



HAL
open science

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

Nouha El Hassan, Anne Spasojevic - de Biré, Jean-Michel Gillet, Nour-Eddine Ghermani, Philippe Espeau, Yohann Corvis, Camille Alzina

► To cite this version:

Nouha El Hassan, Anne Spasojevic - de Biré, Jean-Michel Gillet, Nour-Eddine Ghermani, Philippe Espeau, et al.. High resolution X-ray diffraction, ab initio calculations and thermodynamic measurements to go insight the polymorphism of drugs. Application to paracetamol and piracetam. 6th annual meeting of the “Control and Prediction of the Organic Solid State” (CPOSS) project, Apr 2012, Londres, United Kingdom. hal-02301107

HAL Id: hal-02301107

<https://hal.science/hal-02301107v1>

Submitted on 23 Sep 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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 :

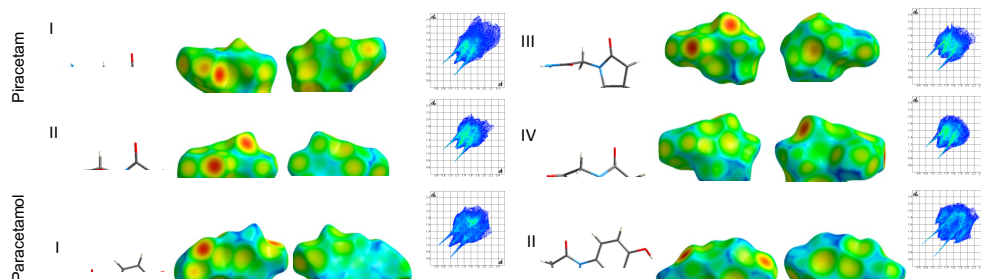
Paracetamol (acetaminophen): antipyretic, analgesic

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

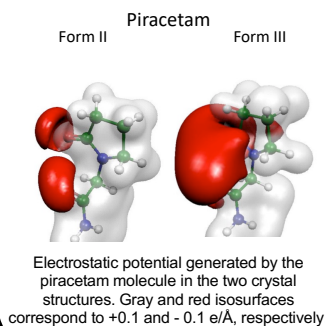
Cristallographic details for piracetam and paracetamol

Form	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= 6,48539°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

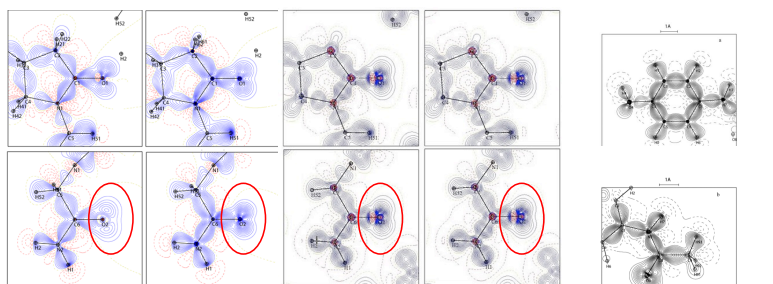
Hirshfeld surfaces and fingerprints for piracetam and paracetamol [3,6]



Electrostatic potential [2]



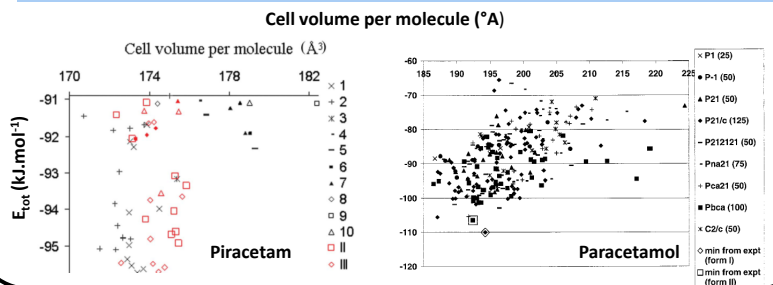
Electron deformation density maps from HR X-ray experiments



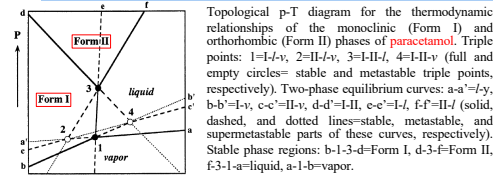
Electrostatic intermolecular energies

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