PCCP

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: G. L. Perlovich, T. V. Volkova, A. Sharapova, V. Kazachenko, N. Strakhova and A. N. Proshin, *Phys. Chem. Chem. Phys.*, 2016, DOI: 10.1039/C6CP00379F.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/pccp

PCCP

ARTICLE

View Article Online
DOI: 10.1039/C6CP00379F

Adamantane Derivatives of Sulfonamides: Sublimation, Solubility, Solvation and Transfer Processes in Biologically Relevant Solvents

G. L. Perlovich,[a,b] T. V. Volkova,[a] A. V. Sharapova,[a] V. P. Kazachenko,[b] N. N. Strakhova[b] and A. N. Proshin[b]

Recevied·00th·January·20xx¶
Accepted·00th·January·20xx¶
¶
DOI:·10.1039/x0xx00000x¶
www.rsc.org/¶

Eight adamantane derivatives of sulfonamides were synthesized and characterized. Temperature dependences of saturation vapor pressure were obtained by the transpiration method and thermodynamic functions of the sublimation processes were calculated. Solubility values of the selected compounds in buffer (pH 7.4), 1-octanol and 1-hexane were determined at different temperatures by the isothermal saturation method. Thermophysical characteristics of fusion processes (melting points and fusion enthalpies) of the substances were measured by the DSC method. Transfer processes from buffer to 1-octanol, from buffer to 1-hexane and 1-hexane to 1-octanol were analyzed. The impact of the molecules structural modification on sublimation, solubility and solvation/hydration processes in the solvents was studied. Correlation equations connecting the thermodynamic functions with physicochemical descriptors were obtained.

Introduction

Aqueous solubility is one of the key physicochemical characteristics of potential drug compounds.[1] High solubility in biological media provides the necessary concentration gradient for effective transport of the drug to the site of its specific action. Despite the fact that the affinity to the receptors in many cases is a key point for potential candidates of drug compounds, however, the solubility, absorption properties, membrane permeability, characteristics of active and passive transport are no less significant for in vivo processes. Unfortunately, these aspects are only taken into account at the final stages of the screening and development of pharmaceutical preparations. Due to this fact, the selected candidates with the best parameters of the receptor affinity exhibit a broad spectrum of undesirable properties when tested *in vitro*: low solubility in physiologically relevant media and extremely low membrane permeability. And solubility improvement by chemical and physicochemical methods at the last stages of the development requires new additional studies aimed at finding an appropriate technology, which makes the whole process much more costly.

No other singular hydrocarbon moiety (apart from the methyl group) is as successful as adamantane in improving or providing pharmacological activity of bestselling pharmaceuticals. Having the "lipophilic bullet" (adamantane is often viewed as providing only the critical lipophilicity) readily available as an "add-on" for known pharmacophors, adamantane was used in the modification of, for example, hypoglycemic sulfonylureas,[2] anabolic steroids,[3] and nucleosides.[4] The adamantane modifications were chosen to enhance lipophilicity and stability of the drugs, thereby improving their pharmacokinetics. Aminoadamantanes, such as amantadine,[5] rimantadine[6] and tromantadine[7] were among the first "hits" that successfully made it to the pharmaceutical market, and most of them are still in use. Adamantane derivatives have been used as antimalarials.[8,9] However, these compounds are poorly soluble in water, so the problem of solubility improvement for this class of compounds is quite urgent.

The objects of the present research are the compounds shown in Figure 1, and this choice was determined by the following considerations. Firstly, the crystal structure and, partly, sublimation processes for these compounds have been described by us earlier.[10] This fact greatly facilitates the analysis of the solvation processes in the selected solvents. Secondly, the substances represent a series of related compounds with a systematic replacement of the substituents

[a] *Department of Physical Chemistry of Drugs, Krestov's Institute of Solution Chemistry, Russian Academy of Sciences, 153045 Akademicheskaya str. 1, Ivanovo, Russia. E-mail: glp@isc-ras.ru*
[b] *Department of Computer-Aided Molecular Design, Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432, Chernogolovka, Russia.*

Electronic Supplementary Information (ESI) available: The relationship between the thermodynamic functions of dissolution processes of the compounds studied in buffer (pH 7.4), 1-octanol and 1-hexane; The temperature dependences of saturation vapor pressure of the compounds studied; The thermodynamic characteristics of sublimation and fusion processes of the compounds studied; The thermodynamic transfer functions of the compounds studied from buffer (pH 7.4) to 1-octanol, buffer (pH 7.4) to 1-hexane, and 1-hexane to 1-octanol at 298 K and p^0 = 0.1 MPa are represented in Figure 1SI and Tables 1SI – 3SI. This material is available free of charge via the Internet at http://pubs.acs.org.

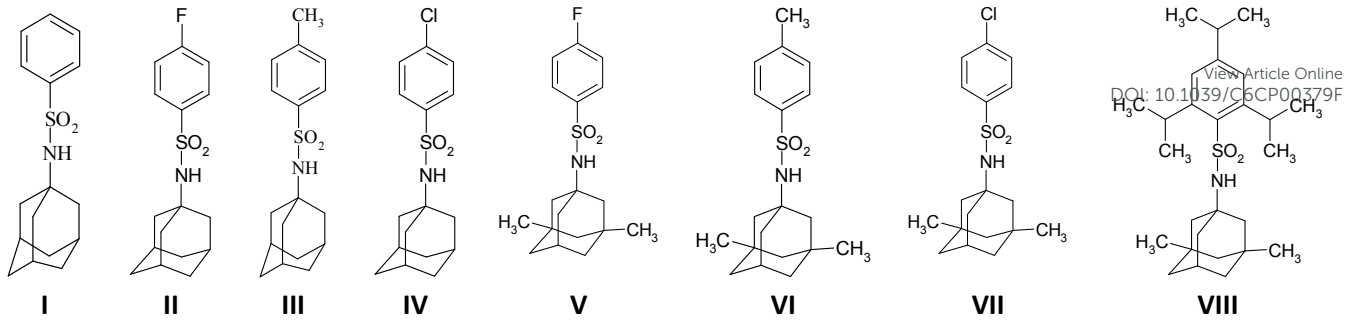


Fig. 1 Structural formulas of the compounds studied

in a strictly fixed position. This will allow us to reveal the behavior regularities of the dissolution, solvation and distribution parameters depending on the nature of the substituents.

A buffer solution pH 7.4, 1-octanol and 1-hexane, which simulate various biological media, were chosen as the solvents.

Moreover, the immiscible liquids: buffer / 1-octanol and buffer /1-hexane are good models to describe the membrane permeability and distribution processes in the gastrointestinal tract and blood-brain barrier, respectively. In this paper, we tried to analyze the effect of sublimation and solvation terms in the dissolution processes as well as the impact of substituents on the variations of the mentioned terms.

Experimental

Solvents

The buffer solutions pH 7.4 were prepared by mixing solutions of appropriate sodium and potassium salts of phosphoric acid manufactured at Chimmed (Moscow, Russia), as described elsewhere.[11] The ionic strength was adjusted by adding potassium chloride. All the chemicals were of AR grade. The pH values were measured by using Electroanalytical Analyser, Type OP-300, Radelkis, Budapest standardized with pH 1.68, 6.86 and 9.22 solutions. 1-Octanol (CH_3-$(CH_2)_7OH$, MW 130.2, 99%) and 1-hexane (C_6H_{14}, MW 86.18, HPLC grade) were received from Sigma Chemical and RCI Labscan, respectively, and used without further purification.

Sublimation experiments

The sublimation experiments were carried out by the transpiration method as described elsewhere.[12] 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 the sublimate and its purity are determined. The vapor pressure over the sample at this temperature can be calculated by the amount of the sublimated sample and the volume of the inert gas used.

The equipment was calibrated using benzoic acid. The standard value of the sublimation enthalpy obtained here was ΔH^0_{sub} = 90.5 ± 0.3 J·mol^{-1}. This was in good agreement with the value recommended by IUPAC of ΔH^0_{sub} = 89.7 ± 0.5 J·mol^{-1}.[13] The saturated vapor pressures were measured 5 times at each temperature with the standard deviation being within 3-5%. Because the saturated vapor pressure of the investigated compounds was low, it could be assumed that the heat capacity change of the vapor with temperature was so small that it could be neglected. The experimentally determined vapor pressure data could be described in (lnP; 1/T) co-ordinates in the following way:

$$\ln(P) = A + B/T \qquad (1)$$

The value of the sublimation enthalpy was calculated by the Clausius-Clapeyron equation:

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

whereas the sublimation entropy at the given temperature *T* was calculated from the following relation:

$$\Delta S^T_{sub} = (\Delta H^T_{sub} - \Delta G^T_{sub})/T \qquad (3)$$

with $\Delta G^T_{sub} = -RT\ln(P/P_0)$, where P_0 was the standard pressure of $1 \cdot 10^5$ Pa.

For experimental reasons, the sublimation data were obtained at elevated temperatures. However, in comparison with effusion methods, the temperatures were much lower, which made extrapolation to room conditions easier. In order to further improve the extrapolation to room conditions, we estimated the heat capacities ($C^{298}_{p,cr}$-value) of the crystals using the additive scheme proposed by Chickos et al.[14] 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 the equation[14]:

$$\Delta H^{298}_{sub} = \Delta H^T_{sub} + \Delta H_{cor} = \Delta H^T_{sub} + (0.75 + 0.15 \cdot C^{298}_{p,cr}) \cdot (T - 298.15) \qquad (4)$$

Solubility Determination

All the experiments were carried out by the isothermal saturation method at several temperature points: 20, 25, 30, 37, 42 ± 0.1° C. All the experimental data was presented/recalculated in molar fraction units. The solid phase was removed by isothermal filtration (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size, Carrigiwohill, Co.Cork, Ireland) or centrifugation (Biofuge pico, Thermo Electron LED GmbH, Germany) at 2000 rpm for 5 min. The experimental results were reported as an average value of at least three replicated experiments. The molar solubilities of drugs were measured spectrophotometrically with an accuracy of 2-2.5 % using a protocol described previously.[15]

The standard Gibbs energies of dissolution processes ΔG^0_{sol} (in kJ·mol^{-1}) were calculated using the following equation:

$$\Delta G^0_{sol} = -RT \ln a_2 \qquad (5)$$

where $a_2 = \gamma_2 \cdot X_2$ is the activity of the solute molecule; X_2 is the drug molar fraction in the saturated solution; γ_2 is the activity coefficient of the solute molecule. The standard solution enthalpies ΔH^0_{sol} (in kJ·mol^{-1}) were calculated using the van't Hoff equation:

$$\partial(\ln a_2)/\partial T = \Delta H^0_{sol}/RT^2 \qquad (6)$$

Due to the poor solubility of the studied drugs, the activity coefficient was equal to 1. It was assumed that the solution enthalpies were independent of the concentration. The temperature dependences of the drug solubilities within the chosen temperature interval could be described by the linear function:

$$\ln X_2 = \mathrm{A} - \mathrm{B}/T \qquad (7)$$

where A is the integral coefficient relating to entropy; $B = \Delta H^0_{sol}/R$.

This indicates that the change in heat capacity of the solutions with the temperature was negligibly small.
The standard solution entropies ΔS^0_{sol} (in J·mol^{-1}·K^{-1}) were obtained from the well-known equation:

$$\Delta G^0_{sol} = \Delta H^0_{sol} - T\Delta S^0_{sol} \qquad (8)$$

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was carried out using a DSC 204 F1 "Foenix" (Netzsch, Germany). DSC runs were performed in the atmosphere of flowing (25 ml·min^{-1}) dry argon gas of high purity 99.996% using standard aluminum sample pans at a heating rate of 10 K·min^{-1}. The DSC was calibrated using five standards: Hg, biphenyl, indium, tin and bismuth. The sample mass was in the range of 1 – 5.5 mg, determined with the accuracy of ± 0.005 mg using the balance Sartorius M2P. The experiment was repeated twice.

Synthesis of compounds

General procedure of the synthesis of the compounds studied

Synthesis of the novel sulfonamide derivatives was carried out according to Scheme 1. Triethylamine (0.04mol) was added to a stirred suspension of 1-aminoadamantane **I** (or Memantine, R^1, R^2 = CH_3) (0.01 mol) in isopropanol (30 ml) at 0°C, followed by solid sulfonyl chloride **II** (R^3 = H, CH_3, Cl, F) (0.01 mol) over a period of 30 minutes. The reaction mixture was heated at 60°C for 2 hours, after which HPLC showed that there was no starting material left. The resulting suspension was cooled to room temperature and the precipitate of triethylamine hydrochloride was removed by filtration. The filtrate was evaporated to dryness to afford a colourless oil which was dissolved in ethyl acetate (50 ml), washed with 0.5N HC1 (50 ml), water (50 m1) and dried over $MgSO_4$. The solvent was evaporated by a rotary evaporator to afford sulfonamide as a white crystalline solid. Yields: 80-90%.

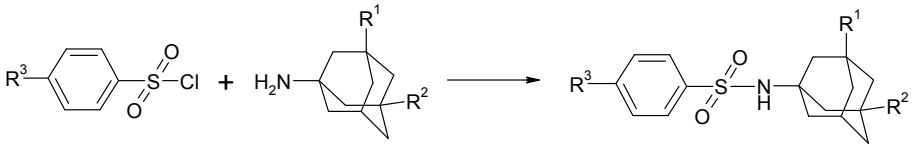
The compounds were carefully purified by re-crystallizing from water-ethanol solution. The precipitate was filtered and dried at room temperature under vacuum until the mass of compounds remained constant. The outlined procedure was repeated several times and the product checked by NMR after each re-crystallization step until the proton NMR signal correspondence to the purity of the compound was over 98 %. The results of the compounds purification are presented at Supporting Information in details (Table 1SI).

NMR Experiments

^{1}H NMR spectra were recorded on Bruker CXP-200 instrument (Germany). $CDCl_3$ was applied as a solvent. Details of the NMR experiments are shown at Supporting Information.

Calculation procedure

All the physicochemical descriptors for the compounds studied were calculated by the program package HYBOT-PLUS (version of year 2003) in Windows.[16]



II I III

Scheme 1

TABLE 1 Temperature dependencies of solubility, X_2 [mol. fraction][a], of compounds **I-VIII** in buffer (pH 7.4), 1-octanol and 1-hexane (p^0 = 0.1 MPa)

	I	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**
				Buffer				
t /°C	$X_2 \cdot 10^7$	$X_2 \cdot 10^6$	$X_2 \cdot 10^7$	$X_2 \cdot 10^5$	$X_2 \cdot 10^6$	$X_2 \cdot 10^6$	$X_2 \cdot 10^5$	$X_2 \cdot 10^6$
20	4.22	2.80	2.01	4.77	4.75	6.48	-	6.48
25	5.01	3.14	2.69	5.12	5.75	6.79	1.77	7.04
30	6.12	3.47	3.58	5.72	-	7.00	1.86	-
32	-	-	-	-	6.73	-	-	8.01
35	-	-	-	-	-	-	1.95	-
37	7.92	3.97	5.45	6.57	7.53	7.44	-	8.51
40	-	-	-	-	-	-	2.07	-
42	9.50	4.62	7.47	7.18	8.51	7.66	-	8.92
45	-	-	-	-	-	-	2.14	-
A[b]	-3.1±0.3	-5.9±0.3	3.4±0.3	-3.9±0.2	-4.1±0.4	-9.52±0.09	-7.9±0.1	-7.2±0.3
B[b]	3393±88	2024±103	5539±98	1768±68	2391±121	711±27	909±33	-1382±104
R[c]	0.9979	0.9961	0.9999	0.9978	0.9962	0.9979	0.9981	0.9916
σ[d]	$1.69 \cdot 10^{-2}$	$1.99 \cdot 10^{-2}$	$1.88 \cdot 10^{-2}$	$1.31 \cdot 10^{-2}$	$2.32 \cdot 10^{-2}$	$5.09 \cdot 10^{-3}$	$5.43 \cdot 10^{-3}$	$2.00\ 10^{-2}$
				1-Octanol				
t /°C	$X_2 \cdot 10^2$	$X_2 \cdot 10^2$	$X_2 \cdot 10^2$	$X_2 \cdot 10^3$	$X_2 \cdot 10^2$	$X_2 \cdot 10^3$	$X_2 \cdot 10^3$	$X_2 \cdot 10^3$
20	1.31	1.50	0.84	3.80	1.16	4.85	4.13	2.36
25	1.44	1.81	1.00	4.81	1.46	5.92	5.35	2.84
30	1.75	2.03	1.21	5.72	-	7.52	-	-
32	-	-	-	-	2.08	-	7.30	3.66
37	2.13	2.45	1.63	7.30	2.65	10.1	9.85	4.34
42	2.72	2.84	1.86	8.28	3.26	12.0	12.3	5.09
A[b]	7.6±0.1	4.7±0.3	7.1±0.4	5.6±0.4	10.6±0.2	7.9±0.2	10.2±0.4	5.05±0.08
B[b]	3469±38	2604±101	3500±113	3266±136	4427±62	3879±71	4592±131	3254±24
R[c]	0.9999	0.9977	0.9987	0.9974	0.9997	0.9995	0.9988	0.9999
σ[d]	$6.57 \cdot 10^{-3}$	$1.95 \cdot 10^{-2}$	$2.17 \cdot 10^{-2}$	$2.61 \cdot 10^{-2}$	$1.19 \cdot 10^{-2}$	$1.36 \cdot 10^{-2}$	$2.51 \cdot 10^{-2}$	$4.61 \cdot 10^{-3}$
				1-Hexane				
t /°C	$X_2 \cdot 10^4$	$X_2 \cdot 10^4$	$X_2 \cdot 10^4$	$X_2 \cdot 10^4$	$X_2 \cdot 10^4$	$X_2 \cdot 10^4$	$X_2 \cdot 10^5$	$X_2 \cdot 10^6$
20	2.33	3.71	1.37	1.02	3.97	1.51	9.81	3.37
25	2.92	4.62	1.77	1.24	5.26	1.92	14.3	4.71
30	3.56	5.93	2.36	1.71	8.01	2.61	22.9	7.97
37	4.62	8.50	3.21	2.40	11.5	3.63	31.6	11.1
42	5.56	10.2	4.22	2.98	14.3	4.39	42.6	15.6
A[b]	3.9±0.2	6.9±0.4	7.1±0.3	6.5±0.5	11.0±0.6	6.9±0.5	11.8±0.2	9.4±0.3
B[b]	3602±53	4349±113	4679±96	4604±162	5514±175	4587±156	6159±76	6472±90
R[c]	0.9997	0.9990	0.9994	0.9982	0.9985	0.9983	0.9998	0.9997
σ[d]	$1.02 \cdot 10^{-2}$	$2.17 \cdot 10^{-2}$	$1.84 \cdot 10^{-2}$	$3.11 \cdot 10^{-2}$	$3.36 \cdot 10^{-2}$	$3.00 \cdot 10^{-2}$	$1.46 \cdot 10^{-2}$	$1.74 \cdot 10^{-2}$

[a] relative standard uncertainty for solubility values $u_r(X_2)$ = 0.03

[b] parameters of the correlation equation: $\ln X_2 = A - B/T$

[c] R – pair correlation coefficient

[d] σ – standard deviation

Results and discussion

The temperature dependences of the compounds solubility in buffer (pH 7.4), 1-octanol and 1-hexane are given in Table 1. The thermodynamic functions of dissolution at 298 K are shown in Table 2. The temperature dependences of saturation vapor pressure **VII** and **VIII** and their thermodynamic functions are presented in Table 3. The thermodynamic parameters of sublimation processes of the compounds **I**-**VI** are described in our previous paper[10] (Tables S2 and S3 of the Supporting Information).

In order to estimate the interaction of compounds with solvents/water on an absolute energy scale, the solvation thermodynamic functions were calculated for the compounds based on the sublimation and solubility experiments results:

$$\Delta Y^0_{solv} = \Delta Y^0_{sol} - \Delta Y^0_{sub} \quad (9)$$

where Y is one of the thermodynamic functions G, H or S; *solv* – solvation, *sol* – solubility and *sub* – sublimation processes.

View Article Online
DOI: 10.1039/C6CP00379F

Table 2 shows the thermodynamic characteristics of solvation processes of the compounds in the selected solvents at 298 K derived with the assistance of the thermodynamic functions of the sublimation processes.

Dissolution and hydration processes in buffer solution

Diagram approach

In order to reveal the influence of the substituents introduced into molecule **I** on the thermodynamic characteristics of dissolution and solvation / hydration, we analysed the differences between the thermodynamic functions of the substituted compounds and the unsubstituted (**I**) one. A diagram approach was used to perform the analysis. Figure 2 shows the marked differences of the thermodynamic functions for the dissolution processes (a) and solvation / hydration (b) in the chosen solvents.

The diagram is divided into eight sectors, each corresponding to a certain ratio of entropy and enthalpy contributions to the Gibbs energy. Each sector of the diagram is bounded by two lines: on the one side – by the line corresponding to a zero value of ΔH^0 or $T\cdot\Delta S^0$; on the other side – by the angles bisector formed at the crossing of the coordinates ($\Delta H^0; T\cdot\Delta S^0$). The isoenergetic lines of the Gibbs energy are marked by the dashed lines. Thus, the diagram can be divided into the following sectors: ($T\cdot\Delta S^0 > \Delta H^0 > 0$) ≡ sector **A**, ($\Delta H^0 < 0$; $T\cdot\Delta S^0 > 0$; $|T\cdot\Delta S^0| > |\Delta H^0|$) ≡ sector **B**, ($T\cdot\Delta S^0 < \Delta H^0 < 0$) ≡ sector **E**, and ($\Delta H^0 > 0$; $T\cdot\Delta S^0 < 0$; $|T\cdot\Delta S^0| > |\Delta H^0|$) ≡ sector **F** corresponding to the entropy determined processes. The sectors of the diagram, where ($\Delta H^0 < 0$; $T\cdot\Delta S^0 > 0$; $|\Delta H^0| > |T\cdot\Delta S^0|$) ≡ sector **C**, ($\Delta H^0 < 0$; $T\cdot\Delta S^0 < 0$; $|\Delta H^0| > |T\cdot\Delta S^0|$) ≡ sector **D**, ($\Delta H^0 > T\cdot\Delta S^0 > 0$) ≡ sector **H** and ($\Delta H^0 > 0$; $T\cdot\Delta S^0 < 0$; $|\Delta H^0| > |T\cdot\Delta S^0|$) ≡ sector **G,** correspond to the enthalpy determined processes.

Dissolution processes

Figure 2a indicates that the insertion of any substituent in molecule **I** improves the solubility in the buffer solution (except compound **III**). In addition, the dissolution enthalpy and entropy of the substituted molecules are reduced in comparison with molecule **I**: the enthalpy terms are reduced more than the entropy ones (all the data points are located in sector D). It means that the dissolution processes become more exothermic and the system (solute - buffer) – more ordered. The negative entropy values for most of the compounds (Table 2) indicate a manifestation of the so-called "hydrophobic effects", i.e. an increase in the ordering of the hydration shells and neighboring water molecules.

The introduction of the halogen atoms (F- and Cl-) in the para- position of the phenyl fragment of molecule **I** increases the solubility ($X_2^{buf}(II)/X_2^{buf}(I)$ =6.3; $X_2^{buf}(IV)/X_2^{buf}(I)$ =102), whereas the insertion of the methyl group produces the opposite effect ($X_2^{buf}(III)/X_2^{buf}(I)$ =0.5).

Introduction of the methyl group in positions *3*- and *5*- of the adamantane fragment produces different effects on solubility as compared to that of the compounds unsubstituted for these positions. For example, the following regularity for the substances with a substituent at the *para*- position of the phenyl moiety is observed: F- $X_2^{buf}(V)/X_2^{buf}(II)$ =1.8; CH_3- $X_2^{buf}(IV)/X_2^{buf}(III)$ =25.2; Cl- $X_2^{buf}(VII)/X_2^{buf}(IV)$ =0.35.

The solubility processes for compounds **I**-**V** are enthalpy determined (Table 2, Figure 1SI), whereas for **VI**-**VIII** – entropy determined. Apparently, for the latter compounds the entropic terms play an important role due to the presence of the hydrophobic methyl groups both in the adamantane and phenyl moieties.

Hydration processes

The thermodynamic functions of hydration are shown in Table 2. Figure 2b shows the relationship between the solvation thermodynamic functions in buffer (pH 7.4) for the substituted adamantane derivatives of sulfonamides (i) relative to unsubstituted compound **I**. The introduction of any substituents in molecule **I** leads to the hydration improvement (a decrease in $\Delta\Delta G_{hydr}^{i-I}$). And the maximal gain in the hydration Gibbs energy is achieved by inserting a Cl- group at the para- position of the phenyl fragment (**IV**) ($\Delta\Delta G_{hydr}^{IV-I}$ =-17 kJ·mol^{-1}), and also for compound **VIII** ($\Delta\Delta G_{hydr}^{IV-I}$ =-19.8 kJ·mol^{-1}). For compounds **II**, **V**, **VI**, the gain $\Delta\Delta G_{hydr}^{i-I}$ is approximately the same and is in the range from -5.6 to -4.6 kJ·mol^{-1}, but the ratio between the enthalpy and entropy terms is different. In accordance with the gain in the hydration enthalpies, the substances are ranged in the following order: $\Delta\Delta H_{hydr}^{VI-I} < \Delta\Delta H_{hydr}^{II-I} < \Delta\Delta H_{hydr}^{V-I}$ (hydration enthalpies of the investigated compounds (negative values) are higher (by the absolute value) that such value for **I**). In its turn, the gain in the entropy terms was revealed to follow the same trend. The enthalpy terms change synchronously with the entropy ones, which results in approximately equal $\Delta\Delta G_{hydr}^{i-I}$-values for the considered compounds. It should be noted that the hydration terms of compounds **I**, **IV** and **V** are approximately the same and, therefore, the gain in the hydration Gibbs energy of **IV** and **V** as compared to **I** is only facilitated by a gain in the hydration enthalpy terms.

As it was mentioned above, dissolution is the result of the imbalance of two fundamental processes: sublimation and solvation/hydration. The results of analysing the Gibbs energies of dissolution, hydration and sublimation of compounds **II**-**VIII** as compared to unsubstituted compound **I** are shown in Figure 3. Introduction of the substituent at the para- position of the phenyl ring of compound **I** increases the sublimation Gibbs energy (reducing the saturated vapor pressure) as compared to the unsubstituted compound (**II**-**IV**). In contrast, the introduction of the methyl groups at positions *3*- and *5*- of the adamantane fragment (**II** and **V**), (**III** and **VI**) and (**IV** and

TABLE 2 Thermodynamic solubility and solvation functions of the compounds studied in buffer (pH 7.4), 1-octanol and 1-hexane at 298 K and p^0 = 0.1 MPa

	X_2^{298} [a] (mol frac)	ΔG^o_{sol} (kJ·mol^{-1})	ΔH^o_{sol} (kJ·mol^{-1})	$T\cdot\Delta S^o_{sol}$ (kJ·mol^{-1})	ΔS^o_{sol} (J·K^{-1}·mol^{-1})	ς_{Hsol} [b] %	ς_{TSsol} [c] %	$-\Delta G^0_{solv}$ (kJ·mol^{-1})	$-\Delta H^0_{solv}$ (kJ·mol^{-1})	$-T\Delta S^0_{solv}$ (kJ·mol^{-1})
					Buffer					
I	5.01·10^{-7}	35.9	28.2 ± 0.7	-7.7	-26 ± 1	78.6	-21.4	23.7	95.4	71.7
II	3.14·10^{-6}	31.4	16.8 ± 0.9	-14.6	-49 ± 2	53.5	-46.5	28.4	104.6	76.2
III	2.69·10^{-7}	37.7	46.1 ± 0.8	8.4	28 ± 1	84.6	15.4	32.5	108.3	75.8
IV	5.12·10^{-5}	24.5	14.7 ± 0.6	-9.8	-33 ± 1	60.0	-40.0	40.7	111.5	70.8
V	5.75·10^{-6}	29.9	19.9 ± 1.0	-10.0	-34 ± 2	66.6	-33.4	28.3	100.9	72.2
VI	6.79·10^{-6}	29.5	5.9 ± 0.2	-23.6	-79 ± 3	20.0	-80.0	29.3	109.2	79.9
VII	1.77·10^{-5}	27.1	7.6 ± 0.3	-19.5	-65 ± 3	28.0	-72.0	36.6	120.7	84.1
VIII	7.04·10^{-6}	29.4	11.5 ± 0.9	-17.9	-60 ± 5	39.1	-60.9	43.5	140.1	96.6
					1-Octanol					
I	1.44·10^{-2}	10.0	28.8 ± 0.3	18.8	63 ± 2	60.5	39.5	49.6	94.8	45.2
II	1.81·10^{-2}	9.9	21.6 ± 0.8	11.7	39 ± 2	64.9	35.1	49.9	99.8	49.9
III	1.00·10^{-2}	11.4	29.1 ± 0.9	17.7	59 ± 3	62.2	37.3	58.8	125.3	66.5
IV	4.81·10^{-3}	13.2	27.2 ± 1.1	14.0	47± 2	66.0	34.0	52.0	99.0	47.0
V	1.46·10^{-2}	10.5	36.8 ± 0.5	26.3	88 ± 4	58.3	41.7	47.7	84.0	35.9
VI	5.92·10^{-3}	12.7	32.3 ± 0.6	19.6	66 ± 4	62.2	37.8	46.1	82.8	36.7
VII	5.35·10^{-3}	13.0	38.2 ± 1.1	25.2	85 ± 5	60.3	39.7	50.7	90.1	39.4
VIII	2.84·10^{-3}	14.6	27.1 ± 0.2	12.5	42 ± 2	68.4	31.6	58.3	124.5	66.2
					1-Hexane					
I	2.92·10^{-4}	20.2	29.9 ± 0.4	9.7	33 ± 1	75.5	24.5	39.4	93.7	54.3
II	4.62·10^{-4}	19.0	36.2 ± 0.9	17.2	58 ± 2	67.8	32.2	40.8	85.2	44.4
III	1.77·10^{-4}	21.4	38.9 ± 0.8	17.5	59 ± 2	69.0	31.0	48.8	115.5	66.7
IV	1.24·10^{-4}	22.3	38.3 ± 1.3	16.0	54 ± 2	70.5	29.5	42.9	87.9	45.0
V	5.26·10^{-4}	18.7	45.8 ± 1.5	27.1	91 ± 6	62.8	37.2	39.5	75.0	35.1
VI	1.92·10^{-4}	21.2	38.1 ± 1.3	16.9	57 ± 3	69.3	30.7	37.6	77.0	39.4
VII	1.43·10^{-4}	21.9	51.2 ± 0.6	29.3	98 ± 4	63.6	36.4	41.8	77.1	35.3
VIII	4.71·10^{-6}	30.4	53.8 ± 0.7	23.4	78 ± 4	69.7	30.3	52.5	97.8	55.3

[a] relative standard uncertainty for solubility values $u_r(X_2)$ = 0.03

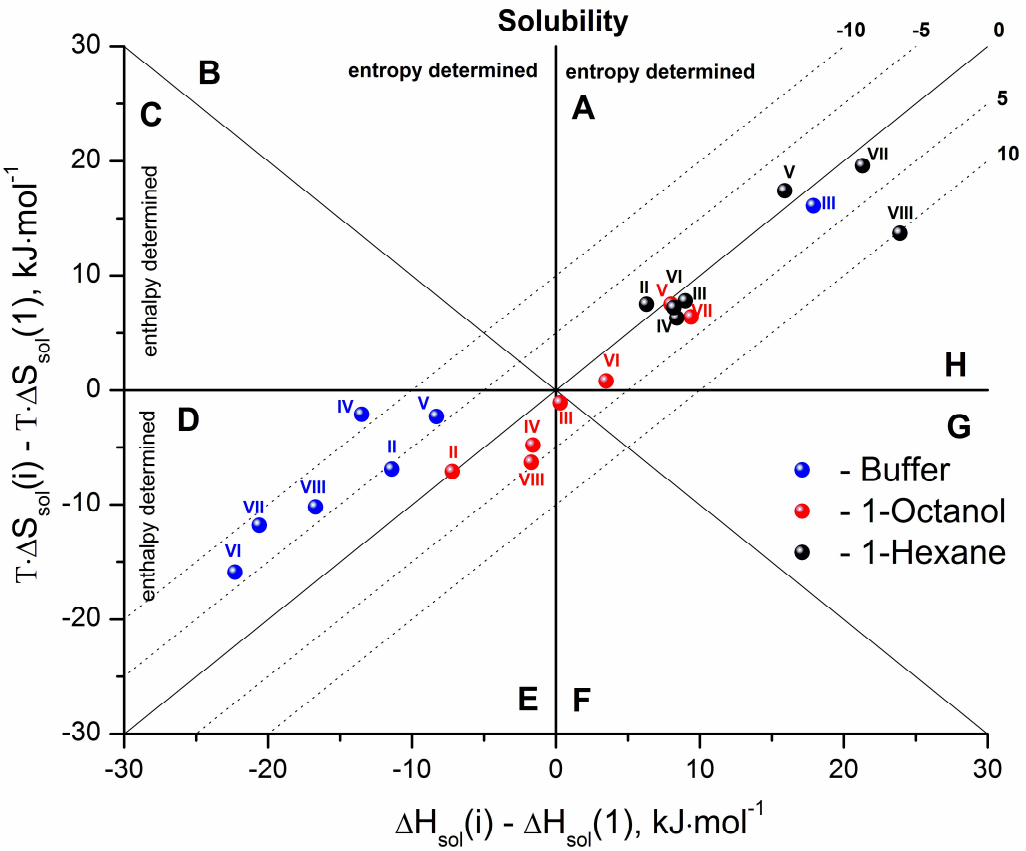
[b] $\varsigma_{Hsol} = (\Delta H^o_{sol}/(|\Delta H^o_{sol}| + |T\cdot\Delta S^o_{sol}|))\cdot 100\%$;

[c] $\varsigma_{TSsol} = (T\cdot\Delta S^o_{sol}/(|\Delta H^o_{sol}| + |T\cdot\Delta S^o_{sol}|))\cdot 100\%$

TABLE 3 Temperature dependencies of saturation vapor pressure of the compounds studied and their thermodynamic characteristics

VII[a]				VIII[b]			
t [°C]	*P* [Pa]	t [°C]	*P* [Pa]	t [°C]	*P* [Pa]	t [°C]	*P* [Pa]
92.0	$6.10\cdot10^{-3}$	118.0	$8.78\cdot10^{-2}$	146.0	$1.93\cdot10^{-1}$	158.0	$5.50\cdot10^{-1}$
96.0	$9.70\cdot10^{-3}$	120.0	$1.10\cdot10^{-1}$	148.0	$2.33\cdot10^{-1}$	160.0	$7.02\cdot10^{-1}$
99.0	$1.38\cdot10^{-2}$	122.0	$1.29\cdot10^{-1}$	150.0	$2.94\cdot10^{-1}$	162.0	$8.76\cdot10^{-1}$
102.0	$1.87\cdot10^{-2}$	125.0	$1.81\cdot10^{-1}$	152.0	$3.38\cdot10^{-1}$	164.0	1.00
104.0	$2.17\cdot10^{-2}$	125.5	$1.88\cdot10^{-1}$	153.0	$3.95\cdot10^{-1}$	165.0	1.14
106.0	$2.77\cdot10^{-2}$	127.0	$2.23\cdot10^{-1}$	154.0	$4.06\cdot10^{-1}$		
109.0	$3.92\cdot10^{-2}$	129.5	$2.60\cdot10^{-1}$	155.0	$4.75\cdot10^{-1}$		
112.0	$5.36\cdot10^{-2}$	135.0	$4.38\cdot10^{-1}$	156.0	$5.03\cdot10^{-1}$		
ΔG^{298}_{sub}	[kJ·mol^{-1}]	63.7 ± 1.9		ΔG^{298}_{sub}	[kJ·mol^{-1}]	72.9 ± 2.1	
ΔH^{T}_{sub}	[kJ·mol^{-1}]	122.3 ± 1.0		ΔH^{T}_{sub}	[kJ·mol^{-1}]	139.7 ± 2.7	
ΔH^{298}_{sub}	[kJ·mol^{-1}]	128.3 ± 1.0		ΔH^{298}_{sub}	[kJ·mol^{-1}]	151.6 ± 2.7	
$C^{298}_{p,cr}$ [c]	[J·mol^{-1}·K^{-1}]	454.9		$C^{298}_{p,cr}$ [c]	[J·mol^{-1}·K^{-1}]	629.6	
$T \cdot \Delta S^{298}_{sub}$	[kJ·mol^{-1}]	64.6 ± 2.4		$T \cdot \Delta S^{298}_{sub}$	[kJ·mol^{-1}]	78.7 ± 3.1	
T_m	[K]	434.9 ± 0.2		T_m	[K]	563.6 ± 0.2	
ΔH^{T}_{fus}	[kJ·mol^{-1}]	37.1 ± 0.5		ΔH^{T}_{fus}	[kJ·mol^{-1}]	-[d]	

[a] $\ln(P[Pa]) = (35.2 \pm 0.2) - (14715 \pm 94)/T$; $\sigma = 1.4\cdot10^{-2}$; $r = 0.9994$; $n=16$;
[b] $\ln(P[Pa]) = (38.5 \pm 0.8) - (16809 \pm 325)/T$; $\sigma = 3.6\cdot10^{-2}$; $r = 0.9980$; $n=13$;
[c] $C^{298}_{p,cr}$ has been calculated by Chikcos additive scheme[14] the error of the calculation procedure corresponds to significant digit;
[d] Complex heat effect.



a

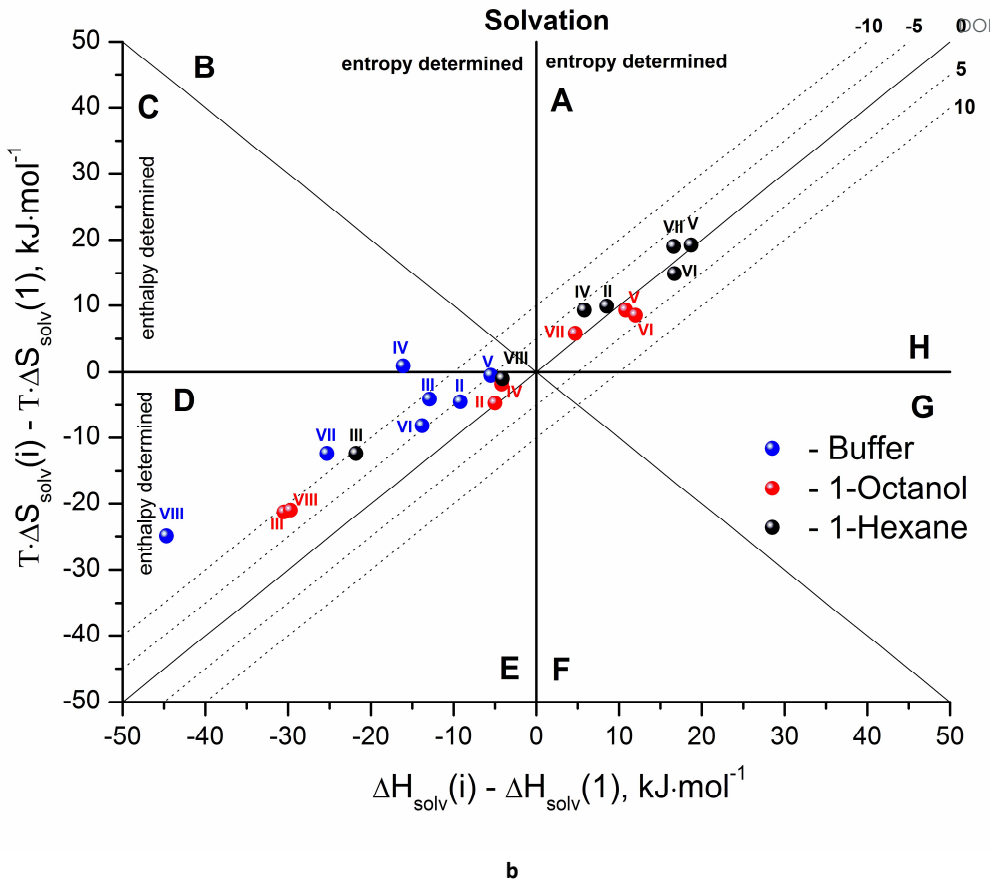
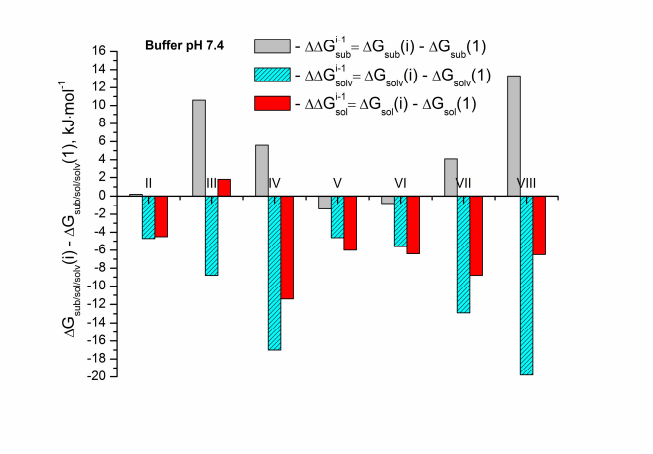


Fig. 2 Relationship between the thermodynamic functions of (a) the dissolution and (b) solvation processes in buffer (pH 7.4), 1-octanol and 1-hexane for the substituted adamantane derivatives of sulfonamides (i) relative to the unsubstituted compound I. The isoenergetic curves of the Gibbs energy are marked by dotted lines. See Figure 1 for numbering of the compounds.

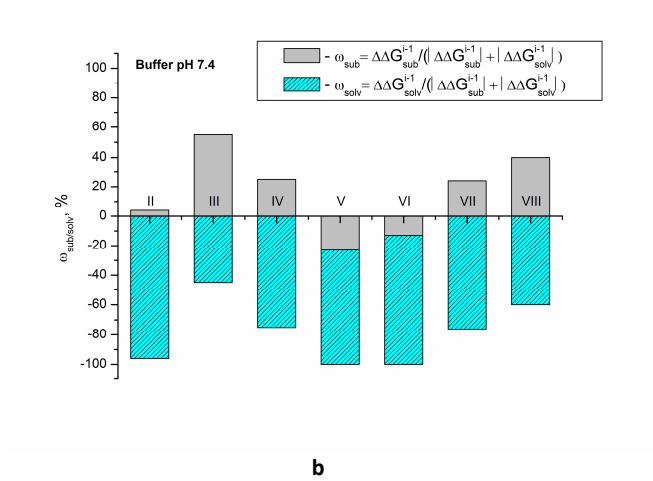
VII) leads to a sublimation Gibbs energy decrease. It is worth noting that the dispersion of the sublimation Gibbs energy values in comparison with the unsubstituted compound is 13.3 kJ·mol^{-1}. This value is less than the energy of a hydrogen bond. Thus, it can be assumed that the design strategy of this class of compounds should be based on the fact that when the substance dissolution (the transition from the crystal to the solution) leads to additional formation of hydrogen bonds.

The analysis of the difference in the hydration Gibbs energy of the substituted and unsubstituted adamantane derivatives of sulfonamide showed a picture significantly different from the previous case. All of the compounds show a decrease in the values of the hydration Gibbs energy in comparison with **I**. The dispersion of these values compared to the unsubstituted compound is 19.8 kJ·mol^{-1}. The sublimation and hydration terms of compounds **II**, **III**, **IV**, **VII** and **VIII** make multi-directional contributions to the dissolution process (i.e. have different signs). Moreover, for compounds **II**, **IV**, **VII** and **VIII**, the hydration contributions are superior to the sublimation ones, which results in the solubility improvement of the substituted molecules as compared to the unsubstituted one. In contrast, for compound **III**, the sublimation contribution is superior to the hydration one, which results in a decrease in the compound solubility in comparison with the unsubstituted one. For compounds **V** and **VI**, the sublimation and hydration terms make equally directional contributions (i.e. those with the same sign) to the dissolution process, reducing the Gibbs energy of both sublimation and hydration during the transition from the unsubstituted to the substituted molecule. In this case, the effects reinforce each other, which are reflected in the improvement of the solubility values. It is this case that is most favorable in designing molecules with improved solubility as it makes the best use of the potential solubility increase both by modifying the crystal lattice and by improving the hydration.

It was interesting to compare the contributions of the Gibbs energy of sublimation and hydration to the process of dissolution in percentage terms. The results are given in Figure 3b. It is evident that the ratio of the considered terms varies widely. For example, in compound **II**, the sublimation term is only 4%, whereas the hydration one – 96%. In turn, for compound **III**, the sublimation term reaches 55%, whereas the hydration one – 45%. In other words, when designing an unsubstituted molecule for compound **II**, the main contribution to the solubility increase is practically made through improvement of the hydration characteristics of the molecule. On the other hand, for compound **III**, the sublimation term exceeds the hydration one, which leads to lowering the solubility values.



a



b

Fig. 3 (**a**) The Gibbs energy differences between the substituted adamantane derivatives of sulfonamides and compound **I** for the following processes: sublimation (grey), hydration (cyan), solubility (red); (**b**) the relative contribution (in percentage) of the sublimation (grey) and hydration (cyan) Gibbs energies to $\Delta\Delta G^{i-I}_{sol}$ of the compounds.

Processes of dissolution and solvation in 1-octanol

In order to reveal the influence of the substituents introduced into molecule **I** on the thermodynamic characteristics of the dissolution and solvation processes in 1-octanol, we used the approach applied in the previous sections.

Dissolution processes

Figure 2a shows that the introduction of the F- atom only in the para- position of the phenyl ring (II) slightly improves the solubility in 1-octanol as compared to the unsubstituted molecule: $X_2^{oct}(II)/X_2^{oct}(I)$=1.3. For compound **V**, the solubility is practically invariable: $X_2^{oct}(V)/X_2^{oct}(I)$=1.01, whereas for the other compounds, the solubility decreases. For all the considered compounds the dissolution processes are enthalpy determined (Table 2, Figure 1SI) with positive dissolution enthalpy and entropy values (the entropy terms for the buffer solutions have a negative sign). It should be noted that the dissolution enthalpies (on average) are higher than the respective values for buffer solutions, while the dissolution entropies are comparable by the absolute values. Only the difference in the entropic term sign explains better solubility of the selected compounds in 1-octanol compared to the buffer (this value ranges from 103 to 4·104 times). Introduction of a methyl group in positions 3- and 5- of the adamantane fragment produces different effects on the solubility in comparison with the compounds unsubstituted for these positions. For example, for the compounds with a substituent in the para- position of the phenyl fragment, the following situation is observed: F- $X_2^{oct}(V)/X_2^{oct}(II)$=0.8 (in buffer – 1.8); CH_3- $X_2^{oct}(VI)/X_2^{oct}(III)$=0.6 (in buffer – 25.2); Cl- $X_2^{oct}(VII)/X_2^{oct}(IV)$=1.1 (in buffer – 0.35).

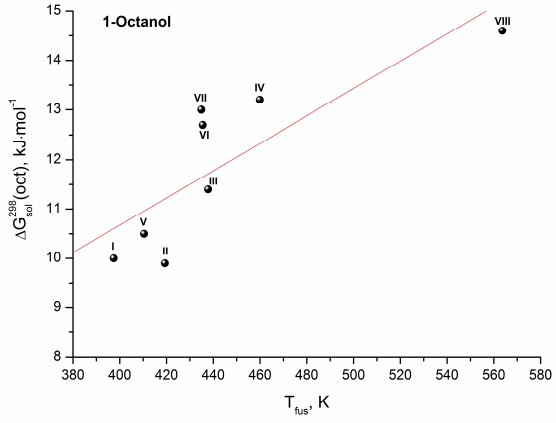
To predict the values of the compounds solubility in 1-octanol, we tried to find a correlation between the dissolution Gibbs energy and different descriptors. In order to describe the process of dissolution, it is quite normal to use the melting point (T_{fus}) as a descriptor,[17,18] as it imitates the sublimation Gibbs energy of the substance (solid-state thermodynamic state) Figure 4a shows a relationship between the above mentioned values that can be described by the following equation:

$$\Delta G^{298}_{sol}(oct) = (-0.4 \pm 3.4) + (0.028 \pm 0.008) \cdot T_{fus} \qquad (10)$$

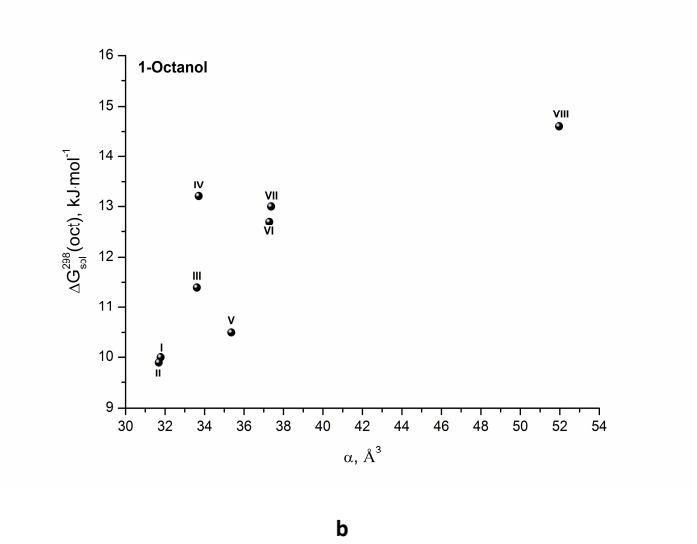
R = 0.8294; σ = 1.04; n = 8

Unfortunately, the correlation coefficient is rather low, but a certain connection between the increase in the dissolution Gibbs energy (reducing the solubility) with the increase in the melting point of the compounds is observed. Moreover, this equation gives an opportunity of $\Delta G^{298}_{sol}(oct)$ prediction with an accuracy of 1.04 kJ·mol^{-1}.

We tried to find correlations between $\Delta G^{298}_{sol}(oct)$ and HYBOT physicochemical descriptors.[16] For this purpose, we tested 13 different descriptors. Unfortunately, a correlation of the analyzed variables was only found between $\Delta G^{298}_{sol}(oct)$ and molecular polarizability (α) (Figure 4b).



a



b

Fig. 4 Dependences of the dissolution Gibbs energies of the compounds in 1-octanol ($\Delta G^{298}_{sol}(oct)$) on the fusing temperatures (T_{fus}) **(a)** and molecular polarizability (α) **(b)**

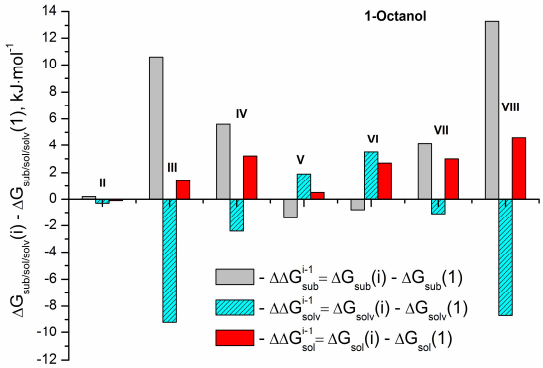
As the molecular polarizability increases, the solubility in 1-octanol goes down and it may be associated with a significant predominance of non-specific van der Waals interactions in the crystal lattice as compared to similar interactions (solute-solvent ones). It should be noted that the correlation coefficient is rather low (0.775), which does not allow the prediction of the solubility with the required accuracy.

Solvation processes

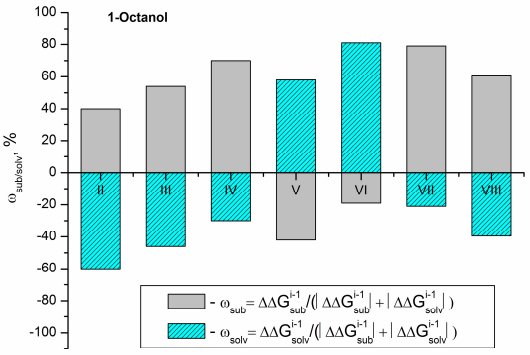
The solvation thermodynamic functions are shown in Table 2. Figure 2b represents the relationship between the solvation thermodynamic functions in 1-octanol for the substituted adamantane derivatives of sulfonamides (i) relative to unsubstituted compound **I**. Introduction of any substituents in the para- position of the phenyl moiety of molecule **I** improves the solvation ($\Delta\Delta G^{i-I}_{solv}$ decreases). And the greatest gain in the solvation Gibbs energy is achieved by placing a methyl group (**III**) in this position ($\Delta\Delta G^{III-I}_{solv}$ =-9.2 kJ·mol^{-1}). A smaller solvation effect is observed for the Cl-substituted compound (**IV**) ($\Delta\Delta G^{IV-I}_{solv}$ =-2.4 kJ·mol^{-1}), whereas for the F- substituted one (**II**) a smaller gain in the solvation Gibbs energy in comparison with the unsubstituted compound ($\Delta\Delta G^{II-I}_{solv}$ =-0.3 kJ·mol^{-1}) is observed. By the gain of the solvation enthalpy, the substances can be ranged as follows: $\Delta\Delta H^{III-I}_{solv} < \Delta\Delta H^{II-I}_{solv} < \Delta\Delta H^{IV-I}_{solv}$ (the solvation enthalpy values of the selected compounds (negative values) are higher (by the absolute value) than the same values for **I**). In turn, the gain in the entropic term has the same tendency.

Analysis of the differences between the two processes (sublimation and solvation) will be carried out in the same way as it was done for the buffer. The results of the dissolution, solvation and sublimation Gibbs energies of compounds **II-VIII** in comparison with unsubstituted compound **I** are summarized in Figure 5. All the data concerning the process of sublimation was presented above when discussing the buffer solutions. Unlike the buffer solution (where the values of the differences in the solvation Gibbs energies of the substituted and unsubstituted compounds were negative for all the compounds); for substances **II-IV**, **VII** and **VIII**, the discussed values are negative, whereas for compounds **V** and **VI** – positive. In turn, for the sublimation terms, the opposite trend is observed. Thus, the sublimation and solvation contributions to the dissolution Gibbs energy of all the considered compounds are oppositely directed, and the final result (i.e. the dissolution Gibbs energy) depends on the ratio of the absolute values of the terms under discussion. Only for compound **II** the solvation contribution exceeds the sublimation one, which improves the solubility values if such structural modification of the molecule takes place. For compounds **III-VIII**, the sublimation contributions exceed the solvation ones. And since the former ones are positive, the solubility values for these compounds decrease. For compounds **V** and **VI**, the solvation contributions exceed sublimation. However, since the solvation contributions have positive signs and the sublimation ones are negative, the resulting value of the solubility of the modified molecules decreases in comparison with **I**.

It was interesting to compare the contributions of the sublimation and solvation Gibbs energies with the dissolution process in percentage terms. The results are presented in Figure 5b. It is evident that the ratios of the considered terms vary widely. For example, for compound **VI** the sublimation term is 19%, whereas the solvation one – 81%. On the other hand, for compound **VII** the sublimation term is 79%, whereas the solvation one – 21%. Thus, we can conclude that if the structural modification of reference molecule **I** occurs, the dissolution processes for compounds **III**, **IV**, **VII** and **VIII** are controlled by the crystal lattice. Whereas for compounds **II**, **V** and **VI**, the dissolution processes are controlled by the solvation phenomena.



a



b

Fig. 5 (**a**) The Gibbs energy differences between the substituted adamantane derivatives of sulfonamides and compound **I** for the following processes: sublimation (grey), solvation (cyan), solubility (red); (**b**) the relative contribution (in percentage) of the sublimation (grey) and solvation (cyan) Gibbs energies to $\Delta\Delta G^{i-I}_{sol}$ of the compounds.

Processes of dissolution and solvation in 1-hexane

As in the previous sections, here we will make a similar analysis of the dissolution and solvation processes in 1-hexane.

Dissolution processes

In order to reveal the influence of the substituents introduced into molecule **I** on the thermodynamic characteristics of the dissolution and solvation / hydration processes, we analyzed the differences of these thermodynamic functions of the substituted and unsubstituted (**I**) compounds. To do this, we used the diagram method. Figure 2 shows the differences of the thermodynamic functions of the dissolution processes (a) and solvation (b) between the substituted and unsubstituted molecules in 1-hexane at 298 K.

Figure 2a shows that the solubility in 1-hexane increases at inserting an F- atom in the *para*- position of the phenyl ring (**II**), and also at the simultaneous introduction of an F-atom in the *para*- position of the phenyl ring and methyl groups in positions *3*- and *5*- of the adamantane fragment (**V**). All the other considered modifications of the molecule lead to a solubility improvement. The solubility processes for all the compounds under consideration are enthalpy determined (Table 2, Figure 1SI) (like those in 1-octanol) with the positive dissolution enthalpy and entropy values. As opposed to 1-octanol, the dissolution enthalpies in 1-hexane are higher, whereas the entropy terms for the two considered solvents are comparable. It is this fact that explains a large difference in the solubility of the chosen compounds in 1-octanol and 1-hexane.

Introduction of an F-atom in the *para*-position of the phenyl fragment of molecule **I** improves the solubility ($X_2^{hex}(II)/X_2^{hex}(I)$=1.6), whereas the insertion of a Cl- atom or methyl group leads to the opposite effect ($X_2^{hex}(IV)/X_2^{hex}(I)$=0.24; $X_2^{hex}(III)/X_2^{hex}(I)$=0.6). Introduction of methyl groups in positions 3- and 5- of the adamantine fragment raises the solubility as compared to the compounds unsubstituted in these positions by approximately the same number of times: for F- $X_2^{hex}(V)/X_2^{hex}(II)$=1.14; for CH_3- $X_2^{hex}(VI)/X_2^{hex}(III)$=1.08; for Cl- $X_2^{hex}(VII)/X_2^{hex}(IV)$=1.15.

To predict the solubility values of the studied compounds in 1-hexane, we tried to find correlations between the dissolution Gibbs energies $\Delta G^{298}_{sol}(hex)$ and different descriptors (as in case with 1-octanol). It should be noted that there is a good correlation between $\Delta G^{298}_{sol}(hex)$ and melting temperatures of the investigated compounds (Figure 6a):

$$\Delta G^{298}_{sol}(hex) = (-9 \pm 3) + (0.069 \pm 0.007) \cdot T_{fus} \qquad (11)$$

R = 0.9710; σ = 0.95; n = 8

The comparison of this correlation equation with the analogous one for 1-octanol clearly demonstrates that the dissolution Gibbs energy is more sensitive to the change of T_{fus} in 1-hexane than in 1-octanol (by more than two times).

We also tried to find correlations between $\Delta G^{298}_{sol}(hex)$ and HYBOT physicochemical descriptors.[16] A correlation between $\Delta G^{298}_{sol}(hex)$ and molecular polarizability (α) was revealed (Figure 6b):

$$\Delta G^{298}_{sol}(hex) = (3 \pm 3) + (0.52 \pm 0.09) \cdot \alpha \qquad (12)$$

R = 0.9256; σ = 1.5; n = 8

Thus, the solubility of the considered compounds in 1-hexane can be assessed based on the melting temperatures and molecular polarizabilities.

Solvation processes

The solvation thermodynamic functions are presented in Table 2. Figure 2b shows the relationship between the solvation thermodynamic functions in 1-hexane for the substituted adamantane derivatives of sulfonamides (i) relative to unsubstituted compound **I**. The introduction of the substituents in the para- position of the phenyl moiety of molecule **I** improves the solvation ($\Delta\Delta G^{i-I}_{solv}$ decreases) (with the exception of **VI**). Moreover, the greatest gain in the solvation Gibbs energy is achieved by placing a methyl group (**III**) in this position ($\Delta\Delta G^{III-I}_{solv}$=-9.4 kJ·mol^{-1}). Then, these effects can be arranged as follows (in descending order): for the Cl- substituted compound (**IV**) – $\Delta\Delta G^{IV-I}_{solv}$ = -3.5 kJ mol^{-1}, for the F- substituted one (**II**) – $\Delta\Delta G^{II-I}_{solv}$ =-1.4 kJ·mol^{-1}. It should be noted that compounds with methyl substituents at positions *3*- and *5*- of the adamantane fragment (**V** and **VI**) are solvated in relation to the initial compound (**I**) as follows: $\Delta\Delta G^{V-I}_{solv}$ = -0.1 kJ·mol^{-1} and $\Delta\Delta G^{VI-I}_{solv}$ = 1.8. The solvation enthalpy and entropy of all the

compounds (except **III** and **VIII**) are lower (by the absolute value) than those of the unsubstituted compound.

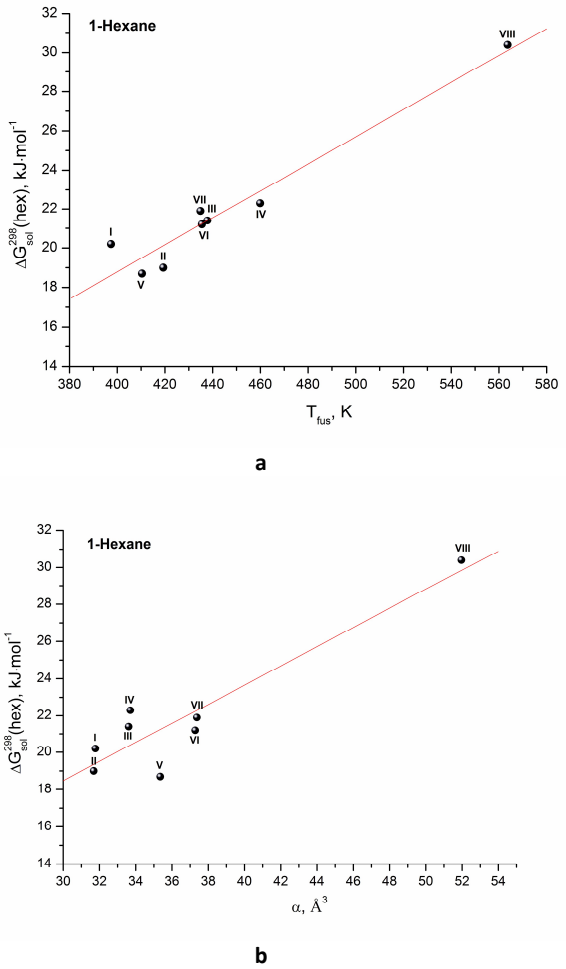


Fig. 6 Dependences of the dissolution Gibbs energies of the compounds in 1-hexane ($\Delta G^{298}_{sol}(hex)$) on the fusion temperatures (T_{fus}) **(a)** and molecular polarizability (α) **(b)**

Analysis of the differences of the two processes (sublimation and solvation) will be carried out in the same way as it was done for the buffer and 1-octanol. The Gibbs energy values of the dissolution, solvation and sublimation processes of compounds **II**-**VIII** as compared to unsubstituted compound **I** are summarized in Figure 7a. Everything that concerns the sublimation process has been described above. The differences of the solvation Gibbs energies of the substituted and unsubstituted compounds **II**-**V**, **VII** and **VIII** are negative, whereas for compound **VI** – positive (the intermediate case is between the buffer and 1-octanol). The sublimation and solvation contributions to the dissolution Gibbs energy of all the compounds considered are oppositely directed, so the final result (i.e. the dissolution Gibbs energy) depends on the ratio of the absolute values of the terms under discussion. An exception is compound **V**, where the modification of the molecule leads to a gain both in the sublimation and solvation terms.

Therefore, such design of the molecule unequivocally improves the solubility in 1-hexane. For compounds **II**-**IV**, **VII** and **VIII** the sublimation term is lower than that of the unsubstituted molecule (the saturated vapor pressure reduction). In turn, these molecules solvate better than the unsubstituted one. However, only for compound **II** the solvation term prevails over the sublimation one (improved solubility). For the other compounds, such effect is not observed and, consequently, the solubility does not increase. The modification of molecule **I** producing molecule **VI** leads to a gain in the sublimation term (the vapor pressure increases), but a significant loss of the solvation term (covering the first term) as well. The result is a solubility decrease.

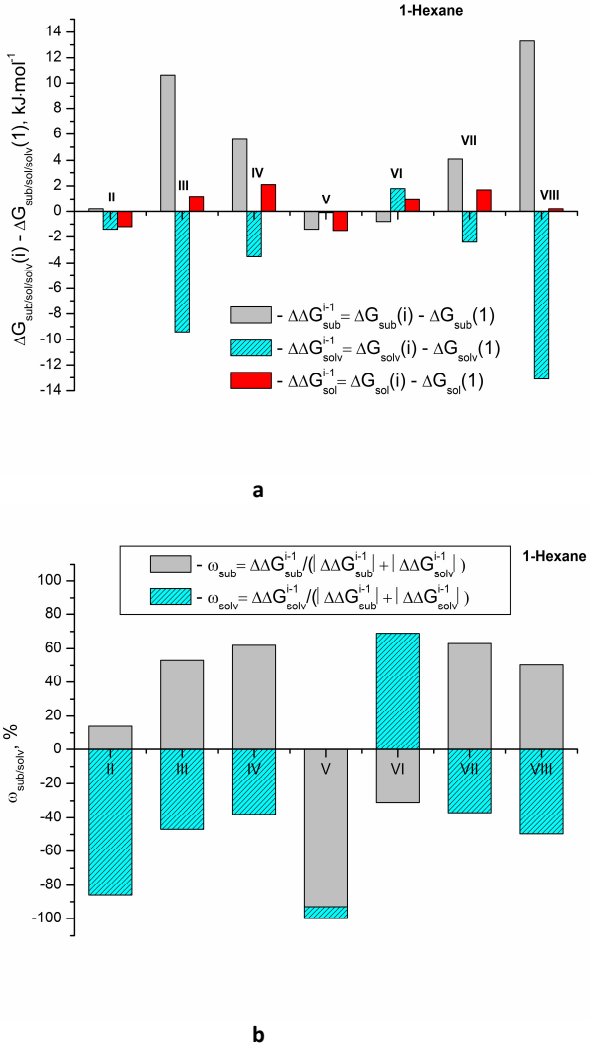


Fig. 7 (**a**) The Gibbs energy differences between the substituted adamantane derivatives of sulfonamides and compound **I** for the following processes: sublimation (grey), solvation (cyan), solubility (red); (**b**) the relative contribution (in percentage) of the sublimation (grey) and solvation (cyan) Gibbs energies to $\Delta\Delta G^{i-I}_{sol}$ of the compounds.

The comparison of the contributions of the Gibbs energies of sublimation and solvation to the dissolution process in percentage terms is shown in Figure 7b. It is

evident that the ratios of the considered terms vary widely. For example, for compound **V** the sublimation term is 93%, whereas the solvation one – 7%. On the other hand, for compound **II** the sublimation term is 14%, whereas the solvation one is 86%.

Transfer processes

Transfer (distribution) of a substance in biological fluids is a vitally important process. These processes are essential steps/stages of passive transport of drug compounds across the membranes of different nature. The distribution processes in biological media are normally simulated by the model immiscible binary solvent systems: (buffer - 1-octanol) – to describe membranes of GIT and (buffer - 1-hexene) – to describe the BBB. It should also be noted that the transfer of a substance from 1-hexane to 1-octanol describes the processes of drug compound penetration from GIT into the brain cortex. On this basis, we will consider all of these processes for the selected compounds. Figure 8 (Table 4SI) summarizes the experimental values of the transfer thermodynamic functions in the coordinates of entropy – enthalpy terms (the approach which was used by us above but in the absolute expression of the values (not relative to compound **I**)).

On average, the compounds considered have higher distribution coefficients in the (buffer → 1-octanol) system in comparison with the (buffer → 1-hexane) one. The transfer Gibbs energies of the system (1-hexane → 1-octanol) are approximately equal (from -8.5 to -10.2 kJ·mol^{-1}) for all the compounds except **VIII** (-15.2 kJ·mol^{-1}). These values coincide with the mean values of the transfer in the system (buffer → 1-hexane), however, they differ significantly by the values of enthalpy and entropy terms. The transfer processes in (buffer → 1-octanol) and (buffer → 1-hexane) are entropy determined (except compound **III** for (buffer → 1-octanol) and **VII** for (buffer → 1-hexane)). And the transfer processes (1-hexane → 1-octanol) are determined by enthalpy (except compound **I**). In other words, the main driving force of the transition of a substance from one phase to another for the entropy determined processes is the increase in the disorder of the system in the octanol and hexane phases as compared to the buffer solution. Moreover, despite the fact that in case of such a transfer in these systems, the interactions of the molecules of the tested substances with 1-octanol and 1-hexane molecules are weaker than those with water, and the entropy factor prevails over the enthalpy one. In case of the molecules transfer from 1-hexane to 1-octanol, the opposite effect/trend is observed.

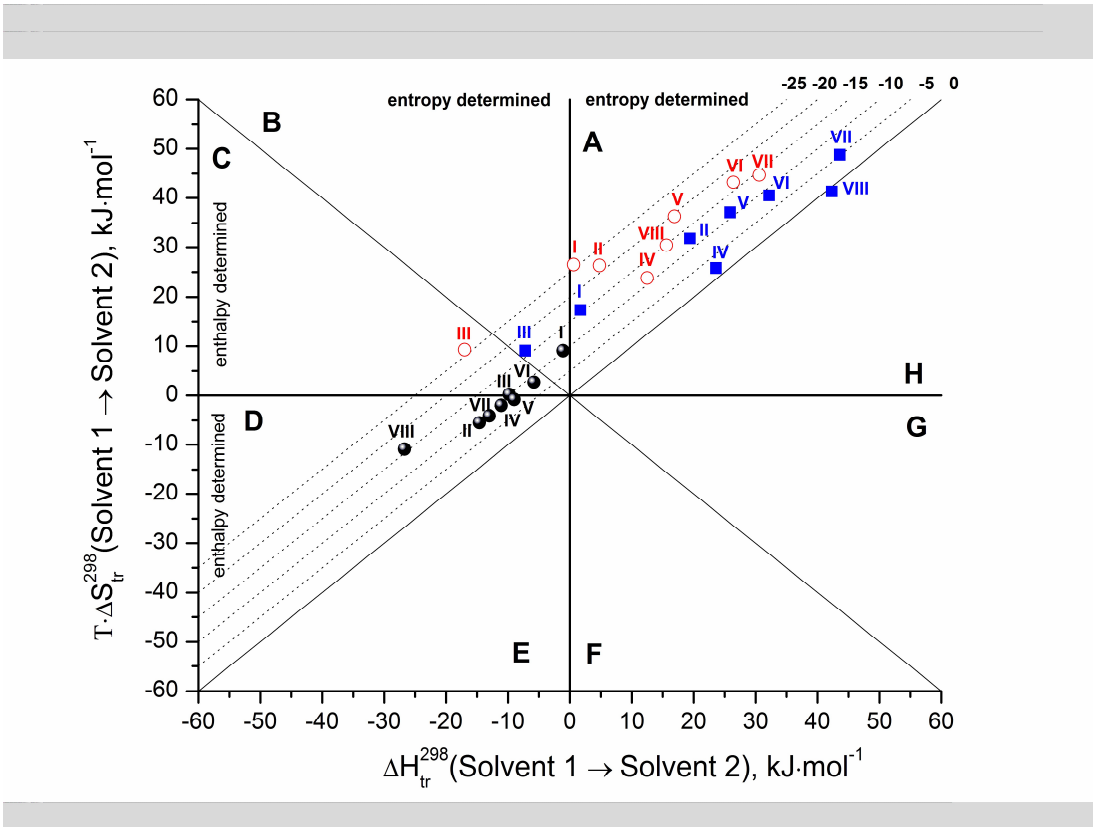


Fig. 8 Experimental data of the transfer processes of the investigated compounds (numbering corresponds to Figure 1) in coordinates of the entropy term on the enthalpy term for the systems: (buffer → 1-octanol) – red circles; (buffer → 1-hexane) – blue squares; (1-hexane → 1-octanol) – black circles.

The interaction of the investigated molecules with the 1-octanol molecules is stronger than with those of 1-hexane (as the first one has hydrogen bonding centers), which entails a decrease in the entropy (system ordering). However, the enthalpy term prevails over the entropy one, which is reflected in the negative values of the transfer Gibbs energy. It should be noted that the transfer processes for compounds **III** and **V** in (1-hexane → 1-octanol) system occur without an entropy change, only by the enthalpy factor (i.e. by enhancing the interactions of the substance with the molecules of 1-octanol as compared to 1-hexane. In turn, compound **I** has approximately the same interaction with the solvent molecules in different phases, but the entropy of transition changes significantly (toward disorder) for all the systems. The transfer of the molecules from 1-hexane to 1-octanol describes specific interactions of the solute with 1-octanol because 1-hexane is a solvent interacting with dissolved molecules only through non-specific (van-der-Waals) interactions. The ratio of the specific interactions (donor-acceptor ones, hydrogen bonds) to the non-specific ones is a very important characteristic of the substance in a certain solvent, which determines all transport properties (diffusion, permeability). In other words, it is this feature that is the clue to understanding membrane permeability processes.

It should be emphasized that the process of the transition from aqueous to octanol phase slightly differs from the distribution process between these phases. First of all this is determined by the existence of the mutual solubility of 1-octanol in water (the octanol content in water is 0.5 M/L) and water in 1-octanol (containing about 2.3 M/L of H_2O in octanol). The experimental distribution coefficients and those derived from the transfer procedure differ not essentially for compounds which are poor soluble in water[19] (The investigated substances belong just to that class of compounds). At that, for the highly soluble in water compounds the considered deviations can be essential and require carefully usage of the obtained parameters.

Conclusions

Eight adamantane derivatives of sulfonamides were synthesized and characterized. Temperature dependences of saturation vapor pressure were obtained by the transpiration method and thermodynamic functions of the sublimation processes were calculated. Thermophysical characteristics of fusion processes (melting points and fusion enthalpies) of the substances were measured by the DSC method. The solubility values of the selected compounds in buffer (pH 7.4), 1-octanol and 1-hexane were determined at different temperatures by the isothermal saturation method. The thermodynamic functions of solubility and solvation/hydration processes were studied. To determine the effect of the substituents introduced in the unsubstituted molecule on the thermodynamic characteristics of dissolution and solvation / hydration, we analysed the differences of these thermodynamic functions for substituted and unsubstituted compounds using the diagrammatic method. The influence of the crystal lattice (sublimation contribution) and solvation / hydration contributions on the solubility values of the investigated compounds in the selected solvent was demonstrated.

The contributions of the Gibbs energy of sublimation and hydration to the process of dissolution in the buffer (in percentage terms) were compared. For compound **II** the sublimation term is only 4%, whereas the hydration one – 96%. In turn, for compound **III**, the sublimation term reaches 55%, whereas the hydration one – 45%. In other words, when designing an unsubstituted molecule for compound **II**, the main contribution to the solubility increase is practically made through improvement of the hydration characteristics of the molecule. On the other hand, for compound **III**, the sublimation term exceeds the hydration one, which leads to lowering the solubility values.

It was compared the contributions of the Gibbs energy of sublimation and solvation to the process of dissolution in 1-octanol. For compound **VI** the sublimation term is 19%, whereas the solvation one – 81%. On the other hand, for compound **VII** the sublimation term is 79%, whereas the solvation one – 21%. Thus, we can conclude that if the structural modification of reference molecule **I** occurs, the dissolution processes for compounds **III**, **IV**, **VII** and **VIII** are controlled by the crystal lattice. Whereas for compounds **II**, **V** and **VI**, the dissolution processes are controlled by the solvation phenomena.

The contributions of the Gibbs energy of sublimation and solvation to the process of dissolution in 1-hexane were assessed. For compound **V** the sublimation term is 93%, whereas the solvation one – 7%. On the other hand, for compound **II** the sublimation term is 14%, whereas the solvation one is 86%.

The relationships between the solubility Gibbs energies in the selected solvents and melting points were obtained. The correlation equation between the solubility Gibbs energies in 1-hexane and molecular polarizability (α) was received. The transfer processes from buffer to 1-octanol, from buffer to 1-hexane and 1-hexane to 1-octanol were analyzed.

Acknowledgements

This work was supported by the Russian Science Foundation (No.14-13-00640).

References

1 G. L. Amidon, H. Lennernäs, V. P. Shah and J. R. Crison, *Pharm. Res.*, 1995, **12**, 413.
2 K. Gerzon, E. V. Krumalns, R. L. Brindle, F. J. Marshall and M. A. Root, *J. Med. Chem.*, 1963, **6**, 760.
3 R. T. Rapala, R. J. Kraay and K. Gerzon, *J. Med. Chem.*, 1965, **8**, 580.
4 K. Gerzon, and D. Kau, *J. Med. Chem.*, 1967, **10**, 189.
5 W. L. Davies, R. R. Grunert, R. F. Haff, J. W. McGahen, E. M. Neumayer, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann and C.E. Hoffmann, *Science*, 1964, **144**, 862.
6 A. Tsunoda, H. F. Maassab, K. W. Cochran and W. C. Eveland, *Antimicrob. Agents Chemother.*, 1965, **5**, 553.

View Article Online
DOI: 10.1039/C6CP00379F

7 K. S. Rosenthal, M. S. Sokol, R. L. Ingram, R. Subramanian and R. C. Fort, *Antimicrob. Agents Chemother.,* 1982, **22**, 1031.
8 Y. Dong, J. Chollet, H. Matile, S. A. Charman, F. C. Chiu, W. N. Charman, B. Scorneaux, H. Urwyler, J. Santo Tomas, C. Scheurer, C. Snyder, A. Dorn, X. Wang, J.M. Karle, Y. Tang, S. Wittlin, R. Brun and J. L. Vennerstrom, *J. Med. Chem.*, 2005, **48**, 4953.
9 X. Wang, Y. Dong, S. Wittlin, D. Creek, J. Chollet, S. A. Charman, J. SantoTomas, C. Scheurer, C. Snyder and J. L. Vennerstrom, *J. Med. Chem.*, 2007, **50**, 5840.
10 G. L. Perlovich, A. M. Ryzhakov, V. V. Tkachev and A. N. Proshin, *CrystEngComm.,* 2015, **17**, 753.
11 G. L. Perlovich, T. V. Volkova, A. N. Proshin, C. Trinh Bui and S. O. Bachurin, *Mol. Pharm.*, 2011, **8**, 1807.
12 W. Zielenkiewicz, G. Perlovich and M. Wszelaka-Rylik, *J. Therm. Anal. Calorim*. 1999, **57**, 225.
13 J. D. Cox and G. Pilcher, *Thermochemistry of Organic and Organometallic Compounds,* Academic Press, London, 1970.
14 J. S. Chickos and W. E. Jr. Acree, *J. Phys. Chem. Ref. Data*, 2002, **31**, 537.
15 G. L. Perlovich and A. Bauer-Brandl, *Curr. Drug Deliv.*, 2004, **1**, 213.
16 O. A. Raevsky, V. J. Grigor'ev and S. V. Trepalin, HYBOT program package, RU990090, 1999.
17 S. H. Yalkowsky and S. C. Valvani, *J. Pharm. Sci.* 1980, **69**, 912.
18 G. L. Perlovich, V. P.Kazachenko, N.N. Strakhova, K.-J. Schaper and O. A.Raevsky, *J. Chem. Eng. Data*, 2013, **58**, 2659.
19 O. A. Raevsky, G. L.Perlovich, V. P.Kazachenko, N. N.Strakhova, K-J. J. Schaper, *J. Chem. Eng. Data,* 2009, **54**, 3121.