Solvent Effects on pK_a values of Some Substituted Sulfonamides in Acetonitrile−Water Binary Mixtures by the UV-Spectroscopy Method

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The examination of the dissociation constants of sulfonamides is essential in drug-design studies and in explaining the biopharmaceutical properties of substances. The dissociation constants of ten common human and veterinary antibiotics, namely, sulfadiazine, sulfamerazine, sulfamethoxazole, sulfathiazole, sulfamonomethoxine, sulfamethoxypyridazine, sulfadimethoxine, sulfafurazole, sulfadoxine, and sulfaquinoxaline, in water and in 15 %, 23 %, and 30 % (v/v) acetonitrile−water mixtures were determined by a UV/pH titration method and correlated with the Kamlet and Taft solvatochromic parameters, π^*, α, and β. Kamlet and Taft's general equation was reduced to two terms by combined factor analysis and target factor analysis in these mixtures: the independent term and polarity/polarizability π^*, which is a solvatochromic parameter. Further, the quasi-lattice quasi-chemical (QLQC) theory of preferential solvation has been applied to quantify the preferential solvation by water of electrolytes in acetonitrile−water mixtures.

Introduction

Sulfonamides are a very important class of antibacterial agents, and they have been used especially in the treatment of urinary tract infections.[1−4] In the field of industrial pharmacy, perhaps the most important physicochemical characteristic property of biologically active molecules is their acidity or basicity expressed by their pK values. Because most molecules have acidic and/or basic functionalities, relationships between dissociation constants and structure may prove useful in drug-design studies and in explaining the biopharmaceutical properties of substances.[5−7]

There are some limitations in determining the acidity constants of molecules such as low solubility in aqueous solutions and low values of acidity constants. Therefore, to enhance the acidity constants on one hand and to increase the solubility on the other, we are forced to choose mixed solvents.[8,9] In addition, the pK of the analytes in the mixed solvent is an important parameter for the optimization of separation techniques such as capillary electrophoresis (CE) and liquid chromatography (LC) of ionizable compounds. An understanding of the factors that determine the acidity or basicity of a solute dissolved in solvent mixtures can be decisive to foresee how the aqueous pK is modified when the organic modifier is added to the aqueous part of the eluent for separation methods and to establish relationships between an aqueous pK and the pK in the organic modifier−water binary mixtures. Moreover, the study of acid−base behavior of analytes in binary organic−water solvent systems could be key in predicting the influence of pH on retention and selectivity in LC.[10,11]

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Previously, the solvent effect on dissociation equilibria was believed to be chiefly guided by electrostatic interactions. However, recent studies[12−14] reveal that the change in the dielectric constant cannot be the sole factor. The variation of the pK values with the content of organic modifier can be explained by consideration of the preferential solvation of electrolytes in organic solvents such as methanol−water and acetonitrile (MeCN)−water mixtures. To elucidate the influence of a change in the medium on the systems studied and on retention in LC, the values of the dissociation constants can be related to macroscopic parameters (cosolvent percentage, the mole fraction of cosolvent (x_2), and the dielectric constant (ε)) and to microscopic parameters (Kamlet and Taft's solvatochromic parameters: α, solvent hydrogen-bond acidity; β, solvent hydrogen-bond basicity; π^* dipolarity/polarizability)[15−17] and the E_T^N parameter which defines the characteristics of the medium studied.[18]

MeCN is one of the most important dipolar aprotic solvents; it is used in many branches of chemistry and, in particular, has proved highly versatile as a mobile phase in LC, for the separation and purification of drugs from a wide variety of sources.[19−21] MeCN is a considerably weaker base and a much weaker acid than water and has a relatively high dielectric constant ($\varepsilon = 36.0$). Therefore, it is a good differentiating solvent for both acids and bases, as reflected by its small autoprotolysis constant ($pK_{HS} = 33.6$). Furthermore, it has low viscosity and ideal UV transparency.[22]

There are large spectra of pK determination techniques such as CE,[23,24] liquid−liquid partitioning,[25] ultraviolet−visible (UV−vis) absorption, and potentiometry.[6−8] Among these, potentiometry and spectrophotometry are methods of choice due to their simplicity, low cost, ease of application, and so on. Very often, the main difficulty in the determination of dissociation constants of drugs is their aqueous insolubility that forces the use of spectroscopic techniques. This technique requires very

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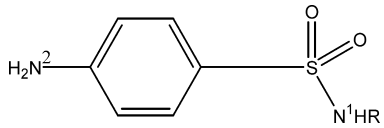


Figure 1. Molecular structures of sulfonamides used in this study.

low analyte concentrations and allows suitable absorbance measurement in aqueous solution even for products with low aqueous solubility.[6,26]

As a continuation of our extensive systematic study[27−29] on the effect of solvent composition on the protonation constants, the purpose of the present study is the determination of the dissociation constants of ten common human and veterinary antibiotics, namely, sulfadiazine, sulfamerazine, sulfamethoxazole, sulfathiazole, sulfamonomethoxine, sulfadimethoxine, sulfadoxine, sulfamethoxypyridazine, sulfafurazole, and sulfaquinoxaline in an MeCN−water medium (0 %, 15 %, 23 %, and 30 % v\v). Despite the importance of sulfonamides as powerful antibacterial agents, it was observed that there is neither a systematic study on the determination of the dissociation constant of these compounds in MeCN−water media nor one on the correlation between the dissociation constant and the most significant solvent properties to determine the influence of each property on the dissociation process.[30−39]

For this study, we chose the sulfonamides including different R groups attached to N^1 of the sulfonamido group (Figure 1) since most bacteriostatic sulfonamides are characterized by a *p*-aminoaryl moiety and structural diversity has been obtained basically by variation of this R group. Generally, this R group is a heterocyclic structure that renders the compound several times more active than the original sulfanilamide. It was suggested that bacteriostatic activity of sulfonamides is favored by decreasing their acidity,[40−43] which was confirmed in very recent works published by Soriano-Correa et al. and Gomes and Gomes.[44,45] Also, distinct therapeutic effects are often associated to different acidity ranges. Thus, it seems that the acidity of the sulfonamido group, and factors affecting it, are key features ruling physicochemical properties such as absorption, distribution, metabolism and toxicity that modulate the sulfonamide bioactivity.[5,46]

In this study, factor analysis (FA) is also used to determine the number of factors involved in the variation of dissociation constants of sulfonamides. The equations obtained permit calculation of the p*K* values of the studied sulfonamides in any MeCN−water mixtures up to 30 % (v/v) MeCN and can help to clarify the acid−base behavior of sulfonamides in these widely used MeCN−water mixtures. Furthermore, the variation in p*K* values obtained over the whole composition range studied has been explained by taking into account the preferential solvation of ions in MeCN−water mixtures; the quasi-lattice quasi-chemical (QLQC) theory[47] was applied to quantify the preferential solvation by water of the hydrogen ions, δ_w, in MeCN−water mixtures.

Experimental Section

Chemicals and Reagents. Analytical reagent grade chemicals were used, unless otherwise indicated. Sulfadiazine, sulfamerazine, sulfamethoxazole, sulfathiazole, sulfafurazole, sulfadoxine, sulfamonomethoxine, sulfamethoxypyridazine, sulfadimethoxine, and sulfaquinoxaline (Merck) were used without further purification. In this study, MeCN (HPLC grade) was selected as the organic modifier. Potassium hydroxide (Titrisol), hydrochloric acid (Titrisol), potassium hydrogen phthalate, and potassium chloride (ionic strength adjuster; 0.1 mol·L^{-1}) were supplied by Merck. All stock solutions of hydrochloric acid, potassium hydroxide, potassium hydrogen phthalate, and potassium chloride were prepared by dilution in water. Water, with a conductivity lower than 0.05 $\mu S \cdot cm^{-1}$, was obtained from a Milli-Q water purification system (Milli Pore Corp.).

Apparatus. Potentiometric measurements were performed with a Mettler-Toledo MA 235 pH/ion (resolution ± 0.1 mV) analyzer system. The UV−vis absorbance spectra were recorded at each pH using a Perkin-Elmer LAMBDA 25 spectrophotometer, equipped with a 1 cm path length cell, controlled by a personal computer. A peristaltic pump was used to circulate the solution from the titration vessel to the spectrophotometer cell, and vice versa, through Teflon or Tygon tubes in a closed loop circuit with continuous flow. All titrations were carried out under N_2 and at (25.0 ± 0.1) °C, which was maintained by circulating water from a constant-temperature thermostat (Heto CBN 8-30 and temperature control unit Heto HMT 200) through the double-wall Pyrex titration cell of 80 mL capacity.

Procedures. Before the spectrometric titration, carbonate-free potassium hydroxide solutions were prepared under a nitrogen atmosphere. The ionic strength of each KOH solution was adjusted to 0.10 mol·L^{-1} by the addition of KCl. The alkali titer and absence of carbonate were periodically checked by pH-metry, using the appropriate Gran function[48] against primary standard oven-dried potassium hydrogen phthalate.

The p*K* values of the sulfonamides were determined by means of the data obtained from spectrometric titrations in water and in 15 %, 23 %, and 30 % (v/v) MeCN−water mixtures at (25.0 ± 0.1) °C and in 0.1 mol·L^{-1} ionic strength (KCl). The spectrophotometric multiple-wavelength pH-titration was carried out as follows: in a first step, the standard electromotive force (e.m.f.) values, $E°$, of the potentiometric cell were evaluated from titrations of a measured amount of an acidic solution, at the same conditions of temperature, ionic strength, and solvent composition to be used in later experiments using KOH solutions in the same solvent and ionic strength as the titrant. The standard e.m.f. of the cell, $E°$, is the average of at least 15 standardizations. The calibration parameters were checked from the Gran plots.[48,49] The standardization of the electrode system was carried out each time the solvent medium was changed and the constancy of $E°$ values ensured by continual surveillance by means of periodic calibrations. In a second step, a solution of fully protonated sulfonamides (42.0 mL containing $1 \cdot 10^{-5}$ mol·L^{-1} drug) at the required conditions of temperature, ionic strength, and solvent composition were titrated using KOH solutions in the same solvent and ionic strength in the pH range of 2.0 to 11.0. After each addition, the potential was allowed to stabilize, its value used, in combination with $E°$ calculated in the calibration step, to calculate the solution pH.

In the UV−vis spectrometric titrations, the test solution was pumped to a spectrometric flow-cell by means of a peristaltic pump. After each addition of titrant, and after waiting for the e.m.f. reading to be stable, UV−vis spectra were recorded with 1 nm resolution over the (190 to 400) nm interval to obtain different spectra around the maximum λ for each sulfonamide.

Data Treatment. Spectrometric titration data were processed using the program STAR (Stability Constants by Absorbance Readings)[50] which calculates stability constants and molar absorptivities of the pure species by multilinear regression. The program STAR requires a previous model of the chemical equilibria, based upon the existence of certain chemical species, to be postulated. The refinement of equilibrium constants is done using the Gauss−Newton nonlinear least-squares algorithm by

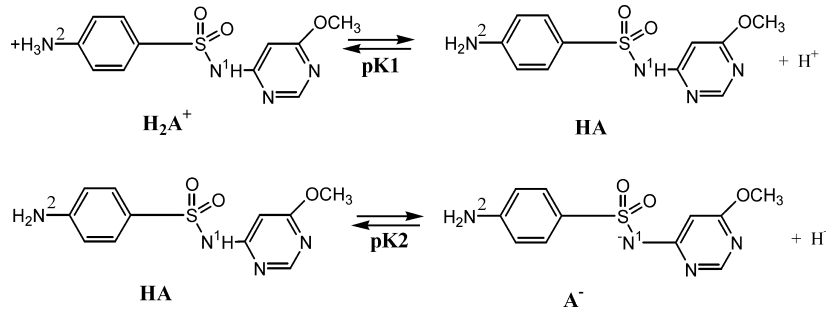


Figure 2. Dissociation equilibrium of sulfamonomethoxine.

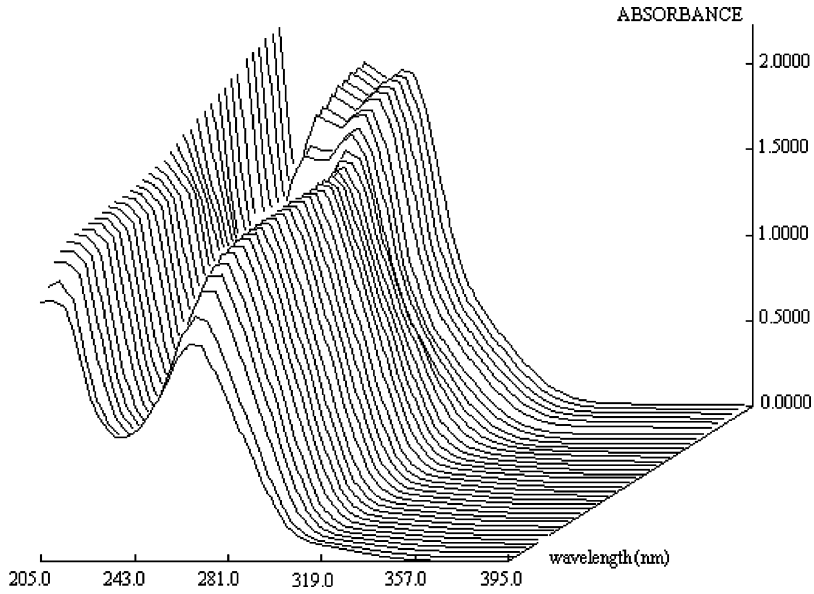


Figure 3. Wavelength (nm) absorbance graphic for sulfomonomethoxine as a function of pH in water.

numerical differentiation, until a minimum in the sum of the squares residual (U) is attained. The optimization is performed by means of a nonlinear least-squares procedure. The minimization process is repeated until the relative change of U between two iterations is ≤ 0.01 %.

Factor analysis has been used as a powerful technique in the study of different chemical phenomena whose interpretation requires multivariate approaches.[51,52] Target factor analysis (TFA) was then applied to identify these factors.[53−55] Input data referring to the pK of substances, which vary according to the composition of the mixed solvent, are collected to build up the experimental data matrix. The principle and methodology of factor analysis and target factor analysis have been described in detail by Malinowski.[56] All calculations, including several tests applied to determine the correct number of factors or to decide whether a proposed target can be accepted as a real factor, were performed through the Holmes 2000 program.[57−59]

Results and Discussion

A sulfonamide contains two important functional groups in the pharmaceutically relevant pH range of 4 to 9 as shown in Figure 1: one acidic amide moiety (N^1) and one basic amine moiety (N^2). The amine nitrogen atom ($-NH_2$) is able to gain a proton, while the amide nitrogen atom ($-NH-$) is able to release a proton under specific pH conditions. Thus, the first dissociation equilibrium refers to the dissociation equilibrium of the amine moiety (pK_1) and the second equilibrium to the dissociation equilibrium of the amide moiety (pK_2). The equilibrium reaction steps are shown in Figure 2.

Figure 3 and Figure 4 show UV−vis spectra of sulfamonomethoxine and sulfadiazine over the (190 to 400) nm interval and different pH values that were given in water and in 30 % MeCN−water mixtures, respectively. The data were processed using the STAR program[50] to obtain the pK values for substances using an iterative procedure.

The dissociation constant values determined for the equilibria involved for sulfadiazine, sulfamerazine, sulfamethoxazol, sulfathiazole, sulfamonomethoxine, sulfamethoxypyridazine, sulfadimethoxine, sulfafurazole, sulfadoxine, and sulfaquinoxaline studied in 0 %, 15 %, 23 %, 30 % (v\v) MeCN−water mixtures at (25.0 ± 0.1) °C are collected in Table 1, together with respective standard deviations. pK values reported in the literature for water are shown in Table 2.[30−35] The difference between the values determined in the present work and the values determined by others is minor and about what would be expected from the difference in conditions employed.

Despite the large distance between the R group and N^2 nitrogen atom, as shown in Table 1, the R substituent seems to have a crucial role in pK_1 values of sulfonamide derivatives. An enhanced effect in the chemical and biological properties that distinguish different sulfonamide-based drugs should be expected if −NH− substitution takes place due to its proximity to the leaving proton. Thus, the role of different R groups attached to the amide nitrogen atom should be equally inspected. In comparison with pK values from Table 1, larger changes in pK_2 values of the sulfonamido group are observed, as expected from the closer distance between the substituent group and the sulfur atom.[45]

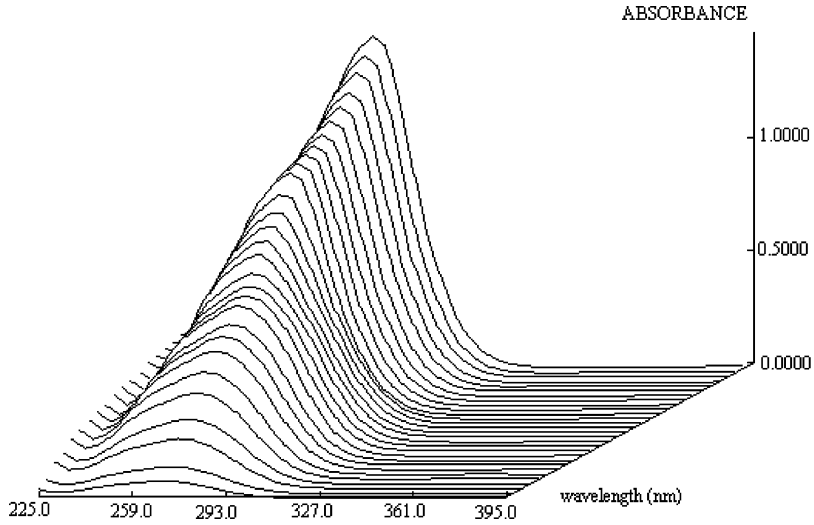
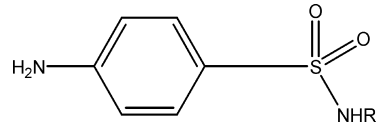
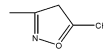
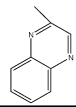


Figure 4. Wavelength (nm) absorbance spectra for sulfadiazine as a function of pH in 30 % (v/v) acetonitrile−water mixtures.

Table 1. pK_1 and pK_2 Values of Sulfonamides in Water and 15 %, 23 %, and 30 % (v/v) MeCN−Water Mixtures



Compounds	R	Water	15 % (v/v) MeCN	23 % (v/v) MeCN	30 % (v/v) MeCN
sulfadiazine		1.94(0.01) 6.33(0.003)	1.62(0.05) 6.62(0.01)	1.47(0.01) 6.88(0.01)	1.43(0.03) 7.11(0.01)
sulfamerazine		2.27(0.02) 6.71(0.04)	1.84(0.01) 7.07(0.01)	1.74(0.01) 7.31(0.01)	1.83(0.02) 7.49(0.01)
sulfamethoxazole		1.49(0.01) 5.41(0.01)	1.39(0.08) 5.65(0.02)	1.30(0.01) 5.87(0.02)	1.28(0.02) 5.91(0.01)
sulfathiazole		1.89(0.05) 7.12(0.01)	1.79(0.01) 7.33(0.01)	1.72(0.02) 7.37(0.03)	1.62(0.01) 7.49(0.01)
sulfamonomethoxine		1.73(0.02) 6.22(0.01)	1.63(0.01) 6.32(0.02)	1.52(0.01) 6.36(0.02)	1.52(0.07) 6.40(0.01)
sulfamethoxypyridazine		2.09(0.02) 6.83(0.07)	2.09(0.09) 7.02(0.05)	2.05(0.05) 7.31(0.02)	1.74(0.10) 7.60(0.01)
sulfadimethoxine		2.11(0.02) 6.17(0.02)	2.18(0.04) 6.40(0.09)	2.19(0.04) 6.51(0.08)	2.20(0.09) 6.60(0.04)
sulfafurazole		2.28(0.06) 5.19(0.03)	2.44(0.01) 5.34(0.01)	2.49(0.04) 5.45(0.03)	2.61(0.03) 5.49(0.02)
sulfadoxine		2.38(0.03) 5.77(0.02)	2.25(0.08) 5.91(0.01)	2.15(0.10) 6.32(0.03)	2.08(0.10) 6.54(0.08)
sulfaquinoxaline		2.34(0.04) 5.97(0.03)	2.24(0.03) 6.16(0.02)	2.40(0.03) 6.27(0.01)	2.34(0.08) 6.33(0.03)

The pK_1 values associated with the amino group (N^1) for the compounds studied were smaller than those generally observed with aniline derivatives in water[26,27] (e.g., aniline in water has a pK = 4.60). This increase in acidity can be attributed to an electron-withdrawing sulfone group in the para position. On the other hand, the pK_2 values in line with the amide nitrogen atom of sulfonamide derivatives were smaller than the dissociation constant of sulfonilamide, pK_a = 10.1.[60] This increase in acidity can be explained by a resonance and steric effect on the dissociation constants because the structures of the sulfonamide derivatives are formed when a heterocyclic molecule is substituted for hydrogen of the sulfamine group.

It is known that one of the most important factors determining equilibrium constants is the reaction medium. The variation of the pK values of sulfonamides versus the mole fraction of MeCN, x_{MeCN}, in the MeCN−water mixtures is presented in Figure 5 and Figure 6. The equations between pK_1 and pK_2 values and mole fraction of organic modifier are shown in Table 3. The variation of pK values with the mole fraction of MeCN is different for each substance although, in general, pK_1 values in line with the anilinium ion decrease with the mole fraction of MeCN, whereas pK_2 values in line with the sulfonamide increase. The different ways in which pK values change might be explained by the fact that the dissociation process is ruled

Table 2. p*K* Values Reported of Sulfonamides in Water

compounds	method	pK_{a1}	pK_{a2}	background	ref
sulfadiazine	CE	2.10	6.28	citrate buffer	34
	CE	2.00	6.4	buffer	37
sulfamerazine	UV/pH	2.22 ± 0.01	6.80 ± 0.02	0.15 M KCl	35
	CE	2.17	6.77	citrate buffer	34
	potentiometry	2.06 ± 0.30	6.90 ± 0.05	(0.01 to 0.05) M $NaClO_4$	30
sulfamethoxazole	potentiometry	1.85 ± 0.30	5.60 ± 0.04	(0.01 to 0.05) M $NaClO_4$	30
	CE	1.7	5.60	buffer	37
	CE	1.83	5.57	citrate buffer	34
	potentiometry	1.85 ± 0.30	5.60 ± 0.04	(0.01 to 0.05) M $NaClO_4$	30
sulfathiazole	potentiometry	2.01 ± 0.30	7.11 ± 0.04	(0.01 to 0.05) M $NaClO_4$	30
sulfamonomethoxine	CE	-	6.03	buffer	35
	CE	1.98	5.96	citrate buffer	34
sulfamethoxypyridazine	potentiometry	1.87 ± 0.30	5.45 ± 0.06	(0.01 to 0.05) M $NaClO_4$	30
	CE	2.09	6.95	citrate buffer	34
	CE	-	5.49	buffer	35
sulfadimethoxine	CE	1.62	6.13	buffer	35
	potentiometry	2.13 ± 0.30	6.08 ± 0.09	(0.01 to 0.05) M $NaClO_4$	30
	CE	1.87	5.86	citrate buffer	34
sulfaquinoxaline	CE	1.86	5.56	citrate buffer	34

by electrostatic interactions as well as by specific solute−solvent interactions. It has been found that in several water−organic binary solvent mixtures pK_a values of a given substance show a linear relationship with the mole fraction of organic solvent.[61] This is indicated by the following expression

$$pK_{a,\varphi} = pK_{a,w} + \varphi\Delta pK \quad (1)$$

where $pK_{a,w}$ indicates the dissociation constant in water, φ the mole fraction of organic solvent, ΔpK the slope of the linear relationship, and $pK_{a,\varphi}$ the pK_a at the corresponding composition.

As shown in Figure 2, the first dissociation equilibrium (pK_1) regarding the N^2 nitrogen atom is the dissociation constant for equilibrium between the positively charged, unionized amino

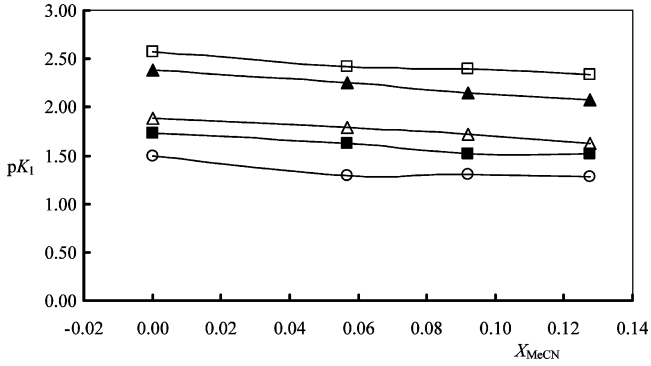


Figure 5. pK_1 values versus mole fraction of water, x_w, in acetonitrile−water mixtures. □, sulfaquinoxaline; ▲, sulfadoxine; Δ, sulfathiazole; ■, sulfamonomethoxine; ○, sulfadiazine.

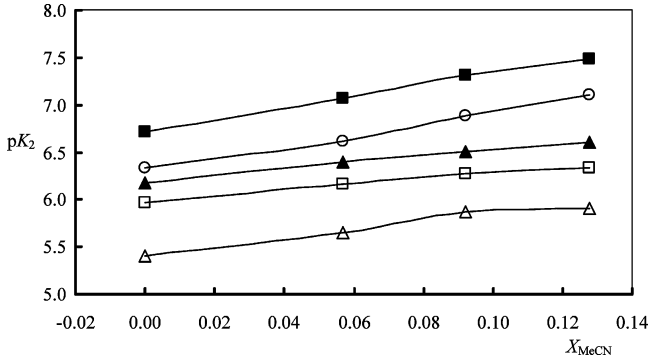


Figure 6. pK_2 values versus mole fraction of water, x_w, in acetonitrile−water mixtures. ■, sulfamonomethoxine; ○, sulfadiazine; ▲, sulfadimethoxine; □, sulfaquinoxaline; Δ, sulfathiazole.

Table 3. Equations between pK_1 and pK_2 Values of Sulfonamides and Mole Fractions of Organic Modifier[a]

substance	equations	regression coefficient
sulfadiazine	$pK_1 = 1.90(0.06) - 4.13(0.75)x$[b]	0.967
	$pK_2 = 6.31(0.03) + 6.17(0.36)x$	0.997
sulfamerazine	$pK_1 = 2.17(0.14) - 3.67(1.69)x$	0.834
	$pK_2 = 6.72(0.02) + 6.20(0.26)x$	0.998
sulfamethoxazole	$pK_1 = 1.49(0.02) - 1.74(0.24)x$	0.981
	$pK_2 = 5.42(0.05) + 4.15(0.62)x$	0.978
sulfathiazole	$pK_1 = 1.90(0.01) - 2.09(0.16)x$	0.994
	$pK_2 = 7.14(0.03) + 2.80(0.33)x$	0.987
sulfamonomethoxine	$pK_1 = 1.72(0.03) - 1.79(0.37)x$	0.960
	$pK_2 = 6.23(0.01) + 1.41(0.13)x$	0.992
sulfamethoxypyridazine	$pK_1 = 2.16(0.12) - 2.43(1.39)x$	0.779
	$pK_2 = 6.77(0.08) + 6.07(0.94)x$	0.977
sulfadimethoxine	$pK_1 = 2.12(0.02) - 0.70(0.19)x$	0.936
	$pK_2 = 6.19(0.02) + 3.40(0.27)x$	0.994
sulfafurazole	$pK_1 = 2.28(0.02) - 2.50(0.20)x$	0.994
	$pK_2 = 5.20(0.02) + 2.44(0.28)x$	0.988
sulfadoxine	$pK_1 = 2.38(0.01) - 2.40(0.11)x$	0.998
	$pK_2 = 5.70(0.11) + 6.31(1.31)x$	0.960
sulfaquinoxaline	$pK_1 = 2.31(0.07) - 0.29(0.84)x$	0.235
	$pK_2 = 5.98(0.02) + 2.89(0.28)x$	0.994

[a] Error associated to values is given in parentheses. [b] x represents the mole fraction of the organic modifier (MeCN).

(−NH_3^+−) group and its electrically neutral conjugate base. Thus, when the amino group is ionized, there is no change in the number of charges involved in the process ($H_2A^+ \leftrightarrow HA+H^+$). Therefore, a change in the polarity of the medium has a minor influence on the dissociation process, which depends only on the solvation of the different species by the solvents of the mixture, and the variation of the dissociation constant with the MeCN content is not linear. This behavior also explains why the pK_1 values of sulfonamides in the range 0 % (v/v) and to approximately 30 % (v/v) of MeCN show small changes.

The appearance of such variation (Figure 5) for the pK_1 values of sulfonamides in MeCN−water mixtures might be due to the fact that these dissociation constants are dependent on solute−solvent interaction effects, and these effects vary with the structural features of the mixtures. If a solute interacts with one solvent more strongly than with the other, the solute will be preferentially solvated by the former.[13] On the water-rich side of MeCN−water mixtures, $x_{MeCN} > 0.15$, the water structure remains more or less intact, and the MeCN molecules gradually occupy the cavities between the water molecules without disrupting the water structure. The (v/v) % limit beyond which the MeCN can no longer be accommodated within the cavities

of the structure of water depends on the pressure and is about 30 % (v/v) in MeCN. In this water-rich region, there are no changes in the pK values of sulfonamides assigned to the dissociation of the protonated amino, but these pK values change if the percentage of MeCN increases (Table 1). This is in accordance with the previously obtained values of preferential solvation, δ_w, of hydrogen ions by water in MeCN−water mixtures.[14,15]

However, in the deprotonation of sulfonamide nitrogene (pK_2), there is a change from a neutral species to two ionic species: a negatively charged one plus a hydrogen ion (HA ↔ $H^+ + A^-$), and therefore, any variation in the polarity of the medium exerts a strong influence on the dissociation process. These pK_2 values, as well as pK_1, are lower than the expected values considering the high pK values expected in pure MeCN. The variation of the pK values of sulfonamides in MeCN−water mixtures could be explained by the fact that there is preferential solvation in these media[14] that is related to structural features of these mixtures.[62] Preferential solvation in MeCN−water mixtures produces lower pK values than expected when the preferred solvent is water. If the solute displays no preference for the solvent molecules, the solvent composition in the cybotactic zone, in the immediate neighborhood of the solute, is the same as in the bulk.

To determine the degree of preferential solvation of hydrogen ions in the MeCN−water solvent mixtures considered, the QLQC theory was used. Evaluation of preferential solvation by water around hydrogen ions, $\delta_w = x_w^L - x$ requires that one knows the molar Gibbs energy of transfer values, ΔG_t^0, of all the individual species involved in the dissociation equilibria from the standard state in water to the standard state in the mixed solvent studied. The standard molar Gibbs energy of transfer for hydrogen ion from water into pure MeCN solvent, $\Delta G_t^0(H^+)$, and the excess of Gibbs energy for mixing MeCN−water equimolar mixtures, $\Delta G_{wMeCN}^0(x = 0.5)$, are (46.4 and 1.32) kJ·mol^{-1}, respectively.[62,63] The results obtained from the QLQC method at 25 °C and for the preferential solvation by water around hydrogen ions, $\delta_w = x_w^L - x$, show that for the MeCN−water mixtures the preferential solvation of hydrogen ions by water is positive; i.e., water molecules show a greater tendency to be in the immediate vicinity of a given hydrogen ion than MeCN molecules do. This preference is maximal at $x_w \approx 0.25$ for the hydrogen ion.[64] Therefore, the pK values of sulfonamide derivatives in these mixtures are expected to be closer to pK values in water than to pK in MeCN.[65]

The preferential solvation in water−organic solvent mixtures may interfere more seriously. Although this problem has not been solved unequivocally, the investigations provide significant evidence that FA techniques can contribute to better understanding of acid−base behavior of substances in these mixtures. The main problem in the study of sulfonamides in MeCN−water mixtures is how a solute species reacts with the solvent that focuses their solvation sphere. There are several empirical methods to correlate the general effects of the solvent in pure solvent and water−organic cosolvent mixtures.[66] The most ambitious and also most successful quantitative treatment of solvent effects using a multiparameter equation is that of Kamlet and Taft,[16−18] also known as the linear salvation-energy relationship (LSER).

$$XYZ = XYZ_o + s\pi^* + a\alpha + b\beta \quad (2)$$

This equation explains any solute property variation with solvent composition in terms of a linear combination of the molecular parameters of the solvent π^* (solvent polarity/polarizability), α (solvent hydrogen-bond-donating acidity, HBD), and β (solvent hydrogen-bond-accepting basicity, HBA). XYZ is the solute property, and XYZ_0 is the value of this property for the same solute in a hypothetical solvent for which $\alpha = \beta = \pi^* = 0$. The values of the solvatochromic parameters π^*, α, and β, in MeCN−water mixtures have been taken from the literature[51] and given in Table 4.

Here, several attempts were made to find the best form of the Kamlet−Taft equation to describe the variation of pK values of sulfonamide derivatives in MeCN−water mixtures. The Kamlet−Taft equations obtained from the results provided, by factor analysis and target factor analysis to the pK value matrices, are shown in Table 5 and Table 6. The coefficients of the parameters are the target loadings, and the values given in parentheses are the errors associated with these values. These loadings (coefficients) are related to the weight of each real factor in each different column (each percentage of MeCN−water in the mixture) of the original data matrix in a similar sense as the "weightings" in regression analysis. Global errors in data reproduction (RMS and RSD) were in agreement with experimental errors. This study also confirms the usefulness of microscopic parameters, such as π^*, α, and β, in the explanation of microscopic processes since the solvent properties in the cybotactic zone are the ones which directly affect the solutes when a process such as acid−base equilibrium occurs.

Table 4. Solvatochromic Parameters for Binary Solvent Mixtures of Acetonitrile with Water[a]

% (v/v) MeCN−water	x_{MeCN}	α	β	π^*
0.00	0.000	1.130	0.58	1.140
15.0	0.0568	1.012	0.60	1.095
23.0	0.0921	0.967	0.61	1.061
30.0	0.1277	0.937	0.61	1.035

[a] Ref 51.

Table 5. Expressions of Kamlet−Taft Equations Obtained through Factor Analysis and Target Factor Analysis Applied to Data Built from pK_1 Values of Sulfonamides[a]

substance	linear solvation energy relationships
sulfadiazine	$pK_1 = -3.38(0.58) + 4.62(0.19)\pi^b$
sulfamerazine	$pK_1 = -2.41(0.45) + 4.00(0.16)\pi^b$
sulfamethoxazole	$pK_1 = -0.78(0.49) + 1.97(0.21)\pi^b$
sulfathiazole	$pK_1 = -0.80(0.51) + 2.36(0.19)\pi^b$
sulfamonomethoxine	$pK_1 = -0.60(0.15) + 2.04(0.32)\pi^b$
sulfamethoxypyridazine	$pK_1 = -1.04(0.25) + 2.80(0.18)\pi^b$
sulfadimethoxine	$pK_1 = -3.01(0.42) - 0.77(0.22)\pi^b$
sulfafurazole	$pK_1 = -5.49(0.56) - 2.80(0.28)\pi^b$
sulfadoxine	$pK_1 = -0.72(0.45) + 2.71(0.23)\pi^b$
sulfaquinoxaline	$pK_1 = -0.34(0.19) + 1.93(0.29)\pi^b$

[a] RMS (root-mean-square error) = 0.06. RSD (residual standard deviation) = 0.07. [b] Error associated to values is given in parentheses.

Table 6. Factor Loadings for the Reproduction of the pK_2 and Matrices of Sulfonamides in Acetonitrile−Water Mixtures[a]

substance	linear solvation energy relationships
sulfadiazine	$pK_2 = 14.33(0.60) - 7.02(0.23)\pi^b$
sulfamerazine	$pK_2 = 14.73(0.57) - 7.00(0.28)\pi^b$
sulfamethoxazole	$pK_2 = 10.81(0.49) - 4.72(0.18)\pi^b$
sulfathiazole	$pK_2 = 10.69(0.42) - 3.11(0.20)\pi^b$
sulfamonomethoxine	$pK_2 = 8.03(0.27) - 1.58(0.14)\pi^b$
sulfamethoxypyridazine	$pK_2 = 14.73(0.55) - 6.96(0.25)\pi^b$
sulfadimethoxine	$pK_2 = 10.55(0.29) - 3.81(0.19)\pi^b$
sulfafurazole	$pK_2 = 8.36(0.24) - 2.76(0.20)\pi^b$
sulfadoxine	$pK_2 = 14.06(0.58) - 7.33(0.27)\pi^b$
sulfaquinoxaline	$pK_2 = 9.70(0.44) - 3.25(0.15)\pi^b$

[a] RMS (root-mean-square error) = 0.06. RSD (residual standard deviation) = 0.07. [b] Error associated to values is given in parentheses.

For the dissociation reactions corresponding to the sulfonamide derivatives, the Kamlet and Taft general equation was reduced to only two terms to describe the modification of the studied property in MeCN−water mixtures: the independent term and π^* (dipolarity/polarizability). Other combinations of factors were tried to explain mixed solvent−solute interactions, but the fit of the model proposed to reproduce experimental data was worse. Although the solvent polarity is identified as the main cause of pK value variation of sulfonamides in MeCN−water mixtures, these results do not justify the assumption that only target π^* and unity are equally valid for explaining the variation of the pK values of sulfonamides in MeCN−water mixtures. It was shown by Barbosa et al.[51] that the linear relationship between pK and π^* can break down when the proportion of organic cosolvent is high, and the data matrices cover up to nearly 60 % (v/v) of MeCN.

The first parameter in the reduced Kamlet and Taft equation determined in this work, derived from the target unity, represents the value of the acid dissociation constant of the different solutes in a hypothetical solvent with $\alpha = \beta = \pi^* = 0$; the second parameter is related to the polarity/polarizability of the solvent, which was well characterized by the π^* parameter. The coefficients of target π^* in the reduced Kamlet−Taft equations are summarized in Table 4 and Table 5. Global errors in data reproduction (RMS and RSD) were in agreement with experimental errors.

The coefficients of target π^* obtained by TFA means that an increase in the polarity of the mixed solvent increases the solvation of ions. Solvation by polarity affects both anions and cations, and this could explain why the target π^* was the main term in the equations obtained in Table 5 and Table 6. There exists a dipole−dipole interaction between the polar sulfonamides and the polar solvent, while an ion−dipole interaction is the important force between the polar solvent and ionized sulfonamides. Since the solute ion−solvent dipole interaction is stronger than the dipole−dipole interaction, increasing the polarity of the solvent causes the ionized form of sulfonamides to become more stable than unionized sulfonamides, thus the degree of ionization increases.

The behavior of the cationic (H_2A^+) sulfonamides differs from that of neutral (HA) as shown in Table 4 and Table 5. The behavior of the cationic sulfonamides in the first dissociation equilibrium (pK_1) regarding the N^2 nitrogen atom differs due to the fact that the π^* are generally positive and a low value. In the dissociation process of these H_2A^+ ions, there is no change in the number of charges, and the change of the polarity of the medium has little influence on the dissociation process. For neutral sulfonamides regarding the N^1 nitrogen atom, electrostatic interaction overwhelms other effects, and this fact is reflected in the greater magnitude of the π^* coefficients with respect to those obtained for amine nitrogen atom of the N^1 of sulfonamides.

This study confirms the usefulness of microscopic parameters, such as π^*, in the explanation of microscopic processes since the solvent properties in the cybotactic zone are the ones which directly affect the solutes. The FA and TFA chemometric techniques enable us to obtain equations (Table 5 and Table 6) that permit the pK values of sulfonamides in any MeCN−water mixtures to be determined. The LSER equations also permit the interpretation of their acid−base behavior in these widely used hydroorganic mixtures. Preferential solvation by water occurs in MeCN−water mixtures, in the range of compositions studied here, for hydrogen ions.

Literature Cited

(1) Owa, T.; Nagasu, T. Novel Sulphonamide Derivatives for the Treatment of Cancer. *Expert Opin. Ther. Pat.* **2000**, *10*, 1725–1740.

(2) Haasnoot, W.; Cazemier, G.; Pre, J. D.; Kemmers-Voncken, A.; Bienenmann-Ploum, M.; Verheijen, R. Sulphonamide Antibodies: From Specific Polyclonals to Generic Monoclonals. *Food Agric. Immunol.* **2000**, *12*, 15–30.

(3) Suganya, K.; Kabilan, S. Substituent and Solvent Effects on Electronic Absorption Spectra of some *N*-(Substitutedphenyl)benzene Sulphonamides. *Spectrochim. Acta A* **2004**, *60*, 1225–1228.

(4) Patel, P.; Korgaokar, S.; Parikh, K.; Parekh, H. Synthesis and Biological Activity of 2-azetidinones, Sulphonamides, Arylamides and Thiourea derivatives. *Indian J. Chem. B* **1999**, *38*, 696–700.

(5) Barbosa, J.; Barron, D.; Jimenez-Lozano, E.; Sanz-Nebot, V. Comparison between Capillary Electrophoresis, Liquid Chromatography, Potentiometric and Spectrophotometric Techniques for Evaluation of pK_a values of Zwitterionic Drugs in Acetonitrile-Water Mixtures. *Anal. Chim Acta* **2001**, *437*, 309–321.

(6) Allen, R. I.; Box, K. J.; Comer, J. E. A.; Peake, C.; Tam, K. Y. Multiwavelength Spectrophotometric Determination of Acid Dissociation Constants of Ionizable Drugs. *J. Pharm. Biomed. Anal.* **1998**, *17*, 699–712.

(7) Fleuren, H. L. J.; Van Ginneken, C. A. M.; Van Rossum, J. M. Differential Potentiometric Method for Determining Dissociation Constants of very Slightly Water-Soluble Drugs Applied to the Sulfonamide Diuretic Chlorthalidone. *J. Pharm. Sci.* **1979**, *68*, 1056–1058.

(8) Almasifar, D.; Forghaniha, F.; Khojasteh, Z.; Ghasemi, J.; Shargi, H.; Shamsipur, M. Spectrophotometric Determination of Acidity Constants of Some Recently Synthesized Anthraquinones in Methanol + Water. *J. Chem. Eng. Data* **1997**, *42*, 1212–1215.

(9) Hemmateenejad, B.; Abbaspour, A.; Maghami, H.; Foroumadi, A. Spectrophotometric Determination of Acidity Constants by Two-Rank Annihilation Factor Analysis. *Anal. Chim. Acta* **2008**, *607*, 142–152.

(10) Evagelou, V.; Tsantili-Kakoulidou, A.; Koupparis, M. Determination of the Dissociation Constants of the Cephalosporins Cefepime and Cefpirome Using UV-Spectrometry and pH-Potentiometry. *J. Pharm. Biomed. Anal.* **2003**, *31*, 1119–1128.

(11) Jiménez-Lozano, E.; Marqués, I.; Barrón, D.; Beltrán, J. L.; Barbosa, J. Determination of pK_a Values of Quinolones from Mobility and Spectroscopic Data Obtained by Capillary Electrophoresis and a Diode Array Detector. *Anal. Chim. Acta* **2002**, *464*, 37–45.

(12) Kan, C. A.; Petz, M. Residues of veterinary drugs in eggs and their distribution between yolk and white. *J. Agric. Food. Chem.* **2000**, *48*, 6397–6403.

(13) Shehatta, I. Effect of Preferential Solvation on the Thermodynamic Properties of Antidepressant Drug Trazodone in Aqueous Ethanol: Linear Free-Energy Relationships. *Helv. Chim. Acta* **2002**, *85*, 2125–2137.

(14) Barbosa, J.; Sanz-Nebot, V. Preferential Solvation in Acetonitrile-Water Mixtures. In: Relationship Between Solvatochromic Parameters and Standard pH Values. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 3287–3292.

(15) Barbosa, J.; Bergés, R.; Toro, I.; Sanz-Nebot, V. Protonation Equilibria of Quinolone Antibacterials in Acetonitrile-Water Mobile Phases Used in LC. *Talanta* **1997**, *44*, 1271–1283.

(16) Kamlet, M. J.; Taft, R. W. The Solvatochromic Comparison Method. I. The Beta-Scale of Solvent Hydrogen-Bond Acceptor (HBA) Basicities. *J. Am. Chem. Soc.* **1976**, *98*, 377–383.

(17) Kamlet, M. J.; Abboud, J. L.; Taft, R. W. The Solvatochromic Comparison Method. The π^* Scale of Solvent Polarities. *J. Am. Chem. Soc.* **1977**, *99*, 6027–6038.

(18) Kamlet, M. J.; Abboud, J. L.; Taft, R. W. *Prog. Phys. Org. Chem.*; Taft, R. W., Ed.; Interscience: NewYork, 1981.

(19) Hearn, M. T. W.; Regnier, F. E.; Wehr, C. T. *High Performance Liquid Chromatography of Proteins and Peptides*, 1st ed.; Academic Press: New York, 1983.

(20) Poole, C. F.; Poole, S. K.; Eds. *Chromatography Today*; Elsevier: Amsterdam, 1991.

(21) Snyder, L. R.; Glaijh, J.; Kirkland, J. J. *Practical HPLC Method Development*; Wiley: 1988.

(22) Marcus, Y.; *The Properties of Solvents, Wiley Series in Solution Chemistry*; John Wiley and Sons: New York, 1998; Vol. 4.

(23) Foulon, C.; Duhal, N.; Lacroix-Callens, B.; Vaccher, C.; Bonte, J. P.; Goossens, J. F. Determination of pK_a Values of Benzoxa-, Benzothia- and Benzoselena - Zolinone Derivatives by Capillary Electrophoresis. Comparison with Potentiometric Titration and Spectrometric Data. *Eur. J. Pharm. Sci.* **2007**, *31*, 165–171.

(24) Gluck, S. J.; Cleveland, J. A. Capillary Zone Electrophoresis for the Determination of Dissociation Constants. *J. Chromatogr.* **1994**, *680*, 43–48.

(25) Hasegawa, J.; Fujita, T.; Hayashi, Y.; Iwamoto, K.; Watanabe, J. Determination of Octanol-Water Partition Coefficients by an HPLC Method for Anticonvulsant Structure-Activity Studies. *J. Pharm. Pharmacol.* **1995**, *47*, 345–347.
(26) Polster, J.; Lachmann, H. *Spectrometric Titrations: Analysis of Chemical Equilibria*; VCH: Weinheim, 1989.
(27) Altun, Y. Study of Solvent Composition Effects on the Protonation Equilibria of Various Anilines by Multiple Linear Regression and Factor Analysis Applied to the Correlation between Protonation Constants and Solvatochromic Parameters in Ethanol-Water Mixed Solvents. *J. Solution Chem.* **2004**, *33*, 477–495.
(28) Altun, Y. Study of Solvent Effects on the Protonation of Functional Group of Disubstituted Anilines: Factor Analysis Applied to the Correlation between Protonation Constants and Solvatochromic Parameters in Ethanol-Water Mixtures. *Monatsh. Chem.* **2005**, *136*, 1993–2006.
(29) Altun, Y.; Köseoğlu, F. Solute-Solvent Interaction Effects on Protonation Equilibrium of Substituted N-benzylidene-2-hydroxyanilines in Aqueous Ethanol: The Application of Factor Analysis to Solvatochromic Parameters and Protonation Equilibria. *Monatsh. Chem.* **2006**, *137*, 703–716.
(30) Qiang, Z.; Adams, C. Potentiometric Determination of Acid Dissociation Constants (pK_a) for Human and Veterinary Antibiotics. *Water Res.* **2004**, *38*, 2874–2890.
(31) Drayton, C. J., Ed. *Comprehensive Medicinal Chemistry*; Pergamon: Oxford, 1990; Vol. 6.
(32) Hansch, C.; Sammes, P. G.; Taylor, J. B. Comprehensive Medicinal Chemistry, the Rational Design, Mechanistic Study and Therapeutic Application of Chemical Compounds. In *Cumulative Subject Index and Drug Compendium*; Drayton, C. J., Ed.; Pergamon: Oxford, 1990; Vol. 6.
(33) Lin, C. E.; Lin, W. C.; Chen, Y. C.; Wang, S. W. Migration Behavior and Selectivity of Sulfonamides in Capillary Electrophoresis. *J. Chromatogr. A* **1997**, *792*, 37–47.
(34) Lin, C. E.; Chang, C. C.; Lin, W. C. Migration Behavior and Separation of Sulfonamides in Capillary Zone Electrophoresis. III. Citrate Buffer as a Background Electrolyte. *J. Chromatogr. A* **1997**, *768*, 105–112.
(35) Völgyi, G.; Ruiz, R.; Box, K.; Comer, J.; Bosch, E.; Takács-Novák, K. Potentiometric and Spectrophotometric pK_a Determination of Water-Insoluble Compounds: Validation Study in a New Cosolvent System. *Anal. Chim. Acta* **2007**, *583*, 418–428.
(36) Van Gogh, H.; Van Deurzen, J. M.; Van Duin, C. T. M.; Van Miert, A. S. J. P. A. M. Influence of Gestation on the Pharmacokinetics of Four Sulfonamides in Goats. *Res. Vet. Sci.* **1989**, *48*, 152–157.
(37) Szczepaniak, W.; Szymañski, A. Relationship between Hydrophobic Properties of Amphoteric Sulfonamides and Their Retention in Micellar Reversed Phase Liquid Chromatography. *J. Liq. Chrom. Rel. Technol.* **2000**, *23* (8), 1217–1231.
(38) Ackermans, M. T.; Beckers, J. L.; Everaerts, F. M.; Hoogland, H.; Tomassen, M. J. H. Determination of Sulfonamides in Pork Meat Extracts by Capillary Zone Electrophoresis. *J. Chromatogr.* **1992**, *596*, 101–109.
(39) Ricci, M. C.; Cross, R. F. Capillary Electrophoresis Separation of Sulphonamides and Dihydrofolate Reductase Inhibitors. *J. Microcol. Sep.* **1993**, *5*, 207–215.
(40) Bell, P. H.; Roblin, R. O. Studies in Chemotherapy. VII. A Theory of the Relation of Structure to Activity of Sulfanilamide Type Compounds. *J. Am. Chem. Soc.* **1942**, *64*, 2905–2917.
(41) Kumler, W. D.; Strait, L. A. The Ultraviolet Absorption Spectra and Resonance in Benzene Derivatives—Sulfanilamide, Metanilamide, p-Aminobenzoic acid, Benzenesulfonamide, Benzoic acid and Aniline. *J. Am. Chem. Soc.* **1943**, *65*, 2349–2354.
(42) Kumler, W. D.; Daniels, T. C. The Relation between Chemical Structure and Bacteriostatic Activity of Sulfanilamide Type Compounds. *J. Am. Chem. Soc.* **1943**, *65*, 2190–2196.
(43) Seydel, J. K. Sulfonamides, Structure-Activity Relationship, and Mode of Action. Structural Problems of the Antibacterial Action of 4-Aminobenzoic Acid (PABA) Antagonists. *Pharm. Sci.* **1968**, *57*, 1455–1478.
(44) Soriano-Correa, C.; Esquivel, R. O.; Sagar, R. P. Physicochemical and Structural Properties of Bacteriostatic Sulfonamides: Theoretical Study. *Int. J. Quantum Chem.* **2003**, *94*, 165–172.
(45) Gomes, J. R. B.; Gomes, P. Gas-Phase Acidity of Sulfonamides: Implications for Reactivity and Prodrug Design. *Tetrahedron* **2005**, *61*, 2705–2712.
(46) Takacs-Novak, K.; Noszal, B.; Hermecz, I.; Kereszturi, G.; Podanyi, B.; Szasz, G. Protonation Equilibria of Quinolone Antibacterials. *J. Pharm. Sci.* **1990**, *79*, 1023–1028.
(47) Marqués, I.; Fonrodona, G.; Butí, S.; Barbosa, J. Solvent Effects on Mobile Phases Used in LC by Factor Analysis Applied to Protonation Equilibria and Solvatochomic Parameters. *TRAC Trends Anal. Chem.* **1999**, *18*, 472–479.
(48) Gran, G. Determination of the Equivalence Point in Potentiometric Titrations-Part II. *Analyst* **1952**, *7*, 661–671.
(49) Marcus, Y. Preferential Solvation. Part 3. Binary Solvent Mixtures. *J. Chem. Soc., Faraday Trans.* **1989**, *85*, 381–388.
(50) Beltfan, J. L.; Codony, R.; Prat, M. D. Evaluation of Stability Constants from Multi-Wavelength Absorbance Data: Program STAR. *Anal. Chim. Acta* **1993**, *276*, 441–454.
(51) Barbosa, J.; Fonrodona, G.; Marques, I.; Sanz-Nebot, V.; Toro, I. Solvent Effects on Protonation Equilibria of Peptides and Quinolones by Factor Analysis Applied to the Correlation between Dissociation Constants and Solvatochromic Parameters in Acetonitrile-Water Mixtures. *Anal. Chim. Acta* **1997**, *351*, 397–405.
(52) Casassas, E.; Fonrodona, G.; de Juan, A.; Tauler, R. Assessment of Solvent Parameters and their Correlation with Protonation Constants in Dioxane-Water Mixtures Using Factor Analysis. *Chemom. Intell. Lab. Syst.* **1991**, *12*, 29–38.
(53) Casassas, E.; Dominguez, N.; Fonrodona, G.; de Juan, A. Factor Analysis Applied to the Study of the Effects of Solvent Composition and Nature of the Inert Electrolyte on the Protonation Constants in Dioxane-Water Mixtures. *Anal. Chim. Acta* **1993**, *283*, 548–558.
(54) Barbosa, J.; Fonrodona, G.; Marquès, I.; Butí, S.; Toro, I. Factor Analysis Applied to the Correlation between Dissociation Constants and Solvatochromic Parameters in Water-Acetonitrile Mixtures, TRAC. *Trends Anal. Chem.* **1997**, *16*, 104–111.
(55) Sindreu, R. J.; Moya, M. L.; Sanchez Burgos, F.; Gonzalez, A. G. Solvent Effects on the Dissociation of Aliphatic Carboxylic Acids in Water-N, N-Dimethylformamide Mixtures: Correlation between Acidity Constants and Solvatochromic Parameters. *J. Solution Chem.* **1994**, *23*, 1101–1109.
(56) Malinowski, E. R. *Factor Analysis in Chemistry*, 2nd ed.; Wiley Interscience: New York, 1991.
(57) González-Arjona, D.; Mejias, J. A.; Gonzalez, A. G. Holmes - A Program for Target Factor Analysis. *Anal. Chim. Acta* **1994**, *295*, 119–125.
(58) Gonzáles-Arjona, D.; Antonio Mejías, J.; Gonzalez, A. G. Corrigendum: Holmes: A Program for Target Factor Analysis. *Anal. Chim. Acta* **1994**, *295*, 119–125by González-Arjona, D.; Antonio Mejías, J.; Gustavo González, A. *Anal. Chim. Acta* **1994**, *297*, 473.
(59) González, A. G.; González-Arjona, D. Advantages of Target Factor Analysis Against Multiple Linear Regression Methods for Testing Model Equations in Linear Free Energy Relationships. *Anal. Chim. Acta* **1995**, *312*, 295–306.
(60) Maren, T. H.; Conroy, C. W. New Class of Carbonic Anhydrase Inhibitor. *J. Biol. Chem.* **1993**, *268*, 26233–26239.
(61) Erdemgil, F. Z.; Sanli, S.; Sanli, N.; Ozkan, G.; Barbosa, J.; Guiteras, J.; Beltran, J. L. Determination of pK_a Values of Some Hydroxylated Benzoic Acids in Methanol-Water Binary Mixtures by LC Methodology and Potentiometry. *Talanta* **2007**, *72*, 489–496.
(62) Marcus, Y.; Migron, Y. Polarity, Hydrogen Bonding, and Structure of Mixtures of Water and Cyanomethane. *J. Phys. Chem.* **1991**, *95*, 400–406.
(63) Barbosa, J.; Marqués, I.; Barrón, D.; Sanz-Nebot, V. The Application of Factor Analysis to Solvatochromic Parameters and pHs Values for the Standardization of Potentiometric Sensors in Mobile Phases Used in Liquid Chromatography. *TRAC Trends Anal. Chem.* **1999**, *18*, 543–549.
(64) Kalidas, C.; Hefter, G.; Marcus, Y. Gibbs Energies of Transfer of Cations from Water to Mixed Aqueous Organic Solvents. *Chem. Rev.* **2000**, *100*, 819–852.
(65) Barbosa, J.; Marqués, I.; Fonrodona, G.; Barrón, D.; Sanz-Nebot, V. Factor Analysis Applied to the Correlation between Dissociation Constants and Solvatochromic Parameters in Water Acetonitrile Mixtures II. Study of Solvent Effects on the Dissociation of Functional Groups of Diuretics, Quinolones, Buffers and Peptides. *TRAC Trends Anal. Chem.* **1997**, *16*, 140–147.
(66) Marcus, Y. Preferential Solvation in Mixed Solvents X. Completely Miscible Aqueous Co-Solvent Binary Mixtures at 298.15 K. *Monatsh. Chem.* **2001**, *132*, 1387–1411.

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