Acta Chemica Scandinavica B 36 (1982) 475–479

Structural Studies of Curcuminoids. I. The Crystal Structure of Curcumin

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The crystal and molecular structure of the food-additive 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione (curcumin) has been determined at 121 K by X-ray crystallographic methods using 3368 reflections observed by counter methods. The crystals are monoclinic, space group $P2/n$ with unit cell dimensions $a=20.028(3)$ Å, $b=7.073(1)$ Å, $c=12.609(2)$ Å, $\beta=94.94(1)°$. The structure was refined to a conventional R-factor of 0.055. Estimated standard deviations are 3×10^{-3} Å and 0.2° in interatomic distances and angles when hydrogen atoms are not involved.

The rhizomes of *Curcuma longa* L. (Zingiberaceae) and extracts of the rhizomes are commercial products produced in large quantities.[1] They are used as ingredients in "Indian curries" and as a natural colouring matter in food processing around the world.[2,3] The yellow compounds of *Curcuma longa* belong to the group of diarylheptanoids. Since many countries have issued a ban on the use of synthetic dyes in food and drugs, the interest in natural colouring matter is increasing. Much to our surprise not too much is known about the stability, analysis and structure of the curcuminoids. As a natural colouring agent it is known to be unstable and has been replaced by stable synthetic dyes when possible.

In addition curcumin is known to possess important pharmacological properties.[4,5] It is known to relieve gastro-intestinal disorders.

During our investigations on the analysis of curcumin and extracts of *Curcuma longa* L. the response of the coloured compounds during HPLC analysis differed from what was expected.[7] The compounds gave considerable negative peaks, not stable signals *etc.* A reason for this may be the fluorescence of the compounds. Curcumin is also known for its ability to make complexes with other molecules and this may also count for the anomalous behaviour during HPLC analysis.

Curcumin is a symmetrical molecule, but – surprisingly – biosynthetic experiments indicate that two different pathways, *e.g.* the phenylpropane and the acetate pathways, contribute to the formation of the molecule.[6] Furthermore, there seems to be some dispute as to which structure can be given to curcumin.[11,13] We therefore found it of interest and a necessity to investigate this before further analysis on the stability could be undertaken.

EXPERIMENTAL

Deep red plate-formed crystals of curcumin were prepared by recrystallization of a sample of Koch-Light quality 1324 h. The compound was dissolved in ethanol at 70 °C in the dark. A small amount of water was added to the solution and after a few days in the refrigerator the crystals separated. A diamond shaped crystal of dimensions $0.6\times0.4\times0.1$ mm. was used for the experimental procedure which is described in Experimental conditions. Cell parameters were determined by a least squares fit to the diffractometer settings for 15 general reflections. The standard deviations in the measured intensities were calculated as $\sigma(I)=[C_T+(0.02C_N)^2]^{\frac{1}{2}}$, where C_T is the total number of counts and C_N is the scan count minus the background count. The intensity data were corrected for Lorentz and polarization effects. The variations in the intensities of the test reflections were between 1 to 2 % and no corrections were made on this basis. Scattering factors used were those of Doyle and Turner[8] for O and C, and of Stewart, Davidson and Simpson[9] for H.

0302-4369/82/070475-05$02.50

CRYSTAL DATA

Curcumin, $C_{21}O_6H_{20}$, monoclinic, $a=20.028(3)$ Å, $b=7.073(1)$ Å, $c=12.609(2)$ Å, $\beta=94.94(1)°$, $V=1779.6$ Å^3, $M=368.37$, $Z=4$, $F_{(000)}=776$, space group $P2/n$.

EXPERIMENTAL CONDITIONS

Instrument	SYNTEX $P\bar{1}$
Radiation	Graphite Crystal Monochromated MoK_α $\lambda=0.71069$ Å
Crystal dimensions/mm	$0.6\times0.4\times0.1$
Scanning mode	$\theta/2\theta$
Scan speed/° min^{-1}	3–6 depending on intensity
Scan range/°	$2\theta_{\alpha_1}-1.1$ to $2\theta_{\alpha_2}+1.3$
Background counts	For 0.35 of scan time at scan limits
Temperature/K	121
2θ range/°	$2<2\theta<60$
Number of reflections meas.	3774
Number of reflections $I>2.5\sigma(I)$	3331
Number of standard reflections	3
Number of reflections between standard reflections	57

STRUCTURE DETERMINATION

The structure was solved by direct methods using the program assembly MULTAN,[10] and a successive Fourier synthesis indicated the positions of all the non-hydrogen atoms. The positions of 17 of the 20 hydrogen atoms were readily found from a difference synthesis. The positions of the hydrogen atoms at O1 and O6 were introduced from con-

Table 1. Fractional atomic coordinates and thermal parameters multiplied by 10.[4] The anisotropic temperature factor is given by $\exp -2\pi^2(U_{11}a^{*2}h^2+\cdots+2U_{12}a^*b^*hk+\cdots)$. Estimated standard deviations in parameters are given in parentheses.

Atom	X	Y	Z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1	5993(1)	6670(2)	0517(1)	198(7)	464(11)	187(7)	39(7)	53(6)	−8(7)
O2	4776(1)	6297(2)	1202(1)	164(7)	435(10)	215(8)	−11(7)	30(6)	−45(7)
O3	5823(1)	8366(2)	7055(1)	128(7)	468(11)	197(7)	9(7)	32(5)	−16(7)
O4	5307(1)	8721(2)	8734(1)	165(7)	478(11)	204(8)	9(7)	32(6)	−31(7)
O5	2272(1)	11231(2)	11201(1)	156(7)	413(10)	345(9)	−53(7)	90(6)	−102(8)
O6	1352(1)	8440(2)	11107(1)	159(7)	392(10)	352(9)	−33(7)	135(6)	−20(8)
C1	5278(1)	6701(3)	1970(2)	168(9)	143(12)	209(10)	16(9)	25(8)	−11(9)
C1	5278(1)	6701(3)	1970(2)	168(9)	143(12)	209(10)	16(9)	25(8)	−11(9)
C2	5211(1)	6928(3)	3040(2)	151(9)	267(12)	211(10)	19(9)	48(8)	−8(9)
C3	5778(1)	7307(3)	3750(2)	164(9)	238(12)	202(10)	36(9)	43(8)	2(9)
C4	6406(1)	7452(3)	3347(2)	139(9)	315(13)	219(10)	−38(9)	12(8)	−7(10)
C5	6473(1)	7247(3)	2267(2)	146(9)	320(13)	236(11)	43(9)	62(8)	−1(10)
C6	5917(1)	6866(3)	1577(2)	207(10)	251(12)	170(10)	35(9)	49(8)	−1(9)
C7	5738(1)	7569(3)	4889(2)	164(9)	271(12)	194(10)	29(9)	12(8)	−20(9)
C8	5186(1)	7651(3)	5429(2)	169(9)	296(13)	193(10)	19(9)	28(8)	−10(9)
C9	5231(1)	8014(3)	6565(2)	175(9)	240(12)	201(10)	35(9)	39(8)	18(9)
C10	4662(1)	8014(3)	7139(2)	138(9)	275(13)	219(10)	2(9)	53(8)	−11(9)
C11	4717(1)	8399(3)	8226(2)	181(10)	232(12)	238(11)	32(9)	61(8)	13(9)
C12	4154(1)	8537(3)	8881(2)	192(10)	292(13)	193(10)	27(9)	55(8)	−9(10)
C13	3540(1)	7835(3)	8601(2)	187(10)	297(13)	135(11)	22(9)	68(8)	−16(10)
C14	2962(1)	8052(3)	9235(2)	157(9)	286(13)	226(10)	18(9)	41(8)	16(9)
C15	2926(1)	9566(3)	9940(2)	124(9)	314(13)	250(11)	−8(9)	46(8)	8(10)
C16	2382(1)	9745(3)	10550(2)	142(9)	296(13)	216(10)	−10(9)	33(8)	−26(10)
C17	1883(1)	8345(3)	10490(2)	126(9)	340(13)	233(10)	−3(9)	54(8)	50(10)
C18	1911(1)	6859(3)	9793(2)	144(9)	316(14)	311(12)	−36(9)	40(8)	11(10)
C19	2448(1)	6717(3)	9154(2)	201(10)	293(13)	289(12)	1(10)	51(9)	−25(10)
C20	4103(1)	6329(4)	1522(2)	159(10)	425(15)	263(11)	−12(10)	19(8)	−19(11)
C21	2729(1)	12788(4)	11209(2)	252(11)	259(15)	353(13)	−36(11)	71(10)	−67(11)

Table 2. Fractional atomic coordinates and isotropic thermal parameters for the hydrogen atoms. Estimated standard deviations given in parentheses.

	X	*Y*	*Z*	*B*
H2	0.478(1)	0.685(3)	0.330(2)	2.4
H4	0.679(1)	0.776(3)	0.386(2)	2.3
H5	0.689(1)	0.734(3)	0.197(2)	1.8
H7	0.615(1)	0.777(3)	0.352(2)	1.7
H8	0.473(1)	0.746(3)	0.506(2)	1.6
H10	0.426(1)	0.780(3)	0.678(2)	2.6
H12	0.427(1)	0.924(3)	0.953(2)	1.6
H13	0.347(1)	0.707(3)	0.796(2)	1.3
H15	0.325(1)	1.056(4)	1.001(2)	2.3
H18	0.157(1)	0.592(4)	0.973(2)	2.8
H19	0.245(1)	0.566(3)	0.862(2)	2.0
H201	0.383(1)	0.610(3)	0.086(2)	1.8
H202	0.397(1)	0.764(4)	0.181(2)	3.1
H203	0.405(1)	0.536(3)	0.205(2)	2.3
H211	0.255(1)	1.385(4)	1.159(2)	3.0
H212	0.277(1)	1.320(3)	1.044(2)	2.9
H213	0.315(1)	1.236(3)	1.166(2)	4.0
HO1	0.569(2)	0.693(5)	0.018(3)	7.2
½HO3	0.577(2)	0.848(6)	0.764(3)	1.6
½HO4	0.560(2)	0.869(6)	0.822(4)	2.5
HO6	0.134(1)	0.947(3)	1.141(2)	3.0

siderations of the hydrogen bond system. A final difference map suggested two possible positions for the last hydrogen atom supposed to be attached to the O3 or O4 atom. The best result was obtained by placing a half hydrogen atom in each of the two positions indicating a statistical distribution of the hydrogen atom at the two positions. All positional parameters, anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms were refined in the final least squares calculations giving an *R*-factor of 0.055 and a goodness of fit $S=(\Sigma w\Delta^2/m-n)^{\frac{1}{2}}=2.52$.

The final parameters are given in Tables 1 and 2. Tables of observed and calculated structure factors are available from the authors.

DESCRIPTION AND DISCUSSION

The labelling of the atoms is indicated in Fig. 1, the bond lengths and angles are given in Table 3 and some torsion angles in Table 4. Fig. 1 illustrates the molecule as it appears in the crystal as well as the molecular packing and the hydrogen bond

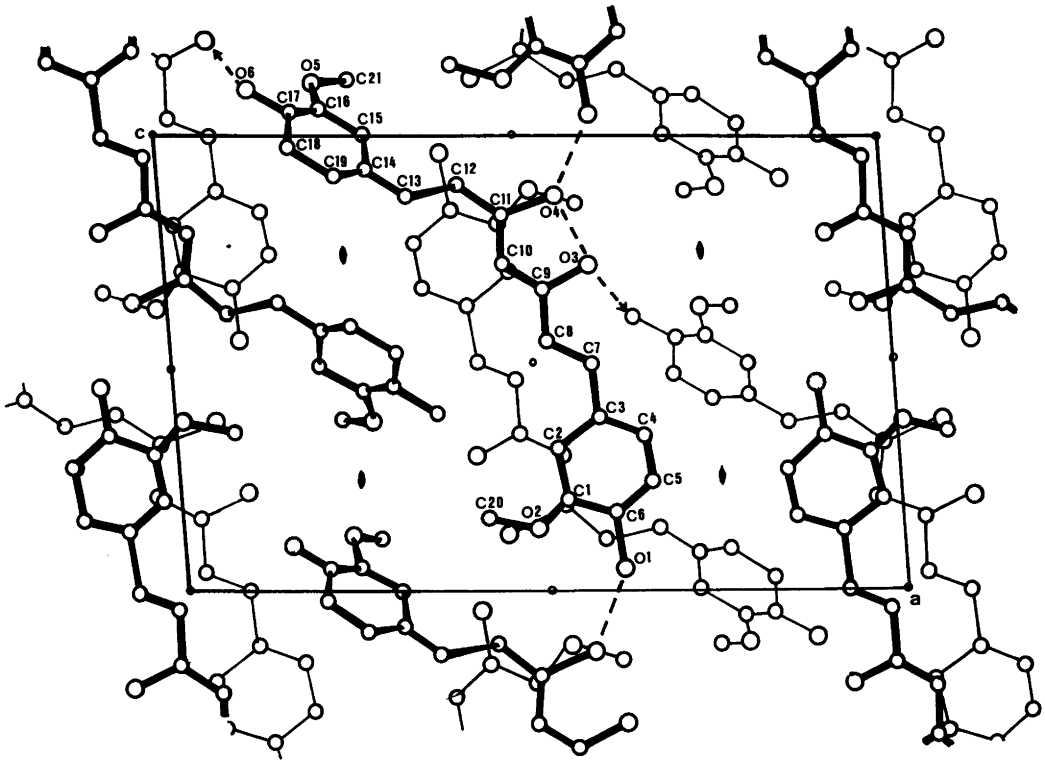

Fig. 1. Numbering of the atoms and the molecular packing in crystals of curcumin.

Table 3. Bond lengths and angles in curcumin. Estimated standard deviations are given in parentheses.

Bond lengths (Å)		Bond angles (°)	
O1 – C6	1.364(2)	C20 – O2 – C1	116.7(2)
O2 – C1	1.366(2)	O2 – C1 – C2	126.2(2)
O2 – C20	1.440(2)	O2 – C1 – C6	113.7(2)
C1 – C2	1.377(3)	C1 – C2 – C3	120.2(2)
C2 – C3	1.410(3)	C2 – C3 – C7	122.7(2)
C3 – C4	1.401(3)	C2 – C3 – C4	118.9(2)
C4 – C5	1.388(3)	C3 – C4 – C5	120.9(2)
C5 – C6	1.379(3)	C4 – C3 – C7	118.4(2)
C6 – C1	1.417(3)	C4 – C5 – C6	120.0(2)
C3 – C7	1.457(3)	C5 – C6 – O1	119.1(2)
C7 – C8	1.348(3)	O1 – C6 – C1	120.9(2)
C8 – C9	1.450(3)	C3 – C7 – C8	128.3(2)
C9 – O3	1.312(2)	C7 – C8 – C9	121.5(2)
C9 – C10	1.403(3)	C8 – C9 – O3	118.4(2)
C10 – C11	1.392(3)	C8 – C9 – C10	121.7(2)
O4 – C11	1.316(2)	O3 – C9 – C10	119.9(2)
C11 – C12	1.457(3)	C9 – C10 – C11	120.7(2)
C12 – C13	1.344(3)	C10 – C11 – O4	120.3(2)
C13 – C14	1.471(3)	C10 – C11 – C12	124.9(2)
C14 – C15	1.397(3)	O4 – C11 – C12	114.8(2)
C15 – C16	1.392(3)	C12 – C13 – C14	124.3(2)
O5 – C16	1.364(2)	C13 – C14 – C15	120.8(2)
O5 – C21	1.432(3)	C13 – C14 – C19	120.0(2)
C16 – C17	1.404(3)	C14 – C15 – C16	120.5(2)
O6 – C17	1.372(2)	C15 – C16 – C17	119.6(2)
C17 – C18	1.375(3)	C15 – C16 – O5	125.3(2)
C18 – C19	1.402(3)	C16 – O5 – C21	117.5(2)
C19 – C14	1.394(3)	C16 – C17 – C18	120.3(2)
		C16 – C17 – O6	121.2(2)
The mean value of		O6 – C17 – C18	118.5(2)
the X – H distances		C17 – C18 – C19	119.9(2)
C – H	0.98(3)	C18 – C19 – C14	120.4(2)
O – H	0.81(7)	C19 – C14 – C15	119.2(2)

Table 4. Torsion angles in curcumin.

Angle	(°)
C20 – O2 – C1 – C2	7.7
C2 – C3 – C7 – C8	– 5.7
C3 – C7 – C8 – C9	– 176.9
C7 – C8 – C9 – C10	– 177.0
C7 – C8 – C9 – O3	3.7
C8 – C9 – C10 – C11	178.8
O3 – C9 – C10 – C11	0.5
C9 – C10 – C11 – O4	– 1.7
C9 – C10 – C11 – C12	176.4
C10 – C11 – C12 – C13	18.4
O4 – C11 – C12 – C13	– 163.3
C11 – C12 – C13 – C14	– 176.9
C12 – C13 – C14 – C15	25.2
C15 – C16 – O5 – C21	4.1

system. The molecule may be described as consisting of three substituted planar groups interconnected through the two double bonds C-7 – C8 and C12 – C13. The two terminal groups are identical but the inherent symmetry of the molecule is distorted in the crystal by a rotation of – 162° about the C11 – C12 bond.

Electron delocalization and intramolecular hydrogen bonding in the fragment – CO – HC = COH – has been studied in a number of molecules.[13] Of the possible tautomeric forms it appears that in the crystal phase, the β-diketones prefer the *cis*-enol configuration stabilized by a strong intramolecular H-bond. This hydrogen bond appears moreover invariably to be asymmetrical, the hydrogen atom always found to be bonded to one unique oxygen atom. A possible exception to this may exist

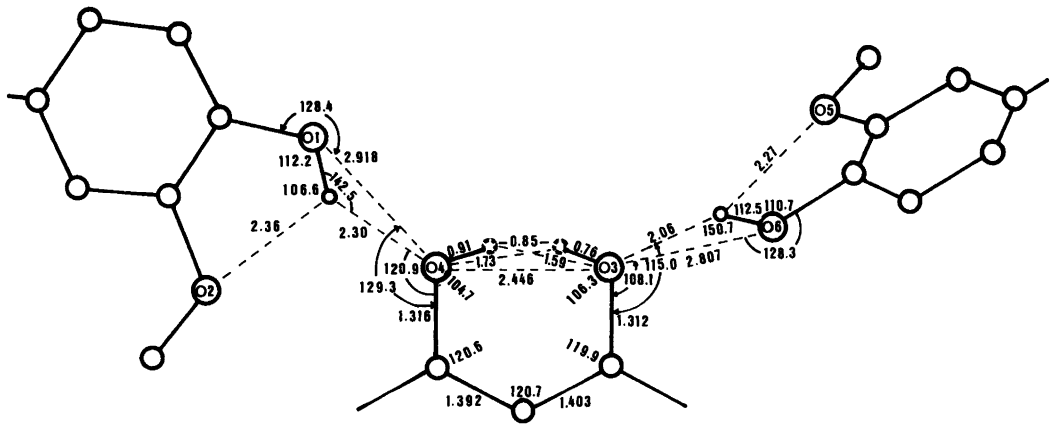

Fig. 2. Geometry in the enol ring and the hydrogen bond system.

in dibenzoylmethane[13] even if the asymmetry in the two C–O bonds seems to be persistent.

In the present structure, the oxygen atoms of the enol-ring are engaged in intermolecular as well as in intramolecular hydrogen bond and the geometry of this particular group and the hydrogen bond system is illustrated in Fig. 2. It may be noticed that both the phenolic hydrogen atoms are oriented towards the neighbouring oxygens, the torsion angles C1–C6–O1–HO1 and C16–C17–O6 –HO6 being 27 and 9°, respectively. The asymmetry of the external angles at C1 and C6 are as expected for such conformations. It may also be seen from Fig. 2 that there are no significant differences in the C–C or the C–O bonds in the enol ring. Furthermore, the best model to fit the data is the one with the hydrogen atom statistically distributed between the two oxygen atoms.

A certain conjugation between the aromatic ring I and the pseudo aromatic ring II seems to be indicated by the distances between the atoms connecting the two ring systems which also are essentially coplanar, the angle between the two ring planes being only about 3°. The interaction between the π-electron systems in ring II and III is probably somewhat less as the angle between these two ring planes is about 45°. The significant difference in the two bond lengths C3–C7 and C13–C14 may be a result of the rotation of 25° about the C13–C14 bond. The total twist of the molecule is indicated by the angle of 47° between ring planes I and III. It is interesting to notice that in the structure of dibenzoylmethane[12] there is a similar difference in the ring twists relative to the enol ring plane; namely −3.8 and 16.9°.

The pseudo aromatic character of the enol ring is finally reflected in the molecular packing in the crystal (Fig. 1). Molecules related by a center of symmetry are stacked along the direction of the *b*-axis, the distance between molecular planes being about 3.45 Å and the respective atomic distances being 3.475 *Å* (C1---C11), 3.517 *Å* (C1---C10), 3.513 *Å* (C2–C10) and 3.650 *Å* (C2–C9). The stacks are finally bonded together by the hydrogen bonds.

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Received January 19, 1982.