Colloid Polym Sci 278:706–709 (2000)

SHORT COMMUNICATION

M. Pérez-Rodríguez
L. M. Varela
P. Taboada
D. Attwood
V. Mosquera

The temperature dependence of the micellisation of chlorpromazine hydrochloride in aqueous solution

Received: 6 January 2000
Accepted: 9 February 2000

M. Pérez-Rodríguez · L. M. Varela
P. Taboada · V. Mosquera (✉)
Grupo de Física de Coloides y Polímeros
Departamento de Física de la Materia Condensada, Universidad de Santiago de Compostela, 15706 Santiago, Spain
e-mail: fmvictor@usc.es

D. Attwood
School of Pharmacy and Pharmaceutical Sciences, University of Manchester
Manchester M13 9PL, UK

Abstract The association characteristics of the weakly associating drug chlorpromazine hydrochloride have been examined over the temperature range 10–35 °C by means of conductimetric measurements. Critical micelle concentrations (cmc) have been determined by the application of a recently developed numerical method [Pérez-Rodríguez et al. (1998) *Langmuir* 14:4422] especially designed for the analysis of the association pattern in highly polydisperse systems of low aggregation number. The cmcs determined in this manner are used in combination with the mass-action model to obtain the thermodynamic parameters of the micellisation process, in particular the surface and hydrophobic contributions to the free energy. The use of exact forms of equations for the thermodynamics of micellisation applicable to systems of low aggregation number leads to values of the enthalpy of micellisation in reasonable agreement with experimentally determined values.

Key words Thermodynamics of micellisation · Critical micelle concentrations · Drugs · Chlorpromazine hydrochloride · Micelles

Introduction

The phenothiazine tranquillising drugs have interesting association characteristics that derive from their rigid, tricyclic hydrophobic groups [1]. Previous studies of the association of amphiphilic drugs have been concerned mainly with the association characteristics of these compounds [2]. Discontinuities in the physicochemical properties of these drugs in aqueous solution at well-defined concentrations led to the assumption of a micellar mode of association [3–5]. Moreover, the concentration dependence of apparent molar thermodynamic parameters [6, 7], vapour pressure data [8] and osmotic coefficient and light-scattering results [9] can be quantitatively described using Burchfield and Woolley's [10, 11] mass-action model of micellisation, which assumes the single-step formation of micelles; however, the values of the monomer–counterion interaction coefficients derived are strongly negative, indicative of possible limited association at concentrations below the critical micelle concentration (cmc).

In the current work, we present an investigation of the association of the phenothiazine drug chlorpromazine hydrochloride in aqueous solution over a wide temperature range by means of conductivity measurements. The data are analysed using the Phillips definition of the cmc combined with a recently developed numerical algorithm [12]. The thermodynamics of micellisation is derived using the usual form of the mass-action model normally applied to micellar systems of high aggregation number and also a more exact form for weakly associating systems. The results are compared with previously reported data [13]. Hydrophobic and surface contributions to the free energy are calculated at each temperature.

Experimental

Materials

The hydrochloride of chlorpromazine [10-(2-dimethylaminopropyl)phenothiazine] (Sigma Chemical Co.) was sufficiently well

characterized to be used as received and it conformed to the purity requirements of the British Pharmacoepia, containing not less than 98.5% of the specified compound.

Experimental methods

Conductivities and dielectric constants of the solutions were measured with a HP 4285A Precision LCR meter 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 polarisation that occurs when the probe is constructed from plain condenser plates. The design of the measurement cell 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 the side. This geometry ensures the probe head is always surrounded by at least 2 cm of solution during the measurement process, so avoiding possible interference from the cell walls. The cell was immersed in a Techne model RB-12A thermostat bath equipped with a Tempunit TU-16A thermostat and an Anton Paar DT 100-30 thermometer, maintaining the temperature constant to ± 0.01 °C. A Variomag 20P shaker was used to homogenise the solution.

Results and discussion

The experimental measurements provide information on the complex electrical conductivity of the solution. The concentration dependence of the real parts of the electrical conductivity (κ') of chlorpromazine at 25 °C is shown in Fig. 1 together with the results of a numerical analysis carried out in the following way. At each temperature the concentration dependence of the electrical conductivity shows a monotonic increase with a gradual decrease in the slope. This is typical behaviour for a weakly associating surfactant. The cmc can be determined by the intersection of the two straight lines of the conductivity–concentration plots above and below the cmc, according to Williams et al. [14], but the precision of the measurement depends on the width of the concentration range over which the change in the physical properties is observed. When this change is gradual, as in the case of drugs and surfactants with a low aggregation number (such as chlorpromazine hydrochloride), it is difficult to obtain a precise cmc value because of the curvature of the plots. Phillips [15] defined the cmc as the concentration corresponding to the maximum change in a gradient in the physical property versus concentration curve ($\phi - c_t$):

$$\left(\frac{\mathrm{d}^3\phi}{\mathrm{d}c_t^3}\right)_{c_t=\mathrm{cmc}} = 0 \ , \tag{1}$$

where

$$\phi = \alpha[S] + \beta[M] \ . \tag{2}$$

α and β are constants of proportionality and $[S]$ and $[M]$ are the concentrations of the monomeric surfactant and the micelle, respectively. We have previously applied the Phillips' definition to obtain the cmc of both classical surfactants and amphiphilic drugs [16–22]. To resolve the problem of the determination of the cmc in weakly associating systems, we recently designed a numerical method that combines the Phillips' definition of the cmc with an analysis of the second derivative of the conductivity–concentration data using the Runge–Kutta method and the Levenberg–Marquardt least-squares fitting algorithm [12]. This method allows the determination of the cmc using a smaller number of points and with greater precision than the Euler method [23]. The cmcs of chlorpromazine hydrochloride determined by this analytical method at various temperatures are listed in Table 1.

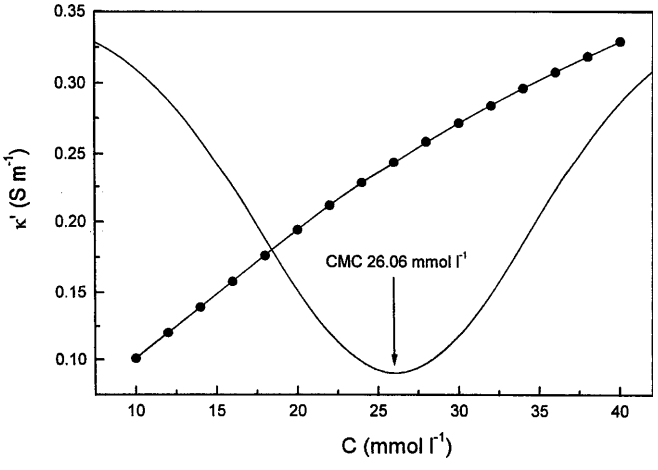

Fig. 1 Real part of the electrical conductivity of an aqueous solution of chlorpromazine hydrochloride at 30 °C versus molar concentration. The *line* connecting the experimental points is shown as a guide to the eye. The *Gaussian fit* corresponds to the second derivative of the conductivity, and the *arrow* shows the critical micelle concentration (cmc)

Table 1 Critical micelle concentration (cmc) and thermodynamic parameters of micellisation of chlorpromazine hydrochloride in aqueous solution. The values shown in *parentheses* correspond to the enthalpies of micellisation calculated using an approximate form of the mass-action equation that assumes micelles of high aggregation number (Eq. 8)

T/°C	cmc/ mmol l^{-1}	ΔG^0_{HP}/ kJ mol^{-1}	ΔG^0_{s}/ kJ mol^{-1}	ΔH^0_{m}/ kJ mol^{-1}	$T\,\Delta S^0_{\mathrm{m}}$/ kJ mol^{-1}
10.00	19.00	−27.19	10.26	−17.21 (−13.11)	9.98
15.00	20.08	−27.47	10.36	−17.83 (−16.02)	9.64
20.00	21.58	−27.67	10.45	−18.45 (−19.11)	9.22
25.00	23.70	−27.78	10.50	−19.08 (−22.38)	8.70
30.00	26.06	−27.88	10.54	−19.73 (−25.84)	8.15
35.00	28.65	−27.97	10.59	−20.39 (−29.50)	7.58

Thermodynamics of micellisation

Micellisation is well characterized by an equation of the form

$$K_m = \frac{[M_n]}{[M_1]^n [S]^{n-p}} \quad , \tag{3}$$

where K_m is the equilibrium constant for the formation of the micelles, $[M_1]$ is the molar concentration of monomers and $[S]$ is the counterion concentration, n being the aggregation number and p the effective charge of the micelle. The validity of Eq. (3) for describing the association process has been demonstrated by a great number of observations on a wide variety of surfactants.

For univalent ions the molar concentrations in Eq. (3) are related through the requirement of charge electroneutrality:

$$c_t = n[M_n] + [M_1] = [S] + p[M_n] - [S'] \quad , \tag{4}$$

where c_t is the total surfactant concentration and $[S']$ is the coion molar concentration. In this model, $p/n = \beta$ is the fraction of counterions bound to the micelle and $1 - \beta$ is the degree of dissociation. The cmc, the concentration at which the number of micelles exhibits a step-function jump from essentially zero, is defined by [24]

$$RT \ln X_{cmc} = \Delta G^0_{HP} + \Delta G^0_s \quad , \tag{5}$$

where X_{cmc} is the mole fraction of surfactant at the cmc. ΔG^0_{HP} and ΔG^0_s are, respectively, the hydrophobic free energy of transfer of a hydrocarbon moiety from water to the oil-like micellar interior (this term drives micellisation) and surface contributions essentially due to repulsion of the monomer head groups (this term opposes micellisation) [25–27].

The standard free energy of micelle formation per monomer unit is given by

$$\Delta G^0_{HP} = -\frac{RT}{n} \ln K_m \quad . \tag{6}$$

Application of the mass-action model leads to a micellisation constant given by [23, 28]

$$\frac{1}{K_m} = n \frac{(2n-p)(4n-2p-1)}{2n-p-2} \times \left[\frac{(2n-p)(4n-2p-1)}{(2n-p-1)(4n-2p+2)} X_{cmc} \right]^{2n-p-1} \quad . \tag{7}$$

In the limit of high aggregation numbers ($n \to \infty$), the above expressions can be approximated by the usual relationship,

$$\Delta G^0_{HP} = (1-\beta) RT \ln X_{cmc} \quad . \tag{8}$$

Operating with Eqs. (6) and (7), we obtained the following expression:

$$\Delta G^0_{HP} = RT \ln X_{cmc} + aRT \ln X_{cmc} + b \quad , \tag{9}$$

a and b being two constants that depend on the magnitudes of aggregation number and micellar charge, whose expressions are

$$a = \left(1 - \frac{1+p}{n}\right) \quad , \tag{10}$$

$$b = RT \left\{ \frac{\ln n + (2n-p)[\ln(2n-p) + \ln(4n-2p-1)] - 2\ln(2n-p-2) - 2(2n-p-1)[\ln(2n-p-1) + \ln(4n-2p+2)]}{n} \right\} . \tag{11}$$

By comparing Eq. (9) with Eq. (5), ΔG^0_s is given by

$$\Delta G^0_s = -(aRT \ln X_{cmc} + b) \quad . \tag{12}$$

The temperature dependence of the Gibbs free energy of micellisation of chlorpromazine hydrochloride solutions is plotted in Fig. 2. The upper line shows results obtained using Eqs. (6) and (7) (for low aggregation numbers) with the values $n = 6$ and $\beta = 0.71$ cited in the literature [13]. As can be seen, the approximate equation normally applied to micellar systems of high

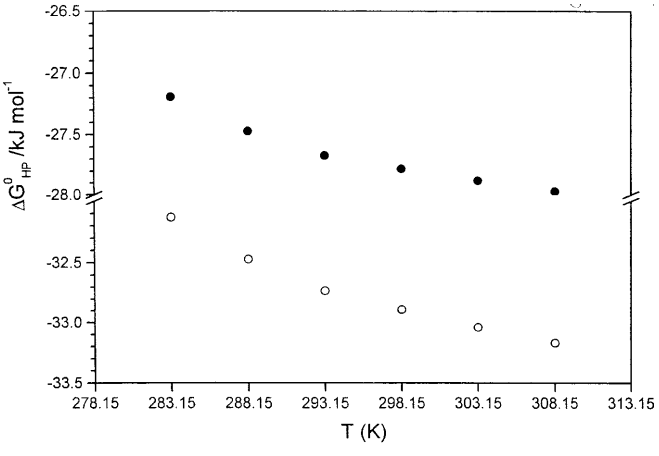

Fig. 2 Temperature dependence of the hydrophobic contribution to the free energy of micellisation of chlorpromazine hydrochloride. *Filled circles* are values calculated using Eqs. (6) and (7) applicable to micelles of low aggregation number, while the *open circles* represent values calculated using an approximate form of the equations derived assuming micelles of high aggregation number (Eq. 8). The scale has been broken for clarity

aggregation number (Eq. 8) leads to lower values of the free energy of micellisation (lower line) and also predicts a more pronounced decrease of this parameter with temperature than the more precise form of the equation.

Table 1 shows the temperature dependence of the thermodynamic parameters of aggregation per mole of chlorpromazine hydrochloride in aqueous solution. ΔG_s^0, calculated by the application of Eqs. (10)–(12), remains almost constant over the range of temperature studied, revealing the small influence of the temperature on the surface energetics. The enthalpy and entropy of micellisation were calculated using the usual thermodynamic relations:

$$\Delta H_m^0 = \left[\frac{\partial\left(\frac{\Delta G_m^0}{T}\right)}{\partial\left(\frac{1}{T}\right)}\right]_p = \frac{RT^2}{n}\left(\frac{\partial \ln K_m}{\partial T}\right)_p \quad (13)$$

$$T\Delta S_m^0 = \Delta H_m^0 - \Delta G_m^0 \ . \quad (14)$$

Table 1 shows that the micellisation of chlorpromazine hydrochloride becomes an increasingly exothermic process with increase of temperature, accompanied by a decrease in ΔS_m^0. For comparison, the enthalpy of micellisation has also been calculated using the approximate form of the equations applicable to micelles of high aggregation number. ΔH_m^0 at 30 °C calculated using the exact forms of the equations is within 5.2% of the reported [13] experimental value ($\Delta H_m^0 = -18.7$ kJ mol^{-1}) for the aggregation of this drug, whereas the value estimated by means of the high-aggregation-number approximation differs from the experimental value by 38%.

Conclusions

The association characteristics of the weakly associating drug chlorpromazine hydrochloride have been analysed over a wide temperature range by means of conductimetric measurements. The use of exact forms of equations for the thermodynamics of micellisation derived from the mass-action model, and cmc values obtained from the application of the Runge–Kutta numerical analysis to the conductimetric data, leads to thermodynamic parameters in reasonable agreement with experimentally determined values.

The micellisation of the drug becomes increasingly exothermic with increase of temperature and the entropy change involved in the formation of the aggregates is progressively lower. The surface and hydrophobic contributions to the free energy are almost constant throughout the temperature range under examination.

Acknowledgement The authors wish to thank the Xunta de Galicia for financial support.

References

1. Attwood D (1995) Adv Colloid Interface Sci 55:271
2. Attwood D, Florence AT (1983) Surfactant systems. Chapman and Hall, London
3. Thoma K, Arning M (1976) Arch Pharmacol 309:837
4. Scholtan W (1955) Kolloid Z Z Polym 142:84
5. Attwood D, Florence AT, Gillan JMN (1974) J Pharm Sci 63:988
6. Attwood D, Boitard E, Dubès J-P, Tachoire H (1992) J Phys Chem 96:11018
7. Attwood D, Blundell R, Mosquera V, García M, Rodríguez J (1994) J Colloid Polym Sci 272:108
8. Attwood D, Dickinson NA, Mosquera V, Pérez-Villar V (1987) J Phys Chem 91:4203
9. Attwood D, Mosquera V, Rey C, Vasquez E (1991) J Chem Soc Faraday Trans 1 87:2971
10. Burchfield TE, Woolley EM (1984) J Phys Chem 88:2149
11. Burchfield TE, Woolley EM (1984) J Phys Chem 88:2155
12. Pérez-Rodríguez M, Prieto G, Rega C, Varela LM, Sarmiento F, Mosquera V (1998) Langmuir 14:4422
13. Attwood D, Boitard E, Dubès J-P, Tachoire H (1997) J Phys Chem B 101:9586
14. Williams RJ, Phillips JN, Mysels KJ (1955) Trans Faraday Soc 51:728
15. Phillips JN (1955) Trans Faraday Soc 51:561
16. Sarmiento F, del Río JM, Prieto G, Attwood D, Jones MN, Mosquera V (1995) J Phys Chem 99:17628
17. del Río JM, Pombo C, Prieto G, Sarmiento F, Mosquera V, Jones MN (1994) J Chem Thermodyn 26:879
18. del Rio JM, Pombo C, Prieto G, Mosquera V, Sarmiento F (1995) J Colloid Interface Sci 172:137
19. del Río JM, Prieto G, Sarmiento F, Mosquera V (1995) Langmuir 11: 1511
20. Attwood D, Mosquera V, García M, Suarez MJ, Sarmiento F (1995) J Colloid Interface Sci 175:201
21. Attwood D, Mosquera V, Novás L, Sarmiento F (1996) J Colloid Interface Sci 179:478
22. Attwood D, Mosquera V, López-Fontán JL,García M, Sarmiento F (1996) J Colloid Interface Sci 184:658
23. Sarmiento F, López-Fontán JL, Prieto G, Attwood D, Mosquera V (1997) Colloid Polym Sci 275:1144
24. Evans DF, Ninham BW (1983) J Phys Chem 87:5025
25. Israelachvili JN, Mitchell DJ, Ninham BW (1976) J Chem Soc Faraday Trans 2 72:1525
26. Mitchell DJ, Ninham BW (1976) J Chem Soc Faraday Trans 2 77:601
27. Wennerström H, Lindman B (1979) Phys Rep 52:1
28. Høiland H (1977) J Solution Chem 6:291