THE PERMEATION OF MOLECULES THROUGH POLYETHYLENE MEMBRANES

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SUMMARY

The permeation of a variety of solutes (in aqueous solution) through a selected polyethylene membrane has been investigated.

Permeation through the membrane is considered to be a three step process: into, through and out of the membrane. In a steady state situation the rates into, through and out of the membrane are the same and this rate is the permeation rate. The rate at which the molecule moves through the membrane prior to the steady state being established is the diffusion rate and this rate is not necessarily the same as the permeation rate.

The permeation rate is affected by the concentration of the solute, the temperature of the system, the pH of the system and its viscosity. The thickness of the membrane is also important. The permeation rate is increased by increase in concentration, increase in temperature and by decrease in the thickness of the membrane.

Relationships between pH and permeation rate and viscosity and permeation rate are more complex. A change of pH which increases the ratio of unionised to ionised species present will increase the permeation rate (provided that the unionised solute will permeate). If the viscosity of the system is changed by the introduction of a solvent which decreases the polarity of the system (relative to water) the permeation rate is decreased.

The hexane water partition coefficient of a solute gives an indication as to whether permeation will occur or not. Expressions which relate the hexane water partition coefficient of a solute to its permeation rate and to its diffusion rate are proposed.

Results obtained in this work suggest that the use of polyethylene membranes may be of some value in work on the *in vitro* prediction of *in vivo* availability of some therapeutically active substances.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University and to the best of my knowledge and belief contains no material previously published or written by another person except where due reference is made in the text.

A. E. Polack.

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ABBREVIATIONS

A	frequency factor
a	area
C (and c)	concentration
C_i	concentration in compartment i
C_o	concentration in compartment o
cms	centimetres
cps	centipoise
D	diffusion coefficient (or diffusion rate)
D'	permeability
$E^{1\%}_{1cm}$	absorbance of a 1% solution in a 1 cm cell
E_a	energy of activation
e	natural logarithm
F	constant
g	grams
in	inches
K_{hw}	hexane water partition coefficient
K_{ow}	oil water partition coefficient
K_{pw}	polyethylene water partition coefficient
K_u	permeation rate
Kcals $mole^{-1}$	kilo calories per mole
k	rate
l	thickness
log	logarithm (to base 10)
M	molarity
MW	molecular weight

m	amount of solute
mg	milligram
mil	1×10^{-3} inches
ml	millilitre
N	normality (in Figure 2.2);
	Avogadro's number (in expressions 3.8 and 5.1)
nm	nanometre
P	permeation rate (under specific conditions)
PC	permeability constant
Pf	permeability factor
pKa	negative logarithm of the dissociation constant
pH	negative logarithm of the hydrogen ion concentration
p	pressure
p'	permeation rate
R	gas constant (1.987 cals degree^{-1} mole^{-1})
RPM	revolutions per minute
r	radius
S	solubility coefficient
T	temperature (in ^{o} Absolute)
t	time
UV	ultraviolet
v	volume
$\bar{v}$	partial specific volume
W	constant
X	thickness

Z	constant
^{o}	degrees Centigrade
^{o}F	degrees Farenheit
η	viscosity
π	3.1412 (in expressions 3.8 and 5.1);
	permachor (in expression 5.5)
τ	lag time
λ_{max}	wavelength of maximum absorption
σ	solubility constant
%	percentage weight in volume (or volume in volume)
%w/w	percentage weight in weight

1. INTRODUCTION

1.1 General

1.2 Membranes

1.2.1 Movement of molecules through naturally occurring membranes

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1.1 General

The movement of molecules through barriers has been of interest for more than two centuries and the earliest reported work appears to be that of Nollet who discovered the process of osmosis in 1748. He placed an alcoholic solution in a bladder, suspended it in a vessel of water and found that the water molecules moved into the sac but that the alcohol did not pass through the membrane (Martin, 1960). The first work on synthetic membranes appears to be that of Deville and Troost (1863) who reported the movement of hydrogen through hot platinum. Pfeffer (1877) measured the osmotic pressure of sugar solutions using a porous cup impregnated with cupric ferrocyanide as the membrane.

The permeation rates of some substances through intact biological membranes was reported by Overton (1895) who measured the time taken for plant cells to break by plasmolysis, the time taken being used as a measure of the permeation rate. Similarly Griyns (1896) used the rate of haemolysis of erythrocytes to measure permeation rates. The first work on the passage of molecules through membranes in living species appears to be that of Baum (1899), Meyer (1899) and Overton (1901) all of whom were concerned with the pharmacological response produced in animals by solutions of selected substances.

All of the early workers who were interested in biological membranes were attempting to elucidate the actual membrane structure. It was not, however, until some time later that a suitable model was proposed. Gorter and Grendel (1925) proposed that the wall of the

red blood cell consisted of a lipid bilayer. Subsequently Davson and Danielli (1935, 1943) proposed that biological membranes consisted of a bimolecular leaflet of phospholipid to which proteins are attached on both surfaces by ionic forces and that fixed electrical charges on external surfaces bind oppositely charged ions forming an electrical double layer and a phase boundary potential. In addition they proposed that the movement of many substances into and out of cells occurs because the membrane is lipid in nature. The membrane structure proposed by Davson and Danielli is still largely accepted (Stein, 1967; Willix, 1971). Specialised regions of the membrane enable the passage of ions and large molecules to occur (Willix, 1971).

The earliest work on synthetic membranes appears to have been that of Deville and Troost (1863) referred to above. That work and much of the subsequent work was concerned with the passage of gases through barriers of various types and was reviewed by Barrer (1939, 1941). Later work on the movement of molecules through synthetic membranes has been extensively reviewed by Lakshminarayanaiah (1969).

Work in which the movement of a solute from one aqueous phase through a polymeric membrane to another aqueous phase has been reported, is considered in Section 1.2.2.

Up to the present time nobody appears to have succeeded in preparing a membrane which can be regarded as being capable of simulating a natural membrane. It has been suggested by some authors that synthetic lipid membranes may simulate the lipid character of natural membranes (for example, Doluisio and Swintosky, 1965; Perrin, 1967) and it is possible that polyethylene is such a membrane.

1.2 Membranes

Barriers (which are either continuous or discontinuous) which are selectively permeable are generally referred to as membranes. The movement of a molecule through a membrane generally takes place by one of two mechanisms - either by passage through pores in the membrane or by a solution process followed by desorption from the distal surface (Herzog and Swarbrick, 1970). The movement of molecules through the gastro intestinal membranes of man may take place by either mechanism but generally does so by the latter process since the diameter of the pores is such that only a limited number of molecules could permeate by the former mechanism (Wagner, 1971). Movement through polymeric membranes is considered to take place by a solution process (Herzog and Swarbrick, 1970) and for this reason discontinuous membranes specially prepared to contain pores of a predetermined size (and often for a predetermined separation purpose), such as sintered glass and sintered discs, are not considered to be relevant and are therefore not considered further.

Much of the work on membranes in recent years has been directed towards specific goals. Amongst these is the continuing desire to fully elucidate the structure of natural membranes and to understand the mechanisms by which molecules pass through membranes in living species. The production of an *in vitro* system which can be closely related to an *in vivo* membrane is the ultimate purpose of much of the current work on membranes.

The use of membranes for selective separation and purification processes has also become more general in recent years. The potential

use of selectively permeable membranes in the production of dosage forms designed for specific purposes has also generated interest in this area.

The specific goals have been summarised by Lakshminarayanaiah (1969) who has classified membranes on the basis of their ultimate use and has placed all membranes into one of three divisions. In general terms these divisions are (1) membranes with favourable electrical performance suitable for use in fundamental transport studies and in some industrial applications, (2) membranes to be used as models for natural membranes and (3) membranes designed to be used to study the physicochemical phenomena associated with the rectification of alternating current.

A review of work on the movement of molecules through various types of membranes follows. In the discussion below (and in subsequent sections and chapters) a distinction is made between permeation and diffusion. In the present context permeation is regarded as the passage of a solute molecule from a solution on one side of a membrane into, through and out of the membrane into a solution on the other side. If the situation is such that a steady state exists (i.e. the rate of entry into the membrane is equal to the rate of exit from the membrane) then the permeation rate is numerically equal to the slope of a plot of the amount of solute which has passed through the membrane against time (in appropriate units). Before a steady state situation can be established the solute must move through the membrane. This process is diffusion and the diffusion rate is not necessarily the same in the period prior to the establishment of the steady state

and in the steady state. This period is generally referred to as the "lag time" or "lag period" and is defined by Rogers (1964) as the time interval between when the solute first enters the membrane and when the steady state of flow is established. The meanings of permeation and diffusion adopted here have been used previously by Nakano and Patel (1970b).

The term "passive diffusion" is used to describe the situation in which the diffusion rate in the steady state (i.e. the permeation rate) is dependent on the physicochemical properties of the solute and of the membrane and on the concentration gradient across the membrane. The permeation rate through a living membrane is often referred to as the absorption rate.

In the steady state of flow the concentration gradient across the membrane is maintained constant. In the quasi steady state of flow the concentration gradient is not maintained constant. For a limited degree of permeation the two stages can be regarded as the same.

1.2.1 Movement of molecules through naturally occurring membranes.

1.2.1.1 *in vivo* membranes

Some of the early work on the movement of molecules through membranes in living species has been referred to in section 1.1. More recently Brodie and Hogben (1957), Schanker (1962), Hogben (1963) and Brodie (1964) have presented extensive general reviews on the physicochemical factors affecting permeation through membranes in higher

animals. All of these authors have emphasised the importance of the lipid water partition coefficient of the molecule and the pH of the medium. The "pH partition theory" of drug absorption (generally attributed to Brodie) was the logical development of much of the work on this subject. Simply stated this theory postulates that the extent of absorption (in a given time) of a substance from the gastro intestinal tract (in higher animals) is dependent on the lipid water partition coefficient of the molecule and that only the unionized species of an acid or a base is capable of permeating the *in vivo* membrane. The greater the lipid water partition coefficient the greater the extent of absorption.

More recently much of the work on living animals has been concerned with the absorption characteristics of individual substances (or classes of substances) through the membranes of the gastro intestinal tract; for example, Levy (1966) has reviewed the absorption of the salicylates and O'Reilly and Aggeler (1970) the absorption of the anticoagulants.

The movement of molecules through living membranes in plants and animals other than man has also been studied. Bates and Gibaldi (1970) have discussed the use of rabbits, pigs, dogs, rats and mice in work concerned with the understanding of the processes by which molecules move across membranes in living species. The monkey has been used by many workers (for example, Nagashima and Levy, 1969). Goldfish have been used to study the effects of various factors on the movement of some substances through membranes in living species.

Levy and Anello (1968) used this animal to examine the effects of various factors on the absorption of barbiturates and similarly Gibaldi and Nightingale (1968) studied the effects of a variety of factors on the absorption of ethanol. Other living animals have also been used (for example, the planarian has been used by Saski, Mannelli, Saettone and Bottari, 1971). Lieb and Stein (1969) reported work on the diffusion of a number of aromatic compounds in some plants.

In a recent review concerned with the permeation of molecules through biological membranes, Teorell (1970) has given particular attention to what he describes as "general factors", these factors being defined by him as the permeability properties of the membrane and the driving forces prevailing across the membrane, and he also gives particular attention to the influence of the membrane solubility (i.e. the solubility of the molecule being considered in the membrane) on the permeation rate.

The works cited above (and others) have not, however, been successful in elucidating the actual mechanism by which molecules move through membranes.

1.2.1.2 *in vitro* membranes

A number of workers have used the "everted sac technique". This involves the removal of a small segment of the intestine of an animal (usually a rat), the everting of the segment and the filling of this sac (after tying off one end) with drug free physiological buffer medium; the other end of the sac is tied off and the sac is immersed in a relatively large volume of the buffer solution (which contains the molecule being investigated) in a suitable container. The concentrations of the solutions are then followed with time under

controlled experimental conditions. This method was originally devised by Wilson and Wiseman (1954). Some modifications of the original method have taken place (e.g. Crane and Wilson, 1958) but the principle remains unaltered. This technique has been used to study the effect of many physicochemical factors on the movement of drug molecules through natural membranes and these factors have been reviewed by Bates and Gibaldi (1970).

Another method involves the use of sections of skin removed from animals - for example Aquiar and Weiner (1969) used skin removed from hairless mice to study the transfer of chloramphenicol.

1.2.2 Movement of molecules through synthetic membranes.

Synthetic membranes which have been used in this type of work can be divided into:

1. Liquid membranes
2. Solid membranes.

1.2.2.1 Liquid membranes

These membranes are used in cells designed such that the liquid membrane is in contact with two separated aqueous layers in a suitably partitioned apparatus. Rosano, Duby and Schulman (1961), Rosano, Schulman and Weisbuch (1961) and Schulman and Rosano (1962) used a cell of this type to investigate the movement of salts and ions (and the effect of some surface active agents on this movement) through short chain alkyl alcohols. Similarly Rosano (1967) used a 1-butanol layer and followed the movement of water through this when different aqueous solutions were placed in the two compartments of the cell.

Doluisio and Swintosky (1964, 1965) used a Y-shaped rocking device based on the same principle and appear to have been the first workers to use this type of apparatus as a model for *in vivo* absorption. They investigated the rate of transfer of salicylic acid, barbital, antipyrine, aminopyrine and tetracycline from an aqueous layer (at a number of different pH's) through a lipid layer (n-octanol or cyclohexane) to another aqueous layer at pH 7.4 and in general found the results to be in agreement with the pH partition theory for movement through living membranes mentioned above (section 1.2.1.1). Khalil and Martin (1967) using the same type of apparatus investigated the transfer of carboxyl salicylic acid, ^{14}C, through a number of non polar liquids (n-pentane, n-hexane, cyclohexane, toluene, benzene, n-octyl alcohol and n-hexyl alcohol) which were chosen to represent a range of "solubility parameters". It was found that the closer the "solubility parameter" of the carboxyl salicylic acid was to that of the lipoidal barrier, the faster was the rate of the disappearance of the acid from the first aqueous layer (pH 2) and the slower its appearance in the other aqueous layer (pH 4).

Perrin (1967) using a "rectangular" partitioned cell studied the transfer of salicylic acid and amidopyrine through layers of 30% dodecanol in cyclohexane and cyclohexane respectively to the other aqueous phase and was able to conclude that the rate of transfer was dependent on the lipid water partition coefficient of the solute and the amount of the unionised form of the acid present.

In this type of apparatus the rate of transfer appears to be dependent on the particular lipoidal layer used and the results of

Khalil and Martin (1967) have been confirmed by Augustine and Swarbrick (1970) who showed that the rate of transfer of salicylic acid from the first aqueous solution to the oil, in an apparatus similar to that used by Perrin (1967), increased as the polarity of the oil increased.

Robertson and Bode (1970) used an apparatus similar to Perrin (1967) in design but different in that the apparatus was continuously rotated about an horizontal axis. This procedure allows for the continuous generation of interfaces and overcomes the difficulty (associated with the apparatus of Doluisio and Swintosky, 1964) of the interface continuously expanding and contracting. The problem associated with the apparatus of Perrin (1967) of the phases tending to emulsify (through vortexing) if the stirring rate is too rapid, is also avoided. The rates of transfer of salicylic acid and three sulphonamides from the one aqueous phase (at pH 2 or pH 5) to the other (at pH 7.4) were found to exhibit the expected pH dependence. Robertson (1971) used the same apparatus to study some of the factors affecting the rate of transfer of erythromycin. It was found that the rate was affected by the pH, the polarity of the lipid phase, the chemical form of the substance and by the presence of protein.

Lakshminarayanaiah (1969) has reviewed much of the work on artificial membranes, but surprisingly makes no mention of the work of Doluisio and Swintosky (1964, 1965), Khalil and Martin (1967) or Perrin (1967).

1.2.2.2 Solid membranes

These membranes are considered in the following categories:

(a) Polyethylene films

(b) Other films

(c) Polyethylene containers.

(a) Polyethylene films

The properties of any sample of polyethylene will depend on the conditions used during the polymerisation process. These conditions will control the degree of crystallinity and the amount of cross linking and therefore many of the properties of the sample.

The diffusion and permeation of substances into and through polyethylene has been the subject of numerous investigations but the majority of these have been concerned with gaseous diffusion. Until relatively recently the permeation of polyethylene by pure liquids and by solutes of aqueous solutions has been largely neglected. In the last decade, however, more attention has been directed to these areas, largely because of the increasing use of polyethylene in a number of everyday applications.

The first report of investigations into the permeation of polyethylene films by pure liquids appear to be those of Parliman (1948, 1949) who using polyethylene bags established "permeability rates" for thirty six polar and twelve non polar liquids. He concluded that permeation was an "activated diffusion process" in which the permeating molecule first dissolved in the polymer and then diffused through it from a region of high concentration to that of low and then evaporated from the outer surface.

Thornton Stannett and Szwarc (1958) investigated the permeation of methanol through thin polyethylene membranes and found the permeation rate to be similar to that found previously by Bent (1957) who had reported the permeation of methanol through polyethylene containers (section 1.2.2.2 c).

Dietrick and Meeks (1959) found that hydrogen peroxide permeated very slowly through a thin polyethylene membrane at room temperature and at an increased rate at higher temperature.

Gonzales, Nematollahi, Guess and Autian (1967) using an apparatus apparently identical to that previously used by Berg, Guess and Autian (1965), Rodell, Bodnar, Guess and Autian (1965) and others from the same laboratory (section 1.2.1.2) set out to determine the diffusion, permeation and solubility of six substances which were structurally similar (benzoic acid, benzyl alcohol, benzaldehyde, acetophenone, 4-methyl benzaldehyde and 4-methyl acetophenone) in and through polyethylene. Part of the study was designed to provide information on the effect of structural factors on the diffusion rates and permeation rates of the parent compounds. These workers plotted amount permeated against time and obtained linear relationships after an initial lag period had elapsed. Results of these experiments revealed that benzyl alcohol and benzoic acid had the smallest permeability constants (P), defined as the amount permeating through a membrane of specified dimensions under specified conditions, and the smallest diffusion coefficients (D) compared to the other compounds in the series. The reason for this was believed to be the intra hydrogen bonding potential of benzyl alcohol and of benzoic acid which allowed the formation of dimers and trimers whose penetration into the polymer was not as easily achieved as that

of the monomer. In the case of the 4-methyl benzaldehyde and the 4-methyl acetophenone, the D values obtained were similar to those of the parent compounds benzaldehyde and acetophenone. The solubility coefficient (S) values, and the P values were, however, found to be larger. The difference in the S and P values was attributed to the effect of methyl substituents, the presence of which was believed to give rise to a higher solubility of the substance in the polyethylene.

These workers were concerned primarily with the effects of temperature and of substituent groups in the molecules considered and did not report on the effect of a number of other factors (for example concentration, volume, pH, viscosity, thickness of membrane) on the diffusion rates and the permeation rates through the polyethylene.

Schoenwald and Belcastro (1969) have reported a study of the sorption of labelled chlorbutanol (from aqueous solution) by polyethylene. They found that the chlorbutanol was taken up under certain conditions of concentration, temperature and time.

(b) Other films

In work on other solid membranes (i.e. not polyethylene) a number of authors have shown that the permeation rate from the one aqueous phase to the other is dependent on a number of factors. In general the apparatus used in this type of work is designed such that the membrane is held vertically between the two parts of the cell which house the aqueous phases. Apparatus used in this type of work is discussed further in Chapter 5.

Weatherby (1943, 1949) using membranes composed largely of biological materials was able to show that a relationship existed between

the pH of the solution and the transport rate of some acids and bases and some organic electrolytes, the greater rate being shown from solutions in which ionisation was suppressed. Similar effects of pH have been shown by Rummel, Buch, Buzello and Neurohr (1969), who used a number of polymeric membranes; by Nakano and Patel (1970a) and by Nakano (1971) using dimethyl polysiloxane membranes. Fites, Banker and Smolen (1970) used four polymeric membranes and were able to show the same effect. Herzog and Swarbrick (1970, 1971a) used a membrane composed largely of biological materials and showed that only the unionised form of salicylic acid was capable of permeating the membrane.

The importance of the partitioning of the solute between the lipid layer (i.e. the membrane) and the aqueous solution has been illustrated by Lueck, Wurster, Higuchi, Lemberger and Busse (1957) and Lueck, Wurster, Higuchi, Finger, Lemberger and Busse (1957) who showed that a plot of the permeation rate (for three different solutes) against the partition coefficient of the solute between the membrane and the aqueous layer was linear. Similarly, Garrett and Chemburkar (1968a,b,c) using a dimethyl polysiloxane membrane found that a plot of the apparent diffusion rates (a function of the diffusion rate) of a number of solutes against the partition coefficients of the solutes between chloroform and the aqueous layer was linear. These workers did not, however, measure the partition coefficient between the membrane itself and the aqueous layer and the partition coefficient measured can therefore be regarded only as a measure of the relative polarity of the solutes.

The two factors considered above (the pH of the solution and the partition coefficient of the solute between the lipid layer and the

aqueous layer) are the main factors in the pH partition theory of drug absorption referred to above (section 1.2.1). The similarities in properties between membranes of the human gastro intestinal tract and synthetic membranes are considered further in Chapter 5.

Lueck and others (1957a) and Lueck and others (1957b) found the permeation rate to be proportional to the reciprocal of the thickness of the membrane.

The effect of the molecular weight of the solute has been reported by Johnson (1965) who found that the diffusion rate through a thiolated gelatin membrane, of five of the seven solutes he used, was related to the molecular weight by the relationship $D(MW)^{\frac{1}{2}} = \text{constant}$.* Garrett and Chemburkar (1968a,b,c) however, found the apparent diffusion rate to be independent of the molecular weight of the solute for diffusion through a dimethyl polysiloxane membrane. Fites, Banker and Smolen (1970) were able to relate the permeation rate through each of four polymeric membranes to the molecular weights of the polymers. They also found the concentration of plasticiser and the degree of hydration of the membrane to be factors which controlled the permeation rate of a solute through the membrane.

Some authors have found the diffusion rate and permeation rate to be related to the temperature of the system by the Arrhenius relationship,

$$k = Ae^{-E_a/RT}.$$

If this relationship holds a plot of the logarithm of the diffusion (or permeation) rate against the reciprocal of absolute temperature should be linear. Rodell, Guess and Autian (1966) found

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* see front of thesis for definition of symbols.

this relationship to be valid for the permeation of a number of solutes through nylon; Garrett and Chemburkar (1968a,b,c) found the same relationship valid for the diffusion of a number of solutes through dimethyl polysiloxane membranes and these workers were able to determine the energies of activation for the processes. Powell, Nematollahi, Guess and Autian (1969) reported on the diffusion and permeation of benzalkonium chloride through nylon and showed the effect of temperature on both diffusion and permeation rates. Both diffusion and permeation rates increased with temperature but in a somewhat erratic manner.

In many investigations of the type being considered a lag time has been reported (for example Rodell, Bodnar, Guess and Autian, 1965; Rodell, Guess and Autian, 1966; Kostenbauder, Boxenbaum and Deluca, 1969; and Nakano, 1971).

Rodell, Guess and Autian (1966) found that the permeation rate was "in general dependent on the quantity of solute originally present in the high concentration side of the cell". Garrett and Chemburkar (1968a,b,c) found the apparent diffusion rate for substances which ionised in solution to be dependent on the concentration of unionised species present. Herzog and Swarbrick (1970, 1971a) found that the disappearance rate of salicylic acid from the first aqueous phase was first order (i.e. a plot of the logarithm of the concentration remaining against time was linear) but Nakano (1971) found that if the logarithm of the concentration remaining in the concentrated aqueous solution was plotted against time (for the permeation of chlorpromazine through a dimethyl polysiloxane membrane) a linear relationship was obtained only

after an initial period during which the rate of disappearance of the solute was greater than that which prevailed in the subsequent steady state. This initial period can be regarded as the lag period during which the solute is being taken up by the membrane. This author also studied the effect of the presence of other substances in the solution and found that the presence of either surface active agents, some insoluble solids or some other soluble substances in the "concentrated solution" generally decreased the permeation rate.

The movement of solute molecules through synthetic membranes has been put to advantage in a number of applications. In laboratory work, dialysis has become an important tool for the separation of the components of mixed systems and many different membranes have been used for a wide variety of separations. The use of membranes in desalination processes has become important. The use of membranes in haemodialysis and in artificial kidneys and in the treatment of drug overdosage and poisoning are all examples of separation processes based on the selective permeation properties of specific membranes.

The use of some membranes for these and other purposes has been discussed by Lakshminarayanaiah (1969) and the dialysis of poisons and drugs has been reviewed by Schreiner (1971). The use of membranes in dosage forms has been of interest to some workers. Chemburkar (1967) attempted to relate the *in vitro* diffusion rate of some solutes through a dimethyl polysiloxane membrane to the diffusion rate of the same solute through the same membrane when it was prepared as a pharmaceutical dosage form. Sundaram and Kincl (1968) and Kincl, Benagiano and Angee (1968) reported work in which they investigated the possibility of formulating

steroids in a long acting form within a polymeric "capsule" and Fites, Banker and Smolen (1970) reported work in which they investigated the possibility of controlling drug release from a tablet by use of an insoluble film around the tablet.

(c) Polyethylene containers

Numerous investigations into the permeation of a variety of substances through polyethylene containers have appeared in the literature. The majority of these have been concerned with pure liquids. Nielsen and Parliman (1950) investigated the relationship between the wall thickness of polyethylene bottles and the permeability rates of selected substances. One of the conclusions reached in this work was that water and alcohol had low permeation rates through polyethylene. The permeation rate of the solvent of aqueous solutions stored in polyethylene containers has been reported by other authors and it has been found that the permeation rate of water is generally sufficiently small to be disregarded except for storage at high temperatures for long periods (Goss, Gregerson and Polack, 1968). In work on the storage of aqueous solutions in polyethylene containers the technique is generally to use an aliquot of the contents of a different container for each sample. This technique assumes that all the containers have identical properties and for this reason the results obtained in this work must be regarded as somewhat crude.

Pinsky, Nielsen and Parliman (1954) reported a long term study of the permeation of sixty-seven "typical" chemicals through polyethylene bottles and were able to conclude that it was possible to predict, fairly accurately, at any selected temperature, the permeability values of the

substances used. Other workers (for example Wright, Tomlinson and Kirmeier, 1953; Bent, 1957) have published permeation figures for a variety of substances, but the experimental methods obviously left much to be desired since expressions such as "ordinary plastic containers filled to the neck ..." were used. Bent (1957) stated "the bottle had an average surface area of 162 mm^2 ...". Nevertheless Bent (1957) drew numerous conclusions from his work and he was able to determine permeability constants, at four temperatures, for twelve organic solvents in three polyethylenes and one irradiated polyethylene. He plotted the logarithms of the permeability constant against the reciprocal of absolute temperature and obtained linear relationships from which he was able to determine energies of the activation for permeation by the use of the Arrhenius relationship given above. Parliman and Pinsky (1957) investigated lined polyethylene containers in an attempt to reduce permeation. Salame (1961) published extensive results for the permeation of organic molecules through polyethylene containers and was able to devise an expression by which he was able to predict the permeation rates of a great number of organic molecules through polyethylene and the correlation between his predicted and experimental results was excellent. The expression included the "permachor" (π) a numerical value devised by him (and applicable to any molecule) which he described as

> "a gross classification of the permeant taking into account its size, shape, polarity and interaction forces with polyethylene".

Salame's method is applicable only to pure liquids and no provision is made for the prediction of permeation rates of organic molecules in

aqueous solutions. Douhairie (1957) appears to have been the first worker to investigate the permeation of solutes of aqueous solutions through polyethylene containers. Subsequently Barkman and Jarnhall (1961), v. Czetch-Lindenwald (1963a,b) and Neuwald (1965) reported losses of solutes of aqueous solutions stored in polyethylene containers. Russell and Stock (1966) reported losses of solutes from aqueous solutions, during autoclaving, in polyethylene containers. Beal Dicenzo, Jannke, Palmer, Pinsky, Salame and Speaker(1967) reported a long term study of a variety of substances (both pure and included in pharmaceutical formulations) stored in polyethylene containers but only a limited number of these were in the form of aqueous solutions. The work of Russell and Stock (1966) was continued by Goss, Gregerson and Polack (1968) and by Polack, Roberts and Schumann(1970). Goss and others (1968) regarded the polyethylene as a water immiscible layer and Polack and others (1970) were able to derive an expression which they used to predict losses under the experimental conditions. This derivation included consideration of the polyethylene water partition coefficient of the solute and the authors chose to represent this value quantitatively by the hexane water partition coefficient of the solute. The agreement between predicted and experimental values was good.

Polack and Roberts (1971) reported further work on the loss of solutes from aqueous solutions stored in polyethylene containers and were able to show that only the unionised species of an acid and a base were able to permeate. They also reported that a plot of the logarithm of the concentration of solute remaining in solution against time was linear only after an initial lag time had elapsed for two selected

solutes (nitrobenzene and chloroxylenol) in aqueous solution. This work showed that some of the factors which are important in the processes by which solute molecules permeate into and through thin polyethylene membranes are also important in the movement of solute molecules from aqueous solutions into polyethylene containers.

Friesen and Plein (1971) have reported a detailed investigation into the storage of aqueous chlorbutanol solutions in polyethylene containers.

1.3 Purpose and scope of the present work

The work of Gonzales and others (1967) only covered the subject of movement of molecules from aqueous solution into and through polyethylene membranes to a limited extent. Similarly Parliman (1948, 1949), Thornton, Stannett and Szwarc (1958) and Dietrick and Meeks (1959) only investigated certain aspects of the problem. For this reason, together with the increasing interest in this area, it was felt that a more detailed investigation of the diffusion and permeation of molecules into and through polyethylene membranes was warranted.

In addition it was felt that information obtained in this work could possibly be of some value in the understanding of permeation through polyethylene containers - the use of polymeric containers (particularly polyethylene) for medicinal substances is viewed with sufficient concern for two major symposia on this subject to have been held in recent years.[1]

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[1] International Pharmaceutical Federation Conference, Montpiellier, 1966 (reported in *J. Mond. Pharm.*, (1966), 4, 257) and British Pharmaceutical Conference, Belfast, 1969 (reported in *Pharm. J.* (1969), 203, 335).

It was also considered possible that information obtained in this study could be of some value in the understanding of the process by which molecules move through *in vivo* membranes.

2. EXPERIMENTAL

2.1 Materials

2.2 Analytical methods

2.3 Heat stability of the substances used

2.4 Determination of permeation rates

2.5 Validity of experimental method

2.6 Other experiments

2.7 Viscosity

2.8 Membrane thickness

2.9 Sorption

2.10 Solubility

2.11 Partition coefficients

2.1 Materials

Substances used in this work were as follows:

Acetic acid glacial, analytical reagent, British Drug Houses, Poole England, Batch 1775.

Acetophenone, laboratory reagent, May and Baker, Dagenham England, Batch 66432 was further purified by distillation as described by Vogel (1956) before use.

Anisaldehyde, laboratory reagent, British Drug Houses, Poole England, Batch 2562430 was further purified by distillation as described by Vogel (1956) before use.

Anisole, laboratory reagent, British Drug Houses, Poole England, Batch 2564310 was further purified by distillation as described by Vogel (1956) before use.

Benzaldehyde, analytical quality, Fluka A.G., Buchs Germany, Batch 96894K.

2,4-Dichlorophenol, laboratory reagent, British Drug Houses, Poole England, Batch 2566250.

Dipotassium hydrogen phosphate, laboratory reagent, Merck A.G., Darmstadt Germany, Batch 70178334.

Glycerin, British Pharmacopoeia quality was dried before use.

Hexane, analytical reagent, Ajax Chemicals, Sydney, Batch 01470 was distilled before use, the fraction of boiling point 67.5°-68.5° being used.

Hydrochloric acid, British Pharmacopoeia quality.

Methyl cellulose, F.H. Faulding, Adelaide, Batch 9B7629.

p-Methyl acetophenone, laboratory reagent, British Drug Houses, Batch 325500 was further purified by distillation as described by Vogel (1956) before use.

Nitrobenzene, laboratory reagent, Merck A.G., Darmstadt Germany, Batch 8612418 was further purified as described by Vogel (1956) before use.

o-Nitrophenol, laboratory reagent, Fluka A.G., Buchs Germany, Batch 432749 was recrystallised from alcohol-water before use.

Potassium dihydrogen phosphate, laboratory reagent, Merck A.G., Darmstadt Germany, Batch 90048.

Sodium acetate, analytical reagent, Standard Laboratories, Melbourne, Batch 3204.

Sodium chloride, analytical reagent, Ajax Chemicals,Sydney, Batch 72585.

Sodium hydroxide, British Pharmacopoeia quality.

p-Tolualdehyde, laboratory reagent, British Drug Houses, Poole England, Batch 2563270.

p-Toluidine, analytical reagent, Ajax Chemicals, Sydney, Batch 71831.

Tris (hydroxymethyl) methylamine, analytical reagent, British Drug Houses, Poole England, Batch 0339812.

Water distilled in an all glass still was used for preparation of all solutions and for the final rinsing of all apparatus.

Buffer solutions are shown in Tables 2.1 and 2.2. pH's were measured on a Radiometer 28 pH meter.

Table 2.1

Buffer systems used for o-nitrophenol solutions.

pH	Buffer system used
3.81	Acetate
3.90	
4.24	
4.70	
5.25	
5.35	
5.71	Phosphate
6.20	
6.30	
6.59	
6.81	
7.06	
7.21	
7.27	
7.40	
7.86	Tris - hydrochloric acid
8.04	

All buffer solutions prepared to be 0.1M and of constant ionic strength (by addition of sodium chloride if necessary) unless otherwise indicated.

Table 2.2

Buffer systems used for p-toluidine solutions.

pH	Buffer system used
4.60	Acetate
5.10	Acetate
5.39	Acetate
5.71	Phosphate
6.08	Phosphate
6.40	Phosphate
6.58	Phosphate
6.80	Phosphate
6.00	p-Toluidine - hydrochloric acid
6.58	p-Toluidine - hydrochloric acid
7.10	Tris - hydrochloric acid
8.32	Tris - hydrochloric acid

All buffer solutions prepared to be 0.5M and of constant ionic strength (by addition of sodium chloride if necessary) unless otherwise indicated.

Polyethylene membrane

"Alkathene"[1] polyethylene (grade XJF 127, thickness 6 mil) which has been used throughout this work, with the exception of part of one set of experiments in which the effect of thickness has been examined (section 2.8), has a number average molecular weight of 28,000-32,000 calculated from measurements of the osmotic pressure of solution in Xylene at 85°.[2] This polyethylene has a nominal density of 0.922 at 23°[3] and at room temperature the degree of crystallinity is in the range of 55-70%[4]. Up to the highest temperature used in this work (40.2°) the degree of crystallinity of the polyethylene is unlikely to alter (Hunter and Oakes, 1945). "Alkathene" XJF 127 has a melt flow index of 3.0, the process by which this is determined being described by the manufacturers as follows:[5]

> "The apparatus is essentially an extrusion plastometer with an orifice 0.315 in (8.1 mm) long and 0.0825 in (2.08 mm) diameter operated at 190° (374°F) under a pressure of 43.2 lbs per sq in (3.0 Kg per sq cm) maintained by a dead weight load on the molten polyethylene. The weight of the material extruded in grammes in ten minutes is the melt flow index of sample."

The melting point of "Alkathene" XJF is 109°.[6] The polyethylene was received in the form of a large rolled sheet.

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[1] Trademark of Imperial Chemical Industries Limited by whom the polyethylene donated.

[2,3,4,5] "Alkathene Brand of Polyethylene", Part 2 published by Imperial Chemical Industries Limited, Plastics Division, Welwyn Garden City, Herts., England (no date given) - pages 10, 6, 8, and 6 respectively.

[6] "Alkathene" Grade XJF 127 Technical Data Sheet issued by Imperial Chemical Industries of Australia and New Zealand, Melbourne 1966.

2.2 Analytical methods

Most of the substances used in the permeation rate determinations obeyed the Beer Lambert Law at their wavelength of maximum absorption. This wavelength was determined initially on a Unicam SP800 recording spectrophotometer and more accurately on a Hitachi Perkin Elmer 139 manual UV visible spectrophotometer.

The wavelengths used are shown in Table 2.3 together with the extinction coefficients of the substances used.

The concentration of unknown solutions and of the amount of solute permeated was determined by measurement of the optical density at the wavelength given in Table 2.3 (after appropriate dilution where necessary) on the Hitachi Perkin Elmer 139 UV visible spectrophotometer and reference to the appropriate Beer Lambert Law plot. The amount of solute which had permeated was calculated taking into account the amount of solute removed in previous samples. An example of the calculation is shown in Appendix 1.

Since the ultraviolet spectra of substances which ionise in solution vary according to the pH of the solution (Ewing, 1960) it was necessary to examine the spectra of o-nitrophenol and p-toluidine over a range of pH.

Solutions of o-nitrophenol exhibited an isosbestic point at 371.5 nm (as can be seen in Figure 2.1). Figure 2.2 is a plot of optical density of o-nitrophenol solutions against concentration at pH 2.35 and pH 12.41. All concentration determinations were carried out at this wavelength since the Beer Lambert Law was obeyed at this wavelength.

Table 2.3

Wavelengths of maximum absorbance for substances used.

	λ_{max} nm	Extinction coefficient $\left(E^{1\%}_{1cm}\right)$
Acetophenone	245	1050
Anisaldehyde	284.5	1330
Anisole	217	550
Benzaldehyde	249	1250
2,4-Dichlorophenol	285	135
p-Methyl acetophenone	256	1020
Nitrobenzene	267	780
o-Nitrophenol	371.5*	130
p-Tolualdehyde	260	1310
p-Toluidine	287†	141[1]
		131[2]
		126[3]
		115[4]
		83[5]
		50[6]
		29[7]
	269[8]	20

* isosbestic point

† all pH's used except pH 4.60

1 pH 8.32 and 7.10

2 pH 6.80

3 pH 6.40

4 pH 6.00

5 pH 5.71

6 pH 5.39

7 pH 5.08

8 pH 4.60

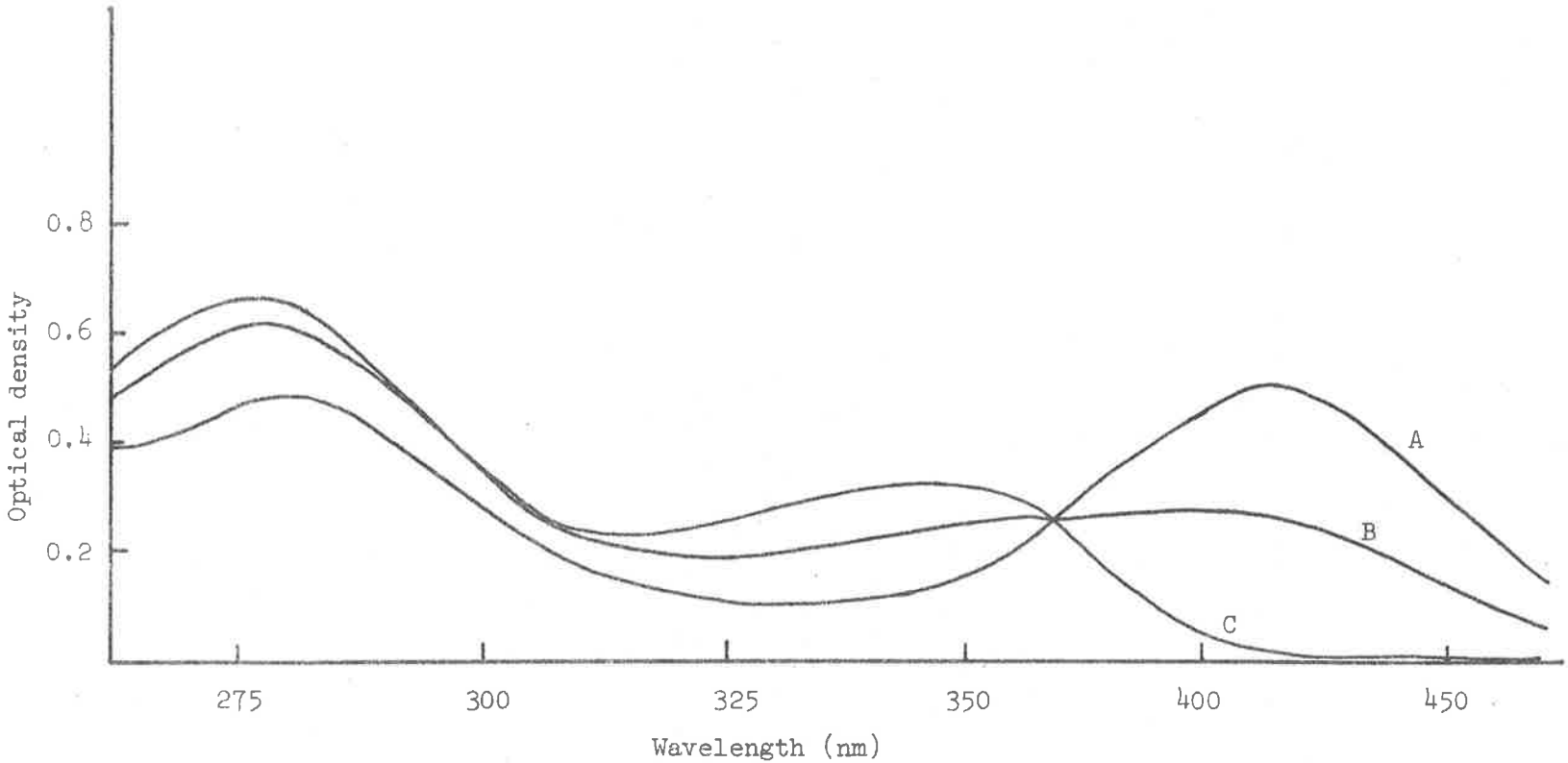

Figure 2.1 Absorption spectra of o-nitrophenol in aqueous solution at three pH's.

A. pH 12.41 (in approx. 0.1N sodium hydroxide)
B. pH 7.03 (in phosphate buffer)
C. pH 4.24 (in acetate buffer)

Concentration of all solutions: 1.44×10^{-4}M.

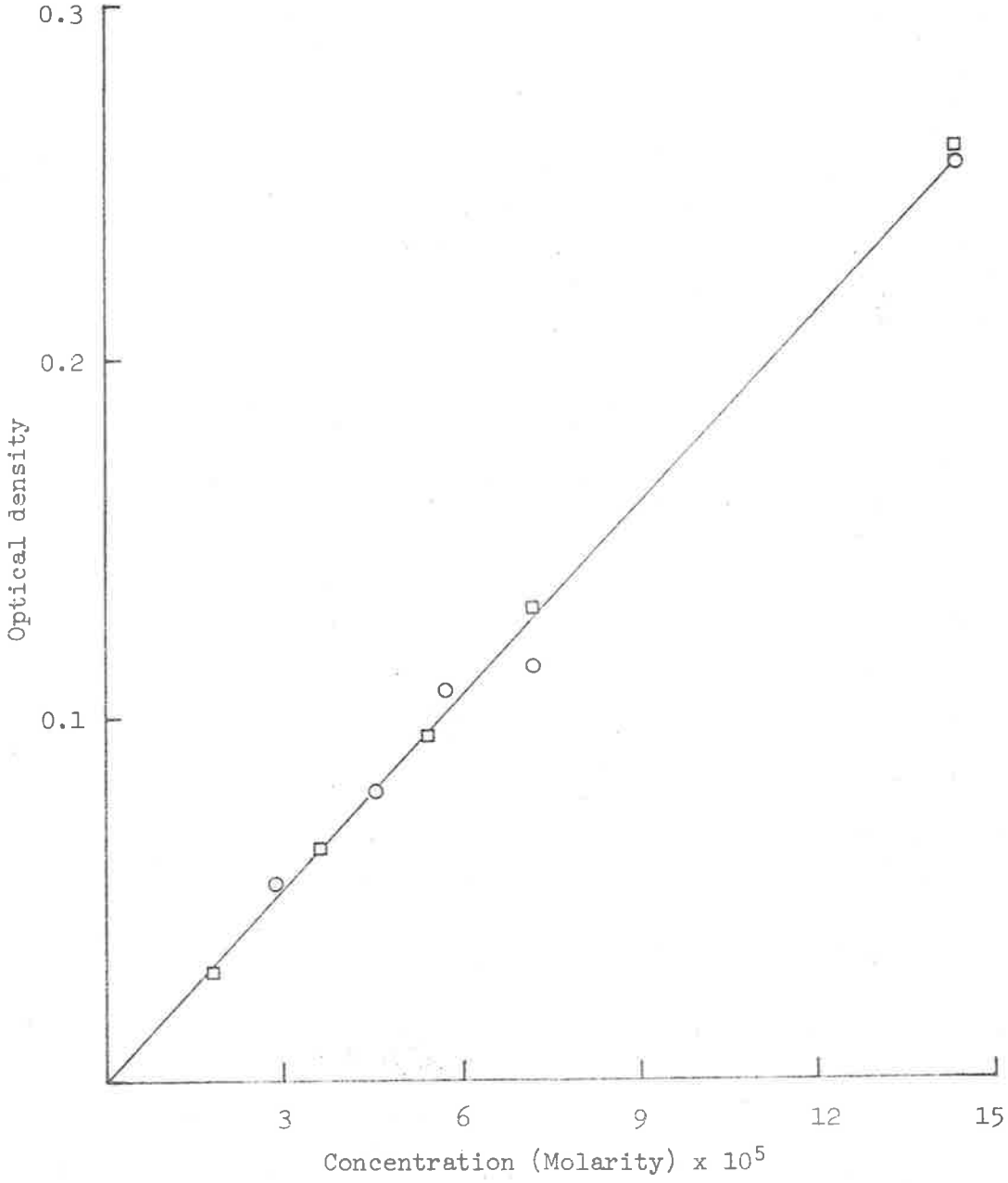

Figure 2.2 Optical density of aqueous solutions of o-nitrophenol at λ = 371.5 nm

○ pH 2.35 in hydrochloric acid (approx. 0.1N)

□ pH 12.41 in sodium hydroxide (approx. 0.1N)

Solutions of p-toluidine did not exhibit an isosbestic point (Figure 2.3) and a separate plot of optical density against concentration was drawn at λ = 287 nm for pH's between 5.08 and 8.32 and λ = 269 nm for pH 4.60. These plots were linear (Figure 2.4) and were used to determine concentration at the appropriate pH. Qualitative tests for acetate phosphate and ammonium ions (section 2.4) were carried out as described by Vogel (1954).

2.3 Heat stability of the substances used.

The stability of all substances used was determined by heating an aqueous solution of the substance in a glass ampoule at a selected temperature (not less than the maximum temperature to be used for permeation rate measurement) for a selected time.

The results of these experiments are shown in Table 2.4.

2.4 Determination of the permeation rates.

Permeation rates were determined using specially constructed glass cells (Figure 2.5). Each compartment of the cell consisted of a Quickfit QF 35 flange joint, the remote end of which had been sealed. Each compartment of the cell had a volume of approximately 90 ml and was fitted with a side arm which could be closed by a ground glass stopper, which could be held in position by springs attached to hooks on the stopper and on the side arm. At the flange end of each side of the cell metal brackets, each consisting of three parts, were placed behind the flange and completely around the glass part of the cell. The two compartments of the cell were clamped together by means of these

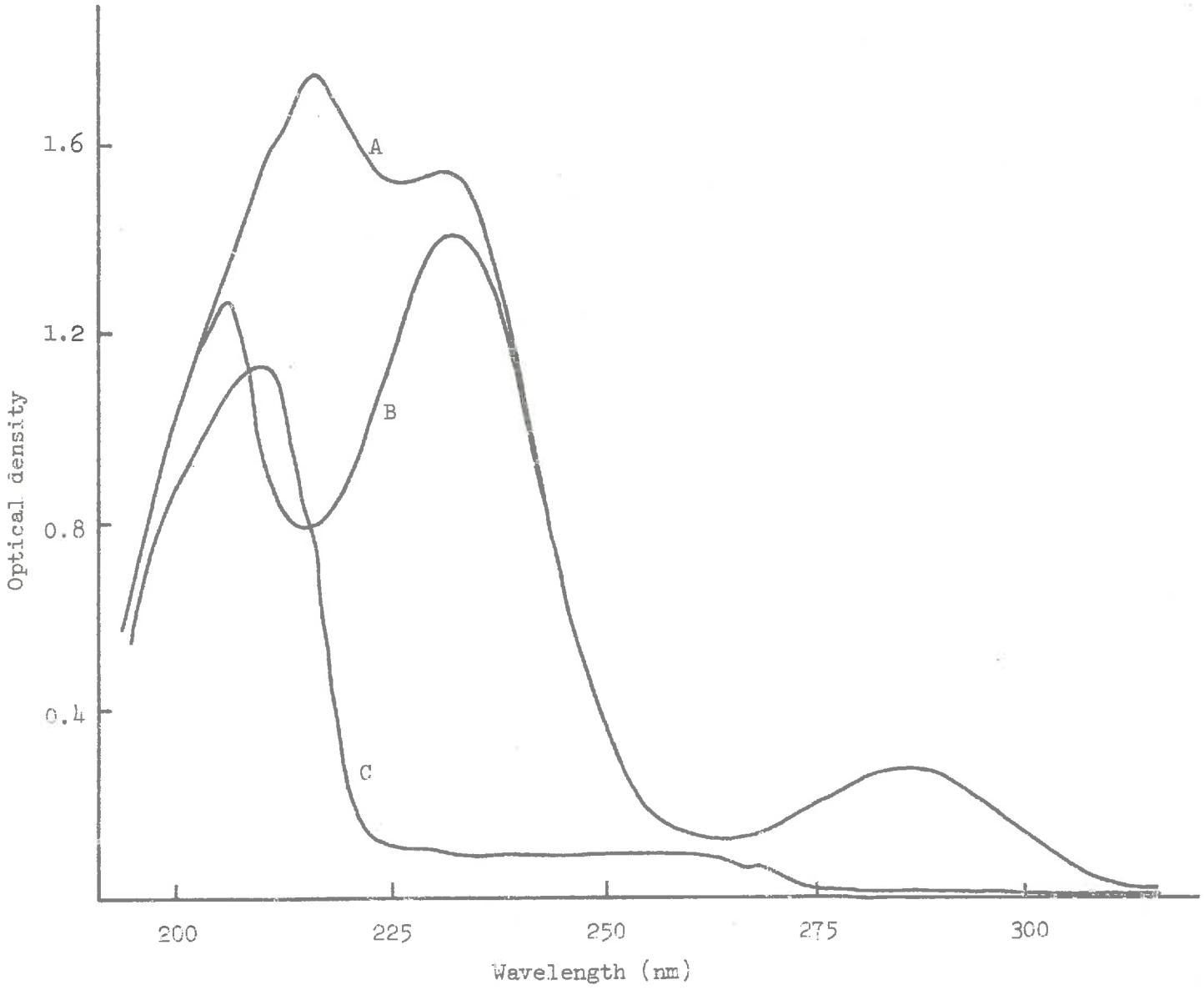

Figure 2.3 Absorption spectra of p-toluidine in aqueous solution at three pH's.
A. pH 13.00 (in approx. 0.1N sodium hydroxide)
B. pH 7.10 (in tris hydrochloric acid buffer)
C. pH 2.01 (in approx. 0.1N hydrochloric acid)
Concentration of all solutions: 1.3×10^{-4} M

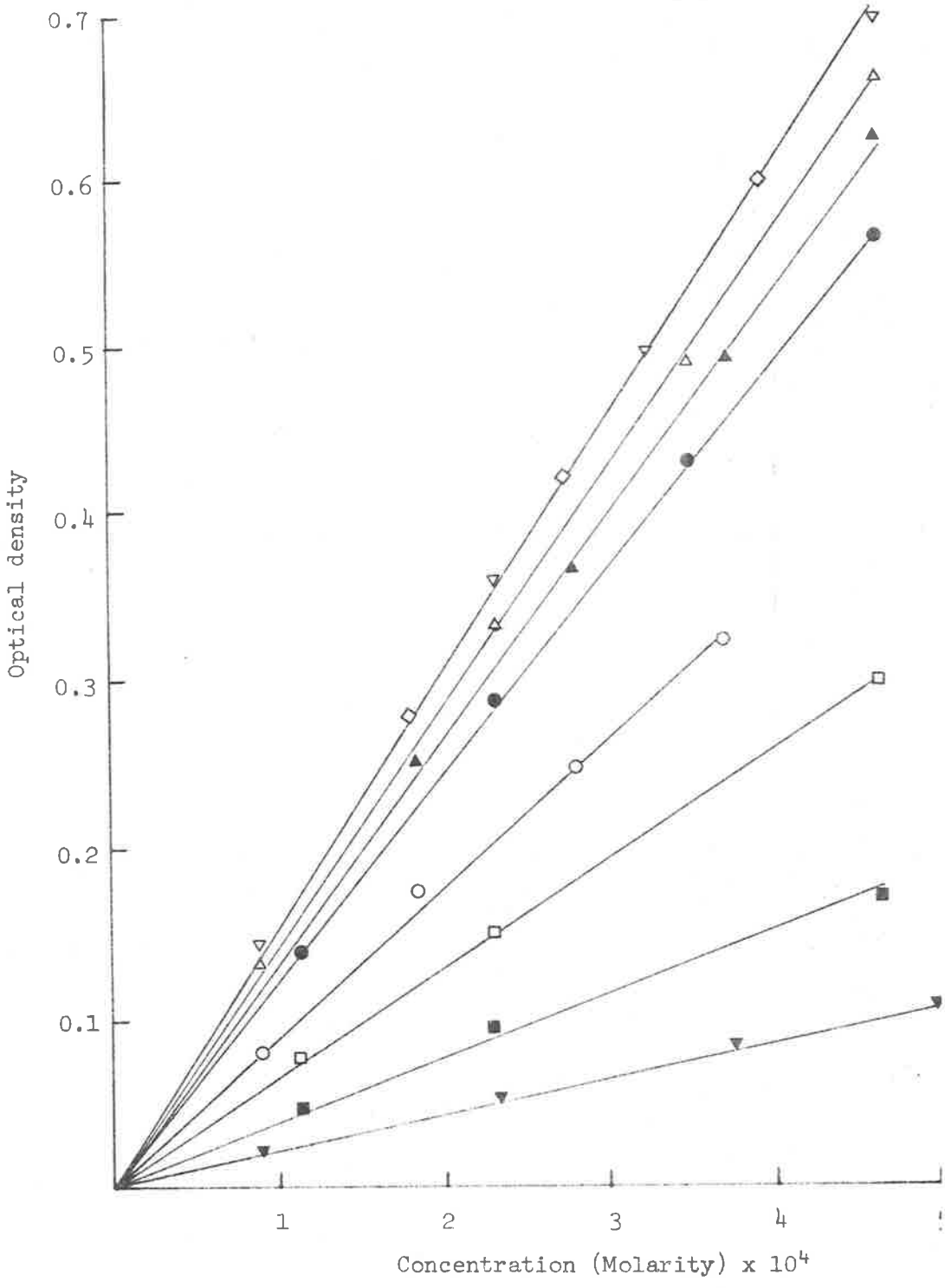

Figure 2.4 Optical density of aqueous solutions of p-toluidine at two wavelengths and a selection of pH's. Details of buffer solutions in Table 2.2.

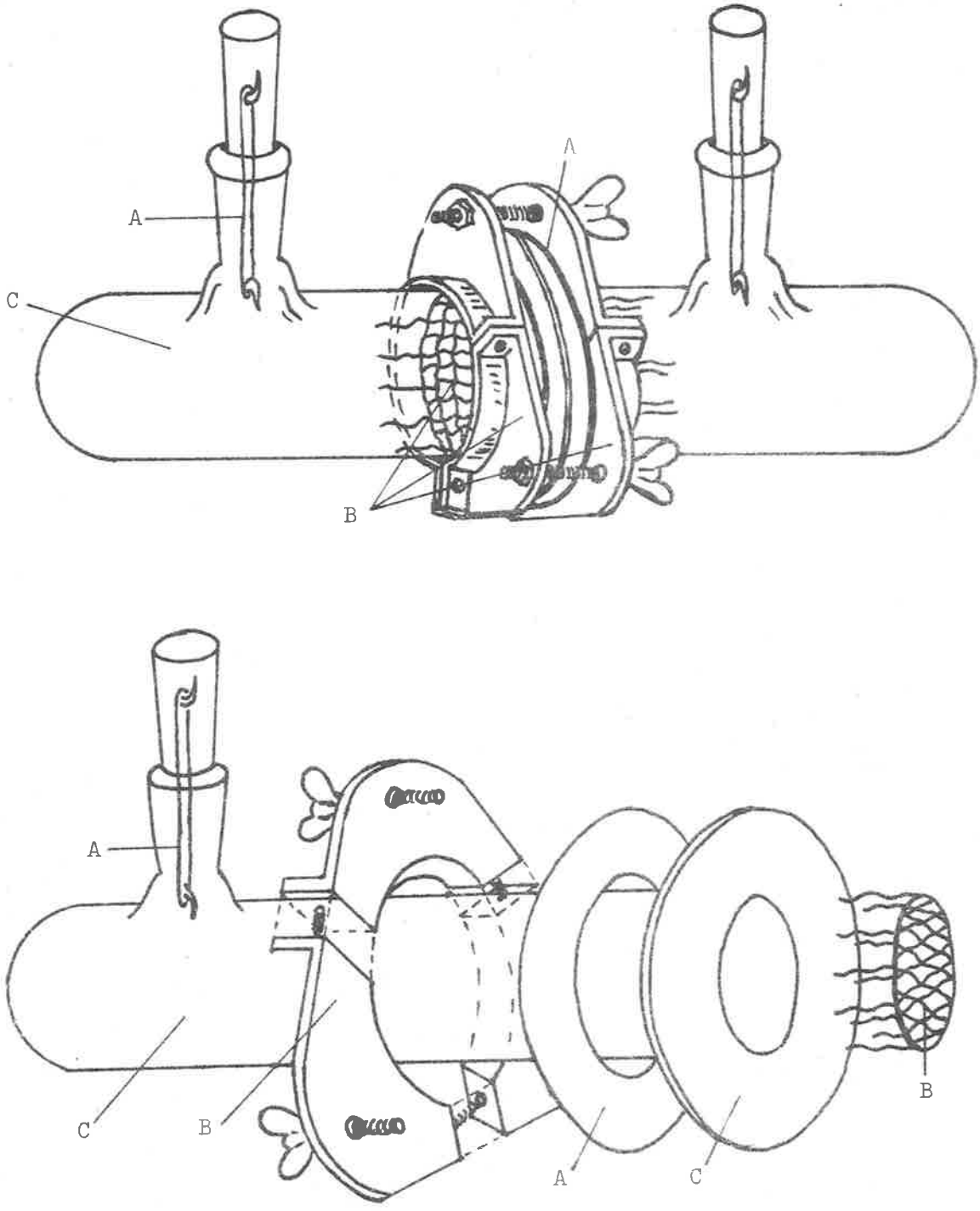

Figure 2.5 Diagrammatic representation of permeation cell.
A: rubber B: metal C: glass

Table 2.4

Stability of substances to heat.

Solute		Temperature	Time of heating (hours)	Optical Density*	
				Before heating	After heating
Acetophenone		48°	6.50	0.453	0.450
Anisaldehyde		48°	5.00	0.254	0.253
Anisole		62°	23.00	0.260	0.260
Benzaldehyde		48°	6.50	0.208	0.209
2,4-Dichlorophenol		42°	6.00	0.214	0.210
p-Methyl acetophenone		47°	5.80	0.201	0.195
Nitrobenzene		48°	5.00	0.310	0.313
o-Nitrophenol	pH 4.24	70°	6.25	0.270	0.272
	pH 8.04	70°	6.25	0.270	0.266
p-Tolualdehyde		47.5°	6.00	0.195	0.199
p-Toluidine	pH 5.39	42°	7.00	0.262	0.255
	pH 7.10	70°	6.25	0.335	0.337

* average of two ampoules after appropriate dilution (same dilution was used before and after heating).

metal brackets (by the use of suitable screws) after the polyethylene had been placed in position between the two flanges. Sufficient polyethylene was used to completely cover the area of the flanges in contact and to protrude beyond the flanges when the cell was fully assembled.

A number of cells were checked for leaks by a known volume of water being placed in one compartment only (stoppered) and being left to stand (with occasional shaking) in an oven at 40° for at least 48 hours. Tested in this way all cells were found to be leakproof and were therefore considered to be satisfactory. The area of membrane available for permeation was 9.625 cm^2.

Permeation rates were measured mostly in duplicate, sometimes in triplicate, in the cells described above in a water bath, which was fitted with a horizontal revolving shaft rotated (from a motor outside the bath) at 19 RPM. Temperature in the bath was controlled by a Jumo thermometer and relay GKT150[1]. Concentrations of all solutions were determined by the methods described in section 2.2. Rotation of the cells in the bath ensured adequate agitation of the water in the bath and therefore accurate control of temperature. The dialysis cells were attached to the shaft by means of screws and wing nuts on the metal brackets, which were used to hold the cell compartments together. The cells were held in the bath in a horizontal position.

Experiments were carried out using either "dry" or "saturated" membranes. In the experiments in which "dry" membranes were used the

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[1] Obtained from Southern Controls Pty Ltd, Mile End South, Adelaide.

polyethylene was cut to the required size and lightly wiped free of dust on each side and placed in position in the cell. Before the two compartments of the cell were clamped into position a stainless steel grid (16 mesh) was placed on each side of the cell close to the end at which the membrane was to be placed. This grid was held in position in such a way that it was unable to move during the actual experiment. The empty cell (with membrane and grid in position) was rotated in the water bath at the required temperature for at least two hours before commencement. At time zero known volumes of solution (of known concentration) and solvent (both previously equilibrated to the required temperature) were poured into the left and right sides of the cell respectively (subsequently referred to as "solution" and "solvent" sides). A number of glass beads (diameter 1/8 inch) were placed in each compartment of the cell before the sample ports were stoppered. The beads moved around in the cell as the cell revolved and kept the contents agitated. The beads were prevented from coming into contact with the membrane by the grid. The motor was switched on. At a suitable time the motor was stopped and a sample of the solution on the "solvent" side removed and its concentration determined. The volume removed for sampling was displaced by the addition of further glass beads to the cell so as to ensure that the membrane remained fully "submerged" throughout. The total time for which the motor was stopped for sampling never exceeded 1.5 minutes.

In the experiments using "saturated" membranes the polyethylene was cut to size and lightly dusted and placed in position in the cell. The fully assembled cell (containing membrane, grid and glass beads) was then placed in the water bath and brought to temperature. Known

volumes of solution and solvent were then placed in the cell and the side arms stoppered. The motor was switched on and the membrane left in contact with the "solution" and "solvent" for at least 24 hours. Not less than 45 minutes before time zero the "concentrated solution" and "solvent" were replaced in the respective compartments by "fresh" equilibrated "solution" and "solvent". At time zero the solution on the "solvent" side was removed; that side of the cell rinsed (as rapidly as possible) three times with glass distilled water and a known volume of solvent, previously heated to the temperature of the bath was placed in the "solvent" compartment. A sample of the solution on the "solution" side of the cell was removed for concentration determination as soon as possible after the filling of the "solvent" side. The volume removed was displaced by glass beads and the side arm stoppered. The motor was then switched on and the procedure described above for "dry" membranes followed.

The permeability of the membranes to buffer salts, to glycerine and to methyl cellulose was checked as follows: a solution of the buffer salt or viscosity producing agent being considered was placed on one side of each of five fully prepared cells (i.e. membrane and grids in position) and water on the other side. The cells were rotated in the water baths described above at 45° for two days. After this time the contents of the side of the cells which originally contained the water only were collected together and in the case of the buffer salts tested qualitatively for the appropriate ion. In the case of the glycerine and methyl cellulose, the viscosity of the collected solutions was determined. The polyethylene was found to be impermeable to all of these substances.

2.5 Validity of the experimental method

Once it was established that the cell did not leak and that the membrane was impermeable to buffer salts, glycerine and methyl cellulose, a series of experiments was carried out to examine the variations of the permeation rate between cells and the variation between different pieces of the polyethylene. The solute chosen for this part of the work was acetophenone because this substance had been found to be stable to heat (section 2.3) and because preliminary work had shown the permeation rate of this substance to be suitable for this particular part of the work. This substance had also been used in a previous investigation of permeation through a polyethylene membrane (Gonzales, Nematollahi, Guess and Autian, 1967).

This work was carried out as follows: Four cells were chosen at random and a membrane, cut from a randomly chosen position on the sheet of polyethylene, placed in each. The permeation rate of the acetophenone was then determined by the method described above for dry membranes for each of the cells on the same day. The procedure was repeated four times using a different "dry" membrane in each cell each time. Permeation rates obtained in different cells on the same day and in the same cell using different membranes are summarised in Table 2.5. It is assumed that there is no significant variation in the permeation rate in any one cell between runs when the same membrane is used (section 3.2.1).

An analysis of variance shows that there is no significant difference in the permeation rate between cells nor is there any significant difference between the rates in any one cell when different

Table 2.5

Permeation Rate, in different cells on the same day and in individual cells on different days, of acetophenone, initial concentration 9.36×10^{-3}M, at 40.2°. Rate in mg$(10^2$ minutes$)^{-1}$.

Cell number	Membrane number				
	1	2	3	4	5
1	0.650	0.640	0.685	0.590	0.640
2	0.590	0.610	0.635	0.623	0.550
3	0.610	0.660	0.600	0.590	0.580
4	0.585	0.635	0.610	0.570	0.612

membranes are used (Appendix 2). The permeation rate for the twenty determinations shown in Table 2.5 is 0.6132 ± 0.0316 mg $(10^2$ minutes$)^{-1}$.

A series of experiments was carried out to investigate the effect of varying volumes on each side of the cell and the effect of the presence of the grids and their distances from the membrane on the permeation rate.

The effect of the volume on the "solvent" side of the cell on the permeation rate of nitrobenzene is shown in Figure 2.6.

The effect of the volume on the "solution" side of the cell on permeation rate of the same substance is shown in Figure 2.7. In all permeation rate determinations a volume of not less than 75 ml and not more than 95 ml was used on both the "solution" and "solvent" sides. It has been assumed from the data of Figures 2.6 and 2.7 that the permeation rate is independent of the volume on either side of the cell. The effect of the volumes on each side of the cell is illustrated by the data given in Appendix 1. Similar results have been obtained throughout the work - i.e. the permeation rate is independent of the volume used.

The effect of the presence of the grids and their distance from the membrane on the permeation rate of acetophenone is shown in Table 2.6.

From the results and observations reported above it seems reasonable to conclude that the apparatus is suitable for the study of permeation rates through polyethylene and that the results obtained in any of the cells can be directly compared.

Table 2.6

Effect of the presence of grids and their distance from the membrane on the permeation rate of acetophenone, initial concentration 1.62×10^{-2}M at 40.2°.

Distance of grid from membrane (cms)		Permeation rate mg $(10^2 \text{minutes})^{-1}$
Solution side	Solvent side	
0	0	1.17
1	1	1.18
1	2	1.22
1	3	1.11
2	1	1.18
2	2	1.16
2	3	1.17
3	1	1.18
3	2	1.19
3	3	1.14

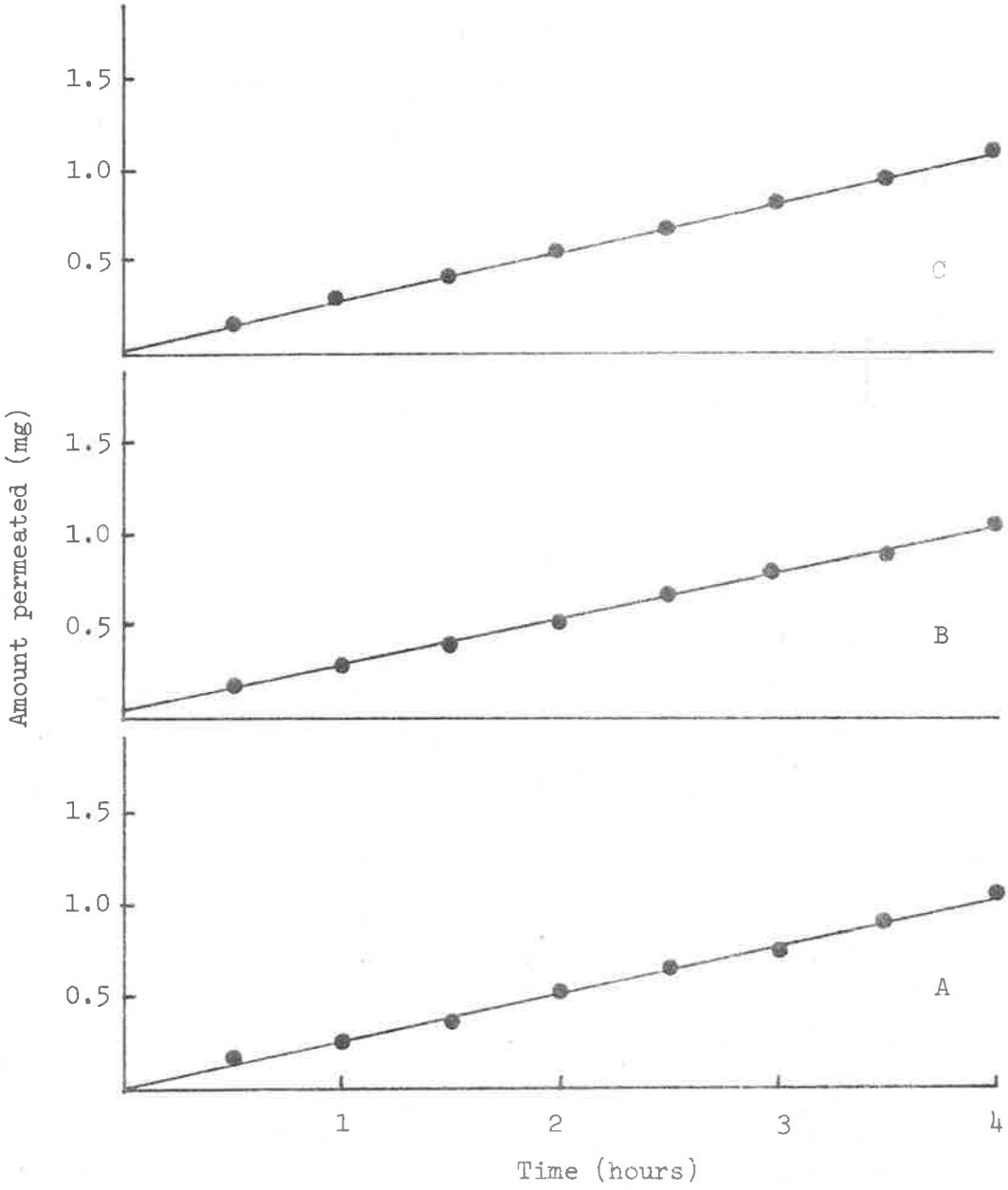

Figure 2.6 Effect of volume on the "solvent" side of the cell on the permeation rate of nitrobenzene through "saturated polyethylene membrane 6 mil. thick at 30.6°.
Initial concentration: 5.12×10^{-3}M.
A. 79.0 ml. Rate 0.433 mg $(10^2$ minutes$)^{-1}$
B. 83.5 ml. Rate 0.429 mg $(10^2$ minutes$)^{-1}$
C. 87.0 ml. Rate 0.433 mg $(10^2$ minutes$)^{-1}$

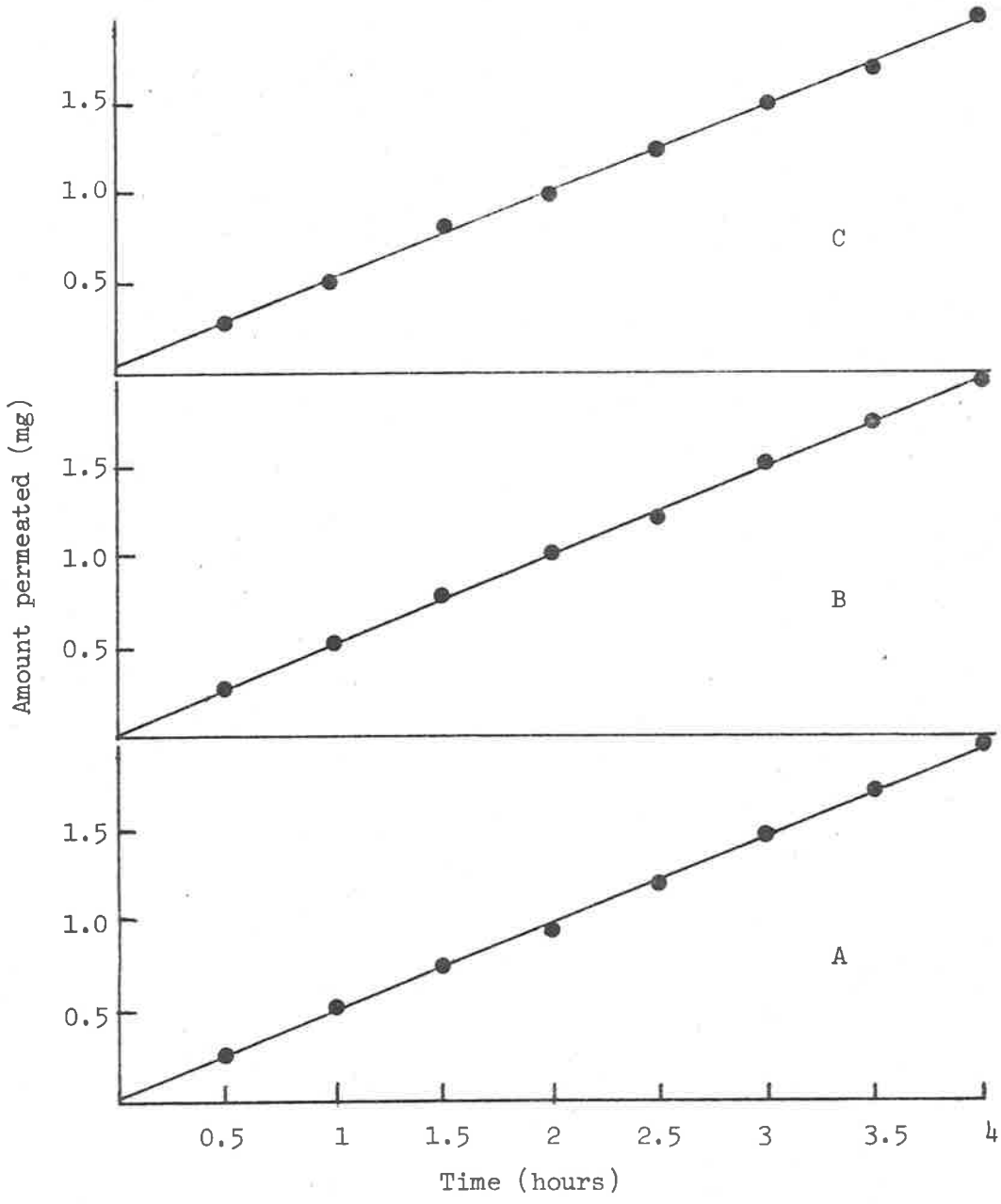

Figure 2.7 Effect of volume on the solution side of the cell on the permeation rate of nitrobenzene through "saturated" polyethylene membrane 6 ml. thick at 35.2°.
Initial concentration: 5.98×10^{-3}M

A. 78.5 ml. Rate 0.821 mg $(10^2$ minutes$)^{-1}$
B. 50.0 ml. Rate 0.825 mg $(10^2$ minutes$)^{-1}$
C. 90.0 ml. Rate 0.825 mg $(10^2$ minutes$)^{-1}$

2.6 Other experiments

Experiments were carried out to investigate the effect of the age of the membrane, of the concentration of the solute, of the temperature of the system, its pH (and ionic strength), its viscosity and the effect of the thickness of the membrane on the permeation rates of a variety of solutes.

2.7 Viscosity

Viscosity was determined on a Brookfield RVT viscometer using spindle No.1 at a speed of 50 RPM.

2.8 Membrane thickness

The thickness of the membrane was measured prior to each experiment as follows: The membrane to be used was cut to the required size and then at least six measurements of the thickness were made (each at a different position) by use of a micrometer screw gauge.

2.9 Sorption

Sorption experiments were carried out (in duplicate) at 24.4° as follows: A piece of polyethylene was cut to approximately the size used in the permeation rate measurements and placed into a 500 ml ground glass stoppered conical flask. An accurately known volume of appropriate solution (previously heated to temperature) was then poured into the flask. The flask was stoppered and placed in a shaking device in a thermostated water bath. The shaking device had a stroke of 2.5 cms and covered this distance 120 times each minute. The level of

the water in the bath exceeded that in the flask at all times. After seven days the shaking device was stopped and the concentration of the solution determined as described above.

2.10 Solubility

Solubilities of the substances in water were determined as follows: For liquids - an excess of the liquid was added to a known volume of water in a 500 ml ground glass stoppered conical flask. The flask was placed in a shaking device in a water bath thermostated at 24.4° and was shaken at 120 strokes of 2.5 cms per minute for at least one week. At the end of this time the flask was removed from the bath and the contents transferred to a separating funnel. After allowing the two layers to separate, the aqueous layer was run off and its concentration determined by the method described previously.

For solids - an excess of solid was added to a known volume of water in a 500 ml ground glass stoppered conical flask and the flask shaken as described above. After a suitable time the excess solid was removed from the suspension by filtration and the concentration of the filtrate determined by the method described previously.

2.11 Partition coefficients

Hexane water partition coefficients were determined (in triplicate) as follows: ten ml of distilled hexane (previously saturated with water) and 10 ml of the appropriate solution (prepared in water previously saturated with hexane) were pipetted into a 100 ml ground glass stoppered test tube. The tube was stoppered and

placed in the shaking device described above (thermostated at 24.4°). The test tubes were shaken overnight and on the next day the aqueous and oily layers were separated and the concentration of the aqueous layer determined by the method described previously and the hexane water partition coefficient calculated. Equal volumes of the aqueous and oily layers were then returned to the test tube, more solute added and the system shaken as before and the partition coefficients determined again. In all cases the partition coefficient values were consistent with those obtained previously.

3. PERMEATION RATES

3.1 Introduction

3.2 Factors affecting the permeation rate

3.2.1 Age of membrane

3.2.2 Concentration and temperature

(a) Saturated membranes

(b) Dry membranes

3.2.3 pH

3.2.4 Viscosity and polarity

3.2.5 Thickness of the membrane.

3.1 Introduction

In the present work the permeation rate is considered to be the rate at which the permeating solution emerges from the membrane after the membrane has become saturated and the diffusion rate to be the rate at which the solute moves through the membrane in the period before the membrane is saturated.

Diagrammatically the diffusion and permeation processes can be represented as shown in Figure 3.1.

The permeation and diffusion rates are not necessarily the same and are often related by the expression

$$P = D \times S \quad * \qquad (3.1)$$

(for example Gonzales and others, 1967). This expression appears to have been developed from the following expression proposed by Barrer (1939) for the permeation of a vapour through a solid membrane.

$$P' = D\sigma \frac{\Delta p}{l} \qquad (3.2)$$

The meaning of P, in current usage, is not uniform and it is therefore not always possible to compare results of different workers directly. Gonzales and others (1967) defined P as the permeability constant (PC) which is the number of mgs of solute passing through a film of 1 cm^2 surface area and 1 cm thick when the concentration gradient is 1 mg per ml. These authors expressed P mathematically as

$$P = \frac{c}{t} \cdot \frac{lv}{ca} \qquad (3.3)$$

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* see front of thesis for definition of symbols.

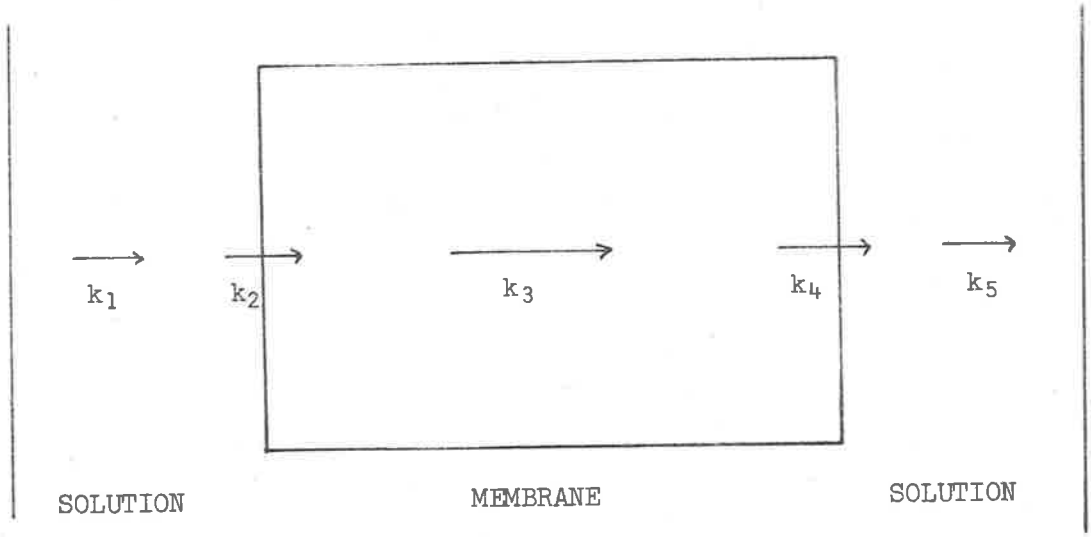

Figure 3.1 Diagrammatic representation of diffusion and permeation through polyethylene membrane.

k_1 represents diffusion of solute molecules through the solution to the membrane.

k_2 represents entry of solute molecules (from solution) into the membrane.

k_3 represents diffusion of solute molecules through the membrane.

k_4 represents exit of solute molecules from the membrane.

k_5 represents diffusion of solute molecules away from the membrane.

Kostenbauder and others (1969) define permeability as follows:

$$\frac{dm}{dt} = D' a (C_i - C_o) / X \qquad (3.4)$$

This expression is essentially the same as that of Gonzales and others (1967) because v is a constant in expression (3.3). However, the numerical value of the permeation rate may be different due to the presence of the factor v unless concentration is expressed in the same units. Both expressions assume ideal behaviour.

Other definitions of P have been used by other authors (for example Salame, 1961; Lebovits, 1966; Masoero, 1967).

The value of D in expression (3.1) has been mathematically defined by Barrer (1939) as

$$D = \frac{l^2}{6\tau} \qquad (3.5)$$

The value of S in expression (3.1) has been defined by Gonzales and others (1967) as

> "the ratio of the amount of solute in a volume of plastic over the amount in a volume of solution at equilibrium."

Permeation data is considered in this chapter as the permeation rate, which is defined for the present purposes (in the same manner as Lueck and others, 1957a,b) as the rate at which the solute molecule emerges from the membrane once a uniform concentration gradient has been established and is equal to $\frac{c}{t}$ which is determined from the slope of the linear portion of the amount permeated against time plot. Rate is expressed in this chapter as the number of mg passing through a

membrane 0.015 cm thick and 9.62 cm^2 in area in 100 minutes. These units are converted by an appropriate factor in Chapter 5 to fit the Gonzales and others (1967) definition of the permeability constant.

The diffusion rates and permeation rates being determined in the present work are quasi steady state rates rather than the steady state rates. The difference between these two situations was given in section 1.2.

Garrett and Chemburkar (1968a,b,c) who used both steady state and quasi steady state systems reported that the diffusion values found in both types of system were essentially the same.

3.2 Factors affecting the permeation rate.

3.2.1 Age of membrane

The effect of the "age" of the membrane in the cell on the permeation rates of anisole when saturated membranes are used is shown in Table 3.1. The permeation rate for the seven determinations shown in Table 3.1 is 8.957 ± 0.01 mg $(10^2$ minutes$)^{-1}$.

3.2.2 Concentration and temperature

(a) Saturated membranes

Plots of the amount of acetophenone passing from the solution side to the solvent side (i.e. permeated) against time for a series of acetophenone solutions at four temperatures are shown in Figures 3.2-3.5.* Similar plots for anisole are shown in Figures 3.6-3.9, for nitrobenzene in Figures 3.10-3.13 and for anisaldehyde at one temperature in Figure 3.14. Similar plots were made at other initial

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* Figures presented at end of section 3.2.2(b) (following page 57).

Table 3.1

Effect of "age" of membrane on permeation rate of anisole, initial concentration 1.25×10^{-2}M, at 35.2°.

"Age" of membrane (at commencement of experiment) (days)	Permeation Rate mg $(10^2$ minutes$)^{-1}$
0	8.89
1	9.00
2	9.05
5	9.08
7	9.00
9	8.78
13	8.90

concentrations for each of these substances and the results are summarised in Figures 3.15-3.18.

The general configuration of the plot of amount permeated against time for all substances, concentrations and temperatures investigated appears to approximate to a linear relationship. Similar results have been reported by Gonzales and others (1967) for a similar quasi steady state system. Provided the concentration in the "solvent" side of the cell is not allowed to exceed about 5% of the initial concentration on the "solution" side the expected decrease in permeation rate with time, due to decreased concentration gradient across the membrane, appears to be negligible and the plot can be regarded as linear. The slope of the line is the permeation rate. In any case if this rate is described (more correctly) as "initial rate" the straight line represents the tangent to a curve. It has been shown above that the quasi steady state rate is very close to the steady state rate. All future reference to permeation rate is regarded as "initial" permeation rate. It can be seen in Figures 3.15-3.18 that the permeation rate is directly proportional to initial concentration only over a limited range of concentration. The concentration at which this relationship ceases to hold is about one third of the aqueous solubility of the solute being considered and it seems reasonable to assume that in solutions of greater concentration the departure from ideal behaviour is due to the differences between concentration and activity in these solutions. When relatively dilute solutions are being considered (i.e. below one third saturation) the effect of temperature on permeation rates is conveniently summarised by the Arrhenius relationship,

$$k = Ae^{-E_a/RT} \qquad (3.6)$$

By rearrangement of expression (3.6), expression (3.7) is obtained.

$$\log k = \log A + \frac{E_a}{2.303R} \times \frac{1}{T} \qquad (3.7)$$

By plotting log k against $\frac{1}{T}$ it is possible to find E_a from the slope of the line. A plot of log k against $\frac{1}{T}$ for acetophenone, anisole and nitrobenzene is shown in Figure 3.19. The activation energies for permeation for the three substances being considered are given in Table 3.2. Gonzales and others (1967) found the activation energy for the permeation of acetophenone through polyethylene to be 17.4 K cals $mole^{-1}$.

(b) Dry membranes

Plots of the amount permeated against time for ten substances are shown in Figures 3.20-3.29, and it can be seen in these Figures that the relationship between amount permeated and time only becomes linear after the initial "lag" period. This lag is due to the time interval between when the permeating solute first enters the membrane and the steady state of flow is established (section 1.2).

The permeation rate (at each of the temperatures used) can be obtained from the slope of the linear portion of the line. Permeation rates (obtained from Figures 3.20-3.29) are given in Table 3.3.

A plot of the logarithm of the permeation rate against the reciprocal of the absolute temperature for each substance listed in Table 3.3 is shown in Figures 3.30-3.31. The activation energies

Table 3.2

Activation energies for permeation through "saturated" polyethylene membranes.

Solute	Activation energy Kcals $mole^{-1}$
Acetophenone	18.81
Anisole	13.45
Nitrobenzene	14.38

Table 3.3

Permeation rates through dry membranes for ten solutes.

Solute	Concentration (M)	Permeation Rate mg $(10^2 \text{ minutes})^{-1}$			
		24.4°	30.6°	35.2°	40.2°
Acetophenone	1×10^{-2}	0.140	0.252	0.384	0.621
Anisaldehyde	5×10^{-3}	0.041	0.077	0.118	0.188
Anisole	1.25×10^{-3}	0.180	0.252	0.352	0.510
Benzaldehyde	1×10^{-2}	0.123	0.220	0.364	0.451
2,4-Dichlorophenol	1×10^{-2}	0.181	0.422	0.821	1.150
p-Methyl acetophenone	2×10^{-3}	0.072	0.117	0.225	0.325
Nitrobenzene	2×10^{-3}	0.080	0.130	0.238	0.342
o-Nitrophenol (pH 3.81)	7.18×10^{-3}	0.350	0.506	0.734	0.922
p-Tolualdehyde	2.08×10^{-3}	0.072	0.107	0.211	0.250
p-Toluidine (pH 8.32)	2.33×10^{-2}	0.100	0.200	0.288	0.531

for permeation of the substances have been calculated from the slopes of the lines and are given in Table 3.4, along with those obtained by Gonzales and others (1967). The activation energies for permeation of acetophenone, anisole and nitrobenzene are similar to those obtained using saturated membranes (Table 3.2).

Permeation rates obtained in the present work and those obtained by Gonzales and others (1967) for acetophenone, benzaldehyde, p-methyl acetophenone and p-tolualdehyde are compared in Figures 3.32, 3.33, 3.34 and 3.35. In all of these Figures it is clear that at the one common temperature (approximately 40°) the permeation rate is very similar and for each of the solutes the activation energies for permeation can be seen to be similar in the two studies.

Lag times and diffusion coefficients (calculated by the use of expression 3.5) are given in Table 3.5.

Plots of the logarithms of the diffusion coefficient against the reciprocal of absolute temperature are shown in Figures 3.36. 3.37 and 3.38, the linear relationship comfirming the Arrhenius expression given previously. Activation energies for diffusion have been calculated from the slopes of the lines in Figures 3.36-3.38 by substitution in the Arrhenius expression and are given in Table 3.6 along with the values obtained for four of the substances by Gonzales and others (1967). The diffusion coefficients and activation energies for diffusion for four substances obtained in the work by Gonzales and others (1967) and in the present work are compared in Figures 3.39, 3.40, 3.41 and 3.42. The activation energies for diffusion are very different and can be seen for three of the four

Table 3.4

Activation energies for permeation through dry polyethylene membranes.

Solute	Activation energy (Kcals mole^{-1})	
	Present work	Gonzales and others (1967)
Acetophenone	17.49	17.4
Anisaldehyde	17.97	
Anisole	12.45	
Benzaldehyde	14.91	15.5
2,4-Dichlorophenol	22.52	
p-Methyl acetophenone	18.64	16.5
Nitrobenzene	16.18	
o-Nitrophenol	12.81	
p-Tolualdehyde	15.92	17.2
p-Toluidine	19.41	

Table 3.5

Lag times and diffusion coefficients for ten solutes.

Solute	Temperature °C	Lag time (τ) minutes	Lag time (τ) seconds	6τ seconds	Diffusion coefficient (cm^2 sec^{-1}) ($\times 10^9$)
Acetophenone	24.4	51	3060	18360	12.25
	30.6	27	1620	9720	23.14
	35.2	18	1080	6480	34.72
	40.2	15	900	5400	41.66
Anisaldehyde	24.4	46	2760	16560	13.58
	30.6	34	2040	12240	18.38
	35.2	27	1620	9720	23.14
	40.2	24	1440	8640	26.04
Anisole	24.4	30	1800	10800	20.83
	30.6	17	1020	6120	36.76
	35.2	9	540	3240	69.44
	40.2	4	240	1440	156.25
Benzaldehyde	24.4	45	2700	16200	13.88
	30.6	25	1500	9000	25.00
	35.2	17	1020	6120	36.76
	40.2	11	660	3960	56.81
2,4-Dichlorophenol	24.4	39	2340	14040	16.02
	30.6	26	1560	9360	24.03
	35.2	20	1200	7200	31.25
	40.2	13	780	4680	48.07

Table 3.5 cont.

Solute	Temperature °C	Lag time (τ) minutes	Lag time (τ) seconds	6τ seconds	Diffusion coefficient ($cm^2\ sec^{-1}$) ($\times 10^9$)
p-Methyl acetophenone	24.4	57	3420	20520	10.96
	30.6	36	2160	12960	17.36
	35.2	28	1680	10080	22.32
	40.2	15	900	5400	41.66
Nitrobenzene	24.4	44	2640	15840	14.20
	30.6	23	1380	8280	27.17
	35.2	15	900	5400	41.66
	40.2	11	660	3960	56.81
o-Nitrophenol (pH 3.81)	24.4	42	2520	15120	14.88
	30.6	24	1440	8640	26.04
	35.2	16	9600	5760	39.06
	40.2	7.5	450	2700	83.33
p-Tolualdehyde	24.4	50	3000	18000	12.50
	30.6	29	1740	10440	21.55
	35.2	23	1380	8280	27.17
	40.2	17	1020	6120	36.76
p-Toluidine (pH 8.32)	24.4	69	4140	24840	9.05
	30.6	47	2820	16920	13.29
	35.2	36	2160	12960	17.36
	40.2	22	1320	7920	28.40

Table 3.6

Activation energies for diffusion through polyethylene membranes.

Solute	Activation energy (Kcals mole)$^{-1}$	
	Present work	Gonzales and others (1967)
Acetophenone	15.14	8.05
Anisaldehyde	7.96	
Anisole	23.95	
Benzaldehyde	17.08	8.16
2,4-Dichlorophenol	12.85	
p-Methyl acetophenone	15.53	10.20
Nitrobenzene	16.73	
o-Nitrophenol	20.07	
p-Tolualdehyde	12.70	6.90
p-Toluidine	13.31	

solutes to be approximately twice as great in the present work as those reported by Gonzales and others (1967). It is suggested that this extra energy required for diffusion is due to the greater thickness of the membrane used in the present work. From the data of Table 3.6 it is apparent that more energy is required by a solute which is relatively soluble in the polyethylene to diffuse through the polyethylene than is required by a solute which is relatively insoluble in the polyethylene (see Table 4.1, particularly values for anisole and anisaldehyde).

The solutes which are the least soluble in the membrane (i.e. acetophenone and anisaldehyde) appear however to require a greater energy (of activation) for permeation than do the other solutes (except p-methyl acetophenone) which are more soluble in the membrane (Table 3.4). In this situation (i.e. permeation) the membrane is completely saturated and the energy required is essentially only that necessary to transfer a molecule from the solution to the membrane. This will be smaller in the case of solutes which are more soluble in the membrane. In diffusion the membrane is becoming saturated during the process (i.e. during the lag time) and it can be assumed that for diffusion to actually take place sufficient energy to remove individual molecules from binding sites in the polyethylene will be necessary and more energy is therefore required for the diffusion of the solutes more soluble in polyethylene.

The supposition that molecules of soluble solutes are strongly bound to the membrane is confirmed by the data of Nakano (1971), and Doluisio, Crouthamel, Tan, Swintosky and Dittert (1970). Both these

groups investigated the movement of solute molecules through membranes, the former using a dimethyl polysiloxane membrane and the latter a rat intestine, *in situ*. Both these groups plotted logarithm of the concentration remaining (on the concentrated side) against time and both found that the plot was linear only after a certain period of time had elapsed and during this time the rate of disappearance of the solute was greater than that which occurred during the subsequent steady state. The solute used by Nakano (1971) was chlorpromazine and by the other group prochlorperazine.

Doluisio and others (1970) regarded the rapid initial rate of disappearance of the solute as being due to a strong binding between the solute and the membrane. These workers found that a similar plot for salicylic acid was linear throughout and it was therefore assumed that salicylic acid was not as strongly bound to the membrane as the prochlorperazine. Herzog and Swarbrick (1971a) also found a plot of the logarithm of the concentration of salicylic acid remaining (on the concentrated side of the membrane) against time to be linear for movement through a different membrane. These workers also measured the solubility of the salicylic acid in the membrane and found it to be relatively small.

Polack and Roberts (1971) found a plot of the logarithm of concentration remaining against time for the movement of nitrobenzene and of chloroxylenol (from aqueous solution) into polyethylene containers to be of a similar configuration to that reported by Doluisio and others (1970) for the movement of prochlorperazine through rat intestine *in situ* and by Nakano (1971) for the movement of

chlorpromazine through a dimethyl polysiloxane membrane. These authors suggested that the reason for the configuration was the same as that proposed by Doluisio and others (1970) i.e. a strong binding of the solute to the membrane.

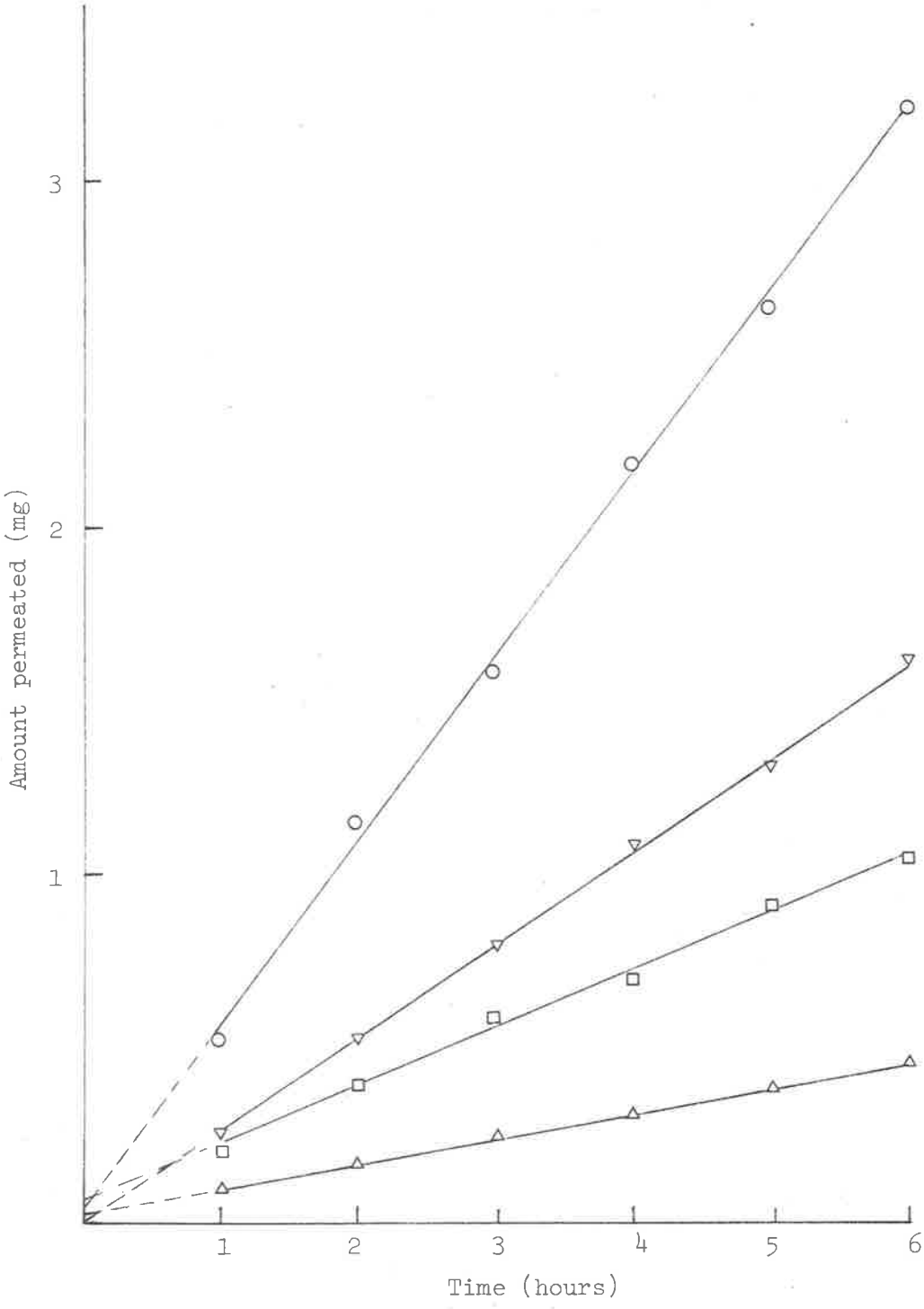

Figure 3.2 Permeation of acetophenone through "saturated" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.)

- ○ 4.08×10^{-2}M
- ▽ 2.66×10^{-2}M
- □ 1.72×10^{-2}M
- △ 0.87×10^{-2}M

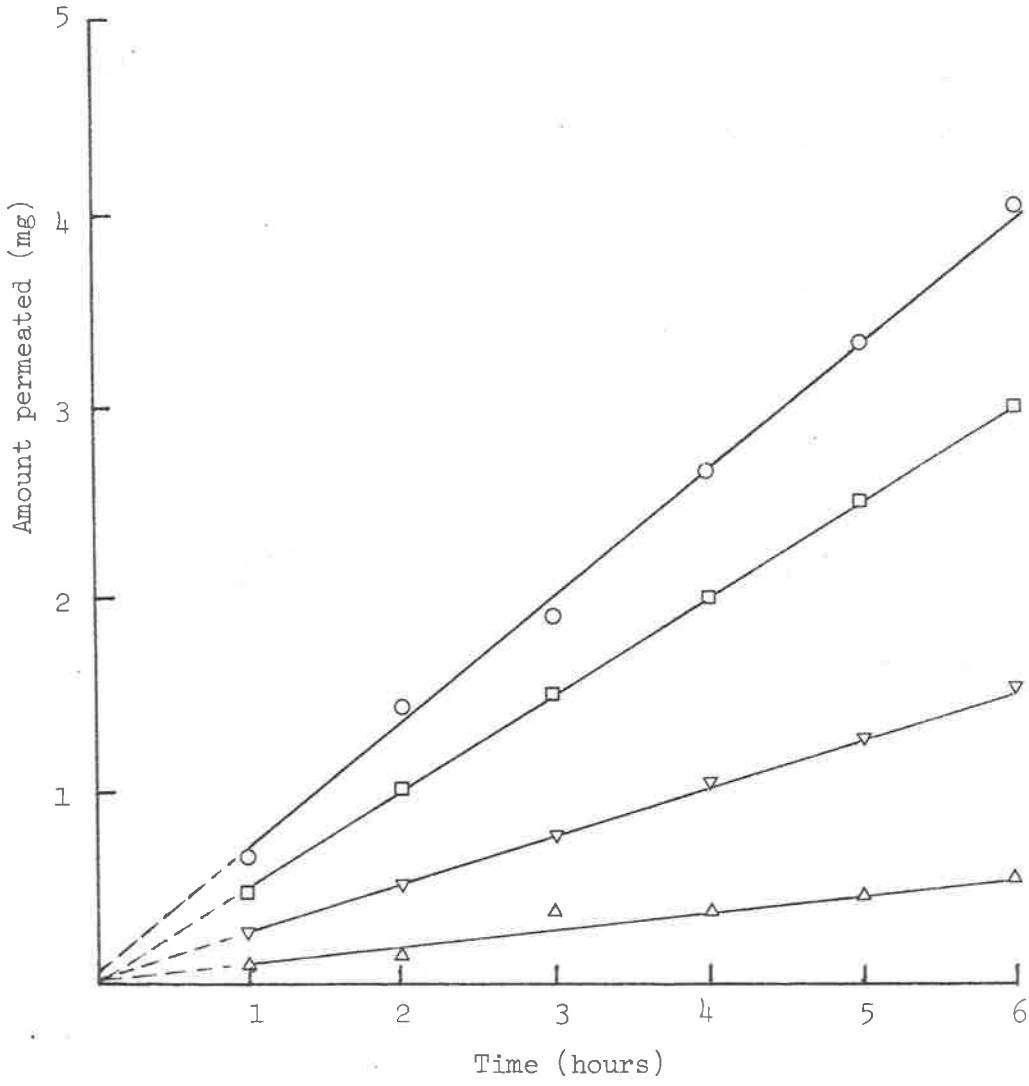

Figure 3.3 Permeation of acetophenone through "saturated" polyethylene membrane 6 mil. thick at 30.6°. (Each point represents average of measurements made in two cells.)

○ 2.79×10^{-2}M

□ 2.37×10^{-2}M

▽ 1.56×10^{-2}M

△ 0.56×10^{-2}M

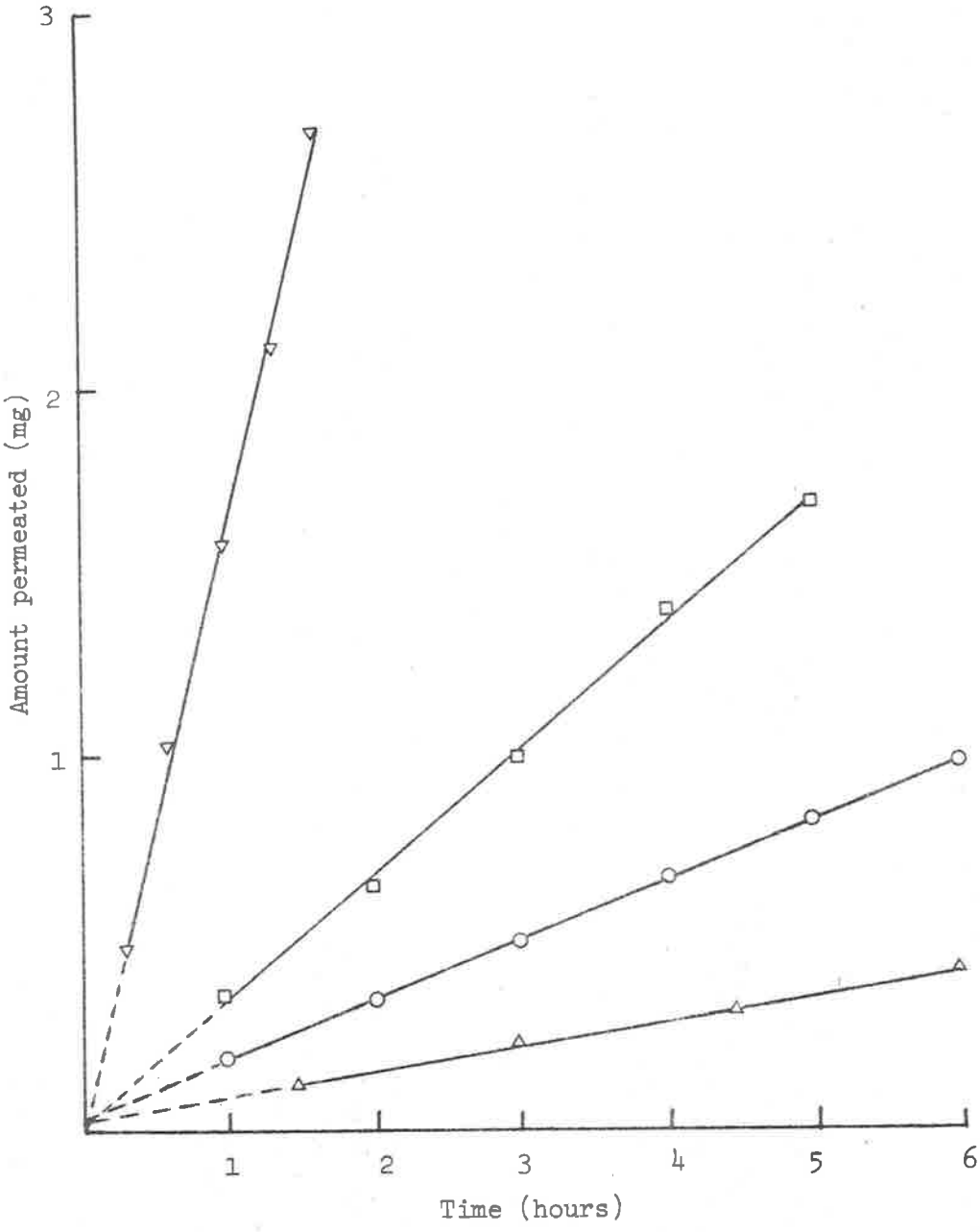

Figure 3.4 Permeation of acetophenone through "saturated" polyethylene membrane 6 mil. thick at 35.2°. (Each point represents average of measurements made in two cells.)

▽ 4.08×10^{-2}M

□ 1.25×10^{-2}M

○ 0.70×10^{-2}M

△ 0.40×10^{-2}M

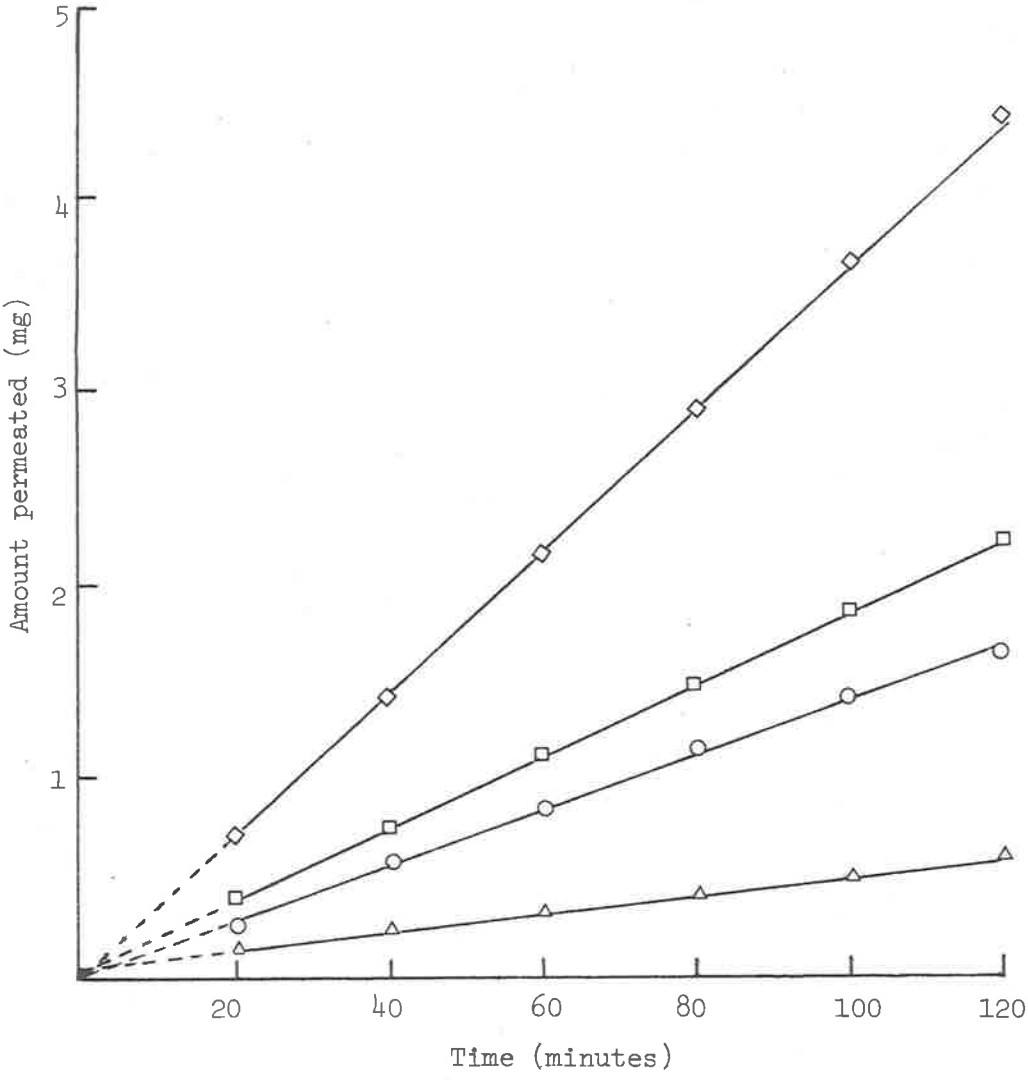

Figure 3.5 Permeation of acetophenone through "saturated" polyethylene membrane 6 mil. thick at 40.2°. (Each point represents average of measurements made in two cells.)

◇ 3.91×10^{-2}M

□ 2.25×10^{-2}M

○ 1.83×10^{-2}M

△ 0.82×10^{-2}M

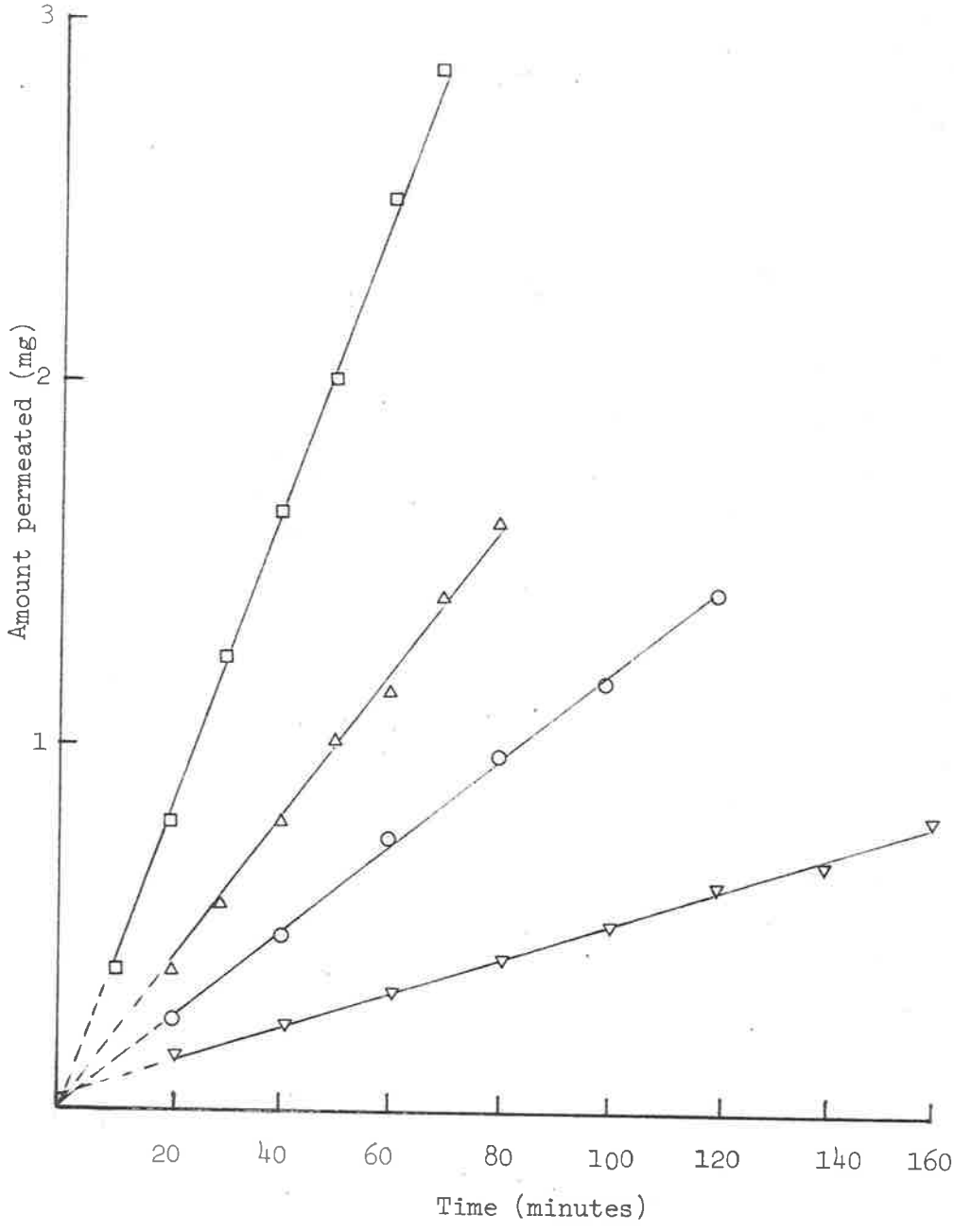

Figure 3.6 Permeation of anisole through "saturated" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.)

□ 1.19×10^{-2}M

△ 0.75×10^{-2}M

○ 0.58×10^{-2}M

▽ 0.22×10^{-2}M

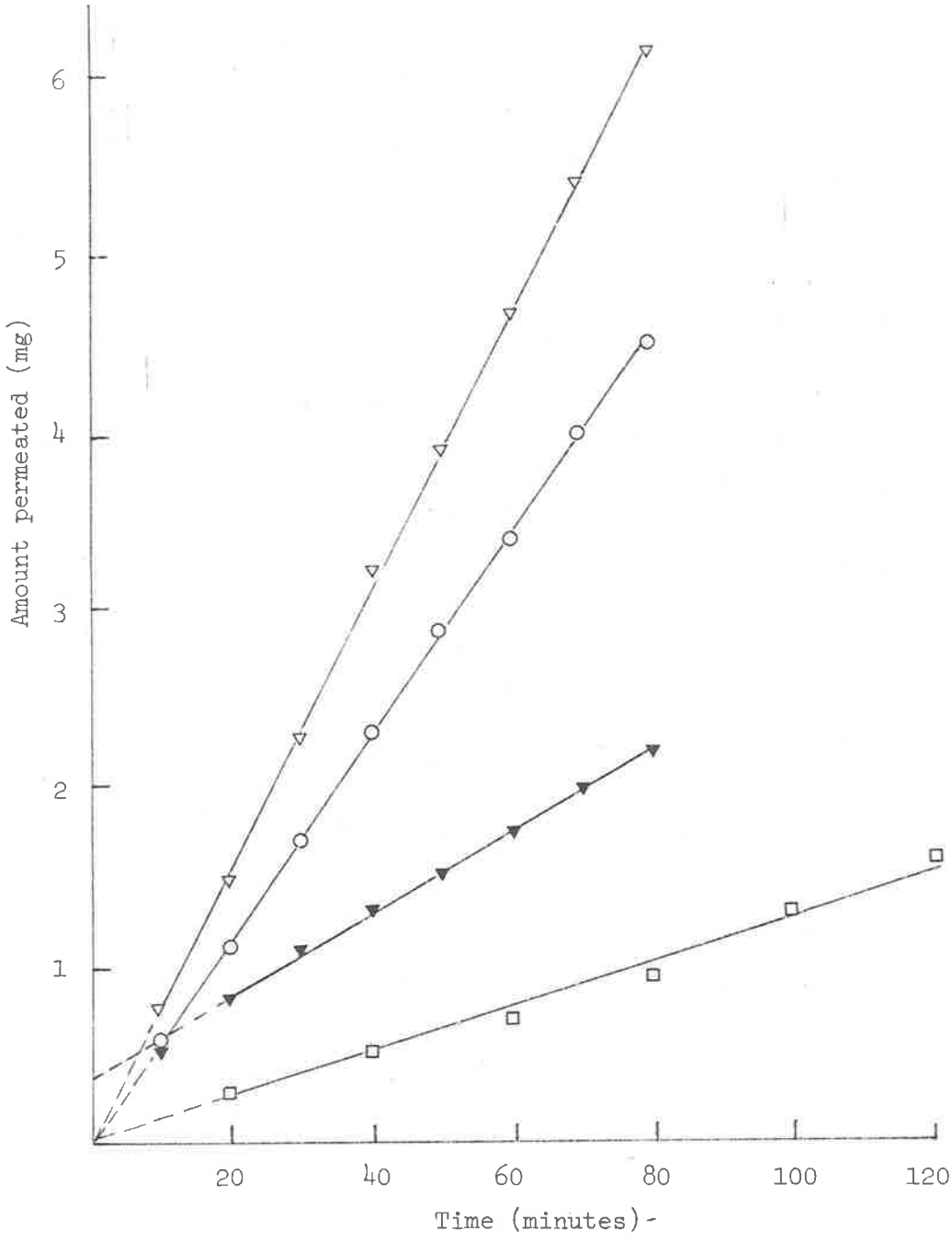

Figure 3.7 Permeation of anisole through "saturated" polyethylene membrane 6 mil. thick at 30.6°. (Each point represents average of measurements made in two cells.)

▽ 1.33×10^{-2}M

○ 1.16×10^{-2}M

▼ 0.61×10^{-2}M

□ 0.42×10^{-2}M

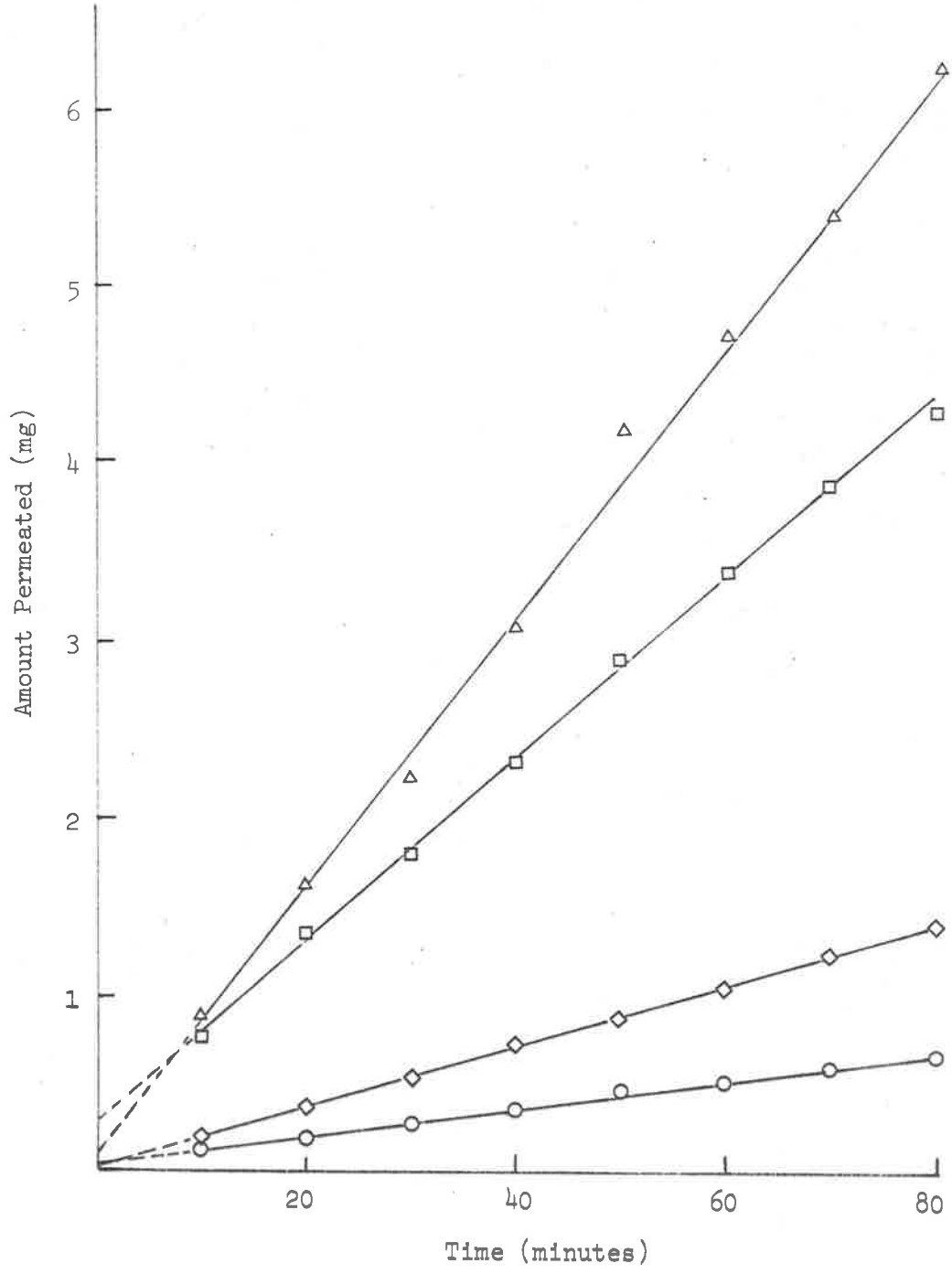

Figure 3.8 Permeation of anisole through "saturated" polyethylene membrane 6 mil. thick at 35.2°. (Each point represents average of measurements made in two cells.)

△ 1.26×10^{-2}M

□ 0.90×10^{-2}M

◇ 0.41×10^{-2}M

○ 0.21×10^{-2}M

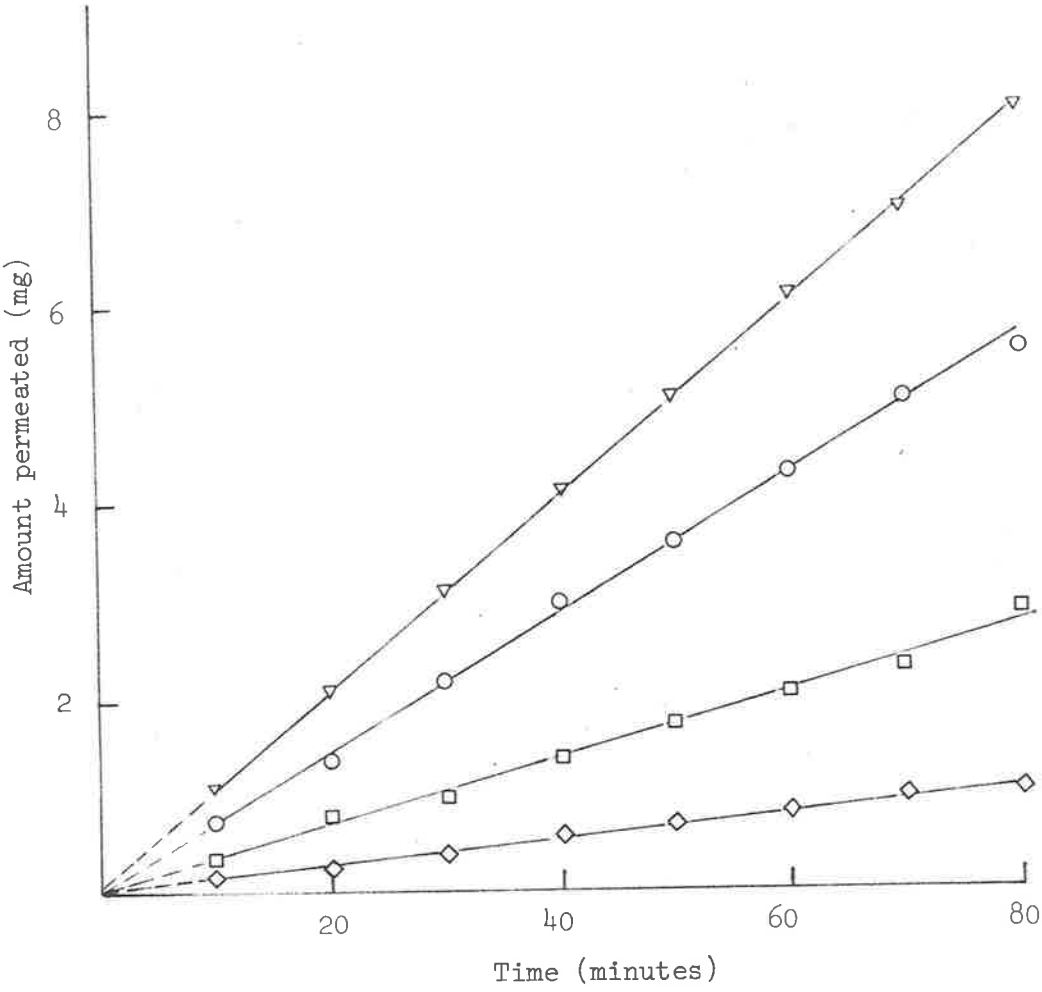

Figure 3.9 Permeation of anisole through "saturated" polyethylene membrane 6 mil. thick at 40.2°. (Each point represents average of measurements made in two cells.)

▽ 1.18×10^{-2}M

○ 0.90×10^{-2}M

□ 0.54×10^{-2}M

◇ 0.22×10^{-2}M

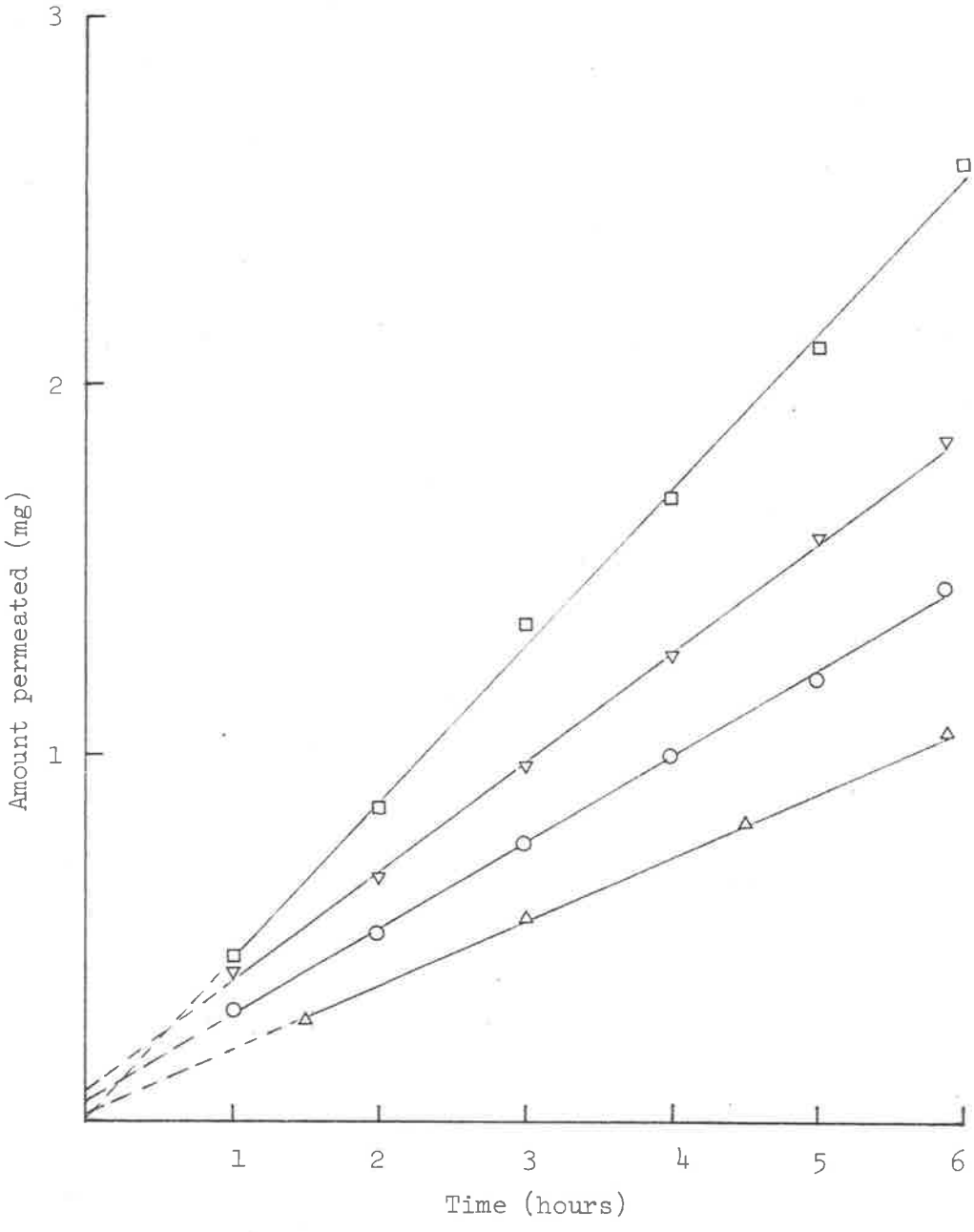

Figure 3.10 Permeation of nitrobenzene through "saturated" polyethylene membrane 6 mil. thick at 24.4°.

□ 1.06×10^{-2}M

▽ 0.86×10^{-2}M

○ 0.68×10^{-2}M

△ 0.56×10^{-2}M

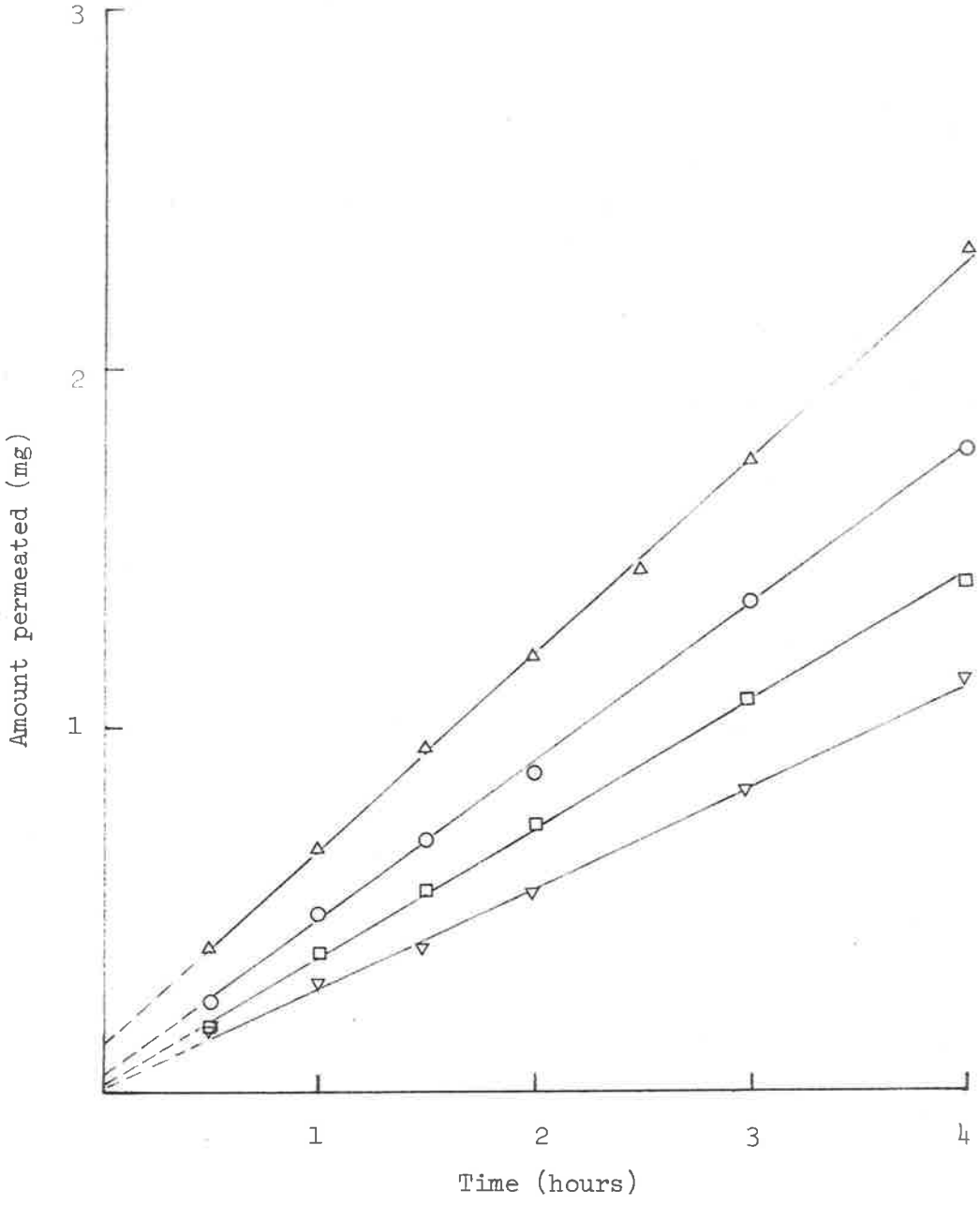

Figure 3.11 Permeation of nitrobenzene through "saturated" polyethylene membrane 6 mil. thick at 35.2°. (Each point represents average of measurements made in two cells.)

△ 0.94×10^{-2}M

○ 0.79×10^{-2}M

□ 0.66×10^{-2}M

▽ 0.51×10^{-2}M

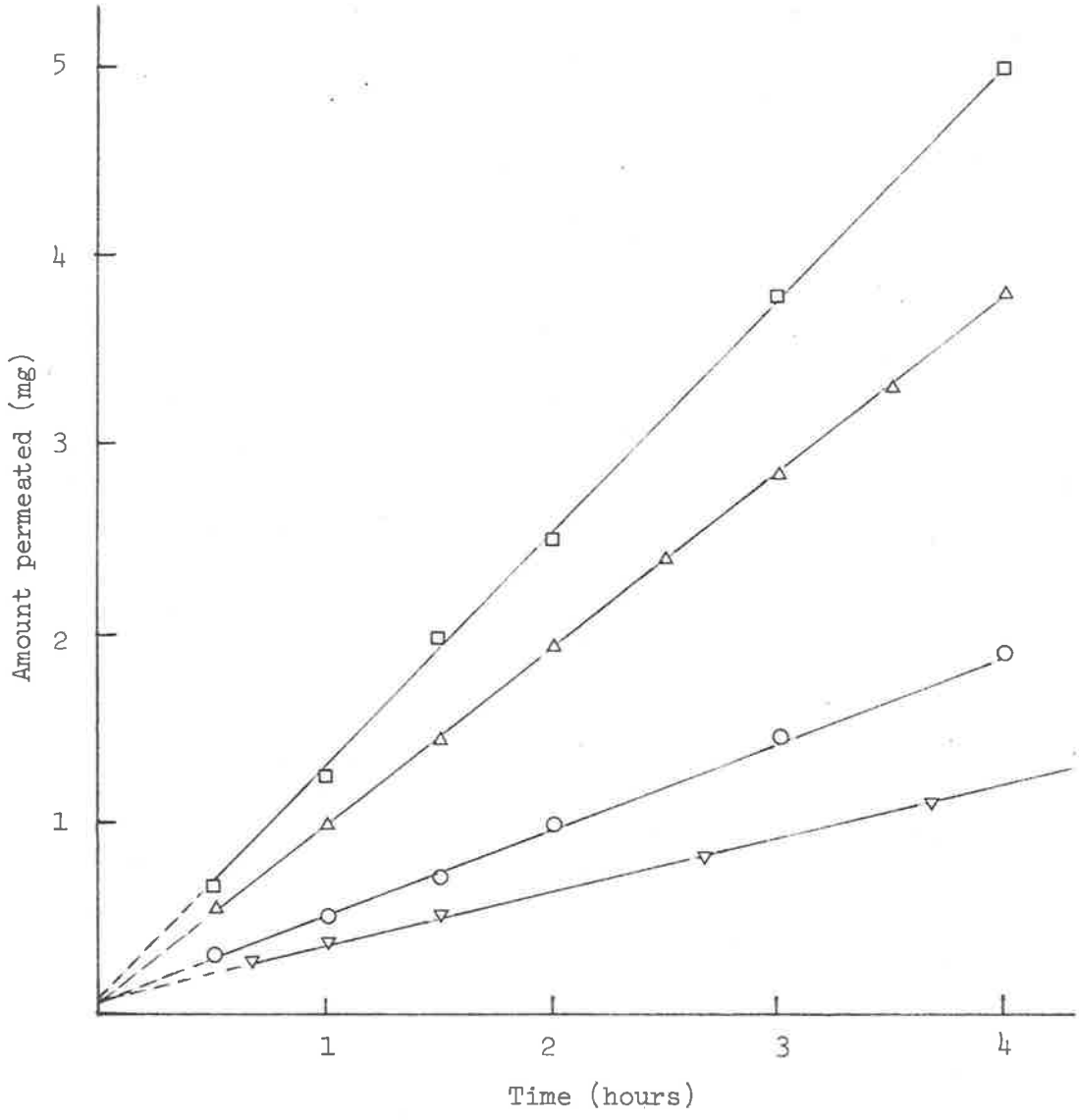

Figure 3.12 Permeation of nitrobenzene through "saturated" polyethylene membrane 6 mil. thick at 35.2°. (Each point represents average of measurements made in two cells.)

- □ 1.16×10^{-2}M
- △ 0.93×10^{-2}M
- ○ 0.59×10^{-2}M
- ▽ 0.38×10^{-2}M

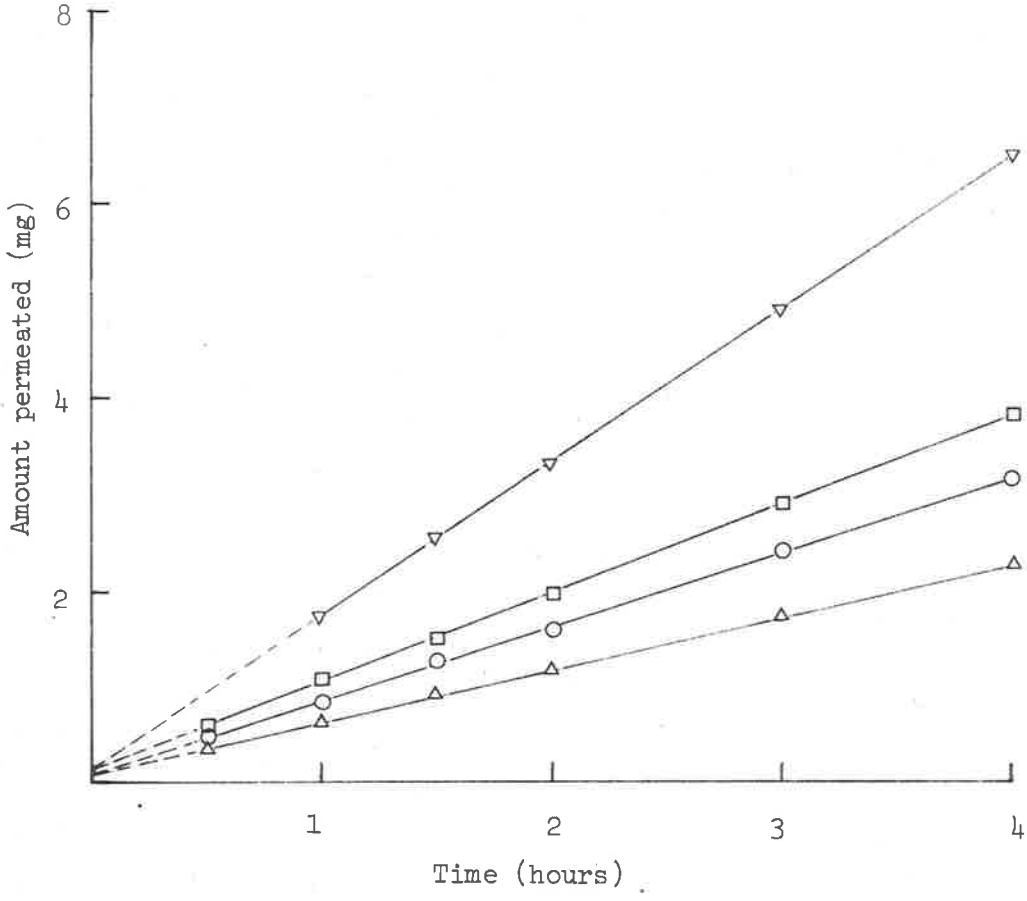

Figure 3.13 Permeation of nitrobenzene through "saturated" polyethylene membrane 6 mil. thick at 40.2°. (Each point represents average of measurements made in two cells.)

▽ 1.14×10^{-2}M

□ 0.71×10^{-2}M

○ 0.60×10^{-2}M

△ 0.48×10^{-2}M

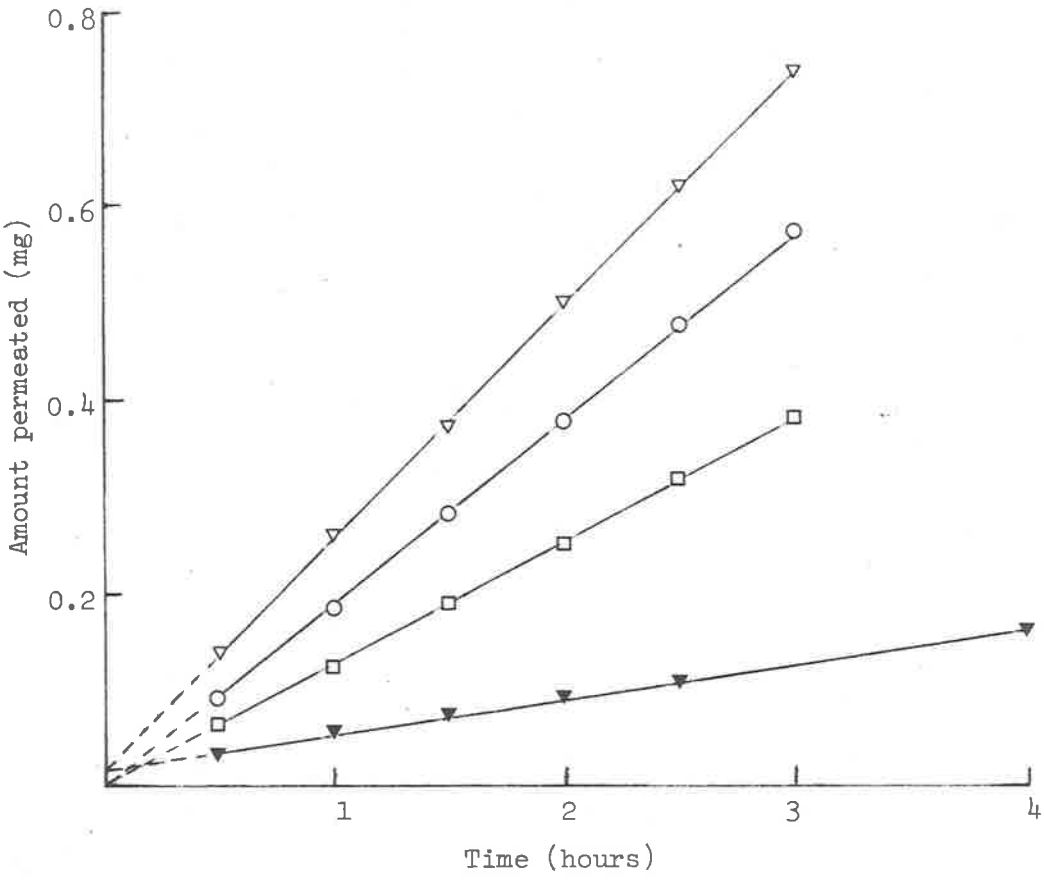

Figure 3.14 Permeation of ansialdehyde through "saturated" polyethylene membrane 6 mil. thick at 35.2°. (Each point represents average of measurements made in two cells.)

▽ 1.47×10^{-2}M

○ 1.18×10^{-2}M

□ 0.87×10^{-2}M

▼ 0.30×10^{-2}M

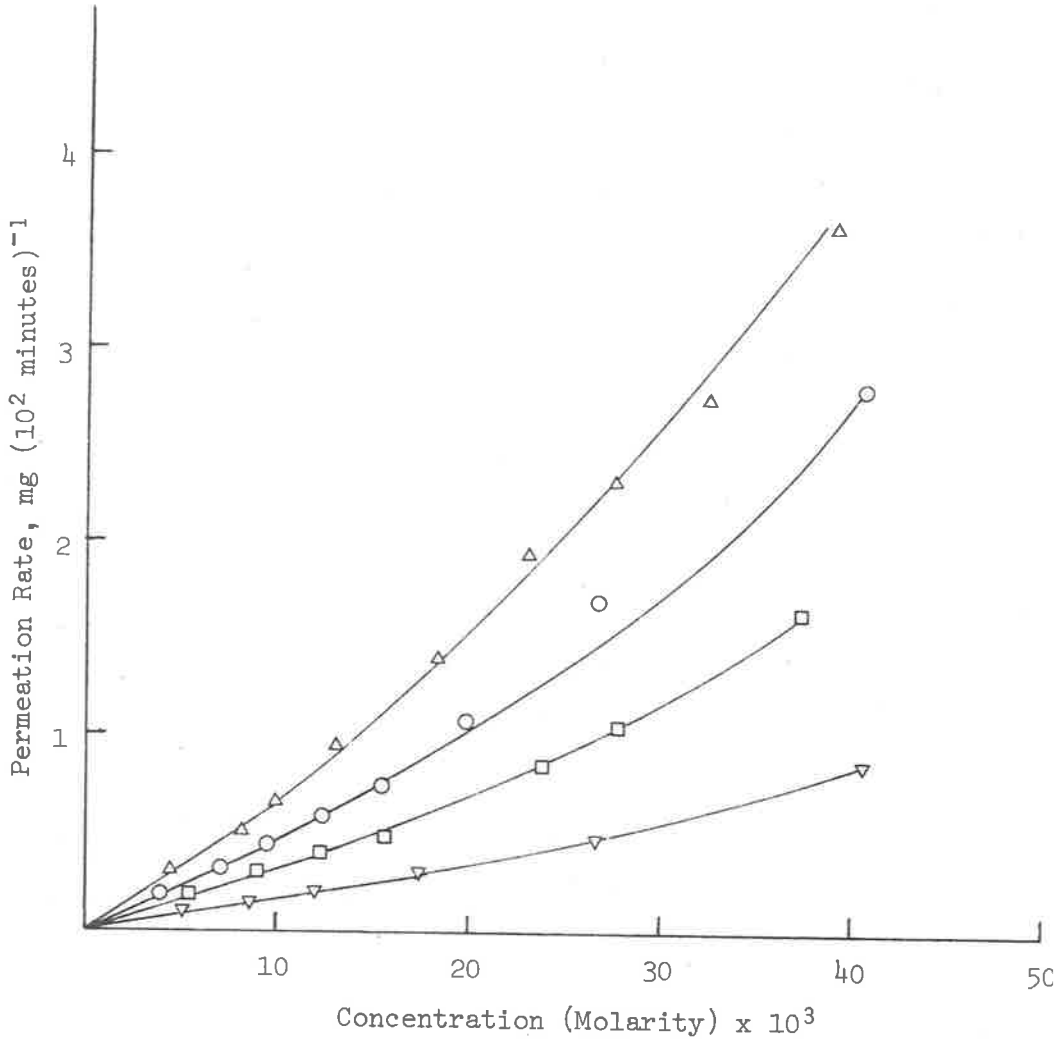

Figure 3.15 Effect of concentration on the permeation rate of acetophenone through "saturated" polyethylene membrane 6 mil. thick. (Each point represents average of measurements made in two cells.)

▽ 24.4°

□ 30.6°

○ 35.2°

△ 40.2°

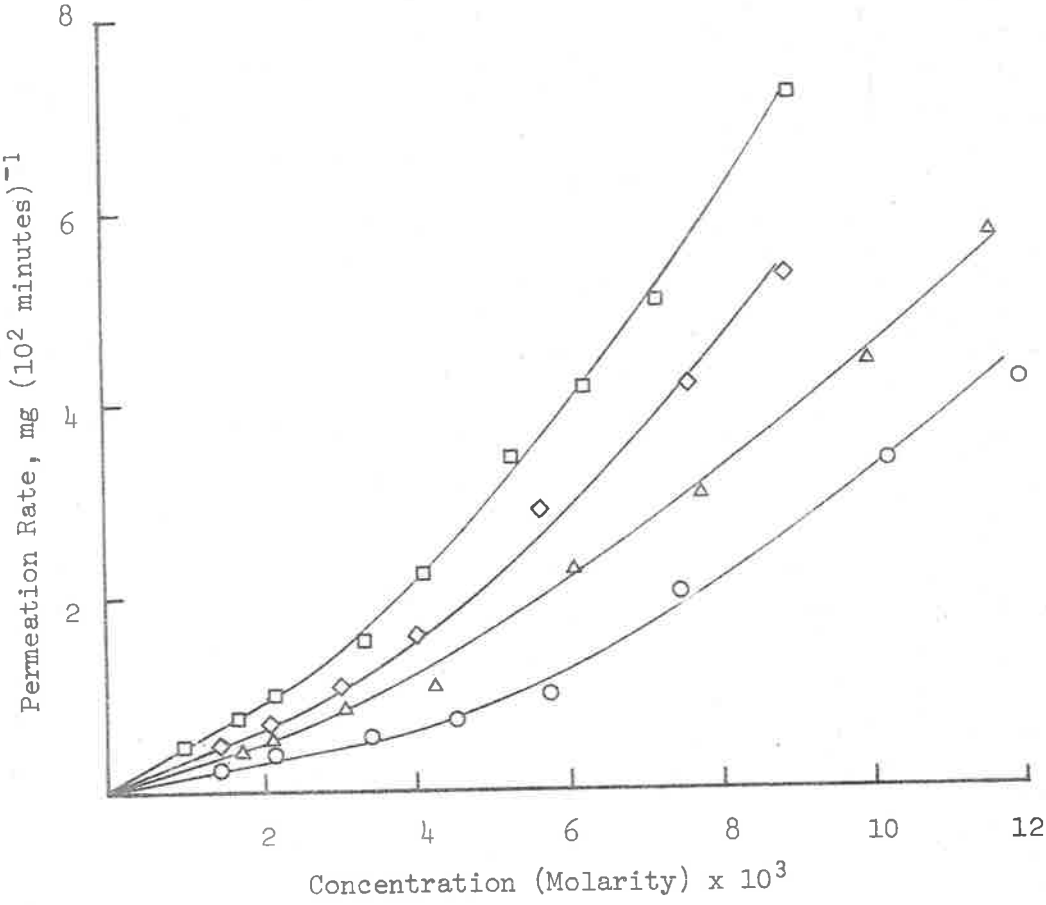

Figure 3.16 Effect of concentration on the permeation rate of anisole through "saturated" polyethylene membrane 6 mil. thick. (Each point represents average of measurements made in two cells.)

○ 24.4°

△ 30.6°

◇ 35.2°

□ 40.2°

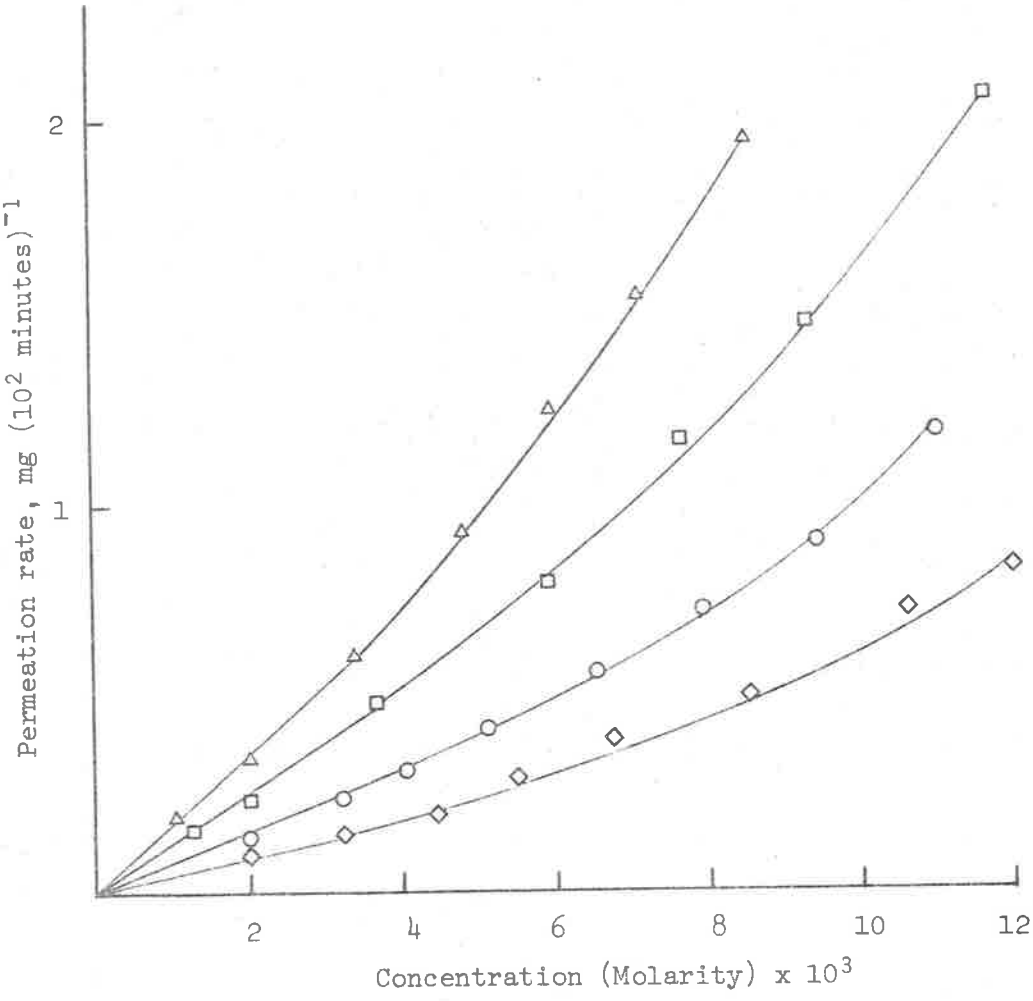

Figure 3.17 Effect of concentration on the permeation rate of nitrobenzene through "saturated: polyethylene membrane 6 mil. thick. (Each point represents average of measurements made in two cells.)

◇ 24.4°

○ 30.6°

□ 35.2°

△ 40.2°

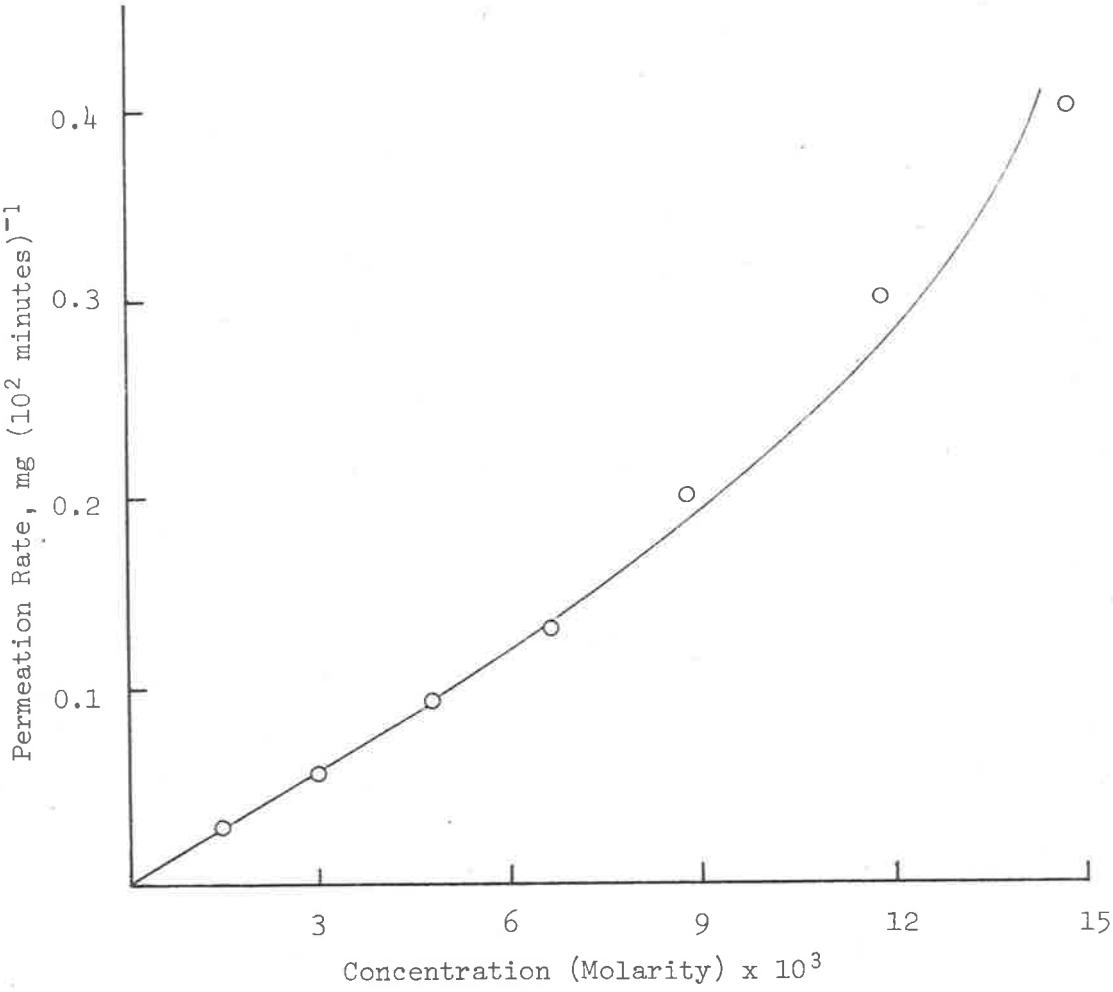

Figure 3.18 Effect of concentration on the permeation rate of anisaldehyde through "saturated" polyethylene membrane 6 mil. thick at 35.2°. (Each point represents average of measurements made in two cells.)

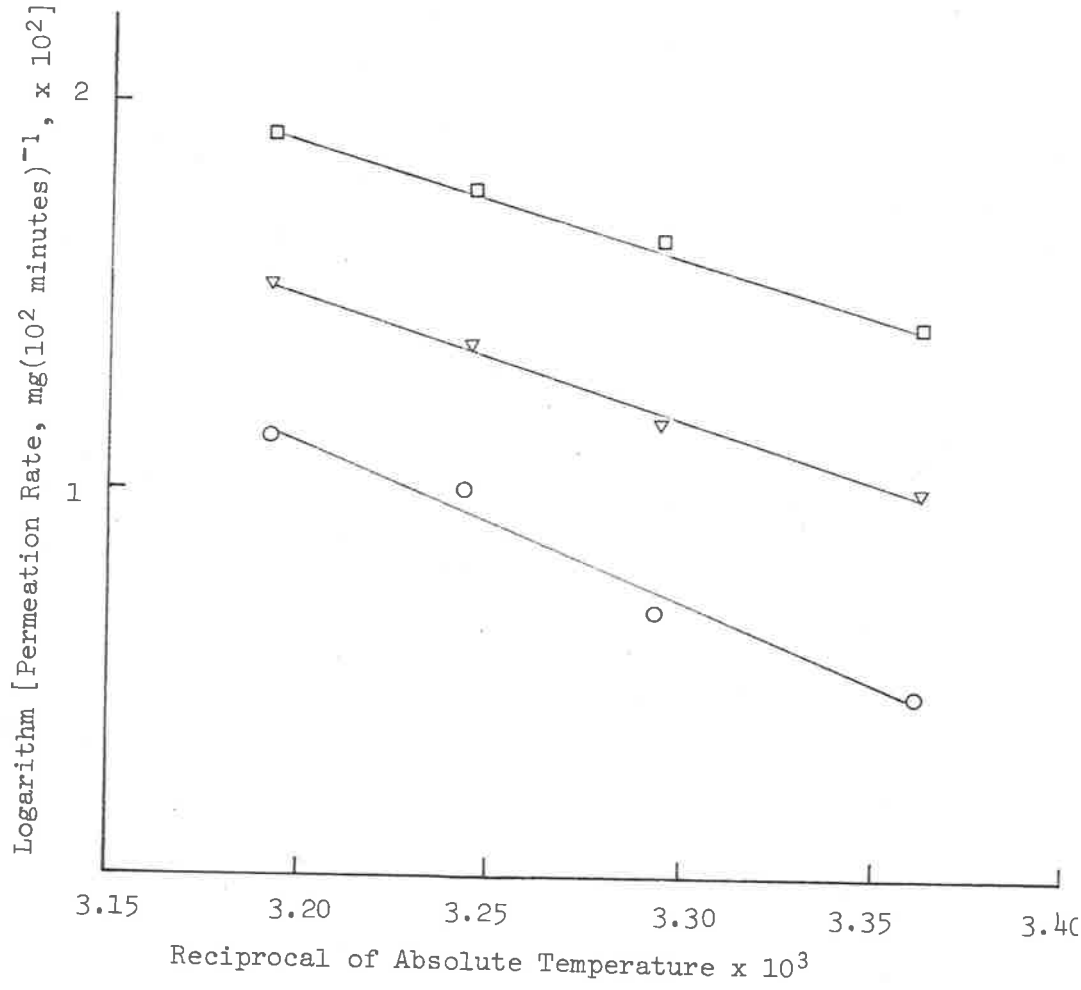

Figure 3.19 Effect of temperature on the permeation rate of three substances through "saturated" polyethylene membrane 6 mil. thick.

□ Anisole

○ Acetophenone

▽ Nitrobenzene

Initial concentration for all determinations: 2×10^{-3}M

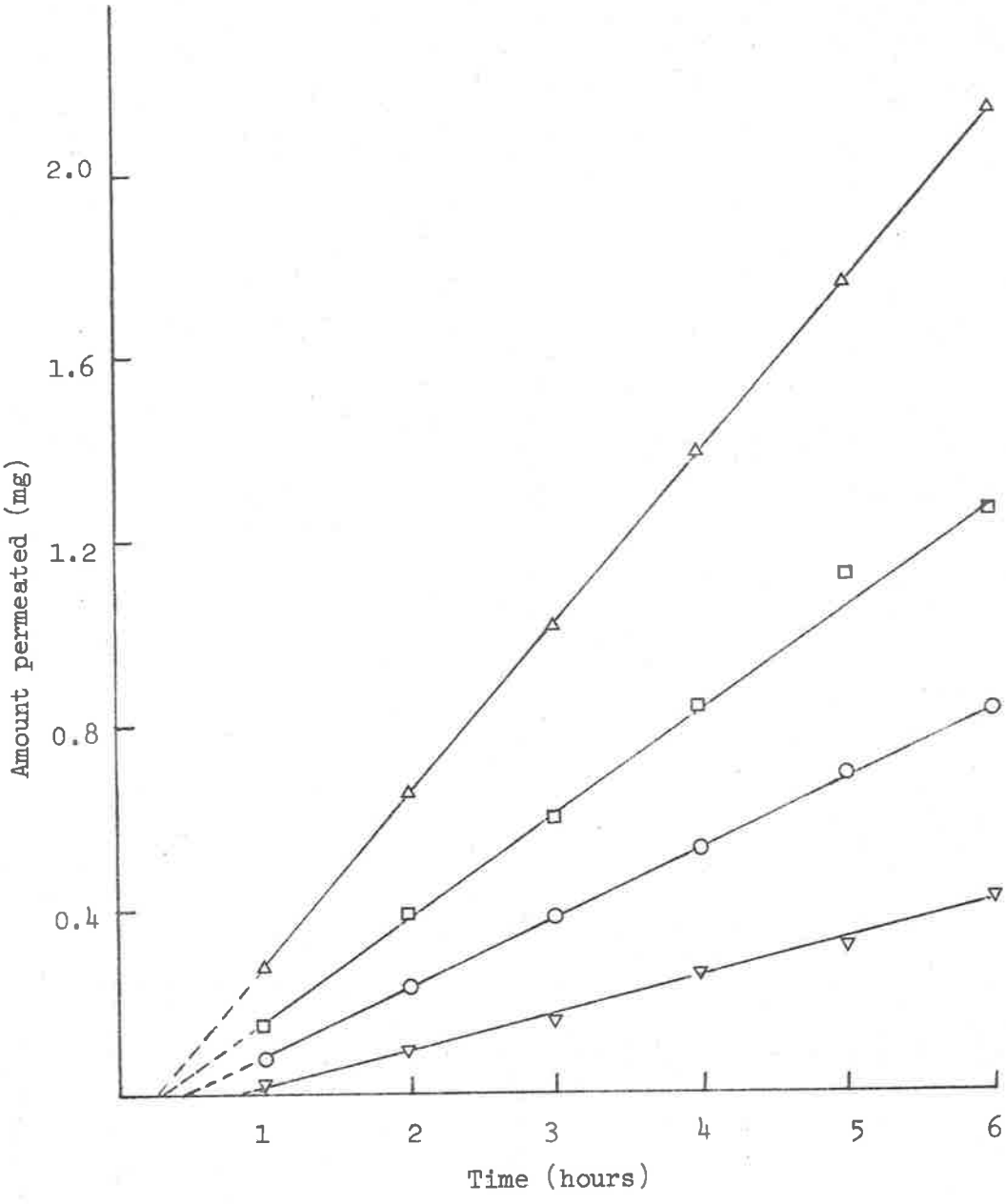

Figure 3.20 Permeation of acetophenone through "dry" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.)
Initial concentration: 1×10^{-2}M

▽ 24.4°

○ 30.6°

□ 35.2°

△ 40.2°

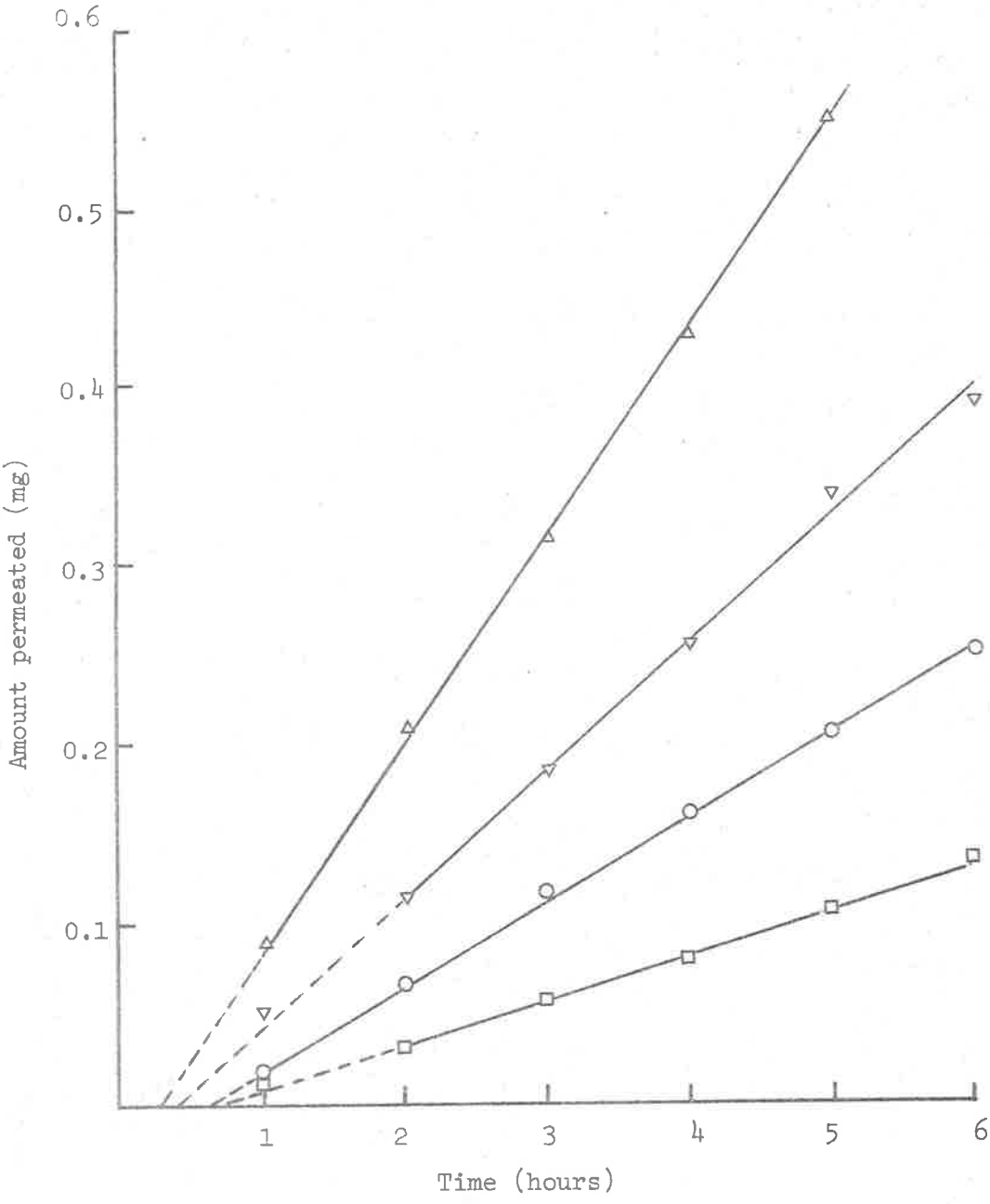

Figure 3.21 Permeation of anisaldehyde through "dry" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.)
Initial concentration: 5×10^{-3}M

□ 24.4°

○ 30.6°

▽ 35.2°

△ 40.2°

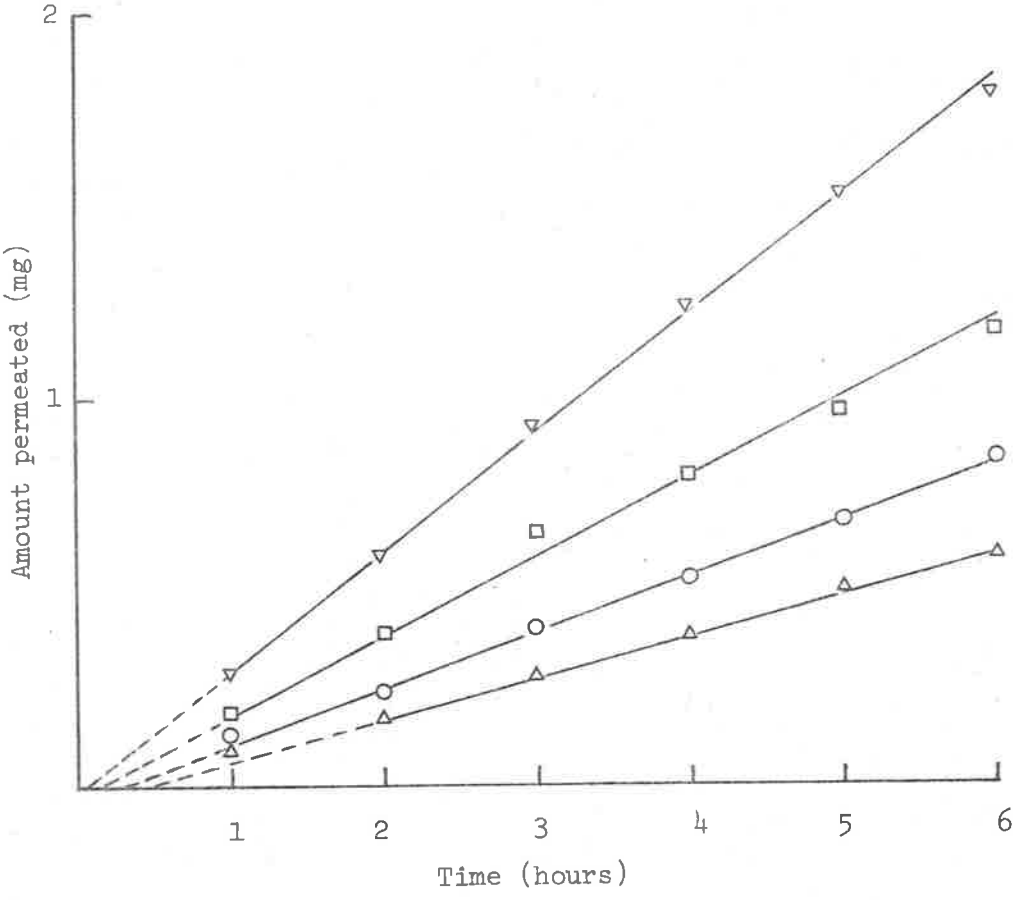

Figure 3.22 Permeation of anisole through "dry" polyethylene membrane 6 mil. thick at 24.4°.
(Each point represents average of measurements made in two cells.)
Initial concentration: 1.25×10^{-3}M

△ 24.4°

○ 30.6°

□ 35.2°

▽ 40.2°

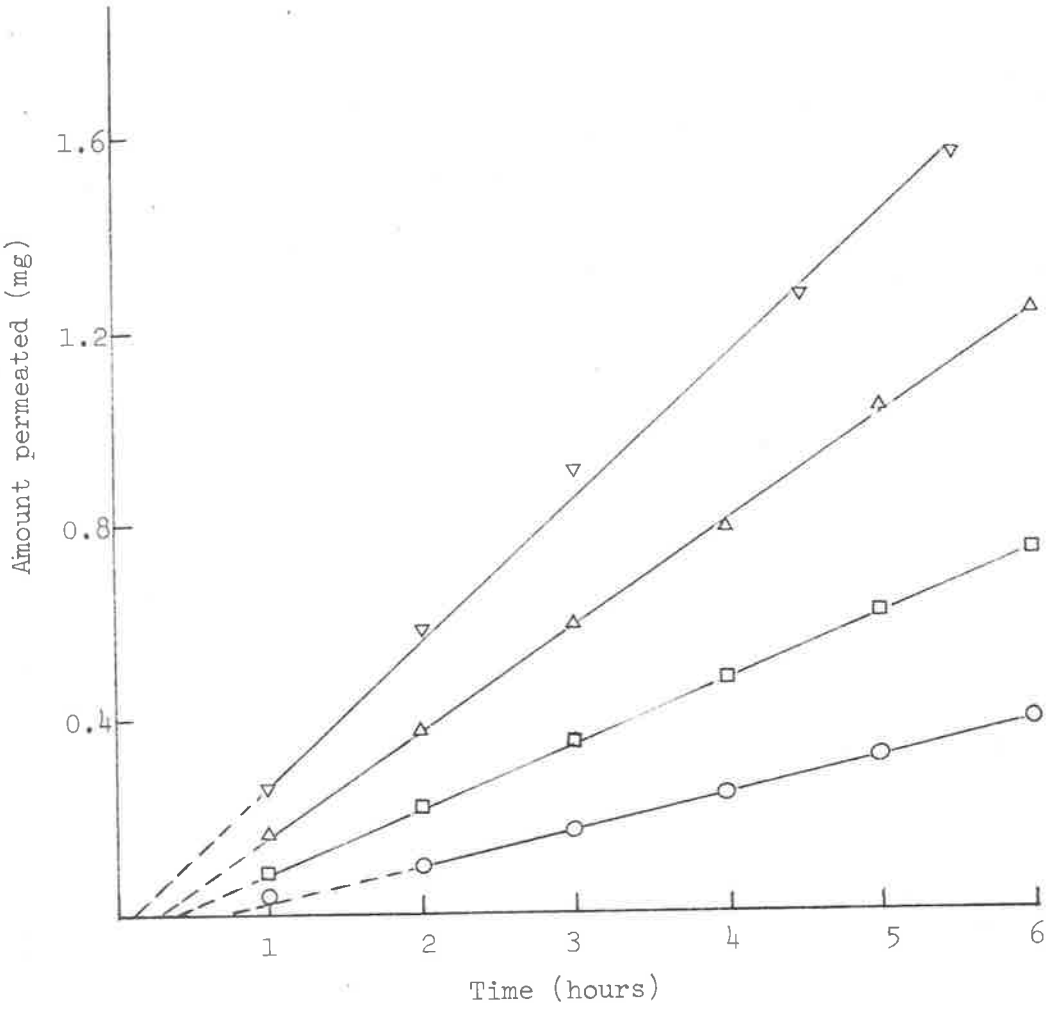

Figure 3.23 Permeation of benzaldehyde through "dry" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.)
Initial concentration: 1×10^{-2}M

○ 24.4°
□ 30.6°
△ 35.2°
▽ 40.2°

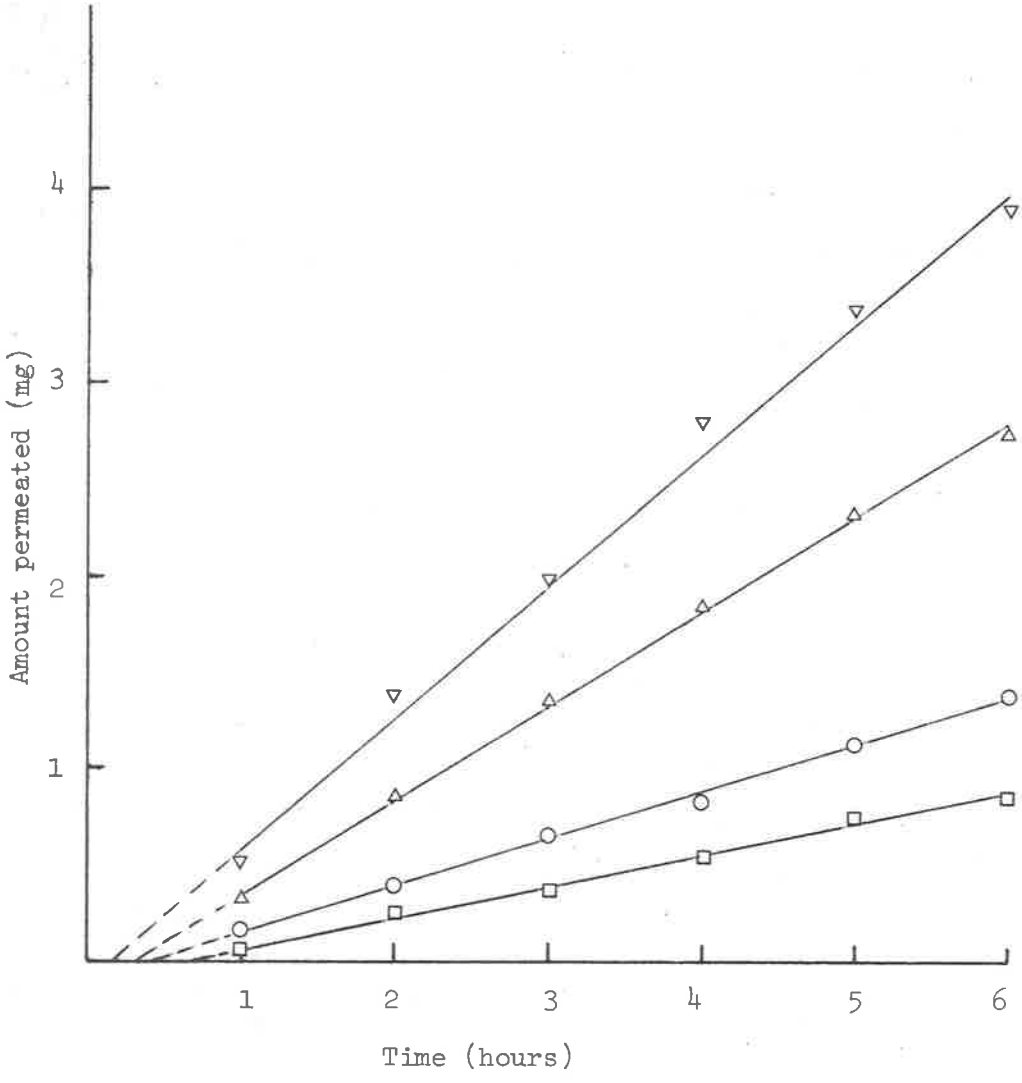

Figure 3.24 Permeation of 2,4-dichlorophenol through "dry" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.)
Initial concentration: 1×10^{-2}M

□ 24.4°
○ 30.6°
△ 35.2°
▽ 40.2°

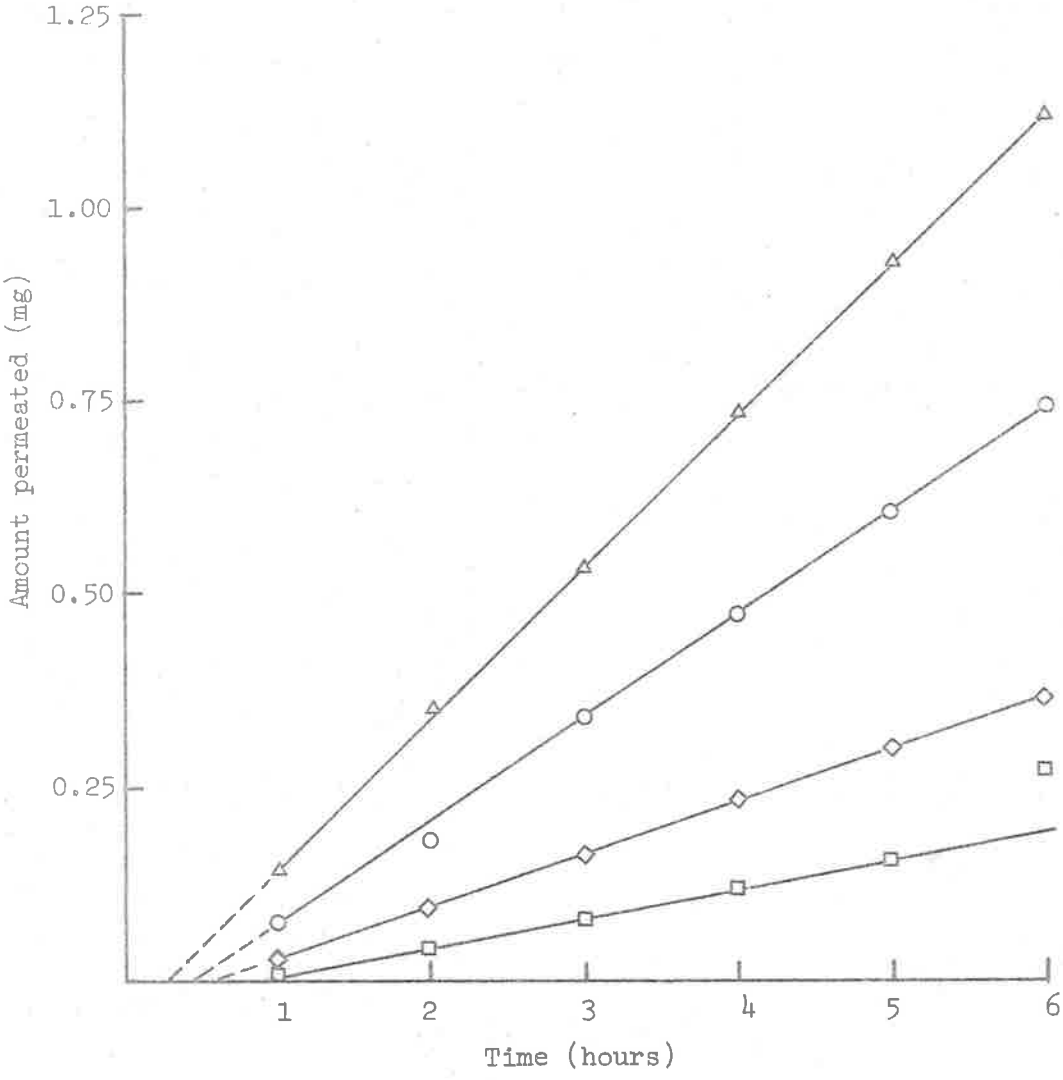

Figure 3.25 Permeation of p-methyl acetophenone through "dry" polyethylene membrane 6 mil. thick at 24.4°.
(Each point represents average of measurements made in two cells.)
Initial concentration: 2×10^{-3}M

□ 24.4°
◇ 30.6°
○ 35.2°
△ 40.2°

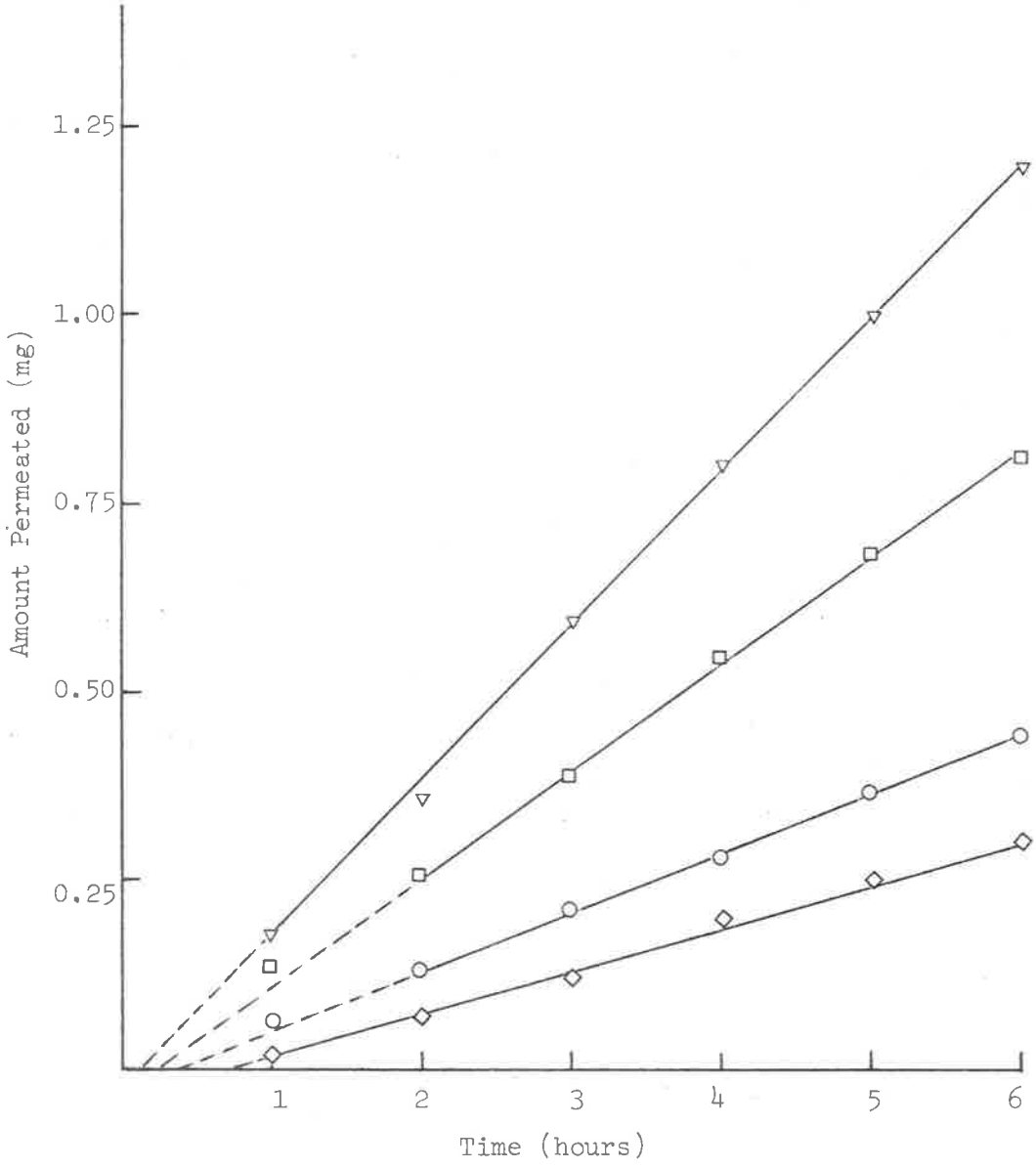

Figure 3.26 Permeation of nitrobenzene through "dry" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.)
Initial concentration: 2×10^{-3}M

◇ 24.4°
○ 30.6°
□ 35.2°
▽ 40.2°

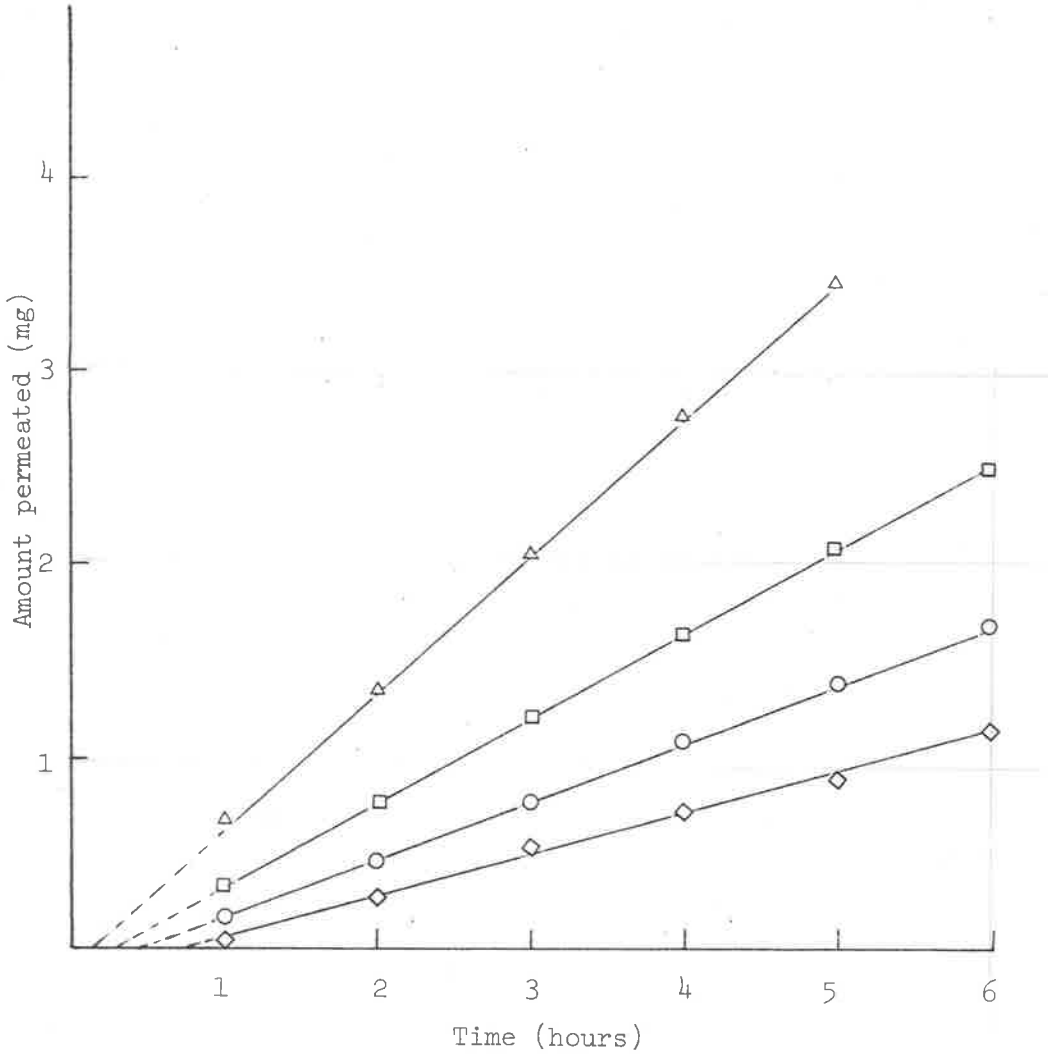

Figure 3.27 Permeation of o-nitrophenol (at pH 3.81), through "dry" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.)
Initial concentration: 7.18×10^{-3}M

◇ 24.4°
○ 30.6°
□ 35.2°
△ 40.2°

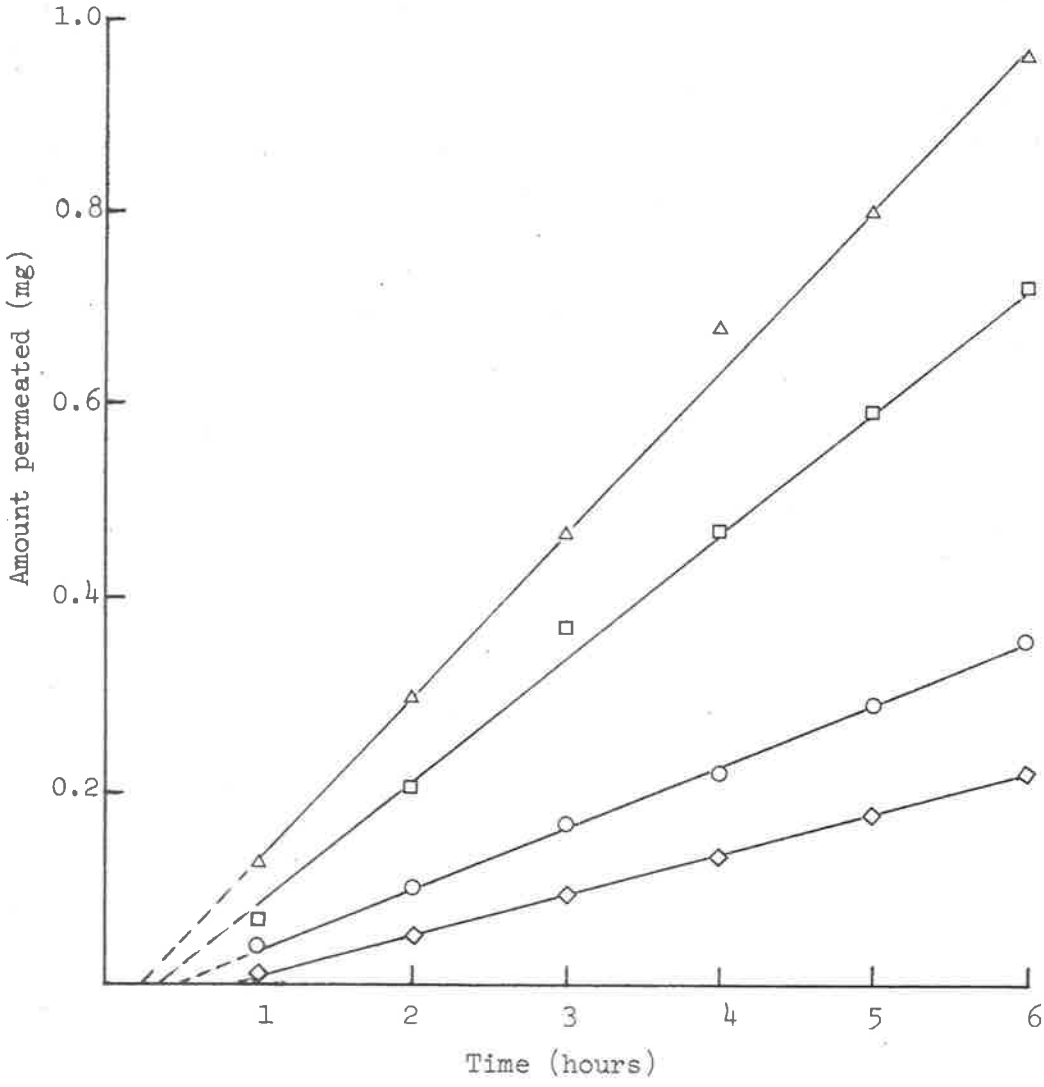

Figure 3.28 Permeation of p-tolualdehyde through "dry" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.)
Initial concentration: 2.08×10^{-3}M

◇ 24.4°

○ 30.6°

□ 35.2°

△ 40.2°

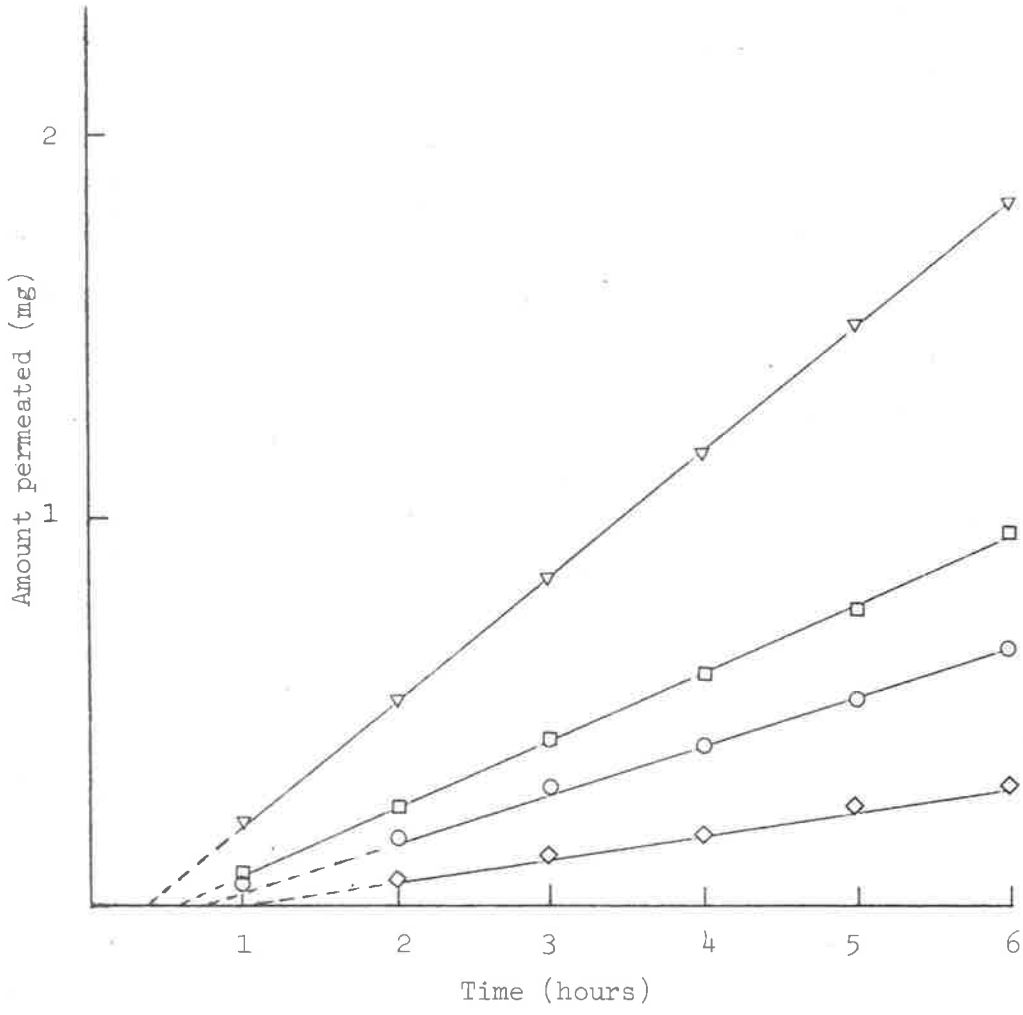

Figure 3.29 Permeation of p-toluidine (at pH 8.32), through "dry" polyethylene membrane 6 mil. thick at 24.4°.
(Each point represents average of measurements made in two cells.)
Initial concentration: 2.33×10^{-2}M

◇ 24.4°
○ 30.6°
□ 35.2°
▽ 40.2°

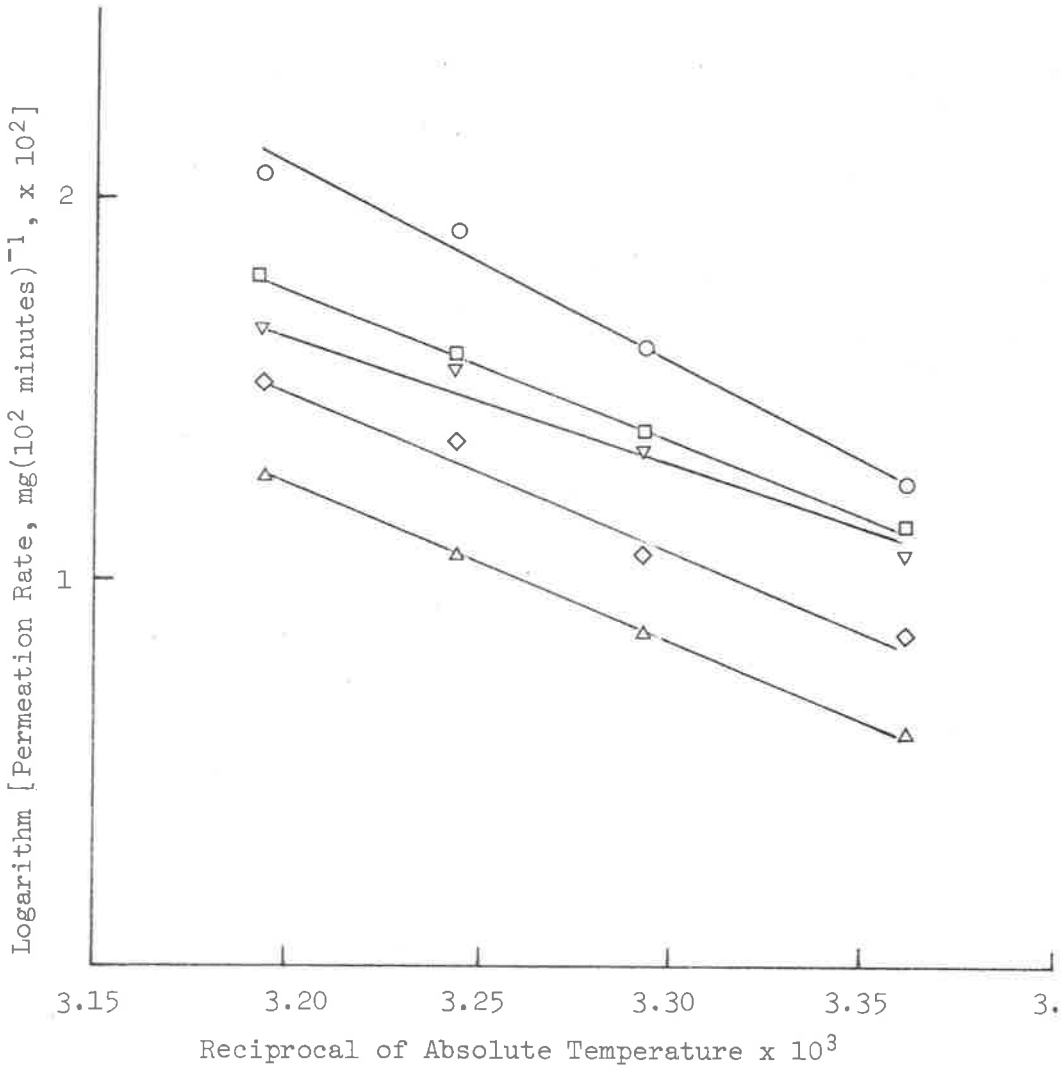

Figure 3.30 Effect of temperature on the permeation rate of five substances through "dry" polyethylene membrane 6 mil. thick.

- □ acetophenone, initial concentration: 1×10^{-2}M
- △ anisaldehyde, initial concentration: 5×10^{-3}M
- ▽ benzaldehyde, initial concentration: 1×10^{-2}M
- ○ 2,4-dichlorophenol, initial concentration: 1×10^{-2}M
- ◇ p-methyl acetophenone, initial concentration: 2×10^{-3}M

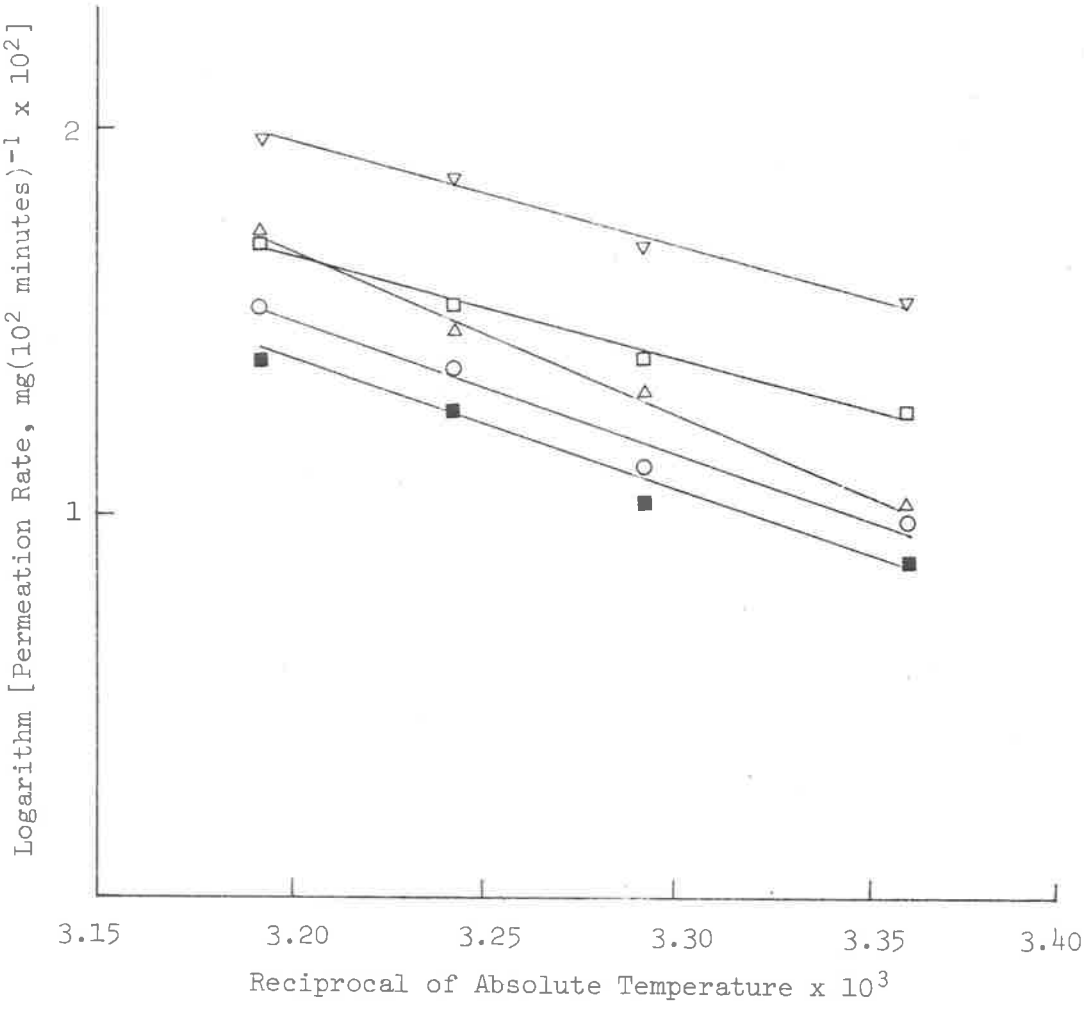

Figure 3.31 Effect of temperature on the permeation rate of five substances through "dry" polyethylene membrane 6 mil. thick.

- □ anisole, initial concentration: 1.25×10^{-3}M
- ○ nitrobenzene, initial concentration: 2×10^{-3}M
- ▽ o-nitrophenol (at pH 3.81), initial concentration: 7.18×10^{-3}M
- ■ p-tolualdehyde, initial concentration: 2.08×10^{-3}M
- △ p-toluidine (at pH 8.32), initial concentration: 2.33×10^{-2}M

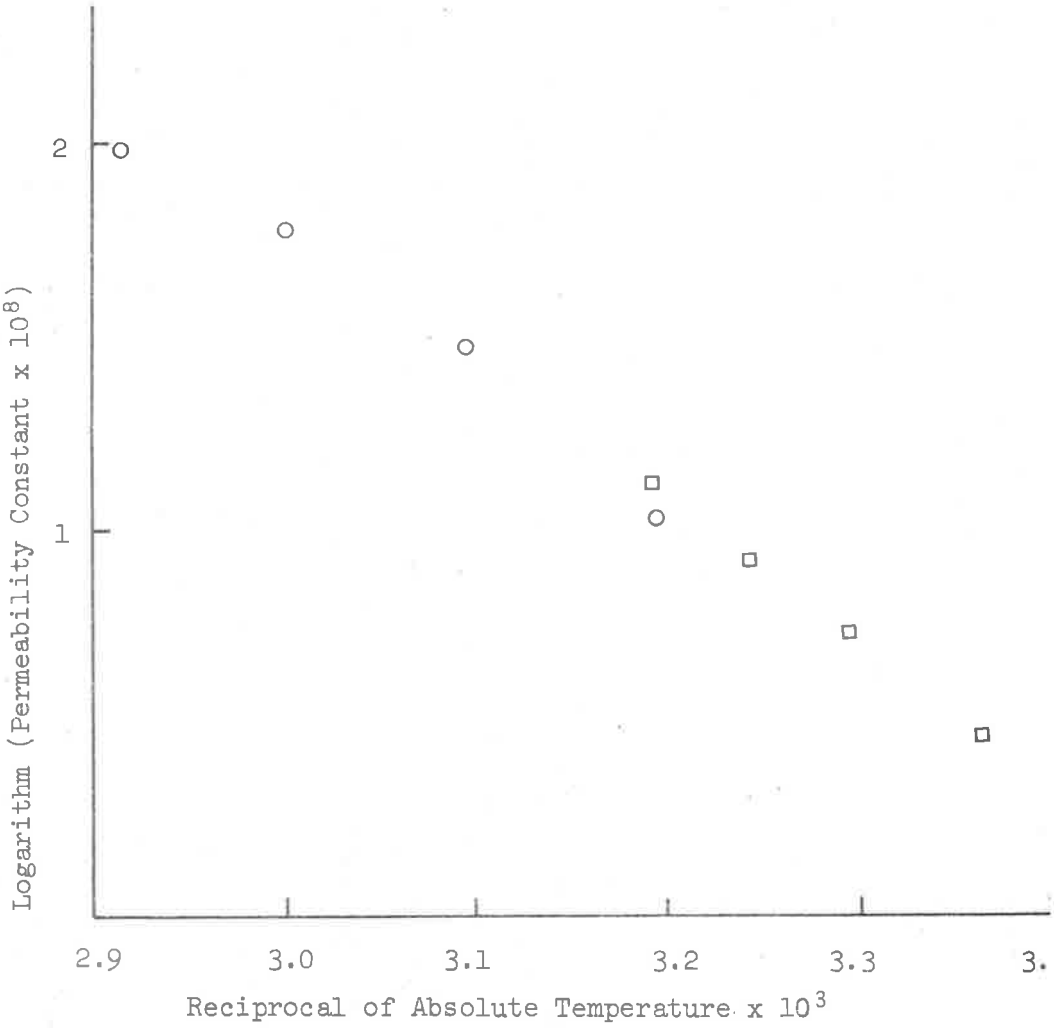

Figure 3.32 Comparison of permeability constants (defined in text in Section 3.1) of acetophenone obtained in present work and those reported by Gonzales and others (1967) at a number of temperatures.

□ present work

○ Gonzales and others (1967)

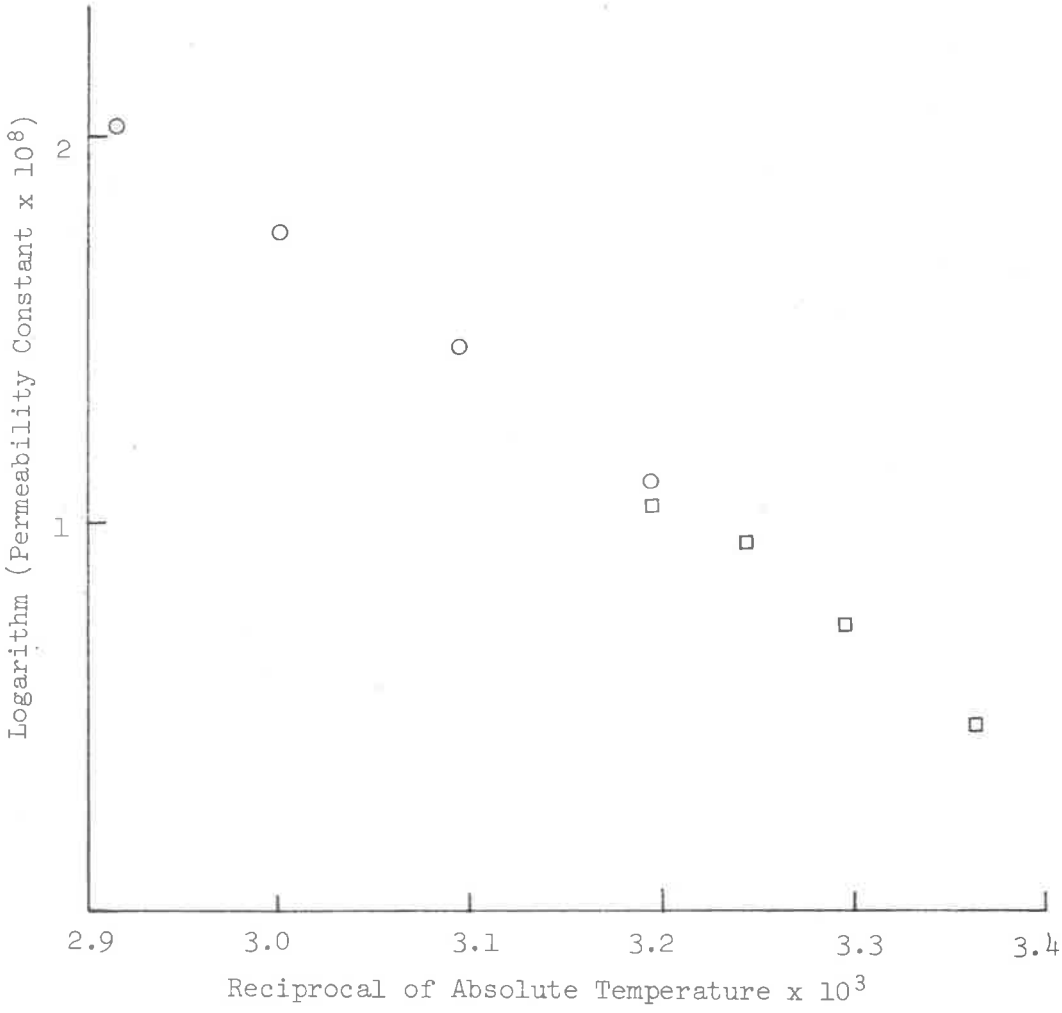

Figure 3.33 Comparison of permeability constants (defined in text in Section 3.1) of benzaldehyde obtained in present work and those reported by Gonzales and others (1967) at a number of temperatures.

□ present work

○ Gonzales and others (1967)

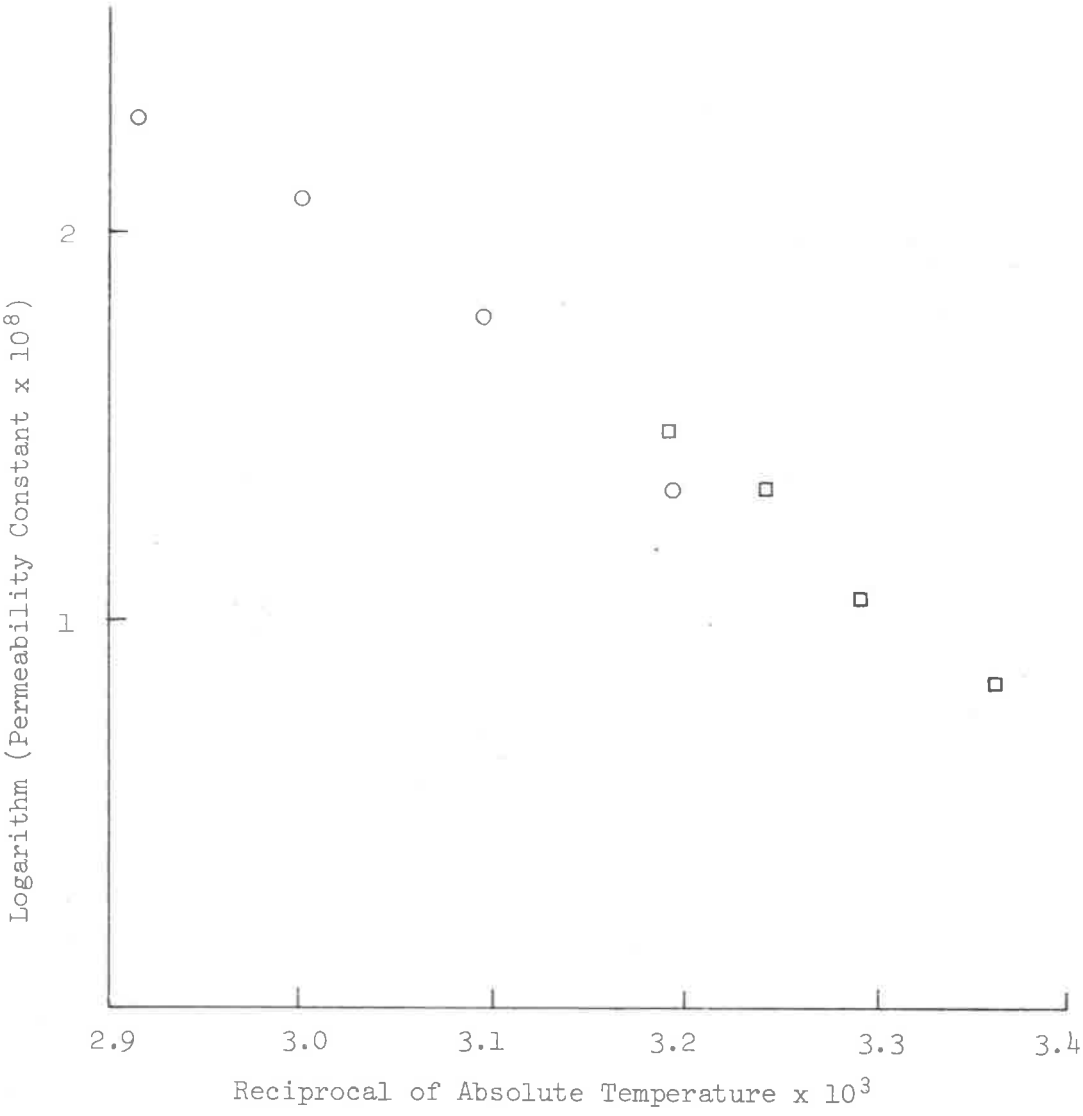

Figure 3.34 Comparison of permeability constants (defined in text in Section 3.1) of p-methyl acetophenone ontained in present work and those reported by Gonzales and others (1967) at a number of temperatures.

□ present work

○ Gonzales and others (1967)

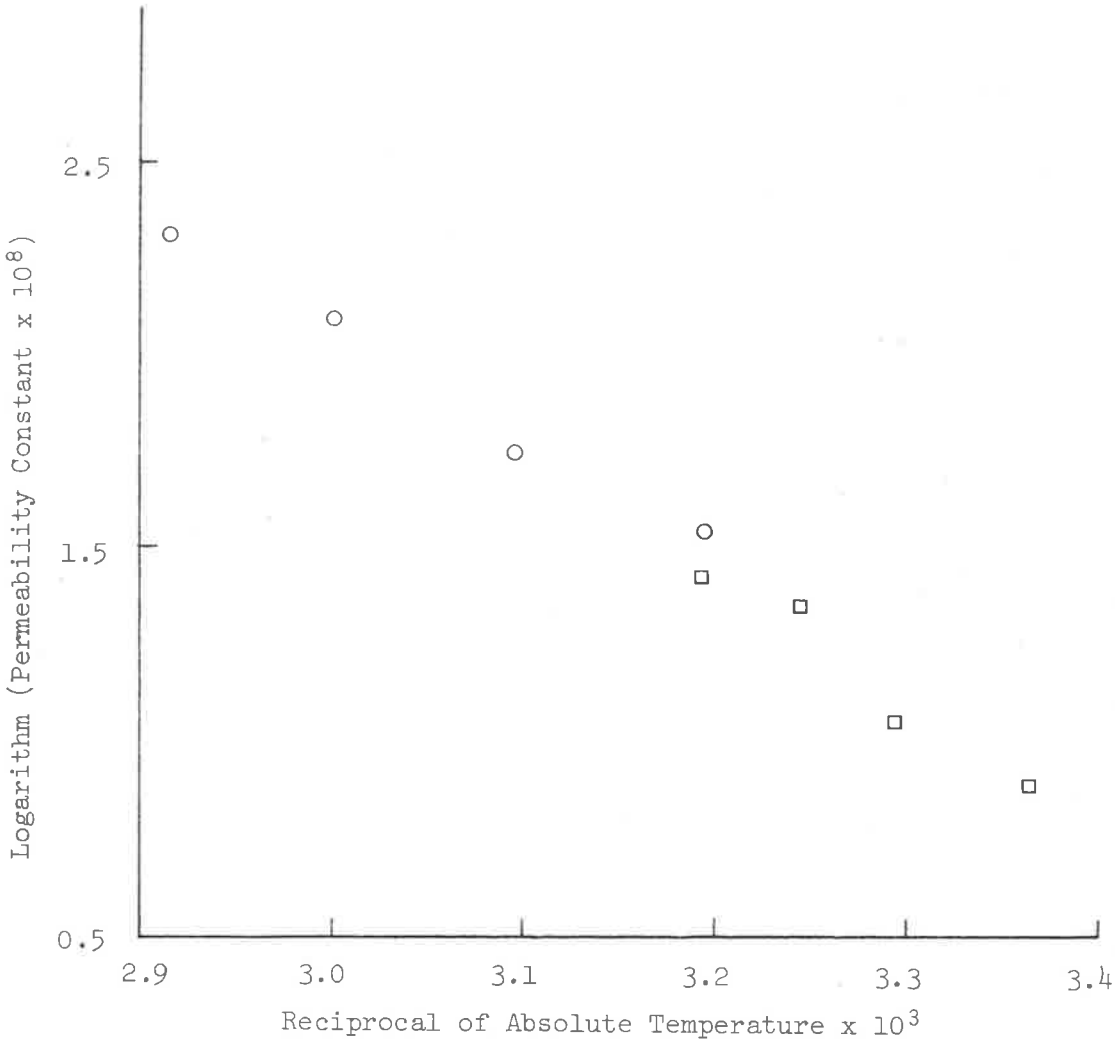

Figure 3.35 Comparison of permeability constants (defined in text in Section 3.1) of p-tolualdehyde obtained in present work and those reported by Gonzales and others (1967) at a number of temperatures.

□ present work

○ Gonzales and others (1967)

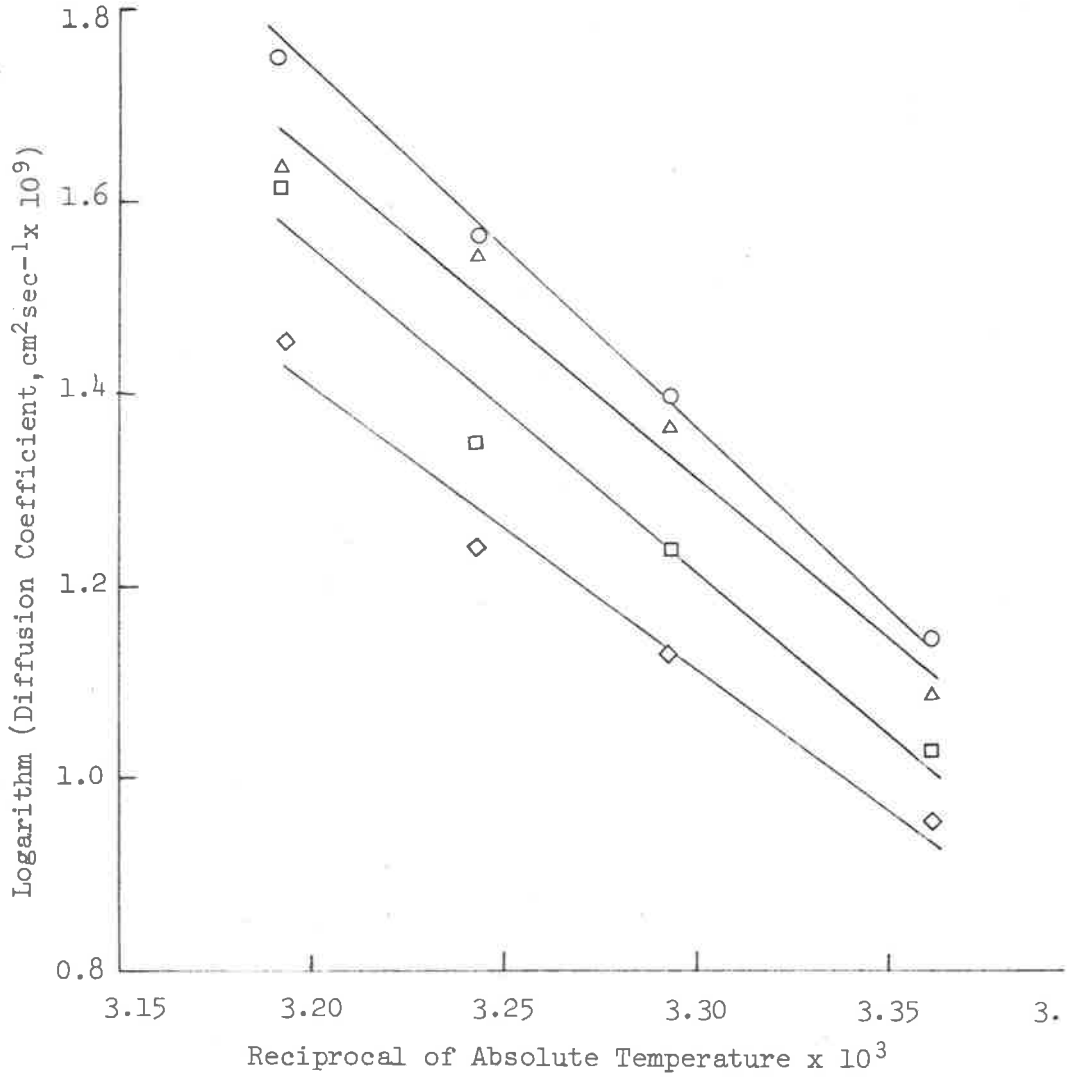

Figure 3.36 Effect of temperature on the diffusion coefficient of four substances through "dry" polyethylene membrane 6 mil. thick.

△ acetophenone, initial concentration: 1 x 10^{-2}M

○ benzaldehyde, initial concentration: 1 x 10^{-2}M

□ p-methyl acetophenone, initial concentration: 2 x 10^{-3}M

◇ p-toluidine (at pH 8.32), initial concentration 2.33 x 10^{-2}M

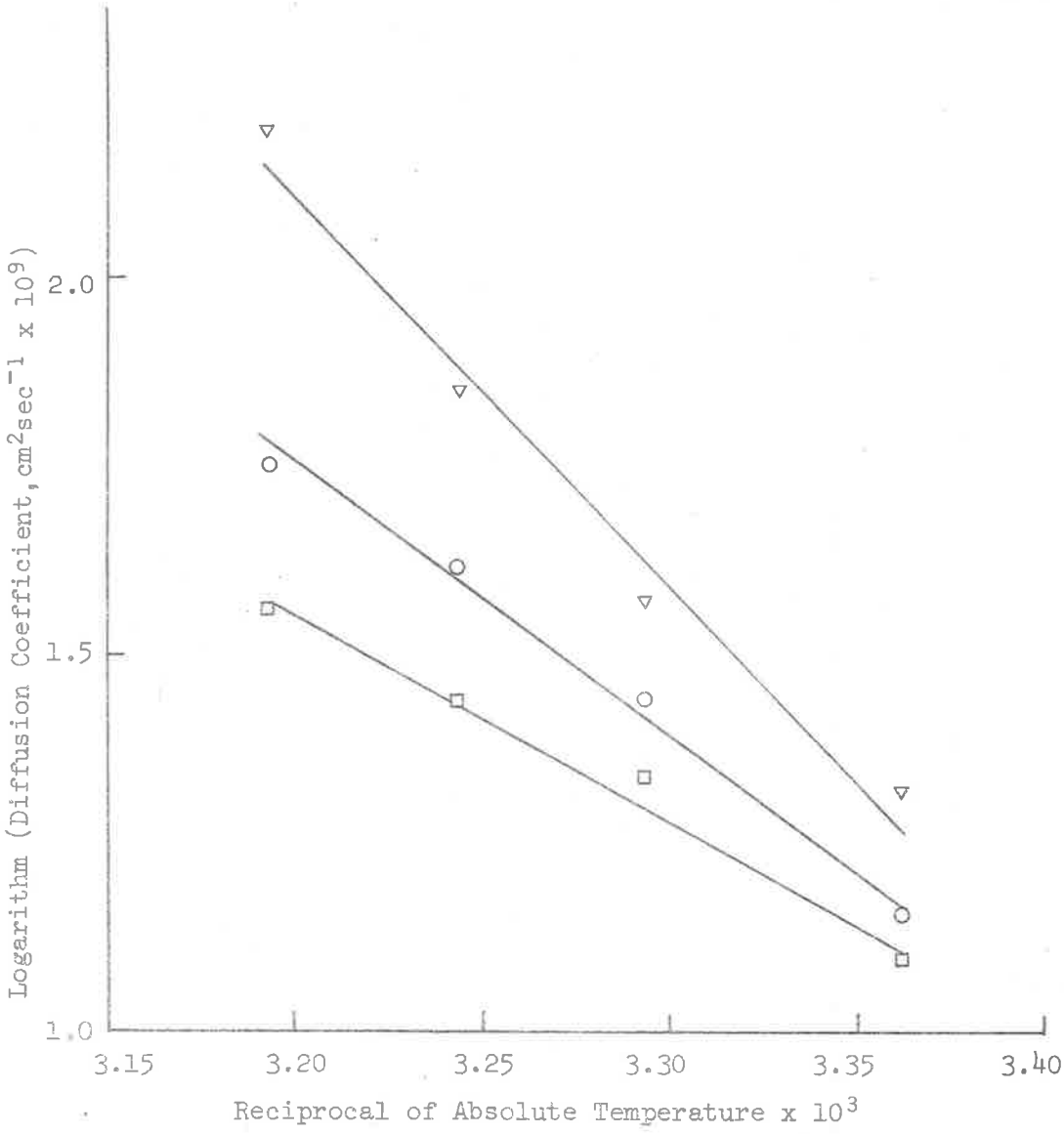

Figure 3.37 Effect of temperature on the diffusion coefficient of three substances through "dry" polyethylene membrane 6 mil. thick.

▽ anisole, initial concentration: 1.25×10^{-3}M

○ nitrobenzene, initial concentration: 2×10^{-3}M

□ p-tolualdehyde, initial concentration: 2.08×10^{-3}M

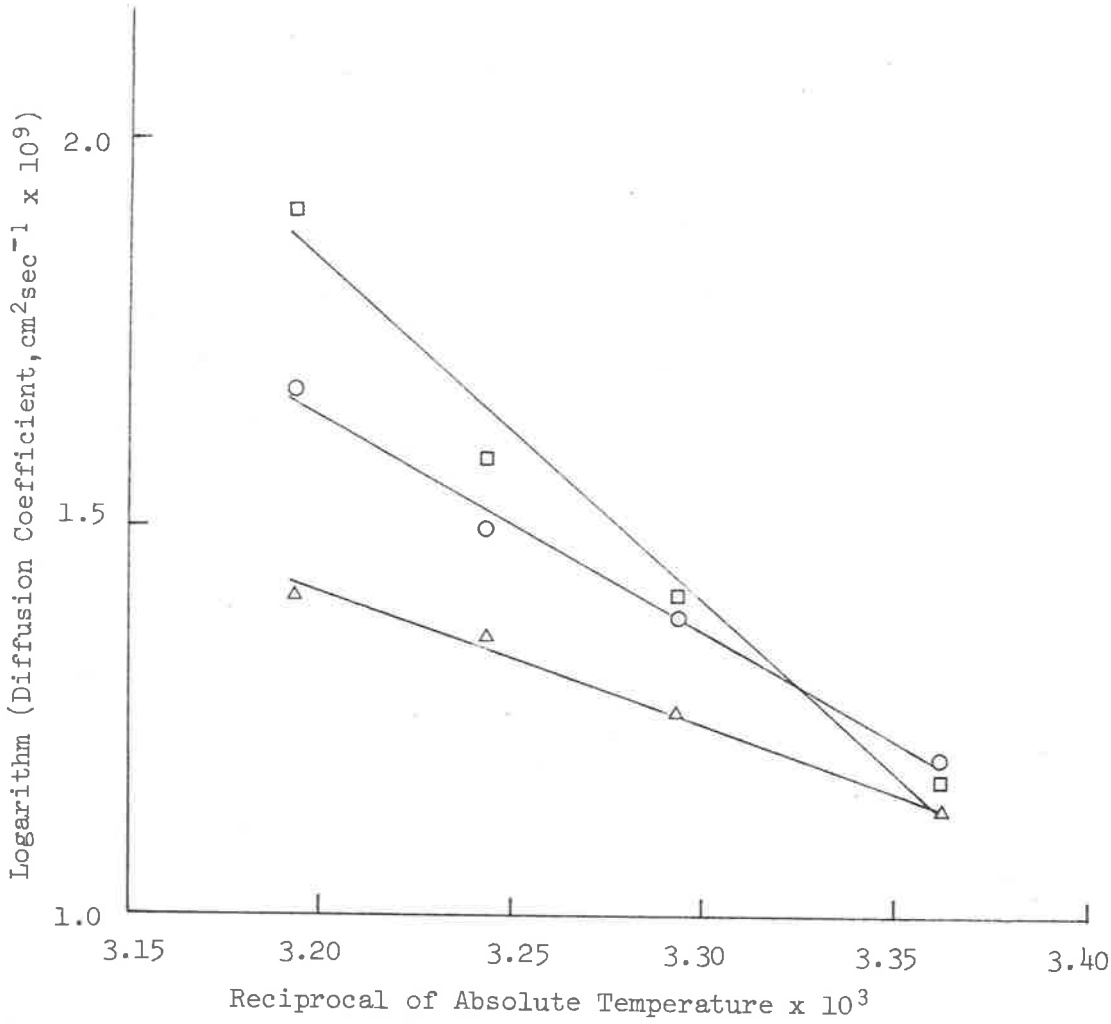

Figure 3.38 Effect of temperature on the diffusion coefficient of three substances through "dry" polyethylene membrane 6 mil. thick.

△ anisaldehyde, initial concentration: 5×10^{-3}M

□ o-nitrophenol, (at pH 3.81), initial concentration 7.18×10^{-3}M

○ 2,4-dichlorophenol, initial concentration: 1×10^{-2}M

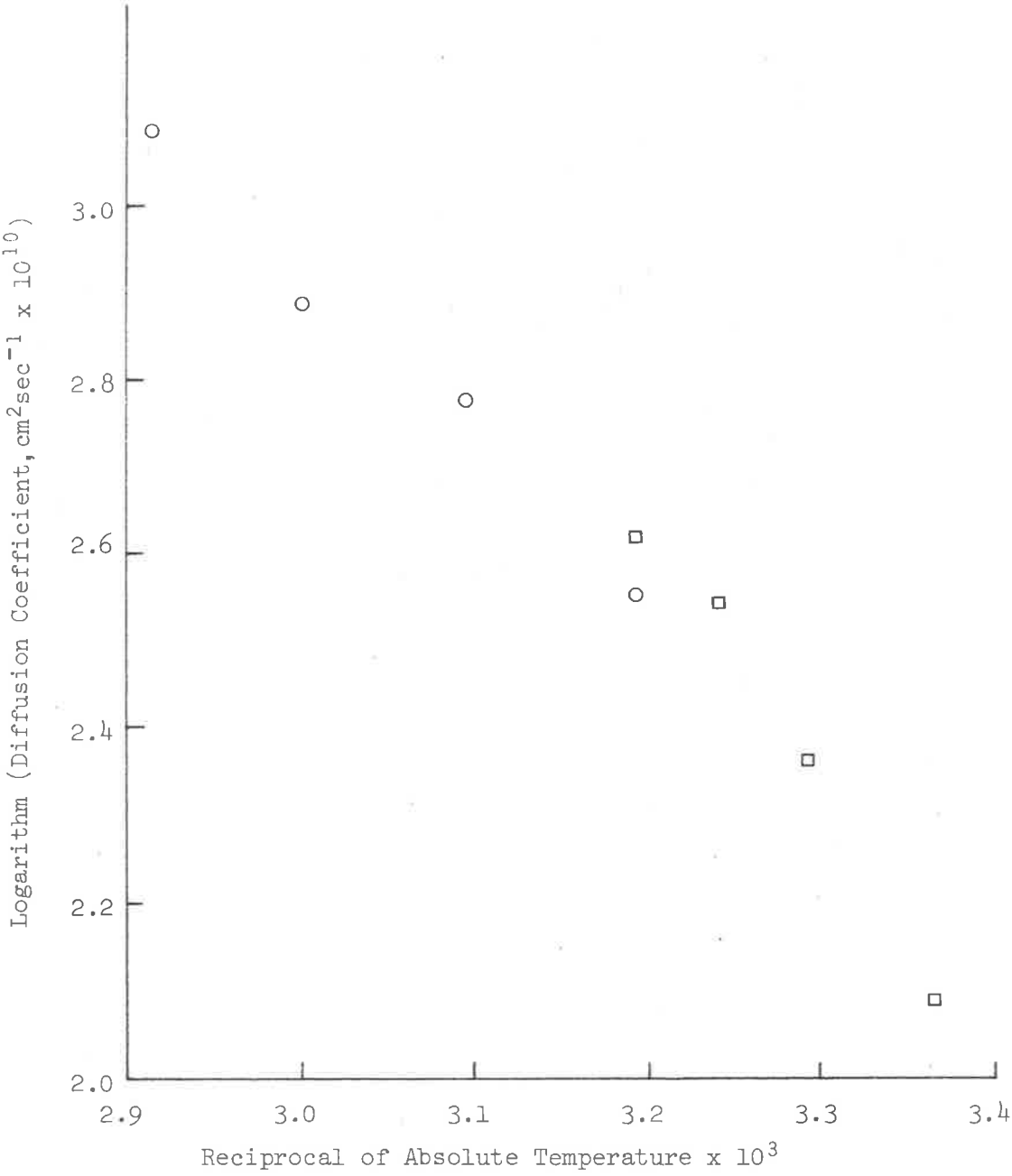

Figure 3.39 Comparison of diffusion coefficients of acetophenone obtained in the present work and those reported by Gonzales and others (1967) at a number of temperatures.

□ present work

○ Gonzales and others (1967)

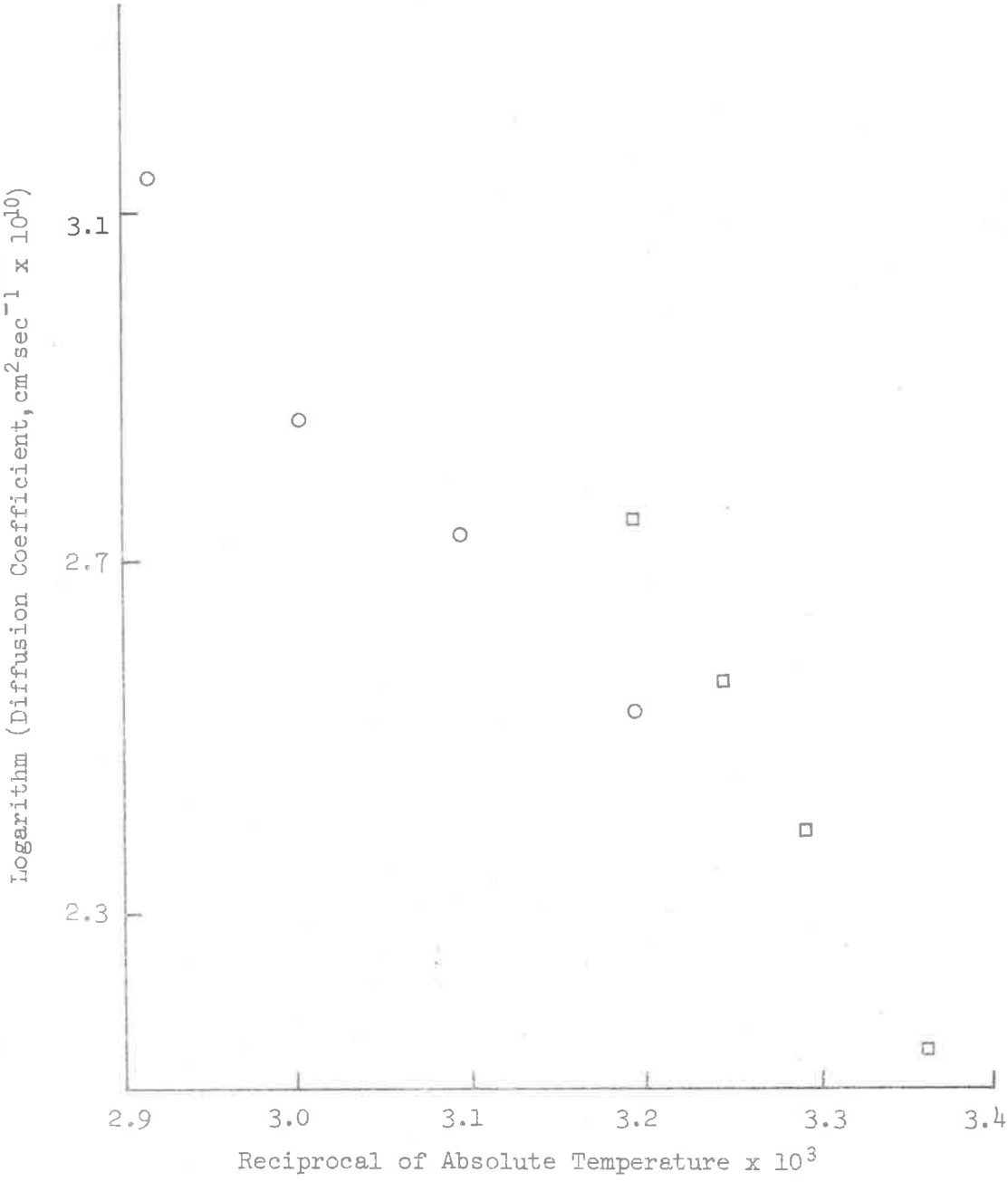

Figure 3.40 Comparison of diffusion coefficients of benzaldehyde obtained in the present work and those reported by Gonzales and others (1967) at a number of temperatures.

□ present work

○ Gonzales and others (1967)

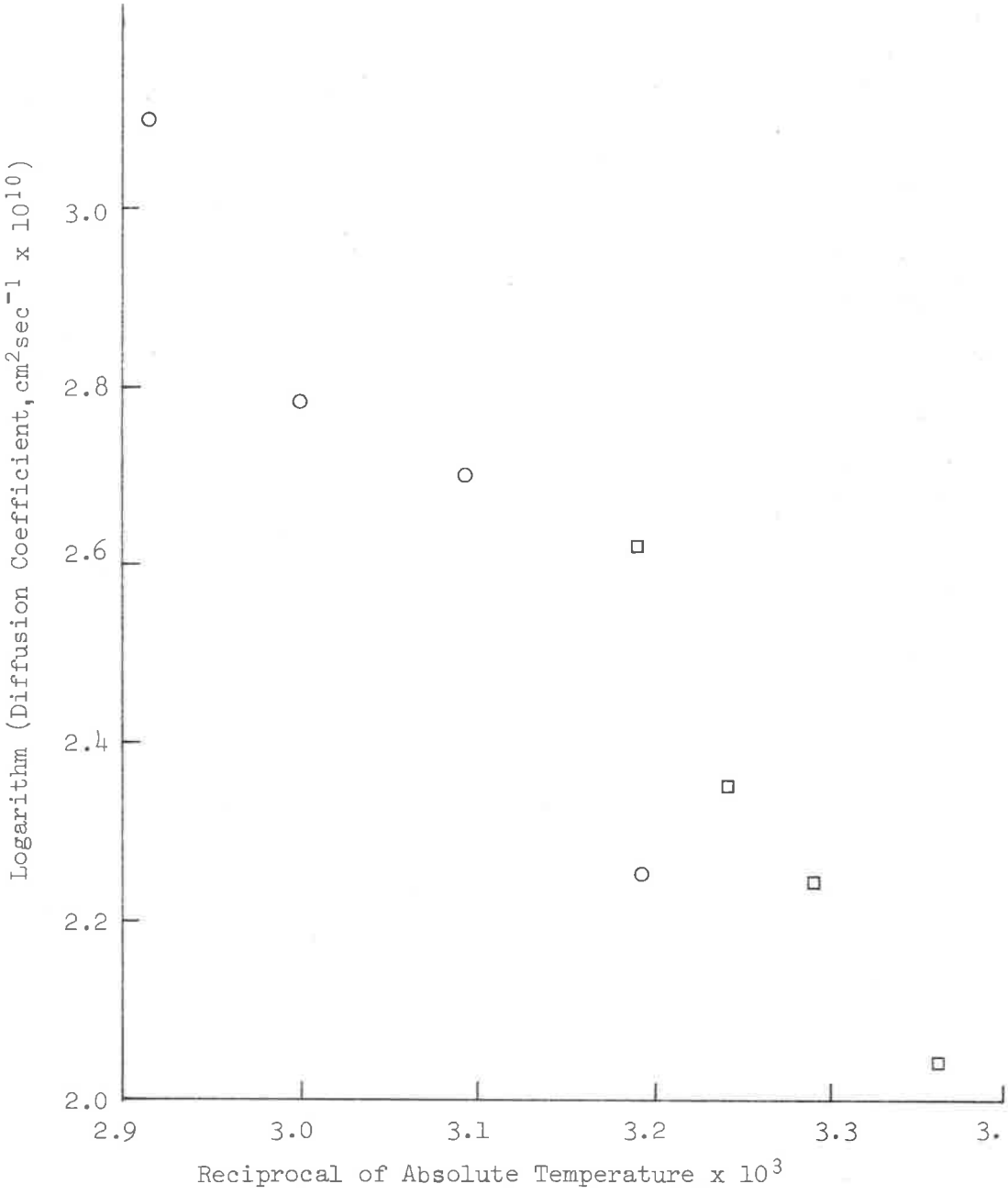

Figure 3.41 Comparison of diffusion coefficients of p-methyl acetophenone obtained in the present work and those reported by Gonzales and others (1967) at a number of temperatures.

□ present work

○ Gonzales and others (1967)

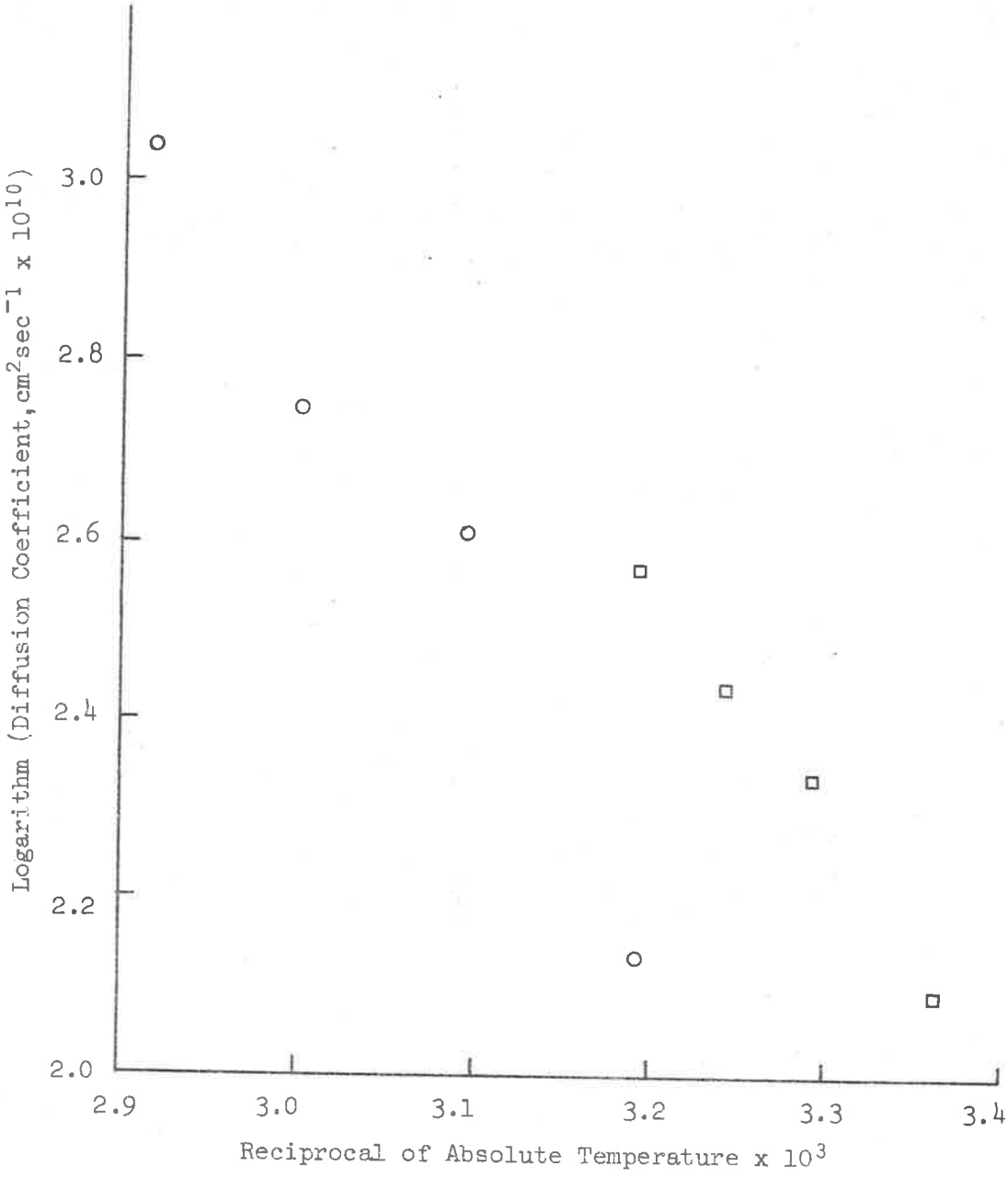

Figure 3.42 Comparison of diffusion coefficients of p-tolualdehyde obtained in the present work and those reported by Gonzales and others (1967) at a number of temperatures.

□ present work

○ Gonzales and others (1967)

3.2.3 pH

The effect of pH was studied using the acid o-nitrophenol and the base p-toluidine. The effect of ionic strength was investigated using o-nitrophenol. The permeation rate of o-nitrophenol at a variety of pH's is shown in Figure 3.43. Also shown in this Figure is the effect of variation in the ionic strength of the buffer solution. It is reasonable to conclude from this Figure that variation in the ionic strength does not appreciably affect the permeation rate and for this reason the effect of the ionic strength has not been considered further.

The permeation rate of p-toluidine at a variety of pH's is shown in Figure 3.44. The relationship between permeation rates and pH is considered further in sections 5.2.3.1, 5.3 and 5.4.

3.2.4 Viscosity and polarity

The effect of viscosity on the permeation rates of three substances is shown in Figures 3.45, 3.46 and 3.47. It can be seen in each of these Figures that the permeation rate is considerably decreased when glycerine is used to increase the viscosity while the use of methyl cellulose does not reduce the permeation rate to the same extent. Obviously this behaviour is due to changes in solvent properties brought about by the addition of glycerine but not by the addition of methyl cellulose. Glycerine has a dielectric constant of 42.5 (Weast, 1968) and water a dielectric constant of 78.54 (Weast, 1968). The addition of glycerine to water can therefore be expected to decrease the dielectric constant of the system and as more glycerine is added the dielectric constant will be further reduced. Methyl cellulose is chemically inert

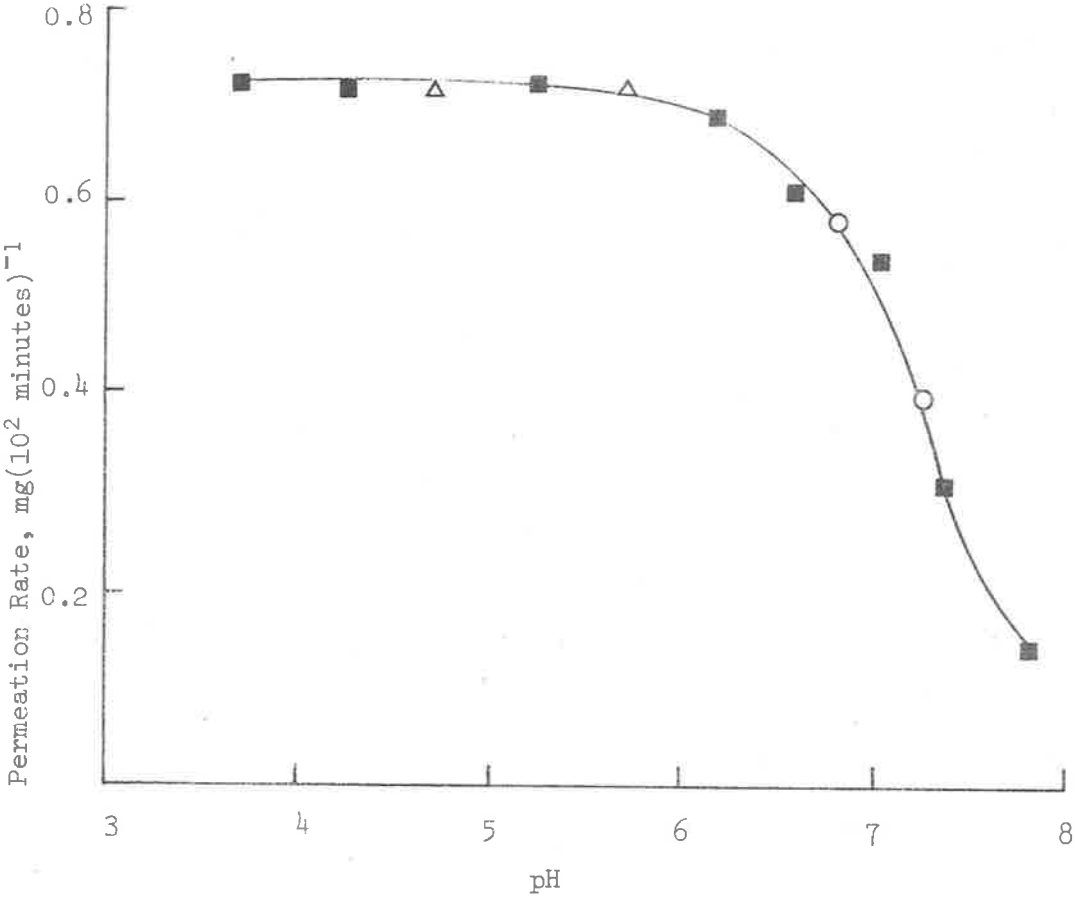

Figure 3.43 Effect of pH and ionic strength on the permeation rate of o-nitrophenol through polyethylene membrane 6 mil. thick at 35.2° - details of buffer systems given in Table 2.1 (Each point represents average of measurements made in two cells.) Initial concentration: 7.18×10^{-3} M (pH 3.81 "dry" membrane, all other pH's "saturated" membrane.)

■ ionic strength of buffer solution: 0.5

△ ionic strength of buffer solution: 1.0

○ ionic strength of buffer solution: 0.25

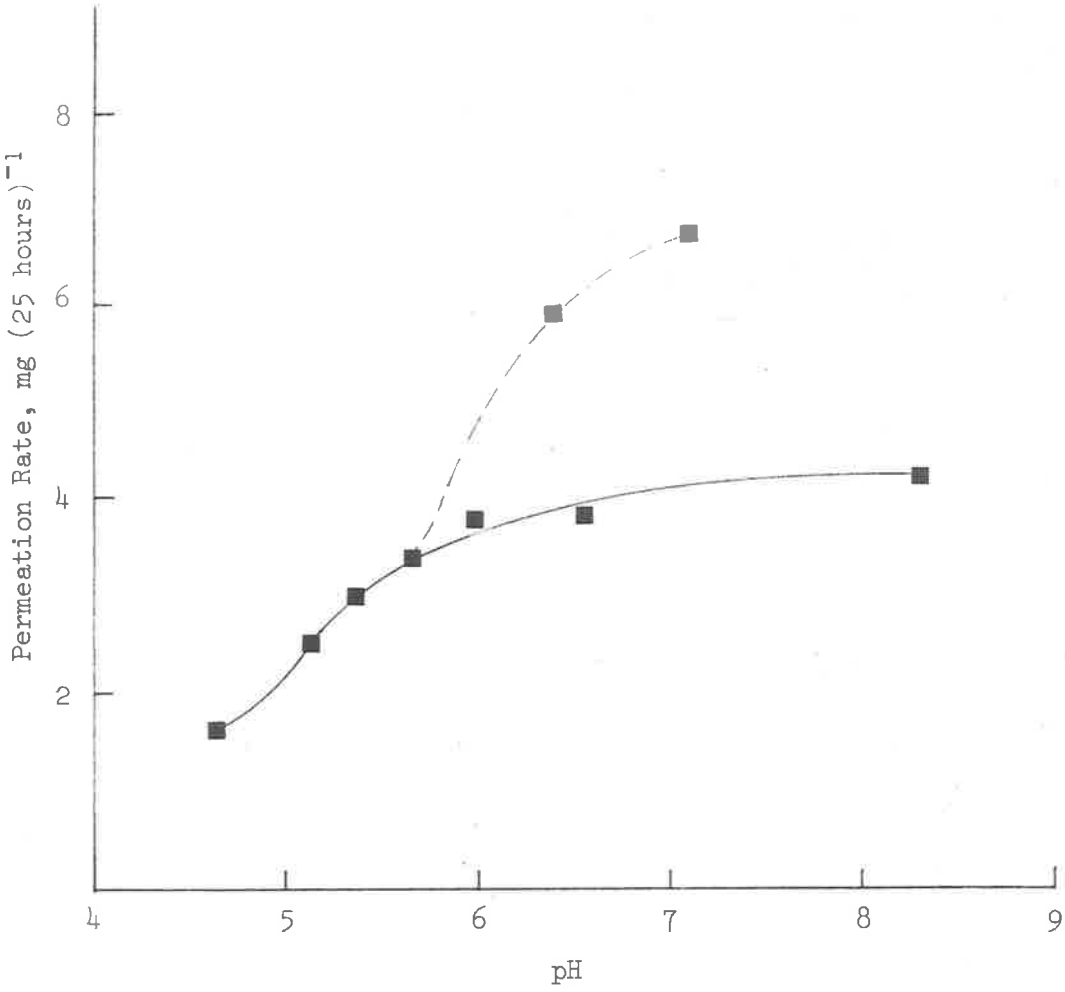

Figure 3.44 Effect of pH on the permeation rate of p-toluidine through polyethylene membrane 6 mil. thick at 35.2° and constant ionic strength - details of buffer systems given in Table 2.2. (Each point represents average of measurements made on two cells.) Initial concentration: $2.33 \times 10^{-}$ M (pH 8.32 "dry" membrane, all other pH's "saturated" membrane.)

(Jenkins, Sperandio and Latiolais, 1966) and when added to water increases viscosity only by virtue of its polymeric properties and is present in the system in a suspended form. The addition of methyl cellulose to water will not change the polarity of the system. This reasoning is confirmed by an examination of Figures 3.48, 3.49 and 3.50 where it can be seen that the hexane water partition coefficients of acetophenone, anisole and nitrobenzene in solutions of varying viscosity, vary according to the viscosity producing agent used. It is realised that these plots (Figures 3.48-3.50) are not physicochemically meaningful.

The expression of Einstein and Sutherland,

$$D = \frac{RT}{N} \cdot \frac{1}{6\pi r\eta} \qquad (3.8)$$

relates the diffusion rate of a solute in a medium to the viscosity of the medium (Martin, 1960). Assuming that this expression can also be applied to the permeation rate (and in the steady state situation the diffusion rate and the permeation rate are the same) and regarding the molecules being considered as having the same radius it is obvious that the expression is not valid in the present circumstances - if it was valid the permeation rate would be independent of the viscosity producing agent used and dependent only on the actual viscosity. In the situation where a glycerine water solvent is used a decrease in permeation rate is noted for all three solutes with increase in viscosity while in all cases with the methyl cellulose water system no appreciable effect on the permeation rate is noted with increase in viscosity.

It is suggested that this apparent anomaly is due to the change in the polarity of the solvent (and also therefore a change in the solubility of the solute) effected by addition of glycerine to water and not by the addition of methyl cellulose. This suggestion is supported by the work of Ostrenga, Steinmetz and Poulsen (1971).

Chemburkar (1967) has presented a plot of the diffusion rate of 4'aminopropiophenone through a dimethyl polysiloxane membrane against time from a phosphate buffer solution containing different concentrations of ethanol and it is clearly seen that with increasing ethanol concentration the diffusion rate is decreased. This data appears to confirm the reasoning above for the effects of glycerine and methyl cellulose on the permeation rates of acetophenone, anisole and nitrobenzene. Chemburkar (1967) does not, however, appear to have considered his data in this way or as being due to a change in the solubility of the solute brought about by the change in the solvent polarity.

3.2.5 Effect of the thickness of the membrane

The effect of the thickness of the polyethylene membrane on the permeation rates of three selected substances is shown in Figure 3.51. The results are consistent with the expected relationship (given by Rogers, 1964) of the permeation rate being proportional to the reciprocal of the membrane thickness. It is interesting to note a departure from expected behaviour at the thickness of 3 mil. The membrane used at this thickness was "Alkathene" XHF 145 and not XJF 127 which was used in all other experiments. This variation illustrates the difference in properties brought about by small changes in composition and this property of plastics has been stressed by a number of authors (for example Marcus, Kim and Autian, 1959).

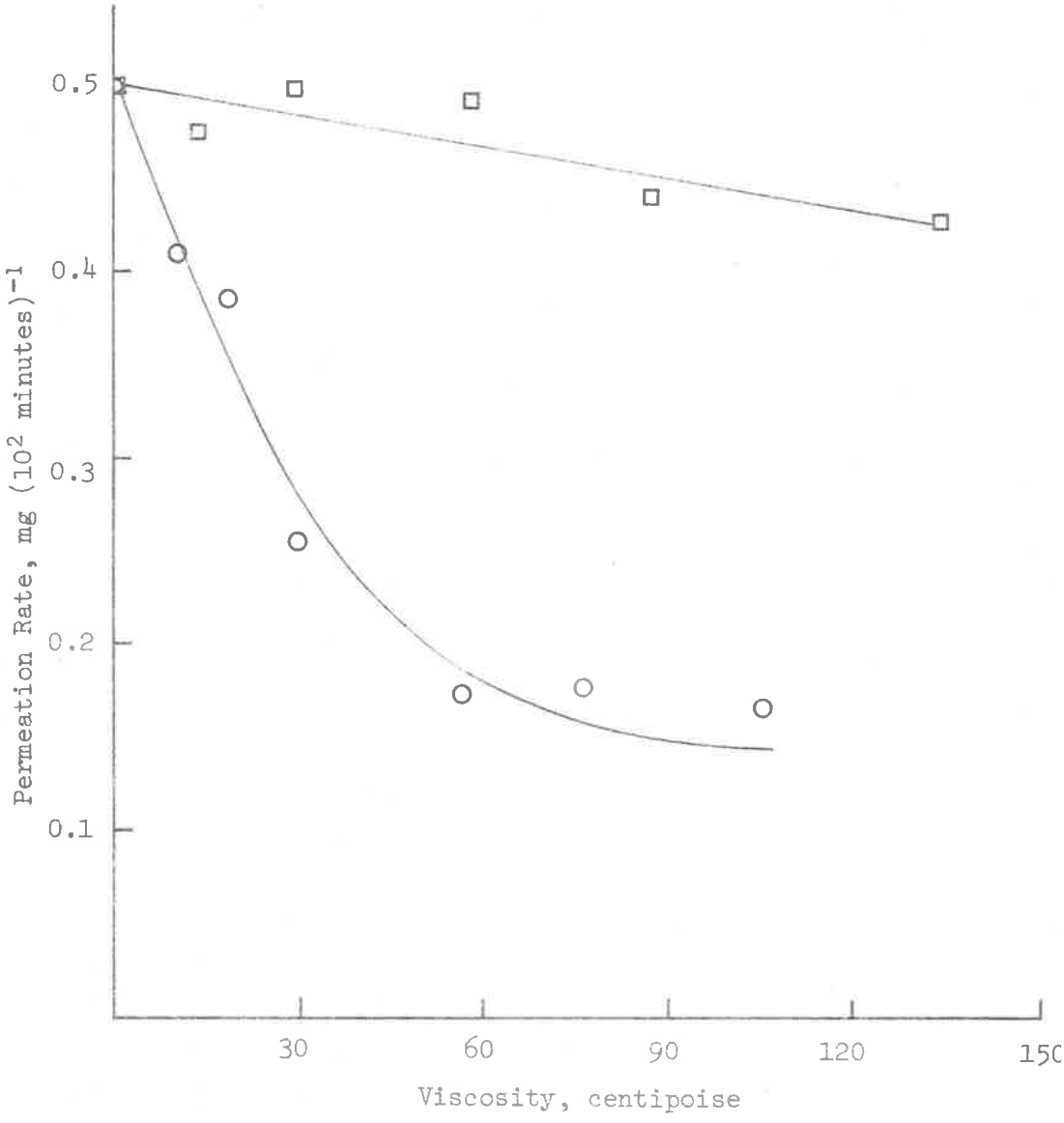

Figure 3.45 Effect of viscosity on the permeation rate of acetophenone through "saturated" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.) Initial concentration: 2.66×10^{-2}M

□ methyl cellulose water solvent

○ glycerin water solvent

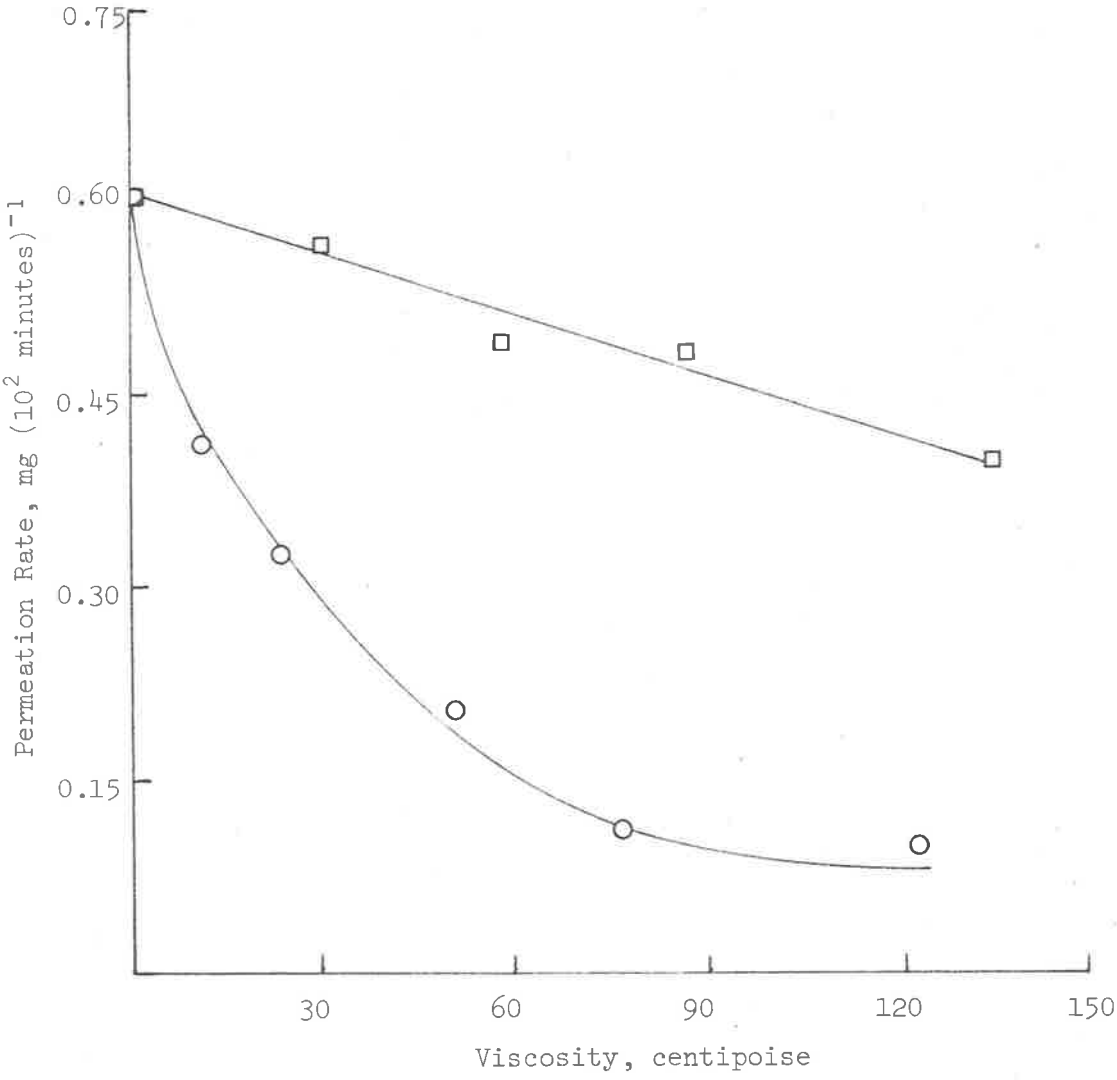

Figure 3.46 Effect of viscosity on the permeation rate of anisole through "saturated" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.) Initial concentration: 3.15×10^{-3}M

□ methyl cellulose water solvent

○ glycerin water solvent

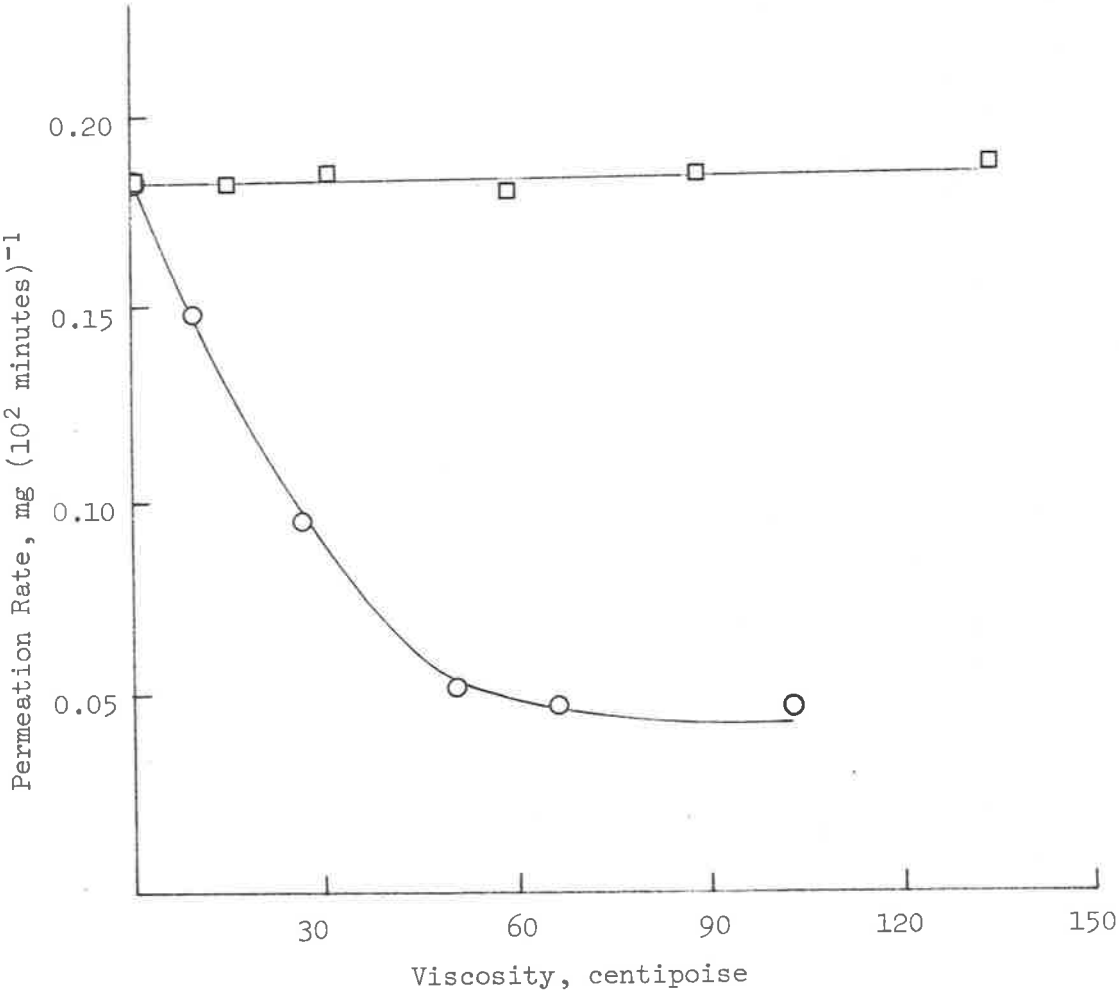

Figure 3.47 Effect of viscosity on the permeation rate of nitrobenzene through "saturated" polyethylene membrane 6 mil. thick at 24.4°. (Each point represents average of measurements made in two cells.) Initial concentration: 4.02×10^{-3}M

□ methyl cellulose water solvent

○ glycerin water solvent

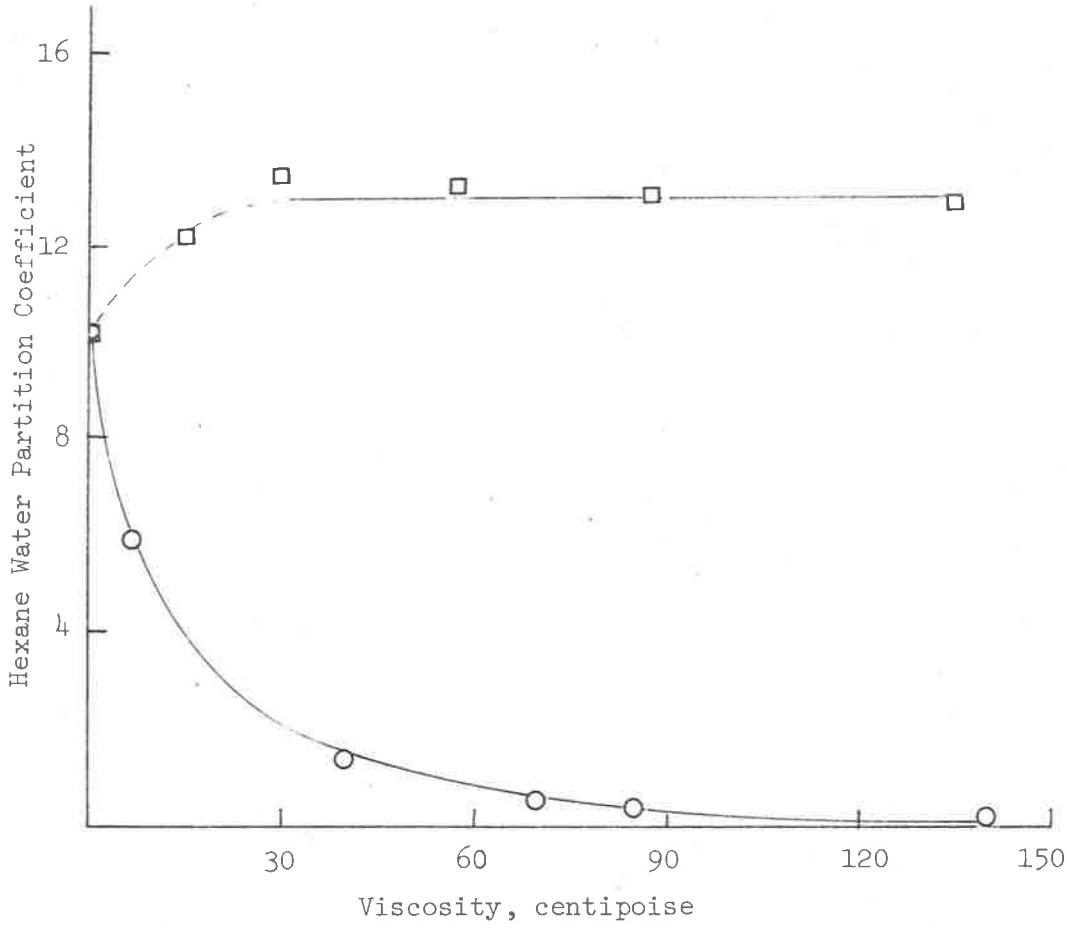

Figure 3.48 Effect of viscosity producing agents on the hexane water partition coefficient of acetophenone at 24.4°.

□ methyl cellulose

○ glycerin

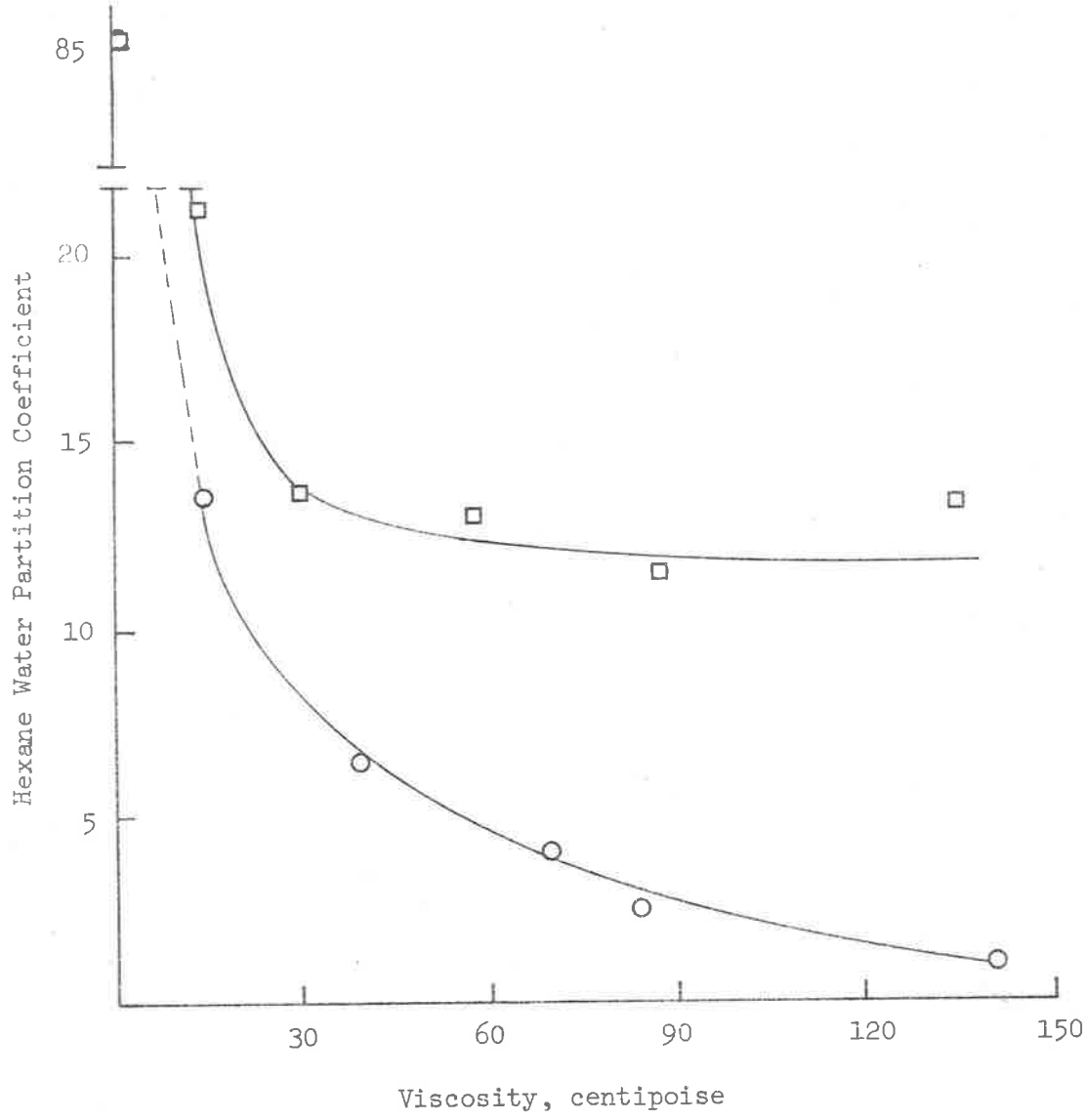

Figure 3.49 Effect of viscosity producing agents on the hexane water partition coefficient of anisole at 24.4°.

□ methyl cellulose

○ glycerin

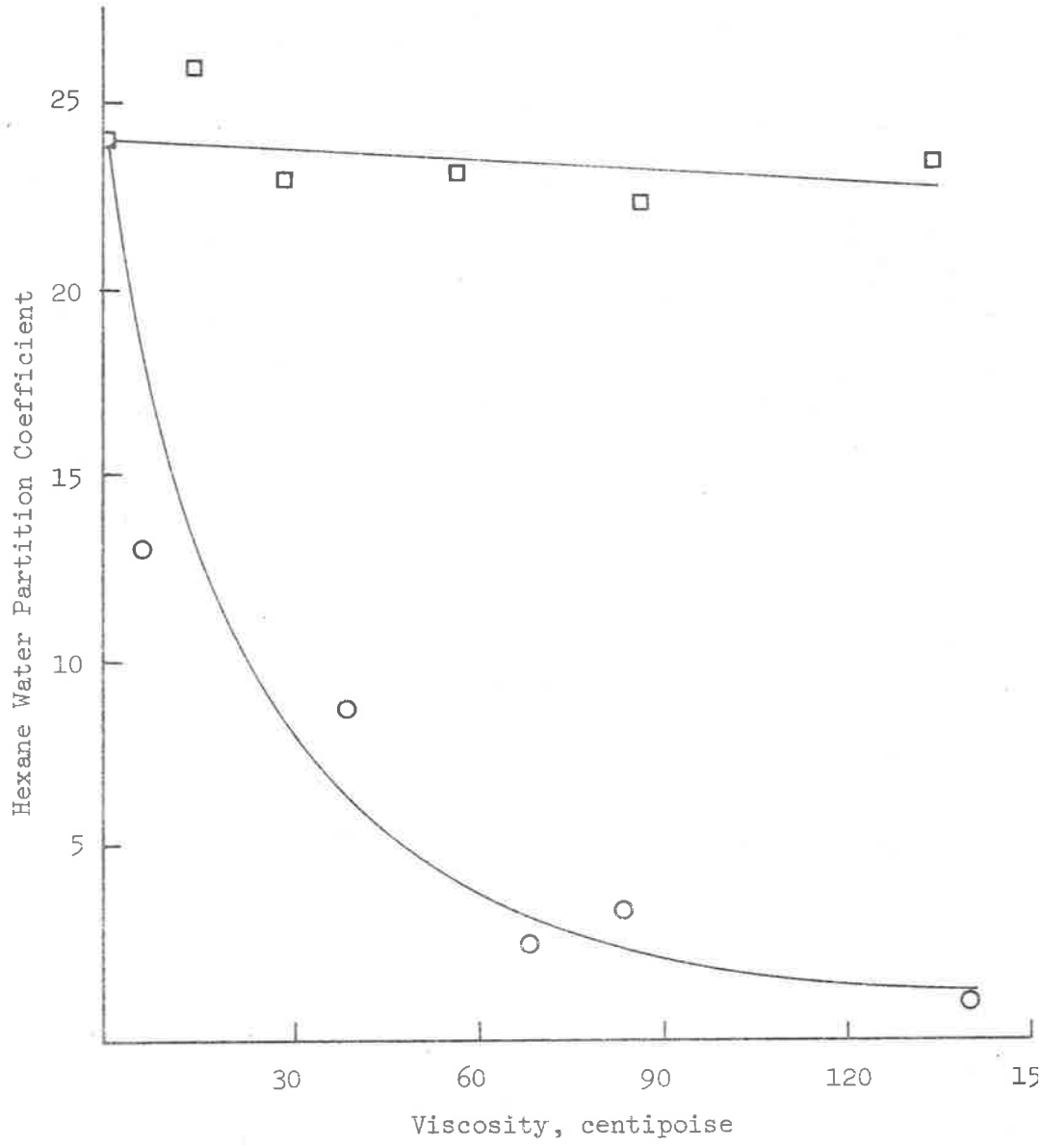

Figure 3.50 Effect of voscosity producing agents on the hexane water partition coefficient of nitrobenzene at 24.4°.

□ methyl cellulose

○ glycerin

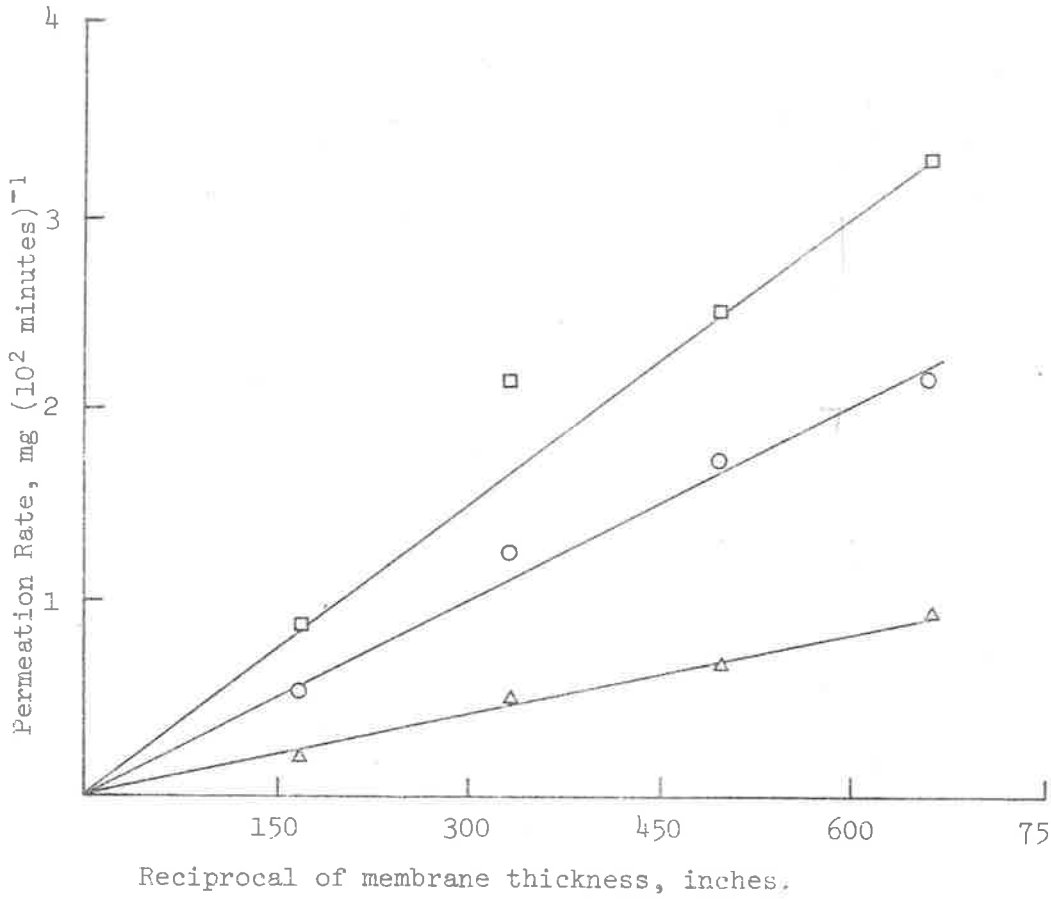

Figure 3.51 Effect of thickness of membrane on permeation rates of three substances through "saturated" polyethylene membranes at 24.4°.

- ○ acetophenone, initial concentration: 3×10^{-2}M
- □ anisole, initial concentration: 4.85×10^{-3}M
- △ nitrobenzene, initial concentration: 4.4×10^{-3}M

4. SORPTION, SOLUBILITY AND PARTITION COEFFICIENT

4.1 Sorption

4.2 Solubility

4.3 Partition coefficient

4.1 Sorption

Sorption experiments were carried out on seven of the ten substances used in this work by the method described in section 2.10. The other substances appeared to interact with the polyethylene when left in contact for one week. The polyethylene was cut to size and weighed before use. In all experiments the polyethylene was cut to weigh 512 mg.

The results of the sorption experiments are given in Table 4.1.

The solubility coefficient (S) is an expression of the solubility of the substance in polyethylene relative to its solubility in the same weight of water and can therefore be regarded as a polyethylene water partition coefficient (section 3.1). This view is supported by Kostenbauder and others (1969) who regarded the S values of Rodell and others (1966) as plastic water partition coefficients even though Rodell and others (1966) did not use the term partition coefficient at all. Herzog and Swarbrick (1971a) have used the term partition coefficient to describe what has previously been referred to as solubility coefficient.

Schoenwald and Belcastro (1969) expressed the sorption of chlorbutanol by polyethylene (and by nylon) as a percentage of the amount of solute originally present - the sorption will therefore vary according to the volume used. Herzog and Swarbrick (1970, 1971a) have shown that the solubility coefficient is independent of the amount of solute present i.e. the solubility coefficient value will be the same irrespective of the volume of the solution - the same cannot be

Table 4.1

Amount of solute sorbed by polyethylene in one week at 24.4°.

	Acetophenone	Anisaldehyde	Anisole	p-Methyl acetophenone	Nitro-benzene	o-Nitrophenol	p-Tolualdehyde
Volume of solution (ml)	200	150	200	150	200	200	150
Initial concentration mg (100 ml)$^{-1}$	91.5	14.8	100.0	20.0	81.8	104.1	17.0
Final concentration mg (100 ml)$^{-1}$	86.0	14.0	77.0	17.0	71.2	92.0	14.8
Amount sorbed (mg)	11.0	1.2	46.0	4.5	21.2	24.2	3.3
Amount sorbed by 1 ml of polyethylene (mg)	19.64	2.14	82.00	8.04	37.86	43.21	5.89
Amount remaining in 1 ml of solution (mg)	0.86	0.14	0.77	0.17	0.71	0.92	0.148
Solubility coefficient	22.84	15.29	106.49	47.29	53.32	46.97	39.79

Weight of polyethylene: 0.512 g
Density of polyethylene: 0.92
(Volume of polyethylene used is therefore 0.56 ml).

said if sorption is expressed as a percentage of the amount originally present. If the sorption values of Schoenwald and Belcastro (1969) are recalculated as solubility coefficients the difference in the sorption of chlorbutanol by polyethylene and by nylon is very much greater than is apparent from the percentage values. In the calculation it is, however, necessary to make an assumption regarding the volume used since no volume is given by the authors. For the greatest apparent amount of sorption reported by Schoenwald and Belcastro (1969) for both polyethylene and nylon and assuming that the same volume was used for both polymers it can be found by calculation that the solubility coefficient of the chlorbutanol between nylon and the water is about five times as great as that between polyethylene and the water - this information is not readily apparent from the data presented.

The solubility coefficients for some of the solutes used in the present study were given in Table 4.1 and appear to be reasonably large, indicating that these solutes are strongly partitioned in favour of the polyethylene. This is surprising if viewed in the light of the statement of Autian (1966) that the sorption of solutes of aqueous solutions by polyethylene could be expected to be very small. This statement might be true for water soluble solutes. The data presented in Table 4.1 suggests that this is apparently not correct for the solutes being considered here. If the polyethylene is regarded as a non polar water immiscible layer as has been suggested previously (Polack and others, 1970; Lees, 1969), the solutes used here could be expected to partition into the polyethylene since (in general) these substances are relatively non polar and relatively water insoluble (section 4.2).

The solubility coefficient is discussed further in Chapter 5.

4.2 Solubility

The aqueous solubilities of substances used in this study are given in Table 4.2.

The relationship between aqueous solubility and permeation rates is considered further in section 5.2.2.1.

4.3 Partition coefficient

The hexane water partition coefficients of the substances used are given in Table 4.3.

The significance of lipid water partition coefficients in the movement of aqueous solutes through non aqueous barriers has been discussed in section 1.2.1.1.

The relationship between the hexane water partition coefficients of the substances used here and the permeation rates of these substances through the polyethylene is discussed in Chapter 5.

Table 4.2

Aqueous solubility of the solutes used.

Solute	Molecular weight[a]	Measured solubility at 24.4° g(100 ml)$^{-1}$	Molar solubility[b] (x 10^2)	Literature value and reference[c] g(100 ml)$^{-1}$
Acetophenone	120.15	0.57	4.74	0.30[1]
Anisaldehyde	136.14	0.25	1.84	
Anisole	108.13	0.15	1.39	
Benzaldehyde	106.12	0.33	3.11	0.29[2]
2,4-Dichlorophenol	163.01*	0.63	3.86	
p-Methyl acetophenone	134.17*	0.12	0.89	0.10[1]
Nitrobenzene	123.11	0.16	1.30	0.19[3]
o-Nitrophenol	139.11	0.47	3.38	0.21[4]
p-Tolualdehyde	120.14	0.14	1.17	0.10[1]
p-Toluidine	107.15	0.83	7.75	0.94[5]

[a] All data except for substances marked * taken from reference [2] below.

[b] Calculated from measured solubility.

[c] References given below:

[1] Gonzales and others (1967).

[2] Merck Index of Chemicals and Drugs. 8th edition (P.G. Stecher, editor). Merck and Co. Inc., Rathway, New Jersey, 1968.

[3] Campetti and Del Grosso (1913).

[4] Vaubel (1895).

[5] Lowenherz (1898).

Table 4.3

Hexane water partition coefficients of the substances used[1] at 24.4°.

Solute		Hexane water partition coefficient
Acetophenone		10.20
Anisaldehyde		7.62
Anisole		85.29
Benzaldehyde		9.53[3]
2,4-Dichlorophenol		7.30[3]
p-Methyl acetophenone		26.10
Nitrobenzene		24.08
o-Nitrophenol[2]	pH 3.90	28.68
	pH 4.70	29.91
	pH 5.35	29.56
	pH 6.30	26.06
	pH 7.21	15.21
	pH 8.04	4.49
p-Tolualdehyde		22.70
p-Toluidine[2]	pH 4.60	0.64
	pH 5.10	1.13
	pH 5.39	2.19
	pH 6.00	2.29
	pH 6.08	5.00
	pH 6.58	2.35
	pH 6.80	5.21
	pH 8.32	2.49

[1] Each value is average of three determinations.

[2] Details of buffer solutions in section 2.1.

[3] From Polack, Roberts and Schumann (1970).

5. DISCUSSION

5.1 Apparatus

5.2 Diffusion and permeation

5.2.1 Introduction

5.2.2 Physicochemical properties of the solute

5.2.2.1 Solubility

5.2.2.2 Molecular weight

5.2.2.3 Lipid water partition coefficient

5.2.2.4 Chemical structure

5.2.3 Physicochemical properties of the system

5.2.3.1 pH

5.3 Mechanism of diffusion and permeation

5.4 Significance of results

5.5 Further work

5.1 Apparatus

The design of the cells used in the present work was based on the apparatus used by Lueck and others (1957a) who measured the permeation of aniline in water containing 1% sodium sulfite, nitrobenzene in 51.4% w/w ethanol and isovaleric acid in 0.001% aqueous sulfuric acid through some semi solid barriers. The authors did not, however, give details of the method used for agitation of the system and for this reason it was decided to use the "rotation" method described in section 2.2. The rotation of the horizontal cells about the central shaft is essentially similar to dialysis methods described (amongst others) by Patel and Foss (1964), Anderson and Morgan (1966) and Mitchell and Brown (1966). The addition of glass beads to the cell ensures adequate mixing. This method of agitation has also been used by Kazmi and Mitchell (1971). The obvious advantage of keeping the cellshorizontal (with rotation about a central shaft) is that very little hydrostatic pressure is exerted on the membrane. In some apparatus used previously in similar work creation of some pressure on the membrane appears to have been possible and even though pressure on each side of the membrane may appear to be "equal" very precise control of stirring rates and stirrer dimensions may be necessary. The apparatus used by Gonzales and others (1967) may possibly have suffered from this drawback and that used by Garrett and Chemburkar (1968a) for quasi steady state diffusion may also have had this defect.

The contents of the cell, described by Holmes, Wilke and Olander (1963), who studied transport through a microporous barrier, which is similar in design to the cell used in the present work was

agitated by a magnetic stirrer located in a special compartment. This design may lead to similar problems due to forced convection.

In some of the apparatus used in this type of work the possibility that part of the membrane is not submerged throughout the experiment appears to be very real. The apparatus used by Garrett and Chemburkar (1968a) for quasi steady state diffusion and that used by Herzog and Swarbrick (1970, 1971a,b) both appear to fall into this category. In both cases the cells are being agitated at a relatively high speed in a shaking device and the volume of the cell compartment is in both cases considerably greater than the volume of solution (or solvent) being used. During agitation there must be a more than even chance that the membrane will not be fully covered by the liquid throughout the duration of the experiment.

In a very recent paper, Flynn and Smith (1971) discussed the design of cells used in this type of work. These workers investigated the effect of a number of cell variables on the permeation rate of p-aminoacetophenone through a dimethyl polysiloxane membrane in a cell which they designed. It was found that the permeation rate was affected by the age of the membrane (section 3.2.1) and also that a change in the stirring rate within the cell had a small (but not significant) effect on the permeation rate. These authors have indicated that further work will be reported in due course.

The effect of different rotation rates of the shaft on the permeation rate has not been investigated in the present work. The degree of agitation within each part of the cell is considered to be satisfactory because the distance of the grids from the membrane makes no difference to the permeation rate (section 2.3). If the degree of

agitation within the cell had not been satisfactory the presence of the grids at different distances from the membrane would have been expected to produce a non homogenous solution at one or more distances and the permeation rates would not have been the same for all positions of the grids.

A disadvantage of the type of apparatus used is the need to stop the rotation mechanism for sampling purposes. The actual time for which the cells are stopped is in practice generally very small relative to the intervals between readings and for this reason it is considered that this is not a particularly serious problem. The apparatus is being adapted so that future work will be able to be done without this difficulty.

These criticisms excepted, this apparatus appears to be satisfactory for the measurement of permeation rates since the data obtained in the experiments designed to investigate the validity of the experimental method and those designed to test the ability of the membrane to prevent permeation of the solvent and added solutes (viscosity producing agents, etc.) (sections 2.4, 2.5) is satisfactory.

5.2 Diffusion and Permeation

5.2.1 Introduction

The meaning of the terms diffusion and permeation were given in section 1.2.

5.2.2 Physicochemical properties of the solute

Numerous workers have related the permeation rates of a number of substances through a variety of barriers to various properties of the permeating molecules. Some of the properties which have been used are solubility, molecular weight and lipid water partition coefficient. The use of combinations of these has also been reported.

5.2.2.1 Solubility

Garrett and Chemburkar (1968a,b,c) found that a plot of the apparent diffusion constant against the reciprocal of the solubility for a number of barbiturates (in acetate buffer pH 4) was linear and a similar plot for 4'aminopropriophenone in a variety of ethanol solutions was also linear.

Herzog and Swarbrick (1971b) have very recently reported a correlation between the transfer rate of a number of benzoic acid derivatives through a polymeric membrane and the reciprocal of the water solubility of the substances.

Figure 5.1 is a plot of the permeation rates against the reciprocal of aqueous solubility of all the substances used in the present work and it is seen that there is no direct relationship between the permeation rate and the reciprocal of aqueous solubility and it can therefore be concluded that the aqueous solubility of a solute is not a rate controlling factor in the permeation of the solute through polyethylene.

5.2.2.2 Molecular weight

The Einstein and Sutherland equation

$$D = \frac{RT}{N} \cdot \frac{1}{6\pi r\eta} \qquad \text{(section 3.2.4)}$$

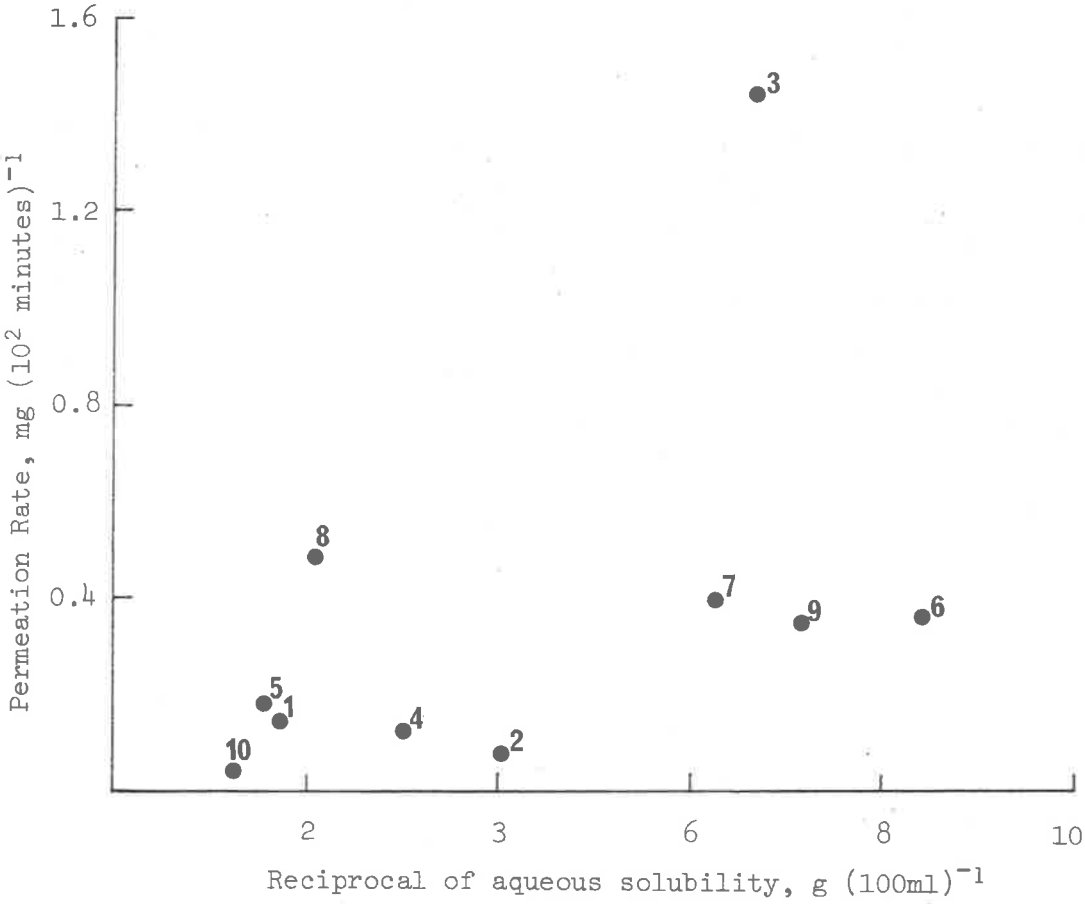

Figure 5.1 Relationship between the reciprocal of aqueous solubility (at 24.4°) and permeation rate through polyethylene membrane 6 mil. thick (at 24.4°) at initial concentration of 1 x 10^{-2}M for ten substances.

1. Acetophenone
2. Anisaldehyde
3. Anisole
4. Benzaldehyde
5. 2,4-Dichlorophenol
6. p-Methyl acetophenone
7. Nitrobenzene
8. o-Nitrophenol (pH 3.81)
9. p-Tolualdehyde
10. p-Toluidine (pH 8.32)

relates the diffusion coefficient of spherical colloidal particles to the viscosity of the medium (Martin, 1960) and since the relationship between radius, molecular weight and partial specific volume is given as

$$\frac{MW\bar{v}}{N} = \frac{4}{3}(\pi r^3)$$

(Chemburkar, 1967), it follows that

$$D = \frac{RT}{6\pi\eta N} \cdot \left(\frac{4\ \pi N}{3M\bar{Wv}}\right)^{1/3} \qquad (5.1)$$

If we assume that all the substances used in the present work have partial specific volumes which are similar then the diffusion coefficient should at constant temperature and constant viscosity be related to the molecular weight of the solute by a relationship of the type

$$D = Z \sqrt[3]{\frac{F}{MW}} \qquad (5.2)$$

If it is assumed that expression 3.1 is valid then since D is linearly related to P a plot of permeation rate against the cube root of the reciprocal of molecular weight should be linear if expression 5.2 is valid. Figure 5.2 is a plot of the permeation rate of a number of solutes (all at the same initial concentration) against the cube root of the reciprocal of the molecular weight of the solute and it can be seen that there is not a linear relationship.

Ballard and Nelson (1962) used the expression

$$D(MW)^{1/2} = Z \qquad (5.3)$$

(originally proposed by Thovert, 1902, for compounds having molecular weights between 60 and 500) and were able to show a linear relationship between the diffusion coefficient and the reciprocal of the square root of the molecular weight for the passage of some molecules through *in vivo* membranes.

If we assume that D is linearly related to P (expression 3.1) a plot of P against the reciprocal of the square root of the molecular weight should be linear if expression 5.3 is valid and Figure 5.3 is such a plot. The fact that the relationships shown in Figures 5.2 and 5.3 are not linear indicates that the permeation rate of a solute through the polyethylene membrane is not dependent on the molecular weight of the solute. Alternatively the assumption that the permeation rate and diffusion coefficient are linearly related (by expression 3.1) may not be valid. The validity of expression 3.1 is considered in section 5.3.

5.2.2.3 Lipid water partition coefficient

The hypothesis that the rate of transfer of a solute from an aqueous system across a non aqueous barrier into another aqueous system is a function of the lipid water partition coefficient of the solute has been proposed by a number of workers. The majority of these workers have been concerned with the passage of substances across membranes in living species.

The first worker to relate these factors appears to have been Meyer (1899) who measured the narcotic effects of a variety of substances in tadpoles and also the olive oil water partition coefficients of the same substances and was able to relate these factors. Baum (1899) appears to have reported a similar effect. Subsequently, Overton (1901)

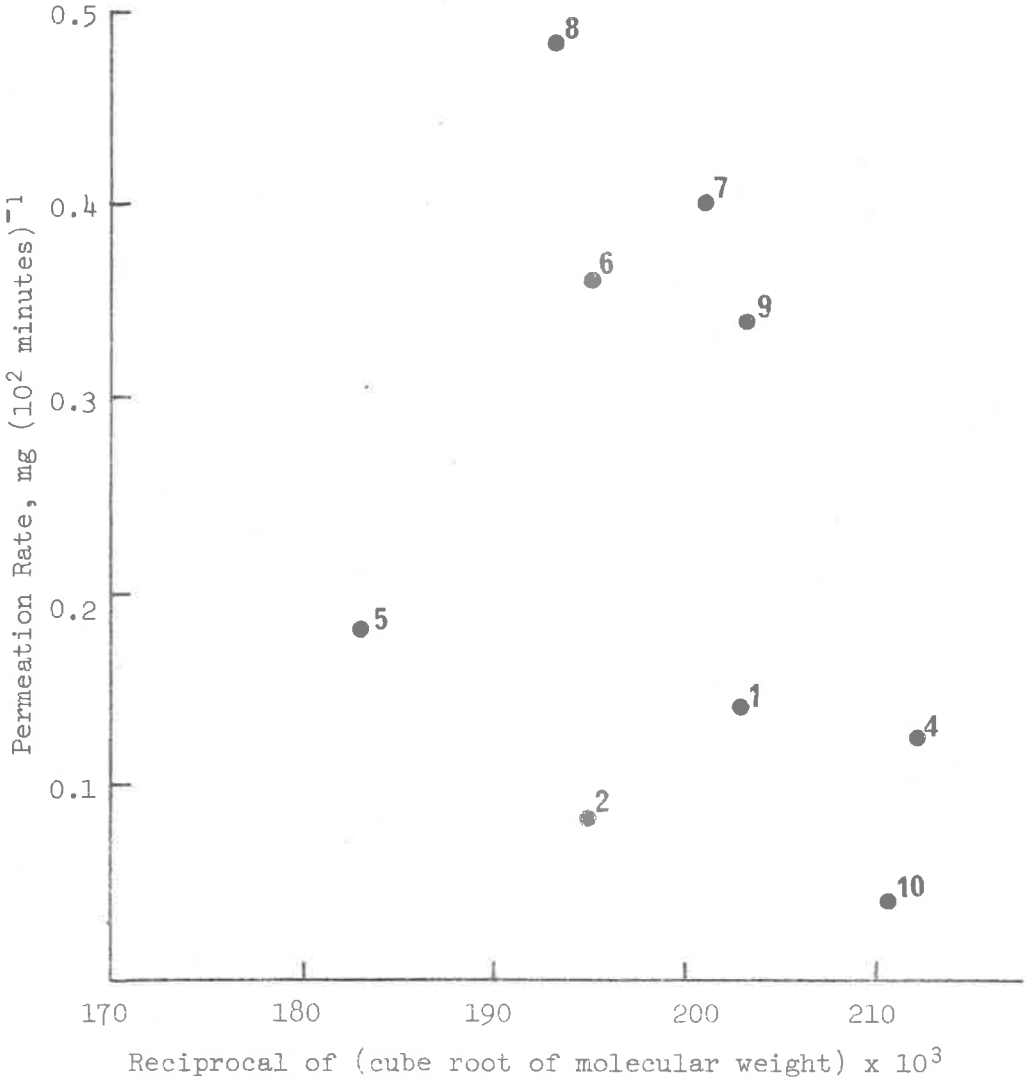

Figure 5.2 Relationship between the reciprocal of the cube root of molecular weight and permeation rate through polyethylene membrane 6 mil. thick (at 24.4°) at initial concentration 1 x 10^{-2}M for nine substances.

1. Acetophenone
2. Ansialdehyde
4. Benzaldehyde
5. 2,4-Dichlorophenol
6. p-Methyl acetophenone
7. Nitrobenzene
8. o-Nitrophenol (pH 3.81)
9. p-Tolualdehyde
10. p-Toluidine (pH 8.32)

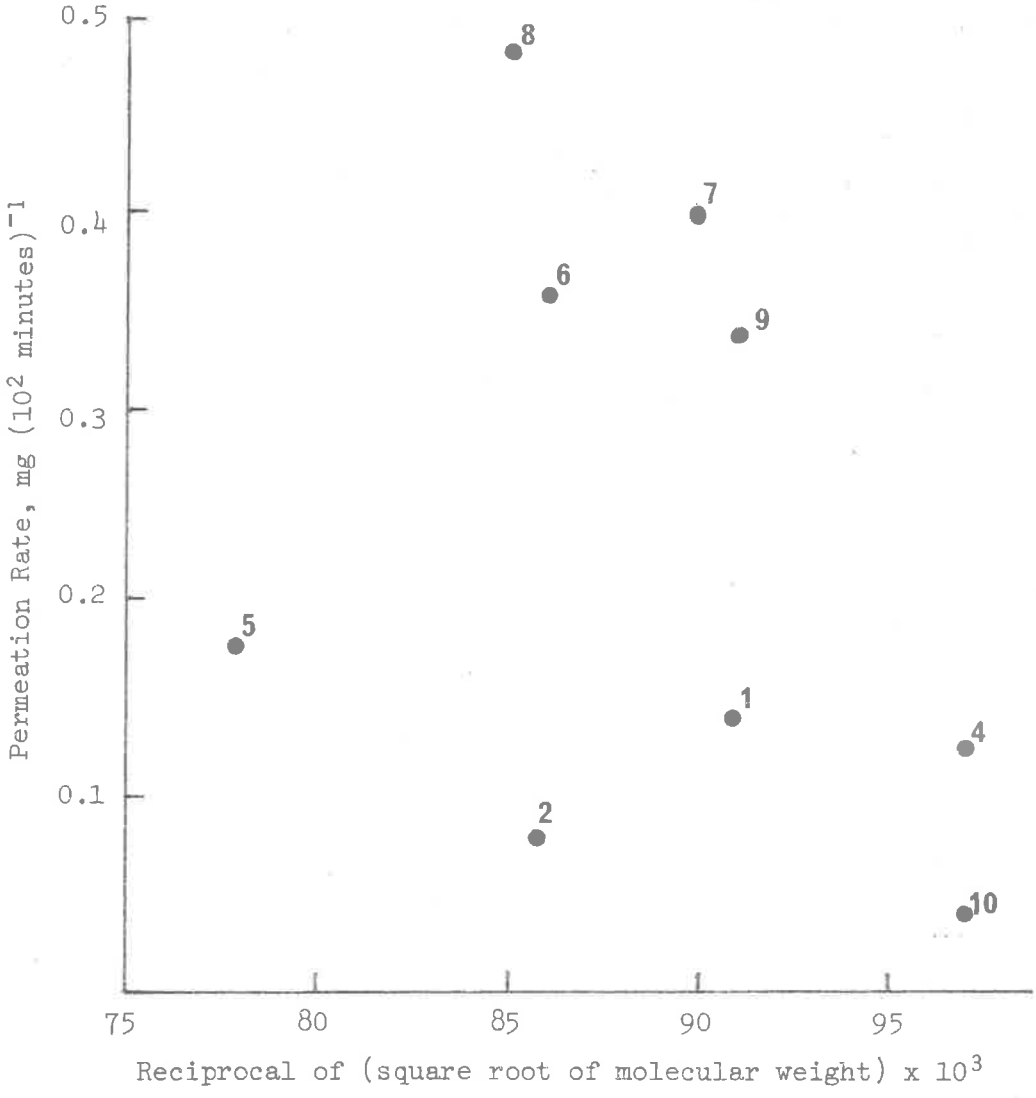

Figure 5.3 Relationship between the reciprocal of the square root of molecular weight and permeation rate through polyethylene membrane 6 mil. thick (at 24.4°) at initial concentration of 1 x 10^{-2}M for nine substances.

1. Acetophenone
2. Anisaldehyde
4. Benzaldehyde
5. 2,4-Dichlorophenol
6. p-Methyl acetophenone
7. Nitrobenzene
8. o-Nitrophenol (pH 3.81)
9. p-Tolualdehyde
10. p-Toluidine (pH 8.32)

who examined the anaesthetic effect of primary alcohol in tadpoles found this effect related to the lipid water partition coefficient of the alcohol. Many other workers have reported a similar correlation between the permeation rates of molecules through *in vivo* barriers and the lipid water partition coefficients of the molecules.

The importance of the lipid water partition coefficient in the ability of an aqueous solute to permeate *in vivo* membranes has been stressed by Schanker (1962) and by Brodie (1964) in reviews of this subject and by others (section 1.2.1.1). It has been reported by Brodie (1964) and others that only the unionised form of an acid or a base is capable of permeating the membranes by a passive diffusion mechanism. (If the ionised moeity is sufficiently small it may penetrate the membrane by other mechanisms.) For the reason given above the pH of the aqueous system in which the acid (or base) is dissolved is an important factor relative to the permeation rate. The permeation rate of solutes through *in vivo* and *in vitro* membranes has been found to be proportional to the concentration of the unionised species present. (section 1.2)

Brodie (1964) stated that the rate of entry of drugs into the cerebro spinal fluid (from the plasma i.e. through an *in vivo* membrane) depends on the lipid solubility of the unionised molecule. Koizumi, Arita and Kakemi (1964) proposed that the absorption rate of an unionised molecule across a lipid barrier (having studied absorption of sulphonamides from the stomach of rats to the blood) was related to the isoamyl acetate water partition coefficient of the molecule by the relationship

$$K_u = \frac{K_{ow}}{\sqrt{MW}} \qquad (5.4)$$

Beckett and Moffat (1969b, 1970) have reported that the absorption rates of a number of substances across the buccal membrane are directly proportional to the logarithms of the partition coefficients of the substances between heptane and an aqueous solution (at a suitable pH).

The partition coefficient principle has been applied to the movement of organic molecules through cells of plants by Collander and Barlund (1933) who reported a correlation between the permeability rate constant for each of a number of molecules in *chara ceratophylla* and the olive oil water partition coefficients of the molecules. Lieb and Stein (1969) measured the diffusion rates of a number of non electrolytes in the same species (and also through some polymers) and were also able to relate the rates to the olive oil water partition coefficients of the molecules. These authors were able to conclude that biological membranes behaved as non porous polymeric sheets with respect to the diffusion of non electrolytes.

The same principle has been found to hold in "*in vitro*" systems. Lueck and others (1957a,b) found a linear relationship between the permeation rate of some aqueous solutes through some semi solid barriers and the partition coefficient of the solute between the actual barrier and water. Similarly the same principle has also been found to hold in an "*in vitro*" system by Garrett and Chemburkar (1968a, b,c).

As a consequence of the establishment of the fact that the movement of molecules through membranes in living species is regarded

as a passage through a lipid layer (section 1.1) some workers have set up models in which organic liquids (which are not miscible with water) have been used to separate two aqueous phases and thus simulate conditions existing in the human gastro intestinal tract. The actual organic liquid used has an effect on the rate of movement of the solute into and through the organic liquid (section 1.2.2.1). The relevance of these models to the present work is considered in more detail later (section 5.4).

In view of the extensive literature dealing with the relationship between lipid water partition coefficients and the movement of molecules through non aqueous barriers it was felt that the possibility of such a correlation should be investigated in the present work. It was also felt that the choice of the organic liquid to be used should be based on a structural similarity (to polyethylene) rather than be purely random as seems to have been the case in some of the work on this subject. For this reason it was decided that an aliphatic hydrocarbon should be used even though Burton, Clarke and Gray (1964) had suggested that

> "inorganic solvents capable of forming hydrogen bonds give better correlation with biological activity than do hydrocarbons."

This choice is supported by the fact that one group of workers (Russell and Stock, 1966) had used the hexane water partition coefficient to express the polarities of some aqueous solutes in polyethylene containers and another group (Polack and others, 1970) had successfully used a function of the hexane water partition coefficient in an expression relating permeation rates (through polyethylene containers) to some properties of the solute molecule. Hexane therefore seemed to

be a logical choice in the present work.

Figure 5.4 relates the permeation rate for a number of solutes (initial concentration 0.01M) to their hexane water partition coefficients. In some cases the actual experiment was performed at a concentration different from 0.01M and the results extrapolated to that concentration. In all the cases where this has been done the actual concentration used was below one third saturation for the particular solute and if the assumption made earlier (section 3.2.2) that a plot of permeation rate against initial concentration is linear when the initial concentration is not greater than one third saturation is valid then the procedure used here is justifiable. A linear relationship appears to hold for the majority of substances used. The deviation from the expected rate of 2,4-dichlorophenol is consistent with the findings of Parliman (1948) who reported that liquids containing halogen atoms permeated through polyethylene at rates greater than expected. A permeation rate greater than expected was also noted for 2,4-dichlorophenol by other workers (Polack and others, 1970).

The linear relationship shown in Figure 5.4 is consistent with the results of Lueck and others (1957a,b) who measured the partition coefficient between the actual barrier and the aqueous solution and also with the results of Nielsen and Parliman (1950), Thornton, Stannett and Szwarc (1958) and Dietrick and Meeks (1959) (sections 1.2.2.2.a and c) all of whom found the permeation rates of water soluble substances (i.e. alcohol, methanol and hydrogen peroxide) to be very small.

A number of authors have however, suggested that the absorption of drugs is related more closely to the logarithm of the lipid water partition coefficient than to the partition coefficient itself. This relationship has been shown for a number of substances. For example,

Schanker (1964) was able to relate these factors for the absorption of some barbiturates in the rat. The work of Beckett and Moffat (1969b, 1970) has been referred to above. Herzog and Swarbrick (1971b) have recently reported similar relationships for an *in vitro* system. In this context it is interesting to record the first few paragraphs from a recent paper by Lien, Koda and Tong (1971), who write as follows:

> "Drug absorption is probably one of the most important factors determining the bioavailability of any drug after its administration. Different models and different mathematical expressions have been used by a number of different investigators in correlating drug absorption with the partition coefficients and pKa values [references cited].
>
> Due to the multiplicity of biological testing methods, in the model systems used and the expressions of the degree of absorption, little generalised information is available to enable one to describe or predict drug absorption quantitatively.
>
> For example in spite of careful study of the percutaneous absorption of steroids and alcohols and even the measurement of the partition coefficients no quantitative correlation was predicted or given [references cited]. This was due to the fact that the authors used the permeability constant (kp) and the partition coefficient (k) rather than the linear free energy related log kp and log k terms; consequently no apparent correlation was observed."

Lien and others (1971) go on to show that for the data on percutaneous absorption of steroids and alcohols to which they refer a log - log plot is linear for each of three different solvent systems used.

The implication by Lien and others (1971) that lipid water partition coefficients and permeability rates cannot be related in a linear manner is shown to be incorrect by some of the work cited above and by the data obtained in the present work. A plot of the logarithm of the permeation rate against the logarithm of the hexane water partition coefficient for the solutes used in the present work is shown

in Figure 5.5 and it can be seen to approximate to a linear relationship - this is to be expected from the linear relationship of Figure 5.4. However the intercept on the log permeation rate axis suggests that permeation will take place even if the molecule does not partition from water into hexane and this would be very surprising.

5.2.2.4 Chemical structure

Salame (1961) predicted the permeation rates of a number of pure liquids through polyethylene by the use of an expression which he derived and into which he incorporated a numerical value for each constituent part of the molecule. The expression used was

$$\log Pf = 16.55 - \frac{3700}{T} - 0.22\pi \qquad (5.5)$$

In the present work all the solutes used are mono, di or tri substituted benzenes and the expression of Salame (1961) should be applicable. The "permachor" values of the solutes used have been calculated from the data given by Salame (1961) and are given in Table 5.1. ("Permachor" defined in section 1.2.2.2.c.)

The experimental and calculated values of the permeation rates are shown in Table 5.2 where it is seen that there is no correlation between the predicted and experimental permeation rates. Following on from what was said in section 3.1 it is interesting to note that the units of permeation given in Table 5.2 were apparently used by Salame (1961) to relate permeation, diffusion and solubility by expression 3.1.

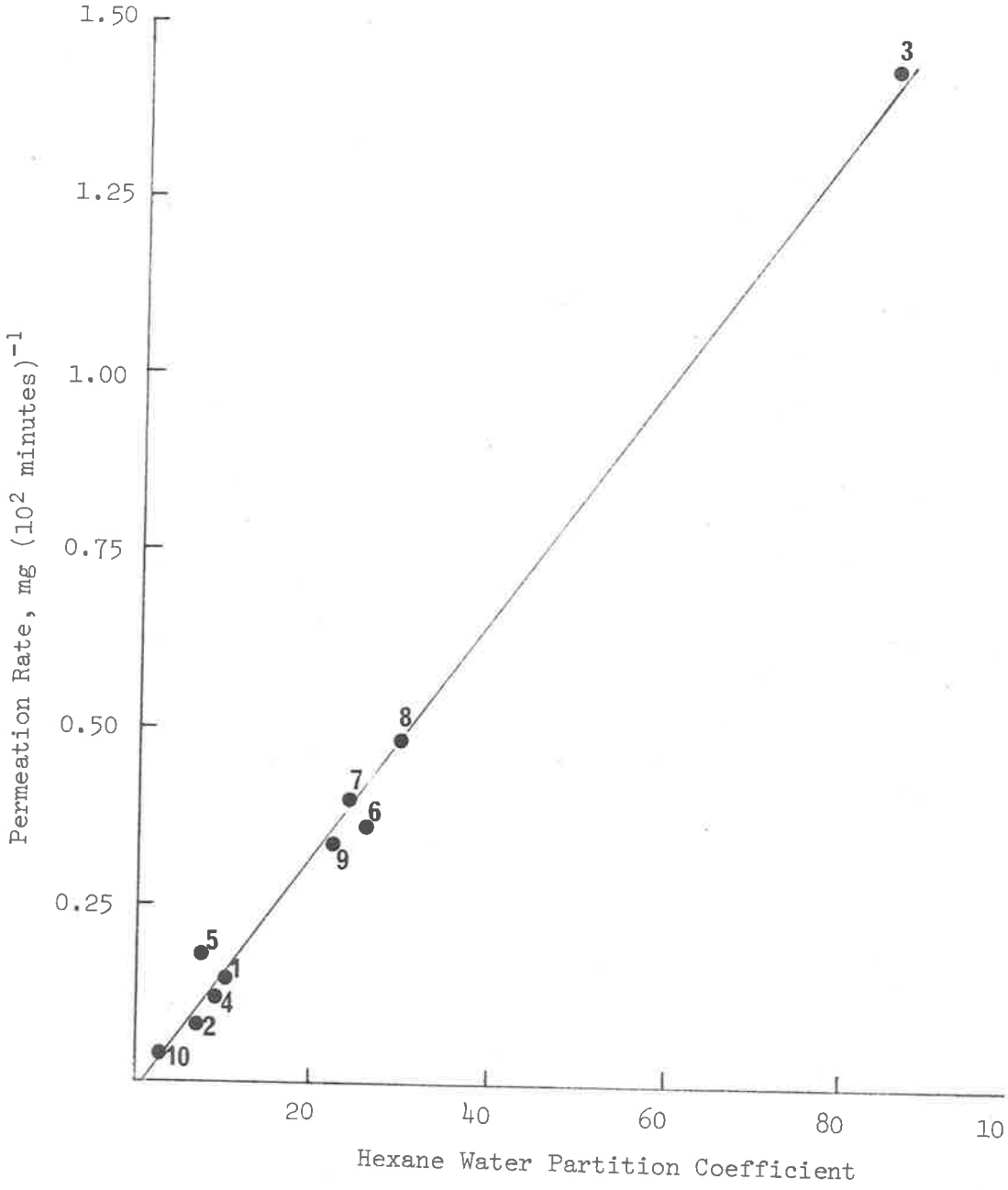

Figure 5.4 Relationship between hexane water partition coefficient (at 24.4°) and permeation rate through polyethylene membrane 6 mil. thick (at 24.4°) at initial concentration of 1×10^{-2}M for ten substances.

1. Acetophenone
2. Anisaldehyde
3. Anisole
4. Benzaldehyde
5. 2,4-Dichlorophenol
6. p-Methyl acetophenone
7. Nitrobenzene
8. o-Nitrophenol (pH 3.81)
9. p-Tolualdehyde
10. p-Toluidine (pH 8.32)

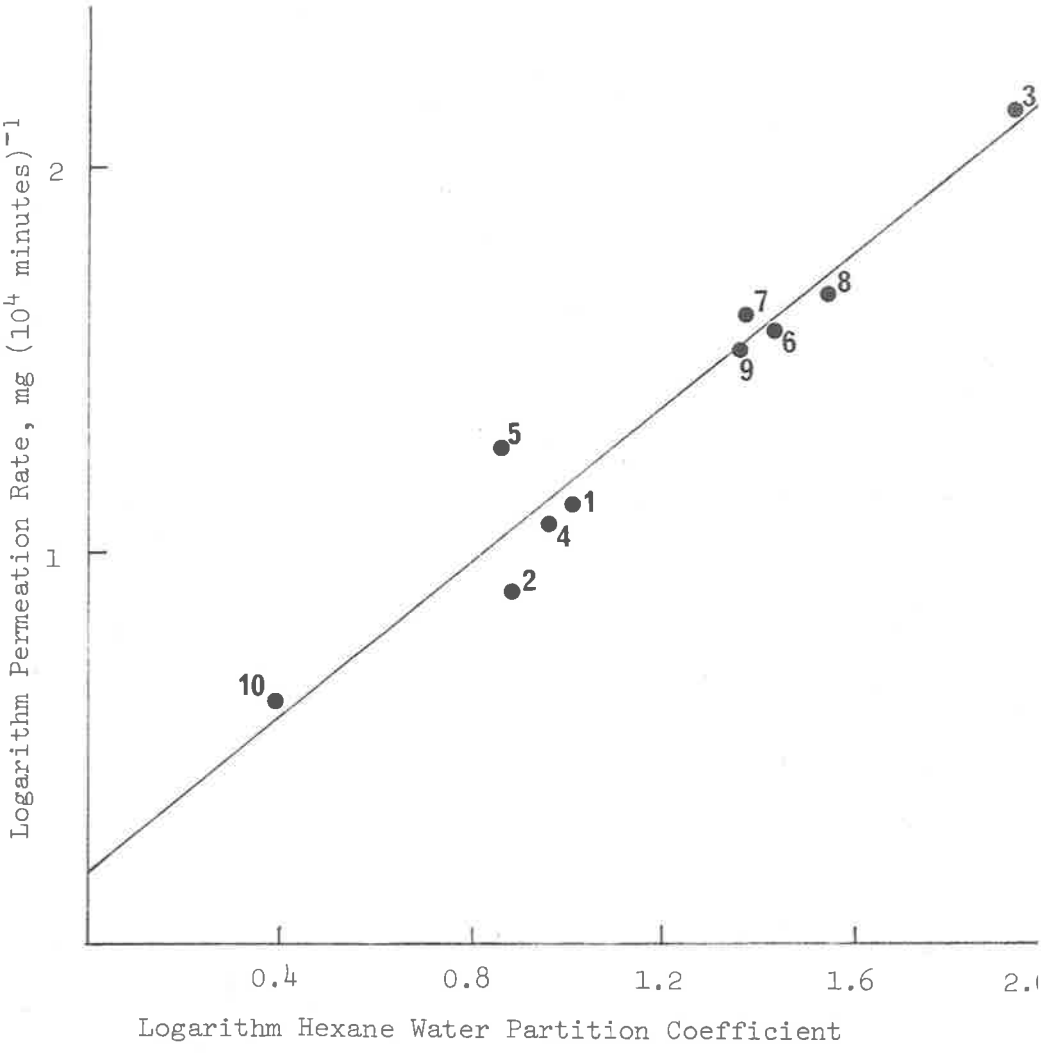

Figure 5.5 Relationship between logarithm of the hexane water partition coefficient (at 24.4°) and the logarithm of the permeation rate through polyethylene membrane 6 mil. thick (at 24.4°) at initial concentration of 1 x 10^{-2}M for ten substances.

1. Acetophenone
2. Anisaldehyde
3. Anisole
4. Benzaldehyde
5. 2,4-Dichlorophenol
6. p-Methyl acetophenone
7. Nitrobenzene
8. o-Nitrophenol (pH 3.81)
9. p-Tolualdehyde
10. p-Toluidine (pH 8.32)

Table 5.1

"Permachor" values of the substances used.

Solute	Permachor value
Acetophenone	15.9
Anisaldehyde	21.2
Anisole	14.0
Benzaldehyde	14.4
2,4-Dichlorophenol	20.8
p-Methyl acetophenone	15.3
Nitrobenzene	15.0
o-Nitrophenol	15.0
p-Tolualdehyde	13.8
p-Toluidine	17.4

Table 5.2

Comparison of permeation rates calculated by Salame's expression and those obtained experimentally for permeation at 24.4°.

Solute	Permeation factor of Salame g/24 hours/001 in/100 in^2	Permeation rate experimental* ($\times 10^{-8}$)
Acetophenone	0.691	0.675
Anisaldehyde	- †	0.348
Anisole	1.029	7.723
Benzaldehyde	1.007	0.672
2,4-Dichlorophenol	- †	0.639
p-Methyl acetophenone	0.743	1.555
Nitrobenzene	0.809	1.880
o-Nitrophenol	0.809	2.028
p-Tolualdehyde	1.073	1.668
p-Toluidine	0.281	0.231

* Calculated to be in the same units as Salame's data. Effect of concentration taken into account by extrapolation of permeation rate in solution (at concentration below one third saturation) to permeation rate for a 100% solution.

† Negative values.

5.2.3 Physicochemical properties of the system

Some of these properties have been considered in section 3.2. The effect of pH on the permeation rate is considered further below.

5.2.3.1 pH

The effect of pH on the permeation rates of an acid and a base were reported in section 3.2.3 where it was seen that at constant initial concentration the permeation rate varied as the pH of the system was changed. It was also seen that the permeation rate of the acid decreased as the pH increased (i.e. as the proportion of unionised species was reduced) and that of the base increased as the pH increased (i.e. as the proportion of the unionised species was increased). These results are consistent with the theory that only the unionised species is capable of permeating through non aqueous barriers (sections 1.2 and 5.2.2.3). This argument is strengthened by consideration of the permeation rates of both the acid and the base at the pH at which unionised and the ionised species are present in equal proportions (i.e. at the pKa of the acid or base). The pKa of o-nitrophenol is given as 7.17 and that of p-toluidine as 5.08 (Weast, 1968). At these pH's the permeation rate is seen to be approximately half of that which occurs when the molecule is fully unionised. The permeation rate of p-toluidine appears to be increased by the presence of phosphate ions at pH's greater than 5.70.

5.3 Mechanism of Diffusion and Permeation

It has been seen above that the permeation rate of the solute is closely related to its hexane water partition coefficient. Further evidence of the relationship is given in Figures 5.6 and 5.7 in which permeation rates of o-nitrophenol and p-toluidine are plotted at a number of pH's and the rates compared with the hexane water partition coefficients of the solute over the same range of pH. Additional evidence is given by examination of the relationship between permeation rates in solutions of varying viscosity and the hexane water partition coefficients of the solutes in those systems - these were presented in Figures 3.48-3.50. It seem reasonable to conclude then that the partition step, k_2, in the permeation process represented diagrammatically in Figure 3.1 (reproduced below) is the step which controls whether the permeation process will proceed or not.

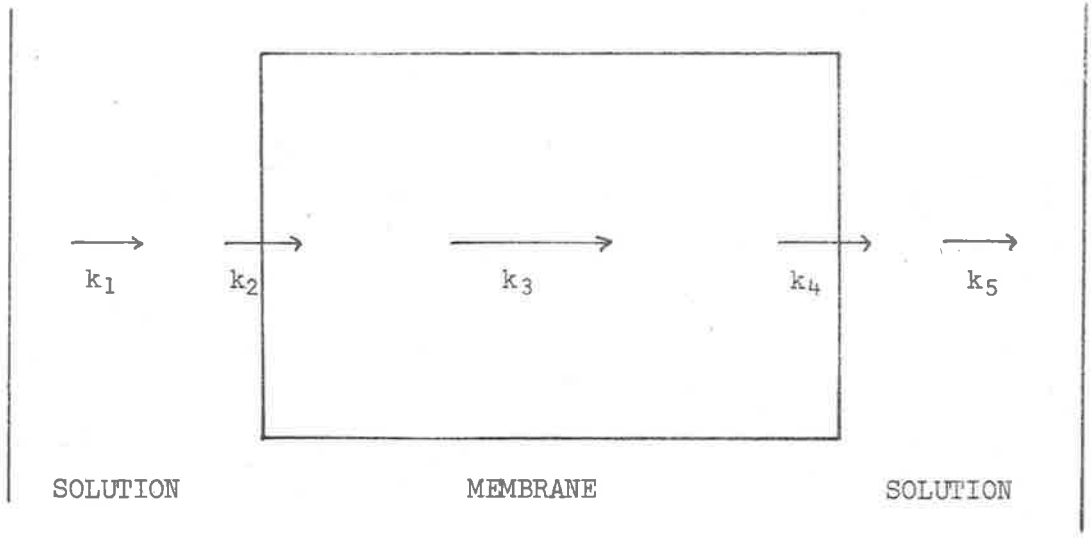

Figure 3.1 Diagrammatic representation of diffusion and permeation through polyethylene membrane.

k_1 represents diffusion of solute molecules through the solution to the membrane.

k_2 represents entry of solute molecules (from solution) into the membrane.

k_3 represents diffusion of solute molecules through the membrane.

k_4 represents exit of solute molecules from the membrane.

k_5 represents diffusion of solute molecules away from the membrane.

For the polyethylene membrane being considered in this work a hexane water partition coefficient of about 1.5 is apparently necessary for the process to take place (Figure 5.4). The fact that the partition step, k_2, is the controlling step appears to confirm the suggestion made earlier (section 3.2.2) that solutes which are soluble in the membrane require less energy (of activation) for permeation than do those which are not - i.e. since permeation is essentially a movement from the solution to the membrane the solutes which partition most readily require the least energy of activation for permeation.

It has generally been the custom in this type of work to use the value of a permeation rate (P) and the diffusion coefficient (D) to calculate the solubility coefficient (S) by substitution in expression 3.1 (i.e. $P = D \times S$).

The solubility coefficient as defined by Gonzales and others (1967) was given above (section 3.1). From this definition we may, in the present context, regard the solubility coefficient as a poly-ehtylene water partition coefficient (section 4.1).

We have seen above that a function of the hexane water partition coefficient of a solute has been used previously to represent a measure of the polyethylene water partition coefficient of the solute (section 5.2.2.3). The relationship between the solubility coefficient (S) or polyethylene water partition coefficient, for some substances and the hexane water partition coefficients for the same substances is given in Figure 5.8 and the relationship

$$S = 14.8 + 1.11\ K_{hw} \qquad (5.6)$$

which is the straight line in Figure 5.8 fits that data.

The permeability factor (P) has been defined differently by different authors (section 3.1) and the use of these different values of P will obviously lead to different values of S, if S is determined by substitution in expression 3.1. For comparative purposes the permeability constant (PC) as defined by Gonzales and others (1967) as the quantity (in mg) of agent passing through a film of 1 cm^2 surface area and 1 cm thickness per second when the concentration gradient is 1 $mg.ml^{-1}$ provides a useful means of expressing the permeation rate. The relationship between the permeation rate used in Chapter 3 [$mg.(10^2\ min)^{-1}\ (9.62\ cm^2)^{-1}\ (0.006")^{-1}$] and the above is a factor of 1/(100 x 66.6 x 9.62 x 60) if the rate is assumed to be linearly related to the surface area available for permeation. The effect of change in thickness from 0.015 cms to 1 cm is, according to the relationship shown in Figure 3.51 a factor of 1/66.6. This value of P (i.e. PC) will, according to Gonzales and others (1967), if divided by the diffusion coefficient (D) be equal to the solubility coefficient (S) according to expression 3.1 (section 3.1).

Table 5.3 shows the experimental values of PC and D for all of the solutes used, at 24.4°, together with the values of S calculated by substitution in expression 3.1. The values of PC and D have been calculated from the data of Figures 3.20-3.29. The assumption has been made that the value of D is independent of concentration (as was done by Gonzales and others, 1967) because the solubility coefficient is an equilibrium value and has been shown to be independent of concentration (Herzog and Swarbrick, 1971a) and because PC is a constant (by

Table 5.3

Permeation, diffusion and solubility values of the substances used.[a]

Substance	Permeation Rate (P)[b] mg(10^2 minutes)$^{-1}$		Permeability constant (PC)[c] (x 10^8)	Diffusion coefficient (D) (x 10^8) (cm^2 sec^{-1})	Partition coefficient polyethylene water (K_{pw})	Permeability constant / Diffusion coefficient (PC/D)	Partition coefficient hexane water (K_{hw})
	1x10^{-1}%	1x10^{-2}M					
Acetophenone	0.117	0.140	3.03	1.22	22.8	2.473	10.20
Anisaldehyde	0.060	0.082	1.56	1.35	15.2	1.152	7.62
Anisole	1.333	1.440	34.64	2.08	106.4	16.629	85.29
Benzaldehyde[d]	0.116	0.123	3.01	1.38			9.53
2,4-Dichlorophenol[d]	0.110	0.180	2.86	1.60			7.30
p-Methyl acetophenone	0.268	0.360	6.97	1.09	47.2	6.36	26.10
Nitrobenzene	0.325	0.400	8.45	1.42	53.3	5.95	24.08
o-Nitrophenol[e]	0.350	0.486	9.09	1.48	46.9	6.17	29.91
p-Tolualdehyde	0.288	0.343	7.48	1.25	39.7	5.98	22.70
p-Toluidine[d,f]	0.040	0.042	1.03	0.90			2.49

[a] All experimental values determined at 24.4°.

[b] P values at concentration indicated through a membrane 9.62 cm^2 in area, 0.006 in thick.

[c] PC is the permeation rate (in mg.sec^{-1}) through a membrane 1 cm^2 in area and 1 cm thick when the concentration gradient is 1 mg.ml^{-1}.

[d] S values not determined for these substances because of apparent interaction with the polyethylene over a period of one week at 24.4°.

[e] All experimental values determined at pH 3.81.

[f] All experimental values determined at pH 8.32.

definition) independent of the actual concentration used, provided the concentration used in the determination is less than one third saturation and earlier arguments are valid (section 3.2.2). It follows, therefore, from expression 3.1 that D must also be independent of concentration.

No work in which the independent determination of PC, D and S has been carried out (for the diffusion and permeation of solutes through polyethylene or other polymeric membrane) appears to have been reported. Salame (1961) appears to have measured all three factors independently but does not appear to have reported his results. In some work the experimental determination of two of the three factors in expression 3.1 and the calculation of the third has produced some unexpected results, which have not been confirmed by experiment and which must, therefore, be of doubtful value. For example, Powell, Nematohalli, Guess and Autian (1969) measured PC and D values for the passage of benzalkonium chloride into and through nylon and calculated the S values from these. The calculated S values appear to be a very irregular set of results and it seems unlikely that the partitioning of the solute between the polymer and the aqueous layer should vary in such a way. If S is to have any meaning it must surely be an equilibrium value and not just the number which relates PC and D for a particular set of conditions.

A plot of $\frac{PC}{D}$ i.e. the calculated value of S against the experimentally determined value of S is shown in Figure 5.9 and the linear relationship is described by the equation,

$$\frac{PC}{D} = -1.52 + 0.16\ S \qquad (5.7)$$

Even though the relationship is linear it is obvious that the experimental and calculated values are very different. It follows that the use of expression 3.1 to calculate S values from experimental PC and D values may not be justifiable - it certainly would not be for the conditions used in this work.

A plot of the calculated S values against the hexane water partition coefficients for the solutes is shown in Figure 5.10 and the relationship is described by the equation,

$$\frac{PC}{D} = 0.88 + 0.18\ K_{hw} \qquad (5.8)$$

Different conditions in the determination of the permeation rate (P) and D (i.e. different polyethylenes, different thickness, etc.) or the use of a different permeability factor (section 3.1) will obviously lead to different values of some of the factors in equations 5.7 and 5.8. It can be seen, however, that it is possible by knowing the hexane water partition coefficient of a particular solute and the relevant equations (i.e. including that shown graphically in Figure 5.4, $P = -0.021 + 0.017\ K_{hw}$) to calculate the permeability constant, the diffusion coefficient and the solubility coefficient (or polyethylene water partition coefficient) of that solute into and through polyethylene. It may be necessary to determine the values in the expressions for each type of polyethylene and it may be necessary to confirm these each time a new batch of polyethylene is used.

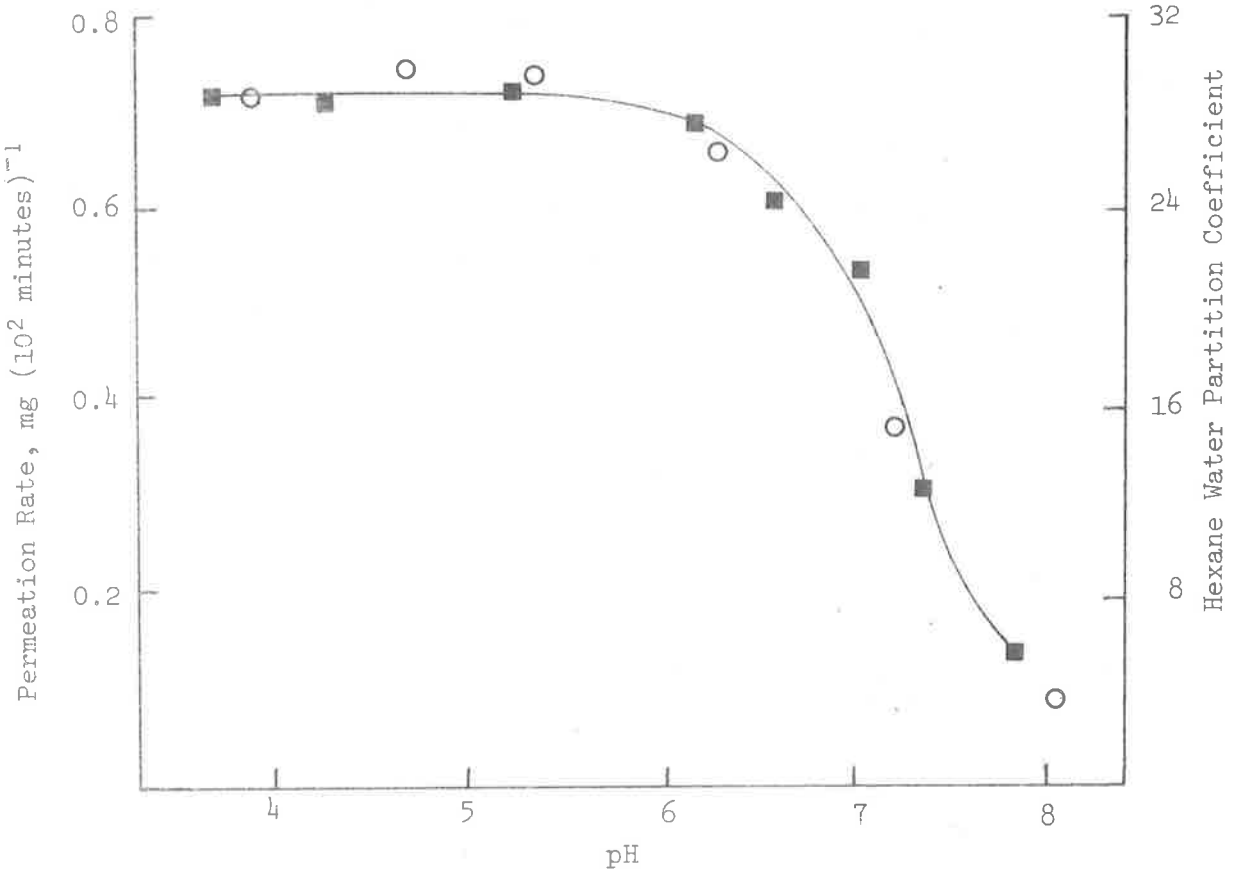

Figure 5.6 Comparison of the effect of pH on the permeation rate of o-nitrophenol through polyethylene membrane 6 mil. thick (at 35.2°) and on the hexane water partition coefficient of the same substance (at 24.4°). Permeation rate measured at initial concentration of 7.18×10^{-3}M. Buffer systems used given in Table 2.1.

■ permeation rate

○ hexane water partition coefficient

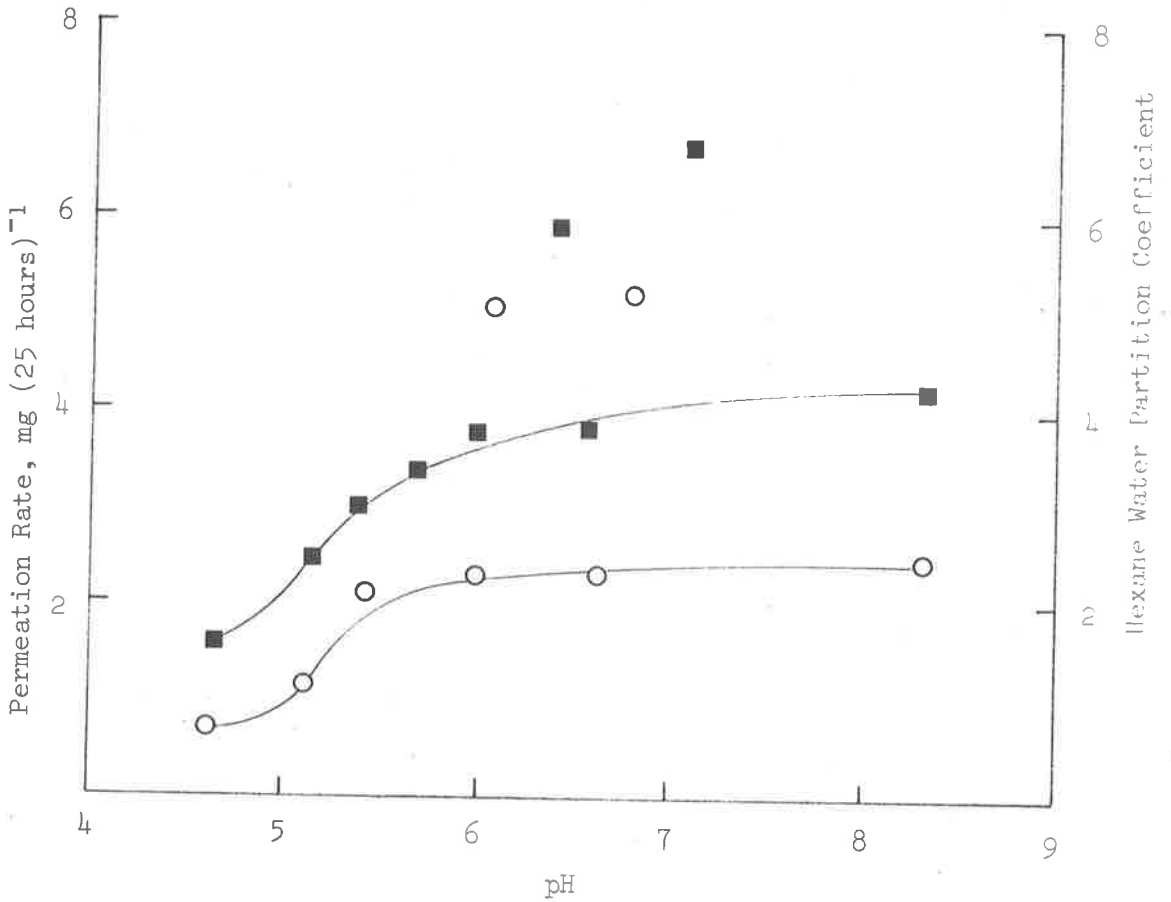

Figure 5.7 Comparison of the effect of pH on the permeation rate of p-toluidine through polyethylene membrane 6 mil. thick (at 35.2°) and on the hexane water partition coefficient of the same substance (at 24.4°). Permeation rate measured at initial concentration of 2.33×10^{-2}M. Buffer systems used given in Table 2.2.

■ permeation rate

○ hexane water partition coefficient

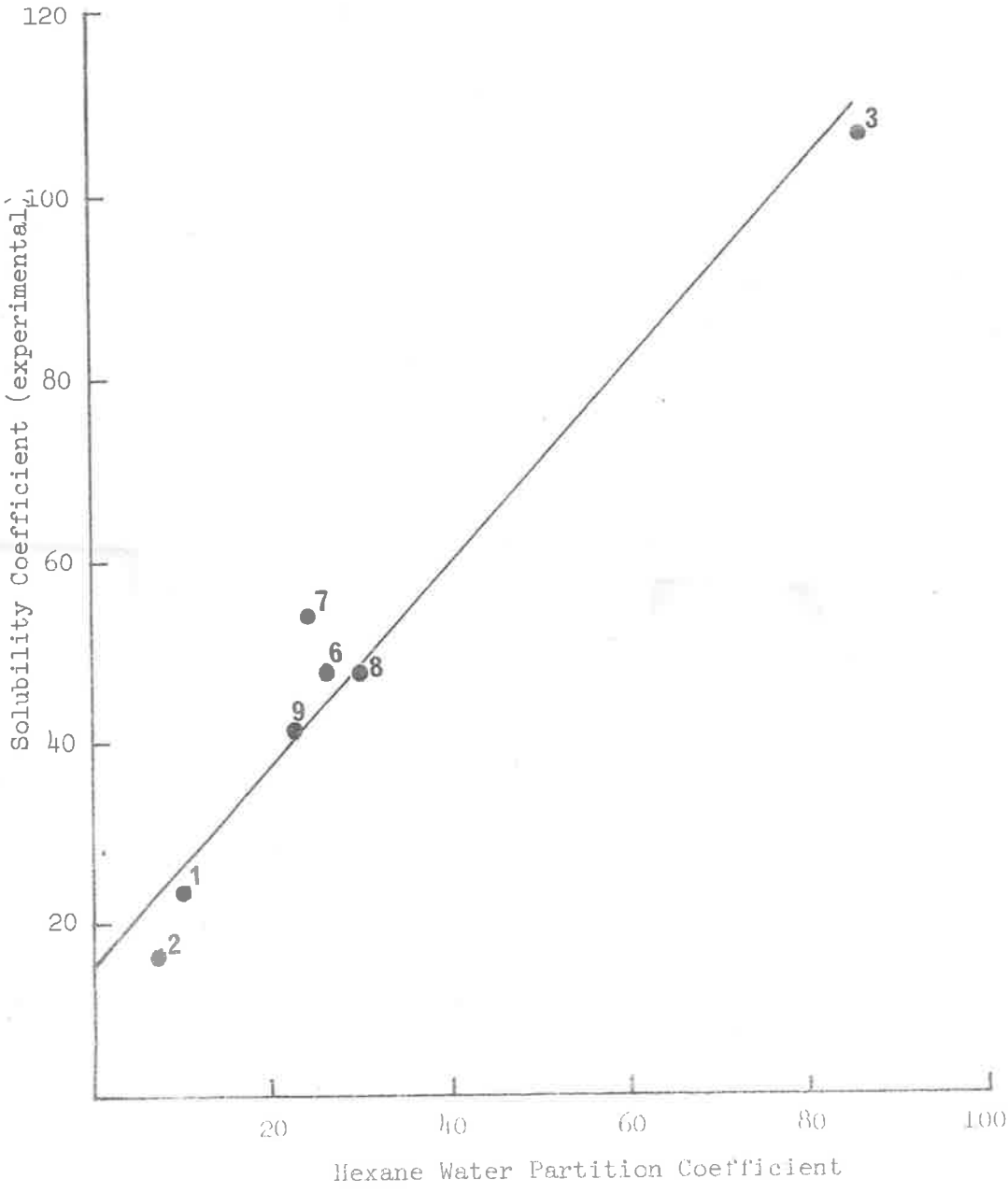

Figure 5.8 Relationship between hexane water partition coefficient (at 24.4°) and experimental solubility coefficient between polyethylene and water (at 24.4°) for seven substances.

1. Acetophenone
2. Anisaldehyde
3. Anisole
6. p-Methyl acetophenone
7. Nitrobenzene
8. o-Nitrophenol (pH 3.81)
9. p-Tolualdehyde

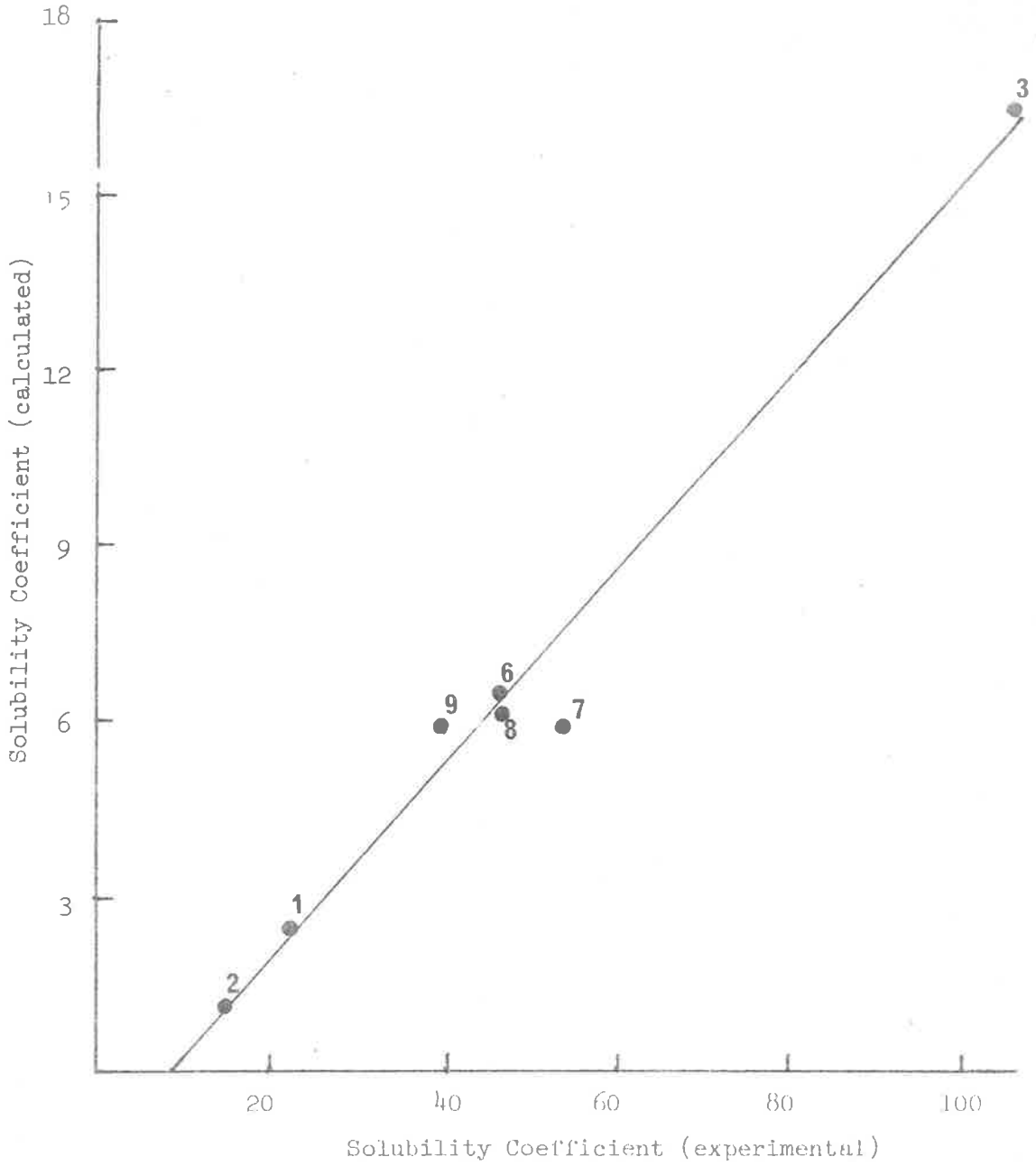

Figure 5.9 Relationship between experimental solubility coefficient and value calculated from diffusion and permeability data for seven substances. (All experimental data obtained at 24.4°.)

1. Acetophenone
2. Anisaldehyde
3. Anisole
6. p-Methyl acetophenone
7. Nitrobenzene
8. o-Nitrophenol (pH 3.81)
9. p-Tolualdehyde

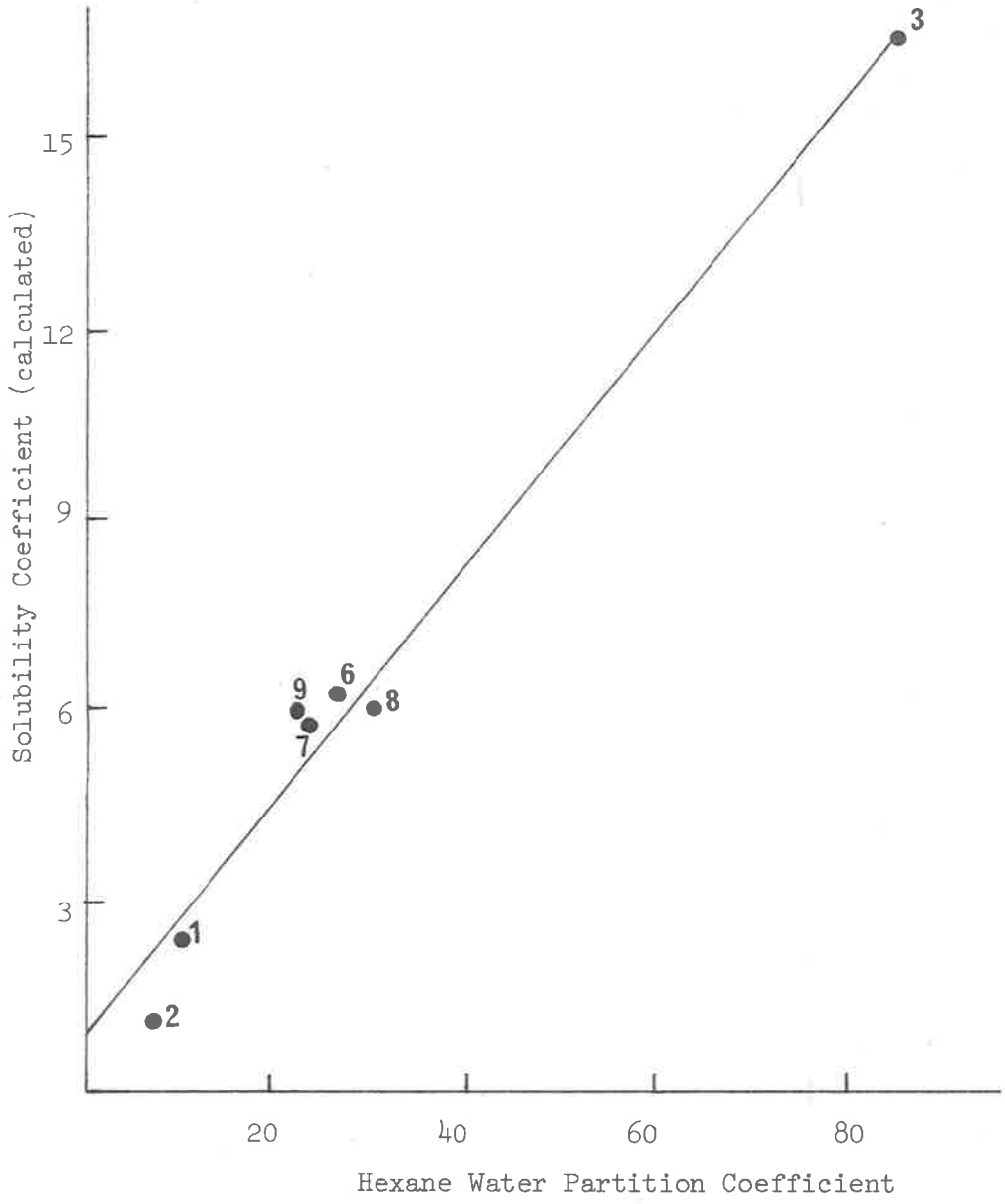

Figure 5.10 Relationship between calculated solubility coefficien and hexane water partition coefficient for seven substances. (All experimental data obtained at 24.4°.)

1. Acetophenone
2. Anisaldehyde
3. Anisole
6. p-Methyl acetophenone
7. Nitrobenzene
8. o-Nitrophenol (pH 3.81)
9. p-Tolualdehyde

5.4 Significance of Results

The fact that the polyethylene behaves in a manner akin to *in vivo* membranes (i.e. permeation is pH and partition dependent etc.) and that the rate of permeation of molecules in aqueous solution through polyethylene can be related to the hexane water partition coefficient of the molecule is of considerable potential significance. In recent years many problems associated with the prediction of the behaviour of therapeutically active substances administered to humans (in solid dosage forms) have arisen. Numerous examples are given in the literature of a variable response produced by the same quantity of the same drug being administered in apparently identical dosage forms (for example see Wagner, 1971). It has been stated earlier (section 1.1) that a therapeutic response following the oral administration of a dosage form is dependent on the active ingredients being able to pass through lipid barriers *in vivo*. Considerable work has taken place in this area and a logical development has been the development of *in vitro* models to simulate conditions *in vivo*.

Doluisio and others (1964, 1965), Perrin (1967) and Robertson and Bode (1970) have all attempted to simulate the *in vivo* process by the use of *in vitro* models which use organic liquids to represent the lipid membrane. A very real objection to some of these models, however, is that the thickness of the membrane which different individual solute molecules have to permeate is not consistent and the permeation rate expressions cannot, therefore include a thickness term.

The use of *in vitro* models has been described by Beckett and Tucker (1967) as being of doubtful value for the prediction of

absorption unless the results obtained can be correlated with *in vivo* data and to the present time no *in vitro* apparatus which is capable of completely simulating the *in vivo* membrane appears to have been developed. For this reason, Beckett and Triggs (1967) proposed the use of the membranes of the buccal cavity (in man) as an *in vivo* model to predict whether or not absorption would take place through the gastro intestinal membranes and if so the absorption rate.

The buccal method of absorption prediction has been developed further by Beckett, Boyes and Triggs (1968) and Beckett and Moffat (1968, 1969a,b, 1970). Beckett and Moffat (1969b, 1970) were able to show a correlation between their buccal absorption data and the heptane aqueous solution partition coefficients of the solutes being considered and they implied, therefore, that a suitable *in vitro* method of absorption prediction could possibly be based on the heptane water partition coefficient of the solute.

Bickel and Weder (1969) compared the gastro intestinal absorption of imipramine and its metabolites with the buccal absorption data of the same substances and found the correlation to be excellent. They were also able to show a correlation between this data and the hexane water partition coefficients of the molecules.

Since Beckett and Moffat (1969b, 1970) were able to correlate buccal absorption data with the heptane aqueous solution partition coefficients of the molecules it follows that buccal absorption data will bear a similar relationship to the hexane water partition coefficients of the molecules since the variation of the logarithm of the oil water partition coefficient of an individual substance between

one pair of liquids and another is given by Collander (1954) as a linear relationship (i.e. the logarithm of the partition coefficient of a substance in one pair of solvents is linearly related to the logarithm of the partition coefficient of the substance in a second pair of solvents). That the use of the hexane water partition coefficient in place of the heptane water partition coefficient is satisfactory, is confirmed by the correlation obtained by Bickel and Weder (1969). Since the hexane water partition coefficients of molecules can be related to the permeation rates of the molecules through polyethylene it follows that polyethylene can be compared to the buccal membrane.

It seems reasonable then to suggest that the apparatus which has been used here may well be a suitable starting point for the development of an *in vitro* drug availability test which has a direct relationship to *in vivo* availability. The actual apparatus used lends itself to a variety of modifications if necessary and a suitable combination of variables (e.g. membrane properties and thickness, membrane area, etc.) may ultimately be achieved so that direct *in vitro-in vivo* correlation may be possible. The use of this apparatus for drug availability work is limited to substances which are absorbed by passive diffusion but since this constitutes the majority of drugs (Vogt, 1965) this is not regarded as a serious limitation.

The comparison of permeation rates through polyethylene with rates through *in vivo* membranes is consistent with the work of Lieb and Stein (1969) who have suggested that biological membranes behave

as non porous polymeric sheets with respect to the diffusion of non electrolytes and that of Teorell (1970) who has suggested that for practical purposes the same general equation may be applied to transport across biological and artificial membranes.

The results reported in this study also appear to have application in the area of interactions between polyethylene containers and their contents and appear to represent an advance in the understanding of this problem.

5.5 Further Work

As a result of the data obtained in this study there appears to be a real possibility that this apparatus may have an application in the *in vitro* prediction of *in vivo* drug absorption. Work in this area is being undertaken at the present time by the author.

Other work which should be undertaken as a result of this study includes the need to investigate the relationship between permeation rates and oil water partition coefficients in other polymeric membranes. The effect of combinations of solutes on permeation rates through polyethylene should also be investigated.

Detailed work on the effect of the structure (and manufacturing process) of polyethylene on the permeation rate could provide useful information.

APPENDIX 1

Typical set of permeation data showing method of calculation of amount permeated.
Data given below: o-Nitrophenol, initial concentration 7.18×10^{-3}M, pH 5.25, temperature 35.2°.
Volume removed at each sampling time: 1.98 ml[1]

Cell number	Time (hours)	Optical density of diluted sample at λ=371.5nm	Dilution used	Conc. of diluted solution[2] g/100 ml	Vol. on solvent side of cell at time of sampling	Amount of solute in "solvent" side of cell (mg)	Amount of solute removed in actual sample (mg)	Cumulative amount of solute removed in samples (mg)	Total amount permeated[3] (mg)
1[a]	1	0.041	1.98→5	0.00032	85.50	0.691	0.016	-	0.691
	2	0.061	1.98→5	0.00048	83.52	1.012	0.024	0.016	1.028
	3	0.096	1.98→5	0.00074	81.54	1.523	0.037	0.040	1.563
	4	0.124	1.98→5	0.00096	79.56	1.928	0.048	0.077	2.005
	5	0.152	1.98→5	0.00117	77.58	2.291	0.059	0.125	2.416
	6	0.184	1.98→5	0.00141	75.60	2.691	0.071	0.184	2.875
	7	0.217	1.98→5	0.00167	73.62	3.104	-	0.255	3.359
2[b]	1	0.035	1.98→5	0.00027	82.00	0.559	0.013	-	0.559
	2	0.064	1.98→5	0.00050	80.02	1.010	0.025	0.013	1.023
	3	0.096	1.98→5	0.00074	78.04	1.458	0.037	0.038	1.496
	4	0.124	1.98→5	0.00096	76.06	1.843	0.048	0.075	1.918
	5	0.155	1.98→5	0.00119	78.08	2.226	0.059	0.123	2.349
	6	0.190	1.98→5	0.00146	76.10	2.648	0.072	0.182	2.831
	7	0.221	1.98→5	0.00169	74.12	2.992	-	0.254	3.246

[1] By calibrated pipette.
[2] From plot of optical density against concentration.
[3] Permeation rate determined from slope of plot of amount permeated against time.
[a] Volume on "solution" side = 89.50 ml.
[b] Volume on "solution" side = 83.00 ml.

APPENDIX 2

Analysis of variance of data given in Table 2.5.

Cell Number	Membrane Number 1	2	3	4	5	Sum
1	0.650	0.640	0.685	0.590	0.640	3.205
2	0.590	0.610	0.635	0.623	0.550	3.008
3	0.610	0.660	0.600	0.590	0.580	3.040
4	0.585	0.635	0.610	0.570	0.612	3.012
Sum	2.435	2.545	2.530	2.373	2.382	12.265

Correction factor = $\frac{(12.265)^2}{20}$ = 7.521511

Total sum of squares = 7.542273 - 7.521511 = 0.020762

Sum of squares between cells =

$1/5(3.205^2 + 3.008^2 + 3.040^2 + 3.012^2) - 7.521511 = 0.005256$

Sum of squares between membranes =

$1/4(2.435^2 + 2.545^2 + 2.530^2 + 2.373^2 + 2.382^2) - 7.521511 = 0.006540.$

Variation	Sum of squares	Degrees of freedom	Mean square
Between cells	0.005256	3	0.001752
Between membranes	0.006540	4	0.001635
Residual	0.008966	12	0.000747
Total	0.020762	19	

F ratio for cells $= \frac{0.001752}{0.000747} = 2.345$

From tables $F_{3,12(0.05)} = 3.49$

F ratio for membranes $= \frac{0.001635}{0.000747} = 2.189$

From tables $F_{4,12(0.05)} = 3.26$

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