Static discrete disorder in the crystal structure of Iododiflunisal: On the Importance of Hydrogen Bond, Halogen Bond and π-Stacking Interactions

Rafael Barbas,[1] Mercè Font-Bardia,[2] Alfredo Ballesteros,[3] Gemma Arsequell,[4] Rafel Prohens[1,*] and Antonio Frontera[5,*]

[1] Unitat de Polimorfisme i Calorimetria, Centres Científics i Tecnològics, Universitat de Barcelona, Baldiri Reixac 10, 08028 Barcelona, Spain.

[2] Unitat de Difracció de Raigs X, Centres Científics i Tecnològics, Universitat de Barcelona, Spain.

[3] Departamento de Química Orgánica e Inorgánica, Instituto de Química Organometálica "Enrique Moles", Universidad de Oviedo, Julián Clavería, Oviedo, 8, 33006-Oviedo, Spain.

[4] Institut de Química Avançada de Catalunya (I.Q.A.C.-C.S.I.C.), E-08034, Barcelona, Spain

[5] Department of Chemistry, Universitat de les Illes Balears, Crta. de Valldemossa km 7.5, 07122 Palma, Spain

Electronic Supplementary Information

Table of contents:

1. Crystal data and structure refinement

1.1 Iododiflunisal (IDIF) (mo_023WB108_0m_a)

Table S1. Crystal data and structure refinement for mo_023WB108_0m_a.

Identification code	mo_023WB108_0m_a	
Empirical formula	C_{13} H_7 F_2 I O_3	
Formula weight	376.09	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P* $2_1/n$	
Unit cell dimensions	a = 16.9777(10) Å	α= 90°.
	b = 4.0424(2) Å	β= 93.412(2)°.
	c = 18.0441(11) Å	γ = 90°.
Volume	1236.18(12) $Å^3$	
Z	4	
Density (calculated)	2.021 Mg/m^3	
Absorption coefficient	2.616 mm^{-1}	
F(000)	720	
Crystal size	0.348 x 0.196 x 0.078 mm^3	
Theta range for data collection	2.404 to 30.592°.	
Index ranges	-24<=h<=24, -5<=k<=5, -25<=l<=25	
Reflections collected	26273	
Independent reflections	3717 [R(int) = 0.0638]	
Completeness to theta = 25.242°	96.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7461 and 0.5695	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3717 / 0 / 189	
Goodness-of-fit on F^2	1.080	
Final R indices [I>2sigma(I)]	R1 = 0.0352, wR2 = 0.0908	
R indices (all data)	R1 = 0.0394, wR2 = 0.0956	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.014 and -1.418 $e.Å^{-3}$	

Table S2. Hydrogen bonds for mo_023WB108_0m_a [Å and °].

Donor --- H....Acceptor	[ARU]	d(D – H)	d(H...A)	d(D...A)	<(D - H...A)
O(2) --H(2O) ..O(1)	[1-x,1-y,-z]	0.68(6)	1.99(5)	2.660(3)	175(8)
Intra O(3) --H(3O) ..O(1)	[x,y,z]	0.76(4)	1.91(4)	2.619(3)	154(4)

2.- Characterization of iododiflunisal bulk powder

Figure S1: Differential Scanning Calorimetry (DSC) of IDIF analysis was carried out by means of a Mettler-Toledo DSC-822e calorimeter. Experimental conditions: aluminum crucibles of 40 μL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10 °C/min. The calorimeter was calibrated with indium of 99.99% purity (m.p.: 156.4 ºC, ΔH: 28.67 J/g).

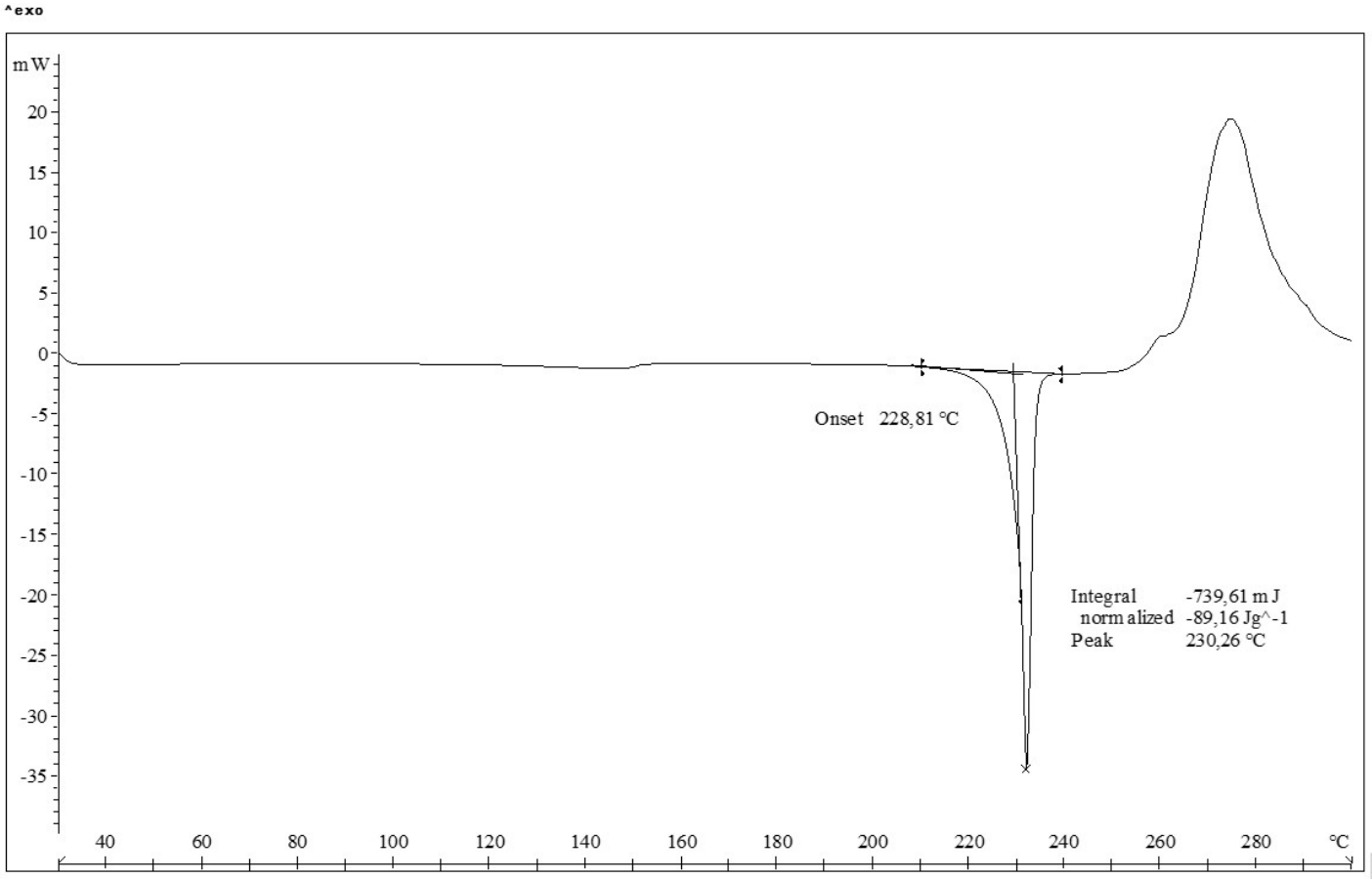


Figure S2: Thermogravimetric Analysis (TGA) of IDIF was performed on a Mettler-Toledo TGA-851e thermobalance. Experimental conditions: alumina crucibles of 70 µL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10 °C/min. SDTA signal is represented in red.

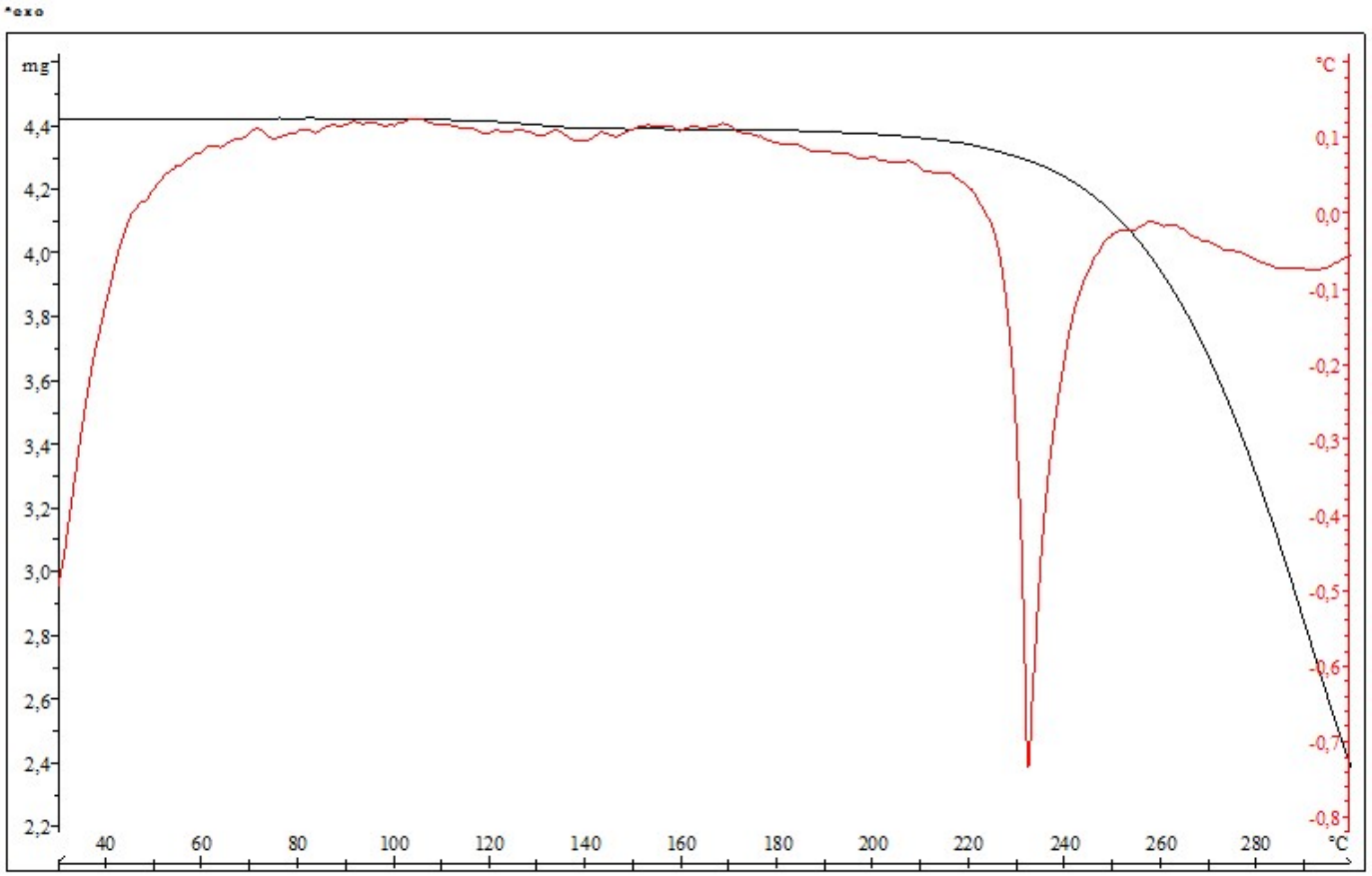
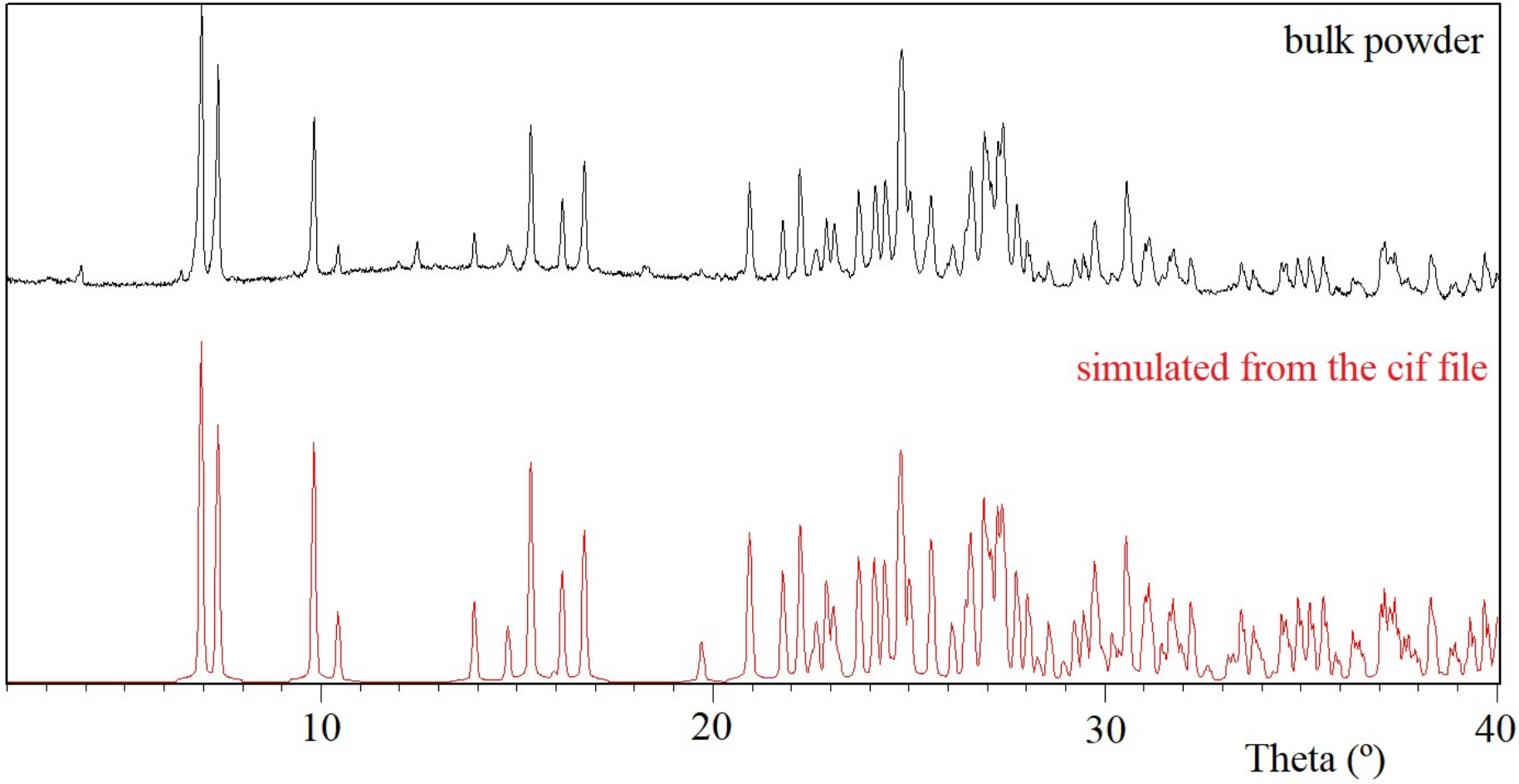
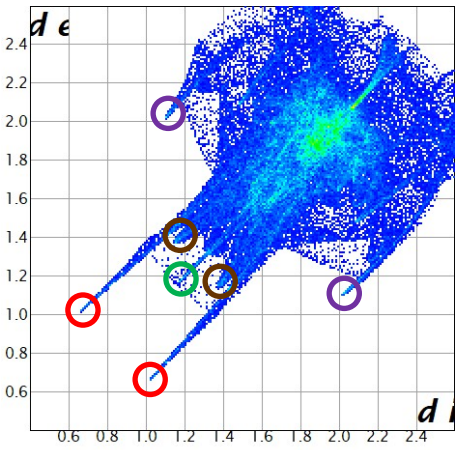


Figure S3: Comparative PXRD diffractograms between bulk IDIF (black) and simulated from the cif file (red). Powder X-ray diffraction (PXRD) pattern was obtained on a PANalytical X'Pert PRO MPD diffractometer in transmission configuration using Cu Kα1+2 radiation (λ = 1.5406 Å) with a focusing elliptic mirror and a PIXcel detector working at a maximum detector's active length of 3.347º. Configuration of convergent beam with a focalizing mirror and a transmission geometry with flat sample sandwiched between low absorbing films measuring from 2 to 40º in 2θ, with a step size of 0.026º and a total measuring time of 30 minutes at room temperature (298 K).

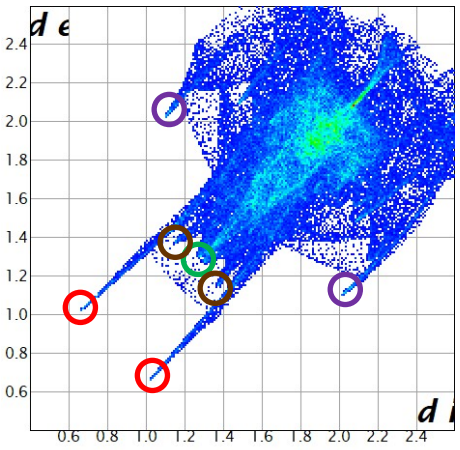


3.- Hirshfeld analysis

Hirshfeld surfaces fingerprint plots of two different asymmetric units of IDIF: comparative footprint and contribution (%) of intermolecular contacts



IDIF_Syn



IDIF_Anti

Table S3. Contribution (%) of intermolecular contacts of two different asymmetric units of IDIF at 296 K

Contacts	IDIF_Syn	IDIF_Anti
H·····H	16.3	19.5
F·····H	15.9	12.1
O·····H	12.2	12.2
C·····H	10.1	7.9
I·····H	8.5	8.5
F·····F	2.7	3.4
Residual	34.3	36.4

4.- Crystal structures of diflunisal reported in the CCDC

Table S4.

CCDC refcode	Space group	Solid form	Temperature (K)	Disorder (in F ortho position)
FAFWIS	*C* 2/*c*	anhydrous (polymorph V)	283-303	Yes
FAFWIS01	*P* -1	anhydrous (polymorph I)	283-303	Yes
FAFWIS02	*P* 2_1 2_1 2_1	anhydrous (polymorph III)	298	No[1]
NUZGUM	*C* 2/*c*	pTHF inclusion complex	100	Yes
NUZHAT	*P* 2_1/*n*	caprolactone inclusion complex	100	Yes
OPOGAD	*P* 2_1/*c*	theophylline cocrystal	150	No
QOQXAV	*C* 2/*c*	monohydrate clathrate	283-303	Yes
RUXRUX	*C* 2/*c*	chloroform solvate	153	Yes
RUXSAE	*P* 2_1/*n*	acetic acid solvate	150	Yes
UWOKEY	*P* -1	1,2-bis(Pyridinium-4-yl)ethene) salt acetonitrile solvate	150	No
UWOKIC	*P* -1	pyrazine cocrystal	283-303	No
UWOKOI	*P* 2_1/*c*	1,3-bis(Pyridinium-4-yl)propane salt	150	No
YEJWEP	*C* 2/*c*	hexane solvate	283-303	Yes

[1] Crystal structure solved from PXRD data, no F atom disorder was considered