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Ibuprofen, a household pharmaceutical belonging to the racemic mimic class-chirality, diastereochemical details, packing and overlay of the pair within the (*S*)(+) crystals

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RESEARCH ARTICLE

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ABSTRACT

We have discovered that enantiopure and racemic Ibuprofen crystallize with nearly the same cell constants, the former in space group $P2_1$, the latter in $P2_1/c$. As expected from a pair that belongs to the racemic mimic class, the values of Z' are 2.0 and 1.0, respectively. Interestingly, despite the fact that one is enantiopure and the other is a racemate, they form the classical dicarboxylate dimer one is familiar with in elemental chemistry and with nearly identical geometrical parameters, the enantiopure sitting at a true lattice inversion center, and the other one at a pseudo-inversion point located at 0.5000, 0.4458, and 0.5000. Packing diagrams are provided that show the remarkable degree to which they agree. Overlay diagrams generated with Mercury illustrate the extent to which the pair of enantiopure species resemble each other; the differences being largely small diastereoisomeric discrepancies and without a doubt the result of anisotropy in packing forces. Finally, within accepted limits for π-π bondings, there are no significant interactions between the phenyl rings in either crystalline form.

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1. Introduction

In the past, we have described our interest in the mode of crystallization described as racemic mimic [1-3] that seems to have been ignored, or gone unnoticed for a long time even though our searches in CCDC [4] suggest that it occurs over the entire spectrum of chemical compounds in that database. So, to begin this report, we state that the most fundamental characteristics of crystalline materials belonging in that class are: (a) racemic materials and their mimic crystals have nearly identical cell constants; (b) racemate crystals contain pairs of molecules related by operations of the second kind; *e.g.*, mirrors, inversions, and roto-inversions; (c) racemic mimic crystals contain the same number of molecules in the unit cell as those in (b); but they support only symmetry operations of the first kind; *e.g.*, translation, rotations, *etc.* Because we have already given the necessary historical recount of how, where, and by whom this was done, we direct the interested reader to those earlier sources [1-3]. The example selected in this case is the widely used drug Ibuprofen [5,6].

2. Experimental

The properties of all substances described here were obtained from the originals provided by the CCDC [4] where we carried out our search. (S)-(+)-Ibuprofen; Dexibuprofen; DrugBank: DB09213; PDB chemical component code: IBP, appearing as JEKNOC12 [5] and *racemic* Ibuprofen; Advil; Motrin; Nurofen; DrugBank: DB01050, appearing as IBPRAC01 [6] are the two species studied here as illustrations of a purely organic racemic mimic pair of drugs. The chiral center assignments and molecular overlay information were obtained with MERCURY [7]. The final figures were drawn with DIAMOND [8].

3. Results and discussion

In Figure 1, we display a picture of the labeled molecule present in the racemic form-space group $P2_1/c$ (note: see below for a comparison of the cell constants of the crystals that have been compared in this publication). The packing characteristics of this species are interesting, as shown in Figure 2.

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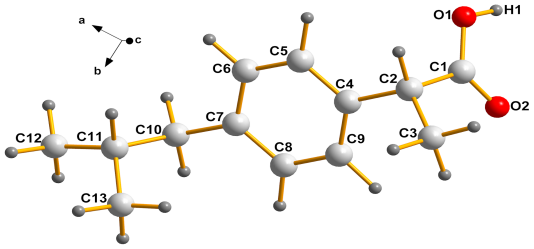

Figure 1. C2 is the chiral center. Note the precision with which the hydrogens of the terminal methyl fragments were located.

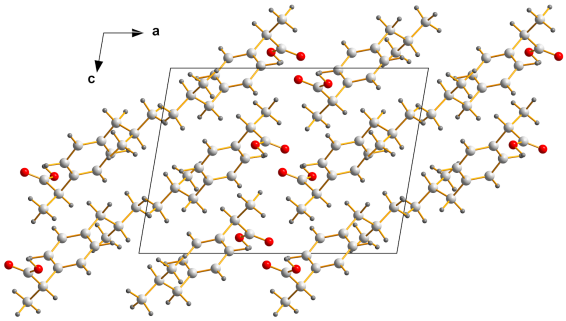

Figure 2. A view of the unit cell projected down the *b*-axis.

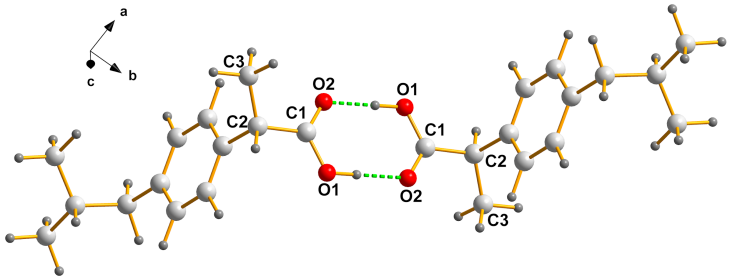

Figure 3. Two molecules of the racemic form of ibuprofen showing the hydrogen-bonded pairs that link the infinite strings.

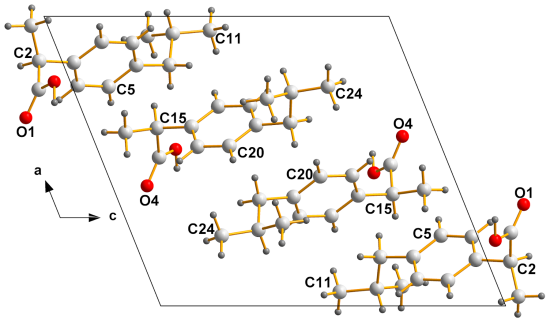

Figure 4. A *b* projection showing how the molecules stack in a view suggesting π-π bonding; however, the ring centroid distances are those of the *a*-unit cell, indicating the stacking expected from packing forces.

The molecules pack in pairs, related by inversion centers, in an interesting tail-to-tail fashion, readily shown on the top left and bottom right, forming infinite rows of such pairs. In turn, adjacent members of such rows form hydrogen bonds in the classical acetic acid dimer mode, Figure 3. Now, we proceed to examine the case of the optically active form, using Figure 4 to illustrate the packing of the molecules in a unit cell.

Let us now investigate the effect of losing the inversion centers- see Figure 5. Here we note that, although crystallographic inversion centers have been lost in space group $P2_1$, pseudo-inversion centers persist, and the center-of-mass of the entire pattern is located approximately at 0.5000, 0.4458, 0.5000; however, recalling that in $P2_1$, the origin in *y* is arbitrary and must be fixed, we can place the center of mass at exactly ½, ½, ½ (or ½,0, ½).

As for the inversion centers at the hydrogen-bonded dimers present in the racemate, those in the (*S*)-enantiomer, they appear atop Figure 5 and are slightly asymmetric, as imperfect centers should be. The O···H distances are 1.648 and 1.776 Å. If the members of the pairs in the chiral sample are different, one can ask the following. How different is this? This question is answered with Figure 6 generated using MERCURY [4] and DIAMOND [5], as mentioned above.

Table 1. Comparison of cell dimensions.

CSD name	a (Å)	b (Å)	c (Å)	β (°)	Volume (Å^3)	Space group	Z	Z'	R	T (K)
IBPRAC01 [3]	14.397(8)	7.818(4)	10.506(6)	99.70(3)	1165.605	$P2_1/c$	4.0	1.0	5.30	100
JEKNOC12 [2]	12.109(1)	7.960(<1)	13.362(1)	111.95(<1)	1194.514	$P2_1$	4.0	2.0	3.80	99

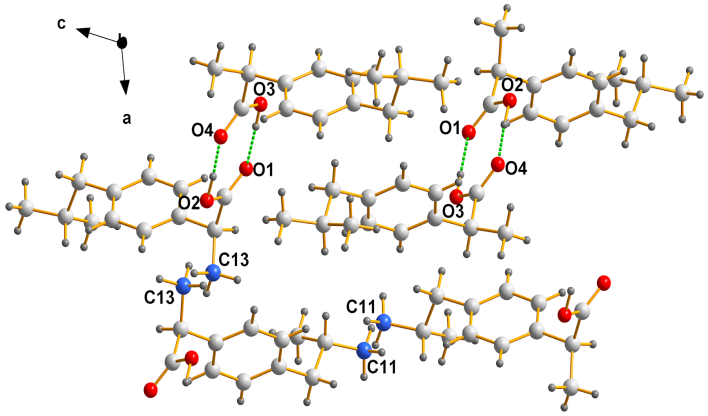

Figure 5. Depicted are areas where one can investigate the inversion-centered hydrogen-bonded and methyl-methyl pairs observed above in **Figure 2**. C11 and C13 methyl group pairs are drawn in blue for the reader's convenience; hydrogen-bonded pairs are joined by dotted lines for the same purpose.

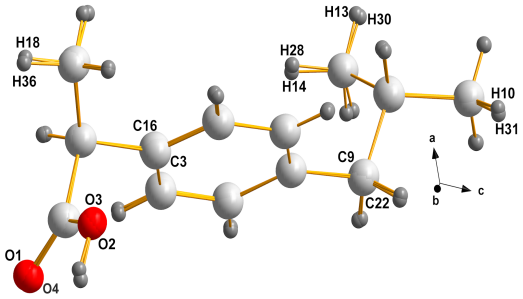

Figure 6. Using MERCURY [4], Molecule 2 was overlayed on Molecule 1 using only the command Flexibility-note that the chiral centers perfectly overlay (even the hydrogens), although refined separately.

Finally, since the fundamental characteristics of a racemic mimic pair are; (a) the pair crystallizes as a racemate and in a Sohncke space group, which is a proper subgroup of the former. This is so in this case. (b) the cell constants are nearly identical in both cases; this is also the case here, as shown in Table 1.

4. Conclusions

The long- and widely-used drug Ibuprofen has been found to crystallize in the *Racemic Mimic* category. Whether or not that is reflected in its biological properties, good or bad, needs to be determined in a suitable environment. We hope that, having provided that clue to the pharmaceutical laboratories, they will decide to proceed accordingly. Hopefully, this idea may have some generality and is found to be valid in additional biologically active compounds currently in use.

Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest. Ethical approval: All ethical guidelines have been adhered.

CRediT authorship contribution statement

Conceptualization: Ivan Bernal and Roger Lalancette; Methodology: Ivan Bernal and Roger Lalancette; Validation: Ivan Bernal and Roger Lalancette; Formal Analysis: Ivan Bernal and Roger Lalancette; Investigation: Ivan Bernal and Roger Lalancette; Resources: Ivan Bernal and Roger Lalancette; Data Curation: Ivan Bernal and Roger Lalancette; Writing - Original Draft: Ivan Bernal and Roger Lalancette; Writing - Review and Editing: Ivan Bernal and Roger Lalancette; Visualization: Ivan Bernal and Roger Lalancette; Funding acquisition: Ivan Bernal and Roger Lalancette; Supervision: Ivan Bernal and Roger Lalancette; Project Administration: Ivan Bernal and Roger Lalancette.

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