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# Structural Motifs in Enantiopure Halogenated Aryl Benzyl Sulfoxides: Effect of Fluorine Substitution

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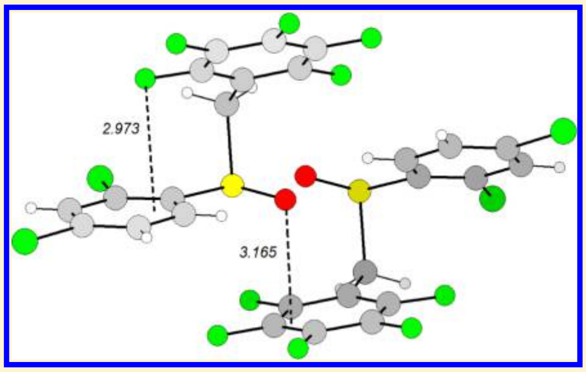
Ⓢ *Supporting Information*

**ABSTRACT:** A series of enantiopure crystalline aryl benzyl sulfoxides, bearing different substituents on both the aryl groups, were synthesized by an enantioselective oxidation of the corresponding sulfides. Structural investigations, achieved by means of single-crystal X-ray diffraction, allowed us to recognize the main assembling interactions. The same procedure was repeated for some corresponding fluorinated aryl benzyl sulfoxides. The synthesis of the enantiomers of a new fluorinated compound, which shows unusual structural patterns, prompted us to compare the structural motifs of the two families of sulfoxides (fluorinated and unfluorinated) and to investigate the changes due to the fluorine substitution. Some short contacts involving the fluorine atom were discussed in more details, taking into account the recent interest in these sometimes controversial interactions.



## INTRODUCTION

Synthetic work performed in these laboratories has led to a conspicuous chemical library of enantiopure sulfoxides, which were produced with our original strategy based upon carbon-for-carbon substitution of suitable carbanionic leaving groups[1−3] or with various enantioselective oxidation reactions of sulfides.[2−7]

In more recent years, among the enantioselective oxidation of sulfides that were scrutinized, we have thoroughly investigated the cheap and straightforward oxidation process performed with hydroperoxides in the presence of catalytic amounts of a complex between titanium and (*S*,*S*)- or (*R*,*R*)-hydrobenzoin,[3−7] a procedure that has yielded a large number of valuable chiral intermediates. In our systematic oxidation of a large set of aryl benzyl sulfides,[3,5,6] we observed that these substrates were invariably oxidized by this procedure with a high enantioselectivity (81 to >98% ee values), regardless of the nature, steric hindrance, and position of many substituents on both aryl groups. Furthermore, a crystallization step of the highly enriched materials (81−95% ee) produced the enantiopure sulfoxides (>98% ee).[3,5,6] The very interesting stereochemical course of the oxidation process was also investigated with DFT methods.[5] Due to the independence of the result from the change of the substituents on the aryl groups, a reliable reaction mechanism was outlined for the simple unsubstituted benzyl phenyl sulfide. According to the calculation, the substrate to be oxidized approaches the chiral titanium complex in a conformation in which the two phenyl groups arrange in an *anti* conformation with respect to the sulfur−methylene carbon bond.[5] When the sulfide is in this conformation, weak interactions involving the aryl groups, among which the T-shaped aryl CH···π interactions are worthy of mention,[8−11] fix it in the effective oxidation position, which discriminates the *pro*-(*R*) from the *pro*-(*S*) pathway.[5] It is worth noting that the weak interactions involving the aryl moieties have gained recent interest both in crystal engineering,[8] and in asymmetric synthesis.[9−11] According to recent publications,[8] these interactions are indicated as "CH···π hydrogen bonds".

When the same oxidizing procedure was applied to fluorinated aryl benzyl sulfides,[6,7] we confirmed the expectation of very high enantioselectivity with a single exception (associated with the oxidation of 2,3,4,5,6-pentafluorobenzyl pentafluophenyl sulfide; ee value 61%).[7] Since the changes due to the fluorine substitution have consequences that are not easily predictable,[12−14] we decided to extend the DFT calculations to the oxidation of these fluorinated substrates. We chose to study the stereochemical course of one of the processes with a higher enantioselectivity and the single case of a less enantioselective oxidation.[7] Both of these new trials were successful, because the stereochemical courses arising from the calculations are in good agreement with the experimental results. We found[7] that the presence of pentafluorophenyl moieties in these sulfides result in new interactions, which complement or modify those that were observed in the case of

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non-fluorinated sulfides. Focusing only on the decreased enantioselectivity in the oxidation of 2,3,4,5,6-pentafluorobenzyl pentafluorophenyl sulfide, we calculated a new reaction pathway in which a *gauche* conformation of the two pentafluorophenyl moieties is involved.[7] Different weak interactions connected to the fluorine atoms are able to stabilize the oxidation process for the sulfide in this conformation, thus altering the stereochemical course that is observed for the other substrates.

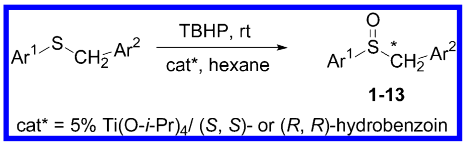
Our research on the enantioselective oxidation has continued, and new fluorinated aryl benzyl sulfoxides have been obtained with the usual high enantioselectivity (>98% ee). However, very few among these compounds yielded crystals that were found to be suitable for X-ray diffraction experiments. In this new series of oxidation reactions, the asymmetric synthesis of 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxides emerged, first because only in this case were satisfactory crystals obtained, and also because the analyzed crystal structure showed new and unexpected weak interactions in comparison with those previously observed.[5−7]

At this point, taking into account the impact that the fluorination had on the reaction mechanism[7] and the recent interest of crystal engineers in the weak interactions involving the fluorine atom,[12−14] we considered it worthy of interest to scrutinize and to compare the new interactions that were found in the crystal structures of enantiopure fluorinated and unfluorinated aryl benzyl sulfoxides from our library, with a particular attention to the former compounds.

## ■ EXPERIMENTAL SECTION

Aryl benzyl sulfoxides (*R*)-**1−11** and (*R*)-**13** (Table 1) were synthesized on a 1 mmol scale by the enantioselective oxidation of the corresponding sulfides with *tert*-butyl hydroperoxide in the presence of 5% of a 1:2 complex formed in situ by mixing titanium isopropoxide and (*S*,*S*)-hydrobenzoin in *n*-hexane, according to our protocol.[5−7] The absolute configurations of the enantiopure synthesized sulfoxides were determined by means of single-crystal X-ray diffraction.

**Table 1. Enantioselective Synthesis of Aryl Benzyl Sulfoxides**



| entry | sulfoxide | Ar$^1$ | Ar$^2$ | torsion[a] | CCDC[b] |
|---|---|---|---|---|---|
| 1 | (*R*)-**1** | 2-MeCOO-$C_6H_4$ | $C_6H_5$ | 66.0,[c] 62.9[d] | 720081 |
| 2 | (*R*)-**2** | 2-MeO-$C_6H_4$ | $C_6H_5$ | 65.6,[c] 65.0[d] | 720083 |
| 3 | (*R*)-**3** | 3-MeO-$C_6H_4$ | $C_6H_5$ | 176.6 | 720084 |
| 4 | (*R*)-**4** | 4-$O_2N$-$C_6H_4$ | $C_6H_5$ | 171.8 | 720082 |
| 5 | (*R*)-**5** | 4-Br-$C_6H_4$ | 2-$O_2N$-$C_6H_4$ | 166.9 | 720085 |
| 6 | (*R*)-**6** | 4-Br-$C_6H_4$ | 4-$O_2N$-$C_6H_4$ | 51.8 | 720086 |
| 7 | (*R*)-**7** | 4-Br-$C_6H_4$ | 2-MeO-$C_6H_4$ | 179.1 | 720087 |
| 8 | (*R*)-**8** | 4-Br-$C_6H_4$ | 3-MeO-$C_6H_4$ | 55.4 | 720088 |
| 9 | (*R*)-**9** | 4-Br-$C_6H_4$ | 3-Cl-$C_6H_4$ | 52.1 | 720089 |
| 10 | (*R*)-**10** | 4-Br-$C_6H_4$ | 2,4-$Cl_2C_6H_3$ | 174.8 | 720090 |
| 11 | (*R*)-**11** | 2-F-$C_6H_4$ | $C_6F_5$ | 64.7 | 876025 |
| 12 | (*R*)-**12** | 2,4-$Cl_2C_6H_3$ | $C_6F_5$ | 69.6 | 992418 |
| 13 | (*S*)-**12** | 2,4-$Cl_2C_6H_3$ | $C_6F_5$ | 68.7 | 992419 |
| 14 | (*R*)-**13** | $C_6F_5$ | $C_6H_5$ | 179.6 | 876664 |

[a] Torsion angle (in deg) for the rotamerism of the aryl groups around the sulfur-methylene carbon (see Scheme 1). [b] Cambridge Crystallographic Data Centre depository number. [c] First molecule in the asymmetric unit. [d] Second molecule in the asymmetric unit.

The synthesis of enantiopure 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (**12**) was set up for the first time for this work. The precursor 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfide was synthesized by a standard reaction of the sodium salt of 2,4-dichlorothiophenol with 2,3,4,5,6-pentafluorobenzyl bromide (see the Supporting Information). The enantioselective oxidation of 2,4 dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfide was performed by employing both enantiomers of hydrobenzoin. In agreement with a rule derived from our previous results,[3−7] (*R*)-sulfoxide was obtained when the (*S*,*S*)-hydrobenzoin was employed (Table 1, entry 12), whereas (*S*)-sulfoxide was obtained if the (*R*,*R*) ligand was used (Table 1, entry 13). The reaction with (*R*,*R*)-hydrobenzoin was repeated also on a larger scale (12 mmol), with a lower catalyst loading (2.5%).[3] These variations caused only a slight decrease of very good isolated yields for these reactions (from 96% to 91%). The multigram experimental procedure follows.

A solution of Ti(O-*i*-Pr)$_4$ (0.085 g, 0.3 mmol) in 20 mL of *n*-hexane was added to a solution of (*R*,*R*)-hydrobenzoin (0.129 g, 0.6 mmol) in 40 mL of *n*-hexane under a nitrogen atmosphere. The mixture was stirred for 1 h at room temperature. A solution of 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfide (4.3 g, 12 mmol) in 80 mL of *n*-hexane was added at this stage, and the mixture was stirred for 30 min. After this time, 1.66 mL (13.2 mmol) of a commercial 80% solution of *tert*-butyl hydroperoxide (in di-*tert*-butyl peroxide/water 3/2) was added and the stirring was continued for 2 days at room temperature. The solvent was removed in vacuo, and the residue was subjected to column chromatography (petroleum ether/ethyl acetate 4/1), yielding (*S*)-2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (**12**; 4.1 g, 91% yield): mp 92−94 °C (*n*-hexane/diethyl ether 95/5). The analytical separation of the enantiomers of a racemic sample of 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (**12**) was performed with HPLC (column, Chiralcel OD-H; eluent, *n*-hexane/isopropyl alcohol 90/10). These conditions were employed in the analysis of the chiral material to check its enantiopurity.

(*S*)-2,4-Dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide: $[\alpha]_D^{25} = -399.6°$ ($c$ = 1.1, $CHCl_3$), ee >98%. (*R*)-2,4-Dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide: $[\alpha]_D^{25} = +400.5°$ ($c$ = 0.9, $CHCl_3$), ee >98%. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.50 (d, $J$ = 8.3 Hz, 1 H), 7.47 (d, $J$ = 1.9 Hz, 1 H), 7.44 (d, $J$ = 8.3 Hz, $J$ = 1.9 Hz, 1 H), 4.46 (dt, $J$ = 13.3 Hz, $J$ = 1.2 Hz, 1 H), 4.23 (dt, $J$ = 13.3 Hz, $J$ = 1.2 Hz, 1 H). $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 145.8 (d-like, $J$ = 255 Hz), 141.2 (d-like, $J$ = 255 Hz), 138.8, 138.7, 137.4 (d-like, $J$ = 253 Hz), 131.1, 129.8, 128.3, 127.2 103.5 (m), 46.8. Anal. Calcd for $C_{13}H_5Cl_2F_5OS$: C, 41.62; H, 1.34. Found: C, 41.32; H, 1.71.

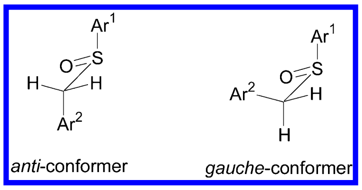
X-ray diffraction data for (*R*)-**12** and (*S*)-**12** were collected on a suitable crystal with a Nonius Kappa CCD area detector diffractometer equipped with Mo K$\alpha$ radiation ($\lambda$ = 0.71073 Å). The structures were solved through the direct methods procedure of SIR2008[15] and refined by the full-matrix least-squares on $F^2$ technique of SHELXL-97.[16] In both cases, the non-hydrogen atoms were refined with anisotropic thermal parameters, while the hydrogen atoms were placed in idealized positions riding on their attached atoms (C−H = 0.93 Å, $U_{iso}(H) = 1.2[U_{iso}(C)]$).

Main crystallographic data for (*R*)-**12**: orthorhombic, space group $P2_12_12_1$, $a$ = 7.7040(10) Å, $b$ = 12.545(2) Å, $c$ = 15.068(3) Å, cell volume 1456.3(4) Å$^3$, R1/wR2 ($I > 2\sigma(I)$) = 0.0633/0.1873, R1/wR2 (all data) = 0.1144/0.2628, Flack parameter −0.01(18). Main crystallographic data for (*S*)-**12**: orthorhombic, space group $P2_12_12_1$, $a$ = 7.7200(5) Å, $b$ = 12.5368(9) Å, $c$ = 15.0423(6) Å, cell volume 1455.86(15) Å$^3$, R1/wR2 ($I > 2\sigma(I)$) = 0.0418/0.0894, R1/wR2 (all data) = 0.0691/0.1006, Flack parameter 0.00(8). Complete crystallographic data (for more details, see the Supporting Information) were deposited at the Cambridge Crystallographic Data Centre with the following depository codes: CCDC-992418 ((*R*)-**12**) and CCDC-992419 ((*S*)-**12**). Copies of available material can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax +44-1223-336033 or e-mail deposit@ccdc.cam.ac.uk).

## RESULTS AND DISCUSSION

**1. Conformer Distribution.** The crystal structures of nonfluorinated aryl benzyl sulfoxides **1**−**10**[5] can be grouped into two main families, if the rotamerism around the bond between the sulfur and the methylene carbon atom is considered. The aryl groups were found to be only in a *gauche* or *anti* position (Scheme 1), with an almost equal number of items populating the two groups (Table 1).

**Scheme 1. *anti* and *gauche* Structures of Aryl Benzyl Sulfoxides**



The torsion angles of the *gauche* family lie in the 51−66° range; the torsion angles of the *anti* family lie in the 167−179° range (Table 1). Taking into account the relevance of the *gauche*/*anti* dichotomy in our mechanism,[7] some further considerations on the conformers in crystal structure are worth a discussion. From a preliminary inspection of the data collected in Table 1, it is not easy to predict the preferred conformer in the crystal structure. However, in our previous work on the comparison between calculated and experimental CD spectra of these molecules,[17] the energies of the main conformers of aryl benzyl sulfoxides **1** and **2** and **4**−**6** had been computed, both under vacuum and in a solvent, at 300 K, together with those of other aryl benzyl sulfoxides whose crystal structure analyses were not available. The energetic differences between the *anti* and the *gauche* rotamers that were calculated were found to be small (less than 0.28 kcal/mol) with a single exception (i.e., the (*R*)-4-bromophenyl 2-nitrobenzyl sulfoxide **5**).[17] Taking into account that the highest energetic differences between the two conformers are related to the presence of moieties in the *ortho* position of the two aryl groups Ar$^1$ and Ar$^2$ of the sulfoxides, thus neglecting the effects of *meta* and *para* substituents, an empirical rule can be derived from the inspection of the structures collected in Table 1: for aryl benzyl sulfoxides **1**−**4** (substitution on the Ar$^1$ aryl moiety, case 1), the preferred conformation is *anti*, but it becomes *gauche* if an *ortho* substituent is present on the Ar$^1$ phenyl moiety. For benzyl 4-bromophenyl sulfoxides **5**−**10** (substitution on the Ar$^2$ benzyl phenyl moiety, case 2), the preferred conformation is *gauche*, but it becomes *anti* if a substituent is present on the *ortho* position of the Ar$^2$ benzyl phenyl group.

**2. Main Interactions in Unfluorinated Aryl Benzyl Sulfoxides 1−10.** Independently from the substituents that are present on both the aryl rings, the peculiarity of the crystal structures of the aryl benzyl sulfoxides **1**−**10** is the pattern of the intermolecular C−H···O short contacts between the sulfinyl oxygen and the hydrogen atom that is in the *ortho* position of the benzyl phenyl group and/or the methylene hydrogen atom (Table 2).

These two contacts are present independently, as in the case of sulfoxides **7**−**10**, or occur contemporarily in sulfoxides **1**−**4** and **6**, thus depicting a characteristic hexagonal pattern (Figure 1), whose vertexes are the oxygen, the two cited hydrogens, the methylene carbon, and two aryl carbon atoms ($C_{ipso}$ and $C_{ortho}$) of the benzyl phenyl group.

With the exception of sulfoxide (*R*)-**5** (see later), the distances between the hydrogen and the oxygen atoms lie in the 2.44−2.87 Å range (Table 2), whereas the angles formed by the C−H···O atoms lies in the 147−167° range (Table 2). Such short contacts were observed in our early crystallographic work on some alkyl aryl sulfoxides[18] and were reviewed by other authors.[19] Taking into account their geometric characteristics, and according to a recent definition,[20] they are a weak form of hydrogen bonding. In the absence of other significant interactions, these hydrogen bonds should provide the largest contribution to the stability of the whole crystal structure.

An interesting exception is observed in the case of (*R*)-4-bromophenyl 2-nitrobenzyl sulfoxide (**5**). The sulfinyl oxygen

**Table 2. Distances (Å) and Angles (deg) of the Intermolecular Interactions Involving the Sulfinyl Oxygen Atom in Sulfoxides 1−11 and 13**

| entry | sulfoxide | $C_{Met}\cdots O^{a}$ | $H_{Met}\cdots O^{b}$ | $\angle C_{Met}HO^{c}$ | $C_{ortho}\cdots O^{d}$ | $H_{ortho}\cdots O^{e}$ | $\angle C_{ortho}HO^{f}$ |
|---|---|---|---|---|---|---|---|
| 1 | (*R*)-**1** | 3.499(3)$^{g}$ | 2.638(25)$^{g}$ | 151(2)$^{g}$ | 3.401(2)$^{g}$ | 2.523(22)$^{g}$ | 154(2)$^{g}$ |
| | | 3.658(3)$^{h}$ | 2.654(28)$^{h}$ | 155(2)$^{h}$ | 3.350(3)$^{h}$ | 2.444(28)$^{h}$ | 159(2)$^{h}$ |
| 2 | (*R*)-**2** | 3.532(3)$^{g}$ | 2.576(33)$^{g}$ | 160(3)$^{g}$ | 3.405(3)$^{g}$ | 2.486(25)$^{g}$ | 147(2)$^{g}$ |
| | | 3.447(3)$^{h}$ | 2.584(30)$^{h}$ | 156(3)$^{h}$ | 3.565(3)$^{h}$ | 2.711(34)$^{h}$ | 153(3)$^{h}$ |
| 3 | (*R*)-**3** | 3.349(4) | 2.507(27) | 159(2) | 3.460(3) | 2.598(24) | 148(2) |
| 4 | (*R*)-**4** | 3.689(3) | 2.869(29) | 149(2) | 3.431(3) | 2.484(26) | 161(2) |
| 5 | (*R*)-**5** | 3.163(4) | 2.240(2) | 159(0) | | | |
| | | 3.433(5)$^{i}$ | 2.540(3)$^{i}$ | 153(0)$^{i}$ | | | |
| 6 | (*R*)-**6** | 3.400(8) | 2.475(4) | 159(0) | 3.480(9) | 2.653(5) | 149(0) |
| 7 | (*R*)-**7** | | | | 3.164(6) | 2.378(39) | 154(4) |
| 8 | (*R*)-**8** | 3.406(5) | 2.510(39) | 167(3) | | | |
| 9 | (*R*)-**9** | 3.382(10) | 2.444(6) | 163(1) | | | |
| 10 | (*R*)-**10** | 3.351(8) | 2.466(5) | 151(0) | | | |
| 11 | (*R*)-**11** | 3.326(5) | 2.281(38) | 168(3) | | | |
| 12 | (*R*)-**13** | 3.434(5) | 2.595(41) | 153(3) | 3.525(5) | 2.707(35) | 149(3) |

[a] Distance between the methylene carbon and the sulfinyl oxygen atom. [b] Distance between the methylene hydrogen and the sulfinyl oxygen atom. [c] Angle of the methylene carbon, the methylene hydrogen, and the sulfinyl oxygen atom. [d] Distance between the aryl *ortho* carbon and the sulfinyl oxygen atom. [e] Distance between the aryl *ortho* hydrogen and the sulfinyl oxygen atom. [f] Angle of the aryl *ortho* carbon, the aryl *ortho* hydrogen, and the sulfinyl oxygen atom. [g] Referring to the first molecule in the asymmetric unit. [h] Referring to the second molecule in the asymmetric unit. [i] Interaction with a different molecule.

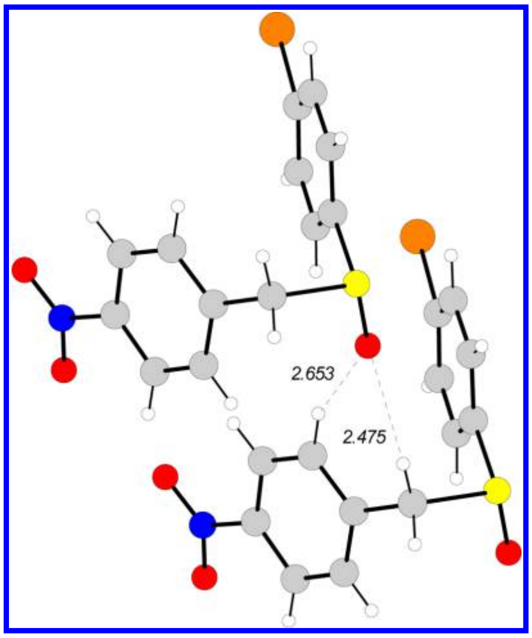


**Figure 1.** Hexagonal pattern formed by weak hydrogen bonding in sulfoxide (*R*)-**6**.

and the methylene hydrogen atom of the same molecule are engaged into two hydrogen bonds with the methylene hydrogen and the sulfinyl oxygen atom, respectively, of two different molecules (Figure 2).

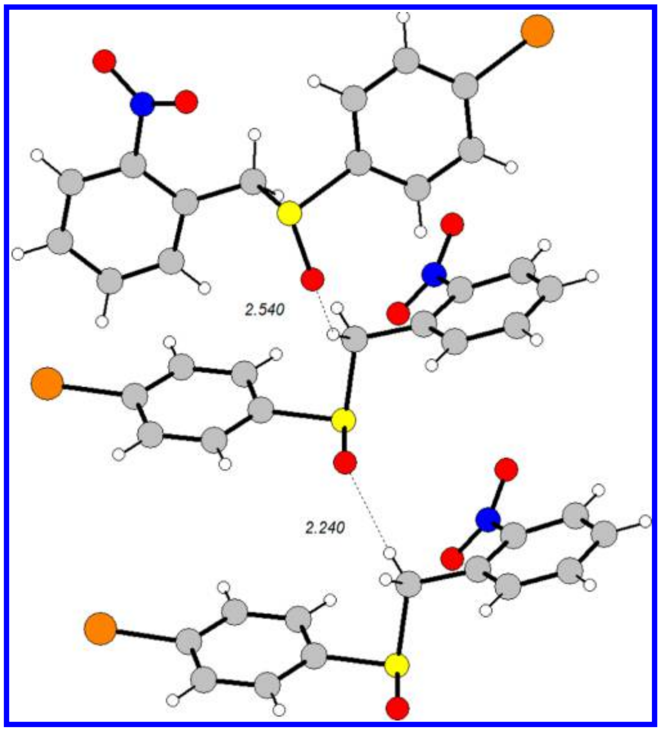


**Figure 2.** Weak hydrogen bonding in sulfoxide (*R*)-**5**.

In one of these interactions, the H···O distance remains in the previously cited range (2.540(2) Å; Table 2, entry 5), whereas in the other hydrogen bond the H···O distance drops to the value 2.240(3) Å, which is the shortest value observed in these molecules.

CH−π hydrogen bonds, which play a crucial role in our theoretical investigation on the enantioselective oxidation of aryl benzyl sulfides,[5−7] are seldom found in the crystals. Exceptions are represented by sulfoxides **4** and **9**.[21] Other forms of short contacts, such as halogen bonding,[13,22] are not general, because they are connected to the contemporary presence of the bromine atom and the methoxy group as a substituent of the aryl moieties, and will not be discussed in the present work.

## 3. Crystal Structures of Fluorinated Aryl Benzyl Sulfoxides.

*3.1. Conformer Distribution.* From a steric point of view, the hydrogen/fluorine exchange is sometimes regarded as an almost isosteric substitution,[23] since the fluorine is only slightly larger than the hydrogen atom. On the other hand, physical, chemical, and biological properties between fluorinated and non-fluorinated compounds are often very different.[12−14] From an inspection of Table 1, the few fluorinated molecules that are listed (entries 11−14) cannot lead to a safe control of our empirical rules for the choice between *gauche* or *anti* conformation in the crystal structure. In the first instance, (*R*)-2-fluorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (**11**) and 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (**12**), which have an *ortho* substituent on the aryl group, should arrange in a *gauche* conformation in their crystal structures, as actually found. Furthermore, as will be reported in the next paragraph, intramolecular interactions, connected with the fluorine atom and the benzyl pentafluorophenyl moiety, contribute to the stability of these *gauche* conformations. On the other hand, the *anti* conformation of sulfoxide **13** could be due to the symmetric *ortho* substitution of both aryl groups. However, more items should be analyzed carefully to check the proposed empirical rule, but this appears to be an uphill task due to the cited difficulty of obtaining fluorinated sulfoxides suitable for X-ray diffraction experiments.

*3.2. Stacking Interactions Involving the Pentafluorophenyl Groups.* The aryl parallel displaced stacking represents a recurring structural motif in molecules in which the pentafluorophenyl group is present.[12−14] Due to the inverted electronic density map of the pentafluorophenyl moiety, the aryl−perfluoroaryl displaced stacking provides a large energetic stabilization for the crystal structure, to such an extent that it is classified among the most robust supramolecular synthons.[20]

Whereas the overlap of the aryl rings in the case of sulfoxides **11** and **12** is not large, due to the *gauche* conformation in which they arrange (Table 1), the canonical form of a stacking interaction was found in the case of benzyl pentafluorophenyl sulfoxide ((*R*)-**13**), in which the aryl groups arrange in the *anti* conformation. The observed intermolecular parallel displaced stacking assembly between two aryl groups of different nature is represented in Figure 3.

The geometric characteristics of this supramolecular assembly are summarized herein. The distance of the *o*-fluorine atom of the pentafluorophenyl group from the centroid of the benzyl phenyl ring is 3.215 Å. The distance of the same atom from the plane of the benzyl phenyl ring is 3.197 Å. Taking into account these distances and the satisfactory overlap between the aryl rings, it is reasonable to believe that the displaced stacking interaction should provide a primary contribution to the stability of the molecule and should dictate the main features of the crystal structures.[20] As reported,[24] the possibility of weaker interactions involving the aryl groups (e.g., C−H···π hydrogen bonds) can be reasonably excluded in the presence of strong stacking interactions.

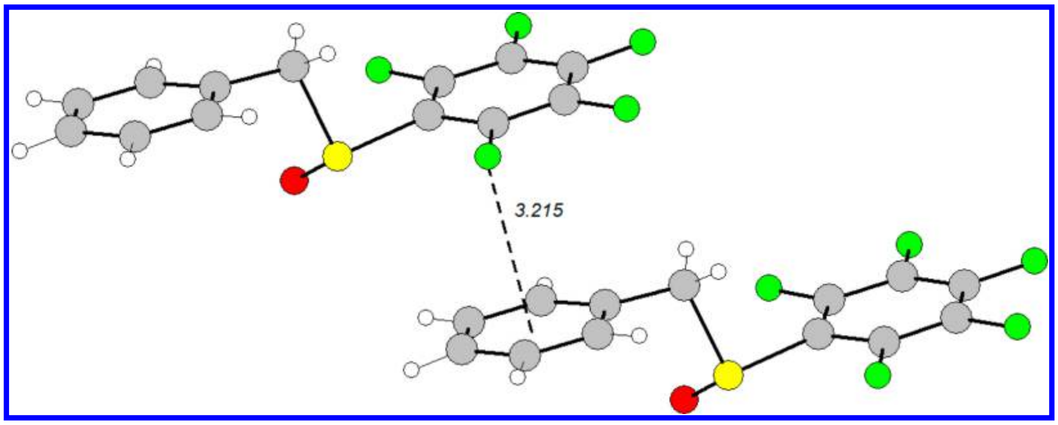


**Figure 3.** $\pi-\pi$ displaced stacking in sulfoxide (*R*)-**13**.

*3.3. Short Contacts Involving the Fluorine Atoms.* New, interesting interactions due to the fluorine atoms were observed in the crystal structures of molecules **11** and **13**. The interaction between the sulfinyl oxygen with the methylene hydrogen atom discussed above was found also in sulfoxides (*R*)-**11** and (*R*)-**13** (Table 2). However, in 2-fluorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide)(*R*)-**11**, this hydrogen bonding (Table 2, entry 11; H··O distance 2.281(38) Å) is accompanied by an F···O short contact (Figure 4) between the same oxygen and the *o*-fluorine atom of the 2-fluorophenyl moiety (F···O distance 2.916(4) Å; C−F···O angle 98.6(2)°; F···O−S angle 113.1(1)°).

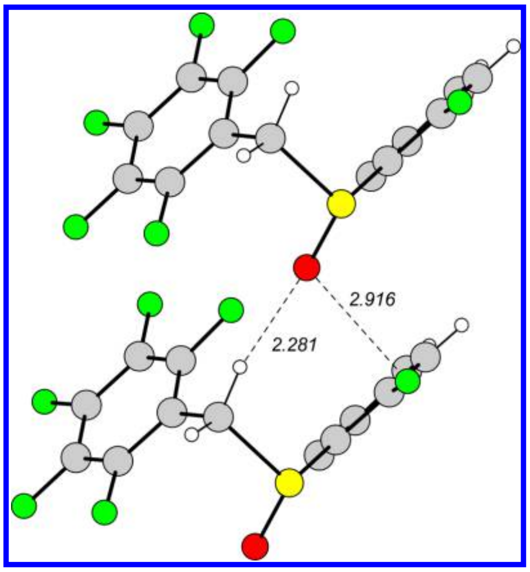


**Figure 4.** Contemporary short contacts of the sulfinyl oxygen atom with hydrogen and fluorine atoms in sulfoxide (*R*)-**11**.

For a long time the interactions involving the fluorine atom have been sources of controversy.[12−14] From an early analysis of the crystallographic database,[25] the short contacts involving halogens were grouped into two main types (I and II) according to the angle of the mutual approach of the halogen atoms toward each other. In type I, the C−$X_1$···$X_2$ and the C−$X_2$···$X_1$ angles are almost equal (not so far from right angles); in type II, one of these angles is almost a right angle, whereas the other is almost linear.

An interesting situation arises if one considers the possibility of an eventual F···O short contact. In earlier times,[26] an intramolecular short contact of this kind in the pentafluorobenzoic acid was considered an energetic disadvantage, compensated by other stronger interactions building the crystal structure. Later, Lyssenko and Antipin reported[27] an intermolecular F···O short contact between a fluorine atom and the carbonyl oxygen of a trifluoromethyl trifluoroacetyl pyrrole (F···O distance 2.897 Å; C−F···O angle 156.4°; F···O−C angle 93.0°). The reported theoretical analysis suggested a binding nature for this interaction.[27] Due to a certain analogy between the carbonyl and the sulfinyl group, we believe that the intermolecular short contact that we observed in sulfoxide (*R*)-**11** resembles the case reported by Lyssenko and Antipin,[27] even though an eventual stabilization is not certain, due to different geometric characteristics.

In benzyl pentafluorophenyl sulfoxide ((*R*)-**13**), the map of the observed short contacts is richer than that in sulfoxide (*R*)-**11** (Figure 5), because the hexagonal pattern formed by the weak hydrogen bonds of the sulfinyl oxygen atom (Table 2, entry 12; H···O distance 2.595(41) Å, H···O distance 2.707(35) Å), similar to those represented in Figure 1 for the unfluorinated sulfoxide (*R*)-**6**, is accompanied by another short contact, having an atomic distance below the sum of the van der Waals radii and involving the oxygen and the *o*-fluorine atom of the pentafluorophenyl group of the same molecule

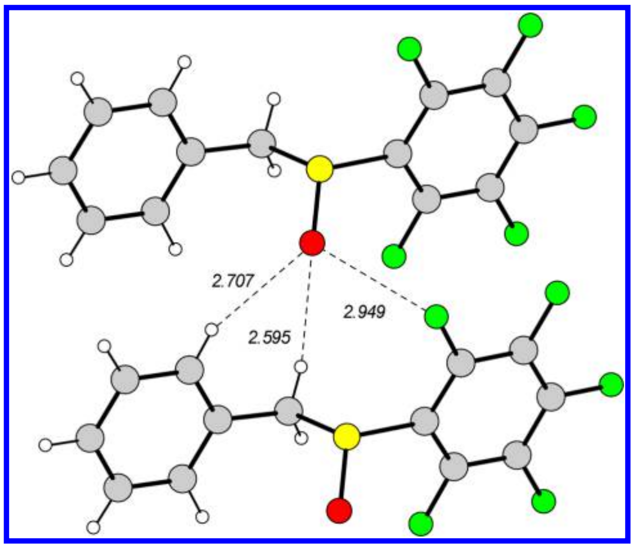


**Figure 5.** Contemporary short contacts of the sulfinyl oxygen atom with two hydrogen and fluorine atoms in sulfoxide (*R*)-**13**.

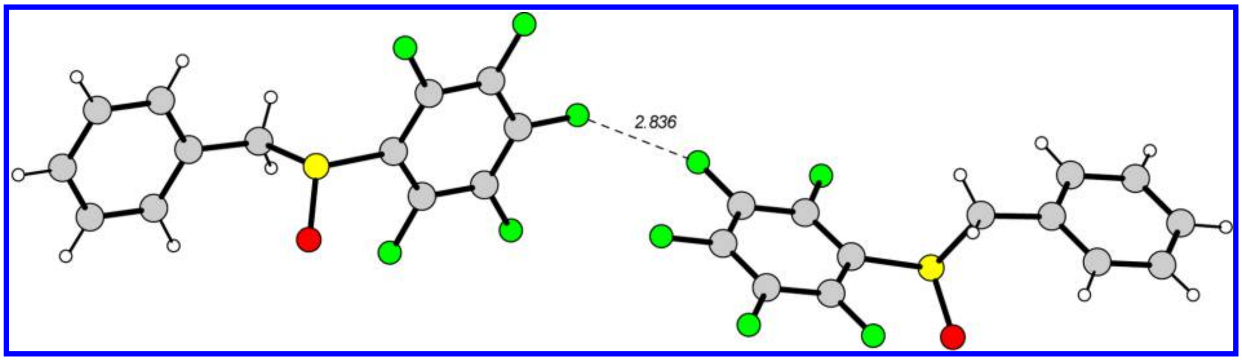


**Figure 6.** C−F···F−C short contact in sulfoxide (*R*)-**13**.

(F···O distance 2.949(3) Å; C−F···O angle 118.0(2)°; F···O−S angle 115.6(1)°). The geometric characteristics of sulfoxide (*R*)-**13** are similar to those that were described for compound (*R*)-**11**, despite the fact that the former arranges in an *anti* conformation, whereas the latter is in a *gauche* conformation.

Structural investigations of (*R*)-**13** (Figure 6) also revealed a C−F···F−C short contact[14] between a fluorine atom in the *meta* position of the pentafluorophenyl moiety with a fluorine atom in the *para* position of the pentafluorophenyl moiety of another molecule (2.836 Å F···F distance; $C_{para}$−F···F angle 150.3(2)°; $C_{meta}$−F···F angle 125.7(2)°). Within these geometric features, a slightly bent type II interaction can be recognized.

The C−F···F−C interaction is one of the most controversial short contacts involving the fluorine atom. In our previous work[18] on the crystal structure of enantiopure halogenated sulfoxides, we recognized a C−Cl···Cl−C interaction between two chlorine atoms with different electronic properties, being bound to two different carbon atoms: one aliphatic and the other aromatic (Cl···Cl distance 3.458(1) Å; $C_{Methylene}$−Cl···Cl angle 167.2(2)°; type II). An interaction of this sort is commonly catalogued among the "halogen bonding" species,[22] because larger halogen atoms (chlorine, bromine, iodine) are more polarizable than fluorine,[12−14] for which, in a first instance, this possibility was excluded. However, after a long debate, at first it was accepted that a type II C−F···F−C interaction could have a slightly stabilizing effect.[12] Later, Quiñonero et al. reported[28] a very short type I F···F contact in a fluorouracil derivative. Also in this case, the subsequent theoretical analysis arrived to the conclusion that there is a slight energetic stabilization even in this situation.[28] Other interesting cases were also reviewed.[14] More recently, the possibility that fluorine atoms could originate halogen bonding was theoretically investigated.[29]

In principle, in the sulfoxide (*R*)-**13**, *m*- and *p*-fluorine atoms are expected to have slightly different electronic densities. Thus, a "weak electrophile−weak nucleophile" type II interaction can be envisaged in this molecule. Moreover, very recently, a precedent for a similar situation was reported in the crystal structure of pentafluorophenyl-appended 2,2′-bithiazoles.[30] As occurs in sulfoxide (*R*)-**13**, the authors observed first the stacking between the thiazole and the pentafluorophenyl rings, which should largely contribute to the energetic stabilization of the structure, and later type I and type II C−F···F−C interactions.[30] Theoretical calculations confirmed the attractive nature of these type II interactions.[30] On the basis of these similarities, we believe that also in sulfoxide (*R*)-**13** the observed type II C−F···F−C interactions should be considered stabilizing.

**4. The Case of Sulfoxide 12.** As anticipated in the Introduction, an unexpected pattern was observed in (*R*)- or (*S*)-2,4-diclorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (**12**). In fact, the sulfinyl oxygen atom is not involved in any interaction with hydrogen atoms. The sulfinyl bond protrudes toward the electron-poor pentafluorophenyl moiety of another molecule,[31] and the oxygen atom reaches a distance of 3.165 Å from the pentafluophenyl plane (Figure 7).

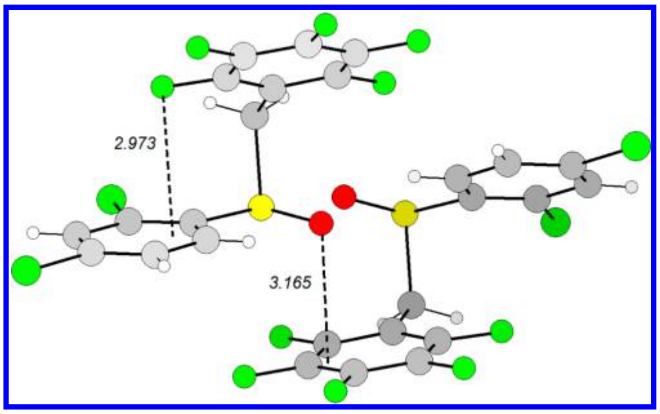


**Figure 7.** Intermolecular protrusion of the oxygen atom toward the pentafluorophenyl moiety and intramolecular projection of the fluorine atom toward the 2,4-dichlorophenyl moiety in sulfoxide (*R*)-**12**.

For a better description, it must be added that the distance between the oxygen and the *p*-carbon atom of the same aryl group is 3.180(8) Å. A similar behavior of the sulfinyl group does not occur often.[31] At the same time, the *o*-fluorine atom of the pentafluorophenyl group, due to the *gauche* conformation, lies projected (Figure 7) toward the plane of the almost electron-poor 2,4-dichlorophenyl group in the same molecule (the distance of the fluorine atom from this plane is 2.973 Å). To complete the description, the distances of the *o*-fluorine atom from the *ipso*-carbon of the 2,4-dichlorophenyl group and from the *o*-carbon bound to the chlorine atom are 3.011(8) and 3.172(8) Å, respectively.

The interactions occurring between an electron-poor aryl group and atoms having unshared electron pairs, but not involved in any hydrogen bonding, were recently investigated and classified.[31] The possible stabilization energies can be estimated on the basis of the geometry of the assembly.[31] In the present case, taking into account the geometrical features of

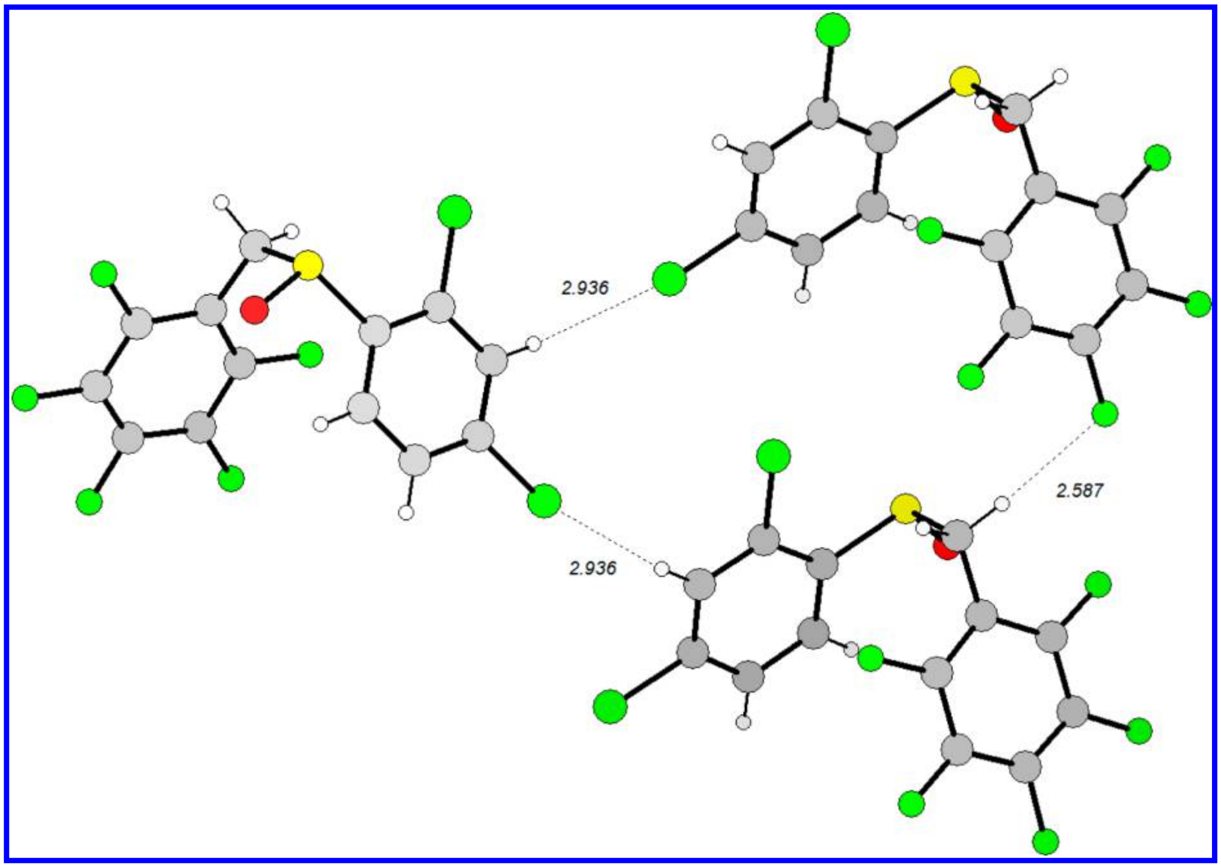


**Figure 8.** Network of three molecules settled by CH···halogen interactions (two CH···Cl and one CH···F short contact) in sulfoxide (*R*)-**12**.

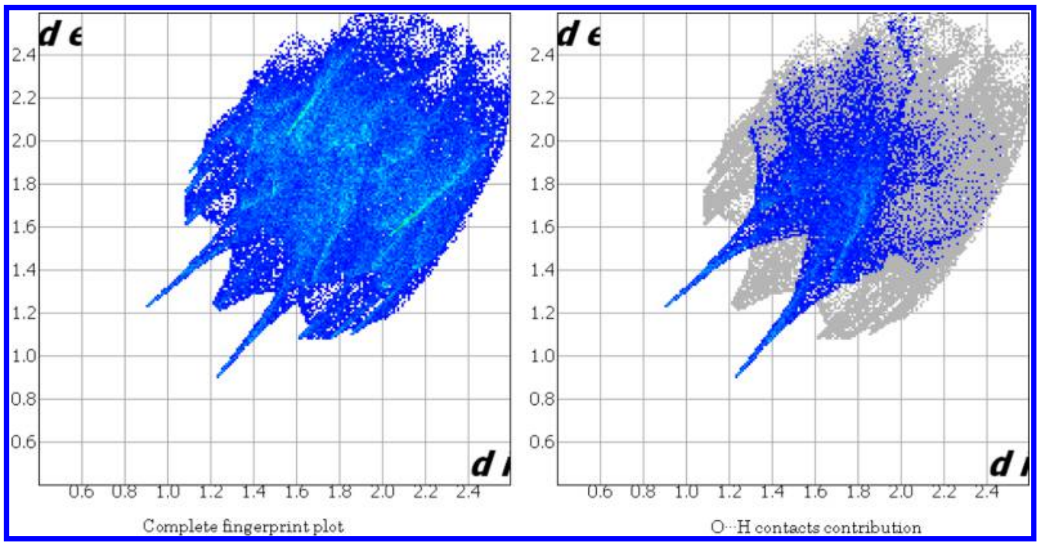
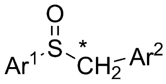


**Figure 9.** Fingerprint plots of *p*-bromophenyl *o*-nitrobenzyl sulfoxide **5**: (left) complete plot; (right) O···H contact contribution.

these sulfoxides, it could be inferred that these interactions should provide a moderate stabilizing contribution.[31] In particular, the intramolecular interaction of the fluorine atom should provide a stabilization, and thus a clear preference, toward the *gauche* conformation of the sulfoxide, also in agreement with our calculation on a structurally related molecule.[7]

However, the most characteristic feature of (*R*)-2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (**12**) is a network of three molecules built up by C−H···halogen interactions (Figure 8).[32] In fact, the hydrogen atom in the *meta* position of one molecule of 2,4-dichlorophenyl moiety interacts with the chlorine atom in the *para* position of the same moiety of another molecule ($H_{meta}\cdots Cl_{para}$ distance 2.936(2) Å; $C{-}H_{meta}\cdots Cl$ angle 173.2(4)°). Conversely, the chlorine atom in the *para* position of the first molecule interacts with the hydrogen atom in the *meta* position of a third molecule with the same geometric features. The three-term ring is closed (Figure 8) between the second and the third molecule by an interaction between the methylene hydrogen atom of the third molecule with the fluorine atom in the *para* position of the pentafluorophenyl group of the second molecule ($H\cdots F_{para}$

Table 3. Percentage of Contribution to the Hirshfeld Surface of Some Atom/Atom Interactions



| sulfoxide | $Ar^1$ | $Ar^2$ | O··H contact | H···H contact | F···H contact | F···F contact |
|---|---|---|---|---|---|---|
| (*R*)-**1** | 2-MeCOO-$C_6H_4$ | $C_6H_5$ | 17.1 | 54.0 | | |
| (*R*)-**2** | 2-MeO-$C_6H_4$ | $C_6H_5$ | 12.8 | 56.5 | | |
| (*R*)-**3** | 3-MeO-$C_6H_4$ | $C_6H_5$ | 16.9 | 48.8 | | |
| (*R*)-**4** | 4-$O_2N$-$C_6H_4$ | $C_6H_5$ | 31.2 | 31.7 | | |
| (*R*)-**5** | 4-Br-$C_6H_4$ | 2-$O_2N$-$C_6H_4$ | 22.0 | 25.1 | | |
| (*R*)-**6** | 4-Br-$C_6H_4$ | 4-$O_2N$-$C_6H_4$ | 29.1 | 24.0 | | |
| (*R*)-**7** | 4-Br-$C_6H_4$ | 2-MeO-$C_6H_4$ | 10.9 | 40.0 | | |
| (*R*)-**8** | 4-Br-$C_6H_4$ | 3-MeO-$C_6H_4$ | 15.1 | 38.7 | | |
| (*R*)-**9** | 4-Br-$C_6H_4$ | 3-Cl-$C_6H_4$ | 10.8 | 28.5 | | |
| (*R*)-**10** | 4-Br-$C_6H_4$ | 2,4-$Cl_2C_6H_3$ | 9.7 | 22.0 | | |
| (*R*)-**11** | 2-F-$C_6H_4$ | $C_6F_5$ | 7.0 | 5.2 | 39.7 | 13.5 |
| (*R*)-**12**,[a] (*S*)-**12** | 2,4-$Cl_2C_6H_3$ | $C_6F_5$ | 5.6 | 3.2 | 24.2 | 9.1 |
| (*R*)-**13** | $C_6F_5$ | $C_6H_5$ | 9.3 | 14.6 | 22.2 | 16.0 |

[a] Coincident values.

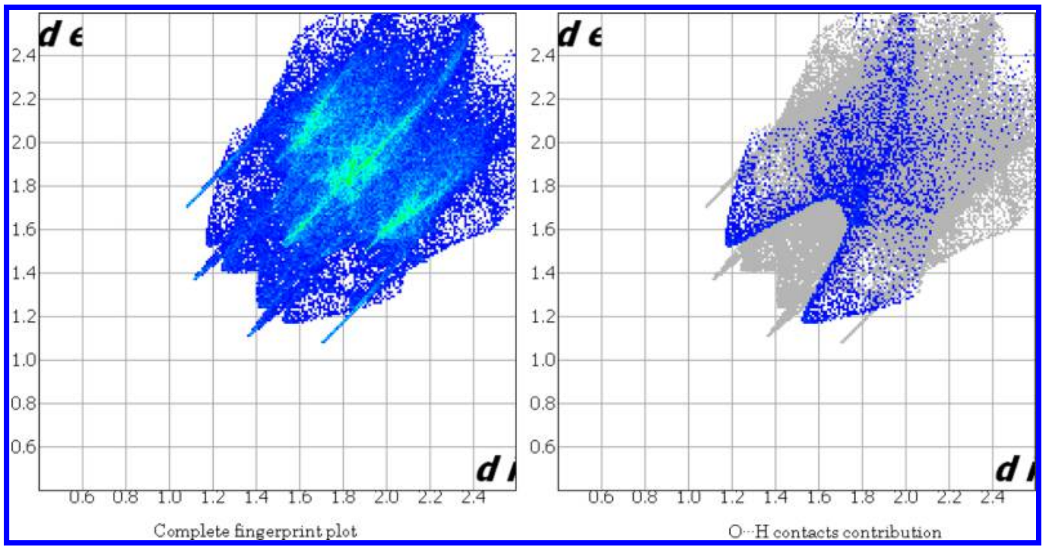


**Figure 10.** Fingerprint plots of 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (**12**): (left) complete plot; (right) O···H contact contribution.

distance 2.587(6) Å; C−H···F angle 163.8(5)°). These interactions involving the hydrogen and the halogen atoms are currently considered a weak form of hydrogen bonding,[32] even in the case of a fluorine atom.[33]

**5. Hirshfeld Surface Analysis.** Recently, Spackman et al. have proposed the application of the Hirshfeld surface of a molecule in a crystal[34] as a new tool, first to summarize and then to gain additional insight into the intermolecular interaction of molecular crystals. The analysis has been developed with the free Crystal Explorer program.[35]

The most innovative feature provided by Crystal Explorer is the so-called "fingerprint analysis", which draws a colored visual summary of the intermolecular interactions and calculates the relative area of the surface corresponding to each type of interaction. This fingerprint analysis is a plot of the distances of the nearest nucleus outside ($d_e$) and inside ($d_i$) the Hirshfeld surface, attributing to each point (defined by $d_e$ and $d_i$ values) a color code (blue for a small contribution, from green to red for the greatest contribution).

The O···H hydrogen bonds in the fingerprint analysis are usually associated with the spikes in the left lower quadrant of the plots.[34] As a representative example, in Figure 9 the whole fingerprint analysis of *p*-bromophenyl *o*-nitrobenzyl sulfoxide **5** is drawn, together with the same analysis restricted to the contribution of the O···H interactions, in which the spikes connected to these hydrogen bonds emerge.

The fingerprint analysis of non-fluorinated aryl benzyl sulfoxides **1**−**10** (see the Supporting Information) are almost homogeneous and confirmed the main characteristics that were discussed in section 2. An interesting complement of this analysis is the calculation of the percentage of how much each interaction contributes to the Hirshfeld surface (Table 3).

In aryl benzyl sulfoxides **1**−**3**, the H···H contacts are predominant (48.8−54.0%), as often occurs,[36] whereas this contribution is lower in the case of sulfoxides **4**−**10**. The O···H contacts have a contribution of 9.7−17.1% in sulfoxides **1**−**3** and **7**−**10** and increase in sulfoxides **4**−**6**, due to the presence of the nitro groups.

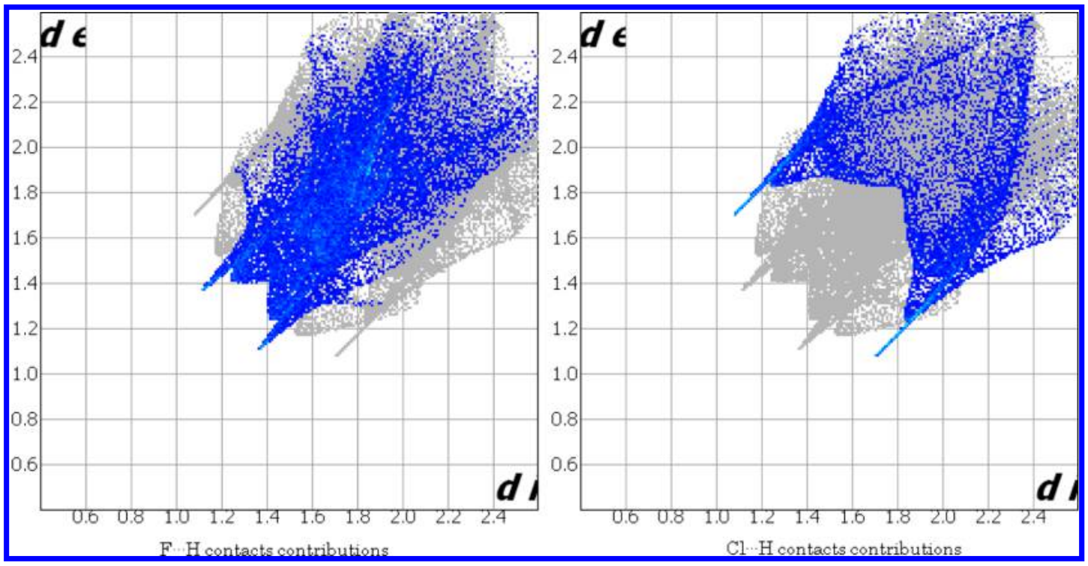


**Figure 11.** Fingerprint plots of 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (**12**): (left) F···H contact contribution; (right) Cl···H contact contribution.

The situation is different in fluorinated sulfoxides **11**−**13**, which are the main topic of this paper. The presence of many fluorine atoms in these molecules alters the observed contribution to the Hirshfeld surface, because in these cases F···H and F···F interactions contributions are predominant (Table 3). In sulfoxides **11** and **13**, in which a hydrogen bond is present (see section 3), the O···H contacts contribute 7 and 9.3%, respectively, not far from the values observed in the case of polyhalogenated non-fluorinated sulfoxides **9** and **10**.

However, the peculiarity of sulfoxides (*R*)- and (*S*)-**12** discussed in section 4 is confirmed also by the fingerprint analysis. In these molecules, in which the oxygen atom is not engaged in any hydrogen bonding, the O···H contact contribution to the surface drops to 5.6%. Furthermore, the fingerprint analysis, restricted to these contacts (Figure 10), confirms that the spikes that were observed in the left lower quadrant of the plot are not related to any hydrogen bonding, as reported above.

The analysis of the F···H and Cl···H contacts (Figure 11) correctly attributes the observed spikes to H···halogen short contacts, as discussed above.

Finally, in (*R*)-benzyl pentafluorophenyl sulfoxide (**13**), the fingerprint analysis (Figure 12) confirmed the presence of a $\pi-\pi$ stacking, identified by the green area around $d_i = d_e \cong 1.8$ Å.[34]

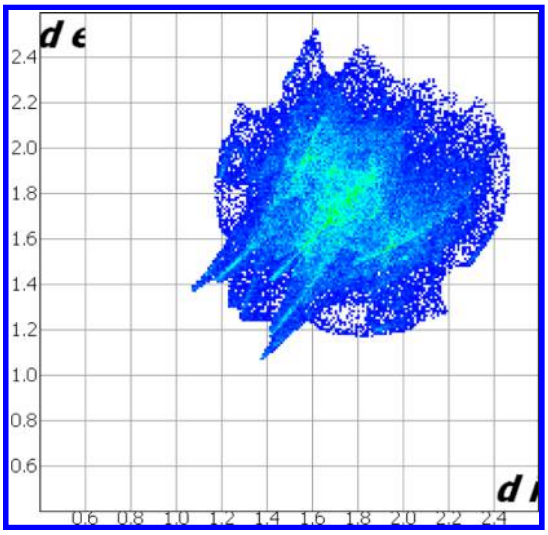


**Figure 12.** Fingerprint plot of (*R*)-benzyl pentafluorophenyl sulfoxide (**13**).

## ■ CONCLUSION

The variety of enantiopure sulfoxides taken from our chemical library allowed us to survey the most relevant interactions assembling the crystal structures of these molecules. Non-fluorinated aryl benzyl sulfoxides show recurrent structural motifs, connected with the weak hydrogen bonding involving the sulfinyl oxygen atom, that depict the characteristic molecular frameworks of these molecules.[18,19] On the other hand, the fluorination of these molecules yielded new and interesting patterns, which are not easily predictable. The pentafluorophenyl moiety induced the formation of parallel displaced aryl $\pi$-stacking, with a notable contribution to the case of a sulfoxide in which the aryl groups are arranged into an *anti* conformation.

The (*R*)- and (*S*)-2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxides that were synthesized showed the unusual case in which the sulfinyl oxygen atom is not involved in any type of hydrogen bonding. On the other hand, a large contribution to the stability of the structure was offered by hydrogen−halogen interactions and by the interactions of oxygen and fluorine atoms with electron-poor aryl groups. Finally, in molecules in which fluorine is the only halogen present, weaker interactions, such as C−F···F−C interactions, should offer their further contribution to the stability of the structures.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Text, tables, figures, and CIF files giving details of the synthesis of 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfide, crystal data, atomic coordinates, and bond lengths and angles for (*R*)-**12** and (*S*)-**12**-sulfoxides, and fingerprint analysis of sulfoxides **1−4** and **6−11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

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