

# Thermodynamics of Adsorption of *N*-Alkyl Betaines at the Air-Water Interface

JAMES SWARBRICK

**Abstract** □ Adsorption studies have been carried out on seven members of a homologous series of *N*-alkyl betaine zwitterionic amphiphiles at the air-water interface. The standard free energies of adsorption have been calculated and resolved into the separate contributions from the polar head group and the methylene groups in the alkyl chain. These contributions are compared with previously published data for the same compounds undergoing micellization.

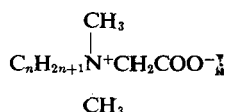
**Keyphrases** □ Betaines, *N*-alkyl—air-water interface adsorption □ Thermodynamics—*N*-alkyl betaines interfacial adsorption □ Surface tension—*N*-alkyl betaine concentration □ Fugacities, surface—methylene free energy change calculation

Adsorption is a phenomenon of increasing significance in the pharmaceutical and biological sciences. Drug adsorption at the surface of a membrane prior to absorption, drug-receptor interactions, and emulsion and suspension technology are some of the contemporary problems which require a knowledge of molecular adsorption at an interface. Associated with adsorption at liquid interfaces are the phenomena of micellization and solubilization which have important biological (1) and pharmaceutical implications (2).

The thermodynamics of micellization in aqueous solution have been reported for a series of synthetic zwitterionic amphiphiles, the *N*-alkyl betaines (3). Since adsorption at the air-water interface is held to precede micellization, the present study was undertaken to investigate the possible relationship between adsorption and micellization. Accordingly, the surface-tension properties of seven homologous *N*-alkyl betaines in dilute aqueous solutions were studied and the thermodynamics of adsorption calculated. These preliminary results are compared with data for the same compounds when undergoing micellization.†

## EXPERIMENTAL

The *N*-alkyl betaines (*N*-alkyl, *N*:*N*-dimethylglycines) have the general formula:



Seven homologs were studied. Those in which  $n = 10, 11, 12, 14,$  and  $16$  have been described previously. Two other homologs ( $n = 13$  and  $15$ ) were synthesized by a method essentially similar to that of Beckett and Woodward (4). Their properties have been described elsewhere (5).

A duNouy tensiometer fitted with a constant-temperature holder was used to determine the surface tensions of the aqueous *N*-alkyl betaine solutions at  $23^\circ$ . The mean scale readings were converted to dynes  $\text{cm}^{-1}$  using the correction tables of Harkins and Jordan (6).

In view of the low solute concentrations employed, all solutions were assumed to have a density equal to that of water.

## RESULTS AND DISCUSSION

Over the low concentration ranges studied (in no case greater than 6–7% of the critical micelle concentration of each homolog), the surface-tension decrease was found to be a linear function of molar concentration. The slopes of these lines are shown in Table I. In all cases, this linearity was maintained for approximately 10 dynes  $\text{cm}^{-1}$ . Accordingly, Table I also contains the concentration of each betaine necessary to cause a surface-tension lowering of 10 dynes  $\text{cm}^{-1}$ .

Several equations apply to adsorption at a sparsely populated interface where the film is ideal, *i.e.*, intermolecular attractions are absent. The first, due to Langmuir (7) is:

$$\Delta G^0 = 2.303RT \log \left[ 1 + \frac{1000}{tRT} (\pi/c) \right] \quad (\text{Eq. 1})$$

When applied to the air-water interface,  $\Delta G^0$  is the standard free energy change,  $\Delta G_{a/w}^0$ , in cal.  $\text{mole}^{-1}$ , when 1 mole of solute is adsorbed from the bulk phase to the interface,  $t$  is the effective thickness of the adsorbed monolayer in  $\text{cm}$ ., and  $\pi/c$  is the change in surface pressure (surface-tension lowering) in dynes  $\text{cm}^{-1}$  with  $c$  the molar concentration of solute. By using a series of homologs and plotting  $\Delta G_{a/w}^0$  as a function of  $n$ , the number of carbon atoms in the alkyl chain, the free energy change on the adsorption of each methylene group,  $\Delta G_{a/w}(\text{—CH}_2\text{—})$ , may be computed from the slope of the line. The extrapolated (*i.e.*,  $n = 0$ ) intercept of such a plot is related to the free energy change on adsorption of the hydrophilic head group,  $\Delta G_{a/w}(W\text{—})$ .

Equation 1 is valid only when (a) the concentration of adsorbed species is sufficiently low that  $\pi/c$  is linear, and (b) when the adsorbed species is a nonelectrolyte. The zwitterionic *N*-alkyl betaines appear to comply with both these criteria. Thus,  $\pi/c$  was linear for all homologs at sufficiently low solute concentrations. Further, these amphiphiles resemble nonelectrolytes in (a) not having any associated counterions, (b) the change in the CMC of these compounds as a function of alkyl chain is quantitatively similar to nonionic surfactants (8), and (c) their solubilizing powers for water-insoluble molecules are insensitive to pH and ionic strength (9).

Examination of Eq. 1 shows that  $\Delta G_{a/w}^0$  is sensitive to  $t$ , the effective monolayer thickness. The disadvantage of having to make a somewhat arbitrary choice of monolayer thickness may be over-

Table I—Adsorption Properties of *N*-Alkyl Betaines at the Air-Water Interface

Number of Carbon Atoms in Alkyl Chain	Molar Concentration Needed to Lower Surface Tension by 10 dynes $\text{cm}^{-1}$	Slope $\pi/c$ ( $\times 10^{-4}$ )	Correlation Coefficient $r$	$\Delta G_{a/w}^0$ (kcal. $\text{mole}^{-1}$ )
10	$9.20 \times 10^{-4}$	1.089	0.97	−5.48
11	$4.30 \times 10^{-4}$	2.314	0.98	−5.92
12	$7.50 \times 10^{-5}$	13.31	0.99	−6.95
13	$2.50 \times 10^{-5}$	40.15	0.94	−7.60
14	$7.17 \times 10^{-6}$	139.4	0.98	−8.33
15	$2.60 \times 10^{-6}$	386.4	0.99	−8.93
16	$6.10 \times 10^{-7}$	1598	0.99	−9.77

† Calculated using either Eq. 1 ( $t = 4\text{Å}$ .) or Eq. 2.

come by using the concept of surface fugacity (10). Based on this concept, the surface-pressure values in the linear  $\pi/c$  region may be regarded as surface fugacities. Consequently, as shown by Weiner and Zografi (11), for a sparsely populated interface and when  $\pi/c$  is linear, then:

$$\Delta G_{a/w}^0 = 2.303RT \log \pi/c \quad (\text{Eq. 2})$$

The free energy change per methylene group may be calculated from the following relationship (12):

$$\Delta G_{a/w}(-\text{CH}_2-) = 2.303 RT \log (c_2/c_1) \quad (\text{Eq. 3})$$

where  $c_1$  is the concentration required to produce a particular surface excess for an amphiphile containing  $m$   $\text{CH}_2$  groups and  $c_2$  is the concentration of the next higher homolog, containing  $(m + 1)$   $\text{CH}_2$  groups, required to produce the same excess. In the region where  $\pi/c$  is linear, the surface excess is proportional to the reduction of surface tension and so  $\Delta G_{a/w}(-\text{CH}_2-)$  can be conveniently obtained from the concentration of the various homologs required to produce an equal lowering of surface tension (Table I). The extrapolated intercept of such a plot has no significance in terms of  $\Delta G_{a/w}(W-)$ .

Equations 1-3 are essentially the same, since in all cases  $\Delta G_{a/w}^0$  is a function of  $\pi/c$ . Consequently,  $\Delta G_{a/w}(-\text{CH}_2-)$  depends on the ratio of the values of  $\pi/c$  for two adjacent homologs. As a result, based on least-squares analysis of the data from the seven homologs,  $\Delta G_{a/w}(-\text{CH}_2-)$  was found to be  $-0.72(4)$  kcal. mole<sup>-1</sup>, regardless of the equation used. The total free energy changes calculated using Eq. 1 ( $t = 4\text{\AA}$ ), and Eq. 2 were identical and are included in Table I.

As mentioned earlier, the free energy change on adsorption of the hydrophilic head group,  $\Delta G_{a/w}(W-)$ , is dependent on the standard free energy when  $n = 0$ . It is, however, necessary to take account of the increased contribution made by the terminal methyl group on the alkyl chain to the total free energy change of the lipophilic moiety. Thus, it follows that:

$$\Delta G^0 = \Delta G(W-) + (n - 1)\Delta G(-\text{CH}_2-) + \Delta G(-\text{CH}_3) \quad (\text{Eq. 4})$$

As discussed by Molyneux *et al.* (3), this reduces to:

$$\Delta G^0 = \Delta G(W-) + n\Delta G(-\text{CH}_2-) - 1.33 \quad (\text{Eq. 5})$$

where 1.33 represents the different in kcal. mole<sup>-1</sup> between  $\Delta G(-\text{CH}_2-)$  and  $\Delta G(-\text{CH}_3)$ , calculated from the solubility of liquid  $n$ -alkanes in water. While there is some doubt as to the absolute value for the terminal methyl group (see Reference 3 for discussion), the figure of 1.33 kcal. mole<sup>-1</sup> has been retained in the present study so as to permit comparison between the behavior of the  $N$ -alkyl betaines on adsorption and when undergoing micellization. Based on this reasoning,  $\Delta G_{a/w}(W-)$  is computed to be  $+3.18$  kcal. mole<sup>-1</sup> when either Eq. 1 ( $t = 4\text{\AA}$ ) or Eq. 2 is used.

As an amphiphile is added to water in increasing concentrations, the surface tension falls until, at the CMC, there is a distinct break

in the slope of the line. In accordance with the Gibbs equation, the decrease in surface tension is due to adsorption of the amphiphile at the air-water interface. This relation implies that the loss in free energy resulting from the adsorption of an amphiphile at the air-water interface is greater than when the same amphiphile undergoes micellization. The free energy changes for the  $N$ -alkyl betaines on micellization have been shown (3) to be  $\Delta G_m(-\text{CH}_2-) = -0.68$  kcal. mole<sup>-1</sup> and  $\Delta G_m(W-) = +3.34$  kcal. mole<sup>-1</sup>. While caution should be exercised in drawing rigid conclusions from these preliminary data, it would appear that the thermodynamic data for the  $N$ -alkyl betaines are consistent with the implication that adsorption at a sparsely populated interface is energetically favored over micellization. Thus, assuming the free energy contributions from the hydrophilic head and the methylene groups in the alkyl chain to be additive, in accordance with Eq. 5 the total free energy change on adsorption [ $\Delta G_{a/w}^0 = +3.18 + n(-0.72) - 1.33$ ] will be consistently more negative than on micellization [ $\Delta G_m^0 = +3.34 + n(-0.68) - 1.33$ ].

## REFERENCES

- (1) A. F. Hofmann and D. M. Small, *Ann. Rev. Med.*, **18**, 333 (1967).
- (2) J. Swarbrick, *J. Pharm. Sci.*, **54**, 1229(1965).
- (3) P. Molyneux, C. T. Rhodes, and J. Swarbrick, *Trans. Faraday Soc.*, **61**, 1043(1965).
- (4) A. H. Beckett and R. J. Woodward, *J. Pharm. Pharmacol.*, **15**, 422(1963).
- (5) J. Daruwala, Ph.D. thesis, University of Connecticut, 1968.
- (6) W. D. Harkins and H. F. Jordan, *J. Am. Chem. Soc.*, **52**, 1751(1930).
- (7) I. Langmuir, *ibid.*, **39**, 1848(1917).
- (8) B. A. Mulley, in "Advances in Pharmaceutical Sciences," H. S. Bean, A. H. Beckett, and J. E. Carless, Eds., Academic Press, New York, N. Y., 1964, chap. 2.
- (9) J. J. Galownia, unpublished results.
- (10) J. Betts and B. Pethica, *Proc. 2nd. Intern. Congr. Surface Activity*, **1**, 152(1957).
- (11) N. D. Weiner and G. Zografi, *J. Pharm. Sci.*, **54**, 436(1965).
- (12) J. T. Davies and E. K. Rideal, "Interfacial Phenomena," Academic Press, New York, N. Y., 1961, chap. 4.

## ACKNOWLEDGMENTS AND ADDRESSES

Received August 27, 1968, from the *Division of Pharmaceutics, School of Pharmacy, University of Connecticut, Storrs, CT 06268*

Accepted for publication October 14, 1968.

Presented to the *Basic Pharmaceutics Section, APHA Academy of Pharmaceutical Sciences, Miami Beach meeting, May 1968.*

The author wishes to acknowledge the able technical assistance of Mr. Ernest M. Mrazik in carrying out the surface-tension determinations.