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ORIGINAL CONTRIBUTION

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Mixed micelles of structurally related antidepressant drugs

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Abstract The composition of micelles in a binary mixture of the amphiphilic antidepressant drugs imipramine hydrochloride and clomipramine hydrochloride has been determined from an analysis of the variation of the critical micelle concentration from conductivity techniques as a function of solution composition. The equilibrium distribution of components between micelle and monomer phases was evaluated using a theoretical treatment based on excess thermodynamic quantities. The nonideality of mixing, expressed in terms of the interaction parameter β, was appreciable in systems containing low imipramine mole fractions, suggesting differences in the packing characteristics within micelles of these two drugs.

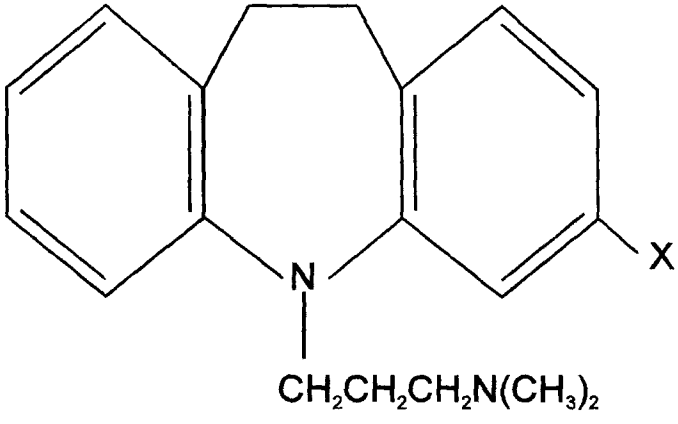
Key words Mixed micelles – drugs – critical micelle concentration

Introduction

In a recent paper [1], we examined the nonideality of mixing within micelles of two structurally similar phenothiazine drugs. This class of drugs have interesting association characteristics which derive from their rigid tricyclic hydrophobic groups [2]. An NMR study of the phenothiazine drug chlorpromazine has indicated vertical stacking of molecules within the micelles in an offset concave-to-convex manner [3]. However, although the association is by a stacking process, similar to that of tricyclic dyes, the association is not continuous but is characterized by a series of inflections in the solution properties with evidence of limited association below the first-critical concentration [4]. As expected from the similarity of their structures, our study showed that mixing of the two phenothiazine drugs was ideal.

In the present study, we have examined the ideality of mixing within micelles formed in a binary mixture of antidepressant drugs. The solution properties of a series of antidepressant drugs, including clomipramine (I) and imipramine (II) which are used in the present study, were reported by Attwood and Gibson [5], and Thoma and Albert [6]. A clear inflection in the concentration dependence of the solution properties from a wide range of techniques suggested a micellar association pattern. However, a more recent calorimetric study has provided evidence for limited association of imipramine below the critical concentration, similar to that noted for the phenothiazine drugs [7]. Moreover, positive deviation of the apparent molar volume of imipramine from the Debye–Hückel limiting law has suggested also premicellar association [8]. No additional inflections in the light-scattering data in water or in dilute electrolyte could be observed for either imipramine or clomipramine over the concentration range in which these are evident for phenothiazine drugs [9]. A detailed comparison of the solution properties of imipramine and clomipramine highlighted differences in the response of the two drugs to the presence of an electrolyte,

which suggests possible differences in the structure of their micelles [9]. An NMR study of proton shifts as a function of concentration [10] showed no clear evidence of the offset stacking of molecules in the micelles of clomipramine, which is a characteristic of the micelles of the phenothiazine drug chlorpromazine. However, because of the difficulty of unambiguous assignment of the ^1H spectrum of imipramine, it was not possible to compare the stacking in micelles of these two antidepressant drugs. The purpose of the present investigation is to examine whether any nonideality of mixing within mixed micelles of the two drugs arises as a result of the observed differences in their micellar properties. The variation of the critical micelle concentration (cmc) with changes in the composition of a binary mixture of these two antidepressant drugs has been used to determine the composition of the mixed micelles and any nonideality of interaction of components in the mixed micelle has been quantified using the dimensionless interaction coefficient, β, introduced by Holland [11].



I: X=Cl, II: X=H

Experimental section

The hydrochlorides of clomipramine (I) [3-chloro-5-(3-dimethylaminopropyl)-10, 11-dihydro-5H-dibenzyl[b, *f*]azepine], and imipramine (II) [5-(3-dimethylaminopropyl)-10, 11-dihydro-5H-dibenzyl[b, *f*]azepine], were obtained from Sigma Chemical Co. and were sufficiently well characterized and purified to be used as received.

The conductivity of the binary mixtures was measured at 25 ± 0.01 °C using a precision LCR meter (HP4285A) with a colloid dielectric probe (HP E5050A). The colloid dielectric probe data measured were controlled with aqueous solutions of KCl over the appropriate concentration range using the molar conductivity data of Shedlovsky [12] and Chambers et al. [13]. Water (twice distilled and degassed) was progressively added to a concentrated aqueous solution of clomipramine/imipramine mixtures of known molality and composition using a peristaltic pump (Dosimat, model-655, Metrohmn AG) under the control of a Hewlett-Packard Vectra computer.

Results and discussion

Figure 1 shows specific conductivity, κ, as a function of molality, m, for imipramine/clomipramine mixtures with 0.5 mole fraction imipramine. Similar plots (not shown) were obtained for mixtures with imipramine mole fractions 0.00, 0.20, 0.40, 0.60, 0.80 and 1.00. In all the cases, curvature in the region of the cmc (indicate by an arrow) was observed making precise determination of the cmc difficult. Such curvature is a consequence not only of a low micellar aggregation number but also reflects changes in the composition of the mixed micelles at concentrations close to the cmc [14]. The cmc values recorded in Table 1 were determined from the clear inflections in plots of molal conductivity as a function of $(\text{molality})^{1/2}$ as recommended by Mysels and Mukerjee [15].

The composition of the monomeric and micellar phases of these systems was evaluated by the treatment of Motomura et al. [16] which is based on excess thermodynamic quantities. The cmc of the mixed system, $\overline{\text{cmc}}$, and the mole fraction of components in the system, $\bar{x}_i$, are

Fig. 1 Conductivity, κ, as a function of molality, m, for a mixture of clomipramine and imipramine with a mole fraction of clomipramine of 0.50

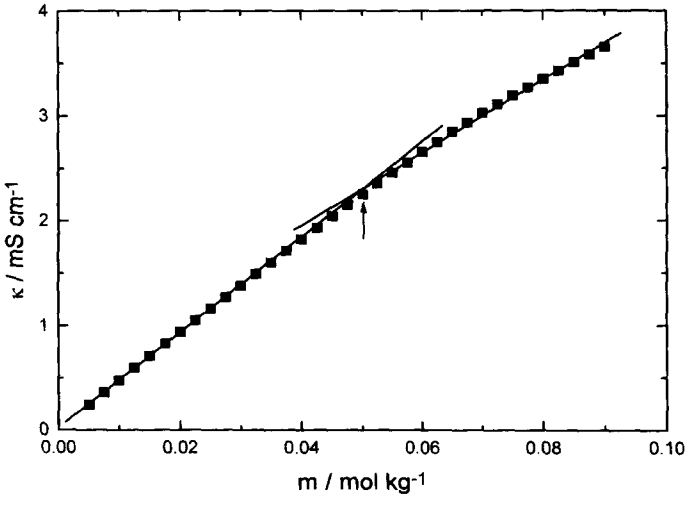


Table 1 Critical micelle concentrations values for the clomipramine/imipramine systems at 25 °C

Mole fraction clomipramine	Mole fraction imipramine	cmc [mol kg^{-1}]
1.00	0.00	0.029
0.82	0.18	0.036
0.63	0.38	0.043
0.53	0.48	0.045
0.40	0.60	0.048
0.22	0.78	0.051
0.00	1.00	0.053

given by

$$\overline{\text{cmc}} = (v_1 x_1 + v_2 x_2)\,\text{cmc}\,, \quad (1)$$

$$\bar{x}_i = v_i x_i/(v_1 x_1 + v_2 x_2) \quad (i = 1, 2)\,, \quad (2)$$

where x_1 and x_2 are the mole fractions of surfactants 1 and 2 and $v_1 = v_{1,a} + v_{1,c}$ and $v_2 = v_{2,b} + v_{2,d}$; $v_{1,a}$ and $v_{1,c}$ are the number of cations and anions produced on dissociation of surfactant 1 and $v_{2,b}$ and $v_{2,d}$ are the number produced on dissociation of surfactant 2.

The drugs under investigation are 1 : 1 electrolytes with identical counterions, i.e.,

$$v_{1,a} = v_{1,c} = v_{2,b} = v_{2,d} = 1 \quad \text{and hence} \quad \overline{\text{cmc}} = 2\,\text{cmc}$$

The composition of the mixed micelle is determined using the relationship

$$\bar{x}_2^{\text{m}} = \bar{x}_2 - (\bar{x}_1 \bar{x}_2/\overline{\text{cmc}})(\partial\overline{\text{cmc}}/\partial \bar{x}_2)_{\text{T,p}} /[1 - \delta_{\text{d}}^{\text{c}} v_{1,c} v_{2,d}/(v_{1,c} v_2 \bar{x}_1 + v_{2,d} v_1 \bar{x}_2)]\,, \quad (3)$$

where

$$\bar{x}_i^{\text{m}} = v_i x_i^{\text{m}}/(v_1 x_1^{\text{m}} + v_2 x_2^{\text{m}}) \quad (i = 1, 2)\,. \quad (4)$$

The Kronecker delta, $\partial_{\text{d}}^{\text{c}}$, for systems investigated here, in which counterions are identical, is 1 and Eq. (3) reduces to

$$\bar{x}_2^{\text{m}} = \bar{x}_2 - (\bar{x}_1 x_2/\overline{\text{cmc}})(\partial\overline{\text{cmc}}/\partial \bar{x}_2)_{\text{T,p}}\,. \quad (5)$$

$\bar{x}_2^{\text{m}}$ was evaluated as a function of $\overline{\text{cmc}}$ by computer analysis of the cmc data. The top line of Fig. 2 shows the variation of the cmc with the composition of the mixed micelle as determined by this method. The bottom curve show the variation of the experimentally measured cmc with the composition of the systems, which was fitted to an equation of the form

$$\overline{\text{cmc}} = a(\bar{x}_2)^2 + b(\bar{x}_2) + c\,, \quad (6)$$

where $a = -0.039 \pm 0.002$, $b = -0.009 \pm 0.002$ and $c = 0.1059 \pm 0.0006$.

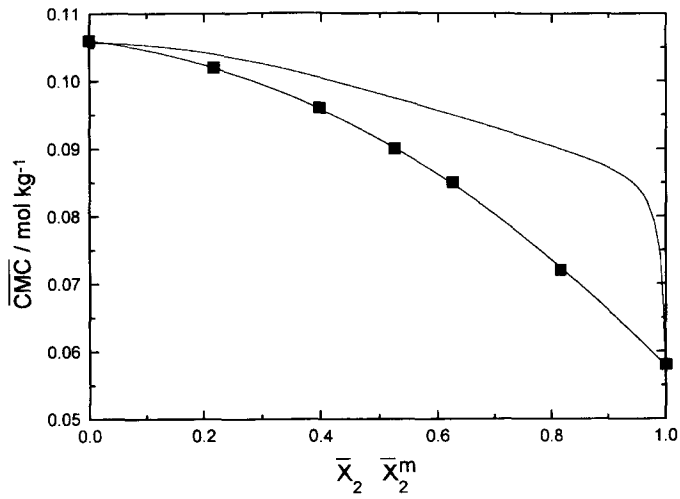


Fig. 2 Variation of $\overline{\text{cmc}}$ ($\overline{\text{cmc}} = 2\,\text{cmc}$) with composition of the clomipramine/imipramine system. The top curve represents the total concentration of free monomeric surfactant against mole fraction of clomipramine in mixed micelle, $\bar{x}_2^{\text{m}}$, as calculated from Eq. (5). The bottom curve represents the variation of $\overline{\text{cmc}}$ with mole fraction of clomipramine in the system, $\bar{x}_2$

Figure 2 may be regarded as a phase diagram, expressing the relationship between the mole fraction of drug in the mixed micelle and that in the solution in equilibrium with it. The upper line shows the equilibrium total concentration of monomeric drug for a given composition of the micelle, while the lower curve gives the mole fraction of each component in monomeric form corresponding to this equilibrium. It is readily seen that for a given composition of the system, the drug with the higher cmc has a higher mole fraction in monomeric form in solution i.e., the micelle is enriched with the drug of the lower cmc. This method of estimation of the equilibrium distribution of components in a mixed system has been shown to give values in good agreement with those derived from direct measurement by gel permeation chromatography [17].

Inspection of Fig. 2 shows that the values of $\bar{x}_2^{\text{m}}$ are close to those of $\bar{x}_2$ at low mole fractions of clomipramine, i.e., the incorporation of this drug into micelles of imipramine is associated with nearly ideal mixing. However, appreciable deviation of the experimental and predicted lines at high mole fractions of clomipramine indicates that the incorporation of small amounts of imipramine into clomipramine micelles is not an ideal process.

To estimate the nonideality of mixing in the mixed micelles, we have used the simplified approach proposed by Holland and Rubingh [18]. According to this model, the monomer concentration of each component in the mixture, C_i^{m}, is given by

$$C_i^{\text{m}} = \alpha_i C^*\,, \quad (7)$$

where α_i is the mole fraction of the ith component in the mixed micelles and C^* the mixed cmc.

In the case of mixtures which contain nonideal surfactants, with respect to each other, the activity coefficients are given by

$$f_i = \alpha_i C^*/x_i C_i \,, \tag{8}$$

C_i being the cmc of pure component.

Using a simple regular solution approximation, the activity coefficients can be expressed as functions of the mole fractions of each of the components in the mixed micelle, x_i, and an appropriate interaction parameter β_{ij}. The β_{ij} parameters are constants related to net (pairwise) interactions in the mixed micelle and they are defined by

$$\beta_{ij} = N(W_{ii} + W_{jj} - 2W_{ij})/RT \,, \tag{9}$$

where W and W/RT being the regular solution theory interactions parameters.

In the case of binary nonideal mixtures of components a single interaction parameter β_{ij} is required and the regular approximation for the activity coefficients in the mixed micelles gives

$$f_1 = \exp \beta_{12}(1 - x_1)^2 \,, \tag{10}$$

$$f_2 = \exp \beta_{12} x_1^2 \,, \tag{11}$$

and the net interaction parameter β_{12} can be readily determined when the mixed cmc for the binary system, C^*_{12}, is known. This requires interactively solving for x_1 at the cmc, using a relationship such as

$$x_1^2 \ln\left[\frac{\alpha_2 C^*_{12}}{x_1 C_1}\right] = (1 - x_1)^2 \ln\left[\frac{\alpha_2 C^*_{12}}{(1 - x_1) C_2}\right], \tag{12}$$

β_{12} can then be directly obtained, given

$$\beta_{12} = \frac{\ln[\alpha_1 C^*_{12}/(x_1 C_1)]}{(1 - x_1)^2} \,. \tag{13}$$

A value of $\beta = -0.9$ was calculated for clomipramine/imipramine system using the computational method proposed by Holland [11], which is based on Eq. (13) using cmc values of the pure components. Application of this procedure to mixtures with a range of compositions gave the β values of -0.59, -0.75, -0.98 and $-1{,}4$ for clomipramine mole fractions of 0.22, 0.40, 0.53 and 0.63, respectively. Values of β for a clomipramine mole fraction of 0.82 were too high to be calculated by this method. The reasons for the significant nonideality of systems containing low imipramine mole fraction are not clear but may reflect differences in the preferred packing within the micelles of each drug as was indicated in our earlier study [1].

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