Magnesium Bis[D(-)-Mandelate] Dihydrate and Other Alkaline Earth, Alkali, and Zinc Salts of Mandelic Acid

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Lithium, sodium, potassium, ammonium, magnesium, calcium, strontium, barium, and zinc D(-)-mandelates have been prepared from the parent mandelic acid and equivalent quantities (1:1 / 2:1) of the corresponding metal hydroxides in water. Colourless polycrystalline products are obtained from the aqueous solutions by evaporation of the solvent. The alkali, ammonium and strontium salts are anhydrous, the calcium and barium salts are monohydrates, the magnesium salt is a dihydrate, and the zinc salt a trihydrate. The crystal and molecular structure of the magnesium salt has been determined by single crystal X-ray diffraction methods (monoclinic, space group P2₁, Z = 2). The lattice contains isolated complexes with hexacoordinate magnesium atoms chelated by two mandelate anions through one of their carboxylate oxygen atoms and the alcoholic hydroxyl group. Two water molecules in cis position are completing the octahedral coordination sphere. [Mg₄(C₄H₈O₄)₃(H₂O)₂] is thus a true mononuclear magnesium complex. Its stability and non-hygrosopic properties suggest its use as a magnesium and/or mandelate drug.

Introduction

α-Hydroxy-carboxylic acids play an important role in many biological processes. Lactic (Scheme 1A) and mandelic acid (Scheme 1B) are the most important members of the series. Apart from this biochemical relevance, mandelic acid derivatives are components of a variety of pharmaceutical formulations, mainly as bacteriostatic and bacteriocidal agents for the renal tract and gall bladder, in ophthalmology, and in spasmyloytic or in antirheumatic drugs [1 - 4].

Scheme 1.

In body fluids with neutral or only slightly acidic or basic pH, mandelic acid is present largely in the form of its salts with the ubiquitous alkali or alkaline earth cations [5, 6]. These metals are also held responsible for the transport of carboxylate substrates through membranes and are co-catalysts for their metabolism [7 - 10].

The nature of alkali or alkaline earth mandelate complexes in aqueous solution or in the solid state has not been investigated systematically, and very little is known about the stoichiometry of these salts. Early studies employed electrochemical methods, infrared spectroscopy, elemental and thermal analysis, but no structural studies have been carried out [11 -15].

Following up our investigation of alkali and alkaline earth compounds of amino acids [16], we have now extended our work into the area of the complexes of analogous hydroxy acids. Current studies have also included e. g. beryllium salts of glycolic [17] and salicylic acid [18].

In these beryllium salts the alcoholic and phenolic functions, respectively, become deprotonated under the influence of the high charge concentration of the Be²⁺ dication with its extremely high charge/radius ratio (6.5). The situation is expected to be completely different for the larger magnesium dication with a charge/radius ratio of only 3.1. In order to confirm this assumption we have now
Fig. 1. Molecular structure of the complex Mg(C_{8}H_{7}O_{3})_{2} \cdot 2 \text{H}_{2}\text{O} (5) (ORTEP, 50\% probability ellipsoids).

Selected bond lengths (Å) and angles (°):

\[
\begin{align*}
\text{Mg-02} & : 2.0699(13), \\
\text{Mg-03} & : 2.0479(14), \\
\text{Mg-05} & : 2.0375(13), \\
\text{Mg-06} & : 2.0542(13), \\
\text{Mg-07} & : 2.0191(14), \\
\text{Mg-08} & : 2.0388(14), \\
\text{02-Mg-03} & : 76.30(5), \\
\text{02-Mg-05} & : 93.37(5), \\
\text{02-Mg-07} & : 167.04(6), \\
\text{05-Mg-07} & : 165.98(6), \\
\text{07-Mg-08} & : 89.87(6), \\
\text{07-Mg-08} & : 91.98(6).
\end{align*}
\]

In the present paper we report the isolation and structural study of magnesium bis[D(-)-mandelate] dihydrate as a prototype of this class of compounds. The stoichiometry of a series of related alkali and alkaline earth salts has also been determined, and the compounds have been characterized by NMR spectroscopy.

Results

Alkali and ammonium D(-)-mandelates

Neutralization of D(-)-mandelic acid in desalinated water with lithium, sodium, potassium, or ammonium hydroxide gives colourless aqueous solutions of the products, which can be isolated in quantitative yield by evaporation of the solvent in a vacuum. According to the elemental analyses the salts (1 - 4) are anhydrous. Their melting/decomposition temperatures are above 250°C. The $^1$H and $^{13}$C NMR spectra of the four products in D$_2$O are very similar and are readily assigned to the structural units of mandelate(-1) anions. No single crystals could be grown of any of the salts.

Alkaline earth and zinc bis[D(-)-mandelates]

Treatment of a slurry or solution of the metal bis(hydroxides) with two equivalents of D(-)-mandelic acid in water affords the metal(II) bis(mandelates) 5 - 9 in high yields. Excess of the hydroxide is removed by filtration, and the products are isolated after concentration of the filtrate in a vacuum. The salts are isolated anhydrous (Sr) or as monohydrates (Ca, Ba), dihydrates (Mg) and trihydrates (Zn). The crystal water is lost upon heating, but no melting is observed below 250°C. All compounds are soluble in water and the solutions in D$_2$O show consistent NMR patterns.

Similar experiments with beryllium hydroxide did not yield any well-defined product.

The crystal and molecular structure of magnesium bis[D(-)-mandelate] dihydrate

Slow evaporation of aqueous solutions of the magnesium salt gives single crystals of the dihydrate (monoclinic, space group P2$_1$, Z = 2), the structure of which has been determined by X-ray diffraction methods at -74°C. Crystal, structure solution and refinement data are summarized in the Experimental Section.

The lattice contains independent mononuclear complexes with no crystallographically imposed symmetry (Fig. 1). The magnesium atom is hexa-

### Table I. Selected hydrogen bond lengths [Å] and angles [°] in the crystal lattice of Mg(C$_8$H$_7$O$_3$)$_2 \cdot 2 \text{H}_{2}\text{O} (5).

<table>
<thead>
<tr>
<th>D-H···A</th>
<th>D···A</th>
<th>D-H</th>
<th>H···A</th>
<th>θ (D-H···A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O3-H3···O4</td>
<td>2.650</td>
<td>0.734</td>
<td>1.936</td>
<td>163.9</td>
</tr>
<tr>
<td>O6-H6···O1</td>
<td>2.723</td>
<td>0.812</td>
<td>1.923</td>
<td>168.4</td>
</tr>
<tr>
<td>O7-H71···O2</td>
<td>2.737</td>
<td>0.804</td>
<td>1.935</td>
<td>174.7</td>
</tr>
<tr>
<td>O7-H72···O1</td>
<td>2.793</td>
<td>0.791</td>
<td>2.007</td>
<td>172.3</td>
</tr>
<tr>
<td>O8-H81···O5</td>
<td>2.695</td>
<td>0.823</td>
<td>1.874</td>
<td>175.2</td>
</tr>
<tr>
<td>O8-H82···O2</td>
<td>2.951</td>
<td>0.806</td>
<td>2.211</td>
<td>152.6</td>
</tr>
</tbody>
</table>
coordinated in a strongly distorted octahedral geometry. Two mandelate anions are chelating the metal atom through one of the carboxylate oxygen atoms (O2, O5) and the hydroxyl oxygen atoms (O3, O6). Unlike the carboxylate groups, the alcoholic hydroxyl oxygen atoms are not deprotonated. This result confirms the observation that two equivalents of mandelic acid are required for neutralization of Mg(OH)2. It should be noted that coordination of alcoholic groups is not very common in aqueous coordination chemistry of magnesium.

Two water molecules (O7, O8), in cis position, complete the coordination sphere of the magnesium atom. These water molecules, the alcoholic hydroxyl groups and both carboxylate oxygen atoms are engaged in a hydrogen bonding network which ties the complexes into a two-dimensional framework (Fig. 2). Details of these hydrogen bonds are summarized in Table I. Selected bond angles and lengths are given in the caption to Fig. 1.

Magnesium bis[D(-)-mandelate] dihydrate is a non-hygroscopic complex of magnesium, which has convenient galenic properties. It is one of the few examples where magnesium is fully chelated by biologically relevant ligands. By contrast, in magnesium salicylate, citrate and aspartate, e.g., the ligands are either mono-dentate anions, appear as free carboxylate anions for the [Mg(H2O)6]2+ dication, or form bridges between the metal atoms to generate a coordination polymer, respectively [19]. The compound can be recommended as both a magnesium and a mandelate source in pharmaceutical preparations.

Experimental Section

General: All experiments were carried out in pure, fully desalinated water. Reagents were commercially available and of p.a. grade. Standard equipment and instrumentation was used throughout. Jeol GX400; 1H NMR: internal standard H2O (δ = 4.6 ppm); 13C{1H} NMR: external standard benzene (δ = 128 ppm). Elemental analyses were performed in the microanalytical laboratory of this Institute by standard procedures.

M(C6H7O5) (M = Li, Na, K, NH4):

To a solution of D(-)-mandelic acid (1.52 g, 10.0 mmol) in 10 ml of water MOH (M = Li, Na, K) or a 25% aqueous solution of NH3 in the molar ratio 1:1 is added. The reaction mixture is stirred at room temperature for 2 h and then filtered. The resulting clear solution is concentrated under reduced pressure to a volume of ca. 5 ml. After layering of this aqueous solutions with acetone/ethanol precipitations of white solids can be obtained. The solids are filtered off, dried in vacuo and identified as M(C6H7O5).

Li(C6H7O5) (1): (yield: 1.52 g, 96.2 %, mp. > 250 °C).
C6H7LiO5 (158.08)
Calc C 60.78 H 4.46 %
Found C 60.92 H 4.53 %

1H NMR (D2O, 20 °C): δ = 7.24-7.14, m, br, 5H, Aryl-H;
δ = 4.80, s, 1H, CH(OH); 13C{1H} NMR (D2O, 20 °C):
δ = 178.81, 1C, COO; δ = 140.21, 1C, C-1; δ = 129.01,
2C, C-3/5; δ = 128.51, 1C, C-4; δ = 127.22, 2C, C-2/6;
δ = 74.72, 1C, CH(OH).

Na(C6H7O5) (2): (yield: 1.62 g, 93.0 %, mp. > 250 °C).
C6H7NaO5 (174.05)
Calc C 55.18 H 4.05 %
Found C 54.13 H 3.92 %

1H NMR (D2O, 20 °C): δ = 7.47-7.38, m, br, 5H, Aryl-H;
δ = 4.99, s, 1H, CH(OH); 13C{1H} NMR (D2O, 20 °C):
δ = 179.55, 1C, COO; δ = 140.65, 1C, C-1; δ = 129.91,
2C, C-3/5; δ = 128.30, 1C, C-4; δ = 127.18, 2C, C-2/6;
δ = 75.11, 1C, CH(OH).

K(C6H7O5) (3): (yield: 1.81 g, 95.1 %, mp. > 250 °C).
C6H7K2O5 (190.24)
Calc C 50.51 H 3.71 %
Found C 51.08 H 4.03 %

1H NMR (D2O, 20 °C): δ = 7.29-7.23, m, br, 5H, Aryl-H;
δ = 4.86, s, 1H, CH(OH); 13C{1H} NMR (D2O, 20 °C):
δ = 179.12, 1C, COO; δ = 140.07, 1C, C-1; δ = 129.07,
2C, C-3/5; δ = 128.49, 1C, C-4; δ = 127.30, 2C, C-2/6;
δ = 75.01, 1C, CH(OH).

NH4(C6H7O5) (4): (yield: 1.56 g, 92.2 %, decomp. > 250 °C).
C6H7NH4O5 (169.18)
Calc C 56.80 H 6.55 N 8.28 %
Found C 56.69 H 6.31 N 8.20 %

1H NMR (D2O, 20 °C): δ = 7.27-7.21, m, br, 5H, Aryl-H;
δ = 4.95, s, 1H, CH(OH); 13C{1H} NMR (D2O, 20 °C):
δ = 177.84, 1C, COO; δ = 139.47, 1C, C-1; δ = 129.11,
2C, C-3/5; δ = 128.78, 1C, C-4; δ = 127.24, 2C, C-2/6;
δ = 74.10, 1C, CH(OH).

M(C6H7O5)n H2O (M = Mg, Ca, Sr, Ba):

To a solution of D(-)-mandelic acid (3.04 g, 20.0 mmol) in 10 ml of water MOH (M = Mg, Ca, Sr, Ba) in the molar ratio 2:1 is added. The reaction mixture is stirred at room temperature for 2 h and then filtered. The resulting clear solution is concentrated under reduced pressure to a volume of ca. 5 ml. After layering of this aqueous solutions with acetone/ethanol precipitation of white solids
is observed. The solids are filtered off, dried in vacuo and identified as \( \text{Mg}_2\text{(C}_6\text{H}_7\text{O}_3)_2 \times n \text{H}_2\text{O} \).

After slow evaporation of aqueous solutions of the magnesium salt single crystals of \( \text{Mg}_2\text{(C}_6\text{H}_7\text{O}_3)_2 \times 2 \text{H}_2\text{O} \) formed within 1 week.

\[ \text{Mg}_2\text{(C}_6\text{H}_7\text{O}_3)_2 \times 2 \text{H}_2\text{O} (5): \text{(yield: 3.41 g, 94.0 %, mp. > 250 °C).} \]

\[ \text{C}_{10}\text{H}_{18}\text{MgO}_8 \ (362.61) \]

Calcd C 53.00 H 5.00 %, Found C 52.10 H 5.16 %.

1H NMR (\( \text{D}_2\text{O}, 20^\circ \text{C} \)): \( \delta = 7.23-7.12, \text{m, br, 5H, Aryl-H;} \)
\( \delta = 4.77, \text{s, 1H, CH(OH)}; \)
\( 13\text{C} \{^1\text{H} \} \) NMR (\( \text{D}_2\text{O}, 20^\circ \text{C} \)):
\( \delta = 179.44, 1\text{C, COO;} \)
\( \delta = 140.45, 1\text{C, C-1;} \)
\( \delta = 128.89, 2\text{C, C-3/5;} \)
\( \delta = 128.34, 1\text{C, C-4;} \)
\( \delta = 127.23, 2\text{C, C-2/6;} \)
\( \delta = 75.08, 1\text{C, CH(OH).} \)

\[ \text{Sr(C}_6\text{H}_7\text{O}_3)_2 \times 2 \text{H}_2\text{O} (6): \text{(yield: 3.35 g, 93.0 %, mp. > 250 °C).} \]

\[ \text{C}_{11}\text{H}_{16}\text{CaO}_7 \ (360.38) \]

Calcd C 53.33 H 4.48 %, Found C 52.27 H 4.17 %.

1H NMR (\( \text{D}_2\text{O}, 20^\circ \text{C} \)): \( \delta = 7.22-7.14, \text{m, br, 5H, Aryl-H;} \)
\( \delta = 4.79, \text{s, 1H, CH(OH)}; \)
\( 13\text{C} \{^1\text{H} \} \) NMR (\( \text{D}_2\text{O}, 20^\circ \text{C} \)):
\( \delta = 179.53, 1\text{C, COO;} \)
\( \delta = 140.46, 1\text{C, C-1;} \)
\( \delta = 128.80, 2\text{C, C-3/5;} \)
\( \delta = 128.24, 1\text{C, C-4;} \)
\( \delta = 127.12, 2\text{C, C-2/6;} \)
\( \delta = 75.08, 1\text{C, CH(OH).} \)

\[ \text{Zn(C}_6\text{H}_7\text{O}_3)_2 \times 3 \text{H}_2\text{O} (9): \text{(yield: 3.96 g, 93.9 %, mp. > 250 °C).} \]

\[ \text{C}_{10}\text{H}_{19}\text{ZnO}_8 \ (421.70) \]

Calcd C 45.57 H 4.78 %, Found C 44.77 H 5.25 %.

1H NMR (\( \text{D}_2\text{O}, 20^\circ \text{C} \)): \( \delta = 7.24-7.20, \text{m, br, 5H, Aryl-H;} \)
\( \delta = 4.81, \text{s, 1H, CH(OH)}; \)
\( 13\text{C} \{^1\text{H} \} \) NMR (\( \text{D}_2\text{O}, 20^\circ \text{C} \)):
\( \delta = 179.37, 1\text{C, COO;} \)
\( \delta = 140.31, 1\text{C, C-1;} \)
\( \delta = 128.85, 2\text{C, C-3/5;} \)
\( \delta = 128.32, 1\text{C, C-4;} \)
\( \delta = 127.22, 2\text{C, C-2/6;} \)
\( \delta = 74.73, 1\text{C, CH(OH).} \)

Crystal structure determination: The sample was mounted in a glass capillary on an Enraf Nonius CAD4 diffractometer and used for measurements of precise cell constants and intensity data collection. During data collection three standard reflections were measured periodically as a general check of crystal and instrument stability. No significant changes were observed. Graphite-monochromated MoK\(_\alpha\) radiation was used. The structure was solved by direct methods and refined by full matrix least-squares calculations on \( F^2 \). Crystal data for \( \text{C}_{10}\text{H}_{16}\text{MgO}_8 \). \( M_r = 362.61 \), colorless crystals, monoclinic, \( a = 9.756(1) \text{ Å}, \beta = 97.92(1)^\circ, \text{space group P 2_1, Z = 2, V = 851.4(2) Å}^3 \).

\( \rho_{calc} = 1.414 \text{ g cm}^{-3}, F(000) = 380; T = -74 ^\circ \text{C} \) Data were corrected for Lorentz and polarization, but not for absorption effects [\( \mu(\text{MoK}\alpha) = 1.46 \text{ cm}^{-1} \)] measured [(\( \sin \theta/\lambda)_{max} = 0.62 \text{ Å}^{-1} \)] and 3725 unique \( (R_{int} = 0.0310) \) reflections; 249 refined parameters, \( wR_2 = 0.0717, R_1 = 0.0295 \) for 3556 reflections with \( F_0 \geq 4\sigma(F_0); \) absolute structure parameter: -0.2(2). Residual electron densities: +0.226/-0.160. The function minimized was: \( wR_2 = [(\Sigma w(F_0^2 - F_c^2)^2)/\Sigma w(F_0^2)]^{1/2}; w = 1/[\sigma^2(F_0^2) + (ap)^2 + bp]; p = (F_0^2 + 2F_c^2)/3; a = 0.0476, b = 0.02 \) All non hydrogen atoms were refined with anisotropic displacement parameters. All C-H atoms were calculated and allowed to ride on their corresponding C atoms with fixed isotropic contributions \( U_{iso(C-H)} = 1.5 \times U_{eq} \) of the attached C; O-H atoms were located and refined with isotropic displacement parameters. Important interatomic distances and angles are shown in the corresponding Figure Caption and in Table I. Anisotropic thermal parameters, tables of interatomic distances and angles, and atomic coordinates have been deposited with the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen. The data are available on request on quoting CSD-410006.
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