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Thermodynamic aspects of solubility and partitioning processes of some sulfonamides in the solvents modeling biological media

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ABSTRACT

The thermodynamic aspects of solubility processes of sulfonamides (SAs) with the general structures 4-NH_2–C_6H_4–SO_2NH–$C_6H_2(R_1)(R_2)$-R_3 (R_1 = 2-CH_3, 2-Cl; R_2 = 4-CH_3, 4-Cl; R_3=5-H, 5-Cl), 4-NH_2-2-Cl–C_6H_3–SO_2NH–$C_6H_3(R_1)$-R_2 (R_1 = 2-H, 2-Cl; R_2 = 4-H, 4-Cl) and 4-NH_2-2-CH_3–C_6H_3–SO_2NH–$C_6H_3(R_1)$-R_2 (R_1 = 2-H, 2-Cl, 2-NO_2; R_2 = 4-H, 4-Cl) in water and 1-octanol (as phases modeling various drug delivery pathways) were studied using the isothermal saturation method. For the sulfonamides with various substituents in phenyl rings the processes of transfer from water to 1-octanol were studied by a diagram method combined with analysis of enthalpic and entropic terms. Distinguishing between enthalpy and entropy, as is possible through the present approach, leads to the insight that the contribution of these terms is different for different molecules (entropy- or enthalpy-determined). Thus, in contrast to the interpretation of only the Gibbs energy of transfer (extensively used for pharmaceuticals in the form of the partition coefficient, logP), the analysis of thermodynamic functions of the transfer process provides additional mechanistic information. This may be important for further evaluation of the physiological distribution of drug molecules and may provide a better understanding of biopharmaceutical properties of drugs.

1. Introduction

The sulfonamide group (–SO_2NH–) is often use in medicinal chemistry for the development of novel drugs with advanced pharmacological characteristics. In spite of the long history of sulfadrug development (wide application in medicine since the 1930ies), the peak of their patenting covers the years 2008–2012. As it has been shown by Carta *et al.* [1], the trend in drug design for the latter period has been focused on compounds incorporating the sulfamoyl moiety: most derivatives reported in the last year in both the scientific and patent literature belong to the aromatic/heterocyclic sulfonamide class. As shown by data of October 2011 [2], the sulfonamide motif occurs in 111 approved drugs or agents in clinical trials. Indeed, the sulfonamides constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial [3], antitumor [4], anti-carbonic anhydrase [5–6], diuretic [6–7], hypoglycemic [8], antithyroid [9], or protease inhibitory [10–12] activity among others.

Although the therapeutic potential of sulfonamides is well studied, nevertheless, the majority of substances of this class have poor solubility in water – an observation that essentially limits the range of their use. The problem of low solubility is associated with significant loss of efficacy of such drugs which reduces the possibility of their market promotion. Thus, the investigation of dissolution, partitioning and permeation processes as well as of their changes caused by structural modifications of substances is an actual problem for development of novel bioavailable drugs.

Knowledge of solubility at various temperatures is useful in physical stability studies of liquid dosage forms, in processes involving temperature changes and in the preformulation stage of a new drug where only a small amount of the drug is available. Unfortunately, only a small number of papers on the temperature dependencies of drug solubility (including sulfonamides) in neat solvents [13–18] and in cosolvent mixtures [19–23] have been published in the literature. Attempts of solubility prediction with use of various approaches for this class of substances are not numerous as well. For instance, in investigations of Zhang *et al.* [15,17] the solubility of some sulfonamides in water and 1-octanol was measured. The experimental data showed good agreement with values calculated by the modified Apelblat equation. Martínez

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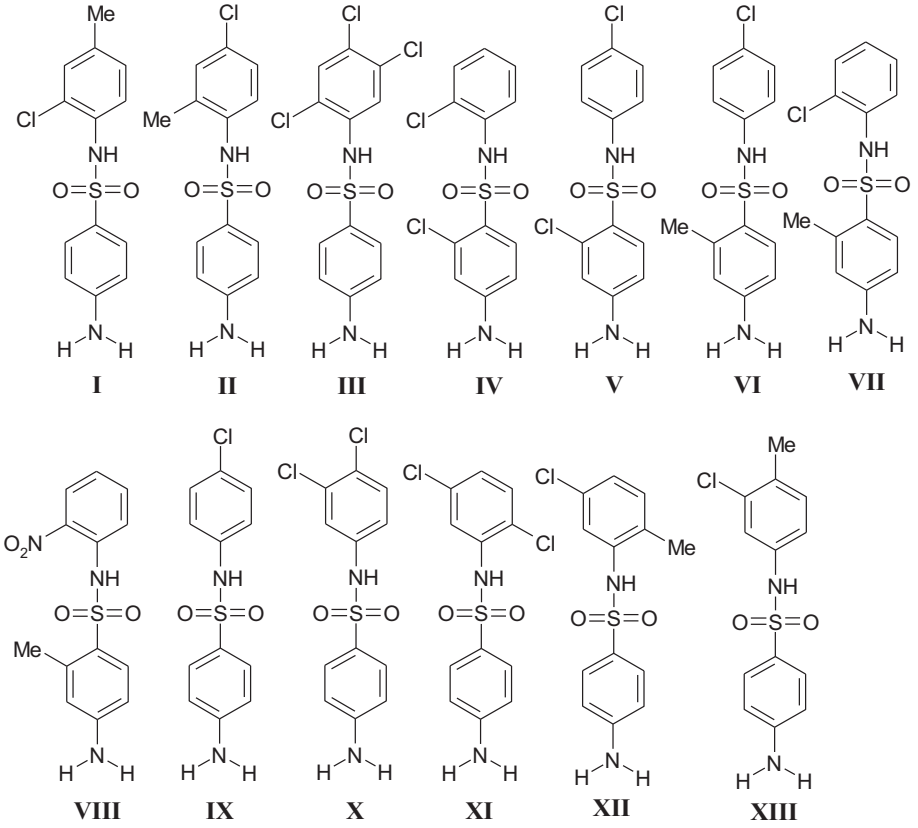
and Gómez [24] had tried to provide a proof of the reliability of the Yalkowsky–Valvani and Jain–Yalkowsky equations for the estimation of the aqueous solubility of some structurally related sulfonamides used as anti-infective agents. As a result of the analysis the authors concluded, that these equations need refinement before they can be used.

A more successful approach to describe sulfonamide solubility was proposed by Regosz *et al.* [18]. As a basis of the method the authors used the Hildebrand-Scatchard equation for regular solutions, which was modified by introduction of dielectric constant and solvatochromic polarity parameters. Comparison of the experimental and calculated data has shown that the used equation is applicable for an estimation of solubility of substances in aqueous and organic solvents in the temperature range from 20 to 75 °C.

In one of our last works [25] the partition coefficients for 38 SA derivatives were measured in the water-octanol system and a correlation equation connecting $\log K_{ow}$ with molecular polarizability and the hydrogen bond acceptor ability was developed. The proposed approach has shown good predictive ability for assessment of partition coefficients of complex organic molecules with a small number of functional groups. Other work [26] deals about the partitioning behavior of eight sulfonamides in 1-octanol buffer and liposome systems. Based on enthalpy–entropy relation authors concluded that the transfer in half of the sulfonamides studied from aqueous media to 1-octanol is mainly driven by hydrogen-bond interactions, whereas the partitioning into liposomes is almost exclusively driven by the hydrophobic immobilization of the solutes in the phospholipidic bilayers.

It should be mentioned, that sulfonamide molecules form branched hydrogen bond networks due to the presence of donor and acceptor atoms. Because of this, the present substances can generate different polymorphs [27,28] as well as be part of various complexes [29–31] and cocrystals [32–34]. Considering such forms allows to improve essentially the solubility of initial compounds, as has been shown for sulfadiazine [30,31], sulfamethazine, sulfamerazine [30], and furosemide [33]. Clearly a detailed study of sulfonamides is of interest not only because of their important practical aspects, but also as objects for understanding the fundamental processes occurring at nucleation and growth of new phases, and also at dissolution and solvation of molecular crystals.

In our previous work [35–38] structures, sublimation, solubility, and solvation characteristics of fourteen sulfonamides have been studied. In continuation of the study, we present in this work a comparative analysis of nine compounds [4-amino-*N*-(2-chloro-4-methylphenyl)-benzene-sulfonamide (**I**), 4-amino-*N*-(4-chloro-2-methyl phenyl)-benzene-sulfonamide (**II**), 4-amino-*N*-(2,4,5-trichlorophenyl)-benzene-sulfonamide (**III**), 4-amino-2-chloro-*N*-(2-chlorophenyl)-benzene-sulfonamide (**IV**), 4-amino-2-chloro -*N*-(4-chlorophenyl)-benzene-sulfonamide (**V**), 4-amino-*N*-(4-chlorophenyl)-2-methyl-benzene-sulfonamide (**VI**), 4-amino-*N*-(2-chlorophenyl)-2-methyl-benzene-sulfonamide (**VII**), 4-amino-2-methyl-*N*-(2-nitrophenyl)-benzene-sulfonamide (**VIII**), and 4-amino-*N*-(3-chloro-4-methylphenyl)-benzene-sulfonamide (**XIII**)] with the following four published ones: 4-amino-*N*-(4-chlorophenyl)-benzene-sulfonamide (**IX**), 4-amino-*N*-(3,4-dichlorophenyl)-benzene-sulfonamide (**X**), 4-amino-*N*-(2,5-dichlorophenyl)-benzene-sulfonamide (**XI**), and 4-amino-*N*-(5-chloro-2-methylphenyl)-benzene-sulfonamide (**XII**), (scheme 1). The choice of the compounds has been dictated by the aim of investigating the impact of substituent nature and their molecular position on thermodynamic properties of solubility and transfer processes in water and 1-octanol, which are model solvents for description of biological media.



SCHEME 1. Structural formulas of the compounds studied.