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Original Citation

Schwalbe, C.H., Ramirez, M., Conway, Barbara R, Bache, C.J., Coles, S.J. and Timmins, P. (2010) Structure and properties of (hydroxy)alkylammonium salts of flurbiprofen. In: Transactions of the Symposium held at the 2010 American Crystallographic Association Annual Meeting. American Crystallographic Association.

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STRUCTURE AND PROPERTIES OF (HYDROXY)ALKYLAMMONIUM SALTS OF FLURBIPROFEN

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1. ABSTRACT

Interactions with hydrogen atoms strongly affect the structure of salts of the anti-inflammatory drug flurbiprofen. With cations of the form $H_3N^+C(CH_3)_{3-n}(CH_2OH)_n$ for n = 0-3 charge-assisted hydrogen bonding is the most obvious feature. In the t-butylammonium (n = 0) salt successive $R_4^3(10)$ rings are formed by $^+$N-H…OCO$^-$ interactions. With n = 1 the additional OH is disordered and has little effect. However, n = 2 changes the pattern: now one $^+$N-H…OCO$^-$ and one O-H…OCO$^-$ hydrogen bond link a cation to a carboxylate anion. When n = 3, this motif persists in one polymorph. However, another polymorph has two independent anions related by pseudo-translation and two independent cations related by a pseudo-glide, while extensive disorder results from application of the "opposite" pseudo-symmetry operation. Enantiomer discrimination at flurbiprofen sites depends on the environment of H and CH_3 in the $HCCH_3$ group. Hirshfeld surfaces show normal van der Waals contacts around ordered methyl groups but tight contacts around major sites for disordered ones, which become worse around the minor sites. Similar effects are observed in the vicinity of the fluorine atoms in the fluorophenyl rings. Whereas the major sites for disordered atoms and the sites for ordered atoms are involved in normal or slightly short van der Waals contacts, the minor sites suffer from tighter contacts.

2. INTRODUCTION

Flurbiprofen [Fbp, (*RS*)-2-(2-fluorobiphenyl-4-yl)propanoic acid] is a non-steroidal anti-inflammatory drug which is useful in the treatment of chronic conditions such as arthritis. However, because of its low aqueous solubility of only 0.03(1) mg mL^{-1} [1] it does not readily provide rapid pain relief. To enhance the solubility we have prepared a series of salts of Fbp with cations of general formula $H_3N^+C(CH_3)_{3-n}(CH_2OH)_n$ for n = 0-3, starting from t-butylammonium and finishing with Tris. Successively changing methyl to hydroxymethyl groups is expected to increase the affinity of the cation for water, but this affinity may not translate into higher solubility if hydrogen bonding sufficiently augments the stability of the crystal. Making this series of salts has increased the solubility of Fbp compared to its free acid form, and in this case the solubility does increase with the number of hydroxymethyl groups [1]:

2.77 mg mL^{-1} with n = 0, 8.9(14) mg mL^{-1} with n = 1, and 11.6(12) mg mL^{-1} with n = 2. The solubility of the Tris salt with n = 3 will be discussed later.
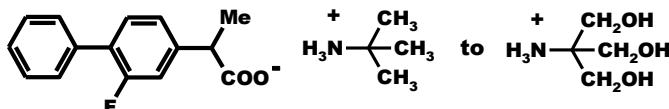
Hydrogen atoms profoundly influence the interactions within the crystal. The numerous possibilities for hydrogen bonding are their most salient feature. In addition, Fbp is a chiral molecule for which the enantiomers can be interchanged by swapping one H atom and a CH$_3$ group.   All our samples were prepared from racemic mixtures and crystallized in centrosymmetric space groups. Enantiomer discrimination depends upon a sufficient difference between the environment of the H site and that of the CH$_3$ site. Insufficient discrimination can lead to disorder with minor occupancy of the Fbp site by the "wrong" enantiomer and, of course, an equal population of the opposite enantiomer at the centrosymmetrically related site.   An additional opportunity for disorder is 180° rotation of the fluorophenyl ring around the axis linking the two rings, which is possible if the surroundings of H and F are permissive.

3. METHODS

Salts were prepared by mixing equimolar quantities of Fbp and base dissolved in acetonitrile. Sample crystals were grown from acetonitrile or methanol.   Wherever possible, data were collected at the National Crystallography Service, Southampton, on a diffractometer equipped with a rotating anode generator and focusing optics.   Two salts (FAmp with n = 1 and one polymorph of FTris with n = 3) diffracted so weakly that synchrotron data were required, which were collected on station I19 at the Diamond synchrotron.

Hirshfeld surfaces [2,3] encoded with d$_{norm}$ [4] were generated with the program Crystal Explorer [5]. The normalization with respect to van der Waals radii embodied in the definition of d$_{norm}$ enables the closeness of intermolecular contacts involving different elements to be compared, e. g. H and F. Contacts shorter than van der Waals separations are represented as red spots on the surface, normal van der Waals contacts appear white, and longer contacts are blue.


4. RESULTS AND DISCUSSION

4.1 Crystal data
Unit cell dimensions of the salts, including two polymorphs of the Tris salt, are given below. The space groups are, respectively, P2$_1$/n, P2$_1$/c, and finally P-1 for the last three. Z' is 1 and one cell dimension falls within the range 6.19-6.29 Å except for FTris polymorph I, where Z' = 2 and all axes are longer.

Abbr.,n	a/Å	b/Å	c/Å	α/Å	β/Å	γ/Å
FTbut,0	15.9343(11)	6.2903(4)	19.1949(11)	90	114.705(3)	90
FAmp,1	16.133(8)	6.270(3)	18.852(3)	90	114.883(5)	90
FAmp2,2	6.1928(2)	9.5205(4)	15.135 (6)	82.627(2)	87.874(3)	89.058(2)
FTrisII,3	6.1930 (1)	9.9421(2)	14.6846(3)	93.937(1)	90.032(2)	90.718(2)
FTrisI,3	10.016(18)	11.073(21)	16.652(29)	84.52(7)	78.81(4)	88.15(8)

<div style="text-align:center">

TABLE 1

Unit cell dimensions and n in the stoichiometry $(CH_3)_{3-n}(CH_2OH)_n$

</div>

Packing diagrams [Figure 1(a-d)] drawn with Mercury [6] in projection down the shortest axis show an almost edge-on view of a pair of Fbp anions with fluorophenyl and phenyl rings juxtaposed but neither parallel nor perpendicular, either in the middle of the cell or straddling one side. Disorder in CH_3 groups and F substituents is evident in FTbut and FAmp but not FAmp2 or FTrisII. Disorder in FTrisI [Figure 1(e)] is so pervasive and extreme that this structure needs to be discussed separately.
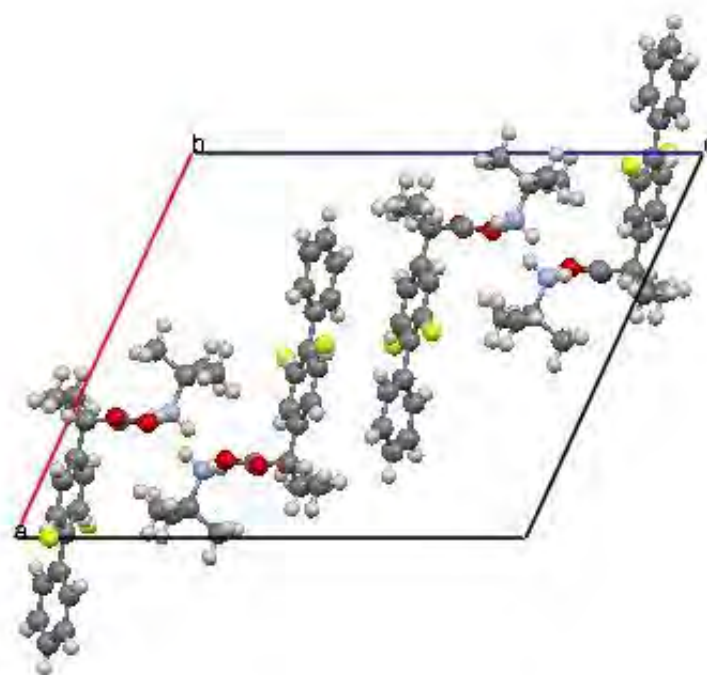
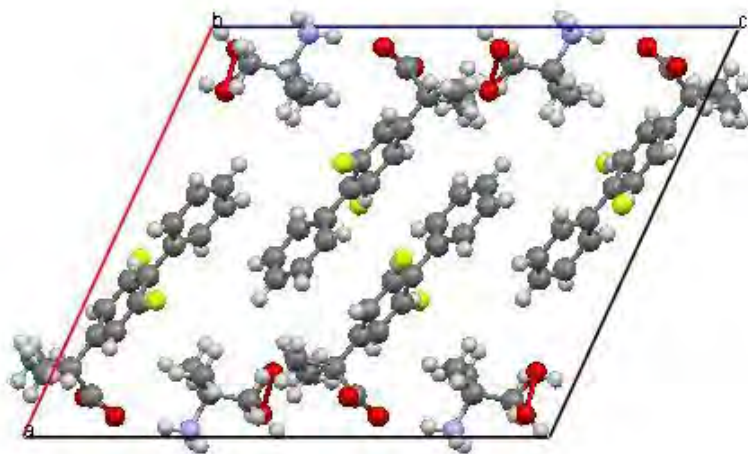**Figure 1.** (a) Packing of FTbut viewed down the *b* axis.

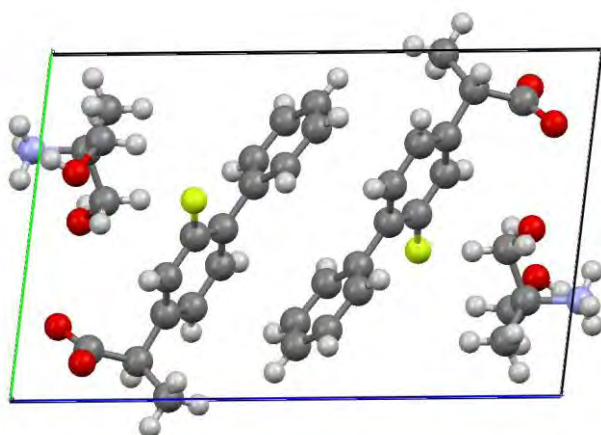**Figure 1.** (b) FAmp viewed down the *b* axis.

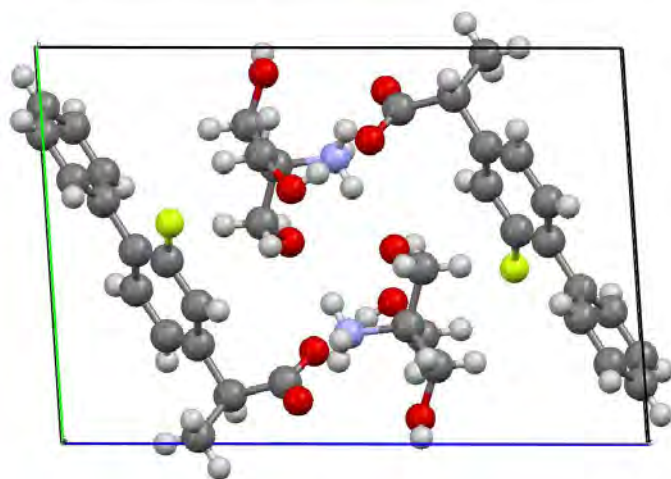**Figure 1.** (c) FAmp2 viewed down the *a* axis.

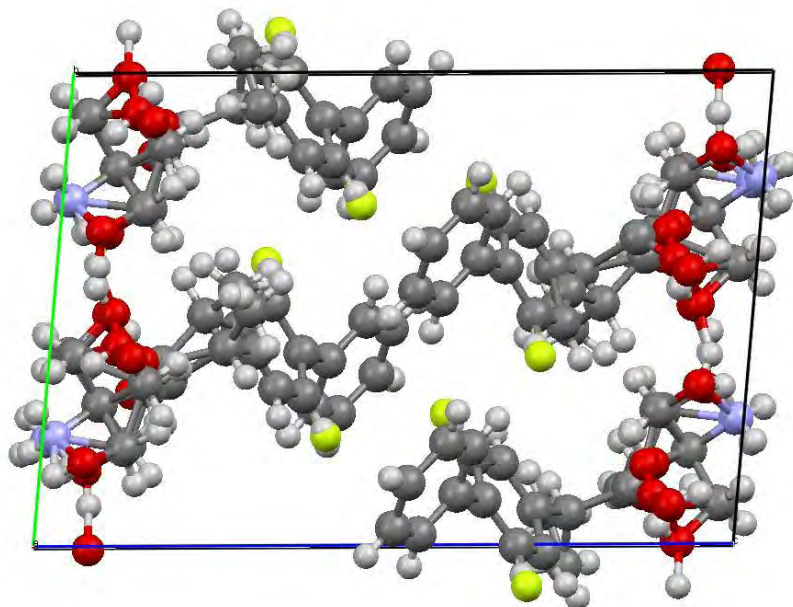**Figure 1.** (d) FTris polymorph II viewed down the *a* axis.

Figure 1. (e) FTris polymorph I viewed down the *a* axis.

4.2 Flurbiprofen geometry

Rotations about the two oppositely directed exit bonds from the fluorophenyl ring are a major influence on the shape of the flurbiprofen anion. Carbon atoms are numbered according to the following scheme: C1 in OCO^-, C2 in CH, C3 in CH_3, C4 to C8 in the fluorophenyl ring with F attached at C6, and C9-C14 in the second ring.

TABLE 2				
C3-C2-C4-C5 torsion angles (in structures where the CH_3 groups are disordered, major C3 then minor) followed by the angle between fluorophenyl and phenyl ring planes				

| Abbr.	Major C3-C2-C4-C5 / °	Minor C3-C2-C4-C5 / °	C1-C2-C4-C5 / °	Interplanar angle / °
FTbut	129.6(5)	58(2)	-104.1(5)	44.4(1)
FAmp	122.9(6)	59(1)	-105.4(6)	43.8(2)
FAmp2	-81.8(2)		42.5(3)	46.0(1)
FTrisII	-81.2(2)		43.7(2)	43.7(1)
FTrisI	-51(2)	-110(2)	79(2)	54.6(3)
	-54(1)		82(1)	61.4(3)

At the propanoic acid end there is a noteworthy pairwise similarity between FTbut and FAmp, and between FAmp2 and FTrisII. The relevant torsion angles in FTrisI are roughly 180° away from those in the first two structures. A clash of H against F or H against H atoms militates against a coplanar arrangement of rings in *ortho*-fluorobiphenyl derivatives. The *ca.* 45° twist between rings in the first four structures is close to the mean value of 43(2)° for 42 observations shown in Figure 2.
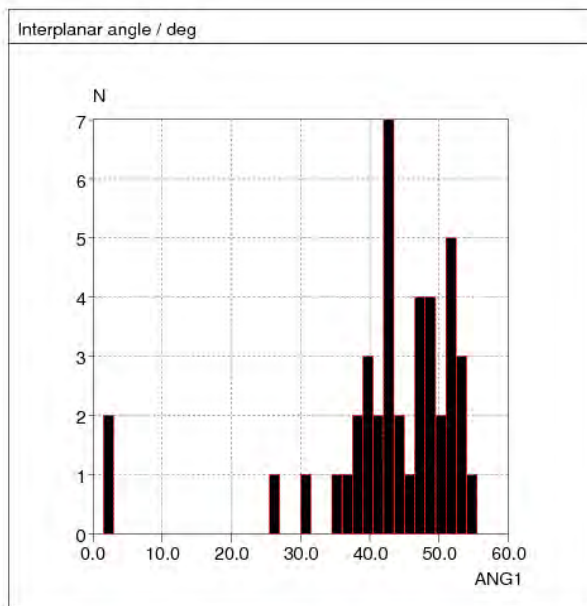
Figure 2. Interplanar angles for *ortho*-fluorobiphenyl structures lacking other *ortho* substituents in the Cambridge Structural Database with R < 10%.
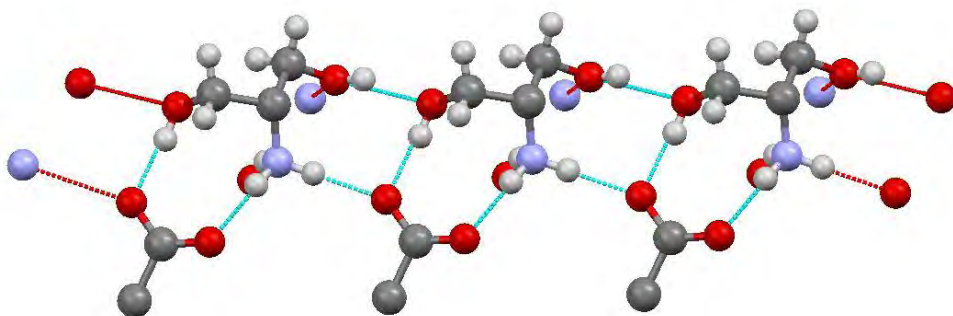
4.3 Hydrogen bonding

In FTbut donation of hydrogen bonds from $^+NH_3$ to COO^- forms ladders built out of $R_4^3(10)$ rings along a 2-fold screw axis, Type II in the classification of Lemmerer et al. [7].
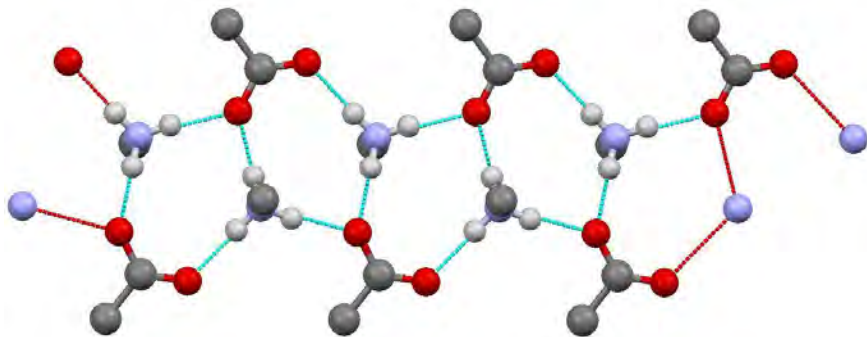
Figure 3. $R_4^3(10)$ rings formed by $C(NH_3)^+$ and $C(OCO)^-$ moieties of FTbut.

Substitution with one OH group to make FAmp does not change this pattern: this OH group lacks a credible hydrogen bond acceptor and is disordered. However, when a second OH group is introduced (FAmp2), the pattern changes fundamentally.

Figure 4. Hydrogen bonds formed by Amp2$^+$ cations (methyl groups omitted for clarity) and C(OCO)$^-$ moieties of FAmp2.

Cations deploy one NH and one OH hydrogen atom in hydrogen bonds to one anion. The other OH group links intermolecularly to the first one while NH finds OCO$^-$. The third amino H atom pairs with OH as acceptor to form a centrosymmetric dimer. Thereby $R_2^2(9)$, $R_3^2(9)$, and $R_2^2(10)$ rings are formed. The well ordered cations and anions in FTris form II create similar hydrogen bonds to those in FAmp2, the additional OH of the cation donating a second hydrogen bond to the carboxylate O atom that previously accepted just one. In the disordered crystals of FTris form I each carboxylate O atom accepts only one hydrogen bond. Remarkably, the two independent anions are related by the translation $x,0.5+y,z$ while cations show the pseudo-glide $0.452-x, 0.5+y,z$! The pivot atom of Tris is suitably positioned to satisfy both. Minor sites in the disorder satisfy the "opposite" pseudo-operation.

### 4.4 Hirshfeld surfaces, environment of H and CH$_3$ groups, and disorder

An overview of the interaction with its surroundings of the entire Fbp anion, not just the polar groups involved in hydrogen bonding, is provided by the Hirshfeld surfaces. These surfaces are presented for 4 of the 5 structures reported here, but the extensive disorder present in FTrisI would make such a calculation unreliable [3].

With the Fbp anions presented in a common orientation (Figure 5) having the C-CH$_3$ pointing vertically upwards the similarity between FTbut and FAmp and between FAmp2 and FTrisII is once again evident. Wherever carboxylate oxygen atoms appear on the visible upper surface, bright red patches show that charge-assisted hydrogen bonding has shrunk the H…O contacts involving these atoms to well below normal van der Waals separations. Such shortening is expected and indicates a favorable interaction, but red patches involving less polar H atoms are likely to indicate unfavorable overcrowding.
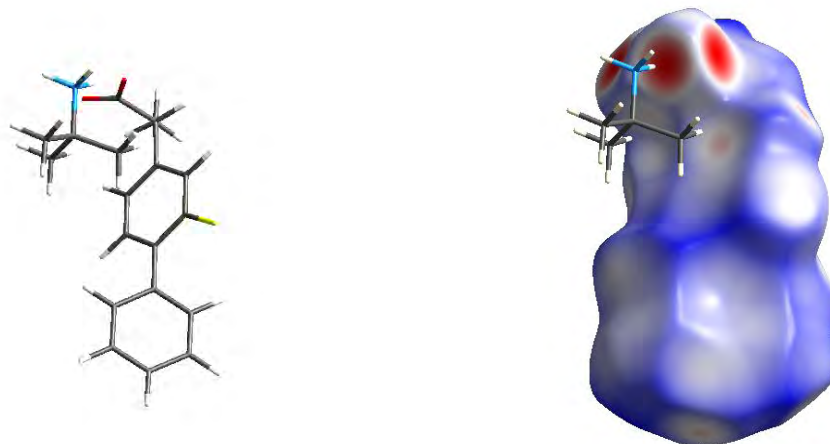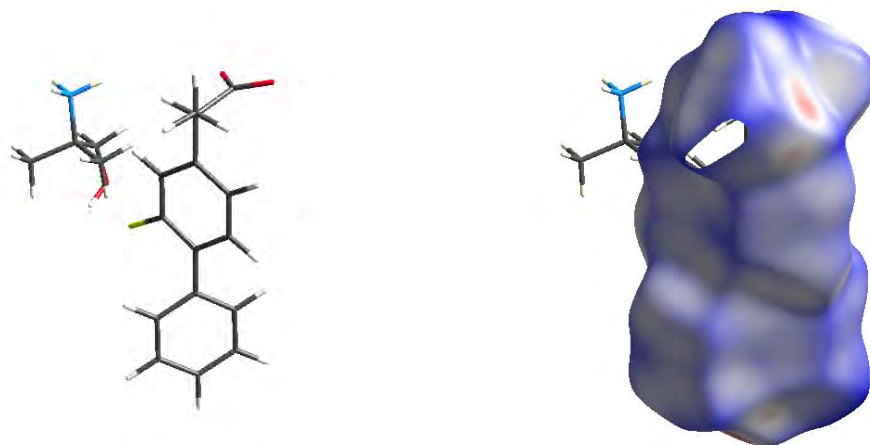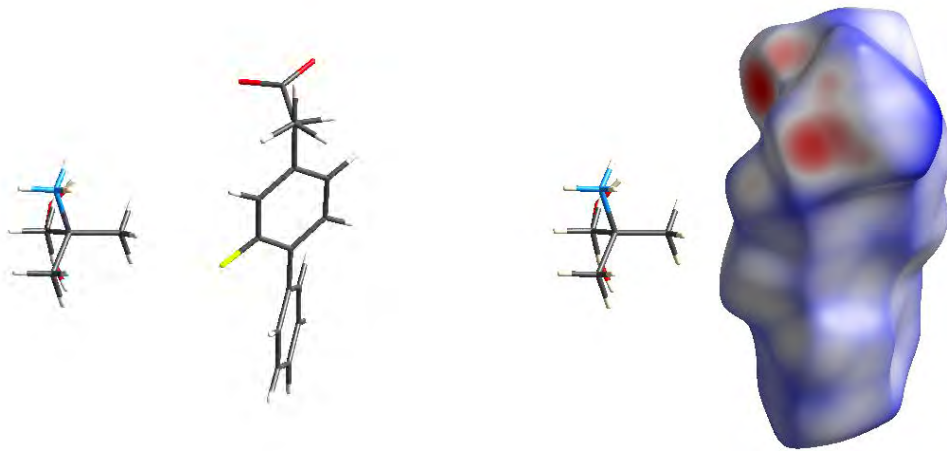
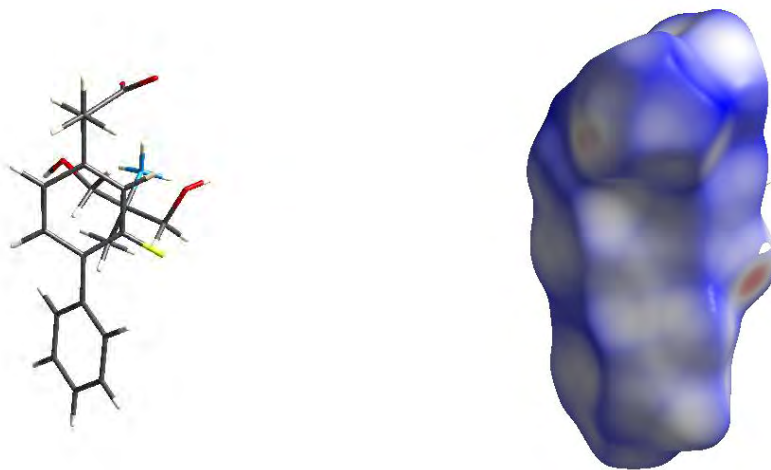**Figure 5.** (a) Stick drawings and Hirshfeld surfaces encoded with d_{norm} for FTbut with its major CH_3 site.
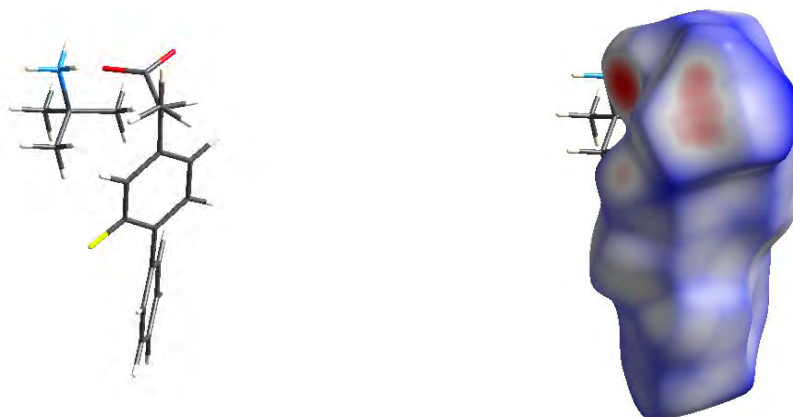
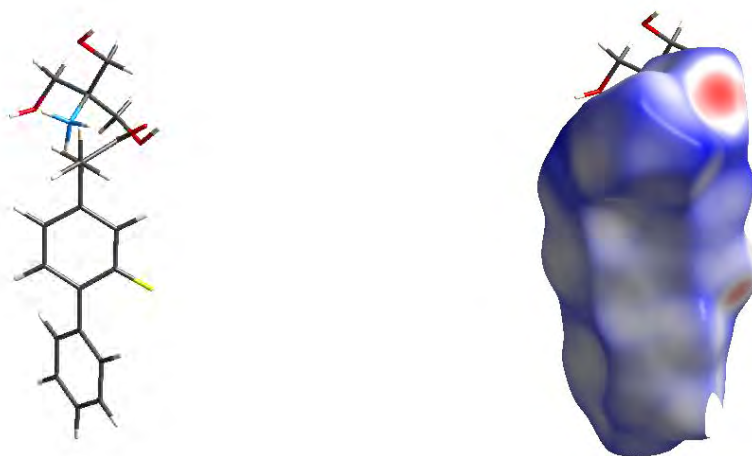**Figure 5.** (b) FTbut with its minor CH_3 site.

Figure 5. (c) FAmp with its major CH_3 site.

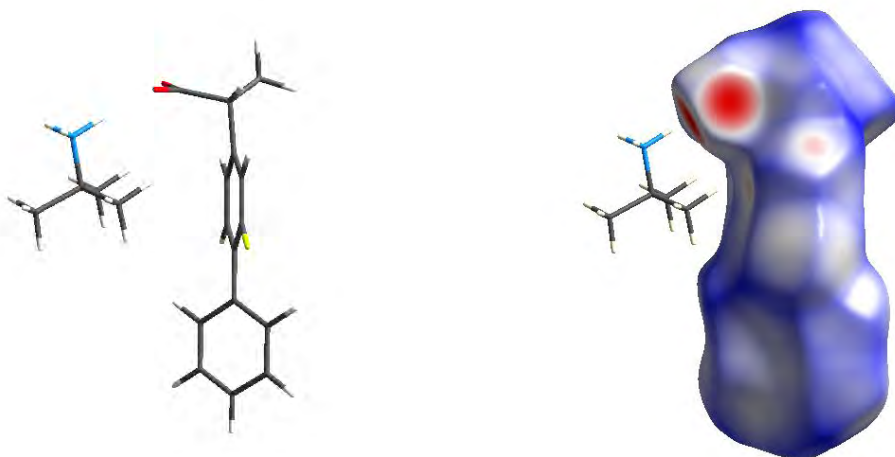**Figure 5.** (d) FAmp with its minor CH$_3$ site.

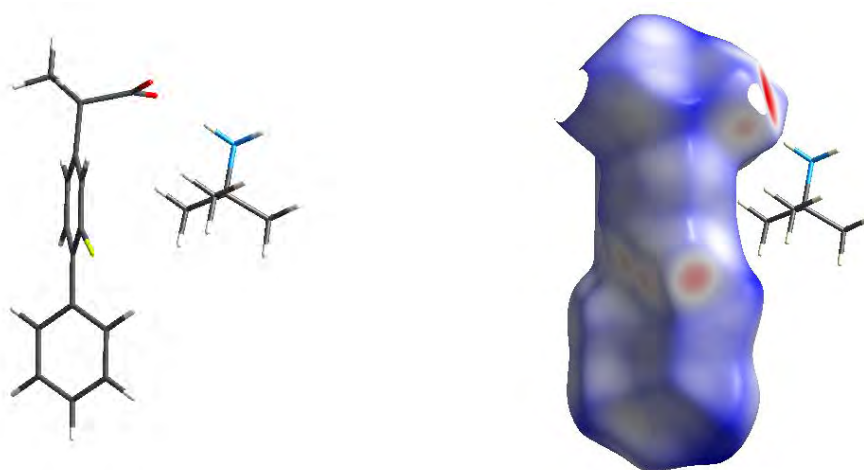**Figure 5.** (e) FAmp2 with no disorder in the CH$_3$ site.

Figure 5. (f) FTrisII with no disorder in the CH$_3$ site.

FTbut and FAmp show two alternative positions for their methyl groups with occupancy factors that refined to 0.882:0.118 and 0.759:0.241 respectively. The major sites are positioned uppermost in Figures 5(a) and 5(c); the minor sites, in 5(b) and 5(d). Small dull red patches suggest that the major sites suffer contacts that are slightly too close, but more extensive and brighter red patches around the minor sites suggest worse crowding. The surfaces around the ordered CH_3 groups in Figures 5(e) and 5(f) mainly have white patches indicating normal van der Waals contacts.
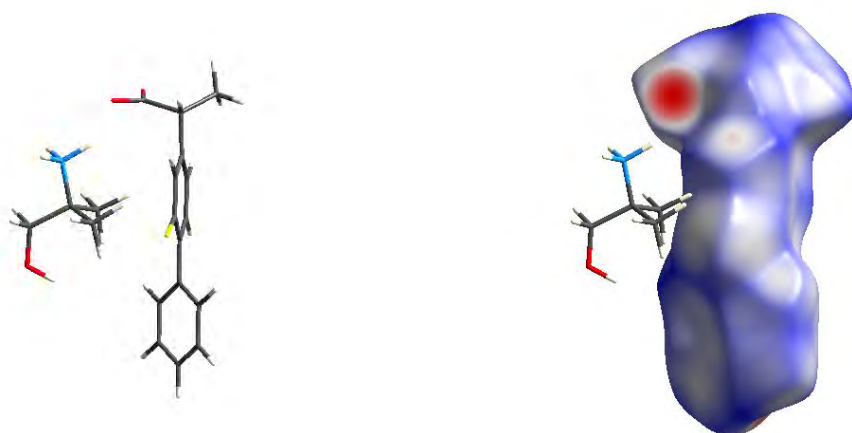
Figure 6 presents a similar graphical analysis of twofold H/F disorder in the fluorophenyl ring. All drawings are in an orientation that places the fluorophenyl ring plane 10° from the vertical with the C-F bond pointing upwards.
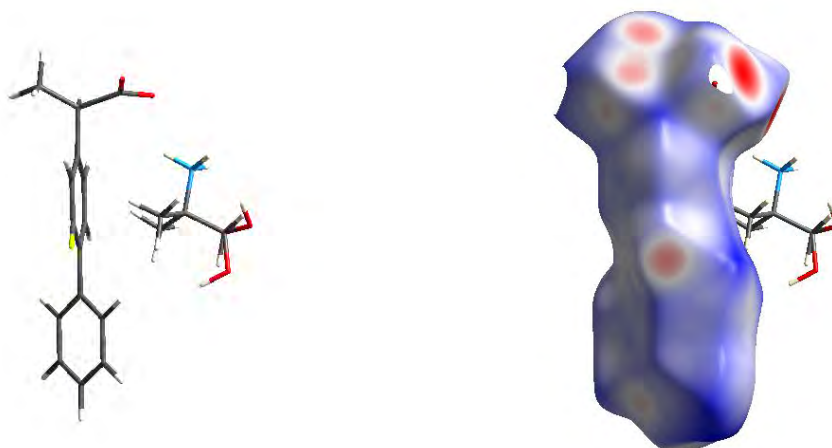

Figure 6. (a) Stick drawings and Hirshfeld surfaces encoded with d_{norm} for FTbut with its major F site.
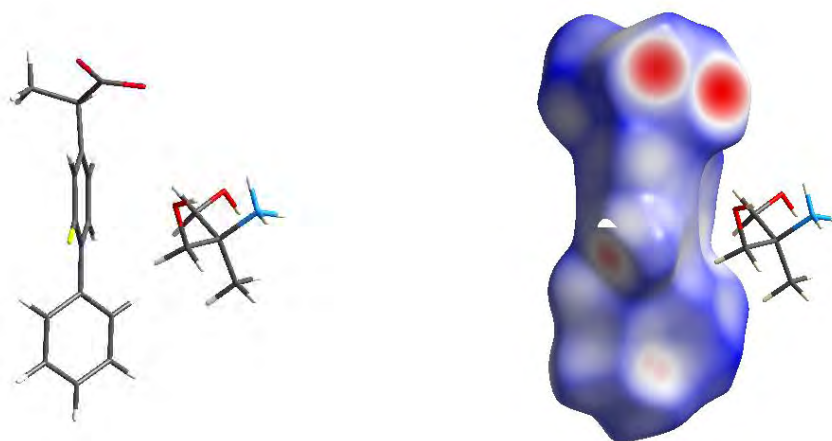

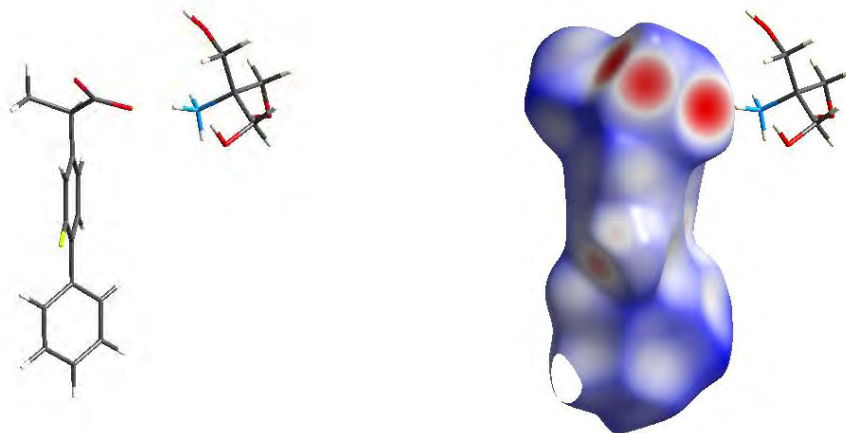**Figure 6.** (b) FTbut with its minor F site.

Figure 6. (c) FAmp with its major F site.

Figure 6. (d) FAmp with its minor F site.

Figure 6. (e) FAmp2 with no disorder in the F site.

Figure 6. (f) FTrisII with no disorder in the F site.

Once again FTbut and FAmp have two alternative sites for a disordered fluorine atom with respective occupancy factors 0.895:0.105 and 0.842:0.158 while Famp2 and FTrisII are ordered. Whereas the Hirshfeld surfaces are white or faint red in the vicinity of ordered and major F sites, stronger red patches indicate close contacts around minor sites of disordered F atoms.

4.5 Pharmaceutical implications

Whereas the twist angle between rings in the biphenyl moiety of Fbp is 44-46° in the other structures and averages ca. 43° in *ortho*-fluorobiphenyl structures in the literature, the higher values of 55° and 61° in FTrisI may imply higher energy. The widespread disorder in this form suggests that intermolecular interactions are suboptimal. Thus there are good grounds for the assumption that FTrisI should have higher energy than FTrisII, yet FTrisI melts at a higher temperature. Both forms show similarly improved aqueous solubility [8] of 14.2(7) mg mL^{-1} for I and 13.6(4) mg mL^{-1} for II. The poor crystal quality of FTrisI matches its poor mechanical properties; it produces weak compacts with troublesome elastic recovery. On the other hand, FTrisII forms strong tablets with shiny faces and excellent mechanical properties [8]. Thus the objective of enhancing the solubility while retaining desirable pharmaceutical properties has been achieved, albeit with the necessity for careful control of crystallization conditions.

5. ACKNOWLEDGMENTS

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