Interfacial Properties of Antimicrobial Long-Chain Quaternary Ammonium Salts II

Soluble Films at the Oil/Water Interface

By NORMAN D. WEINER, HELIO C. PARREIRA*, and GEORGE ZOGRAFI†

The adsorption of 3 quaternary ammonium salts, dodecylpyridinium chloride, dodecyltrimethylammonium chloride, and dodecyldimethylethylammonium chloride, has been measured at the hexane-, octane-, decane-, dodecane-, and tetradecane-0.1 M KCl interface. Adsorption appears to be influenced by interaction between the oil and both the nonpolar and polar portions of the surface-active agents, even though the surface-active agents are not soluble in the oils. The relative effect of chain length of the oil on surface concentration is a function of the bulk concentration of the quaternary ammonium salts.

IN A PREVIOUS publication (1) a study was reported concerning the adsorption of 3 quaternary ammonium salts, dodecylpyridinium chloride (DPC), dodecyltrimethylammonium chloride (DTAC) and dodecyldimethylethylammonium chloride (DEAC), at the air/water interface. The present study is concerned with the properties of these compounds at a number of different oil/water interfaces.

It is well recognized that the interfacial properties of surface-active agents at the air/water surface are quite different than their properties at the oil/water interface (2–6). Hutchinson (3) has suggested that oil molecules are present at the interface along with adsorbed surface-active molecules, and that a competition exists at the interface between the nonpolar portions of like molecules and the nonpolar portions of the oil and surface-active agents. He came to this conclusion by comparing the π-A characteristics of fatty acids adsorbed at various oil/water interfaces and their relative solubility in the oils. Schulman et al. (7) have studied the effect of the oil phase on microemulsion formation, and have concluded that oil molecules associate at the interface with surface-active agents. The presence of oil at any particular surface pressure was said to depend on the oil's ability to interact with film molecules and thus resist ejection with increasing film pressure. Zisman (8) has reported that mineral oil molecules appear to penetrate long-chain alcohol monolayers adsorbed at the oil/water interface, and remain as part of the surface film up to surface pressures of about 30 dynes/cm.

Davies (9) has suggested that compounds having the same polar group, but differing in chain-length, should have the same π-A relationships at an oil/water interface since interactions between hydrocarbon chains of the compounds do not exist or are very weak. Brooks and Pethica (10, 11) have recently compared π-A curves at heptane–water interfaces for dodecyl, octadecyl, and docosyltrimethylammonium bromides. These π-A curves were obtained by applying the Gibbs adsorption equation in the case of the dodecyl compound, and by spreading insoluble monolayers of the other compounds. The π-A curves for these compounds were in good agreement, thus apparently verifying Davies' conclusions. Since the effect of changing the oil phase has not been considered in these systems, the authors chose to measure adsorption from aqueous solution in the presence of a series of straight-chain hydrocarbons, ranging from hexane to tetradecane. Since the quaternary ammonium salts are not soluble in the oils, it was felt that any effect on adsorption, due to changing oils, must be due to changes occurring in the interfacial region. The use of the 3 compounds under consideration also allowed the authors to observe differences due to the polar group, since chain-length and counter-ion were the same in all cases.

EXPERIMENTAL

Materials.—Hexane,[1] octane,[2] decane,[2] dodecane,[2] and tetradecane[2] were purified as follows: 25 ml. of fuming sulfuric acid was added to 500 ml. of oil, and the mixture was shaken in a separator for 5 min. The fuming sulfuric acid layer, which darkened considerably, was then discarded. This procedure was repeated until 3 successive additions of fuming sulfuric acid produced no visible darkening of the acid layer. The oil phase was then washed

[1] Hexane (spectroanalyzed, certified reagent) was purchased from Fisher Scientific Co.
[2] Each of these hydrocarbons (practical grade) was purchased from Eastman Organic Chemicals.

with water 5 times, with 5% sodium bicarbonate solution 5 times, and with water again 5 times. Charcoal and anhydrous sodium sulfate were then added to the oil, and the mixture was allowed to stand overnight. The oil was then filtered and distilled under vacuum. Only the middle 80% was collected. The surface tension of each oil agreed with reported data (12, 13).

Interfacial Tension Measurements.—The drop-volume method was used for all interfacial tension measurements. The apparatus used is the same as that described previously (1). It is a modification of one described recently by Parreira (14).

Calculations of interfacial tension from the drop-volume method were carried out with the Harkins and Brown equation (15),

$$\gamma = \frac{V(d - d')g}{2\pi r \theta} \qquad \text{(Eq. 1)}$$

where V = volume of the drop, cm.^{3}
  g = gravity constant (980.3), cm./sec.^{2}
  d = density of the aqueous phase, Gm./cm.^{3}
  d' = density of the oil phase, Gm./cm.^{3}
  π = 3.142
  r = radius of the syringe tip, cm.
  θ = correction factor obtained from the data of Harkins and Brown (15) for various values of $(r/V^{1/3})$

A syringe tip having a radius of 0.1895 cm. was used for all interfacial tension measurements. A 0.1895-cm. tip allowed at least 3 drops to form without refilling the syringe, even for the most dilute solutions. As with studies at the air/water interface (1), all values for $r/V^{1/3}$ that resulted from interfacial tension measurements with this syringe tip were within the range that allowed a second-order polynomial expression to be used for the calculation of θ.

The densities of hexane, octane, decane, dodecane, and tetradecane are 0.6595, 0.6986, 0.7258, 0.7459, and 0.7610 Gm./ml., respectively. These values do not change, within experimental error, if the oil is saturated with water. The density of water was also unaffected by saturation with oil.

It was observed that, if the syringe was not thoroughly cleaned between fillings, the volumes of the drops varied considerably, even with the same solution. This phenomenon did not occur in previous surface tension studies. It was possible that, if the syringe was not thoroughly cleaned between runs, a small amount of oil remaining on the tip might have been drawn into the syringe with the sample. If proper technique was used, however, the precision of the measurement was always within 0.2 dynes/cm., and in most cases to within 0.1 dynes/cm. In regions of very low interfacial tension, *i.e.*, below 7 dynes/cm., the results were erratic, apparently due to nonuniform wetting of the tip. A change in the size of the tip or the use of a stainless steel tip did not alleviate this difficulty.

It is interesting to note that the interfacial tensions of DPC, DTAC, and DEAC solutions, at all concentrations, were unaffected by the lack of mutual saturation of the aqueous and oil phases. All interfacial tension measurements, therefore, were made in solutions that were not saturated, with frequent checks being made on saturated systems. All solutions were prepared in duplicate. The volumes of at least 3 drops were measured for each sample; the

volume of a drop was independent of time if the drop was allowed at least 5 min. to form. All interfacial tension measurements were, therefore, considered to be equilibrium measurements.

Interfacial tension *versus* concentration data were obtained for DPC and DEAC at the hexane–0.1 M KCl and dodecane–0.1 M KCl interfaces, and for DTAC at the hexane–0.1 M KCl, octane–0.1 M KCl, decane–0.1 M KCl, dodecane–0.1 M KCl, and tetradecane–0.1 M KCl interfaces. All measurements were carried out at 25 ± 0.1°.

RESULTS

In order to obtain values for the surface concentration and the surface area of each compound at the various interfaces, the Gibbs adsorption equation was applied. Since all measurements were made in the presence of excess electrolyte, the following form of the equation (16) was used:

$$\Gamma = 1/A = (1/kT)(d\pi/d \ln c) \qquad \text{(Eq. 2)}$$

where

  Γ = surface concentration (molecules/cm.^{2})
  A = surface area (cm.^{2}/molecule)
  k = Boltzmann's constant (ergs/degree-molecule)
  T = absolute temperature
  π = surface pressure (ergs/cm.^{2})
  c = bulk concentration (moles/L.)

The slopes of the surface pressure *versus* log bulk concentration plots were estimated with polynomial equations using the least squares method (1). An IBM 7090 digital computer was utilized to obtain the required data. Fourth-order polynomial equations gave the best fit to experimental data; a typical set of interfacial pressure *versus* logarithm molar concentration curves are shown in Fig. 1. The lines represent the empirical polynomial curves and the points represent experimental data.
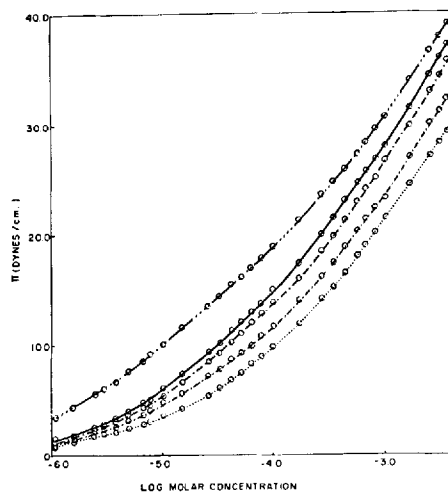

Fig. 1.—Surface pressure (π) *vs.* logarithm molar concentration of DTAC at various interfaces at 25°. (Lines represent empirical polynomial curves.) Key: ··——, hexane–0.1 M KCl; ———, octane–0.1 M KCl; —·—·—, decane–0.1 M KCl; – – – –, dodecane–0.1 M KCl; ......, tetradecane–0.1 M KCl.
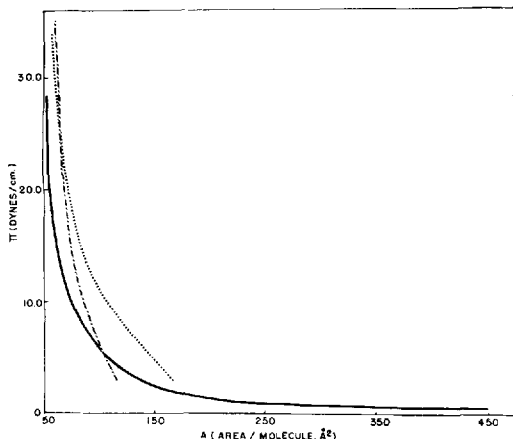
Fig. 2.—Surface pressure (π) *vs.* surface area (A) for DPC at various interfaces at 25°. Key: ———, air–0.1 M KCl; ......, dodecane–0.1 M KCl; – – – –, hexane–0.1 M KCl.

Fig. 4.—Surface pressure (π) *vs.* surface area (A) for DEAC at various interfaces at 25°. Key: ———, air–0.1 M KCl; ......, dodecane–0.1 M KCl; – – – –, hexane–0.1 M KCl.
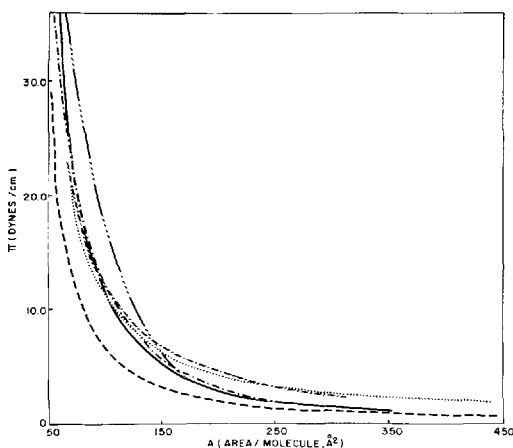

Fig. 3.—Surface pressure (π) *vs.* surface area (A) for DTAC at various interfaces at 25°. Key: – – – –, air–0.1 M KCl; —··, hexane–0.1 M KCl; ———, octane–0.1 M KCl; ·—·—·, decane–0.1 M KCl; – –– ––, dodecane–0.1 M KCl; ......, tetradecane–0.1 M KCl.

The π-A curves of DPC, DTAC, and DEAC at the various interfaces are shown in Figs. 2–4. These curves generally indicate that more "condensed" films occur with the lower molecular weight oils (*i.e.*, a marked increased in the surface pressure for a small change in the area per molecule) particularly in regions of high area. The π-A curves for the quaternary ammonium compounds at the air–0.1 M KCl, hexane–0.1 M KCl, and dodecane–0.1 M KCl interfaces are shown in Figs. 5–7, respectively. Whereas the π-A curves of the 3 quaternary ammonium compounds are quite similar at the air/water surface, the π-A curves of DPC appear to be more "condensed" than those of DTAC and DEAC at the oil/water interfaces, particularly at the hexane–0.1 M KCl interface.

A region where surface pressure changed linearly with concentration (Traube region) was not observed at any of the oil/water interfaces tested.
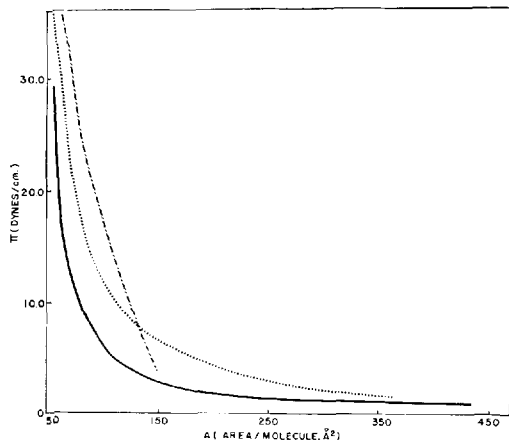
This observation appears to substantiate Hutchinson's hypothesis (3) that, even for low concentrations of surface-active agents, the hydrocarbon group is immersed in the oil phase, rather than lying parallel to the interface.

DISCUSSION

The greater complexity of the oil/water interface as compared to the air/water surface and differences with different oils is to be expected when one considers the possible interactions between the hydrocarbon portion of the surface-active agent and the oil. Furthermore, it appears that interactions between the polar group of the surface-active agent and the oil are responsible for marked changes in the nature of the surface film. This aspect has not been considered previously.

In order to evaluate the effect of the oil phase, as observed in this study, it will be worthwhile looking at 2 extreme situations. First, the oil does not interact with the hydrocarbon portion of the surface-active agent, and the only interactions of interest are those between the hydrocarbon portion and water at high surface areas, and those between surface-active agent hydrocarbon portions at low areas. In the second case, the oil strongly interacts with the hydrocarbon portion of the surface-active agent and there is minimal hydrocarbon–water interaction at high surface areas, as well as little or no cohesive interaction between surface-active molecules.

If the first case occurs, the hydrocarbon portion of the surface-active agent should be aligned approximately parallel to the interface at high surface areas. This would result in a linear change in surface pressure with concentration (Traube region), as observed at the air/water interface (1), and would mean that the oil phase does not affect the nature of the film. This, of course, is contrary to what is seen in Figs. 3 and 4. At lower areas interaction between the hydrocarbon portions of surface-active agent should result in π-A curves which are the same as those observed at the air/water interface. Again, Figs. 3 and 4 indicate that this is not the case, although at very low areas, expulsion of oil molecules from the surface may be occurring to some extent.
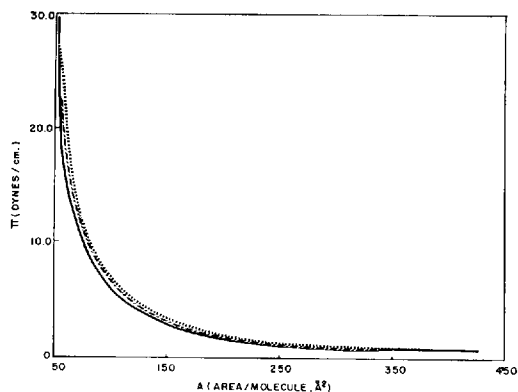
Fig. 5.—Surface pressure (π) *vs.* surface area (A) for the air −0.1 M KCl interface at 25°. Key:
———, DPC; − − − −, DEAC; ......, DTAC.
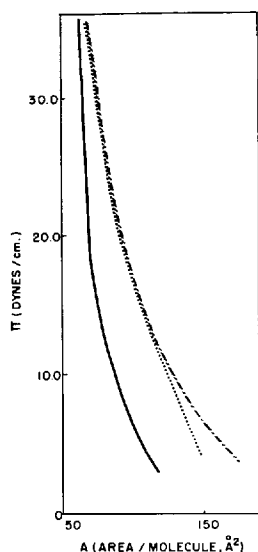

Fig. 6.—Surface pressure (π) *vs.* surface area (A) for the hexane-0.1 M KCl interface at 25°. Key: ———, DPC; − − − −, DEAC; ...., DTAC.
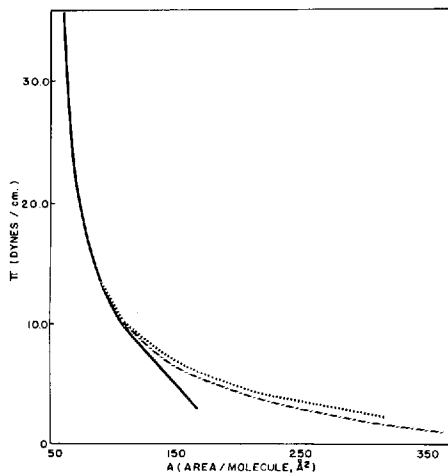

Fig. 7.—Surface pressure (π) *vs.* surface area (A) for the dodecane–0.1 M KCl interface at 25°. Key: ———, DPC; − − − −, DEAC; ......, DTAC.
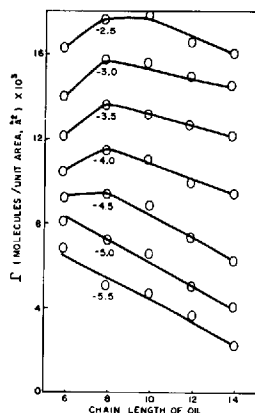

Fig. 8.—Surface concentration (Γ) at the 0.1 M KCl–hydrocarbon interface at 25° *vs.* chain length of hydrocarbon for various bulk concentrations of DTAC (expressed as log of molarity).

If the oil interacts strongly with the surface-active agent, the strong interaction between the hydrocarbon portion of the surface-active agent and the oil should result in an alignment of surface-active molecules approximately perpendicular to the interface, even at high surface areas. It would then be reasonable to expect that the most "condensed" film would result in the dodecane/water interface, since the dodecane–dodecyl quaternary ammonium compound interaction would allow stronger attractive forces than would the other oils tested. Figures 2–4 indicate that this is not the case. In fact, the hexane/water interface results in the most "condensed" films for all 3 quaternary ammonium compounds tested. This extreme would also necessitate the absence of a transition from an "expanded" region (a region where hydrocarbon–water interactions are predominent and small changes in surface pressure produce large changes in area per molecule) to one of saturation adsorption (a region where hydrocarbon–hydrocarbon interactions are predominant and changes in pressure do not produce significant changes in area). Figures 2–4 show that this transition does not always occur, and, in fact, whereas the dodecane/water interface does show such a transition for DTAC and DEAC, the hexane/water interface, at the pressures tested, does not. It therefore appears that the nature of the film is intermediate between the 2 extremes cited. The alignment of the surface-active molecules at the oil/water interface is neither parallel nor perpendicular to the interface, but intermediate between the two.

Plots of the chain length of the oil *versus* the surface concentration of DTAC at various bulk concentrations (Fig. 8) appear to give some indication as to the role of the oil. At low bulk concentrations the surface concentration of DTAC is inversely proportional to the chain length of the oil. At higher bulk concentrations, the octane/water interface contains the highest surface concentration of DTAC. At even higher bulk concentrations, the decane/water interface contains surface concentrations of DTAC which are of equal magnitude to that of the octane/water interface. It seems possible, therefore, that as the bulk concentration of DTAC increases, there is a tendency for the higher chain length hydrocarbons to interact to a greater extent with the DTAC film.

This trend could be accounted for by the fact that, at low bulk concentrations, the DTAC molecules are not aligned perpendicularly to the interface due to

some interaction with water, coiling of the hydrocarbon chains, or both. The size of hexane, as compared to the other hydrocarbons, could make it best suited to interact with the DTAC film at these low concentrations. As the surface concentration increases, it is reasonable to expect that the hydrocarbon portions of the surface-active agents will orient in a more perpendicular direction to the interface. This should improve the chances for the longer-chain hydrocarbons to interact with the exposed groups of the surface-active agents.

The preceding discussion considered only the interactions between the oil and the hydrocarbon group of the surface-active agent. It is important, however, not to neglect the possibility of an interaction between the polar group of the surface-active agent and the oil. Figures 5–7 show that, although the π-A curves of DPC, DTAC, and DEAC are quite similar at the air/water surface, differences between the 3 quaternary ammonium compounds at an oil/water interface do exist. The π-A curves for DPC are "compressed" to a greater extent than those for DTAC and DEAC at the oil/water interfaces, especially at the hexane/water interface. This effect may be due to a dipole-induced dipole interaction between the planer aromatic pyridinium ion and the oil, which is less possible in the case of DTAC or

DEAC. Once again, the steric nature of the hexane molecule probably makes it best suited for this interaction.

It appears, therefore, that the nature of the oil phase influences adsorption of water-soluble substances, such as quaternary ammonium salts, and that the oil used in such studies must be considered in any discussion.

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Solubilizing Properties of Bile Salt Solutions I

Effect of Temperature and Bile Salt Concentration on Solubilization of Glutethimide, Griseofulvin, and Hexestrol

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Data on the micellar solubilization of the poorly water-soluble drugs, griseofulvin, hexestrol, and glutethimide, in 0–0.6 M aqueous solutions of the sodium salts of cholic, desoxycholic, taurocholic, and glycocholic acids at 3 temperatures are presented. Employing the pseudo two-phase model for micellar solubilization, the thermodynamic functions, ΔF^0, ΔS^0, and ΔH^0 of partitioning of the drug molecule between the aqueous phase and the micellar phase have been determined for hexestrol and griseofulvin. The physical-chemical ramifications and biological implications in these systems are considered.

A QUEOUS solutions of surfactants exhibit a more or less abrupt change in their physical properties over a narrow concentration range. This distinct change in properties is generally accepted to be due to the formation of oriented aggregates or micelles. The narrow surfactant concentration range at which micelles begin to form is referred to as the critical concentration for micelle formation or CMC. Among the more

interesting properties of micellar solutions is their ability to solubilize water-insoluble materials.

Micellar solubilization has been defined by McBain (1) as "the spontaneous passage of solute molecules of a substance, insoluble in water, into an aqueous solution of a surfactant in which a thermodynamically stable solution is formed." This process essentially involves the diffusion of the added solubilizate molecules (*i.e.*, the water-insoluble material being solubilized) from the bulk phase into the surfactant micelle. The solubilized system is in a state of equilibrium.

Micellar solubilization has been broadly classified into 3 types (1–3). (*a*) *Nonpolar (nonspecific) solubilization:* the solubilizate is in-