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Surface Tension Measurements on the Penicillin Sodium Nafcillin

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The surface behavior and the critical micelle concentrations of the penicillin sodium nafcillin monohydrate in aqueous electrolyte solution (0.00–0.40 mol kg⁻¹ NaCl) at 303.15 K were determined by surface tension measurements. From the magnitude of the surface properties and using the values of the standard Gibbs energy of micellization of this penicillin, the standard Gibbs energies of adsorption of this drug were calculated at each electrolyte concentration.

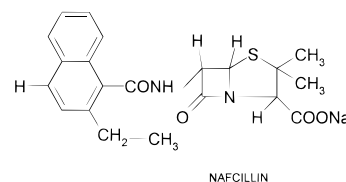
Introduction

A large number of drugs have been found to exhibit typical amphiphilic behavior in aqueous solution in that they accumulate at interfaces, depressing the surface tension, and form aggregates in solution at sufficiently high concentrations.¹ Of the drugs studied, much attention has been paid over the years to the colloidal behavior exhibited by penicillins. McBain and co-workers² and Few and Schulman³ demonstrated the colloidal nature of penicillin G. Later studies reported the micellar behavior of several synthetic penicillins by light-scattering measurements.⁴ The self-association of penicillins G and V was examined by gel filtration chromatography,⁵ and NMR techniques have been used in a study of penicillin G⁶ and cloxacillin.⁷ In recent papers we have reported the aggregation properties and intermolecular interactions of cloxacillin, dicloxacillin, and flucloxacillin penicillins,⁸ the thermodynamic and surface properties of these drugs,^{9,10} and the effect of the nature of the hydrophobe on the ideality of mixing of binary mixtures of these compounds.¹¹

However, the presence of highly surface active impurities and the difficulties experienced in the purification processes of these antibiotics in early works did not allow the correct determination of the surface properties of these drugs, leading to conflicting opinions about the surface activity of these antibiotics.^{12,13}

In this study we report the critical micelle concentrations (cmc's) and the surface properties of sodium nafcillin monohydrate (see Chart 1) in aqueous electrolyte solution (concentration range 0.00–0.40 mol kg⁻¹) at 303.15 K. We have previously shown¹⁴ that this drug forms small micelles with aggregation numbers ranging from only 3 in water to 11 in 0.4 mol kg⁻¹ NaCl. From the surface tension data, we have calculated the excess surface concentration, Γ_2 , and the minimum area per molecule, A . Using the standard Gibbs energy of micellization previously calculated⁹ and the surface tension data, the standard Gibbs energy of adsorption ($\Delta G_{\text{ads}}^\circ$) of this antibiotic has been calculated at each electrolyte concentration.

Chart 1



Materials and Methods

Sodium nafcillin monohydrate [6-(2-ethoxy-1-naphthamido)penicillin] was obtained from Sigma Chemical Co. The drug conformed to the purity requirements of the British Pharmacopoeia and as such contained $\geq 98.5\%$ of the specified compound. Water was doubly distilled, deionized, and degassed before use. Sodium chloride was of Analar grade.

Surface tensions were measured by the Wilhelmy plate method using a Kruss K-12 surface tension apparatus, equipped with a processor to acquire the data automatically. The reproducibility of the surface tension was ± 0.01 mN m⁻¹. The equipment was connected to a circulating water bath to keep the temperature constant at (303.15 \pm 0.01) K.

Penicillin solutions of known molality were progressively diluted with water or electrolyte solution using an automatic pump (Dosimat 665 Mettrom). The usual precautions were taken to ensure cleanliness.

Results and Discussion

Tables 1 and 2 show the experimental surface tension data for sodium nafcillin monohydrate in aqueous electrolyte solution (concentration range 0.00–0.40 mol kg⁻¹) at 303.15 K. To obtain the critical micelle concentrations, the surface pressure, π ($\pi = \gamma_0 - \gamma$, where γ_0 is the surface tension of the solvent and γ is that of the solution), was plotted against logarithm of molality, $\log m$, for this antibiotic at each salt concentration (see Figure 1). For clarity, the data are displaced vertically by (8, 6, 4, and 2) mN m⁻¹ for (0.4, 0.2, 0.1, and 0.05) mol kg⁻¹ NaCl, respectively. The critical micelle concentrations were calculated as the intersection points of the linear fits corre-

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Table 1. Surface Tension, γ , As a Function of Molality, m , of Sodium Nafcillin Monohydrate in Aqueous Electrolyte Solution of (0.00, 0.05, and 0.10) mol kg⁻¹ NaCl at 303.15 K

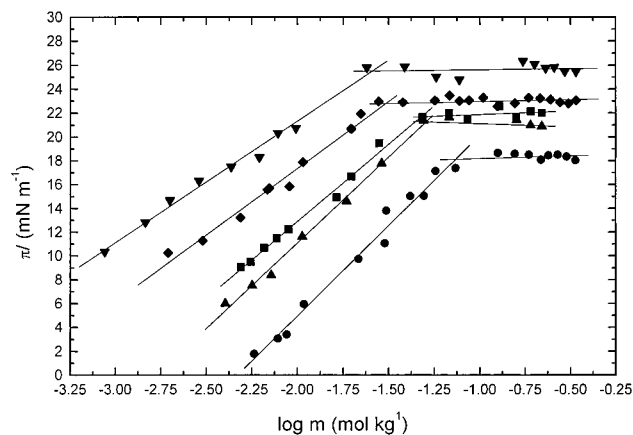
0.00 mol kg ⁻¹ NaCl		0.05 mol kg ⁻¹ NaCl		0.10 mol kg ⁻¹ NaCl	
$m/\text{mol kg}^{-1}$	$\gamma/\text{mN m}^{-1}$	$m/\text{mol kg}^{-1}$	$\gamma/\text{mN m}^{-1}$	$m/\text{mol kg}^{-1}$	$\gamma/\text{mN m}^{-1}$
0.336	53.12	0.219	52.30	0.220	53.18
0.300	52.82	0.190	52.20	0.191	53.04
0.268	52.67	0.159	51.78	0.159	53.52
0.238	52.71	0.068	51.25	0.128	52.63
0.217	53.09	0.049	51.79	0.085	53.74
0.186	52.67	0.029	55.39	0.068	53.20
0.156	52.60	0.019	58.58	0.048	53.53
0.126	52.40	0.011	61.56	0.028	55.71
0.073	53.79	0.007	64.79	0.020	58.50
0.057	54.03	0.006	65.66	0.016	60.25
0.049	56.12	0.004	67.18	0.009	62.94
0.042	56.13			0.008	63.69
0.031	57.36			0.007	64.50
0.030	60.11			0.006	65.68
0.022	61.43			0.005	66.12
0.011	65.22				
0.009	67.77				
0.008	68.10				
0.006	69.38				

Table 2. Surface Tension, γ , As a Function of Molality, m , of Sodium Nafcillin Monohydrate in Aqueous Electrolyte Solution of 0.20 and 0.40 mol kg⁻¹ NaCl at 303.15 K

0.20 mol kg ⁻¹ NaCl		0.40 mol kg ⁻¹ NaCl	
$m/\text{mol kg}^{-1}$	$\gamma/\text{mN m}^{-1}$	$m/\text{mol kg}^{-1}$	$\gamma/\text{mN m}^{-1}$
0.339	54.10	0.338	53.72
0.307	54.36	0.293	53.71
0.277	54.29	0.256	53.34
0.244	54.03	0.230	53.42
0.215	53.92	0.200	53.10
0.186	53.91	0.173	52.84
0.156	54.36	0.077	54.40
0.125	54.61	0.058	54.15
0.104	53.87	0.039	53.29
0.087	54.11	0.024	53.38
0.077	54.18	0.010	58.43
0.068	53.72	0.008	58.86
0.057	54.13	0.006	60.90
0.038	54.27	0.004	61.68
0.029	54.19	0.003	62.85
0.022	55.22	0.002	64.49
0.020	56.5	0.001	66.35
0.011	59.29	0.0009	68.82
0.009	61.32		
0.008	61.46		
0.007	61.61		
0.005	63.93		
0.003	65.89		
0.002	66.91		

sponding at each branch of the π -log m curves. The values of the critical micelle concentrations so obtained (see Table 3) are slightly lower than those previously determined by light-scattering measurements.¹⁴ A reasonable explanation of the discrepancies between the values from these two experimental methods might be the differently weighted averages from these techniques that become significant for the weakly associating polydisperse systems under investigation. As expected, as the electrolyte concentration is increased, the cmc values are decreased due to the shielding of the electrostatic repulsion between the polar head groups, allowing the monomers to be more closely packed in the micelles and, thus, decreasing the cmc values.

The Gibbs surface excess concentrations, Γ_2 , of the monomers at the air/water interface were evaluated,

**Figure 1.** Surface pressure, π , versus logarithm of molality for sodium nafcillin monohydrate in aqueous electrolyte solution of (●) 0.00, (▲) 0.05, (■) 0.10, (◆) 0.20, and (▼) 0.40 mol kg⁻¹ at 303.15 K. For clarity, the data are displaced vertically by (8, 6, 4, and 2) mN m⁻¹ for (0.4, 0.2, 0.1, and 0.05) mol kg⁻¹ NaCl, respectively.**Table 3. Critical Micelle Concentration, cmc, Maximum Surface Excess Concentration, Γ_2 , Minimum Area per Molecule, A , and Gibbs Free Energy of Adsorption, ΔG_{ads} , of Sodium Nafcillin Monohydrate in Aqueous Electrolyte Solution (Concentration Range of NaCl 0.00–0.40 mol kg⁻¹) at 303.15 K**

	[NaCl]				
	0.00	0.05	0.10	0.20	0.40
cmc ^a /(mol kg ⁻¹)	0.076	0.051	0.048	0.031	0.027
Γ_2^b /(mol m ⁻²)	1.32	1.67	1.70	1.71	1.65
A^b /(nm ²)	1.26	1.00	0.98	0.98	1.00
ΔG_{ads} /(kJ mol ⁻¹)	-36.7	-36.8	-37.0	-38.2	-39.7

^a Estimated uncertainties $\pm 10\%$. ^b Estimated uncertainties $\pm 15\%$.

assuming ideality, by application of the Gibbs equation in the form

$$\Gamma_2 = -\frac{1}{2.3RTx}(\text{d}\gamma/\text{d log } m) \quad (1)$$

where Γ_2 is the Gibbs surface excess concentration, R is the gas constant, and T is the temperature in kelvins. The variable x is introduced to allow for the simultaneous adsorption of cations and anions and has the expression¹

$$x = 1 + \frac{m}{(m + m_s)} \quad (2)$$

where m_s is the concentration of added electrolyte. Thus, x has a value of 2 in water and approaches 1 in the presence of excess inert electrolyte. The values of Γ_2 so obtained are shown in Table 3. The area per molecule, A , of the amphiphilic drug ions at the air/water interface was calculated from eq 1 using

$$A = 1/N_A\Gamma_2 \quad (3)$$

where N_A is Avogadro's constant. The data (see Table 3) show the expected decrease with an increase of the electrolyte concentration due to a progressive charge shielding and a closer packing of the drug ions in the surface in the presence of swamping electrolyte. The values of A in the presence of swamping amounts of electrolyte are similar to those reported for other drug molecules; the phenothiazine drugs, for example, have areas per molecule of between (0.66 and 0.77 nm²).¹⁵

The standard Gibbs energies of adsorption, $\Delta G_{\text{ads}}^{\circ}$, in water for these drugs were calculated from the standard Gibbs energies of micellization at different electrolyte concentrations previously obtained¹⁰ and the surface tension data through the equation¹⁶

$$\Delta G_{\text{ads}}^{\circ} = \Delta G_{\text{m}}^{\circ} - \frac{\pi_{\text{cmc}}}{\Gamma_2} \quad (4)$$

where π_{cmc} is the surface pressure at the critical micelle concentration. The values are shown in Table 3. All the values are negative, indicating that the hydrophobicity of the molecules primarily leads them toward the air–water interface, and then the formation of micelles occurs above the critical micelle concentration. Moreover, $\Delta G_{\text{ads}}^{\circ}$ values are larger as the electrolyte concentration increases. Values in water can be compared with those of other penicillins:⁹ cloxacilin (−42.2 kJ/mol), dicloxacilin (−43.0 kJ/mol), and flucloxacilin (−38.8 kJ/mol).

As mentioned above, the electrolyte decreases the electrostatic repulsion and allows the monomers to pack more closely at the air/water monolayer, favoring the increase of the number of molecules on the solution surface and, thus, increasing the magnitude of $\Delta G_{\text{ads}}^{\circ}$. This can also be confirmed from Figure 1: a comparison of the initial pressure changes indicates that nafcillin is more surface active at high electrolyte concentrations (0.4 mol kg^{−1}) and, therefore, the “escaping tendency” from the aqueous environment to the air–water monolayer is more marked due to the greater hydrophobicity of the molecule with the presence of electrolyte.

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Received for review December 14, 1999. Accepted February 23, 2000. The authors thank the Xunta de Galicia for financial support. P.T. also thanks Fundación Caixa Galicia for his grant.

JE990323E