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Thermodynamics of Solubility Processes of Novel Drug-like Spiro-Derivatives in Model Biological Solutions

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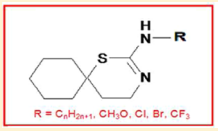
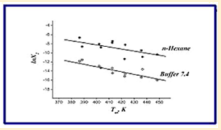
ABSTRACT: The solubility of 11 new drug-like spiro-compounds in buffer solution (pH 7.4) and hexane was measured by the isothermal saturation technique in the temperature range of (293 to 315) K. The influence of substituent chemical nature, branching of aliphatic chain, and inclusion of oxygen and halogen atoms in molecule structure were investigated. The correlation dependences of the solubility on molecular descriptors and thermophysical properties were estimated. Standard thermodynamic solubility functions for the test compounds were calculated. The conclusion reveals the dominant contribution of dispersion forces in the solution process.





INTRODUCTION

The solubility of organic compounds has always been of great interest for both fundamental and applied sciences since it is a key feature underlying production and utilization of drug compounds.[1,2] The solubility of the latter has an effect on the processes occurring in a human organism such as adsorption, distribution, and membrane permeability which are responsible for their biological activity.[3,4]

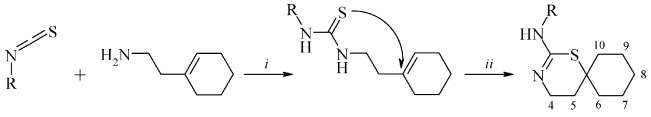
Drugs based on heterocyclic substances are widely used in medicine due to their high biological activity inherent to natural molecules.[5] Spiro-derivatives with oxygen, nitrogen, and sulfur atoms in the cycles are among the chemical substances concerned and have a range of applications to treat cancer and cardiovascular diseases.[6] Studies are in progress on the successful usage of spiro-compounds to treat Alzheimer's disease, diabetes, atherosclerosis, schizophrenia, and receptor activity modulators.[7−10]

The pharmacological effect of heterocyclic drug substances is determined both by the cyclic system itself and by the nature of substituents present in it. Carbon atom substitution by a heteroatom in aromatic series, the increase in the number of chains in the cycle, and lengthening or branching of aliphatic chains result in structural and stereochemical changes in a molecule. These changes, in turn, cause a change in physicochemical properties and pharmacological effects. Therefore, establishing interrelations between a drug's chemical structure and its solubility is a task of prime importance in pharmaceutics.[11]

The present paper is a continuation of the investigation we undertook to study the solubility and partitioning of drug and drug-like compounds in biological media.[12,13] The effects of chemical nature and structure of new spiro-compound derivatives on their solubility in model biological media (hexane and a buffer with pH 7.4) have been studied in the present paper. The choice of the solvents was dictated by the fact that hexane and the buffer are a model pair of solvents that imitate the properties of a blood−brain barrier.[14,15] The examination of the properties of the molecules in these media gives insight into the processes of passive transport through organism membranes and allows imparting the desired design to bioavailable drug molecules.

EXPERIMENTAL SECTION

Materials. Synthetic approaches to 11 novel spiro-derivatives were carried out according to the scheme:



I II III IV

***N*-Substituted 1-Thia-3-azaspiro[5.5]undec-2-en-2-yl-amines (IV).** To a stirred solution of 2-(1-cyclohexenyl)-ethylamine (II; 1.25 g, 0.01 mmol) in diethyl ether (20 mL), a solution of appropriate isothiocyanate (I) in diethyl ether (0.01 mmol) was added dropwise. Then the reaction mixture was stirred for (2 to 5) h at ambient temperature until formation of the precipitate. The precipitate of thiourea (III) was filtered off, dried, suspended in 48 % aqueous HBr (10 mL), and refluxed for 5 h; the precipitate dissolved during the reaction. After the completion of the reaction, the mixture was cooled to ambient temperature and diluted with water (20 mL) and dichloromethane (50 mL), and then saturated aqueous $NaHCO_3$ was carefully added until the solution was basic. The organic layer was separated and dried with Na_2SO_4. The drying agent was filtered off, and the solvent was removed. The residue was recrystallized from propane-2-ol to give *N*-substituted 1-thia-3-azaspiro[5.5]undec-2-en-2-ylamine (IV).[16]

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^{1}H NMR spectra were recorded on Bruker CXP-200 instrument (Karlsruhe, Germany) in $CDCl_3$, the chemical shifts are given in the d scale relative to Me_4Si. The solvents were removed using a rotary evaporator under water pump vacuum.

Phenyl-(1-thia-3-aza-spiro[5.5]undec-2-en-2-yl)-amine (1). The overall yield for the two steps was 79 %, mp (melting point) 113.5 °C. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 1.22 (1H, m, C(8)H*H*) (numbering of the atoms corresponds to the scheme (IV); the chemical shift fits to the italicized proton), 1.50 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 1.78 (4H, m, C(5)H_2, C(6)*H*H, C(10)*H*H), 3.55 (2H, m, C(4)H_2), 6.20 (1H, br s, NH), 6.90 (1H, m, ArH), 7.19 (4H, m, ArH).

Anal. (elemental analysis). Calcd for $C_{15}H_{20}N_2S$: C, 69.19; H, 7.74; N, 10.76. Found: C, 69.30; H, 7.85; N, 10.85. Calcd mass: 260.4041; found: 260.4040.

Methyl-(1-thia-3-aza-spiro[5.5]undec-2-en-2-yl)-amine (2). Yield 72 %, mp 108.3 °C. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 1.30 (1H, m, C(8)H*H*), 1.58 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 1.71 (2H, t, J = 5.8 Hz, C(5)H_2), 1.88 (2H, m, C(6)*H*H, C(10)*H*H), 2.81 (3H, s, CH_3), 3.66 (2H, t, J = 5.8 Hz, C(4)H_2), 3.88 (1H, br s, NH).

Anal. Calcd for $C_{10}H_{18}N_2S$: C, 60.56; H, 9.15; N, 14.12. Found: C, 60.59; H, 9.33; N, 14.05. Calcd mass: 198.3324; found: 198.3327.

Ethyl-(1-thia-3-aza-spiro[5.5]undec-2-en-2-yl)-amine (3). Yield 62 %, mp 139.5 °C. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 1.16 (3H, t, J = 7.2 Hz, CH_3), 1.32 (1H, m, C(8)H*H*), 1.58 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 1.72 (2H, t, J = 5.8 Hz, C(5)H_2), 1.88 (2H, m, C(6)*H*H, C(10)*H*H), 3.28 (2H, q, J = 7.2 Hz, NHCH_2), 3.61 (1H, br s, NH), 3.64 (2H, t, J = 5.8 Hz, C(4)H_2).

Anal. Calcd for $C_{11}H_{20}N_2S$: C, 62.22; H, 9.49; N, 13.19. Found: C, 62.33; H, 9.43; N, 13.05; Calcd mass: 212.3595; found: 212.3598.

(4-Isopropyl-phenyl)-(1-thia-3-aza-spiro[5.5]undec-2-en-2-yl)-amine (4). Yield 73 %, mp 139.7 °C. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 1.21 (6H, d, J = 6.7 Hz, C$(CH_3)_2$), 1.30 (1H, m, C(8)H*H*), 1.56 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 1.84 (2H, t, J = 5.9 Hz, C(5)H_2), 1.88 (2H, m, C(6)*H*H, C(10)*H*H), 2.84 (1H, m, C*H*$(CH_3)_2$), 3.65 (2H, t, J = 5.9 Hz, C(4)H_2), 7.10 (2H, m, ArH).

Anal. Calcd for $C_{18}H_{26}N_2S$: C, 71.47; H, 8.66; N, 9.26. Found: C, 71.40; H, 8.85; N, 9.25. Calcd mass: 302.4853; found: 302.4852.

1-[4-(1-Thia-3-aza-spiro[5.5]undec-2-en-2-ylamino)-phenyl]-ethanone (5). Yield 69 %, mp 163.6 °C. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 1.29 (1H, m, C(8)H*H*), 1.56 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 1.85 (2H, t, J = 5.9 Hz, C(5)H_2), 1.88 (2H, m, C(6)*H*H, C(10)*H*H), 2.55 (3H, s, C(O)CH_3), 3.61 (2H, t, J = 5.9 Hz, C(4)H_2), 6.25 (1H, br s, NH), 7.24 (2H, d, J = 8.6 Hz, ArH), 7.87 (2H, d, J = 8.6 Hz, ArH).

Anal. Calcd for $C_{17}H_{22}N_2OS$: C, 67.51; H, 7.33; N, 9.26. Found: C, 67.40; H, 7.45; N, 9.28. Calcd mass: 302.4417; found: 302.4422.

***N*-(1-Thia-3-aza-spiro[5.5]undec-2-en-2-yl)-benzamide (6).** Yield 79 %, mp 130.4 °C. ^{1}H NMR [200 MHz, DMSO-d_6] δ: 1.36 (1H, m, C(8)H*H*), 1.68 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 2.00 (4H, m, C(5)H_2, C(6)*H*H, C(10)*H*H), 3.64 (2H, m, C(4)H_2), 7.40 (3H, m, ArH), 8.08 (2H, m, ArH), 11.52 (1H, br s, NH).

Anal. Calcd for $C_{16}H_{20}N_2OS$: C, 66.63; H, 6.99; N, 9.71. Found: C, 66.55; H, 6.85; N, 9.70. Calcd mass: 288.4146; found: 288.4146.

(4-Methoxyphenyl)-(1-thia-3-aza-spiro[5.5]undec-2-en-2-yl)-amine (7). Yield 65 %, 115.5 °C. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 1.33 (1H, m, C(8)H*H*), 1.60 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 1.88 (4H, m, C(5)H_2, C(6)*H*H, C(10)*H*H), 3.61 (2H, m, C(4)H_2), 3.81 (3H, s, OCH_3), 4.50 (1H, br s, NH), 6.84 (2H, d, J = 8.8 Hz, ArH), 7.13 (2H, d, J = 8.8 Hz, ArH).

Anal. Calcd for $C_{16}H_{22}N_2OS$: C, 66.17; H, 7.64; N, 9.65. Found: C, 66.22; H, 7.66; N, 9.69. Calcd mass: 290.4305; found: 290.4310.

(3-Chloro-4-methylphenyl)-(1-thia-3-aza-spiro[5.5]-undec-2-en-2-yl)-amine (8). Yield 74 %, mp 149.3 °C. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 1.28 (1H, m, C(8)H*H*), 1.55 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 1.87 (4H, m, C(5)H_2, C(6)*H*H, C(10)*H*H), 2.29 (3H, s, CH_3), 3.54 (2H, m, C(4)H_2), 6.88 (1H, dd, J = 1.1 8.1 Hz, ArH), 7.08 (1H, d, J = 8.1 Hz, ArH), 7.18 (1H, d, J = 1.1 Hz, ArH).

Anal. Calcd for $C_{16}H_{21}ClN_2S$: C, 62.22; H, 6.85; N, 9.07. Found: C, 62.30; H, 6.85; N, 9.05. Calcd mass: 308.8762; found: 308.8766.

(4-Bromophenyl)-1-thia-3-aza-piro[5.5]undec-2-en-2-yl)-amine (9). Yield 72 %, mp 175.3 °C. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 1.32 (1H, m, C(8)H*H*), 1.61 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 1.91 (4H, m, C(5)H_2, C(6)*H*H, C(10)*H*H), 3.59 (2H, m, C(4)H_2), 7.08 (2H, d, J = 8.6 Hz, ArH), 7.39 (2H, d, J = 8.6 Hz, ArH).

Anal. Calcd for $C_{15}H_{19}BrN_2S$: C, 53.10; H, 5.64; N, 8.26. Found: C, 53.30; H, 5.65; N, 8.15; Calcd mass: 339.3001; found: 339.3000.

(4-Chlorophenyl)-1-thia-3-aza-piro[5.5]undec-2-en-2-yl)-amine (10). Yield 75 %, mp 162.7 °C. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 1.29 (1H, m, C(8)H*H*), 1.59 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 1.89 (4H, m, C(5)H_2, C(6)*H*H, C(10)*H*H), 3.57 (2H, m, C(4)H_2), 7.06 (2H, d, *m*, ArH), 7.35 (2H, m, ArH).

Anal. Calcd for $C_{15}H_{19}ClN_2S$: C, 61.10; H, 6.50; N, 9.50. Found: C, 61.22; H, 6.53; N, 9.45. Calcd mass: 294.8491; found: 294.8495.

(1-Thia-3-aza-spiro[5.5]undec-2-en-2-yl)-(4-trifluoro-methylphenyl)-amine (11). Yield 77 %, mp 149.8 °C. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 1.29 (1H, m, C(8)H*H*), 1.58 (7H, m, C(6)H*H*, C(7)H_2, C(8)*H*H, C(9)H_2, C(10)H*H*), 1.85 (4H, t, J = 5.9 Hz, C(6)*H*H, C(10)*H*H, C(5)H_2), 3.60 (2H, t, J = 5.9 Hz, C(4)H_2), 6.11 (1H, br s, NH), 7.25 (2H, d, J = 8.4 Hz, ArH), 7.49 (2H, d, J = 8.4 Hz, ArH).

Anal. Calcd for $C_{16}H_{19}F_3N_2S$: C, 58.52; H, 5.83; N, 8.53. Found: C, 58.33; H, 5.85; N, 8.65. Calcd mass: 328.4024; found: 328.4028.

The purity of the spiro-derivatives determined by size exclusion chromatography (SEC) was 0.98 (mass fraction). SEC was performed using two 600 × 8 mm columns, filled with polystyrene gel (5 μm particle size, 50 nm and 10 nm pore size, Polymer Laboratories). The eluant was tetrahydrofuran at 0.5 mL·min^{-1}. Chromatograms (one single peak) were registered using a Waters 440 absorbance detector at 245 nm and a Waters 410 differential refractometer at 30 °C.

Hexane (C_6H_{14}, MW 86.18, 99 % purity) was received from Aldrich (St. Louis, MO, USA). The buffer solutions were prepared by mixing solutions of appropriate sodium and potassium salts of phosphoric acid pH 7.4, as described

elsewhere.[17] Ionic strength was adjusted by adding potassium chloride. All chemicals were of analytical reagent grade. The pH values were measured by using electroanalytical analyzer (type OP-300, Radelkis, Budapest) standardized with pH 1.68, 6.86, and 9.22 solutions.

Apparatus and Procedure. All of the experiments were carried out by the isothermal saturation method at five temperature points: (293, 298, 303, 310, and 315 ± 0.1) K.The essence of the above method includes the determination of the compound concentration in the saturated solution. Glass ampules containing the tested substance and the solvent were placed into the air thermostat supplied by the stirring device. The point of the solution thermodynamic equilibrium was determined from the solubility kinetic dependences and averaged for 24 h. After saturation was achieved the solution aliquot was taken and centrifugated in a centrifuge under the temperature control Biofuge stratos (Germany) during 5 min under a fixed temperature. The solid phase was removed by isothermal filtration with a 0.45 μm filter MILLEXHA (Cork, Ireland). The saturated solution was diluted with the correspondent solvent to the required concentration. The molar solubilities of drugs were measured by means of spectrophotometer Cary-50 (CIIIA) in UV spectral region (λ = 190 to 400 nm) with an accuracy of (2 to 4) %. The experimental results are reported as an average value of at least three replicated experiments. It should be noted that sediment differential scanning calorimetry (DSC) analysis showed the absence of crystallosolvates for all of the tested compounds.

The temperatures and enthalpies of fusion of the substances under study have been determined by DSC using a DSC 204 F1 "Foenix" (Netzsch, Germany). The experiment was carried out in an atmosphere of flowing (25 mL·min^{-1}) dry argon gas of high purity (99.996 %) using standard aluminum sample pans and a heating rate of 10 K·min^{-1}. The DSC was calibrated using five standards: mercury, biphenyl, indium, tin, and bismuth. The sample mass was determined with the accuracy of $1 \cdot 10^{-5}$ g using the balance Sartorius M2P.

Background. The standard Gibbs energies of dissolution processes ΔG^0_{sol} were calculated using the following equation:

$$\Delta G^0_{sol} = -RT \ln a_2 \quad (1)$$

where $a_2 = \gamma_2 \cdot x$ is the activity of the solute molecule; x 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} were calculated using the van't Hoff equation:

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

Due to very low solubilities of the compounds under investigation in a buffer and hexane, it was assumed that γ_2 = 1. The temperature dependencies of drug solubilities within the chosen temperature interval can be described by the linear function:

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

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:

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

RESULTS AND DISCUSSION

The objects of the studies were new isothiourea spiro-derivatives in a number of 1,3-thiazines. The general central fragment of these molecules is linked with a radical through an amine group (Figure 1).

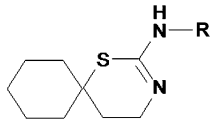


Figure 1. Molecular structure of spiro-compounds.

The diversity of molecular structures is achieved by increasing the length and branching of the aliphatic chain, changing the position and the number of substituents, and introducing oxygen, chlorine, bromine, and fluorine atoms into structure. Structural formulas of radicals, polarizability, and thermophysical parameters of fusion of the compound concerned are given in Table 1. Substance **1** has an unsubstituted phenyl ring as a radical and can be used as a model compound when comparing the contribution of individual functional groups into the processes of dissolution. The first group of the compounds investigated is represented by the substances with alkyl substituents (**2** to **4**). An oxygen atom is incorporated into the structure of substituents of group II compounds) (**5** to **7**); atoms of halogens (chlorine, bromine, fluorine) are added to compounds of group III (**8** to **11**).

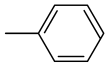
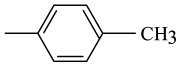
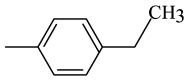
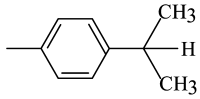
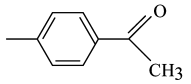
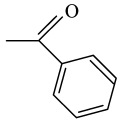
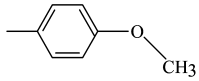
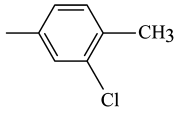
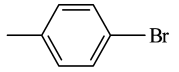
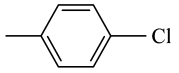
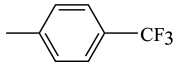
Solubility values of the compounds studied in hexane and the buffer have been obtained by the isothermal saturation method at five temperatures (Table 2).

Solubility values are known to be connected with physicochemical properties of compounds, which are responsible for the pattern of intermolecular interactions both in crystals and in the solute−solvent system. This is why we analyzed parameters of molecular crystal fusion and established the way they are related to solubility. Use is made of the crystal fusion temperature to evaluate crystal lattice energy.[18,19] Figure 2 shows solubilities of the compounds under study in hexane and a buffer solution at 298 K as a function of fusion temperature. As one can see from the data presented, the increase in fusion temperature results in the decrease of compound solubility. The rise in fusion temperature is likely to result from crystal lattice energy content which, in turn, prevents the passing of a molecule from the crystal state into the solution.

The dependences of solubility in buffer and hexane for the substances under study on molecule polarizability are presented in Figure 3. It has been established that for compounds **2** to **4** with alkyl substitutes the linear growth in solubility in hexane with polarizability increasing is observed. Since molecule polarizability can be used to evaluate nonspecific intermolecular interactions, the results we obtained are in good agreement with the ideas of a decisive role of disperse interactions during *n*-alkane dissolution in solvents with various polarity.[20]

To assess the effect of a chemical nature of a substituent on spiro-derivative solubility in hexane, use was made of group II and III compounds. Having a similar structure to a central molecule fragment, these compounds are distinguished by the fact that the outlying alkyl radicals of group I compounds are replaced by substituents containing oxygen and halogen atoms. As one can see from the data presented in Table 2, solubility

Table 1. Structural Formulas of the Radicals, Thermophysical Parameters of Melting, and the Polarizability of the Spiro-Compounds

Compound	-R	T_m/K	ΔH^{Tm}_{fus} / kJ·mol^{-1}	ΔS^{Tm}_{fus} /J·mol^{-1}·K^{-1}	$\alpha \cdot 10^2$/nm^{3*}
1		386.5 ± 0.2	21.6 ± 0.5	55.8± 2.5	3.05
			I		
2		381.3 ± 0.2	29.7 ± 0.5	73.8 ± 2.5	3.23
3		412.5 ± 0.2	42.82 ± 0.5	40.5 ± 2.5	3.41
4		412.7 ± 0.2	29.2 ± 0.5	70.8 ± 2.5	3.60
			II		
5		436.6 ± 0.2	32.5 ± 0.5	74.4 ± 2.5	3.43
6		403.4 ± 0.2	27.9 ± 0.5	69.2 ± 2.5	3.24
7		388.5 ± 0.2	29.3 ± 0.5	75.4 ± 2.5	3.26
			III		
8		422.3 ± 0.2	33.2 ± 0.5	78.6 ± 2.5	3.42
9		448.3 ± 0.2	44.3 ± 0.5	98.8 ± 2.5	3.31
10		435.7 ± 0.2	41.9 ± 0.5	96.2 ± 2.5	3.24
11		422.8 ± 0.2	32.9 ± 0.5	77.8 ± 2.5	3.20

[a]Polarizability calculated by program HYBOT [Raevsky, O. A.; Grigor'ev, V. J.; Trepalin, S. V. *HYBOT program package*, Registration by Russian State Patent Agency No. 990090; Feb 26, 1999].

values for alkyl substituted group I compounds in hexane are higher than those of group II and III.

Irrespective of the structure of a terminal substituent, one observes a linear dependence between solubilities in hexane and buffer of spiro-compounds with atoms of oxygen and halogens and the polarizability of the molecules within each group (Figure 3).

Particular emphasis must be given to the comparatively high solubility of compound **11** in group III (a fluorinated analogue of methyl-substituent **2**) in hexane. Thus, complete substitution of hydrogen atoms in alkyl substituent by highly negative fluorine atoms increases the solubility.

The effect of the benzene fragment position in a terminal substituent on the solubility of spiro-derivatives in hexane can be followed using model compounds containing keto-groups in the structure of substituents **5** and **6**. The change in benzene fragment position and its migration to the terminal part of the molecule increase the solubility of compound **6** as compared to **5**.

Being a water-based polar solvent in contrast to hexane, the buffer is able to interact with substances being investigated not only owing to dispersion forces but to specific ones as well.[21] Amino groups, atoms of oxygen, chlorine, bromine, fluorine, sulfur, and nitrogen, are active centers in the structure of compounds being dissolved. Despite the presence of highly specific polar functional groups in the structure of all of the compounds, their solubility (except for **7**) is lower than that of compound **1**. The linear correlation between solubility and polarizability of compounds of each group presented demonstrates that the effect of dispersion forces on spiro-derivative solubility in the buffer may be crucial. For all groups of compounds studied, except group II, $R \geq 0.985$ (greater than or equal to 0.985).

Table 2. Experimental Mole Fraction Solubilities x of Spiro-Compounds in Buffer and Hexane[a]

	1		2		3		4		5		6	
	buffer	hexane	buffer	hexane	buffer	hexane	buffer	hexane	buffer	hexane	buffer	hexane
T/K	$x\cdot10^6$	$x\cdot10^3$	$x\cdot10^6$	$x\cdot10^4$	$x\cdot10^6$	$x\cdot10^4$	$x\cdot10^7$	$x\cdot10^4$	$x\cdot10^6$	$x\cdot10^5$	$x\cdot10^5$	$x\cdot10^5$
293.15	7.14	1.15	2.42	2.80	1.47	3.65	4.91	5.14	1.10	1.56	0.14	12.4
298.15	7.28	1.30	2.50	3.26	1.57	4.31	5.28	6.10	1.22	1.93	0.16	15.3
303.15	7.43	1.48	2.60	3.79	1.75	5.08	5.66	7.42	1.26	2.42	0.17.	18.9
310.15	7.58	1.90	2.78	4.45	1.94	6.17	6.52	9.19	1.46	3.23	0.20	25.0
315.15	7.69	2.15	2.95	5.20	2.09	8.85	6.79	11.00	1.55	3.95	0.22	29.5
A	-10.8 ± 0.1	2.5 ± 0.2	-10.2 ± 0.1	0.5 ± 0.02	-8.3 ± 0.1	1.2 ± 0.3	-9.7 ± 0.1	2.8 ± 0.2	-8.9 ± 0.2	2.3 ± 0.1	-7.7 ± 0.1	3.4 ± 0.2
B[b]	313 ± 11	2687 ± 58	815 ± 20	2546 ± 69	1515 ± 39	2664 ± 65	1423 ± 31	3043 ± 75	1417 ± 60	3918 ± 27	1686 ± 40	3645 ± 57
R[c]	0.99854	0.99932	0.99872	0.99889	0.99899	0.99913	0.99930	0.99907	0.99806	0.9999	0.99914	0.99952
σ[d]	$0.2\cdot10^{-2}$	$1.1\cdot10^{-2}$	$1.1\cdot10^{-2}$	$1.3\cdot10^{-2}$	$1.0\cdot10^{-2}$	$1.2\cdot10^{-2}$	$1.0\cdot10^{-2}$	$1.4\cdot10^{-2}$	$1.1\cdot10^{-2}$	$0.53\cdot10^{-2}$	$0.8\cdot10^{-2}$	$1.1\cdot10^{-2}$

	7		8		9		10		11	
	buffer	hexane	buffer	hexane	buffer	hexane	buffer	hexane	buffer	hexane
T/K	$x\cdot10^5$	$x\cdot10^5$	$x\cdot10^7$	$x\cdot10^5$	$x\cdot10^7$	$x\cdot10^5$	$x\cdot10^7$	$x\cdot10^5$	$x\cdot10^7$	$x\cdot10^4$
293.15	0.94	14.93	2.44	0.86	1.11	2.46	1.94	6.09	2.65	2.14
298.15	0.97	18.22	2.65	1.15	1.13	3.31	2.14	7.93	4.43	2.72
303.15	1.01	22.06	2.80	1.48	1.26	4.34	2.39	10.1	5.30	3.45
310.15	1.03	29.46	3.08	2.15	1.31	6.54	2.75	13.6	6.98	4.24
315.15	1.08	35.71	3.28	2.68	1.42	8.27	2.97	17.0	8.23	5.70
A	-9.8 ± 0.1	3.5 ± 0.2	-11.0 ± 0.1	4.8 ± 0.2	-12.8 ± 0.1	6.8 ± 0.3	-9.2 ± 0.1	4.9 ± 0.2	-2.7 ± 0.2	5.5 ± 0.1
B[b]	519 ± 16	3598 ± 54	1229 ± 37	4835 ± 67	926 ± 25	5103 ± 78	1827 ± 38	4281 ± 61	3547 ± 64	4089 ± 28
R[c]	0.99846	0.99967	0.99863	0.99942	0.99884	0.99965	0.99934	0.99969	0.99951	0.99991
σ[d]	$0.3\cdot10^{-2}$	$1.1\cdot10^{-2}$	$0.7\cdot10^{-2}$	$1.5\cdot10^{-2}$	$0.5\cdot10^{-2}$	$1.5\cdot10^{-2}$	$0.7\cdot10^{-2}$	$1.2\cdot10^{-2}$	$1.2\cdot10^{-2}$	$0.6\cdot10^{-2}$

[a]Standard uncertainties u are $u(T) = 0.05$ K, $u_r(x) = 0.02$. [b]Parameters of the correlation equation: $\ln x = A - B/T$. [c]R is the pair correlation coefficient. [d]σ is the standard deviation.

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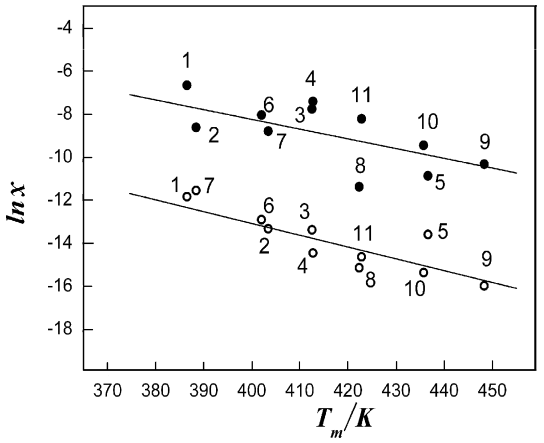

Figure 2. Correlation between the solubility and the melting temperature ($R \geq 0.750$) for spiro-compounds: ●, hexane; ○, buffer 7.4.

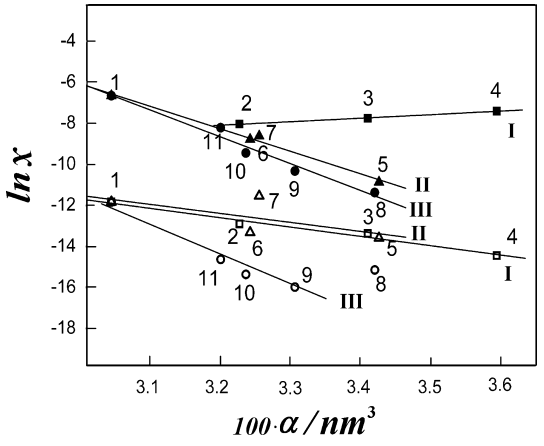

Figure 3. Correlation between the solubility spiro-compounds groups I to III in hexane (■, ●, ▲) and buffer 7.4 (□, ○, △) and polarizability.

Compound **8** with methyl and chlorine substituents stands midway between alkyl- and halogen-derivatives. Of special importance is the position of a model compound **1** on the scheme that corresponds to intersection points of the dependences between a decrease in solubility and increase in polarizability of compounds in hexane and the buffer. This fact demonstrates the right choice of a model substance and necessity of division of spiro-derivatives studied in individual groups.

Thus, the close relationship between solubility, polarizability and thermophysical parameters of the systems investigated allows the value of solubility for the compounds belonging to the same class to be semiempirically calculated.

Thermodynamic functions of solubilization of the compounds in hexane and the buffer have been calculated in terms of solubility−temperature dependences. They are presented in Table 3. As one can see from Table 3, Gibbs energy values of spiro-derivatives in hexane are positive and show the reaction to be endothermic. These values are higher in the buffer than in hexane, which means that the latter solvent is better than the former one. Taking into consideration the fact that this pair of solvents is most frequently used as a model system to describe the blood−brain barrier, one can draw a conclusion that the most preferable paths of passive transport of the substances concerned will be accomplished through the least susceptible to specific interactions phase.

A diagram method applied by us earlier[13] was used to match entropy and enthalpy terms of dissolution. The diagram portrayed in Figure 4 highlights contributions of thermody-

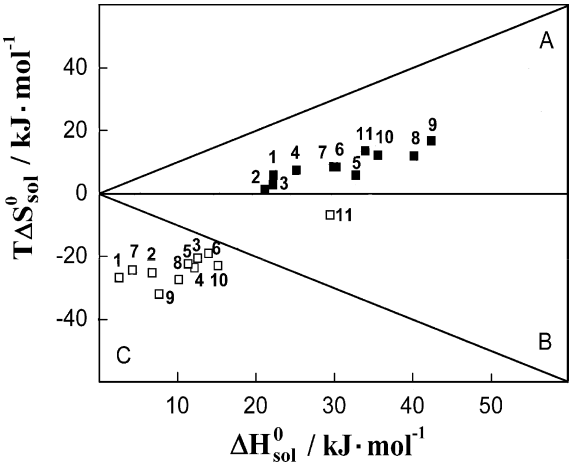

Figure 4. Relationship between the enthalpic and the entropic terms of Gibbs energy of solubility spiro-compounds in hexane (■) and buffer (□).

Table 3. Thermodynamic Solubility Functions of Spiro-Compounds in Buffer and Hexane at 298 K

	hexane				buffer 7.4			
	ΔG^0_{sol}	ΔH^0_{sol}	$T\Delta S^0_{sol}$	ΔS^0_{sol}	ΔG^0_{sol}	ΔH^0_{sol}	$T\Delta S^0_{sol}$	ΔS^0_{sol}
compound	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}	J·K^{-1}·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}	J·K^{-1}·mol^{-1}
1	16.5	22.3 ± 0.8	5.9	19.7 ± 3	29.3	2.6 ± 0.1	−26.7	−89.5 ± 5
2	19.9	21.2 ± 0.5	1.3	4.3 ± 0.2	32.0	6.8 ± 0.4	−25.2	−84.6 ± 5
3	19.2	22.2 ± 0.8	2.9	9.9 ± 0.5	33.1	12.6 ± 0.5	−20.5	−68.8 ± 7
4	17.7	25.2 ± 0.8	7.5	25.1 ± 1.2	35.8	12.2 ± 1.4	−23.6	−79.6 ± 5
5	26.9	32.8 ± 1.1	5.9	19.7 ± 0.8	33.7	11.4 ± 1.3	−22.3	−74.7 ± 4
6	21.8	30.3 ± 0.5	8.5	28.5 ± 1.0	33.0	14.0 ± 0.8	−19.0	−63.7 ± 5
7	21.3	29.9 ± 0.7	8.5	28.9 ± 1.2	28.6	4.3 ± 0.4	−24.3	−81.5 ± 9
8	28.2	40.2 ± 0.6	12.0	40.3 ± 1.2	37.5	10.2 ± 0.3	−27.3	−91.6 ± 4
9	25.6	42.4 ± 0.6	16.8	56.5 ± 1.9	39.6	7.7 ± 0.4	−31.9	−107.0 ± 7
10	23.4	35.6 ± 0.5	12.2	40.9 ± 1.4	38.1	15.2 ± 0.3	−22.9	−76.8 ± 3
11	20.3	34.0 ± 0.2	13.7	45.8 ± 1.2	36.3	29.5 ± 0.5	−6.7	−22.7 ± 1

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namic functions in the process of dissolution of the compounds under study. Sector A where ($\Delta H^0_{sol} > T\Delta S^0_{sol} > 0$) and sector B where ($\Delta H^0_{sol} > 0$; $T\Delta S^0_{sol} < 0$; $|\Delta H^0_{sol}| > |T\Delta S^0_{sol}|$) correspond to the enthalpy of the process studied. Sector C of the diagram where ($\Delta H^0_{sol} > 0$; $T\Delta S^0_{sol} < 0$; $|\Delta H^0_{sol}| < |T\Delta S^0_{sol}|$) corresponds to the entropy of the process. Isoenergetic curves of ΔG^0_{sol} functions are marked as dotted lines in Figure 3. A comparison of enthalpy and entropy contributions into the Gibbs energy of dissolution demonstrates that it is entropy contributions that are critical for the buffer solution (sector C). Alternatively, remarkable positive enthalpy and entropy contributions (sector **A**) are characteristic for nonassociated solvent hexane, the former ones dominating in the process.

A comparison of entropy dissolution values in the buffer and hexane reveals some specific characteristics of the dissolution process. Positive $T\Delta S^0_{sol}$ values of compounds in hexane and negative ones in the buffer are due to ordering of spatial lattices of the solvents. This alters the pattern in the solvent—the solute interacts and causes relatively high enthalpies and positive entropies of dissolution to appear. These specific features of the thermodynamics of dissolution in water and some other associate media are associated with the cultrate mechanism of dissolution, solvophobic effect, and domination of interstitial solutions in these solvents, that is, by instillation (introduction) of a dissolved substance molecule into interassociated and intra-associated cavities of the elements with nonequilibrium free volume.

CONCLUSIONS

Solubilities of advanced drug-like isothiourea spiro-derivatives in a number of 1,3-thiazines in pharmaceutically meaningful solvents of hexane and the buffer (pH 7.4) have been measured in the temperature range (293 to 315) K by the isothermal saturation method using spectrophotometric analysis.

The effects of lengthening and branching of a terminal substituent alkyl chain as well as the introduction of atoms of oxygen, chlorine, bromine, and fluorine have been studied. The solubility data have been correlated with molecular descriptors of the substances, namely, molecular mass and polarizability. A thermodynamic description of solubility was made using thermophysical properties obtained with the DSC technique. It has been stated that solubilities of all poorly soluble drug-like substances are higher in hexane that those in an aqueous buffer. Standard thermodynamic functions of dissolution of drug-like substances in saturated solutions were calculated from the experimental data. Enthalpy and entropy factors of intermolecular interaction in hexane and the buffer respectively contribute to the nonideal character of the solute−solvent system. The conclusion is made that it is dispersion forces which significantly contribute to the solubility of spiro-derivatives.

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Notes

The authors declare no competing financial interest.

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