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Potentiometric Study of Acetylsalicylic Acid: Solubility and Acid−Base Equilibria in Different Saline Media at 298 K

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A simultaneous study of acid−base and solubility equilibria of acetylsalicylic acid has been carried out by potentiometry with a glass electrode in NaCl and KNO_3 at several ionic strengths and 25 °C. The dependence of the stoichiometric equilibrium constant on ionic strength has been analyzed according to different specific interaction theories. The experimental data also allow one to estimate both the salting coefficient of acetylsalicylic acid in the studied electrolytes and the specific interaction parameters of acetylsalicylate ion with cations of the support electrolyte.

Introduction

Acetylsalicylic acid ($2\text{-}CH_3CO_2C_6H_4CO_2H$), commonly known as aspirin, is a simple aromatic carboxylic acid with acid−base chemistry that is represented by the dissociation equilibrium $AH = A^- + H^+$. Despite the importance of the compound, it is surprisingly difficult to find in the literature the values of dissociation constants associated with this equilibrium, and when they are found, salinity conditions, among others, used to determine these values, are not given. Hence, available data from different sources are sparse and confusing.

Acid−base properties are known to be strongly affected by the nature and concentration of the electrolyte medium concerned. The effects of ionic strengh and ionic medium were recently reviewed by Daniele et al.[1] and Sastre de Vicente.[2] This work focuses on the systematic study of aspirin solubility and acid−base chemistry in two different saline media, sodium chloride and potassium nitrate. Experimental data obtained potentiometrically allow us to describe the dependence of the stoichiometric equilibrium constant on the concentration of the electrolyte medium and to obtain an extrapolated value for the thermodynamic equilibrium constant, as well as to calculate solubilities and the Setchenow (or salting) coefficient of acetylsalicylic acid in aqueous solutions of NaCl and KNO_3. Finally, specific interaction parameters (acetylsalicylate/Na^+, K^+), which are very difficult to obtain by other procedures, can be calculated from estimated dissociation constants and solubilities.

Theory

The dissociation of a weak monobasic acid can be represented by the following equilibrium reaction:

$$AH \leftrightarrow A^- + H^+ \qquad (1)$$

having a thermodynamic dissociation constant of the form

$$K^{T}_{AH} = \frac{(A^-)(H^+)}{(AH)} = \frac{[A^-][H^+]}{[AH]}\frac{\gamma_{A^-}\gamma_{H^+}}{\gamma_{AH}} = K^{*}_{AH}Q^{\gamma}_{AH} \qquad (2)$$

where K^{*}_{AH} is the stoichiometric dissociation constant of the species AH and Q^{γ}_{AH} is the quotient of the activity coefficients of the present species; both are dependent on the ionic strength of the medium.

Two different ionic interaction theories for activity coefficients, those developed by Guggenheim and Pitzer, have been employed in this work to get the expressions for the dependence of pK^{*}_{AH} on ionic strength.

The Guggenheim model[3] leads to the expression

$$pK^{*}_{AH} = pK^{T}_{AH} - \frac{2A\sqrt{I}}{1 + 1.5\sqrt{I}} + BI \qquad (3)$$

with A, the Debye−Hückel limiting slope, being 0.509 at 25 °C in aqueous media and B, a constant parameter, being the linear combination of β parameters of specific interaction between ions of opposite sign:

$$B = 2(\beta_{A^-,C} + \beta_{H^+,X} - \lambda^{\log}_{AH,CX}) \qquad (4)$$

where $\lambda^{\log}$ is the parameter of interaction between the neutral species and the ions present in the medium and CX refers to the background electrolyte.

Under experimental working conditions (support electrolyte 1:1 at ionic strength below 2 M), the following expression[3] is deduced from the Pitzer model

$$pK^{*}_{AH} = pK^{T}_{AH} + \frac{2}{\ln 10}f^{\gamma} + H_1 I + H_2 g + \frac{2}{\ln 10}\beta^{1}_{C,X}h \qquad (5)$$

where f^{γ}, g, and h are functions of the ionic strength, while the constants H_1 and H_2 are linear combinations of the β coefficients of binary interactions between ions and the $\lambda^{\ln}$ coefficient of the neutral species:

$$f^{\gamma} = -A_{\phi}\left[\frac{\sqrt{I}}{1 + 1.2\sqrt{I}} + \frac{2}{1.2}\ln(1 + 1.2\sqrt{I})\right] \qquad (6)$$

$$g = [1 - (1 + 2\sqrt{I})e^{-2\sqrt{I}}] \qquad (7)$$

$$h = Ie^{-2\sqrt{I}} \qquad (8)$$

$$H_1 = \frac{2}{\ln 10}(\beta^{0}_{A^-,C} + \beta^{0}_{H^+,X} - \lambda^{\ln}_{AH,CX}) \qquad (9)$$

$$H_2 = \frac{1}{\ln 10}(\beta^{1}_{A^-,C} + \beta^{1}_{H^+,X} - \beta^{1}_{C,X}) \qquad (10)$$

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where A_ϕ is analogous to the Debye–Hückel limiting slope, having a value of 0.391 at 25 °C.

On the other hand, the salting coefficient can be determined experimentally by using a method based on solubility measurements,[4] presenting the advantage that acid solubility measurements in saline media can be realized with simple titrations with a base of known concentration.

The solubility of neutral species in aqueous solutions is altered by the presence of a salt. This effect corresponds with variations in the activity coefficient of the neutral molecule. In most cases, the solubility of the neutral species decreases as the concentration of the ions in the medium increases, corresponding with an increase in the activity coefficient of the neutral species, known as the salting out effect.[5]

Setchenow proposed an experimental expression that linearly relates the logarithm of the activity coefficient of the neutral species with the electrolyte concentration in solution using a parameter known as the salting coefficient, also referred to as the Setchenow coefficient. Relations of this type are found in later works on many different neutral species in a wide variety of electrolyte media.[6,7]

The relation employed in this study has the form

$$\log \frac{y_i^{\mathrm{S}}}{y_i^{\circ}} = \log \frac{S_{c,i}^{\circ}}{S_{c,i}^{\mathrm{S}}} = k_c C_{\mathrm{el}} \tag{11}$$

where y_i^{S} and y_i° are the activity coefficients on the molarity scale of substance i in the presence of a salt and in pure water, respectively, S_i^{S} and S_i° are the respective solubilities in the two media (in mol·L^{-1}), C_{el} is the molar concentration of the electrolyte, and k_{c} is a constant known as the salting or Setchenow coefficient, since eq 11 is of the same form as that proposed empirically by the author.

The expression is represented similarly in the molal scale as

$$\log \frac{\gamma_i^{\mathrm{S}}}{\gamma_i^{\circ}} = \log \frac{S_{m,i}^{\circ}}{S_{m,i}^{\mathrm{S}}} = k_m m_{\mathrm{el}} \tag{12}$$

where m represents the molalities of the species, γ is the activity coefficient in the molal scale, and k_m is the Setchenow coefficient in the molal scale.

The relation between the Setchenow coefficient in the molality scale k_m and the interaction parameters of the neutral species i is, in accordance with the two theories,

$$k_m = \frac{2}{\ln 10}\lambda_i^{\ln} = 2\lambda_i^{\log} \tag{13}$$

Setchenow equations can be expressed in the form

$$\log S_{c,\mathrm{AH},n}^{\mathrm{S}} = -k_c C_{\mathrm{el}} + \log S_{c,\mathrm{AH},n}^{\circ} \tag{14}$$

$$\log S_{m,\mathrm{AH},n}^{\mathrm{S}} = -k_m m_{\mathrm{el}} + \log S_{m,\mathrm{AH},n}^{\circ} \tag{15}$$

where c and m indicate molar or molal concentration, respectively, and the subscript n represents the solubility of the nondissociated part of the carboxylic acid, which is the fraction that actually corresponds with the solubility of the neutral species present in the solution.

Thus, a linear fit of the data of the logarithm of the solubility of the nondissociated part as a function of ionic strength will provide the salting coefficient of acetylsalicylic acid in the working medium and the solubility of the nondissociated part in pure water.

Experimental Section

The experimental data were obtained from potentiometric titrations, which allow the simultaneous study of acid–base and solubility equilibria. A saturated solution of acetylsalicylic acid (Aldrich, >99.0% purity) was first prepared and then titrated with solutions of known concentration of KOH or NaOH (Merck p.a.). An appropiate amount of inert electrolyte, KNO_3 or NaCl (Merck p.a.), was added to all solutions in order to maintain a constant ionic strength. All solutions were prepared using water purified by passage through a Millipore Milli-Q system. The equipment and experimental methodology of titrations have been described elsewhere.[8]

To obtain a saturated acetylsalicylic acid system, a sufficient quantity of acid is weighed and support electrolyte is added to get the desired working ionic strength. Because of the low solubility and relatively low dissociation constant value of this carboxylic acid, its contribution to the total ionic strength of the solution is assumed to be negligible. The solution is covered, thoroughly stirred, and warmed to facilitate carboxylic acid solvation and increase solubility, thus ensuring obtaining a solution that will later be oversaturated at the working temperature. Later, the solution is maintained at constant temperature (25 ± 0.1 °C) for 2 h under a nitrogen stream and magnetic mixing to allow the solubility equilibrium to be reached at that temperature. Excess carboxylic acid precipitates, and an aliquot is pipetted from the liquid phase.

Given that acetylsalicylic acid undergoes hydrolysis at its acetyl group in aqueous medium, titrations can only be carried out up to the equivalence point, since the potential of the electrode varies rapidly without reaching stability from this point on. Abnormal variations in the potential measured are not observed in the acid region. It was proved experimentally that, under titration conditions, a saturated solution of acetylsalicylic acid does not undergo potential variations greater than ±0.1 mV in 2 h.

The equivalence point was determined by use of the Gran method,[9] which presents clear advantages over others because it allows us to calculate the aforementioned point without having to reach it during the titration, as is our case.

The SUPERQUAD program[10] was used to calculate the stoichiometric equilibrium constants from experimental data. This program is based on the least-squares minimization of residuals in the emf readings.

Before titrations, the glass electrode must be calibrated on the proton concentration scale to estimate the value of the reference potential and to check the Nernstian behavior in the electrode. Calibrations are done over the pH range from 2.3 to 2.9, where the electrode response is found to be optimal. Known volumes of a 0.1 M solution of HCl at the desired ionic strength are added to a solution of the background electrolyte at the same ionic strength, and the potential of the mixed solution is measured upon each addition. Proton concentration and potential data pairs are then fitted to the equation $E = E° + s \log [\mathrm{H}^+]$, where E represents the measured formal potential, $E°$ the electrode reference potential, s the Nernst slope, and $[\mathrm{H}^+]$ the proton concentration.

Results and Discussion

The experimental data of stoichiometric equilibrium constant and total solubility for acetylsalicylic acid are

Table 1. Experimental Data (molal scale) of Stoichiometric Constants and Solubilities of Total (T) and Nondissociated (n) Fraction for Acetylsalicylic Acid in KNO_3 and NaCl at 25 °C[a]

I/mol·kg^{-1}	pK^*_m	$S^S_{m,T}$	$S^S_{m,n}$
		KNO_3	
0.152	3.410 ± 0.010	0.0234 ± 0.0005	0.0206 ± 0.0004
0.511	3.359 ± 0.005	0.0229 ± 0.0001	0.0200 ± 0.0001
0.829	3.348 ± 0.008	0.0224 ± 0.0003	0.0194 ± 0.0002
1.155	3.364 ± 0.005	0.0217 ± 0.0001	0.0189 ± 0.0001
1.603	3.379 ± 0.005	0.0209 ± 0.0003	0.0182 ± 0.0003
2.186	3.407 ± 0.004	0.0195 ± 0.0004	0.0170 ± 0.0004
		NaCl	
0.151	3.403 ± 0.001	0.0220 ± 0.0005	0.0193 ± 0.0005
0.302	3.365 ± 0.003	0.0203 ± 0.0001	0.0176 ± 0.0001
0.405	3.346 ± 0.002	0.0194 ± 0.0001	0.0167 ± 0.0001
0.608	3.331 ± 0.002	0.0182 ± 0.0002	0.0155 ± 0.0002
0.814	3.327 ± 0.007	0.0167 ± 0.0001	0.0141 ± 0.0001
1.022	3.326 ± 0.015	0.0157 ± 0.0006	0.0132 ± 0.0005

[a] The error in the average value corresponds to the standard deviation of the data.

Table 2. Fitting Parameters and pK^T Values for Acetylsalicylic Acid in KNO_3 and NaCl at 25 °C Obtained by Use of Guggenheim and Pitzer Theories[a]

	KNO_3	NaCl
	Guggenheim Model (Eq 3)	
pK^T	3.653 ± 0.006	3.642 ± 0.002
B	0.105 ± 0.005	0.092 ± 0.004
σ	0.008	0.003
	Pitzer Model (Eq 5)	
pK^T	3.637 ± 0.008	3.636 ± 0.006
H_1	0.124 ± 0.008	0.104 ± 0.017
H_2	0.32 ± 0.03	0.30 ± 0.04
σ	0.004	0.002

[a] The error in the average value corresponds to the standard deviation of the data.

given in Table 1 as a function of ionic strength of the corresponding saline medium.

The solubility of the nondissociated acetylsalicylic acid in the saline medium S^S_n is also given in the same table. As acetylsalicylic acid is a weak acid, there are two fractions in solution, one of the dissociated form and the other neutral. Though different approximations have been used to calculate this concentration,[4,6] none of them are necessary in this case given that it can be determined straightforwardly from the stoichiometric constant of the dissociation equilibrium of the acid at the working ionic strength:

$$K^*_{AH} = \frac{[A^-][H^+]}{[AH]} = \frac{[A^-]^2}{[AH]_T - [A^-]} \qquad (16)$$

where $[AH]_T$ and $[A^-]$ represent the total concentration of acid and the concentration of the dissociated fraction, respectively. The dissociated part of the acid is obtained from this expression by simply solving a quadratic equation. The solubility of the nondissociated fraction, described in Table 1, is obtained by subtracting the dissociated part from the total concentration of carboxylic acid.

The experimental pK^*−I data were fitted according to Guggenheim and Pitzer theories (eqs 3 and 5), respectively. The parameters obtained are given in Table 2. From the analysis of the tabulated data and the graphs obtained by applying both models (Figures 1 and 2), it follows that the fitting equations tested accurately reproduce the experimental facts.

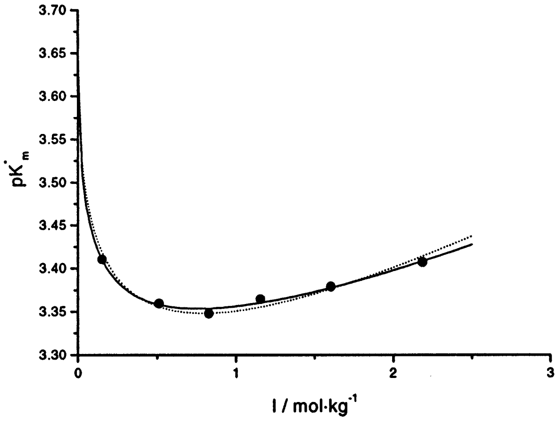

Figure 1. Experimental pK^*−I data (●) of acetylsalicylic acid in KNO_3 at 25 °C fitted according to Pitzer (−) and Guggenheim (- - -) models.

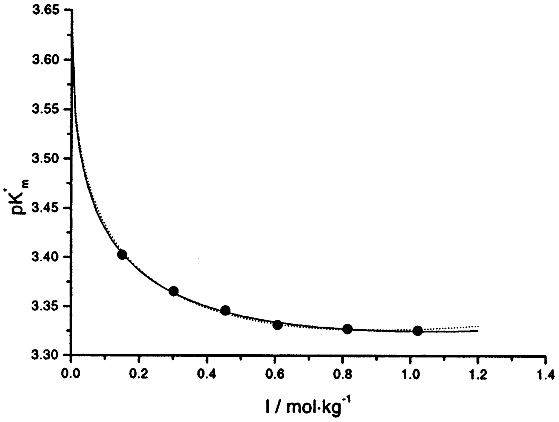

Figure 2. Experimental pK^*−I data (●) of acetylsalicylic acid in NaCl at 25 °C fitted according to Pitzer (−) and Guggenheim (- - -) models.

Table 3. Data of the Equilibrium Constant of Acetysalicylic Acid Found in the Literature[a]

pK	ref
3.49	12
3.5	11
3.55	13

[a] Experimental conditions: T = 25 °C except for the value from ref 11, where the temperature is not specified. The ionic strength is not reported for any of the values.

The values obtained for the pK^T of acetylsalicylic acid in the present work are concordant with one another, as the differences between them are always smaller than ±0.06,[11] although the divergence from the few data found in the literature (see Table 3) is significantly greater. It should be pointed out that rigorous studies on the acid behavior of acetylsalicylic acid were not found and the few data available on its acidity constant are either confusing or concern values obtained from a specific electrolyte medium. Thus, the experimental conditions under which either the value found in the *Merck Index*[12] or that proposed by Albert and Serjeant[11] was determined are not known, whereas Issopoulos[13] uses a pK_a value in a nonmicellar medium as all indication.

The results of the present work suggest that the data obtained in the literature correspond with values of stoichiometric constants at low ionic strengths, but not zero, that very often are essential requirements for carrying out experiments. A typical example would be the determination of stoichiometric constants at an ionic strength of 0.1 M

Table 4. Salting Coefficient of Acetylsalicylic Acid and Solubility of the Nondissociated Part in Pure Water Obtained from a Linear Fit According to Eqs 14 and 15[a]

	KNO_3	NaCl
k_c	0.063 ± 0.003	0.202 ± 0.008
$\log S^\circ_{c,n}$	−1.679 ± 0.003	−1.692 ± 0.005
r^2	0.993	0.995
k_m	0.041 ± 0.002	0.189 ± 0.008
$\log S^\circ_{m,n}$	−1.679 ± 0.002	−1.692 ± 0.005
r^2	0.994	0.994

[a] The error in the average value corresponds to the standard deviation of the data.

Table 5. Specific Interaction Parameters for Acetylsalicylic Acid in KNO_3 and NaCl at 25 °C According to Guggenheim and Pitzer Theories[a]

	KNO_3	NaCl
	Guggenheim Model (Eq 4)	
β_{H^+,X^-}	0.032 21 ± 0.000 09	0.0552 ± 0.0003
β_{A^-,C^+}[b]	0.041 ± 0.003	0.085 ± 0.004
$\lambda^{\log}_{AH,CX}$[b]	0.0203 ± 0.0008	0.095 ± 0.004
	Pitzer Model (Eqs 9 and 10)	
$\beta^0_{H^+,X^-}$	0.1168 ± 0.0010	0.1775 ± 0.0010
$\beta^1_{H^+,X^-}$	0.3546 ± 0.0010	0.2945 ± 0.0010
$\beta^1_{C^+,X^-}$	0.0494 ± 0.0010	0.2664 ± 0.0010
$\beta^0_{A^-,C^+}$[b]	0.073 ± 0.009	0.16 ± 0.02
$\beta^1_{A^-,C^+}$[b]	0.43 ± 0.07	0.66 ± 0.09
$\lambda^{\ln}_{AH,CX}$[b]	0.047 ± 0.002	0.218 ± 0.009

[a] The error in the average value corresponds to the standard deviation of the data. [b] Parameters obtained in this work.

(often of $NaClO_4$). Such experimental conditions would provide a clear explanation for values of around 3.5 that appear repeatedly in the literature.

The linear fit of the data of logarithm of solubility of the nondissociated part as a function of ionic strength according to eqs 14 and 15 provides a slope whose value, opposite in sign, is the salting coefficient of acetylsalicylic acid in the working medium. The logarithm of solubility of the nondissociated part in pure water is obtained from the intercept. Table 4 shows the results obtained. It should be pointed out that works on the solubility of acetylsalicylic acid were not found in the literature.

Finally, in accordance with the expressions of the adjustable parameters, B in the Guggenheim model (eq 4) and H_1 and H_2 in the Pitzer model (eqs 9 and 10), and by use of their numerical values obtained from the respective fittings, the specific interaction parameters of the acetylsalicylate anion with each cation of the working media can be calculated for both models.

In each case, the values of the specific interaction parameters of the ions of the support electrolyte, β_{H^+,X^-}, $\beta^0_{H^+,X^-}$, $\beta^1_{H^+,X^-}$, $\beta^1_{C^+,X^-}$, are necessary for these calculations. With regard to the Pitzer model,[3] these data are tabulated for numerous salts, and in the case of the Guggenheim model, they have been calculated by applying this model to tabulated activity coefficients data of HNO_3 and HCl as a function of ionic strength.[14] The specific interaction parameters of the neutral species λ_i are also required, and these can be calculated from the Setchenow k_m coefficient data obtained in this work, in accordance with eq 13.

Table 5 shows all the known specific interaction parameters together with those new calculated parameters.

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