Complexation Constants of Procaine with β-Cyclodextrin in NaCl Media

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The complexation constants of neutral and protonated procaine (also called novocaine) with β-cyclodextrin have been obtained as a function of sodium chloride concentration, at 25 °C, using the potentiometric technique with a glass electrode. It was found that the formation of the complex with protonated procaine is not altered by the presence of the salt and the logarithm of the formation constant of the neutral complex increases slowly with ionic strength, varing linearly with salt concentration.

Introduction

Cyclodextrins are very important molecules in supramolecular chemistry.[1,2] Their ability to form inclusion complexes with a great variety of hosts has found multiple applications. One is to act as drug-delivery systems. This ability is due to their conical cylinder shape with a cavity capable of accommodating a guest molecule. In this sense, it is considered interesting to study the interaction of procaine (4-aminobenzoic acid diethylaminoethyl ester), a well-known local anesthetic, with cyclodextrins. Two amino groups are present in the procaine molecule, a primary amine and a tertiary amine. Therefore, depending on the acidity of the medium, procaine can be exist as a neutral molecule (No), a monocation (NoH^+), or a dication (NoH_2^+). The formation of inclusion complexes of these species with cyclodextrins has been studied previously in this laboratory.[3,4] It was concluded that the stability constants are higher for β-cyclodextrin (β-CD) than for α-cyclodextrin and that the dication does not form complexes with neutral β-CD, whereas both the monocation and the neutral molecule of procaine form 1:1 complexes. Our studies have indicated that procaine penetrates β-cyclodextrin with the H_2N group end first, with the aromatic ring of the drug and the ester group inside the cavity. Different techniques have been used to obtain this information: fluorescence and UV−vis spectroscopy, electrical conductivity, and even kinetic experiments. In the present article, our studies are completed with a different technique, widely used in the determination of equilibrium constants, namely, potentiometry with a glass electrode. A matter not addressed in the earlier works,[3,4] that is, the variation of complexation constants with ionic strength *I*, is studied here. Potentiometry has been extensively used in this laboratory to obtain acid−base equilibrium constants of different systems in various saline media.[5−7] In fact, we previously determined the acid−base equilibrium constants for the two amino groups of the procaine molecule at 25 °C in NaCl solutions.[8] These data are necessary in order to obtain the complexation constants of No and NoH^+ with β-CD as a function of sodium chloride concentration, the aim of this work. This salt was chosen as an inert electrolyte because no complexation of Cl^- with β-CD has been observed.[9]

The complexation equilibrium of the procaine cation can be represented by

$$NoH^+ + \beta\text{-CD} = NoH{\cdot}CD^+ \quad (1)$$

where the constant is given by

$$K_2^T = \frac{[NoH{\cdot}CD^+]}{[NoH^+][\beta\text{-CD}]}\frac{\gamma_{NoH\cdot CD^+}}{\gamma_{NoH^+}\gamma_{\beta\text{-CD}}} = K_2^c\frac{\gamma_{NoH\cdot CD^+}}{\gamma_{NoH^+}\gamma_{\beta\text{-CD}}} \quad (2)$$

or, taking logarithms,

$$\log K_2^c = \log K_2^T + \log \gamma_{NoH^+} + \log \gamma_{\beta\text{-CD}} - \log \gamma_{NoH\cdot CD^+} \quad (3)$$

where K^T represents the thermodynamic equilibrium constant, K^c represents the stoichiometric constant, and γ_i is the activity coefficient of the species indicated by the subscript. The constant K_2^c is used in accordance with ref 4; K_1^c was used to denote the hypothetical complex between β-CD and the procaine dication (NoH_2^+). It was also concluded that the fully protonated procaine molecules do not form inclusion complexes.

On the other hand, the complexation equilibrium of neutral procaine can be represented by

$$No + \beta\text{-CD} = No{\cdot}CD \quad (4)$$

where the constant is given by

$$K_3^T = \frac{[No{\cdot}CD]}{[No][\beta\text{-CD}]}\frac{\gamma_{No\cdot CD}}{\gamma_{No}\gamma_{\beta\text{-CD}}} = K_3^c\frac{\gamma_{No\cdot CD}}{\gamma_{No}\gamma_{\beta\text{-CD}}} \quad (5)$$

or, taking logarithms,

$$\log K_3^c = \log K_3^T + \log \gamma_{No} + \log \gamma_{\beta\text{-CD}} - \log \gamma_{No\cdot CD} \quad (6)$$

The activity coefficients can be expressed as a function of the concentration of the salt used to keep ionic strength constant by means of different approaches. The Pitzer model[10,5−8] is often used to describe the experimental behavior, although a simpler model for activity coefficients, specifically, a model with a Debye−Hückel term plus a linear parameter (DH + L), will suffice for the interpretation of the results found in this system, as explained in the discussion. Several models for activity coefficients can be found in refs 10 to 12.

Experimental Section

A 40 mL aqueous aliquot containing procaine hydrochloride, NoHCl (0.0100 mol·L^{-1}) (Aldrich), and β-CD (0.0050

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Table 1. Logarithms of the Complexation Constants of Protonated Procaine with β-Cyclodextrin versus Salt Concentration or Ionic Strength in NaCl at 25 °C[a,b]

c_{NaCl}	log K_2^{c*}
0.10	2.28 ± 0.01
0.25	2.32 ± 0.01
0.50	2.29 ± 0.01
0.75	2.26 ± 0.01
1.00	2.29 ± 0.01

[a] See eqs 1 and 2. [b] Molarity scale used.

Table 2. Logarithms of the Complexation Constants of Neutral Procaine with β-Cyclodextrin versus Salt Concentration or Ionic Strength in NaCl at 25 °C[a,b]

c_{NaCl}	log K_3^{c*}
0.10	3.062 ± 0.008
0.25	3.070 ± 0.009
0.50	3.139 ± 0.005
0.75	3.120 ± 0.006
1.00	3.187 ± 0.007

[a] See eqs 4 and 5. [b] Molarity scale used.

mol·L^{-1}) (Fluka) was titrated with a standard solution of hydrochloric acid (Merck p.a.) to determine log K_2^c and with a standard solution of sodium hydroxide (Merck p.a.) in order to determine log K_3^c. The necessary amount of NaCl (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 [(25.0 ± 0.1) °C] by circulating water from a thermostat. Purified nitrogen was bubbled through the solutions in order to ensure thorough homogenization and CO_2 removal. A Crison microBu 2030 automatic buret furnished with a 2.5 mL syringe for dispensing the titrant was used. The buret was controlled with 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).

Acid−base equilibrium constants of procaine in NaCl at 25 °C were determined previously[8] in the absence of β-CD. When the latter species is present, it forms complexes with procaine (No and/or NoH$^+$) disturbing the acid−base equilibria. If NoHCl + β-CD is titrated with HCl, the complex NoH·CD$^+$ is formed, and its stability constant, log K_2^c, can be obtained; when it is titrated with NaOH, NoH·CD$^+$ and No·CD are formed, and log K_3^c can be determined from this titration (using the log K_2^c value obtained previously). Equilibrium constants were calculated from the potentiometric titration data by means of the Hyperquad[13] program. Titrations in acid and basic media were introduced simultaneously into the program to refine both constants. The electrode response at constant ionic strength is given by $E = E^{0'} + s \log [H^+]$, where E is the emf,[14] and the electrode parameters, the formal potential, $E^{0'}$, and the slope, s, are required by the program to determine the constants. A separate experiment was carried out to obtain the electrode parameters: emf was measured in solutions of known proton concentration, at the desired ionic strength, and $E^{0'}$ was obtained from a linear regression; see ref 14.

Results and Discussion

Data for log K^c are listed in Tables 1 and 2 on the molarity scale. As can be appreciated from Tables 1 and 2 and Figures 1 and 2, log K_2^c remains constant, within the experimental error and within the ionic strength range used in this study, whereas log K_3^c increases slowly with the ionic strength, a variation of 0.13 pK units from $I = c_{NaCl} = (0.1 \text{ to } 1)$ mol·L^{-1}; in contrast,

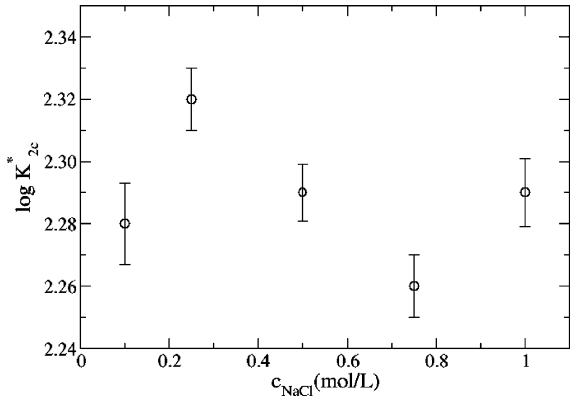

Figure 1. log K_2^{c*} versus I at 25 °C. Symbols represent experimental data.

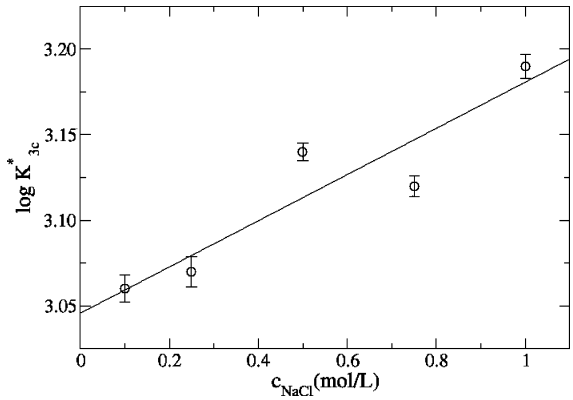

Figure 2. log K_3^{c*} versus I at 25 °C. Symbols represent experimental data, and solid lines correspond to the linear fit.

for example, the logarithms of the acidity constants of NoH_2^+ and NoH^+ vary by 0.45 and 0.33 log units, respectively, over the same range, as can be seen in Table 1 of ref 8.

The constants determined in this work are in good agreement with those found by means of different techniques in refs 3 and 4 (fluorescence measurements, reaction kinetics, conductivity measurements), where log K_2^c ranged from 2.3 to 2.4, whereas here, its value is 2.3 (this is the average of the values presented in Table 1), and log K_3^c found previously was 3.19, and here, it varies from 3.06 to 3.19. The ionic strength used in the previous studies[3,4] was less than 0.1 mol·L^{-1}.

In view of eq 3, log K_2^c is a function of the activity coefficient of the neutral species, log $\gamma_{\beta\text{-CD}}$, and of the difference (log γ_{NoH^+} − log $\gamma_{NoH\cdot CD^+}$). The activity coefficient for a neutral molecule, N, depends linearly on the ionic strength or salt concentration[12,15−17]

$$\ln \gamma_N = K_{N,salt} c_{salt} \quad (7)$$

This is the well-known Setschenow equation, valid for low nonelectrolyte concentrations. Of course, K is a constant that depends on the neutral molecule and on the salt, and c represents the concentration of salt, which can be expressed in molarity or molality.[16] The simplest way to deal with the activity coefficient of an ion at moderate salt concentration is to add a linear term with respect to the ionic strength to the Debye−Hückel equation; more sophisticated models are useful to treat more complex mixtures and/or solutions with high concentration of salt, i.e. the Pitzer model.[10,12] In an expression such as log γ_{NoH^+} − log $\gamma_{NoH\cdot CD^+}$ where the charges of the ions are equal, the Debye−Hückel terms cancel out, leaving just linear parameters, whose sum is ap-

proximately zero if we consider that log K_2^c does not vary with c. Taking into account that there is no variation with salt concentration, the Pitzer model was not applied to this system; in any case, the equilibrium considered in eq 1 is similar to that shown in eq 2 of ref 8 (neutral species + charged species = charged species), and the Pitzer equation for this system would be similar to eq 18 of ref 8 changing the subscripts.

On the other hand, in the complexation equilibrium of neutral procaine, only neutral species are present. Using eq 7, one finds that the dependence of log K_3^c on c_{NaCl} or I ($I = c$) is linear

$$\log K_3^c = \log K_3^T + (K_{No} + K_{\beta\text{-CD}} - K_{No\cdot CD})c_{NaCl} \quad (8)$$

When the data of Table 2 are fitted to eq 8, the result is

$$\log K_3^{c*} = 3.05\ (\pm\ 0.02) + 0.13\ (\pm\ 0.03)c_{NaCl} \quad (9)$$

where the standard errors are in parentheses and the molarity scale is used. This line and experimental data are represented in Figure 2. Of course, the Pitzer equations can be used to fit the data; the only difference would be that, in the Pitzer model, the molality scale is used and the salting coefficients are slightly different depending on whether they are expressed in molality or molarity.[16]

Therefore, as can be seen from Tables 1 and 2 and Figures 1 and 2, the complexation equilibrium of the procaine cation with β-CD does not vary with NaCl up to a concentration of 1 mol/L, whereas the equilibrium constant of the complexation of neutral procaine with β-CD varies slowly with salt concentration. The interest of this study is double: on one side, procaine is a local anesthetic and it can be used in media where sodium chloride is present, and on the other hand, potentiometry is widely employed to determine equilibrium constants. In the potentiometric technique, some amount of salt has to be added to keep the ionic strength constant, and its influence should be considered. In this case, the presence of salt does not change the complexation constants in an important way; in fact, the effect of the salt is much greater in the acid−base constants of procaine determined in ref 8 than here. Of course, a completely different situation appears if any of the ions of the electrolyte is capable of forming complexes with β-CD, in which case, the salt can exert a great influence. It is well-known that some anions tend to form complexes with cyclodextrins as can be seen in refs 2 and 9.

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