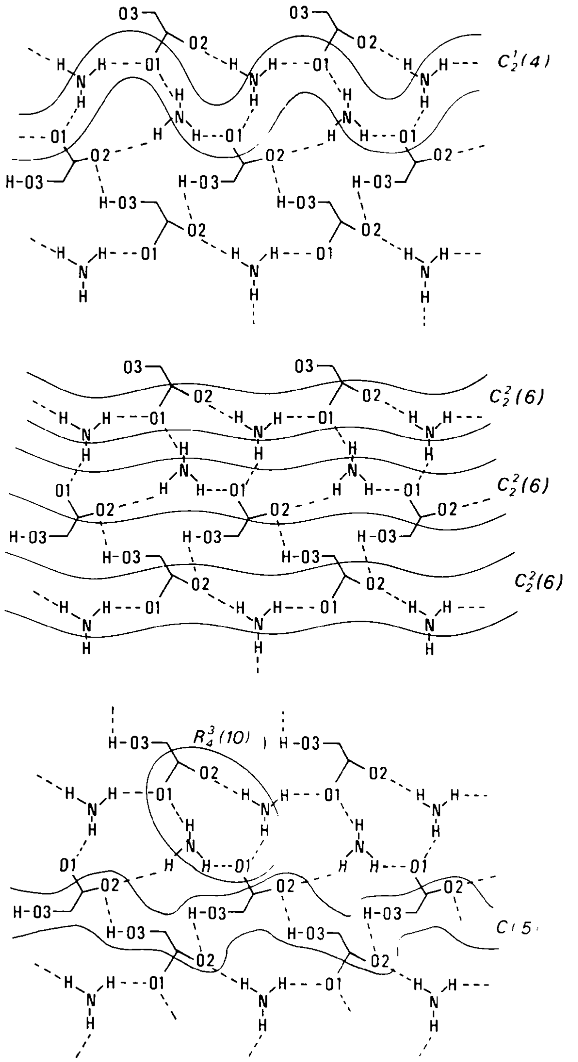

Fig. 5. Illustration of motifs and graph sets in monoclinic and orthorhombic (*S*)-1-phenylethylammonium (*S*)-mandelate. Only the hydrogen-bonding parts of the molecules are drawn, for clarity.

length, defined as the number of bonds if a and d are not written $a = d = 1$. In the case of infinite chains the lengths of the translational units are given. After the assignment of graph sets the total hydrogen-bonded network, N_1, is stated as a series of the graph sets, specifying motifs with N—H— first and O—H— last.

In (*S*)-1-phenylethylammonium (*S*)-mandelate two types of hydrogen bonds are found, N—H···O(carboxylate) and O—H···O(carboxylate). The motif of the first type includes two different infinite chains and a ring. These are illustrated Fig. 5. The second motif is an infinite chain with graph set $C(5)$ and is also illustrated in Fig. 5. The network is $N_1 = C_2^1(4)C_2^2(6)[R_4^3(10)]C(5)$. Similar analyses have been performed on the 23 salts and their graph sets are given in Table 5. The salts are grouped according to the functionality of the base, *e.g.* tertiary, secondary and primary amines and amidines. For comparison the hydrogen-bond patterns in optically active and racemic mandelic acid were also analysed. In both of them a $C(5)$ chain along a 2_1 axis is found. Furthermore an $R_2^2(10)$ ring is found in the racemic mandelic acid. An analysis of the 23 mandelate structures showed that the following graph sets occur frequently: D, $C_2^2(6)$, $C_2^1(4)$, $S(5)$, $C(5)$, $R_2^2(10)$.

The D type corresponds to motifs in which the hydrogen bonds cannot be connected *via* non-hydrogen bonds. If the salts of tertiary amines are excluded, Table 5 shows that the chains $C_2^2(6)$ or $C_2^1(4)$ are found in all but one of the mandelates. In this exception the chain $C_4^3(10)$ occurs which is the sum of the translational units of $C_2^2(6)$ and $C_2^1(4)$. These chains cannot exist in mandelates of a tertiary amine, because only one amine proton is available. The $C_2^2(6)$ motif in mandelate No. 8 is a chain of mandelate ions and water molecules.

Three different motifs are found in the hydrogen bonds between mandelate ions: $S(5)$, $C(5)$, $R_2^2(10)$. They are observed in all but two mandelate structures. There is no indication of systematic behaviour in the occurrences of the three motifs, *e.g.* Nos. 12, 13 and 14 differ from each other only in the chirality of their asymmetric carbon atoms, but the motifs for hydrogen bonds between anions are all different.

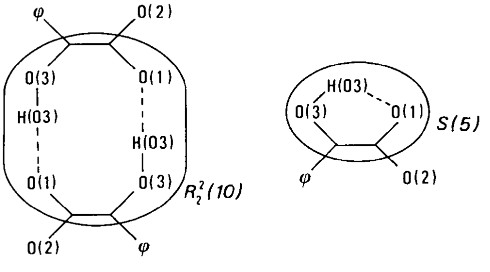

Fig. 6. Illustration of $R_2^2(10)$ and $S(5)$.

The $C(5)$ motif observed in the free mandelic acid is retained in six of the 23 mandelates. It is also found in No. 23, but here the chain goes through the cation. The $R_2^2(10)$ motif occurs twice and the intramolecular ring $S(5)$ is found in 13 mandelates. These two motifs are illustrated in Fig. 6.

As shown in Fig. 4, the torsion angle O(1)—C(1)—C(2)—O(3) is so small in all the examined mandelates that an intramolecular hydrogen bond is possible. The formation of the five-membered ring $S(5)$ would lead to a hydrogen bond where the O—H—O angle is significantly smaller than the one usually observed in hydrogen bonds. In addition, H(O3) appears to have a preference for intermolecular hydrogen bonds, which are generally strong (short, with an O—H—O angle close to 180°). The proton of the hydroxy group is involved in hydrogen bonds in all the mandelates, but the intramolecular hydrogen bond seems only to be formed when this is not at the expense of intermolecular hydrogen bonds. In two of the structures (Nos. 10 and 11) the $S(5)$ form part of a bifurcated hydrogen bond.

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