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High resolution X-ray diffraction, ab initio calculations and thermodynamic measurements to go insight the polymorphism of drugs. Application to paracetamol and piracetam

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HAL Authorization

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Introduction

➤ Studying polymorphism of pharmaceutical compounds is a growing field of activity. This is due to the economic pressure of the pharmaceutical industry and the more important awareness of the polymorphism consequences on the medicament properties, in particular chemical and physical stability

➤ We have developed a fundamental approach to study polymorphism, which combines high-resolution X-ray diffraction, thermodynamic experiments and *ab-initio* calculations

➤ Application to :

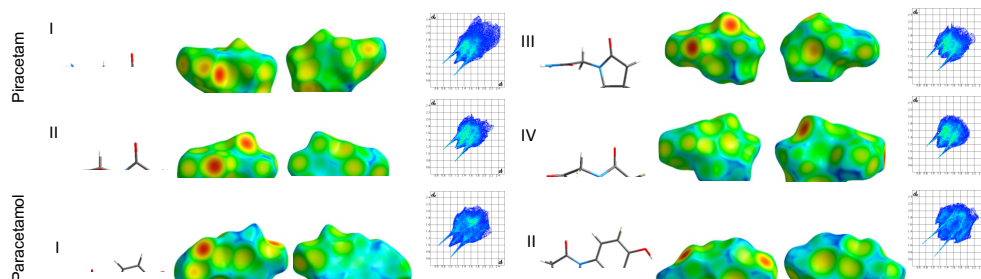
Paracetamol (acetaminophen): antipyretic, analgesic

Piracetam (2-oxo-1-pyrrolidine acetamide): Nootropic drug

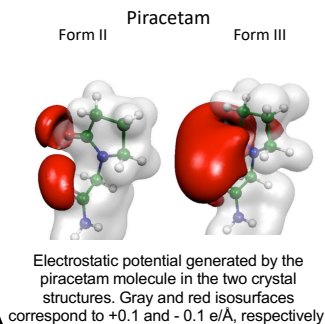
Cristallographic details for piracetam and paracetamol

Form	Piracetam				paracetamol	
	I [1]	II [2]	III [2]	IV [3]	I [4]	II [5]
Empirical formula	C ₆ H ₁₀ N ₂ O ₂	C ₆ H ₁₀ N ₂ O ₂	C ₆ H ₁₀ N ₂ O ₂	C ₆ H ₁₀ N ₂ O ₂	C ₈ H ₉ N ₁ O ₂	C ₈ H ₉ N ₁ O ₂
Crystal system	monoclinic	triclinic	monoclinic	monoclinic	monoclinic	orthorhombic
Space group	P2 ₁ /n	P-1	P2 ₁ /n	P2 ₁ /c	21/n	Pbca
Unit cell dimensions	a= 6,7254°Å b= 13,2572°Å c= 8,0529°Å α= 90° β= 98,603° γ= 90°	a= 6,3530°Å b= 6,5278°Å c= 8,3716°Å α= 80,297° β= 78,226° γ= 89,048°	a= 6,4539°Å b= 6,3857°Å c= 16,1814°Å α= 90° β= 92,057° γ= 90°	a= 5,4541°Å b= 8,9537°Å c= 13,61°Å α= 104,93° β= 90° γ= 90°	a= 6,820°Å b= 8,374°Å c= 11,559°Å α= 90° β= 99,32° γ= 90°	a= 11,7636°Å b= 7,2863°Å c= 17,1041°Å α= 90° β= 90° γ= 90°
Volume (°Å ³)	709,918	334,956(17)	666,45(8)	642,199	651,428	1466,046
Z	4	2	4	4	4	8
Density (calculated) (Mg/m ³)	1,33	1,410	1,417	1,47	1,541	1,37

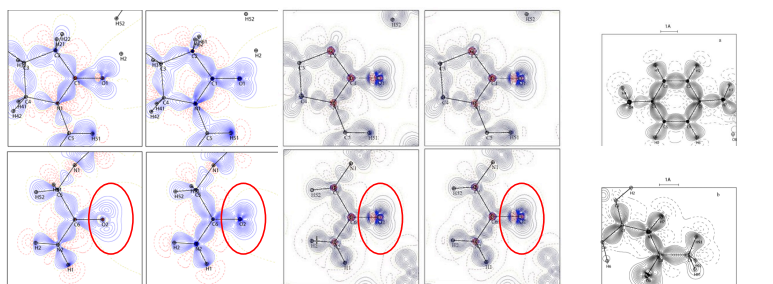
Hirshfeld surfaces and fingerprints for piracetam and paracetamol [3,6]



Electrostatic potential [2]



Electron deformation density maps from HR X-ray experiments

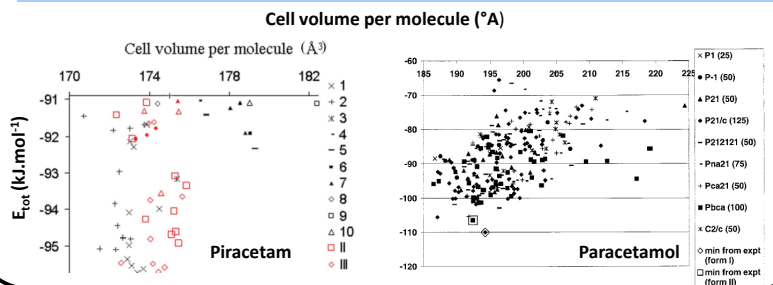


Experimental (blue) and Theoretical (black) electron deformation density maps for form II (left) and form III (right) of piracetam [2]. Experimental electron deformation density maps for form I of paracetamol [4]. Contour levels are ± 0.05 e/Å³ (negative contours are dashed)

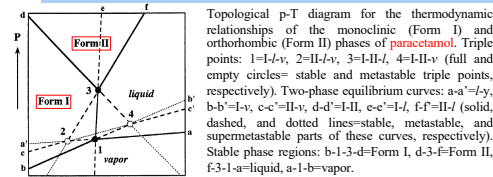
Electrostatic intermolecular energies

Atom 1	Atom2	D (°Å)	Symmetry Operation	Energy (kJ.mol ⁻¹)
Piracetam form II				
O2	H1	1.92	X ₁ -Y ₁ -Z ₁	-33.3
O1	H2	1.95	X ₁ -Y ₁ -Z ₁	-41.0
O1	H1	2.29	X ₁ -Y ₁ -Z ₁	-27.4
H2	H1	2.62	X ₁ -Y ₁ -Z ₁	-7.9
O2	H3	2.78	X ₁ -Y ₁ -Z ₁	-1.5
H3	H2	2.80	X ₁ -Y ₁ -Z ₁	-25.6
H1	H1	2.61	X ₁ -Y ₁ -Z ₁	-9.5
H1	H1	2.55	X ₁ -Y ₁ -Z ₁	-1.6
H1	H1	2.64	X ₁ -Y ₁ -Z ₁	-0.8
H1	H2	2.81	X ₁ -Y ₁ -Z ₁	-1.7
Sum				-110.0
Piracetam form III				
O2	H1	1.92	X ₁ -Y ₁ -Z ₁	-80.7
O2	H1	1.95	X ₁ -Y ₁ -Z ₁	-45.0
H2	H1	2.56	X ₁ -Y ₁ -Z ₁	-30.4
O1	H1	2.62	X ₁ -Y ₁ -Z ₁	-21.9
H3	O1	2.46	X ₁ -Y ₁ -Z ₁	-1.8
O4	H4	2.89	X ₁ -Y ₁ -Z ₁	-5.9
H2	H3	2.57	X ₁ -Y ₁ -Z ₁	-5.5
H2	H3	2.48	X ₁ -Y ₁ -Z ₁	-1.5
N1	H1	2.52	X ₁ -Y ₁ -Z ₁	0.0
Sum				-131.9
Paracetamol form I				
O4	H7	1.9275	X ₁ -Y ₁ -Z ₁	-15.23
O8	H4	1.6966	X ₁ -Y ₁ -Z ₁	-11.15
H92	O8	2.7902	X ₁ -Y ₁ -Z ₁	-9.86
H92	H4	2.6565	X ₁ -Y ₁ -Z ₁	-5.69
H93	H2	2.5015	X ₁ -Y ₁ -Z ₁	-0.32
H96	H6	2.2083	X ₁ -Y ₁ -Z ₁	-0.01
H5	H4	2.7269	X ₁ -Y ₁ -Z ₁	1.71
Sum				-40.55

Cristal Structure Prediction [7,8]



Thermodynamic measurements [9]



Conclusion