Crystal Structure and Pseudopolymorphism of Bisdemethoxycurcumin-Alcohol Solvates

* KASAI Kayoko, * SAITO Atsushi and * SATO Shun

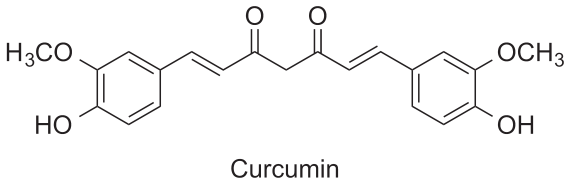
Abstract

Crystal structures of pseudopolymorphic (1*E*,6*E*)-1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (bisdemethoxycurcumin, BDMC) methanol solvate BDMC•CH_3OH (**1**) and 2-propanol solvate BDMC•$(CH_3)_2CHOH$ (**2**) were determined.

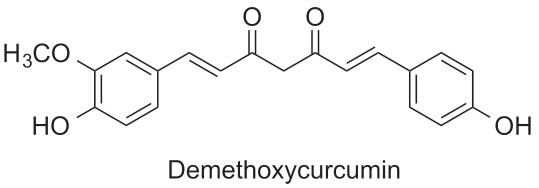
Key words：Bisdemethoxycurcumin（ビスデメトキシクルクミン）
X-ray Crystal Structure Analysis（X 線結晶構造解析）
Pseudopolymorphism（擬似結晶多形）
Keto-enol Tautomer（ケト―エノール互変異性体）
Hydrogen Bond Network（水素結合ネットワーク）

1. Introduction

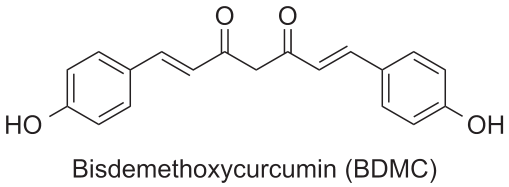
The yellow-orange pigment, obtained from the rhizome of the plant *Curcuma longa* L. (Zingiberaceae), commonly known as turmeric, consists of three important analogues: curcumin ((1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione), demethoxycurcumin ((1*E*,6*E*)-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione), and bisdemethoxycurcumin ((1*E*,6*E*)-1,7-bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione). Commercially available curcumin mixtures contain 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin [1]. These curcuminoids exhibit notable effects such as anti-inflammatory, antioxidant, antitumor, anti-Alzheimer, and antidepressant activities [2, 3]. Because the molecular mechanisms underlying their biological activities have not yet been fully clarified, it is important to investigate their chemical properties.



Curcumin



Demethoxycurcumin



Bisdemethoxycurcumin (BDMC)

The X-ray crystal struture of curcumin was first determined in 1982 [4] and was redetermined in 2007 [5]. Despite of the systematic name for curcumin, (1*E*,6*E*)-1,7-bis(4-hydroxy-3-

* Department of Science Education, Miyagi University of Education

methoxyphenyl) hepta-1,6-diene-3,5-dione, and its classification as a β-diketone -CO-H_2C-CO, the X-ray structure analyses clearly confirm that curcumin exists in the keto-enol form -CO-HC=C-OH in the crystal phase. Many curcumin derivatives such as bisdemethoxycurcumin (BDMC) [6, 7], tetrahydrocurcumin [8], and bis (acetoxy) curcumin [9] also exist in the keto-enol form. Three possible structures of BDMC are the β-diketone tautomer and two equivalent keto-enol tautomers, as shown in Figure 1. The crystal structures of BDMC including methanol and water molecules are nearly identical: both are monoclinic, belong to the space group $P2_1/c$, and have similar unit-cell dimensions [6, 7]. We report here the crystal structures of BDMC methanol solvate (**1**) and 2-propanol solvate (**2**).

2. Experimental

2.1. Materials and Methods

Bisdemethoxycurcumin was purchased from Tokyo Chemical Industry Co., Ltd. Methanol and 2-propanol were purchased from Kanto Chemical Co., Ltd. Single crystals of **1** and **2** were grown by slow evaporation of solutions in methanol and 2-propanol, respectively. Elemental analysis was performed at the Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University (Japan). Anal. Calcd for $C_{20}H_{20}O_5$ (**1**) : C, 70.57; H, 5.92; N, 0.00. Found: C, 70.48; H, 5.93; N, 0.00%. Anal. Calcd for $C_{19}H_{16}O_4$ (**2**) : C, 74.01; H, 5.23; N, 0.00. Found: C, 73.90; H, 5.36; N, 0.00%.

2.2. Crystallographic Data Collection and Refinement

Single crystals of **1** and **2** with appropriate dimensions were mounted on a glass fiber and used for data collection. Crystal data for all the structures were collected with a Bruker-AXS SMART-APEXII CCD diffractometer ($Mo_{K\alpha}$ radiation, λ = 0.71073 Å) by the φ and ω scans ($1.23 \leq \theta \leq 27.61°$ for **1**; $1.86 \leq \theta \leq 27.67°$ for **2**). Multi-scan absorption corrections were applied using the SADABS program. The structures were solved by the direct method and refined by full-matrix least-squares against F^2 of all data using the SHELXS 97 and SHELXL 2013 programs [10]. The positions of the hydrogen atoms bonded to carbon were generated geometrically, assigned isotropic thermal parameters, and allowed to ride on their respective parent atoms before the final cycle of least-squares refinements. Hydrogen atoms bonded to oxygen except for keto-enol moieties were located in a difference Fourier map and their coordinates refined freely. Hydrogen atoms bonded to oxygen in keto-enol moieties were located in a difference Fourier map, and their coordinates

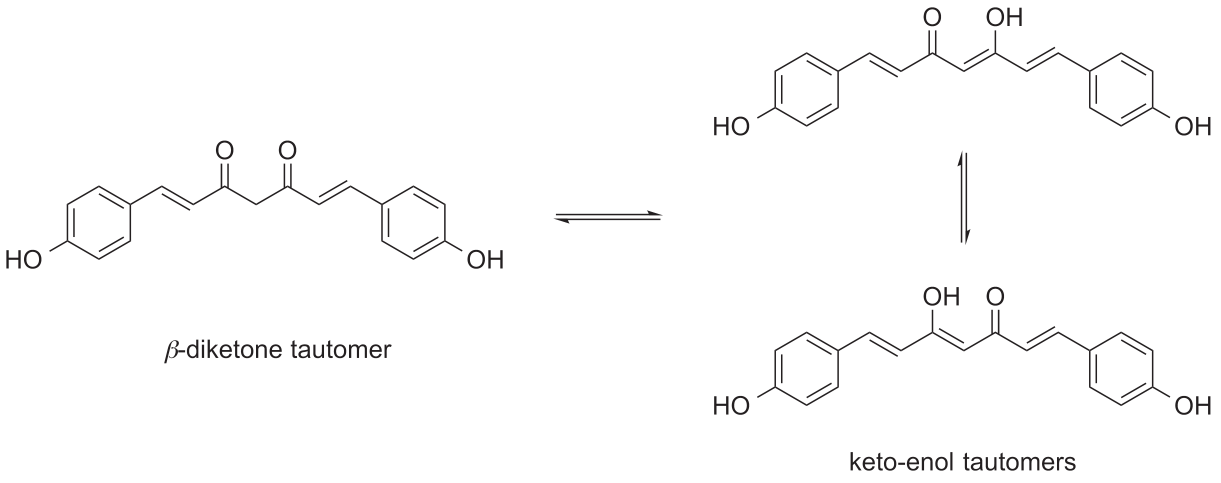


Figure 1. Three possible structures of bisdemethoxycurcumin

refined with restricted bond length (O-H = 0.82 Å). Crystallographic data for **1** and **2** are listed in Table 1. Molecular graphics were created by VESTA 3 for three-dimensional visualizations of crystal, volumetric, and morphology data [11].

Table 1. Crystallographic data for **1** and **2**.

	1	**2**
Formula	$C_{20}H_{20}O_5$	$C_{22}H_{24}O_5$
*M*r	340.36	368.41
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/n$	$Pna2_1$
a [Å]	6.7875(5)	7.5312(5)
b [Å]	7.6241(5)	11.9297(8)
c [Å]	33.064(2)	21.8675(15)
β [°]	93.7090(10)	—
V [Å^3]	1707.4(2)	1964.7(2)
Z	4	4
T [K]	130	130
ρ_{calcd} [Mg m^{-3}]	1.324	1.246
Crystal description	plate	pillar
Crystal color	yellow	orange
Crystal size [mm]	0.49 × 0.47 × 0.18	0.53 × 0.20 × 0.16
μ ($Mo_{K\alpha}$) [mm^{-1}]	0.095	0.088
F(000)	720	784
Reflections collected	8660	9803
Independent reflections	3615 (R_{int} = 0.0167)	3168 (R_{int} = 0.0208)
Completeness to θ = 25.242° [%]	99.8	99.9
Max/min transmission	0.983 / 0.820	0.986 / 0.819
Data / restraints / parameters	3615 / 2 / 243	3168 / 3 / 262
Goodness-of-fit	1.086	1.123
Final *R* indices ($I > 2\sigma(I)$)	R_1 = 0.0417, $_wR_2$ = 0.0960	R_1 = 0.0373, $_wR_2$ = 0.0801
R indices (all data)	R_1 = 0.0504, $_wR_2$ = 0.1011	R_1 = 0.0447, $_wR_2$ = 0.0843
Absolute structure parameter	—	0.3(5)
Largest diff. peak/hole [eÅ^{-3}]	0.259 / -0.289	0.208 / -0.226

3. Results and Discussion

The structures of **1** and **2** are shown in Figure 2 clearly indicate that **1** and **2** exist in the keto-enol form in the crystal structure. Selected bond lengths and angles are given in Table 2. The methanol solvate **1** crystallizes in the primitive monoclinic space group $P2_1/n$ with Z = 4 formula units in the unit cell, which is identical to that previously reported [6]. The 2-propanol solvate **2** crystallizes in the primitive orthorhombic space group $Pna2_1$ with Z = 4 formula units in the unit cell. It is clear that pseudopolymorphism occurs [12]. As shown in Figure 2, the orientations of the two phenolic OH groups are the same in **1**, whereas they point in the opposite direction in **2**. Comparison of those side views in Figure 2 shows that **2** is somewhat flat, whereas **1** is relatively distorted. The angles between the planes of the two benzene rings in the BDMC molecules of **1** and **2** are 14.84 ° and 6.50 °, respectively. Their difference maps calculated in the latter stage of refinement indicate that the two H atoms are in appropriate positions between O3 and O4 of the keto-enol moiety. The respective H atom occupancy factors are 0.79 (H3) and 0.21 (H4) in **1** and 0.71 (H3) and 0.29 (H4) in **2**, showing unequal disordering.

Table 2. Selected bond lengths (Å) and angles (°) of **1** and **2**.

	1	**2**		**1**	**2**
O3–C9	1.3296(17)	1.337(3)	O3–C9–C10	121.19(13)	120.9(2)
O4–C11	1.2777(18)	1.283(3)	C8–C9–C10	122.50(13)	122.6(2)
C4–C7	1.4612(19)	1.464(4)	C9–C10–C11	121.21(13)	121.9(2)
C7–C8	1.345(2)	1.338(4)	O4–C11–C12	120.22(12)	120.5(2)
C8–C9	1.4523(19)	1.448(4)	O4–C11–C10	120.87(13)	120.7(2)
C9–C10	1.380(2)	1.376(4)	C10–C11–C12	118.91(13)	118.8(2)
C10–C11	1.4244(19)	1.419(4)	C3–C4–C5	117.74(13)	117.5(2)
C11–C12	1.4630(19)	1.464(4)	C3–C4–C7	117.85(13)	120.1(2)
C12–C13	1.337(2)	1.336(4)	C5–C4–C7	124.38(13)	122.4(2)
C13–C14	1.4575(19)	1.463(3)	C15–C14–C19	117.58(13)	118.2(2)
			C13–C14–C15	119.18(13)	118.5(2)
O3–C9–C8	116.31(12)	116.6(2)	C13–C14–C19	123.24(13)	123.2(2)

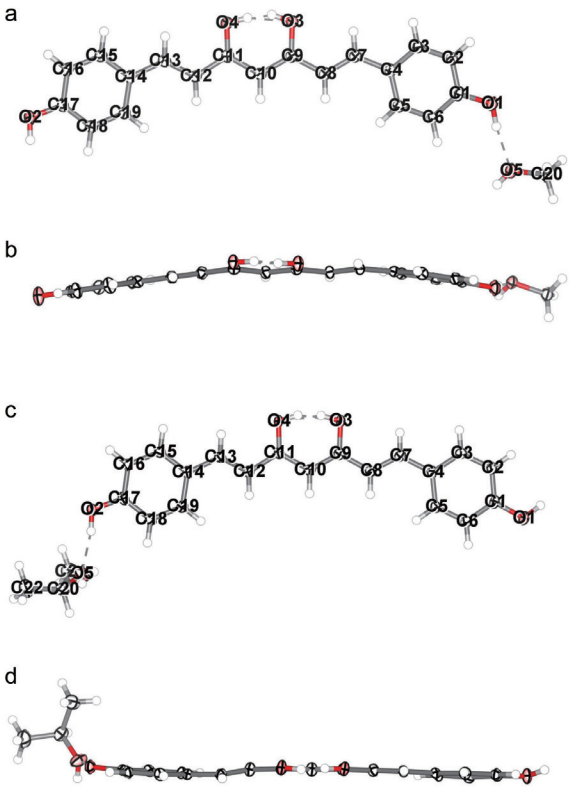


Figure 2. The moclecular structures of **1** and **2**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn as small spheres of arbitrary radii. Hydrogen bonds are shown as dashed lines. (a) Top view of **1**. (b) Side view of **1**. (c) Top view of **2**. (d) Side view of **2**.

Intra- and intermolecular O-H···O hydrogen bonds in **1** and **2** are summarized in Tables 3 and 4. Whereas hydrogen bonds between methanol and BDMC exist in **1**, those between BDMC molecules also exist in **2**. The packing of **1** is extended into a two-dimensional network by intermolecular hydrogen bonds between O5 of the alcoholic OH group and H1 of the phenolic OH group and H2, and between O4 on the keto-enol moiety and H5 attached to alcoholic O5. From this arrangement, channels are formed along the *a*-axis, in which the methanol molecules are located as shown in Figure 3. The packing of **2** is extended into a three-dimensional network by intermolecular hydrogen bonds between O5 of the alcoholic OH group and H2 of the phenolic OH group, O2 of the phenolic OH group and H5 attached to alcoholic O5, and O4 of the keto-enol moiety and H1 of the phenolic OH group. From this arrangement, channels are also formed along the *a*-axis, in which the 2-propanol molecules are located as shown in Figure 4. The bulkier structure of 2-propanol than methanol seems to cause the pseudopolymorphism.

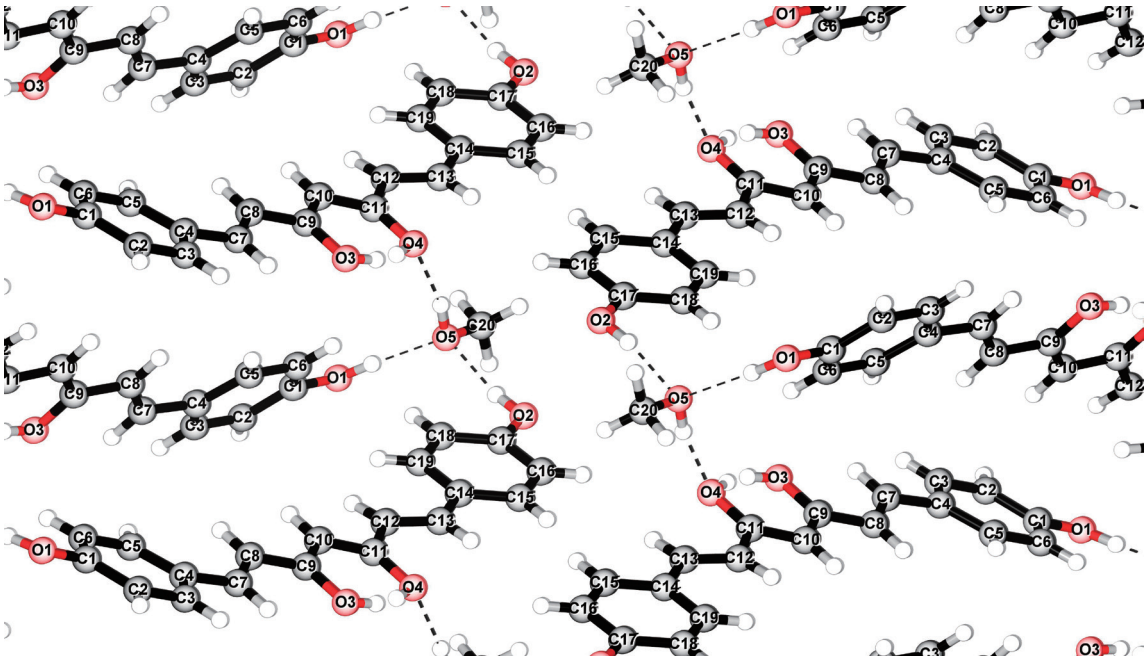


Figure 3. A partial packing diagram of **1**, indicating intermolecular O-H···O hydrogen bonds (dashed lines).

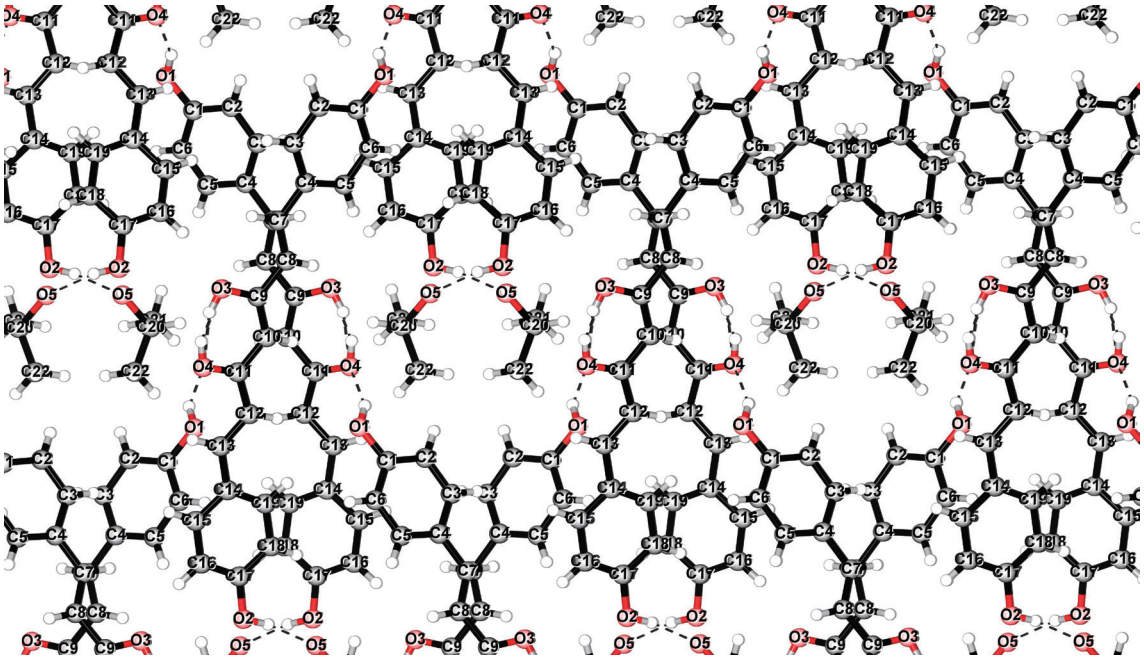


Figure 4. A partial packing diagram of **2**, indicating intermolecular O-H···O hydrogen bonds (dashed lines).

Table 3. Hydrogen-bond geometry (Å, °) of **1**.

D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
O5–H5···O4$^{(i)}$	0.85(2)	1.89(2)	2.7211(16)	165(2)
O2–H2···O5$^{(ii)}$	0.86(2)	1.91(2)	2.7584(17)	170(2)
O1–H1···O5$^{(iii)}$	0.90(2)	1.83(2)	2.7223(17)	171.6(19)
C20–H20A···O2$^{(iv)}$	0.98	2.65	3.1388(19)	111.4

Symmetry codes: (i) x, y+1, z; (ii) x-1, y, z; (iii) -x+3/2, y-1/2, -z+1/2; (iv) -x-1, -y+1, -z.

Table 4. Hydrogen-bond geometry (Å, °) of **2**.

D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
O5–H5···O2$^{(i)}$	0.82(4)	2.00(4)	2.785(3)	161(5)
O2–H2···O5$^{(ii)}$	0.88(4)	1.79(4)	2.652(3)	169(5)
O1–H1···O4$^{(i)}$	0.89(5)	1.90(5)	2.732(3)	154(4)
C16–H16A···O3$^{(iii)}$	0.95	2.52	3.260(3)	135.0
C12–H12A···O1$^{(ii)}$	0.95	2.58	3.499(3)	163.2
C8–H8A···O3$^{(iv)}$	0.95	2.58	3.314(3)	133.7

Symmetry codes: (i) -x+3/2, y-1/2, z+1/2; (ii) -x+1, -y+1, z-1/2; (iii) -x+1, -y+2, z-1/2; (iv) x-1/2, -y+3/2, z.

4. Conclusions

In summary, the single crystal X-ray structures of two pseudopolymorphs of BDMC were determined. The methanol solvate has a two-dimensional network structure formed by intermolecular hydrogen bonds between methanol and BDMC molecules. The 2-propanol solvate has a novel three-dimensional network structure formed by intermolecular hydrogen bonds between not only propanol and BDMC but also BDMC molecules with each other.

Acknowledgement

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References

[1] P. Anand, S. G. Thomas, A. B. Kunnumakkara, C. Sundaram, K. B. Harikumar, B. Sung, S. T. Tharakan, K. Misra, I. K. Priyadarsini, K. N. Rajasekharan, B. B. Aggarwal, Biochem. Pharmacol. 76 (2008) 1590.

[2] K. Bairwa, J. Grover, M. Kania, S. M. Jachak, RSC Adv. 4

(2014) , 13946.
[3] V. Katsidoni, P. Alexiou, M. Fotiadou, M, Pelecanou, M. Sagnou, G. Panagis, Psychopharmacology 231 (2014) 4467.
[4] H. H. Tønnesen, J. Karlsen, A. Mostad, Acta Chem. Scand. B 36 (1982) 475.
[5] S. P. Parimita, Y. V. Ramshankar, S. Suresh, T. N. Guru Row, Acta Cryst. E63 (2007) o860.
[6] H. H. Tønnesen, J. Karlsen, A. Mostad, U. Pedersen, P. B. Rasmussen, S.-O. Lawesson, Acta Chem. Scand. B 37 (1983) 179.
[7] J. Karlsen, A. Mostad, H. H. Tønnesen, Acta Chem. Scand. B 42 (1988) 23.
[8] C. R. Girija, N. S. Begum, A. A. Syed, V. Thiruvenkatam, Acta Cryst. C60 (2004) o611.
[9] J. T. Mague, W. L. Alworth, F. L. Payton, Acta Cryst. C60 (2004) o608.
[10] G. M. Sheldrick, Acta Cryst. A64 (2008) 112.
[11] K. Momma, F. Izumi, J. Appl. Crystallogr. 44 (2011) 1272.
[12] A. Nangia, G. R. Desiraju, Chem. Commun. (1999) 605.

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