

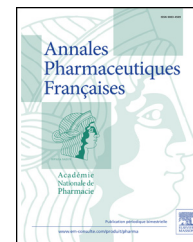


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UPDATE

# X-ray crystallography, an essential tool for the determination of thermodynamic relationships between crystalline polymorphs



*La radiocristallographie, un outil incontournable pour décrire la thermodynamique du polymorphisme cristallin*

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Received 15 September 2015; accepted 19 October 2015  
Available online 19 November 2015

## KEYWORDS

Crystallography;  
Thermodynamics;  
Polymorphism;  
Phase diagram

**Summary** After a short review of the controversies surrounding the discovery of crystalline polymorphism in relation to our present day understanding, the methods of how to solve the stability hierarchy of different polymorphs will be briefly discussed. They involve either theoretical calculations, or, more commonly, experimental methods based on classical thermodynamics. The experimental approach is mainly carried out using heat-exchange data associated to the transition of one form into another. It will be demonstrated that work-related data associated to the phase transition should be taken into account and the role of X-ray crystallography therein will be discussed. X-ray crystallography has become increasingly precise and can nowadays provide specific volumes and their differences as a function of temperature, and also as a function of pressure, humidity, and time.

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**MOTS CLÉS**

Cristallographie ;  
Thermodynamique ;  
Polymorphisme ;  
Diagramme de phases

**Résumé** Après un très bref rappel sur les controverses ayant accompagné la mise en évidence du polymorphisme cristallin et de sa réalité, on rappelle comment on répond à la question de la hiérarchie de stabilité des polymorphes ou bien par des calculs théoriques ou bien, et surtout, par des méthodes expérimentales inspirées de la thermodynamique classique. Ces dernières ont d'abord été utilisées en ne tenant compte que des effets thermiques associés à la transition d'une forme à l'autre. On montre ensuite comment le « travail » qui accompagne cette transition doit être pris en compte. On montre enfin comment la radiocristallographie le permet grâce à des mesures, devenues suffisamment précises, des volumes spécifiques et de leurs différences en fonction de la température mais aussi d'autres paramètres (pression, humidité, temps).

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## The emergence of crystallography and the notion of crystalline polymorphism

The conception of (geometrical) crystallography practically coincided with the appearance of the then controversial notion of crystalline polymorphism. At the end of the 18th century, as ‘‘professor of Humanities in [sic] the University of Paris’’, Abbé René-Just Haüy (1743–1822) formulated two hypotheses in his book on the structure of crystals [1]. The first stated that a crystal is the result of a three-dimensional repetition of an elementary unit, which he labeled ‘‘integral molecule’’. The second stated that there exists only one single elementary unit for a given chemical species.

Only a little later in 1788, Martin Heinrich Klaproth (1743–1817), pharmacist and professor of Chemistry at the University of Berlin, refuted the second hypothesis, not questioning however the correctness of the first one. He claimed that calcium carbonate exists in at least two different crystalline forms in nature: calcite and aragonite [2].

A persistent controversy arose, at times bitter, and exchanges were not always polite, as Robert W. Cahn asserts [3]. The controversy lasted until Eilhard Mitscherlich (1794–1863), successor of Klaproth at the University of Berlin, provided irrefutable proof of polymorphism, i.e., the capability of a substance to crystallize in at least two different crystalline forms. In 1823, he convincingly demonstrated the existence of dimorphism for sulfur [4], which finally settled the issue for the scientific community.

It took at least another century before X-ray crystallography allowed 3D visualization of the elementary units (the so-called ‘‘integral molecules’’) and demonstrated the difference between isomers and polymorphs. Nowadays, owing to X-ray crystallography, polymorphism has become a visible reality, with crystal structures often represented at the atomic scale by a variety of three-dimensional collections of spheres (the atoms) interconnected by sticks (the chemical bonds). Crystallography allows the observation of the changes in molecular conformation [5] for flexible molecules and variations in molecular packing, which can also occur in structures with inflexible molecules (for example in the case of benzene [6]), both causes of crystalline polymorphism.

However, this approach only leads to a model (the perfect crystal) that is a representation of discrete quantum states, averaged over space and time, corresponding to the

energy states of a specific sample within the conditions of observation. In other words, the unit cell and the underlying structure correspond to a specific energy level and as a result, if two polymorphs are observed under the same experimental conditions, their respective energies must be different. Thus, only a single crystalline form can be stable under a given set of conditions, which must be the one with the lowest energy. Gibbs already came to this conclusion in his classical phase theory, independent of any hypothesis about the microscopic nature of matter [7].

When applied to polymorphism in active pharmaceutical ingredients (APIs), this inference leaves the pharmaceutical industry with the following, often-difficult question: which form is the stable one [8]?

## Thermodynamics and the initial approaches to determine polymorph stability

It is clear that in the case of energy differences, the answer will be given by thermodynamics and currently two approaches to answer the foregoing question are being pursued.

Owing to the increased computation power of computers, one approach involves methods to calculate and compare the energies of polymorphs whose structures are known under the same conditions. It is nowadays also possible to predict structures of potential polymorphs of a given compound through its chemical formula and to deduce the energy differences [9]. The computational approach is described elsewhere in great detail and will not be discussed in this text [9b–f]. Nevertheless, it still has some shortcomings. For example, it is still difficult to determine the energy differences between polymorphs as a function of temperature and the energy differences are so far not extremely precise. Moreover, polymorphs of molecular salts, possessing a combination of ionic and weaker interactions are still very difficult to evaluate *in silico*. On the other hand, computational methods can nowadays provide possible crystal structure solutions for a given API. This, in turn, allows calculation of X-ray powder diffraction patterns, which can be compared to those obtained by high resolution X-ray diffraction of powder samples. In this way, it has become

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