Thermodynamics at the Cloud Point of Phenothiazine Drug Chlorpromazine Hydrochloride−Additive Systems

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An amphiphilic drug chlorpromazine hydrochloride (CPZ), a phenothiazine with neuroleptic activity, undergoes clouding phenomena, which depend upon the physicochemical conditions (e.g., concentration, pH, temperature, etc.). The clouding components release their solvated water and separate out from the solution. Therefore, the cloud point (CP) of an amphiphile can be considered as the limit of its solubility. Herein, we report the energetics of clouding in CPZ in the presence of additives (viz., alcohols, surfactants, and polymers). The standard Gibbs energy change of solubilization (ΔG^0_s) for all of the additives is found to be positive. However, the standard enthalpy change (ΔH^0_s) and the product of the temperature and the standard entropy change ($T\Delta S^0_s$) values are negative as well as positive, depending upon the type and nature of the additive, and the results are discussed on the basis of these factors.

Introduction

In an aqueous environment, amphiphilic molecules (viz., surfactants, drugs, polymers, etc.) can form micelles, a kind of self-organized molecular assembly, above their critical micelle concentrations (cmc's).[1] Self-assembly and self-organization are natural and spontaneous processes occurring mainly through noncovalent interactions, such as van der Waals, hydrogen bonding, hydrophilic/hydrophobic, electrostatic, donor, and acceptor, and metal−ligand coordination networks.[2] The interest in micelle solutions stems from their potential as functional molecular assemblies for use in many fields in pure and applied science because they can be used as models for several biochemical and pharmacological systems and they can solubilize water-insoluble substances (including certain medicines or drugs) in their hydrophobic cores.[3]

Many drug molecules are amphiphilic and, like surfactants, self-associate in aqueous environments to form small aggregates.[4−8] The colloidal properties of amphiphilic drugs are largely determined by the nature of the aromatic ring system of their hydrophobic moieties, and such drugs are useful in probing the relationship between the molecular architecture and the physicochemical properties.[4] In pharmacy, the interaction of small molecules with drugs is one of the most extensively studied topics. In this respect, many drugs, particularly those with local anesthetic, tranquillizer, antidepressant, and antibiotic actions, exert their activity by interaction with biological membranes, which can be considered as a complex form of amphiphilic bilayers. Thus, a full knowledge of the mechanism of the interactions of drugs with other foreign materials is required before the actual application in human body. This is due to the fact that drugs are always used in the presence of a variety of additives (excipients).

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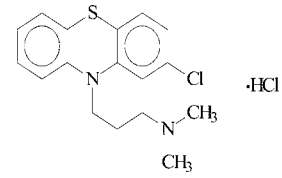

Figure 1. Molecular structure of the amphiphilic phenothiazine drug chlorpromazine hydrochloride (CPZ) used in the present study.

Drug association depends not only upon structure but also on physicochemical conditions, such as temperature, pH, and electrolyte concentration.[4,5] Because of having low viscosity, small aggregate size, simple preparation, and long shelf life,[9] surfactant aggregates have been widely used as drug delivery vehicles. In fact, micellar solubilization is one of the most important properties of surfactant solutions, widely used in the pharmaceutical, food, detergency, cosmetic industries, enhanced oil recovery, and so forth.

Clouding is a well-known phenomenon observed in nonionic surfactants; upon raising the temperature, the system becomes cloudy and phase-separates at a well-defined temperature (i.e., cloud point, CP).[10] The mechanism of clouding in nonionic surfactants, however, is not yet very clear and continues to be a source of controversy among different research groups. However, the occurrence of the CP in ionic surfactant solutions is not usual except under special conditions, for example, high salt concentration,[11−13] salt-free aqueous solutions of certain surfactants with large headgroups[14] or large counterions,[15] and some mixed cationic and anionic surfactant solutions. The CP appearance in these systems is explained in terms of increased hydrophobic interactions, the dehydration of the hydrophilic group,[12] and the formation of large aggregates or clusters.[13,14]

Some amphiphilic drugs, like ionic surfactants, undergo pH-, concentration-, and temperature-dependent phase separation.[16−27] It was observed that their CP can vary with additives.

The amphiphilic drug chlorpromazine hydrochloride (CPZ; see Figure 1), a phenothiazine with neuroleptic activity, shows

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a large capacity to interact with biological membranes and can sometimes be used as a local anesthetic.[28] CPZ has an amino group and is essentially in its charged form at physiological pH.[29] CPZ is often regarded as a model drug for the investigation of interactions between drugs and biological or model membranes.[5,30] Phenothiazine drugs aggregate in a micelle-like manner with the value of N_{agg} (aggregation number) being of the order of 6 to 15.[4,5,30] It is essential to have a knowledge of the clouding behavior of the drug under varying conditions (viz., concentration, pH, temperature, etc.).

In our previous studies,[18,23,25,26] we examined the clouding behavior of CPZ in aqueous buffer solution (10 mM sodium phosphate, SP) in the presence and absence of additives. In the present paper, we report the energetics of phase separation of the amphiphilic drug CPZ (the CP data were taken from literature[23,26]) in the presence and absence of additives. The results have relevance in drug delivery and model drug delivery.

Materials and Methods

We have given details of the materials in our previous papers.[23,26] The cmc of CPZ in pure water was determined by measuring the surface tension of pure drug solutions of various concentrations at (303 ± 0.5) K. The drug cmc was obtained by plotting surface tension (γ) against log[CPZ]. The constancy in the γ versus log[CPZ] plot was taken as the cmc of CPZ.

Ten millimole SP buffer solutions were prepared[23,26] and subsequently used for preparing CPZ samples for CP determinations. CPs were obtained by placing Pyrex glass tubes (containing the drug solutions) into a temperature-controlled bath, the temperature of which was ramped at the rate of 0.1 K·min^{-1} near the CP. The temperature at the onset of turbidity in the solution on heating was noted. The heating was continued well above the temperature and then discontinued until the solution became clear—this temperature was also noted. The temperature was cycled twice in this way. The values of the two steps agreed within 0.5 K. The uncertainty in the measured CP was ± 0.5 K, and the standard deviations were in between $1.10 \cdot 10^{-4}$ and $3.25 \cdot 10^{-4}$.

The CP of an amphiphile can be considered as the limit of its solubility as it phase-separates at temperatures above CP. The clouding components release their solvated water and separate out from the solution. For calculation, we consider that the phase equilibrium is an ideal one. In an ideal condition, concentration and activity are both equal. Hence, the standard Gibbs energy change of solubilization (ΔG^0_s) of the surfactant can be evaluated from the relation

$$\Delta G^0_s = -RT \ln X_s \quad (1)$$

where X_s is the mole fraction concentration of additive at the CP, R is the gas constant, and T is the clouding temperature in Kelvin scale.

The standard enthalpy and entropy of clouding, ΔH^0_s and $T\Delta S^0_s$, respectively, can be calculated by

$$\Delta H^0_s = \frac{\partial(\Delta G^0_s/T)}{\partial(1/T)} \quad (2)$$

$$T\Delta S^0_s = \Delta H^0_s - \Delta G^0_s \quad (3)$$

The thermodynamic parameters were calculated using eqs 1 to 3. $\Delta G^0_s/T$ versus $1/T$ curves have two stages (a representative plot is shown in Figure 2): the first stage is enthalpy-controlled, that is, $\Delta H^0_s > T\Delta S^0_s$, whereas the second stage is controlled by both enthalpy and entropy.

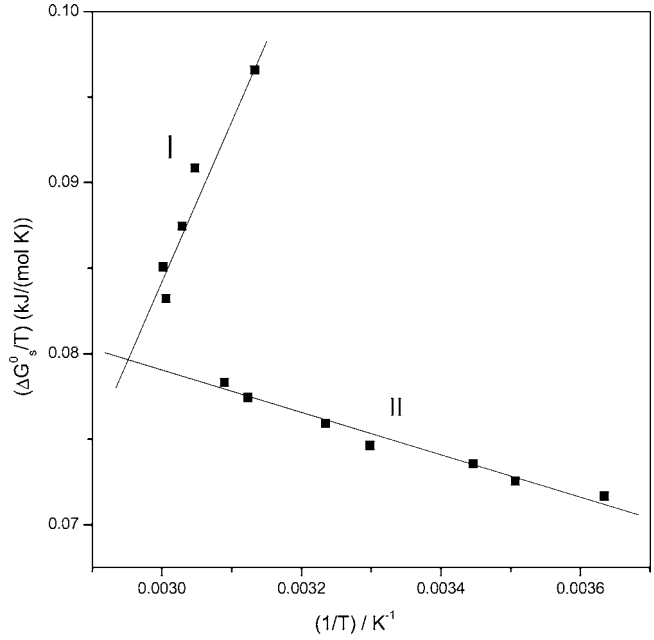

Figure 2. $\Delta G^0_s/T$ vs $1/T$ plot of the CPZ + SDS system to derive the enthalpy change of clouding (ΔH^0_s). The stages are denoted by I and II.

Results and Discussion

The thermodynamics of clouding data for the drug CPZ in the presence of additives are given in Tables 1 to 3. These thermodynamic parameters reveal that for all additives ΔG^0_s is positive. However, ΔH^0_s and $T\Delta S^0_s$ values are negative or positive, depending upon the type and nature of the additives.

A. Effect of Alcohols. Alcohols (up to C_7OH) have changed the ΔH^0_s and $T\Delta S^0_s$ values from positive to negative (Table 1), whereas for long-chain alcohol (C_8OH), these values are negative at all mole fractions. For the latter class, the instability or insolubility of drug−additive systems takes place with self-association and structural changes that dominate over other related processes like desolvation and dislocation, making the overall enthalpy change negative. For cyclopentanol and cyclohexanol, these values (ΔH^0_s and $T\Delta S^0_s$) change sign from positive to negative according to their insolubility or solubility.

Additives which act as water-structure breakers increase the randomness in the system, and for such additives ΔH^0_s and $T\Delta S^0_s$ both become positive (Table 1). Additives like short-chain alcohols are highly miscible in water and, therefore, disrupt the water structure; their presence always results in a decrease in the aggregation number.[31] The micelles even disappear when enough alcohol is added to the micellar solution.[32] These alcohols adsorb at the micelle−water interface[12] and would hinder the micellar aggregation. Hence, $T\Delta S^0$ values come out to be positive and large in magnitude.

At standard conditions, the dissolution of 1 mol of drug in the presence of additives releases heat with an overall ordering of the drug−additive system. These additives, like long-chain alcohols, cycloalkanols, are only partially soluble in water and, hence, solubilize more in micelles with their headgroups toward the surface and alkyl chain penetrating into the micelles. This results in the formation of larger aggregates that ends up with the release of heat with overall ordering in the system.

B. Effect of Surfactants. i. Anionic Surfactants. In the presence of anionic surfactants (both SDS and SDBS), the values of ΔH^0_s change sign from positive to negative in the concentration range used. For SDS, the values of $T\Delta S^0_s$ change from positive to negative, whereas in case of SDBS, these values

Table 1. CP and Energetic Parameters for Clouding in 50 mmol·L^{-1} CPZ Prepared in 10 mmol·L^{-1} SP Buffer Solutions (pH = 6.7) in the Presence of Alcohols[a]

mole fraction of alcohol	CP[b] / K	ΔG^0_s / kJ·mol^{-1}	ΔH^0_s / kJ·mol^{-1}	$T\Delta S^0_s$ / kJ·mol^{-1}	mole fraction of alcohol	CP[b] / K	ΔG^0_s / kJ·mol^{-1}	ΔH^0_s / kJ·mol^{-1}	$T\Delta S^0_s$ / kJ·mol^{-1}
		$\chi_{C_5OH}\cdot10^4$					$\chi_{C_8OH}\cdot10^5$		
0	310.65				0	310.65			
8.99	311.15	18.15	367.32	349.17	3.60	310.15	26.38	−60.71	−87.09
17.97	311.65	16.38		350.94	7.20	309.65	24.56		−85.26
26.93	312.65	15.38		351.94	9.00	309.15	23.94		−84.65
35.87	313.15	14.66		352.66	1.26	308.15	23.00		−83.71
44.79	311.65	14.01	−19.52	−33.53	1.80	306.15	21.95		−82.65
53.71	309.15	13.43		−32.96	2.70	302.15	20.64		−81.35
62.60	303.15	12.78		−32.31	3.60	297.15	19.59		−80.29
71.48	295.15	12.12		−31.64	4.50	290.65	18.62		−79.33
89.19	289.15	11.34		−30.87	5.40	280.15	17.53		−78.23
106.80	281.15	10.61		−30.13					
		$\chi_{C_6OH}\cdot10^4$					$\chi_{pent\text{-}4\text{-}en\text{-}1\text{-}ol}\cdot10^4$		
0	310.65				0	310.65			
0.90	310.65	24.06	1295.40	1271.33	4.49	314.65	20.16	45.504	25.34
2.70	311.15	21.26		1274.14	8.99	320.15	18.67		26.83
4.50	311.65	19.97		1275.43	13.48	328.15	18.03		27.47
8.99	314.15	18.32		1277.08	17.96	340.15	17.88		27.63
13.48	315.15	17.32		1278.08	26.92	338.65	16.66	−28.47	−45.12
17.97	307.15	16.14	−11.19	−27.33	35.87	336.15	15.74		−44.20
22.45	293.15	14.86		−26.05	44.79	332.65	14.96		−43.43
25.13	285.15	14.19		−25.38	53.71	328.15	14.26		−42.73
26.93	273.15	13.44		−24.63	62.60	326.15	13.76		−42.23
					71.48	323.15	13.27		−41.74
					89.19	312.15	12.24		−40.72
					106.80	300.65	11.35		−39.81
		$\chi_{C_7OH}\cdot10^4$					$\chi_{cyclopentanol}\cdot10^4$		
0	310.65				0	310.65			
0.90	311.15	24.09	188.23	164.13	4.49	310.65	19.90	12.20	−7.70
1.80	311.15	22.31		165.92	8.99	310.65	18.12		−5.92
2.70	311.65	21.29		166.94	17.97	310.65	16.33		−4.13
3.60	311.65	20.55		167.68	35.87	310.15	14.52	−96.62	−111.14
5.40	312.15	19.53		168.70	53.71	307.15	13.34		−109.97
7.19	313.15	18.84		169.39	71.48	305.65	12.56		−109.17
8.99	314.15	18.32		169.91	89.19	303.65	11.91		−108.53
10.79	315.15	17.90		170.33	106.80	301.15	11.36		−107.98
13.48	310.15	17.04	−20.03	−37.07			$\chi_{cyclohexanol}\cdot10^4$		
17.97	301.15	15.83		−35.86	0	310.65			
22.45	291.15	14.76		−34.79	4.49	312.15	20.00	110.55	90.55
26.93	277.15	13.63		−33.66	8.99	313.65	18.29		92.26
					13.48	317.15	17.43		93.13
					17.97	322.15	16.93		93.62
					26.92	323.15	15.89		94.65
					35.87	320.15	14.98	−26.23	−41.22
					44.79	316.15	14.22		−40.44
					53.71	311.65	13.54		−39.77
					71.48	305.15	12.53		−38.76
					89.19	298.15	11.69		−37.93
					106.80	288.15	10.87		−37.10

[a] 1-Pentanol, C_5OH, hexan-1-ol, C_6OH, heptan-1-ol, C_7OH, 1-octanol, C_8OH, pent-4-en-1-ol, cyclopentanol, and cyclohexanol. [b] Ref 26.

are negative in all mole fractions (Table 2). This may be because of the presence of the benzene ring (which is more hydrophobic) in SDBS. First they have positive ΔH^0_s and $T\Delta S^0_s$ values, and then after a certain concentration (cmc), the values of ΔH^0_s and $T\Delta S^0_s$ become negative. At low concentrations of anionic surfactants, ΔH^0_s and $T\Delta S^0_s$ come out to be positive, and $\Delta H^0_s > T\Delta S^0_s$. At low concentrations, these surfactants hinder micelle formation, and the overall system is in a vdisordered state. As the concentration of surfactant increases, micellar growth increases, and large aggregates form; ΔH^0_s and $T\Delta S^0_s$ become negative.

ii. Cationic Surfactants. a. Conventional Surfactants. At all mole fractions of conventional cationic surfactants, the thermodynamic parameters, both ΔH^0_s and $T\Delta S^0_s$, are positive (Table 2). The added cationic surfactants exist in the solution as monomers, micelles, or mixed micelles,[7] which increase the interaggregate repulsion. With the longer alkyl chain of the cationic surfactant, the values of ΔH^0_s and the $T\Delta S^0_s$ values are lower. It can be seen (from Table 2) that the addition of bromide surfactants increases the CP more than chloride surfactants and decreases ΔH^0_s. The presence of Cl^- or Br^- ions is responsible for the decrease in the surface area occupied per headgroup (a_o) with the increase in the Mitchell−Ninham parameter, the R_p ($= V_c/a_o l_c$ where V_c is the volume of the alkyl part of the drug) value. The degree of counterion binding has an effect on the size and shape of micelles. As the Br^- ion has a stronger binding effect than Cl^-, addition of Br^- causes an increase in R_p and, therefore, produces lower ΔH^0_s than Cl^- ions.

b. Gemini Surfactants. Like conventional cationic surfactants, the presence of cationic gemini surfactants also has positive thermodynamic parameters at all mole fractions.

Table 2. CP and Energetic Parameters for Clouding in 50 mmol·L^{-1} CPZ Prepared in 10 mmol·L^{-1} SP Buffer Solutions (pH = 6.7) in the Presence of Surfactants[a]

mole fraction of surfactant	CP[b] / K	ΔG^0_s / kJ·mol^{-1}	ΔH^0_s / kJ·mol^{-1}	$T\Delta S^0_s$ / kJ·mol^{-1}	mole fraction of surfactant	CP[b] / K	ΔG^0_s / kJ·mol^{-1}	ΔH^0_s / kJ·mol^{-1}	$T\Delta S^0_s$ / kJ·mol^{-1}
		Anionic					Nonionic		
		$\chi_{SDS}\cdot10^5$					$\chi_{TX\text{-}100}\cdot10^7$		
0	310.65				0	310.65			
0.89	319.15	30.83	86.53	55.71	0.17	312.15	46.39	60.40	14.01
1.80	328.15	29.81		56.73	0.34	314.15	44.93		15.47
2.70	330.15	28.87		57.66	0.49	316.15	44.19		16.20
3.60	333.15	28.34		58.19	0.79	319.65	43.43		16.97
4.49	332.65	27.68	−16.49	−44.17	1.15	324.65	43.13		17.27
5.39	331.15	27.05		−43.54	1.47	331.15	43.32		17.08
6.29	328.15	26.39		−42.87	1.58	333.15	43.36		17.03
7.19	327.15	25.94		−42.43	1.76	336.65	43.53		16.87
8.09	323.65	25.35		−41.84	2.03	344.65	44.16		16.24
8.99	320.15	24.79		−41.28			$\chi_{Brij\text{-}30}\cdot10^7$		
10.80	309.15	23.47		−39.96	0	310.65			
12.60	303.15	22.63		−39.12	0.14	312.15	46.98	119.91	72.93
14.40	290.15	21.34		−37.83	0.38	313.15	44.46		75.45
16.20	285.15	20.69		−37.18	0.57	313.65	43.49		76.41
18.00	275.15	19.72		−36.12	0.66	316.15	43.45		76.46
		$\chi_{SDBS}\cdot10^5$			1.37	318.15	41.81		78.10
0	310.65				1.78	320.15	41.37		78.54
0.89	313.15	30.25	0.96	−29.28	1.55	322.15	42.00		77.90
1.35	314.15	29.29		−28.32	2.55	324.15	40.91		78.99
1.80	312.15	28.35	−47.50	−75.85	2.92	327.15	40.93		78.98
2.25	306.15	27.24		−74.74	2.32	330.65	41.99	80.85	38.85
2.70	288.15	25.20		−72.70	3.59	333.65	41.16		39.68
3.15	286.15	24.66		−72.16	2.78	337.15	42.31		38.53
3.60	284.65	24.22		−71.72	4.22	341.15	41.63		39.22
4.05	282.65	23.77		−71.27	4.52	345.15	41.92		38.92
4.49	281.15	23.39		−70.89	3.41	349.15	43.23		37.62
4.95	279.65	23.05		−70.55	5.08	356.15	42.92		37.93
5.39	278.15	22.72		−70.22			$\chi_{Brij\text{-}35}\cdot10^7$		
6.29	277.15	22.29		−69.79	0	310.65			
7.19	275.15	21.82		−69.32	0.19	312.15	46.13	109.79	63.65
		Cationic (conventional)			0.37	313.15	44.53		65.26
		$\chi_{CPC}\cdot10^4$			0.55	314.15	43.66		66.13
0	310.65				0.72	315.15	43.09		66.69
0.18	313.15	28.44	65.61	37.16	0.88	316.65	42.76		67.03
0.36	314.15	26.72		38.88	1.27	319.65	42.21		67.58
0.54	316.15	25.83		39.78	1.62	322.15	41.88	75.89	34.01
0.89	319.65	24.76		40.85	1.94	324.65	41.71		34.18
1.26	324.65	24.24		41.37	2.24	328.15	41.77		34.12
1.80	331.15	23.74		41.87	2.52	331.65	41.89		33.99
2.16	337.15	23.66		41.95	2.77	335.65	42.13		33.76
2.69	345.15	23.58		42.03	3.01	340.15	42.46		33.43
		$\chi_{CPB}\cdot10^4$			3.24	344.65	42.82		33.07
0	310.65						$\chi_{Tween20}\cdot10^7$		
0.18	313.15	28.44	35.11	6.66	0	310.65			
0.36	315.15	26.81		8.29	0.08	312.65	48.52	140.05	92.12
0.54	316.65	25.87		9.24	0.19	314.15	46.44		93.61
0.89	320.15	24.79		10.31	0.36	316.15	45.03		95.02
1.26	326.15	24.35		10.76	0.52	318.15	44.36		95.69
1.80	333.65	23.92		11.19	0.66	320.15	43.99		96.06
2.16	340.15	23.87		11.24	0.92	323.15	43.53		96.52
2.69	349.15	23.85		11.25	1.14	325.65	43.28		3.29
		$\chi_{TTAB}\cdot10^4$			1.33	328.65	43.26		3.32
0	310.65				1.49	331.15	43.26		3.31
0.18	312.15	28.35	48.48	20.12	1.64	334.15	43.39		3.18
0.36	313.15	26.64		21.84	1.77	336.15	43.44		3.13
0.54	315.15	25.75		22.77	1.89	338.15	43.52		3.05
0.89	319.15	24.72		23.76	1.99	340.15	43.63		2.95
1.26	323.15	24.12		24.35	2.18	343.15	43.77		2.81
1.80	329.65	23.63		24.84	2.33	345.15	43.83		2.75
2.16	334.65	23.48		24.99	2.45	347.15	43.93		2.65
2.69	341.15	23.31		25.17	2.56	349.15	44.05		2.53
3.06	345.65	23.25		25.22	2.66	351.15	44.20		2.38
3.24	348.15	23.26		25.22			$\chi_{Tween40}\cdot10^7$		
		$\chi_{CTAB}\cdot10^4$			0	310.65			
0	310.65				0.07	312.65	48.99	83.02	34.02
0.18	313.15	28.44	32.66	4.22	0.13	313.65	47.37		35.65
0.36	315.15	26.81		5.85	0.19	314.65	46.49		36.53
0.54	317.15	25.91		6.75	0.25	315.65	45.90		37.12
0.72	319.15	25.31		7.35	0.31	317.15	45.56		37.46
0.89	321.15	24.87		7.79	0.37	318.15	45.24	55.88	10.63

Table 2. Continued

mole fraction of surfactant	CP[b] / K	ΔG^0_s / kJ·mol^{-1}	ΔH^0_s / kJ·mol^{-1}	$T\Delta S^0_s$ / kJ·mol^{-1}	mole fraction of surfactant	CP[b] / K	ΔG^0_s / kJ·mol^{-1}	ΔH^0_s / kJ·mol^{-1}	$T\Delta S^0_s$ / kJ·mol^{-1}
1.08	324.15	24.61		8.05	0.46	319.65	44.90		10.98
1.26	327.15	24.42		8.24	0.52	320.65	44.73		11.15
1.44	329.65	24.24		8.42	0.59	322.15	44.54		11.33
1.62	332.65	24.14		8.52	0.73	325.15	44.42		11.46
1.80	335.15	24.02		8.65	0.86	328.15	44.39		11.49
1.98	338.15	23.97		8.69	0.98	331.15	44.43		11.45
2.16	342.15	24.01		8.65	1.09	334.15	44.52		11.36
2.34	345.15	23.99		8.67	1.18	337.65	44.77		11.11
2.52	348.65	24.02		8.64	1.32	341.15	44.94		10.94
2.69	352.15	24.06		8.60	1.52	345.15	45.05		10.83
		Cationic (gemini)			1.71	349.15	45.24		10.64
		$\chi_{16\text{-}6\text{-}16} \cdot 10^5$			1.88	353.65	45.53		10.35
0	310.65				2.04	358.65	45.93		9.95
0.89	313.15	30.25	68.22	37.97			$\chi_{Tween60} \cdot 10^8$		
1.80	316.15	28.72		39.50	0	310.65			
2.70	319.15	27.91		40.31	0.66	312.65	48.96	64.46	15.50
3.60	322.15	27.40		40.81	1.31	315.15	47.56		16.90
4.49	325.15	27.06		41.16	1.92	316.65	46.77		17.69
5.39	327.15	26.73		41.49	2.54	318.65	46.33		18.13
6.29	328.65	26.43		41.79	3.18	321.15	46.09		18.37
7.19	330.15	26.18		42.04	3.78	323.15	45.92		18.54
8.99	335.15	25.96		42.26	4.66	325.65	45.70		18.75
10.80	340.15	25.83		42.39	5.23	327.65	45.67		18.79
12.60	346.15	25.84		42.38	6.07	330.65	45.68		18.78
		$\chi_{16\text{-}5\text{-}16} \cdot 10^5$			7.42	334.65	45.67		18.78
0	310.65				8.71	341.15	46.11		18.35
0.89	313.15	30.25	71.85	41.60	9.95	346.15	46.40		18.06
1.80	316.15	28.72		43.14			$\chi_{Tween80} \cdot 10^8$		
2.70	318.15	27.82		44.03	0	310.65			
3.60	320.15	27.23		44.62	0.65	313.15	49.08	56.37	7.29
4.49	322.15	26.81		45.04	1.61	314.15	46.87		9.49
5.39	325.15	26.56		45.29	2.24	316.15	46.30		10.07
6.29	327.15	26.31		45.54	3.16	319.15	45.82		10.55
7.19	329.15	26.10		45.75	3.77	321.15	45.64		10.73
8.99	333.15	25.80		46.05	4.67	323.65	45.42		10.95
10.80	338.15	25.68		46.17	5.26	323.65	45.31		11.06
12.60	343.15	25.62		46.23	6.13	325.15	45.17		11.19
		$\chi_{16\text{-}4\text{-}16} \cdot 10^5$			6.70	328.65	45.13		11.24
0	310.65				7.55	331.15	45.15		11.22
0.89	312.65	30.20	61.78	31.58	8.10	332.65	45.16		11.21
1.80	315.15	28.63		33.15	8.92	335.15	45.23		11.14
2.70	317.15	27.74		34.04	9.46	337.15	45.34		11.03
3.60	319.15	27.15		34.63	10.20	339.65	45.44		10.92
4.49	320.65	26.68		35.09	10.80	342.15	45.64		10.73
5.39	322.65	26.36		35.42	11.50	345.15	45.84		10.53
6.29	324.15	26.07		35.71					
7.19	325.65	25.83		35.95					
8.99	329.15	25.49		36.28					
10.80	332.15	25.22		36.56					
12.60	336.15	25.09		36.68					
14.40	341.15	25.09		36.69					
16.20	346.15	25.12		36.66					
18.00	352.15	25.24		36.53					

[a] Sodium dodecyl sulfate, SDS; sodium dodecylbenzene sulfonate, SDBS; cetyltrimethylammonium bromide, CTAB; tetradecyltrimethylammonium bromide, TTAB; cetylpyridinium chloride, CPC; cetylpyridinium bromide, CPB; *t*-octylphenoxypolyethoxyethanol, TX-100; poly(ethylene glycol dodecylether), Brij 30/35; poly(oxyethylenesorbitan monolaurate), Tween 20; poly(oxyethylenesorbitan monopalmitate), Tween 40; poly(oxyethylenesorbitan monostearate), Tween 60; poly(oxyethylenesorbitan monooleate), Tween 80; 1,4-butanediyl-α,ω-bis(*N*-hexadecyl-*N*,*N*-dimethylammonium bromide), 16-4-16; 1,5-pentanediyl-α,ω-bis(*N*-hexadecyl-*N*,*N*-dimethylammonium bromide), 16-5-16; and 1,6-hexanediyl-α,ω-bis(*N*-hexadecyl-*N*,*N*-dimethylammonium bromide), 16-6-16. [b] Ref 23.

Cationic (conventional and gemini) surfactants form mixed micelles with drugs.[7] Above the cmc values of gemini surfactants, the gemini micelles could be present in the solution along with the drug micelles. This would increase the intermicellar repulsions, which causes both ΔH^0_s and $T\Delta S^0_s$ to be positive (Table 2). A large effective charge is expected for spheroidal micelles and small effective charge for an ellipsoidal morphology.[33] The hydrophobic or hydrophilic nature of the spacer *s* can dramatically affect the physicochemical properties of the gemini surfactants, presumably because of the modification of the mobility and packing of surfactant monomers within the aggregate. Gemini surfactants with short spacers show a strong tendency for micellar growth and formation of micelles of low curvature, and this ability decreases with the increase in spacer chain length.[34] A surfactant with spacer 4 forms larger micelles than one of spacer 6. It has been reported that the cmc values show a peaked behavior with the number of carbon atoms in the spacer and the maximum appears at a spacer of 5 or 6 (in the 16-*s*-16 gemini series).[33,34] This is the equilibrium distance between the two head groups, and

Table 3. CP and Energetic Parameters for Clouding in 50 mmol·L^{-1} CPZ Prepared in 10 mmol·L^{-1} SP Buffer Solutions (pH = 6.7) in the Presence of Polymers[a]

mole fraction of polymer	CP[b] / K	ΔG^0_s / kJ·mol^{-1}	ΔH^0_s / kJ·mol^{-1}	$T\Delta S^0_s$ / kJ·mol^{-1}
		$\chi_{PVP15}\cdot 10^7$		
0	310.65			
0.11	310.65	47.29	−609.15	−656.44
0.22	310.65	45.59		−654.75
0.31	310.65	44.64		−653.79
0.40	310.65	43.99		−653.14
0.48	310.15	43.43		−652.58
0.67	310.15	42.59		−651.74
0.83	310.15	42.04		−651.19
0.97	309.65	41.57		−650.73
1.09	309.65	41.27		−650.42
1.19	309.15	40.96		−650.12
1.29	309.15	40.77		−649.92
1.38	309.65	40.67		−649.82
1.45	310.15	40.59		−649.75
1.52	311.15	40.60	6.89	−33.71
1.59	312.15	40.63		−33.74
1.64	314.15	40.80		−33.90
1.69	316.15	40.98		−34.08
1.74	318.65	41.23		−34.33
1.79	320.65	41.42		−34.52
1.83	323.15	41.68		−34.78
1.87	326.15	42.01		−35.11
1.90	329.15	42.34		−35.45
1.94	332.65	42.75		−35.85
1.97	336.65	43.22		−36.32
1.99	341.15	43.75		−36.86
		$\chi_{PVP25}\cdot 10^7$		
0	310.15			
0.07	310.65	48.63	−69.89	−118.52
0.16	310.65	46.41		−116.30
0.29	310.15	44.77		−114.66
0.39	309.15	43.79		−113.68
0.49	308.15	43.10		−112.99
0.58	306.65	42.49		−112.39
0.65	304.15	41.85		−111.75
0.71	303.15	41.48		−111.37
0.77	302.15	41.15		−111.04
0.82	301.15	40.85		−110.75
0.87	300.15	40.58		−110.48
0.91	299.15	40.33		−110.23
0.94	299.65	40.30	8.84	−31.46
0.98	300.65	40.35		−31.50
1.01	303.15	40.60		−31.76
1.06	306.15	40.87		−32.02
1.11	309.65	41.22		−32.38
1.15	313.15	41.59		−32.75
1.22	317.15	41.97		−33.13
1.29	322.15	42.47		−33.63
1.34	327.65	43.12		−34.27
1.38	335.15	44.01		−35.16
1.81	310.15	45.97	−35.32	−81.28
3.10	308.15	44.29		−79.61
4.07	306.15	43.31		−78.63
4.83	303.15	42.46		−77.77
5.43	300.65	41.81		−77.13
5.69	299.15	41.49		−76.80
5.92	298.15	41.25		−76.57
6.14	298.65	41.23	9.09	−32.13
6.34	300.65	41.43		−32.33
6.68	304.15	41.77		−32.68
7.24	312.15	42.67		−33.57
7.67	317.15	43.20		−34.10
8.15	323.15	43.85		−34.76
8.39	330.15	44.72		−35.62
8.69	337.65	45.64		−36.54
		$\chi_{PVP60}\cdot 10^8$		
0	310.15			
0.13	308.15	52.33	−93.21	−145.54
0.32	306.15	49.79		−143.01
0.58	304.15	47.94		−141.15
1.00	300.15	45.96		−139.18
1.31	297.15	44.83		−138.05
1.56	296.65	44.34		−137.55
1.75	295.65	43.89		−137.11
1.91	294.65	43.54		−136.75
2.04	295.65	43.52	25.03	−18.49
2.15	297.15	43.61		−18.58
2.25	298.15	43.65		−18.62
2.34	299.15	43.70		−18.68
2.41	300.65	43.85		−18.82
		$\chi_{PVP90}\cdot 10^9$		
0	310.15			
1.03	304.15	52.32	−37.93	−90.25
2.36	301.15	49.73		−87.66
4.13	298.15	47.85		−85.78
5.51	295.65	46.74		−84.67
6.61	292.15	45.74		−83.68
7.51	289.65	45.05		−82.98
8.26	285.65	44.20		−82.13
8.89	280.65	43.25		−81.18
9.44	279.15	42.88		−80.82

[a] Poly(vinyl pyrrolidones), PVPs (PVP 15, PVP 25, PVP 30, PVP 60, and PVP 90). [b] Ref 23.

a spacer of up to six carbon atoms prefers to lie in a stretched rather than in a curved form. Therefore, micelles with spacer 4 carry less effective charge and would create less repulsion, producing lower $T\Delta S^0_s$ values.

iii. Nonionic Surfactants. For nonionic surfactants the thermodynamic parameters (ΔH^0_s and $T\Delta S^0_s$) are positive (Table 2). These surfactants possess hydrophilic oxyethylene chains and form mixed micelles.[7] These drug−surfactant mixed micelles would be highly hydrated. The CP increase with the addition of nonionic surfactants is obviously due to this headgroup hydration, which increases the randomness (i.e., $T\Delta S^0_s$) of the systems.

C. Effect of Polymers. Like anionic surfactants, in the presence of polymers poly(vinyl pyrrolidone), PVPs (biocompatible and a prospective material for use as serum for artificial blood preparation),[35] the values of ΔH^0_s change sign (except for PVP 90, the highest molecular weight polymer) but in the opposite manner (i.e., from negative to positive; see Table 3). They have negative $T\Delta S^0_s$ for all PVPs in all mole fractions. First, they have negative ΔH^0_s, and then, after a certain concentration (different for different PVPs), the values become positive (except for the highest molecular weight polymer, PVP 90). Polymers with lower molecular weights have a larger value of $T\Delta S^0_s$ (the value is the highest for the lowest molecular weight polymer PVP 15). Here, it is clear that polymer size has a role to play in changing the thermodynamic parameters. Polymers interact with CPZ micelles and vary the water of hydration to a different extent.

There is no doubt that the exothermicity of the clouding phenomenon is due to the aggregation of weakly solvated

amphiphile molecules and their phasing-out into the condensed phase. This is a simplified explanation: otherwise, various environmental and structural factors and their combinations (like desolvation, solvent modification, micellar growth, morphological transition, intermicellar interactions, etc.) have their due share on the energetics of clouding.

Conclusions

An amphiphilic phenothiazine drug, CPZ, undergoes clouding phenomena in the presence and absence of additives. Additives which increase the micelle size decrease the randomness of the system, and hence the $T\Delta S^0_s$ value becomes negative. On the other hand, additives which cause the breakdown of micelles and are water-structure breakers give positive ΔH^0_s and $T\Delta S^0_s$ values. The above two points have clearly been demonstrated by studying the CP of the drug CPZ in the presence of various additives.

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