Energetics of Drug-Additive Systems at the Cloud Point†

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The energetics of clouding in amphiphilic drugs, promazine hydrochloride and nortriptyline hydrochloride, in the presence of additives, such as alcohols and surfactants, are reported. The additives which assist in micellar growth like long-chain alcohols and cyclohexanol give negative $\Delta_s H^0$ and $T\Delta_s S^0$ values, whereas cationic and nonionic surfactants increase the randomness in the system and hence $T\Delta_s S^0$ becomes positive. Anionic surfactants at low concentrations retard micellar growth and hence on increasing the concentration $T\Delta_s S^0$ values change from positive to negative.

Introduction

Amphiphiles such as surfactants, copolymers, drugs, and some proteins have a strong tendency to be adsorbed at interfaces. The surface activity of amphiphiles is due to the fact that the different molecular segments have affinity for different environments. This stress can be relieved by adsorbing at interfaces between the media or by molecular self-assembly into nanophases.

It is clear from a large number of studies on phenothiazine drugs that these amphiphiles form micelles.[1−4] These drugs possess an almost planar tricyclic ring system with a short hydrocarbon chain carrying a terminal, charged nitrogen atom (depending upon the solution pH). For example, the pK_a of both promazine hydrochloride (PMZ) and nortriptyline hydrochloride (NOT) is 9.4,[5,6] and at physiological condition, the drug molecules exist in cationic form.

It is well-known that aqueous solutions of certain polymers and nonionic surfactants have a lower consolute temperature.[7−9] The temperature at which the solution separates into surfactant-rich and surfactant-lean phases is known as cloud point (CP) since this process involves an increase in turbidity of the solution. The CP is very sensitive to the interactions in the system and is also affected by the presence of other compounds.[10] Initially, this clouding was ascribed to an increase in size and aggregation number of the micelles and to the formation of giant micelles which were believed eventually to become insoluble in water. Later it was realized that the clouding results from the clustering of micelles as a result of attractive intermicellar interactions. Clouding is attributed to the dehydration of hydrophilic groups of the amphiphiles.[11] It has also been reported that the increase of hydrophobicity near the headgroup region in an ionic surfactant increases the tendency to phase separate.[12,13] However, despite a number of theories put forward to explain the occurrence of CP, it is still not completely resolved.[14,15]

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. Hence, the standard Gibbs energy of solubilization ($\Delta_s G^0$) of the surfactant can be evaluated from the relation

$$\Delta_s G^0 = -RT \ln x \quad (1)$$

where x is the mole fraction solubility at CP; R is gas constant; and T is the clouding temperature in Kelvin scale. The standard enthalpy of clouding, $\Delta_s H^0$, can then be calculated from the slope of the $\Delta_s G^0/T$ vs $1/T$ plot (see eq 2) and standard entropy of clouding $T\Delta_s S^0$, by use of the Gibbs−Helmholtz relation (eq 3)

$$\Delta_s H^0 = \partial(\Delta_s G^0/T)/\partial(1/T) \quad (2)$$

$$\Delta_s S^0 = (\Delta_s H^0 - \Delta_s G^0)/T \quad (3)$$

Like surfactants, some drugs also exhibit phase separation which can be tuned with the help of additives.[16−19] Here we report the energetics of phase separation of the amphiphilic drugs, 10-(3-dimethylamino propyl) phenothiazine hydrochloride, commonly known as promazine hydrochloride and 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-*N*-methylpropylamine hydrochloride, commonly known as nortriptyline hydrochloride (abbreviated as PMZ and NOT, respectively, in this article and schematically shown in Scheme 1).

Experimental Section

Materials. The chemicals were used as received. Their details are given below.

Sigma, U.S.A.: NOT (≥ 98 %), PMZ (≥ 98 %), sodium dodecyl sulfate (SDS, 99 %), tetradecyltrimethylammonium

Scheme 1. Molecular Structure of the Drugs (A) Promazine Hydrochloride (PMZ) and (B) Nortriptyline Hydrochloride (NOT)

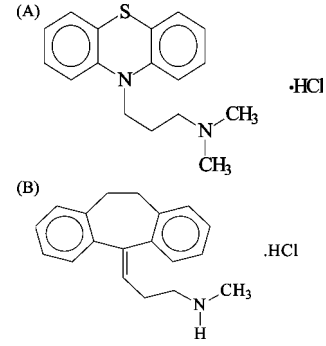

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Table 1. Cloud Point (CP) and Energetic Parameters for Clouding in Promazine Hydrochloride (PMZ) and Nortriptyline Hydrochloride (NOT) Aqueous Solutions in the Presence of Additives

	PMZ ($50.0 \cdot 10^{-3}$ mol·L^{-1} at pH = 6.67)					NOT ($30.0 \cdot 10^{-3}$ mol·L^{-1} at pH = 7.07)			
mole fraction of additive	CP[21,23] / K	$\Delta_s G^0$ / kJ·mol^{-1}	$\Delta_s H^0$ / kJ·mol^{-1}	$T\Delta_s S^0$ / kJ·mol^{-1}	mole fraction of additive	CP[22] / K	$\Delta_s G^0$ / kJ·mol^{-1}	$\Delta_s H^0$ / kJ·mol^{-1}	$T\Delta_s S^0$ / kJ·mol^{-1}
$10^3 x_{\text{Pentanol}}$					$10^3 x_{\text{Pentanol}}$				
0.90	306.15	17.9	−103.1	−121.0	0.63	317.15	19.4	−350.7	−370.1
1.80	305.65	16.0		−119.2	0.90	316.15	18.4		−369.1
3.59	304.15	14.2		−117.3	1.80	314.15	16.5		−367.2
5.37	299.15	13.0		−116.1	2.69	311.15	15.3	−35.5	−50.8
7.15	296.15	12.2		−115.3	3.39	304.15	14.4		−49.9
8.92	292.15	11.5		−114.6	4.48	298.15	13.4		−48.9
					5.37	293.15	12.7		−48.2
					7.15	290.15	11.9		−47.5
					8.92	286.15	11.2		−46.8
$10^3 x_{\text{Hexanol}}$					$10^3 x_{\text{Hexanol}}$				
0.27	305.65	20.9	−144.0	−164.9	0.09	317.15	24.6	−67.8	−92.3
0.45	304.15	19.5		−163.5	0.18	315.15	22.6		−90.4
0.63	303.15	18.6		−162.6	0.27	312.15	21.3		−89.1
1.17	300.15	16.8		−160.8	0.36	308.15	20.3		−88.1
1.35	298.15	16.4		−160.4	0.45	305.15	19.6		−87.3
1.80	296.15	15.6		−164.7	0.63	302.15	18.5		−86.3
2.69	292.15	14.4	−14.0	−28.4	0.90	300.15	17.5		−85.3
3.59	278.15	13.0		−27.0	1.80	293.15	15.4		−83.2
					2.70	281.15	13.8		−81.6
$10^3 x_{\text{Heptanol}}$					$10^3 x_{\text{Heptanol}}$				
0.45	304.15	19.5	−146.3	−165.8	0.09	305.15	23.6	−618.7	−642.3
0.63	302.15	18.5		−164.8	0.27	308.15	20.8		−639.4
0.81	301.15	17.8		−164.1	0.45	303.15	19.4		−638.1
					0.63	293.15	18.0	−24.3	−42.3
					0.90	281.15	16.5		−40.8
$10^3 x_{\text{Octanol}}$					$10^3 x_{\text{Octanol}}$				
0.36	302.15	19.9	−18.8	−38.8	0.27	306.15	21.3	−43.9	−65.1
0.45	293.15	18.8		−37.6	0.45	294.15	19.6		−63.5
0.63	281.15	17.2		−36.1	0.63	291.15	18.0		−61.9
					0.90	282.15	17.0		−65.1
$10^3 x_{\text{Cyclohexanol}}$					$10^3 x_{\text{Cyclohexanol}}$				
0.09	306.15	23.7	−723.4	−747.1	0.18	314.15	22.5	−37.9	−60.5
0.45	305.65	19.6		−743.0	0.34	303.15	20.1		−58.1
0.81	304.15	18.0		−741.4	0.53	292.15	18.3		−56.2
0.9	299.15	17.4	−17.2	−34.7	0.70	288.15	17.4		−55.3
1.1	293.15	16.6		−33.8					
1.3	280.15	15.5		−32.7					
1.8	275.15	14.5		−31.7					
$10^3 x_{\text{SDS}}$									
0.01	306.65	29.4	385.9	356.5					
0.014	307.15	28.5		357.3					
0.02	308.15	28.0		357.9					
0.03	309.15	27.0		358.8					
0.036	309.65	26.3		359.6					
0.07	310.15	24.6		361.3					
0.11	311.15	23.6		362.3					
0.14	305.15	22.5	−14.7	−37.2					
0.18	297.15	21.3		−36.0					
0.22	292.15	20.5		−35.1					
0.25	278.15	19.2		−33.9					
$10^3 x_{\text{SDBS}}$									
0.01	308.15	29.5	133.2	103.7					
0.014	310.15	28.8		104.4					
0.02	306.15	27.8	−32.3	−60.1					
0.027	298.15	26.1		−58.4					
0.03	291.15	25.1		−57.4					
0.04	286.15	24.3		−56.7					
0.07	278.15	22.1		−54.4					
$10^3 x_{\text{CPB}}$					$10^3 x_{\text{CPB}}$				
0.036	310.15	26.4	120.3	93.9	0.04	322.15	27.4	103.3	75.8
0.07	314.15	24.9		95.4	0.07	325.15	25.8		77.5
0.11	316.15	24.0		96.3	0.11	329.15	24.9		78.4
0.14	319.15	23.5		96.8	0.14	331.15	24.4		78.8
0.18	321.15	23.0		97.3	0.18	336.15	24.1		79.2
$10^3 x_{\text{CPC}}$					$10^3 x_{\text{CPC}}$				
0.04	309.15	26.3	180.8	154.5	0.04	320.65	27.3	175.0	147.7
0.07	312.15	24.8		156.0	0.07	323.15	25.6		149.4
0.11	314.65	23.8	80.8	57.0	0.11	326.15	24.7		149.4
0.14	317.65	23.4		57.4	0.14	329.15	24.3		150.7
0.18	319.65	22.9		57.9	0.18	332.15	23.8		151.2

Table 1 Continued

mole fraction of additive	PMZ ($50.0 \cdot 10^{-3}$ mol·L^{-1} at pH = 6.67) CP[21,23] / K	$\Delta_s G^0$ / kJ·mol^{-1}	$\Delta_s H^0$ / kJ·mol^{-1}	$T\Delta_s S^0$ / kJ·mol^{-1}	mole fraction of additive	NOT ($30.0 \cdot 10^{-3}$ mol·L^{-1} at pH = 7.07) CP[22] / K	$\Delta_s G^0$ / kJ·mol^{-1}	$\Delta_s H^0$ / kJ·mol^{-1}	$T\Delta_s S^0$ / kJ·mol^{-1}
$10^3 x_{CTAB}$					$10^3 x_{CTAB}$				
0.04	309.65	8.3	164.2	155.9	0.04	321.15	27.3	106.1	78.8
0.07	311.65	6.9		157.3	0.07	324.15	25.7		80.4
0.11	313.65	5.8		158.4	0.11	328.15	24.9		81.2
0.14	315.15	5.2		159.0	0.14	332.15	24.5		81.6
0.18	317.15	4.5		159.7					
$10^3 x_{TTAB}$					$10^3 x_{TTAB}$				
0.04	320.15	27.2	372.9	345.0	0.04	320.15	27.2	479.0	451.8
0.07	321.15	25.5		347.4	0.07	321.15	25.5		453.5
0.11	322.65	24.5	45.3	20.8	0.11	322.65	24.4		454.6
0.14	327.15	24.1		21.2	0.14	327.15	24.1	53.1	29.0
0.18	330.15	23.7		21.6	0.18	330.15	23.7		29.4
$10^3 x_{16-4-16}$					$10^3 x_{16-4-16}$				
0.07	311.15	24.7	68.8	44.0	0.04	340.15	28.9	92.8	63.9
0.11	316.15	23.9		44.8	0.07	346.15	27.5		65.4
0.14	319.15	23.5		45.3	0.11	352.15	26.7		66.1
0.18	322.65	23.1		45.7					
$10^3 x_{16-5-16}$					$10^3 x_{16-5-16}$				
0.04	310.15	26.4	96.5	70.1	0.04	342.15	29.1	80.9	51.8
0.07	313.15	24.8		71.6	0.07	349.15	27.7		53.3
0.11	317.15	24.0		72.5	0.11	356.15	27.0		53.9
0.14	319.65	23.6		72.9					
0.18	323.65	23.2		73.3					
$10^3 x_{Tween\ 60}$					$10^3 x_{Tween\ 60}$				
0.06	322.15	26.0	46.2	20.2	0.03	342.15	29.6	57.1	27.5
0.09	330.15	25.6		20.6	0.05	347.15	28.9		28.2
0.12	337.15	25.3		20.9	0.06	353.15	28.5		28.5
0.15	339.15	24.8		21.4	0.08	357.15	28.2		28.9
					0.09	361.65	28.0		29.1
$10^3 x_{Tween\ 40}$					$10^3 x_{Tween\ 40}$				
0.04	316.15	26.4	67.8	41.4	0.04	338.15	28.5	95.3	66.7
0.09	322.15	25.1		42.7	0.06	341.15	27.6		67.8
0.13	328.15	24.4		43.4	0.09	344.65	26.7		68.6
0.17	333.15	24.0		43.8	0.11	348.65	26.4		68.9
0.21	336.15	23.7		44.1					
$10^3 x_{Tween\ 20}$					$10^3 x_{Tween\ 20}$				
0.07	315.15	24.9	87.6	62.6	0.07	335.15	26.7	67.9	41.2
0.15	320.15	23.4		64.2	0.11	339.15	25.7		42.2
0.22	323.15	22.6		65.0	0.15	344.15	25.2		42.7
0.29	327.15	22.2		65.4	0.19	349.15	24.9		43.0
0.37	331.15	21.8		65.8					

bromide (TTAB, ≥ 99 %). Merck, Germany: Cetylpyridinium bromide monohydrate (CPB, ≥ 99 %). BDH, England: Cetylpyridinium chloride (CPC, ≥ 98 %), cetyltrimethylammonium bromide (CTAB, ≥ 99 %). TCI, Japan: Sodium dodecylbenzenesulfonate (SDBS, ≥ 99 %). Fluka, Switzerland: 1-Pentanol (C_5OH, ≥ 99 %), 1-octanol (C_8OH, > 97 %). Koch-Light, England: Polyoxyethylenesorbitan monopalmitate (Tween 40). BDH, India: Cyclohexanol (> 98 %). Loba Chemie, India: Polyoxyethylenesorbitan monolaurate (Tween 20), polyoxyethylenesorbitan monostearate (Tween 60). Merck, India: Trisodium phosphate dodecahydrate (TSP), sodium dihydrogen monohydrate (SDP).

The gemini surfactants, 1,5-bis(*N*-hexadecyldimethylammonium)pentane dibromide (16-5-16) and 1,4-bis(*N*-hexadecyldimethylammonium)butane dibromide (16-4-16) were prepared and characterized by the reported method[20] using dimethylhexadecylamine and the appropriate dibromoalkane. Sodium phosphate (SP) buffer (10 mmol·L^{-1}), prepared in deionized and doubly distilled water (specific conductivity = (1 to 2) μS·cm^{-1}), was used as the solvent. The pH of the drug solutions was measured with an ELICO pH meter (model LI 120, Hyderabad, India) using a combined electrode (ELICO CH-41).

Methods. The CP measurements were performed by visual observation. The sample solutions (pure drug or drug + additive) were taken in securely stoppered Pyrex glass tubes which were then placed in a controlled stirring and heating device. The temperature was slowly raised. The heating was regulated to about 0.5 °C·min^{-1} around the CP. The temperature at the onset of turbidity in the solution on heating was noted.[21−23] The heating was continued well above this temperature and then discontinued until the solution became clear—this temperature was also noted. The procedure was cycled twice in this way, and the mean value of appearance and disappearance of turbidity was taken as the CP. The uncertainty in the measured CP was ± 0.5 °C.

The energetic parameters were calculated using eqs 1 to 3. $\Delta_s G^0/T$ vs $1/T$ curves have two stages (a representative plot is shown in Figure 1): the first stage (I) is enthalpy controlled, i.e., $\Delta_s H^0 > T\Delta_s S^0$, whereas the second stage (II) is controlled by both enthalpy and entropy, i.e., $\Delta_s H^0 \approx T\Delta_s S^0$.

Results and Discussion

Data of energetics for the two drugs PMZ and NOT in the presence of additives are given in Tables 1 to 3. These

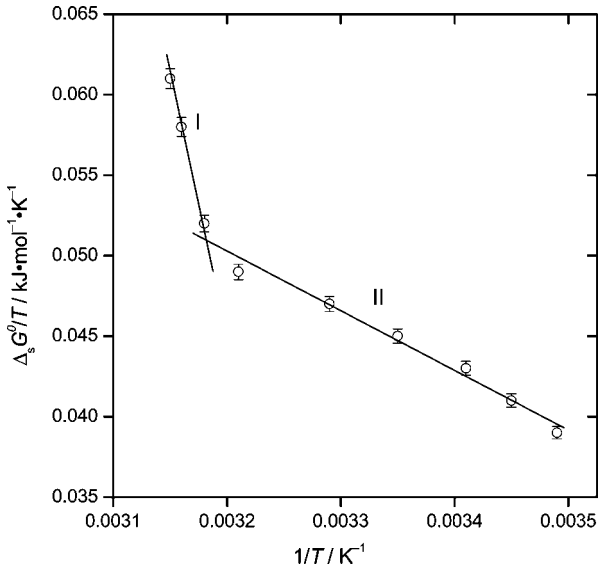

Figure 1. $\Delta_s G^0/T$ vs $1/T$ plot of the nortriptyline hydrochloride (NOT)−pentanol system to derive the enthalpy of clouding ($\Delta_s H^0$). The lines show two stages denoted as I and II.

Table 2. Cloud Point (CP) and Energetic Parameters for Clouding in Different Concentrations (y) of Promazine Hydrochloride (PMZ) Solutions Containing Varying Mole Fractions (x) of Cetyltrimethylammonium Bromide (CTAB) at pH = 6.67

mole fraction of the additive	CP / K	$\Delta_s G^0$ / kJ•mol^{-1}	$\Delta_s H^0$ / kJ•mol^{-1}	$T\Delta_s S^0$ / kJ•mol^{-1}
		y = 100 mM		
$10^3 x_{CTAB}$				
0.04	319.65	26.9	144.1	117.2
0.07	322.15	25.6		118.5
0.11	325.15	24.6		119.5
0.14	327.15	24.1		120.0
		y = 75 mM		
$10^3 x_{CTAB}$				
0.04	315.15	26.8	139.4	112.9
0.07	317.15	25.2		114.1
0.11	319.65	24.2		115.2
0.14	322.65	23.8		115.6
		y = 50 mM		
$10^3 x_{CTAB}$				
0.04	309.65	8.3	164.2	155.9
0.07	311.65	6.9		157.3
0.11	313.65	5.8		158.4
0.14	315.15	5.2		159.0

parameters reveal that for all additives $\Delta_s G^0$ is positive. However, $\Delta_s H^0$ and $T\Delta_s S^0$ values are negative or positive, depending upon the type and nature of the additive. For long chain alcohols and cyclohexanol, these values are negative at all mole fractions. For cationic and nonionic surfactants the values are positive, while for anionic ones, i.e., SDS and SDBS, the values change sign from positive to negative in the concentration range used. For the former class, the instability/insolubility of drug−additive systems takes place with self-association, and structural changes that dominate over other related processes like desolvation and dislocation make the overall enthalpy change negative.

(i) Negative $\Delta_s H^0$ and $T\Delta_s S^0$. At standard condition, the dissolution of one mole of drug in the presence of additives releases heat with an overall ordering of the drug−additive system. Alcohols 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.[24] This

Table 3. Cloud Point (CP) and Energetic Parameters for Clouding in Different Concentrations (y) of Nortriptyline Hydrochloride (NOT) Solutions Containing Varying Mole Fractions (x) of Cetyltrimethylammonium Bromide (CTAB) at pH = 7.07

mole fraction of the additive	CP / K	$\Delta_s G^0$ / kJ•mol^{-1}	$\Delta_s H^0$ / kJ•mol^{-1}	$T\Delta_s S^0$ / kJ•mol^{-1}
		y = 40 mM		
$10^3 x_{CTAB}$				
0.07	331.15	26.3	103.5	77.2
0.11	336.15	25.5		78.0
0.14	338.15	24.9		78.6
0.18	339.15	24.3		79.2
		y = 35 mM		
$10^3 x_{CTAB}$				
0.04	327.15	27.5	129.2	101.7
0.07	330.15	26.3		102.9
0.11	334.15	25.3		103.9
0.14	336.15	24.8		104.4
0.18	337.15	24.2		105.0
		y = 30 mM		
$10^3 x_{CTAB}$				
0.04	321.15	27.3	106.1	78.8
0.07	324.15	25.7		80.4
0.11	328.15	24.9		81.2
0.14	332.15	24.5		81.6

results in the formation of larger aggregates that end up with release of heat with overall ordering in the system.

(ii) Positive $\Delta_s H^0$ and $T\Delta_s S^0$. Cationic as well as nonionic surfactants form mixed micelles with drugs.[25,26] As these surfactants contain hydrophilic headgroups, their incorporation into the drug micelles increases the number of water molecules near the headgroups of the micelles. This affects the water structure also, and the system becomes disordered thereby increasing the overall entropy of the system. Also, repulsion among the drug molecules is expected to increase. Since CP occurs when the net interaction between micelles becomes attractive, the presence of these surfactants increases the CP (Tables 2 and 3).[17,22] Further, at low concentration of anionic surfactants, $\Delta_s H^0$ and $T\Delta_s S^0$ come out to be positive and $\Delta_s H^0 > T\Delta_s S^0$. At low concentrations, these surfactants hinder micelle formation, and the overall system is in a disordered state.[17,27] As the concentration of the surfactant increases, micellar growth increases; larger aggregates form;[27] and $\Delta_s H^0$ and $T\Delta_s S^0$ become positive with $\Delta_s H^0 \approx T\Delta_s S^0$.

Tables 2 and 3 contain the results of energetic parameters of PMZ and NOT, respectively, in CTAB at different fixed drug concentrations. The trend is similar to that of Table 1, and only the values of the parameters change with the variation of drug concentration. An increase in drug concentration in the presence of CTAB leads to a decrease in overall ordering.

No doubt, 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

Alcohols (pentanol and beyond) increase the micelle size and decrease the randomness of the system, hence $T\Delta_s S^0$ values become negative. On the other hand, cationic and nonionic

surfactants give positive $\Delta_s H^0$ and $T\Delta_s S^0$. With the addition of anionic surfactants, $\Delta_s H^0$ and $T\Delta_s S^0$ values first become positive and then negative. The above points have clearly been demonstrated by studying the cloud point of drugs, PMZ and NOT, in the presence of various additives

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