

## Weak intermolecular interactions in isomorphous 5-(2-chloroethoxy)-2,3-dihydro-1,4-benzodioxine and 5-(2-bromoethoxy)-2,3-dihydro-1,4-benzodioxine: bonding or nonbonding interactions

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The title compounds,  $C_{10}H_{11}ClO_3$ , (I), and  $C_{10}H_{11}BrO_3$ , (II), are isomorphous and effectively isostructural; all of the interatomic distances and angles are normal. The structures exhibit long intermolecular  $C-H \cdots O$  and  $C-H \cdots \pi$  contacts with attractive energies ranging from 1.17 to 2.30 kJ mol<sup>-1</sup>. Weak  $C-H \cdots O$  hydrogen bonds form  $C(3)$  and  $C(4)$  motifs, combining to form a two-dimensional  $R_3^4(12)$  net. No face-to-face stacking interactions are observed.

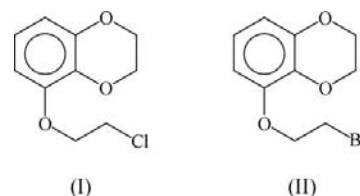
### Comment

Hydrogen bonding is a phenomenon crucial in chemical, catalytic and biochemical processes, chemical and crystal engineering, and supramolecular chemistry (Jeffrey & Saenger, 1991; Jeffrey, 1997; Epstein & Shubina, 2002). Nowadays much attention is focused on the nature and properties of weak hydrogen bonds because they strongly influence the behaviour of many organic molecules and biomolecules (Szatyłowicz, 2008).

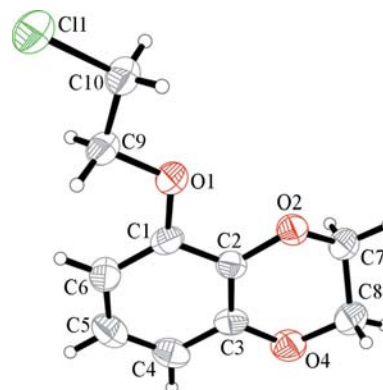
5-(2-Chloroethoxy)-2,3-dihydro-1,4-benzodioxine, (I), is an important compound used in the synthesis of second generation antidepressants responsible for 5-HT<sub>1A</sub> antagonism in serotonin reuptake inhibitors (Mewshaw *et al.*, 2002, 2004). 5-(2-Bromoethoxy)-2,3-dihydro-1,4-benzodioxine, (II), is a reactant utilized in the synthesis of tetrahydroquinoline-based protein farnesyltransferase inhibitors used as antimalarials (Bendale *et al.*, 2007). Compounds (I) and (II) are also excellent for the study of weak hydrogen bonding because they contain only weak  $C-H$  donors and weak ether O,  $\pi$ (arene) and halogen acceptors.

Compounds (I) and (II) (Figs. 1 and 2) are isomorphous and effectively isostructural; the atomic coordinates of (I) may be used as a starting point for the refinement of the structure of

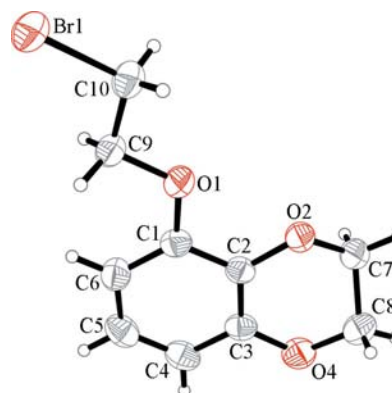
(II), although refinement of the absolute structure parameter (Flack, 1983) then indicates that inversion of the atomic coordinates is required to complete the refinement for (II).



All the interatomic distances and angles in (I) and (II) are normal, and the typical shortening of the  $C_{phenyl}-O$  ether bonds (Tables 1 and 2) is observed [the mean value is 1.38 (2) Å for 27 688 structures found in the Cambridge Structural Database (CSD; Version 5.29 plus one update; Allen, 2002)]. The 2-chloroethoxy and 2-bromoethoxy substituents are almost planar (Tables 1 and 2) and they are almost coplanar with the adjacent aryl rings [the dihedral angle between the corresponding least-squares planes is 4.9 (3)° for (I) and 5.5 (3)° for (II)]. In both compounds, the conformation of the heteroatomic ring is an unsymmetrical



**Figure 1**  
The molecular structure of (I). Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary radii.



**Figure 2**  
The molecular structure of (II). Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary radii.

half-chair, with a local pseudo-twofold axis across the mid-points of the C2—C3 and C7—C8 bonds. This is distorted toward a sofa conformation, with a pseudo-mirror plane perpendicular to the ring plane on the line C3...C7 (Duax & Norton, 1975; Duax *et al.*, 1976). The values of the smallest asymmetry parameters are  $C_2(\text{C2}\cdots\text{C3}, \text{C7}\cdots\text{C8}) = 10.5 (3)^\circ$  [for both (I) and (II)] and  $C_s(\text{C3}\cdots\text{C7}) = 13.5 (3)$  and  $13.9 (2)^\circ$  for (I) and (II), respectively. The values of the ring-puckering angles  $\theta$  and  $\varphi$  (Cremer & Pople, 1975) for the atom sequence O2—C2—C3—O4—C8—C7 are, respectively,  $130.1 (4)$  and  $101.2 (4)^\circ$  in (I), and  $129.3 (3)$  and  $101.2 (3)^\circ$  in (II).

This ring conformation is relatively uncommon in comparison with the conformations of 129 2,3-dihydro-1,4-benzodioxine ring systems found in the CSD, where the O—C...C—O torsion angle has a mean absolute value of  $2.0 (2)^\circ$  and the O—C—C—O torsion-angle distribution can be divided into two distinct sets, one close to  $60^\circ$  and the second close to  $0^\circ$ ; the mean absolute values are  $58.1 (8)$  and  $4.3 (10)^\circ$ , respectively. The C—C—O—C torsion angles are spread over a wider range (Fig. 3), but again preferred values can be detected, namely  $17.0$  and  $47.4^\circ$ , respectively, for the C...C—O—C and C<sub>phenyl</sub>—O—C—C torsion angles. In general, an increase in one angle is associated with an increase in the second (Fig. 3). In (I) and (II), the O—C—C—O torsion angles are close to typical values (Tables 1 and 2). The C—C—O—C torsion angles differ considerably from the preferred ones (Fig. 3), and only in four structures (Chekhlov *et al.*, 1993; Donnelly *et al.*, 1987; Kuipers *et al.*, 1997; Nicolaou *et al.*, 2004) are the torsion angles within  $2^\circ$  of those found for (I) and (II).

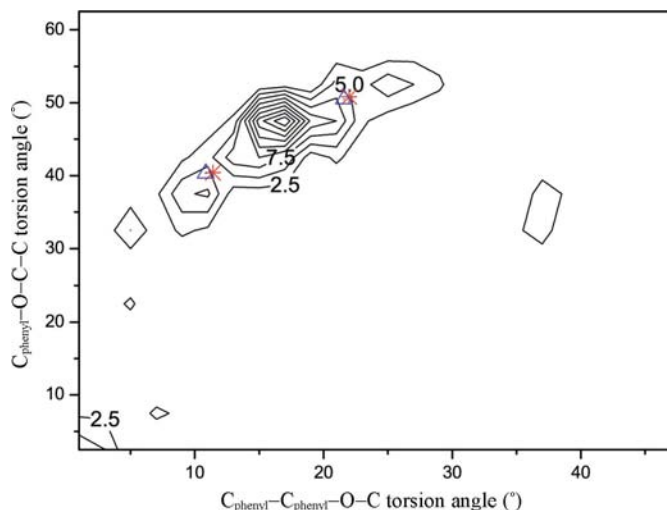
Each structure contains very long C—H...O and two C—H... $\pi$ (arene) intermolecular interactions (Table 3), which could be considered as very weak hydrogen bonds (Desiraju & Steiner 1999). The C—H...O contacts generate C(3) and C(4) first-level graph-set motifs (Bernstein *et al.*, 1995), along [100]

and [101], respectively, and the resulting second-level graph-set motif is  $R_3^4(12)$ , giving a two-dimensional net parallel to (010). However, no face-to-face stacking interactions are observed in the structures of (I) and (II).

The molecular electronic properties have been calculated at a single point from the experimental coordinates, as well as for optimized structures. The structural parameters were a starting model in each calculation. The optimized geometrical parameters were in good agreement with those found from X-ray measurements, although the geometrically optimized molecules typically show an elongation of the C—H bonds (from 0.07 to 0.16 Å). This effect leads to a slight narrowing of the  $D\cdots H\cdots A$  angles, but the  $D\cdots A$  distances remains unchanged.

The intermolecular interactions were calculated for molecular sets containing from two to 13 molecules. The sets were constructed using a single molecule as the starting point and adding extra molecules one-by-one along intermolecular interactions in both hemispherical and linear modes. The first completed hemisphere contained the central molecule and four satellites at  $(x-1, y, z)$ ,  $(x-\frac{1}{2}, -y+\frac{1}{2}, z-\frac{1}{2})$ ,  $(x+1, y, z)$  and  $(x+\frac{1}{2}, -y+\frac{1}{2}, z+\frac{1}{2})$ , and the second contained an additional eight satellites. In linear mode, the sets were constructed along the hydrogen-bonded chain directions and they contained between two and ten molecules. Both restricted Hartree–Fock and density functional methods (B3LYP functional) in the triple-zeta 6-311++G(3df,2p) basis set were used as implemented in GAUSSIAN03 (Frisch *et al.*, 2004). In all cases, the differences in electronic properties and energies originating from the different numbers of molecules used in the calculation and the differences between the various methods (as described above) are given in parentheses as standard deviations of the mean values. Where a deviation is not given, the values were the same within their range of reported precision. The energies of the hydrogen bonds calculated in terms of natural bond orbital (NBO) energetic analysis,  $E$  (Foster & Weinhold, 1980; Reed & Weinhold, 1985; Reed *et al.*, 1988), are collected in Table 3. The atomic and molecular properties were calculated at 298.15 K.

In general, all hydrogen bonds in (I) and (II) must be considered as very weak. The second-order perturbation theory analysis of the Fock matrix in the NBO basis leads to the conclusion that the C—H...O interactions are formed mostly by hydrogen-bond-acceptor lone pairs donating electron density to the antibonding orbitals of  $D\cdots H$  bonds, and these ‘delocalization’ energies,  $E_{\text{del}}$ , are collected in Table 3. In these hydrogen bonds, the second most energetic interactions (but distinctly smaller than the above-mentioned first ones) are interactions between acceptor lone pairs and one-centre Rydberg antibonding orbitals of H atoms (e.g.  $0.46 \text{ kJ mol}^{-1}$  for the C8—H8B...O2<sup>i</sup> hydrogen bond; symmetry code as in Table 3). The C—H... $\pi$  interactions are formed only by  $\pi$ -bonding orbitals of the aromatic ring donating electron density to the one-centre Rydberg antibonding orbitals of H atoms. The principal ‘delocalization’ energies  $E_{\text{del}}$  of these C—H... $\pi$  interactions are collected in Table 3. The energies of the intermolecular interactions, calculated on the basis of the total



**Figure 3**

Contour plot showing the relationship between the C—O—C—C and C—O—C=C torsion angles in 2,3-dihydro-1,4-benzodioxine ring systems. The values for (I) are indicated by asterisks and the contours are frequency of occurrence.

self-consistent field energy ( $E_{\text{SCF}}$ ) [corrected for the basis set superposition error estimated by use of the counterpoise method (Boys & Bernardi, 1970)], are very close to the sum of the respective NBO total energies ( $E_{\text{C8-H8B}\cdots\text{O2}^{\text{i}}} + E_{\text{C9-H9B}\cdots\text{C6}^{\text{iii}}}$  and  $E_{\text{C8-H8B}\cdots\text{O4}^{\text{ii}}} + E_{\text{C7-H7A}\cdots\text{C6}^{\text{ii}}}$  for (I);  $E_{\text{C8-H8B}\cdots\text{O2}^{\text{iii}}} + E_{\text{C9-H9B}\cdots\text{C6}^{\text{i}}}$  and  $E_{\text{C8-H8B}\cdots\text{O4}^{\text{iv}}} + E_{\text{C7-H7A}\cdots\text{C6}^{\text{iv}}}$  for (II); symmetry codes are as in Table 3). The differences are not larger than  $0.04 \text{ kJ mol}^{-1}$ , but in all cases,  $E_{\text{SCF}}$  is slightly larger than the value obtained on the NBO basis as a result of the contributions of acceptors occupied orbitals other than lone pairs (e.g. one-centre Rydberg anti-bonding orbitals). In general, the strength of the  $\text{C-H}\cdots\text{O}$  interactions decreases with the lengthening of the  $\text{D}\cdots\text{A}$  distance (even if the  $\text{D-H}\cdots\text{A}$  angle is larger). The  $\text{C-H}\cdots\pi$  interactions depend distinctly less on the  $\text{D}\cdots\text{A}$  distance than the  $\text{C-H}\cdots\text{O}$  interactions, but a similar relationship is observed, especially for larger  $\text{D-H}\cdots\text{A}$  angles.

Analysis of the NBO charges and those derived from the electrostatic properties using Breneman radii shows that H atoms involved in weak hydrogen bonds have a charge of 0.16 (4) atomic units (a.u.), O atoms have a  $-0.49$  (6) a.u. charge and the aromatic ring C atoms have a total charge of  $-0.35$  (9) a.u. divided almost equally among the six C atoms. It is noteworthy that in the case of calculations performed for a single molecule, the corresponding positive charges are about 0.02 a.u. larger and the negative charges are about 0.01 a.u. smaller. These values confirm that during the formation of weak intermolecular interactions some transfer of electron density occurs. The *ab initio* results show that the observed interactions are bonding in character, but they are very weak, with a total interaction energy gain during crystal formation of about  $6.28 \text{ kJ mol}^{-1}$ .

## Experimental

The syntheses of both (I) and (II) have been reported previously (Daukshas *et al.*, 1965; Mewshaw *et al.*, 2002, 2004; Charton *et al.*, 2000), but in all reported procedures, (I) was synthesized in a two-stage method *via* 5-hydroxy-2,3-dihydro-1,4-benzodioxine as the intermediate product. The procedure reported here is a one-pot synthesis giving the products in high yield and high purity. Commercially available 1,2,3-trihydroxybenzene (0.05 mol, 6.3055 g) was mixed with 0.10 mol of the appropriate 1,2-dihalogenoethane (7.90 ml of 1,2-dichloroethane or 8.64 ml of 1,2-dibromoethane), 8 ml of a 40% aqueous solution of NaOH and 1.0 g of *tert*-butylammonium bromide. The mixture was stirred vigorously for 20 h using a magnetic stirrer. The dark-brown reaction mixture was extracted four times with 10 ml of pentane. The combined extracts were washed with 10 ml of water and then evaporated to dryness under reduced pressure. The resulting products were recrystallized from laboratory ethanol (97%) [total yield: 96.3% for (I) and 97.1% for (II)]. Diffraction quality crystals were selected directly from these solutions after 2 h of standing at ambient temperature. The yields of both compounds can be increased to greater than 99.4% by increasing the reaction time to 7 d. Changing the molar ratio of the reactants (1,2,3-trihydroxybenzene–1,2-dihalogenoethane) in the range 1:1 to 1:3 leads to the formation of the same products with yields between 93.0 and 99.7% for a 20 h reaction.

## Compound (I)

### Crystal data

$\text{C}_{10}\text{H}_{11}\text{ClO}_3$   
 $M_r = 214.64$   
 Monoclinic,  $Cc$   
 $a = 5.0961$  (7) Å  
 $b = 25.0840$  (19) Å  
 $c = 8.0217$  (6) Å  
 $\beta = 104.637$  (8)°

$V = 992.14$  (17) Å<sup>3</sup>  
 $Z = 4$   
 Mo  $K\alpha$  radiation  
 $\mu = 0.36 \text{ mm}^{-1}$   
 $T = 291 \text{ K}$   
 $0.28 \times 0.27 \times 0.24 \text{ mm}$

### Data collection

Kuma KM-4 CCD diffractometer  
 Absorption correction: numerical  
 ( $X\text{-RED}$ ; Stoe & Cie, 1999)  
 $T_{\text{min}} = 0.897$ ,  $T_{\text{max}} = 0.918$

5173 measured reflections  
 1540 independent reflections  
 1410 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.046$

### Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$   
 $wR(F^2) = 0.080$   
 $S = 1.08$   
 1540 reflections  
 127 parameters  
 2 restraints

H-atom parameters constrained  
 $\Delta\rho_{\text{max}} = 0.13 \text{ e Å}^{-3}$   
 $\Delta\rho_{\text{min}} = -0.18 \text{ e Å}^{-3}$   
 Absolute structure: Flack (1983),  
 650 Friedel pairs  
 Flack parameter: 0.09 (7)

## Compound (II)

### Crystal data

$\text{C}_{10}\text{H}_{11}\text{BrO}_3$   
 $M_r = 259.10$   
 Monoclinic,  $Cc$   
 $a = 5.0911$  (8) Å  
 $b = 25.4143$  (18) Å  
 $c = 8.0469$  (5) Å  
 $\beta = 104.690$  (9)°

$V = 1007.13$  (18) Å<sup>3</sup>  
 $Z = 4$   
 Mo  $K\alpha$  radiation  
 $\mu = 4.06 \text{ mm}^{-1}$   
 $T = 291 \text{ K}$   
 $0.11 \times 0.10 \times 0.10 \text{ mm}$

### Data collection

Kuma KM-4 CCD diffractometer  
 Absorption correction: numerical  
 ( $X\text{-RED}$ ; Stoe & Cie, 1999)  
 $T_{\text{min}} = 0.640$ ,  $T_{\text{max}} = 0.677$

8036 measured reflections  
 1746 independent reflections  
 1712 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.020$

### Refinement

$R[F^2 > 2\sigma(F^2)] = 0.018$   
 $wR(F^2) = 0.048$   
 $S = 1.09$   
 1746 reflections  
 127 parameters  
 2 restraints

H-atom parameters constrained  
 $\Delta\rho_{\text{max}} = 0.32 \text{ e Å}^{-3}$   
 $\Delta\rho_{\text{min}} = -0.18 \text{ e Å}^{-3}$   
 Absolute structure: Flack (1983),  
 854 Friedel pairs  
 Flack parameter: 0.039 (8)

**Table 1**

Selected geometric parameters (Å, °) for (I).

C1—O1	1.378 (3)		
O2—C2—C3—O4	−1.5 (4)	C8—C7—O2—C2	−50.8 (3)
C2—C3—O4—C8	11.4 (3)	C7—O2—C2—C3	22.0 (3)
C3—O4—C8—C7	−40.4 (3)	C6—O1—C9—C10	−179.48 (19)
O4—C8—C7—O2	61.4 (3)	O1—C9—C10—Cl1	−175.80 (17)

**Table 2**

Selected geometric parameters (Å, °) for (II).

C1—O1	1.374 (3)		
O2—C2—C3—O4	−0.6 (3)	C8—C7—O2—C2	−50.5 (3)
C2—C3—O4—C8	10.9 (3)	C7—O2—C2—C3	21.6 (3)
C3—O4—C8—C7	−40.3 (3)	C6—O1—C9—C10	179.28 (18)
O4—C8—C7—O2	61.4 (3)	O1—C9—C10—Br1	−174.32 (15)

**Table 3**

Experimental hydrogen-bond geometry ( $\text{\AA}$ ,  $^\circ$ ), total energy  $E$  ( $\text{kJ mol}^{-1}$ ) and principal 'delocalization' energy  $E_{\text{del}}$  calculated on the NBO basis for (I) and (II).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$	$E$	$E_{\text{del}}$
(I)						
$C8-H8B\cdots O2^i$	0.97	2.72	3.497 (4)	138	2.05 (1)	1.42 (1)
$C8-H8B\cdots O4^{ii}$	0.97	2.67	3.383 (4)	131	3.51 (1)	2.09 (1)
$C7-H7A\cdots Cg^{ii}$	0.97	3.28	4.208 (6)	160	1.72 (1)	1.21 (1)
$C9-H9B\cdots Cg^{iii}$	0.97	2.75	3.551 (6)	140	1.59 (1)	1.17 (1)
(II)						
$C8-H8B\cdots O2^{iii}$	0.97	2.71	3.488 (3)	137	2.18 (1)	1.51 (1)
$C8-H8B\cdots O4^{iv}$	0.97	2.66	3.372 (3)	131	3.64 (2)	2.30 (1)
$C7-H7A\cdots Cg^{iv}$	0.97	3.22	4.151 (5)	160	2.51 (1)	1.63 (1)
$C9-H9B\cdots Cg^v$	0.97	2.71	3.525 (5)	142	1.63 (1)	1.17 (1)

Note:  $Cg$  is the centroid of the aromatic ring. Symmetry codes: (i)  $x-1, y, z$ ; (ii)  $x-\frac{1}{2}, -y+\frac{1}{2}, z-\frac{1}{2}$ ; (iii)  $x+1, y, z$ ; (iv)  $x+\frac{1}{2}, -y+\frac{1}{2}, z+\frac{1}{2}$ .

All H atoms were treated as riding atoms, with C—H distances of 0.93 or 0.97  $\text{\AA}$  and with  $U_{\text{iso}}(\text{H})$  values set at  $1.2U_{\text{eq}}(\text{C})$ .

For both compounds, data collection: *CrysAlis CCD* (UNIL IC & Kuma, 2000); cell refinement: *CrysAlis RED* (UNIL IC & Kuma, 2000); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *XP* in *SHELXTL/PC* (Sheldrick, 2008) and *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2009).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3288). Services for accessing these data are described at the back of the journal.

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