GI tract, production of undetected metabolites, and/or biliary secretion of metabolites.

No intact I or free III was detectable in serum samples collected over an 8-hr. period following oral administration of 1500 mg. of I (analytical sensitivity $\geq$ 8 mcg./ml.). Extensive distribution, analogous to that reported for salicylamide in animals (7), apparently occurred.

***In Vivo* Studies with II**—Urinary excretion of II and its detected metabolites is shown in Table II. On the basis of the *in vitro* kinetics studies, absorption of intact II was predicted. This was supported by the detection of small but significant amounts of II in the urine (mean: 0.40% of the dose). Overall mean 24-hr. excretion of II, of its hydrolysis product, IV (1.14%), and of conjugated IV (40.0%) was 41.5% of the administered dose, suggesting considerably more efficient absorption of II than was found in the case of I. This observation also was consistent with the stability of II which would present a neutral molecule for diffusion across the intestinal barrier as contrasted to III, produced from I, which would exist at least partially in the anionic form at the pH of the intestine. Extensive enzymatic hydrolysis of II was indicated, in agreement with the reported *in vivo* hydrolysis of aryl carbamates (8) as opposed to the stability of aliphatic carbamates (9, 10).

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Anesthetic Gas Absorption Properties of Surfactant Systems

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Abstract □ Studies were undertaken to determine the possibility of solubilization being a method of gas transport in biological systems by aggregation through associated micelle formation. Specific gases, surfactant concentration, type of structure in surfactant systems, and biopharmaceutical and physiological aspects were considered in determining the transport mechanism of water-insoluble anesthetic gases. Gas solubilization was analyzed by GC with a modified tonometer as an absorption chamber. Halothane, ethyl ether, trichloroethylene, and nitrous oxide were used with surfactant systems of polysorbate 80, dioctyl sodium sulfosuccinate, and bovine albumin. The surfactant concentration was an important factor in anesthetic gas absorption, since increased gas absorption was observed with concentrations of surfactant above the CMC. The mechanism of absorption tends to indicate solubilization of the gases through the formation of micelles.

Keyphrases □ Anesthetic absorption, gaseous—effect of surfactant systems □ Surfactant effect—absorption of gaseous anesthetics □ Solubilization, micelle formation—possible mechanism of gaseous anesthetic absorption

The fact that most inhaled anesthetic gases and many physiologically important gases are nonpolar and have poor solubility in highly polar water must be considered in attempting to understand their possible transport mechanism. The generally accepted hypothesis of gases diffusing through the lung lining presents some theoretical difficulties. Not only are these gases insoluble in water, they would be diffusing through media containing carbon dioxide and carbonates which could greatly reduce the degree of permeability, solubility, and rate of diffusion. It appears unlikely that simple partition and diffusion mechanisms can account for the large quantities of nonpolar anesthetic gases transported through lung tissue to the bloodstream.

Although solubilization of micelles is a reasonably well-established concept, its application as an alternate mechanism of solubilization through the formation of micelles has now been proposed for the rapidity of gas absorption (1, 2). An important factor which has emerged from general studies is that these surfactant solutions become significant solvents at a stage where surfactant molecules begin aggregating. The surfactant molecules acting as aggregated units become excellent solvents (3).

EXPERIMENTAL

The concept of solubilization, which has been defined as "the spontaneous dissolving of a normally water-insoluble substance by an aqueous solution of surfactant" (4), was utilized in these laboratories as a means of explaining the nature of the data obtained on gas absorption. Studies were undertaken to obtain gas absorption data on several surfactant systems and to expand a previous concept by experimentally using several anesthetic gases for observation of gas absorption on different surfactant systems. The surfactants

Table I—GC Operating Temperatures

Gas	Ports					
	Injection	Column	Internal Detector	Duct	Outlet	External Oven
Ethyl ether	150°	100°	101°	—	—	—
Halothane	165°	125°	130°	—	—	—
Trichloroethylene	180°	152°	156°	—	—	—
Nitrous oxide	172°	140°	147°	206°	255°	238°

were prepared in concentrations well above the CMC for these studies.

Equipment[1]—Gas solubilization was analyzed by GC. The absorption chamber was a modified tonometer, constructed of glass and fitted with rubber stoppers for the extraction of nonpolar gas samples (Fig. 1). Gas syringes were used to transfer the gas volume from the preparation tonometer to that containing gas samples. These were fitted with 22-gauge, 6.4-cm. (2.5-in.) needles. Hamilton gastight syringes (50, 100, 250, and 500 μl.), fitted with Teflon hub needles [24 gauge, 3.8 cm. (1.5 in.)], were used for removal of gas analysis samples from the second tonometer and for injection of these samples into the gas chromatograph. A gas chromatograph equipped with dual hydrogen flame-ionization detectors and a thermal conductivity detector was utilized to follow the course of gas uptake. The hydrogen flow rate was maintained at 10 ml./min., air was at 350 ml./min., and nitrogen was 60 ml./min. Helium, when used as the carrier gas with the thermal conductivity detector, was maintained at a flow rate of 40 ml./min. The stainless steel columns used for analysis of gas uptake were 1.8 m. by 0.64 cm. (6 ft. by 0.25 in.). These were packed with 25% silicone gum rubber SE-30 on Anakron (70–80 mesh) for analysis of the ethyl ether, halothane, and trichloroethylene. Poropak-Q was used for packing with the nitrous oxide samples. See Table I for operating temperatures used in the gas chromatograph.

Gas analysis samples were removed at intervals of approximately 1 min. for 20 min. The experiments were conducted at room temperature. Liquid systems to be studied were first warmed in a water bath at 40° to permit escape of any dissolved gases and then were placed in the sample tonometer through which helium had been passed to clean the atmosphere.

The anesthetic gases[2] (halothane, ethyl ether, trichloroethylene, and nitrous oxide) were studied in relation to the amount of gas uptake occurring in surfactant systems of polysorbate 80, dioctyl sodium sulfosuccinate, and bovine albumin[3]. These samples were

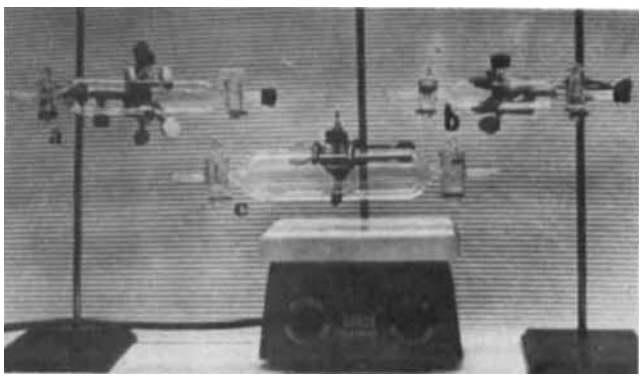

Figure 1—*Modified tonometer. Key: a, 150-ml. sample tonometer; b, 50-ml. sample tonometer; and c, 300-ml. preparation and storage tonometer.*

[1] Sources of the equipment used were as follows: gas chromatograph, WCLID 1670 model, purchased from Warner-Chilcott Laboratories, Richmond, Calif.; and columns, HCl Scientific, Inc., Rockford, Ill.

[2] Halothane (Fluothane), Ayerst Laboratories, New York, N. Y.; ethyl ether USP, Squibb & Sons, New York, N. Y.; nitrous oxide USP, (from size E tanks), University of Illinois; and trichloroethylene (trichloroethene), analytical grade, Fisher Scientific Co., Chicago, Ill.

[3] Polysorbate 80 (Tween 80), liquid, Atlas Chemical Co., Wilmington, Del.; dioctyl sodium sulfosuccinate (Aerosol-OT), solid, American Cyanamid Co., New York, N. Y.; and bovine albumin, powder, Armour Pharmaceutical Co., Kankakee, Ill.

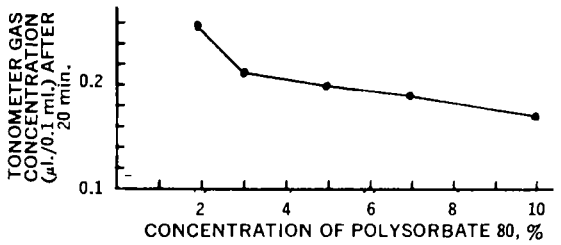

Figure 2—*Halothane gas sorption by polysorbate 80 after 20 min.*

analyzed for each gas studied by GC and quantified by comparison with a freshly prepared standard.

Halothane, ethyl ether, and trichloroethylene were originally in the liquid state. In preparing the anesthetics for the desired vapor volume, the following formula was used:

$$\frac{(A)(B)(C)}{(D)(E)} = \text{volume of liquid anesthetic (ml.)} \quad \text{(Eq. 1)}$$

where A = percent of gas concentration, B = volume (ml.) of tonometer, C = molecular weight of anesthetic agent, D = specific gravity of anesthetic agent, and E = gas constant (22,400 ml.).

These experiments were expanded from earlier work (2) in which a lung surfactant was used with halothane vapor absorption. The studies were intended to show this as a general phenomenon applicable to gas uptake on favorable surfactant systems.

RESULTS AND DISCUSSION

The tonometer gas concentration (microliters) in the vapor phase above the liquid sample *versus* the time (minutes) that vapor gas was present in the closed system was the method used for graphically following gas uptake. It was determined during experimentation that a 20-min. time period was adequate for observation of a significant quantity of gas uptake. These data were initially converted to gas concentration (microliters per milliliter) remaining after 20 min. *versus* surfactant concentration to obtain relative studies (Fig. 2). For consolidation purposes, the percentage of gas concentration *versus* surfactant concentration was plotted for each surfactant.

Figure 3 illustrates gas uptake results using halothane, trichloroethylene, ethyl ether, and nitrous oxide on polysorbate 80 solutions in concentrations of 2, 3, 5, 7, and 10%. Note that the 3and 10% w/v appear to have absorbed a relatively higher gas concentration as shown by discontinuities in the curve.

Figure 4 shows results of similar studies performed with dioctyl sodium sulfosuccinate solutions, which indicate increased gas absorption properties with increasing concentrations of dioctyl sodium sulfosuccinate. These solutions were prepared in distilled water rather than isotonic saline since a precipitate formed in the saline solution. The graphs follow the decrease in anesthetic gas concentration in the vapor phase and, thereby, the gas absorbed by the solution.

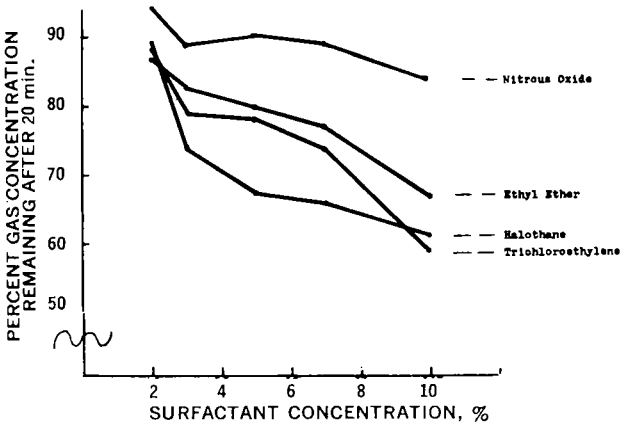

Figure 3—*Gas sorption by polysorbate 80.*

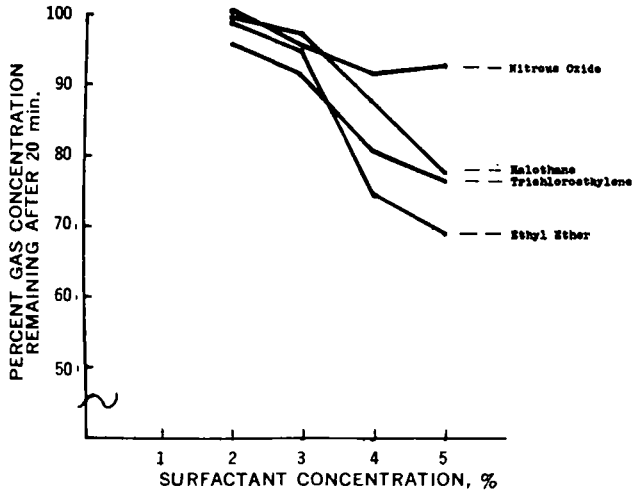

Figure 4—*Gas sorption by dioctyl sodium sulfosuccinate.*

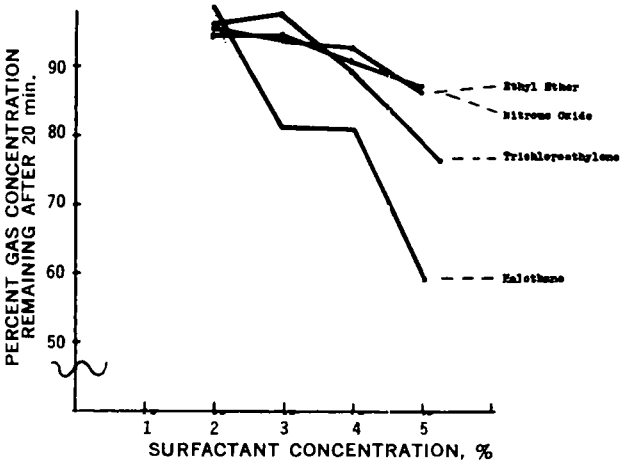

Figure 5—*Gas sorption by bovine albumin.*

A similar observation was previously reported (2); however, this work dealt only with halothane vapor. Thus, these studies agree with reported data and, in addition, expand the hypothesis by its application to the other anesthetic gases used in these experiments.

Another system used to determine gas uptake was bovine albumin. Previous work by Featherstone and coworkers (5, 6) showed a significant discontinuance in the solubility of cyclopropane in albumin at a concentration of 5%. Serum albumin solutions were used in their experiments to determine the amount of cyclopropane gas that would go into solution. Results indicated that very little uptake occurred from 0 to 4%. However, from 5 to 10%, there was a significant increase in the dissolving ability of cyclopropane.

The present studies were performed with concentrations of bovine albumin varying from 1 to 5%. As can be seen from Fig. 5, absorption of each gas showed a disproportionate increase as the concentration of albumin approached the 5.0% level. Thus, at concentrations from 4 to 6%, there was a significant discontinuity or rise in the ability to dissolve nonpolar gases, which indicates that micellar aggregation is taking place. The experimental data using several nonpolar gases on bovine albumin solutions of various concentrations verify that the primary aggregation point is at 5.0%.

Gas uptake increased with increasing concentrations of each solution system used, although not in direct proportion. No appreciable gas uptake was observed, however, when distilled water or normal saline was used as standards for control or with solution systems below the CMC.

In all of these absorption studies, the lower percent concentrations showed absorption that paralleled that of saline or distilled water. With increasing concentrations, it became apparent that increasingly larger aggregates (micelles) form, as demonstrated by the sudden increase in gas absorption. The marked ability of these systems to absorb or solubilize the anesthetic gases is highly indicative of solubilization by micelles.

In samples with an aqueous surface containing little or no amount of surfactant, there was little or no gas absorption. The surfactant solutions are in differing states of aggregation. Surfactants dispersed principally as individual molecules in water or saline give a medium that absorbs little or no nonpolar molecules. As the concentration of surfactant molecues was increased to reach a saturation point, they aggregated into units of micelles. After reaching the CMC, micelles increased in size with the addition of surfactant and aggregated to form continuous structures (3). At this stage the increased ability to solubilize nonpolar substances was most significant.

SUMMARY

It becomes evident from these studies and other published data (6) that while dispersed systems of lipids in water cannot account for the quantities of nonpolar gases present in the blood, the aggregated molecules of surfactants can dissolve large quantities of solute. These results can be of significance in molecular biology and should be worthy of consideration.

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