



# Alkoxy-benzoic acids: Some lacking structures and rationalization of the molecular features governing their crystalline architectures



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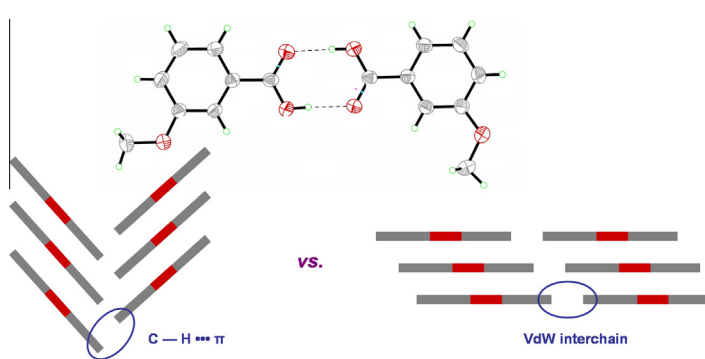
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## HIGHLIGHTS

- The crystalline structures of four selected (alkoxy)benzoic acids have been solved.
- Trends along the whole set of known structures of such compounds were analyzed.
- Dimeric synthons organize either in parallel or perpendicular architectures.
- The influence of molecular features driving to one or the other was established.
- A specific aromatic C–H··· $\pi$  interaction plays a major role.

## GRAPHICAL ABSTRACT



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## ABSTRACT

The crystalline structure of four alkoxy-substituted benzoic acids, namely 3-(methoxy)benzoic acid (**I**), (with two independent molecules in the asymmetric unit); 3,4-di(ethoxy)benzoic acid (**II**), 3,5-di(ethoxy)benzoic acid (**III**) and 3,4,5-tri(ethoxy)benzoic acid (**IV**) are presented, and the details of their packing arrangements discussed. In all cases the synthon is a H-bonded head-to-head dimer. C–H··· $\pi$  interactions involving C atoms at the 4-positions of neighbouring molecules organize the dimeric synthons in a perpendicular orientation in the case of **I**. These interactions being blocked for **II**, Van der Waals interchain interactions organise synthons therein in parallel orientation. In the case of **III**, although C–H··· $\pi$  interactions at the 4-positions are possible in principle, interchain interactions prevail, giving rise to a parallel arrangement of linear strands. Finally, compound **IV** with all three 3,4,5 substituted sites reduces its interaction scheme to stacking contacts, and the columns thus formed are essentially non interacting. An attempt to rationalize the molecular factors influencing the structures of the whole set of 3-, 4- and/or 5-methoxy- and ethoxy-substituted benzoic acids reported so far in the literature is performed.

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## Introduction

Stacking of aromatic compounds have been the subject of intense experimental research, crystallographic studies being by

far the major and most informative ones. The general trends are nowadays well understood: [1–7] provided that the ratio of “C” to “exposed H” atoms ( $C/H_{\text{exposed}}$ ) is low, as in small polyaromatics like naphthalene or pyrene, molecules tend to adopt non-parallel mutual orientations, the so called T-shaped (edge-to-face) being the paradigmatic one. It is nowadays accepted that this perpendicular orientation results from close-packing considerations and

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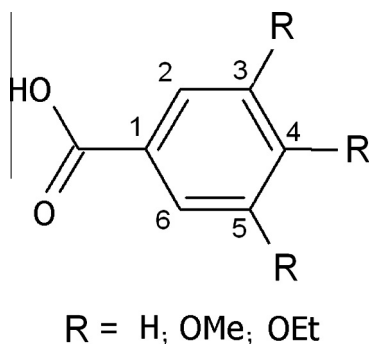
aromatic C–H··· $\pi$  interactions. [7–9] If the extent of C–H··· $\pi$  interactions is limited (high C/H<sub>exposed</sub> ratio, like in highly condensed polyaromatics or highly substituted aromatic compounds), molecules tend to stack with parallel orientations, like in tribenzopyrene. This structure is often associated to the so-called  $\pi$ – $\pi$  stacking. Intermediate structures (cf. coronene) have also been found in systems with intermediate C/H<sub>exposed</sub> ratios.

If the aromatic compounds under consideration bear a carboxylic group, the general trends discussed above remain valid. However, the presence of the carboxylic group introduces two main differences: as a result of the strong O–H···O<sub>carbox</sub> H-bond, synthons are the head-to-head dimers; moreover, C–H···O<sub>carbox</sub> interactions may also be present and contribute to the structure. These features have been thoroughly analyzed by Desiraju in a systematic study dealing with methoxy substituted cinnamic and propiolic acids [2]; on this basis, stereoselective topochemical photoreactions have been achieved. In those compounds, the presence of methoxy groups allowed additional C–H···O<sub>methoxy</sub> interactions to take place. Additionally, a correlation between structures with a short axis shorter than 5 Å and parallel geometries has been evidenced.

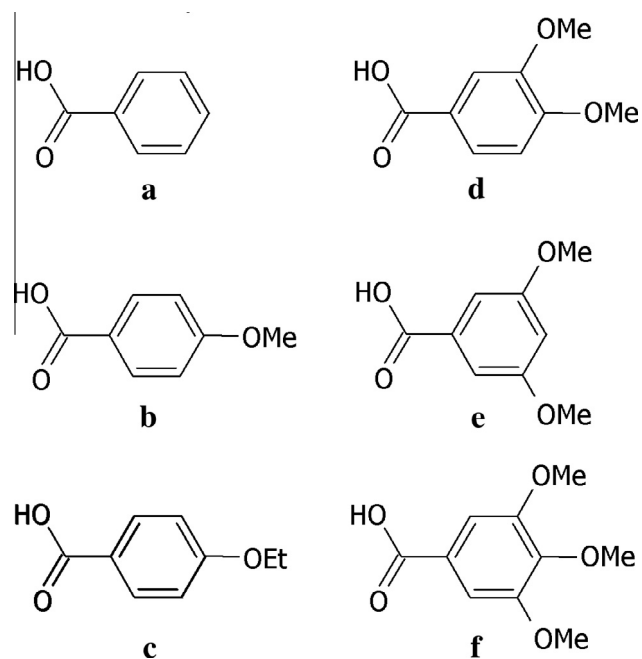
We turned our attention to the crystalline structure of related but simpler compounds: methoxy- and ethoxy-substituted benzoic acids, and focused on compounds substituted in 3-, 4- and/or 5-positions (Scheme 1); 2- and 2,6-derivatives have not been considered as the proximity of carboxyl and ether groups can substantially modify the interplay of intermolecular interactions. Indeed, the structures of some such derivatives showed no dimeric synthons, but catemers [10]. Scheme 2 shows the unsolvated structures of the sort so far solved and published, viz., (a) benzoic acid [11]; (b) 4-(methoxy)benzoic acid [12] (*p*-anisic acid); (c) 4-(ethoxy)benzoic acid [13]; (d) 3,4-di(methoxy)benzoic acid [14]; (e) 3,5-di(methoxy)benzoic acid [15]; (f) 3,4,5-tri(methoxy)benzoic acid [16] though almost no discussion on their supra-molecular interactions is available.

In order to fill some gaps in the sequence we decided to solve four of the lacking structures which would allow for a progressive analysis of the molecular features contributing to their building-up. We thus present in this report the crystalline structures of 3-(methoxy)benzoic acid (I), 3,4-di(ethoxy)benzoic acid (II), 3,5-di(ethoxy)benzoic acid (III) and 3,4,5-tri(ethoxy)benzoic acid (IV) (Scheme 3), along with a global analysis which rationalize the crystalline structures of this kind of compounds in terms of the driving intermolecular interactions. For the later task, C–H··· $\pi$  and  $\pi$ – $\pi$  stacked interactions will be analyzed in detail.

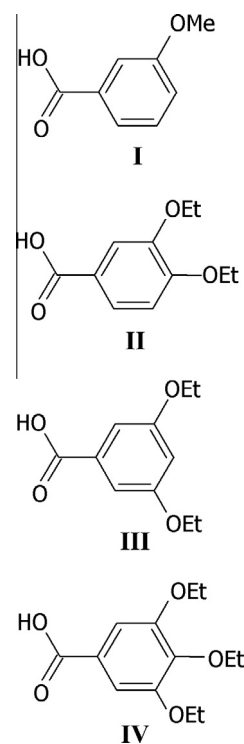
Their precise nature has been discussed in the literature, and is still matter of active debate. In a significant step, Hunter and Sanders [17] proposed an electrostatic + Van der Waals simultaneous interpretation for both parallel and T-shaped geometries, although more recent calculations suggest [18] this approach overestimates the electrostatic contribution. It is nowadays accepted that



Scheme 1. 3-, 4- and/or 5-methoxy- and ethoxy-benzoic acids.



Scheme 2. Molecular sketch of the so far reported 3-, 4- and/or 5- methoxy- and ethoxy-benzoic acids.



Scheme 3. Molecular sketch of the studied compounds.

C–H··· $\pi$  interactions arise mainly from dispersion forces, with electrostatic terms playing a secondary role on interaction's energy although a more important one on their directionality [19,20]. From a crystallographic viewpoint, the occurrence of C–H··· $\pi$  interactions is often suggested on the basis of the main geometric parameters involved: some authors take H··· $\pi$  and C··· $\pi$  distances shorter than certain values (usually 3.05 Å and 3.5 Å respectively) as the frontier between “true” H-bonds and purely Van der Waals type interactions; others extend these limits well beyond these

values, or take the  $C_{ar}-H \cdots \pi$  interaction as a whole, independently of its deep physical nature. In our opinion, the H-bond nature of such  $C-H \cdots \pi$  interactions is well established on firm basis, as comprehensively and convincingly reviewed by Nishio et al. [8,19,21], although we should recognize this viewpoint is not yet unanimously accepted. Following the IUCr recommendations on H-bonds [22] we have adopted the “chemist viewpoint” suggested by Desiraju and others [7] thus using the “ $C-H \cdots \pi$  interactions” expression in a wide sense -including those mainly arising from van der Waals interactions-, provided the following conditions are fulfilled: (i)  $H \cdots A$  and  $C \cdots A$  distances (A: H-acceptor) not substantially longer than expected from Van der Waals radii considerations. (ii) appropriate  $C-H \cdots A$  directionality and (iii) crystallographic evidence of this interaction being relevant for the structure.

## Experimental

### Crystallization

3-(Methoxy)benzoic acid, 3,4-di(ethoxy)benzoic acid, 3,5-di(ethoxy)benzoic acid and 3,4,5-tri(ethoxy)benzoic acid were purchased from Sigma–Aldrich and used without further purification. Single crystals were grown in all cases by slow cooling (less than 1 K per day) of concentrated solutions from appropriate solvents.

Crystallization experiments from different solvents (methanol, ethanol, acetone, dichloromethane, toluene, hexane, cyclohexane and mixtures) were conducted in a parallel way for each compound, using the same cooling rate (same oil bath); the final choice was: cyclohexane, hexane, cyclohexane:ethanol 10:2 and hexane for **I**, **II**, **III** and **IV** respectively. In all cases the crystals were screened by optical examination, and the best ones selected for data acquisition.

### X-ray crystallography

For all crystals, Crystal Data were collected on a Oxford Gemini CCD S Ultra diffractometer at room temperature using Mo  $K\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ) [23]. The structure was solved by direct methods and refined by full-matrix least squares on  $F^2$  using the SHELXS-97 software [24]. All non-hydrogen atoms were refined anisotropically. The structural analysis was performed with the help of the multipurpose PLATON program [25] and the molecular representations shown in the figures were generated using XP in the SHELXTL package [24]. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 985637–985640. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

**Table 1**  
Data collection and refinement details.

	(I)	(II)	(III)	(IV)
<i>Crystal data</i>				
Chemical formula	$C_8H_8O_3$	$C_{11}H_{14}O_4$	$C_{11}H_{14}O_4$	$C_{13}H_{18}O_5$
$M_r$	152.14	210.22	210.22	254.27
Crystal system, space group	Monoclinic, $P2_1/n$	Triclinic, $P1$	Triclinic, $P1$	Triclinic, $P1$
$a, b, c$ (Å)	13.8034 (17), 5.0275 (5), 21.446 (3)	4.869 (3), 7.365 (4), 15.665 (5)	6.6934 (6), 8.4801 (7), 10.5732 (9)	4.3355 (3), 9.1635 (8), 18.0798 (12)
$\alpha, \beta, \gamma$ (°)	90, 99.320 (13), 90	87.561 (5), 89.030 (5), 75.030 (4)	101.203 (7), 101.796 (7), 99.968 (6)	90.415 (6), 94.032 (6), 95.009 (7)
$V$ (Å <sup>3</sup> )	1468.6 (3)	542.2 (5)	561.94 (8)	713.71 (9)
$Z$	8	2	2	2
No. of measured, independent and observed [ $I > 2\sigma(I)$ ] reflections	9723, 3478, 1853	5871, 2538, 1630	6706, 2585, 1475	9428, 3354, 1766
$R_{int}$	0.064	0.068	0.047	0.034
$R[F^2 > 2\sigma(F^2)]$ , $wR(F^2)$ , $S$	0.067, 0.224, 1.10	0.068, 0.220, 1.08	0.049, 0.145, 1.00	0.055, 0.169, 1.02
# Reflections, parameters, restraints	3478, 207, 2	2538, 140, 1	2585, 141, 2	3354, 169, 1
$\Delta\rho_{max}$ , $\Delta\rho_{min}$ (e Å <sup>-3</sup> )	0.23, -0.26	0.25, -0.29	0.16, -0.20	0.16, -0.16

**Table 2**  
Hydrogen-bond geometry (Å, °) for compounds (I) to (IV).

	D–H	H $\cdots$ A	D $\cdots$ A	D–H $\cdots$ A
<i>(I)</i>				
O1A–H1A $\cdots$ O2B	0.85 (2)	1.80 (3)	2.649 (3)	173 (3)
O1B–H1B $\cdots$ O2A	0.85 (2)	1.77 (2)	2.619 (3)	172 (2)
<i>(II)</i>				
O1–H1 $\cdots$ O2i	0.86 (1)	1.75 (1)	2.614 (2)	173 (3)
C10–H10B $\cdots$ Cg1ii	0.97	2.79	3.613	143
Symmetry codes: (i) $-x+2, -y+2, -z$ ; (ii) $x-1, y, z$				
<i>(III)</i>				
O1–H1 $\cdots$ O2i	0.86 (1)	1.78 (1)	2.6385 (17)	173 (2)
C11–H11B $\cdots$ O2ii	0.96	2.54	3.408 (2)	151
C4–H4 $\cdots$ O3iii	0.93	3.02	3.948 (2)	175
C9–H9A $\cdots$ O4iii	0.96	3.01	3.444 (2)	109
C9–H9C $\cdots$ Cg1iv	0.96	2.97	3.765 (2)	141
C10–H10A $\cdots$ Cg1v	0.97	2.87	3.732 (2)	148
Symmetry codes: (i) $-x+1, -y+1, -z$ ; (ii) $-x+2, -y+1, -z+1$ ; (iii) $-x, -y, -z+1$ ; (iv) $x-1, y, z$ ; (v) $-x+1, -y+1, -z+1$				
<i>(IV)</i>				
O1–H1 $\cdots$ O2i	0.92 (3)	1.70 (3)	2.617 (2)	177 (3)
C10–H10A $\cdots$ O4ii	0.97	2.51	3.441 (3)	162
Symmetry codes: (i) $-x+1, -y+1, -z+1$ ; (ii) $x+1, y, z$				

All H atoms were found in a difference map, C–H's being further idealized and finally allowed to ride, while the carboxylic H was refined with a restrained O–H distance. CH<sub>3</sub> groups were in turn allowed to rotate. Displacement parameters were taken as  $U_{iso}(H) = X \times U_{eq}(Host)$  [Parameters used:  $(C-H)_{methyl} = 0.96 \text{ \AA}$ ,  $X = 1.5$ ;  $d(C-H)_{arom} = 0.93 \text{ \AA}$ ,  $X = 1.2$ ,  $d(O-H) = 0.85 (1) \text{ \AA}$ ,  $X = 1.2$ ]. Data collection and refinement parameters are summarized in Table 1, while the most significant non covalent interactions are presented in Table 2 (H-bonds) and Table 3 ( $\pi \cdots \pi$  contacts).

## Results and discussion

Fig. 1a–d shows the molecular diagrams of **I**, **II**, **III** and **IV**, respectively. Bonds distances and angles are, as expected,

unexceptional for what they will not be discussed in any detail; we shall analyze internal geometries only marginally and focus instead on the supramolecular structures and the interactions responsible for their building up. An obvious common feature in all four structures is the closed  $[(O-H)_{carboxy} \cdots O_{carboxy}]_2$  synthon (Table 2(I, II, III, IV) first entries) leading to H-bonded head-to-head dimers, the *leit motives* for all four packing arrangements.

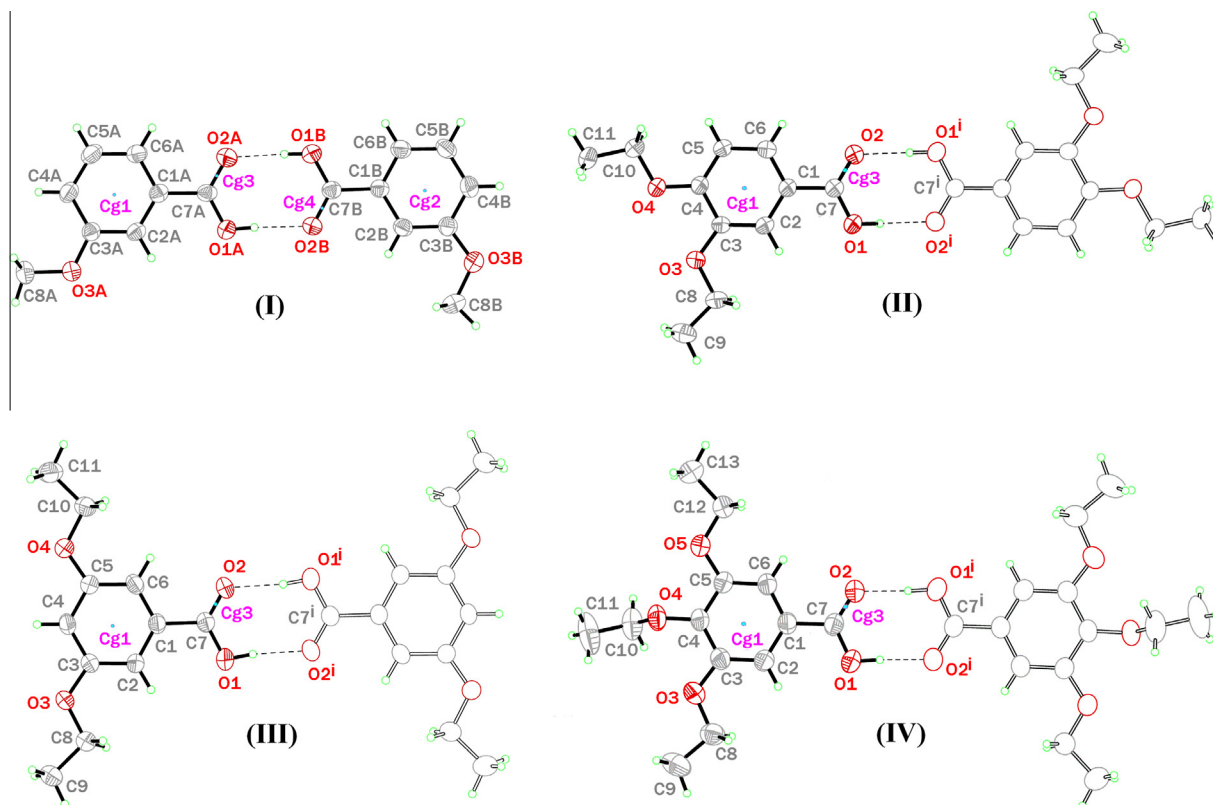
In the case of **I** the dimer is not symmetric and formed by two independent molecules in the asymmetric unit; in the remaining three structures they are built up around inversion centers. Deviation from planarity in the dimers is uneven, the mean plane through both aromatic rings plus carboxy groups giving maximum deviations of 0.076 Å in **I** (for O1B), 0.233 Å in **II** (for O1/O1A), 0.151 Å in **III** (for O2/O2A) and 0.131 Å in **IV** (for O2/O2A). In spite

**Table 3**

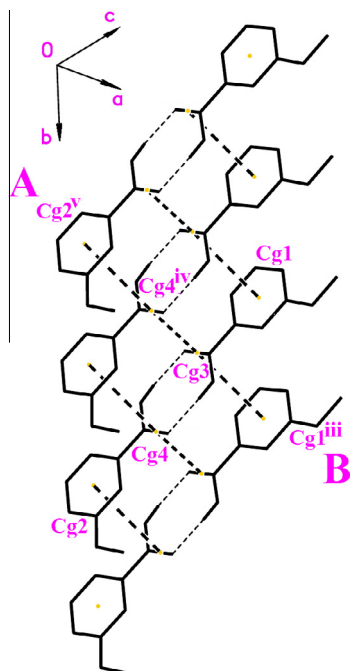
$\pi$ – $\pi$  contacts (Å, °).

	ccd(Å)	ipd(Å)	sa(°)
<i>(I)</i>			
Cg3...Cg1 <sup>iii</sup>	3.785	3.411	36
Cg3...Cg4 <sup>iv</sup>	3.287	3.286	3
Cg4 <sup>iv</sup> ...Cg2 <sup>v</sup>	3.804	3.378	28
Symmetry codes: (iii): $x, y + 1, z$ ; (iv): $x, y - 1, z$ ; (v): $x, y - 2, z$ . Centroid codes: Cg1: C1A → C6A; Cg2: C1B → C6B; Cg3: C7A–O2A; Cg4: C7B–O2B			
<i>(II)</i>			
Cg3...Cg1 <sup>iv</sup>	3.969	3.135	37
Cg3...Cg3 <sup>v</sup>	3.185	3.173	5
Symmetry codes: (iv): $x + 1, y, z$ ; (v): $1 - x, 2 - y, -z$ . Centroid codes: Cg1: C1 → C6; Cg3: C7–O2			
<i>(IV)</i>			
Cg1...Cg1 <sup>i</sup>	4.336	3.617	34
Symmetry codes: (i): $-1 + x, y, z$ . Centroid codes: Cg1: C1 → C6			

ccd: center-to-center distance (distance between ring(bond) centroids); ipd: mean inter-planar(bond) distance (distance from one plane(bond) to the neighbouring centroid); sa: mean slippage angle (angle subtended by the intercentroid vector to the plane(bond)).



**Fig. 1.** Molecular diagrams for the four reported structures. a: (I); b: (II); c: (III); d: (IV). Displacement ellipsoids drawn at a 40% level. Broken lines stand for O–H...O bonds. Symmetry codes: (i)  $-x + 1, -y + 1, -z$ .

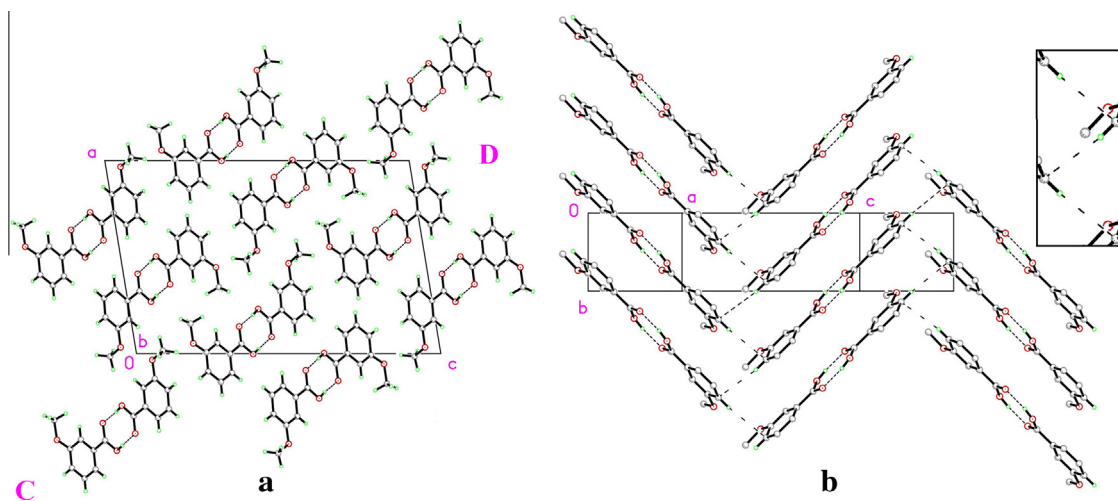


**Fig. 2.** Columnar array in **I**, showing their linkage along the A ↔ B line. Broken lines stand for non-covalent interactions discussed in the text. Symmetry codes: (iii):  $x, y + 1, z$ ; (iv):  $x, y - 1, z$ ; (v):  $x, y - 2, z$ .

of structural similarities, the way in which these dimers interact with each other is fairly different and this will be the main scope of the following discussion.

Compound **I** features two independent molecules in the asymmetric unit, defining the H-bonded dimers which pile in a (slanted)  $\pi$ -stacked fashion to form columnar ribbons along the short  $b$  axis (5.0275 (5) Å). These columns are built up *via*  $\pi_{\text{carbox}} \cdots \pi_{\text{arom}}$  and  $\pi_{\text{carbox}} \cdots \pi_{\text{carbox}}$  interactions “threading” 4 different molecules (along the A–B axis in Fig. 2; see also Table 2(I)). There are tail-to tail links (described in the next paragraph), which associate columns into slim planar arrays parallel to  $(\bar{1}01)$  (Fig. 3a); no direct interactions between planes seem to be in force, the linkage being of a diffuse Van der Waals nature instead.

The tail-to tail links in **I** likely arise from aromatic C–H  $\cdots \pi$  interactions (very weak CH/ $\pi$  bonds) involving the 4-position of both neighbouring molecules, with the C–H bond of one molecule pointing toward the C atom in the 4-position of the other one, generating a C2 catemeric structure (Inset in Fig. 3b; for Graph set notation see Bernstein et al. [26]). This geometry slightly differs from the one associated to the conventional description usually given to these interactions, viz., as a C–H  $\cdots$  Cg one, or, in simpler words, one with the C–H vector pointing towards the ring centroid. Nevertheless, this type of interaction is extremely similar to the one responsible for the so called [27] 5–5–22 structure of benzoic acid [11], (a) in Scheme 2, and that of 3,5-di(methoxy)benzoic acid [15], (e) in Scheme 2. In all three cases the herringbone disposition of dimers is sustained by an almost exactly similar interaction, where a C4–H4 bond points to a C4' atom in the acceptor ring. Table 4 shows some illuminating figures evidencing the extreme similarity of all three cases, as well as the prevalence of a C–H  $\cdots$  C description over a C–H  $\cdots$  Cg one, based on a shorter H  $\cdots$  A distance, a larger C–H  $\cdots$  A angle and an H  $\cdots$  A vector almost perpendicular to the acceptor ring plane. Ciunik and Desiraju [28] suggested that even if the  $\theta$  vs.  $d$  scatter-plot for these C–H  $\cdots \pi$

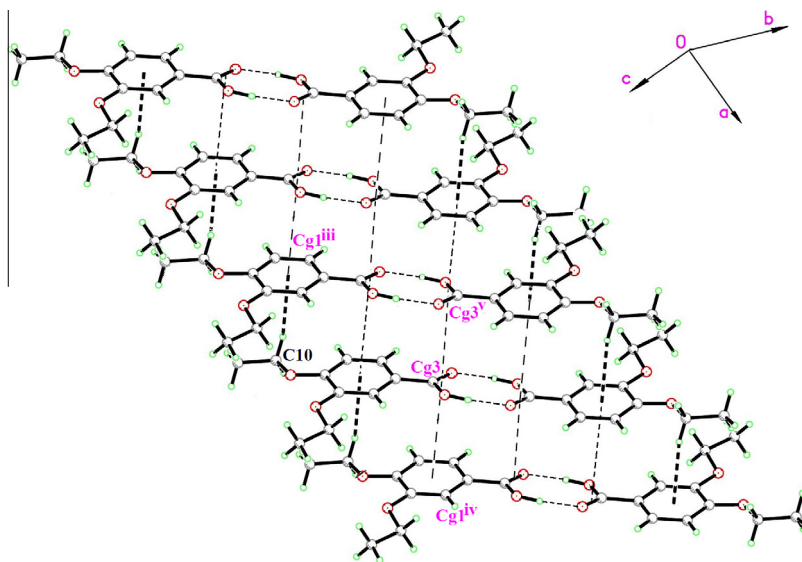


**Fig. 3.** Packing diagrams of **I** (a) viewed along the  $b$  axis, showing columns in projection, and their alignment along the C ↔ D line into  $(\bar{1}01)$  planes. Broken lines stand for non-covalent interactions discussed in the text. (b) Showing one isolated (C ↔ D) plane, rotated 90° horizontally in order to display details of the catemeric C–H  $\cdots$  C interaction. Broken lines stand for non-covalent interactions discussed in the text. Inset: the C<sup>2</sup> synthon.

**Table 4**  
Tail-to-tail interactions (Å, °).

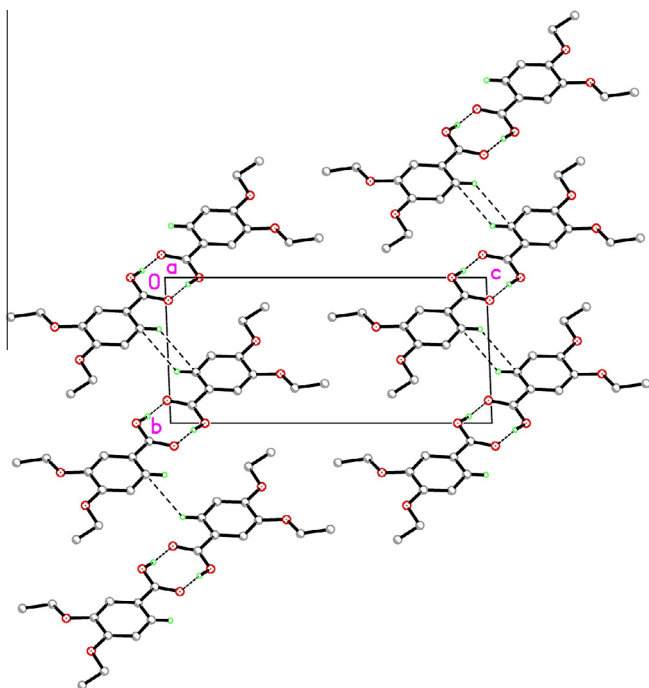
(I) This work	Interplanar angle: 94.3°		
C4a–H4a $\cdots$ C4b'	3.062 Å/164.5°/9.6°	C4a–H4a $\cdots$ Cg1b'	3.552 Å/149.6°/31.8°
C4b–H4b $\cdots$ C4a'	3.179 Å/164.3°/6.7°	C4b–H4b $\cdots$ Cg1a'	3.594 Å/149.4°/38.5°
(a) BENZAC	Interplanar angle: 98.0°		
C4–H4 $\cdots$ C4'	3.046 Å/164.4°/8.8°	C4–H4 $\cdots$ Cg1'	3.475 Å/145.3°/30.3°
(e) HEKMOZ	Interplanar angle: 91.8°		
C4–H4 $\cdots$ C4'	3.016 Å/167.4°/9.9°	C4–H4 $\cdots$ Cg1'	3.521 Å/147.8°/32.4°

For each (C–H  $\cdots$  A) group, the three numbers given (X1/X2/X3) have the following meaning. X1: (H  $\cdots$  A) distance (Å), X2: (C–H  $\cdots$  A) angle (°); X3: (H  $\cdots$  A  $\cdots$  Ring-Normal) angle (°).



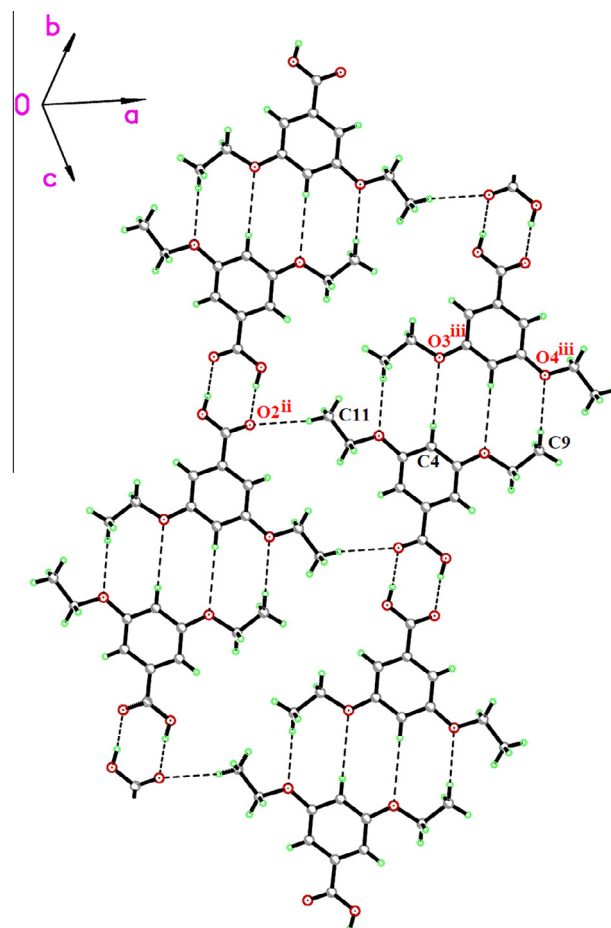
**Fig. 4.** Columnar array in **II**. Broken lines stand for non-covalent interactions discussed in the text. Symmetry codes: (iii)  $x - 1, y, z$ ; (iv):  $x + 1, y, z$ ; (v):  $1 - x, 2 - y, -z$ .

interactions is sensibly more diffuse than, for instance, the O–H... $\pi$  one, the essential nature of the interaction is electrostatic with the predominant pointing of the C–H bond towards the centroid of the  $\pi$  system. The relatively long C4a...C4b' distance (3.98 Å) found in **(I)** (the range of C...C or C...PLANE distances reported for systems for which aromatic CH/ $\pi$  bonds have been claimed spans a ca. 3.40–4.11 Å range) [19,29,30] points toward an interaction dominated by dispersion components rather than electrostatic ones, as reviewed by Nishio for most CH/ $\pi$  bonds. For the three compounds analyzed in Table 4, this C–H...C interaction meets the three criteria stated in the Introduction; indeed, for **(I)**, the sum of the C–H distance (0.93 Å) and the Van der Waals radii for H (1.20 Å) and C (1.77 Å) amounts 3.90 Å, well within the 0.7 Å margin suggested by Alvarez [31].

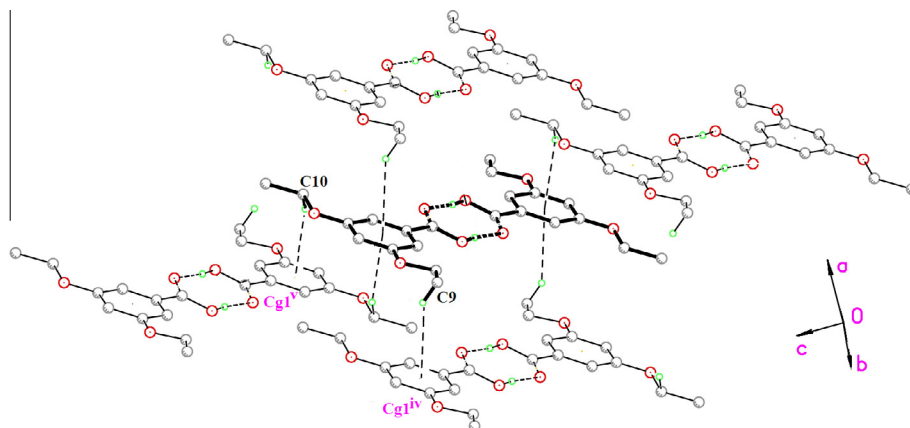


**Fig. 5.** Packing diagram of **II** viewed along the short  $a$  axis, showing columns in projection, and their linkage into (001) planes. Broken lines stand for non-covalent interactions discussed in the text.

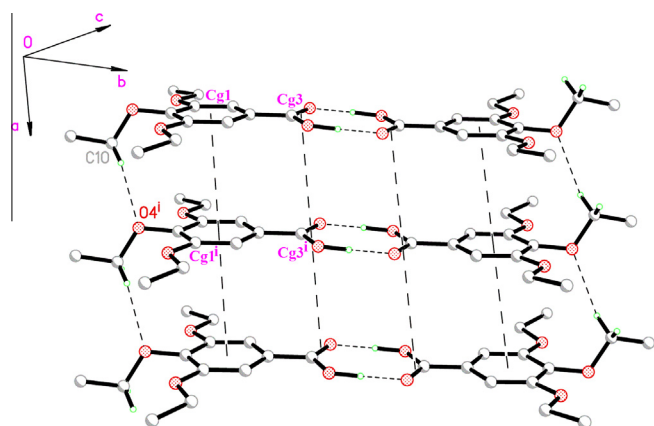
Following with our analysis, and within this overall framework, the structure of benzoic acids with alkoxy-substituents in the 4-position, precluding this C<sub>ar</sub>–H... $\pi$  interaction, looks interesting. Indeed, the structure of 4-(methoxy)benzoic acid (structure **(b)** in Scheme 2) exhibits tail-to-tail C<sub>methoxy</sub>–H...O<sub>methoxy</sub> dipolar and



**Fig. 6.** The  $(\bar{1}21)$  strand in **III**. Broken lines stand for non-covalent interactions discussed in the text. Symmetry codes: (ii)  $-x + 2, -y + 1, -z + 1$ ; (iii)  $-x, -y, -z + 1$ .



**Fig. 7.** Packing diagram of **III** showing the way in which planar strands interact. Broken lines stand for non-covalent interactions discussed in the text. Symmetry codes: (iv)  $x - 1, y, z$ ; (v)  $-x + 1, -y + 1, -z + 1$ .



**Fig. 8.** Columnar array in **IV**. Broken lines stand for non-covalent interactions discussed in the text. Symmetry codes: (i):  $x + 1, y, z$ .

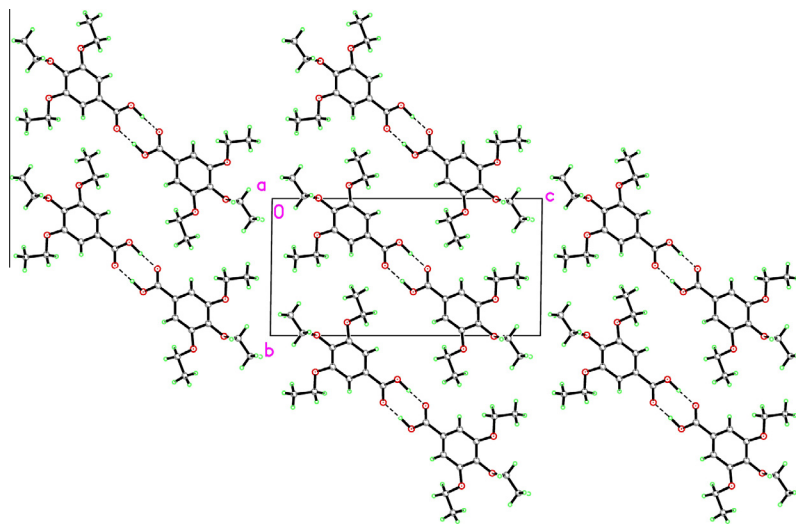
Van der Waals-type interactions giving rise to straight “strands” of dimeric synthons, in turn laterally associated by  $C_{ar}-H \cdots \pi$  interactions in a nearly corrugated-sheet structure, and stacked via  $\pi_{arom} \cdots \pi_{arom}$  and  $\pi_{carbox} \cdots \pi_{carbox}$  interactions along the short  $c$  axis (3.980 (10) Å); 4-(ethoxy)benzoic acid, in turn, (C2/c, short

axis  $b = 4.013$  (1) Å) forms singly corrugated sheets, as pointed out by Sarma and Desiraju [1].

In our case, 3,4-di-(ethoxy)benzoic acid **II** crystallizes in the triclinic P-1 group space. As already said, dimeric synthons are not strictly planar but nevertheless they stack along the short  $a$  axis (4.869 (5) Å) via  $\pi_{carbox} \cdots \pi_{arom}$ ,  $\pi_{carbox} \cdots \pi_{carbox}$  and  $C_{methylene}-H \cdots \pi_{arom}$  interactions (Table 2(II), Table 3(II) and Fig. 4), resulting in (100) columnar arrays. These columns interact only weakly with each other; in particular, a rather short  $C6-H6 \cdots C6^i$  [i:  $1 - x, 1 - y, -z$ ] contact appears between chains and around an inversion center ( $H6 \cdots C6^i = 2.80$ Å) giving raise to a  $R_2^2(4)$  loops connecting chains along the  $b$  direction (Fig. 5). Finally, organization of these structures along  $c$  seems to result from a large number of Van der Waals  $C \cdots O$  and  $C \cdots C$  interactions in the tails region.

The third compound studied here, 3,5-di(ethoxy)benzoic acid **III**, has no substitution on the 4-position and could, in principle, give rise again to perpendicular structures. In fact, this is the case for the already discussed 3,5-di(methoxy)benzoic acid (structure (e) in Scheme 2), where dimeric synthons stack along the short  $b$  axis (4.9238 (3) Å), these stacks being mutually perpendicular at the 4-positions.

Nevertheless, the structure of **III** (triclinic, space group P-1) consists of parallel straight (101) strands of dimeric synthons



**Fig. 9.** Packing diagram of **IV** viewed along the short  $a$  axis, showing the non-interacting columns in projection.

(Fig. 6), built up by tail-to-tail  $C_{ar}-H \cdots O_{ethoxy}$  and  $C_{methyl} \cdots O_{ethoxy}$  interactions (Table 2(III), 3rd and 4th entries, and Fig. 6, broken lines running top to bottom). These strands associate laterally via  $CH_3 \cdots O_{carbox}$  interactions (Table 2(III), 2nd entry and Fig. 6, broken lines running left to right) to define planar arrays parallel to  $(\bar{1}21)$ . These planes stack parallel to each other exclusively via  $C_{methyl}-H \cdots \pi$  interactions (Table 2(III), entries 5th and 6th, and Fig. 7).

Finally, compound IV (also triclinic, space group P-1) with all three 3,4,5 substituted sites reduces its interaction scheme (in addition to the ever-present dimeric synthon, Table 2(IV), first entry) to the interactions shown in Fig. 8 and presented in Table 2(IV), second entry and Table 3(IV). The columns thus formed are essentially non interacting (Fig. 9).

## Conclusions

A global analysis of the whole set of known structures of 3-,4- and/or 5-methoxy- or ethoxy-substituted benzoic acids suggests the following general rules: the head-to-head hydrogen-bonded dimeric synthon is always present. Intermolecular interactions in the radial part of the synthons determine if they associate as parallel strands or perpendicular moieties. When the 4-position involves an alkoxy group, these driving interactions are tail-to-tail interactions, as in the already discussed 4-methoxy, 3,4-di(ethoxy) and 3,4,5-tri(ethoxy) derivatives as well as in the 3,4,5-tri(methoxy) compound (LIJKOF); if the 4-position is not substituted,  $C_{ar,4}-H \cdots C_{ar,4}(\pi)$  interactions give rise to perpendicular arrangements of synthons (3-methoxy and 3,5-di(methoxy) derivatives), provided tail-to tail interactions are not prevailing; otherwise, they will drive the structure, as in the case of the 3,5-di(ethoxy) derivative. Parallel stacking of synthons and lateral association seem to play a minor role in these structures, eventually present if the orientation of the synthons resulting from the main described interactions is appropriate.

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