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SHORT COMMUNICATION

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Comparison of the thermodynamic properties of structurally related amphiphilic antidepressants in aqueous solution

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Abstract The critical concentrations of amitriptyline, desipramine and nortriptyline hydrochlorides in aqueous solution were determined over the temperature range 288–313 K by a method based on deconvolution into Gaussians of the second derivate of the measured specific conductivity data. The mass-action model was used to calculate the thermodynamic quantities: standard free Gibbs energy, standard enthalpy and standard entropy of aggregate formation. The results are discussed in terms of the structure of the drug aggregates.

Key words Amitriptyline · Desipramine · Nortriptyline · Critical micelle concentration · Thermodynamic parameters

Introduction

The dualistic character of amphiphilic compounds in having both hydrophilic and hydrophobic parts is the basis of their relation to both external and internal interfaces in aqueous systems. Self-association of the amphiphilic compounds is a possible way of eliminating the energetically unfavourable contact between the nonpolar part and water while simultaneously retaining the polar part in an aqueous environment. The physical phenomenon responsible for such behaviour is referred to as the hydrophobic effect and arises from a subtle balance between intermolecular energies and entropies [1]. An equilibrium solution of amphiphiles in water corresponds to a system of aggregates, coexisting with a nearly constant concentration of monomers. Unlike in ordinary solutions, the solute particles in amphiphile solutions can respond to variations in thermodynamic parameters (such as total concentration, temperature or ionic strength) by changing their size and shape distributions. This behaviour resembles that of a system governed by multiple chemical equilibria [2].

Typical colloidal behaviour is exhibited by a large number of drugs from many pharmacological groups of compounds. For example, various studies have been performed to study the association characteristics of phenothiazine tranquillizer drugs [3–7]. Other workers have reported the amphiphilic character of several penicillins and their colloidal properties and have related the existence of a second critical concentration critical concentration with the halogen substituent existing in their hydrophobic core [8, 9].

However, the stability of aggregates from a thermodynamics perspective has not yet been quantified sufficiently. An important contribution to the free energy of formation of aggregates is the enthalpy change involved in this process. This is linked directly to

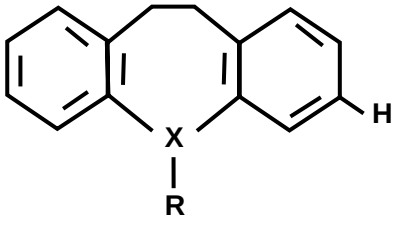
intermolecular interactions and is most directly influenced by changes in the nature of the amphiphile.

In the present work we present an investigation of the association of three antidepressant drugs, desipramine, amitriptyline and nortriptyline, in aqueous solution over a wide temperature range by means of conductivity measurements. These drugs under investigation are amphiphilic in nature, possessing an almost planar tricyclic ring system with a short hydrocarbon chain carrying a terminal, charged N atom. This provides an opportunity to investigate the influence of structure of the hydrophobe on the mode of association of these amphiphilic drugs. The thermodynamics of aggregate formation is derived using the usual form of the mass-action model.

Experimental

Materials

The following drugs were sufficiently well characterized and purified by the manufacturers to be used without further purification. The hydrochlorides desipramine (10,11-dihydro-*N*-methyl-5*H*-dibenz-[*b*,flazepine hydrochloride) amitriptyline [1-propanamine, 3-(10, 11-dihydro-5*H*-dibenzo(*a*,*d*)cyclohepten-5-yledine)-*N*,*N*-dimethyl hydrochloride] and nortriptyline [3-(10, 11-dihydro-5*H*-dibenz[*a*,*d*] cyclohepten-5-ylidine)-*N*-methyl-1-propanamine hydrochloride) were purchased from Sigma Chemical Co. All concentrations were determined by weight using double-distilled and sometimes, when necessary, triple-distilled and degassed water.



	X	*R*
Desipramine HCl	N	$-[CH_2]_3NH(CH_3)$
Amitriptyline HCl	C	$=CH[CH_2]_2N(CH_3)_3$
Nortriptyline HCl	C	$=CH[CH_2]_3NH(CH_3)$

Experimental methods

The conductance was measured with a conductivity meter (Kyoto Electronics type C-117) whose cell (Kyoto, type K-121) was calibrated with KCl solutions in the appropriate concentration range. The cell constant was calculated using molar conductivity data published by Shedlovsky [10] and Chambers et al. [11]. Concentrated solutions of drug systems of known concentration were progressively added to the solution using an automatic pump (Dosimat 665 Methohm). The measuring cell was immersed in a thermostatted bath, and the temperature was maintained constant to within ± 0.01 K.

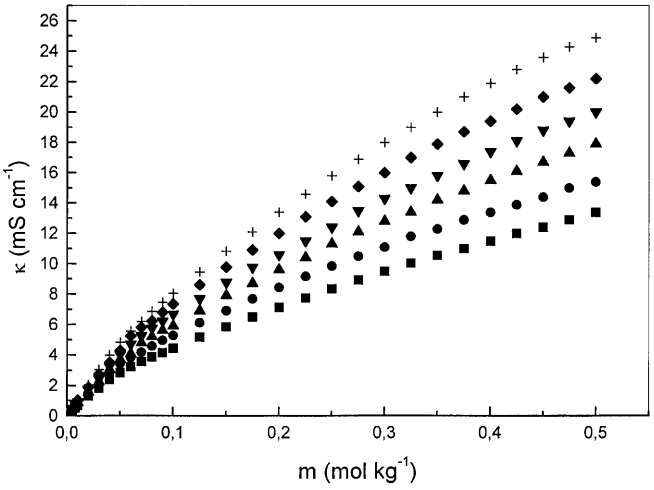


Fig. 1 Plots of specific conductivity against molal concentration of amitriptyline hydrochloride in aqueous solution at different temperatures: 288.15 K (■); 293.15 K (●); 298.15 K (▲); 303.15 K (▼); 308.15 K (◆); 313.15 K (+)

Results and discussion

Plots of specific conductivity, κ, of amitriptyline against drug concentration for different temperatures are illustrated in Fig. 1. Similar plots were obtained for desipramine and nortriptyline. For each temperature, the concentration dependence of the electrical conductivity shows a monotonic increase with a gradual decrease in the slope, the behaviour being typical for a weakly associating amphiphilic [12]. The variation of the specific conductivity with temperature shows a gradual increase for the amitriptyline, which is due to an increase in the thermal energy of the counterions; however, the conductivities of desipramine show a discontinuity in this behaviour between 288 and 293 K. The study of nortriptyline was only possible in the range of temperatures from 288 to 303 K; at higher temperatures the solutions have a cloudy aspect, a prelude of the coagulation and precipitation of the drug.

The results obtained for each drug were analysed to detect the presence of any critical concentration (CC) using the Phillips definition [13] of the critical micelle concentration as the concentration corresponding to the maximum change in the gradient in plots of the solution specific conductivity versus concentration:

$$\left(\frac{d^3\kappa}{dc^3}\right)_{c=\mathrm{cmc}} = 0 \quad , \tag{1}$$

where

$$\kappa = a[S] + b[M] \tag{2}$$

with a and b being proportionality constants and S and M the concentration of the monomers and the aggregates, respectively.

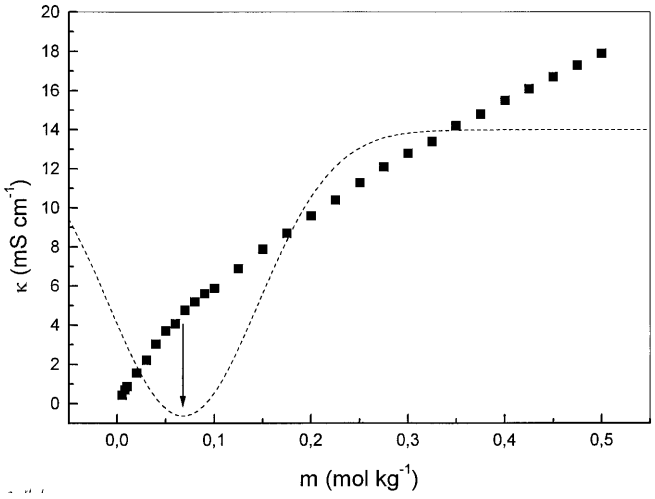


Fig. 2 Plot of specific conductivity against molal concentration of amitriptyline hydrochloride in aqueous solution at a temperature of 288.15 K. The Gaussian fit corresponds to the second derivate of the conductivity. The *arrow* denotes the critical concentration

Table 1 Critical aggregation and thermodynamic parameters of aggregation of amitriptyline hydrochloride in aqueous solution at different temperatures

T (K)	Critical concentration (mol kg^{-1})	ΔG_m^0 (kJ mol^{-1})	ΔH_m^0 (kJ mol^{-1})	$T\Delta S_m^0$ (kJ mol^{-1})
288.15	0.059	−25.46	−9.86	15.60
293.15	0.057	−26.04	−14.17	11.87
298.15	0.063	−26.06	−16.17	9.89
303.15	0.067	−26.24	−17.89	8.35
308.15	0.074	−26.25	−18.34	7.91
313.15	0.081	−26.32	−19.52	6.80

Table 2 Critical aggregation and thermodynamic parameters of aggregation of desipramine hydrochloride in aqueous solution at different temperatures

T (K)	Critical concentration (mol kg^{-1})	ΔG_m^0 (kJ mol^{-1})	ΔH_m^0 (kJ mol^{-1})	$T\Delta S_m^0$ (kJ mol^{-1})
288.15	0.085	−23.80	−13.47	10.33
293.15	0.083	−24.31	−16.26	8.05
298.15	0.085	−24.63	−18.84	5.79
303.15	0.088	−24.93	−21.23	3.71
308.15	0.089	−25.24	−23.40	1.84
313.15	0.094	−25.44	−24.51	0.93

The numerical analysis of the data was made by means of a recently developed algorithm based on the Runge–Kutta numerical integration method and the Levenberg–Marquardt least-squares fitting algorithm, which allows the determination of precise values of the CCs of drugs and surfactants of low aggregation [14]. The measured conductivity and a Gaussian fit of its second derivative from which the critical micelle concentrations was obtained in the case of amitriptyline at 15 °C are shown in Fig. 2.

Table 3 Critical aggregation and thermodynamic parameters of aggregation of nortriptyline hydrochloride in aqueous solution at different temperatures

T (K)	Critical concentration (mol kg^{-1})	ΔG_m^0 (kJ mol^{-1})	ΔH_m^0 (kJ mol^{-1})	$T\Delta S_m^0$ (kJ mol^{-1})
288.15	0.038	−28.22	−3.39	24.83
293.15	0.037	−28.59	−4.21	24.38
298.15	0.044	−28.97	−4.95	24.02
303.15	0.049	−28.99	−5.65	23.34

The critical micelle concentrations for amitriptyline, desipramine and nortriptyline are listed in Tables 1, 2 and 3, respectively. Comparison of the CC values indicates that the hydrophobicity follows the sequence nortriptyline > amitriptyline > desipramine. The differences in the CC values arise solely from the different substituents in the molecular structure of these drugs; all the drugs have Cl^- counterions and all are fully ionised at the pH of the solutions. However, these values are higher than those reported using other techniques [15, 16]. The spread of values for each compound might be a consequence not only of inherent differences in the solution properties measured by each of the experimental methods but also of the difficulty in locating inflection points in experimental data for systems of low aggregation number.

The variation of X_{CC} (where X_{CC} is the CC expressed as a mole fraction) with temperature for desipramine is shown in Fig. 3. A similar plot was obtained for amitriptylie. Both curves pass through a minimum close to 293.15 K and were fitted to the equation

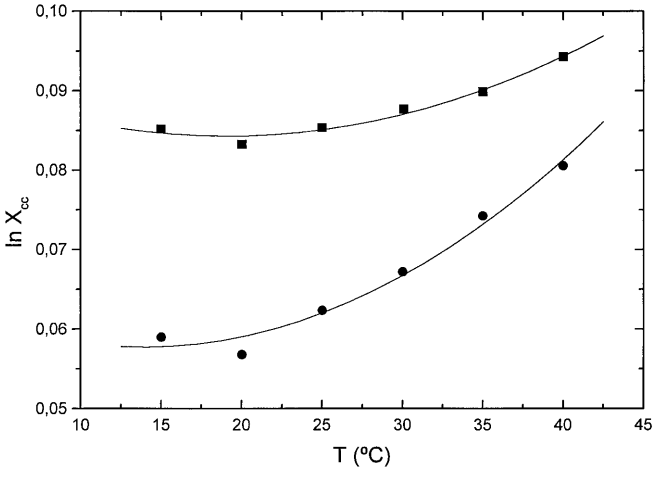


Fig. 3 Temperature dependence of critical concentration as mole fraction, $\ln X_{CC}$, of amitriptyline (●) and desipramine (■) in water. *Continuous lines* calculated from Eq. (3)

$$\ln X_{CC} = aT^2 + bT + c \ , \quad (3)$$

with values of the coefficients of a of $3.5 \times 10^{-5} \pm 2 \times 10^{-5}$ K^{-2} and $2.3 \times 10^{-5} \pm 5 \times 10^{-6}$ K^{-2}, of b of $-9 \times 10^{-4} \pm 3 \times 10^{-4}$ K^{-1} and $-8 \times 10^{-4} \pm 2 \times 10^{-4}$ K^{-1} and of c of $63 \times 10^{-3} \pm 6 \times 10^{-3}$ and $92 \times 10^{-3} \pm 7 \times 10^{-3}$ for amitriptyline and desipramine, respectively.

For our drugs under study, the equilibrium between monomers and aggregates is represented by Eq. (4):

$$nS^+ + (n-p)G^- \leftrightarrow Mp^+ \ , \quad (4)$$

where S^+ represent the drug ion, G^- the counterion and M^{p+} the aggregate formed by n monomers (quantity defined as the aggregation number) with net charge p. The aggregation constant is written as

$$K_m = \frac{[M^p]}{[G^-]^{n-p}[S^+]^n} \ . \quad (5)$$

In order to calculate K_m it is necessary to know, in addition to the values of n and p taken from the literature [15], the concentration of both the single ion and the aggregates at any total drug concentration. Nevertheless, this difficulty may be overcome by making use of the Phillips method explained earlier. The mass balances for drug ions (c_t) and counterions (c_g), respectively, are expressed as

$$c_t = [S^+] + n[M^{p+}] \ , \quad (6)$$

$$c_g = [S^+] + p[M^{p+}] \ , \quad (7)$$

and by simultaneously solving Eqs. (1), (2), (3), (4), (5), (6) and(7), with the assumption $p[M^{p+}] \ll [S^+]$, the following equilibrium constant can be obtained

$$\frac{1}{K_m} = n\frac{(2n-p)(4n-2p-1)}{2n-2p-2}\left[\frac{(2n-p)(4n-2p-1)}{(2n-p-1)(4n-2p+2)}X_{cmc}\right]^{2n-p-1} \ . \quad (8)$$

The standard Gibbs energy change per mole of monomer is given by

$$\Delta G_m^0 = -\frac{RT}{n}\ln K_m \quad (9)$$

and the standard enthalpy of aggregation follows from the application of the Gibbs–Helmholtz equation to Eq. (9) giving

$$\Delta H_m^0 = \left(\frac{\partial \Delta G_m^0/T}{\partial(1/T)}\right)_p = -\frac{RT^2}{n}\left(\frac{\partial \ln K_m}{\partial T}\right)_p \ . \quad (10)$$

The entropy of aggregation can hence be obtained from

$$T\Delta S_m^0 = \Delta H_m^0 - \Delta G_m^0 \ . \quad (11)$$

The temperature dependences of the thermodynamic quantities of aggregation per mole for the three drugs under study are shown in Tables 1, 2 and 3. These values are similar to those calculated for other antidepressants and for the phenothiazine drugs [5, 17–19] with also a tricyclic ring system forming the hydrophobic core of the molecules. The aggregation of the three drugs becomes increasingly exothermic with increase of temperature (negative ΔH_m^0 values), suggesting the importance of the London-dispersion interactions as the major force for aggregation [20]. ΔS_m^0 calculated from ΔG_m^0 and ΔH_m^0 for these three drugs decrease progressively with the temperature, showing that at temperatures below the CC minimum the aggregation is driven solely by the positive ΔS_m^0.

Since amitriptyline and nortriptyline have a similar ionic head group, as commented on earlier, any differences in the thermodynamic parameters will be a consequence of differences in their hydrophobic groups, in this case resulting from a hydrogen atom instead of a methyl group in the hydrocarbon side chain of amitriptyline. This structural difference gives rise to lower standard Gibbs energies for nortriptyline as expected for this more hydrophobic drug. Substitution of the carbon atom in the X position for a nitrogen atom and the existence of an extra singly bound methyl group in the side chain instead of the double bond if compared with nortriptyilne results in a more hydrophilic character of this drug, as demonstrated by the higher CC and standard Gibbs energy values.

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References

1. Lindman B, Wennerström H, Eicke HF (1980) Micelles. Springer, Berlin Heidelberg New York
2. Gelbert WM, Ben-Shaul A, Roux D (1994) Micelles, membranes, microemulsions, and monolayers. Springer, Berlin Heidelberg New York
3. Attwood D, Doughty D, Mosquera V, Perez Villar V (1991) J Colloid Interface Sci 141:316
4. Attwood D, Blundell R, Mosquera V (1993) J Colloid Interface Sci 157:50
5. Attwood D, Fletcher P, Boitard E, Dubès JP, Tachoire H (1990) J Phys Chem 94:6034
6. Attwood D, Dickinson NA, Mosquera V, Perez Villar V (1987) J Phys Chem 91:4203
7. Taboada P, Attwood D, Ruso JM, Sarmiento F, Mosquera V (1999) Langmuir 15:2022
8. Taboada P, Attwood D, Ruso JM, Suárez M J, Sarmiento F, Mosquera V (1999) J Chem Eng Data 44:820
9. Taboada P, Attwood D, Ruso JM, García M, Sarmiento F, Mosquera V (1999) J Colloid Interface Sci 216:270
10. Shedlovsky T (1932) J Am Chem Soc 54:1411
11. Chambers JF, Stokes JM, Stokes RH (1956) J Phys Chem 60:985

12. Sarmiento F, del Rio JM, Prieto G, Attwood D, Jones MN, Mosquera V (1995) J Phys Chem 99:17628
13. Phillips JN (1955) Trans Faraday Soc 51:561
14. Pérez-Rodriguez M, Prieto G, Rega C, Varela LM, Sarmiento F, Mosquera V (1998) Langmuir 14:4442
15. Attwood D, Gibson J (1978) J Pharm Pharmacol 30:176
16. Taboada P, Attwood D, Ruso JM, García M, Mosquera V (2001) Langmuir 17:173
17. Attwood D, Mosquera V, García M, Suarez MJ, Sarmiento F (1995) J Colloid Interface Sci. 175:201
18. Attwood D, Blundell R, Mosquera V, Garcia M, Rodriguez J (1994) Colloid Polymer Sci 272:108
19. Attwood D, Mosquera, V, Rey C, García M (1991) J Colloid Interface Sci 147:316
20. Nusselder JJH, Engberts JBFN (1992) J Colloid Interface Sci 148:353