

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

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Summary. The stoichiometric protonation constants ($\log \beta$) of some disubstituted aniline derivatives in ethanol–water mixtures (0–90% ethanol by volume) at $25.0 \pm 0.1^\circ\text{C}$ were firstly submitted to factor analysis in order to obtain the number factors which affect the variation of the whole data sets and, afterwards, submitted to target factor analysis to identify these factors. The influence of solvatochromic parameters in the interactions between aniline derivatives and the solvent studied was identified and quantified. The general equation of *Kamlet* and *Taft* was reduced for these mixtures to two terms using combined factor analysis (FA) and target factor analysis (TFA): the independent term and the hydrogen-bond donating ability, α (HBD), solvatochromic parameters. Further, the quasi-lattice quasi-chemical (QLQC) theory of preferential solvation has been applied to quantify the preferential solvation by water of electrolytes in ethanol–water mixtures. The effects of the substituents on the protonation constants, the additivities of these effects, and the applicability of the *Hammett* equation to the behavior of substituents are also discussed. Further, *Hammett's* reaction constant for the protonation of disubstituted anilines has been obtained for all the solvent mixtures and correlates well with α (HBD) of the solvent.

Keywords. Protonation constants; Ethanol–water mixtures; Solvent effect; Factor analysis; Preferential solvation.

Introduction

Water is generally regarded as the solvent that represents biological conditions. Contrary to this assumption, comparatively low polarity has been detected in some

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biological microenvironments, such as active sites of enzymes and side chains in proteins, sometimes hidden in lower dielectric cavities [1–4]. In these cases, the selection of other solvent mixtures such as ethanol, methanol, and acetonitrile–water seems recommendable in order to emulate the medium's real features properly. For example, the behavior of many solutes in plasma samples is closer to that in alcohol than to that in H₂O [5–7]. In this manner, EtOH/H₂O mixtures can offer a suitable medium for modeling biological interactions because they exhibit low polarity while water is present as always in biological systems.

The solvent mixtures such as methanol–water, ethanol–water, acetonitrile–water, *etc.* are characterized by dramatic changes in the physical constants of solvent (*i.e.*, their melting and boiling point, dielectric constants, *etc.*) and macroscopic solvent parameters (mol fraction of co-solvent, x_2 , *etc.*), upon modification of their compositions that influence many solute properties of these mixtures. Previously, the solvent effect on the electrolyte behavior (*e.g.*, acid–base properties) was believed to be chiefly guided by electrostatic interactions (*Born* model). However, inconsistencies in the behavior of solutes were often found regarding the properties of the solvents used [8]. These apparent contradictions revealed that solvents should not be considered as macroscopic continua, but as dynamic structures having molecules that interact differently with each other and with solutes. The macroscopic parameters can thus be used as descriptors of the bulk solvent but are able to provide a reliable picture of the solvent structure around the solutes, in their solvation sphere [9–15].

The main problem in the study of electrolyte behavior in water/organic solvent mixtures is how a solute species reacts with the solvent that focuses their solvation sphere. Factor analysis (FA) is a powerful technique for explaining solute–solvent interactions and a helpful tool in the field of linear solvation relationships (LSER) for better understanding of solvent effects on solute physico-chemical properties. It is especially powerful in the study of solvent composition effects on different characteristics of solutes, such as protonation constants in organic-water solvent mixtures [14, 15].

The approach involved the application of the hypothesis-free model technique, FA, in establishing how many sources of variation affect the solute property studied. Thereafter, these factors were identified using TFA and combined to yield the best model for the type of substance studied. The target vectors used in this work, which depend on the characterization of the solvent mixture, were of two kinds: macroscopic parameters (cosolvent percentage, the molar fraction of ethanol (x_{EtOH}) and the dielectric constant (ϵ)), and microscopic parameters (*Kamlet* and *Taft*'s solvatochromic parameters: α , β , and π^* [16–18] and either *Reichardt*'s E_T^{30} parameter [19] or its normalized form, E_T^N), which define the characteristic of this medium [20]. These solvatochromic parameters, together with macroscopic parameters and an independent term were tested as targets and the *Kamlet-Taft* equation (also known as the linear solvation-energy relationship, LSER, $XYZ = XYZ_o + s\pi^* + a\alpha + b\beta$) [16–18] appropriate to each substance was worked out.

As a continuation of our study [9] on the effect of solvent composition on the protonation equilibria of some substituted anilines in ethanol–water mixed solvents, in this work, the study was extended to several disubstituted anilines with methyl-

and methoxy-groups, in order to propose a more general model for anilines. The disubstituted anilines studied in this work are chemical intermediates used principally in the production of dyes and are also a component of tobacco smoke, a degradation product of aniline-based pesticides, and a metabolite of certain drugs, particularly the xylide group of local anesthetics. The protonation constant or dissociation constant values of disubstituted anilines are physical properties that are applied to dispensing problems and are used to decide what pH should be adjusted to provide optimum bioavailability, and to predict the solubility in aqueous solution at a given pH and concentration [7].

All coefficients of *Kamlet-Taft* equation have to be found, either through multi-linear regression, or as in this work, using factor analysis techniques. The advantages of this procedure are that it is a model free technique, *i.e.*, it does not need prior postulation of a chemical model, and the results can be achieved for each substance from simultaneous treatment of compounds' sets that present similar behaviour, which enables the influence of each macroscopic and solvatochromic property of the solvent mixture on the protonation process to be determined.

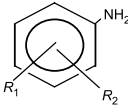
In order to determine the degree of preferential solvation of hydrogen ions in the *EtOH*-water solvent mixtures, the quasi-lattice quasi-chemical QLQC theory was applied in this work [22, 23]. The equations obtained allow evaluation of the most important solvent properties that affect protonation of the studied substances in any ethanol-water mixture.

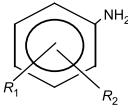
In addition, it is known that the structural effect is one of the major factors that influence the basicity of a compound. Therefore in this study, the substituent effect on the protonation constants of disubstituted anilines has been investigated and the additivity effects of substituents have been discussed. Moreover, some attempts have been made for evaluation whether the *Hammett* equation could be used to predict the effect of the substituent on the protonation equilibrium of disubstituted anilines in ethanol-water mixtures just like in monosubstituted anilines' case [9]. Finally, few attempts have been also made to determine the influence of solvents on *Hammett's* reaction parameter [24]. Thus, it is useful to obtain as much information as possible by varying the nature of the base and solvent composition.

Results and Discussions

Table 1 shows the stoichiometric protonation constant values determined using the BEST program for the series of seven disubstituted anilines (2,3-dimethylaniline, 2,4-dimethylaniline, 2,5-dimethylaniline, 2,6-dimethylaniline, 3,4-dimethylaniline, 2,4-dimethoxyaniline, and 3,4-dimethoxyaniline) studied in 0, 10, 20, 30, 40, 50, 60, 70, 80, and 90% (*v/v*) ethanol-water mixtures at $25.0 \pm 0.1^\circ\text{C}$. Since the solubility of 2,4- and 3,4-dimethoxyanilines in water media is too low, the protonation constant values of these compounds couldn't be determined in this media. The values of $\log \beta$ found in water are in good agreement with the data reported in the literature [35-42]. There are published data for only a few of the substituted anilines studied in only 50% ethanol-water compositions or other solvent compositions [36]. The difference in the constants in Tables 1 and 2, between the values determined in the present work and the values determined by others, are

Table 1. The stoichiometric protonation constants ($\log \beta$) for aniline and disubstituted anilines in ethanol water solvents at $25.0 \pm 0.1^\circ\text{C}$ and $I = 0.10\text{ M}$ (NaClO_4)*

		<i>EtOH</i> (% <i>v/v</i>) (x_{EtOH}) ^a				
<i>R</i> ₁	<i>R</i> ₂	$\log \beta$				
		0(0.00) ^a	10(0.033) ^a	20(0.072) ^a	30(0.117) ^a	40(0.170) ^a
H	H	4.60	4.56	4.44	4.30	4.13
2-CH ₃	3-CH ₃	4.78(4.65) ^b	4.70(4.60) ^b	4.60(4.43) ^b	4.53(4.40) ^b	4.42(4.29) ^b
2-CH ₃	4-CH ₃	4.99(5.06) ^b	4.90(4.96) ^b	4.80(4.70) ^b	4.70(4.68) ^b	4.56(4.63) ^b
2-CH ₃	5-CH ₃	4.68(4.65) ^b	4.60(4.60) ^b	4.48(4.43) ^b	4.36(4.40) ^b	4.24(4.29) ^b
2-CH ₃	6-CH ₃	3.98(4.32) ^b	3.90(4.24) ^b	3.78(4.00) ^b	3.65(4.02) ^b	3.52(3.95) ^b
3-CH ₃	4-CH ₃	5.26(5.39) ^b	5.18(5.32) ^b	5.08(5.13) ^b	5.00(5.06) ^b	4.90(4.97) ^b
2-OCH ₃	4-OCH ₃	(5.31) ^b	5.30(5.14) ^b	5.20(5.14) ^b	5.06(5.09) ^b	4.96(5.09) ^b
3-OCH ₃	4-OCH ₃	(5.01) ^b	4.95(4.83) ^b	4.87(4.78) ^b	4.77(4.72) ^b	4.68(4.77) ^b

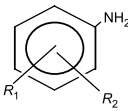
		<i>EtOH</i> (% <i>v/v</i>) (x_{EtOH}) ^a				
<i>R</i> ₁	<i>R</i> ₂	$\log \beta$				
		50(0.236) ^a	60(0.316) ^a	70(0.418) ^a	80(0.552) ^a	90(0.736) ^a
H	H	4.08	3.98	3.86	3.76	3.92
2-CH ₃	3-CH ₃	4.26(4.17) ^b	4.16(4.02) ^b	4.06(4.17) ^b	3.99(3.84) ^b	4.12(3.95) ^b
2-CH ₃	4-CH ₃	4.45(4.54) ^b	4.32(4.44) ^b	4.26(4.32) ^b	4.24(4.22) ^b	4.36(4.33) ^b
2-CH ₃	5-CH ₃	4.10(4.17) ^b	3.98(4.02) ^b	3.90(4.01) ^b	3.82(3.84) ^b	3.94(3.95) ^b
2-CH ₃	6-CH ₃	3.36(3.84) ^b	3.2(3.70) ^b	3.08(3.70) ^b	3.01(3.52) ^b	3.18(3.72) ^b
3-CH ₃	4-CH ₃	4.78(4.87) ^b	4.69(4.76) ^b	4.59(4.63) ^b	4.53(4.54) ^b	4.65(4.56) ^b
2-OCH ₃	4-OCH ₃	4.88(4.94) ^b	4.71(4.73) ^b	4.62(4.74) ^b	4.57(4.68) ^b	4.67(4.78) ^b
3-OCH ₃	4-OCH ₃	4.54(4.66) ^b	4.48(4.55) ^b	4.42(4.53) ^b	4.38(4.44) ^b	4.43(4.47) ^b

* Uncertainties in the protonation constants are 0.05 or lower ($\sigma_{\text{fit}} < 0.02$); ^a the mol fraction of ethanol; ^b $\log \beta_{\text{calc}} = \log \beta(\text{aniline}) + \Sigma \Delta \log \beta$ ($\log \beta$ values of aniline and $\Delta \log \beta$ values of monosubstituted anilines were taken from Ref. [9])

minor and about what would be expected from the difference in conditions employed ($I = 0.10\text{ M}$ NaClO_4 and 25°C).

The variation of the $\log \beta$ values of some disubstituted anilines *versus* the mol fraction of ethanol, x_{EtOH} , in ethanol–water mixtures is presented in Fig. 1. As seen from Table 1 and Fig. 1, protonation constants, $\log \beta$ values of disubstituted aniline derivatives decrease at the beginning (lower percentage of ethanol) and pass through a minimum around the mol fraction of ethanol of 0.50–0.60 and then increase slowly. This characteristic variation in the $\log \beta$ curves for the protonation equilibria of monosubstituted anilines has been observed also in a recent study about aqueous mixtures of ethanol [9] and studies about other organic solvent mixtures [43–46].

Table 2. Literature pK_a values of some aniline derivatives in water and various ethanol–water mixtures

			
R_1	R_2	0% v/v EtOH	50% v/v EtOH
2-CH ₃	3-CH ₃	4.72 ^b	4.42 ^b
2-CH ₃	4-CH ₃	5.0 ^a 4.84 ^b	4.61 ^b
2-CH ₃	5-CH ₃	4.60 ^a 4.57 ^b	4.23 ^b
2-CH ₃	6-CH ₃	4.10 ^a 3.89 ^b 3.94 ^c	3.49 ^b
3-CH ₃	4-CH ₃	5.22 ^b 5.17 ^d	
2-OCH ₃	4-OCH ₃		
3-OCH ₃	4-OCH ₃		

^a Ref. [35]; ^b Ref. [36]; ^c Ref. [37]; ^d Ref. [38]

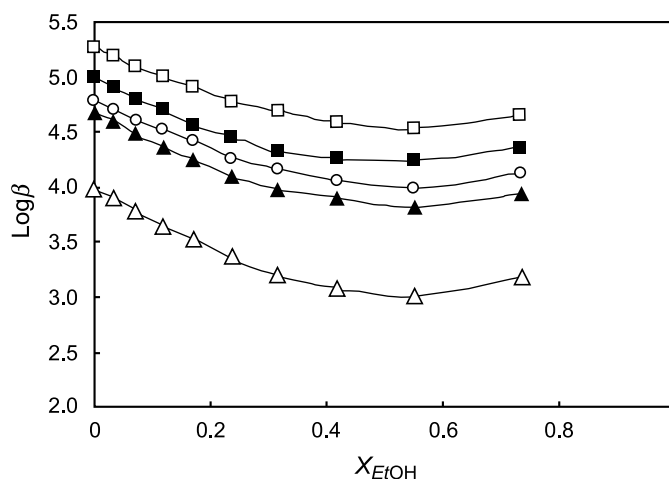


Fig. 1. Plot of $\log \beta$ values of 2,3-dimethyl, 2,4-dimethyl, 2,5-dimethyl, 2,6-dimethyl, and 3,4-dimethyl substituted anilines versus the mol fraction of ethanol, x_{EtOH} , in ethanol–water mixtures (\square = 3,4-dimethylaniline; \blacksquare = 2,4-dimethylaniline; \circ = 2,3-dimethylaniline; \blacktriangle = 2,5-dimethylaniline; \triangle = 2,6-dimethylaniline)

The macroscopic properties of the EtOH/water mixtures are inadequate to explain this variation in $\log \beta$ values of anilines. Accordingly, the electrostatic effect has considerably less importance in explaining solvent effects on the iso-electric protonation reaction ($B + SH^+ \leftrightarrow BH^+ + S$), as indicated previously [9, 44, 47, 48]. Thus, the effect of the dielectric constant on the action of various solvents in this reaction has no consequence, and the chemical effects on the acid–base equilibrium can be studied independently from electrostatic complications. The application of 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 the acid–base behavior of substances in these

mixtures. *Taft et al.* proposed the use of solvatochromic parameters in order to evaluate solute–solvent interactions for many *Gibbs* free energy-related properties, including protonation of bases in water and water organic solvent mixtures, [17, 49] through correlation analysis, Linear Solvation Energy Relationships (LSER).

Several attempts were made to find the best form of *Kamlet-Taft* equation to describe the variation of $\log \beta$ values of the disubstituted anilines in ethanol–water mixtures. The study carried out in this work can be made, on the one hand, by including $\log \beta$ values in 90% (v/v) of ethanol and, on the other hand, by excluding these values in the data matrix. The results obtained in both cases do not differ significantly so that those matrices wherein $\log \beta$ values in 90% (v/v) of ethanol are available were considered.

A summary of factor analysis is reported in Table 3. Residual standard deviation (RSD) corresponds to the real error in the data matrix. IND, which is an empirical function that reaches a minimum at the correct number of factors, is employed. It can be seen that in Table 3 and Fig. 2, IND function reaches a minimum at 2, which means that we have two factors responsible of the variation of $\log \beta$ in different ethanol–water mixtures.

Table 4 shows the results of testing the *Kamlet-Taft* parameters, with x_{EtOH} and unity as targets. In this table α , β , x_{EtOH} , and unity was found to be successful,

Table 3. Determination of number of factors (NF) by using IND function

Number factors	IND	RSD
1	$1.7862 \cdot 10^{-3}$	$6.4304 \cdot 10^{-2}$
2	$6.4674 \cdot 10^{-4}$	$1.6169 \cdot 10^{-2}$
3	$8.6148 \cdot 10^{-4}$	$1.3784 \cdot 10^{-2}$
4	$1.1982 \cdot 10^{-3}$	$1.0784 \cdot 10^{-2}$
5	$1.5919 \cdot 10^{-3}$	$6.3677 \cdot 10^{-3}$

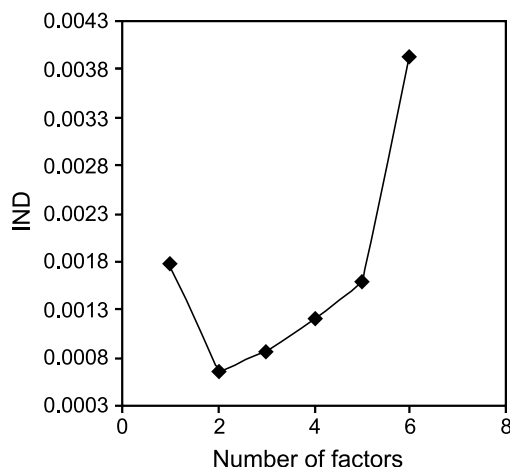


Fig. 2. Evaluation of the IND function *versus* number of factors

Table 4. Determination of factors lying in the vector space

Factor	SPOIL	F-test	SL	Targeting
α	5.5893	59.704	0.069444	successful
β	2.8597	16.996	0.46035	successful
x_{EtOH}	5.5586	59.071	0.070367	successful
π^*	9.2980	161.95	0.024404	unsuccessful
unity	0.54718	1.2974	40.273	successful

SPOIL: spoil associated with the target; SL: significance level

Table 5. Expressions of *Kamlet-Taft* equations obtained through factor analysis and target factor analysis

Substance	Linear solvation energy relationships
2,3-Dimethylaniline	$\log \beta = 1.74(0.23) + 2.61(0.22)\alpha$
2,4-Dimethylaniline	$\log \beta = 2.02(0.15) + 2.53(0.15)\alpha$
2,5-Dimethylaniline	$\log \beta = 1.35(0.20) + 2.85(0.19)\alpha$
2,6-Dimethylaniline	$\log \beta = 2.02(0.26) + 3.25(0.26)\alpha$
3,4-Dimethylaniline	$\log \beta = 2.48(0.19) + 2.37(0.19)\alpha$
2,4-Dimethoxyaniline	$\log \beta = 2.22(0.21) + 2.71(0.21)\alpha$
3,4-Dimethoxyaniline	$\log \beta = 2.50(0.13) + 2.14(0.13)\alpha$

RMS (root-mean-square error) = 0.06; RSD (residual standard deviation) = 0.07; errors assigned to values are given in parenthesis

which means these factors were accepted as targets lying in the factor space. Once this had been determined, TFA was applied for identification of the chemical nature of these factors. The validity of each target was analyzed by evaluating its SPOIL function (Table 4). After recombination of the selected target factors, the factors which provided a lower value for RMS, hydrogen-bond donating ability, α (HBD), and unity were determined to be responsible factors for the variation of $\log \beta$ values of disubstituted anilines in ethanol–water mixtures, the same result was found for monosubstituted anilines [9]. Other combinations of factors were tried, but the fit to the experimental data was always worse.

In Table 5, the *Kamlet-Taft* [16–18] equations obtained from the results found by application of factor analysis and target factor analysis, are shown. Coefficients of parameters are target loadings and the value given in parentheses are the errors assigned to these values. These loadings are related to the weight of each real factor in each different column 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 confirms the usefulness of microscopic parameters such as α in explanation of microscopic processes, since the solvent properties in cybotactic zone are the ones, which directly affect the solutes when a process such as acid–base equilibrium occurs. The factor loadings obtained by the TFA (Table 5) also lead to some important conclusions: firstly, the protonation constants of disubstituted aniline derivatives are influenced by specific solute–solvent interactions as

indicated in monosubstituted anilines [9] by the contribution of the α parameter. Secondly, the factor loadings obtained by the TFA (Table 5) are positive in all instances, meaning that an increase in solvation of the unprotonated species (B) of the base by hydrogen-bond donation (HBD) from the solvent to the base decreases electrolyte protonation. Thus, an increase in hydrogen-bond donating acidity of solvent mixtures decreases the solvation (stabilization) of H^+ and B (unprotonated aniline derivative), and concomitantly protonation as well as spontaneous transfer of BH^+ (protonated aniline derivative) from H_2O to $EtOH/H_2O$ mixtures. The presence of the positive charge of the BH^+ ions decreases their interactions with the H-bond donor groups of the solvent mixture, and, thus, protonation is hindered. Finally, the second term, derived from target unity, represents the value of the protonation constant of the different solutes in a hypothetical solvent with $\alpha = \beta = \pi^* = 0$. In the protonation process of anilines, because there is no change in the number of charges ($B + H^+ = BH^+$), it is likely that the change of the polarity (π^*) of the medium has no important influence on the protonation process.

The appearance of such a variation and a minimum (Fig. 1) for the protonation of disubstituted anilines (B) in water–ethanol mixtures could be explained by the fact that these protonation constants are dependent on the solute–solvent interaction effects and these effects vary with the structural features of the mixtures. In ethanol–water mixtures there are three regions [50, 51]. In the water-rich region of ethanol–water mixtures ($x_{EtOH} \leq 0.07$), the ethanol gradually occupies the cavities between water molecules without disrupting the water structure [50, 51]; and in the range about $0.07 \leq x_{EtOH} \leq 0.45$, there are clusters of molecules of the same kind surrounded by a region where molecules of both kinds are near each other, which is called a microheterogeneity region. In these regions, preferential solvation by water of hydrogen and anilines (B) continuously increases, which might explain the decrease in the $\log \beta$ values of anilines when the percentage of ethanol increases (Table 1). This is consistent with values of the preferential solvation, δ_w ,

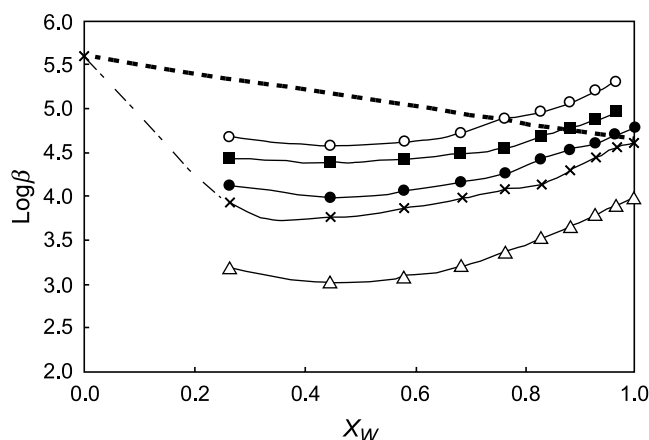


Fig. 3. Plot of $\log \beta$ values of 2,3-dimethyl, 2,6-dimethyl, 2,4-dimethoxy, and 3,4-dimethoxy substituted anilines versus the mol fraction of water, x_w in ethanol–water mixtures (○ = 2,4-dimethoxyaniline; ■ = 3,4-dimethoxyaniline; ● = 2,3-dimethylaniline; × = aniline; △ = 2,6-dimethylaniline)

of hydrogen by water in *EtOH*–water mixtures [50]. The boundaries of the regions are, of course, not sharp [52]. In the *EtOH*-rich region ($x_{EtOH} > 0.55$), the water–*EtOH* interactions that could be discounted in the middle range should now be considered. This is a region in which preferential solvation by water decreases; a concave variation of $\log \beta$ values of disubstituted aniline derivatives (Fig. 1) versus x_{EtOH} may be expected with an inflection point at $x_{EtOH} = 0.55$ where preferential solvation by water is maximal.

Furthermore, it can be seen in Fig. 3 that the $\log \beta$ values of substances obtained in ethanol–water mixtures decrease with the percentage of ethanol (see Table 1), but they are lower than expected values if we consider the high $\log \beta$ values in pure ethanol. Figure 2 shows $\log \beta$ values of aniline ($\log \beta = 5.60$ in pure ethanol) [9, 44] and some disubstituted anilines in ethanol–water mixtures, as a function of x_W , the bulk mol fraction of water, where the dashed line represents the expected variation of $\log \beta$ values between $x_{EtOH} \approx 0.7$ and pure ethanol solvent and the dotted straight line corresponds to the ideal variation of the $\log \beta$ values of aniline. In all cases, the deviation to lower $\log \beta$ values from the ideal dependence on the mixture composition indicates preferential solvation by water. These $\log \beta$ values are lower than the theoretical values because of preferential solvation in this media, which is related to structural features of these mixtures [28]. Any deviation from the ideal dependence on the composition of the mixtures suggests that the composition in the immediate surroundings of a solute may be different from the composition of the bulk mixture.

Evaluation of the preferential solvation from QLQC [50], the difference between the mol fraction of water around hydrogen ions (x_W^L) and the bulk mol fraction of water (x_W), requires the standard molar *Gibbs* free energy of transfer for a hydrogen ion from water into pure ethanol solvent, $\Delta G_t^\circ (H^+, W \rightarrow EtOH, kJ mol^{-1}) = 11.1$, and the excess of *Gibbs* energy for mixing ethanol–water equimolar mixtures $\Delta G_{WEtOH}^E (x = 0.5, kJ mol^{-1}) = -4.2$ [53]. The obtained results from the QLQC method at 25°C, and for the preferential solvation by water around hydrogen ions, $\delta_W = x_W^L - x_W$, show that for the ethanol–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 ethanol molecules do. This preference is maximal at $x_W \approx 0.45$ for hydrogen ion [50]. Therefore, the $\log \beta$ values of aniline derivatives in these mixtures are expected to be closer to $\log \beta$ values in water than to $\log \beta$ in ethanol. This is different for compositions close to the ethanol-pure solvent, where the preferential solvation by water decreases quickly [50].

The substituent effects of methyl and methoxy groups on the basicity of disubstituted anilines in ethanol–water mixtures have been discussed by using the data obtained in this study. The basicity orders similar to those of monosubstituted anilines [9] were also defined for disubstituted anilines and the related order was found to be as follows for all of the media studied: $2,6\text{-diCH}_3 < \text{aniline} \leq 2,5\text{-diCH}_3 < 2,3\text{-diCH}_3 < 2,4\text{-diCH}_3 < 3,4\text{-diCH}_3$. Similarly, the order of basicity was found to be as $3,4\text{-diOCH}_3 < \text{aniline} < 2,4\text{-diOCH}_3$ for dimethoxy anilines. The comparison of the basicity orders obtained for disubstituted anilines with those obtained for monosubstituted anilines revealed that the order thus obtained is the expected one.

Two or more substituents were found to exert an additive effect upon the basicity [54, 55]. However, there are no systematic studies upon the additivities of substituent effects on the basicity of aniline in ethanol–water media. In order to elucidate the additive effects of substituents in these media, the protonation constants ($\log \beta_{\text{calc}}$) values were calculated for each disubstituted aniline by the use of $\Delta \log \beta$ values in Table 1 according to equation $\log \beta_{\text{calc}} = \log \beta(\text{aniline}) + \Sigma \Delta \log \beta$ and tabulated in Table 1. As seen from Table 1 the experimental $\log \beta$ values were found to be in accordance with $\log \beta_{\text{calc}}$ at the level of $\pm 0.30 \log \beta$ unit except for 2,6-dimethylaniline. The fact that there was no additive effect for 2,6-dimethylaniline may be due to the steric interaction of two methyl groups located at ortho positions.

The effect of substituents on the $\log \beta$ values of aniline derivatives in any given solvent can be rationalized using the *Hammett* equation [56, 57]. Only the data given in Table 1 for 3,4-dimethylaniline and 3,4-dimethoxyaniline could be used to test the applicability of the *Hammett* equation to the behavior of substituents in anilines in ethanol–water mixtures. Since these two values are not sufficient for this test plots of $\log \beta$ values for 3,4-dimethylaniline and 3,4-dimethoxyaniline, together with meta- and para-monosubstituted anilines [9] against the *Hammett* substituent constants (σ) [29] are obtained for each ethanol–water mixture studied (Fig. 4). The linear plots were statistically analyzed using the least square method ($\log \beta(s) = \log \beta_o(s) - \rho(s) \Sigma \sigma$) by SPSS software. The relevant reaction constants (ρ) and the usual parameters (the correlation coefficient, r , standard error of regression, SE, and variance ratio, F -value) describing the precision with which the data are represented by the *Hammett* equation are given Table 6. The $\log \beta$ values follow *Hammett's* equation, the plots of $\log \beta$ vs. σ in each solvent mixture studied are linear, with correlation coefficients always higher than 0.98 and, generally, 0.99. It is worth mentioning that these plots are in accordance with the

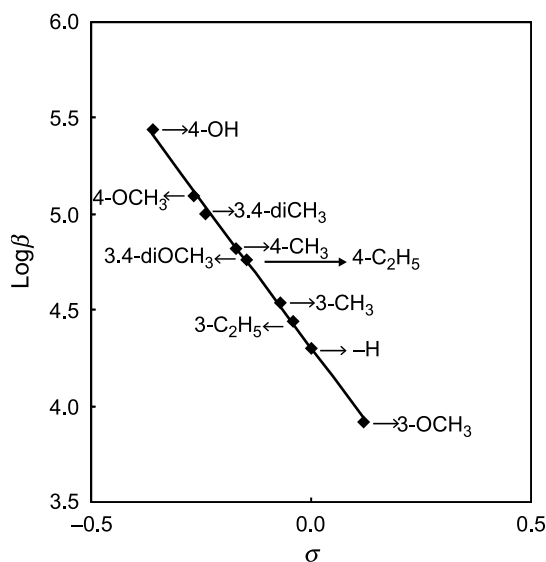


Fig. 4. Plot of $\log \beta$ values of aniline and monosubstituted anilines versus *Hammett* substituent constants (σ) for 30% ethanol–70% water

Table 6. Reaction constants for the reactivity of monosubstituted [9] and disubstituted aniline derivatives at $25.0 \pm 0.1^\circ\text{C}$ and $I = 0.10\text{ M NaClO}_4$ ($n = 10$)^a

Reaction	Ethanol (% v/v EtOH)	ρ (slope)	Intercept	SE ^b	F^c	$(r^2)^d$
B + H ⁺ \rightleftharpoons BH ⁺	0	2.73(0.12)	4.63(0.02)	0.049	540.987	0.987
	10	2.83(0.13)	4.54(0.02)	0.053	516.493	0.985
	20	2.94(0.09)	4.42(0.02)	0.039	1059.853	0.992
	30	3.07(0.06)	4.30(0.01)	0.024	2948.047	0.997
	40	3.17(0.09)	4.19(0.02)	0.0409	1104.531	0.992
	50	3.20(0.12)	4.11(0.02)	0.0522	666.082	0.987
	60	3.24(0.14)	4.01(0.03)	0.0572	572.482	0.984
	70	3.27(0.17)	3.91(0.03)	0.0711	377.659	0.979
	80	3.32(0.17)	3.81(0.03)	0.0729	369.552	0.979
	90	3.28(0.13)	3.92(0.02)	0.0535	668.481	0.988

^a n is the number of compounds; ^b the standard error of regression; ^c variance ratio; ^d the correlation coefficients

obtained plots for only monosubstituted anilines. Furthermore, with the addition of values of 3,4-dimethylaniline and 3,4-dimethoxyaniline to the values of monosubstituted anilines, the scores for the correlation coefficient (r^2), F -value (variance ratio), and the standard error of regression (SE) were found to be statistically better.

The ρ values obtained in our study range from 2.73 to 3.32 and increase concomitantly with the ethanol content. The obtained ρ values for *Hammett's* reaction constant for disubstituted anilines in water and other ethanol–water mixtures are close to values obtained for monosubstituted anilines [9, 38]. In conclusion, our observations support that the *Hammett* equation very adequately represents the basicity of both mono and disubstituted anilines in ethanol–water mixtures like it does for water.

It is also interesting to investigate the effect of the different solvent properties (quantified through solvatochromic parameters) upon *Hammett* reaction constants, ρ . The effects of the solvent on *Hammett* reaction constants can be explained by using *Kamlet* and *Taft's* [16–18] multiparameter approach, in which α , β , and π^* are the possible independent variables, whose significances are tested. $\rho(s) = 4.73(0.06) - 1.61(0.06)\alpha$, where the standard error of the fitting = 0.023, $F = 689.658$, and $r = 0.994$. Other fittings obtained using the other parameters always lead to poorer statistical results. As can be seen, the solvent effects on the $\rho(s)$ values are mainly due to the hydrogen-bond donating ability (HBD, α) term and not to the polarity/polarizability term and hydrogen-bond accepting ability (HBA). In addition, the coefficient of the α term has a negative sign. This is the reason for $\rho(s)$ to increase concomitantly with the ethanol content of the mixture. Similar correlations have been obtained between ρ and π^* and $E_T^N(30)$ for some phenol derivatives in water-1,4-dioxan mixtures [13] and ρ and α in water–ethanol mixtures [9].

These results contribute to a better understanding of the acid–base behavior of the substances in the widely used ethanol–water mixtures. The basicity or acidity of the compounds in a particular medium is influenced not only by the structure of the molecules, but also, very importantly, by the nature of any solute–solvent

interactions that might exist. The results given in this study are of interest for finding out the origin of solvent effects, but other different solvents and protonation processes must be studied to complete our information on the subject.

Experimental

Reagents

All of the disubstituted anilines (2,3-dimethylaniline, 2,4-dimethylaniline, 2,5-dimethylaniline, 2,6-dimethylaniline, 3,4-dimethylaniline, 2,4-dimethoxyaniline, 3,4-dimethoxyaniline) were reagent grade from Merck. The compounds were purified by standard methods [25] and their purity was controlled by potentiometric titration. Ethanol was dried over 4 Å type molecular sieves before use. Perchloric acid, sodium perchlorate, and potassium hydrogenphthalate (G.R., all from Merck) were used without further purification. All solutions were prepared by mixing double-distilled and freshly boiled water, whose conductivity did not exceed $0.5 \mu\text{Scm}^{-1}$. Carbonate-free sodium hydroxide solutions were prepared under a nitrogen atmosphere as 0, 10, 20, 30, 40, 50, 60, 70, 80, and 90% (v/v) aqueous (freshly boiled doubly-deionised water) ethanol solutions. The alkali titer and absence of carbonate were periodically checked by *pH*-metry, using the appropriate *Gran* function against primary standard oven-dried potassium hydrogenphthalate. The ionic strength of each NaOH solution was adjusted to 0.10 M by the addition of NaClO₄ as supporting electrolyte. When not in use, they were stored at 4°C. The accurate concentration of stock solutions of perchloric acid and sodium hydroxide is determined by potentiometric titration [26].

Apparatus

Potentiometric measurements were performed with an Orion 960 automatic titrator equipped with Orion EA 940 *pH* meter (resolution 0.1 mV, accuracy 0.2 mm³). All titrations were carried out under N₂ and at $25.0 \pm 0.1^\circ\text{C}$, which was maintained by circulating water from a constant-temperature thermostat (Haake, precision $\pm 0.1^\circ\text{C}$) through the double-wall Pyrex titration cell of 80 cm³ capacity. The electrode was modified by substituting its aqueous KCl solution for the mixture 0.01 M NaCl + 0.09 M NaClO₄. The apparatus is described in detail elsewhere [9].

Procedure

The protonation constants of disubstituted anilines studied were determined by means of the data obtained from potentiometric titrations in 0, 10, 20, 30, 40, 50, 60, 70, 80, and 90% (v/v) aqueous ethanol solutions at $25.0 \pm 0.1^\circ\text{C}$ and 0.1 M ionic strength (NaClO₄) in a manner essentially similar to that described earlier [9].

In a first step, the potentiometric cell was calibrated for use of the combined *pH* electrode as a hydrogen ion concentration probe rather than as an activity probe before each experiment to obtain *pH* ($-\log[\text{H}^+]$) values for the titration medium [9]. For this purpose, a measured amount of an acidic solution at the same conditions of temperature, ionic strength, and solvent composition to be used in later experiments, was placed in a double-walled Pyrex cell, and it was titrated with a strong base (NaOH, 0.1 M). The potential was allowed to stabilize after each addition of titrant and its value was then used to obtain E_{cell}° and electrode calibration slope, *s* (*Nernstian* factor). Usually, about 10 or 12 additions suffice for E_{cell}° and electrode calibration slope to be accurately determined, provided that the *pH* of the background solution changes from the initial *pH* 2 to a value about two units lower than the protonation constant's, $\log \beta$, value of the compound to be studied. Also, by assuming the E_{cell}° value determined in the acidic range to be reliable and $[\text{OH}^-]$ = concentration of base added in excess, we calculated reproducible values of the stoichiometric ion products ($K'_{\text{ap}} = [\text{H}^+][\text{OH}^-]$) for all of the solvent mixtures at ionic strength of 0.10 M NaClO₄ in several series of experiments.

In a second step, for all of the anilines, an excess of HClO₄ solution was added so that these substances were fully protonated at the beginning of the titrations and titrated by incremental additions

of carbonate-free and standard NaOH solution. After each addition, the potential was allowed to stabilize and its value was used, in combination with E^o and the electrode calibration slope calculated in the calibration step, to calculate the pH of the solution.

Values of the *Kamlet-Taft* solvatochromic parameters (α , π^* [27], β [28], and E_T^N [28]) and *Hammett* substituent constants (σ) [29] were taken from the literature.

Date Treatment

The calculation of the stoichiometric protonation constants of disubstituted aniline derivatives has been carried out with the FORTAN program BEST [30]. The error in the constants listed in Table 1 is estimated as 0.02 log unit on the basis of the σ_{fit} value, which measures the deviation of the experimental curve and the curve calculated from the equilibrium constants, being less than 0.01 pH unit in all potentiometric determinations. The equilibrium constants reported in this paper were obtained as averaged values of four titrations.

The principle and methodology of FA and TFA are described in detail by Malinowski [31]. Input data referring to $\log \beta$ values of disubstituted anilines, which vary with composition of the mixed solvent, were collected to build up the experimental data matrix such that each row concerned a particular solvent mixture composition and each column concerned a particular substance. Factor analysis was used first, to determine how many sources of independent variation were involved in the varying data. Afterwards, target factor analysis, a technique especially valuable for achieving meaningful transformations of the abstract factors emerging after the *Eigen* analysis of the cases, was applied to identify the chemical nature of these factors. The TFA enables us to test individually suspected parameters, the target vectors (*i.e.*, physical properties) as possible real factors that may be responsible for trends in the data matrix. This individual testing ability is one of the most valuable features of TFA.

Finally, the coefficients involved in the model equation that fit the data were evaluated as factor loadings and their standard deviations were given. They allowed expressions to be obtained that describe the variation of $\log \beta$ with respect to the percentage of ethanol in the solvent mixture. The best combination of the tested target vectors, which describe accurately the data matrix, was the combination that gives the smallest error on the estimation of loadings and the smallest root-mean squares error (RMS) in data reproduction. In addition, the residual standard deviation value (RSD) was calculated since it gave a more realistic precision in the fit.

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 [21, 32, 33]. Also, MATLAB functions [34] were used to check the number of factors through singular value decomposition.

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