

Nouha EL HASSAN¹, Anne SPASOJEVIĆ – DE BIRÉ¹, Jean-Michel GILLET¹, Nour Eddine GHERMANI^{1,2}, Philippe ESPEAU³, Yohann CORVIS³ and Camille ALZINA³

¹ Laboratoire Structures et Propriétés des Matériaux Solides (SPMS), UMR CNRS 8580, Ecole Centrale Paris, Grande Voie des Vignes, 92290 Châtenay-Malabry, France

² Laboratoire Physico-Chimie-Pharmacotechnie-Biopharmacie (PPB), UMR CNRS 8612, Université Paris-Sud 11, Faculté de Pharmacie, 5 rue Jean-Baptiste Clément, 92296 Châtenay-Malabry, France,

³ Laboratoire de chimie physique, Faculté de Pharmacie de l'Université Paris 5, 4 avenue de l'Observatoire, 75006 Paris, France

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 :

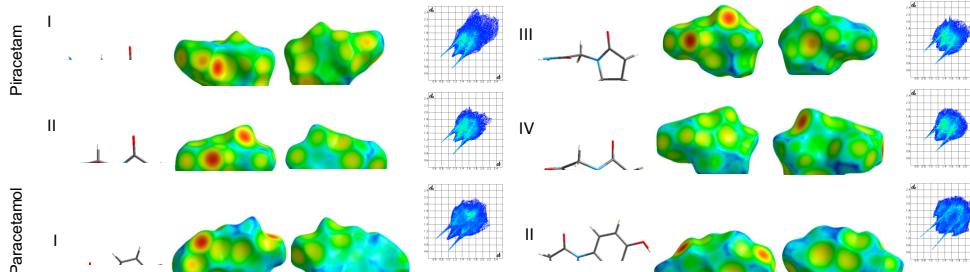
Paracetamol (acetaminophen): antipyretic, analgesic

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

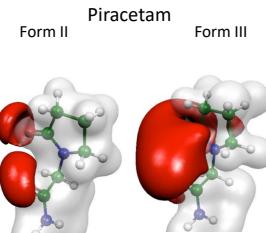
Cristallographic details for piracetam and paracetamol

Form	Piracétam			paracétamol		
	I [1]	II [2]	III [2]	IV [3]	I [4]	
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	
Crystal system	monoclinic	triclinic	monoclinic	monoclinic	monoclinic	
Space group	P2 ₁ /n	P $\bar{1}$	P2 ₁ /n	P2 ₁ /c	21/n	
Unit cell dimensions	a = 6.7254 ¹ \AA b = 13.2572 ¹ \AA c = 8.0529 ¹ \AA α = 90° β = 98.603° γ = 90°	a = 6.3530 ¹ \AA b = 6.5278 ¹ \AA c = 8.3716 ¹ \AA α = 80.297° β = 78.226° γ = 89.048°	a = 6.4539 ¹ \AA b = 6.3857 ¹ \AA c = 16.1814 ¹ \AA α = 90° β = 92.057° γ = 90°	a = 5.4541 ¹ \AA B = 8.9537 ¹ \AA c = 13.61 ¹ \AA α = 104.93 ° β = 90° γ = 90°	a = 6.820 ¹ \AA B = 8.374 ¹ \AA c = 11.559 ¹ \AA α = 90° β = 99.32° γ = 90°	a = 11.7636 ¹ \AA b = 7.2863 ¹ \AA c = 17.1041 ¹ \AA 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]

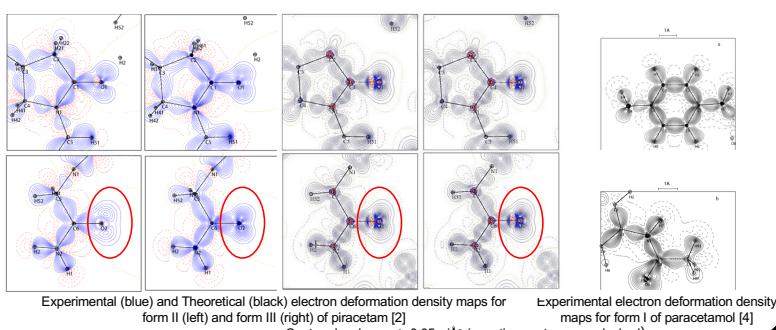


Electrostatic potential [2]



Electrostatic potential generated by the piracetam molecule in the two crystal structures. Gray and red isosurfaces correspond to +0.1 and -0.1 e/Å, respectively.

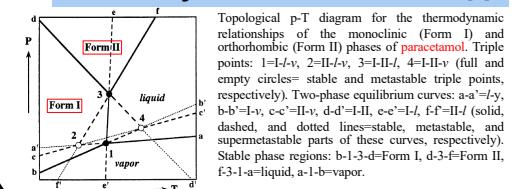
Electron deformation density maps from HR X-ray experiments



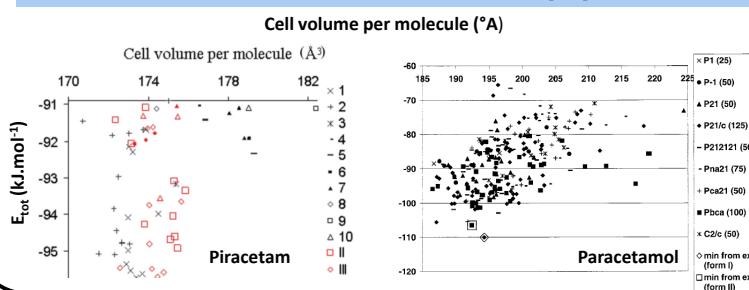
Electrostatic intermolecular energies

Atom 1	Atom 2	D (Å)	Symmetry Operation	Energy (kJ.mol ⁻¹)	Atom 1	Atom 2	D (Å)	Symmetry Operation	Energy (kJ.mol ⁻¹)
O2	H1	1.92	-X, Y+1, Z-1	-73.3	O4	H7	1.9375	X+1, -Y+1, Z+1	-17.32
O1	H2	1.95	-X+1, Y, Z	-41.9	O8	H4	1.6966	X+1, -Y+1, Z+1	-11.15
H3	O2	2.12	-X+1, Y-1, Z-2, inv	-27.4	H9	O8	2.7062	X+2, -Y+1, Z+2	-9.86
H2	O1	2.16	-X, Y+1, Z-2, inv	-1.5	H9	H4	2.6565	X-2, -Y, Z-1 (inv)	-5.69
H1	O2	2.30	-X+1, Y-1, Z-2, inv	-25.6	H9	H2	2.5015	X-2, -Y, Z-1 (inv)	-0.32
H3	H1	2.55	-X+1, Y-1, Z-1, inv	-0.5	H6	H6	2.2263	X-2, -Y-1, Z-1 (inv)	-0.01
H2	H1	2.81	-X, Y-1, Z-2, inv	-1.6	H5	H4	2.7269	X-2, -Y-1, Z-1	1.71
			Sum	-116.0				Sum	-40.55

Thermodynamic measurements [9]



Cristal Structure Prediction [7,8]



Conclusion