

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

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Studying the polymorphism of pharmaceutical compounds is a growing field of activity. This is due, on one hand, to the economic pressure of the pharmaceutical industry, and on the other hand, to the more important awareness of the consequences of polymorphism on the properties of a medicine.

A good knowledge of molecular interactions and crystal energies is essential for the determination of relative polymorph stability. We have developed a fundamental approach to study polymorphism, which combines high-resolution X-ray diffraction and *ab-initio* calculations. This approach would enable us to study the consequences of drug polymorphism on the physical and chemical properties of drugs.

Piracetam is a small and flexible molecule, used against several neurodegenerative disorders such as Alzheimer's disease. We will present the results we have obtained for Piracetam (figure). In particular, we will compare electrostatic energies obtained from X ray diffraction experiments [1] with crystal structure prediction from *ab-initio* calculations [2]. We will show also thermodynamic aspect of the relative stability for piracetam.

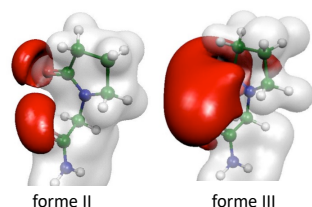


Figure. Experimental electrostatic potential isosurface (red $-0.1 \text{ e.}\text{\AA}^{-1}$ grey $+0.1 \text{ e.}\text{\AA}^{-1}$) for piracetam polymorphs I and II

[1] Chambrier, M.-H. ; Bouhaida, N. ; Bonhomme, F. ; Lebègue, S. ; Gillet J.-M., Jelsch, C. and Ghermani N.E. ; Cryst. Growth Des., 2011, 11,6, 2528-2538 [2] Nowell, H. and Price S.L., Acta Cryst., 2005, B61, 558–568

Rendgenska difrakcija visoke rezolucije, *ab initio* izračunavanja i termodinamička merenja u ispitivanju polimorfizma kod lekova. Primena na priacetamu.

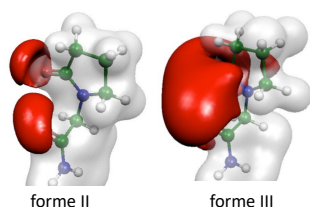
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Ispitivanje polimorfizma kod jedinjenja koja se koriste u farmaciji je u porastu. Razlog je svakako ekonomski pritisak na farmaceutsku industriju, ali takodje i svest o posledicama koje polimorfizam može imati na svojstva medikamenata.

Poznavanje molekulskih interakcija i energije kristala je od suštinskog značaja za određivanje relativne stabilnosti polimorfa. Razvili smo fundamentalni pristup u proučavanju polimorfizma koji kombinuje rendgensku strukturnu analizu visoke rezolucije i *ab initio* metode. Ovakav pristup omogućuje proučavanje polimorfizma kod lekova kao i posledica koje polimorfizam može imati na njihova fizička i hemijska svojstva.

Piracetam je mali i fleksibilni molekul koji se koristi protiv nekoliko neurodegenerativnih poremećaja kao što je Alchajmerova bolest. Ovom prilikom izložićemo rezultate koje smo dobili za Piracetam (slika) poredeći, pre svega, elektrostatičke energije dobijene eksperimentima rendgenske difrakcije [1] sa kristalnom strukturom predviđenom *ab initio* izračunavanjima [2]. Pokazaćemo takođe, termodinamičke aspekte relativne stabilnosti piracetama.



Slika. Eksperimentalno određeni elektrostatički potencijal za polimorfe piracetama I i II (izopovršine: crvena -0.1 e.Å^{-1} ; siva $+0.1 \text{ e.Å}^{-1}$)

[1] Chambrier, M.-H. ; Bouhaida, N. ; Bonhomme, F. ; Lebègue, S. ; Gillet J.-M., Jelsch, C. and Ghermani N.E. ; Cryst. Growth Des., 2011, 11,6, 2528-2538 [2] Nowell, H. and Price S.L., Acta Cryst., 2005, B61, 558–568