A Calorimetric Study on the Self-Association of Amphiphilic Drugs in Aqueous Solution

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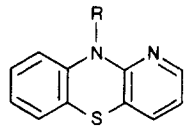
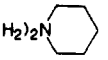
The technique of heat conduction calorimetry has been applied to a study of the self-association of two amphiphilic drugs in aqueous electrolyte solution. Deconvolution of the calorimetric response has permitted the continuous determination of the variation of apparent molar enthalpy with concentration extending to regions of high dilution. A theoretical treatment is presented of the thermogenesis in solutions of amphiphilic compounds undergoing self-association by a process of stepwise addition of monomers. This treatment has been applied in a study of the association of the two azaphenothiazine drugs, isothipendyl hydrochloride and pipazethate hydrochloride, in dilute electrolyte solutions. The calorimetric data for all systems could be satisfactorily described by using an association model with stepwise equilibrium constants of equal magnitude. Values are presented for the molar enthalpy change on association and for the stepwise equilibrium constants.

Introduction

It is clear from a large number of investigations on the physicochemical properties of phenothiazine drugs[1,2] that these amphiphilic compounds form micelles in water and in the presence of low concentrations of added electrolyte. Recent light-scattering studies[3] have shown that the presence of a pyridine-like N atom in the phenothiazine ring system causes a change to a continuous association pattern, which in the case of the two azaphenothiazine drugs, isothipendyl hydrochloride, I, and pipazethate hydrochloride, II, could be described by a stepwise association model



I: R = $-CH_2CH(CH_3)N(CH_3)_2$

II: R = $-COO(CH_2)O(CH_2)_2N$ 

with equilibrium constants of equal magnitude. Such association models have been widely used to describe the stacking of cationic dyes and nucleotides. Other structural features of drug molecules which are thought to influence the association pattern, and analytical methods for derivation of stepwise association constants, are reviewed in ref 1 and 2.

Recent work on the deconvolution of instrumental response has allowed the transformation of a calorimeter, normally used in an integral manner, into an instrument capable of giving an instantaneous measurement of the thermal power associated with a given process, i.e., a "thermal oscilloscope".[4] Such modification has permitted the examination of the thermodynamics of solutions in regions of low concentration.[5] We now report the application of this technique in a study of the self-association of the two azaphenothiazine drugs examined previously. Although recent papers[6-9] report systematic measurements of the enthalpies of dilution of a series of alkyltrimethylammonium bromides, there are no previous reports of similar measurements on the type of continuously associating system under investigation here. Measurements of the instantaneous thermal power, i.e., thermogenesis, associated with the molecular aggregation in these systems have been treated theoretically to determine the pattern of association and to derive values of the stepwise equilibrium constants and the molar enthalpy changes of association.

Experimental Section

Calorimetric Equipment. Calorimetric measurements were performed at 30 °C on a modified Arion-Electronique conduction calorimeter (Type BCP). The principle of the calorimetric system is illustrated in Figure 1. The mixing process takes place in a measurement cell (25 mm diameter and 80 mm height) surrounded successively by semiconductor thermocouples and by an isothermal calorimetric block (thermal heat sink). This element is differentially related to a twin reference cell in such a way that a possible drift of the experimental zero, caused by a corresponding drift of the room temperature, is minimized. Mixing of the contents of both cells was effected by paired paddles driven by a common motor. Reactant was continuously injected by paired glass syringes.[10] Equipping the test and control cells in an identical manner in this way allowed compensation for the parasitic effects due to mixing.

Deconvolution of Instrumental Response. The response $h(t)$ of a linear system such as this to an impulse may be described by an exponential sum

$$h(t) = \sum_{i=0}^{i=n} a_i \exp(-t/\tau_i) \qquad (1)$$

where τ_i are the instrumental constants and a_i their amplitude coefficients. The instrumental response to any signal input only represents this input (with a small time delay) when the signal shows a slow variation with time.[11] In general, however, the transfer function of the equipment leads to signal deformation and, in order to measure the instantaneous power, P, absorbed by the environment of the reaction during the course of an experiment, it is essential to deconvolve the response by compensation of the principal time constants. Since the series (τ_i) declines rapidly, compensation of the first two constants generally gives

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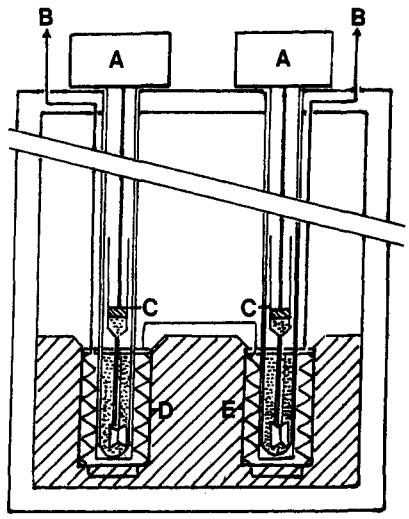

Figure 1. Diagram to show the principle of the calorimetric system. Key: A, stirrer and mixing system; B, to amplifier; C, syringe; D, measurement cell; E, reference cell.

a satisfactory reconstitution of the thermogenesis of the phenomenon under study.[12] The raw instrumental response, $s(t)$, (the experimental thermogram) was corrected by using the expression $s(t) + \tau_1\, ds(t)/dt$ to obtain a signal, $s_1(t)$, free of the influence of the time constants τ_1. Similarly, application of the correction $s_1(t) + \tau_2\, ds_1(t)/dt$ eliminated the influence of τ_2. This procedure may be applied by an analogue technique or by a numerical correction to a sampled thermogram.[13] In this study, the calorimetric output was directed to an amplifier (Ancom 15C3-a) and, thence, to a digital voltmeter (Enertec-Schlumberger 7060) linked to a minicomputer (Digital Minc 23). Analogue filtering was achieved by a two-stage filter[14] which corrected the first two time constants on line. The method of determination of τ_1 and τ_2 without systematic error has been discussed elsewhere.[15] This is a critical stage in the general process of deconvolution upon which the quality of reconstitution of the thermogram is highly dependent.

Calibration. The instrument was calibrated by using a chemical process, which gives a better representation of the dynamic properties of the equipment than an electrical calibration procedure. The concept of apparent molar enthalpy, ϕL_2, of a solute allows tabulation of the enthalpies of dilution. Dilution from an initial molality m_I to a final molality m_F is given by[16]

$$[\Delta_{dln}H]_{m_I}^{m_F} = \phi L_2(m_F) - \phi L_2(m_I) \qquad (2)$$

An expression for $\phi L_2(m)$ for sodium chloride at 25 °C has been reported by Fortier and co-workers.[17] Messikomer and Wood[18] have published a series of numerical values for this system at 30 °C. These data have been fitted to an expression of the form used by Fortier and co-workers; thus

$$\phi L_2(m) = 2109(d_0 m)^{1/2} - 3318.1m + 2625.6m^{3/2} - 2096.3m^2 + 802.4m^{5/2} \qquad (3)$$

where d_0 is the mass per unit volume of water at 30 °C and

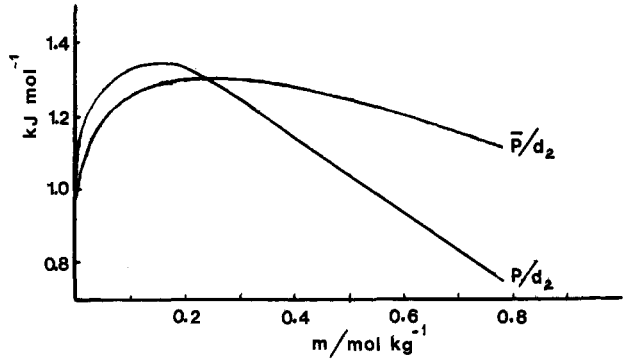

Figure 2. Variation of the functions P/d_2 and $\bar{P}/d_2$ with concentration, m, for the dilution of an aqueous sodium chloride solution at 30 °C.

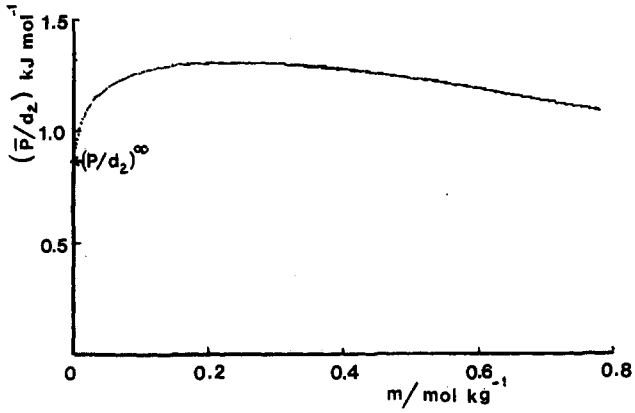

Figure 3. Experimental values of $\bar{P}/d_2$ for sodium chloride solutions, used in the determination of the instrumental calibration constant, S. The mean standard deviation of the fit to eq 7 was ±1.4 J mol^{-1}.

$\phi L_2(m)$ is the apparent molar enthalpy of a solute in a solution of molality, m.

It may be shown[19] that at infinite dilution (at the commencement of the experiment when the experimental cell contains only solvent) the ratio of the power absorbed, P, to the rate of addition of solute, d_2, is numerically equal (though of opposite sign) to the apparent molar enthalpy of the solute in the titrant solution; that is,

$$\left(\frac{P}{d_2}\right)^{\infty} = -\phi L_2(m_I) \qquad (4)$$

At a time t after the commencement of the dilution process, when the molality of the solute in the cell is m, the average power absorbed $\bar{P}$ is given by

$$(\bar{P}/d_2)_m = \phi L_2(m) - \phi L_2(m_I) \qquad (5)$$

where

$$\bar{P} = (1/t)\int_0^t P\, dt$$

and hence

$$\phi L_2(m) = (\bar{P}/d_2)_m + \phi L_2(m_I) = (\bar{P}/d_2)_m - (P/d_2)^{\infty} \qquad (6)$$

Figure 2 presents a graphical representation of this expression for the dilution of an aqueous solution of sodium chloride at 30 °C. If $(\bar{e}(t)/d_2)_m$ and $(e(t)/d_2)^{\infty}$ are calculated from the signal $e(t)$ obtained by deconvolution of the calorimetric response $s(t)$, then

$$\phi L_2(m) = (\bar{P}/d_2)_m - (P/d_2)^{\infty} = [(\bar{e}(t)/d_2)_m - (e(t)/d_2)^{\infty}]S \qquad (7)$$

The calibration constant S of the instrument was determined by

(12) Cesari, E.; Torra, V.; Macqueron, J. L.; Prost, R.; Dubès, J. P.; Tachoire, H. *Thermochim. Acta*, **1982**, *53*, 1, 17.
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(16) Tachoire, H.; Torra, V. "Progress Report on Thermokinetics by Heat-Conduction-Calorimetry"; *Proceedings of the ICTA 8, Bratslava, August 1985*. Boitard, E.; Dubès, J. P.; Kêchavarz, R.; Tachoire, H. *Thermochim. Acta*, in press.
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(19) Boitard, E.; Dubès, J. P.; Kêchavarz, R.; Tachoire, H. *Thermochim. Acta*, in press.

fitting the experimental data points of Figure 3 to eq 7. The standard deviation of the fitted line was ±1.4 J mol^{-1} over the whole concentration range.

During the course of the experiment the value of τ_1 increases due to an increase in the volume contained in the cell whilst the higher constants remain essentially invariant. It has been shown previously that the variation of τ_1 is linear[20] and hence, in order to reconstitute the thermogenesis, we have applied an evolving inverse filtering which accounts for this variation.

Calorimetric Measurements on Drug Solutions. The two cells initially contained 15 g of aqueous sodium chloride of the required molarity (0.1 mol dm^{-3} or 0.2 mol dm^{-3}). The injection apparatus delivered this same solution into the control cell and a solution of the drug (0.25 mol kg^{-1}) in the aqueous sodium chloride solution into the test cell at an identical rate (2 cm^3 h^{-1}).

Materials. Isothipendyl hydrochloride [10-(2-dimethylamino-2-methylethyl)-10*H*-pyrido[3,2-*b*][1,4]benzothiazine hydrochloride] (ICI plc) and pipazethate hydrochloride [10*H*-pyrido[3,2-*b*][1,4]benzothiadiazine-10-carboxylic acid, 2-[(2-piperidinoethoxy)]ethyl ester hydrochloride (Chemiewerk-Homburg) were sufficiently well characterized and purified to be used as received. Sodium chloride was of AnalaR grade.

Theoretical Section

The association of the two amphiphilic drugs was assumed to occur by stepwise addition of monomers according to

$$A_1 + A_1 \rightleftharpoons A_2$$

$$A_2 + A_1 \rightleftharpoons A_3$$

$$\vdots$$

$$A_{i-1} + A_1 \rightleftharpoons A_i$$

If $m_i(t)$ represents the molality of the species A_i at time t, the total molality $m(t)$ in terms of monomer of all the species present is given by

$$m(t) = \sum_{i=1}^{\infty} i m_i(t) = m_1(t) + 2m_2(t) + \ldots + i m_i(t) + \ldots \quad (8)$$

The quantity of heat $Q_i(t)$ absorbed by the system during the formation of $N_i(t)$ moles of A_i in the time interval between t = 0 (infinite dilution) and t is given by

$$Q_i(t) = N_i(t)[\Delta H_i + \Delta H_{i-1} + \ldots + \Delta H_2] \quad (9)$$

where ΔH_i represents the molar enthalpy change during the formation of A_i. At time t there are also present in the solution, $N_2(t)$ moles of A_2, $N_3(t)$ moles of A_3, ... The corresponding thermal effects are

$$Q_2(t) = N_2(t)\Delta H_2$$

$$Q_3(t) = N_3(t)[\Delta H_2 + \Delta H_3]$$

$$\vdots$$

$$Q_i(t) = N_i(t)[\Delta H_i + \ldots + \Delta H_2] \quad (10)$$

The global thermal effect $Q_T(t)$ is thus

$$Q_T(t) = \sum_{i=2}^{\infty} Q_i(t) = \sum_{i=2}^{\infty}[N_i(t)\sum_{j=2}^{i}\Delta H_j] = \sum_{i=2}^{\infty}[\Delta H_i \sum_{j=i}^{\infty} N_j(t)] \quad (11)$$

The corresponding thermogenesis $P_T(t)$ (power absorbed by the system) has the form

$$P_T(t) = \sum_{i=2}^{\infty}[(dN_i(t)/dt)\sum_{j=2}^{i}\Delta H_j] \quad (12)$$

Expressing $m(t)$, $Q_T(t)$, and $P_T(t)$ in terms of the association constants K_i and the molality $m_1(t)$ of monomer A_1, we obtain

$$m(t) = m_1(t)[1 + 2K_2m_1(t) + 3K_2K_3[m_1(t)]^2 \ldots + iK_2K_3\ldots K_i[m_1(t)]^{i-1} + \ldots] \quad (13)$$

$$m(t) = m_1(t) + \sum_{i=2}^{\infty}(i[m_1(t)]^i \prod_{k=2}^{i} K_k) \quad (14)$$

$$Q_T(t) = M_T(t)(\sum_{i=2}^{\infty}([m_1(t)]^i \prod_{k=2}^{i} K_k)\sum_{j=2}^{i}\Delta H_j) \quad (15)$$

$$P_T(t) = \sum_{i=2}^{\infty}((d(M_T(t)[m_1(t)]^i)/dt \prod_{k=2}^{i} K_k)\sum_{j=2}^{i}\Delta H_j) \quad (16)$$

$M_T(t)$ represents the total molar mass of solvent at time t

$$M_T(t) = M_0 + M(t) \quad (17)$$

where M_0 is the mass of solvent initially present in the cell.

Knowing the relationship between the constant K_i and K_{i+1} allows the deduction of that between ΔH_i and ΔH_{i+1}. Assuming that these enthalpies remain almost constant in the infinitesimal interval between T_1 and T_2, one may express the van't Hoff equation in the form

$$\ln (K_i(T_2)/K_i(T_1)) = -(\Delta H_i/R)[(1/T_2) - (1/T_1)] \quad (18)$$

and

$$\ln (K_{i+1}(T_2)/K_{i+1}(T_1)) = -(\Delta H_{i+1}/R)[(1/T_2) - (1/T_1)] \quad (19)$$

Substracting eq 19 from eq 18 gives

$$\ln [(K_i/K_{i+1})_{T_2}(K_{i+1}/K_i)_{T_1}] = (-1/R)((1/T_2) - (1/T_1))(\Delta H_i - \Delta H_{i+1}) \quad (20)$$

Postulating a fixed relationship between successive equilibrium constants gives

$$\ln 1 = (-1/R)((1/T_2) - (1/T_1))(\Delta H_i - \Delta H_{i+1}) = 0 \quad (21)$$

$$\Delta H_i = \Delta H_{i+1} = \Delta H \quad (22)$$

Equation 15 now becomes

$$Q_T(t) = \Delta H M_T(t)(\sum_{i=2}^{\infty}(i-1)[m_1(t)]^i \prod_{k=2}^{i} K_k) \quad (23)$$

since the equality of all the enthalpy changes entrains the corollary

$$\sum_{j=2}^{i}\Delta H_j = (i-1)\Delta H \quad (24)$$

In the same way

$$P_T(t) = \Delta H(\sum_{i=2}^{\infty}(i-1)(dM_T(t)[m_1(t)]^i/dt)\prod_{k=2}^{i} K_k) \quad (25)$$

The experimental data may be fitted to the preceding equations by assuming a fixed relationship between the equilibrium constants K_i and K_{i+1} and, in this way, the enthalpies of formation may be calculated. The following association models were considered.

Model 1

This model assumes the equality of all stepwise association constants

$$K_i = K_{i+1} = K, \quad \Delta H_i = \Delta H_{i+1} = \Delta H \quad (26)$$

The total molality of amphiphile may be expressed in terms of that, $m_1(t)$, of the monomer A_1 by using eq 14.

$$m(t) = m_1(t) \times (1 + 2Km_1(t) + 3K^2[m_1(t)]^2 + \ldots + iK^{i-1}[m_1(t)]^{i-1} + \ldots) = m_1(t)(\sum_{i=1}^{\infty} i[Km_1(t)]^{i-1}) \quad (27)$$

Let $X = Km_1(t)$, then

$$m(t) = \left(\frac{X}{K}\right)(1 + 2X + 3X^2 + \ldots + iX^{i-1} + \ldots) = \frac{X}{K}\sum_{i=1}^{\infty} iX^{i-1} \quad (28)$$

(20) Rey, C.; Rodriguez, J. R.; Perez-Villar, V.; Ortín, J.; Torra, V.; Dubès, J. P.; Kéchavarz, R.; Tachoire, H. *Thermochim. Acta*, **1984**, *81*, 97. Ortín, J.; Ramos, A.; Torra, V. *Thermochim. Acta*, **1985**, *84*, 255. Ortín, J.; Rey, C.; Torra, V. *Thermochim. Acta*, **1985**, *96*, 37.

whence

$$m(t) = N(t)/M_T(t) = (X/K)/(1 - X)^2 \quad (29)$$

The molality of the monomer, $m_1(t)$, may be obtained by solution of eq 29 giving

$$m_1(t) = [1 + 2Km(t) - (1 + 4Km(t))^{1/2}]/2K^2m(t) \quad (30)$$

The total quantity of heat absorbed by the system between times $t = 0$ and t is given by eq 23 as

$$Q(t) = \Delta HM_T(t)(\sum_{i=2}^{\infty}(i - 1)[m_1(t)]^iK^{i-1}) \quad (31)$$

since for this model

$$\prod_{k=2}^{i} K_k = K^{i-1} \quad (32)$$

$$Q_T(t) = (\Delta HX^2M_T(t)/K)(\sum_{i=1}^{\infty} iX^{i-1}) \quad (33)$$

Thus

$$Q_T(t) = \Delta HX^2M_T(t)/K(1 - X)^2 \quad (34)$$

Substituting for $M_T(t)$ from eq 29 gives

$$Q_T(t) = \Delta HXN(t) \quad (35)$$

The power $P_T(t)$ relative to the formation of the associated species is thus of the form

$$P_T(t) = \Delta H\, d(N(t)X)/dT = \Delta H(N(t)(dX/dt) + Xd_2) \quad (36)$$

where $d_2 = dN(t)/dt$.

Differentiation of eq 29 and substitution into eq 36 yields

$$P_T(t) = \Delta H[Km_1(t)/(1 + Km_1(t)](2d_2 - m_1(t)d_1/(1 - Km_1(t)) \quad (37)$$

Equation 30 may be used to calculate $m_1(t)$ for any given value of K. Similarly, $P_T(t)$ may be calculated from eq 37 for a given value of ΔH. The values of K and ΔH may then be adjusted until a satisfactory representation of the function $P_T(t)$ is achieved.

The relative apparent molar enthalpy $\phi L(m)$ of the amphiphilic solute represents the sum per mole of solute of the thermal effects resulting from the self-association; that is,

$$\phi L(m) = Q_T/N(t) = \Delta HKm_1(t) \quad (38)$$

The evolution of this function as determined from eq 6 may be utilized as an alternative means of extracting values of K and ΔH. Both this method and the use of eq 37 are equivalent.

Model 2

This model represents a mildly cooperative association process which has been found to satisfactorily describe the association characteristics of several drugs[21,22]

$$K_i = K(i - 1)/i \quad (39)$$

For this model

$$m(t) = m_1(t)(1 + Km_1(t)) + K^2[m_1(t)]^2 + ... + K^{i-1}(m_1(t)^{i-1} + ...)$$

$$= (X/K)\sum_{i=1}^{\infty} X^{i-1} \quad (40)$$

$$m(t) = (N(t)/M_T(t)) = X/K(1 - X) = m_1(t)/(1 - Km_1(t)) \quad \text{for } X < 1 \quad (41)$$

$$m_1(t) = m(t)/(1 + Km(t)) \quad (42)$$

(21) Attwood, D.; Tolley, J. A. *J. Pharm. Pharmacol.* **1980**, *32*, 761.
(22) Attwood, D.; Agarwal, S. P.; Waigh, R. D. *J. Chem. Soc., Faraday Trans. 1* **1980**, *76*, 2187.

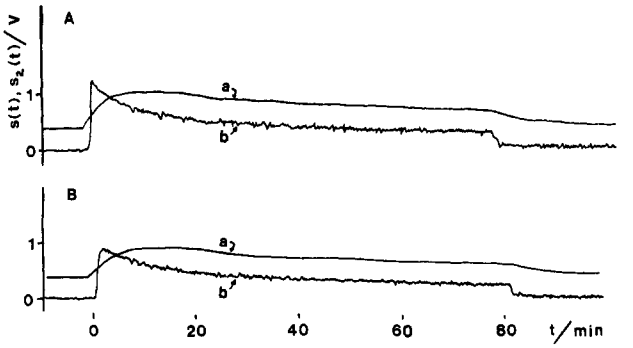

Figure 4. Thermograms at 30 °C for the dilution of aqueous solutions of (A) isothipendyl hydrochloride (0.25 mol kg^{-1}) in 0.1 M NaCl and (B) pipazethate hydrochloride (0.25 mol kg^{-1}) in 0.2 M NaCl: (a) raw thermogram $s(t)$; (b) signal $s_2(t)$ obtained after deconvolution by inverse filtering. $s_2(t)$ is equivalent to the input signal $e(t)$ whose amplitude is proportional to the thermogenesis (power P absorbed).

The total quantity of heat $Q_T(t)$ absorbed by the system between times $t = 0$ and t is given by eq 23 as

$$Q_T(t) = \Delta HM_T(t)(\sum_{i=1}^{\infty}[(i - 1)/i]m_1(t)^iK^{i-1}) \quad (43)$$

or

$$Q_T(t) = \Delta H(M_T(t)/K)(\sum_{i=1}^{\infty}(i - 1)X^i/i) \quad (44)$$

whence

$$Q_T(t) = \Delta H(M_T(t)/K)([X/(1 - X)] + \ln(1 - X)) \quad (45)$$

Substituting from eq 41 gives

$$Q_T(t) = \Delta H[(M_T(t)/K)\ln(1 - X) + N(t)] \quad (46)$$

The power is thus given by

$$P_T(t) = \Delta H[d((M_T(t)/K)\ln(1 - X))/dt + d_2] \quad (47)$$

from which

$$P_T(t) = \Delta H[Xd_2 + [X + \ln(1 - X)](d_1/K)] \quad (48)$$

or, as a function of $m_1(t)$

$$P_T(t) = \Delta H[Km_1(t)d_2 + [Km_1(t) + \ln(1 - Km_1(t))](d_1/K)] \quad (49)$$

Values of K and ΔH were derived by the analysis of the experimental data using eq 49 or, alternatively, by the use of the function $\phi L(m)$ which for this model becomes

$$\phi L(m) = \Delta H[(M_T(t)/N(t)\ K)\ln(1 - X) + 1] \quad (50)$$

Substituting from eq 41 yields

$$\phi L(m) = \Delta H[1 + [(1 - X)\ln(1 - X)]/X] \quad (51)$$

or

$$\phi L(m) = [\Delta H/Km(t)][Km(t) - \ln(1 + Km(t))] \quad (52)$$

Results and Discussion

Parts A and B of Figure 4 show typical plots of the uncorrected instrumental response $s(t)$ and the deconvolved signals $s_2(t)$ as derived from inverse filtering of this signal for the dilution of isothipendyl hydrochloride and pipazethate hydrochloride, respectively. $s_2(t)$ is equivalent to the input signal $e(t)$ whose amplitude is proportional to the thermogenesis P. The observed effects were always endothermic. The power P declined continuously from the value equivalent to infinite dilution with increase in the concentration of drug in the cell. Division of P by the rate of addition d_2 of the drug yields the function $f(m) = P/d_2$, the

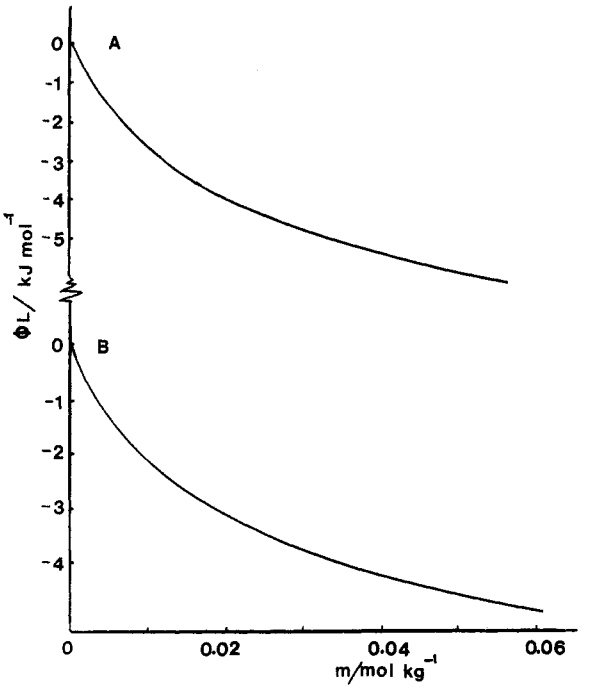

Figure 5. Variation of the function ϕL with concentration, m, at 30 °C for (A) isothipendyl hydrochloride in 0.1 M NaCl and (B) pipazethate hydrochloride in 0.2 M NaCl.

value of which at infinite dilution represents (with inversion of sign) the apparent relative molar enthalpy, ϕL, of the amphiphile in the titrant.

$$(P/d)^{\infty} = \phi L^{\infty} - \phi L'(\text{titrant}) = -\phi L' \qquad (\text{since } \phi L^{\infty} = 0) \tag{53}$$

At any given point in the titration, when the concentration is m and the average power is $\bar{P}$,

$$(\bar{P}/d)_m = \phi L(m) - \phi L' \tag{54}$$

then

$$\phi L(m) = (\bar{P}/d_2)_m - (P/d_2)^{\infty} \tag{55}$$

Parts A and B of Figure 5 show plots of the function $\phi L(m)$ against molality for isothipendyl hydrochloride in 0.1 M NaCl and pipazethate hydrochloride in 0.2 M NaCl, respectively.

It is evident that the calorimetric technique used in this study permits the generation in one continuous experiment of the function $\phi L(m)$ even in very dilute solution. With classical calorimetric techniques, the construction of such plots would necessitate many individual measurements. For example, in a comparable study by Berg[23] of the apparent molar enthalpy of solute in aqueous solutions of sodium dodecyl sulfate, a flow calorimeter was used which allowed discontinuous measurements of the integral enthalpies of dilution ΔH_{dln} between an initial molality m_I and several final molalities m_F both above and below the critical micelle concentration. The apparent relative molar enthalpy $\phi L(m_F)$ was then calculated from values of $\phi(m_I)$ derived by extrapolation of this function to infinite dilution according to

$$\phi L(m_F) = [\Delta_{dln}H]_{m_I}^{m_F} + \phi L(m_I) \tag{56}$$

$$= [\Delta_{dln}H]_{m_I}^{m_F} - [\Delta_{dln}H]_{m_I}^{0} \tag{57}$$

The theoretical treatment of thermogenesis in solutions of associating amphiphiles as outlined in the theoretical section was applied to the calorimetric data. The model which assumed equality of association constants (model 1) gave an excellent representation of the data for all systems. Figure 6 shows a typical

(23) Berg, R. L. "Thermodynamics of Aqueous Solutions of Sodium Dodecyl Sulphate"; Bartlesville Energy Research Center, Report TPR-73/3, 1977.

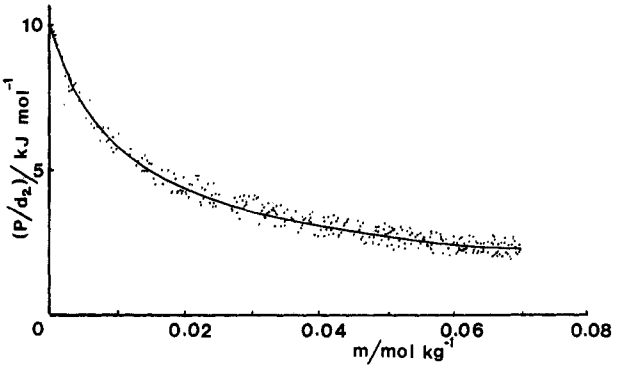

Figure 6. Variation of the function P/d_2 with concentration for isothipendyl hydrochloride in 0.1 M NaCl at 30 °C. Continuous line represents theoretical variation as calculated by model 1.

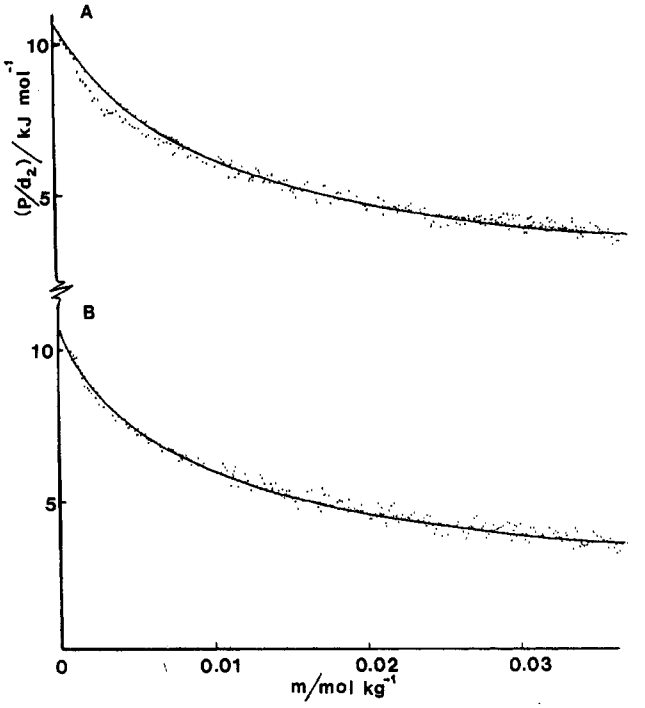

Figure 7. Variation of the function P/d_2 with concentration for isothipendyl hydrochloride in 0.1 M NaCl at 30 °C at low concentration. Continuous lines represent theoretical variation as calculated by (A) model 2 and (B) model 1.

TABLE I: Stepwise Association Constants and Molar Enthalpies for the Association of Isothipendyl Hydrochloride and Pipazethate Hydrochloride in Aqueous Electrolyte at 30 °C

	light scattering[a]		calorimetry		
NaCl concn, mol dm^{-3}	max concn, mol kg^{-1}	K, kg mol^{-1}	max concn, mol kg^{-1}	K, kg mol^{-1}	ΔH, kJ mol^{-1}
			Isothipendyl Hydrochloride		
0.1	0.05	19	0.04	40 ± 1	−12.1 ± 0.2
	0.08	16	0.07	40 ± 1	−12.0 ± 0.2
0.2	0.05	24	0.03	37 ± 1	−12.1 ± 0.2
	0.08	26	0.06	33 ± 1	−12.9 ± 0.2
			Pipazethate Hydrochloride		
0.1	0.05	23	0.03	31 ± 1	−10.3 ± 0.2
	0.12	17	0.07	30 ± 1	−10.1 ± 0.2
0.2	0.06	48	0.03	31 ± 1	−10.3 ± 0.2
	0.11	41	0.07	31 ± 1	−10.3 ± 0.2

[a] Recalculated from light-scattering data of ref 3.

fit of the data for isothipendyl hydrochloride in 0.1 M NaCl. Model 2 was unable to adequately describe the data for these systems in the region of high dilution, although the fit to the data at higher concentrations was satisfactory. (Figure 7). Values

of K and ΔH derived from the analysis of the calorimetric data using model 1 are given in Table I. The influence of concentration range upon the optimum parameters has been investigated by fitting the curves over their full concentration range ($m \leq 0.07$ mol kg^{-1}) and over the half-width. Inspection of the results shows little significant concentration dependence.

Included in Table I are values of K derived by the analysis of light-scattering results for these systems. It is encouraging to note that these very different experimental techniques have both indicated the same association model. The data previously reported by Attwood did not include the pipazethate–0.2 M NaCl system. Light-scattering measurements have been carried out on this system and the data for the other systems investigated here have been reanalyzed over similar concentration ranges to those of the calorimetric measurements to avoid possible influence of nonideality effects at high concentration on the values calculated from the light-scattering data. The concentration dependence of K from this technique was more marked than that noted for calorimetry, particularly for the pipazethate systems. In view of the difficulties in obtaining precise light-scattering data at such low concentrations, it is considered that the difference in magnitude between the K values from the two experimental techniques is probably within the limits of error of the light-scattering measurements.

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The Mean Activity Coefficient of an Electrolyte Solution Inside a Charged Cylindrical Micropore. Effect of the Counterions

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The Poisson–Boltzmann equation for the ionic distribution inside a charged cylindrical micropore is solved variationally by minimizing the associated electrostatic free energy. A new expression for the mean ionic activity coefficient is obtained from the free energy expression for the system with fixed surface charge density, and the effect of the counterions on this property is discussed. It is found that the counterion screening is significant for large surface charge densities and small values of the concentration parameter κR.

Introduction

The problem of a charged cylindrical micropore in equilibrium with an external electrolyte solution has a number of chemical, colloidal, and engineering applications and has been the subject of several studies.[1] The simplest approach to the calculation of the electrostatic properties of the ions inside the micropores is the use of the nonlinear Poisson–Boltzmann equation, and special attention has been given to its variational solution.[2] The electroneutrality condition inside the cylinder requires the consideration of the presence of ions of opposite charge to that of the wall, i.e., the counterions, whose concentration depends on the magnitude of the surface charge density and should become particularly important for high charges and low external electrolyte concentration. This gives rise to an additional term in the Poisson–Boltzmann equation which has been often overlooked in the literature.

In the next section we start with the electrostatic free energy of the system and derive a new expression for the activity coefficient inside a charged micropore.

We then use the variational principles of Arthurs and Robinson,[8] successfully used by one of us[2] in the study of electrokinetic flux in microcapillaries, to solve the corresponding standard Poisson–Boltzmann equation.

The Electrostatic Mean Activity Coefficient

Let us consider an infinite cylinder of radius R with a fixed and uniformly smeared surface charge density σ. The cylinder is immersed in an aqueous electrolyte solution, considered in the restricted primitive model, which is allowed to fill the interior. The description of the interaction of the surface charge with the ions outside the cylinder is referred to as the outer problem while the description of the properties of the ions inside the micropore, which is the interest of this work, is referred to as the inner problem.[3] The mean electrostatic potential inside the cylinder, $\psi(r)$, is assumed to be given by the Poisson–Boltzmann equation

$$\nabla^2\psi = -\frac{4\pi}{\epsilon}\sum_i z_j e \rho_j \exp[-\beta z_j e \psi] \qquad (1)$$

where ϵ is the dielectric constant, $z_j e$ is the ionic charge, ρ_j is the number density of ionic species j, e is the electron's charge, and $\beta = 1/kT$, where k is Boltzmann's constant and T the temperature. We assume that the charge on the cylinder arises from the dissociation of the polarizable groups on its surface. The sum in eq 1 then is over all ionic species in solution and includes the counterions and the ions coming from the dissociation of the added electrolyte. This equation is subjected to the boundary condition

$$(\nabla\cdot\psi)\cdot\hat{n} = \frac{4\pi}{\epsilon}\sigma \qquad (2)$$

where $\hat{n}$ denotes the outward normal vector and σ the charge surface density of the micropore.

The electrical free energy of this system can be obtained by adding the work necessary to charge the ions in solution in the volume V inside the cylinder plus the work used to charge the surface. Using the charging process described by Levine,[4] we calculated the electrical free energy as

$$A_e = \int_0^1 \frac{d\lambda}{\lambda} \int_V \psi \rho_c(r)\, d\vec{r} + \int_0^1 d\lambda \int_S \psi\sigma\, dS \qquad (3)$$

where λ is the charging parameter and $\rho_c(r)$ is the local charge density of the electrolyte.

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