



Deprotonation of salicylic acid and 5-nitrosalicylic acid in aqueous solutions of ethanol

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Abstract: The protonation constant values of two hydroxybenzoic acids (salicylic acid and 5-nitrosalicylic acid) were studied in some water–ethanol solutions using spectrophotometric and potentiometric methods at 25 °C and in an ionic strength of 0.1 M sodium perchlorate. The results indicated that the pK_a values increase with increasing proportion of ethanol in mixed solvent. The dependence of the protonation constants on the variation of the solvent were correlated by the dielectric constants of the media. Furthermore, for a better understanding of the solvent influence, the obtained results were explained in terms of the Kamlet–Taft parameters α (hydrogen-bond donor acidity), π^* (dipolarity/polarizability) and β (hydrogen-bond acceptor basicity) by means of linear solvation energy relationships. The multiple linear regression analysis indicated that the pK_a values of salicylic acid were strongly dependent on the non-specific electrostatic solvent–solute interactions, whereas specific hydrogen bonding interactions controlled the protonation of nitrosalicylic acid in water–ethanol binary mixtures.

Keywords: pK_a ; hydroxybenzoic acids; binary mixtures; solvent effects.

INTRODUCTION

The value of the protonation constant of compounds, pK_a , is a key parameter for predicting the extent of ionization of their functional groups with respect to the proton concentration of a medium. This parameter is essential in a wide range of research areas, such as chemistry, biochemistry and pharmacology. The fundamental physicochemical properties of drugs such as solubility and permeability are influenced by pH. Thus these properties for a diverse set of acidic or basic drug are directly related to their pK_a values.¹ It has been shown that the activity of enzymes and acid–base homeostasis of living organisms are prominently dependent on the protonation constants of the compounds present in the cell and in

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the body.² Hence, knowledge of pK_a values is necessary for the quantitative understanding and stability constant determination of the interactions between acidic or basic ligands and metal ions in complexes.^{3–7}

Solvent mixtures, especially binary solutions of water and organic solvents, are widely used in a variety of chemical fields, such as solvent extraction, chemical synthesis and liquid chromatography. Furthermore, a pure solvent can frequently be mixed with others in order to obtain solutions with a variety of physical properties. Systematic investigations of solvent effects on thermodynamic and kinetic functions are interesting both from experimental and theoretical perspectives in chemical and biochemical analysis. The study of solvent effects in binary solvent mixtures is more complicated than in pure solvents because the solute–solvent and solvent–solvent interactions can create new solvent properties leading to preferential solvation. Preferential solvation occurs when solutes interact stronger with one of the components of the mixture and then this difference in the interactions is reflected in the composition of solute microenvironment.^{8,9}

The use of empirical scales obtained from solvatochromic compounds is a suitable method for explaining solute–solvent interactions at a microscopic level. Some of the most extensively used parameters are the solvatochromic parameters which take into account all possible specific and non-specific interactions between solute and solvent molecules. Kamlet and Taft scaled their solvatochromic solvent parameters by introducing a developed solvatochromic comparison method.^{10–14} The parameters α , β and π^* are a measure of the hydrogen bond donor acidity, hydrogen bond acceptor basicity and dipolarity–polarizability of the solvent, respectively. The sum of these solvent properties can be used to treat molecular solvent effects with the framework of the concept of linear solvation energy relationships.^{15,16}

In continuation of previous studies,^{17–21} in this study, the protonation constants of salicylic and 5-nitrosalicylic acid were determined in various mixtures of water–ethanol solvents to examine the solvent dependence of their acid–base equilibria properties. Salicylic and 5-nitrosalicylic acid are organic phenolic compounds which are widely used in organic drug synthesis. Their chemical structures are presented in Fig. 1.

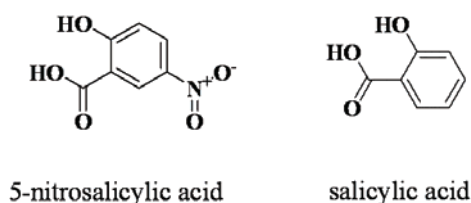


Fig. 1. Chemical structure of salicylic and 5-nitrosalicylic acid.

EXPERIMENTAL

Salicylic and 5-nitrosalicylic acid were obtained from Sigma–Aldrich. Ethanol was of the highest available purity (Merck) and was used without further purification. Stock solutions of NaOH and HCl were prepared from titrisol solutions (Merck). The water used was double-distilled water with a conductivity of $1.3 \pm 0.1 \mu\Omega^{-1} \text{ cm}^{-1}$. Sodium perchlorate was supplied by Merck as an analytical reagent grade material and was used without further purification.

Potentiometric measurements were performed in a double-walled electrochemical cell thermostated at 25 °C. The ionic strength of the mixtures was maintained to 0.1 M with sodium perchlorate. A Jenway Research potentiometer, model 3520, with a combination of glass and reference electrode was used for the measurement of the electromotive force (*emf*) in potentiometric titrations of acidic solution mixtures.

Spectrophotometric measurements were performed on a UV–Vis Shimadzu 2100 spectrophotometer with a Pentium 4 computer using thermostated matched 10 mm quartz cells. A flow type measurement cell was used. A peristaltic pump allowed for the circulation of the solution under study from the electrochemical cell to the spectrophotometric cell; thus, the absorbance and the *emf* of the solution could be measured simultaneously. To exclude carbon dioxide from the system, a stream of purified nitrogen was passed through a sodium hydroxide solution and then bubbled slowly through the reaction solution.

Prior to each spectrophotometric titration, the electrochemical cell was calibrated to obtain the formal electrode potential emf° .^{22,23} Approximately 20 ml of solutions of HCl in water–ethanol systems were titrated by the stepwise addition of NaOH solution. The equilibrium emf° values of the cell were recorded after allowing potential stabilization. The *emf* values in each of binary mixtures were computed from the Nernst equation knowing the exact concentration of H^+ at each titration point and the reference electrode potential. In the next step, 25 mL of an acidic solution of hydroxybenzoic acid was titrated with a sodium hydroxide solution (0.1 mol dm^{-3}). The absorbance data were recorded in the interval of 200–400 nm after reading the *emf* values of the electrochemical cell. Then, the spectroscopic titration data were introduced to the Star program²⁴ to calculate the pK_a values of the two investigated compounds.

RESULTS AND DISCUSSION

Calibration of the electrochemical cell in water–ethanol mixtures

According to the Nernst equation, the potential of a glass electrode can be presented as:

$$emf = emf^\circ + k \log [\text{H}^+] + k \log \gamma_{\text{H}^+} + E_{\text{LJ}} \quad (1)$$

where E_{LJ} is the liquid junction potential, $k = 2.303RT/F$ in which R , T and F have their usual meanings and γ_{H^+} is the activity coefficient of the hydrogen ions. Difficulties in computing the activity coefficients of hydrogen ion in various aqueous mixtures of organic solvents lead to measuring *emf* vs. the H^+ concentration in solution. As the ionic strength of the solution was kept constant, the activity coefficient of the hydrogen ion was also constant. The non-ideality of the solutions is then included in k_a (the specific constant of a glass electrode in the acidic region), and thus:

$$emf = k_a + k \log [\text{H}^+] \quad (2)$$

with k_a being $emf^\circ + k \log \gamma_{H^+} + E_{LJ}$. The use of a glass electrode (with an aqueous inner solution) in non-aqueous media introduces a deviation from ideality. However, it was shown that the deviation is negligible and that a glass electrode is always usable in such media to measure H^+ concentration with a linear relation of E_{cell} vs. $\log [H^+]$.²⁵

Thus, the hydrogen ion concentration can be easily calculated by:

$$[H^+] = (M_{HCl}V_0 - M_{NaOH}V_1)/(V_0 + V_1) \quad (3)$$

where M_{HCl} and M_{NaOH} are the molarities of the acid and base, V_0 and V_1 are the initial volume of acid and the added volume of sodium hydroxide solution, respectively. The k_a values were calculated from measured emf and the known concentration of solvated proton at every titration point by linear regression analysis. The derived linear equations are reported in Table I.

TABLE I. The calibration equation of the electrochemical cell in different water-ethanol mixtures at 25 °C

Ethanol content, % (v/v)	Cell calibration equation
0	$emf = 365.20 + 59.11 \log [H^+]$
10	$emf = 362.15 + 58.53 \log [H^+]$
20	$emf = 360.34 + 59.21 \log [H^+]$
30	$emf = 359.33 + 59.27 \log [H^+]$
40	$emf = 358.48 + 59.22 \log [H^+]$
50	$emf = 354.31 + 59.87 \log [H^+]$

For all the binary mixtures, the slopes obtained from the least squares analysis were close to the theoretical Nernst value (59.167 mV at 25 °C) with correlation coefficients of nearly $r^2 = 0.99$. Therefore the pH values of the binary mixtures can be properly measured according to:

$$p_cH = (k_a - emf)/k \quad (4)$$

Computing protonation constants

The absorption spectra for salicylic acid and 5-nitrosalicylic acid at varying pH values in 50 % (v/v) ethanol are shown in Figs. 2 and 3, respectively.

For each binary solvent, the spectral absorbance in different pH values were used to construct a matrix \mathbf{R} of size $m \times n$, where m is the number of different pH values in which the absorbance was determined at n wavelengths at 0.5 nm intervals. According to the Beer law, a least squares analysis was performed in the Star program environment to decompose the data matrix \mathbf{R} into a matrix of pure concentration, \mathbf{C} , and a matrix of pure spectral profiles, \mathbf{S} , with the optimal residual error matrix \mathbf{E} .

$$\mathbf{R} = \mathbf{CS} + \mathbf{E} \quad (5)$$

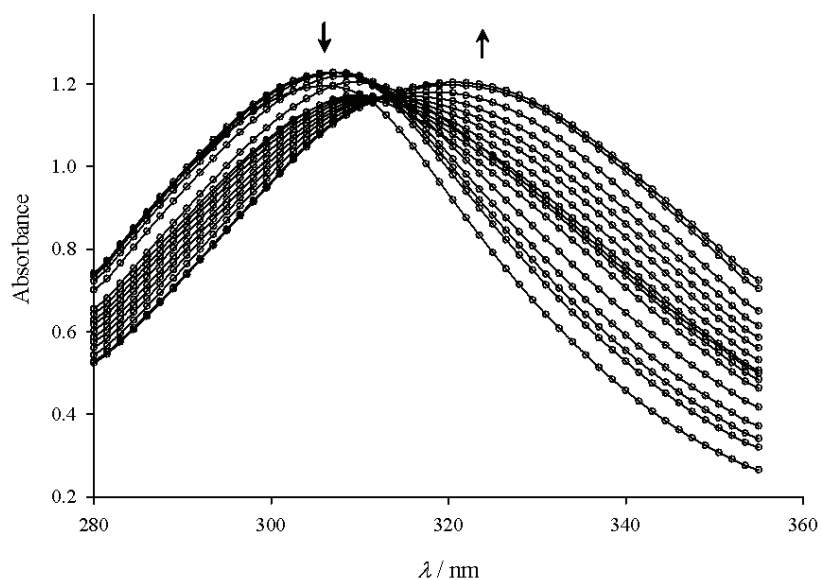


Fig. 2. Spectral change of salicylic acid ($2.2 \times 10^{-4} \text{ mol dm}^{-3}$) with decreasing pH in 50 % (v/v) ethanol.

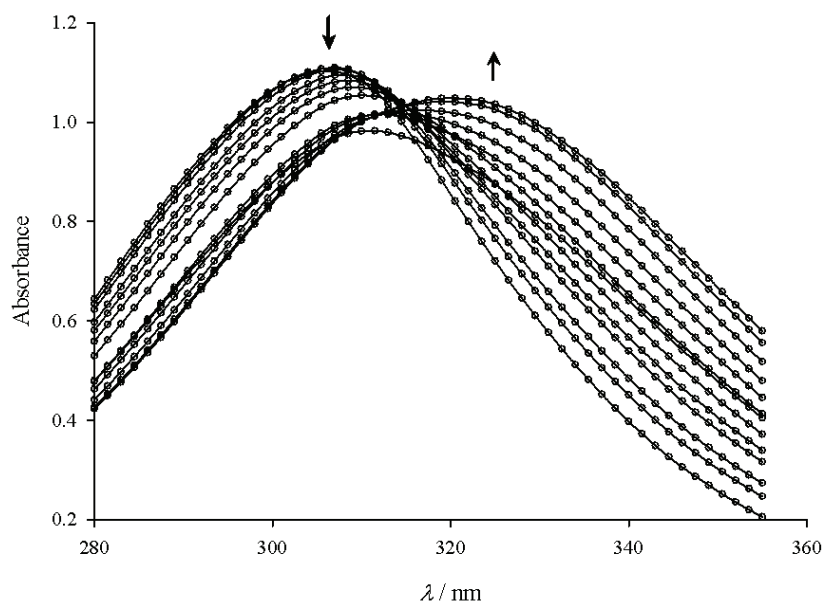


Fig. 3. Spectral change of 5-nitrosalicylic acid ($8.5 \times 10^{-5} \text{ mol dm}^{-3}$) with decreasing pH in 50 % (v/v) ethanol.

In iterative cycles, the matrices **C** and **S** were determined which best represent the original matrix **R**. These procedures were realized for a known number

of components and using the initial estimation of the two **C** and **S** matrices. The matrix of pure concentration profiles is related to the protonation constant and the total concentration of the compounds. Under suitable constraints, the nonlinear least-squares fitting continues until the best set of parameters (pK_a and molar absorptivities of the species) is obtained that result in a minimum of **E**.

The protonation constants determined by the Star program are listed in Table II with the solvent parameters, dielectric constant (ϵ_r) and KAT parameters in various water–ethanol solvents mixtures.^{26,27}

TABLE II. Protonation constants of salicylic acid and 5-nitrosalicylic acid with the KAT parameters and dielectric constants of different water–ethanol mixtures at 25 °C and constant ionic strength (0.1 mol dm⁻³ NaClO₄); the KAT solvatochromic parameters and the dielectric constants were taken from refs. 27 and 26, respectively

Ethanol content, % (v/v)	pK_a		α	β	π^*	ϵ
	Salicylic acid	5-Nitrosalicylic acid				
0	2.916±0.072	2.017±0.010	1.17	0.47	1.09	78.56
10	2.873±0.011	2.093±0.009	1.11	0.38	1.13	73.95
20	2.927±0.009	2.189±0.009	1.04	0.40	1.15	69.05
30	3.052±0.009	2.250±0.010	1.01	0.48	1.14	63.85
40	3.252±0.007	2.262±0.012	0.98	0.54	1.12	58.36
50	3.465±0.009	2.320±0.014	0.98	0.59	1.08	52.62

Effect of the solvent

As shown in Table II, the pK_a values of salicylic acid and 5-nitrosalicylic acid increase with increasing volume percentage of ethanol. The electron withdrawing nitro functional group in 5-nitrosalicylic acid leads to lower pK_a values in comparison to salicylic acid. The deprotonation equilibrium of the two hydroxybenzoic acids can be represented by $HA \rightleftharpoons H^+ + A^-$. It is expected that because of solute–solvent electrostatic interactions, the neutral species (HA) are thermodynamically more stable than the ionic species (H^+ and A^-) in media with higher percentages of ethanol in which the dielectric constants are lower. In order to explore the possibility of this hypothesis, the pK_a values of substances were correlated to the reciprocal of the dielectric constants of the binary mixtures and their dependence interpreted according to the Born equation.²⁸ In the absence of the specific solute–solvent interactions, a plot of pK_a values vs. the reciprocal dielectric constant of the media, ϵ , should be linear:

$$pK_a = (121.6n/r)(1/\epsilon - 0.0128) \quad (6)$$

where r is the common radius of the ions and n is the square summation of the charges involved in the protonation equilibrium. In this work, a linear regression analysis was performed between pK_a and $1/\epsilon$ values in different water–ethanol mixtures by using the Linest function in the Microsoft Excel program.²⁹ The following expressions were obtained in accordance with the Born equation, where

the quantities shown in brackets are the standard deviation of the corresponding coefficients:

$$pK_a(\text{salicylic acid})=1.60(0.20) + 59.97(12.72)1/\varepsilon \quad r^2 = 0.93 \quad (7)$$

$$pK_a(5\text{-nitrosalicylic acid})=1.53(0.19) + 43.46(12.04)1/\varepsilon \quad r^2 = 0.77 \quad (8)$$

The squared correlation coefficient, r^2 , measures the goodness-of-fit of the experimental data to the theoretical equation. These results indicate that the protonation constants of salicylic acid depend on the electrostatic forces and can be explained based on the Born equation, whereas the pK_a values of 5-nitrosalicylic acid do not follow the same order, indicating the existence of additional factors that influence the solute-solvent interactions. This observation is consistent with a previous study on the behavior of salicylic acid in water-DMSO mixtures.¹⁹

For a better evaluation of the solute-solvent interactions at the molecular level, the most significant KAT parameters were used. A multi-parametric equation was proposed to evaluate specific and nonspecific interactions within the framework of the linear solvation energy relationships (LSER) concept. The number of parameters in the equation depends on the significance of the solute-solvent interactions.^{30,31} However, the general equation for LSER is usually expressed as:

$$pK_a = A_0 + a\alpha + b\beta + p\pi^* \quad (9)$$

where A_0 , a , b and p are independent coefficients characteristic of the process which indicate their sensitivity to the accompanying solvent properties. In order to explain the obtained pK_a values through the KAT solvent parameters, the protonation constants were correlated with solvent properties by means of multiple linear regressions in the Microsoft Excel program.²⁹ The fitted single, dual and multiparametric equations are tabulated together with their regression statistics (r^2 , standard deviations and F -statistic) in Table III for each substance.

TABLE III. The linear regression analysis of the KAT equation for the values of the protonation constant of salicylic acid and 5-nitrosalicylic acid in water-ethanol mixtures

LSER correlation equation	r^2	F -statistic
Salicylic acid		
$pK_a = 20.37(14.29) - 2.64(2.72)\alpha - 8.54(5.51)\pi^* - 9.18(9.56)\beta$	0.99	52.25
$pK_a = 6.66(0.36) - 0.04(0.22)\alpha - 3.28(0.49)\pi^*$	0.98	79.99
$pK_a = -1.74(1.16) + 5.59(1.05)\beta + 1.52(0.55)\alpha$	0.97	52.53
$pK_a = 6.58(1.43) + 0.07(0.79)\beta - 3.27(0.91)\pi^*$	0.98	79.43
$pK_a = 4.39(0.42) - 1.29(0.41)\alpha$	0.71	9.84
$pK_a = 1.45(0.27) + 2.79(0.46)\beta$	0.90	36.57
$pK_a = 6.70(0.25) - 3.35(0.23)\pi^*$	0.98	211.28
5-Nitrosalicylic acid		
$pK_a = -5.14(9.17) + 0.83(1.74)\alpha + 3.05(3.53)\pi^* + 5.44(6.14)\beta$	0.98	30.09
$pK_a = 2.98(0.23) - 0.71(0.14)\alpha - 0.07(0.31)\pi^*$	0.97	48.18
$pK_a = 2.76(0.59) + 0.16(0.53)\beta - 0.66(0.28)\alpha$	0.97	48.90

TABLE III. Continued

LSER correlation equation	r^2	F -statistic
5-Nitrosalicylic acid		
$pK_a = -0.80(0.80) + 2.53(0.44)\beta + 1.40(0.51) \pi^*$	0.98	60.68
$pK_a = 2.94(0.07) - 0.74(0.07)\alpha$	0.97	126.39
$pK_a = 1.38(0.12) + 1.37(0.21)\beta$	0.92	43.07
$pK_a = 3.69(0.48) - 1.39(0.44) \pi^*$	0.71	9.81

The F -statistic values were used to assess which of the LSER equations is statistically the optimum model. The best predictive mathematical equations in the fitted models were those that have highest F -statistic values and small standard deviation (Table III). In the case of salicylic acid, the non specific dipolarity–polarizability interactions have the most important effect on the pK_a values, whereas the deprotonation of 5-nitrosalicylic acid is extensively sensitive to specific hydrogen bonding interactions. The π^* scale for salicylic acid in the correlated model has a negative effect which means a decrease in the polarity of the media increases the pK_a values. The coefficient of the α term for 5-nitrosalicylic acid in the LSER equation is also negative, meaning a lower deprotonation of compound with decreasing solvent hydrogen bond acidity. These results are in complete agreement with the above assumption derived from the Born equation.

CONCLUSIONS

The protonation constants of salicylic acid and 5-nitrosalicylic acid were successfully determined in water and water–ethanol mixtures of 0–50 % ethanol (v/v) by spectrophotometric and potentiometric methods at 25 °C and at an ionic strength of 0.1 M sodium perchlorate. Generally, it was observed that the pK_a values of substances increase with increasing volume fraction of ethanol. The high correlation coefficients between the pK_a values and solvatochromic parameters of the binary mixtures (α and π^*) demonstrate the existence of a linear relationship between these magnitudes in these media.

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ИЗВОД

ДЕПРОТОНОВАЊЕ САЛИЦИЛНЕ И 5-НИТРОСАЛИЦИЛНЕ КИСЕЛИНЕ У РАСТВОРИМА У СМЕШИ ВОДА–ЕТАНОЛ

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Испитиване су вредности констате протоновања две хидроксибензове киселине (салицилна и 5-нитросалицилна) у различитим растворима у смеси вода–етанол, потенциометријски на 25 °C у раствору 0,1 М натријум-перхлората. Добијени резултати указују на то да

pK_a вредности расту повећањем удела етанола у смеси растварача. Зависност константе протоновања од састава растварача корелисана је са диелектричном константом средине. У циљу бољег разумевања утицаја растварача, добијени резултати објашњени су линеарном зависношћу Камлет–Тафтових параметара α (киселост донора водоничне везе), π^* (диполарност/поларизабилност) и β (базност акцептора водоничне везе) и енергије солватације. Вишеструка линеарна регресиона анализа указује да pK_a вредности салицилне киселине значајно зависе од неспецифичних електростатичких интеракција растварач–растворена супстанца, док специфичне интеракције водоничних веза утичу на протоновање нитросалицилне киселине у бинарним смешама вода–етанол.

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