

Interrelation between Thermodynamic Parameters of the Fusion Process and Crystal Structure of Drugs and Drug-like Molecules

German Perlovich ^{a,b}, Annette Bauer-Brandl ^a

^a Department of Pharmaceutics & Biopharmaceutics, Institute of Pharmacy, University of Tromsø, 9037 Tromsø, Norway

^b Institute of Solution Chemistry, Russian Academy of Sciences, 153045 Ivanovo, Russia

Thermodynamic characterisation of the fusion process of molecular crystals is a well established and informative method. However, it is still an open question how melting point and enthalpy of fusion interrelate with the crystal structure. The present work tries to fill this gap with specific information exemplified by NSAIDs, hydroxybenzoic acids, and parabens.

Materials, Methods and Approaches. Acetylsalicylic acid; Ibuprofen (+)-IBP; (±)-IBP; Flurbiprofen; Ketoprofen; Naproxen; Diflunisal; Acetanilide; Paracetamol; Phenacetine; 2-, 3-, 4-Hydroxy Benzoic acids, and Parabens (MePB; EtPB; PrBP; BuPB) were chosen as subjects of investigation. Heats and temperatures of fusion were obtained by differential scanning calorimetry (Perkin Elmer Analytical Instruments, Norwalk, Connecticut, USA) with a heating rate of 10 K·min⁻¹. Thermodynamic parameters of sublimation were obtained using the transpiration method described elsewhere [1]. Crystal lattice parameters were received from Cambridge data base, measured during the present work, and/or kindly provided by Caira [2], respectively. Hydrogen bond network topologies of the respective crystal lattices were studied using the approach proposed by Etter [3] and based on the analysis of graph set assignments. Molecular van der Waals's volumes and surfaces were calculated by the GEPOL program package [4].

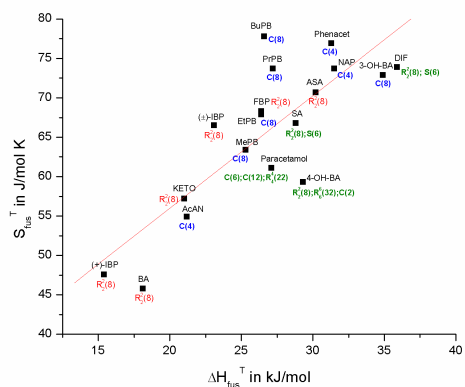


Figure 1

the fusion process, are maintained to a maximum extent also in the liquid state. Substances on the trend line, probably, completely realize their degrees of freedom (if one takes into account the hydrogen bond networks in the melt). Those compounds deviating from the trend line to increased fusion entropy are conformational more flexible molecules compared to the others. Probably, during their fusion process, and while the hydrogen bonds are broken off, additional degrees of freedom appear due to conformational (structural) disordering.

Results and Discussion. Dependence of entropies of fusion on fusion enthalpies for the discussed compounds is shown in Figure 1, together with the information of the graph set assignment. (Figure legend: The respective graph set assignment is given under the respective drug name. Red: compounds with dimer packing; Blue: infinite chains; Green: set of motifs.) Drugs with a complex structure of their hydrogen bond network (green symbols in Figure 1) deviate most from the common trend line, with a tendency of decreased fusion entropy. Probably, the hydrogen bond networks, after

Comparing the enthalpies of evaporation and sublimation, a linear correlation between these two is derived, with a slope =1 (within experimental errors). This indicates that the mechanisms of sublimation and evaporation processes reflect identical types of defects. Dependencies of the melting points on the molecular free volumes in crystal lattices of the drugs under investigation are presented in Figure 2. It is not difficult to see that there is the following regularity: increasing V^{free} -values lead to a decreased melting temperature, with an essential exception for Diflunisal and Naproxen due to structurally disordered molecules in the respective crystal lattices.

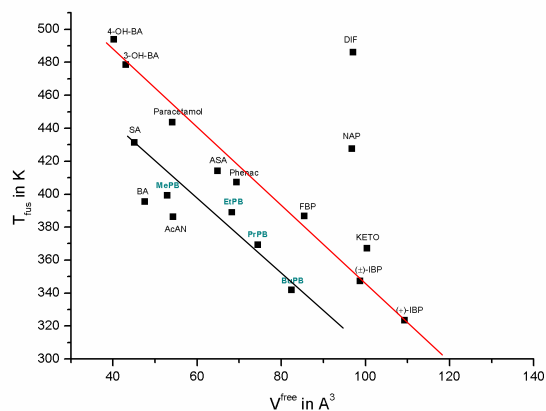


Figure 2

References

- [1] Perlovich, G.L., Bauer-Brandl, A., 2004. *Current Drug Delivery* 1(3):213-226.
- [2] Caira, M.R., 2003. - Personal communication.
- [3] Etter M., 1990. *Acc. Chem. Res.* 23:120-126.
- [4] Pascual-Ahuir, J.L., Silla, E., 1990. *J. Comp. Chem.* 11:1047.