

## Prediction, Crystallization and Stability of Polymorphs: Influenced by the Entropy Differences of their Solid States

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The existing solid state variety of organic and inorganic substances in forms of stoichiometric entities such as polymorphs and co-crystals is a fact of nature. Specifically, no explanations based on theories were presented hitherto for the existence of substances revealing only one crystal form. It would be an academic challenge to be able to give rules for the existence of a substance revealing only one stable crystal form based on the molecular structure of the substance and the corresponding crystal lattice.

Computational crystallographer developed algorithms for lattice energy calculations with the attempt to predict crystal structures. The first blind test in cooperation with the Cambridge Crystallographic Data Centre was published in 2000 [1]. J. D. Dunitz [2] and H.-B. Bürgi presented their critical views about the prediction as invited lecturers at two PhandTA Conferences. The conclusion given by Dunitz was: Too many crystal structures for a single chemical substance exist within a narrow lattice energy band.

The stability relation of two or more polymorphs of a substance in respect to temperature or pressure is crucial for research and development activities as well as for any application. Two thermodynamic functions could be used for the description of their stability relation, namely the Helmholtz free energy  $A(T,V)$  and the Gibbs free energy  $G(T,P)$  in form of

a definition	or in form of a differential expression
$A = U - TS$	$dA = - SdT - PdV$
$G = H - TS$	$dG = - SdT + VdP$

The two functions differ in their parameters, namely the Helmholtz function is related to the intensive parameter  $T$  and the extensive parameter  $V$ . The intensive one is scale-invariant and the extensive is scaling with the amount of material in the system. The Gibbs function, however, is depending on the intensive parameters  $T$  and  $P$ .

The chemical potential, the driving force, or the difference of the molar Gibbs free energy functions of two polymorphs are different expressions for the same quality. It is the absolute measure for the degree of instability of the corresponding metastable polymorph in respect to the stable one. Our investigations concerning the Gibbs free energy were restricted to temperature [3-5]. A specific example about the polymorphs A and D of Cimetidine will be presented among others [6]. A. Bauer in cooperation with theoretical chemists calculated the crystal energies of the A and D forms. The polymorph A was found as the stable one with an energy difference of  $6 \text{ kJ mol}^{-1}$ . In contrary, Marti's group proved with DCS that the D form is the stable one.

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