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Sublimation thermodynamics of four fluoroquinolone antimicrobial compounds

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ABSTRACT

The transpiration method was used to measure the vapor pressures as a function of temperature of the following antimicrobial drugs: ciprofloxacin, enrofloxacin, norfloxacin and levofloxacin. Based on these results standard molar enthalpies, entropies and Gibbs energies of sublimation at T = 298.15 K were calculated and a correlation between the crystal lattice energy and the saturation vapor pressure in a number of fluoroquinolones was found. The thermophysical characteristics of the compounds studied were determined by DSC. The influence of different structural fragments of molecules substituents and the effects of hydrogen bonds in crystal lattices on the sublimation enthalpy was discussed.

1. Introduction

Fluoroquinolones are synthetic antibiotics chemically related to nalidixic acid of the first generation DNA gyrase inhibitor and active against both Gram-positive and Gram-negative bacteria [1]. Among the most important structural fragments of the drug compounds of this type are the fluorine atom and the piperazinyl ring at positions 6 and 7 of quinolone-3-carboxylic acid which considerably widen their activity range considerably and improve their pharmacokinetic profile [2]. The rational design of fluoroquinolone molecules has resulted in compounds with a new biological action [3].

As fluoroquinolone molecules possess donor and acceptor groups, they can participate in formation of branched hydrogen bond networks in the solid state. Owing to this fact, the compounds are able to crystallize in various polymorphic forms [4], as well as to become components of complexes [5], cocrystals [6], salts [7] and crystalline hydrates and solvates [8]. The crystal structure of such compounds was analyzed in references [9–12]. The aromatic groups of fluoroquinolones are usually assembled by π-π stacking dimers in which the charged groups are parallel forming polar channels within the crystal structure. Moreover the charged-assisted hydrogen bonding interactions contribute the most relevant contributions for the crystal lattice energy [6]. The typical O—H···O intramolecular bond was found in all the structures of the studied neutral fluoroquinolone forms [10,11,13]. As has been obtained, in most cases the carboxylic group is not deprotonated and is linked by a hydrogen bond with the nearest 4-oxy atom [14]. In some fluoroquinolone structures, the carboxyl group is ionized and, thus, the molecule is in a zwitterionic form with a protonated terminal nitrogen of the piperazinyl ring in the solid state [15,16].

A great number of studies deal with fluoroquinolone solubility [17,18]. This is quite natural as solubility is one of the main properties determining the drug's bioavailability, optimal therapeutic doses and possible side effects [19]. According to the thermodynamic cycle, the fundamental aspects of solubility are directly related to sublimation and solvation studies [20]. But, as there has been no data reported about the sublimation and crystal lattice energy, fluoroquinolone solvation parameters have not been investigated. Besides, it should be mentioned that the crystal lattice energy of a drug is of primary importance in pharmaceutics, crystal engineering and modeling because it affects chemical, physical and biological properties of a drug [21].

The aim of the present work was, first of all, to determine the crystal lattice energy of the drug compounds belonging to the fluoroquinolone group with different types and positions of substituents and, secondly, to find a correlation between the physico-chemical properties of the substances and the crystal structure. This work is a continuation of our studies of physico-chemical properties of drug and drug-like compounds in the solid state and in solution [22,23].

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2. Experimental

2.1. Materials

Ciprofloxacin, enrofloxacin, norfloxacin and levofloxacin were obtained from commercial sources. The origin, CAS numbers and purity of all samples are presented in Table 1.

2.2. Differential scanning calorimetry

Fusion temperatures and enthalpies of the compounds under investigation have been determined using a Perkin-Elmer Pyris 1 DSC differential scanning calorimeter (Perkin-Elmer Analytical Instruments, Norwalk, Connecticut, USA) with Pyris software for Windows NT. DSC runs were performed in an atmosphere of flowing dry helium gas (20 cm^3 min^{-1}) of high purity 0.99996 (mass fraction) using standard aluminum sample pans and a heating rate of 2 K min^{-1}. The accuracy of weight measurements was 0.005 mg. The DSC was calibrated with an indium sample from Perkin-Elmer (P/N 0319-0033). The value determined for the enthalpy of fusion corresponded to 28.48 J g^{-1} (reference value 28.45 J g^{-1}). The fusion temperature was 429.5 ± 0.1 K (determined by at least ten measurements).

2.3. Vapor pressures measurements

Sublimation experiments were carried out by the transpiration method. This method consists in passing a stream of an inert gas over a sample at a constant flow rate and temperature, the rate being low enough to practically achieve the saturation state of the gas with the substance's vapor. Then the vapor is condensed and the sublimed quantity determined. The vapor pressure over the sample at this temperature can be calculated from the amount of the sublimed material and the volume of the inert gas used.

Details of the technique are given in the literature [24]. The inert gas (nitrogen) from the tank flows through a column packed with silica to adsorb any water vapor. The gas temperature is stabilized in a water thermostat. The stability of the gas flow with the precision over 0.01% is maintained by using a mass flow controller MKS type 1259CC-00050SU. The inert gas of constant temperature and velocity passes then to the glass tube, which is placed in an air thermostat. Three zones of the glass tube can be distinguished: a starting zone for inert gas stabilization; a transitional zone in which the sublimation process takes place ensuring slow sublimation of the investigated substance, and the finishing zone in which the inert gas together with the sublimated substance is overheated by 4–5 K, controlled by a platinum resistance thermometer. The determined temperature of the air thermostat is kept constant with a precision of 0.01 K by the temperature controller PID type 650 H UNIPAN equipped with a resistance thermometer. The finishing zone is coupled with a condenser built from glass helix, placed outside the thermostat located in a Dewar vessel filled with liquid nitrogen.

The equipment was tested with benzoic acid (V). The vapor pressure values were measured in the temperature range of 307–355 K. We obtained the following values of the vapor pressure at a fixed temperatures: p = 0.285 Pa (T = 307.15 K); p = 1.674 Pa (T = 323.15 K); p = 7.513 Pa (T = 338.15 K); p = 31.599 Pa (T = 354.15 K). Relative standard uncertainty for experimental pressure $u_r(p) = 0.05$. The standard value of the sublimation enthalpy obtained in our experiments was $\Delta^g_{cr}H^o_m = 90.5 \pm 0.3$ kJ mol^{-1}. This is in good agreement with the value recommended by IUPAC ($\Delta^g_{cr}H^o_m = 89.7 \pm 0.5$ kJ mol^{-1}) [25].

From the experimentally determined pressure – flow rate relationship, the optimal flow rate of 1.2–1.8 dm^3 h^{-1} has been identified. At this flow rate, the saturated vapor pressure is independent of the flow rate and, thus, the thermodynamic equilibrium is realized.

The amount of sublimated substance is determined by following procedure. The condensed substance is dissolved in a defined volume of solvent V_{sol}. The determination of the mass of the substance is based on the measuring of absorbance A of its solution by means of spectrophotometer Cary-50 (Varian, USA) with an accuracy of 2–4%. Knowing a value of the extinction coefficient ε (dm^3 mol^{-1} cm^{-1}) of the studied compound dissolved in the solvent one can express the concentration of the solution c (mol dm^{-3}) according to the Lambert-Beer law, by the following relation:

$$A = \varepsilon c l \quad (1)$$

whereas the mass of sublimated substance is calculated from:

$$m = c V_{sol} M \quad (2)$$

where l is an absorbing path length; M is a molar mass of studied substance. The time required for each experiment ranged from 2 to 6 h depending on the selected temperature. The mass of sublimated substance per hour was (0.1–1.0) 10^{-2} mg which is two orders lower than for benzoic acid.

Each experiment was repeated five times at a fixed temperature with the standard deviation of up to 5%. Assuming the sublimation enthalpy to be independent of temperature the experimentally determined vapor pressure data may be described in the following way:

$$\ln(\rho/\mathrm{Pa}) = A + B/T \quad (3)$$

The value of the sublimation enthalpy at the mean temperature T was calculated by the Clausius–Clapeyron equation:

Table 1
Source, CAS numbers and purity of compounds studied.

Compound	Chemical name	CAS register No.	Source	Initial mass fraction purity	Method purification	Final mass fraction purity	Analysis method
I	Ciprofloxacin	85721-33-1	Acros	⩾0.98	Sublimation	0.995	Gas chromatography
II	Enrofloxacin	93106-60-6	Sigma-Aldrich	⩾0.98	Sublimation	0.995	Gas chromatography
III	Norfloxacin	70458-96-7	Acros	⩾0.98	Sublimation	0.994[a] (0.992)[b]	Gas chromatography Thermogravimetric analysis
IV	Levofloxacin	100986-85-4	Sigma-Aldrich	⩾0.98	Sublimation	0.995[a] (0.969)[b]	Gas chromatography Thermogravimetric analysis
V	Benzoic acid	242381	Sigma-Aldrich	⩾0.995	–	–	–

[a] Purity for anhydrous forms of compounds.
[b] Purity of compounds considering water content.