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Studying thermodynamic aspects of sublimation, solubility and solvation processes and crystal structure analysis of some sulfonamides

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Abstract

Crystal structures of *N*-(2-chlorophenyl)-benzene-sulfonamide (**I**), *N*-(2,3-dichlorophenyl)-benzene-sulfonamide (**II**), *N*-(4-chlorophenyl)-benzene-sulfonamide (**III**) were solved by X-ray diffraction method. Temperature dependencies of saturated vapor pressure and thermodynamic functions of sublimation process were calculated (**I**: $\Delta G^{298}_{sub} = 50.4$ kJ mol^{-1}; $\Delta H^{298}_{sub} = 114 \pm 1$ kJ mol^{-1}; $\Delta S^{298}_{sub} = 213 \pm 3$ J mol^{-1} K^{-1}; **II**: $\Delta G^{298}_{sub} = 54.1$ kJ mol^{-1}; $\Delta H^{298}_{sub} = 124.9 \pm 1.6$ kJ mol^{-1}; $\Delta S^{298}_{sub} = 237 \pm 5$ J mol^{-1} K^{-1}; **III**: $\Delta G^{298}_{sub} = 49.9$ kJ mol^{-1}; $\Delta H^{298}_{sub} = 98.6 \pm 1.9$ kJ mol^{-1}; $\Delta S^{298}_{sub} = 163 \pm 5$ J mol^{-1} K^{-1}). Thermochemical parameters of fusion process for the compounds were obtained. Enthalpies of evaporation were estimated from enthalpies of sublimation and fusion. Temperature dependencies of the solubility in water, *n*-octanol and *n*-hexane were measured. The thermodynamic functions of solubility and solvation processes were deduced. Specific and non-specific solvation terms were distinguished using the transfer from the "inert" *n*-hexane to the other solvents. The transfer processes of the molecules from water to *n*-octanol were analyzed and main driven forces were established.

Keywords: *N*-(2-Chlorophenyl)-benzene-sulfonamide; *N*-(2,3-Dichlorophenyl)-benzene-sulfonamide; *N*-(4-Chlorophenyl)-benzene-sulfonamide; Sublimation thermodynamics; Solubility; Solvation; Crystal structure; Specific and non-specific interactions; Transfer process

1. Introduction

Sulfonamides are drugs extensively used for the treatment of certain infections caused by Gram-positive and Gram-negative microorganisms, some fungi, and certain protozoa. Although the advent of antibiotics has diminished the usefulness of sulfonamides, they still occupy a relatively small but important place in the therapeutic resources of physicians. It should be mentioned, that there are some attempts to correlate different physico-chemical characteristics of these compounds with chemotherapeutic activity: pK_a, protein binding, and electronic charge distribution (Korolkovas, 1988; Mandell and Sande, 1992). Unfortunately, the action of sulfonamides is complicated and cannot be described in a simple way. There is not enough information to propose suitable mechanisms for the transfer process of sulfonamides between immiscible liquid phases, and between aqueous media and biological membrane models, in order to explain the differences in the pharmacological power as a function of the molecular structure (Ucucu et al., 1995). Moreover, due to lack of thermodynamic sublimation data of the outlined class of compounds, analysis of solvation parameters of the drugs has not been carried out yet.

One of the key issues in drug design is to let the molecules actually reach their target. Each stage of the processes involved,

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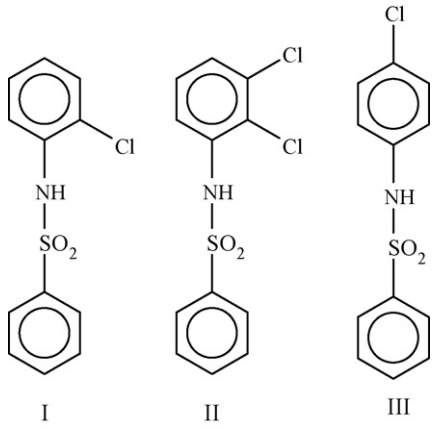


Scheme 1.

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 (Perlovich and Bauer-Brandl, 2004; Perlovich et al., 2005; Perlovich et al., 2006), 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.

As a subject of this investigation three compounds have been chosen: *N*-(2-chlorophenyl)-benzene-sulfonamide (**I**), *N*-(2,3-dichlorophenyl)-benzene-sulfonamide (**II**), *N*-(4-chlorophenyl)-benzene-sulfonamide (**III**) (Scheme 1). Analysis of the literature data has shown, that these compounds are not described in the literature with point of view neither of studying thermodynamics of solubility and solvation processes (Martinez and Gomez, 2001; Martinez and Gomez, 2002a; Martinez and Gomez, 2002b; and references within), nor of characterization of crystal structures (Adsmond and Grant, 2001 and references therein). Moreover, the outlined substances are interesting with a point of view on fundamental aspects of the influence of nature and position of the substituent (in this case Cl-group) on: (a) architecture of crystal lattice; (b) geometry and topology of hydrogen bond networks; (c) energetics of the crystal lattices; (d) thermodynamics of solubility and partitioning processes in pharmaceutically relevant solvents.

2. Material and methods

2.1. Compounds and solvents

The chemical synthesis of *N*-(2-chlorophenyl)-benzene-sulfonamide (**I**), *N*-(2,3-dichlorophenyl)-benzene-sulfonamide (**II**) and *N*-(4-chlorophenyl)-benzene-sulfonamide (**III**) has been performed in analogy to procedures described in papers of (Crosley et al., 1940; Anderson et al., 1942; Gutsche et al., 1974) by reaction of a substituted aromatic amine (here chloroaniline) with benzenesulfonyl chloride in dry pyridine, followed by precipitation of the end product by pouring the reaction mixture into water and by acidification to pH ~ 5. The compounds have been carefully purified by re-crystallization from water–ethanol solution. The initial substances have been dissolved in ethanol in order to get saturated solutions. After that the water has been added until occurrence of a white precipitation. The precipitate has been filtered and dried at room temperature under vacuum until the mass was constant. The outlined procedure has been repeated several times with carrying out of NMR experiments after each re-crystallization stage until the NMR signal of the impurities protons corresponded to purity of the compound better than 99%.

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).

2.2. Solubility determination

All the experiments were carried out by the isothermal saturation method at five temperature points: 20, 25, 30, 37, 42 ± 0.1 °C. The solid phase was removed by isothermal filtration (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size) or centrifugation (Biofuge pico). The experimental results are stated as the average of at least three replicated experiments. The molar solubilities of the drugs were measured spectrophotometrically with an accuracy of 2–2.5% using a protocol described previously (Perlovich and Brandl-Bauer, 2003).

Standard Gibbs energies of the dissolution processes ΔG°_{sol} were calculated using the following equation:

$$\Delta G^{\circ}_{sol} = -RT \ln X_2 \quad (1)$$

where X_2 is the drug molar fraction in the saturated solution. The standard solution enthalpies ΔG°_{sol} were calculated using the van't Hoff equation:

$$\frac{d(\ln X_2)}{dT} = \frac{\Delta H^{\circ}_{sol}}{RT^2} \quad (2)$$

assuming that the activity coefficients of the considered drugs in the solvents are equal to one and solution enthalpies are independent of concentration. The temperature dependencies of the solubilities of the drugs within the chosen temperature interval can be described by a linear function:

$$\ln X_2 = A - \frac{B}{T} \quad (3)$$

This indicates that the change in heat capacity of the solutions with the temperature is negligibly small.

The standard solution entropies ΔG°_{sol} were obtained from the well-known equation:

$$\Delta H^{\circ}_{sol} = \Delta H^{\circ}_{sol} - T\Delta S^{\circ}_{sol} \quad (4)$$

2.3. Sublimation experiments

Sublimation experiments were carried out by the transpiration method as was described elsewhere (Zielenkiewicz et al., 1999). In brief: a stream of an inert gas passes above the sample

at a constant temperature and at a known slow constant flow rate in order to achieve saturation of the carrier gas with the vapor of the substance under investigation. The vapor is condensed at some point downstream, and the mass of sublimate and its purity determined. The vapor pressure over the sample at this temperature can be calculated from the amount of sublimated sample and the volume of the inert gas used.

The equipment was calibrated using benzoic acid. The standard value of sublimation enthalpy obtained here 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} (Cox and Pilcher, 1970). The saturated vapor pressures were measured at each temperature five times with the standard deviation being within 3–5%. Because the saturated vapor pressure of the investigated compounds is low, it may be assumed that the heat capacity changes of the vapor with temperature is so small that it can be neglected. The experimentally determined vapor pressure data may be described in ($\ln P$; $1/T$) co-ordinates in the following way:

$$\ln(P) = A + \frac{B}{T} \quad (5)$$

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

$$\Delta H^{T}_{sub} = RT^2 \frac{\partial(\ln P)}{\partial T} \quad (6)$$

whereas, the entropy of sublimation at a given temperature T was calculated by the following relation:

$$\Delta S^{T}_{sub} = \frac{\Delta H^{T}_{sub} - \Delta G^{T}_{sub}}{T} \quad (7)$$

with $\Delta G^{T}_{sub} = -RT \ln(P/P_0)$, where P_0 is the standard pressure of 1.013×10^5 Pa.

For experimental reasons the sublimation data were obtained at elevated temperatures. However, in comparison to fusion methods, the temperatures are much lower, which makes extrapolation to room conditions easier. In order to further improve the extrapolation to room conditions, heat capacities ($C^{298}_{p,cr}$ − value) of the crystals were estimated using the additive scheme proposed by Chickos and Acree (2002). The heat capacity was introduced as a correction for the recalculation of the sublimation enthalpy ΔH^{T}_{sub} − value at 298 K (ΔH^{298}_{sub} − value), according to Eq. (8) (Chickos and Acree, 2002) (the procedure of calculation of $C^{298}_{p,cr}$ values is presented in Table 4):

$$\Delta H^{298}_{sub} = \Delta H^{T}_{sub} + \Delta H_{cor} = \Delta H^{T}_{sub} + (0.75 + 0.15C^{298}_{p,cr})\ (T - 298.15) \quad (8)$$

2.4. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was carried out 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 (20 ml min^{-1}) dry helium gas of high purity 99.996% using standard aluminium sample pans and a heating rate of 10 K min^{-1}. The accuracy of weight measurements was ±0.0005 mg. The DSC was calibrated with the indium 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 melting point was 156.5 ± 0.1 °C ($n = 10$). The enthalpy of fusion at 298 K was calculated by the following equation:

$$\Delta H^{298}_{fus} = \Delta H_{fus} - \Delta S_{fus}(T_m - 298.15) \quad (9)$$

where the difference between heat capacities of the melt and solid states has been approximated by entropy of fusion (as an upper estimate). This approach has been used by Dannenfelser and Yalkowsky (1999) and Verevkin and Schick (2004).

The enthalpy of vaporization has been calculated as:

$$\Delta H^{298}_{vap} = \Delta H^{298}_{sub} - \Delta H^{298}_{fus} \quad (10)$$

2.5. X-ray diffraction experiments

Single-crystal X-ray measurements were carried out using a Nonius CAD-4 diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). Intensity data were collected at 25 °C by means of a ω–2θ scanning procedure. The crystal structures were solved using direct methods and refined by means of a full-matrix least-squares procedure. CAD-4 Software (1989) was applied for data collection, data reduction and cell refinement. Programs SHELXS-97 and SHELXL-97 (Sheldrick, 1997) were used to solve and to refine structures, respectively.

3. Results and discussion

3.1. Crystal structure analysis

Before discussing thermodynamic characteristics of **I**–**III**, a detailed description of their crystal structures is needed. The X-ray diffraction experiment was carried out at 293(2) K. The results of the experiments are presented in Table 1.

In order to characterize conformational states of the molecules a view of **I**–**III** molecules with the atomic numbering is shown on Fig. 1a–c, respectively. Based on the presented numbering a comparative analysis of both conformational states of the molecules and geometric parameters of the hydrogen bonds may be carried out. The results are summarized in Table 2.

Differences of conformational states of the molecules in the crystal lattices can be characterized in the following way. The angle between SO_2-group and the phenyl motif Ph1 (C1–C2–C3–C4–C5–C6) ∠O1–S–C1–C2 can be arranged as: **I** < **II** < **III**. The angle ∠N1–S–C1–C2 (describing orientation of NH-group relative to Ph1) is essentially less for **III** in comparison with **I** and **II**. Thus, it may be noted, that introducing an additional Cl-substituent in meta-position of the second phenyl motif (compounds **II** and **I**) does not promote a noticeable change in orientation of SO_2- and NH-groups with respect to Ph1. However, the discussed parameters are different from each other for the substituents situated at ortho- (**I**) and para- (**II**) positions. The second phenyl ring Ph2 (C7–C8–C9–C10–C11–C12)

Table 1
Crystal lattice parameters of the substances under investigation[a]

	I	II	III
Crystal data	Perlovich et al. (2006a)	Tkachev et al. (2006)	Perlovich et al. (2006b)
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/a$	$P2_1/c$	$Pbca$
Description	Colourless prism	Colourless prism	Colourless prism
Crystal size (mm)	$0.4 \times 0.3 \times 0.2$	$0.28 \times 0.2 \times 0.11$	$0.5 \times 0.4 \times 0.1$
a (Å)	14.821(3)	8.466(1)	10.840(2)
b (Å)	9.656(2)	9.805(1)	9.740(1)
c (Å)	8.365(2)	15.876(2)	23.596(3)
β (°)	92.46(3)	92.10(1)	90.00
Volume (Å^3)	1196.0(4)	1317.0(3)	2491.3(6)
Z	4	4	8
D_{calc} (g cm^{-3})	1.487	1.524	1.428
Radiation	Mo Kα	Mo Kα	Mo Kα
T (K)	293(2)	293(2)	293(2)
μ (mm^{-1})	0.48	0.64	0.46
Data collection			
Measured reflections	2262	2824	1838
Independent reflections	2108	2022	1838
Independent reflections with $>2\sigma(I)$	1727	1152	1568
R_{int}	0.027	0.042	
θ_{max} (°)	25.1	25.0	23.5
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$	0.035	0.049	0.038
$\omega R(F^2)$	0.100	0.103	0.127
S	1.05	1.00	1.15
Reflections	2108	2022	1838
Parameters	194	167	158
$(\Delta/\sigma)_{max}$	0.001	0.001	0.001
$\Delta\rho_{max}$ (e Å^{-3})	0.33	0.24	0.41
$\Delta\rho_{min}$ (e Å^{-3})	−0.26	−0.21	−0.34

[a] Brackets display the standard deviations.

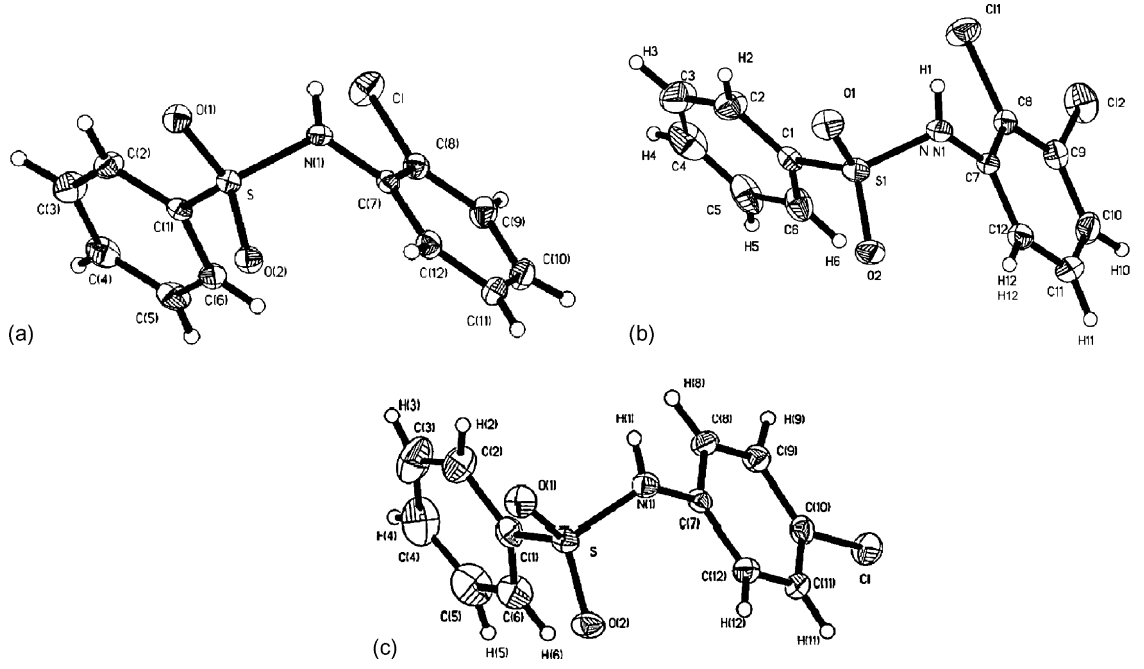


Fig. 1. A view of **I** (a), **II** (b) and **III** (c) molecules with the atomic numbering.

Table 2
Some parameters, which characterize of the conformational states and hydrogen bond geometry of molecules **I–III** in the crystal lattice

	I	**II**	**III**
∠O1–S–C1–C2 (°)	5.83(19)	7.4(4)	30.7(4)
∠N1–S–C1–C2 (°)	−108.50(17)	−106.8(3)	−83.5(3)
∠S–N1–C7–C12 (°)	−68.3(2)	−63.8(4)	−71.1(4)
∠Ph1–Ph2 (°)	49.14(9)	54.8(2)	54.39(15)

	Hydrogen bond geometry				
	D–H···A[a]	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
I	N1–H1···O2^{i}	0.75(2)	2.26(2)	2.994(2)	167(2)
II	N1–H1···O2^{ii}	0.76(4)	2.30(4)	3.039(4)	166(4)
III	N1–H1···O2^{iii}	0.78(3)	2.21(3)	2.993(4)	175(4)

[a] Symmetry code: (i) 3/2 − *x*, *y* − 1/2, 1 − *z*; (ii) 2 − *x*, *y* − 1/2, 3/2 − *z*; (iii) 1/2 − *x*, *y* − 1/2, *z*.

is turned relatively to the NH-group in the following way (absolute value of the torsion angles) ∠S–N1–C7–C12: **II** < **I** < **III**. The phenyl fragments are rotated relatively to each other by 49.14(9)° (**I**) < 54.39(15)° (**III**) < 54.8(2)° (**II**). It is not difficult to see, that the location of a Cl-atom in para-position (**III**) in comparison with ortho- (**I**) leads to a stronger turn of the phenyl fragment (this angle is a characteristic of conformational flexibility of the –SO_2–NH– bridge, which connects the two phenyl rings). It is interesting to note, that the introduction of an additional Cl-substituent in meta-position (compare **I** and **II**) leads to a considerable change of this angle. Probably due to packing energy, the conformational state of the bridge is very sensitive to the presence of substituents at the periphery region of Ph2 (meta- and para-positions) in contrast to ortho-position.

Each molecule of the outlined crystal structures has one hydrogen bond: N1–H1···O2^{i}. Comparative characteristics of the hydrogen bonds geometric parameters are summarized in Table 2. As follows from Table 2, the hydrogen bonds of **III** are more planar than those of **I** and **II**. If we suppose that the H1···O2^{i} distance characterizes the strength of hydrogen bonding, then the substances can be arranged in the following way (increasing hydrogen bond energy): **II** < **I** < **III**.

The molecular packing architectures of the noted crystal lattices are different (Fig. 2a–c). The molecules of **I** form chains with adjacent molecules by means of the above described hydrogen bonds. The hydrogen bonds create infinite helicoids along the OY-axis. The hydrogen bond network can be described by the graph set assignment introduced by Etter (1990) as C4 (infinite chain with four involved atoms). In one turn the chains of the molecules interact with adjacent chains only by van der Waals forces between approximately coplanar chlorophenyl fragments. It should be mentioned, that the unsubstituted phenyl rings of the molecules are arranged approximately coplanar to the analogous fragments of the neighbours.

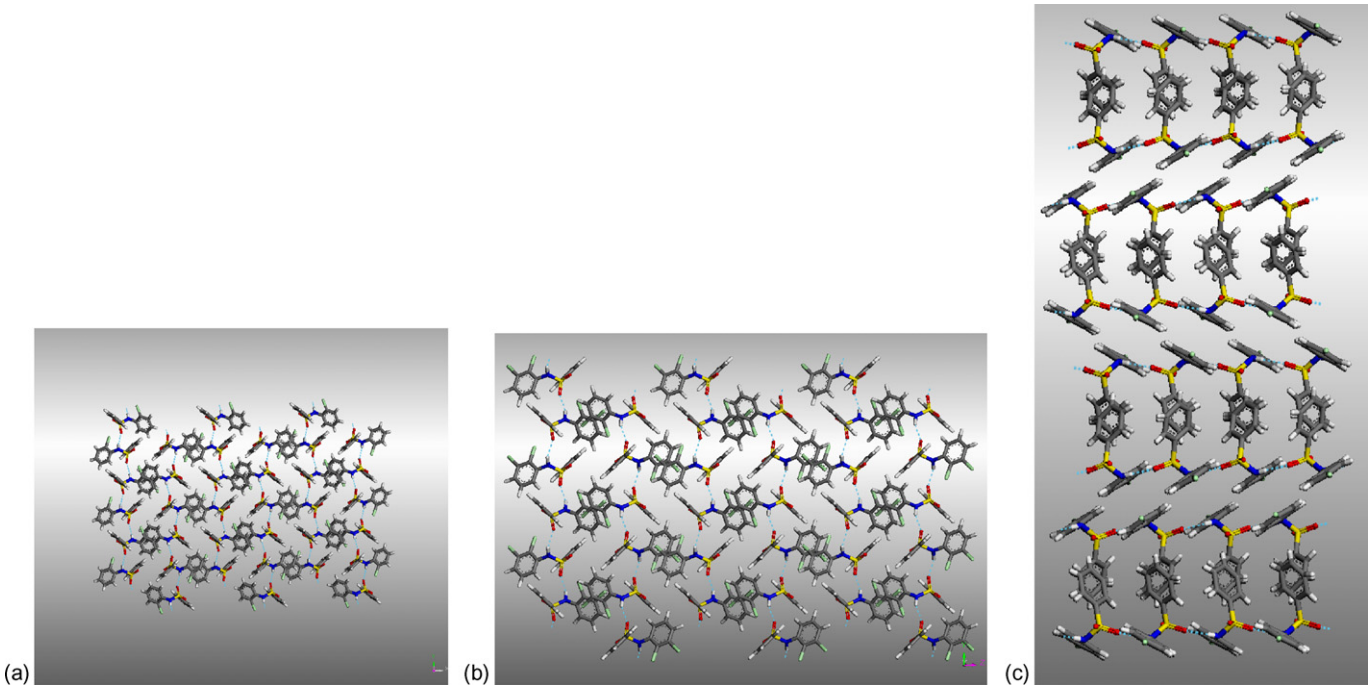


Fig. 2. Molecular packing architectures of **I** (a), **II** (b) and **III** (c) crystal lattices.

Table 3
Temperature dependencies of saturation vapor pressure of compounds **I–III**

I[a]		**II**[b]		**III**[c]	
T (°C)	P (Pa)	T (°C)	P (Pa)	T (°C)	P (Pa)
50.0	5.14×10^{-3}	55.0	3.06×10^{-3}	54.0	6.87×10^{-3}
54.0	8.65×10^{-3}	56.0	3.35×10^{-3}	58.0	9.10×10^{-3}
57.0	1.32×10^{-2}	58.0	4.80×10^{-3}	60.0	1.32×10^{-2}
59.0	1.83×10^{-2}	62.0	8.40×10^{-3}	63.0	1.53×10^{-2}
61.5	2.25×10^{-2}	65.0	1.29×10^{-2}	65.5	2.02×10^{-2}
62.5	2.63×10^{-2}	68.0	2.09×10^{-2}	68.0	2.60×10^{-2}
66.0	4.00×10^{-2}	70.0	2.60×10^{-2}	71.0	3.34×10^{-2}
68.0	5.29×10^{-2}	71.0	2.76×10^{-2}	73.0	4.69×10^{-2}
70.0	5.96×10^{-2}	73.5	3.69×10^{-2}	75.0	5.50×10^{-2}
71.0	6.72×10^{-2}	76.0	5.08×10^{-2}	79.0	7.43×10^{-2}
73.0	9.44×10^{-2}	78.0	6.86×10^{-2}	80.0	9.07×10^{-2}
74.0	8.80×10^{-2}	82.0	7.81×10^{-2}	82.5	1.16×10^{-1}
76.0	1.22×10^{-1}	83.0	1.11×10^{-2}	87.0	1.70×10^{-1}
77.0	1.27×10^{-1}	85.0	1.42×10^{-1}		
80.0	1.88×10^{-1}	88.0	2.17×10^{-1}		
82.0	2.42×10^{-1}	89.0	2.10×10^{-1}		
85.0	3.61×10^{-1}	90.5	2.78×10^{-1}		
86.0	3.40×10^{-1}	94.0	3.83×10^{-1}		
89.5	5.12×10^{-1}	96.0	5.08×10^{-1}		
92.0	6.54×10^{-1}				
94.0	8.44×10^{-1}				

[a] $\ln(P\ (\text{Pa})) = (36.7 \pm 0.3) - (13562 \pm 119)/T$; $\sigma = 5.64 \times 10^{-2}$; $r = 0.9993$; $F = 13079$; $n = 21$.
[b] $\ln(P\ (\text{Pa})) = (39.5 \pm 0.6) - (14844 \pm 198)/T$; $\sigma = 9.02 \times 10^{-2}$; $r = 0.9984$; $F = 5605$; $n = 19$.
[c] $\ln(P\ (\text{Pa})) = (30.6 \pm 0.7) - (11684 \pm 228)/T$; $\sigma = 6.80 \times 10^{-2}$; $r = 0.9978$; $F = 2622$; $n = 13$.

The molecular packing architecture of **II** (Fig. 2b) is similar to **I**. First of all, the hydrogen bonds create helicoids, which are oriented along the OY-axis with C4 graph set assignment. Secondly, the discussed molecular chains of both structures interact with each other by van der Waals forces only.

The molecules of **III** form chains by hydrogen bonds with adjacent molecules (Fig. 2c). The hydrogen bonds topology is analogous to the one described above and creates infinite helicoids along the OY-axis with C4 graph set assignment. The chains form a complex layer structure, which can be characterized as follows. In contrast to the previous structure, the layer includes two types of chains which are situated in such way that the periphery consists of the chlorophenyl motifs, whereas, the inside part of the unsubstituted phenyl rings. The chlorophenyl fragments of the adjacent layers are approximately parallel and interact with each other only by van der Waals forces. The unsubstituted phenyl ring of the considered molecules interact with each other by van der Waals forces as well, but due to non coplanar arrangement the energy of these interactions is lower to the analogous one for the chlorophenyl fragments. These conclusions are confirmed by the sublimation data presented below.

3.2. Sublimation characteristic

The temperature dependencies of saturated vapor pressure of the considered compounds are shown in Table 3. The thermodynamic functions of the drugs sublimation, fusion and vaporization processes are presented in Table 4.

Table 4
Thermodynamic characteristics of processes of sublimation, fusion and vaporization of the studied compounds

	I	**II**	**III**
$\Delta G^{298}_{\text{sub}}$ (kJ mol^{-1})	50.4	54.1	49.9
$\Delta H^{\text{T}}_{\text{sub}}$ (kJ mol^{-1})	113 ± 1	123.4 ± 1.6	97.3 ± 1.9
$\Delta H^{298}_{\text{sub}}$ (kJ mol^{-1})	114 ± 1	124.9 ± 1.6	98.6 ± 1.9
$C^{298}_{\text{p,cr}}$ (J K^{-1} mol^{-1})[a]	301.9	322.2	301.9
$T\Delta S^{298}_{\text{sub}}$ (kJ mol^{-1})	63.6	70.8	48.7
$\Delta S^{298}_{\text{sub}}$ (J K^{-1} mol^{-1})	213 ± 3	237 ± 5	163 ± 5
ς_H (%)[b]	64.2	63.8	66.9
ς_{TS} (%)[b]	35.8	36.2	33.1
T_{m} (K)	398.2 ± 0.2	387.2 ± 0.2	394.6 ± 0.2
$\Delta H^{\text{T}}_{\text{fus}}$ (kJ mol^{-1})	33.5 ± 0.5	27.2 ± 0.5	25.8 ± 0.5
$\Delta H^{298}_{\text{fus}}$ (kJ mol^{-1})	25.1	21.0	19.5
$\Delta S^{\text{T}}_{\text{fus}}$ (J K^{-1} mol^{-1})[c]	84 ± 2	70 ± 2	65 ± 2
$\Delta H^{298}_{\text{vap}}$ (kJ mol^{-1})	88.9	103.9	79.1

[a] $C^{298}_{\text{p,cr}}$ has been calculated by additive scheme with the following group values (in J K^{-1} mol^{-1}): C_{p}(–SO$_2$–) = 88.7; C_{p}(internal quaternary aromatic = C–) = 9.1; C_{p}(tertiary aromatic C sp^3 = C$_a$H–) = 17.5; C_{p}(–NH–) = –0.3; C_{p}(–Cl) = 28.7; the error of the calculation procedure corresponds to significant digit.
[b] $\zeta_H = (\Delta H^{298}_{\text{sub}}/(\Delta H^{298}_{\text{sub}} + T\Delta S^{298}_{\text{sub}})) \times 100\%$;
$\zeta_{TS} = (T\Delta S^{298}_{\text{sub}}/(\Delta H^{298}_{\text{sub}} + T\Delta S^{298}_{\text{sub}})) \times 100\%$.
[c] $\Delta S_{\text{fus}} = \Delta H_{\text{fus}}/T_{\text{m}}$.

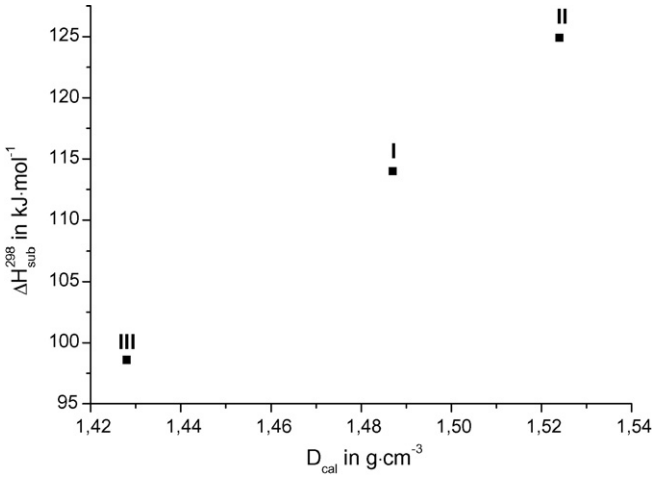


Fig. 3. Dependence between the sublimation enthalpies (ΔH^{298}_{sub}) and the calculated densities of molecules in the crystal lattices (D_{cal}) of the compounds.

It should be noted that the crystal lattice energies of the compounds are essentially different. For example, replacement of the Cl-substituent from ortho- to para-position leads to a decrease of the crystal lattice energy from 114 to 98.6 kJ mol^{-1}. As follows from X-ray diffraction experiments, the architecture of the crystal lattices is quite different (Fig. 2a and c) and, in consequence, this fact influences the outlined values essentially (around 15 kJ mol^{-1}). It is interesting to mention that introduction of the second Cl-substituent in the meta-position of the phenyl ring of **II** leads to an increase of crystal lattice energy by approximately 11 kJ mol^{-1}. So it may be concluded that the energetic scale of influence of the considered substituent on the crystal lattice energy is comparable in both the position and addition amount of the substituent. From Table 4 it follows as well, that the sublimation process for the compounds is enthalpy controlled. However, the contribution of the enthalpy term of the substance **III** to the energetic process is higher in comparison with the other ones.

It is interesting to note, that a correlation is observed between the experimental sublimation enthalpy values and the calculated values of the crystal lattice density (Fig. 3). Probably, this fact can be explained by the predominating van der Waals packing term in comparison to the hydrogen bonding energy (where the last term is approximately the same for the considered compounds).

3.3. Solubility and solvation thermodynamics

The temperature dependencies of solubility of the three sulfonamides in water, *n*-hexane and *n*-octanol solutions are summarized in Table 5. The thermodynamic functions of the drugs solubility process in the solutions at 25 °C are presented in Table 6.

Firstly, the compounds under investigation can be arranged by increasing solubility in the solvents in the following way: water < *n*-hexane < *n*-octanol. Secondly, the solution enthalpies for all substances have positive values, and it means that the

Table 5
The temperature dependencies of solubility, X_2 (mol fraction), of compounds **I**–**III** in water, *n*-hexane and *n*-octanol

T (°C)	**I**			**II**			**III**		
	Water ($X_2 \times 10^7$)	*n*-Hexane ($X_2 \times 10^6$)	*n*-Octanol ($X_2 \times 10^3$)	Water ($X_2 \times 10^7$)	*n*-Hexane ($X_2 \times 10^5$)	*n*-Octanol ($X_2 \times 10^2$)	Water ($X_2 \times 10^6$)	*n*-Hexane ($X_2 \times 10^7$)	*n*-Octanol ($X_2 \times 10^3$)
17	–	–	2.39	–	–	1.07	–	–	3.32
18	–	5.62	–	–	3.47	–	–	8.74	–
20	7.52	5.96	2.75	3.46	3.79	1.21	1.37	9.56	3.71
25	8.64	7.73	3.60	4.06	4.92	1.41	1.68	13.7	4.21
30	9.43	10.1	4.26	4.89	6.13	1.66	2.24	20.7	5.16
37	10.2	14.4	5.72	6.32	8.52	1.95	3.22	34.7	6.31
42	11.6	17.2	–	7.74	10.9	–	3.94	45.1	–
A[a]	−8.1 ± 0.3	3.1 ± 0.4	7.5 ± 0.4	−3.3 ± 0.3	4.7 ± 0.2	4.8 ± 0.4	2.0 ± 0.5	8.4 ± 0.6	6.7 ± 0.4
B[a]	1762 ± 96	4437 ± 111	3926 ± 129	3400 ± 91	4369 ± 54	2709 ± 125	4564 ± 163	6512 ± 179	2929 ± 128
R[b]	0.9955	0.9988	0.9984	0.9989	0.9967	0.9968	0.9981	0.9985	0.9972
σ[c]	1.85×10^{-2}	2.57×10^{-2}	2.28×10^{-2}	1.74×10^{-2}	1.25×10^{-2}	2.215×10^{-2}	3.14×10^{-2}	4.15×10^{-2}	2.267×10^{-2}

[a] Parameters of the correlation equation: $\ln X_2 = A - B/T$.
[b] Pair correlation coefficient.
[c] Standard deviation.

Table 6
Thermodynamic solubility functions of the studied drugs in *n*-hexane, water and *n*-octanol solutions at 298 K

Drugs	X_2	ΔG°_{sol} (kJ mol^{-1})	ΔH°_{sol} (kJ mol^{-1})	$T\Delta G^{\circ}_{sol}$ (kJ mol^{-1})	ΔS°_{sol} (J K^{-1} mol^{-1})
n-Hexane					
I	7.73×10^{-6}	29.2	36.9 ± 0.9	7.7	25.8
II	4.92×10^{-5}	24.6	36.4 ± 0.4	11.8	39.6
III	1.37×10^{-6}	33.5	54.1 ± 1.5	20.6	69.1
Water					
I	8.64×10^{-7}	34.6	14.6 ± 0.8	−20.0	−67 ± 3
II	4.06×10^{-7}	36.4	28.3 ± 0.8	−8.1	−27 ± 2
III	1.68×10^{-6}	33.0	37.9 ± 1.4	4.9	17 ± 2
n-Octanol					
I	3.6×10^{-3}	13.9	33 ± 1	19.1	64.1
II	1.41×10^{-2}	10.6	23 ± 1	12.4	41.6
III	4.21×10^{-2}	7.85	24 ± 1	16.15	54.2

crystal lattice energy outweighs the solvation energy. It is interesting to note, that entropies of solubility in water have opposite sign (negative) in comparison with the analogous values for *n*-hexane and *n*-octanol. Probably, in water the observed ranking of the solubility process is due to hydrophobic effects in comparison with other solvents. It is not difficult to see that the entropic term of the solubility process (in absolute value) is lower than the enthalpic one (with exception for compound **I** in water). This fact confirms that the solubility process for the substances is enthalpy controlled.

In order to estimate the interaction of the drugs with the solvents on the absolute energy scale, solvation thermodynamic functions have been calculated for the compounds. The thermodynamic functions of solvation processes for the studied compounds in *n*-hexane, water and *n*-octanol at 298 K are presented in Table 7. The interaction of the substances with the solvents (ΔH°_{solv}) can be arranged (by decreasing absolute values) as follows: *n*-octanol > water > *n*-hexane. Thus, the substances interact with "inert" solvent molecules (*n*-hexane) on a lower level than with solvents having specific centers of interactions (*n*-octanol and water). In order to compare contributions of enthalpic and entropic solvation terms the parameters $\zeta_{H_{solv}}$ and $\zeta_{TS_{solv}}$ have been introduced (Perlovich and Bauer-Brandl, 2004) (Table 7). From analysis of these values it follows, that the enthalpic term is the dominant contribution to the solvation Gibbs energy. Nevertheless, it should be mentioned, that the entropic term in water is essentially higher than the analogous terms in *n*-hexane and *n*-octanol. This fact is a consequence of hydrophobic effects. If the contribution of enthalpic (entropic) solvation terms is taken into account, then *n*-hexane is situated between *n*-octanol and water for the considered compounds.

The strength of specific interactions may be estimated by a transfer procedure from a solvent, which interacts with solute molecules only by non-specific forces, to considered solvent (*n*-hexane → *n*-octanol (water)). The thermodynamic functions of transfer process from *n*-hexane to the solvents are summarized in Table 8. It is not difficult to see, that the ΔH_{tr} and $T\Delta S_{tr}$ functions have a negative sign in water for these substances. Moreover, the enthalpic terms of **I** and **II** outweigh the entropic ones, whereas, the discussed terms of **III** are practically coincident. Thus, specific interactions of **I** and **II** compounds with water molecules occur with changing of ordering (entropy) of the system, whereas, for **III** the both terms make approximately equivalent contribution. If **I** and **III** are compared, then, probably, the location of the Cl-substituent in para-position of Ph2 has an essential influence on the distribution of hydropho-

Table 7
Thermodynamic solvation functions of the studied compounds in *n*-hexane, water and *n*-octanol solutions at 298 K

Compound	ΔG°_{solv} (kJ mol^{-1})	ΔH°_{solv} (kJ mol^{-1})	$T\Delta S^{\circ}_{solv}$ (kJ mol^{-1})	ΔS°_{solv} (J K^{-1} mol^{-1})	$\zeta_{H_{solv}}$ [a] (%)	$\zeta_{TS_{solv}}$ [b] (%)
n-Hexane						
I	−21.2	−77.1	−55.9	−187	58.0	42.0
II	−29.5	−88.5	−59.0	−198	60.0	40.0
III	−16.4	−44.5	−28.1	−94	61.3	38.7
Water						
I	−15.8	−99.4	−83.6	−280	54.3	45.7
II	−17.7	−96.6	−78.9	−265	55.0	45.0
III	−16.9	−60.7	−43.8	−147	58.1	41.9
n-Octanol						
I	−36.5	−81.0	−44.5	−149	64.5	35.5
II	−43.5	−101.9	−58.4	−196	63.6	36.4
III	−42.05	−74.6	−32.55	−109	69.6	30.4

[a] $\zeta_{H_{solv}} = (|\Delta H^{\circ}_{solv}|/(|\Delta H^{\circ}_{solv}| + |T\Delta S^{\circ}_{solv}|)) \times 100\%$.
[b] $\zeta_{TS_{solv}} = (|T\Delta S^{\circ}_{solv}|/(\Delta H^{\circ}_{solv}| + |T\Delta S^{\circ}_{solv}|)) \times 100\%$.

Table 8
Thermodynamic functions of transfer from *n*-hexane to the solvents of studied compounds at 298 K

Solvents	$-\Delta G_{tr}$ (kJ mol^{-1})	$-\Delta H_{tr}$ (kJ mol^{-1})	$-T\Delta S_{tr}$ (kJ mol^{-1})	ε_H[a] (%)	ε_S[b] (%)
I					
n-Hexane	(21.2)[c] 0	(77.1)[c] 0	(55.9)[c] 0	0	0
Water	−5.4	22.3	27.7	28.9	49.6
n-Octanol	15.3	3.9	−11.4	5.1	−20.4
II					
n-Hexane	(29.5)[c] 0	(88.5)[c] 0	(59.0)[c] 0	0	0
Water	−11.8	8.1	19.9	9.2	33.7
n-Octanol	14	13.4	−0.6	15.1	−1.1
III					
n-Hexane	(16.4)[c] 0	(44.5)[c] 0	(28.1)[c] 0	0	0
Water	0.5	16.2	15.7	36.4	55.9
n-Octanol	25.65	30.1	4.45	67.6	15.8

[a] $\varepsilon_H = (\Delta H_{spec}/\Delta H_{non\text{-}spec}) \times 100\%$.
[b] $\varepsilon_S = (\Delta S_{spec}/\Delta S_{non\text{-}spec}) \times 100\%$.
[c] Non-specific interactions: ΔY°_{solv} (*n*-hexane).

Table 9
Thermodynamic functions of transfer from water to *n*-octanol of studied compounds at 298 K

Compounds	$\Delta G_{tr}^{w\to o}$ (kJ mol^{-1})	$\Delta H_{tr}^{w\to o}$ (kJ mol^{-1})	$T\Delta S_{tr}^{w\to o}$ (kJ mol^{-1})	$\Delta S_{tr}^{w\to o}$ (J mol^{-1} K)	$\zeta_{H_{tr}}$[a] (%)	$\zeta_{TS_{tr}}$[b] (%)
I	−20.7	18.4	39.1	131	32.0	68.0
II	−25.8	−5.3	20.5	68.8	−20.5	79.5
III	−25.15	−13.9	11.25	37.7	−55.3	44.7

[a] $\zeta_{H_{tr}} = (\Delta H^{\circ}_{tr}/(|\Delta H^{\circ}_{tr}| + |T\Delta S^{\circ}_{tr}|)) \times 100\%$.
[b] $\zeta_{TS_{tr}} = (T\Delta S^{\circ}_{tr}/(|\Delta H^{\circ}_{tr}| + |T\Delta S^{\circ}_{tr}|)) \times 100\%$.

bic properties of the molecule (in comparison to its location in ortho-position) towards their decreasing.

The specific interaction terms for *n*-octanol are different from the previous case. Firstly, the enthalpic terms are negative for the considered compounds, whereas, the entropic ones are positive for **I** and **II** and negative for **III**. Secondly, $|\Delta H_{tr}| < |T\Delta S_{tr}|$ for **I** and $|\Delta H_{tr}| > |T\Delta S_{tr}|$ for **II** and **III**. Thus, the compactness of molecular structure (comparison of **I** and **III**), i.e. location of Cl-substituent at ortho-position, leads to redistribution of the specific interaction terms towards dominance of the entropic term (i.e. possible blocking centers of the specific interactions and hydrogen bonding).

To estimate the relationship between specific and non-specific solvation thermodynamic terms the following parameters ε_H for the enthalpic term and ε_S for the entropic term have been introduced:

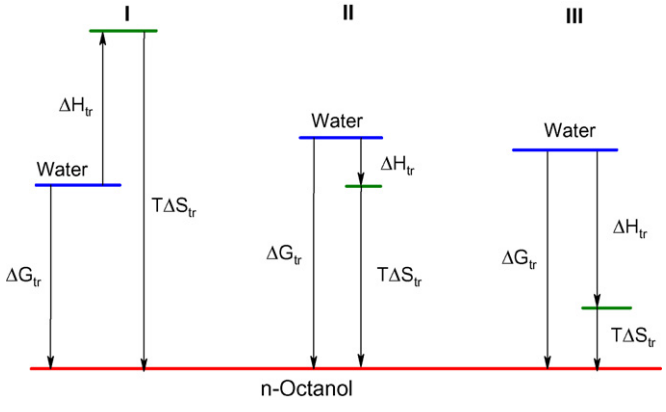
$$\varepsilon_H = \frac{\Delta H_{spec}}{\Delta H_{non\text{-}spec}} \times 100\% \quad (11)$$

$$\varepsilon_S = \frac{\Delta S_{spec}}{\Delta S_{non\text{-}spec}} \times 100\% \quad (12)$$

As it follows from Table 8, the ratio of enthalpies of specific to non-specific interactions for the substance **I** is 28.9% and 5.1% for water and *n*-octanol, respectively. Introduction of a Cl-substituent in para-position (**III**) instead of ortho (**I**), leads to an essential change of these terms: $\varepsilon_H = 36.4\%$ and 67.6% for water and *n*-octanol, respectively. Introduction of an additional Cl-substituent in meta-position (**II**) in comparison with (**I**) leads to decreased ε_H for water (9.2%) and increased ε_H for *n*-octanol (15.1%).

3.4. Partitioning process

In the next step of our investigations we tried to analyze the process of partitioning of our substances in the water-octanol system by analyzing the hypothetic transfer from water to *n*-octanol. The results are presented in Table 9 and Scheme 2. It should be mentioned that the partitioning processes for these compounds have different driving forces and, as consequence,



Scheme 2.

different mechanism. For example, for the compound **I** the enthalpic and entropic terms have the same sign, whereas, for the compounds **II** and **III**—opposite sign. Moreover, the absolute values of these terms for drugs **II** and **III** are different: for **II** the entropic term overweighs the enthalpic one, whereas, for **III** the opposite is observed. For compounds **I** and **II** the partitioning process is entropy driven, whereas, for **III**—enthalpy driven. Thus, the presented technique gives the opportunity to analyze the nature of distribution processes in a deeper way.

4. Conclusion

It is useful to investigate the thermodynamic functions of drugs and drug-like molecules in the solid state and in solutions thoroughly. Energies of dissolution are accessible by classical methods, whereas, energies for the sublimation process were obtained by the transpiration method. These enable to quantify solvation energies in different solvents. The respective fractions of the enthalpy and entropy terms of solvation can be deduced, which provide information about the mechanism of the solvation process. Transfer functions (calculated form the respective energetic states in the pure solvents), using hexane as a standard, distinguish between specific and non-specific interaction. For drugs, the water–solvent transfer energies are often studied using octanol as a model for a lipophilic compartment in the form of partition coefficients. In the current study, for three closely related molecules, transfer from water to octanol was found. However, distinguishing between enthalpy and entropy, as is possible through the present approach, leads to the insight that the mechanism is different for the different molecules (entropy- or enthalpy-driven). Thus, in contrast to interpretation of Gibbs energy of transfer, being excessively used for pharmaceuticals in the form of the partition coefficient and $\log P$, analysis of thermodynamic functions of the transfer process, as outlined in the present work, provides additional mechanistic information. This may be of importance for further evaluation of distribution of drug molecules and provide a better understanding of biopharmaceutical properties of drugs.

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