Protonation Constants of Procaine in Different Salts

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Acid−base equilibrium constants for the two amino groups of the procaine molecule have been determined at 25 °C in different saline media (NaCl, KCl, and $CaCl_2$), by means of potentiometric titrations. The Pitzer model has been used to deal with the ionic strength dependence of activity coefficients, and the parameters proposed by this theory have been obtained, including the thermodymanic dissociation constants, pK^T. Equations describing the dependence of stoichiometric acid−base equilibrium constants versus ionic strength are given.

Introduction

Procaine or novocaine has been used as a local anesthetic for a long time. The dissociation equilibria of this substance are important to understand its behavior;[1] therefore, it has been considered of interest to study the variation of its acid−base equilibrium constants with salt concentration in different ionic media at 25 °C.

Two amino groups are present in the procaine molecule, a primary and a tertiary amine, and therefore, depending on the acidity of the medium, procaine may exit as a neutral molecule, N, a monocation, C^+, or a dication, D^{2+} (Figure 1). The deprotonation equilibria of procaine may be represented by

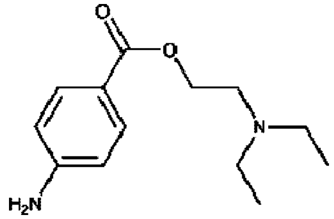

Figure 1. Structure of the procaine molecule.

$$D^{2+} = C^+ + H^+ \tag{1}$$

$$C^+ = N + H^+ \tag{2}$$

where D^{2+} is $H_3N^+{-}R{-}N^+HEt_2$, C^+ is $H_2N{-}R{-}N^+HEt_2$, and N is $H_2N{-}R{-}NEt_2$.

The first acid dissociation constant is given by

$$K_1^T = \frac{[C^+]\cdot[H^+]}{[D^{2+}]}\cdot\frac{\gamma_{C^+}\cdot\gamma_{H^+}}{\gamma_{D^{2+}}} = K_1^*\frac{\gamma_{C^+}\cdot\gamma_{H^+}}{\gamma_{D^{2+}}} \tag{3}$$

and the second by

$$K_2^T = \frac{[N]\cdot[H^+]}{[C^+]}\cdot\frac{\gamma_N\cdot\gamma_{H^+}}{\gamma_{C^+}} = K_2^*\frac{\gamma_N\cdot\gamma_{H^+}}{\gamma_{C^+}} \tag{4}$$

where K^T represents the thermodynamic equilibrium constant; K^* is the stoichiometric constant; and γ_i is the activity coefficient of the species indicated by the subscript that can be expressed by means of the Pitzer model[2] as a function of the concentration of the salt used to keep ionic strength constant and the corresponding ionic interaction parameters that can be estimated on this basis. Systematic studies of the dependence of the amines pK^* with ionic strength by means of the Pitzer theory can be found in the literature.[3,4]

Experimental

A 40 mL aqueous aliquot, containing procaine hydrochloride (0.0100 mol·L^{-1}) (Aldrich), was titrated with a standard solution of hydrochloric acid (MERCK p.a.) to determine pK_1 and with a standard solution of potassium hydroxide (MERCK p.a.) to determine pK_2. The necessary amount of salt (NaCl, KCl, or $CaCl_2$, MERCK, p.a.) to adjust the ionic strength to the desired value was added to all solutions. Titrations were carried out in a dual-wall cell that was kept at constant temperature (25 °C) by circulating water from a thermostat. Purified nitrogen was bubbled through the solutions to ensure thorough homogenization and CO_2 removal. A Crison microBu 2030 automatic burette furnished with a 2.5 mL syringe for dispensing the titrant was used. The burette was controlled via a computer that was used to read the emf values from a Crison micropH 2000 pH-meter, connected to two electrodes: a glass electrode Radiometer pHG211 and a reference electrode Radiometer REF201.

Equilibrium constants were obtained from the potentiometric titration data as described elsewhere:[5] (a) a calibration of the electrode using the proton concentration was performed to obtain the electrode parameters, formal potential, $E^{0\prime}$, and slope, s (because the electrode response, at constant ionic strength, is given by $E = E^{0\prime} + s \log [H^+]$, where E is emf),[6–8] and (b) potentiometric titration data for procaine and calibration parameters were used to calculate the protonation constants by means of the MINIQUAD program.[9] Data for pK^* versus I are listed in Table 1.

The NaCl and KCl solutions were made by weight, while a stock solution of known molarity (standardized by density measurements) of $CaCl_2$ was used to dilute to the desired concentration[10] using an automatic burette. Densities were measured with a Anton Paar digital densimeter (model 60/602) or taken from the literature.[11]

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10.1021/je800061h CCC: $40.75

Table 1. Acid−Base Equilibrium Constants of Procaine versus Ionic Strength, In Different Media, at 25 °C (see Equations 1 and 2)[a]

NaCl		KCl		$CaCl_2$	
I	pK_1^*	I	pK_1^*	I	pK_1^*
0.100	2.015	0.101	2.030	0.091	2.054
0.252	2.123	0.252	2.099	0.229	2.152
0.506	2.303	0.509	2.227	0.458	2.250
1.021	2.464	1.033	2.444	0.919	2.343
1.548	2.585	1.573	2.548	1.382	2.428
				1.849	2.501

NaCl		KCl		$CaCl_2$	
I	pK_2^*	I	pK_2^*	I	pK_2^*
0.100	8.961	0.101	8.919	0.091	8.938
0.252	8.990	0.252	9.008	0.231	8.974
0.506	9.086	0.509	9.113	0.462	9.023
1.021	9.291	1.033	9.313	0.917	9.136
1.548	9.466	1.573	9.448	1.385	9.223

[a] Molality scale is used.

Results and Discussion

From eq 3 and taking logarithms one obtains

$$-\ln K_1^* = -\ln K_1^{\mathrm{T}} + \ln \gamma_{\mathrm{H}^+} + \ln \gamma_{\mathrm{C}^+} - \ln \gamma_{\mathrm{D}^{2+}} \tag{5}$$

where activity coefficients can be expressed by means of the Pitzer model,[2] which yields for the proton activity coefficient in NaCl solution[5]

$$\ln \gamma_{\mathrm{H}^+} = f^{\gamma} + I^2 B'_{\mathrm{NaCl}} + 2IB_{\mathrm{HCl}} + 2I\theta_{\mathrm{HNa}} \tag{6}$$

or

$$\ln \gamma_{\mathrm{H}^+} = f^{\gamma} + 2I(\beta^0_{\mathrm{HCl}} + \theta_{\mathrm{NaH}}) + \beta^1_{\mathrm{HCl}} \cdot g + \frac{1}{2}\beta^1_{\mathrm{NaCl}}(2I\mathrm{e}^{-2\sqrt{I}} - g) \tag{7}$$

B and f^{γ} are functions of the ionic strength commonly used in the Pitzer theory

$$B_{\mathrm{Ma}} = \beta^{(\mathrm{o})}_{\mathrm{Ma}} + \frac{\beta^{(1)}_{\mathrm{Ma}}}{2I} g$$

being

$$g = \left[1 - (1 + 2\sqrt{I})\mathrm{e}^{-2\sqrt{I}}\right]$$

B' is the derivative of B, and

$$f^{\gamma} = -0.3915\left[\frac{\sqrt{I}}{1 + 1.2\sqrt{I}} + \frac{2}{1.2}\ln(1 + 1.2\sqrt{I})\right]$$

The expression for $\ln \gamma_{\mathrm{C}}{}^+$ is exactly equal to eq 7 but replacing H^+ by C^+. With respect to the dication, it should be noticed that the f^{γ} and B' terms are multiplied by z^2 where z is the charge number of the ion.[2] However, taking into account the distance between charges, it may be supposed that they behave independently[12,13] and D^{2+} should not be considered as an ion of charge +2, but as an ion with two independent charges +1. The electrical work involved in charging this ion is twice that of charging a monocharged ion, and as a consequence, a factor of 2 rather than 4 should multiply the f^{γ} and B' terms

$$\ln \gamma_{\mathrm{D}^{2+}} = 2(f^{\gamma} + I^2 B'_{\mathrm{NaCl}}) + 2IB_{\mathrm{DCl}} + 2I\theta_{\mathrm{DNa}} \tag{8}$$

or

$$\ln \gamma_{\mathrm{D}^{2+}} = 2f^{\gamma} + 2I(\beta^0_{\mathrm{DCl}} + \theta_{\mathrm{DNa}}) + \beta^1_{\mathrm{DCl}} g + \beta^1_{\mathrm{NaCl}}(2I\mathrm{e}^{-2\sqrt{I}} - g) \tag{9}$$

Substituting in eq 5 the activity coefficients given by the Pitzer model, the result for the dissociation constant is

$$\mathrm{p}K_1^* = \mathrm{p}K_1^{\mathrm{T}} + \frac{2I}{\ln 10}(\beta^0_{\mathrm{HCl}} + \theta_{\mathrm{NaH}} + \beta^0_{\mathrm{CCl}} + \theta_{\mathrm{NaC}} - \beta^0_{\mathrm{DCl}} - \theta_{\mathrm{DNa}}) + \frac{g}{\ln 10}(\beta^1_{\mathrm{HCl}} + \beta^1_{\mathrm{CCl}} - \beta^1_{\mathrm{DCl}}) \tag{10}$$

This equation is valid for KCl when Na is substituted by K. Proceeding in the same way for $CaCl_2$, the following equation is obtained

$$\mathrm{p}K_1^* = \mathrm{p}K_1^{\mathrm{T}} + \frac{4I}{3\ln 10}\left(\beta^0_{\mathrm{HCl}} + \frac{1}{2}\theta_{\mathrm{CaH}} + \beta^0_{\mathrm{CCl}} + \frac{1}{2}\theta_{\mathrm{CaC}} - \beta^0_{\mathrm{DCl}} - \frac{1}{2}\theta_{\mathrm{DCa}}\right) + \frac{2}{3}\frac{g}{\ln 10}(\beta^1_{\mathrm{HCl}} + \beta^1_{\mathrm{CCl}} - \beta^1_{\mathrm{DCl}}) \tag{11}$$

From these equations, it is obvious that the term $(\beta^1_{\mathrm{HCl}} + \beta^1_{\mathrm{CCl}} - \beta^1_{\mathrm{DCl}})$ appears in the equation of all electrolytes (with 2/3 factor in $CaCl_2$); $\mathrm{p}K_1^{\mathrm{T}}$ is the same in all equations; and the linear terms are relatively similar. $(\beta^0_{\mathrm{HCl}} + \beta^0_{\mathrm{CCl}} - \beta^0_{\mathrm{DCl}})$ appears always accompanied by different θ parameters. Taking into account that these θ parameters can be important to explain experimental data as seen in refs 14, 5, and 15, a fit has been performed using data for the three salts (Table 1) considering that the linear terms are different for all the electrolytes, but $\mathrm{p}K_1^{\mathrm{T}}$ and $(\beta^1_{\mathrm{HCl}} + \beta^1_{\mathrm{CCl}} - \beta^1_{\mathrm{DCl}})$ are the same. The method of *dummy* variables in multiple regression has been used to achieve this goal,[16] and some subroutines of Press et al.[17] were used to perform the linear fit. The result is given by the following equations

$$\mathrm{p}K_1^*(\mathrm{NaCl}) = 1.96 + \frac{2I}{\ln 10}0.13 + \frac{g}{\ln 10}1.46 \tag{12}$$

$$\mathrm{p}K_1^*(\mathrm{KCl}) = 1.96 + \frac{2I}{\ln 10}0.09 + \frac{g}{\ln 10}1.46 \tag{13}$$

$$\mathrm{p}K_1^*(\mathrm{CaCl_2}) = 1.96 + \frac{4I}{3\ln 10}0.23 + \frac{2}{3}\frac{g}{\ln 10}1.46 \tag{14}$$

From these data, the curves $\mathrm{p}K^*$ versus I are plotted in Figure 2, together with the experimental data from Table 1. The parameters in the parentheses in eqs 10 and 11 can be compared with eqs 12 to 14.

The same procedure can be applied to the second equilibrium constant. Therefore, taking logarithms of eq 2, one obtains

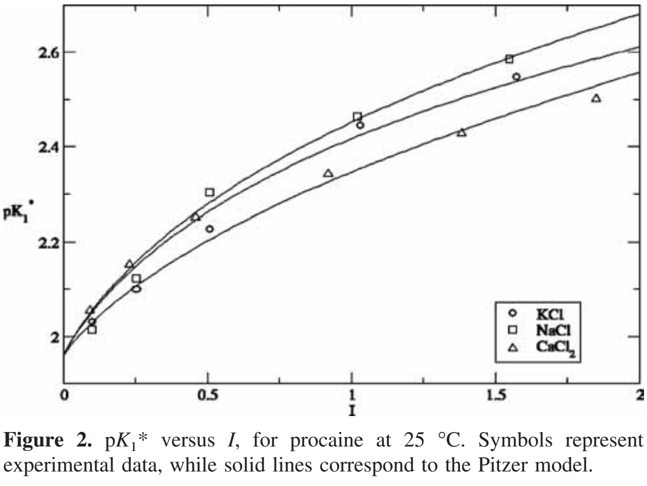

Figure 2. $\mathrm{p}K_1^*$ versus I, for procaine at 25 °C. Symbols represent experimental data, while solid lines correspond to the Pitzer model.

$$-\ln K_2^* = -\ln K_2^{\mathrm{T}} + \ln \gamma_{\mathrm{N}} + \ln \gamma_{\mathrm{H}^+} - \ln \gamma_{\mathrm{C}^+} \qquad (15)$$

The activity coefficients for the H^+ and C^+ ions, using the Pitzer model, are given by eq 7, and the activity coefficient of the neutral molecule is

$$\ln \gamma_{\mathrm{N}} = 2m(\lambda_{\mathrm{NNa}} + \lambda_{\mathrm{NCl}}) = 2I(\lambda_{\mathrm{NNa}} + \lambda_{\mathrm{NCl}}) = 2I\lambda_{\mathrm{NaCl}} \qquad (16)$$

The corresponding expression for KCl is obtained by changing Na for K, while in $CaCl_2$ medium

$$\ln \gamma_{\mathrm{N}} = \frac{2}{3}I(\lambda_{\mathrm{NCa}} + 2\lambda_{\mathrm{NCl}}) = \frac{2}{3}I\lambda_{\mathrm{CaCl}} \qquad (17)$$

Linear dependence of $\ln \gamma_{\mathrm{N}}$ on ionic strength was proposed by Setschenow, and this proportionality constant is usually known as the salting coefficient or Setschenow constant and is equivalent to λ in the Pitzer model.[18,2]

Substituting in eq 15 the activity coefficients, the result for the dissociation constant is

$$\mathrm{p}K_2^* = \mathrm{p}K_2^{\mathrm{T}} + \frac{2I}{\ln 10}(\lambda_{\mathrm{NaCl}} + \beta^0_{\mathrm{HCl}} + \theta_{\mathrm{NaH}} - \beta^0_{\mathrm{CCl}} - \theta_{\mathrm{NaC}}) + \frac{g}{\ln 10}(\beta^1_{\mathrm{HCl}} - \beta^1_{\mathrm{CCl}}) \qquad (18)$$

This equation is valid for KCl when Na is substituted by K. Proceeding in the same way for $CaCl_2$, the following equation is obtained

$$\mathrm{p}K_2^* = \mathrm{p}K_2^{\mathrm{T}} + \frac{4I}{3\ln 10}\left(\frac{1}{2}\lambda_{\mathrm{CaCl}} + \beta^0_{\mathrm{HCl}} + \frac{1}{2}\theta_{\mathrm{CaH}} - \beta^0_{\mathrm{CCl}} - \frac{1}{2}\theta_{\mathrm{CaC}}\right) + \frac{2g}{3\ln 10}(\beta^1_{\mathrm{HCl}} - \beta^1_{\mathrm{CCl}}) \qquad (19)$$

Comparing the equations for the three salts, one finds that, $\mathrm{p}K_2^{\mathrm{T}}$ and $(\beta^1_{\mathrm{HCl}} - \beta^1_{\mathrm{CCl}})$ are common to all of them, while the linear terms are different because of the λ and θ parameters. Using data for $\mathrm{p}K_2^{\mathrm{T}}$ versus I in Table 1, the method of *dummy* variables in multiple regression yields the following equations

$$\mathrm{p}K_1^*(\mathrm{NaCl}) = 8.90 + \frac{2I}{\ln 10}0.35 + \frac{g}{\ln 10}0.33 \qquad (20)$$

$$\mathrm{p}K_1^*(\mathrm{KCl}) = 8.90 + \frac{2I}{\ln 10}0.34 + \frac{g}{\ln 10}0.33 \qquad (21)$$

$$\mathrm{p}K_1^*(\mathrm{CaCl_2}) = 8.90 + \frac{4I}{3\ln 10}0.34 + \frac{2}{3}\frac{g}{\ln 10}0.33 \qquad (22)$$

The Pitzer functions for $\mathrm{p}K_2^*$ versus I and the experimental data are displayed in Figure 3. It can be appreciated that the linear terms including the salting coefficients, λ, are equal (within experimental error) for the three salts. The values obtained in eqs 12 to 14 and 20 to 22 correspond to the sums of parameters within parenthesis in eqs 10 and 11 and 18 and 19. Some of these terms are known from the literature[2]

$$\beta^0_{\mathrm{HCl}} = 0.1775, \quad \beta^1_{\mathrm{HCl}} = 0.2945, \quad \theta_{\mathrm{KH}} = 0.005, \quad \theta_{\mathrm{NaH}} = 0.036$$

Using these values and those in eqs 12 to 14 and 20 to 22, the parameters in Table 2 have been calculated.

The value obtained for $\mathrm{p}K_2^{\mathrm{T}} = 8.90 \pm 0.02$ shows resonable agreement with that found in the literature,[19] $\mathrm{p}K_2^{\mathrm{T}} = 8.96 \pm 0.02$, that was determined using data of $\mathrm{p}K_2^*$ versus I, in NaCl, with a different model to deal with activity coefficients of the ions (Debye−Hückel plus a linear term) while we are using Pitzer theory. Our data for procaine (or isocaine) in NaCl agree well with those obtained in the paper mentioned above;[19] for example, $\mathrm{p}K_2^*(I = 1) = 9.30$ on the molar scale is equal in both studies, and sometimes there is a small difference, $\mathrm{p}K_2^*$ $(I = 0.09) = 8.99$ in ref 19 while our value is $\mathrm{p}K_2^*$ $(I = 0.10) = 8.96$ on the molar scale. It is interesting to notice that although the potentiometric technique was used in both cases the formal potential, $E^{0\prime}$, has been estimated in very different ways. In ref 19, an internal calibration of the electrode was performed and $E^{0\prime}$ was simultaneously refined with the constants, while a separate experiment to calibrate the electrode has been carried out in this paper. A correct calibration is really important to obtain reliable equilibrium constants,[19,20,7] and as has been shown, different approaches can be used to achive this goal.

We have chosen the Pitzer model to describe the experimental behavior. A simpler model for activity coefficients could have been used to achive this goal, i.e., a model with a Debye−Hückel term plus a linear parameter (DH + L). The great advantages of the Pitzer model are, in the authors' opinion:

(1) Its versatility to explain the behavior of different systems, so that it has been shown to be quite reliable in accounting for the interactions of nonelectrolytes and electrolytes in aqueous solutions[21] but can be used when there is a strong association of ions, for example, an acid−base equilibrium, as has been shown in this paper.[2]

(2) No matter how complex the mixture of electrolytes may be, Pitzer equations can be applied to it. If the properties of a pure component are known, the properties of mixed electrolytes can be predicted with considerable accuracy.[2] This theory deals with adjustable parameters that are supposed to take into account the interaction among specific ions.[22,2] We consider it interesting to tabulate as many as possible of the Pitzer parameters that could be used in different systems.

(3) It can be applied to high ionic strength with the inclusion of the proper parameters, without disturbing the basic pattern.[2]

Taking all these points into account, the Pitzer model has been used for a long time. The objection that can be made to the Pitzer theory is that it is more complicated than a "DH + L" model, and it needs more paramaters; however, in fact, there

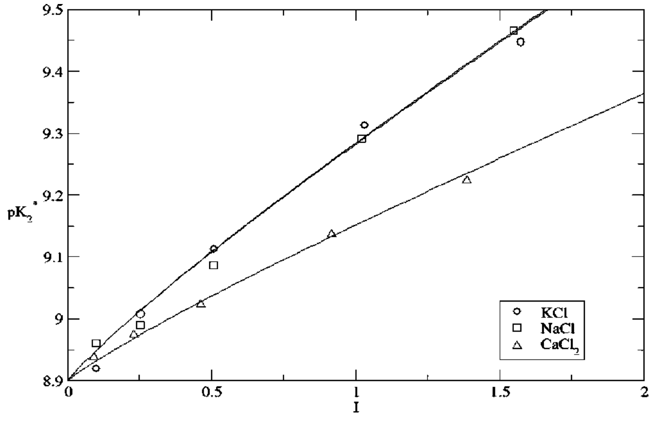

Figure 3. pK_2* versus I, for procaine at 25 °C. Symbols represent experimental data, while solid lines correspond to the Pitzer model.

Table 2. Pitzer Parameters, at 25 °C

$\mathrm{p}K_1^{\mathrm{T}} = 1.96 \pm 0.03$; $\mathrm{p}K_2^{\mathrm{T}} = 8.90 \pm 0.02$
$\beta^1_{\mathrm{DCl}} = -1.2 \pm 0.7$
$\beta^1_{\mathrm{DCl}} = -0.03 \pm 0.22$
$(\beta^0_{\mathrm{CCl}} + \theta_{\mathrm{NaC}} - \beta^0_{\mathrm{DCl}} - \theta_{\mathrm{DNa}}) = -0.08 \pm 0.09$
$(\beta^0_{\mathrm{CCl}} + \theta_{\mathrm{KC}} - \beta^0_{\mathrm{DCl}} - \theta_{\mathrm{DK}}) = -0.09 \pm 0.09$
$(\beta^0_{\mathrm{CCl}} + 0.5\theta_{\mathrm{CaC}} - \beta^0_{\mathrm{DCl}} - 0.5\theta_{\mathrm{DCa}} + 0.5\theta_{\mathrm{CaH}}) = 0.06 \pm 0.09$
$(\lambda_{\mathrm{NaCl}} - \beta^0_{\mathrm{CCl}} - \theta_{\mathrm{NaC}}) = 0.13 \pm 0.05$
$(\lambda_{\mathrm{KCl}} - \beta^0_{\mathrm{CCl}} - \theta_{\mathrm{KC}}) = 0.16 \pm 0.05$
$(0.5\lambda_{\mathrm{CaCl}} + 0.5\theta_{\mathrm{CaH}} - \beta^0_{\mathrm{CCl}} - 0.5\theta_{\mathrm{CaC}}) = 0.16 \pm 0.09$

is not much difference, in this case, when the equations are examined carefully.

pK_1^* vs I for the Pitzer model is

$$pK_1^* = pK_1^T + aI + bg(I)$$

For the DH + L model

$$pK_1^* = pK_1^T + dI$$

where a, b, and d are constants. Linear terms depend on the inert electrolyte, while pK_1^T and b are always the same. So, using the method of dummy variables, we estimate five parameters (pK_1^T, a_{NaCl}, a_{KCl}, a_{CaCl}, b). In the DH + L model, four parameters are estimated (pK_1^T, d_{NaCl}, d_{KCl}, d_{CaCl}), just one less parameter, which is not a great simplification.

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Received for review January 25, 2008. Accepted April 19, 2008. Financial support from the Dirección General de Investigación (Ministerio de Educación y Ciencia) of Spain and FEDER (Project CTQ2005-07428/BQU) and from Xunta de Galicia (PGIDIT06PXIC103152PN) is gratefully acknowledged.

JE800061H