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## Effects of Structure on Permeability of Substituted Anilines from Aqueous Solutions through Polyethylene

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**Abstract** □ Permeation studies were undertaken with aqueous solutions of aniline and various substituted anilines to ascertain the effect of chemical structure on the permeation of these agents through polyethylene. The permeation studies permitted the estimation of steady-state rates of permeation and calculation of the permeability constants. Permeability constants varied from a low of  $1.61 \times 10^{-9}$  cm.<sup>2</sup>/sec. for 2-anilinoethanol to a high of  $3.58 \times 10^{-6}$  cm.<sup>2</sup>/sec. for *N,N*-dimethylaniline. When the permeability constants of the compounds were compared with their hexane-water partition coefficients, a very high correlation resulted, leading to an empirical expression which may be useful in predicting the permeability constants of similar types of compounds having partition coefficients in the range of the values reported.

**Keyphrases** □ Permeability constants, substituted anilines—from aqueous solution through polyethylene, effects of different aniline structures, correlated with hexane-water partition coefficients □ Anilines, substituted—effects of structure on permeability, from aqueous solution through polyethylene, correlated with hexane-water partition coefficients □ Plastics—effect of aniline structure on its permeability, hexane-water partition coefficient correlated with structure of aniline □ Polyethylene—effect of structure of substituted anilines on permeability, correlated with hexane-water partition coefficient

One of the most used plastics for containers and packaging systems for all types of drug, cosmetic, and household products is polyethylene. The excellent moisture-vapor barrier properties of polyethylene have encouraged the use of this specific plastic by the pharmaceutical and cosmetic industries as well as by the hospital pharmacist for the packaging of a host of aqueous products. Salame and Pinsky (1) contributed a great deal of information concerning the permeation of a large number of organic liquids stored in polyethylene containers. They developed a method (permachor method) for predicting the permeation of an organic solvent from the structure of the compound.

Much less information on the permeability of solutes in aqueous systems stored in polyethylene containers is available. Polack *et al.* (2) formulated a method for predicting the permeation of selected solutes in aqueous systems when the products (in polyethylene containers) were autoclaved. Gonzales *et al.* (3) studied the permeation of aqueous solutions of selected compounds through polyethylene and reported that structure in-

fluences the permeability constant. Other investigators (4-7) studied the permeation of solute molecules through different types of polymeric materials.

The loss of an ingredient from a drug product can lead to a decrease in the potency of the product or render the product pharmaceutically unacceptable. A definite need, therefore, exists to generate qualitative and quantitative permeation data for groups of solutes to guide the pharmaceutical scientist and packaging engineer in deciding which of a number of polymeric materials might be the most useful for a specific packaging application.

This report concerns a permeation study of aqueous solutions of aniline and various substituted anilines using polyethylene film as the specific plastic. The primary objectives of this study were to discern what effects the structure of solutes have on permeation and to see to what extent permeability through polymeric films can be correlated with partition coefficients obtained in a convenient solvent system such as hexane-water. In the ideal case the mechanics of the diffusional process within a polymeric barrier are unaffected by the nature of the adjacent phases and, therefore, basic data obtained from a liquid-membrane-liquid model system may be applicable to the packaging system in which one surface is in contact with air.

#### EXPERIMENTAL

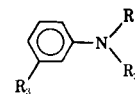
**Materials**—The polyethylene film<sup>1</sup> had a 0.0127-cm. thickness and a 0.924 density. All chemicals employed in this study were analytical reagent grade or the highest available purity. Table I lists the compounds studied along with their structures and molecular weights.

**Analytical Methods**—The absorbance of aqueous solutions was determined with a spectrophotometer<sup>2</sup> at the wavelength of maximum absorption for each compound. The concentration of each solution was calculated from Beer's law plots prepared for each compound under study.

**Conditioning of Film**—The polyethylene film was cut into 10 × 10-cm. squares and soaked in 95% ethanol for 24 hr. The film was rinsed with distilled water and further soaked in 50% ethanol for

<sup>1</sup> Obtained from Gulf Oil Corp., Chemicals Department, Orange, Texas.

<sup>2</sup> Hitachi-Perkin-Elmer model 139.



**Table I**—Molecular Structures of Compounds Investigated of the General Formula:

Compound	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Molecular Weight
Aniline	—H	—H	—H	93.12
<i>N</i> -Methylaniline	—H	—CH <sub>3</sub>	—H	107.16
<i>N,N</i> -Dimethylaniline	—CH <sub>3</sub>	—CH <sub>3</sub>	—H	121.18
<i>N</i> -Ethylaniline	—H	—CH <sub>2</sub> —CH <sub>3</sub>	—H	121.18
<i>N</i> -Propylaniline	—H	—(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	—H	135.21
2-Anilinoethanol	—H	—(CH <sub>2</sub> ) <sub>2</sub> OH	—H	137.18
Acetanilide	—H	—C(=O)—CH <sub>3</sub>	—H	135.16
<i>m</i> -Nitroaniline	—H	—H	—NO <sub>2</sub>	138.13
<i>m</i> -Chloroaniline	—H	—H	—Cl	127.57
<i>m</i> -Toluidine	—H	—H	—CH <sub>3</sub>	107.16
<i>m</i> -Anisidine	—H	—H	—OCH <sub>3</sub>	123.16

1 hr. The film was rinsed with distilled water, and the ethanol soaking-water washing procedure was repeated three times. After the final rinse with distilled water, the film was dried overnight at  $50 \pm 0.5^\circ$  in a drying oven and stored in a desiccator.

**Permeation Studies**—The permeation experiments were conducted in a two-chambered glass cell as described by Rodell *et al.* (4). The chambers were separated by a square of polyethylene film and secured in place with the aid of a rubber O-ring and a clamp. The permeation chambers were covered with aluminum foil to prevent any light-catalyzed degradation of the compounds under study. The cell was equilibrated in a constant-temperature water bath for 1 hr. and examined for leaks. The permeation process was initiated by simultaneously adding 500 ml. of solution and 500 ml. of distilled water, each heated to the temperature of the water bath, to the left and right chambers of the cell, respectively. Both chambers were agitated with glass stirrers, equipped with Teflon paddles, driven by laboratory motors at approximately 300 r.p.m. At various time intervals, 4-ml. aliquots were removed from the distilled water chamber and the amount of the compound that permeated across the plastic film was determined spectrophotometrically. The observed concentration was corrected for the amount of solute removed with the previous aliquots. Sampling was continued for a sufficient time to ensure that a steady-state permeation had been achieved. In all of the studies, the final concentration of the permeating solution, at the termination of the experiment, was far in excess of the concentration of the desorbing solution; thus the concentration gradient remained essentially invariant during the experiment.

Permeation studies for each compound were performed at least in duplicate, and the observed amounts of solute permeating the membrane during each time interval were averaged. All studies were conducted at  $50 \pm 0.2^\circ$ . The pH of each solution was determined before and after each permeation experiment and was sufficiently high so that all compounds under study were at least 99% in the unionized form. The initial concentration of each solution was 0.008 *M*, with the exception of *N*-propylaniline which, due to limited solubility, was studied at 0.002 *M*. In addition, the influence of initial concentration on the permeation process was examined using aniline solutions with initial concentrations of 0.004, 0.008, 0.011, or 0.043 *M*.

**Partition Coefficients**—Ten milliliters of hexane and 10 ml. of aqueous solute solution were placed into a ground-glass-stoppered test tube. Each stopper was secured by adhesive tape and a strong rubber band. Duplicate samples were equilibrated by rotating the tubes at  $27 \pm 0.2^\circ$  in a water bath for 48 hr. The tubes were then fixed in a stationary position in the bath, and two phases were allowed to separate. A sample was withdrawn from the water phase, and its concentration was determined spectrophotometrically. The concentration of solute in the hexane phase was calculated from the initial and final concentrations of the chemical in the water phase.

## RESULTS AND DISCUSSION

**Characterization of Permeation**—Several models have been proposed to describe permeation through membranes. Salame and Pinsky (1) studied the permeation of organic liquids through polyethylene film and related the permeation process to the size,

shape, and polarity of the permeating species. Solute permeation through relatively thick barriers, such as were employed in the present study, may be described by the following sequence of events: absorption of the permeant into the plastic surface, diffusion of the permeant through the plastic, and desorption of the permeant from the outer surface. The absorption and desorption steps are affected by the relative affinity of the permeant for the aqueous or solvent phase and the membrane. The diffusion process is regulated by the effective size of the permeant species, the extent of the plastic-permeant interaction, and the structural characteristics of the plastics.

Stehle and Higuchi (8) proposed a more detailed diffusional model for transport rate studies across membranes, which includes diffusional resistance terms resulting from the presence of diffusion layers on either side of a lipoidal membrane. They reported that steady-state transport rates are linear with increasing partition coefficients up to a point, beyond which the flux levels off as a result of diffusion layer resistance becoming the dominant effect.

The permeation process in the steady state may be characterized by Eq. 1, as described by Daynes (9), when the diffusional gradient is solely within the membrane:

$$Q = (A/L)(D)(PC)(C)(T - T_L) = (c)(V) \quad (\text{Eq. 1})$$

where  $Q$  is the cumulative amount of solute penetrated;  $A$  is the surface area of film exposed to the solution;  $L$  is the thickness of the film;  $D$  is the diffusion coefficient in the membrane;  $PC$  is the membrane-solvent partition coefficient of the permeant species;  $C$  is the initial concentration of the permeating solution;  $c$  and  $V$  are the concentration and volume, respectively, of the desorption solution;  $T$  is the time elapsed since the permeation process was initiated; and  $T_L$  is the time lag or the time required for steady state to be achieved.

The product of  $D$  and  $PC$  is defined as the permeability constant ( $P$ ), as given in Eq. 2:

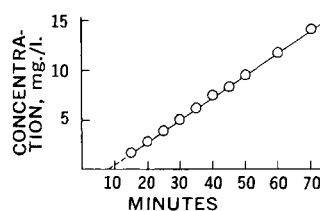
$$P = (D)(PC) \quad (\text{Eq. 2})$$

The permeability constant may be evaluated from the slope of a plot of  $c$  versus time, during steady state, as given in Eq. 3:

$$P = (c/T)(LV/CA) \quad (\text{Eq. 3})$$

The  $P$  values are expressed as square centimeters per second. The permeation rates were determined by a least-squares analysis of the steady-state portion of the permeation curves. Figure 1 illustrates a typical permeation curve.

Daynes (9) and Barrer (10) developed an expression which permits the evaluation of the diffusion coefficient when a time lag is



**Figure 1**—Permeation of *N*-ethylaniline through polyethylene showing a positive intercept ( $50^\circ$ ).

**Table II**—Effect of Concentration on the Permeation of Aniline ( $50 \pm 0.2^\circ$ )

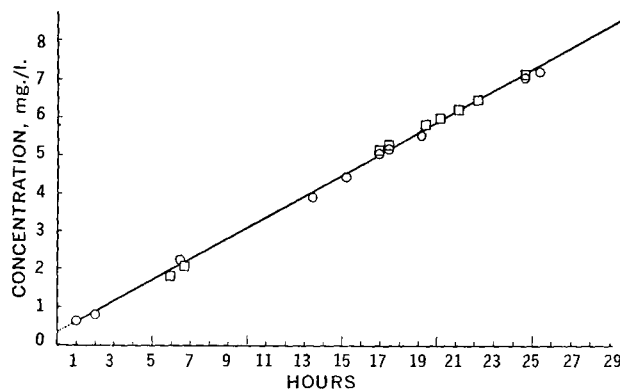
Molar Concentration	Rate of Permeation, mg./l./hr.	Permeability Constant, $\times 10^8$ cm. <sup>2</sup> /sec.
0.004	0.159	3.50
0.008	0.300	3.24
0.011	0.422	3.11
0.043	1.79	3.37

observed in the permeation plot. For a number of the compounds under study, extrapolation of the linear portion of the curve to the time axis (time-lag point) resulted in a small time lag (Fig. 1). For the other compounds, however, the extrapolation led to a negative intercept, preventing the direct calculation of the diffusion coefficient using the time-lag equation. A representative plot of data exhibiting this type of behavior is illustrated in Fig. 2. Anomalous permeation curves for certain organic compounds were also observed by others using several different systems. Park (11), in a study of methylene chloride permeation through polystyrene films at  $25^\circ$ , and Mears (12), in a study of the permeation of allyl chloride in polyvinyl acetate films at  $40^\circ$ , observed permeation curves which were concave, rather than convex, toward the time axis. Fujita (13) speculated on three possible causes for this type of behavior. He suggested: (a) the presence of a convective flow or two or more diffusion flows having different diffusion coefficients, (b) a time dependence of the diffusion coefficient, or (c) a stress effect relating to an alteration in the polymeric structure of the barrier upon contact with the permeant molecules prior to the attainment of steady state.

Observations of negative time lags in aqueous systems similar to those employed in the present study have not been previously reported. It may be noted from Table III that only those compounds listed below *N*-methylaniline demonstrated this phenomenon. It could be speculated that the structural characteristics of the polymeric barrier may have been altered prior to steady state due to rearrangement of the polymer chains as the more hydrophilic anilines began permeating the barrier. This mechanism, however, requires considerable investigation before a suitable model can be developed to quantitate this unusual behavior.

With all of the compounds reported in this study, the permeation curves were linear after steady-state permeation had been achieved and the permeability constants were evaluated using Eq. 3.

**Effect of Concentration**—The effect of concentration on permeation was investigated for four concentrations of aniline to establish that the permeability constant was concentration independent, as suggested by Eq. 2. Table II summarizes the results of these studies. The permeation rates were determined from the steady-state portion of the permeation curves, and the permeability constants were computed from Eq. 3. The volume of the solutions and the membrane surface area and thickness were constant for each concentration studied. These data illustrate the expected results that the rate of permeation is directly proportional to the initial concentration of the permeating species and that the permeability constant is essentially invariant with concentration within



**Figure 2**—Permeation of *m*-anisidine through polyethylene showing a negative intercept ( $50^\circ$ ).

experimental error. Garrett and Chemburkar (6) reported similar results in their study of silastic membranes. Therefore, the comparison of the *P* value for *N*-propylaniline, determined using an initial concentration of 0.002 *M*, with the *P* values for the other substituted anilines, determined at 0.008 *M*, would appear to be valid.

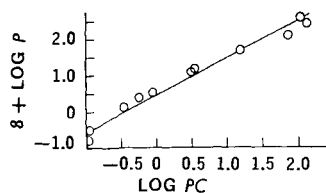
**Effect of Structure**—Table III summarizes the permeation data obtained for the aniline compounds under study, along with their experimentally determined hexane-water partition coefficients. With the exception of the *N,N*-dimethylaniline, there is a rank order correlation between permeability constant and partition coefficient. These data are in general agreement with Pinsky's (14) observations with polyethylene of increasing permeability of classes of chemicals in the order of alcohols, acids, nitro derivatives, aldehydes, ketones, esters, ethers, and hydrocarbons. Similarly, Nielsen and Temple (15) found that polar substances, such as water and methanol, exhibited slow permeation rates through polyethylene, while nonpolar substances, such as *n*-heptane, exhibited rapid permeation rates. It is to be expected that the permeation of a molecule through a homogeneous membrane, such as polyethylene, will be related to the relative affinity of the molecule for its aqueous environment and the hydrophobic membrane up to the point of diffusion layer control. Since there is a greater tendency for a nonpolar molecule to leave the water phase and enter such a membrane, nonpolar species should generally exhibit relatively rapid permeation rates.

Examination of the data presented in Table III reveals that *N,N*-dimethylaniline and *N*-propylaniline have similar partition coefficients, but the disubstituted compound has a significantly higher permeability constant. This observation may be the result of a steric hindrance to diffusion or an increased solute-polymer chain interaction for the *N*-propylaniline, or it may reflect a non-linearity between the hexane-water and the polyethylene-water partition coefficient values for this compound. The remainder of the compounds exhibited decreasing permeability constants as the relative affinity of the aqueous solvent for the diffusants increased. Between classes of compounds, this relative affinity may be attributable to an ability to form hydrogen bonds. Acetanilide, con-

**Table III**—Experimental Constants Evaluated from Permeation and Partitioning Studies<sup>a</sup> ( $50 \pm 0.2^\circ$ )

Compound	Permeation Rate, mg./l./hr.	Time Lag, min.	Diffusion Coefficient, $\times 10^8$ cm. <sup>2</sup> /sec.	Permeability Constant, $\times 10^8$ cm. <sup>2</sup> /sec.	Partition Coefficient
<i>N,N</i> -Dimethylaniline	46.0	6.36	6.29	358	125
<i>N</i> -Propylaniline	7.59	7.32	6.51	232	130
<i>N</i> -Ethylaniline	14.6	8.82	4.54	113	76.1
<i>N</i> -Methylaniline	4.44	11.9	4.20	44.8	16.4
<i>m</i> -Chloroaniline	1.77	-4.44	—	15.0	3.71
<i>m</i> -Toluidine	1.15	-3.12	—	11.5	3.24
Aniline	0.300	-100	—	3.24	0.940
<i>m</i> -Anisidine	0.269	-84.3	—	2.33	0.602
<i>m</i> -Nitroaniline	0.165	-204	—	1.23	0.360
Acetanilide	0.040	-1604	—	0.307	0.113
2-Anilinoethanol	0.022	-919	—	0.161	0.111

<sup>a</sup> Concentration of *N*-propylaniline was 0.002 *M*. All others were 0.008 *M*.



**Figure 3**—Correlation of the permeability constants of a series of substituted anilines with their hexane-water partition coefficients.

taining a ketone group, and *m*-anisidine, containing an ether linkage, would be expected to have increasing permeation rates. *m*-Chloroaniline and *m*-toluidine have similar partition coefficients and similar permeation characteristics. Hydrogen bonds do not form with atoms such as chlorine and, since chlorine generally increases relative lipid solubility, it would thus be expected that *m*-chloroaniline would exhibit a more rapid permeation rate than the compounds containing an oxygen atom.

**Correlation of Permeability Constants with Partition Coefficients**—In view of the good rank order correlation evident in Table III between permeability constants and partition coefficients, a regression analysis of these data was undertaken, based on Eq. 4:

$$\log(P) = A \cdot \log(PC) + B \quad (\text{Eq. 4})$$

where *A* and *B* are empirical coefficients, representing the slope and *Y*-intercept of a plot of  $\log P$  versus  $\log PC$ . The coefficients computed<sup>3</sup> for this equation were *A* = 0.9647 and *B* = -7.5534. The multiple-correlation coefficient (*r*) of the regression was 0.990. The *F*-test for the regression was significant at the 99.9% confidence level. The "explained variance" (the fraction of the data variance attributed to the regression equation) was 97.9%.

Figure 3 illustrates the relationship expressed by Eq. 4 and indicates that this equation would be useful for the estimation of the permeability constants of similar types of compounds at 50° having hexane-water partition coefficients in the range reported in this study.

#### SUMMARY

Permeation studies were conducted on aniline and various substituted anilines using a specific polyethylene as the plastic. Permeation plots for each compound permitted the calculation of the steady-state rates of permeation and the permeability constants. When the permeability constants were compared to the partition

coefficients, a high correlation resulted, leading to an expression which would appear to be useful in helping predict the permeability of similar types of compounds from known or readily determined hexane-water partition coefficients in the range reported in this study. Permeation studies of other groups of compounds through polyethylene, as well as other plastics, are continuing and the results will be reported in subsequent papers.

#### REFERENCES

- (1) M. Salame and J. Pinsky, *Mod. Packag.*, **36**, 153(1962).
- (2) A. E. Polack, M. S. Roberts, and F. E. Schumann, *Amer. J. Hosp. Pharm.*, **27**, 638(1970).
- (3) M. A. Gonzales, J. Nematollahi, W. L. Guess, and J. Autian, *J. Pharm. Sci.*, **56**, 1288(1967).
- (4) M. B. Rodell, W. L. Guess, and J. Autian, *ibid.*, **55**, 1429 (1966).
- (5) E. R. Garrett and P. B. Chemburkar, *ibid.*, **57**, 944(1968).
- (6) *ibid.*, **57**, 949(1968).
- (7) *ibid.*, **57**, 1401(1968).
- (8) R. G. Stehle and W. I. Higuchi, *J. Pharm. Sci.*, **56**, 1367 (1967).
- (9) H. A. Daynes, *Proc. Roy. Soc., A*, **97**, 286(1920).
- (10) R. M. Barrer, *Trans. Faraday Soc.*, **35**, 644(1939).
- (11) G. S. Park, *ibid.*, **48**, 11(1952).
- (12) P. Mears, *J. Polym. Sci.*, **27**, 405(1958).
- (13) H. Fujita, *Fortschr. Hochpolym.-Forsch.-Bd.*, **3**, S.1(1961).
- (14) J. Pinsky, *Mod. Plast.*, **34**, 145(1957).
- (15) A. R. Nielsen and E. J. Temple, *Package Eng.*, **3**, 21(1958).

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<sup>3</sup> Using an IBM 1620 computer.