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ON THE CRYSTALLOGRAPHIC POLYMORPHISM OF PHARMACEUTICS – A QUANTUM CHEMICAL AND CHEMOMETRIC TREATMENT

By Bojidarka Ivanova and Michael Spiteller

PREFACE

In this work we discuss certain consideration for quantum chemical and chemometric assessing in the crystallographic polymorphism. It is aimed primarily at researchers in ‘Analytical chemistry’ and is designed to help readers’ understanding of the implications of the different quantum chemical theories in the chemical crystallography. The focal part of the discussion sets out the polymorphism of aspirin. The other parts of the paper extend the scope of the contribution considering crystallographic, quantum chemical and chemometric data about pharmaceutics. In the corresponding results–sections we present discussion concentrating on subtle electronic effects in polymorphs, thus illustrating the great capability of the computational quantum chemistry to distinguish between modifications showing perturbations of the atomic positions in the crystals.

TABLE OF CONTENT

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Keywords

Polymorphism; Pharmaceutics; Quantum chemistry; Crystallography; Chemometrics

Abstract

That paper deals extensively with relations between '*molecular structure*'–'*electronic structure*'–'*energy*' of pharmaceutics such as salicylic acid **(1)**, polymorphs (**I–III**) of aspirin **(2)**, 5–hydroxy thryptophan crystalizing as crystallohydrate **(3)**, 5-hydrohy-L-tryptophan barbituric acid co–crystal **(4)** and 5-hydroxy-L-tryptophan 1,3-dimethylbarbituric acid dihydratemolecule co–crystal **(5)**; tyrammonium iodide (**6**), 3,5–diiodotyrosine **(7),** tyrammonium 5–sulfosalicylate (**8**), dopammonium 5–sulfosalicylate dihydrate (**9**)) and 2',3'-*o*-isopropylideneadenosine **(10)**, using crystallographic, quantum chemical *ab initio* and DFT molecular dynamics – adiabatic and diabatic computations – and chemometrics. Structures **(1)** and **I** have been redeterminated (**(1)**: Monoclinic $P2_1/c$; a = 4.9293(8), b = 11.232(2), c = 11.602(2) Å, β = 90.648(6)°; V = 642.314 $Å^3$, Z = 4; **(2)**: Monoclinic $P2_1/c$; a = 11.4511(18), b = 6.6028(9), c = 11.4182(18) Å, β = 95.690(5)°, V = 859.069 $Å^3$; Z = 4). The theoretical analyses have accounted for whether high resolution crystallographic measurements of disordered systems can be treated theoretically, producing distinguishable quantitatively trajectory of energetics accounting for subtle electronic effects. The results have contributed insights *into* the followings: *(i)* The total energy appears sensitive parameter towards subtle electronic effects; *(ii)* As far as the total energy difference between two independent crystallographic solutions of **I** of aspirin is $\Delta(E^{TOT})$ = |0.24701| a.u. The latter is lower than $\Delta(E^{TOT})$ of modifications **I** and **II** ($E^{TOT} \in$ 0.4780–0.5975 kcal.mol^{-1}), but in parallel is higher than $\Delta(E^{TOT})$ = |0.1573| a.u. of disordered **II**, the evaluation of total energy parameters as only a quantity prevents a reliable study of subtle electronic effects; but *(iii)* the chemometrics of the trajectory profile of the total energy provides meaningful statistical information allowing us to distinguish between the electronic effects due to perturbations and atomic positions; disorders; plane stacking effect, and more.

Abbreviations and acronyms

ADMP – Atom-Centered Density Matrix Propagation (quantum chemical method); AIM – Atoms in molecules; ANOVA – Analysis of variance; BDE – Bond dissociation energy; BOMD – Born Oppenheim Molecular Dynamics (quantum chemical method); BOs – Bond orders; BCP – Bond critical point (analysis); BVM - Bond valence model; CT – Charge transfer effects; DFT – Density functional theory; ED – Electron density; ESPs – Electrostatic potentials; FBO – Fuzzy bond order; IR – Infrared (spectroscopy); LBO – Laplacian bond order; LPA – Lowdin population analysis; MD – Molecular dynamics; MM – Molecular mechanics; MOs – Molecular orbitals; MS – Mean square; NBO – Natural bond orbital (analysis); NCE – Natural Columbic energy (potential); NLMO – Natural local molecular orbitals; NEC – Natural electronic configuration; PCM – Polarizable continuum model; SS – Sum of squares; SD – standard deviations; TSH – Trajectory surface hopping; V_{NCE} – Columbic potential energy term; UV–VIS–NIR – Ultraviolet-visible-Near infrared (spectroscopy); XRD – X-ray diffraction (in context measurements of powders).

Introduction

The term '*polymorphism'* reflects molecular ability to crystalize in more than one structure (Bond et al; 2007; Higashi et al. 2017). Since, properties of polymorphs can vary, their quantification becomes an important task to manufacturing pharmaceutics. It affects packing properties *via* molar volume and crystal density; optical properties and refractive index; electrical and thermal properties; conductivity; hydroscopicity; other differences associated with *thermodynamics*; *kinetics*; *surface* and *mechanical* properties, and more (Datta and Grant, 2004). In order to make a complex prediction of correlation among '*molecular structure*'–'*electronic structure*'–'*energetics*' using crystallographic and quantum chemical data it should be taken *into* consideration various polymorph modifications. On this view, we have struggled with an analytical chemical problem to define quantitatively borders of perturbation of electronic structure and energetics of polymorphs, using as molecular templates crystals of **(1)** and **(2) (Scheme 1)**, respectively. Compound **(1)** appears a structural analogous of aspirin, but is a conformational blocked, due to presence of intramolecular (OH···O=C) hydrogen bond.

Aspirin is a remarkable example of a bestselling pharmaceutics, which is broadly used to treat cardiovascular diseases, in addition to reduce angiogenesis of cancer (Xie et al. 2021). It is already implemented in the practice, however, shows complex polymorphism, including few known polymorphs (Bond et al. 2007a,b, 2011; Vishweshwar et al. 2005; Bag and Reddy, 2012; Wen and Beran, 2012; Shtukenberg et al. 2017; Arputharaj et al. 2012; LeBlanc et al. 2016); Price et al. 2009; Ouvrard and Price, 2004; Brela et al. 2016). The employment of crystallographic data for purposes of computational chemistry needs a detail assessment of variations of experimental crystallographic parameters, in order to, determine the error contribution to energy – the major parameter assessing bonding properties of molecules and thus their biological activity – and/or molecular properties, in parallel to, error contributions from theoretical methods. Despite, numerous efforts devoted to quantify accuracy of