

65°. However, at higher temperatures the samples containing 15 mg. dextroamphetamine sulfate should show a faster rate of browning (Fig. 8). At higher temperatures, sufficient energy was obtained to enable additional intact drug molecules to interact with the lactose. Therefore, the rate of the browning reaction in solid-solid mixtures of dextroamphetamine sulfate and spray-dried lactose is dependent on the concentration of drug in the mixture and the temperature at which the mixture is stored.

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Permeation of Aromatic Organic Compounds from Aqueous Solutions through Polyethylene

K. NASIM*, M. C. MEYER, and J. AUTIAN▲

Abstract □ The permeation, through polyethylene, of various aromatic acids, alcohols, amines, esters, aldehydes, and ketones in aqueous solution was investigated at 50°. The studies were conducted in a glass cell with two chambers separated by a thin film of polyethylene. Studies at several temperatures indicated activation energies ranging from 12.9 to 21.4 kcal./mole. The applicability of Fick's first law was established with solutions of varying initial concentrations. An inverse relationship was observed between the permeability constant of several compounds and the proportion of ethanol present in the solvent. Studies at various pH's demonstrated transport of only the unionized species. Films exposed to permeant solutions, prior to the permeation experiments, exhibited reduced permeation rates. Experimental permeability constants (P) and hexane-water partition coefficients (PC) were subjected to

regression analysis. A good correlation was obtained with the empirical equation: $\log(P) = 1.06 \cdot \log(PC) - 7.76$.

Keyphrases □ Permeation—aromatic organic compounds from aqueous solutions through polyethylene films □ Partition coefficients, hexane-water—used to study permeation of aromatic acids, alcohols, amines, esters, aldehydes, and ketones in aqueous solutions through polyethylene films □ Polyethylene films—permeation of aromatic organic compounds from aqueous solutions, hexane-water partition coefficients, permeability constants □ Organic aromatic compounds—permeation from aqueous solutions through polyethylene films □ Films, polyethylene—permeation of aromatic organic compounds from aqueous solutions, hexane-water partition coefficients, permeability constants

A previous report in this series (1), involving polyethylene films, demonstrated a relationship between hexane-water partition coefficients and permeability constants obtained for aqueous solutions of aniline and various substituted anilines. As an extension of this work, the permeation of 19 aromatic compounds,

representing various chemical classes, was studied in a similar system. The objective of these investigations was the development of correlations, between the physicochemical properties of the compounds and their permeation from aqueous solution through polyethylene, that might serve for the convenient prediction of

Table I—Chemical Structure and Molecular Weight of the Compounds Investigated

Compound	R ₁ ^a	R ₂ ^a	Molecular Weight
Benzoic Acids and Benzoates			
Benzoic acid	H	COOH	122.12
<i>p</i> -Hydroxybenzoic acid	OH	COOH	138.12
Methyl <i>p</i> -hydroxybenzoate	OH	COOCH ₃	152.14
Ethyl <i>p</i> -hydroxybenzoate	OH	COOC ₂ H ₅	166.18
<i>n</i> -Propyl <i>p</i> -hydroxybenzoate	OH	COOC ₃ H ₇	180.21
<i>p</i> -Aminobenzoic acid	NH ₂	COOH	137.13
Methyl <i>p</i> -aminobenzoate	NH ₂	COOCH ₃	151.17
Ethyl <i>p</i> -aminobenzoate	NH ₂	COOC ₂ H ₅	165.19
Isobutyl <i>p</i> -aminobenzoate	NH ₂	COOC ₄ H ₉	193.24
Phenols			
Phenol	OH	H	94.11
<i>p</i> -Bromophenol	OH	Br	173.01
Anilines			
Aniline	NH ₂	H	93.13
<i>p</i> -Nitroaniline	NH ₂	NO ₂	138.12
<i>p</i> -Anisidine	NH ₂	OCH ₃	123.15
Benzaldehydes			
Benzaldehyde	CHO	H	106.12
<i>p</i> -Chlorobenzaldehyde	CHO	Cl	140.57
<i>p</i> -Methylbenzaldehyde	CHO	CH ₃	120.14
<i>p</i> -Nitrobenzaldehyde	CHO	NO ₂	151.12
<i>p</i> -Hydroxybenzaldehyde	CHO	OH	122.12
Acetophenones			
Acetophenone	COCH ₃	H	120.15
<i>p</i> -Nitroacetophenone	COCH ₃	NO ₂	165.18
<i>p</i> -Methylacetophenone	COCH ₃	CH ₃	134.12
<i>p</i> -Methoxyacetophenone	COCH ₃	OCH ₃	150.17
<i>p</i> -Aminoacetophenone	COCH ₃	NH ₂	135.16

^a Substitutions on the benzene ring at the *para*-position.

permeation tendencies of related compounds. In addition, it seemed desirable to elucidate the influence of some experimental variables on the permeation process.

EXPERIMENTAL

Materials—A polyethylene film¹, 0.0127 cm. thick and 0.924 dense, was used. All chemicals employed in this study were analytical reagent grade or the highest available purity. Table I lists the 24 compounds considered. As described later, only 19 of these were employed experimentally. The remaining five are discussed in terms of literature data.

Analytical Methods—All solute concentrations were determined, using a spectrophotometer², from Beer's law plots prepared for each compound at the wavelength of maximum absorption.

Routine Conditioning of Film—Except in studies to investigate the effect of various pretreatments of the films, a standard procedure was employed in the preparation of each film. Squares of the polyethylene film, 10 × 10 cm., were soaked in 95% ethanol for 24 hr. The film was rinsed with distilled water and then soaked in 50% ethanol for 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 ± 0.5° in a drying oven and stored in a desiccator until used.

Permeation Studies—The permeation experiments were conducted, essentially as previously described (1), in a two-chamber glass cell as illustrated by Rodell *et al.* (2). The solutions in each cell were well stirred with the aid of magnetic stirring bars and micro-submersible magnetic stirrers, set at approximately 200 r.p.m. The compounds were studied as 0.1% (w/v) solutions in distilled water, with the exception of *n*-propyl *p*-hydroxybenzoate and isobutyl *p*-aminobenzoate which were studied as water-ethanol

Table II—Effect of Concentration on the Permeation of Aqueous Solutions of Acetophenone through Polyethylene at 50°

Concentration (w/v), %	Permeation Rate, mg./min.	Permeability Constant, cm. ² /sec. × 10 ⁸
0.01	0.0049	22.4
0.05	0.0228	20.7
0.10	0.0511	23.1
0.20	0.0890	21.9
0.30	0.1280	19.3

systems because of limited solubility. The permeation experiments were conducted at 50 ± 0.2°, except for those involving studies of temperature effects; studies of isobutyl *p*-aminobenzoate were conducted at 60 ± 0.2° to accelerate the slow permeation rate. Several studies were designed to discern the influence of pH on the permeation rate, but in the majority of the permeation experiments the pH of each solution was sufficiently high so that the compound was at least 99% in the unionized form.

Sampling during each study was continued for a sufficient time to ensure that steady-state permeation was achieved. In all experiments, the final concentration of the permeating or donor solution, at the termination of the experiment, was far in excess of the concentration of the desorbing or receptor solution. This resulted in an essentially invariant concentration gradient throughout the experiment. Each permeation experiment was performed at least in duplicate, and the observed amounts of solute permeating the film during each time interval were averaged.

Partition Coefficients—The hexane-water partition coefficients for the compounds were determined at 27 ± 0.2° by equilibration of the samples, containing 10 ml. of each solvent, in a constant-temperature water bath.

Effect of Concentration—Studies of the influence of concentration on the permeation process were conducted at 50 ± 0.2° with aqueous acetophenone solutions at concentrations of 0.01, 0.05, 0.1, 0.2, and 0.3% (w/v).

Effect of Temperature—The influence of temperature was studied with methyl *p*-aminobenzoate, methyl *p*-hydroxybenzoate, and ethyl *p*-hydroxybenzoate, in aqueous solution, using initial concentrations of 0.1% (w/v).

Effect of Solvent—Mixed ethanol-water systems were employed as the donor and receptor solutions in investigations of the influence of solvent polarity on the permeation process. Experiments were performed with 0.1% (w/v) *n*-propyl *p*-hydroxybenzoate in 2, 5, 10, and 20% (v/v) ethanol solutions at 50 ± 0.2° and with 0.1% (w/v) isobutyl *p*-aminobenzoate in 20, 30, 40, and 50% (v/v) ethanol solutions at 60 ± 0.2°. The permeation cells were tightly sealed, except during brief periods of sampling, to minimize evaporation of ethanol.

Effect of pH—The effect of pH on the permeation process was studied with 0.1% (w/v) solutions of aniline and benzoic acid in 0.1 M dibasic sodium phosphate buffer. The donor buffer solution containing aniline was adjusted to pH 2.6, 3.6, 4.6, 5.6, and 6.6, and the receptor buffer solution was adjusted to pH 6.6. The solutions containing benzoic acid were adjusted to pH 2.2, 4.2, and 5.0, and the receptor solution for this compound was adjusted to pH 2.2. The pH's of the donor and receptor solutions were measured at the termination of each study and showed no change.

Effect of Pretreatment of Polyethylene Film—In addition to the conditioning procedures for the films outlined earlier, two other treatments were employed to investigate certain anomalous behavior observed with some compounds. The first type of special treatment involved reusing a film that had been employed in a prior experiment. At the termination of permeation studies with methyl *p*-aminobenzoate, ethyl *p*-aminobenzoate, and ethyl *p*-hydroxybenzoate, the three films were removed from the permeation cells, rinsed with distilled water, and dried at room temperature. A second series of permeation studies was then conducted using these same films, with each film employed in connection with the compound with which it had previously been exposed. The experimental conditions were identical to those of the original experiment for each compound.

A second pretreatment procedure was also utilized in which the polyethylene film was immersed for 48 hr. in distilled water at 50 ±

¹ Chemicals Department, Gulf Oil Corp., Orange, Tex.

² Hitachi Perkin-Elmer model 139.

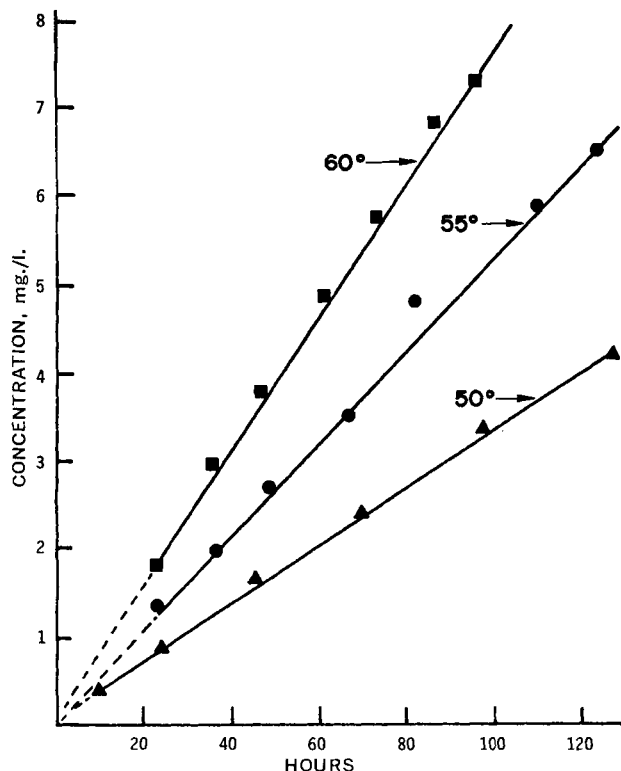


Figure 1—Influence of temperature on the permeation of 0.1% (w/v) ethyl *p*-hydroxybenzoate.

0.2°. This film was then employed in a permeation study conducted at the same temperature with a 0.1% solution of methyl *p*-aminobenzoate.

RESULTS AND DISCUSSION

In each study, the permeation process was characterized in terms of a permeability constant (P) determined, as previously described (1), from the least-squares analysis of the steady-state portion of a plot of milligrams per liter of compound permeated across the polyethylene film *versus* time.

Effect of Concentration—The influence of initial solute concentration was studied with five different concentrations of acetophenone, ranging from 0.01 to 0.3% (w/v). The observed permeation rates and permeability constants are summarized in Table II. As anticipated from a consideration of Fick's first law (3-5) for a system with an invariant concentration gradient and constant surface area, the permeation rate of this compound was directly proportional to the initial concentration present in the system. However, the permeability constant was essentially invariant with changes in initial concentration. A similar observation was also reported by Garrett and Chemburkar (6) for the permeation of certain drug molecules through silastic membranes.

Effect of Temperature—Permeation studies were conducted for methyl and ethyl *p*-hydroxybenzoates and methyl *p*-aminobenzoate at 50, 55, and 60°. A representative permeation plot at the three temperatures is given in Fig. 1 for ethyl *p*-hydroxybenzoate. The activation energies of permeation, as determined from the slope of a plot of $\log(P)$ *versus* the reciprocal of the absolute temperature illustrated in Fig. 2, were 12.88, 19.46, and 21.44 kcal./mole for methyl *p*-aminobenzoate, ethyl *p*-hydroxybenzoate, and methyl *p*-hydroxybenzoate, respectively. There is an inverse relationship between the permeability constant and the energy of activation for permeation. The linear increase in permeability with increasing temperature, up to 60°, suggests that the permeability characteristics of the polymer film were not altered significantly over the temperature range studied.

Effect of Solvent—Two compounds having very low water solubilities were studied in various water-ethanol solutions. Permeability constants were evaluated from studies of *n*-propyl

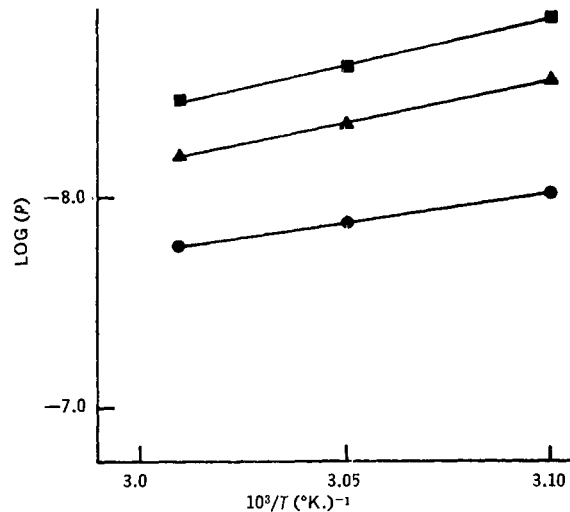


Figure 2—Arrhenius plots of the logarithm of the permeability constant versus the reciprocal of the absolute temperature for 0.1% (w/v) solutions. Key: ●, methyl *p*-aminobenzoate; ▲, methyl *p*-hydroxybenzoate; and ■, ethyl *p*-hydroxybenzoate.

p-hydroxybenzoate in ethanol solutions ranging in concentration from 2 to 20% (v/v); the isobutyl *p*-aminobenzoate in ethanol solutions ranged in concentration from 20 to 50% (v/v). Figures 3 and 4 illustrate the relationship between the permeability constant and the concentration of ethanol present in the system.

Garrett and Chemburkar (6) reported that the permeation rate of *p*-aminopropiophenone through a silastic membrane decreased with an increasing ethanol concentration in the permeation solution, but it was independent of the ethanol concentration in the desorbing solutions. In the present study, the observed decrease in the permeation rate of the solutes through the polyethylene film, with an increasing ethanol concentration, can be explained on the basis of changes in the solvent-membrane partition coefficient. The increased solubility of the compounds in the solvent, with an increasing ethanol concentration, relative to a constant solubility in the membrane slowed the permeation of the compounds.

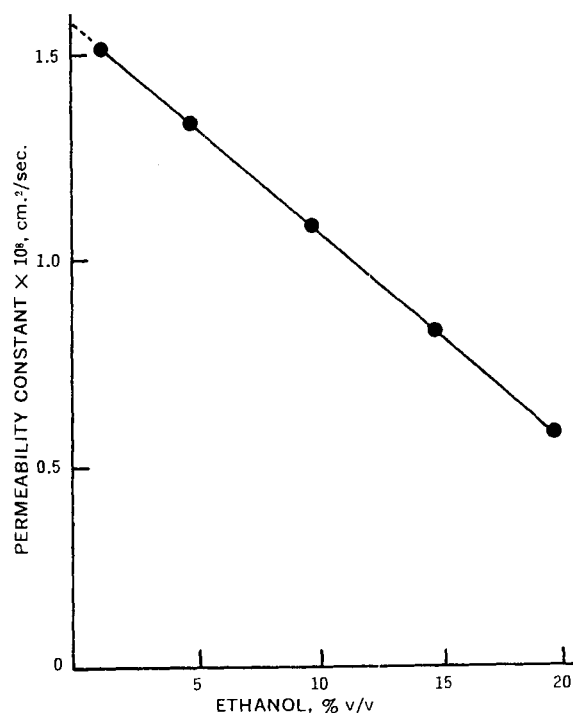


Figure 3—Influence of the ethanol concentration on the permeation of 0.1% (w/v) *n*-propyl *p*-hydroxybenzoate at 50°.

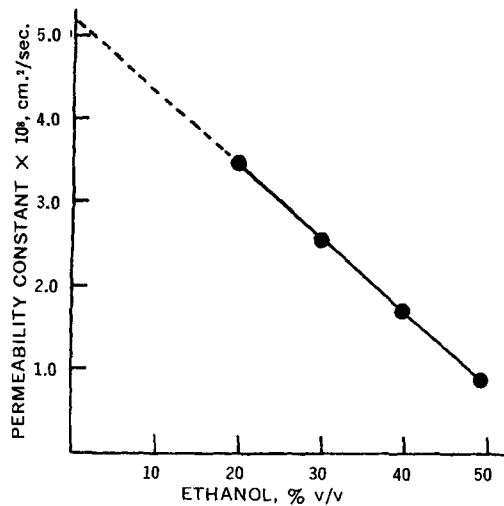


Figure 4—Influence of the ethanol concentration on the permeation of 0.1% (w/v) isobutyl p-aminobenzoate at 60°.

Effect of pH—If the permeation rate (R) of a weak acid depends on both the concentration of the ionized species (A^-) and the concentration of the unionized species (HA) in the permeation solution, then:

$$R = k(HA) + k'(A^-) \quad (\text{Eq. 1})$$

where k and k' are the rate constants for the permeation of unionized and ionized species, respectively. By expressing the concentrations of the unionized and ionized species in terms of total concentration (HA_i) and the fraction unionized (f), where $(f) = (HA)/(HA_i)$, Eq. 2 may be readily obtained:

$$R = f[k(HA_i) - k'(HA_i)] + k'(HA_i) \quad (\text{Eq. 2})$$

The fraction of benzoic acid that was unionized at each pH was calculated from its pKa value of 4.2, which is applicable to the experimental studies conducted at 50° (7, 8). A plot of benzoic acid permeation rate (R) versus fraction unionized (f), with (HA_i) held constant, resulted in a linear relationship (Fig. 5) in accordance with Eq. 2. The ordinate intercept was zero, indicating negligible

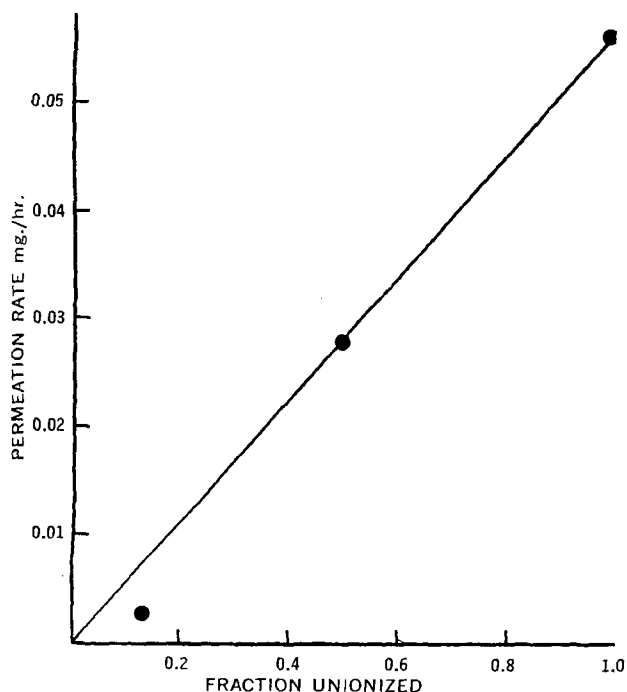


Figure 5—Effect of the degree of ionization, at various pH's, on the permeation rate of 0.1% (w/v) benzoic acid at 50°.

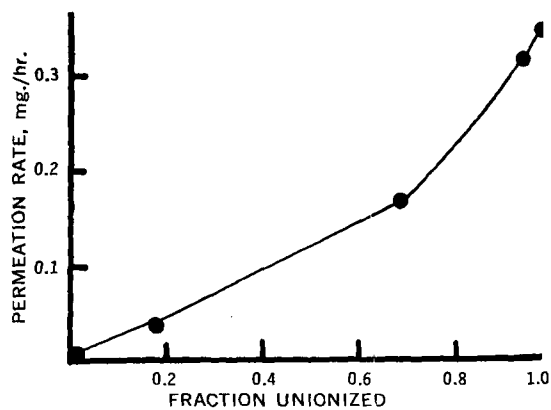


Figure 6—Effect of the degree of ionization, at various pH's, on the permeation rate of 0.1% (w/v) aniline at 50°.

permeation of the anionic species. Benzoic acid could not be conveniently studied above pH 5.0 because of very slow permeation. The permeation rate at pH 5.0 is somewhat less than predicted from a consideration of the fraction unionized only. Pinsky (9) showed that benzoic acid dimers permeate faster than the monomers. Therefore, the observed permeation rate may reflect a decrease in the formation of dimers with increasing pH and ionization.

Equation 2 should also be applicable to the permeation of a weak base such as aniline, with $(f) = (B)/(B_i)$ and substitution of (B_i) for (HA_i) , where $(B_i) = (B) + (BH^+)$. The fraction unionized at each pH was calculated from the pKa value of 4.25, which had been corrected to the 50° experimental conditions (7). A plot of aniline permeation rate (R) versus fraction unionized (f), with (B_i) held constant, is given in Fig. 6. It can be seen that there is an unexplained deviation from the linear relationship expected from a consideration of Eq. 2, as the compound approaches a totally unionized state, but the data indicate that the permeation rate is highly dependent on the concentration of the unionized species.

Effect of Pretreatment of Polyethylene Film—All compounds under study yielded linear permeation curves after steady-state permeation was achieved. The permeability constant was determined from the least-squares analysis of the slope of this portion of the plot. Unexpectedly, however, the majority of the studies yielded data that were concave rather than convex toward the time axis during the initial portion of the permeation curve. This resulted in an

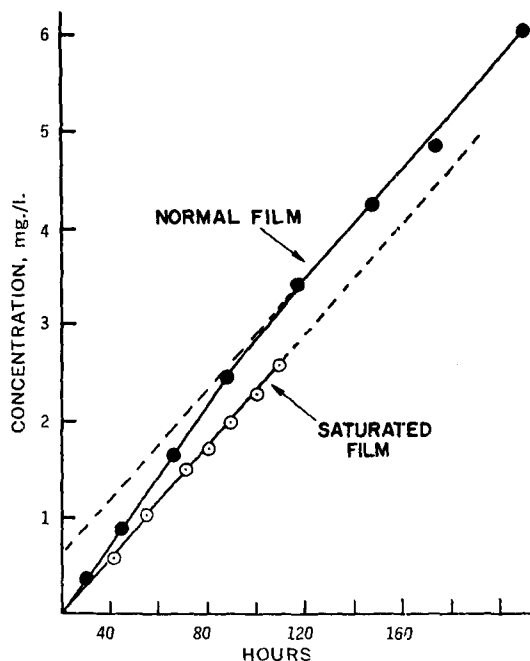


Figure 7—Influence of polyethylene film pretreatment on the permeation of 0.1% (w/v) ethyl p-hydroxybenzoate at 50°.

Table III—Effect of Film Treatment

Compound	Permeation Rate, mg./hr.		Permeability Constant, cm. ² /sec. × 10 ⁸	
	Normal Film	Satu- rated Film	Normal Film	Satu- rated Film
Ethyl <i>p</i> -aminobenzoate	0.251	0.240	2.06	1.81
Methyl <i>p</i> -aminobenzoate	0.112	0.084	0.920	0.690
Ethyl <i>p</i> -hydroxybenzoate	0.031	0.028	0.256	0.225

apparent positive intercept on the *Y*-axis upon extrapolation of the steady-state portion of the curve (Fig. 7). A similar observation was previously noted in the study of several substituted anilines (1). Since these results suggested an initial permeation rate which was greater than the rate observed during steady state, studies were initiated to determine if this phenomenon was related to the initial entry of the permeant species into polyethylene film and subsequent alteration of the permeation characteristics of the polymer. Representative data are illustrated in Fig. 7 for the permeation of ethyl *p*-hydroxybenzoate through a film treated in the routine manner. This same section of film was then reemployed in a subsequent study under identical conditions. One possible explanation for the observed results is an alteration in the permeation characteristics of the film as the solute continued to permeate the film. The data (Fig. 7) suggest that the initial relatively rapid permeation rate decreased with time as the film became saturated with the solute. This may be due to a rearrangement of the polymer molecules prior to steady state or to a blocking of permeation routes within the polymer due to interaction of the solute with the polymer. Table III summarizes the results of these studies, including those conducted with methyl and ethyl *p*-aminobenzoates. As can be seen, there was a decrease in the steady-state permeation rate and the permeability constant for each compound when the saturated film was employed. This is in contrast to the observation of Flynn and Smith (10) who reported increased permeability rates for *p*-aminoacetophenone when dimethylpolysiloxane films were reused in their diffusion system.

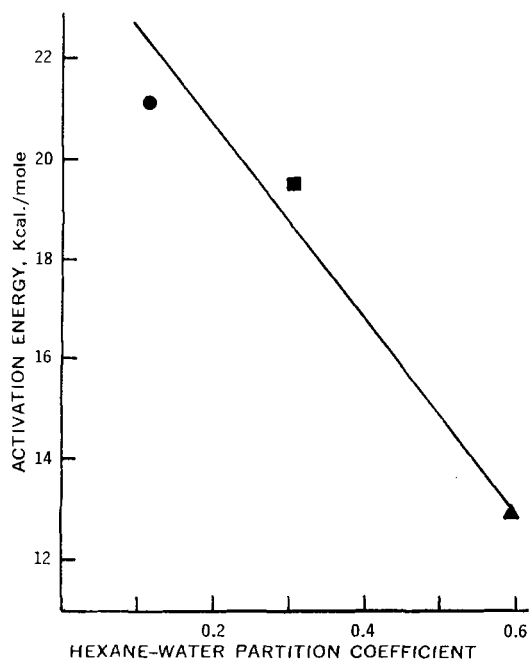


Figure 8—Relationship between the apparent activation energy for permeation and the hexane-water partition coefficient for 0.1% (w/v) solutions at 50°. Key: ●, methyl *p*-hydroxybenzoate; ■, ethyl *p*-hydroxybenzoate; and ▲, methyl *p*-aminobenzoate.

Table IV—Experimental Constants Evaluated from Permeation and Partitioning Studies (50 ± 0.2°)

Chemical	Permeability Constant × 10 ⁸ cm. ² /sec.	Hexane- Water Partition Coefficient
Benzoic Acids and Benzoates		
<i>p</i> -Hydroxybenzoic acid	0.00156	— ^a
<i>p</i> -Aminobenzoic acid	0.00330	— ^a
Methyl <i>p</i> -hydroxybenzoate	0.126	0.118
Ethyl <i>p</i> -hydroxybenzoate	0.256	0.310
Methyl <i>p</i> -aminobenzoate	0.920	0.600
Benzoic acid	1.00 ^b	0.720 ^c
Propyl <i>p</i> -hydroxybenzoate	1.60 ^d	0.800
Ethyl <i>p</i> -aminobenzoate	2.06	0.900
Isobutyl <i>p</i> -aminobenzoate	5.25 ^e	13.7
Benzaldehydes		
<i>p</i> -Hydroxybenzaldehyde	0.0370	0.111
<i>p</i> -Nitrobenzaldehyde	6.20	2.66
Benzaldehyde	27.7 ^b	12.5
<i>p</i> -Methylbenzaldehyde	55.3 ^b	28.7
<i>p</i> -Chlorobenzaldehyde	117	40.0
Acetophenones		
<i>p</i> -Aminoacetophenone	0.940	0.232
<i>p</i> -Nitroacetophenone	7.80	5.32
<i>p</i> -Methoxyacetophenone	10.6	8.60
Acetophenone	30.3 ^b	14.0
<i>p</i> -Methylacetophenone	62.3 ^b	45.0
Anilines		
<i>p</i> -Nitroaniline	0.470	0.240
<i>p</i> -Anisidine	1.60	0.746
Aniline	2.60	0.953
Phenols		
Phenol	0.640	0.200
<i>p</i> -Bromophenol	2.33	0.818

^a Partition coefficients were too low to be determined accurately. ^b Values taken from the work of Gonzales *et al.* (11). ^c Values taken from the work of Polack *et al.* (12). ^d Value determined by extrapolation to 0% ethanol (Fig. 3). ^e Value determined at 60° in 20% ethanol.

One additional approach was also undertaken to determine if perhaps the exposure of the film to the solvent for a prolonged period contributed to an alteration of the permeation characteristics of the polymer. The permeation of methyl *p*-aminobenzoate was studied with a film that had been soaked in distilled water at 50 ± 0.2° for 48 hr. The steady-state permeation rate and permeability constant obtained in this study approached the results previously obtained with this solute using saturated film (Table III). The observed permeation rate was 0.101 mg./hr. and the permeability constant was 0.830 × 10⁻⁸ cm.²/sec. These data suggest that some change in the permeation characteristics of the polymer occurred with time. However, the particular film section was not the same as the one employed in the routine and saturated studies. Therefore, the data may not be strictly comparable between the three studies.

Influence of Structure and Partition Coefficient on Permeation—One objective of this investigation was to determine if the relationships observed in the previous study (1) between the permeation of a series of substituted anilines and their physicochemical properties could be extended to various other chemical classes. Prior to the onset of diffusion layer control, it may be anticipated

Table V—Regression Analysis Data

Series	α^a	β^a	r^b	$F^c, \%$	EV^d
Benzoic acid and benzoates	1.3699	-7.7245	0.9736	99.8	0.9350
Benzaldehydes	1.3299	-8.0418	0.9928	99.9	0.9809
Acetophenones	0.7988	-7.5777	0.9844	99.5	0.9587
All 21 compounds	1.0621	-7.7602	0.9683	99.9	0.9343

^a α and β are constants given in Eq. 3. ^b The multiple correlation coefficient. ^c The level of significance for the *F* test of the regression analysis. ^d Explained variance, the fraction of the experimental data variance that is explained by the regression equation.

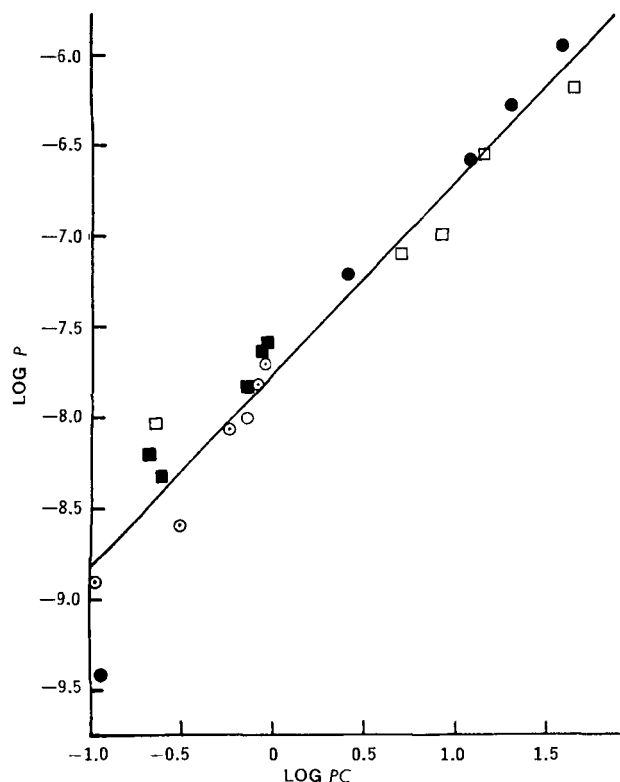


Figure 9—Correlation of permeability constants with hexane-water partition coefficients. Key: ○, benzoic acids and benzoates; ●, benzaldehydes; □, acetophenones; and ■, anilines and phenols.

that the permeation of various solutes through a homogeneous membrane such as polyethylene could be related to the relative affinity of the solute for the solvent phase in which it is located and the membrane phase through which it is permeating. Hexane-water was selected as the model partitioning system because polyethylene is considered to be a relatively nonpolar polymer.

Table IV summarizes the data obtained in the present study and reveals a good rank-order relationship within several chemical classes between the permeability constant (P) and the hexane-water partition coefficient (PC) of the solutes. It is apparent that the less polar a compound is, the more rapid will be its permeation through the polyethylene film. Figure 8 shows the relationship between the permeation activation energies determined from Fig. 2 and the respective hexane-water partition coefficients for the three compounds.

It is apparent that introduction of certain functional groups on the parent molecule will alter the permeation of the parent compound in accordance with relationships that are well known for the effects of various substituents on the polarity of a compound. For example, *p*-hydroxybenzoic acid, with two polar groups, is considerably less lipid soluble and slower permeating than benzoic acid. As the relatively polar *p*-hydroxy substituted acid is esterified, the permeability of the compound continues to increase in the order: propyl > ethyl > methyl. Furthermore, compounds with an amino group, which is less polar than the hydroxyl group, exhibit a greater permeability than the corresponding *p*-hydroxy substituted species. Within the benzaldehyde and acetophenone series, the introduction of polar hydroxy, nitro, amino, or methoxy groups decreases the permeability of the parent compounds, and the relatively nonpolar methyl and chloro derivatives exhibit increased permeability.

The apparent correlation evident in Table IV between the permeability constant (P) and the partition coefficient (PC) suggested that an empirical relationship might be obtained to quantitate the data and facilitate the prediction of the permeability of a compound from its hexane-water partition coefficient. A regression analysis of the data in Table IV was undertaken based on Eq. 3:

$$\log(P) = \alpha \log(PC) + \beta \quad (\text{Eq. 3})$$

where α and β are empirical coefficients representing the slope and Y intercept, respectively, of a plot of $\log(P)$ versus $\log(PC)$. The

data were analyzed in terms of the three groups of compounds with related structures, *i.e.*, the benzoic acids and benzoates, the benzaldehydes, and the acetophenones. In addition, 21 of the compounds listed in Table IV were grouped together for analysis. For the regression calculations, *p*-hydroxy- and *p*-aminobenzoic acids were not considered because of the lack of an accurate partition coefficient. Isobutyl *p*-aminobenzoate was also omitted since the permeability constant for this compound was determined at 60° in 20% ethanol. The empirical coefficients for Eq. 3 were computed using a computer³. The statistical analysis of the data included the multiple correlation coefficient (r) of the regression, the F test, and the "explained variance" or the fraction of the data variance attributed to the regression equation.

Table V summarizes the results of the regression analysis. The parameters for each of the three individual groups, as well as the entire group of compounds, were well correlated using Eq. 3. In Fig. 9, the data for the entire group of compounds are plotted in accordance with Eq. 3. The line given in the figure was obtained from the regression equation using the coefficients given in Table V for all 21 compounds.

The results of this analysis suggest that the permeation of these and related compounds, with partition coefficients ranging from less than 0.1 to 45, could be estimated under similar experimental conditions from their hexane-water partition coefficients.

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