

Separation and Structure of Chiral *S*-Malic Acid Hydrate

NIE, Jing-Jing^a(聂晶晶) XU, Duan-Jun^{*a}(徐端钧) WU, Jing-Yun^b(吴景云)
 CHIANG, Michael Y.^b(蒋燕南)

^a Department of Chemistry, Zhejiang University, Hangzhou Zhejiang 310027, China

^b Department of Chemistry, National Sun Yat-Sen University, Kaohsiung, Taiwan, China

Crystals of the chiral malic acid hydrate ($C_4H_6O_5 \cdot H_2O$) were unexpectedly obtained from an ethanol/water solution containing racemic *D*, *L*-malic acid and *L*-asparagine. The crystal belongs to orthorhombic space group $P2_12_12_1$ with cell dimensions of $a = 0.5576(1)$, $b = 0.9818(2)$, $c = 1.1793(2)$ nm, $V = 0.6455(2)$ nm³, $Z = 4$, $\mu(Mo K\alpha) = 0.152$ mm⁻¹, $F(000) = 320$, $D_c = 1.565$ g·cm⁻³, $R = 0.051$, $wR = 0.136$ for 657 observed reflections [$I > 2\sigma(I)$]. The significant difference in bond distances for carboxyl groups suggests that the crystal consist of malate anion and protonized crystalline water. This is a report for direct separation of racemic mixture, *i. e.*, without the formation of a molecular complex of raceme with a chiral separating reagent.

Keywords crystal structure, *R*-malic acid, chiral compound, separation, H-bonding

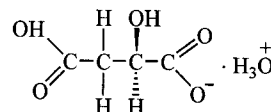
Introduction

The method of separating a racemic mixture into its enantiomers through the formation of diastereomeric molecular complex by reaction with an optically active compound has been widely investigated. From the point of view of crystallography, an essential prerequisite of the successful separation is the formation of two kinds of crystals by enantiomers and a separating reagent, which have a significantly different solubility or melting point. Following the crystal with less solubility being precipitated from the mixture solution, an enantiomer together with the separating reagent is separated from racemic mixture.¹

Although a lot of racemic mixture has been success-

fully separated based on the above simple principle, in fact, the chiral separation procedure may be more complicated. An example is the crystal structure of the molecular complex formed by *R*, *S*-mandelic acid and 1*S*, 3*R*-camphoramic acid. It showed a pair of diastereomers forming a co-crystal with different molar ratio of diastereomers in a unit cell, resulting in an incomplete separation of racemic mixture.²

Recently, during the investigation of separation of racemic malic acid, another novel phenomenon has been discovered. An enantiomer of malic acid unexpectedly crystallized with a crystalline water from a solution containing racemic malic acid and separating reagent. To our knowledge, this is the first report for directly separating raceme (without forming a molecular complex with a separating reagent). This note will report the separation procedure and the single crystal structure of the title compound on purpose to present a novel experimental result for chiral separation procedure.



Experimental

Preparation

D, *L*-Malic acid and *L*-asparagine were available

* E-mail: xudj@mail.hz.zj.cn

Received July 24, 2001; revised and accepted November 27, 2001.

Project supported by the National Natural Science Foundation of China (No. 29973036).

commercially. The specific optical rotation of an aqueous solution of *D, L*-malic acid was determined using a WZZ-1S instrument at 20 °C and the value of 0.0 confirmed that the sample is surely a raceme.

D, L-Malic acid (600 mg) and *L*-asparagine (0.4 g) with approximate molar ratio of 1.5:1 were dissolved in a mixture solution of ethanol (2.5 mL) and water (10 mL) at room temperature. Prismatic single crystals were obtained by slow vaporization of solvent. The specific optical rotation of an aqueous solution of the crystalline sample was determined by a WZZ-1S instrument and the $[\alpha]_D^{20}$ value of -26° agrees with -27° reported for *L*-malic acid with *S*-configuration.

Crystal structure determination

A single crystal of the title compound with an approximate dimensions of $0.25 \times 0.35 \times 0.45$ mm³ was mounted on a glass fiber. X-ray diffraction intensity data were collected on a Rigaku AFC-7S diffractometer up to 2θ value of 50.0° with graphite-monochromatized Mo K_α radiation using the ω - 2θ scan technique at 293 K. A total of 674 independent reflections were collected, of which 657 reflections were considered as observed [$I > 2\sigma(I)$] and used for the structure solution and refinements. Usual Lp and empirical absorption corrections were applied.

The structure was solved by direct methods followed by Fourier syntheses and refined by full-matrix least squares procedures using the SHELX-93 program package.³ H atoms were located in a difference Fourier map and fixed during the refinements. Anisotropic refinement including all the non-H atoms converged to agreement factors $R = 0.051$ and $wR = 0.136$ for 657 observed reflections, where $w = 1/[\sigma^2(F_o^2) + (0.0610 P)^2 + 1.0174 P]$ and $P = (F_o^2 + 2F_c^2)/3$. Atomic scattering factors were taken from International Tables for X-ray Crystallography.⁴

Crystal data $C_4H_6O_5 \cdot H_2O$, $M_r = 152.10$, orthorhombic, $P2_12_12_1$, $a = 0.5576(1)$, $b = 0.9818(2)$, $c = 1.1793(2)$ nm, $V = 0.6455(2)$ nm³, $Z = 4$, $\mu(\text{Mo } K_\alpha) = 0.152$ mm⁻¹, $F(000) = 320$, $D_c = 1.565$ g·cm⁻³, $S = 1.164$, $(\Delta/\sigma)_{\max} = 0.001$, $(\Delta\rho)_{\max} = 432$, $(\Delta\rho)_{\min} = -326$ e/nm³.

Results and discussion

The space group of $P2_12_12_1$ shows that the structure

is chiral. The structure refinements based on *L*- and *D*-configuration gave Flack parameter $+2.1$ and -2.1 respectively, which means that the absolute configuration of the compound can not be determined reliably. The specific optical rotation value of -26° suggests that the chiral molecule should be *L*-configuration in this work.

The coordinates and thermal parameters are presented in Table 1. Selected bond distances and angles are listed in Table 2.⁹ The molecule structure for *L*-configuration is illustrated in Fig. 1.

Although structures of racemic malic acid⁵ and chiral anhydrous malic acid⁶ were reported previously, the structure of the chiral malic acid hydrate has not appeared at Cambridge Structure Database up to now. The molecular structure of the present malic acid is much different from those of both chiral malic acid and racemic malic acid re-

Table 1 Atomic fractional coordinates ($\times 10^4$) and thermal parameters ($\times 10^5$) of non-H atoms

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq} (nm ²)
O(1)	53(6)	5430(3)	6(3)	30(1)
O(2)	1184(5)	3256(3)	-38(2)	26(1)
O(3)	-1111(5)	3945(3)	2392(3)	27(1)
O(4)	-1035(7)	5639(4)	3687(3)	43(1)
O(5)	4151(6)	3432(3)	1727(3)	35(1)
O _w	-3037(7)	7299(4)	1126(3)	39(1)
C(1)	1239(7)	4425(4)	358(3)	19(1)
C(2)	3064(7)	4726(4)	1291(3)	19(1)
C(3)	2098(7)	5569(4)	2273(3)	20(1)
C(4)	-174(8)	4979(4)	2793(3)	18(1)

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 2 Selected bond lengths (nm) and angles (°)

O(1)—C(1)	0.1258(5)	O(2)—C(1)	0.1240(5)
O(3)—C(4)	0.1236(5)	O(4)—C(4)	0.1328(5)
O(5)—C(2)	0.1498(5)	C(1)—C(2)	0.1528(5)
C(2)—C(3)	0.1522(5)	C(3)—C(4)	0.1521(6)
O(1)—C(1)—O(2)	126.1(4)	O(2)—C(1)—C(2)	117.8(4)
O(1)—C(1)—C(2)	115.8(3)	O(5)—C(2)—C(3)	110.1(3)
O(5)—C(2)—C(1)	110.6(3)	C(3)—C(2)—C(1)	114.7(3)
C(4)—C(3)—C(2)	113.2(3)	O(3)—C(4)—O(4)	123.4(4)
O(3)—C(4)—C(3)	120.7(4)	O(4)—C(4)—C(3)	115.8(3)

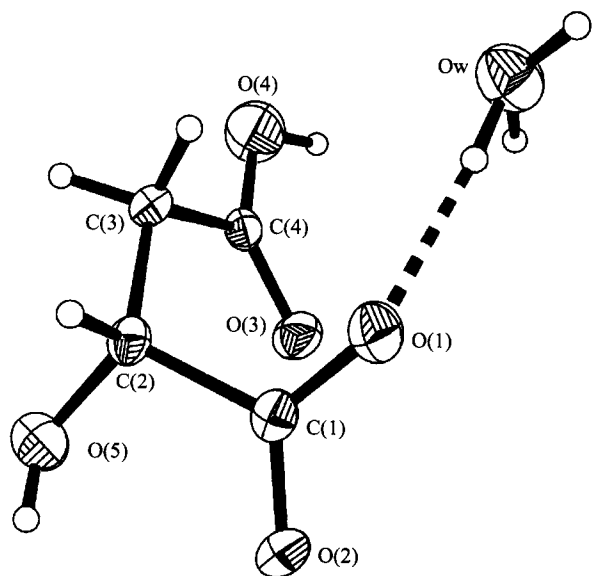


Fig. 1 An ORTEP drawing of the title *S*-compound showing 30% probability displacement ellipsoids.

ported previously. A comparison of structures is summarized in Table 3. Firstly, the conformation of the malic

acid in the present work is completely different from those reported. For reported structures, torsion angles of the carbon skeleton all are close to 180° , showing a coplanar carbon skeleton, whereas the torsion angle 52.9° shows a more stable conformation for the carbon skeleton in the title compound. The molecule of the present malic acid is not coplanar. The structure consists of two planes, C(1)-C(2)-O(1)-O(2)-O(5) plane (with maximal atomic deviation of 0.0079 nm) and C(2)-C(3)-C(4)-O(3)-O(4) plane (with maximal atomic deviation of -0.0026 nm). These two planes are almost perpendicular to each other, dihedral angle being 96.4° . Secondly, it is notable that bond distances within the carboxyl moiety are much different. A lot of structure determinations showed a general rule for C—O bond distances of carboxyl group, *i. e.*, both C—O bond distances are almost identical in a carboxylate anion but significantly different in a neutral carboxylic acid.⁷⁻⁸ As shown in Table 3, bond distances of two carboxyl groups in the title compound are significantly different, almost identical for C(1) carboxyl but

Table 3 A comparison of this structure with those from literature

Compound	Bond distance in carboxyl (nm)				Torsion angle ($^\circ$) C(1)-C(2)-C(3)-C(4)	Ref.
	C(1)—O(1)	C(1)—O(2)	C(4)—O(3)	C(4)—O(4)		
(-)-Malic acid ^a	0.1313	0.1220	0.1227	0.1282	180.4	6
	0.1297	0.1224	0.1201	0.1288	182.4	
(±)-Malic acid	0.1312	0.1208	0.1221	0.1288	184.5	5
<i>L</i> -Malic acid hydrate	0.1258	0.1240	0.1236	0.1328	52.9	this work

^a Two crystallographic independent molecules in a unit cell.

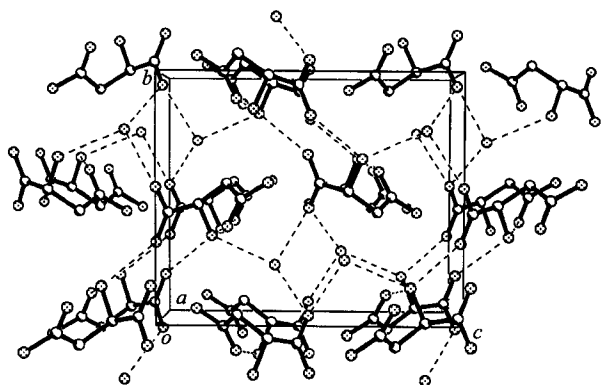


Fig. 2 Molecular packing diagram viewed along the axis *a* with dashed lines showing the intermolecular H-bonding.

much different for C(4) carboxyl. This fact strongly suggests that the present malic acid like a mono-anion but not a neutral molecule. Although it is difficult for us to completely understand this separation procedure at this moment, the ionization of malic acid in the solution of racemic malic acid containing *L*-asparagine may be a reason for fortunately obtaining crystals of the title chiral *S*-compound.

While the deprotonation of the C(1) carboxyl group, crystalline water became protonized one. The third H atom around the Ow atom was found in a difference Fourier map with a longer Ow—H(3)_w distance of 0.134 nm.

As shown in the crystal packing diagram (Fig. 2), the extensive H-bonding network exists in the crystal structure.

References and notes

- 1 Kinbara, K.; Sakai, K.; Hashimoto, Y.; Norita, H.; Saigo, K. *J. Chem. Soc., Perkin Trans.* **1996**, 2615.
- 2 Hu, Z.; Nie, J. J.; Xu, D. J.; Xu, Y. Z.; Wu, J. Y.; Chiang, M. Y. *J. Chem. Cryst.* in press.
- 3 Sheldrick, G. M. *SHELX-93, Program for Crystal Structure Refinement*, University of Gottingen, Germany, **1993**.
- 4 *International Tables for X-ray Crystallography*, Vol. IV, Kynoch Press, Birmingham, England (Present distributor: Kluwer Academic Publishers, Dordrecht), **1974**. p. 72.
- 5 Sluis, P.; Kroon, J. *Acta Crystallogr.* **1985**, *C41*, 956.
- 6 Sluis, P.; Kroon, J. *Acta Crystallogr.* **1989**, *C45*, 1406.
- 7 Nie, J. J.; Xu, D. J.; Wu, J. Y.; Chiang, M. Y. *Acta Crystallogr.* **2001**, *E57*, o428.
- 8 Nie, J. J.; Xu, D. J.; Wu, J. Y.; Chiang, M. Y. *Chin. J. Struct. Chem.* **2001**, *20*, 401.
- 9 Full crystallographic data has been deposited at Cambridge Crystallographic Data Center with the deposition number of CCDC 167452.

(E0107241FZ DONG, H. Z.)