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Permitivity of penicillin V: a thermodynamic study

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Abstract

A method of determining critical concentrations for aggregation in self-associating systems of low aggregation number by dielectric constant measurement has been applied in a study of the self-association of penicillin V as a function of temperature. Dielectric properties of penicillin V are more sensitive to structural modifications in bulk amphiphilic solutions than the electrical conductivity and provide a simpler method for the determination of critical concentrations of such systems without the necessity of the complex numerical data analysis required in the determination of inflection points in electrical conductivity data, which show a more gradual change throughout the measured concentration.

Thermodynamic parameters of micelle formation were derived from the variation of the first critical concentration using a modified form of the mass action model applicable to systems of low aggregation number. The good agreement between the experimental and theoretical standard enthalpies of aggregation, ΔH°_{m}, supports the validity of the proposed model to predict thermodynamic parameters of aggregation.

Keywords: Penicillin V; Dielectric permitivity; Critical micelle concentration; Standard enthalpy of aggregation

1. Introduction

Interest in the colloidal properties of penicillins dates from the late 1940s and early 1950s and includes studies by McBain et al. [1], Hauser and Marlow [2], and Few and Schulman [3]. These investigations were strongly affected by surface-active impurities that complicate the characterization of the self-association process. Recently, we have studied in detail the self-assembly of amphiphilic anionic penicillins [4–7] and have shown that in common with some of the phenothiazine drugs [8–12], some penicillins exhibit a multiple association pattern [4,5] with more than one inflection in the concentration dependence of their solution properties. These inflections points were indentified as the critical micelle concentrations (CMC) of these kind of compounds. However, as CMC's are usually determined on the basis of a change in the physicochemical properties of the amphiphilic drug solution due to cooperative formation of aggregates in the bulk solution, and such changes in properties do not occur at a single concentration but rather over a range of concentration, a spread of critical micelle concentration values is produced as a consequence not only of inherent differences on the solution properties measured by each of the experimental techniques but also of the difficulty in locating inflection points in experimental

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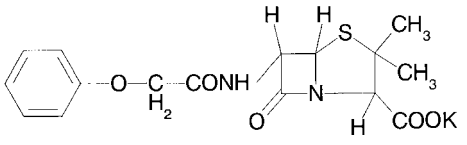

Scheme 1.

data in systems of low aggregation number as those of this study.

In an earlier paper [13] we demonstrated the potential of dielectric constant measurement as a means of detecting critical concentrations of such systems avoiding the use of complex mathematical algorithms for their determination. We now report the use of this technique in the determination of the thermodynamics of the self-association of the amphiphilic drug penicillin V (Scheme 1) from measurements over a temperature range of 15–40 °C and concentrations between 0 and 0.20 mol kg^{-1}. Precise determination of the CMC at different temperatures allows the calculation of the thermodynamic functions of aggregation using the mass action model of micelle formation [14]. An important contribution to the free energy of formation of aggregates is the enthalpy change involved in the process. This is linked directly to intermolecular interactions and is most directly influenced by changes in the nature of the amphiphile. In the present work, we have derived the enthalpy change on association for penicillin V from the variation of first critical concentration with temperature and compared this value with an experimental one obtained by microcalorimetry at 25 °C.

2. Experimental

2.1. Materials

Penicillin V (potassium salt) of at least 98.5% purity was obtained from Sigma and was used as received. Solutions were made in double-distilled, deionised and degassed water before use.

2.2. Apparatus and procedure

Conductivities and dielectric constants of the drug solutions were measured with a HP 4285A Precision LCR meter (±0.1% accuracy) equipped with a HP E5050A colloid dielectric probe operating in a frequency range between 200 kHz and 20 MHz. The probe is especially designed to measure inductances and to avoid the polarization that occurs in the plain condenser probe. The measurement cell design was conceived to obtain the highest degree of accuracy. It consists of a cylinder of 8 cm diameter and 5 cm height with the probe entrance at a side. This geometry ensures the probe head to be always surrounded by at least 2 cm of solution during the measurement process, which avoids possible interferences of the cell walls. The cell was immersed in a Techne, model RB-12A thermostated bath equipped with a Tempunit TU-16A thermostat. Temperature control was achieved using an Anton Paar DT 100-30 thermometer, maintaining the temperature constant to within ±0.01 °C. A Variomag 20P shaker was used to homogenize the solution.

3. Results and discussion

3.1. Conductivity measurements

Fig. 1 shows a representative plot of the concentration of the measured real part of the electrical conductivity, κ, of aqueous solutions of penicillin V at 25 °C (similar plots, not shown, were obtained at selected temperatures over the range 15–40 °C) and concentrations up to 0.20 mol kg^{-1}. The curve shows a gradual change over the concentration range examined and no clear inflection points can be detected by visible inspection. So, determination of critical concentration value for this drug from conductivity data have involved the numerical analysis of data using an algorithm based on the Runge–Kutta numerical integration method and the Levenberg–Marquardt least-squares fitting algorithm to identify inflections in the conductivity/concentration plots. The CMC values, expressed as mole fractions, so obtained at the defined temperature range are plotted in Fig. 2.

3.2. Dielectric constant measurements

The concentration dependence of the real part of the dielectric constant, ε', of aqueous solution of penicillin V over a wide concentration range at 25 °C are plotted in Fig. 3 as a function of concentration. The dielectric property of the amphiphile exhibits an abrupt transition in the neighbourhood of the critical concentration. Similar plots were obtained for the other selected

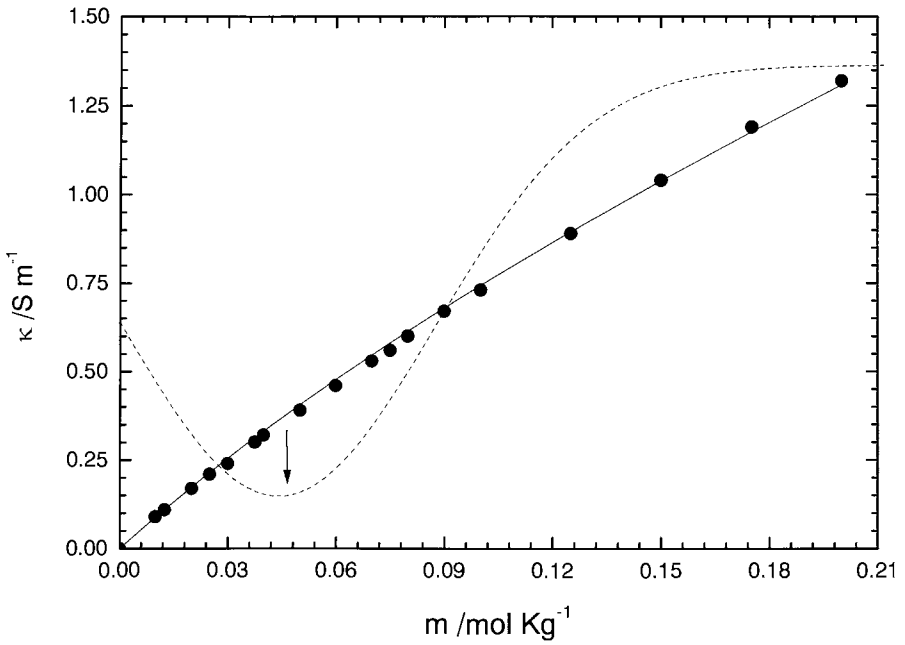

Fig. 1. Plot of the real part of the electrical conductivity (κ') of an aqueous solution of penicillin V against concentration at 25 °C. The dashed line corresponds to the Gaussian fit of the second derivative. Arrow denotes the CMC.

temperatures. The concentration-dependence of ε' at concentrations below the critical concentration is similar to that observed for solutions of the cationic surfactant *n*-dodecyl trimethylammonium bromide and also the phenothiazine drug chlorpromazine [13] and may be a consequence of premicellar association. The values of the critical concentrations at selected temperatures, (Fig. 2), were obtained as the intersections of polynomials above and below each transition as shown in Fig. 3. Good agreement was noted between critical concentrations measured in this way (0.040 mol kg^{-1}) and those derived previously at 25 °C by numerical analysis of conductivity data (0.045 mol kg^{-1}) and by light scattering techniques (0.040 mol kg^{-1}) [5] at the selected concentration range. In contrast to electrical conductivity, the dielectric constant shows a greater sensitivity to concentration changes [13], and should, therefore, provide a more sensitive technique of examining structural changes of polydisperse media.

3.3. Thermodynamics of micellization

Assuming that the mass action equation is applicable to this system, the equilibrium between the anionic monomers and aggregates may be represented by:

$$nS^- + (n-p)G^+ \leftrightarrow M^{p-} \tag{1}$$

where S^- represents the drug ion, G^+ the counterion and M^{p-} the aggregate formed by *n* monomers with net charge *p*. The equilibrium constant K_m for the formation of the micelles is:

$$K_m = \frac{[M^{p-}]}{[S^-]^n[G^+]^{n-p}} \tag{2}$$

where $[M^{p-}]$, $[S^-]$ and $[G^+]$ are the molar concentration of micelles, monomers and counterions, respectively. The expression used for the calculation of K_m was [15]

$$\frac{1}{K_m} = n\frac{(2n-p)(4n-2p-1)}{2n-p-2} \times \left[\frac{(2n-p)(4n-2p-1)}{(2n-p-1)(4n-2p+2)}x_{CMC}\right]^{2n-p-1} \tag{3}$$

where x_{CMC} is the CMC expressed as a mole fraction. Values of *n* and *p* were derived from light scattering measurements [5].

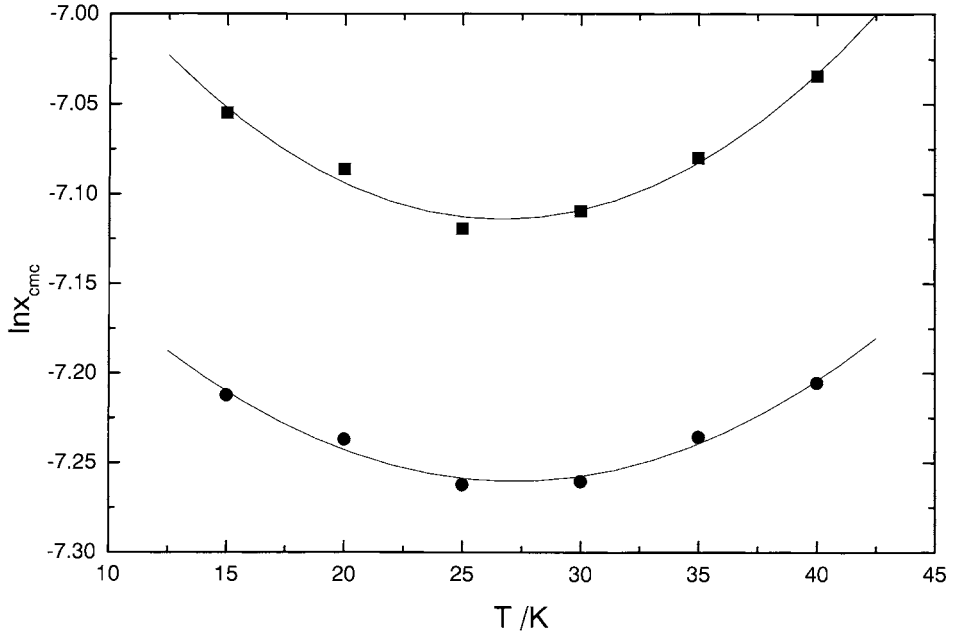

Fig. 2. Temperature dependence of critical micelle concentration as mole fraction, $\ln x_{CMC}$, of penicillin V obtained by (●) conductivity and (■) permitivity measurements in water.

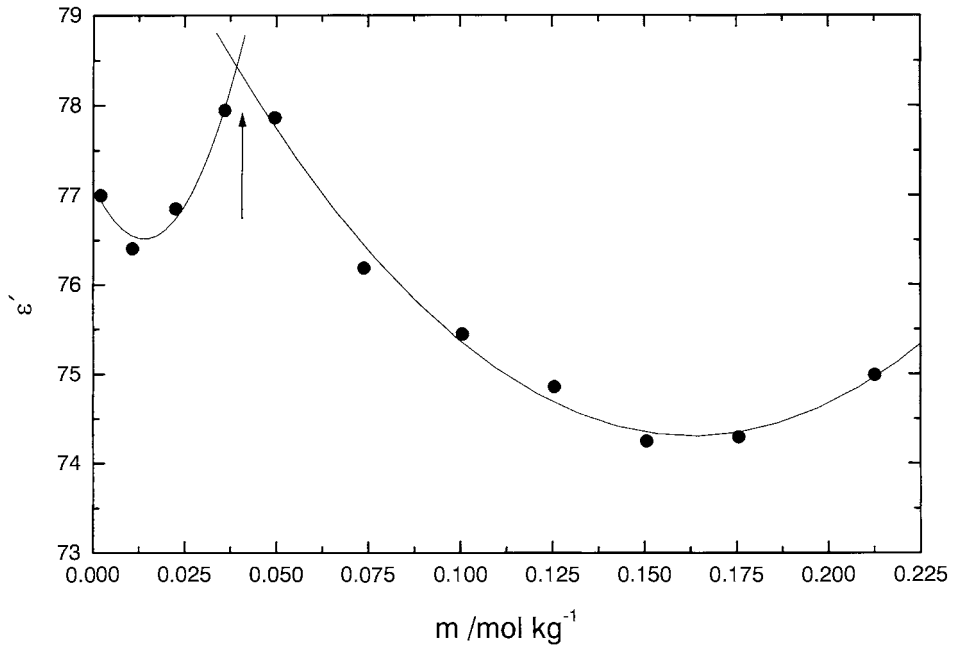

Fig. 3. Plot of the permittivity (ε') of an aqueous solution of penicillin V against concentration at 25 °C. Solid line represents the quadratic fitting curves. The arrow denotes CMC.

Table 1
Calculated and experimental standard enthalpy changes, ΔH°_{m}, for penicillin V, cloxacillin, dicloxacillin and nafcillin at 25 °C

Compound	ΔH°_{m} (kJ mol^{-1}, calculated)	ΔH°_{m} (kJ mol^{-1}, experimental)
Penicillin V	0.70	0.76
Cloxacillin	−0.50[a]	−0.53[a]
Dicloxacillin	−0.30[a]	−0.25[a]
Nafcillin	−0.30[b]	−0.30[b]

[a] Ref. [6].
[b] Ref. [7].

The enthalpy of formation of the aggregate was calculated from the temperature dependence of the CMC using the Gibbs–Helmholtz relation:

$$\Delta H^{\circ}_{m} = \left[\frac{\partial}{\partial(1/T)}\left(\frac{\Delta G^{\circ}_{m}}{T}\right)\right]_{p} = \frac{RT^{2}}{n}\left(\frac{\partial \ln K_{m}}{\partial T}\right)_{p} \quad (4)$$

Table 1 shows the calculated values for ΔH°_{m} for penicillin V at 25 °C. Comparison with other penicillins (sodium cloxacillin, dicloxacillin and nafcillin) is also established. The ΔH°_{m} values were in good agreement with those determined experimentally by calorimetric measurements [5–7]. The low and positive value of the enthalpy of aggregation formation of penicillin V shows that the process is endothermic and mainly entropic. Positive values of ΔH°_{m} are generally attributed to the release of structured water from the hydration layers around the hydrophobic parts of the molecule [16] during the formation of the aggregates. However, the negative value of ΔH°_{m} for cloxacillin, dicloxacillin and nafcillin indicates that the aggregation proccess is exothermic and primarily enthalpic, in which hydrophobic interactions become less important, suggesting the mainly importance of the London-dispersion interactions as the major force for aggregation [17].

Acknowledgements

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