International Journal of Pharmaceutics, 6 (1980) 339–348

THE TEMPERATURE DEPENDENCE AND THERMODYNAMICS OF PARTITIONING OF PHENOLS IN THE n-OCTANOL–WATER SYSTEM

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(Received August 6th, 1980)
(Revised version received August 25th, 1980)
(Accepted August 28th, 1980)

SUMMARY

The temperature dependency of the *n*-octanol–water partition coefficient and the hydrophobic substituent constant, π, for a series of substituted phenols has been determined. The thermodynamics of transfer of *p*-alkylphenols revealed both a favorable enthalpic and entropic contribution whereas xylenols having an ortho substituted methyl group reduced the enthalpic and increased the entropic contributions. Polar substituents in the para position of the ring, such as halogen, nitro or methyl ester, increased the free energy of transfer of phenol through increased enthalpy and in spite of an unfavorable entropy. Para-methoxy or ethoxy groups caused a reversal of the enthalpy of transfer from negative to positive and at the same time increased the entropic contribution. A comparison of the *n*-octanol–water system results with those obtained using artificial membranes suggests that the bulk organic phase–water system can serve as a good model for distribution only when specific polar group interaction between the compound and the phospholipid bilayer is minimal or absent.

INTRODUCTION

The *n*-octanol–water system is frequently employed as a model system for measuring the partitioning of solutes in biological membranes (Hansch and Fujita, 1964; Lien et al., 1968; Roberts et al., 1977; Wallace et al., 1978). This has led to usage of the π substituent constant in predicting partition coefficients of classes of solutes (Fujita et al., 1964; Machleidt et al., 1972). The importance of having reliable partition coefficient data in the *n*-octanol–water system is apparent, although it has been argued that other non-polar organic solvents may serve as better models (Rytting et al., 1972).

Very few studies have been made on the temperature dependency of the oil–water

partition coefficient (Schumacher and Nagwekar, 1974; Davis et al., 1976). The available evidence suggests that the effect of temperature is not great (Leo et al., 1971) and that temperature variation within several degrees may be neglected (Korenman, 1972a). But wide variations in reported partition coefficients of solutes, particularly the phenols, may be partly attributed to studies at different 'ambient' temperatures. In addition, it is possible that discrepancies in reported values may be due to lack of equilibration. It has been suggested by Leo et al. (1971) that equilibrium is normally achieved in a matter of a few minutes of shaking the two phases. However, the influence of various functional groups may prolong the equilibration period. Initial studies using various phenols in the present study indicated that several hours were necessary to achieve equilibrium. Schumacher and Nagwekar (1974) reported that 8 h was required to reach equilibrium of sulfonamides in a *n*-octanol–buffer system. These reasons may be responsible for a partition coefficient for *p*-methylphenol in a *n*-octanol–water system of 87.1 (Fugita et al., 1964) and 108.5 (Korenman, 1972b) and 1660 (calculated value, Hansch and Fujita, 1964) and 3767 [1] (Korenman, 1972c) for *p*-*n*-butylphenol.

The thermodynamics of transfer of a solute from an aqueous phase to an organic phase is readily obtained from partition coefficient data because it is a free energy-related property (Leo et al., 1971). However, the free energy of partitioning of a solute expresses only the extent of spontaneity of the net process and reveals little about the underlying mechanisms involved. Thus, although *p*-ethylphenol exhibits a free energy of transfer between an aqueous phase and *n*-octanol (this study) similar to that in dimyristoylphosphatidylcholine liposomes (Rogers and Davis, 1980), a comparison of the two systems shows that large differences in the enthalpy and entrophy of transfer exist. A study of the thermodynamics of partitioning in various organic phase–water systems may lead to a greater understanding of the manner by which molecules interact with biological membranes.

The results presented in this paper are part of a continuing study of the influence of various functional groups on the partitioning behavior of lipid-soluble molecules. The phenols constitute excellent model compounds for this purpose because numerous ring substitutions are possible, but they are also of pharmacological interest as insecticides, bactericides and preservatives. Data on the interaction of compounds with model membrane systems are scarce. Only when sufficient data become available will it be possible to determine to what extent a bulk organic solvent may serve as a valid model for distribution studies in biological systems.

MATERIALS AND METHODS

All solutions were prepared using double-distilled water and high-grade *n*-octanol (Fisher Scientific, certified reagent). Sodium chloride (BDH reagent) and the following

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[1] This value was calculated from $\log P = a + \log P_0$ which was shown by Korenman (1972c) to hold for *p*-alkylphenols independent of the extractant used, where P = partition coefficient of the *p*-alkylphenol and P_0 = partition coefficient of phenol using the same extractant and a = 3.576 for 4-*n*-butylphenol.

phenols were used without further purification: *o*-methylphenol, 99⁺%; *m*-methylphenol, 99⁺%; *p*-methylphenol, 99⁺%; *p*-ethylphenol, 97%; *p*-*n*-propylphenol; 2,6-dimethylphenol, 99%; 2,4-dimethylphenol, 99%; 3,5-dimethylphenol, 99⁺%; *p*-fluorophenol, 99%; *p*-chlorophenol, 99⁺%; *p*-bromophenol, 99%; *p*-iodophenol; 97%; *p*-nitrophenol, *p*-methoxyphenol, 98%; all of the Aldrich Chemicals; *p*-*n*-butylphenol; *p*-ethoxyphenol (Eastman Kodak); phenol (Fisher Scientific, A.C.S. reagent) and *p*-hydroxymethylbenzoate (BDH).

Stock solutions of the phenols were prepared in 0.15 M sodium chloride [2] at a concentration of 0.1 mg · ml^{-1}. Beer's law plots were obtained for each phenol at λ_{max} by measuring absorbances of standard solutions on a Beckman Model 25 spectrophotometer using 1 cm cells.

Samples for equilibration were prepared on a weight basis. Thus, 10 g of stock solution were weighed into glass vials fitted with screw caps followed by 0.1 g *n*-octanol (previously equilibrated with 0.15 M sodium chloride solution). The vials were shaken at constant temperature (±0.2°C) (Dubnoff metabolic shaker, Precision Scientific) over the range 20–50°C until equilibrium was reached. The aqueous phase was then carefully transferred by pipet to cells and the absorbance recorded. Dilutions were made where appropriate. Molal concentrations of phenol in the aqueous phase were determined from the Beer's law plots, and molal concentrations in the *n*-octanol phase were determined by difference, the ratio of the respective concentrations (oil : water) yielding the partition coefficient (K^0_ω). The results are the averages of duplicate determinations.

RESULTS AND DISCUSSION

Equilibrium partition coefficients were obtained by shaking at the required temperature for the appropriate period. However, the period was found to vary for different solutes. Generally, alkylphenols required the longest equilibration times and equilibration was achieved more rapidly at higher temperatures. This is illustrated for *p*-methylphenol and *p*-ethylphenol in Fig. 1. At least 18 h was required in all cases, but many solutes at 20°C required 40 h. When the effect of concentration of *p*-methylphenol on its K^0_ω was examined over the range of 0.08 mg · ml^{-1} to 0.48 mg · ml^{-1}, constant results were obtained. The results of K^0_ω for many of the phenols were higher than corresponding literature values. If the solute is placed initially in the aqueous phase, then the latter may represent non-equilibrium K^0_ω values. A plot of log K^0_ω vs hydrocarbon chain length of the *p*-alkylphenols was linear having a slope of 0.53 and a correlation coefficient of 0.999. The K^0_ω of members in this series differs by a factor of 3.4 which agrees with a factor of about 3 observed by others for a variety of homologous series (Aranow and Witten, 1960; Hansch and Anderson, 1967).

An increase in temperature resulted in a decrease in the K^0_ω for each of the phenolic solutes except *p*-methoxy and *p*-ethoxyphenol for which the K^0_ω increased. Plots of log K^0_ω against the reciprocal of the absolute temperature were linear and had a high correlation ($r > 0.90$). In the *n*-octanol–water system, variation of temperature produced an

[2] In addition, stock solutions of *p*-nitrophenol and 2,6-dimethylphenol were acidified with HCl to pH 2.

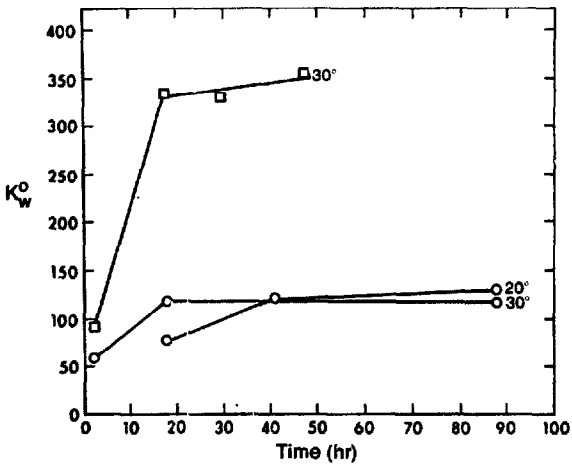

Fig. 1. Demonstration of the time required to obtain equilibrium partition coefficients of substituted phenols in a *n*-octanol–water system. ○, *p*-methylphenol; □, *p*-ethylphenol.

average change of the K^0_ω by 0.007 log unit deg^{-1}. The most pronounced effects were observed with the *p*-halophenols, *p*-nitrophenol, *p*-methoxyphenol and *p*-hydroxymethylbenzoate.

The thermodynamics of partitioning of phenolic solute in the *n*-octanol–0.15 M NaCl system are described by Eqns. 1, 2 and 3:

$$\Delta G^0_{\omega\to 0} = -RT \ln K^0_\omega \tag{1}$$

$$\Delta H^0_{\omega\to 0} = T\Delta S^0_{\omega\to 0} - RT \ln K^0_\omega \tag{2}$$

$$\Delta S^0_{\omega\to 0} = \frac{\Delta H^0_{\omega\to 0} - \Delta G^0_{\omega\to 0}}{T} \tag{3}$$

where $\Delta G^0_{\omega\to 0}$, $\Delta H^0_{\omega\to 0}$ and $\Delta S^0_{\omega\to 0}$ are the standard partial molar energy, enthalpy and entropy of partition, respectively. Results at 20°C appear in Table 1 along with corresponding values of the K^0_ω. Except for *p*-methoxyphenol, all substituted phenols demonstrate a more favorable energy of transfer ($\Delta G^0_{\omega\to 0} < 0$) from aqueous to oil phase than phenol. It is also seen that $\Delta G^0_{\omega\to 0}$ for the phenols is very similar in magnitude, perhaps giving an impression that the various substituted functional groups operate to increase the K^0_ω by similar mechanisms. However, examination of the corresponding values of $\Delta H^0_{\omega\to 0}$ and $\Delta S^0_{\omega\to 0}$ in Table 1 indicate that the individual substituents exert different influences on the partitioning behavior of phenol.

The partitioning of phenol in the *n*-octanol–0.15 M NaCl system is accompanied by a negative $\Delta G^0_{\omega\to 0}$ and $\Delta H^0_{\omega\to 0}$ and a positive $\Delta S^0_{\omega\to 0}$. This can be compared to the cyclohexane–water system where $\Delta G^0_{\omega\to 0} = -0.48$ kJ · mol^{-1} (mole fraction concentration scale), $\Delta H^0_{\omega\to 0} = +22.60$ kJ · mol^{-1} and $\Delta S^0_{\omega\to 0} = +77.4$ kJ^{-1} · mol^{-1} (Davis et al., 1976). Thus, the partitioning of phenol in a water–cyclohexane system is entropy-controlled whereas in a water–*n*-octanol system it is mainly enthalpy-controlled. This suggests that

TABLE 1

PARTITION COEFFICIENTS (K^0_ω), SUBSTITUENT CONSTANTS (π) AND THERMODYNAMIC CONSTANTS FOR PARTITIONING OF PHENOLS IN THE n-OCTANOL–WATER SYSTEM AT 20°C

Compound	K^0_ω	π	$\Delta G^0_{\omega\to 0}$ (kJ mol^{-1})	$\Delta H^0_{\omega\to 0}$ (kJ mol^{-1})	$\Delta S^0_{\omega\to 0}$ (J mol^{-1} K^{-1})
phenol	34.3	0	−8.7	−8.3	1.4
o-methylphenol	102.4	0.45	−11.2	−5.5	19.4
m-methylphenol	113.8	0.50	−11.5	−6.5	17.0
p-methylphenol	125.4	0.55	−11.8	−8.7	10.6
p-ethylphenol	395.3	1.04	−14.5	−11.1	11.6
p-*n*-propylphenol	1570.9	1.67	−18.0	−14.7	11.5
p-*n*-butylphenol	4365.4	2.11	−20.5	−11.2	31.8
2,6-dimethylphenol	250.2	0.85	−13.5	−3.2	35.2
2,4-dimethylphenol	348.0	1.00	−14.3	−3.3	48.8
3,5-dimethylphenol	355.0	1.01	−14.4	−10.8	12.1
p-fluorophenol	78.8	0.36	−10.7	−15.3	−15.7
p-chlorophenol	354.2	1.00	−14.3	−16.9	−8.8
p-bromophenol	398.6	1.04	−14.5	−16.8	−7.6
p-iodophenol	679.4	1.27	−15.8	−15.4	1.5
p-nitrophenol	122.9	0.55	−11.7	−15.6	−13.1
p-hydroxymethylbenzoate	101.3	0.46	−11.3	−21.8	−36.0
p-methoxyphenol	36.8	0.01	−8.7	16.2	85.0
p-ethoxyphenol	89.7	0.40	−10.9	10.6	73.3

solute–solvent interactions are important in *n*-octanol, likely arising from hydrogen bonding forces. The observed small gain in entropy can be explained as the net effect when the usually large positive entropy gain resulting from transfer of hydrocarbon out of water (Frank and Evans, 1945) is balanced by an almost equal loss of entropy due to restriction of movement of phenol molecules as a result of their interaction with *n*-octanol molecules.

Functional group contributions

The incremental thermodynamic parameters for partitioning of phenols at 20°C are given in Table 2. These have been calculated as the difference between the thermodynamic constants for the substituted phenol and phenol given in Table 1. Thus, a measure of the partial molar free energy, enthalpy and entropy of the various functional groups on the transfer of a mole of phenol from aqueous phase to *n*-octanol is obtained.

(1) Alkyl group substitution. Methyl group substitution in the ortho or meta position of the ring yields a positive $\delta\Delta H^0_{\omega\to 0}$ which decreases as the methyl group is moved further away from the phenolic -OH group. This suggests an interference of the phenolic -OH group in forming intermolecular hydrogen bonds in either water or *n*-octanol, probably due to intramolecular hydrogen bond formation. The effect this has on entropy is apparent in that a large positive $\delta\Delta S^0_{\omega\to 0}$ results after *o*-methyl substitution and which

TABLE 2

INCREMENTAL THERMODYNAMIC FUNCTIONS FOR PARTITIONING OF PHENOLS AT 20°C

Functional group	$\delta\Delta G^0_{\omega\to 0}$ (kJ mol^{-1})	$\delta\Delta H^0_{\omega\to 0}$ (kJ mol^{-1})	$\delta\Delta S^0_{\omega\to 0}$ (J mol^{-1} K^{-1})
o-methyl	−2.5	+2.8	+18.0
m-methyl	−2.8	+1.8	+15.6
p-methyl	−3.1	−0.4	+9.2
p-ethyl	−5.8	−2.8	+10.2
p-*n*-propyl	−9.3	−6.4	+10.1
p-*n*-butyl	−11.8	−2.9	+30.4
2,6-dimethyl	−4.8	+5.1	+33.8
2,4-dimethyl	−5.6	+5.2	+47.4
3,5-dimethyl	−5.7	−2.5	+10.7
p-fluoro	−2.0	−7.0	−17.1
p-chloro	−5.6	−8.6	−10.2
p-bromo	−5.8	−8.5	−9.0
p-iodo	−7.1	−7.1	+0.1
p-nitro	−3.0	−7.3	−14.5
p-methyl ester	−2.6	−13.5	−37.4
p-methoxy	0	+24.5	+83.6
p-ethoxy	−2.2	+18.9	+71.9

decreases after *m*-methyl or *p*-methyl substitution. Increasing the chain length of the alkyl group in the para position augments a negative $\delta\Delta H^0_{\omega\to 0}$ probably as a result of increased van der Waals forces of attraction between the hydrocarbon chains in the oil phase. A deviation from the trend is observed with the *p*-*n*-butyl substituent which is again possibly due to partial steric hindrance of the phenolic -OH group in forming hydrogen bonds. Dimethyl substitution of phenol, where one methyl group is in the ortho position, also yields a positive $\delta\Delta H^0_{\omega\to 0}$ but becomes a negative value when substitution is at the 3,5 positions. The thermodynamic functions of 3,5-dimethylphenol are very similar to the values obtained after *p*-ethyl substitution. The symmetry of the 3,5-dimethylphenol molecule may be responsible in offsetting the hindrance of the phenolic -OH group as observed after only meta-methyl substitution.

(2) Halogen group substitution. A halogen atom is reported to alter the partitioning behavior of a parent compound by virtue of its ability to form hydrogen bonds, by virtue of an inductive effect on adjacent groups and by virtue of a direct methylene-like effect in solvents (Diamond and Wright, 1969). Values of $\delta\Delta H^0_{\omega\to 0}$ for halogen groups in Table 2 are approximately equal. In the halogen series, strength of hydrogen bonds and electron-withdrawing effect on adjacent groups are in the order F > Cl > Br > I. Fluorine substitution in a solute normally reduces intermolecular forces between the solute and hydrocarbon phases, such as *n*-octanol. The significance for partition coefficient studies is that the decrease in K^0_ω after *p*-fluoro substitution of phenol brought about the weakened interactions with *n*-octanol nearly offsets the increase in K^0_ω due to its inductive effect on the phenolic -OH group. Hydrogen bonding in *n*-octanol must, however, be substantial

(causing restriction of movement of solute molecules) since a large negative $\delta\Delta S^0_{\omega\to 0}$ is obtained. Thus, transfer of a halogen group from water to *n*-octanol is driven mainly by enthalpy contributions and this, in spite of an unfavorable change in entropy.

(3) Nitro group substitution. The nitro group behaves similarly to a halogen atom in that it has a strong electron-withdrawing character but it forms weak hydrogen bonds (Nagakura and Gouterman, 1957). As seen in Table 2, the $\delta\Delta H^0_{\omega\to 0}$ of the nitro group is similar to *p*-fluoro, thus *p*-nitrophenol is likewise transferred into a more ordered environment ($\delta\Delta S^0_{\omega\to 0} < 0$) in the *n*-octanol phase. The nitro group has a considerably higher dipole moment than most other substituent groups and, therefore, would tend to promote alignment of the phenol molecule with *n*-octanol molecules resulting in less freedom of movement.

(4) Methyl ester group substitution. The transfer of phenol having this substituent is associated with a net gain in enthalpy. This is attributed to increased hydrogen bonding and alkyl group interaction in the *n*-octanol phase. Again, the solute–solvent interactions give rise to a large negative $\delta\Delta S^0_{\omega\to 0}$ and energetically, a significant compensation of the enthalpy occurs. The net result is a modest increase in the K^0_ω.

(5) Methoxy and ethoxy group substitution. The resultant $\delta\Delta H^0_{\omega\to 0}$ and $\delta\Delta S^0_{\omega\to 0}$ attributed to *p*-methoxy and *p*-ethoxy group substitution are large and positive. Thus, partitioning is mainly under entropy control. Although the -O- group is able to participate in hydrogen bond formation, in comparison to the hydroxyl group, two ether links tend to be slightly less in their hydrogen bonding effect than one hydroxyl group, probably because of greater steric hindrance to hydrogen bonding at the ether oxygen (Diamond and Wright, 1969). In the *n*-octanol–water system, hydrogen bonding of this group with *n*-octanol is probably absent whereas it is more likely to occur in the enviroment of the smaller water molecules. Thus, the energy required to break hydrogen bonds in water is not gained back after transfer into *n*-octanol. However, the large positive enthalpy is counterbalanced by an equal, large gain in entropy. Consequently, a *p*-methoxy group neither increases nor decreases the K^0_ω whereas a slight increase is obtained with the *p*-ethoxy substituent because of the increased van der Waals' forces of attraction with *n*-octanol molecules.

The π substituent constant

The hydrophobic bonding or π substituent constant for functional groups allows the prediction of partition coefficients of compounds (Fujita et al., 1964; Hansch and Fujita, 1964; Flynn, 1971). The majority of data of π for functional groups have been obtained in the *n*-octanol–water system. Values of π at 20°C for the various phenols obtained in this study are shown in Table 1, and are somewhat larger than those reported by Hansch and Fujita (1964) but undergo regular change within the various series of phenols.

On the whole, the temperature dependency of the K^0_ω is not great, but as shown in Table 1 (as revealed in the magnitude of $\Delta H^0_{\omega\to 0}$), distinct differences in the dependence on temperature occur among the phenols. Thus, for some functional groups substituted on phenol, a significant variation in π with temperature will be observed. In these cases, the π substituent constant at the appropriate temperature must be chosen in making calculations of the K^0_ω. These are obtainable by substitution into the corresponding linear regression equations given in Table 3. The temperature variation of π is least significant

TABLE 3

REGRESSION ANALYSIS OF THE TEMPERATURE VARIATION OF π OF SUBSTITUTED PHENOLS [a]

Group	Slope	Intercept	Correlation
o-methyl	0.0016	0.42	0.992
m-methyl	0.0009	0.49	0.923
p-methyl	0	0.55	1.00
p-ethyl	−0.0014	1.07	−0.990
p-*n*-propyl	−0.0031	1.74	−0.998
p-*n*-butyl	−0.0020	2.15	−0.976
2,6-dimethyl	0.0030	0.79	1.00
2,4-dimethyl	0.0027	0.95	0.996
3,5-dimethyl	−0.0014	1.09	−0.990
p-fluoro	−0.004	0.44	−1.00
p-chloro	−0.0047	1.09	−0.999
p-bromo	−0.0046	1.13	−0.999
p-iodo	−0.0040	1.35	−1.00
p-nitro	−0.0040	0.63	−0.994
p-$COOCH_3$ [b]	−0.0075	0.61	−0.999
p-methoxy	0.0136	−0.25	0.999
p-ethoxy	0.0103	0.20	1.00

[a] Over the temperature range 20–50°C.
[b] Over the temperature range 20–40°C.

for the *o*-methyl, *m*-methyl, *p*-methyl, *p*-ethyl and 3,5-dimethyl substituted phenols and most significant for the *p*-methoxy and *p*-ethoxy derivatives.

Comparison of the n-octanol–water system with biological systems

In a previous study, Rogers and Davis (1980) demonstrated that the partitioning of phenolic solutes in dimyristoylphosphatidylcholine liposomes resembled partitioning into a more polar environment than bulk non-polar solvents, such as cyclohexane (ϵ = 2.02), carbon tetrachloride (ϵ = 2.24) or chlorobenzene (ϵ = 5.71). Thus, a structured organic phase such as *n*-octanol (ϵ = 10.3) yielded a better correlation for partitioning into a lipid bilayer when it was in the gel or 'frozen' state. However, in the liposome system (below the lipid phase transition temperature) $\Delta H^0_{\omega\to\ell} > 0$ and $\Delta S^0_{\omega\to\ell} > 0$ for *p*-alkyl- and *p*-halophenols whereas in the *n*-octanol–water system, $\Delta H^0_{\omega\to 0} < 0$ for *p*-alkyl- and *p*-halophenols but $S^0_{\omega\to 0} > 0$ for *p*-alkylphenols and $\Delta S^0_{\omega\to 0} < 0$ for the *p*-halophenols. Thus, using a thermodynamic approach, it is possible to gain an understanding of the different mechanisms involved in the partitioning of solutes in the two systems, viz. entropy-controlled partitioning in a lipid bilayer system (below the lipid phase transition temperature) vs enthalpy-controlled partitioning in a *n*-octanol–water system. Above the phase transition temperature of the lipid, the enthalpy of partitioning in liposomes is dominant for both *p*-alkyl- and *p*-halophenols and increases are observed in each series. Although the enthalpy is also negative in the *n*-octanol–water system, it remains constant in the *p*-halophenol series and increases slightly in the *p*-alkylphenol

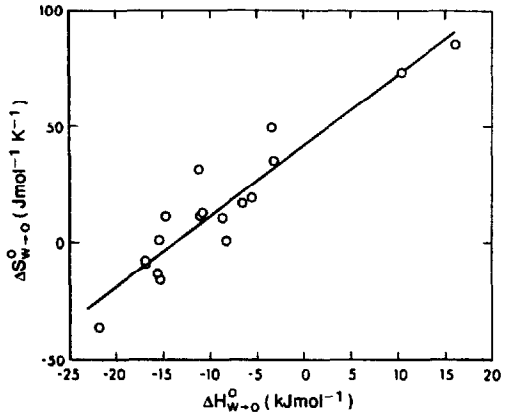

Fig. 2. The entropy vs enthalpy of transfer of substituted phenols in a *n*-octanol–water system. Each point represents one solute. The straight line gives the least mean-squares fit.

series. It is suggested, therefore, that correlation between *n*-octanol–water and biological membrane partition coefficients is obtained only when there is no specific polar interaction of functional groups of a solute molecule with the polar groups of the lipid molecules in the membrane. This will be the case for non-polar functional groups and also, when the polar regions of the lipid bilayer in the gel or 'frozen' state are inaccessible to the solute.

Comparisons of the solubilities of polar solutes in lecithin and bulk solvents reveal that structured solvents, such as water, yield similar slopes in the linear relationship between ΔS^0 and ΔH^0 (Barclay and Butler, 1938; Katz and Diamond, 1974). Likewise, it can be shown that linearity between $\Delta S^0_{\omega\to\ell}$ and $\Delta H^0_{\omega\to\ell}$ is obtained if the Barclay–Butler slopes are approximately equal (Katz and Diamond, 1974). Fig. 2 shows that linearity is also obtained from a plot of $\Delta S^0_{\omega\to 0}$ vs $\Delta H^0_{\omega\to 0}$ employing all 18 phenols studied in the *n*-octanol–water system. The slope of 0.00301 ($r = 0.942$) is comparable to the slope of 0.00312 obtained from the liposome studies (Rogers and Davis, 1980) and is higher than the value of 0.00235 for polar solutes in liposome systems and 0.0014 in bulk organic solvent–water systems (Katz and Diamond, 1974). Hence, from a structural point of view, it would appear that *n*-octanol serves as a good model of a biological membrane, but it should be expected that greater deviations will occur when polar functional groups of molecules are free to interact with phospholipids in membranes.

ACKNOWLEDGEMENTS

The authors are grateful for an M.R.C. Summer Research Studentship awarded to A.W.

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