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4-[2-(*o*-Carboxybenzamido)ethyl]phenoxyacetic Acid Dihydrate

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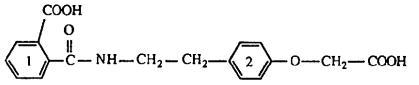
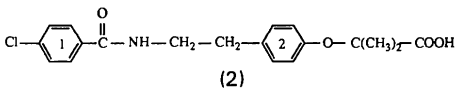
Abstract. $C_{18}H_{17}NO_6.2H_2O$, $M_r = 379{\cdot}386$, monoclinic, $P2_1/c$, $a = 7{\cdot}161\ (5)$, $b = 12{\cdot}997\ (2)$, $c = 20{\cdot}290\ (3)$ Å, $\beta = 99{\cdot}22\ (2)°$, $V = 1861{\cdot}4$ Å^3, $Z = 4$, $D_x = 1{\cdot}354$ g cm^{-3}, Cu $K\alpha$ radiation, $\lambda = 1{\cdot}5418$ Å, $\mu = 9{\cdot}2$ cm^{-1}, $F(000) = 800$, $T = 293$ K, final $R(F) = 0{\cdot}051$ for 2262 observed reflections. The structure was solved by direct methods and compared to the previously determined structure of the analogous drug molecule, bezafibrate. The structural characteristics of the two compounds are then correlated to their relative activities as allosteric effectors of hemoglobin. The molecule adopts a synplanar–antiplanar conformation unlike other phenoxyacetic acids.

Introduction. 4-[2-(*o*-Carboxybenzamido)ethyl]phenoxyacetic acid, AM49 (1), is an analog of the antihyperlipoproteinemic agent bezafibrate, BZF (2).



(1)



(2)

BZF has been shown to bind to the central water cavity of deoxyhemoglobin (Perutz, Fermi, Abraham, Poyart & Bursaux, 1986) and acts as an allosteric effector of hemoglobin. The crystal structure of bezafibrate has previously been reported [$P2_12_12_1$; $a = 10{\cdot}319\ (1)$, $b = 17{\cdot}823\ (2)$, $c = 19{\cdot}842\ (1)$ Å] (Hegde, Sawzik, McClure & Abraham, 1988) and later confirmed by Djinovic, Globokar & Zupet (1989) [$P2_12_12_1$; $a = 10{\cdot}222\ (2)$, $b = 17{\cdot}826\ (3)$, $c = 19{\cdot}921\ (4)$ Å]. In a continuing effort to design compounds with enhanced allosteric activity, AM49 introduces an ortho acid functionality tailored to interact electrostatically with the positive charge on Lys99α of hemoglobin. The crystal structure of AM49 is reported here along with a comparison of its features with those of the parent compound BZF.

Experimental. The title compound was crystallized from methanol at room temperature. Data were collected on a Rigaku AFC5 diffractometer equipped with a rotating-anode X-ray source. The crystal had dimensions $0{\cdot}2 \times 0{\cdot}2 \times 0{\cdot}5$ mm. Cell parameters were measured on the diffractometer using 25 reflections in the 2θ range 50–80°. Range of indices $0 < h < 9$, $0 < k < 16$, $-24 < l < 24$ ($\theta < 60°$). Empirical absorption correction was applied based on ψ scans of three reflections with minimum and maximum transmission coefficients of 0·84 and 1·00. Three standard reflections ($03\bar{1}$, $13\bar{1}$, 112) measured every 150 reflections showed no decrease in intensity (99·7, 100·3

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Table 1. *Fractional atomic coordinates for* AM49 *and* B_{eq} *values with e.s.d.'s in parentheses*

$B_{eq} = (4/3)\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}(Å^2)
C(1)	1·0086 (5)	−0·1944 (2)	0·1999 (1)	3·7 (9)
C(2)	0·8328 (5)	−0·1668 (2)	0·1629 (1)	3·4 (8)
C(3)	0·6899 (6)	−0·2381 (2)	0·1506 (2)	4·5 (10)
C(4)	0·7185 (7)	−0·3389 (3)	0·1736 (2)	5·4 (12)
C(5)	0·8909 (7)	−0·3663 (3)	0·2098 (2)	5·7 (13)
C(6)	1·0348 (6)	−0·2953 (2)	0·2233 (2)	4·7 (11)
C(7)	1·1705 (5)	−0·1217 (2)	0·2102 (2)	3·9 (9)
C(8)	0·7900 (4)	−0·0573 (2)	0·1414 (2)	3·3 (8)
C(9)	0·7178 (5)	0·0616 (2)	0·0468 (2)	3·9 (9)
C(10)	0·8901 (5)	0·1301 (2)	0·0550 (2)	4·4 (10)
C(11)	0·8439 (5)	0·2374 (2)	0·0278 (2)	3·6 (8)
C(12)	0·8116 (5)	0·2565 (2)	−0·0403 (2)	3·8 (9)
C(13)	0·7714 (5)	0·3540 (2)	−0·0656 (2)	3·8 (9)
C(14)	0·7586 (4)	0·4353 (2)	−0·0226 (2)	3·4 (8)
C(15)	0·7893 (5)	0·4186 (2)	0·0457 (2)	4·0 (9)
C(16)	0·8300 (5)	0·3195 (2)	0·0700 (2)	4·0 (10)
C(17)	0·7217 (5)	0·6163 (2)	−0·0093 (2)	3·7 (9)
C(18)	0·6873 (4)	0·7144 (2)	−0·0487 (2)	3·5 (9)
N(1)	0·7584 (4)	−0·0402 (2)	0·0761 (1)	3·7 (7)
O(1)	1·1884 (4)	−0·0524 (2)	0·1725 (1)	5·0 (7)
O(2)	1·2916 (4)	−0·1403 (2)	0·2650 (1)	6·5 (9)
O(3)	0·7745 (3)	0·0100 (1)	0·1832 (1)	4·2 (6)
O(4)	0·7166 (3)	0·5301 (1)	−0·0527 (1)	3·9 (6)
O(5)	0·6869 (4)	0·7956 (2)	−0·0199 (1)	4·7 (7)
O(6)	0·6585 (4)	0·7041 (2)	−0·1138 (1)	4·6 (7)
O*W*(1)	0·3988 (4)	0·4677 (2)	0·2063 (2)	4·9 (8)
O*W*(2)	0·4244 (5)	0·1243 (2)	0·1751 (1)	5·5 (8)

and 100·4% of initial intensity at the end of data collection). Of the 3150 reflections measured, 2262 were observed with $I > 2{\cdot}0\sigma(I)$ and were used in the structure refinement. Direct methods (*SHELX*76; Sheldrick, 1976) were used for structure determination. H atoms located by difference Fourier synthesis. Anisotropic full-matrix least-squares refinement (on F) for non-H atoms, isotropic for H atoms. $\sum[w(k|F_o| - |F_c|)^2]$, where $w = 1/\sigma(|F_o|)^2$ was minimized (*UPALS*; Lundgren, 1978). $R = 0{\cdot}051$, $wR = 0{\cdot}067$, $S = 1{\cdot}589$, ratio of maximum least-squares shift to e.s.d. = 0·02, maximum peak height in the final difference Fourier map = 0·25 e Å^{-3}. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, pp. 71, 148). Atomic parameters are given in Table 1,* selected bond lengths, bond angles and relevant torsion angles are presented in Table 2. The atom-numbering scheme is shown in Fig. 1.

Discussion. The bond distances and angles in the structure are within the expected ranges of values. The atoms of the peptide group are planar and the least-squares plane of the peptide group forms angles of 69·1 (1) and 3·7 (3)° with phenyl rings 1 and 2

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53826 (13 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond lengths* (Å), *bond angles* (°), *selected torsion angles* (°), *and hydrogen-bond geometry* (Å, °)

C(1)—C(2)	1·399 (4)	C(1)—C(6)	1·396 (5)
C(1)—C(7)	1·483 (4)	C(2)—C(3)	1·372 (5)
C(2)—C(8)	1·505 (4)	C(3)—C(4)	1·394 (6)
C(4)—C(5)	1·373 (6)	C(5)—C(6)	1·376 (6)
C(7)—O(2)	1·312 (4)	O(1)—C(7)	1·202 (4)
O(3)—C(8)	1·236 (4)	N(1)—C(8)	1·324 (4)
C(10)—C(9)	1·508 (5)	N(1)—C(9)	1·460 (5)
C(10)—C(11)	1·516 (5)	C(11)—C(12)	1·386 (4)
C(12)—C(13)	1·378 (5)	C(13)—C(14)	1·384 (4)
C(14)—C(15)	1·383 (4)	C(14)—O(4)	1·385 (4)
C(15)—C(16)	1·392 (5)	C(11)—C(16)	1·381 (5)
C(17)—C(18)	1·504 (5)	C(17)—O(4)	1·421 (4)
C(18)—O(5)	1·207 (4)	C(18)—O(6)	1·308 (4)

C(1)—C(2)—C(3)	120·0 (3)	C(2)—C(3)—C(4)	120·7 (3)
C(3)—C(4)—C(5)	119·4 (4)	C(4)—C(5)—C(6)	120·5 (4)
C(5)—C(6)—C(1)	120·6 (3)	C(6)—C(1)—C(2)	118·7 (3)
C(2)—C(1)—C(7)	121·5 (3)	C(1)—C(7)—O(1)	123·5 (3)
C(1)—C(7)—O(2)	113·0 (3)	C(2)—C(8)—O(3)	120·6 (3)
C(2)—C(8)—N(1)	116·1 (3)	O(3)—C(8)—N(1)	123·2 (3)
C(8)—N(1)—C(9)	123·3 (3)	N(1)—C(9)—C(10)	112·8 (3)
C(9)—C(10)—C(11)	112·3 (3)	C(10)—C(11)—C(12)	121·1 (3)
C(11)—C(12)—C(13)	121·6 (3)	C(12)—C(13)—C(14)	120·0 (3)
C(13)—C(14)—C(15)	119·7 (3)	C(14)—C(15)—C(16)	119·2 (3)
C(15)—C(16)—C(11)	121·9 (3)	C(16)—C(11)—C(12)	117·6 (3)
C(14)—O(4)—C(17)	116·6 (2)	O(4)—C(17)—C(18)	110·7 (3)
C(17)—C(18)—O(5)	119·8 (3)	C(17)—C(18)—O(6)	115·8 (3)
O(5)—C(18)—O(6)	124·4 (3)		

C(7)—C(1)—C(2)—C(8)	−10·0 (5)	C(10)—C(9)—N(1)—C(8)	73·2 (4)
C(1)—C(2)—C(8)—O(3)	−68·2 (4)	C(9)—C(10)—C(11)—C(12)	−75·7 (4)
C(3)—C(2)—C(8)—N(1)	−69·6 (4)	C(13)—C(14)—O(4)—C(17)	−173·8 (3)
C(2)—C(8)—N(1)—C(9)	−179·0 (3)	O(4)—C(17)—C(18)—O(5)	−179·9 (3)
O(3)—C(8)—N(1)—C(9)	5·4 (5)	O(4)—C(17)—C(18)—O(6)	0·3 (4)
N(1)—C(9)—C(10)—C(11)	−176·8 (3)		

Donor atom	H(*D*)	Acceptor atom	*D*···*A*	*D*—H···*A*	Code
N(1)	H(N1)	O(5)	2·877 (4)	164·61	i (0 −1 0)
O(*W*2)	H(O*W*2)	O(1)	2·847 (4)	173·17	i (−1 0 0)
O(2)	H(O2)	O(*W*1)	2·605 (4)	164·05	ii (2 −1 0)
O(*W*2)	H(O*W*2)	O(3)	2·895 (4)	164·93	i (0 0 0)
O(6)	H(O6)	O(*W*2)	2·573 (4)	177·47	iii (1 1 0)
O(*W*1)	H″(O*W*1)	O(6)	2·901 (4)	137·40	iii (1 1 0)
O(*W*1)	H′(O*W*1)	O(3)	2·795 (4)	160·36	ii (1 0 0)

Symmetry codes: (i) x, y, z; (ii) $-x, y+\frac{1}{2}, -z+\frac{1}{2}$; (iii) $-x, -y, -z$.

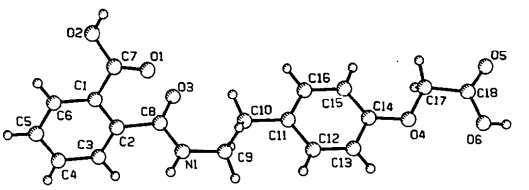
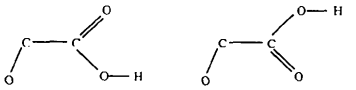


Fig. 1 Atom-numbering scheme of AM49.

respectively. The corresponding angles in the crystal structure of BZF were 14·0 (11) and 82·2 (11)° for molecule *A* and 21·6 (14) and 83·3 (14)° for molecule *B*. Steric hinderance from the *ortho* carboxylic acid group probably accounts for the larger angle between the plane of the peptide group and the benzamido moiety. The torsion angle about the N(1)—C(9) bond which was found to be 176·5 and −177·2° for the two independent molecules of BZF (Hegde, Sawzik, McClure & Abraham, 1988) is 73·2°

in AM49. The terminal carboxyl group adopts a synplanar–antiplanar conformation (*a*), unlike the synplanar–synplanar (*b*) conformation found in the analogous α,β-saturated carboxylic acids (Leiserowitz, 1976), in other phenoxyacetic acids (Kennard, Smith & White, 1982) and for both molecules *A* and *B* in the crystal structure of BZF (Hegde, Sawzik, McClure & Abraham, 1988; Djinovic, Globokar & Zupet, 1989).



(*a*) (*b*)

The non-bonding distance O(ether)···O(carbonyl) is 3·528 Å, as opposed to 2·671 Å in phenoxyacetic acid. The O(ether)···O(hydroxyl) distance is 2·580 Å. The O(4)—C(17)—C(18)—O(6) torsion angle is 0·33° in AM49 compared to 179·2° in phenoxyacetic acid. There is no disorder in the terminal carboxylic acid group [C=O and C—O(H) distances are listed in Table 2]. The water molecules are tethered to AM49 by hydrogen bonds (distances and angles listed in Table 2). The only direct intermolecular hydrogen bond is between the carbonyl O(5) and peptide N(1). All other hydrogen bonds are water mediated.

The two phenyl rings are at a dihedral angle of −67·9 (1)° to each other. The corresponding angle for BZF was found to be 68·3 (11) and 62·1 (14)° for the two independent molecules in the asymmetric unit and 33·5° in the BZF–deoxyhemoglobin structure. The phenyl rings of protein-bound BZF (Perutz, Fermi, Abraham, Poyart & Bursaux, 1986) are more planar than the phenyl rings in the BZF

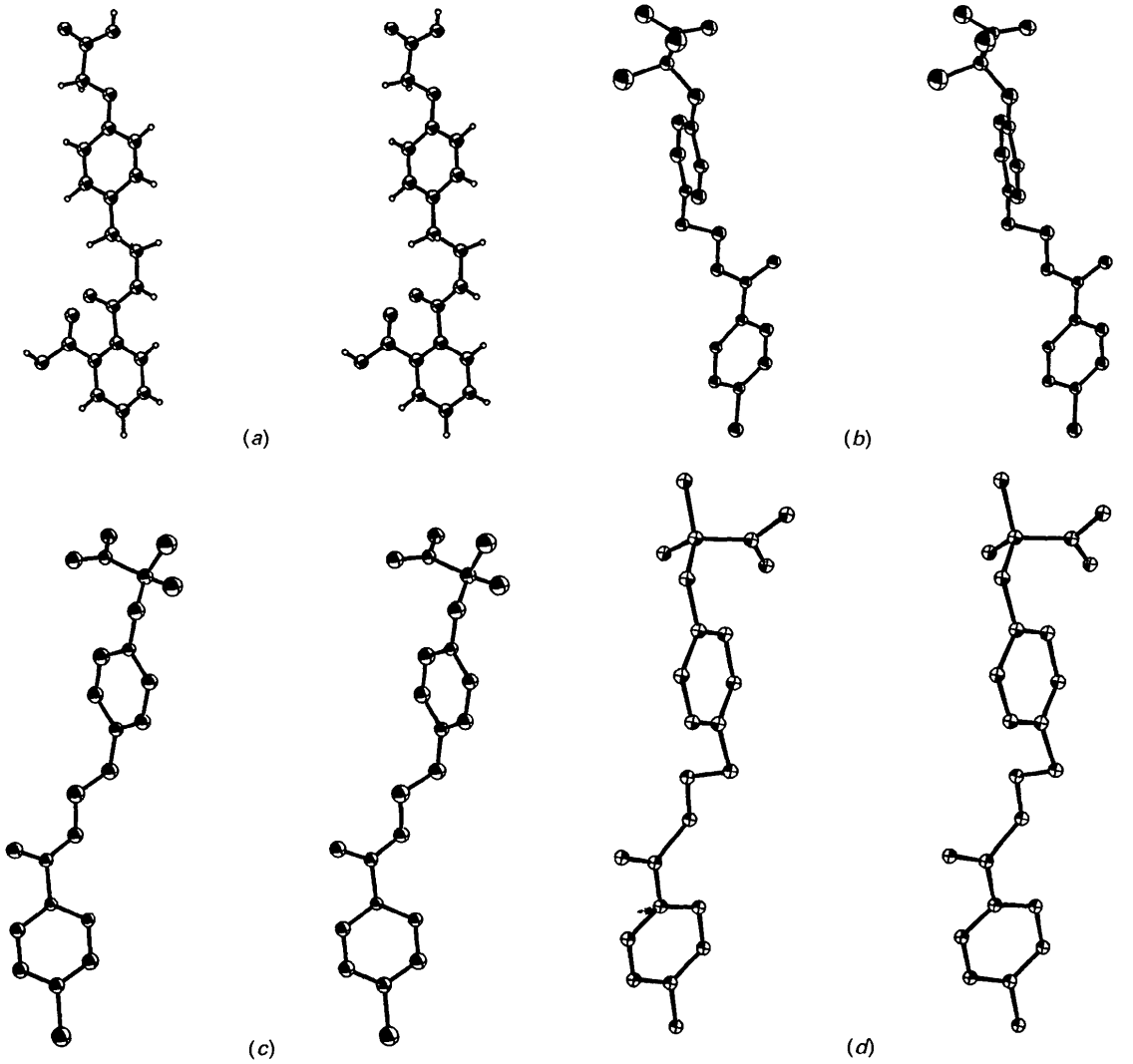


Fig. 2. *PLUTO* (Motherwell & Clegg, 1978) plots of (*a*) the conformation of AM49, (*b*) and (*c*) the conformations of the two independent molecules of BZF and (*d*) the conformation of BZF bound to deoxyhemoglobin.

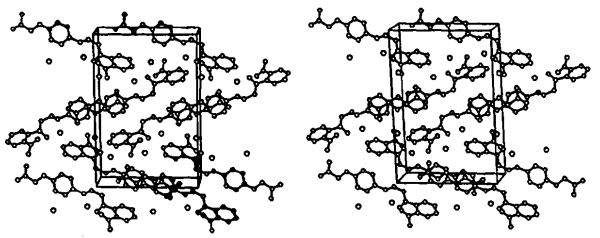


Fig. 3. Molecular packing of AM49 (*ORTEP*; Johnson, 1965). *a* is into the plane of the paper, *b* is horizontal and *c* is vertical.

crystal forms. Fig. 2 compares the conformation of AM49 (Fig. 2*a*) with the two independent molecules of BZF (Figs. 2*b* and 2*c*), and the deoxyhemoglobin-BZF bound conformation (Fig. 2*d*). The decrease in oxygen affinity for hemoglobin (a measure of allosteric effector activity) was equivalent for BZF and AM49, with $\Delta P_{50} = 10$ mm of Hg at 10 m*M* drug concentration and 2·7 m*M* hemoglobin. Thus it appears that the addition of an *o*-COOH group did not change the allosteric effector activity as envisioned.

Fig. 3 shows the molecular packing of AM49, drawn using *ORTEP* (Johnson, 1965).

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Lattice Inclusion Compounds of Gossypol. Structure of 2/1 Gossypol/Di-*n*-propyl Ether Coordinatoclathrate

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Abstract. $C_{30}H_{30}O_8.1/2C_6H_{14}O$, $M_r = 569{\cdot}65$, monoclinic, $C2/c$, $a = 11{\cdot}544\ (3)$, $b = 30{\cdot}602\ (7)$, $c = 16{\cdot}472\ (4)$ Å, $\beta = 90{\cdot}84\ (2)°$, $V = 5818\ (3)$ Å^3, $Z = 8$, $D_x = 1{\cdot}30$ g cm^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}5418$ Å, $\mu = 7{\cdot}28$ cm^{-1}, $F(000) = 2424$, $T = 293$ K, $R = 0{\cdot}078$ for 1998 observed reflections. Despite its potential C_2 symmetry, the di-*n*-propyl ether molecule is statistically disordered in the cage with C_2 symmetry; it is non-symmetrical, with C—C torsion angles (+)antiperiplanar and one C—O torsion angle (−)anticlinal, the other (+)synclinal. The guest molecule is hydrogen bonded to one of the two O(5)—H hydroxyls located on the wall of the cage. Crystal data for some other inclusion compounds, isostructural with gossypol/di-*n*-propyl ether crystals, are also given.

Introduction. Gossypol [1,1′,6,6′,7,7′-hexahydroxy-5,5′-diisopropyl-3,3′-dimethyl-(2,2′-binaphthalene)-8,8′-dicarboxaldehyde] shows remarkable inclusion ability towards a number of chemically different guest substrates (Ibragimov, Talipov, Dadabaev, Nazarov & Aripov, 1988). The host structure is easily rearranged to accommodate guests of proper size, shape and chemical nature and therefore numerous structural types of gossypol inclusion compounds are observed. Some carboxylic acid esters and ketones with carbon–oxygen or carbon chains, five, six or seven atoms long form isostructural inclusion compounds of a cage type (Ibragimov, Talipov & Gdaniec, 1990; Ibragimov, Talipov & Dadabaev, 1988). The presence of a carbonyl group in the guest molecule was believed to be a necessary condition for formation of inclusion compounds of this structural type. Recently, inclusion compounds of gossypol with di-*n*-propyl ether, butyl ethyl ether, propyl butyrate, acetonylacetone and methyl (*S*)-(−)-2-chloroacetate were crystallized. Space group and

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