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Short communication

Thermodynamic aspects of solubility process of some sulfonamides

German L. Perlovich[a,b,*], Alex M. Ryzhakov[b], Nadezda N. Strakhova[a], Vladimir P. Kazachenko[a], Klaus-Jürgen Schaper[c], Oleg A. Raevsky[a]

[a] Department of Computer-Aided Molecular Design, Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432 Chernogolovka, Russia
[b] Institute of Solution Chemistry, Russian Academy of Sciences, 153045 Ivanovo, Russia
[c] Research Center Borstel, Leibniz Center for Medicine and Biosciences, D-23845 Borstel, Germany

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ABSTRACT

The thermodynamic aspects of solubility process of sulfonamides with the general structures $C_6H_5–SO_2NH–C_6H_4–R$ (R = 4-NO_2; 4-Cl) and 4-$NH_2–C_6H_4–SO_2NH–C_6H_4–R$ (R = 4-NO_2; 4-CN; 4-Cl; 4-OMe; 4-C_2H_5) in water, phosphate buffer with pH 7.4 and n-octanol (as phases modeling various drug delivery pathways) were studied using the isothermal saturated method.

1. Introduction

Sulfonamides (SAs) are of fundamental chemical interest as many of them possess pharmacological, fungicidal, or herbicidal activities [1]. The chemotherapeutic activity of sulfonamides has been found in the early thirties of the last century. They are the first group of modern chemotherapeutic antibacterial drugs. Although the extensive use of antibiotics has diminished the usefulness of SAs, they still occupy a relatively small but important place in the therapeutic resources of physicians.

In our previous work [2–4] structures, sublimation, solubility, and solvation characteristics of 10 sulfonamides have been studied. As a continuation of the study, we present in this work a comparative analysis of published compounds (N-(4-chlorophenyl)-benzene-sulfonamide (**I**), 4-amino-N-(4-chlorophenyl)-benzene-sulfonamide (**II**), 4-amino-N-(4-ethylphenyl)-benzene-sulfonamide (**III**), 4-amino-N-(4-methoxyphenyl)-benzene-sulfonamide (**IV**)) with the following three new ones: N-(4-nitrophenyl)-benzene-sulfonamide (**V**), 4-amino-N-(4-nitrophenyl)-benzene-sulfonamide (**VI**), 4-amino-N-(4-cyanophenyl)-benzene-sulfonamide (**VII**) (Fig. 1). The choice of the compounds has been dictated by the following aims. Firstly, we wanted to investigate the impact of the nature of the substituents at para-position on thermodynamic and thermophysical properties. Secondly, we intended to recognize the influence of these substituents on solubility and partitioning processes in water, buffer and n-octanol, which are model solvents for description of biological membranes.

2. Experimental

2.1. Compounds and solvents

The chemical synthesis of SAs (**VI**–**VII**) has been performed according to procedures described earlier [5–7].

1-Octanol (lot 11K3688) was obtained from Sigma Chemical Co. (USA). The buffer solutions were prepared by mixing solutions of appropriate sodium and potassium salts of phosphoric acid to obtain pH 7.4, as described elsewhere [8]. The ionic strength (IS = 0.15) was adjusted by addition of sodium chloride. All chemicals were of AR grade. The pH values were measured using Electroanalytical Analyser, Type OP-300, Radelkis, Budapest, standardized with pH 1.68, 6.86 and 9.22 solutions.

2.2. Methods

Solubility determination. All the experiments were carried out by the isothermal saturation method at several temperature points: 20, 22, 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

* Corresponding author at: Institute of Solution Chemistry, Russian Academy of Sciences, 153045 Ivanovo, Russia. Tel.: +7 4932 533784; fax: +7 4932 336237.
E-mail address: glp@isc-ras.ru (G.L. Perlovich).

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Table 1
Temperature dependencies of solubility, X_2 [mol. fraction], of compounds **I–VII** in buffer pH 7.4 and **V–VII** in water and n-octanol.

	I	**II**	**III**	**IV**	**V**		**VI**			**VII**			
	Buffer pH 7.4				pH 7.4	Water	n-Octanol	pH 7.4	Water	n-Octanol	pH 7.4	Water	n-Octanol
t (°C)	$X_2 \times 10^6$	$X_2 \times 10^7$	$X_2 \times 10^7$	$X_2 \times 10^7$	$X_2 \times 10^6$	$X_2 \times 10^6$	$X_2 \times 10^3$	$X_2 \times 10^6$	$X_2 \times 10^6$	$X_2 \times 10^3$	$X_2 \times 10^6$	$X_2 \times 10^6$	$X_2 \times 10^3$
20	1.17	9.28	2.83	7.55	8.97	1.45	9.58	10.1	2.72	2.60	3.64	4.11	1.12
25	1.58	13.4	3.94	10.7	12.0	1.85	11.6	13.8	3.64	3.00	5.35	5.47	1.29
30	2.21	18.0	5.68	12.9	18.0	2.32	13.9	21.0	4.88	3.61	6.86	7.58	1.58
37	3.42	30.1	8.57	21.0	28.4	3.19	18.0	32.4	7.63	4.65	10.2	11.6	1.97
42	4.35	42.5	13.0	26.9	38.9	3.71	22.2	41.0	8.29	5.62	14.7	14.5	2.34
A[a]	5.5 ± 0.4	7.8 ± 0.5	6.5 ± 0.7	4.0 ± 0.8	9.7 ± 0.5	−0.5 ± 0.2	7.3 ± 0.3	9.1 ± 0.8	4.7 ± 0.5	5.3 ± 0.4	6.8 ± 0.7	6.4 ± 0.2	3.8 ± 0.3
B[a]	5607 ± 114	6363 ± 150	6315 ± 217	5317 ± 252	6263 ± 148	3799 ± 61	3497 ± 82	6042 ± 242	5120 ± 142	3307 ± 117	5653 ± 226	5518 ± 67	3101 ± 87
R[b]	0.999	0.999	0.998	0.997	0.999	0.99962	0.99918	0.998	0.9988	0.99812	0.998	0.99978	0.99883
σ[c]	2.2×10^{-2}	2.88×10^{-2}	4.2×10^{-2}	4.84×10^{-2}	2.8×10^{-2}	1.17×10^{-2}	1.57×10^{-2}	4.7×10^{-2}	2.73×10^{-2}	2.25×10^{-2}	4.34×10^{-2}	1.28×10^{-2}	1.66×10^{-2}

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

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 [9].

Standard Gibbs energies of the dissolution processes ΔG^0_{sol} were calculated using the following equation:

$$\Delta G^0_{sol} = -RT \ \ln X_2 \quad (1)$$

where X_2 is the drug molar fraction in the saturated solution. The standard solution enthalpies ΔH^0_{sol} were calculated using the van't Hoff equation:

$$d(\ln \ X_2)/dT = \Delta H^0_{sol}/RT^2 \quad (2)$$

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 dependence of the solubility of drugs within the chosen temperature interval can be described by a linear function:

$$\ln \ X_2 = A - B/T \quad (3)$$

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

The standard solution entropies ΔS^0_{sol} were obtained from the well-known equation:

$$\Delta G^0_{sol} = \Delta H^0_{sol} - T\Delta S^0_{sol} \quad (4)$$

3. Results and discussion

The temperature dependencies of solubility of sulfonamides **V–VII** in water and n-octanol are summarized in Table 1. The solubility data obtained in buffer with pH 7.4 are presented in Table 1. The thermodynamic functions of the drugs solubility process in the solutions at 298 K are shown in Table 2.

The investigated compounds can be arranged by increasing solubility in the solvents in the sequence water < buffer pH 7.4 < n-octanol. The solution enthalpies of **I–VII** in all three solvents have positive values, and this means that the crystal lattice energy outweighs the energy required for solvation. It is interesting to note, that the entropies of the solubility process (ΔS^0_{sol}) in these solvents have a positive sign. The positive value of the solution entropy can be explained by the higher degree of order of the molecules in the crystal than in solution.

On the basis of decreasing solubility in buffer at 298 K (Table 1) the sulfanilamide derivatives can be arranged in the sequence: **VI** (NO_2–) > **VII** (CN–) > **II** (Cl–) > **IV** (OCH_3–) > **III** (C_2H_5–). Obviously this sequence reflects the increasing p*K*a values (i.e. decreasing SO_2NH-acidity) shown in Table 6 and the corresponding decreasing fractions of ionized compounds in buffer, also presented in Table 6. Introducing an amino group into compound **I** (to obtain substance **II**) slightly decreases solubility: $X_2^{298}(\mathbf{I}) = 1.58 \times 10^{-6} > X_2^{298}(\mathbf{II}) = 1.34 \times 10^{-6}$. On the other hand, introducing the same group into compound **V** (to obtain substance **VI**) slightly increases solubility: $X_2^{298}(\mathbf{V}) = 1.20 \times 10^{-5} < X_2^{298}(\mathbf{VI}) = 1.38 \times 10^{-5}$. If one compares the solubility of the non-sulfanilamides **I** and **V**, then the value for the second one is higher than the first. The same trend is observed for the solubility values of the amino derivatives (sulfanilamides **II** and **VI**).

The solubility relationship of the para-derivatives in water is different from that in buffer: **VII** (CN–) > **VI** (NO_2–) > **IV** (OCH_3–, $X_2 = 1.32 \times 10^{-6}$ [4]) > **II** (Cl–, $X_2 = 1.19 \times 10^{-6}$ [3]) > **III** (C_2H_5–, $X_2 = 5.09 \times 10^{-7}$ [4]). Clearly this sequence reflects the increasing lipophilicity (hydrophobicity) of the substituents, which can be expressed by their increasing Hansch Π values (CN: −0.57; NO_2: −0.28; OCH_3: −0.02; Cl: 0.71; C_2H_5: 1.02). Introducing an NH_2 group into **I** and **V** shows the same trend both for water and buffer:

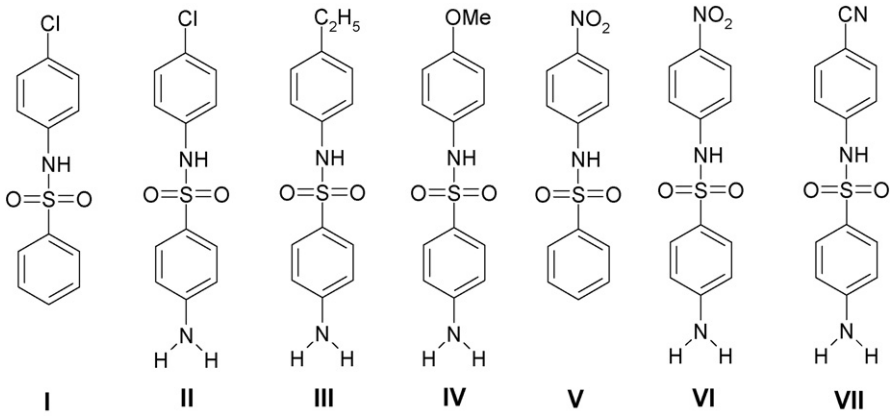

Fig. 1. Structural formulas of studied sulfonamides.

Table 2
Thermodynamic solubility functions of the compounds studied in water, buffer 7.4, and n-octanol at 298 K.

	X_2^{298} mol frac	ΔG^0_{sol} kJ mol^{-1}	ΔH^0_{sol} kJ mol^{-1}	$T\Delta S^0_{sol}$ kJ mol^{-1}	ΔS^0_{sol} J K^{-1} mol^{-1}	ς_{Hsol} [a] %	ς_{TSsol} [b] %
Water							
V	1.85×10^{-6}	32.7	36.1 ± 0.4	3.4	11 ± 2	91.4	8.4
VI	3.64×10^{-6}	31.0	43.0 ± 1.0	12.0	40 ± 2	78.2	21.8
VII	5.47×10^{-6}	30.0	45.9 ± 0.6	15.9	53 ± 2	74.3	25.7
Buffer 7.4							
I	1.58×10^{-6}	33.2	46.6 ± 0.9	13.4	45 ± 2	77.7	22.3
II	1.34×10^{-6}	33.5	52.9 ± 1.2	19.4	65 ± 3	73.2	26.8
III	3.94×10^{-7}	36.4	52.5 ± 1.8	16.1	54 ± 3	76.5	23.5
IV	1.07×10^{-6}	34.0	44.2 ± 2.1	10.2	34 ± 2	81.3	18.7
V	1.20×10^{-5}	28.0	52.1 ± 1.2	24.1	81 ± 3	68.4	31.6
VI	1.38×10^{-5}	27.8	50.2 ± 2.0	22.4	75 ± 4	69.1	30.9
VII	5.35×10^{-6}	30.0	47.0 ± 1.9	17.0	57 ± 3	73.4	26.6
n-Octanol							
V	1.16×10^{-2}	11.1	29.1 ± 0.7	18.0	60 ± 2	61.8	38.2
VI	3.00×10^{-3}	14.4	27.5 ± 1.0	13.1	44 ± 2	67.7	32.3
VII	1.29×10^{-3}	16.4	25.8 ± 0.7	9.4	32 ± 2	73.3	26.7

[a] $\varsigma_{Hsol} = (\Delta H^0_{sol}/(|\Delta H^0_{sol}| + |T\Delta S^0_{sol}|))100\%$.
[b] $\varsigma_{TSsol} = (T\Delta S^0_{sol}/(|\Delta H^0_{sol}| + |T\Delta S^0_{sol}|))100\%$.

X_2^{298}(**I**) $= 1.68 \times 10^{-6}$ [2] > X_2^{298}(**II**) $= 1.19 \times 10^{-6}$ [3], X_2^{298}(**V**) $= 1.85 \times 10^{-6} > X_2^{298}$(**VI**) $= 3.64 \times 10^{-6}$. Again the solubility values of NO_2 derivatives (**V**, **VI**) in water (due to the Π-effect) exceed the values of the Cl derivatives (**I**, **II**).

The solubility values at 298 K in n-octanol (Tables 1, 2 and [3,4]) can be arranged in the following sequence: **VI** > **II** (Cl–, $X_2 = 1.45 \times 10^{-3}$ [3]) > **VII** > **III** (C_2H_5–, $X_2 = 1.04 \times 10^{-3}$ [4]) > **IV** (OCH_3–, $X_2 = 2.33 \times 10^{-4}$ [4]). It is not difficult to see that the para-amino derivatives (**II**, **VI**) have lower solubility than the unsubstituted compounds (**I**: $X_2 = 4.21 \times 10^{-2}$ [2]; **V**: $X_2 = 1.16 \times 10^{-2}$). Moreover, replacement of the NO_2 group in (**V**) by Cl– in (**I**) leads to increasing solubility, whereas the analogous procedure for the para-derivatives (**VI**, **II**) has the opposite effect.

In order to estimate the contribution of enthalpic and entropic terms to the solubility process the parameters of relative contribution of enthalpic, ς_{Hsol}, and entropic, ς_{TSsol}, terms have been introduced (Table 2). For all considered compounds the solubility process are determined approximately by the fraction of 2/3 by the enthalpy term and by 1/3 by entropy.

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