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CRYSTAL STRUCTURES OF 4-(OXIRAN-2-YLMETHOXY)BENZOIC ACID AND 4-ACETOXYBENZOIC ACID

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Compounds 4-(oxiran-2-ylmethoxy)benzoic acid (**2**) and 4-acetoxybenzoic acid (**4**) are synthesized by a new synthetic route and studied by X-ray crystallography. Compound **2** crystallizes in the monoclinic system, $P2_1/n$ space group, $a = 5.1209(2)$ Å, $b = 30.3429(16)$ Å, $c = 5.9153(3)$ Å, $\beta = 96.725(3)°$, $V = 912.81(8)$ Å^3, $Z = 4$. Compound **4** crystallizes in the triclinic system, P-1 space group, $a = 7.3400(4)$ Å, $b = 8.0819(3)$ Å, $c = 15.6548(9)$ Å, $\alpha = 85.754(3)°$, $\beta = 84.268(2)°$, $\gamma = 70.023(3)°$, $V = 867.63(8)$ Å^3, $Z = 4$. The crystal structure of **2** comprises two crystallographically independent molecules of the compound. In the crystal structures of **2** and **4**, pairs of molecules form carboxyl dimers.

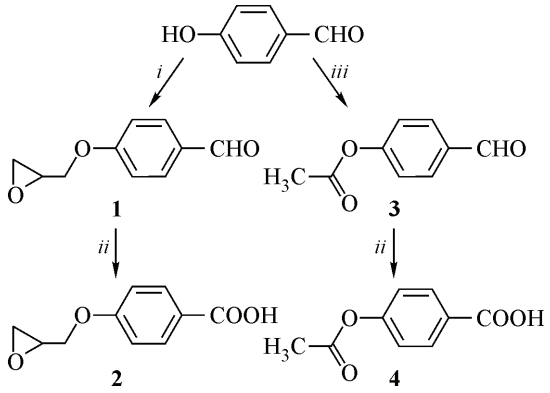
K e y w o r d s: crystal structure, epoxide, hydrogen bond, carboxylic acid.

INTRODUCTION

The emergence of new pathogenic bacterial strains with high resistance to antibacterial agents constitutes a serious public health threat. Not only the currently used antimicrobial drugs (β-lactams, macrolides, and quinolones), but also drugs considered to be the last line of defence (linezolid and vancomycin) are becoming less effective. This situation strongly supports the search for novel antibacterial agents [1, 2].

The peptidoglycan biosynthetic pathway is one of the best known and most validated targets for antibacterial therapy. Peptidoglycan confers a defined cell shape and preserves cell integrity by compensating internal osmotic pressure. Therefore it is an essential component of the bacterial cell wall for both Gramm positive and negative microorganisms. Any perturbation of the multi-step peptidoglycan biosynthesis may lead to cell death [3]. Peptidoglycan polymer consists of a linear chain of repeating *N*-acetylglucosamine (Glc*N*Ac) and *N*-acetylmuramic acid (Mur*N*Ac) monomeric units, interconnected by short peptide chains. The assembly of the peptide moiety by the successive additions of amino acids L-alanine, D-glutamate, *meso*-diaminopimelate (or L-lysine) and D-alanyl-D-alanine to UDP-Mur*N*Ac is catalyzed by four ADP-forming ligases (MurC, MurD, MurE and MurF). These essential cytoplasmic enzymes are present only in bacteria and are highly specific, thus making them attractive as targets for the development of new therapeutic agents to counter bacterial infections [4].

Based on our previous studies in the field of new antimicrobial drug design [5—7] and further docking studies we came across three useful intermediates for the synthesis of our compounds: 4-(oxiran-2-ylmethoxy)benzaldehyde (**1**), 4-(oxiran-2-ylmethoxy)benzoic acid (**2**), and 4-acetoxybenzoic acid (**4**).



Scheme 1. Synthesis of compounds **2** and **4**:
(*i*) 1. NaOH, 2. epichlorohydrin; (*ii*) 30 % H_2O_2; (*iii*) Ac_2O, pyridine

EXPERIMENTAL

Chemicals and solvents from Fluka and Sigma-Aldrich Chemical Co. were used without further purification. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel ($60F_{254}$) plates (0.25 mm). Flash column chromatography was performed on flash column silica gel 60 (Merck, particle size 40—60 mesh). Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H-, COSY-, HMQC-, and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX_{300} spectrometer in the DMSO-d_6 solution with TMS as the internal standard. Chemical shifts were reported in ppm (δ) downfield from TMS. All the coupling constants (*J*) are in Hertz. IR spectra were recorded on a Perkin-Elmer FTIR 1600 spectrometer. Mass spectra were obtained with a VG-Analytical Autospec Q mass spectrometer with ESI ionization (MS Centre, Jožef Stefan Institute, Ljubljana). Elemental analyses were performed by the Department of Organic Chemistry, Faculty of Chemistry and Chemical Technology, Ljubljana, on a Perkin Elmer elemental analyzer 240 C. All reported yields are the yields of purified products.

4-(Oxiran-2-ylmethoxy)benzaldehyde (1). 4-Hydroxybenzaldehyde (6.10 g, 50.0 mmol) was dissolved in 2 M NaOH (30 ml). Epichlorohydrin (4.68 g, 50.0 mmol) was added dropwise to the solution stirred at 0 °C. Reaction mixture was stirred overnight at room temperature. The solution was extracted with dichloromethane (3×25 ml) and the combined organic phases washed with 1 M HCl (3×40 ml), water (40 ml), and brine (25 ml). The organic phase was dried with Na_2SO_4, and the solvent removed under reduced pressure. The crude product was purified with flash column chromatography on silica (MF: petrolether/ethyl acetate = 2:1). Yield 79 %. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.73 (m, 1H, CH_2, (C10)), 2.87 (m, 1H, CH_2, (C10)), 3.37 (m, 1H, CH, (C9)), 3.96 (m, 1H, CH_2, (C8)), 4.47 (m, 1H, CH_2, (C8)), 7.16 (A_2X_2, J = 8.7 Hz, Δν = 214 Hz, 2H, Ar—H, (C4, C6)), 7.87 (A_2X_2, J = 8.7 Hz, Δν = 214 Hz, 2H, Ar—H, (C3, C7)), 9.88 (s, 1H, CHO) ppm. ^{13}C NMR (300 MHz, DMSO-d_6): 44.6 (C10), 50.3 (C9), 70.3 (C8), 115.9 (C4, C6), 130.8 (C2), 132.7 (C3, C7), 164.0 (C5), 192.2 (C1) ppm. MS *m*/*z* (rel. intensity): 178(M^+, 100). IR (KBr): ν 3675, 3069, 1681, 1600, 1576, 1424, 1303, 1246, 1163, 1024, 911, 837 cm^{-1}. Elemental analysis for $C_{10}H_{10}O_3$: Calculated: 67.41 % C, 5.66 % H, 0 % N, measured: 67.77 % C, 5.78 % H, 0 % N, mp = 32—34 °C [8].

4-(Oxiran-2-ylmethoxy)benzoic acid (2). 4-(Oxiran-2-ylmethoxy)benzaldehyde (5.80 g, 32.6 mmol) was pulverized in a 100 ml flask and 30 % hydrogen peroxide (50 ml) was added. The reaction mixture was stirred vigorously for 30 min at room temperature. Dichloromethane (100 ml) was added and the phases were separated. The organic phase was washed with brine, dried over Na_2SO_4, and the solvent removed under reduced pressure to yield white solid. Yield 86 %. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.74 (m, 1H, CH_2, (C10)), 2.86 (m, 1H, CH_2, (C10)), 3.37 (m, 1H, CH, (C9)), 3.93 (m, 1H, CH_2, (C8)), 4.44 (m, 1H, CH_2, (C8)), 7.21 (A_2X_2, J = 8.7 Hz, Δν = 279 Hz, 2H, Ar—H, (C4, C6)), 8.14 (A_2X_2, J = 8.7 Hz, Δν = 214 Hz, 2H, Ar—H, (C3, C7)), 12.63 (s, 1H, COOH)

ppm. ^{13}C NMR (300 MHz, DMSO-d_6): 43.9 (C10), 52.7 (C9), 70.0 (C8), 116.2 (C4, C6), 122.7 (C2), 133.5 (C3, C7), 164.9 (C5), 172.4 (C1) ppm. MS *m*/*z* (rel. intensity): 193 ((M-1)$^+$, 100). IR (KBr): ν 3445, 3072, 3004, 2933, 2739, 1690, 1600, 1508, 1456, 1314, 1260, 1160, 1023, 837, 760, 615, 509 cm^{-1}. Elemental analysis for $C_{10}H_{10}O_4$: Calculated: 61.85 % C, 5.19 % H, 0 % N, measured: 61.32 % C, 5.24 % H, 0 % N, mp = 212—213 °C.

4-Acetoxybenzaldehyde (3). 4-Hydroxybenzaldehyde (2.45 g, 20.0 mmol) was dissolved in pyridine (30 ml) and acetanhydride (10.2 g, 0.1 mol) was added slowly at room temperature. The mixture was stirred for 2 h at room temperature until the starting compound was no longer detected with TLC and concentrated in vacuo. The crude product was dissolved in dichloromethane (30 ml), extracted with 1 M HCl (3×25 ml), water (25 ml), and brine (25 ml). The organic phase was dried with Na_2SO_4, and the solvent removed under reduced pressure to yield orange oil. Yield 92 %. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 8.14 (A_2X_2, J = 8.5 Hz, Δν = 179 Hz, 2H, Ar—H), 8.32 (A_2X_2, J = 8.5 Hz, Δν = 179 Hz, 2H, Ar—H), 10.01 (s, 1H, CHO) ppm. ^{13}C NMR (300 MHz, DMSO-d_6): 19.6 (C9), 121.5 (C4, C6), 129.8 (C3, C7), 133.5 (C2), 155.8 (C5), 169.4 (C8), 190.3 (C1) ppm. MS *m*/*z* (rel. intensity): 165 (MH, 100). IR (KBr): ν 3308, 2847, 1764, 1692, 1603, 1512, 1369, 1217, 912, 875, 732 cm^{-1} [9].

4-Acetoxybenzoic acid (4). 30 % Hydrogen peroxide (15 ml) was added to 4-acetoxybenzaldehyde (1.79 g, 10.0 mmol) and stirred vigorously for 30 min at room temperature. Dichloromethane (25 ml) was added and the phases were separated. The organic phase was washed with brine, dried over Na_2SO_4, and the solvent removed under reduced pressure to yield white solid. Yield 94 %. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30 (s, 3H, CH_3), 7.26 (A_2X_2, J = 8.6 Hz, Δν = 219 Hz, 2H, Ar—H), 8.00 (A_2X_2, J = 8.6 Hz, Δν = 219 Hz, 2H, Ar—H), 12.97 (s, 1H, COOH) ppm. ^{13}C NMR (300 MHz, DMSO-d_6): 19.6 (C9), 121.3 (C4, C6), 127.4 (C2), 130.5 (C3, C7), 156.0 (C5), 169.3 (C8), 171.2 (C1) ppm. MS *m*/*z* (rel. intensity): 179 ((M-1)$^+$, 100). IR (KBr): ν 3314, 3027, 1758, 1678, 1602, 1431, 1371, 1294, 1188, 1012, 915, 862 cm^{-1}, mp = 189—191 °C.

X-Ray diffraction analysis. Single crystal X-ray diffraction data were collected at room temperature on a Nonius Kappa CCD diffractometer with graphite monochromated MoK_α radiation (λ = = 0.71073 Å). The data were processed by DENZO [10]. Structures were solved by direct methods implemented in SHELXS-97 [11] and refined by a full-matrix least-squares procedure based on F^2 with SHELXL-97 [12]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were readily located in difference Fourier maps and were placed at calculated positions and treated using appropriate riding models. In molecule **2**, the O3 oxygen atom is disordered over two positions in a refined ratio of 0.88:0.12. Hydrogen atoms (H1 and H2) involved in hydrogen bonding in the molecule of **4** are disordered over two positions in a refined ratio of 0.50:0.50. Crystallographic data are listed in Table 1. The geometry parameters of **2** and **4** are very close to the corresponding ones found in the Cambridge structural database [13]. The structural data for compounds **2** and **4** were deposited with the Cambridge Crystallographic Data Center under the number CCDC 816654-816655. CIF files containing complete information on the studied structures may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, fax +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or from the following web site: www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

Compounds **1** and **3** were readily obtained by the reaction of 4-hydroxybenzaldehyde with epichlorohydrin and acetanhydride respectively. For further transformation a novel synthetic route using simple one step oxidation with hydrogen peroxide was developed, and carboxylic acids **2** and **4** were isolated in high yield. The structures of both acids were revealed by single crystal XRD.

The molecule of **2** is nearly planar, except the C10 and O3a,b atoms in the epoxy ring (Fig. 1). The mean plane through the acid group (O1/O2/C1) is inclined to the benzene ring by 3.10(2)°. Such small deviations from planarity of the benzene ring and the carboxylic group are often observed; see, for example, [14—19]. Similarly, only a small deviation of planarity is observed between the benzene ring and the O4/C8/C9 mean plane (2.28(10)°). The non-planarity of the molecule is due to the disor-

Table 1

Crystal Data and Structure Refinement for **2** *and* **4**

Parameters	**2**	**4**
Empirical formula	$C_{10}H_{10}O_4$	$C_9H_8O_4$
Formula weight, g/mol^{-1}	194.18	180.15
Temperature, K	293(2)	293(2)
Radiation wavelength, Å	0.71073	0.71073
Crystal size, mm	0.25×0.12×0.08	0.60×0.60×0.08
Crystal color	colorless	colorless
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	P-1
a, b, c, Å	5.1209(2), 30.3429(16), 5.9153(3)	7.3400(4), 8.0819(3), 15.6548(9)
α, β, γ, deg.	90, 96.725(3), 90	85.754(3), 84.268(2), 70.023(3)
Unit cell volume, Å^3	912.81(8)	867.63(8)
Z	4	4
Calculated density, g/cm^{-3}	1.413	1.379
Absorption coefficient, mm^{-1}	0.110	0.110
F(000)	408	376
θ range for data collection, deg.	3.53—26.73	3.26—27.52
Index ranges h, k, l (min/max)	–6/6, –37/38, –7/7	–8/9, –10/10, –20/19
Reflections collected	3382	5428
Independent reflections	1887	3700
R(int)	0.0286	0.0278
Completeness to θ, deg.	96.6 % to 26.73	92.1 % to 27.52
Reflections used	1151	2793
Refined parameters	138	242
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0553$, $wR2 = 0.1292$	$R1 = 0.0527$, $wR2 = 0.1370$
R indices (all data)	$R1 = 0.1003$, $wR2 = 0.1511$	$R1 = 0.0708$, $wR2 = 0.1548$
GOOF on F^2	1.038	1.037
Largest diff. peak and hole, e/Å^{-3}	0.331 and –0.233	0.203 and –0.216

dered epoxy ring (C9/C10/O3A and C9/C10/O3B) oriented at an angles of 62.2(3)° and 76.9(10)° against the benzene ring respectively. In the crystal structure of **2**, pairs of molecules are linked into dimers by O—H···O hydrogen bonding, with an O···H distance of 1.83 Å and an O···O distance of 2.635(2) Å. The O—H···O angle of 168.0° indicates strong hydrogen bonding and the dimers are located around the centers of inversion (Table 2). Benzene rings in a dimer are coplanar; the distance between the mean planes is 0.342 Å.

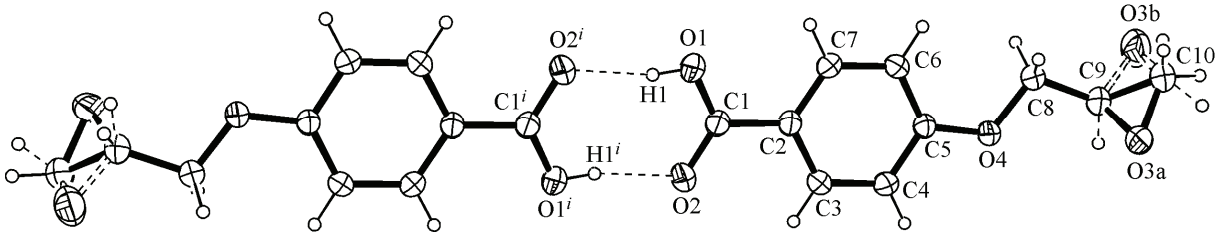


Fig. 1. X-Ray crystal structure of **2**, showing a hydrogen-bonded dimer with labeling and atomic displacement parameters at the 30 % probability level.

Hydrogen bonding is indicated by dashed lines [symmetry code: (i) x, $-y$, $1-z$]. Bond of the disordered O3 and H atoms with the minor site occupation factor are drawn with a broken line

Table 2

Hydrogen bond geometry in **2** (Å, deg.)

D—H···A	D—H, Å	H···A, Å	D···A, Å	D—H···A, deg	Symmetry code
O1—H1···O2	0.82	1.83	2.635(2)	168.0	–*x*, –*y*, 1–*z*
C9—H9A···O3A	0.98	2.50	3.384(4)	149	1/2+*x*, 1/2–*y*, 1/2+*z*
C10—H10A···O3A	0.97	2.52	3.191(5)	126	1/2+*x*, 1/2–*y*, –1/2+*z*

Table 3

Hydrogen bond geometry in **4** (Å, deg.)

D—H···A	D—H, Å	H···A, Å	D···A, Å	D—H···A, deg.	Symmetry code
O1—H1A···O6	0.82	1.83	2.6272(19)	163.0	*x*, *y*, *z*
O2—H1B···O5	0.82	1.82	2.6222(18)	167.0	*x*, *y*, *z*
O5—H2A···O2	0.82	1.82	2.6222(18)	165.5	*x*, *y*, *z*
O6—H2B···O1	0.82	1.82	2.6272(19)	167.1	*x*, *y*, *z*
C3—H3···O6	0.93	2.56	3.418(3)	154	–1+*x*, *y*, *z*
C4—H4···O1	0.93	2.52	3.370(3)	152	–1+*x*, *y*, *z*
C9—H9C···O4	0.96	2.52	3.477(3)	176	–1–*x*, 1–*y*, 2–*z*
C15—H15···O5	0.93	2.59	3.409(3)	147	1+*x*, *y*, *z*
C16—H16···O2	0.93	2.58	3.440(3)	154	1+*x*, *y*, *z*
C18—H18B···O4	0.96	2.54	3.500(3)	175	1+*x*, 1+*y*, –1+*z*

Compound **4** crystallizes with two independent molecules in the asymmetric unit (Fig. 2). These two molecules are almost identical. The mean plane through the O1/O2/C1 carboxyl group is inclined to the benzene ring by 2.00(12)°, which is less than in compound **2**. Interestingly, the mean plane through the O5/O6/C10 carboxyl group of the second molecule in the asymmetric unit of crystal structure **4** is inclined to the benzene ring by 10.23(11)°. This value is markedly higher than that in the case of compound **2**, but still smaller than in *ortho* substituted benzoic acids, see for example [20—22]. The acetyl group in *para* position is not coplanar with the benzene ring. The C8/O3/C5/C6 torsion angle is 55.2(2)°, and C17/O7/C14/C15 is 67.9(2)°. In the crystal structure of **4**, two independent molecules are linked into dimers by O—H···O hydrogen bonding. Hydrogen atoms involved in hydrogen bonding are disordered over two positions with the refined occupation factor of 0.50. For the hydrogen bonding geometry see Table 3. Contrary to the molecule of **2**, benzene rings in the dimers of **4** are inclined by 11.46(9)° rather than coplanar.

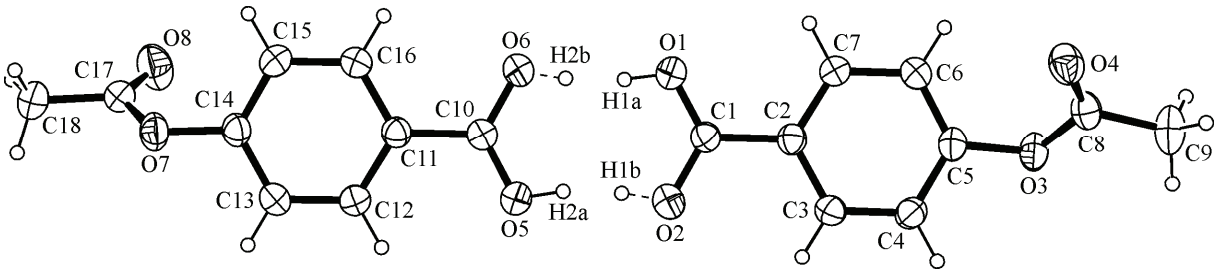


Fig. 2. Asymmetric unit in the X-ray crystal structure of **4**, showing a hydrogen bonded dimer with labeling and atomic displacement parameters at the 30 % probability level.
Bonds of the disordered H atoms with the minor site occupation factor are drawn with a broken line. Hydrogen bonding is not indicated due to disorder

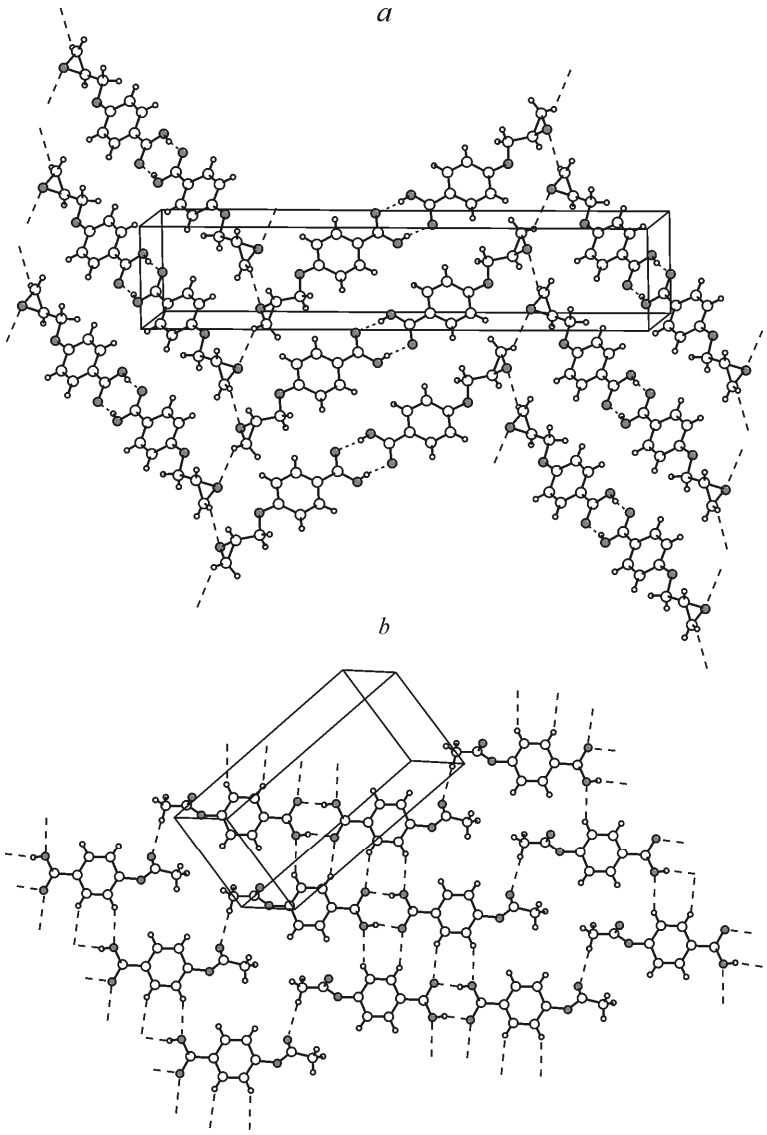


Fig. 3. Layer formation *via* O—H···O and C—H···O interactions in **2** (*a*), **4** (*b*)

Carboxyl dimers in **2** and **4** form layers via several C—H···O interactions. In **2**, dimers are arranged in a zigzag fashion with the interaction of O3A epoxy oxygen with the C9—H9A unit (Table 2, Fig. 3, *a*). On the other hand, dimers in **4** are parallel with interactions between carbonyl oxygen (O4) and the C18—H18B unit (Table 3, Fig. 3, *b*). Additional interactions of benzene CH units with carboxyl oxygen atoms (O1, O2) are present in **4**, but were not found in **2**. For interactions between layers the C10—H10A···O3A interaction is responsible in **2** and C9—H9C···O4 in the crystals of **4**.

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