SHORT PAPER

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Optical resolution of mandelic acid by complexation with *(S)*-(+)-alanine†

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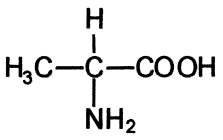
Racemic mandelic acid (**2**) was resolved efficiently by complexation with *(S)*-(+)-alanine (**1**) and the crystal structure of 2:2:1 complex of *(S)*-(+)-alanine (**1**), *(R)*-(-)-mandelic acid (**2**) and H_2O was determined characterizing the hydrogen bond network in the solid state.

Keywords: mandelic acid, (s)-(+)-alanine

Racemic mandelic acid (**2**) has been resolved by diastereomeric salt formation with α-phenylethyl amine[1] or ephedrin.[2] We have now found that *(S)*-(+)-alanine **1** forms a stable inclusion complex with *(R)*-(-)-mandelic acid **2**, and the latter can be resolved efficiently by inclusion crystallisation. For example, when a mixture of *(S)*-(+)-**1** (5.0 g, 0.06 mol) and (±)-**2** (17.0 g, 0.11 mol) was recrystallised from water (20 ml), a 2:2:1 inclusion complex of *(S)*-(+)-**1**, *(R)*-(–)-**2** (30% ee) and H_2O was obtained in 84% yield. After three recrystallisations of the complex from water, a pure inclusion complex of *(S)*-(+)-**1**, *(R)*-(–)-**2** and H_2O was obtained as colourless prisms (5.0 g, m.p. 182–187°C) in 37% yield. Dissolving the pure complex in H_2O (30 ml) and extracting with ether gave *(R)*-(–)-**2** ($[\alpha]_D$ -148.6 (*c* 8.1, H_2O))of 100% ee in 31% yield. The optical purity was determined by comparison with the reported $[\alpha]_D$ value.[1]

The structure analysis showed that two crystallographically independent molecules of **1** and **2** exist together with one water molecule in the unit cell. The molecules of **1a** and **1b** are zwitterionic. The carboxylate groups form intermolecular hydrogen bonds with the carboxyl groups of **2** (**1a**….**2a** = 2.472 (5), **1b**….**2b** = 2.538 (6) Å), respectively (Fig. 1). The hydrogen bonds are significantly shorter than the others found in the crystal (Table 2), formation of discrete molecular complexes of **1**–**2** being suggested.



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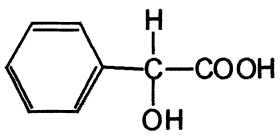

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Table 1 Selected bond lengths (Å)

1a–2a		**1b–2b**	
O1 – C7	1.416 (6)	O6 –C18	1.418 (6)
O2 – C8	1.219 (6)	O7 – C19	1.212 (6)
O3 – C8	1.297 (5)	O8 – C19	1.309 (6)
O4 – C11	1.229 (5)	O9 – C22	1.218 (6)
O5 – C11	1.276 (6)	O10 – C22	1.255 (6)

1a–**2a** and **1b**–**2b** are arranged to form hydrogen bonding networks in different layers alternatively atacked in the *c* direction (Fig. 2). Proton donating and accepting groups lie on one surface (hydrophilic) of the layer and phenyl groups lie on the other surface (hydrophobic). Between the layers, head-to-head or tail-to-tail contacts are found: hydrogen bonding networks are formed on the hydrophilic side, while no contacts shorter than Van der Waals contacts are formed on the hydrophobic side.

Table 2 Hydrogen bonding geometry (Å, °)

D-H…A		D-H	H…A	D…A	D-H…A
O1 – H10	O9i	0.89 (5)	2.15 (5)	2.905 (5)	142 (5)
O1W – H1W	O6ii	0.91 (7)	2.28 (7)	3.033 (6)	140 (5)
O1W – H1W	O7ii	0.91 (7)	2.43 (6)	3.276 (6)	155 (4)
O1W – H1W′	O9i	0.87 (6)	2.20 (7)	2.898 (6)	137 (5)
O3 – H3O	O5	1.21 (6)	1.27 (6)	2.472 (5)	171 (4)
O6 – H6O	O2	0.98 (6)	2.17 (6)	2.841 (6)	124 (3)
O6 – H60	O9i	0.98 (6)	2.50 (6)	3.326 (6)	142 (3)
O8 – H80	O10	0.93 (6)	1.77 (6)	2.538 (6)	138 (4)
N1 – H1N	O1Wiii	0.84 (6)	2.35 (6)	2.957 (7)	130 (4)
N1 – H1N	O2iii	0.84 (6)	2.75 (6)	3.000 (6)	99 (3)
N1 – H1N	O7iii	0.84 (6)	2.37 (6)	3.038 (7)	137 (4)
N1 – H1N′	O5iii	0.80 (5)	2.09 (6)	2.869 (6)	164 (4)
N1 – H1N″	O1iv	0.81 (6)	2.20 (6)	2.863 (6)	139 (4)
N2 – H2N	O6v	0.84 (5)	2.07 (6)	2.894 (6)	167 (4)
N2 – H2N′	O1v	0.99 (5)	2.66 (5)	3.057 (8)	104 (5)
N2 – H2N′	O4ii	0.99 (5)	1.84 (5)	2.791 (6)	160 (4)
N2 – H2N″	O7ii	1.15 (5)	2.44 (5)	3.038 (6)	110 (2)
N2 – H2N″	O10ii	1.15 (5)	1.72 (5)	2.820 (6)	158 (3)

Symmetry code: (i) x, y+1, z; (ii) x-1, y, z; (iii) x+1, y, z; (iv) x+1, y-1, z; (v) x-1, y-1, z

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

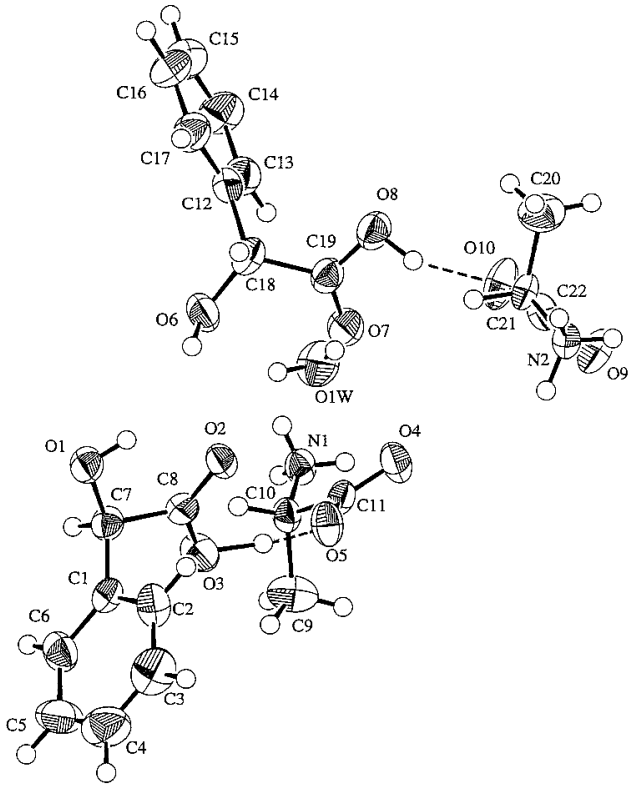

Fig. 1 The molecular structures showing 50% probability displacement ellipsoids and the atom-numbering scheme. Shortest hydrogen bonds are represented by broken lines.

Experimental

Optical resolution of (R)-(-)-mandelic acid ***2*** *by inclusion complexation with (S)-(+)-alanine* ***1***: when a mixture of *(S)*-(+)-**1** (5.0 g, 0.06 mol) and (±)-**2** (17.0 g, 0.11 mol) in water (20 ml) was kept at room temperature for 2 h , a 2:2:1 inclusion complex of *(S)*-(+)-**1**, *(R)*-(–)-**2** (30% ee) and H_2O was obtained as colorless prisms (11.3 g) in 84% yield. After three recrystallisations of the complex from water, a pure inclusion complex of *(S)*-(+)-1, *(R)*-(-)-**2** and H_2O was obtained as colorless prisms (5.0 g, m.p. 182–187°C) in 37% yield. Dissolving the pure complex in H_2O (30 ml) and extracting with ether gave *(R)*-(–)-**2** (2.6 g, $[\alpha]_D$ -148.6 (*c* 8.1, H_2O))of 100% ee in 31% yield. The optical purity was determined by comparison with the reported $[\alpha]_D$ value.[1]

Crystal data of the 2:2:1 complex of (S)-(+)-alanine ***1*** *and (R)-(-)-mandelic acid* ***2*** *and* H_2O: $C_{11}H_{16}NO_{5.5}$, Mr = 250.25, Platelet, colourless, 0.2 x 0.10 x 0.03, Triclinic, P1, a = 6.0200 (5) Å, b = 8.181 (1) Å, c = 12.5380 (8) Å, V = 610.9 (1) Å^3, Dx = 1.360 Mg m^{-3}, Z = 2, μ = 0.109 mm^{-1}, $F(000)$ = 2660, T = 296 (1) K, final R = 0.063, Rw = 0.106 for 349 variables and 1567 reflections with $I > 2\sigma$ (I). The H atoms bound to N or O atoms were located from difference electron density maps and refined on their positional parameters using the reflections in the range of $2\theta < 33°$. All other H atoms were placed in calculated positions and refined using a riding model (C–H = 0.95 Å). H atoms were given isotropic displacement parameters equal to 1.2 times the equivalent isotropic displacement parameters of their bonding atoms. Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (CCDC 166936).

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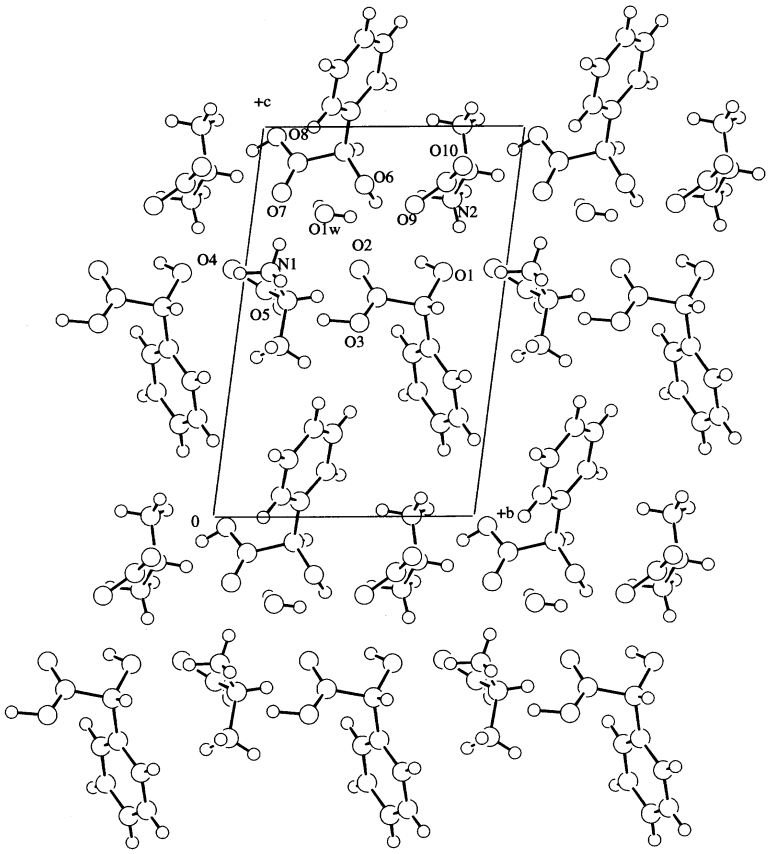

Fig. 2 The crystal packing viewed down *a*-axis. H atoms bound to C atoms are not shown for clarity.