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Thermodynamic properties of flufenamic and niflumic acids—Specific and non-specific interactions in solution and in crystal lattices, mechanism of solvation, partitioning and distribution

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Abstract

Temperature dependency of saturated vapour pressure and the thermochemical characteristics of the fusion process were measured for flufenamic acid and niflumic acid, and thermodynamic functions of sublimation, fusion and evaporation calculated. An approach to split specific and non-specific energetic terms in crystal lattices is developed. The melting points of the considered molecules correlate with the ratio between specific and non-specific interactions in crystal lattices. Temperature dependencies of the solubility in buffers with pH 2.0 and 7.4, in *n*-octanol and in *n*-hexane were measured. The thermodynamic functions of solubility, solvation and transfer processes were deduced. Specific and non-specific solvation terms were distinguished by the transfer from "inert" *n*-hexane to the other solvents. Comparison of the ratio between specific and non-specific interactions in solid state and in the solutions was carried out. A diagram to analyse energetic terms of partitioning and distribution processes is introduced.

Keywords: Flufenamic acid; Niflumic acid; Sublimation thermodynamics; Solubility; Solvation; Transfer; Crystal lattice energy; Specific and non-specific interactions; Partitioning; Distribution

1. Introduction

One of the key issues in drug design is to let the molecules actually reach their target. Each stage of the processes involved, as there are liberation (dissolution), absorption, distribution, and passive transport, is determined by the solvation characteristics of the drug molecules. So far, these questions have been addressed mainly from the point of view of relative thermodynamic functions in the form of partitioning and distribution coefficients (log *P*, log *D*). In our previous work [1–3] we have approached this problem by analysis of the thermodynamic functions in absolute energetic scales, in order to understand the mechanisms and driving forces of the drug transport and drug delivery processes.

The subjects for the present investigation are flufenamic acid and niflumic acid (Fig. 1) as further examples of NSAIDs (non-steroidal antiinflammatory drugs). These molecules were chosen because they are structurally closely related and differ only by the aromatic motif, being a phenyl or a pyridin ring, respectively. It is interesting to analyse the effect of this structural difference on crystal lattice energies, solubility in different solvents, solvation energies in these solvents, and on the partitioning (distribution) properties. It should be noted that in the literature there are some articles devoted to studies of the crystal lattice structures of niflumic acid [4] and flufenamic acid [5]. Thermochemical characteristics of the fusion process of niflumic acid have been investigated by Pinvidic et al. [6] using DTA, DSC, and TG methods. Solubility of niflumic acid has been analysed in solvent mixtures and has been related to the polarity of these mixtures by Bustamante et al. [7]. Protonation constants of niflumic acid in various solutions and in octanol/water, as well as partitioning and distribution coefficients of different molecular forms have been studied by Takacs-Novak et al. [8].

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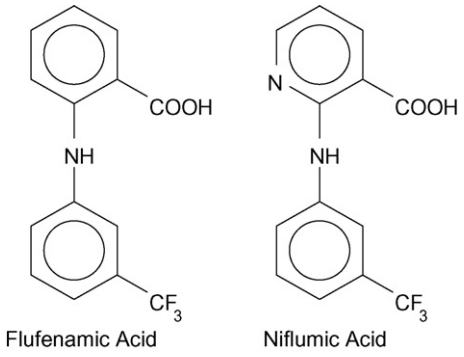

Fig. 1. Structure formula of flufenamic and niflumic acids.

In the present study we try: (a) to split specific and non-specific interaction terms in the crystals with those in pharmaceutical important media (aqueous buffers with pH 2.0 and 7.4 and *n*-octanol) in absolute energetic scale values and compare the relative fractions thereof; (b) to study the mechanism and driving forces of partitioning (distribution) processes.

2. Materials and methods

Flufenamic acid (2-[[3-(trifluoromethyl)phenyl]amino]benzoic acid, $C_{14}H_{10}F_3NO_2$, FW 281.23, lot 122K1018) and niflumic acid (2-[3-(trifluoromethyl)anilino]nicotinic acid, $C_{13}H_9F_3N_2O_2$, FW 282.2, lot 12K1486) were from Sigma Chemical Co., St. Louis, USA.

1-Octanol (*n*-octanol, $CH_3(CH_2)_7OH$, MW 130.2, lot 11K3688) ARG from Sigma Chemical Co. (USA). *n*-Hexane (C_6H_{14}, MW 86.18, lot 07059903C) ARG from SDS (Peypin, France). Buffer solutions were prepared by mixing solutions of hydrochloric acid and potassium chloride for pH 2.0, and appropriate sodium and potassium salts of phosphoric acid for pH 7.4. All the chemicals were of AR grade. The pH values were controlled using a pH meter (Electroanalytical Analyser, Type OP-300, Radelkis, Budapest) calibrated with solutions of pH 1.68 and 9.22.

Sublimation experiments were carried out by the transpiration method as previously described [2]. In brief: a stream of an inert gas passes the sample at a given constant temperature and at a known slow constant flow rate in order to achieve saturation of the carrier gas with the vapour of the substance under investigation. The vapour is condensed at some point downstream, and the mass of the sublimate and its purity determined. The vapour pressure above the sample at this temperature can be calculated from the amount of sublimated material and the volume of the inert gas used.

The equipment was calibrated using benzoic acid. The standard value of sublimation enthalpy obtained was $\Delta H^\circ_{sub} = 90.5 \pm 0.3\,kJ\,mol^{-1}$. This is in good agreement with the value recommended by IUPAC of $\Delta H^\circ_{sub} = 89.7 \pm 0.5\,kJ\,mol^{-1}$ [9]. The saturated vapour pressures were measured at least five times at each temperature, with the statistical error being within 3–5%. The experimentally determined vapour pressure data are described in ($\ln P$; $1/T$) co-ordinates by Eq. (1):

$$\ln(P) = \frac{A + B}{T} \tag{1}$$

The value of the enthalpy of sublimation is calculated by the Clausius–Clapeyron equation:

$$\Delta H^T_{sub} = -\frac{R\partial(\ln P)}{\partial(1/T)} \tag{2}$$

The entropy of sublimation at a given temperature T was calculated from the following relationship:

$$\Delta S^T_{sub} = \frac{\Delta H^T_{sub} - \Delta G^T_{sub}}{T} \tag{3}$$

where $\Delta G^T_{sub} = -RT\ln(P/P_0)$ and $P_0 = 1.013 \times 10^5$ Pa.

Solubility experiments. All the experiments were carried out by the isothermal saturation method at five temperature points: $20, 25, 30, 37, 42 \pm 0.1\,^\circ C$. The solid phase was removed by both centrifugation and isothermal filtration (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size). The experimental results stated are the average of at least five replicated experiments. The molar solubilities of the drugs studied were measured spectrophotometrically with an accuracy of 2–2.5% using a protocol described previously [1].

Differential scanning calorimetry (DSC) was carried out using a Perkin-Elmer Pyris 1 DSC differential scanning calorimeter (Perkin-Elmer Analytical Instruments, Norwalk, CT, USA) and Pyris software for Windows NT. DSC runs were performed in an atmosphere of flowing ($20\,ml\,min^{-1}$) dry nitrogen gas of high purity 99.990% using standard closed aluminum sample pans. The DSC was calibrated with indium from Perkin-Elmer (P/N 0319-0033). The value of the determined enthalpy of fusion corresponded to $28.48\,J\,g^{-1}$ (reference value $28.45\,J\,g^{-1}$). The melting point was $429.7 \pm 0.1\,K$ ($n = 10$). All the DSC-experiments were carried out at a heating rate of $10\,K\,min^{-1}$. The accuracy of weight measurements was ±0.005 mg (Sartorius M2P semi-microbalance).

3. Results and discussion

Before starting to study the solvation process, let us first introduce some basic definitions. The solvation of 1 mol of solute molecules in the solvent can be defined as the total change of the standard thermodynamic functions (ΔG°, ΔH°, ΔS°) of the compound when transferring it from the gas phase (ideal gas; single molecules without interaction) into the solvent. The thermodynamic cycle of solvation is illustrated in Scheme 1, from which it follows that

$$\Delta Y^\circ_{solv} = \Delta Y^\circ_{sol} - \Delta Y^\circ_{sub} \tag{4}$$

where ΔY° is the standard change of any of the thermodynamic functions of the solvation (ΔY°_{solv}), dissolution (ΔY°_{sol}), or sublimation (ΔY°_{sub}) process. Therefore, the following equations may be defined

$$\Delta G^\circ_{solv} = \Delta G^\circ_{sol} - \Delta G^\circ_{sub} \tag{5}$$