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Thermodynamic Study of Self-Assembly Behavior of Propranolol Hydrochloride in Aqueous Solutions as a Function of Electrolyte Concentration and Temperature

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Density and ultrasound measurements of propranolol hydrochloride in aqueous solutions were carried out as functions of the drug molality, in the presence of different concentrations of added electrolyte (0.00, 0.01, 0.03, and 0.05) mol kg^{-1} NaCl and at the temperatures (288.15, 293.15, 298.15, 303.15, 308.15, and 313.15) K. The critical micelle concentrations were determined using the Phillips definition. To calculate changes in the thermodynamics properties of micellization, the mass action model was applied.

Introduction

The importance of surfactants arises from their widespread applications (shampoos, soaps, detergents). However, some drugs exhibit the same behavior as that of traditional surfactants, due to their ability to spontaneously form aggregates when dispersed in aqueous solutions. This property arises form their amphiphilic structure,[1] and it is really important for their pharmacological applications. The association of drugs has been examined by several workers,[2−4] finding a change in the slope of some physicochemical properties of these drugs in aqueous solutions which is indicative of a self-aggregation. This discontinuity is identified with the critical micelle concentration, and the shape and size of these aggregates depend mainly on the surfactant structure, ionic strength, temperature, and so forth.

Classical models of micelle formation can be divided into two broad categories: the pseudophase separation model and the mass action model. The phase separation model assumes that the micelles are a separate (pseudo)phase commencing at the cmc, representing the saturation concentration for monomeric surfactants. The simple mass action model considers an average micelle that is in equilibrium with surfactant monomers in a dilute aqueous solution. In this model, the micelle formation is reversible. In this paper we report determinations of ultrasound velocity and densities of propranol hydrochloride in the presence of added electrolyte in the concentration range (0.00 to 0.50) mol kg^{-1} and at the range temperatures from (288.15 to 303.15) K. For each system critical micelle concentrations were calculated and from these values thermodynamic parameters of micellization, such as free energy, enthalpy, and entropy, have been calculated by using a modified mass action model. This model has been successfully applied in the calculation of the thermodymamics of association of several amphiphilic drugs, such as chlorhexidene digluconate[5] or amphiphilic penicillins.[6]

Experimental Section

Ultrasound velocities and densities were continuously, simultaneously, and automatically measured using an DSA 5000 Anton Paar density and sound velocity analyzer with a resolution of ±10^{-6} g cm^{-3} and 10^{-2} m s^{-1}, respectively. Both the speed of sound and density are extremely sensitive to the temperature, so this was kept constant within 10^{-3} K. The reproducibility of the density and ultrasound velocity measurements is ±10^{-6} g cm^{-3} and 10^{-2} m s^{-1}, respectively. Measurements of densities and ultrasound velocities of the aqueous solutions of propranolol hydrochloride in the presence of added electrolyte (0.00, 0.10, 0.30, and 0.50) mol kg^{-1} NaCl in the range of temperatures (288.15 to 313.15) K were performed as a function of their concentration.

Propranolol (1-[isopropylamino]-3-[1-naphthyloxy]-2-propranol) hydrochloride (No. P-0884) was purchased from Sigma Chemical Co. and sufficiently well characterized and purified to be used as received. Sodium chloride (Fluka) was of analytical grade. Water was double distilled, deionized, and degassed before use.

Results and Discussion

Experimental results are given in Table 1. The first column of the table shows the molality of propranolol hydrochloride, and the density and ultrasound velocity are listed below the corresponding temperature. Figure 1 shows plots of ultrasound velocity, *u*, as a function of molality in the absence of NaCl; similar plots were obtained for the other electrolyte concentrations. The results obtained for each temperature and electrolyte concentration were analyzed, using the Phillips definition,[7] to detect the presence of critical micelle concentrations corresponding to the maximum change in gradient in plots of the ultrasound velocity versus concentration:

$$\left(\frac{\mathrm{d}^3 u}{\mathrm{d}m^3}\right)_{m=\mathrm{cmc}} = 0 \qquad (1)$$

The numerical analysis of the data was made by means of a 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 critical micellar concentrations of amphiphiles with weak aggregation characteristics.[8] The dotted line in Figure 2 is a Gausssian fit of the second derivative of the curve, with the minimum

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Table 1. Densities, ρ, and Ultrasound Velocities, u, as a Function of Concentration, m, of Propranolol Hydrochloride at Different Temperatures

	T/K = 288.15		T/K = 293.15		T/K = 298.15		T/K = 303.15		T/K = 308.15		T/K = 313.15	
m	ρ	u	ρ	u	ρ	u	ρ	u	ρ	u	ρ	u
mol kg^{-1}	g cm^{-3}	m s^{-1}	g cm^{-3}	m s^{-1}	g cm^{-3}	m s^{-1}	g cm^{-3}	m s^{-1}	g cm^{-3}	m s^{-1}	g cm^{-3}	m s^{-1}
0.00 mol kg^{-1} NaCl												
0.01	0.999 524	1470.07	0.998 626	1485.13	0.997 465	1499.25	0.996 066	1511.57	0.994 447	1522.10	0.992 593	1530.93
0.02	0.999 975	1471.67	0.999 070	1486.44	0.997 910	1500.55	0.996 511	1512.87	0.994 883	1523.41	0.993 015	1532.25
0.03	1.000 440	1473.31	0.999 548	1488.25	0.998 381	1502.33	0.996 985	1514.23	0.995 358	1524.68	0.993 455	1533.51
0.05	1.001 421	1476.36	1.000 529	1491.21	0.999 368	1505.49	0.997 934	1516.98	0.996 292	1527.49	0.994 339	1536.12
0.07	1.002 432	1479.82	1.001 521	1494.16	1.000 355	1508.60	0.998 937	1520.01	0.997 261	1530.47	0.995 251	1538.92
0.09	1.003 453	1482.87	1.002 553	1497.48	1.001 378	1511.52	0.999 949	1522.93	0.998 267	1532.90	0.996 166	1540.84
0.11	1.004 491	1486.35	1.003 587	1500.38	1.002 420	1514.76	1.000 971	1525.77	0.999 246	1536.30	0.997 099	1544.22
0.13	1.005 531	1489.22	1.004 606	1503.81	1.003 421	1517.53	1.001 999	1528.40	1.000 263	1538.53	0.997 994	1546.56
0.15	1.006 576	1492.46	1.005 632	1506.27	1.004 444	1519.54	1.003 029	1530.50	1.001 244	1540.46	0.998 891	1548.20
0.17	1.007 580	1494.59	1.006 631	1507.82	1.005 464	1520.81	1.004 022	1532.11	1.002 220	1541.62	0.999 780	1549.40
0.19	1.008 588	1495.92	1.007 654	1509.64	1.006 474	1522.76	1.005 031	1533.45	1.003 215	1543.44	1.000 683	1550.99
0.21	1.009 564	1497.20	1.008 655	1511.81	1.007 454	1524.44	1.006 028	1535.31	1.004 217	1544.90	1.001 548	1552.24
0.23	1.010 528	1498.13	1.009 596	1513.26	1.008 387	1525.92	1.006 950	1536.93	1.005 149	1546.36	1.002 409	1553.99
0.10 mol kg^{-1} NaCl												
0.01	1.003 912	1475.21	1.002 957	1490.40	1.001 746	1509.86	1.000 301	1516.36	0.998 647	1527.41	0.996 768	1535.40
0.02	1.004 330	1476.77	1.003 362	1491.97	1.002 158	1511.13	1.000 705	1517.62	0.999 049	1528.65	0.997 189	1536.67
0.03	1.004 772	1478.06	1.003 772	1493.66	1.002 564	1512.80	1.001 125	1519.25	0.999 465	1529.99	0.997 601	1538.17
0.05	1.005 648	1481.49	1.004 631	1496.47	1.003 414	1515.97	1.001 963	1522.00	1.000 309	1532.80	0.998 444	1541.12
0.07	1.006 491	1484.69	1.005 499	1499.69	1.004 265	1519.08	1.002 815	1524.79	1.001 153	1535.56	0.999 303	1544.10
0.09	1.007 369	1488.00	1.006 348	1502.76	1.005 101	1522.13	1.003 651	1527.96	1.002 001	1538.21	1.000 167	1547.23
0.11	1.008 218	1491.21	1.007 198	1505.78	1.005 959	1524.64	1.004 471	1530.08	1.002 847	1540.73	1.001 011	1549.40
0.13	1.009 067	1493.96	1.008 040	1507.94	1.006 783	1526.58	1.005 298	1532.00	1.003 659	1542.30	1.001 842	1550.87
0.15	1.009 896	1495.80	1.008 861	1510.14	1.007 601	1528.60	1.006 104	1533.86	1.004 458	1544.24	1.002 679	1552.67
0.17	1.010 730	1497.42	1.009 695	1512.20	1.008 408	1530.46	1.006 883	1535.70	1.005 246	1546.05	1.003 504	1553.88
0.19	1.011 563	1499.12	1.010 483	1514.14	1.009 190	1532.42	1.007 685	1537.52	1.006 039	1547.76	1.004 333	1555.47
0.21	1.012 368	1500.91	1.011 287	1516.31	1.009 961	1534.32	1.008 431	1539.49	1.006 781	1549.45	1.005 138	1556.72
0.23	1.013 172	1502.75	1.012 054	1518.66	1.010 746	1536.28	1.009 193	1541.36	1.007 563	1551.35	1.005 930	1558.13
0.30 mol kg^{-1} NaCl												
0.01	1.011 730	1488.99	1.010 583	1504.26	1.009 486	1517.62	1.008 181	1529.24	1.006 334	1539.17	1.004 312	1547.49
0.02	1.012 134	1490.53	1.010 982	1505.50	1.009 888	1519.14	1.008 571	1530.78	1.006 726	1540.42	1.004 712	1548.69
0.03	1.012 533	1492.02	1.011 383	1507.23	1.010 292	1520.51	1.008 971	1532.03	1.007 126	1541.82	1.005 110	1549.98
0.05	1.013 374	1495.07	1.012 223	1510.16	1.011 135	1523.28	1.009 795	1534.61	1.007 920	1544.24	1.005 912	1552.30
0.07	1.014 228	1497.94	1.013 070	1512.55	1.011 972	1525.60	1.010 600	1536.42	1.008 744	1546.13	1.006 716	1554.68
0.09	1.015 042	1499.72	1.013 891	1514.56	1.012 790	1527.46	1.011 424	1538.60	1.009 551	1547.85	1.007 514	1556.29
0.11	1.015 875	1501.72	1.014 724	1516.41	1.013 619	1529.20	1.012 220	1540.33	1.010 368	1549.56	1.008 309	1557.81
0.13	1.016 691	1503.74	1.015 548	1518.34	1.014 436	1530.88	1.013 040	1542.13	1.011 156	1551.29	1.009 092	1559.36
0.15	1.017 507	1505.53	1.016 355	1520.32	1.015 241	1533.03	1.013 821	1543.82	1.011 946	1553.03	1.009 877	1561.13
0.17	1.018 302	1507.60	1.017 152	1522.05	1.016 049	1534.42	1.014 639	1545.50	1.012 724	1554.67	1.010 641	1562.49
0.19	1.019 099	1509.44	1.017 944	1524.00	1.016 830	1536.42	1.015 408	1547.34	1.013 560	1556.45	1.011 415	1563.97
0.21	1.019 882	1511.20	1.018 711	1526.05	1.017 592	1538.17	1.016 152	1549.12	1.014 272	1558.16	1.012 172	1565.64
0.23	1.020 645	1513.35	1.019 470	1527.77	1.018 360	1540.21	1.016 914	1550.98	1.015 015	1559.97	1.012 907	1567.29
0.50 mol kg^{-1} NaCl												
0.01	1.020 031	1500.65	1.018 850	1515.65	1.017 461	1528.30	1.015 866	1539.99	1.014 088	1549.74	1.012 132	1557.68
0.02	1.020 395	1503.25	1.019 220	1518.39	1.017 829	1531.10	1.016 237	1542.04	1.014 451	1551.74	1.012 498	1559.24
0.03	1.020 764	1505.92	1.019 581	1521.05	1.018 196	1533.44	1.016 620	1543.81	1.014 813	1553.37	1.012 857	1561.02
0.05	1.021 495	1509.14	1.020 329	1523.56	1.018 939	1535.92	1.017 341	1546.23	1.015 563	1556.06	1.013 590	1564.22
0.07	1.022 236	1510.14	1.021 063	1524.73	1.019 662	1536.93	1.018 078	1547.23	1.016 307	1557.00	1.014 349	1565.09
0.09	1.022 962	1511.29	1.021 797	1525.69	1.020 396	1537.99	1.018 803	1548.35	1.017 039	1557.97	1.015 085	1565.95
0.11	1.023 678	1512.33	1.022 511	1526.75	1.021 120	1539.05	1.019 528	1549.43	1.017 775	1558.93	1.015 824	1566.86
0.13	1.024 382	1513.35	1.023 211	1527.74	1.021 833	1540.18	1.020 241	1550.56	1.018 488	1559.92	1.016 552	1567.76
0.15	1.025 075	1514.44	1.023 917	1528.71	1.022 532	1541.11	1.020 930	1551.72	1.019 183	1560.91	1.017 258	1568.52
0.17	1.025 772	1515.50	1.024 614	1529.75	1.023 232	1542.22	1.021 631	1552.71	1.019 881	1561.76	1.017 959	1569.44
0.19	1.026 445	1516.61	1.025 296	1530.66	1.023 920	1543.28	1.022 319	1553.88	1.020 568	1562.74	1.018 653	1570.22
0.21	1.027 123	1517.54	1.025 975	1531.55	1.024 604	1544.37	1.022 996	1554.97	1.021 265	1563.65	1.019 343	1571.17
0.23	1.027 788	1518.50	1.026 638	1532.64	1.025 261	1545.38	1.023 656	1556.02	1.021 920	1564.57	1.020 021	1571.68

value corresponding to the cmc. Values for all the electrolyte concentrations and temperatures can be obtained from Table 2.

The variation of the cmc with the temperature of propranolol is shown in Figure 3 and passes through a minimum around 295 K for the four electrolyte concentrations. These plots were fitted to the equation

$$\ln \chi_{\mathrm{cmc}} = a(T/\mathrm{K})^2 + b(T/\mathrm{K}) + c \qquad (2)$$

where χ_{cmc} is the mole fraction of the cmc. Values for the three coefficients a, b, and c are shown in Table 3.

Figure 4 shows plots of density, ρ, against molality. Similar behavior was found for the other electrolyte concentrations. The variation of density with the molal concentration below the cmc was fitted to the empirical equation[9]

$$\rho = \rho_0 + (Am + Bm^{3/2} + Cm^2 + Dm^{2/5})/10^3 \qquad (3)$$

where ρ_0 is the density of pure electrolyte at each temperature. Values of the least-squares parameters, A, B, C, and D are given in Table 4, together with the variance for the fits.

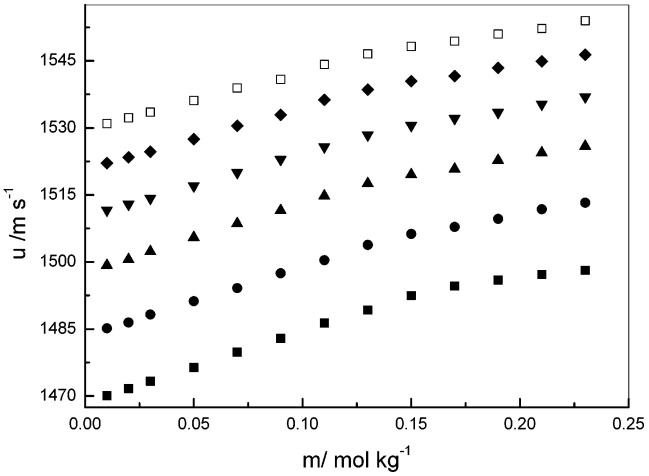

Figure 1. Ultrasound velocities, *u*, as a function of propranolol hydrochloride molality, *m*, for an aqueous solution containing 0.00 mol kg^{-1} NaCl: ■, 288.15 K; ●, 293.15 K; ▲, 298.15 K; ▼, 303.15 K; ◆, 308.15 K; □, 313.15 K.

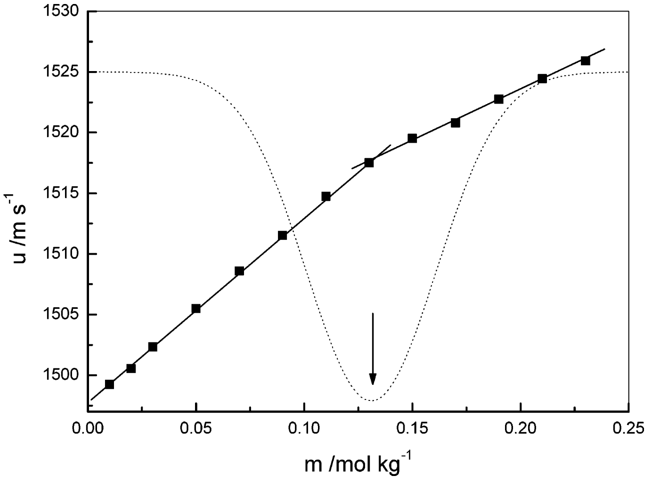

Figure 2. Ultrasound velocities, *u*, as a function of propranolol hydrochloride molality, *m*, for an aqueous solution containing 0.00 mol kg^{-1} NaCl at 298.15 K. The dotted line represents the second derivative of the ultrasound−concentration curve. The arrow denotes the cmc.

Table 2. Critical Micelle Concentrations of Propranolol Hydrochloride as a Function of NaCl Concentration (*m*)

	m_{cmc}/(mol kg^{-1}) at the following *m*/(mol kg^{-1})			
T/K	0.00	0.10	0.30	0.50
288.15	0.138	0.102	0.057	0.039
293.15	0.133	0.098	0.052	0.035
298.15	0.131	0.097	0.050	0.034
303.15	0.134	0.103	0.056	0.039
308.15	0.148	0.108	0.061	0.043
313.15	0.159	0.122	0.068	0.049

Table 3. Coefficients *a*, *b*, and *c* for Fits of Eq 2 as a Function of NaCl Concentration (*m*)

m/(mol kg^{-1})	*a*/K^{-2}	*b*/K^{-1}	*c*
0.00	0.00071 ± 0.00010	−0.42 ± 0.06	56 ± 9
0.10	0.00074 ± 0.00008	−0.43 ± 0.05	58 ± 7
0.30	0.0011 ± 0.00023	−0.63 ± 0.14	87 ± 20
0.50	0.0012 ± 0.00027	−0.719 ± 0.16	99 ± 24

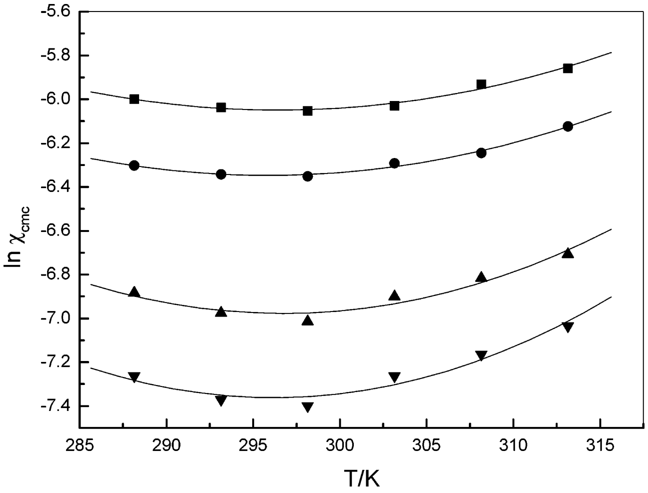

Figure 3. Natural logarithm of the critical micellar concentrations in mole fractions, ln χ_{cmc}, of propranolol hydrochloride in aqueous solutions containing ■, 0.00 mol kg^{-1}; ●, 0.10 mol kg^{-1}; ▲, 0.30 mol kg^{-1}; or ▼, 0.50 mol kg^{-1} NaCl, as a function of temperature. The continuous lines were calculated from eq 2.

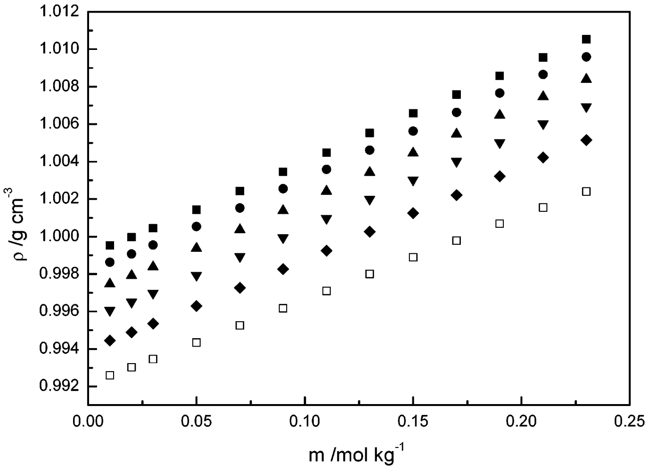

Figure 4. Density of an aqueous solution of propranolol hydrochloride containing 0.00 mol kg^{-1} NaCl: ■, 288.15 K; ●, 293.15 K; ▲, 298.15 K; ▼, 303.15 K; ◆, 308.15 K; □, 313.15 K.

The thermodynamic properties of aggregation were derived by application of the mass action model[10−12] as follows. Assuming that the ultrasound velocity of propranolol solutions, *u*, is a linear function of the concentration of all species that take part in the aggregation process, we can write

$$u = q[\mathrm{S}] + h[\mathrm{M}] \tag{4}$$

where *q* and *h* are proportionality constants and [S] and [M] are the concentrations of the monomer and aggregate, respectively. For our system, the equilibrium between ions and aggregates is represented by

$$n\mathrm{S}^{+} + (n - p)\mathrm{G}^{-} \Leftrightarrow \mathrm{M}^{p+} \tag{5}$$

where G^-, S^+, and M^{p+} represent the counterion, drug ion, and aggregates of aggregation number *n* and charge *p*. The equilibrium constant is written as

$$K_{\mathrm{m}} = \frac{[\mathrm{M}^{p+}]}{[\mathrm{G}^{-}]^{n-p}[\mathrm{S}^{+}]^{n}} \tag{6}$$

To calculate K_m in addition to *n* and *p*, the concentrations of both single ions and the aggregates at any one total ion concentration are required, for which we use the definition of Phillips, eq 1, of critical micellar concentration.

Table 4. Parameters for Fits of Eq 3 as a Function of NaCl Concentration (m)

m^a	T^b	A^c	B^d	C^e	D^f
0.0	288.15	30 ± 2	88 ± 12	−107 ± 19	0.27 ± 0.09
	293.15	35 ± 10	59 ± 57	−63 ± 10	0.07 ± 0.4
	298.15	27 ± 9	104 ± 50	−139 ± 50	0.35 ± 0.36
	303.15	37 ± 12	43 ± 12	−30 ± 17	0.06 ± 0.51
	308.15	45 ± 13	−5.6 ± 76	47 ± 17	−0.24 ± 0.5
	313.15	39 ± 2	26 ± 13	−27 ± 12	−0.27 ± 0.09
0.1	288.15	50 ± 15	−27 ± 82	34 ± 11	−0.68 ± 0.59
	293.15	20 ± 3	118 ± 19	−182 ± 31	0.52 ± 0.14
	298.15	23 ± 9	99 ± 51	−158 ± 42	0.46 ± 0.37
	303.15	36 ± 9	36 ± 50	−60 ± 21	−0.06 ± 0.36
	308.15	37 ± 5	27 ± 27	−38 ± 14	−0.03 ± 0.19
	313.15	45 ± 5	−22 ± 25	52 ± 10	−0.25 ± 0.18
0.3	288.15	18 ± 10	133 ± 57	−218 ± 93	0.54 ± 0.41
	293.15	22 ± 7	102 ± 37	−165 ± 40	6.33 ± 0.26
	298.15	25 ± 5	90 ± 27	−146 ± 35	0.29 ± 0.19
	303.15	35 ± 10	37 ± 56	−64 ± 22	−0.10 ± 0.40
	308.15	44 ± 8	−21 ± 41	40 ± 17	−0.34 ± 0.29
	313.15	39 ± 5	14 ± 26	−31 ± 12	−0.22 ± 0.18
0.5	288.15	24 ± 3	15 ± 19	−26 ± 11	−0.07 ± 0.14
	293.15	24 ± 4	15 ± 25	−28 ± 11	−0.07 ± 0.18
	298.15	33 ± 3	23 ± 18	−43 ±21	0.018 ± 0.13
	303.15	41 ± 8	−19 ± 47	23 ± 17	−0.21 ± 0.34
	308.15	21 ± 4	86 ± 21	−138 ±34	0.52 ± 0.15
	313.15	33 ± 10	14 ± 52	−14 ± 5	0.10 ± 0.38

[a] In mol kg^{-1}. [b] In K. [c] In g cm^{-3} mol^{-1} kg. [d] In g cm^{-3} $mol^{-3/2}$ $kg^{3/2}$. [e] In g cm^{-3} mol^{-2} kg^2. [f] In g cm^{-3} $mol^{-2/5}$ $kg^{2/5}$.

The mass balance for drug ions (c_t) is expressed as

$$c_t = [S^+] + n[M^{p+}] \tag{7}$$

and simultaneously solving eqs 1 and 4−7, the following equilibrium constant K_m can be obtained

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

Experimental data of n and p were available for this systems from static light scattering measurements.[13] The variation of ln K_m with temperature was attributed only to the temperature coefficient of the cmc and was fitted to a second-order polynomial of the form

$$\ln K_m = s(T/K)^2 + r(T/K) + t \tag{9}$$

The values of s, r, and t are listed in Table 5. The plot of ln K_m against T is shown in Figure 5.

Values (per mole of monomer) of the standard Gibbs energy change, ΔG_m°, the standard enthalpy change, ΔH_m°, and the standard entropy change, ΔS_m°, on aggregation (see Table 6) were calculated from the following expressions:

$$\Delta G_m^\circ = -\left(\frac{RT}{n}\right)\ln K_m \tag{10}$$

$$\Delta H_m^\circ = \left[\frac{\partial(\Delta G_m^\circ)/T}{\partial\left(\frac{1}{T}\right)}\right]_p = -\frac{RT^2}{n}\left(\frac{\partial \ln K_m}{\partial T}\right)_p \tag{11}$$

$$\Delta S_m^\circ = -\frac{1}{T}(\Delta G_m^\circ - \Delta H_m^\circ) \tag{12}$$

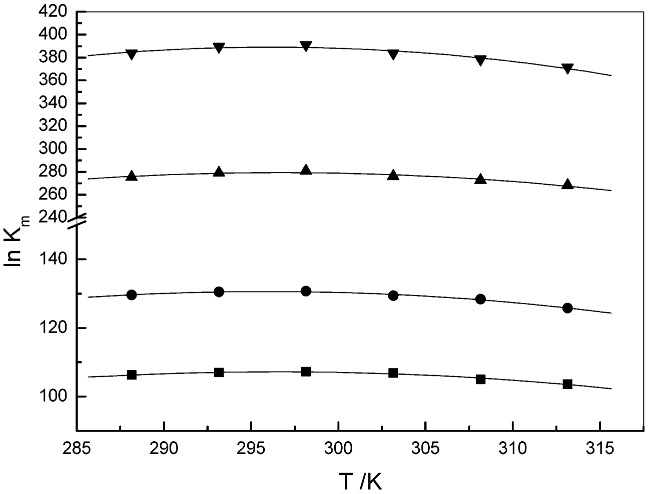

Figure 5. Natural logarithm of the aggregation equilibrium constant, ln K_m, of propranolol hydrochloride in aqueous solutions containing ■, 0.00 mol kg^{-1}; ●, 0.10 mol kg^{-1}; ▲, 0.30 mol kg^{-1}; or ▼, 0.50 mol kg^{-1} NaCl, as a function of temperature. The continuous lines were calculated from eq 9.

Table 5. Coefficients *a*, *b*, and *c* for Fits of Eq 9 as a Function of NaCl Concentration (m)

m/(mol kg^{-1})	s/K^{-2}	r/K^{-1}	t
0.00	−0.0133 ± 0.0019	7.9 ± 1.1	−1060 ± 170
0.10	−0.0159 ± 0.0017	9.4 ± 1.1	−1263 ± 150
0.30	−0.0499 ± 0.0095	26.1 ± 5.7	−3587 ± 860
0.50	−0.062 ± 0.015	38.6 ± 8.9	−5337 ± 1300

Table 6. Standard Gibbs Energy, ΔG_m°, Enthalpy, ΔH_m°, and Entropy, ΔS_m°, of Micelle Formation Per Mole for Propranolol Hydrochloride in Aqueous Solution at Different Temperatures[a]

T/K	ΔG_m°/(kJ mol^{-1})	ΔH_m°/(kJ mol^{-1})	ΔS_m°/(J mol^{-1} K^{-1})
		0.00 mol kg^{-1} of NaCl	
288.15	−25.41	22.84	167.64
293.15	−26.04	14.33	137.82
298.15	−26.56	5.19	106.57
303.15	−26.90	−4.58	73.65
308.15	−26.87	−15.02	38.46
313.15	−26.96	−26.13	2.62
		0.10 mol kg^{-1} of NaCl	
288.15	−25.85	14.17	138.95
293.15	−26.47	5.19	108.06
298.15	−26.97	−4.44	75.62
303.15	−27.15	−14.72	41.03
308.15	−27.38	−25.68	5.52
313.15	−27.26	−37.34	−32.19
		0.30 mol kg^{-1} of NaCl	
288.15	−27.46	21.62	170.44
293.15	−28.32	9.31	128.46
298.15	−28.97	−3.88	84.21
303.15	−28.97	−17.98	36.28
308.15	−29.08	−33.01	−12.78
313.15	−29.07	−49.00	−63.70
		0.50 mol kg^{-1} of NaCl	
288.15	−29.67	20.73	171.61
293.15	−29.64	8.13	128.91
298.15	−30.26	−5.36	83.56
303.15	−30.19	−19.79	34.34
308.15	−30.27	−35.16	−15.88
313.15	−30.20	−51.51	−68.12

[a] Experimental uncertainties: ±10% for ΔG_m°; ±20% for $\Delta S_m^\circ \Delta H_m^\circ$ and $\Delta S_m^\circ \Delta S_m^\circ$.

We can see that Gibbs energy and enthalpy decrease with temperature. The enthalpy of micellization shows a change from positive to negative values close to 298.15 K. Positive values are generally attributed to the release of structural water from the hydration layers around the hydrophobic parts of the molecule.[14] As the temperature

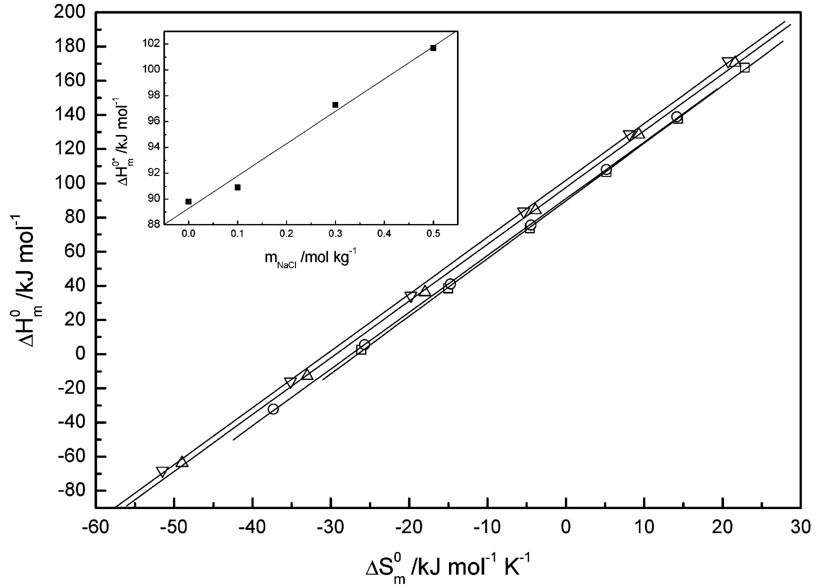

Figure 6. Enthalpy−entropy coJmpensation plot for aqueous solutions of propranolol hydrochloride containing □, 0.00 mol kg^{-1}; ○, 0.10 mol kg^{-1}; △, 0.30 mol kg^{-1}; or ▽, 0.50 mol kg^{-1} NaCl. The inset shows the variation of $\Delta H^{\circ}_{m}{}^{*}$ with electrolyte concentration.

Table 7. Values Obtained from the Linear Fit of the Compensation Plots (Figure 6) as a Function of NaCl Concentration (*m*)

m/(mol kg^{-1})	$\Delta H^{\circ}_{m}{}^{*}$/(kJ mol^{-1})	T_c/K
0.00	89.8 ± 0.3	337 ± 2
0.10	90.9 ± 0.4	332 ± 2
0.30	97.5 ± 0.6	332 ± 2
0.50	101.7 ± 0.6	333 ± 2

is increased, the structure of water is partially broken-down, and hydrophobic interactions become less significant. The negative values of enthalpy suggest the importance of the London-dispersion interactions as an attractive force for micellization.[15] The entropy values calculated by this model decrease progressively with temperature (see Table 6), showing that at temperatures below the cmc minimum the aggregation is driven solely by the positive ΔS°_{m}.

The values for the thermodynamic functions become increasingly negative with an increase of electrolyte concentration as the system becomes more hydrophobic.[16]

To correlate the enthalpic and entropic contributions to micellization, ΔH°_{m} versus ΔS°_{m}, the so-called compensation phenomenon,[17−19] has been plotted in Figure 6. The results were fitted to the equation $\Delta H^{\circ}_{m} = \Delta H^{\circ}_{m}{}^{*} + T_c\Delta S^{\circ}_{m}$. T_c is the compensation temperature and reflects the cooperation of enthalpy with entropy for the micellization process of propranolol. When hydrated ionic groups of surfactants are bound with surrounding water molecules, the process leads to an energetic stabilization (negative enthalpy changes). At the same time, the motion of water molecules bound to ionic groups causes a decrease in entropy. The value of T_c remains constant when the electrolyte concentration is increased (see Table 7), and it is quite close to values reported for alkyltrimethylammonium bromides,[19] 308 ± 4 K. In this situation, the driving force of micelle formation comes only from the enthalpic term; that is, the standard Gibbs energy of micellization only has an enthalpic term. $\Delta H^{\circ}_{m}{}^{*}$ is related with the hydrophobic moiety and decreases when the alkyl chain is increased. However, maintaining the same hydrophobic moiety, this value increases with the electrolyte concentration almost linearly (see the inset in Figure 6).

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