# A Novel Method for Measuring Membrane–Water Partition Coefficients of Hydrophobic Organic Chemicals: Comparison with 1-Octanol–Water Partitioning

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**Abstract** □ A novel method of measuring membrane–water partitioning characteristics of very hydrophobic organic chemicals is described. Partition coefficients are reported for a series of halogenated aromatic hydrocarbons of varying molar volume between water and L-α-phosphatidylcholine dimyristoyl (DMPC) membrane vesicles and two solvents, *n*-hexane and 1-octanol. The results indicate that *n*-hexane and 1-octanol are satisfactory surrogates for DMPC membranes for chemicals with 1-octanol–water partition coefficients (log $K_{OW}$) <5.5 or molar volumes <230 $cm^3$/mol. Chemicals with higher log $K_{OW}$ or molar volume values display marked differences in membrane–water, 1-octanol–water, and *n*-hexane–water partitioning. Implications for lipid– and organism–water partitioning of hydrophobic chemicals are discussed.

The ability of organic chemicals to elicit certain therapeutic or toxic effects, such as narcosis, and to bioaccumulate in organisms is strongly influenced by the partitioning tendency of these chemicals between the organism or a certain target site within the organism and water. Since partitioning of organic chemicals is predominantly into the organic or lipid phases of the organism (e.g., membranes), for which 1-octanol is generally believed to be a satisfactory surrogate phase, various drug activities, toxicities, and distribution processes have been successfully correlated with the 1-octanol–water partition coefficient,[1-5] $K_{OW}$. However, when $K_{OW}$ becomes relatively large (i.e., for compounds which are very hydrophobic and have high molar volumes), a loss of linear correlation is often observed.[5-13] This limits the predictive ability of these relationships and raises uncertainties about the mechanisms involved. The relatively slow transport characteristics of these very hydrophobic compounds have been recognized as an important contributing factor to this loss of linear correlation.[2,7,9,11,13] But, it can also be argued that the partitioning behavior of chemicals with large $K_{OW}$ values into the lipid phases of the organism and 1-octanol may no longer be similar. This may be due to the fact that membranes and other lipid phases in organisms have a more definite structure than 1-octanol. To test the hypothesis that membranes and 1-octanol show a different phase behavior towards chemicals of larger molar volume, partition coefficients between L-α-phosphatidylcholine dimyristoyl (DMPC) membrane vesicles and water were measured for a series of halogenated aromatic hydrocarbons. Since the existing techniques[14-18] are not well suited for this purpose, due to the very low aqueous solubilities of these chemicals, a method was developed to measure partition coefficients of highly hydrophobic compounds (log $K_{OW} > 3$) between membrane vesicles or liposomes and water. We describe the method and discuss partitioning data for 54 chemicals in total between water and *n*-hexane, 1-octanol, and DMPC membranes.

## Theoretical Section

The logarithm of partition coefficients between an organic phase such as 1-octanol and water have often been shown to be linear functions of the molecular properties of the solute, such as molecular weight, volume, surface area, and molar volume.[19-22] Also, numerous linear "Collander-type" correlations have been reported between partition coefficients of two organic phase–water systems.[2] But, as pointed out earlier, a breakdown of these correlations may occur for membrane–water systems. To establish the cause of such a phenomenon, it is useful to explore the fundamental basis of organic phase–water partitioning and "Collander" equations.

The partition coefficient $K_{AW}$, between an organic phase, A, and water, W, can be expressed as

$$K_{AW} = C_A/C_W = (V_W\gamma_W)/(V_A\gamma_A) \quad (1)$$

where $C_A$ and $C_W$ are the concentrations (mol/$m^3$) of the chemicals in the organic phase and water, respectively, $V_A$ and $V_W$ ($cm^3$/mol) are the molar volumes of the organic phase and water, respectively, and $\gamma_W$ and $\gamma_A$ are the activity coefficients of the solute (based on Raoult's law) in these phases.[19] The activity coefficients are the reciprocals of the mole fraction solubilities (i.e., $1/x$) of the chemical in the respective phases when the chemical is a liquid, or $F/x$ when the chemical is a solid.[19,23,24] The term $F$ is the fugacity ratio and can be calculated from

$$F = \exp([-\Delta S_f/R][T_m/T - 1]) \quad (2)$$

where $\Delta S_f$ is the entropy of fusion, $T_m$ is the melting point (K) of the solute, $T$ is the temperature (K) of the system, and $R$ is the gas constant. For the nonpolar chemicals in this study, the ratio $\Delta S_f/R$ is approximately constant with a value of 6.79.[19,24] The activity coefficients $\gamma_W$ and $\gamma_A$ can be shown to correspond to the molar Gibbs free energy of solution, $\Delta G_s$, in the respective phases according to

$$\ln \gamma_W = \Delta G_{s,W}/RT \quad (3)$$

$$\ln \gamma_A = \Delta G_{s,A}/RT \quad (4)$$

A thermodynamic cycle (Figure 1) shows that $\Delta G_s$ can be expressed as the sum of the free energy of vaporization, $\Delta G_v$, and the free energy of solvation (i.e., $\Delta G_{sv}$). Following Butler and Harrower, the solvation process can be treated as a "two-step" process, each with its own free energy.[25,26] In step 1, a cavity is created in the solvent that is large enough to accommodate the solute molecule. The (endoergic) free energy associated with this process of cavity formation, $\Delta G_c$, is believed to be due to a combination of breaking solvent–

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solvent interactions and a loss of entropy as a result of the restricted spatial distribution of the solvent molecules. It is thus approximately proportional to the molecular volume of the solute or molar volume.[20] In step 2, the solute is introduced into the cavity. The free energy associated with step 2, $\Delta G_i$, is due to the formation of interactions between the solute and solvent molecules and may not display a similar molar volume dependence. The free energy of solution in each phase can therefore be expressed as

$$\Delta G_s = \Delta G_v + \Delta G_{sv} = \Delta G_v + \Delta G_c + \Delta G_i \quad (5)$$

Combining eqs 1, 3, 4, and 5 gives an expression for $K_{AW}$ in terms of these free energies, that is

$$-RT \ln K_{AW} = RT \ln (V_A/V_W) + (\Delta G_{c,A} - \Delta G_{c,W}) + (\Delta G_{i,A} - \Delta G_{i,W}) \quad (6)$$

This equation demonstrates that the free energy of solute transfer between an organic phase and water is determined by the free energy of cavity formation and solute–solvent interactions in the two phases. If $\Delta G_{c,A}$ and $\Delta G_{c,W}$ are proportional to the molar volume of solute ($V_S$), and can thus be replaced by, respectively, $AV_S$ and $WV_S$, where A and W are constants (i.e., the free energies of cavity formation per unit of cavity volume for the organic phase and water, respectively), eq 6 can be rewritten as

$$\ln K_{AW} = [(W - A)V_S]/RT + \ln (V_W/V_A) + (\Delta G_{i,W} - \Delta G_{i,A})/RT \quad (7)$$

Equation 7 then shows that for a series of solutes, $\ln K_{AW}$ is linearly dependent on the molar volume of the solute, $V_S$, when the solutes are chemically similar (i.e., $\Delta G_{i,A}$ and $\Delta G_{i,W}$ are approximately constant for all solutes) and/or when the free energies of interaction of the solutes are much smaller than their free energies of cavity formation. Congeneric series of chemicals such as polychlorinated benzenes, biphenyls, and dibenzo-*p*-dioxins are examples of such solutes, and correlations between log $K_{OW}$ and $V_S$ are observed to be linear.[19,20–22]

Equation 7 can also be written for a partition coefficient, between another organic phase, B, and water ($K_{BW}$), that is,

$$\ln K_{BW} = [(W - B)V_S]/RT + \ln (V_W/V_B) + (\Delta G_{i,W} - \Delta G_{i,B})/RT \quad (8)$$

Therefore, it follows that after substitution of eq 8 in eq 7, that

$$\ln K_{AW} = [(W - A)/(W - B)] \ln K_{BW} + P + Q \quad (9)$$

where $P = [(W - A)/(W - B)] \ln V_B + [(A - B)/(W - B)] \ln V_W - \ln V_A$ and $Q = ([(W - A)/(W - B)]\Delta G_{i,B} + [(A - B)/(W - B)]\Delta G_{i,W} - \Delta G_{i,A})/RT$.

Equation 9 is equivalent with the empirical Collander-type equations,[2] that is

$$K_{AW} = X(K_{BW})^Y \quad (10)$$

or

$$\log K_{AW} = Y \log K_{BW} + \log X \quad (11)$$

where $Y$ equals $[(W - A)/(W - B)]$ and $X$ is $(P + Q)$. It follows from eq 9 that correlations between log $K_{AW}$ and log $K_{BW}$ are linear when, for a series of solutes in both organic phases, the free energy of cavity formation is linearly dependent on the molar volume of the solute, and the free energies of interaction are either negligible with respect to the free energy of cavity formation or approximately constant for all solutes. Loss of linearity between log $K_{AW}$ and log $K_{BW}$ can thus be expected for solutes which have relatively small molar volumes and are chemically different in nature. For such chemicals, the free energy of cavity formation is relatively small and solute–solvent interactions may have a major effect on the free energy of solution. The chemical natures of the solvents A and B may then profoundly affect the relationship between the partition coefficients. A loss of linear relationship may thus be expected, especially when solute–solvent interactions are strong. Loss of linear correlation can also occur when in one of the two organic phases the free energy of cavity formation is nonlinearly related to molar volume. In that case, the slope $Y$ in eq 11 becomes a function of the molar volume of the solute. This may occur for high molar volume solutes, for which the free energy of solution is predominantly a function of cavity formation.

## Experimental Section

**Reagents**—L-α-Phosphatidylcholine dimyristoyl (DMPC) was obtained from Sigma. Mono-, di-, tri-, tetra-, and pentachlorobenzenes, 1,4-di- and 1,3,5-tribromobenzene, and 99+% 1-octanol were obtained from Aldrich. Hexachlorobenzene was obtained from BDH Chemicals. Hexabromobenzene, 2,4,6,2′,4′,6′-hexachlorobiphenyl, octachloronapthalene, and 1,2,4-trichloro-, 1,2,3,4-tetrachloro-, and octachlorodibenzo-*p*-dioxin were kindly provided by the Department of Environmental and Toxicological Chemistry of the University of Amsterdam. All other polychlorinated biphenyls, polybrominated biphenyls, and polychlorinated dibenzo-*p*-dioxins came from Analabs Foxboro. Glass-distilled *n*-hexane was obtained from Baker. All chemicals had a minimal purity of 98%, as indicated by the suppliers and confirmed by GC-ECD analysis.

**Preparation of Lipid Vesicles**—Membrane vesicles were prepared according to a method described by Bangham et al.[27] Briefly, DMPC was dissolved in chloroform (10 mg DMPC per 5 mL), and then evaporated to dryness in a round-bottomed flask on a rotary evaporator at 40 °C for 30 min. Distilled water was added to the lipid layer in the round-bottomed flask, and the solution was shaken slowly in a waterbath at 40 °C. This solution was ultrasonicated in a waterbath sonicator at ~30 °C for 75 min under helium, and then further diluted in distilled water before being used for partitioning measurements.

**Measurement of Membrane–Water Partition Coefficients**—A two-phase system consisting of a membrane vesicle solution (0.1–1 mg DMPC/mL of distilled water) and a solution of the test chemical(s) in *n*-hexane was created in an aspirator bottle with a bottom tap. The lower membrane vesicle solution was stirred slowly throughout the experiment which was performed at 26.5 ± 0.5 °C. After 3 and 5 d, which appeared to be well beyond the time for the system to reach equilibrium, samples were taken of both the membrane vesicle and hexane solutions. Samples taken from the *n*-hexane solution were diluted and analyzed directly by GC-ECD. Samples taken from the membrane vesicle solution (10–250 mL) were extracted twice with 10–50 mL of *n*-hexane. The extract was then concentrated by evaporation on a rotary evaporator at 30 °C and analyzed by GC-ECD.

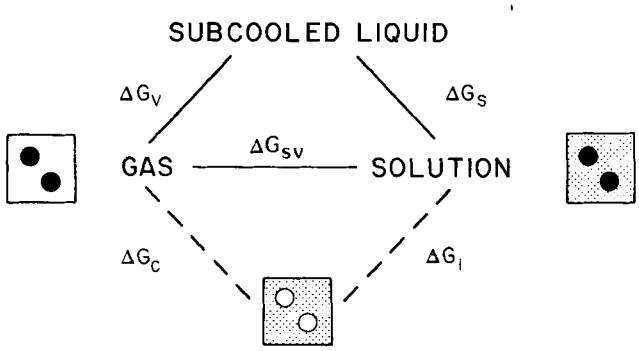


**Figure 1**—*Thermodynamic cycle for a dissolving solute.*

**Table I—Partition Coefficients between Water and L-α-Phosphatidylcholine Dimyristoyl Membranes ($K_{MW}$), *n*-Hexane ($K_{HW}$), and 1-Octanol ($K_{OW}$), and Aqueous Solubilities ($S_W$) for Selected Halogenated Aromatic Hydrocarbons**

| Compound | $V_S$, $cm^3/mol$ | $M_w$, g/mol | $T_m$, K | log $K_{HW}$ | log $K_{MW}$ | log $K_{OW}$ | log $S_W$, $mol/m^3$ | $F$ | log $\gamma_W$ | log $\gamma_H$ | log $\gamma_M$ | log $\gamma_O$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Monochlorobenzene | 116.9 | 112.6 | 227.4 | 3.00 ± 0.02 | 3.00 ± 0.03 | 2.98[a] | 0.418[a] | 1.000 | 4.33 | 0.47 | −0.24 | 0.50 |
| 1,2-Dichlorobenzene | 137.8 | 147.0 | 220.2 | 3.60 ± 0.01 | 3.64 ± 0.01 | 3.38[a] | −0.202[a] | 1.000 | 4.95 | 0.48 | −0.26 | 0.72 |
| 1,3-Dichlorobenzene | 137.8 | 147.0 | 248.3 | 3.81 ± 0.01 | 3.71 ± 0.03 | 3.48[a] | −0.072[a] | 1.000 | 4.82 | 0.15 | −0.46 | 0.49 |
| 1,4-Dichlorobenzene | 137.8 | 147.0 | 326.1 | 3.70 ± 0.01 | 3.57 ± 0.02 | 3.38[a] | −0.678[a] | 0.527 | 5.14 | 0.59 | 0.00 | 0.92 |
| 1,2,3-Trichlorobenzene | 158.7 | 181.5 | 325.8 | 4.16 ± 0.02 | 4.16 ± 0.04 | 4.04[a] | −1.170[a] | 0.531 | 5.64 | 0.62 | −0.09 | 0.75 |
| 1,2,4-Trichlorobenzene | 158.7 | 181.5 | 290.0 | 4.30 ± 0.01 | 4.20 ± 0.02 | 3.98[a] | −0.595[a] | 1.000 | 5.34 | 0.18 | −0.43 | 0.51 |
| 1,3,5-Trichlorobenzene | 158.7 | 181.5 | 337.0 | 4.53 ± 0.02 | 4.32 ± 0.04 | 4.02[a] | −1.644[a] | 0.411 | 6.00 | 0.61 | 0.11 | 1.14 |
| 1,2,3,5-Tetrachlorobenzene | 179.6 | 215.9 | 323.9 | 4.86 ± 0.02 | 4.91 ± 0.04 | 4.65[a] | −1.873[a] | 0.554 | 6.36 | 0.65 | −0.12 | 0.87 |
| 1,2,4,5-Tetrachlorobenzene | 179.6 | 215.9 | 412.2 | 4.86 ± 0.02 | 4.87 ± 0.04 | 4.51[a] | −1.963[a] | 0.074 | 5.58 | −0.14 | −0.86 | 0.22 |
| Pentachlorobenzene | 200.5 | 250.3 | 357.7 | 5.32 ± 0.02 | 5.26 ± 0.04 | 5.03[a] | −2.479[a] | 0.257 | 6.63 | 0.45 | −0.20 | 0.76 |
| Hexachlorobenzene | 221.4 | 284.8 | 501.5 | 5.69 ± 0.02 | 5.43 ± 0.04 | 5.47[a] | −4.783[a] | 0.010 | 7.51 | 0.96 | 0.51 | 1.20 |
| 1,4-Dibromobenzene | 142.6 | 235.8 | 360.2 | 4.33 ± 0.02 | 4.30 ± 0.14 | 3.89[b] | −1.070[g] | 0.242 | 5.20 | 0.01 | −0.67 | 0.46 |
| 1,3,5-Tribromobenzene | 165.9 | 314.7 | 395.2 | 5.01 ± 0.02 | 5.21 ± 0.07 | 5.26[b] | −2.600[g] | 0.109 | 6.38 | 0.51 | −0.40 | 0.28 |
| Hexabromobenzene[i] | 235.8 | 551.5 | 579.0 | 5.81 ± 0.02 | 5.64 ± 0.04 | 6.80[c] | — | — | — | — | — | — |
| 2,4,5-trichlorobiphenyl | 247.3 | 257.5 | 351.0 | 5.76 ± 0.02 | 5.51 ± 0.04 | 5.60[d] | −3.268[d] | 0.299 | 7.49 | 0.87 | 0.41 | 1.04 |
| 2,2′,5,5′-tetrachlorobiphenyl | 268.2 | 292.0 | 360.0 | 6.28 ± 0.03 | 5.88 ± 0.08 | 6.10[d] | −3.987[d] | 0.243 | 8.12 | 0.98 | 0.67 | 1.17 |
| 2,2′,4,4′,6,6′-hexachlorobiphenyl | 310.0 | 360.9 | 387.0 | 6.50 ± 0.02 | 5.93 ± 0.04 | 7.00[d] | −5.721[d] | 0.132 | 9.59 | 2.23 | 2.08 | 1.74 |
| Decachlorobiphenyl | 393.6 | 498.7 | 578.9 | 7.14 ± 0.07 | 5.39 ± 0.10 | 8.26[d] | −8.620[d] | 0.002 | 10.58 | 2.59 | 3.62 | 1.48 |
| 2,7-Dichlorodioxin | 233.8 | 253.0 | 483.2 | 5.60 ± 0.05 | 5.90 ± 0.10 | 5.75[e] | −4.830[e] | 0.015 | 7.74 | 1.28 | 0.27 | 1.15 |
| 1,2,4-Trichlorodioxin | 254.7 | 287.5 | 402.2 | 5.87 ± 0.07 | 5.58 ± 0.11 | 6.45[e] | −4.583[e] | 0.093 | 8.30 | 1.57 | 1.15 | 1.00 |
| 1,2,3,4-Tetrachlorodioxin | 275.6 | 322.0 | 463.2 | 5.93 ± 0.05 | 5.21 ± 0.10 | 6.70[e] | −5.706[e] | 0.023 | 8.82 | 2.03 | 2.04 | 1.27 |
| Octachlorodioxin | 359.2 | 460.0 | 605.2 | 6.90 ± 0.05 | 4.96 ± 0.20 | 8.40[e] | −8.793[e] | 0.001 | 10.50 | 2.74 | 3.97 | 1.25 |
| Octachloronaphthalene[i] | 314.8 | 404.0 | — | 6.00 ± 0.05 | 5.50 ± 0.11 | 8.40[c] | — | — | — | — | — | — |
| 4,4′-Dibromobiphenyl | 231.2 | 311.8 | 422.0 | 5.61 ± 0.02 | 6.01 ± 0.09 | 5.72[f] | −4.735[h] | 0.055 | 8.22 | 1.75 | 0.64 | 1.65 |
| 2,4,6-Tribromobiphenyl | 254.5 | 390.7 | 337.0 | 6.21 ± 0.04 | 6.00 ± 0.10 | 6.03[b] | −4.386[h] | 0.389 | 8.72 | 1.65 | 1.15 | 1.84 |
| 2,2′,5,5′-Tetrabromobiphenyl | 277.8 | 469.6 | 409.0 | 6.72 ± 0.02 | 6.05 ± 0.04 | 6.50[b] | −5.064[h] | 0.074 | 8.68 | 1.10 | 1.06 | 1.33 |
| 2,2′,4,4′,6,6′-hexabromobiphenyl | 324.4 | 627.4 | 449.0 | 7.52 ± 0.03 | 5.96 ± 0.07 | 7.20[b] | −6.002[h] | 0.030 | 9.22 | 0.84 | 1.69 | 1.17 |

[a] From ref 19. [b] Measured by reversed-phase HPLC retention time as described in ref 28. [c] From ref 29. [d] From ref 30. [e] From ref 22. [f] From ref 31. [g] From ref 32. [h] Measured by a generator column method as described in ref 22. [i] Data not included in the correlations shown in eqs 14–25.

Concurrently, and under exactly the same conditions, the *n*-hexane–water partition coefficients of the test chemicals were measured. Samples ranging from 10 to 1000 mL were taken from the water phase and extracted twice with *n*-hexane. The extract was concentrated on a rotary evaporator at 30 °C, and then analyzed by GC-ECD. Samples from the *n*-hexane phase were diluted and then analyzed by GC-ECD.

Partition coefficient measurements for all test chemicals were performed in a similar fashion, but volume ratios were different depending on the aqueous solubility of the compound. *n*-Hexane–water partition coefficients, $K_{HW}$, were calculated from the chemical concentration in the *n*-hexane ($C_H$) and water ($C_{WH}$) of the *n*-hexane–water system as $C_H/C_{WH}$. This $K_{HW}$ was then used to determine the dissolved chemical concentration in the water of the *n*-hexane–water–membrane system (i.e., $C_{WM}$ which equals $C_{HM}/K_{HW}$, where $C_{HM}$ is the chemical concentration in the *n*-hexane phase above the membrane vesicle suspension in the *n*-hexane–water–membrane system). The chemical concentration in the membrane vesicles, $C_M$, was then calculated as the difference of the total chemical concentration in the membrane vesicle suspension (i.e., water and membranes, $C_{MS}$ and $C_{WM}$) from

$$C_M = V_{WM}(C_{MS} - C_{WM})/V_M \quad (12)$$

where $V_{WM}$ is the volume of the water phase in the membrane vesicle suspension, and $V_M$ is the volume of the membrane phase in the membrane vesicle suspension (i.e., the mass of phospholipids, $M_M$, divided by the membrane vesicle density, $d_M$, $M_M/d_M$). The membrane vesicle density was assumed to be 1.014 g/mL.[14] The membrane–water partition coefficient, $K_{MW}$, was then calculated as the ratio of $C_M$ and $C_{WM}$ (i.e., $K_{MW} = C_M/C_{WM}$). In summary, $K_{MW}$ was calculated from

$$K_{MW} = V_{WM}(C_{MS} - [C_{HM}/K_{HW}])/([M_M/d_M][C_{HM}/K_{HW}]) \quad (13)$$

**Determination of Chemical Solubilities in 1-Octanol**—Saturated solutions were prepared in dry 1-octanol by adding an excess amount of the test chemical to ~1 mL of 1-octanol in a 1.5-mL vial that was capped with a screw-top teflon septum. The vials were shaken gently for 24 h, then centrifuged at 4000 rpm for 1 h and left to settle for at least 48 h before analysis by GC-ECD.

**Gas Chromatographic Analyses**—All samples were analyzed on a HP 5890 gas chromatograph equipped with a $^{63}$Ni-electron capture detector (300 °C) and an OGSE on-column injector. A 30-m J&W DB 17+ fused silica capillary column (film thickness: 0.25 μm) was used. The carrier gas was helium, used at a linear velocity of 30 cm/s (at 50 °C), and the make up gas was 5% methane:argon, used at a flow rate of 60 mL/min.

Temperature programs from 50 to 300 °C were used, depending on the chemical of interest.

## Results

Experimentally determined membrane–water and *n*-hexane–water partition coefficients with their 95% confidence intervals are listed in Table I. In all experiments, loss of phospholipids from the membrane vesicle solution to the *n*-hexane phase was <5% at the experimental temperature, as determined by spectrophotometric analysis, and no accumulation of phospholipids at the *n*-hexane–water interface was observed throughout the course of the experiment. The efficiency of the extraction procedures ranged from 90 to virtually 100%. In Figure 2, the measured membrane–water and *n*-hexane–water partition coefficients, as well as 1-octanol–water partition coefficients obtained from the literature (Table I), are plotted versus the molar volume of the solute, $V_S$, calculated according to the LeBas method.[33] This plot shows that the logarithm of the *n*-hexane–water, 1-octanol–water, and membrane–water partition coefficients increase with molar volume in a linear fashion from values of ~3 at a molar volume of 115 cm$^3$/mol to 5.7 at a molar volume of 230 cm$^3$/mol. Beyond 230 cm$^3$/mol, this linear behavior continues for 1-octanol–water and *n*-hexane–water partition coefficients, resulting in the following correlations for all solutes. Confidence intervals having a 95% probability are included in parentheses.

$$\log K_{HW} = 0.0152\ (\pm 0.0018)V_S + 1.977\ (\pm 0.668) \quad (14)$$
$$n = 25,\ r = 0.95$$

$$\log K_{OW} = 0.0198\ (\pm 0.0015)V_S + 0.975\ (\pm 0.534) \quad (15)$$
$$n = 25,\ r = 0.98$$

Log $K_{HW}$ shows a slight (but statistically nonsignificant) tendency to level off from the linear correlation for larger values of $V_S$. This may be caused by experimental error or other factors.[22] Figure 2 shows that in contrast to log $K_{HW}$ and log $K_{OW}$, log $K_{MW}$ values level off beyond 230 cm$^3$/mol and even seem to fall near 400 cm$^3$/mol. Thus, log $K_{MW}$ follows an apparent parabolic relationship with respect to $V_S$, with a maximum $K_{MW}$ for solutes with molar volumes of ~300 cm$^3$/mol; that is,

$$\log K_{MW} = 0.0527\ (\pm 0.0092)V_S - 0.00908\ (\pm 0.00187)(V_S^2/100) - 1.73\ (\pm 1.05) \quad (16)$$
$$n = 25,\ r = 0.94$$

This loss of linear correlation between log $K_{MW}$ and $V_S$ for high molar volume compounds cannot be attributed to the presence of phospholipids in the water phase since the membrane–water partition coefficients are measured as a

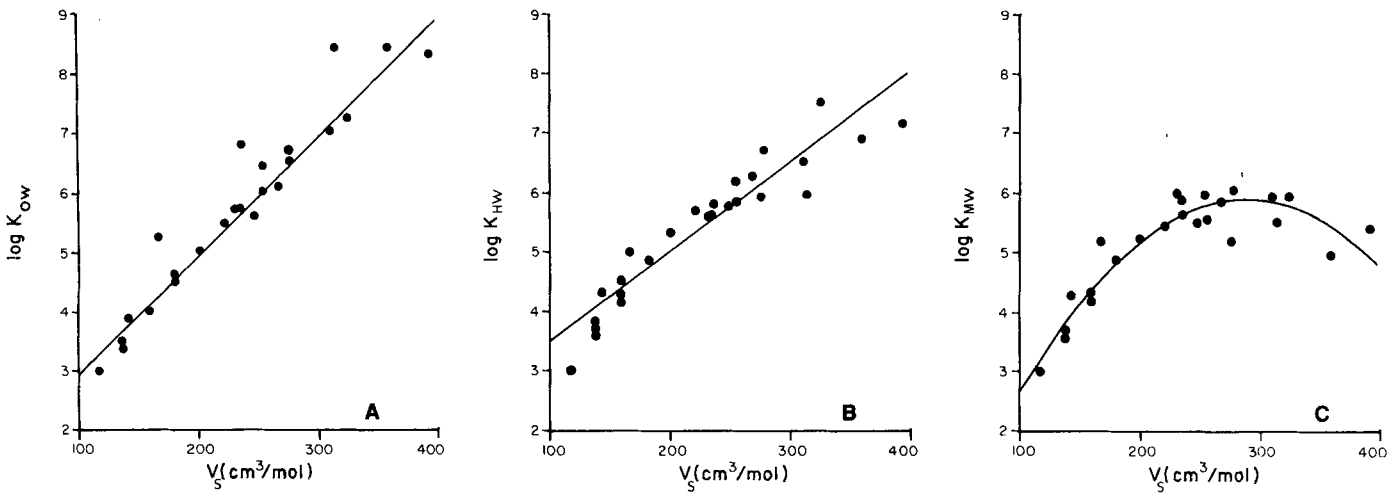


**Figure 2**—*Octanol–water* (A), *n-hexane–water* (B), *and DMPC membrane–water* (C) *partition coefficients as a function of the molar volume of the solute* ($V_S$).

ratio of the concentrations in the membrane vesicles and *n*-hexane- (not DMPC) saturated water. Recoveries of extraction procedures were carefully checked to ensure that the relatively low membrane–water partition coefficients are not the result of losses during extraction. It is therefore believed that the low membrane–water partition coefficients for high molar volume solutes are due to the relatively low solubilities or high activity coefficients of these solutes in membranes compared with 1-octanol or *n*-hexane. Apparently the free energy of cavity formation (and thus the free energy of solution) in the membrane phase per unit of volume increases with increasing volume. It is thus instructive to analyze these data in terms of activity coefficients and free energies.

In Table II, 1-octanol solubilities are listed and combined with data from two other studies.[19,34] Fugacity ratios, $F$, were calculated and activity coefficients in 1-octanol ($\gamma_O$) were deduced as $\gamma_O = F/X_O$, where $x_O$ is the mole fraction solubility in 1-octanol. Figure 3 gives a plot of log $\gamma_O$ versus molar volume.

Similarly, activity coefficients in water ($\gamma_W$) were calculated from independently determined water solubilities (Table I). Activity coefficients in membranes ($\gamma_M$), 1-octanol ($\gamma_O$), and *n*-hexane ($\gamma_H$) were then calculated from $\gamma_W$ and, respectively, $K_{MW}$, $K_{OW}$, and $K_{HW}$ (following eq 1) with molar volumes of 669 cm$^3$/mol for DMPC membranes, 126 cm$^3$/mol for water-saturated 1-octanol, 130 cm$^3$/mol for *n*-hexane, and 18 cm$^3$/mol for water (listed in Table I and plotted versus molar volume in Figure 4). The activity coefficients thus determined in membranes, 1-octanol, and *n*-hexane contain a considerable error since they are derived from two experimental observations instead of one (for $\gamma_W$), and they are

**Table II—Solubilities (log $S_O$) and Activity Coefficients (log $\gamma_O$) of Selected Aromatic Hydrocarbons in 1-Octanol**

| Compound | $M_w$, g/mol | $T_m$, K | $V_S$, cm$^3$/mol | log $F$ | log $S_O$, mol/L | log $\gamma_O$ |
|---|---|---|---|---|---|---|
| 1,4-Dichlorobenzene | 147.0 | 326 | 137.8 | −0.30 | 0.25 | 0.35 |
| 1,2,3-Trichlorobenzene | 181.5 | 326 | 158.7 | −0.30 | 0.25 | 0.35 |
| 1,3,5-Trichlorobenzene | 181.5 | 337 | 158.7 | −0.41 | | |
| 1,2,3,5-Tetrachlorobenzene | 215.9 | 324 | 179.6 | −0.28 | 0.15 | 0.47 |
| 1,2,4,5-Tetrachlorobenzene | 215.9 | 412 | 179.6 | −1.16 | −0.76 | 0.50 |
| Pentachlorobenzene | 250.3 | 358 | 200.5 | −0.62 | −0.49 | 0.77 |
| Hexachlorobenzene | 284.8 | 502 | 221.4 | −2.06 | −1.84 | 0.68 |
| Hexabromobenzene | 551.5 | 579 | 250.8 | −2.83 | −3.14 | 1.20 |
| 4-Monochlorobiphenyl | 188.7 | 351 | 205.5 | −0.55 | −0.22 | 0.56 |
| 4,4′-Dichlorobiphenyl | 223.1 | 422 | 226.4 | −1.26 | −1.15 | 0.78 |
| 2,4,5-Trichlorobiphenyl | 257.5 | 351 | 247.3 | −0.54 | −0.75 | 1.12 |
| 2,2′,5,5′-Tetrachlorobiphenyl | 292.0 | 360 | 268.2 | −0.64 | −0.63 | 0.89 |
| 2,3,4,5-Tetrachlorobiphenyl | 292.0 | 364 | 268.2 | −0.68 | −0.85 | 1.07 |
| Decachlorobiphenyl | 487.7 | 579 | 393.6 | −2.83 | −2.77 | 0.84 |
| Naphthalene | 128.2 | 353 | 148 | −0.57 | −0.02[b] | 0.34 |
| Biphenyl | 154.2 | 343 | 185 | −0.47 | −0.16[b] | 0.59 |
| Acenaphtene | 154.2 | 369 | 173 | −0.73 | −0.59[b] | 0.76 |
| Fluorene | 154.2 | 389 | 188 | −0.93 | −0.65[b] | 0.62 |
| 1-Methylfluorene | 168.2 | 358 | 210 | −0.62 | −0.53[b] | 0.80 |
| Anthracene | 178.2 | 489 | 197 | −1.93 | −1.93[b] | 0.89 |
| Phenanthrene | 178.2 | 374 | 199 | −0.78 | −0.40[b] | 0.51 |
| Fluoranthene | 202.3 | 384 | 217 | −0.88 | −0.76[b] | 0.78 |
| Pyrene | 202.3 | 429 | 214 | −1.33 | −0.85[b] | 0.42 |
| Chrysene | 228.3 | 528 | 251 | −2.32 | −2.70[b] | 1.28 |
| 2,3-Benzofluorene | 216.3 | 482 | 240 | −1.86 | −1.75[b] | 0.79 |
| Perylene | 252.3 | 550 | 263 | −2.54 | −2.52[b] | 0.87 |
| 1,2,5,6-Dibenzanthracene | 278.4 | 539 | 300 | −2.43 | −3.03[b] | 1.49 |
| Atrazine | 215.7 | 450 | 262.6 | −1.54 | −1.32 | 0.67 |
| DDT | 354.5 | 382 | 363.5 | −0.86 | −1.09 | 1.12 |
| Hexachlorocyclohexane | 290.8 | 433 | 258.6 | −1.37 | −1.29 | 0.81 |
| Hexachlorobenzene | 284.8 | 503 | 221.4 | −2.07 | −1.82 | 0.64 |
| 1,4-Dichlorobenzene | 147.0 | 326 | 137.8 | −0.30 | 0.25 | 0.35 |
| Dyes:[a] | | | | | | |
| I | 516.4 | 448 | 535 | −1.52 | −3.80[c] | 3.18 |
| II | 303.0 | 498 | 322 | −2.02 | −3.48[c] | 2.36 |
| III | 306.5 | 498 | 365 | −2.02 | −3.41[c] | 2.28 |
| IV | 311.7 | 492 | 308 | −1.96 | −3.26[c] | 2.20 |
| V | 418.5 | 421 | 526 | −1.25 | −3.01[c] | 2.65 |
| VI | 393.3 | 457 | 514 | −1.61 | −2.69[c] | 1.98 |
| VII | 396.9 | 443 | 438 | −1.47 | −2.62[c] | 2.05 |
| VIII | 498.0 | 390 | 503 | −0.94 | −2.47[c] | 2.43 |
| IX | 343.8 | 419 | 404 | −1.23 | −2.21[c] | 1.88 |
| X | 381.5 | 446 | 479 | −1.50 | −2.20[c] | 1.59 |
| XI | 371.0 | 549 | 371 | −2.53 | −4.60[c] | 2.96 |
| XII | 307.3 | 563 | 326 | −2.67 | −4.26[c] | 2.48 |
| XIII | 486.8 | 563 | 486 | −2.67 | −4.80[c] | 3.02 |
| XIV | 629.5 | 593 | 675 | −2.97 | −6.10[c] | 4.02 |
| XV | 726.4 | 593 | 763 | −2.97 | −6.20[c] | 4.12 |
| XVIII | 439.8 | 603 | — | −3.07 | −5.10[c] | 2.92 |
| XIX | 312.3 | 673 | 267 | −3.77 | −5.26[c] | 2.39 |
| XX | 1100.0 | 753 | 933 | −4.57 | −7.20[c] | 3.52 |

[a] No systematic names are reported by the authors, but structural formulas of the listed dyes can be found in ref 34. [b] From ref 19. [c] From ref 34.

calculated as the ratio of two error-containing numbers.

Figure 4 shows that log $\gamma_W$ increases linearly with $V_S$, that is

$$\log \gamma_W = \Delta G_{s,W}/RT = 0.0240\ (\pm 0.0019)V_S + 1.892\ (\pm 0.69) \quad (17)$$

$$n = 25,\ r = 0.98$$

Each 1.0-cm$^3$/mol increase in $V_S$ thus causes an increase in $\Delta G_{s,W}$ of 60 (±5) J/mol, in log $\gamma_W$ of 0.024 (±0.0019), and a corresponding reduction in subcooled liquid solubility. There is no evidence of a significant change in the slope of the log $\gamma_W$ versus $V_S$, plot, except for chemicals with molar volumes >300 cm$^3$/mol. For these chemicals, the experimental error in $\gamma_W$ measurements is rather large and likely to result in values lower than the actual values, thus slightly reducing the slope.

Since $\gamma_O$ and $\gamma_H$ data are less accurate, their interpretation is more difficult. Figures 3 and 4, however, indicate that log $\gamma_O$ and log $\gamma_H$ also increase linearly with $V_S$, that is

$$\log \gamma_O = \Delta G_{s,O}/RT = 0.00540\ (\pm 0.00075)V_S - 0.281\ (\pm 0.865) \quad (18)$$

$$n = 48,\ r = 0.87$$

$$\log \gamma_O = \Delta G_{s,O}/RT = 0.00418\ (\pm 0.00148)V_S + 0.0716\ (\pm 0.541) \quad (19)$$

$$n = 25,\ r = 0.71$$

$$\log \gamma_H = \Delta G_{s,H}/RT = 0.00884\ (\pm 0.00202)V_S - 0.948\ (\pm 0.739) \quad (20)$$

$$n = 25,\ r = 0.84$$

Also, no profound change in behavior occurs when $V_S$ becomes large. Equation 18 applies to data derived from 1-octanol solubilities and eq 19 applies to data deduced from $K_{OW}$. The striking feature is that a 1.0-cm$^3$/mol increase in $V_S$ causes $\Delta G_{s,O}$ and $\Delta G_{s,H}$ to increase by 12 ±4 and 22 ±5 J/mol, respectively, and log $\gamma_O$ and log $\gamma_H$ to increase by 0.0048 (±0.0015) and 0.0088 (±0.0020), respectively, effects that are much less than that in water.

Figure 4 shows that log $\gamma_M$ tends to follow a parabolic relationship with respect to $V_S$, that is,

$$\log \gamma_M = \Delta G_{s,M}/RT = 0.00320\ (\pm 0.00040)(V_S^2/100) - 1.11\ (\pm 0.262) \quad (21)$$

$$n = 25,\ r = 0.94$$

This results in an increase in $\Delta G_{s,M}$ and log $\gamma_M$, for a 1.0-cm$^3$/mol increase in $V_S$, which is approximately linearly dependent on $V_S$ [i.e., respectively, 0.16 (±0.02)$V_S$ J/mol and 6.4 (±0.8)$10^{-5}V_S$]. For chemicals with $V_S$ values ranging from 100 to 230 cm$^3$/mol, this implies that a 1.0-cm$^3$/mol increase in $V_S$ causes $\Delta G_{s,M}$ to increase by 16 to 37 J/mol, and log $\gamma_M$ to increase by 0.0064 to 0.015, increases that are approximately similar to those in 1-octanol and *n*-hexane. Although similar in slope, $\gamma_M$ for chemicals with $V_S$ values <230 cm$^3$/mol tend to be lower in magnitude than $\gamma_O$ and $\gamma_H$ (i.e., the solutes show a greater affinity for DMPC than for 1-octanol and *n*-hexane). For some chemicals, $\gamma_M$ is even lower than unity (i.e., a negative deviation from Raoult's law). This corresponds to the behavior of activity coefficients in glyceryltrioleate.[35] Beyond 230 cm$^3$/mol, $\gamma_M$ increases markedly, resulting in an increase in $\Delta G_{s,M}$ of 37 J/mol, and in log $\gamma_M$ of 0.015 for a 1.0 cm$^3$/mol increase in $V_S$ of a solute of ~230 cm$^3$/mol, to respectively 64 J/mol and 0.026 for the same increase in $V_S$ for a solute of 400 cm$^3$/mol.

Introducing solvatochromic parameters to quantify solute–solvent interactions did not significantly improve the correlations shown in eqs 18–21.[36,37] This may be interpreted as a confirmation that solute–solvent interactions are relatively unimportant with respect to cavity formation for the chemically closely related solutes in this study. It is believed that experimental error is a major factor affecting the quality of the correlations. We can thus conclude that chemicals with molar volumes between 115 and 230 cm$^3$/mol show approximately the same behavior in 1-octanol, *n*-hexane, and DMPC membranes. Chemicals with molar volumes in the range of 230 to 400 cm$^3$/mol show a marked difference in solubility between membranes and *n*-hexane or 1-octanol, probably as a result of a profound increase in free energy of cavity formation in the membranes.

## Discussion

Since this study indicates that, within the molar volume

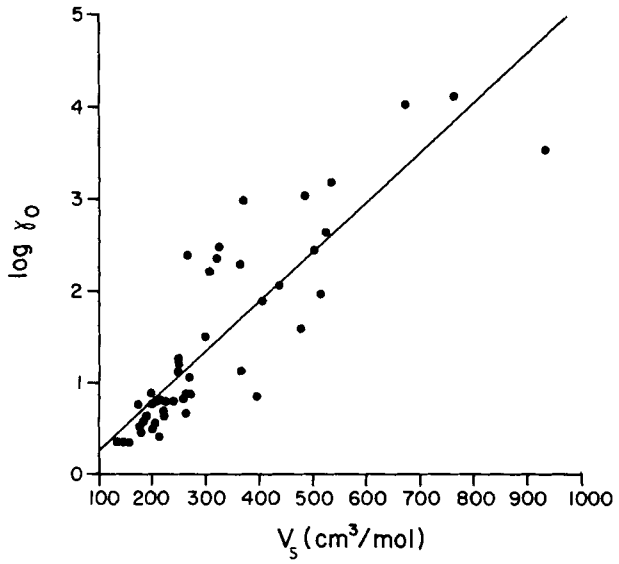


**Figure 3**—*Logarithm of the activity coefficients in 1-octanol (log $\gamma_O$) versus the molar volume of the solute ($V_S$).*

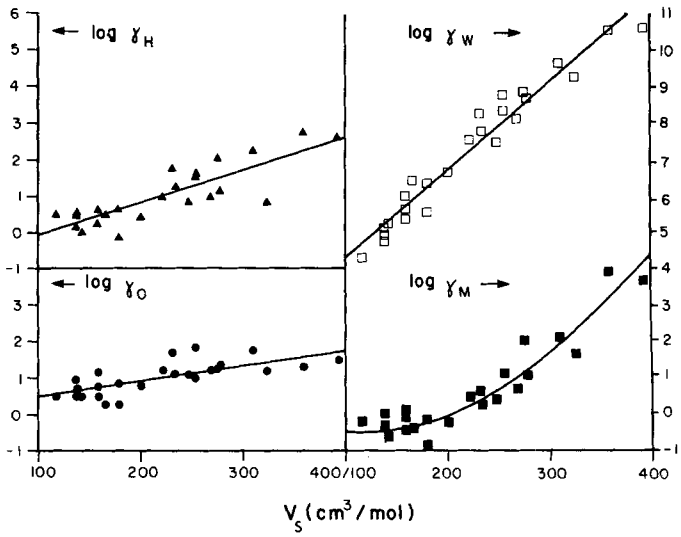


**Figure 4**—*Logarithms of the activity coefficients in 1-octanol (log $\gamma_O$), n-hexane (log $\gamma_H$), DMPC membranes (log $\gamma_M$), and water (log $\gamma_W$) versus the molar volume of the solute.*

range studied, activity coefficients of nonpolar hydrophobic organic chemicals in 1-octanol and *n*-hexane are linearly related to the molar volume of the solute, a linear correlation between log $K_{OW}$ and log $K_{HW}$, based on eq 9, may be expected and is actually observed:

$$\log K_{OW} = 1.21\ (\pm 0.13)\log K_{HW} - 1.10\ (\pm 0.763) \quad (22)$$

$$n = 25,\ r = 0.96$$

For chemicals with molar volumes below ~230 $cm^3$/mol, the behavior of the activity coefficient in membranes with increasing molar volume corresponds to that in 1-octanol and *n*-hexane. Satisfactory correlations between partitioning in 1-octanol or *n*-hexane and biological phases similar to those studied here can be expected and indeed are found.[2,38] Under those conditions, 1-octanol and *n*-hexane are satisfactory surrogate phases for biological phases. This is illustrated in Figure 5 where DMPC vesicles– and liposome–water partition coefficients, determined by different methods at temperatures between 25 and 28 °C (Table III), are combined with the DMPC vesicle–water partition coefficients measured in this study and plotted versus log $K_{OW}$. Figure 5, which shows the relationship between log $K_{MW}$ and log $K_{OW}$ over 11 orders of magnitude in $K_{OW}$, demonstrates that for chemicals with log $K_{OW}$ between 1 and 5.5, log $K_{MW}$ and log $K_{OW}$ are approximately equal and follow a linear correlation:

$$\log K_{MW} = 1.19\ (\pm 0.13)\log K_{OW} - 0.645\ (\pm 0.682) \quad (23)$$

$$n = 25,\ r = 0.96$$

For chemicals with a log $K_{OW}$ of <1, and thus with relatively high aqueous solubilities, this linear relation curves off, possibly as a result of the different water contents of 1-octanol and DMPC membranes. For chemicals with log $K_{OW}$ >5.5, and thus with molar volumes >230 $cm^3$/mol, the linear correlation breaks down and $K_{OW}$ does not adequately reflect the partitioning tendency in membranes any more. Since for these chemicals membrane activity coefficients seem to follow a distinct parabolic relationship with molar volume, it follows, after substitution of eq 6 with $\Delta G_{c,A} = AV^2$ in eq 8, that correlations between log $K_{MW}$ and log $K_{OW}$ or log $K_{HW}$ or any other bulk organic phase–water partition coefficient are nonlinear and are dependent on the molar volume of the solute according to

$$\log K_{MW} = [1.66\ (\pm 0.42) - 0.00237\ (\pm 0.00080)V_S]\log K_{OW} - 0.850\ (\pm 1.25) \quad (24)$$

$$n = 25,\ r = 0.91$$

and

$$\log K_{MW} = [1.61\ (\pm 0.276) - 0.00175\ (\pm 0.000487)V_S]\log K_{HW} - 1.36\ (\pm 0.908) \quad (25)$$

$$n = 25,\ r = 0.96$$

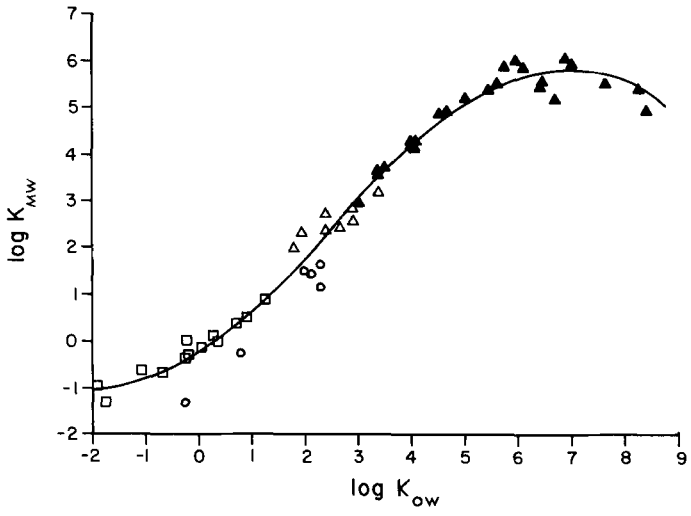


**Figure 5**—*Relationship between the 1-octanol–water partition coefficient (log $K_{OW}$) and the DMPC membrane–water partition coefficient (log $K_{MW}$).*

The reason for the breakdown in the relationship between log $K_{OW}$ and log $K_{MW}$ appears to be that when solute size increases, relatively more energy per unit of volume is required to form a cavity in the structured membrane phase to accomodate the solute. This is likely to be the result of the structured nature of the phospholipids in the membrane phase, and agrees with observations by several authors that more voluminous branched molecules have lower lecithin–water partition coefficients than their straight chain analogues, and that the extent to which branching lowers the partition coefficient is higher in membranes than in bulk solvents.[43–45] Molecular volume and shape thus affect activity coefficients in a structured liquid, such as membranes, differently from bulk phases, such as 1-octanol and *n*-hexane, and these differences tend to become larger with increasing solute size. This phenomenon may cause a loss of linear correlation between partition coefficients between "bulk organic solvents" and water, and "membrane tissue" and water for fairly large size solutes. This may then cause a breakdown of linear $K_{OW}$-based structure–activity relationships.

Finally, we emphasize that the results and discussion

**Table III—Literature Data on Partition Coefficients between Water and L-*a*-Phosphatidylcholine Dimyristoyl Membranes ($K_{MW}$) and 1-Octanol ($K_{OW}$)**

| Compound | log $K_{MW}$ | log $K_{OW}$ |
|---|---|---|
| Methanol | −0.680[a] | −0.70[d] |
| Ethanol | −0.350[a] | −0.26[d] |
| *n*-Propyl alcohol | 0.123[a] | 0.28[d] |
| Isopropyl alcohol | −0.145[a] | 0.05[d] |
| *t*-Butyl alcohol | 0.027[a] | 0.36[d] |
| Cyclohexanol | 0.906[a] | 1.23[d] |
| Urea | −0.632[a] | −1.09[d] |
| Ethylene glycol | −0.930[a] | −1.93[e] |
| Glycerol | −1.290[a] | −1.76[e] |
| Butyramide | −0.289[a] | −0.21[d] |
| Ethylacetate | 0.407[a] | 0.70[d] |
| *n*-Butyl alcohol | 0.506[a] | 0.88[d] |
| Acetone | 0.027[a] | −0.24[d] |
| Ethrane | 1.450[b] | 2.10[d] |
| Trichloroethylene | 1.040[b] | 2.29[d] |
| Halothane | 1.170[b] | 2.30[d] |
| Chloroform | 1.470[b] | 1.96[d] |
| Diethylether | −0.274[b] | 0.80[d] |
| Ethanol | −1.320[b] | −0.26[d] |
| *p*-Fluorophenol | 2.010[c] | 1.79[d] |
| *p*-Chlorophenol | 2.390[c] | 2.40[d] |
| *p*-Bromophenol | 2.450[c] | 2.66[d] |
| *p*-Iodophenol | 2.610[c] | 2.92[d] |
| *p*-Methylphenol | 2.350[c] | 1.94[d] |
| *p*-Ethylphenol | 2.750[c] | 2.42[d] |
| *p*-(*n*-Propyl)phenol | 2.890[c] | 2.90[f] |
| *p*-(*n*-Butyl)phenol | 3.190[c] | 3.38[f] |

[a] From ref 39 and (□) in Figure 5. [b] From ref 18 and (○) in Figure 5. [c] From ref 40 and (△) in Figure 5. [d] From ref 41. [e] From ref 42. [f] Calculated from log $K_{OW}$ of *p*-ethylphenol with a $\pi$-value of 0.48 for each $-CH_2-$ group.

presented here are based on data obtained from relatively few solutes and solvents. In particular, the solutes comprise a relatively restricted class of chemicals which are nonpolar in nature. Other classes of chemicals may behave differently. It is thus essential to obtain data from a wider range of chemicals before the generality of this approach can be ascertained. If it can be demonstrated for chemicals of different chemical nature that the model membranes used in this study indeed resemble the partitioning characteristics of membrane or lipid tissue in organisms, membrane–water partition coefficients may be a more reliable predictor and basis for QSARs than $K_{OW}$, especially for high molar volume chemicals.

## References and Notes


1. Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1972**, *71*, 525–555.
2. Dearden, J. C. *Environ. Health Persp.* **1985**, *61*, 203–228.
3. Seeman, P. *Pharmacol. Rev.* **1972**, 583–655.
4. Neely, W. B. *Environ. Sci. Technol.* **1979**, *13*, 1506–1510.
5. Veith, G. D.; Call, D. J.; Brooke, L. T. *Can. J. Fish Aquat. Sci.* **1983**, *40*, 743–748.
6. Lien, E. J. *Environ. Toxicol. Chem.* **1985**, *4*, 259–271.
7. Lien, E. J.; Wang, P. H. *J. Pharm. Sci.* **1980**, *69*, 648–650.
8. Hansch, C.; Clayton, J. M. *J. Pharm. Sci.* **1973**, *62*, 1–21.
9. Kubinyi, H. *Arzneim.-Forsch.* **1976**, *26*, 1991–1997.
10. Franke, R.; Oehme, P. *Pharmazie* **1973**, *28*, 489–508.
11. Lipnick, R. L.; Pritzker, C. S.; Bentley, D. L. *Proceedings, 6th European QSAR Symposium*, Pontorose, September 1986; Elsevier: Amsterdam, 1987, in press.
12. Bruggeman, W. A.; Opperhuizen, A.; Wijbenga, A.; Hutzinger, O. *Toxicol. Environ. Chem.* **1984**, *7*, 173–189.
13. Gobas, F. A. P. C.; Shiu, W. Y.; Mackay, D. In *QSAR in Environmental Toxicology*; Kaiser, K. L. E., Ed.; D. Reidel: Dordrecht, 1987; pp 107–123.
14. Katz, Y.; Diamond, J. M. *J. Membr. Biol.* **1974**, *17*, 69–86.
15. Papahadjopoulos, D.; Jacobson, K.; Poste, G.; Shephard, G. *Biochim. Biophys. Acta* **1975**, *394*, 504–519.
16. Hill, M. W. *Biochim. Biophys. Acta* **1974**, *356*, 117–124.
17. Oman, G.; Lakowicz, J. R. *Biochim. Biophys. Acta* **1982**, *684*, 83–95.
18. VanderKooi, J. M.; Landesberg, R.; Selick, H., II; McDonald, G. G. *Biochim. Biophys. Acta* **1977**, *464*, 1–16.
19. Miller, M. M.; Wasik, S. P.; Huang, G. L.; Shiu, W. Y.; Mackay, D. *Environ. Sci. Technol.* **1985**, *19*, 522–529.
20. Pearlman, R. S. In *Partition Coefficient*; Dunn, W. J., III; Block, J. H.; Pearlman, R. S., Eds.; Pergamon: New York, 1986; pp 3–20.
21. Leo, A.; Hansch, C.; Jow, P. Y. C. *J. Med. Sci.* **1976**, *5*, 611–615.
22. Shiu, W. Y.; Doucette, W.; Gobas, F. A. P. C.; Andren, A.; Mackay, D., *Environ. Sci. Technol.*, in press.
23. Valvani, S. C.; Yalkowsky, S. H. In *Physical Chemical Properties of Drugs*; Yalkowsky, S. H.; Sinkula, A. A.; Valvani, S. C., Eds.; Marcel Dekker: New York, 1980; pp 201–227.
24. Prausnitz, J. M. *Molecular Thermodynamics of Fluid-Phase Equilibria*; Prentice-Hall: New Jersey, 1969; pp 385–406.
25. Butler, J. A. V. *Trans. Faraday Soc.* **1937**, *33*, 229–237.
26. Butler, J. A. V.; Harrower, P. *Trans. Faraday Soc.* **1937**, *33*, 171–178.
27. Bangham, A. D.; Standish, M. M.; Watkins, J. C. *J. Mol. Biol.* **1965**, *13*, 238–253.
28. Veith, G. D.; Austin, N. M.; Morris, R. T. *Water Res.* **1979**, *13*, 43–47.
29. Bruggeman, W. A.; van der Steen, J.; Hutzinger, O. *J. Chromatogr.* **1982**, *238*, 335–346.
30. Shiu, W. Y.; Mackay, D. *J. Phys. Chem. Ref. Data* **1986**, *15*, 911–929.
31. Doucette, W. J. Ph.D. Thesis, University of Wisconsin, Madison, WI, 1985.
32. Yalkowsky, S. H.; Orr, R. J.; Valvani, S. C. *Ind. Eng. Chem. Fundam.* **1979**, *18*, 351–353.
33. Reid, R. C.; Prausnitz, J. M.; Sherwood, T. K. *The Properties of Gases and Liquids*, 3rd Ed.; McGraw Hill: New York, 1977.
34. Anliker, A.; Moser, P. *Ecotox. Environ. Safety* **1987**, *13*, 43–53.
35. Chiou, C. T.; Manes, M. J. *J. Chem. Soc., Faraday Trans 1* **1986**, *82*, 243–246.
36. Kamlet, J. M.; Abboud, J. L. M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877–2887.
37. Kamlet, M. J., personal communication.
38. Hansch, C.; Dunn, W. J. *J. Pharm. Sci.* **1972**, *61*, 1–19.
39. Katz, Y.; Diamond, J. M. *J. Membr. Biol.* **1974**, *17*, 101–120.
40. Rogers, J. A.; Davis, S. S. *Biochim. Biophys. Acta* **1980**, *598*, 392–404.
41. Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.
42. Cornford, E. *J. Membr. Biol.* **1982**, *64*, 217–224.
43. Diamond, J. M.; Katz, Y. *J. Membr. Biol.* **1974**, 121–154.
44. Hingson, D. J.; Diamond, J. M. *J. Membr. Biol.* **1972**, *10*, 93–135.
45. Diamond, J. M.; Wright, E. M. *Ann. Rev. Physiol.* **1969**, *31*, 581–646.


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