nonlinear heterogeneous one-compartment—one type of tissue—model to the dog intravenous studies.

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Use of Thermal Gravimetric Analysis in Sorption Studies II: Evaluation of Diffusivity and Solubility of a Series of Aliphatic Alcohols in Polyurethan

G. W. C. HUNG and J. AUTIAN▲

Abstract ☐ A thermogravimetric analysis method was used to evaluate the diffusion and solubility of a series of aliphatic alcohols in a specific polyurethan film at several different temperatures. The diffusion coefficients were calculated from desorption curves by the use of a specific equation applied to the early stages of desorption. In general, the diffusion coefficients of the straight-chain alcohols increased with temperature and decreased with molecular weights. The branched-chain alcohols had diffusion coefficients lower than the nonbranched isomers. Activation energies of diffusion were also calculated and fell into the range of 9.16–14.5 kcal./mole. By knowing the diffusion and the solubility coefficients, the permeability constants were estimated.

Keyphrases ☐ Alcohols, aliphatic—diffusivity and solubility in polyurethan films, thermogravimetric analysis ☐ Polyurethan films—diffusivity and solubility of aliphatic alcohols, thermogravimetric analysis ☐ Diffusion coefficients of aliphatic alcohols—polyurethan films, thermogravimetric analysis ☐ Thermogravimetric analysis—diffusivity and solubility of aliphatic alcohols in polyurethan films

Greater attention is now being paid to the possible interaction of drugs with various plastics and elastomers used for packaging of drugs or as various types of collection and administration devices. Reduction of potency of the drug or a preservative in the product due to an interaction with the plastic can pose from minor to serious consequences to the patient. A previous communication (1) from these laboratories reported on the use of thermogravimetric analysis (TGA) as a rapid and simple means of studying drug–plastic interactions. In that study a group of liquid compounds were first placed in contact with a specific plastic (nylon 66) until equilibrium was attained. The material was then placed into the TGA instrument, and the desorption was followed in a dynamic manner by increasing the temperature at a constant rate. The resultant thermogram then permitted an evaluation of the equilibrium sorption concentration and the energy of activation of desorption which, in turn, permitted a qualitative insight as to the role the structure of the compound played in the sorption process.

The present report extends these TGA studies on the interaction of a series of aliphatic alcohols with a specific plastic, polyurethan. Desorption experiments permitted the calculation of the diffusion coefficients of these alcohols and the activation energies of diffusion. The equilibrium sorption concentration of each compound at different temperatures was also evaluated.

EXPERIMENTAL

Materials—The following eight alcohols were used in this study: methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-methyl-1-propanol, 1-pentanol, and 1-octanol. All of these compounds were of reagent grade or of the highest purity obtainable commercially. They were used as such without further purification. Table I lists the alcohols and summarizes some physical properties for each compound.

Table I—Some Physical Properties of Alcohols

Compound	Formula Weight	Melting Point[a]	Boiling Point[a]	Density[a], g./cu. cm.	Dipole Moment[b] (Debye)	Molecular Volume[c], $V \times 10^{23}$, cu. cm./Molecule	Heat of Vaporization[d], ΔH_v, kcal./mole
Methanol	32.04	−97.8°	64.55°	0.793	1.71	6.71	8.4
Ethanol	46.07	−114.6°	78.4°	0.789	1.73	9.69	9.4
1-Propanol	60.09	−127.0°	97.2°	0.804	1.67	12.4	8.8
2-Propanol	60.09	−89.0°	82.3°	0.785	1.70	12.7	9.6
1-Butanol	74.12	−89.5°	117.7°	0.180	1.81	15.2	10.5
2-Methyl-1-propanol	74.12	−108.0°	108.4°	0.801	1.66	15.4	—
1-Pentanol	88.15	−78.5°	138.0°	0.817	1.66	18.0	10.7
1-Octanol	130.23	−16.3°	195.0°	0.825	1.72	26.2	12.7

[a] Values obtained from "Handbook of Chemistry and Physics," 44th ed., The Chemical Rubber Publishing Co., Cleveland, Ohio, 1963. [b] Values obtained from A. L. McClelland, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963. [c] Molecular volume calculated from the relationship $d = M/V$ by dividing the molecular weight by the density and the Avogadro number to yield the volume per molecule. [d] Heat of vaporization obtained from "Lange's Handbook of Chemistry," 9th ed., McGraw-Hill, New York, N. Y., 1956.

The polyurethan was obtained[1] as a thin film. It is a thermoset solid polyurethan prepared by reacting a polyurethan prepolymer with 4,4′-methylenebis(2-chloroaniline). Its general properties are those of an elastomer.

Preparation of Samples—Test samples were punched from the film with a paper punch [No. 1, 0.63-cm. (0.25-in.) diameter] to produce a definite size and shape (0.640-cm. diameter, 0.0770–0.0778-cm. thickness, and 27.5–28.0-mg. weight). In all instances, test samples for each specific alcohol at a specified temperature were kept as uniform as possible and never exceeded 0.5% (thickness or weight) from sample to sample. Individual thicknesses and weights of the samples were always used, however, in the treatment of the thermogram data for obtaining the diffusion coefficient and solubility coefficient. Prior to use in any experiment, the test samples were soaked in 95% alcohol for 48 hr. and then rinsed repeatedly with distilled water. An additional soaking in 50% ethyl alcohol for 24 hr. with subsequent rinsing with distilled water was performed. Finally the test samples were rinsed with acetone and dried to constant weight. These samples were then stored in a desiccator until ready for use.

For each alcohol, a test sample was removed, weighed on an analytical balance to establish its initial dry weight, and then placed into an all-glass sorption tube to which was added 10.0 ml. of the specific alcohol. The tube was then stoppered (screwcap with Teflon-faced rubber liner) and placed into a thermally controlled water bath adjusted to 24.0 ± 0.2°. Similar samples with the same alcohol were entered into water baths at 30.0, 40.0, and 50.0 ± 0.2°.

Preliminary runs indicated that equilibrium sorption occurred within a few days to several weeks, depending upon the alcohol and the storage conditions. For uniformity, however, the sorption tubes with samples were kept in the water baths for exactly 30 days. After this time the plastic sample was removed from the test alcohol and excess liquid was blotted with tissue paper. Immediately (within 70 sec.) the plastic sample was introduced into the TGA instrument, the sample weight was recorded, and a thermogram was run. This same procedure was used for each alcohol studied.

TGA for Desorption Studies—The TGA instrument and the method of running a desorption experiment were presented in a previous paper (1), but certain modifications were made in the present study. In this case, the sample, the quartz hangdown tube, and the thermocouple (to measure the temperature of the sample) were all contained in a chamber which could be immersed into a constant-temperature bath[2] adjusted to the same temperature of the initial 30-day sorption experiments (i.e., 20, 30, 40, and 50 ± 0.1°). A schematic diagram of this arrangement is shown in Fig. 1.

A stream of nitrogen was passed through concentrated sulfuric acid and then into the chamber containing the test sample, at a constant flow rate of 100 ml./min., to flush and remove any adhering gases or decomposed gaseous products evolved during the desorption experiment. The gas (nitrogen), in turn, was led out of
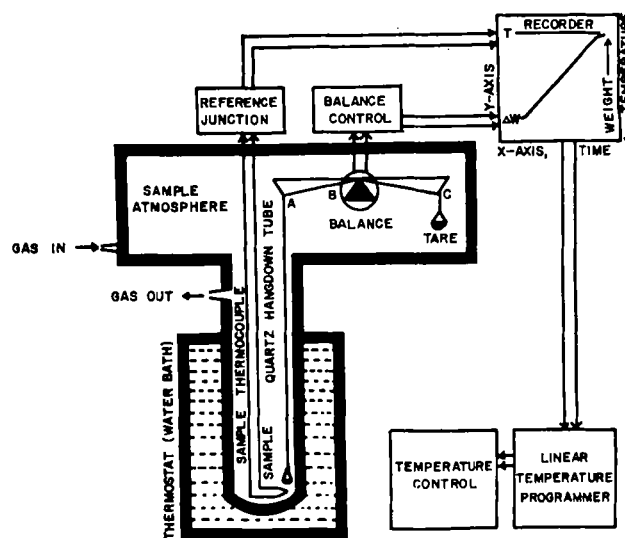
the chamber into a series of gas-washing bottles. When equilibrium temperature was achieved in the chamber (2 min.), the instrument was turned on and the weight loss versus time was recorded on chart paper until a constant weight was obtained. This isothermal thermogram was used for evaluation of the diffusivity of the compound being studied. To ensure reproducibility, at least two test samples for each alcohol (at each sorption temperature) were run. The relative precision of the calculated diffusion coefficients for each alcohol was 3.0% or less between and among test samples run, indicating an acceptable level of reproducibility.

Analysis of Thermograms to Calculate Diffusion Coefficient—For many solute–polymer systems, the diffusion coefficient will be a function of penetrant concentration and will require (for the appropriate boundary conditions and concentration dependence) a solution to Fick's second law of diffusion:

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left[D(C)\,\frac{\partial C}{\partial x}\right] \qquad \text{(Eq. 1)}$$

where C is the concentration of the solute, t is the time, x is the distance along the direction of diffusion, and $D(C)$ is the concentration-dependence differential diffusion coefficient. Since sorption data will generally not reveal the boundary conditions, Eq. 1 cannot be solved in a straightforward manner. Other mathematical approaches must be used to evaluate the diffusion coefficient, which then can be considered as some average value depending upon the specific method of analysis. These approaches were reviewed by several authors (2–5).

In this paper the diffusion coefficient has been calculated from desorption data taken from the early stages of desorption, in which

[1] From Molded Products Co., Easthampton, Mass., under the code number M P950.
[2] Sero-Utility Bath, model 82, Precision Scientific Co., Chicago, Ill.

Figure 1 *Schematic representation of the TGA instrument in a desorption experiment.*
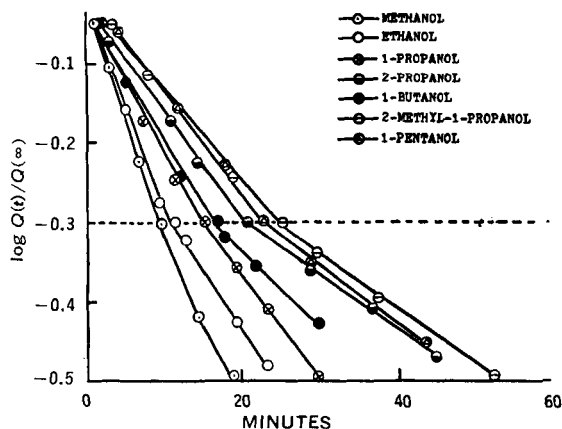
Figure 2—*Plots of fractional loss of alcohols from polyurethan versus time during desorption experiments (50°).*

time period the situation approximates the diffusion out of a semi-infinite medium. The mathematical expressions were then modified from the approximated numerical solution of Eq. 1 for particles diffusing into or out of a plane sheet in the form:

$$\frac{(\bar{C} - C_f)}{(C_i - C_f)} = \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp - \left[\frac{(2n+1)^2 \pi^2 D}{L^2} (t) \right] \quad \text{(Eq. 2)}$$

where $\bar{C}$ is the total average concentration per unit area measured at time t; C_f and C_i are the final and initial concentrations, respectively, per unit area within the plane sheet; $(\bar{C} - C_f)$ is the quantity of liquid per unit area of the plane sheet remaining in the solid at time t; and L is the thickness of the plane sheet.

For the TGA method used in this study, however, one can measure $(\bar{C} - C_f)$ as a function of time during the desorption process by simply weighing a sheet of solid that previously was soaked in the testing liquids until the establishment of equilibrium. If the weight is represented by $W(t)$ at time t, then:

$$\bar{C} - C_f = W(t) - W(\infty) = Q(t) \quad \text{(Eq. 3)}$$

and:

$$C_i - C_f = W(0) - W(\infty) = Q(\infty) \quad \text{(Eq. 4)}$$

and Eq. 2 becomes:

$$\frac{Q(t)}{Q(\infty)} = \frac{W(t) - W(\infty)}{W(0) - W(\infty)} =$$

$$\frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp - \left[\frac{(2n+1)^2 \pi^2 D}{L^2} (t) \right] \quad \text{(Eq. 5)}$$

where $Q(t)$ is the weight of liquid per unit area of the plane sheet remaining in the solid at time t, and $Q(\infty)$ is the total weight of liquids diffusing out of the plane sheet at infinite time. If t is suffi-
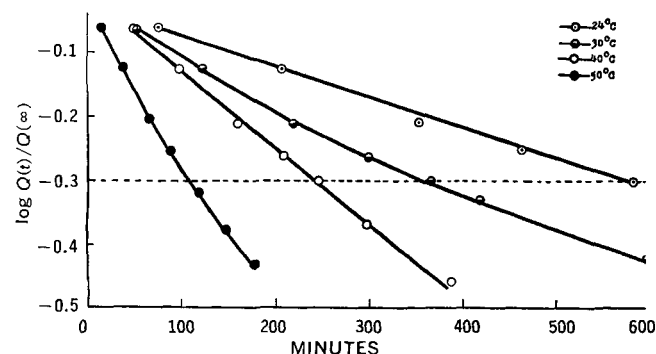

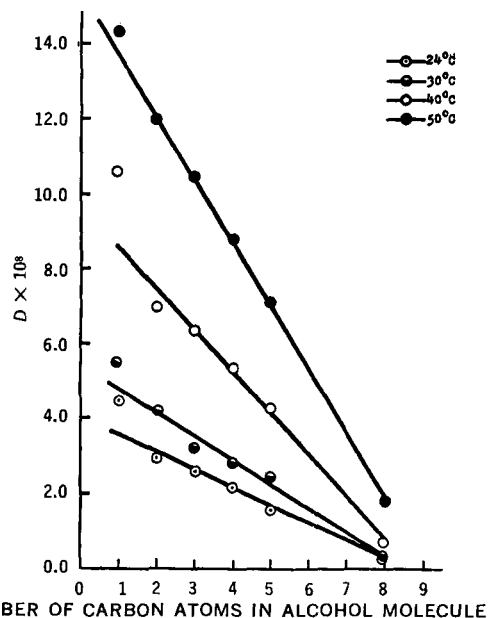Figure 3—*Plots of fractional loss of 1-octanol from polyurethan versus time at 24, 30, 40, and 50°.*

Figure 4—*Effect of the number of carbon atoms on the diffusion o alcohols in polyurethan at 24, 30, 40, and 50°.*

ciently large, Eq. 5 can be reduced to:

$$\frac{Q(t)}{Q(\infty)} = \frac{8}{\pi^2} \exp - \left[\frac{\pi^2 D}{L^2} (t) \right] \quad \text{(Eq. 6)}$$

or, in logarithmic form, to:

$$\log \frac{Q(t)}{Q(\infty)} = \log \left(\frac{8}{\pi^2} \right) - \frac{\pi^2 D}{2.303 L^2} (t) \quad \text{(Eq. 7)}$$

Equation 7 is a linear equation; thus, for any desorption exper-

Table II—Diffusion and Solubility Coefficients of a Series of Aliphatic Alcohols in a Polyurethan

Alcohol	Temperature	$D \times 10^8$, cm.^{2}/sec.	S, g. Solute/g. Plastic
Methanol	24°	4.44	0.2336
	30°	5.42	0.2400
	40°	10.6	0.2631
	50°	14.3	0.2698
Ethanol	24°	2.88	0.2760
	30°	4.20	0.2686
	40°	6.84	0.2786
	50°	11.9	0.2893
1-Propanol	24°	2.55	0.2602
	30°	3.16	0.3221
	40°	6.21	0.3527
	50°	10.4	0.3882
2-Propanol	24°	0.970	0.2115
	30°	2.20	0.2356
	40°	4.24	0.2722
	50°	8.09	0.2806
1-Butanol	24°	2.16	0.3461
	30°	2.83	0.3343
	40°	5.26	0.3647
	50°	8.80	0.3825
2-Methyl-1-propanol	24°	1.00	0.2765
	30°	1.85	0.2920
	40°	3.56	0.3595
	50°	6.93	0.4106
1-Pentanol	24°	1.56	0.3641
	30°	2.47	0.3711
	40°	4.27	0.3811
	50°	7.02	0.3940
1-Octanol	24°	0.295	0.2670
	30°	0.497	0.3060
	40°	0.713	0.3021
	50°	0.810	0.3412

14.0

12.0

10.0

$D \times 10^8$

8.0

6.0

4.0

2.0

0.0

0   5.0   10.0   15.0   20.0   25.0

MOLECULAR VOLUME OF ALCOHOLS, $V \times 10^{23}$ (cu. cm./MOLECULE)

—○— 24°C
—●— 30°C
—○— 40°C
—●— 50°C
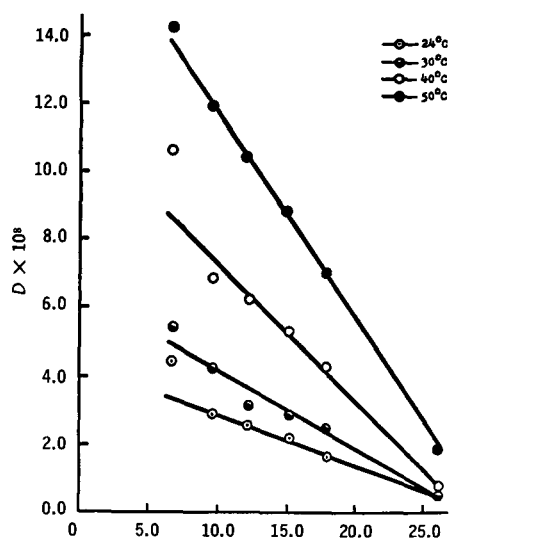
Figure 5—*Effect of molecular volume on the diffusion of alcohols at 24, 30, 40, and 50°.*

iment, a plot of log $Q(t)/Q(\infty)$ versus time should reveal a linear relationship from which D can be calculated from the slope.

In practice, desorption data were taken directly from the thermograms, recalculated as log $Q(t)/Q(\infty)$ versus time, and the slopes were calculated by the least-squares method by means of an IBM 360 computer using FORTRAN IV. Linear relations for Eq. 7 were found to exist in the range of 0 to approximately 50% desorption, so only these values were used for calculating the slopes.

RESULTS AND DISCUSSION

Figure 2 shows a plot of log $Q(t)/Q(\infty)$ versus time for methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-methyl-1-propanol, and 1-pentanol derived from desorption thermograms at 50°. The results reveal the general linearity as predicted by Eq. 7 during the early stages of desorption, with the lines becoming slightly curved as desorption extends past log $Q(t)/Q(\infty)$ equal to -0.3 (or 50% desorption). Similar data for 1-octanol are presented in Fig. 3 for desorption studies at 24, 30, 40, and 50°. Calculated D values for each alcohol at each temperature are included in Table II. In the same table are included the solubility coefficient of the penetrant in the polyurethan at each temperature.

Activation energies of diffusion (E_d) for each alcohol were also evaluated from the Arrhenius relation by plotting log D versus the reciprocal of absolute temperature. These values are shown in Table III.

As might be expected, the diffusivity increased with temperature (Table II). If one excludes 2-propanol and 2-methyl-1-propanol from the series, the addition of another carbon in the alcohol chain increases the diffusion coefficient by a nearly constant factor at each specific temperature (Fig. 4). The two branched alcohols (2-propanol and 2-methyl-1-propanol) have D values lower than their straight-chain isomers (Table II). This indicates that as the cross-sectional areas of these alcohols increase, greater hindrance is presented for passage through the polymer. Similar results were reported by others (6, 7) for different penetrant–polymer systems.

Table III—Activation Energies of Diffusion for a Series of Aliphatic Alcohols in a Polyurethan

Alcohol	E_d, kcal./mole
Methanol	9.16
Ethanol	9.93
1-Propanol	10.4
2-Propanol	14.5
1-Butanol	10.2
2-Methyl-1-propanol	13.4
1-Pentanol	10.5
1-Octanol	12.1

Table IV—Permeability Coefficients of a Series of Aliphatic Alcohols through a Polyurethan

Alcohol	Temperature	$P \times 10^8$, cm.²/sec.
Methanol	24°	1.04
	30°	1.30
	40°	2.80
	50°	3.87
Ethanol	24°	0.795
	30°	1.13
	40°	1.91
	50°	3.45
1-Propanol	24°	0.664
	30°	1.02
	40°	2.19
	50°	4.05
2-Propanol	24°	0.205
	30°	0.518
	40°	1.15
	50°	2.27
1-Butanol	24°	0.748
	30°	0.946
	40°	1.92
	50°	3.37
2-Methyl-1-propanol	24°	0.277
	30°	0.54
	40°	1.28
	50°	2.85
1-Pentanol	24°	0.568
	30°	0.917
	40°	1.63
	50°	2.77
1-Octanol	24°	0.0787
	30°	0.152
	40°	0.215
	50°	0.618

Figure 5 shows the relationship of D to the molecular volume of each alcohol studied in the series. It is obvious that all lines show the same general linearity as those for D versus carbon length (Fig. 4), indicating that both factors (chain length and molecular volume in the homogeneous liquid phase) are directly correlated with each other and that their effects on diffusivity in the heterogeneous solid state are similar. The effect of chain length on the diffusivity may be interpreted as a direct reflection of the molecular motion of the molecule in the polymer matrix, while the effect of molecular volume on the diffusivity is generally correlated with the availability of the free volume between polymer chains for diffusion flow following the "hole theory" of Glasstone et al. (8).

The activation energies (Table III) for straight-chain aliphatic alcohols diffusing in polyurethan film ranged from 9.16 kcal./mole (for methanol) to 12.1 kcal./mole (for 1-octanol). Since the energy required to "open a hole" in the polymer to accommodate a diffusing molecule will bear a direct relationship to the activation energy of diffusion, larger molecules in a related series will have larger activation energies and slower diffusion rates. This is in conformity with the observations made here.

A comparison of the heat of vaporization (ΔH_v) listed in Table I to the activation energies (E_d) shown in Table III reveals an approximate correlation, suggesting but not proving that bonding or interaction of these alcohols with the polyurethan chains may be similar to intermolecular bonding of the alcohols in the liquid state, namely, hydrogen bonding. Since polyurethan has a number of polar groups (such as urethan groups), the alcohols could interact with these groups primarily through hydrogen-bond formation. It is also possible that other secondary forces, such as hydrophobic bonding, play a role in the interaction. Hydrophobic bonding for solute–polymer interactions was discussed by other investigators (5).

The importance of the hydrophobic character of the straight-chain alcohols in the series studied could not be proved from the present experimental data. Some minor support for the importance of the hydrophobic character of the alcohols was reflected in the solubility coefficients shown in Table II. If one excludes 1-propanol and the two isomeric alcohols (2-propanol and 2-methyl-1-propanol), the solubility increased as the hydrophobic character in-

creased up to 1-octanol, which then showed a decrease. The decrease in the solubility coefficient for 1-octanol simply may reflect that the number of "holes" in the polymer to accommodate the larger 1-octanol molecule is less than for the smaller molecular weight alcohols.

Since the permeability coefficient is a product of the diffusion coefficient and the solubility coefficient or $P = DS$, the permeability coefficients for the group of alcohols were calculated (Table IV). This simple relationship holds for the permeation process when D obeys Fick's diffusion law and S obeys Henry's law (5, 9). It is not certain with the penetrant–polymer system used in this study if in fact one or both laws are actually obeyed, particularly since it is known that penetrant–polymer interactions generally lead to variable D values. Therefore, the P values shown in Table IV should be considered as estimates of the permeability coefficients.

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ACKNOWLEDGMENTS AND ADDRESSES

Interactions of Dimethyl Sulfoxide with Lipid and Protein Monolayers

N. D. WEINER▲, M. Y. LU, and M. ROSOFF

Abstract ☐ Phospholipids, cholesterol, protein, and mixed phospholipid–protein monolayers were used as models to study interactions between dimethyl sulfoxide and cell membranes. Surface pressure measurements were used to study these dimethyl sulfoxide–film interactions. While films of dipalmitoyl lecithin, egg lecithin, and cholesterol showed no interaction with dimethyl sulfoxide, films of bovine serum albumin exhibited a significant condensation effect. The degree of film condensation was found to be a function of pH and dimethyl sulfoxide concentration in the subphase. It was postulated that the observed effect of dimethyl sulfoxide on albumin films is due to the loss of protein from the surface. Lipid–protein films showed only small condensation effects in the presence of dimethyl sulfoxide, indicating that the phospholipids protect the protein from attack by dimethyl sulfoxide. These studies indicate that the remarkable penetration abilities of dimethyl sulfoxide may be due to some alteration of protein structure as a result of dehydration at the biomembrane.

Keyphrases ☐ Lipid monolayer films—interactions with dimethyl sulfoxide, surface pressure–surface area curves ☐ Protein monolayer films—interactions with dimethyl sulfoxide, surface pressure–surface area curves ☐ Lipid–protein monolayer films—interactions with dimethyl sulfoxide, surface pressure–surface area curves ☐ Dimethyl sulfoxide—interactions with lipid, protein, and lipid–protein monolayer films, surface pressure–surface area curves ☐ Monolayers, lipid and protein—interactions with dimethyl sulfoxide, surface pressure–surface area curves

its use (4) have limited its widespread use in humans. There have also been numerous reports concerning the ability of dimethyl sulfoxide to penetrate rapidly human skin and to enhance the percutaneous absorption of materials dissolved therein (5, 6). While the utility of dimethyl sulfoxide in promoting percutaneous absorption is well documented, few studies have appeared concerning its mechanism of action upon the barrier to absorption through the skin. While it has been suggested that dimethyl sulfoxide exerts its effect by causing a swelling or expansion of the protein fibers of the skin barrier (7), a lipid extraction effect (8) also has been implicated to account for the rapid penetration effects caused by dimethyl sulfoxide.

Monomolecular films have been widely used to elucidate interactions that occur between various substances and membrane components. The mechanisms of action of polyene antibiotics (9), anesthetics (10), air pollutants (11), and other agents have been elucidated, to some degree, at the cellular level by the use of monomolecular films.

Since the activity of dimethyl sulfoxide seems to be related to its ability to permeate cell membranes (12, 13), it is of interest to investigate the effects of dimethyl sulfoxide on monolayers of components found in biological membranes. This paper presents data on the interactions of dimethyl sulfoxide with monolayers of lipids, protein, and lipid–protein mixed films.

Although dimethyl sulfoxide has been reported to possess a number of desirable therapeutic properties (1–3), the potential medical hazards associated with