

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/215477027>

Thermodynamic Properties of Some Antidepressant Drugs in Aqueous Solution

ARTICLE in *LANGMUIR* · JANUARY 2001

Impact Factor: 4.46 · DOI: 10.1021/la0007325

CITATIONS

39

READS

42

5 AUTHORS, INCLUDING:



Pablo Taboada

University of Santiago de Compostela

149 PUBLICATIONS **2,317** CITATIONS

SEE PROFILE



Juan M. Ruso

University of Santiago de Compostela

163 PUBLICATIONS **2,042** CITATIONS

SEE PROFILE



Víctor Mosquera

University of Santiago de Compostela

170 PUBLICATIONS **3,114** CITATIONS

SEE PROFILE

Thermodynamic Properties of Some Antidepressant Drugs in Aqueous Solution

Pablo Taboada,[†] David Attwood,[‡] Juan M. Ruso,[†] Manuel García,[†] and Víctor Mosquera^{*,†}

Grupo de Física de Coloides y Polimeros, Departamentos de Física de la Materia Condensada y Física Aplicada, Facultad de Física, Universidad de Santiago de Compostela, Spain, and School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PL, U.K.

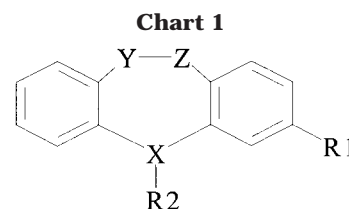
Received May 30, 2000. In Final Form: September 12, 2000

The apparent molal volumes and adiabatic compressibilities of aqueous solutions of the amphiphilic antidepressants amitriptyline, nortriptyline, and desipramine have been determined from density and ultrasound velocity measurements. Critical concentrations were obtained from both techniques. Positive deviations of the apparent molal volume of nortriptyline from the Debye–Hückel limiting law in dilute solution indicate premicellar association. The changes of molal volume accompanying aggregate formation suggest a tightly packed aggregate. Isentropic apparent molal adiabatic compressibilities were calculated by combining the ultrasound velocity and density data. Changes of this quantity were similar to those of typical surfactants, indicating a decrease of hydrophobic hydration in the association of the monomers of these drugs.

Introduction

The colloidal properties of amphiphilic drugs are largely determined by the nature of the aromatic ring systems of their hydrophobic moieties, and such drugs are useful in probing the relationship between molecular architecture and physicochemical properties.¹ Antidepressant compounds are a family of drugs which allow the elucidation of this relationship. These substances possess an almost planar tricyclic ring system with a short hydrocarbon chain carrying a terminal, charged nitrogen atom (see Chart 1 for the structures). These drugs form aggregates of approximately 8–10 monomers in water at a critical concentration, which can be detected by a discontinuity of the concentration dependence of the physicochemical properties of the solution.¹ The presence of substituents in the hydrophobic core or variations of the hydrocarbon chain length results in modifications of the behavior of these drugs in solution, altering their chemical stability and pharmacological activity.^{2–6}

One of the mechanisms to establish relationships between molecular architecture and physicochemical properties is the study of the thermodynamics of aggregation of amphiphilic compounds and the understanding of the factors governing this process. Systematic studies of the factors influencing the apparent molal volume and compressibility of drug aggregates are of



	X	Y-Z	R ₁	R ₂
Imipramine HCl	N	CH ₂ -CH ₂	H	-(CH ₂) ₃ N(CH ₃) ₂
Clomipramine HCl	N	CH ₂ -CH ₂	Cl	-(CH ₂) ₃ N(CH ₃) ₂
Desipramine HCl	N	CH ₂ -CH ₂	H	-(CH ₂) ₃ NH(CH ₃)
Amitriptyline HCl	C	CH ₂ -CH ₂	H	=CH[(CH ₂) ₃ N(CH ₃) ₂]
Nortriptyline HCl	C	CH ₂ -CH ₂	H	=CH[(CH ₂) ₃ NH(CH ₃)]

importance in defining the thermodynamics of aggregation. Many publications on homologous series of typical surfactants have highlighted the structural factors which influence these parameters.^{7–10} However, fewer studies have been carried out for amphiphilic drugs and, specifically, for antidepressant compounds. Attwood et al. reported the dependence of apparent molal volumes and adiabatic compressibilities of the phenothiazine tranquilizer drugs promethazine, promazine, and chlorpromazine with temperature,^{11,12} and also the influence of an extra Cl atom in the phenyl ring system of the antidepressant drug clomipramine when compared with its structurally related compound imipramine.^{12,13}

* To whom correspondence should be addressed. E-mail: fmvector@usc.es.

[†] Universidad de Santiago de Compostela.

[‡] University of Manchester.

(1) Attwood, D.; Florence, A. T. *Surfactant Systems*; Chapman and Hall: London, 1983.

(2) Attwood, D.; Gibson, J. *J. Pharm. Pharmacol.* **1978**, *30*, 176.

(3) Attwood, D.; Dickinson, N. A.; Mosquera, V.; Pérez Villar, V. *J. Phys. Chem.* **1987**, *91*, 4203.

(4) Attwood, D.; Doughty, D.; Mosquera, V.; Pérez Villar, V. *J. Colloid Interface Sci.* **1991**, *141*, 316.

(5) Attwood, D. *Adv. Colloid Interface Sci.* **1995**, *55*, 271.

(6) Taboada, P.; Attwood, D.; Ruso, J. M.; Sarmiento, F.; Mosquera, V. *Langmuir* **1999**, *15*, 2022.

(7) Musbally, G. M.; Perron, G.; Desnoyers, J. E. *J. Colloid Interface Sci.* **1974**, *48*, 494.

(8) Corkill, J. M.; Goodman, J. F.; Walker, T. *Trans. Faraday Soc.* **1967**, *63*, 768.

(9) Bloor, D. M.; Gormally, J.; Wyn-Jones, E. *J. Chem. Soc., Faraday Trans. 1* **1984**, *80*, 1915.

(10) Zielinski, R.; Ikeda, S.; Nomura, H.; Kato, S. *J. Chem. Soc., Faraday Trans. 1* **1988**, *84*, 151.

(11) Attwood, D.; Mosquera, V.; Rey, C.; García, M. *J. Colloid Interface Sci.* **1991**, *147*, 316.

(12) Attwood, D.; Blundell, R.; Mosquera, V.; García, M.; Rodríguez, J. *Colloid Polym. Sci.* **1994**, *272*, 108.

In the present work we have examined the apparent molal volumes and adiabatic molal compressibilities of the antidepressant drugs amitriptyline, nortriptyline, and desipramine hydrochlorides at 298.15 K from density and ultrasound velocity measurements, with particular emphasis on the effect of substituents on the association behavior of these drugs. Critical concentrations were detected from apparent molal volumes and ultrasound.

Experimental Section

Materials. Amitriptyline, nortriptyline, and desipramine hydrochlorides of at least 98.5% purity were purchased from Sigma Chemical Co. and used as received. Water was double-distilled and degassed before use.

Density Measurements. Density was measured at 298.15 K using an Anton Paar DMA 60/602 densimeter with a resolution of $\pm 10^{-6}$ g cm $^{-3}$. The temperature control was maintained within ± 0.005 K, giving rise to uncertainties in density of ca. $\pm 1.5 \times 10^{-6}$ g cm $^{-3}$. The temperature was maintained constant by a HETO proportional temperature controller and checked with an Anton Paar DT100-30 digital precision thermometer. The densimeter was calibrated with air at known pressure and water, where the density of water was assumed to be 0.997 043 g cm $^{-3}$. To ensure the complete absence of microbubbles in the solutions, samples were kept for 30 min in Branson 5200 ultrasound equipment at 298.15 K.

Ultrasound Velocity Measurements. Ultrasound velocity was measured at 298.15 K at a frequency of 2 MHz using a Nusonic model 6380 concentration analyzer (Nusonic Inc.) with a temperature transducer connected to a Hewlett-Packard 3455A digital microvoltmeter. Errors in ultrasound velocity measurements arise mainly from variations of temperature, and in this study temperature was controlled to within ± 0.005 K with a HETO temperature controller. The sound velocity transducer was connected to a Hewlett-Packard 3437A multimeter, whose output was assessed continuously by a computer, averaging 100 measurements and giving an accuracy in the velocity of ± 0.01 m s $^{-1}$. The uncertainties in the ultrasound velocity measurements were ca. ± 0.05 m s $^{-1}$ at molalities above the critical concentration. Measurements on more dilute solutions were subject to increased error associated with the adsorption of antidepressant from solution onto the walls of the cell.

Results and Discussion

A. Densities and Molal Apparent Volumes. The apparent molal volume was calculated from the experimental density data by means of the equation

$$V_\phi = \frac{M}{\rho} - \frac{10^3(\rho - \rho_0)}{m\rho\rho_0} \quad (1)$$

where M is the molecular weight of the solute, ρ the density of the solution, m the molality, and ρ_0 the density of pure water. Figure 1 shows the apparent molal volumes of each drug. For nortriptyline, in the preaggregation region V_ϕ increases until the critical concentration and experiences a slight decrease at a higher concentration. From approximately 0.05 mol kg $^{-1}$, V_ϕ increases sharply, indicating the onset of the precipitation of the drug. Amitriptyline and desipramine have a much higher aqueous solubility, and it was possible to measure V_ϕ up to concentrations of at least 0.25 mol kg $^{-1}$. These drugs show a decrease of V_ϕ with concentration, which becomes less important at higher concentrations of drug and almost levels off at concentrations close to 0.35 and 0.17 mol kg $^{-1}$, respectively.

In Figure 1, the gradient of the plots of amitriptyline and desipramine approaches zero at high drug concentration, and many workers have subjectively chosen the

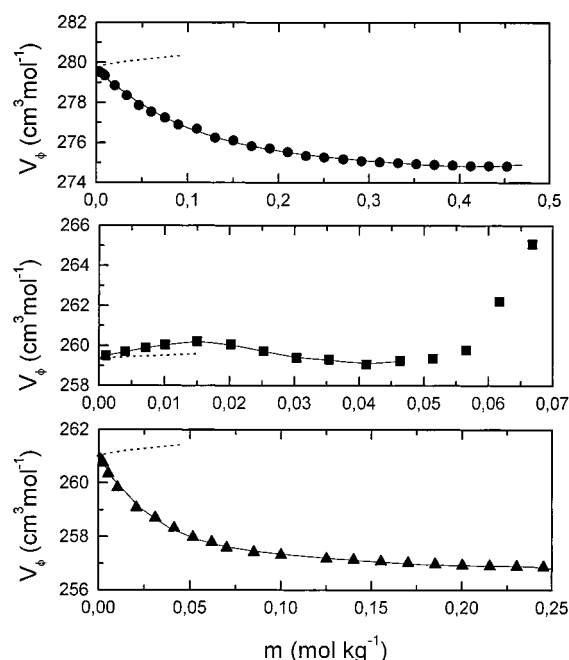


Figure 1. Apparent molal volume, V_ϕ , as a function of m for aqueous solutions of (●) amitriptyline, (■) nortriptyline, and (▲) desipramine hydrochlorides at 298.15 K. Dotted lines are values from the Debye–Hückel limiting law fit.

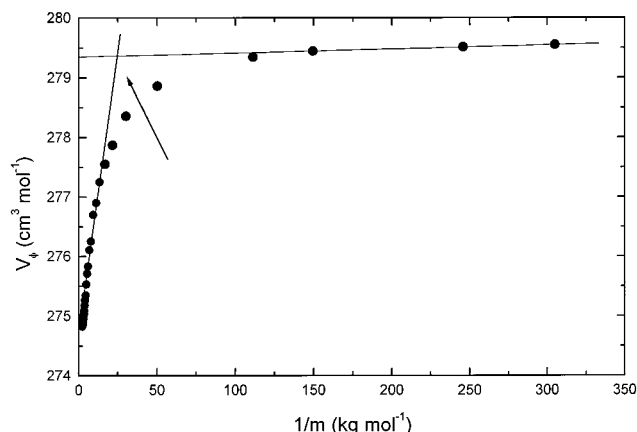


Figure 2. Apparent molal volume, V_ϕ , against $1/m$ for aqueous solutions of amitriptyline hydrochloride at 298.15 K. The arrow denotes the critical concentration.

approximately constant or limiting values as the apparent molal volume of the aggregates, V_ϕ^{mic} . An alternative approach¹⁴ is to consider the pseudophase model of micellization. Assuming this model, the apparent molal volume of these antidepressants can be expressed as

$$V_\phi = V_\phi^{\text{mic}} + \frac{cc}{m} [V_\phi^0 - V_\phi^{\text{mic}}] \quad (2)$$

where V_ϕ^0 is taken as the apparent molal volume for monomers. Figure 2 shows a representative plot of V_ϕ against $1/m$ for amitriptyline hydrochloride. Values obtained for the critical concentration (cc), V_ϕ^{mic} , and V_ϕ^0 by this model for all three drugs are shown in Table 1.

A more exact way to calculate V_ϕ^0 is to assume that solutions of amphiphilic compounds behave as solutions of 1:1 electrolytes up to the critical concentration; the

(13) Attwood, D.; Mosquera, V.; García, M.; Suárez, M. J.; Sarmiento, F. *J. Colloid Interface Sci.* **1995**, *175*, 201.

(14) Brun, T. S.; Hoiland, H.; Vikingstad, E. *J. Colloid Interface Sci.* **1978**, *63*, 89.

Table 1. Critical Concentrations, cc, Apparent Molal Volumes at Infinite Dilution, V_ϕ^0 , Micellar Apparent Molal Volumes, V_ϕ^{mic} , Changes in Apparent Molal Volumes upon Aggregation, ΔV_m , and the B_v Parameter of Amitriptyline, Nortriptyline, and Desipramine Hydrochlorides in Aqueous Solution at 298.15 K

	cc (mol kg ⁻¹)	V_ϕ^0 (cm ³ mol ⁻¹)		V_ϕ^{mic} (cm ³ mol ⁻¹)	ΔV_m (cm ³ mol ⁻¹)		B_v (cm ³ kg mol ⁻²)
		pseudo	limiting law		pseudo	limiting law	
amitriptyline	0.038	279.4	279.6	274.1	-5.3	-5.5	-49.5
nortriptyline	0.026	259.5	259.4	258.2	-1.3	-1.2	39.1
desipramine	0.045	260.7	260.8	256.6	-4.1	-4.2	-89.2

apparent molal volumes may then be described in the premicellar region by the equation¹⁵

$$V_\phi = V_\phi^0 + A_v m^{1/2} + B_v m \quad (3)$$

where V_ϕ^0 is the apparent molal volume at infinite dilution, A_v is the Debye–Hückel limiting law coefficient, and B_v is an adjustable parameter related to a pair interaction¹⁴ and equivalent to the second virial coefficient which measures the deviation from the limiting law due to the nonelectrostatic solute–solute interactions. This parameter has been studied systematically for volumes.^{7,15–17} For 1:1 electrolytes in water at 298.15 K, $A_v = 1.868 \text{ cm}^3 \text{ kg}^{1/2} \text{ mol}^{-3/2}$ and B_v is generally negative except for hydrogen-bonding interactions.⁷ Values of V_ϕ^0 and B_v obtained, with the standard deviations, are shown in Table 1. V_ϕ^0 values are in close agreement with those derived from the application of the pseudophase model. From Table 1, it can be seen that nortriptyline has a positive B_v , possibly as a consequence of nonelectrostatic solute–solute interactions such as hydrogen-bonding, which lead to dimerization in the premicellar region.⁷ Positive B_v values have also been obtained for other amphiphilic drugs including the tranquilizer phenothiazine drugs promazine, chlorpromazine, and promethazine¹² and the antidepressant imipramine hydrochloride.¹² With such drugs, calorimetric^{18,19} and osmotic techniques⁵ have demonstrated the existence of a preaggregation process determined at concentrations well below the critical concentration. Other amphiphilic substances, such as the bile salts potassium cholate and sodium deoxycholate,²⁰ and sodium octyl sulfate,⁷ also show positive deviations from the limiting law. In the case of the bile salts, this was attributed to continuous association in a manner similar to a stacking process. On the other hand, amitriptyline and desipramine show negative B_v values, typical of more conventional surfactants such as the alkyl sulfates or tetraalkylammonium salts.^{7,21,22} Premicellar association has important implications for the transport of the drug molecules through biological membranes since this may occur at the low concentrations prevalent in vivo. The differences in the association characteristics indicated for the antidepressant drugs of this study may therefore be of importance from a pharmacological viewpoint and require further investigation.

(15) Desnoyers, J. E.; De Lisi, R.; Ostiguy, C.; Perron, G. *Solution Chemistry of Surfactants*; Plenum Press: New York, 1979; Vol. 1.

(16) Harned, H. S.; Owen, B. B. *Physical Chemistry of Electrolyte Solutions*; Chapman and Hall: London, 1957; Chapter 8.

(17) Desnoyers, J. E.; Perron, G.; Roux, A. H. *Surfactant Solutions: New Methods of Investigation*; Marcel Dekker: New York, 1987.

(18) Attwood, D.; Boitard, E.; Dubès, J. P.; Tachoire, H. *Colloid Surf.* **1990**, 48, 35.

(19) Attwood, D.; Fletcher, P.; Boitard, E.; Dubès, J. P.; Tachoire, H. *J. Phys. Chem.* **1990**, 94, 6034.

(20) Djavanbakhsh, A.; Kale, K. M.; Zana, R. *J. Colloid Interface Sci.* **1977**, 59, 139.

(21) De Lisi, R.; Ostiguy, C.; Perron, G.; Desnoyers, J. E. *J. Colloid Interface Sci.* **1979**, 71, 147.

(22) Franks, F.; Quickenden, M. J.; Ravenhill, J. R.; Smith, H. T. *J. Phys. Chem.* **1968**, 72, 2668.

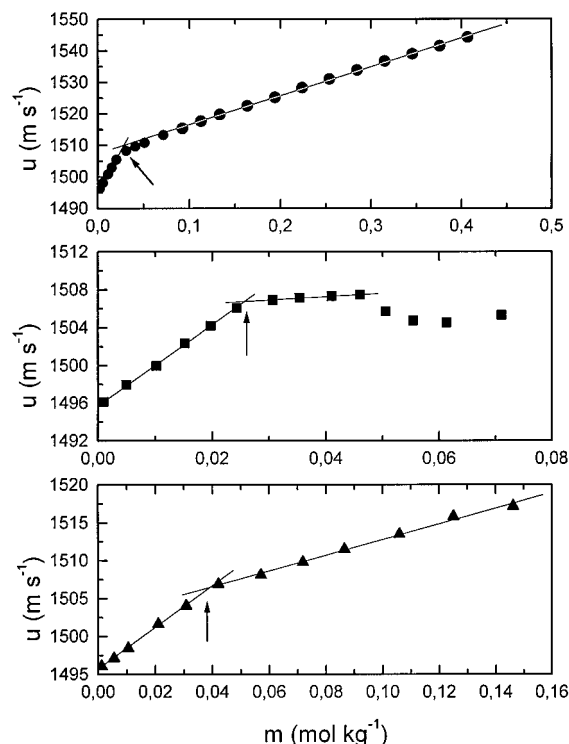


Figure 3. Ultrasound velocity, u , of (●) amitriptyline, (■) nortriptyline, and (▲) desipramine hydrochlorides in aqueous solution as a function of molality, m , at 298.15 K. The arrow denotes the critical concentration.

The change in volume associated with the formation of the stable aggregate from a monomeric drug was taken to be $\Delta V_m = V_\phi^{\text{mic}} - V_\phi^0$. The ΔV_m values for each compound determined in this way using V_ϕ^0 from the pseudophase model and the limiting law are in good agreement, as shown elsewhere.^{12,23} Moreover, the ΔV_m values for amitriptyline, nortriptyline, and desipramine are lower than those obtained for typical surfactants (for example, for sodium dodecyl sulfate, $10.8 \text{ cm}^3 \text{ mol}^{-1}$ at 298.15 K)⁷ and negative. These results suggest that there is less free space in the interior of the aggregates than in typical micelles, as might be expected if a stacked aggregate was formed. A similar conclusion was reached previously for the antidepressant imipramine hydrochloride.¹² Since these drugs have similar ionic headgroups, any differences in their ΔV_m values will be a consequence of differences in their hydrophobic groups. The higher ΔV_m for amitriptyline reflects a greater hydrophobic hydration of this drug, resulting from the presence of the extra methyl group in the hydrocarbon side chain compared with nortriptyline. Desipramine has structural differences in both the tricyclic ring system and the side chain, resulting in a slightly lower ΔV_m than that of amitriptyline (4.2 compared to 5.5 $\text{cm}^3 \text{ mol}^{-1}$). Since amitriptyline, nortriptyline, and de-

(23) Kale, K. M.; Zana, R. *J. Colloid Interface Sci.* **1977**, 61, 312.

Table 2. Critical Concentrations, cc, from Ultrasound Velocity Measurements and Adiabatic Molal Compressibilities, Isentropic Apparent Molal Adiabatic Compressibilities at Infinite Dilution, $K_{\phi(S)}^0$, Micellar Isentropic Apparent Molal Adiabatic Compressibilities, $K_{\phi(S)}^m$, and Changes in Isentropic Apparent Molal Adiabatic Compressibilities, $\Delta K_{\phi(S)}$ of Amitriptyline, Nortriptyline, and Desipramine Hydrochlorides in Aqueous Solution at 298.15 K

	cc (mol kg ⁻¹)	$10^3 K_{\phi(S)}^0$ (cm ³ bar ⁻¹ mol ⁻¹)	$10^3 K_{\phi(S)}^m$ (cm ³ bar ⁻¹ mol ⁻¹)	$10^3 \Delta K_{\phi(S)}$ (cm ³ bar ⁻¹ mol ⁻¹)
amitriptyline	0.030	-13.3	3.2	16.5
nortriptyline	0.026	-14.1	-3.6	10.5
desipramine	0.040	-5.6	1.5	7.1

sipramine have identical counterions, differences in the V_{ϕ}^0 values arise from structural differences of the drug cations. Comparison of amitriptyline and nortriptyline, or desipramine and imipramine¹² ($V_{\phi}^0 = 274.7$ cm³ mol⁻¹), shows a contribution to the volume at infinite dilution of 20.2 and 13.9 cm³ mol⁻¹, arising from the extra CH₃ group. This increment is in reasonable agreement with the increase of volume of *n*-alkylamine bromides and tetraalkylammonium salts arising from an extra methyl group (16 cm³ mol⁻¹).^{24,25}

B. Sound Velocity and Compressibilities. The dependence of the sound velocity, u , of the drug solutions at 298.15 K on the concentration, m , is shown in Figure 3. The two linear segments of the plots, corresponding to the monomeric and micellar forms of the compound, intersect at the critical concentration, showing a clear and well-defined break. The values so obtained (see Table 2) show a close agreement with those calculated from the application of the pseudophase model to the apparent molal volume values.

Density and ultrasound velocity measurements were combined to calculate adiabatic compressibilities using the Laplace equation¹⁶

$$k_s = - \frac{1}{V} \left(\frac{\partial V}{\partial p} \right)_S = \frac{10^6}{\rho u^2} \quad (4)$$

where V , p , and S refer to volume, pressure, and entropy, respectively. k_s is the adiabatic compressibility coefficient, expressed in bar⁻¹ when the ultrasound velocity u is expressed in cm s⁻¹ and the density in g cm⁻³. A plot of k_s against molality for each compound is shown in Figure 4.

The isentropic apparent molal compressibility, $K_{\phi(S)}$, can be calculated from ultrasound measurements:²²

$$K_{\phi(S)} = \frac{10^3(k_s - k_s^0)}{m\rho_0} + k_s V_{\phi} \quad (5)$$

where k_s and k_s^0 are the isentropic coefficients of compressibility of the solution and solvent, respectively. Figure 5 shows plots of $K_{\phi(S)}$ vs molality for the three antidepressants.

Previous studies of $K_{\phi(S)}$ have shown that this quantity is large and negative for ionic compounds in water, positive for mainly hydrophobic solutes, and intermediate, small, and negative for uncharged hydrophilic solutes such as sugars.^{26,27} Within a homologous series of tetra-*n*-alkylammonium salts,²⁵ alkyltrimethylammonium bromides,^{10,28} and *n*-alkyl sulfates,^{14,29} the isentropic apparent molal compressibilities of the surfactant monomers de-

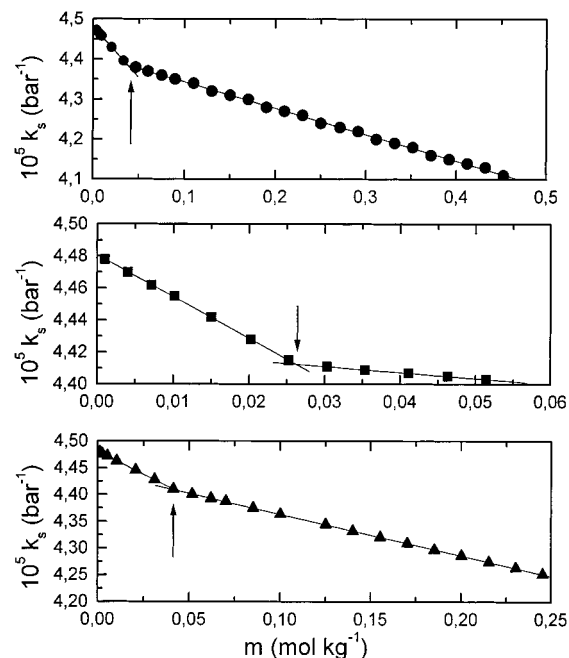


Figure 4. Adiabatic compressibility, k_s , of (●) amitriptyline, (■) nortriptyline, and (▲) desipramine hydrochlorides in aqueous solution as a function of molality, m , at 298.15 K. The arrow denotes the critical concentration.

creased with increasing chain length due to an increase in the amount of structured water in the vicinity of the hydrocarbon chains, which is less compressible than bulk water. Therefore, it might be expected that the drug cations would have lower compressibilities than these surfactants because of their larger hydrophobic groups. The isentropic apparent molal compressibilities at infinite dilution, $K_{\phi(S)}^0$, confirm this hypothesis (see Table 2): (a) the large and negative values of $K_{\phi(S)}^0$ are a consequence of a higher resistance to pressure of the structured water around the monomer compared to that of bulk water, and (b) the hydrophobic character of the aggregates of amitriptyline and desipramine is indicated by the positive values of the apparent molal adiabatic compressibility of the aggregates, $K_{\phi(S)}^m$. However, the $K_{\phi(S)}^m$ values are lower than those obtained for penicillin V (65×10^{-4} bar⁻¹ cm³ mol⁻¹)³⁰ or typical surfactants such as SDS (146×10^{-4} bar⁻¹ cm³ mol⁻¹).¹⁴ The high compressibilities of the latter are explained in terms of van der Waals interactions between the solute and solvent and imply that the micellar interior resembles a bulk liquid phase.³¹ It is interesting to note the similarity of the $K_{\phi(S)}^m$ values of the antidepressant

(28) Mosquera, V.; del Río, J. M.; Attwood, D.; García, M.; Jones, M. N.; Prieto, G.; Suárez, M. J.; Sarmiento, F. *J. Colloid Interface Sci.* **1998**, *206*, 66.

(29) Suárez, M. J.; López-Fontán, J. L.; Sarmiento, F.; Mosquera, V. *Langmuir* **1999**, *15*, 5265.

(30) Varela, L. M.; Rega, C.; Suárez, M. J.; Ruso, J. M.; Prieto, G.; Attwood, D.; Sarmiento, F.; Mosquera, V. *Langmuir* **1999**, *15*, 6285.

(31) Tanford, C. *The Hydrophobic Effect*; Wiley: New York, 1973.

(24) Desnoyers, J. E.; Are, M. *Can. J. Chem.* **1967**, *45*, 359.

(25) Conway, B. E.; Verall, R. E. *J. Phys. Chem.* **1966**, *70*, 3952.

(26) Hoiland, H.; Vikingstand, E. *J. Chem. Soc., Faraday Trans. 1* **1976**, *72*, 1441.

(27) Franks, F.; Ravenhill, J. R.; Reid, D. S. *J. Solution Chem.* **1972**, *1*, 3.

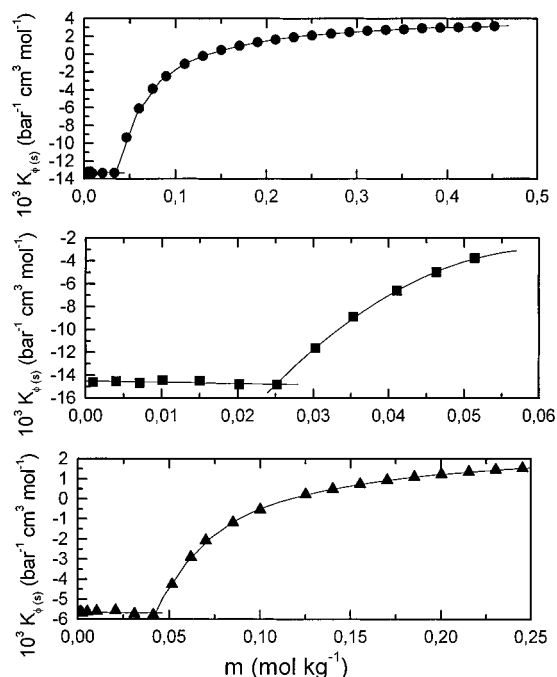


Figure 5. Isentropic apparent molal compressibility, $K_{\phi(S)}$, of (●) amitriptyline, (■) nortriptyline, and (▲) desipramine hydrochlorides in aqueous solution as a function of molality, m , at 298.15 K.

drugs and those of the phenothiazine drugs ($K_{\phi(S)}^m$ of chlorpromazine is $39 \times 10^{-4} \text{ bar}^{-1} \text{ cm}^3 \text{ mol}^{-1}$),¹² the association of which has been shown to occur by a stacking

process.³² Therefore, although the structure of the aggregates of the antidepressant drugs was not explored here, the low compressibility of the drug aggregates suggests a stacked aggregate which does not possess the looseness of structure associated with the micelles of typical surfactants.

The change in the partial molal isentropic compressibility of aggregation, $\Delta K_{\phi(S)}$, can be evaluated from

$$\Delta K_{\phi(S)} = K_{\phi(S)}^m - K_{\phi(S)}^0 \quad (6)$$

Table 2 shows a comparison between the values obtained in this work for $K_{\phi(S)}^m$ and $K_{\phi(S)}^0$ of each drug. $\Delta K_{\phi(S)}$ is positive for all drugs, as was found previously for imipramine and clomipramine,^{12,13} indicating the predominant role of the decrease of hydrophobic hydration in the association process. This decrease is mainly due to an appreciable dehydration of the aromatic rings and the polar headgroups of antidepressant molecules during association such as might occur as a consequence of stacking of the molecules in the aggregate with the polar groups and the side chains arranged around the periphery of the stack, as demonstrated for phenothiazine drugs³² and some penicillins.^{6,33}

Acknowledgment. We thank the Xunta de Galicia for financial support.

LA0007325

(32) Attwood, D.; Waigh, R.; Blundell, R.; Bloor, D.; Thévand, A.; Boitard, E.; Dubès, J. P.; Tachoire, H. *Magn. Reson. Chem.* **1994**, *32*, 468.

(33) Taboada, P.; Attwood, D.; Ruso, J. M.; García, M.; Mosquera, V.; Sarmiento, F. *Langmuir* **2000**, *16*, 3175.