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Note

Sulfonamides as a subject to study molecular interactions in crystals and solutions: Sublimation, solubility, solvation, distribution and crystal structure

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Abstract

Crystal structures of 4-amino-*N*-(4-chlorophenyl)-benzene-sulfonamide (**IV**), 4-amino-*N*-(2,3-dichlorophenyl)-benzene-sulfonamide (**V**), 4-amino-*N*-(3,4-dichlorophenyl)-benzene-sulfonamide (**VI**) and 4-amino-*N*-(2,5-dichlorophenyl)-benzene-sulfonamide (**VII**) were solved by X-ray diffraction method. Temperature dependencies of saturated vapour pressure and thermodynamic functions of sublimation process were calculated (**IV**: $\Delta G^{298}_{sub} = 74.0\,kJ\,mol^{-1}$, $\Delta H^{298}_{sub} = 134.1 \pm 1.2\,kJ\,mol^{-1}$, $\Delta S^{298}_{sub} = 202 \pm 3\,J\,mol^{-1}\,K^{-1}$; **V**: $\Delta G^{298}_{sub} = 61.7\,kJ\,mol^{-1}$, $\Delta H^{298}_{sub} = 141.1 \pm 0.7\,kJ\,mol^{-1}$, $\Delta S^{298}_{sub} = 266 \pm 2\,J\,mol^{-1}\,K^{-1}$; **VI**: $\Delta G^{298}_{sub} = 85.8\,kJ\,mol^{-1}$, $\Delta H^{298}_{sub} = 167.5 \pm 3.6\,kJ\,mol^{-1}$, $\Delta S^{298}_{sub} = 274 \pm 8\,J\,mol^{-1}\,K^{-1}$; **VII**: $\Delta G^{298}_{sub} = 75.7\,kJ\,mol^{-1}$, $\Delta H^{298}_{sub} = 155.4 \pm 1.6\,kJ\,mol^{-1}$, $\Delta S^{298}_{sub} = 268 \pm 4\,J\,mol^{-1}\,K^{-1}$). Thermochemical parameters of fusion and evaporation processes for the compounds were obtained. Temperature dependencies of the solubility in water, *n*-octanol were measured. The thermodynamic functions of solubility and solvation processes were deduced. The transfer processes of the molecules from water to *n*-octanol were analysed by diagram method and main driven forces were established.

Keywords: 4-Amino-*N*-(4-chlorophenyl)-benzene-sulfonamide; 4-Amino-*N*-(2,3-dichlorophenyl)-benzene-sulfonamide; 4-Amino-*N*-(3,4-dichlorophenyl)-benzene-sulfonamide; 4-Amino-*N*-(2,5-dichlorophenyl)-benzene-sulfonamide; Sublimation thermodynamics; Solubility; Solvation; Crystal structure; 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 use 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 physic-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 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).

Analysis of the crystal lattice structures published in literature has been carried out by Adsmond and Grant (Adsmond and Grant, 2001). Especial attention in this work it has been pointed out on characterization and systematization of hydrogen bond networks by using graph set notations. Moreover, the authors tried to describe donor and acceptor affinities of atoms in the molecules studied on basis of statistical analysis of the hydrogen bonds created.

One of the key issues in drug design is to let the molecules actually reach their target. The dissolution, absorption, distribution and passive transport are important components of the drug

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delivery process and pharmacokinetics. Understanding of main characteristics of the outlined processes is determined resolution of following questions: how strongly the drug molecules interact with the neighbors (solvation shells); what is the nature of the interactions and ratio between specific and non-specific interactions; how strong the drug molecules have an influence on disordering of the medium molecules and what are the disordering effects at transfer molecules from lipophilic to hydrophilic phases; what is the structural unit taking part in the passive diffusion process – molecule or molecule together with their solvation shell (partly solvation shell); what is the time-life of the solvation shell. The answers of the mentioned questions are determined by the solvation characteristics of the drug molecules. However, due to lack of thermodynamic sublimation data of drug and drug-like compounds, analysis of solvation parameters stayed outside of the focus of investigators. In our previous work (Perlovich and Bauer-Brandl, 2004; Perlovich et al., 2006a,b,c,d, 2007a,b) 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 solvation characteristics of some sulfonamides such as *N*-(2-chlorophenyl)-benzene-sulfonamide (**I**), *N*-(2,3-dichlorophenyl)-benzene-sulfonamide (**II**), *N*-(4-chlorophenyl)-benzene-sulfonamide (**III**) (Scheme 1) have been described by us before (Perlovich et al., 2007a,b). As a continuation of this study, the solvation and structural aspects of 4-amino-*N*-(4-chlorophenyl)-benzene-sulfonamide (**IV**), 4-amino-*N*-(2,3-dichlorophenyl)-benzene-sulfonamide (**V**), 4-am-ino-*N*-(3,4-dichlorophenyl)-benzene-sulfonamide (**VI**) and 4-amino-*N*-(2,5-dichlorophenyl)-benzene-sulfonamide (**VII**) (Scheme 1) are presented in this work. The choice of the compounds has been dictated by the following aims: to analyze how the additional amino group in the (**IV–VII**) structures influences on: (a) architecture of the crystal lattices; (b) geometry and topology of the hydrogen bond networks; (c) energetic aspects of the crystal lattices; (d) thermodynamics of solubility, solvation and partitioning processes in pharmaceutically relevant solvents in comparison with (**I–III**).

2. Materials and methods

2.1. Compounds and solvents

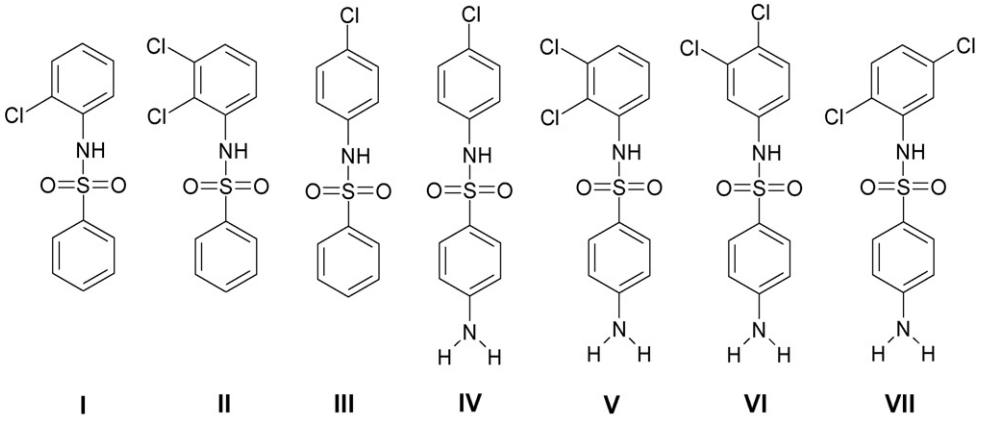
The chemical synthesis of 4-amino-*N*-(4-chlorophenyl)-benzene-sulfonamide (**IV**), 4-amino-*N*-(2,3-dichlorophenyl)-benzene-sulfonamide (**V**), 4-amino-*N*-(3,4-dichlorophenyl)-benzene-sulfonamide (**VI**) and 4-amino-*N*-(2,5-dichlorophenyl)-benzene-sulfonamide (**VII**) has been performed in analogy 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 chloro- or dichloroaniline) with 4-acetylaminobenzenesulfonyl chloride in dry pyridine, followed by hydrolytic deacetylation in alkaline aqueous medium (∼1 M NaOH) and precipitation of the end product by acidification (∼1 M HCl) to pH 5. The compounds have been carefully purified by re-crystallization from water–ethanol solution. The initial substances dissolve in ethanol in order to get saturation solutions. After that the water has been added until occurrence of a white precipitation. The precipitation has been filtered and dried at the room temperature under vacuum until the mass of the compounds remained 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 corresponds to purity of the compound better than 99%.

Single crystals of the title compounds were grown from a water–ethanol solution (20:1) by vapour diffusion of ethanol vapour into an aqueous solution (Guillory, 1999).

1-Octanol (*n*-octanol, $CH_3(CH_2)_7OH$, MW 130.2, lot 11K3688) ARG from Sigma Chemical Co. (USA).

2.2. X-ray diffraction experiments

Single-crystal X-ray measurements were carried out using a Nonius CAD-4 diffractometer with graphite-monochromated Mo K_α radiation ($\lambda = 0.71069$ 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. Enraf-



Scheme 1.

Nonius *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.

2.3. Solubility determination

All the experiments were carried out by the isothermal saturation method at several temperature points: 17, 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 (Zielenkiewicz et al., 1999a).

Standard Gibbs energies of the dissolution processes ΔG^0_{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 $\Delta H^\circ{}_{sol}$ 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 1 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 $\Delta S^\circ{}_{sol}$ were obtained from the well-known equation:

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

2.4. Sublimation experiments

Sublimation experiments were carried out by the transpiration method as was described elsewhere (Zielenkiewicz et al., 1999b). 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 $\Delta H^\circ{}_{sub} = 90.5 \pm 0.3\ J\ mol^{-1}$. This is in good agreement with the value recommended by IUPAC of $\Delta H^\circ{}_{sub} = 89.7 \pm 0.5\ J\ mol^{-1}$ (Cox and Pilcher, 1970). The saturated vapor pressures were measured at each temperature 5 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 change 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 following way:

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

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

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

Whereas the entropy of s+ublimation at a given temperature *T* was calculated from the following relation:

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

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

Sublimation data are yielded at elevated temperatures for experimental reasons. However, in comparison to effusion 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). 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 equation (Chickos and Acree, 2002) (the procedure of $C^{298}_{p,cr}$ − values calculation is presented in Table 5):

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

2.5. 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 ±0.005 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 Dannenfelser and

Yalkowsky (Dannenfelser and Yalkowsky, 1999) and Verevkin and Schick (Verevkin and Schick, 2004).

The enthalpy of vaporization has been calculated as:

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

3. Results and discussion

3.1. Crystal structure analysis

The results of the X-ray diffraction experiments are presented in Table 1. It should be mentioned that there are two independent molecules in asymmetric unit for **IV**, **V** and **VI**.

In order to characterize conformational states of the molecules a view of two independent **V** molecules, as an example, with the atomic numbering are shown on Fig. 1a and b. This numbering was used for everything drugs under investigation. Based on the presented numbering it may carry out comparative analysis of conformational states of the **I–VII** molecules. The results are summarized in Table 2.

Table 2
Some parameters (°) describing molecular conformational states in the crystal lattices

	∠O1–S1–C1–C2	∠N1–S1–C1–C2	∠S–N1–C7–C12	∠Ph1–Ph2
I[a]	5.8(2)	−108.5(2)	−68.3(2)	49.14(9)
II[b]	7.4(4)	−106.8(3)	−63.8(4)	54.8(2)
III[c]	30.7(4)	−83.5(3)	−71.1(4)	54.4(2)
IV(A)	39.2(4)	−74.4(3)	−79.1(4)	60.5(2)
IV(B)	41.2(4)	−71.3(4)	−36.4(5)	80.7(1)
V(A)	47.3(2)	−64.8(2)	−28.1(2)	81.56(6)
V(B)	37.4(2)	−75.6(2)	−43.0(2)	79.11(7)
VI(A)	45.2(9)	−66.7(9)	−33(1)	84.7(3)
VI(B)	41.6(9)	−71.2(8)	−80(1)	60.7(4)
VII	40.6(3)	−72.4(3)	−65.9(3)	64.9(1)

[a] Ref. Perlovich et al. (2006c).
[b] Ref. Tkachev et al. (2006).
[c] Ref. Perlovich et al. (2006d).

The packing molecules in the crystal lattices of the substances under investigation are presented in Fig. 2.

To describe conformational state of the molecules the four parameters have been chosen: the angle between SO_2-group and

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

	IV tw	**V** Perlovich et al.[b]	**VI** tw	**VII** Perlovich et al.[c]
Crystal data				
Crystal system	Orthorhombic	Triclinic	Orthorhombic	Monoclinic
Space group	$Pna2_1$	P1bar	$Pna2_1$	$P2_1/c$
Description	Colourless prism	Colourless prism	Colourless prism	Colourless prism
Crystal size (mm)	0.05 × 0.05 × 0.03	0.4 × 0.2 × 0.2	0.06 × 0.04 × 0.026	0.27 × 0.18 × 0.13
a (Å)	15.460(3)	7.4700(8)	15.407(3)	12.848(2)
b (Å)	6.0500(12)	13.613(1)	6.233(1)	7.262(1)
c (Å)	27.370(6)	14.548(1)	27.409(6)	14.993(2)
α (°)	90.00	110.91(1)	90.00	90.00
β (°)	90.00	90.51(1)	90.00	105.72(1)
γ (°)	90.00	102.42(1)	90.00	90.00
Volume (Å^3)	2560.0(9)	1343.6(2)	2632.1(9)	1346.4(3)
Z	8	4	8	4
D_{calc} (g cm^{-3})	1.467	1.568	1.601	1.565
Radiation	Mo K_α	Mo K_α	Mo K_α	Mo K_α
T (K)	293(2)	200(2)	293(2)	293(2)
μ (mm^{-1})	0.456	0.64	0.649	0.64
Data collection				
Measured reflections	2405	5502	2472	2895
Independent reflections	1765	4499	1909	2149
Independent reflections with >2σ(I)	1704	4325	1280	1527
R_{int}	0.0332	0.011	0.0454	0.028
θ_{max} (°)	24.88	25.0	25.0	25.0
Refinement				
Refinement on	F^2	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$	0.0297	0.029	0.0448	0.040
$\omega R(F^2)$	0.0779	0.080	0.0875	0.105
S	1.010	1.10	1.016	1.02
Reflections	1765	4499	1909	2149
Parameters	344	362	344	181
$(\Delta/\sigma)_{max}$	0.001	0.001	0.006	0
$\Delta\rho_{max}$ (e Å^{-3})	0.231	0.31	0.28	0.25
$\Delta\rho_{min}$ (e Å^{-3})	−0.262	−0.31	−0.23	−0.42

[a] Brackets display the standard deviations.
[b] Ref. Perlovich et al. (2006b).
[c] Ref. Perlovich et al. (2007a).

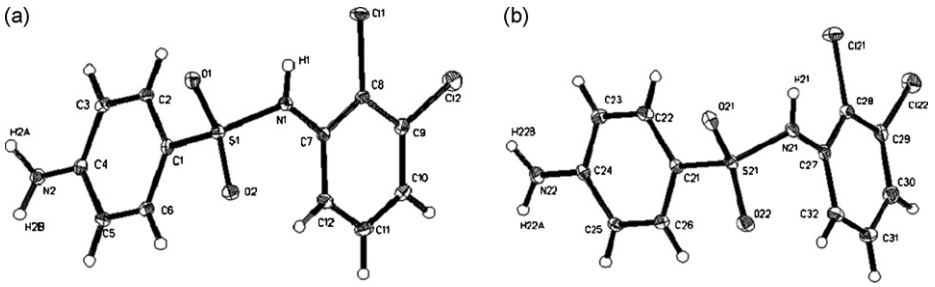


Fig. 1. A view of two independent molecules **V(A)** – (a) and **V(B)** – (b) with the atomic numbering.

the phenyl motif Ph1 (C1-C2-C3-C4-C5-C6) ∠O1–S1–C1–C2; the angle ∠N1–S1–C1–C2, describing orientation of NH-group relatively to Ph1; the torsion angle ∠S1–N1–C7–C12, which characterizes location of the second phenyl ring Ph2 (C7-C8-C9-C10-C11-C12) in respect to NH-group and, finally, the angle between the two phenyl rings ∠Ph1–Ph2.

Introducing additional NH_2-group (**III** and **IV** as an example of mono-Cl-substituted compounds) leads to essential change of the molecular conformational states. The outlined parameters can be arranged by following way for ∠O1–S1–C1–C2: 30.7(4)° (**III**) <39.2(4)° (**IV**(A)) <41.2(4)° (**IV**(B)); for the dihedral angle ∠N1–S1–C1–C2 (absolute values): 71.3(4)° (**IV**(B)) <74.4(3)° (**IV**(A)) <83.5(3) (**III**) and for the dihedral angle ∠S–N1–C7–C12 (absolute values): 36.4(5)° (**IV**(B)) <71.1(4)° (**III**) <79.1(4)° (**IV**(A)). The angles between the phenyl rings for **III** and **IV**(A) are differed on 5°, whereas for **III** and **IV**(B) – more than 25°. At other side, introducing NH_2-group in the di-Cl-substituted sulfonamides (**II** and **V**) leads to bigger molecular conformational changes in comparison with the previous case for the dihedral angle ∠O1–S1–C1–C2: 7.4(4)° (**II**) <41.2(4)° (**V**(B)) <47.3(2)° (**V**(A)); for the dihedral angle ∠N1–S1–C1–C2 (absolute values): 64.8(2)° (**V**(A)) <75.6(2)° (**V**(B)) <106.8(3)° (**II**); for the dihedral angle ∠S–N1–C7–C12 (absolute values): 28.1(2)° (**V**(A)) <43.0(2)° (**V**(B)) <63.8(4)°

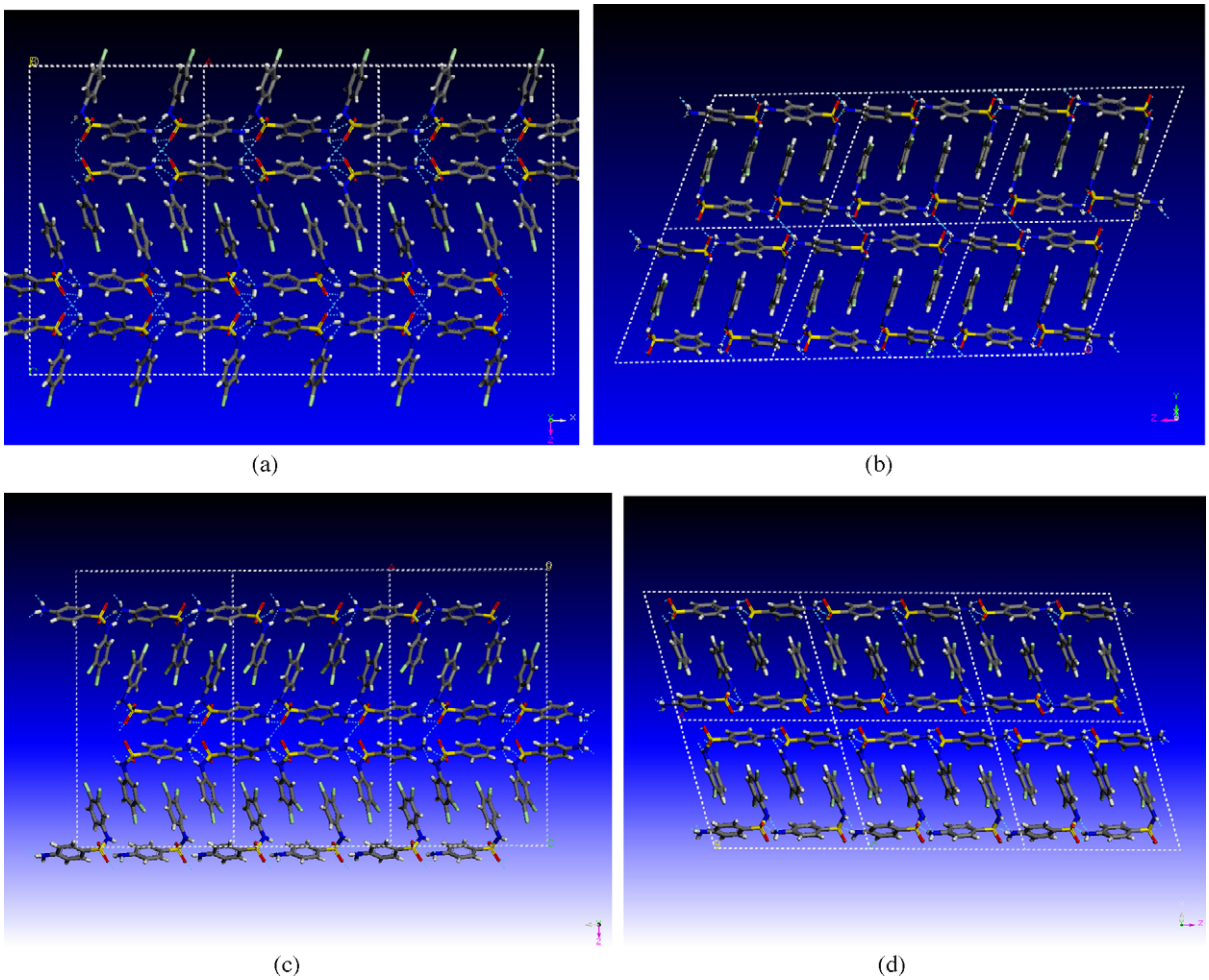
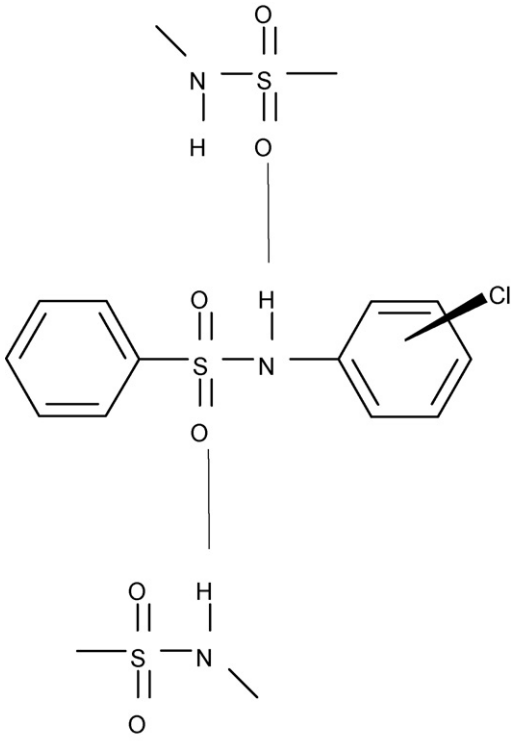


Fig. 2. Molecular packing architectures of (**IV**) – a, (**V**) – b, (**VI**) – c and (**VII**) – d crystal lattices.



I, II, III

Scheme 2.

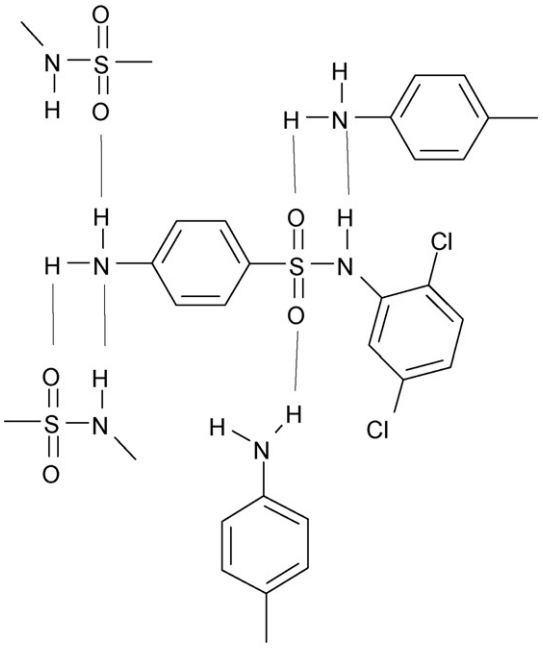
(**II**). The angles between the phenyl rings for **V**(A) and **V**(B) are differed on 2°, whereas for **II** and **V**(A) – on 25°.

The three compounds (**IV–VI**) from the considered amino-derivatives of the sulfonamides have two independent molecules in the asymmetric unit. Moreover, the compound **IV** is mono-chloride-substituted in contrast to other ones, which are di-chloride-substituted. It is interesting to note, that for the outlined compounds the angles between the phenyl rings of the molecules A and B in asymmetric unit are differed not essential for the drug **V** (within 2°), whereas for the substances **IV** and **VI** these differences reach more than 20°. It is not difficult to see that the molecular conformational states in the crystals depend on location of Cl-substitutes for the isomers of the considered compounds (**V–VII**). This fact can be connected both with topological structure of the molecules and hydrogen bonds network. Therefore, in the next step of our investigation we tried to analyze these questions.

Comparative characteristics of the hydrogen bonds geometric parameters and graph set notations (Etter, 1990) for the two levels are summarized in Table 3.

The easiest picture of the hydrogen bonds networks is observed for compounds **I–III**, which can be described by graph set assignment introduced by Etter (Etter, 1990) as C(4) (infinite chain with 4 involved atoms). The schematic depicture of the hydrogen bonds is presented on Scheme 2.

For the compound **VII** (where there are three different hydrogen bonds) the diagonal elements (first level) of the graph set notation matrix include only infinite chains with 8 involved atoms, C(8). Whereas the rest elements of the matrix consist

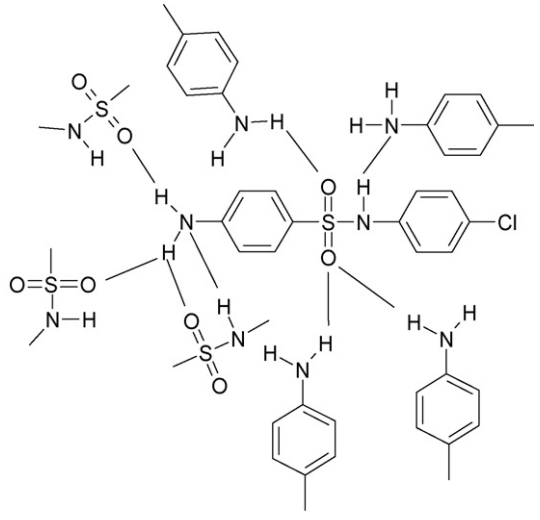


VII

Scheme 3.

of both infinite chains and intermolecular rings with 6 involved atoms (Scheme 3, Table 3).

The most complicated hydrogen bonds network is observed for the compounds with two independent molecules in asymmetric unit (**IV–VI**). For drug **IV** the diagonal elements of the graph set notation matrix include mainly C(8) and diads (D). Moreover, the diads are formed by the hydrogen bonds, which link each other the two independent molecules in the asymmetric unit (Scheme 4). The elements of second level can be briefly characterized as a set of two kinds of the chains: one of the chains is created by atoms belonging to the molecules A, whereas the



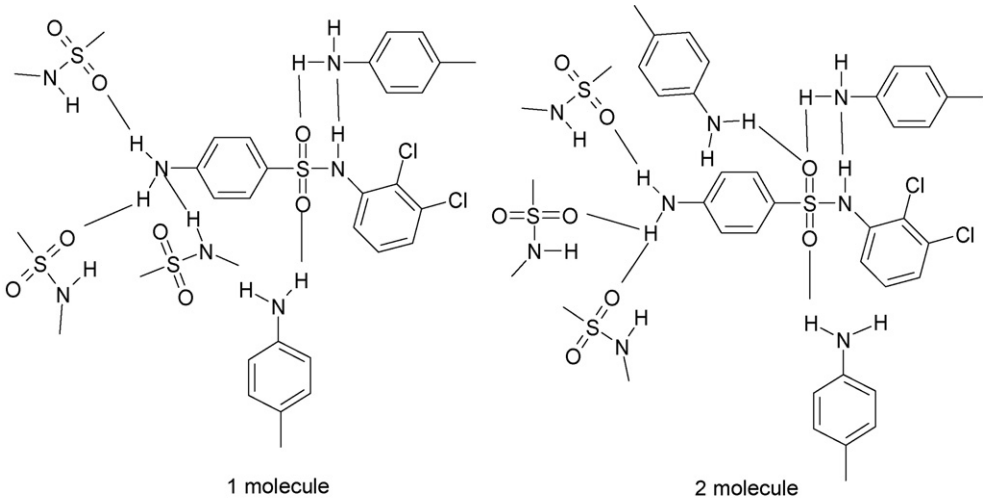
IV

Scheme 4.

Table 3
Hydrogen bonds geometry of the molecules studied

	D–H. . .A[a]	D–H [Å]	H. . .A [Å]	D. . .A [Å]	D–H. . .A [°]		a							
I	N1–H1. . .O2^{i}	0.75(2)	2.26(2)	2.994(2)	167(2)	a	C(4)							
II	N1–H1. . .O2^{ii}	0.76(4)	2.30(4)	3.039(4)	166(4)	a	C(4)							
III	N1–H1. . .O2^{iii}	0.78(3)	2.21(3)	2.993(4)	175(4)	a	C(4)							
IV	D—H. . .A[b]	D—H	H. . .A	D. . .A	D—H. . .A		a	b	c	d	e	f	g	h
a	N1-H1. . .N2^{i}	1.01(5)	2.05(5)	3.049(5)	166(4)	a	C(8)							
b	N2-H2a. . .O1^{ii}	0.98(5)	2.64(5)	3.185(5)	115(3)	b	$R_2^2(6)$	C(8)						
c	N2-H2a. . .O21^{iii}	0.98(5)	2.36(5)	2.979(5)	120(4)	c	C(8);D	C(8);D	D					
d	N2-H2b. . .O2^{iv}	0.89(5)	2.30(5)	3.138(5)	156(4)	d	C(7) or $R_4^4(22)$	C(6) or $R_4^4(22)$	C(8);D	C(8)				
e	N21-H21. . .N22^{ii}	0.75(5)	2.28(5)	3.007(5)	161(5)	e	C(8);C(8)	C(8);C(8)	C(8);D	C(8);C(8)	C(8)			
f	N22-H22a. . .O1^{v}	0.87(6)	2.53(5)	2.962(5)	112(4)	f	C(8);D	C(8);D	C(16);C(16)	C(8);D	C(8);D	D		
g	N22-H22a. . .O21^{i}	0.87(6)	2.57(5)	3.172(5)	127(4)	g	C(8);C(8)	C(8);C(8)	C(8);D	C(8);C(8)	$R_2^2(6)$	C(8);D	C(8)	
h	N22-H22b. . .O22^{vi}	0.90(5)	2.33(5)	3.165(5))	154(4)	h	C(8);C(8)	C(8);C(8)	C(8);C(8)	C(8);C(8)	C(6);C(6) or $R_4^4(22)$	$R_4^4(22)$	$R_4^4(22)$	C(8)
V	D—H. . .A[c]	D—H	H. . .A	D. . .A	D—H. . .A		a	b	c	d	e	f	g	
a	N2-H2a. . .O1^{ii}	0.86(3)	2.466(24)	3.126(2)	134(2)	a	$R_2^2(16)$							
b	N2-H2a. . .O21^{ii}	0.86(3)	2.446(24)	3.066(2)	130(2)	b	$R_2^2(16)$;D;D	D						
c	N2-H2b. . .O22^{iii}	0.86(2)	2.219(25)	3.047(2)	161(2)	c	$R_2^2(16)$;D;D	C(5)	D					
d	N22-H22a. . .O2^{iv}	0.83(2)	2.411(25)	3.190(2)	156(2)	d	$R_2^2(16)$;D;D	C(8)	C(16)	D				
e	N22-H22b. . .O1^{i}	0.84(2)	2.397(24)	2.999(2)	129(2)	e	$R_2^2(16)$;D;D	C(16)	C(16)	C(6)	D			
f	N1-H1. . .N22^{i}	0.79(2)	2.325(25)	3.083(2)	160(2)	f	$R_2^2(16)$;D;D	C(16)	C(16)	C(6)	$R_2^2(6)$	D		
g	N21-H21. . .N2^{ii}	0.82(2)	2.245(25)	3.034(2)	160(2)	g	$R_2^2(16)$;D;D	$R_2^2(6)$	C(6)	C(16)	C(16)	C(16)	D	
VI	D—H. . .A[d]	D—H	H. . .A	D. . .A	D—H. . .A		a	b	c	d	e	f		
a	N1-H1. . .N2^{i}	0.96	2.13	3.007(12)	151	a	C(8)							
b	N2-H2a. . .O21^{ii}	0.97	2.37	2.917(10)	115	b	D	D						
c	N2-H2b. . .O2^{iii}	0.99	2.29	3.255(11)	164	c	C(6)	C(8);D	C(8)					
d	N21-H21. . .N22^{iv}	0.91	2.21	3.076(12)	153	d	C(8);C(8)	C(8);D	C(8);C(8)	C(8)				
e	N22-H22a. . .O21^{i}	0.98	2.49	3.276(12)	138	e	C(8);C(8)	C(8);D	C(8);C(8)	C(8);C(8)	C(8)			
f	N22-H22b. . .O22^{v}	0.98	2.32	3.188(11)	148	f	C(8);C(8)	C(8);D	C(8);C(8)	C(8);C(8) or $R_2^2(6)$	C(8);C(8)	C(8)		
VII	D—H. . .A[e]	D—H	H. . .A	D. . .A	D—H. . .A		a	b	c					
a	N1-H1. . .N2^{i}	0.74(4)	2.394(36)	3.116(4)	157(4)	a	C(8)							
b	N2-H2a. . .O1^{ii}	0.86(4)	2.331(37)	3.062(4)	143(3)	b	$R_2^2(6)$	C(8)						
c	N2-H2b. . .O2^{iii}	0.82(4)	2.317(37)	3.118(4)	166(3)	c	C(6)	C(4)	C(8)					

[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.
[b] Symmetry code:(i) x-1/2,1/2-y,z; (ii) 1/2 + x,1/2-y,z; (iii) 1-x,1-y,1/2 + z; (iv)1/2 + x,3/2-y,z; (v)-x,1-y,z-1/2; (vi) x-1/2, 3/2-y, z.
[c] Symmetry code: (i) -x,-y, 1-z; (ii) -x,-y,-z; (iii) 1-x,-y,-z; (iv) 1-x,-y,1-z.
[d] Symmetry code: (i) x-1/2,-y + 1/2,z; (ii) -x + 1,-y + 1,z-1/2; (iii) x + 1/2,-y + 3/2,z; (iv) x + 1/2,-y + 1/2,z; (v) x-1/2,-y + 3/2,z.
[e] Symmetry code: (i) x,-y + 1/2, z-1/2; (ii) x,-y + 1/2,z + 1/2; (iii) x,-y-1/2,z + 1/2.



V

Scheme 5.

other one – by atoms belonging to the molecules B. It should be noted that the some double chains can be presented in equivalent form as intermolecular rings $R_4^4(22)$.

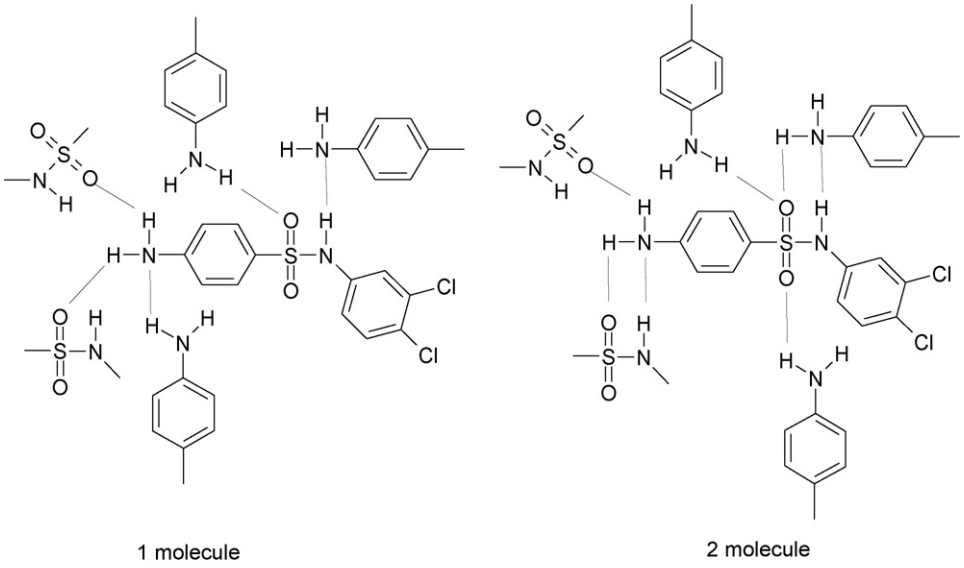
The hydrogen bonds network of **V** is essentially differed from the previous one (**IV**) (Scheme 5).

Practically, the whole diagonal elements are presented by diads (D). The second level elements of the hydrogen bonds can be described by motif $R_2^2(16)$;D;D. Whereas the rest of the elements of the matrix consist on infinite chains with various included atoms.

The hydrogen bonds network of **VI** (Scheme 6) can be characterized by matrix with C(8) diagonal elements and with adjacent elements as double chains C(8);C(8) or C(8);D.

The packing architectures of the molecules in the crystal lattices **IV**–**VII** (Fig. 2) are similar and can be characterized in the following way. The molecules create chains by forming hydrogen bonds between NH_2- and SO_2-groups. Chlorophenyl fragments of the molecules are situated at the angle of the chains and interact with the analogous motifs of the adjacent molecules by van der Waals forces only. At the opposite side of the chlorophenyl location, the chains interact with each other by van der Waals forces as well, if in the asymmetric unit there is just one molecule (**VII**, Fig. 5d). If in the asymmetric unit there are two molecules (**IV**–**VI**), then in addition to the outlined van der Waals interactions it is accrued the hydrogen bond interactions between H–N–H. . .O=S=O groups belonging to different molecules in the asymmetric unit.

The packing density of the molecules in the crystals depends on geometry and topology of the molecule and hydrogen bonds network as well. The free molecular volume in the crystal lattice has been estimated on basis of the X-ray diffraction data and van der Waals's molecular volume (V^{vdw}), calculated by GEPOL



VI

Scheme 6.

Table 4
Temperature Dependencies of Saturation Vapor Pressure of Compounds **IV–VII**

IV[a]		**V**[b]		**VI**[c]		**VII**[d]	
t (°C)	P (Pa)	t (°C)	P (Pa)	t (°C)	P (Pa)	t (°C)	P (Pa)
127.0	6.10×10^{-3}	72.0	3.21×10^{-3}	145.0	7.75×10^{-3}	105.5	2.48×10^{-3}
130.0	8.15×10^{-3}	74.0	4.09×10^{-3}	149.0	1.30×10^{-2}	109.0	3.35×10^{-3}
130.5	9.28×10^{-3}	77.0	6.10×10^{-3}	151.0	1.38×10^{-2}	112.0	5.30×10^{-3}
134.0	1.20×10^{-2}	80.0	9.75×10^{-3}	152.0	1.64×10^{-2}	118.0	1.10×10^{-2}
138.0	1.85×10^{-2}	82.0	1.17×10^{-2}	152.5	2.07×10^{-2}	120.0	1.27×10^{-2}
141.0	2.28×10^{-2}	89.5	3.24×10^{-2}	155.0	2.33×10^{-2}	124.0	2.28×10^{-2}
144.0	2.93×10^{-2}	94.0	5.78×10^{-2}	157.0	2.76×10^{-2}	129.0	3.84×10^{-2}
148.0	4.20×10^{-2}	97.0	7.35×10^{-2}	159.0	3.51×10^{-2}	133.0	6.33×10^{-2}
149.5	4.99×10^{-2}	99.0	1.00×10^{-1}	161.0	4.16×10^{-2}	137.0	8.98×10^{-2}
151.0	5.61×10^{-2}	105.0	2.12×10^{-1}	164.5	6.79×10^{-2}	138.0	1.04×10^{-1}
152.0	6.08×10^{-2}	107.0	2.47×10^{-1}	168.0	9.83×10^{-2}	139.0	1.22×10^{-1}
158.0	1.04×10^{-1}	109.0	3.30×10^{-1}	169.0	9.07×10^{-2}	144.5	2.00×10^{-1}
159.0	1.11×10^{-1}	113.3	5.12×10^{-1}	170.0	1.01×10^{-1}		
		116.0	7.19×10^{-1}	175.0	1.81×10^{-1}		
		118.0	9.05×10^{-1}				

[a] $\ln P$ (Pa) = (33.8 ± 0.3) − (15538 ± 141)/T; $\sigma = 3.04 \times 10^{-2}$; $r = 0.9995$; $F = 12067$; $n = 13$.
[b] $\ln P$ (Pa) = (42.1 ± 0.2) − (16534 ± 87)/T; $\sigma = 3.82 \times 10^{-2}$; $r = 0.9999$; $F = 35914$; $n = 15$.
[c] $\ln P$ (Pa) = (42 ± 1) − (19411 ± 437)/T; $\sigma = 7.59 \times 10^{-2}$; $r = 0.9974$; $F = 1976$; $n = 14$.
[d] $\ln P$ (Pa) = (42.0 ± 0.5) − (18200 ± 186)/T; $\sigma = 5.07 \times 10^{-2}$; $r = 0.99948$; $F = 9511$; $n = 12$.

(Pascual-Ahuir and Silla, 1990):

$$V^{\text{free}} = \frac{(V_{\text{cell}} - Z \cdot V^{\text{vdw}})}{Z} \quad (11)$$

where V_{cell} is a volume of the unit cell, Z is a number of molecule in the unit cell.

Dependence of the free versus the van der Waals volumes for the discussed compounds is shown in Fig. 3. It is interesting to note that the free volume per molecule of the drugs **II–V** and **VII** in the crystal lattices are differed each from other not essentially (within 2 Å^3). Therefore, it may suppose that there is the maximal critical free volume when the molecules change packing architecture. The crystal lattices of **IV** and **VI** are isomorphic; therefore accommodation of the additional Cl-atom of compound **VI** (in comparison with **IV**) occurs into the free volume of the unit cell, which is obtained from packing of molecules of substance **IV**.

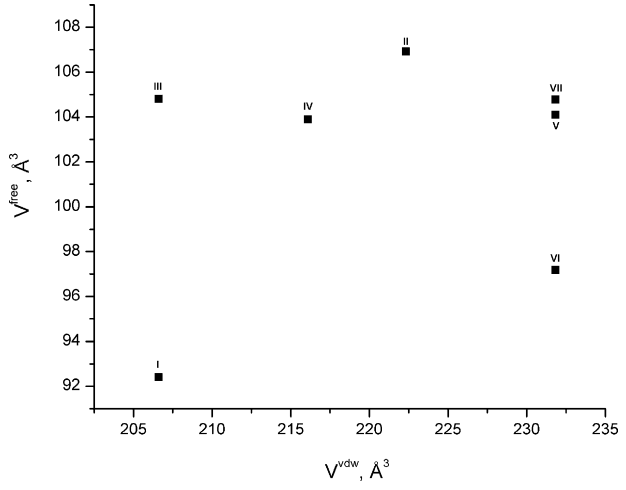


Fig. 3. Dependence between the free molecular volumes in the crystal lattices (V^{free}) and the van der Waals volumes of the compounds (V^{vdw}).

3.2. Sublimation characteristics

The temperature dependencies of saturated vapor pressure of the considered compounds are shown in Table 4. The thermodynamic functions of the drugs sublimation, fusion and vaporization processes are presented in Table 5.

Introducing additional amino-group in the drug **II** (Perlovich et al., 2007b) ($\Delta H^{298}_{\text{sub}} = 124.9 \pm 1.6$ kJ mol^{-1}) increases the

Table 5
Thermodynamic characteristics of processes of sublimation, fusion and vaporization of the studied compounds

	IV	**V**	**VI**	**VII**
$\Delta G^{298}_{\text{sub}}$ (kJ mol^{-1})	74.0	61.7	85.8	75.7
$\Delta H^{T}_{\text{sub}}$ (kJ mol^{-1})	129.2 ± 1.2	137.5 ± 0.7	161.4 ± 3.6	151.3 ± 1.6
$\Delta H^{298}_{\text{sub}}$ (kJ mol^{-1})	134.1 ± 1.2	141.1 ± 0.7	167.5 ± 3.6	155.4 ± 1.6
$C^{298}_{\text{p,cr}}$ (J mol^{-1} K^{-1})[a]	315.1	335.3	335.3	335.3
$T\Delta S^{298}_{\text{sub}}$ (kJ mol^{-1})	60.1	79.4	81.7	79.7
$\Delta S^{298}_{\text{sub}}$ (J mol^{-1} K^{-1})	202 ± 3	266 ± 2	274 ± 8	268 ± 4
ς_{H} (%)[b]	69.1	64.0	67.2	66.1
ς_{TS} (%)[b]	30.9	36.0	32.8	33.9
T_{m} (K)	467.9 ± 0.2	454.3 ± 0.2	497.9 ± 0.2	445.9 ± 0.2
$\Delta H^{T}_{\text{fus}}$ (kJ mol^{-1})	37.3 ± 0.5	40.9 ± 0.5	51.5 ± 0.5	41.3 ± 0.5
$\Delta H^{298}_{\text{fus}}$ (kJ mol^{-1})	23.8	26.8	30.8	27.6
$\Delta S^{T}_{\text{fus}}$ (J mol^{-1} K^{-1})[c]	79.7	90.0	103.4	92.6
$\Delta H^{298}_{\text{vap}}$ (kJ mol^{-1})	110.3	114.3	136.7	127.8

[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] $\varsigma_H = (\Delta H^{298}_{\text{sub}}/(\Delta H^{298}_{\text{sub}} + T\Delta S^{298}_{\text{sub}})) \times 100\%$;
$\varsigma_{\text{TS}} = (T\Delta S^{298}_{\text{sub}}/(\Delta H^{298}_{\text{sub}} + T\Delta S^{298}_{\text{sub}})) \times 100\%$..
[c] $\Delta S_{\text{fus}} = \Delta H_{\text{fus}}/T_{\text{m}}$.

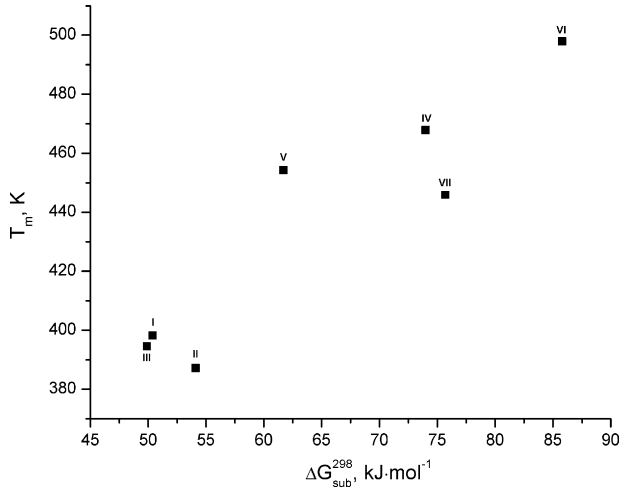


Fig. 4. Dependence between the melting points (T_m) and the sublimation Gibbs energies (ΔG^{298}_{sub}) (see text for numbering of the compounds).

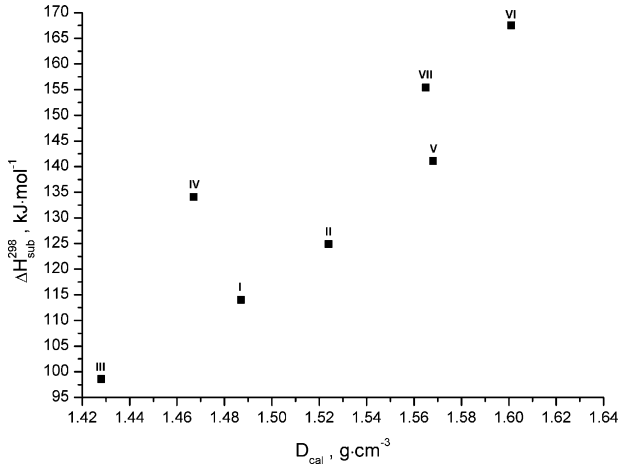


Fig. 6. Dependence between the sublimation enthalpies (ΔH^{298}_{sub}) and the calculated molecular densities in the crystal lattices (D_{cal}) (see text for numbering of the compounds).

crystal lattice energy on 16.2 kJ mol^{-1} (drug **V**: $\Delta H^{298}_{sub} = 141.1 \pm 0.7$ kJ mol^{-1}). The analogous introducing amino-group in drug **III** (Perlovich et al., 2007b) ($\Delta H^{298}_{sub} = 98.6 \pm 1.9$ kJ mol^{-1}) increases the crystal lattice energy on 35.5 kJ mol^{-1} (drug **IV**: $\Delta H^{298}_{sub} = 134.1 \pm 1.2$ kJ mol^{-1}).

Comparative analysis of thermodynamic parameters of sublimation and fusion processes of the discussed compounds leads to the following results. It is observed correlation between the melting points and sublimation Gibbs energies (Fig. 4). At other side, there is correlation between the sublimation enthalpies and the fusion enthalpies at 298 K (Fig. 5). Thus if the thermo chemical parameters of the fusion process are known, the thermodynamic parameters of the sublimation process of the considered class of the compounds can be estimated.

It is interesting to mentioned, that there is regularity between the sublimation enthalpies and the theoretical calculated densities of the crystals, D_{cal}, derived from X-ray diffraction experiments (Fig. 6): while the density increases the sublimation enthalpy value increases as well (with exception for the drug **IV**). Probably, this fact can be explained due to essential overweighting of the van der Waals packing term in comparison to the hydrogen bonding energy.

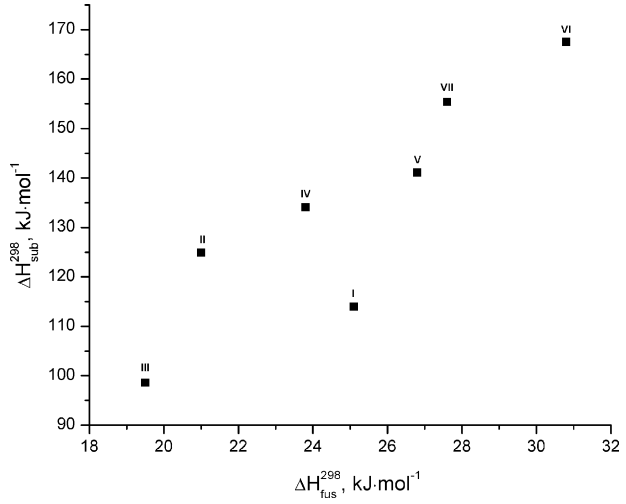


Fig. 5. Dependence between the sublimation enthalpies (ΔH^{298}_{sub}) and the fusion enthalpies (ΔH^{298}_{fus}) (see text for numbering of the compounds).

3.3. Solubility and solvation thermodynamics

The temperature dependencies of solubility of some sulfonamides in water and *n*-octanol solutions are summarized in Table 6. The thermodynamic functions of the drugs solubility process in the solutions at 298 K are presented in Table 7.

Firstly, the compounds under the investigation are more soluble in *n*-octanol than in water. Secondly, the solution enthalpies for every substance have positive values, and it means that the crystal lattice energy overweighs the solvation one. It is interesting to note, that entropies of the solubility process in water have opposite sign in comparison with the analogous values for *n*-octanol. The negative values of the solution entropies of the **V–VII** compounds in water mean that at transfer of the molecules from the solid state to the solute, ordering of (drug-water) system becomes stronger in comparison to the crystal. This behavior can be connected with hydrophobic effects, which appears from interaction of the hydrophobic fragments of the molecules studied with water. The positive value of the solution entropy is observed for drug **IV** and this regularity can be explained by stronger ordering the molecules in the crystal than in the solution. The stronger order of the molecules of drug **IV** in the crystal lattice in comparison with **V–VII**. In Goodman and Gilman ones can be connected with a bigger number of hydrogen bonds per molecule and, as consequences, with more complicated topology of the hydrogen bonds networks (discussed above). The positive values of the solution entropies for the drugs **V–VII** in *n*-octanol can be connected with essential disordering of the solvent molecules at the solubility process due to comparable size of the solute molecules with parameters of the *n*-octanol molecule. Moreover, the topological peculiarities of the drugs (especially with the two Cl-atoms) intensify the process. Solubility processes in water are enthalpy determined for

Table 6
The temperature dependencies of solubility, X_2·(mol. frac.), of compounds **IV**–**VII** in water and *n*-octanol

t (°C)	**IV**		**V**		**VI**		**VII**	
	Water	*n*-Octanol	Water	*n*-Octanol	Water	*n*-Octanol	Water	*n*-Octanol
	$X_2 \times 10^6$	$X_2 \times 10^3$	$X_2 \times 10^7$	$X_2 \times 10^4$	$X_2 \times 10^7$	$X_2 \times 10^4$	$X_2 \times 10^7$	$X_2 \times 10^4$
17	–	1.26	–	4.44	–	3.17	–	3.47
20	0.918	1.32	3.10	5.15	1.67	3.56	6.12	4.12
25	1.19	1.45	3.32	6.81	2.05	4.22	7.25	5.29
30	1.51	1.53	3.72	8.58	2.48	5.01	8.98	6.67
37	2.02	1.67	4.23	11.8	3.26	6.17	10.3	8.90
42	2.84	–	4.56	–	3.89	–	12.4	–
A[a]	1.7 ± 0.8	-2.2 ± 0.3	-9.3 ± 0.2	7.4 ± 0.3	-3.3 ± 0.3	2.32 ± 0.17	-4.4 ± 0.4	6.6 ± 0.3
B[a]	4590 ± 230	1288 ± 86	1683 ± 67	4396 ± 87	3605 ± 97	3011 ± 52	2910 ± 112	4224 ± 97
R[b]	0.9963	0.99339	0.9977	0.9994	0.99892	0.99955	0.9978	0.99921
σ[c]	4.42×10^{-2}	1.52×10^{-2}	1.28×10^{-2}	1.55×10^{-2}	1.86×10^{-2}	9.19×10^{-3}	2.15×10^{-2}	1.72×10^{-2}

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

IV, **VI** and **VII**, whereas for compound **V** – entropy determined. In octanol the solubility processes are enthalpy determined for everything compounds studied.

In order to estimate interaction of the drugs with the solvents in absolute energetic scale, solvation thermodynamic functions have been calculated for the compounds on base of the results of the sublimation and solubility experiments:

$$\Delta Y^\circ_{solv} = \Delta Y^\circ_{sol} - \Delta Y^{298}_{sub} \quad (12)$$

where Y are one from the thermodynamic functions G, H or S.

The thermodynamic functions of solvation processes for the studied compounds in water and *n*-octanol at 298 K are presented in Table 7.

Interaction of the studied substances with the solvents (ΔH°_{solv}) can be arranged in decreasing way (absolute value) as follows: for water **VI** > **VII** > **V** > **IV** and for *n*-octanol **VI** > **IV** > **VII** > **V**. In order to compare contributions of enthalpic and entropic solvation terms the parameters ς_{Hsolv} and ς_{TSsolv} have been introduced (Perlovich and Bauer-Brandl, 2004) (Table 7). From analysis of these values it can be concluded that the enthalpic term contributes a dominant part to the solvation Gibbs energy. It is interesting to mention, that the ς_{Hsolv} and ς_{TSsolv}-parameters are approximately equal for every compound studied for the solvation processes in *n*-octanol.

3.4. Partitioning process

The thermodynamic functions of transfer of the studied compounds from the buffers to *n*-octanol, being widely discussed as reflecting some biopharmaceutical properties of drugs, were studied (Table 8). The experimental data of the thermodynamic functions of the compounds under investigation are collected in Fig. 7. The regions where ($T\Delta S^\circ_{tr} > \Delta H^\circ_{tr} > 0$) ≡ sector **I**, and ($\Delta H^\circ_{tr} < 0$; $T\Delta S^\circ_{tr} > 0$; $|T\Delta S^\circ_{tr}| > |\Delta H^\circ_{tr}|$) ≡ sector **II** correspond to entropy determined processes. The regions of the diagram where ($\Delta H^\circ_{tr} < 0$; $T\Delta S^\circ_{tr} > 0$; $|\Delta H^\circ_{tr}| > |T\Delta S^\circ_{tr}|$) ≡ sector **III** and ($\Delta H^\circ_{tr} < 0$; $T\Delta S^\circ_{tr} < 0$; $|\Delta H^\circ_{tr}| > |T\Delta S^\circ_{tr}|$) ≡ sector **IV** correspond to enthalpy determined processes. A schematic depiction of these relationships is given in Scheme 7. Isoenergetic curves of the ΔG°_{tr} function are marked as dotted lines in Fig. 7.

Studying the enthalpic and entropic terms of the transfer process is a convenient tool to analyze the size of a substructure unit which takes part in a partitioning process. If the transfer enthalpy is positive then it may be assumed that the drug molecule interacts more strongly with the solvate shell in the water phase in comparison with the octanol one. Therefore there is a high probability of transferring of the drug molecule together/partly with the solvation shell (water molecules). In this case the substructure transferring unit is a drug molecule + solvation shell. At $\Delta H^\circ_{tr} < 0$ the opposite picture is observed: the total resolvation of drug molecule in water phase occurs at the transferring process. Thus the substructure transferring unit is just a drug molecule. The entropic term shows changing ordering of the system at transferring the substructure unit from one phase

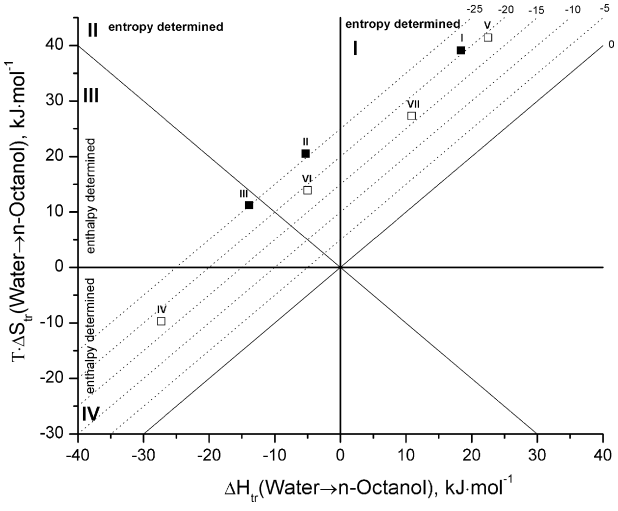


Fig. 7. Relationship between the enthalpic and entropic terms of transfer functions from the water to *n*-octanol for the compound studied (see text for numbering of the compounds). The isoenergetic curves of ΔG°_{tr} function are marked by dotted lines.

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

	X_2^{298} mol frac	ΔG^0_{sol} (kJ mol^{-1})	ΔH^0_{sol} (kJ mol^{-1})	$T\Delta S^\circ_{sol}$ (kJ mol^{-1})	ΔS°_{sol} (J K^{-1} mol^{-1})	ΣH_{sol}[a] (%)	ΣTS_{sol}[b] (%)	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})	ΣH_{solv}[c] (%)	ΣTS_{solv}[d] (%)
Water													
IV	1.19×10^{-6}	33.8	38 ± 2	4.2	14 ± 2	90.0	10.0	−41.0	−96.1	−55.1	−185	63.6	36.4
V	3.32×10^{-7}	37.0	14.0 ± 0.6	−23.0	−77 ± 2	37.8	−62.2	−24.7	−127.1	−102.4	−343	55.4	44.6
VI	2.05×10^{-7}	38.2	30.0 ± 0.8	−8.2	−28 ± 2	78.5	−21.5	−47.6	−137.5	−89.9	−302	60.5	39.5
VII	7.25×10^{-7}	35.1	24.2 ± 0.9	−10.9	−37 ± 2	68.9	−31.1	−40.6	−131.2	−90.6	−304	59.2	40.8
n-Octanol													
IV	1.45×10^{-3}	16.2	10.7 ± 0.7	−5.5	−18 ± 1	66.0	−34.0	−57.8	−123.4	−65.6	−220	65.3	34.7
V	6.81×10^{-4}	18.1	36.5 ± 0.7	18.4	62 ± 1	66.5	33.5	−43.6	−104.6	−61.0	−205	63.2	36.8
VI	4.22×10^{-4}	19.3	25.0 ± 0.4	5.7	19 ± 1	81.4	18.6	−66.5	−142.5	−76.0	−255	65.2	34.8
VII	5.29×10^{-4}	18.7	35.1 ± 0.8	16.4	55 ± 1	68.2	31.8	−57.0	−120.3	−63.3	−212	65.5	34.5

[a] $\Sigma H_{sol} = (|\Delta H^\circ_{sol}|/(|\Delta H^\circ_{sol}| + |T\Delta S^\circ_{sol}|)) \times 100\%$.
[b] $\Sigma TS_{sol} = (|T\Delta S^\circ_{sol}|/(|\Delta H^\circ_{sol}| + |T\Delta S^\circ_{sol}|)) \times 100\%$.
[c] $\Sigma H_{solv} = (|\Delta H^\circ_{solv}|/(|\Delta H^\circ_{solv}| + |T\Delta S^\circ_{solv}|)) \times 100\%$.
[d] $\Sigma TS_{solv} = (|T\Delta S^\circ_{solv}|/(|\Delta H^\circ_{solv}| + |T\Delta S^\circ_{solv}|)) \times 100\%$.

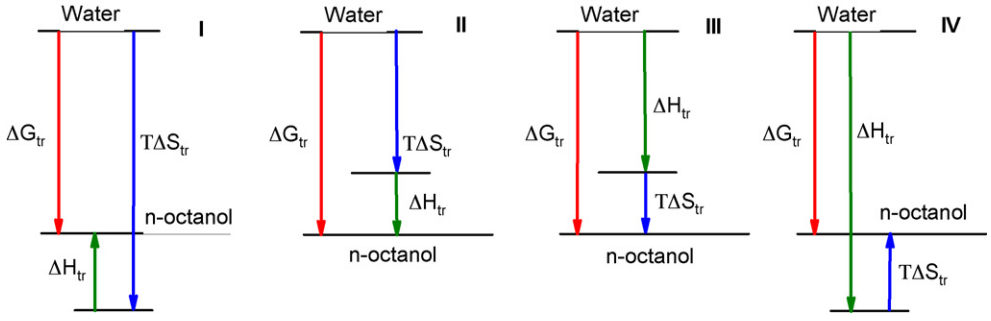
to the other. Thus, the first sector corresponds to transfer of (drug + solvation shell) from the water to octanol phase with essential disordering of the last one. The second sector corresponds to transfer of an individual drug molecule with essential disordering of the octanol phase. The third sector corresponds to transfer of an individual drug molecule with not essential disordering of the octanol phase. Finally, the fourth sector corresponds to transfer of an individual drug molecule ordering of the octanol phase. This information can be useful to analyze diffusion processes of drug molecules through biological barriers (passive transport), because the size of the substructure unit plays a key role and determines coefficient diffusion values and mechanism of it.

It is not difficult to see, that the transfer processes are very sensitive to structure of the compounds. The transfer processes of **I**, **II**, **V–VII** are entropy determined. Moreover, the enthalpic term for **I**, **V**, **VII** has positive sign, whereas for **II** and **VI** – negative. The entropy determined process corresponds to essential changing of the entropy term at transfer drug molecule from water to *n*-octanol phases (in comparison to the enthalpy term). One from the explanation of the regularity can be connected with the strong hydrophobic effect of the compounds, which cannot be compensated by introducing in the molecule the hydrogen bonding substituent (amino-group). For two compounds (**III** and **IV**) the transfer processes are enthalpy determined. However, as like in previous case, for drug **III** the entropic term is positive, whereas for **IV** – negative. The maximal driving force of the transfer process ($\Delta G_{tr}^{w\rightarrow o}$) is observed for the sulfonamides without amino-groups in the molecular structure (**I**, **II**, **III**). Moreover, the outlined substances are located in the different sectors of the diagram (Fig. 7) and this situation corresponds to various contributions of the thermodynamic terms in the discussed process. The analogous situation is observed for amino-derivatives of the sulfonamides. The driving forces of the transfer processes for these compounds ($\Delta G_{tr}^{w\rightarrow o}$) are approximately the same (within 1 kJ mol^{-1}), but the ratios and signs of the enthalpic and entropic terms are differed essentially. Introducing amino-group in the molecule **III** (compound **IV**) keeps the transfer process as enthalpy determined, however, the entropic term changes the sign from positive to negative. Introducing amino-group in the molecule **II** (drug **V**) keeps the transfer process as entropy determined, however, the enthalpic term change the sign from negative to positive. Introducing additional Cl-atom both for the compounds without the amino-groups (**I** and **II**, **III**) and with the groups (**IV** and **V–VII**) makes the transfer process from enthalpy determined to entropy determined. It is interesting to note that the maximal dispersion of $T\Delta S_{tr}$ and ΔH_{tr} values corresponds to drugs **I** and **III** for the group of substances without amino-substitute and drugs **IV** and **V** for the group of substances with amino-substitute. If it considers comparable variants of the molecules (**I** and **II**) and (**IV** and **V**) (another words, pair of the compounds with and without amino group), then it may suppose that in particular the amino-group promotes to essential dispersion of $T\Delta S_{tr}$ and ΔH_{tr} values. Thus, the presented approach gives opportunity to analyze contributions of various substitutes in changing of mechanism of the transfer processes.

Table 8
Transfer thermodynamic functions from water to *n*-octanol of compounds studied at 298 K

Compound	$\Delta G_{tr}^{w\to o}$ (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)	ς_{Htr}[a] (%)	ς_{TStr}[b] (%)
I[c]	−20.7	18.4	39.1	131	32.0	68.0
II[c]	−25.8	−5.3	20.5	68.8	−20.5	79.5
III[c]	−25.15	−13.9	11.25	37.7	−55.3	44.7
IV	−17.6	−27.3	−9.7	−32.5	−73.8	−26.2
V	−18.9	22.5	41.4	138.8	35.2	64.8
VI	−18.9	−5.0	13.9	46.6	−26.5	73.5
VII	−16.4	10.9	27.3	91.6	28.5	71.5

[a] $\varsigma_{Htr} = (\Delta H^{\circ}_{tr}/(|\Delta H^{\circ}_{tr}| + |T\Delta S^{\circ}_{tr}|)) \times 100\%$.
[b] $\varsigma_{TStr} = (T\Delta S^{\circ}_{tr}/(|\Delta H^{\circ}_{tr}| + |T\Delta S^{\circ}_{tr}|)) \times 100\%$.
[c] Ref. Perlovich et al. (2007b).



Scheme 7.

4. Conclusion

The four new crystal structures of the sulfonamides have been solved by X-ray diffraction experiments and comparative analysis of molecular conformational states and hydrogen bonds networks by graph set notations in the crystal lattices has been carried out. The correlations between the sublimation Gibbs energies and the melting points and between the sublimation enthalpies and the fusion enthalpies at 298 K have been derived. These dependencies give opportunity to predict the sublimation thermodynamic parameters on the basis of fusion experiments only. The correlation between the sublimation enthalpies and densities of the crystals under the investigation obtained by X-ray diffraction experiments has been received. The thermodynamic functions of solubility and solvation processes have been analyzed using temperature dependencies of solubility in water and n-octanol and sublimation characteristics of the compounds. The enthalpic term contributes a dominant part to the solvation Gibbs energy. Studying the transfer processes has been carried out by diagram method with analysis of the enthalpic and entropic terms. Introducing additional Cl-atom both for the compounds without the amino-groups and with the groups makes the transfer process from enthalpy determined to entropy determined. Introducing amino-group in the compounds studied promotes to essential dispersion of $T\Delta S_{tr}$ and ΔH_{tr} values. 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-determined). 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.

Acknowledgments

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