

during which we, too, observed only a hypotensive (initial) response to the monomer. In addition, a secondary rise in blood pressure, above control values, which occurred a few minutes after injection of the methacrylate, was observed in the present study.

Powell *et al.* (11) suggested that the hypotensive effect may result from a vasodilatory action of the methacrylate. In a previous study on the isolated guinea pig ileum (10), these methacrylates (Types I and II) induced relaxation of the smooth muscle of the intestine; thus Powell's postulate that such an effect may also be produced on the smooth musculature of the vascular system would not be inconsistent with the reported effects of these methacrylate monomers upon intestinal smooth muscle.

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## Direct Estimation of Hexadecyltrimethylammonium-Ion Adsorption at Liquid Interfaces by a Radioisotope Technique I: Specific Ion Effects at Air-Water Interface

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**Abstract** □ The adsorption of the surfactant <sup>14</sup>C-hexadecyltrimethylammonium ion at the air-water interface was measured directly by detecting radioactivity emitted by adsorbed molecules. This was accomplished by placing a gas flow detector above the surface containing surfactant of known specific activity. Adsorption in the presence of potassium halide ions was found to change in the order bromide > chloride > fluoride, indicating specific ion interactions at the surface. Tetraalkylammonium halides produced the same order of effect for halide ions, but an inhibitory effect on adsorption was noted with increasing alkyl chain length. This effect appears to be related to their salting-in properties. Large hydrophobic anions, such as some alkyl- and arylsulfonates, produce two effects, depending on the concentration of surfactant and sulfonate. Ion association at the surface occurs

at low sulfonate concentrations, whereas at higher sulfonate concentrations the ion association in bulk solution occurs, leading to less adsorption.

**Keyphrases** □ Hexadecyltrimethylammonium ion, adsorption—radioisotope technique for direct estimation at air-water interface, specific ion effects □ Surfactants, adsorption—radioisotope technique for direct estimation of hexadecyltrimethylammonium ion at air-water interface, specific ion effects □ Adsorption—radioisotope technique for direct estimation of hexadecyltrimethylammonium ion at air-water interface, specific ion effects □ Radiolabeling—used to measure hexadecyltrimethylammonium-ion adsorption at air-water interface

In recent years it has become increasingly apparent that the therapeutic potency of many drug molecules is related to their hydrophobic behavior or their tendency to leave an aqueous environment for one that is more nonpolar (1). At the molecular level, a number of processes may be responsible for this behavior. For example, (a) the drug may interact with a specific receptor or enzyme with a consid-

erable contribution from hydrophobic interactions; (b) a rate-limiting barrier to the site of action may exist which is lipoidal and hence more limiting to less lipoidal molecules; and (c) there may be an interaction of the drug directly with biological membranes, causing a change in membrane permeability either by direct interaction with membrane molecules or by an indirect effect due to competition or

interaction with substances normally membrane bound, *e.g.*, calcium or some enzymes.

Previous studies from this laboratory were concerned with the interfacial activity of various drugs at the air-solution interface and at interfaces covered with insoluble monomolecular films, with particular interest in the substituted phenothiazines (2-6). The position has been taken that studies at the air-water interface can give useful information about factors influencing hydrophobic behavior of drugs in aqueous solution. Studies using the monomolecular film technique, on the other hand, provide the opportunity to present a well-defined array of molecules placed in such a position that microenvironmental factors at the surface can be controlled. For example, by judicious choice of film substances and by compression of the monomolecular film, one can alter the chemical composition, molecular orientation, charge density, and, perhaps, interfacial water structure in such a way as to produce different drug-"film molecule" interactions. In this way, one can simulate the conditions a drug will encounter as it acts on a biological membrane. Some studies involving the surface activity of drugs recently were reviewed (7, 8).

Of major interest is an understanding of the kinetic and equilibrium relationship between molecules at an interface and those in the bulk aqueous solution. To obtain such information, one must be able to measure the surface concentration of drug molecules, *i.e.*, molecules per unit area in excess of the bulk drug concentration. An approach traditionally used at various liquid interfaces is to measure surface tension change with increasing drug concentration with the assumption that reduction in surface tension reflects increasing surface concentration. The more correct approach involves the use of the Gibbs (9) equation:

$$-d\gamma = \sum \Gamma_i d\mu_i \quad (\text{Eq. 1})$$

where  $\Gamma_i$  and  $\mu_i$  are the surface concentration and chemical potential, respectively, of each species present. For a system containing a solute of activity  $a_s$  and an insoluble film having activity  $a_f$ , one can write:

$$-d\gamma = RT\Gamma_s d \ln a_s + RT\Gamma_f d \ln a_f \quad (\text{Eq. 2})$$

where  $R$  is the gas constant, and  $T$  is the absolute temperature.

In the absence of an insoluble film, the second term is missing and the major problem is to account properly for the activity change,  $d \ln a_s$ . For dilute solutions of nonelectrolyte, one can utilize the solute concentration; but for higher concentrations where solution activity is not equal to concentration or for electrolytes, there is a fair degree of uncertainty in the use of concentration (10, 11). In the case of drug molecules, such as the phenothiazines, there is good evidence to suggest self-association at relatively low concentrations, even below an apparent critical micelle concentration (CMC) (12), so that a great deal of uncertainty exists in such cases when attempting to apply the Gibbs equation.

To begin to apply Eq. 2 to the case where film molecules are present, one is forced to assume that no perturbation of the film occurs with a change in solute activity or bulk concentration and that only solute concentration changes influence the surface tension. Pethica (13) suggested that this assumption was only approached for penetration of a solute into a highly compressed film, where the number of penetrating molecules is small and where no change in the area per film molecule (the reciprocal of  $\Gamma_f$ ) can occur. Consequently, much work that only measures surface tension change when adding drugs beneath monomolecular films is of little direct use in the estimation of drug-monomer interaction. Another major problem encountered specifically when studying cationic substances is the difficulty of measuring surface tension accurately because of strong adsorption on the glass or platinum surfaces used in various surface tension measuring devices.

To obviate these difficulties, a technique was needed that allowed for the direct estimation of molecules adsorbed to a liquid surface. One attractive approach, first reported in 1949 (14-16), involves the use of radiolabeled compounds and the detection of weak  $\beta$ -particles emitted from the solution surface. This technique was used at the air-water interface to confirm the Gibbs equation with sodium lauryl sulfate (17, 18), as well as with multicomponent systems where different species compete for the surface (19, 20). A few studies with monomolecular films also were reported, but these were confined to the detection of some  $^{14}\text{C}$ -labeled proteins or  $^{45}\text{Ca}^{+2}$  at surfaces covered with phospholipid films (21-23).

To develop this technique for studying drug adsorption to various interfaces, it was decided to use  $^{14}\text{C}$ -labeled hexadecyltrimethylammonium ion, a highly surface-active molecule. In this first report, studies concerned with adsorption at the air-water interface are presented. In a subsequent report, adsorption at interfaces covered with lipid monomolecular films will be considered.

## EXPERIMENTAL

**Chemicals**—The  $^{14}\text{C}$ -labeled compounds<sup>1</sup> used were: hexadecyl-1- $^{14}\text{C}$ -trimethylammonium bromide, specific activity 11.3 mCi/mmmole; urea- $^{14}\text{C}$ , specific activity 58.5 mCi/mmmole; and glycerin, specific activity 11.7 mCi/mmmole, uniformly  $^{14}\text{C}$ -labeled. Radiochromatograms confirmed that each compound was chemically pure. Reagent grade urea and glycerin and chemically pure hexadecyltrimethylammonium bromide<sup>2</sup> served as the unlabeled carriers. All electrolytes used were of reagent grade, and double-distilled water was utilized as the solvent.

**Radioactivity Detection**—The radiation detector consisted of a thin formvar-ethylene dichloride end window (less than 150  $\mu\text{g}/\text{cm}^2$ ), gas flow detector connected to a series decade scaler<sup>3</sup>. The flow gas was commercial "Q-Gas"<sup>4</sup>; the flow rate was 50 ml/min.

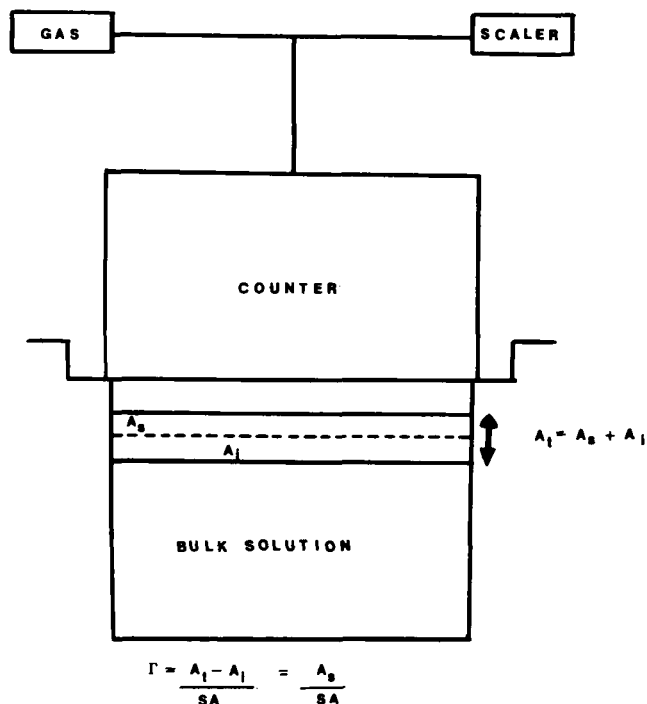
All solutions to be counted were placed into a Teflon dish (subsequently referred to as a cuve), which was 6.0 mm deep and 5.7 cm in diameter. The counting area exposed to the detector was

<sup>1</sup> All of the labeled compounds were supplied by Amersham Searle, Arlington Heights, Ill.

<sup>2</sup> Calbiochem, La Jolla, Calif.

<sup>3</sup> Nuclear-Chicago 8703, Nuclear Chicago, Des Plaines, Ill.

<sup>4</sup> Nuclear Chicago, Des Plaines, Ill.



Scheme I—Counting apparatus used to detect radiolabeled molecules at a solution surface

25.9 cm<sup>2</sup>. A constant solution volume of 10.0 ml was used throughout the study, and the detector was placed over the solution at a fixed distance from the surface (about 2 mm). Thus, constant counting geometry was maintained. All studies were conducted at a room temperature of 23 ± 1°. A schematic representation of this setup is given in Scheme I.

**Determination of Surface Concentration**—Because of the relatively large range of <sup>14</sup>C-β-particles with respect to the thickness of the surface region, when the detector is placed over the surface of a solution containing <sup>14</sup>C-labeled solute, the total counts per minute recorded represent the molecules present down to some depth within the solution. Thus, a certain proportion of the total counts, A<sub>T</sub>, is due to molecules counted merely because of bulk concentration of solute; this is expressed as A<sub>1</sub> (Fig. 1). To be able to measure counts due to those molecules present at the surface in excess of the bulk concentration A<sub>s</sub>, A<sub>T</sub> and A<sub>1</sub> must be determined independently and A<sub>s</sub> must be obtained by their differ-

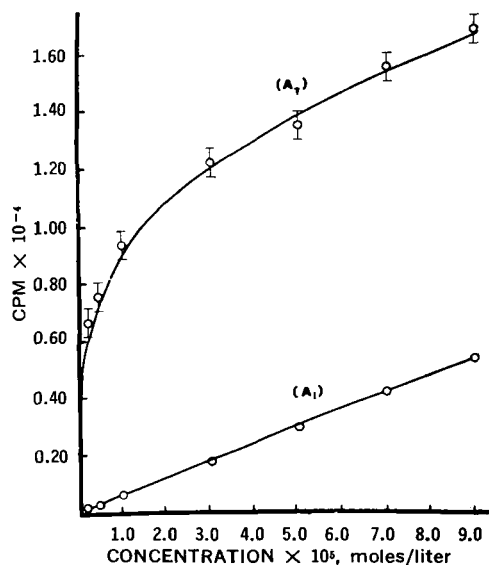


Figure 1—Counts per minute versus solute concentration. Ionic strength = 0.10, ammonium bromide.

Table I—Hexadecyltrimethylammonium–Urea System in the Presence of 0.10 M Ammonium Bromide

Hexadecyltrimethylammonium Concentration, moles/liter	$\Gamma \times 10^{-9}$ , moles/cm <sup>2</sup>	Å <sup>2</sup> /Ion
1.0 × 10 <sup>-6</sup>	1.05 ± 0.03	158.0
3.0 × 10 <sup>-6</sup>	1.99 ± 0.06	83.4
5.0 × 10 <sup>-6</sup>	2.22 ± 0.01	74.8
7.0 × 10 <sup>-6</sup>	2.59 ± 0.04	64.1
1.0 × 10 <sup>-5</sup>	2.63 ± 0.03	63.1
3.0 × 10 <sup>-5</sup>	3.19 ± 0.05	(48.9) <sup>a</sup> 52.1
5.0 × 10 <sup>-5</sup>	3.32 ± 0.05	(46.4) 50.0
7.0 × 10 <sup>-5</sup>	3.49 ± 0.04	(43.3) 47.6
9.0 × 10 <sup>-5</sup>	3.56 ± 0.06	(42.1) 46.7

<sup>a</sup> Numbers in parentheses obtained from parabolic fit (Fig. 2).

ence. Values of A<sub>1</sub> are determined by using solutions of a nonsurface-active radiolabeled compound, having the same specific activity and molar concentration as the surfactant solution. In this way the difference between A<sub>1</sub> and A<sub>T</sub> has to be due only to the presence of adsorbed hexadecyltrimethylammonium ions. Radiolabeled solutions of urea and/or glycerin were used to determine A<sub>1</sub> for all concentrations of surfactant and all solution conditions considered. Since various solution conditions were to be used, e.g., different electrolytes, varying ionic strength, and pH, a systematic check on the effect of such changes on A<sub>1</sub> was made. Under no conditions used was the value of A<sub>1</sub> altered by varying solution conditions.

Once the counts per minute due to adsorbed molecules, A<sub>s</sub>, have been determined, the surface concentration of surfactant, Γ, in moles per square centimeter, can be estimated by the following expression:

$$\Gamma = \frac{A_s}{SA} \quad (\text{Eq. 3})$$

where A equals total surface area of the solution in square centimeters, and S represents the specific activity of surfactant molecules at the surface in units of counts per minute per mole.

To evaluate S in Eq. 3, known amounts of labeled hexadecyltrimethylammonium ion were spread as an insoluble monomolecular film on the surface of an almost saturated solution of ammonium bromide (76.2 g/100 ml); this was done to ensure that the surfactant molecules remained on the surface and did not dissolve. Approximately 5 min elapsed before counting was initiated to allow

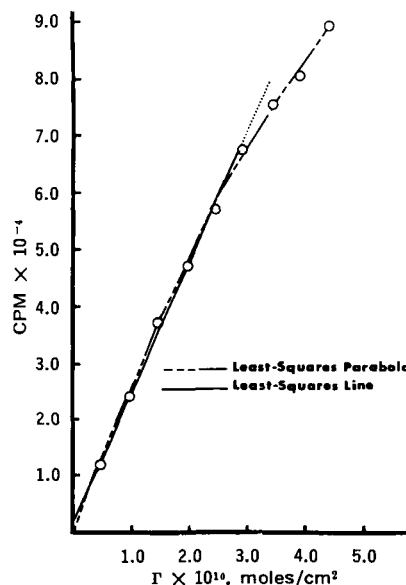


Figure 2—Counts per minute versus amount of hexadecyltrimethylammonium ion applied to the surface of an almost saturated solution of ammonium bromide.

**Table II**—Surface Concentration  $\times 10^{10}$  (Moles per Square Centimeter) for Hexadecyltrimethylammonium Adsorption in Aqueous Solutions of 0.10 M Tetraalkylammonium Bromide, and Data for Hexadecyltrimethylammonium Adsorption in 0.10 M KBr

Hexadecyltrimethylammonium Concentration, moles/liter	Potassium Bromide	Tetramethyl	Tetrapropyl	Tetrabutyl
$7.0 \times 10^{-6}$	$2.09 \pm 0.04$	$2.11 \pm 0.02$	$2.03 \pm 0.05$	$1.43 \pm 0.02$
$1.0 \times 10^{-5}$	$2.27 \pm 0.03$	$2.22 \pm 0.02$	$2.19 \pm 0.03$	$1.58 \pm 0.02$
$3.0 \times 10^{-5}$	$2.77 \pm 0.04$	$2.62 \pm 0.02$	$2.54 \pm 0.03$	$2.07 \pm 0.04$
$5.0 \times 10^{-5}$	$2.92 \pm 0.06$	$2.78 \pm 0.04$	$2.77 \pm 0.03$	$2.27 \pm 0.03$

**Table III**—Surface Concentration  $\times 10^{10}$  (Moles per Square Centimeter) for Hexadecyltrimethylammonium Adsorption in Aqueous Solutions of Tetraalkylammonium Chloride, and Data for Hexadecyltrimethylammonium Adsorption in 0.10 M KCl

Hexadecyltrimethylammonium Concentration, moles/liter	Potassium Chloride	Tetramethyl	Tetrapropyl	Tetrabutyl
$7.0 \times 10^{-6}$	$1.63 \pm 0.02$	$1.24 \pm 0.02$	$1.22 \pm 0.04$	$1.21 \pm 0.03$
$1.0 \times 10^{-5}$	$1.87 \pm 0.03$	$1.67 \pm 0.04$	$1.38 \pm 0.03$	$1.37 \pm 0.05$
$3.0 \times 10^{-5}$	$2.22 \pm 0.03$	$1.92 \pm 0.03$	$1.70 \pm 0.03$	$1.79 \pm 0.03$
$5.0 \times 10^{-5}$	$2.42 \pm 0.06$	$2.12 \pm 0.03$	$1.88 \pm 0.04$	$1.88 \pm 0.04$

time for the spreading solvent, chloroform, to evaporate. Values were constant over 15 min and did not change by more than 5% over 1 hr. The value of  $S$  was obtained from the slope of a plot of the surface radioactivity,  $A_s$ , versus the moles per square centimeters of surfactant spread after appropriate correction for non-radioactive species present. As later results indicated, a possible difference in counting geometry because of the saturated solution used was not an important factor. Also, no significant difference in  $S$  was found using a nearly saturated potassium bromide solution rather than one containing ammonium bromide.

## RESULTS

**Preliminary Studies**—To demonstrate the suitability of this technique, initial measurements were made on a system consisting of hexadecyltrimethylammonium ion in 0.1 M  $\text{NH}_4\text{Br}$  solution. The concentration of the surfactant ranged from  $1 \times 10^{-6}$  to  $9.0 \times 10^{-5}$  M; the CMC of this surfactant under these conditions is  $8.0 \times 10^{-5}$  M (24). Unless otherwise specified, urea was used to determine  $A_i$ .

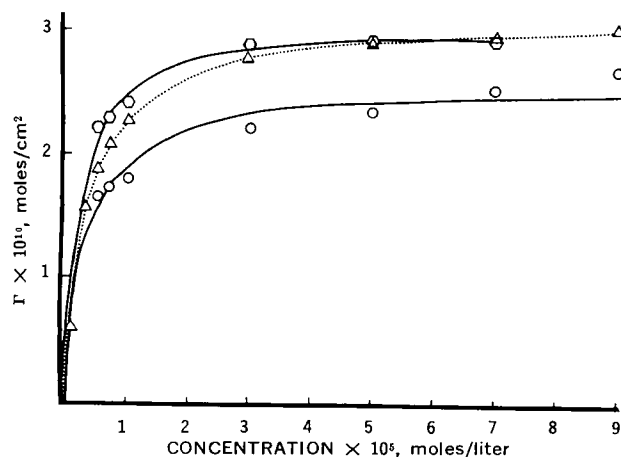
Figure 1 illustrates plots of  $A_T$  and  $A_i$  versus bulk surfactant concentration and urea concentration, respectively. These counts represent the average of ten 1-min counts run on at least duplicate solutions, after correcting for background and detector dead-

time. The error bars represent three standard deviations. From these data,  $A_s$  was obtained for each molar concentration by taking the difference between  $A_T$  and  $A_i$ . Essentially identical results were obtained when glycerin was substituted for urea.

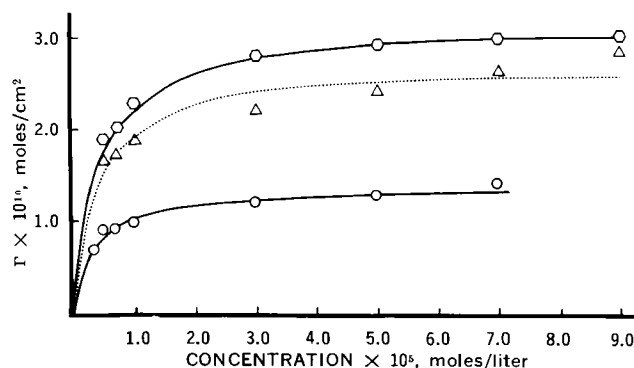
Figure 2 contains the "standard plot" used to convert  $A_s$  to  $\Gamma$ . The counts per minute of spread surfactant increased proportionally to the amount on the surface up to about  $3.0 \times 10^{-10}$  mole/cm<sup>2</sup>; beyond this value a significant decrease in slope occurred. Similar results were observed by others working with sodium lauryl sulfate and were attributed to dissolution of film molecules into the underlying solution (17). To obtain a good estimate of the slope, a least-squares line was fitted to the data up to about  $3.0 \times 10^{-10}$  mole/cm<sup>2</sup> while a parabola was used to include all of the data points.

Table I summarizes the results of preliminary analyses of data presented in Fig. 1, utilizing the linear standard curve. The data are presented as  $\pm 1$  SD. Note that the values of area per molecule (reciprocal of  $\Gamma$ ) in parenthesis were obtained by parabolic fit and that reasonable agreement is seen up to  $3.5 \times 10^{-10}$  mole/cm<sup>2</sup>. The absolute values of area per molecule obtained at the higher concentrations (40–50 Å<sup>2</sup>) are in good agreement with those obtained for shorter chain alkylammonium ions using surface tension measurements and applying the Gibbs equation (25, 26).

**Effect of Ionic Strength**—To test the applicability of this technique further, the influence of ionic strength on hexadecyltrimethylammonium ion adsorption was considered. As seen in Fig.



**Figure 3**—Surface concentration versus bulk concentration as a function of ionic strength. Key:  $\circ$ , 0.01 M KBr;  $\Delta$ , 0.10 M KBr; and  $\square$ , 0.20 M KBr.



**Figure 4**—Surface concentration versus bulk concentration in the presence of 0.10 M halide counterions. Key:  $\circ$ , potassium fluoride;  $\Delta$ , potassium chloride; and  $\square$ , potassium bromide.

**Table IV**—Surface Concentration  $\times 10^{10}$  (Moles per Square Centimeter) for Hexadecyltrimethylammonium Adsorption in Aqueous Solutions of 0.10 M Sodium Benzenesulfonate and 0.10 M Sodium Naphthalenesulfonate

Hexadecyltrimethylammonium Concentration, moles/liter	0.01 M Sodium		0.1 M Sodium	
	Benzenesulfonate	Naphthalenesulfonate	Benzenesulfonate	Naphthalenesulfonate
$1.0 \times 10^{-6}$	$0.926 \pm 0.01$	$0.484 \pm 0.01$	$0.873 \pm 0.01$	$0.469 \pm 0.01$
$3.0 \times 10^{-6}$	$1.32 \pm 0.01$	$1.26 \pm 0.02$	$1.45 \pm 0.03$	$0.999 \pm 0.02$
$5.0 \times 10^{-6}$	$1.40 \pm 0.02$	$1.32 \pm 0.03$	$1.56 \pm 0.02$	$1.21 \pm 0.04$
$1.0 \times 10^{-5}$	$1.37 \pm 0.02$	$1.48 \pm 0.02$	$1.68 \pm 0.02$	$1.33 \pm 0.03$
$3.0 \times 10^{-5}$	$1.53 \pm 0.02$	$2.73 \pm 0.02$	$1.95 \pm 0.02$	$1.51 \pm 0.02$
$5.0 \times 10^{-5}$	$1.58 \pm 0.03$	$3.06 \pm 0.03$	$1.86 \pm 0.04$	$1.64 \pm 0.03$

**Table V**—Surface Concentration  $\times 10^{10}$  (Moles per Square Centimeter) for Hexadecyltrimethylammonium Adsorption in Aqueous Arylsulfonate–Potassium Fluoride Solutions<sup>a</sup>

Hexadecyltrimethylammonium Concentration, moles/liter	Potassium Fluoride	Benzenesulfonate Ion		
		$10^{-5} M$	$10^{-4} M$	$10^{-3} M$
		$1.0 \times 10^{-6}$	$0.646 \pm 0.02$	$0.529 \pm 0.02$
$5.0 \times 10^{-6}$	$0.894 \pm 0.02$	$0.922 \pm 0.02$	$0.977 \pm 0.03$	$1.28 \pm 0.03$
$3.0 \times 10^{-5}$	$1.19 \pm 0.03$	$1.24 \pm 0.02$	$1.36 \pm 0.03$	$1.52 \pm 0.03$
		Naphthalenesulfonate Ion		
		$10^{-5} M$	$10^{-4} M$	$10^{-3} M$
$1.0 \times 10^{-6}$	$0.646 \pm 0.02$	$0.560 \pm 0.01$	$0.709 \pm 0.01$	$1.07 \pm 0.02$
$5.0 \times 10^{-6}$	$0.894 \pm 0.02$	$1.11 \pm 0.02$	$1.40 \pm 0.03$	$1.49 \pm 0.03$
$3.0 \times 10^{-5}$	$1.19 \pm 0.03$	$1.26 \pm 0.02$	$1.68 \pm 0.03$	$2.04 \pm 0.03$

<sup>a</sup> A constant ionic strength of 0.10 is maintained with fluoride ion while varying the concentration of arylsulfonate.

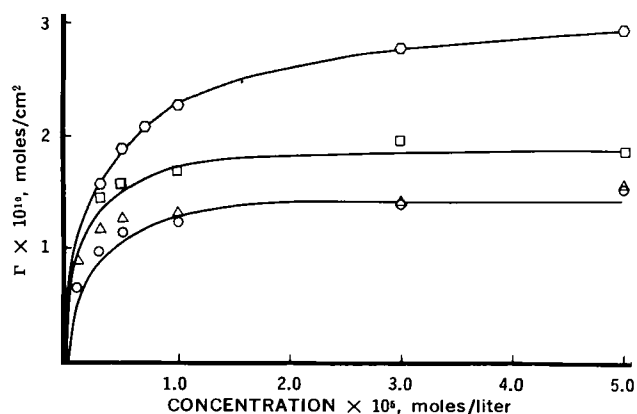
3, the amount of adsorption increased with increasing ionic strength, going from 0.01 to 0.1 M KBr, and then changed much less above 0.1 M. This is expected if one considers that the major effect of the electrolyte on the adsorption of a surface-active cation is due to the screening of repulsive interactions between the ions already adsorbed at the surface. At lower ionic strength and particularly in the absence of an electrolyte, a significantly increased time period for the attainment of an apparent equilibrium value was found. Such slow rates, again, are expected because of the repulsion of the like-charged surfactant coming to the surface. In all subsequent studies, therefore, with a few exceptions, an ionic strength of 0.1 was used, and consideration of kinetic aspects of adsorption was not necessary.

**Specific Ion Effects**—Earlier work from this laboratory had demonstrated that the surface activity of some substituted phenothiazines was significantly influenced by the presence of specific ions in solution (4, 5). The present technique appeared to offer an opportunity to get a more direct estimate of specific ion effects on the number of molecules adsorbing and, at the same time, to see whether the technique was sensitive enough to see such changes. Based upon the earlier studies, therefore, the effects of fluoride, chloride, bromide, several tetraalkylammonium halides, and several alkyl- and arylsulfonates on the adsorption of hexadecyltrimethylammonium ion were measured.

Figure 4 illustrates the effect of specific halide ions at 0.1 M, with the order of adsorption being bromine > chlorine > fluoride. Unfortunately, at all practical concentration levels, the iodide ion produced a very insoluble salt with the surfactant (CTA<sup>+</sup>) and thus it could not be included in this part of the study. Tables II and III indicate for four surfactant concentrations the effect of adding tetraalkylammonium ions instead of potassium. In general, one can see a retardation of adsorption relative to potassium with increasing tetraalkyl chain length. However, the patterns differ when either chloride or bromide is present. This will be discussed more fully later, but significant retardation occurs only with tetrabutyl ion in the presence of bromide ion, whereas retardation is seen with tetramethyl ion in the presence of chloride ion and this retardation levels off at the tetrapropyl ion.

Previous studies of the surface tension of substituted phenothiazine solutions indicated that some alkyl- and arylsulfonates change the concentration of drug required to produce a given de-

gree of surface tension lowering (5). It seemed of interest to quantify these effects by direct measurement of surface concentration. In the first series of experiments, counting studies were conducted with a series of 0.1 M sodium alkylsulfonates, including methane-, ethane-, 2-propane-, butane-, pentane-, hexane-, and benzenesulfonates. Figure 5 depicts the results of this experiment, indicating reduction in all cases relative to potassium bromide, little difference between the various alkylsulfonates, and more adsorption in the presence of benzenesulfonate than with the alkylsulfonates. In Table IV, the adsorption of surfactant in the presence of benzenesulfonate and naphthalenesulfonate at 0.01 and 0.1 M levels is compared. Note that 0.1 M naphthalenesulfonate produces less adsorption than 0.1 M benzenesulfonate, but at 0.01 M this order of effect is seen only at lower surfactant concentrations. At higher surfactant concentrations, naphthalenesulfonate produces more adsorption than benzenesulfonate. Further comparison of the two arylsulfonates was made by using concen-



**Figure 5**—Surface concentration versus bulk concentration in solutions of 0.10 M sulfonate ion. Also included for comparison are adsorption data in 0.10 M KBr. Key: O, methanesulfonate;  $\Delta$ , hexanesulfonate;  $\square$ , benzenesulfonate; and  $\circ$ , potassium bromide.

**Table VI**—Surface Concentration  $\times 10^{10}$  (Moles per Square Centimeter) for Hexadecyltrimethylammonium Adsorption in Aqueous Solutions of 0.10 *M* Sodium Naphthalenesulfonate and 0.10 *M* Orange II

Hexadecyltrimethylammonium Concentration, moles/liter	0.01 <i>M</i> Sodium Naphthalenesulfonate		0.01 <i>M</i> Orange II
$1.0 \times 10^{-6}$	$0.484 \pm 0.01$		$0.199 \pm 0.01$
$3.0 \times 10^{-6}$	$1.26 \pm 0.02$		$0.793 \pm 0.02$
$5.0 \times 10^{-6}$	$1.32 \pm 0.03$		$1.13 \pm 0.01$
$1.0 \times 10^{-5}$	$1.48 \pm 0.02$		$1.31 \pm 0.02$
$3.0 \times 10^{-5}$	$2.73 \pm 0.02$		$1.44 \pm 0.02$
$5.0 \times 10^{-5}$	$3.06 \pm 0.03$		$1.47 \pm 0.03$

trations lower than 0.01 *M* but maintaining the ionic strength at 0.1 with potassium fluoride. In all of these cases, increasing levels of sulfonate increased adsorption of surfactant, and the naphthalenesulfonate always produced more adsorption than the benzenesulfonate (Table V). It appears from these results that a critical excess of naphthalenesulfonate over hexadecyltrimethylammonium ion causes a reduction in adsorption, but as the ratio of surfactant to sulfonate gets closer to 1, a marked increase in adsorption occurs.

To check out this behavior further, it was decided to study a sulfonate of large molecular weight, the dye Orange II [*p*-(2-hydroxy-1-naphthylazo)benzenesulfonic acid sodium salt]. Its ability to interact with long chain quaternary ammonium ions was studied previously (27). Because of the combined salt's low solubility product, a concentration only up to 0.01 *M* Orange II could be used in this study. Table VI compares the effect of naphthalenesulfonate and Orange II at a 0.01 *M* level. At all concentrations, adsorption was significantly reduced by Orange II relative to naphthalenesulfonate. Table VII lists the results of using lower amounts of Orange II at constant ionic strength. Once again one can see increased adsorption relative to no sulfonate (all potassium fluoride) but a definite decrease with increasing Orange II, except for higher surfactant concentrations where lower Orange II produced increased adsorption. Clearly, one is observing the same trend of retarded adsorption when the sulfonate is in excess of surfactant but a reversal if the ratio is closer to 1. A comparison of the three arylsulfonates reveals that the higher the molecular weight the greater is the effect when both retardation and accentuation of surfactant adsorption occur.

## DISCUSSION

**General Considerations**—The results obtained in this study indicate that with the radioisotope technique one can measure directly the adsorption of hexadecyltrimethylammonium ion at the air-water interface as well as the effect of specific ions on this process. It must be kept in mind that experimental variation in these measurements is on the order of 10%, with the most serious problems occurring at low concentrations because of low counting rates. At high concentrations, there is also some error because of a greater contribution percentagewise to total counts by unadsorbed molecules. However, the differences reported are significant and they do indicate that one can study some effects specific

**Table VII**—Surface Concentration  $\times 10^{10}$  (Moles per Square Centimeter) for Hexadecyltrimethylammonium in Aqueous Orange II—Potassium Fluoride Solutions<sup>a</sup>

Hexadecyltrimethylammonium Concentration, moles/liter	Potassium Fluoride	Orange II		
		$10^{-5}$ <i>M</i>	$10^{-4}$ <i>M</i>	$10^{-3}$ <i>M</i>
$1.0 \times 10^{-6}$	$0.646 \pm 0.02$	$0.919 \pm 0.02$	$0.656 \pm 0.01$	$0.393 \pm 0.01$
$3.0 \times 10^{-6}$	$0.812 \pm 0.02$	$1.52 \pm 0.03$	$1.33 \pm 0.01$	$1.10 \pm 0.03$
$5.0 \times 10^{-6}$	$0.894 \pm 0.02$	$1.58 \pm 0.02$	$1.51 \pm 0.02$	$1.30 \pm 0.02$
$1.0 \times 10^{-5}$	$0.994 \pm 0.03$	$1.51 \pm 0.02$	$1.46 \pm 0.02$	$1.29 \pm 0.02$
$3.0 \times 10^{-5}$	$1.19 \pm 0.03$	$1.64 \pm 0.03$	$2.69 \pm 0.02$	$1.47 \pm 0.04$
$5.0 \times 10^{-5}$	$1.21 \pm 0.03$	$1.74 \pm 0.03$	$2.70 \pm 0.04$	$1.71 \pm 0.03$

<sup>a</sup> A constant ionic strength of 0.10 is maintained with fluoride ion while varying the concentration of Orange II. Included are data for hexadecyltrimethylammonium adsorption in 0.10 *M* KF.

**Table VIII**—Association Constants for Some Cation-Anion Interactions in Aqueous Solution Taken from Data of Packter and Donbrow (40)<sup>a</sup>

ArSO <sub>3</sub> . . . N(CH <sub>3</sub> ) <sub>3</sub> R		<i>K</i> <sub>a</sub> , liters/mole
Ar	R	
Benzene	C <sub>10</sub> H <sub>21</sub>	7.2
Naphthalene-1	C <sub>8</sub> H <sub>17</sub>	7.2
Naphthalene-1	C <sub>10</sub> H <sub>21</sub>	20
Anthraquinone-1	C <sub>8</sub> H <sub>13</sub>	9.7
Anthraquinone-1	C <sub>8</sub> H <sub>17</sub>	25
Anthraquinone-1	C <sub>10</sub> H <sub>21</sub>	263
Azobenzene-4	C <sub>4</sub> H <sub>9</sub>	5.5
Azobenzene-4	C <sub>6</sub> H <sub>13</sub>	19.6
Azobenzene-4	C <sub>8</sub> H <sub>17</sub>	102
Azobenzene-4	C <sub>10</sub> H <sub>21</sub>	4000

<sup>a</sup> *K*<sub>a</sub> was calculated by taking the reciprocal of instability constants given in this study (40).

ions produce on the adsorption of hexadecyltrimethylammonium ion to liquid interfaces.

To understand how the various ions can influence the adsorption of hexadecyltrimethylammonium ion to the air-water interface, it is first convenient to have an expression that relates surface concentration to bulk concentration. Davies (28) derived such an expression for the adsorption of charged surfactants to liquid interfaces, taking into account the influence of the electrical double layer produced as charged molecules are adsorbed, which is expressed as:

$$\Gamma = \frac{k'c \exp\left(\frac{W - Z_1e\psi_0}{kT}\right)}{1 + k'\Gamma_0c \exp\left(\frac{W - Ze\psi_0}{kT}\right)} \quad (\text{Eq. 4})$$

where  $\Gamma$  is the number of molecules adsorbed per square centimeter,  $c$  is the bulk concentration,  $\Gamma_0$  is the maximum number of molecules per square centimeter that can be adsorbed,  $k'$  is a constant related to hydrodynamic factors,  $W$  is the free energy of desorption (minus free energy of adsorption) due essentially to the alkyl chain,  $Z$  is the valency of the long chain ion,  $e$  is the charge of an electron,  $\psi_0$  is the electrical potential of the surface,  $k$  is the Boltzmann constant, and  $T$  is the absolute temperature. Basically, the equation indicates that a long chain compound with a large negative free energy of adsorption,  $W$ , will exhibit a large tendency to adsorb but that an ionic species will produce a surface potential,  $\psi_0$ , that will retard further adsorption due to repulsive effects. Consequently, it is not surprising that excess electrolyte or specific counterion interactions that reduce the effect of  $\psi_0$  provide enhanced adsorption of surfactant at a given bulk concentration,  $c$ . At the present time with the data collected, it is very difficult to test this equation quantitatively because of a number of factors. First, the technique prevents working at low enough concentrations to simplify the expression (surface concentrations  $<10^{14}$  molecules/cm<sup>2</sup>) (28). Second, the potential term,  $Ze\psi_0$ , is difficult to evaluate because of limitations in the Guoy-Chapman model at higher potentials (28). Third, this equation does not take into account the very specific interactions involving counterions which are being observed. Further compli-

cations come from some uncertainties related to the state of the hexadecyltrimethylammonium ion in bulk solution so that concentration is not necessarily related to activity. For example, there is good evidence for dimerization of such surfactants below the CMC (29), as well as some "ion-pairing" in aqueous solution when relatively large hydrophobic counterions are present (30). Such evidence will be presented when discussing the various specific ion effects.

**Specific Effect of Halide Ions**—The influence of halide ions on the adsorption of surfactant, as measured directly in this study, is consistent with earlier results of surface tension measurement using quaternary dodecylammonium salts (31) and chlorpromazine ion (5). These results also agree with those obtained for micelle formation (32) and for oil-water partitioning of protonated amine ion-pairs (33). When hexadecyltrimethylammonium ion is adsorbed to the interface, it must have counterions in its vicinity. If these counterions tend to interact with surfactant at the surface so as to reduce effectively the positive charge there, the free energy term in Eq. 4 must be reduced, leading to enhanced adsorption.

A number of factors can determine the extent of the interaction between ions at an interface, including a lower local dielectric constant relative to water (34), a tendency of anions to leave an aqueous environment for one that is more nonpolar (hydrophobic properties, *i.e.*, the state of hydration (35), and the tendency of the ion to be polarized and to interact specifically by noncoulombic forces of attraction (32). Indeed, halide ions have a tendency to accumulate at the air-water interface, even in the absence of an opposite charge, in the order bromine > chlorine > fluorine; this is the order of increasing hydration and decreasing size (35). Thus, one can conclude that, whereas simple ions such as the halides have no tendency to pair with hexadecyltrimethylammonium ion in aqueous solution, the nature of the air-water interface is such that it favors such ion-pairing. With the radioisotope technique, one is able to detect differences between the three halides studied and it now remains to quantitate this in future work by working at lower levels of adsorption where Eq. 2 is applicable.

In the series of experiments with the tetraalkylammonium bromides and chlorides, there appears to be an effect due to the coion as well as the counterion. The specific effect of bromine *versus* chlorine, noted earlier, is apparent from a comparison of surfactant adsorption in the presence of the same coion but different counterions; bromine favors adsorption over chlorine (Tables II and III). The second effect at constant counterion is a reduction in surfactant adsorption relative to that seen in the presence of potassium, with an increased effect at higher tetraalkylammonium-ion chain length. Some general questions one can ask first are how does an ion of similar charge cause a reduction in adsorption of surfactant and why does the effect increase with increasing alkyl chain length. One also can ask why the relative effect noted for the series of tetraalkylammonium ions does not occur to the same extent for bromine and chlorine.

First, it is possible that some competition exists for the surface between the surfactant and the other tetraalkylammonium ions. Indeed, tetrabutylammonium ion in the presence of chloride and bromide does produce a 10- and 13-dynes/cm change, respectively, in the surface tension of water (5). However, the tetramethylammonium chloride system suppresses adsorption quite significantly, yet it exhibits little surface activity (5). Further evidence against simple competition is seen from work on the effect of these coions on the oil-water partitioning of protonated amine ion-pairs (33). It was shown by direct measurement that these tetraalkylammonium ions reduced the partitioning of chlorpromazine ion into *n*-octanol in the same order noted here, but that no tetraalkylammonium ion partitioned into the oil phase.

In view of these observations, it seems most probable that inhibition of adsorption occurs in the bulk aqueous solution. The most likely possibility would seem to be an effect on water structure by the tetraalkylammonium ions such that the hydrophobic properties of the surfactant are reduced. Steigman *et al.* (36) measured the effect of these tetraalkylammonium ions on the CMC of hexadecyltrimethylammonium ion with the same general result seen here, namely, increased CMC with increasing alkyl chain length and thus reduced hydrophobic behavior. They attributed this effect to the presence of alkyl groups in addition to those of the surfactant which organize water structures in such a way as to reduce the tendency for nonpolar groups to leave an

aqueous environment. Apparently, this structuring of water offsets the favorable entropy change ordinarily occurring when water structure breaks down after a long chain group goes to a micelle or interface. This would explain the enhanced effect when increasing alkyl chain length. Lindenbaum (37) measured increased hydrogen bonding of water in the presence of tetraalkylammonium salts.

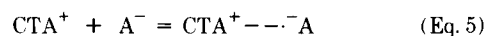
The other question centers on the different patterns of chain length effect with bromine and chlorine. If it is assumed that both counterion and coion effects act in opposite directions, one might expect such differences. For example, bromine produces ion-pairing to a greater extent than chlorine and, hence, one might have to go to tetrabutylammonium bromide before seeing a significant reduction. On the other hand, tetramethylammonium chloride is able to offset these ion-pairing effects to some extent.

**Effects of Alkyl- and Arylsulfonates**—The results of experiments involving the organic sulfonates support an earlier conclusion that adsorption of hexadecyltrimethylammonium ion is enhanced by ion-pairing at the surface but retarded by conditions in the bulk aqueous phase. Whereas the most likely explanation for the retarding effect of the tetraalkylammonium ions is their effect on water structure, an additional possibility exists when considering the effect of sulfonates, *i.e.*, the formation of ion-pairs in water as a competitive equilibrium to the adsorption process. Ordinarily, ion-pairs do not form in water because of the high dielectric constant and hydrating capacity of water which offsets coulombic attraction of opposite charges. However, when these ions both contain hydrophobic groups, there is an enhanced possibility of interaction. A number of factors are probably responsible for this, all centering on hydrophobic interactions. Diamond (38) suggested that a major factor is the reduced extent of the bulk water structuring brought about by having two closely placed hydrophobic groups rather than two hydrophobic ions, resulting in a favorable increase in entropy to the system. He referred to this as water-structure-enforced ion-pairing. Since increased hydrophobicity would also favor such association at the surface, ion-pairing at the surface and bulk aqueous solution would be favored with increasing size of the sulfonate ion, possibly producing competitive effects on surfactant adsorption.

A few studies included association constants in aqueous solution for systems related to those used in the present study. Mukerjee and Mysels (30) determined association constants for tetraalkylammonium ions, up to propyl, with lauryl sulfate ion in the range of 12.5–21 at 25°; Modin and Schill (39) measured association constants for these cations with toluenesulfonate and naphthalenesulfonate, ranging from 5.0 to 30. Table VIII presents some association constants for systems of much closer relationship to the present work; these were obtained by Packter and Donbrow (40). In general, one observes that increasing the size of either ion has a significant effect on association; for systems similar to hexadecyltrimethylammonium ion and Orange II, one can expect a relatively high association constant on the order of 10<sup>5</sup>–10<sup>6</sup>. This upper limit is believed to be reasonable based on a value reported for octadecyltrimethylammonium ion and the dye methyl orange of about 10<sup>6</sup>–10<sup>7</sup> (41).

Assuming that there is good evidence for association in aqueous solution as well as at the surface, how does this explain the results of this study? First, one can consider the situation where going from methanesulfonate to hexanesulfonate has little effect on adsorption of surfactant. There is always the possibility that these effects are too small to be separated by the present technique. However, it is also highly probable that compensating effects due to surface and bulk ionic association are occurring. More revealing is the effect of going from hexanesulfonate to benzenesulfonate (Fig. 5). It is suggested here that association in solution and/or other water-structuring effects are greater for the hexanesulfonate ion because of greater hydrophobicity. Thus, a greater adsorption of surfactant with benzenesulfonate occurs.

Following this idea, one can see similar patterns with the other systems. For example, in Tables IV–VII, with naphthalenesulfonate, benzenesulfonate, and Orange II, a situation exists where the larger, more hydrophobic ion always retards surfactant adsorption if the concentration of anion is in large enough excess of the surfactant. However, at lower anion concentrations, the reverse, enhancing effect is noted. Assuming association to be described by a simple expression, with CTA<sup>+</sup> representing the surfactant:



and considering the relatively low concentration of hexadecyltrimethylammonium ion used, a significant excess of anion would be needed to influence the surfactant monomer concentration enough to reduce "normal" adsorption, hence the dependency of extent of retardation on anion concentration or ratio of surfactant to anion.

That ion association of hexadecyltrimethylammonium ion and Orange II can occur in aqueous solution and can interfere with "extraction" of both species to a nonpolar phase was shown in the work of Scott (42). He measured the percent of this surfactant extracted into chloroform in the presence of Orange II (not soluble in chloroform) and found an inefficiency of extraction when less than a 50% excess of Orange II was present. The inefficiency was attributed to association of surfactant and Orange II in aqueous solution, as suggested here. Unfortunately, to quantitate this picture completely, it will be necessary to get a better measure of the equilibrium constants describing what occurs at the surface. In addition, one must somehow account for the many equilibria involving ion-pairing in water, as well as the self-association of hexadecyltrimethylammonium ion and anions such as Orange II (29, 43). It is clear, however, that this method in conjunction with other techniques and with more refinement can be used to answer these questions.

### CONCLUSIONS

1. In this study the adsorption of a long chain ion, hexadecyltrimethylammonium, was measured at the air-water interface using a radiotracer technique. The applicability of this technique was tested by observing changes in adsorption due to the presence of various ionic species.

2. Adsorption of surfactant was shown to be dependent on the type of halide ion present; the halide ion apparently forms an ion-pair at the surface, thus increasing the extent of adsorption in the order bromine > chlorine > fluorine. A secondary retarding effect was noted with the use of tetraalkylammonium halides up to the tetrabutyl derivative. This effect is best explained by changes due to water structuring in conjunction with surface ion-pairing.

3. Adsorption of surfactant is greatly influenced by hydrophobic sulfonate ions. Here, the problem is complicated apparently by a combination of enhanced adsorption due to ion-pairing at the surface and reduced adsorption due to association of oppositely charged ions in aqueous solution.

4. This radioisotope technique can detect subtle changes in adsorption at the air-water interface due to specific ions and it can be used with other hydrophobic molecules, including many drugs, to evaluate their fundamental properties at interfaces.

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