Octanol-Water Partition Coefficients of Simple Organic Compounds

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Octanol-water partition coefficients ($\log P$) for 611 simple organic compounds representing all principal classes have been retrieved from the literature. Available experimental details of measurement are documented from original articles. Pertinent thermodynamic relations are presented, with a discussion of direct and indirect methods of measurement. Reported $\log P$ data for each compound have been evaluated according to stated criteria, and recommended values (with uncertainty) are given.

Key words: octanol-water partition coefficient; organic compounds; hydrophobicity; hydrophilicity

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List of Symbols and Abbreviations

a	= activity
AMB	= ambient temperature
AQ	= octanol-saturated water phase
AS	= absorption spectrophotometry
B	= organic base
c	= concentration
C_p	= heat capacity at constant pressure
CR	= chemical reaction
D	= direct method
FL	= fluorescence
G	= Gibbs energy

GC	= generator column		x	= mole fraction
GLC	= gas-liquid chromatography		X	= solute
h	= chromatographic peak height, Eq. (28)		?	= doubtful Log P value; Code uncertain
H	= enthalpy			
HA	= organic acid		**Greek**	
H_M	= Henry's law constant		Δ	= difference in thermodynamic function
(RP)-HPLC	= (reverse-phase) high pressure liquid chromatography		γ	= volume-fraction activity coefficient
I	= indirect method		μ	= chemical potential
K	= Kjeldahl method		φ	= volume fraction
K_a	= acid ionization constant		ζ	= solubility (mol L^{-1})
l	= liquid			
m,n	= correlation constants, Eq. (10)		**Superscripts**	
NS	= neutral salt solution		aq	= octanol-saturated water phase
ORG	= water-saturated octanol phase		0	= standard state
p	= pressure		oct	= pure octanol phase
P	= partition coefficient		org	= water-saturated octanol phase
P_{app}	= apparent partition coefficient		sat	= phase saturated with solute
RC	= radiochemical method		w	= pure water phase
s	= solid		*	= Hansch & Leo "selected" Log P value
S	= entropy			
SF	= shake-flask method		**Subscripts**	
T	= temperature (kelvin)		app	= apparent (partition coefficient)
Temp.	= temperature of log P measurement (°C)		fus	= fusion
TN	= titration		f	= final
v	= volume (general)		i	= initial
V	= molar volume (L mol^{-1})		org	= water-saturated octanol phase
W	= octanol-saturated water solvent		tr	= transfer process
			X	= solute

1. Introduction

1.1. General

1.1.a. Definition

A pure substance may distribute itself between two partially miscible solvents in intimate contact, and the equilibrium ratio of solute concentrations in the two phases has come to be known as the distribution coefficient or partition coefficient.[1] In preparative organic chemistry, the use of solvents of greatly differing polarity (e.g., hydrocarbon and water) facilitates the extraction and purification of desired products. In addition, the biological activity of simple organic compounds was early found to correlate with their oil-water partition coefficients.[2] It became apparent that, for biological purposes a partition coefficient based on long-chain ester or alcohol solvents was more appropriate. After some deliberation, 1-octanol was chosen as the most useful lipophile solvent in these applications. Most correlation work has been done using the octanol-water pair, and this is the reason for its wide use and the existence of a great quantity of data on the subject.

The octanol-water partition coefficient of a substance X at a given temperature is, by general consent,[1] represented by P and defined by (for reasons explained later, the superscripts "org" and "aq" are used to denote mutually saturated phases, and "oct" and "w" for the pure solvents.)

$$P = [X]^{org}/[X]^{aq}, \tag{1}$$

i.e., the ratio of concentrations (mole/volume) at equilibrium; it is therefore unitless. In the interest of standardization and precision in interpretation, the partition coefficient is defined for the same species on both phases.[1] This is important in considering P of ionizable compounds such as organic

acids, amines, and quaternary ammonium salts, which may also form dimers or ion-pairs. This is discussed further in this Introduction.

In addition, the solvents represented in Eq. (1) are those mutually saturated with each other at the temperature of measurement. This is a natural consequence of the classical "shake-flask" or extraction method used in experimental measurement of P, and is to be taken into account for accuracy in measurement and thermodynamic interpretation.

Further, P is preferably defined as the quantity which is independent of concentration, i.e., that value for which the solute obeys Henry's law in both solvents simultaneously. In practice, this means a P determined at high dilution, or extrapolated to zero concentration. Since P as measured can range over many orders of magnitude (10^{-2} to 10^6), it is usually expressed as its decadic logarithm, log P.

1.1.b. Scope of this evaluation

This work proposes to have retrieved and evaluated most of the significant published experimentally determined values of log P of simple organic molecules. The word "simple" is taken here to indicate molecules containing no or only one polar functional group, i.e., a group having N,O,S and/or halogen atom. A few well-known exceptions (chloroform, CCl_4) have been included. This limits the number of substances involved and, as far as possible, avoids complications of interpretation due to the presence of neighboring polar groups. The compounds are those which are liquids or solids at ordinary temperatures and pressures, and no arbitrary upper carbon number cutoff limit has been imposed. Elements, inorganic, metal-organic and unstable species have been excluded, as well as quaternary ammonium and similar salts.

1.1.c. Need for critical evaluation

The partition coefficient, as properly defined, is a definite equilibrium physico-chemical property of a pure substance under specified conditions. It provides a useful quantitative parameter for representing the lipophilic/hydrophilic nature of the substance. It is a function of the Gibbs energy of transfer from water to octanol and hence describes the thermodynamic tendency for the compound to partition preferentially in different media. It is not surprising, therefore, that it has been widely used in many areas such as:

-design of drugs and pharmaceuticals,[4]
-prediction and correlation of bioconcentration[5] and soil and sediment sorption of organic pollutants,
-research on medicinal chemicals,
-modelling of environmental fate of organic chemicals,[6]
-toxicology of substances.

For many substances, $\log P$ has been measured by different laboratories and by different methods. The reported $\log P$ values of a single substance can sometimes vary a great deal; for example, those of p,p'-DDT cover a range of a factor of one hundred.[2] Large uncertainties in $\log P$ are undesirable in general. The accuracy of the simulation, by calculation, of the environmental fate of an organic chemical may become quite sensitive to uncertainties of input parameters (e.g., Mirex in Lake Ontario[7]). The successful development of additive-constitutive calculational schemes[2,8] for $\log P$, based on molecular structure, requires a database of assessed accuracy. Finally, it is difficult, if not impossible, for the uninitiated user of $\log P$ data to distinguish accurate and inaccurate data by simple inspection.

1.2 Thermodynamics

The thermodynamic relationships between $\log P$ and other quantities will be examined in some detail in this section. Many experimental data on $\log P$ related thermodynamic quantities have appeared recently, some of high quality. Since these were not discussed in any detail in former compilations and reviews,[1,2] the following exposition is meant to summarize the important thermodynamic relations in a concise and rigorous manner.

1.2.a. General equilibrium relations

The present thermodynamic analysis is a slightly edited restatement of the one currently being used to describe the two-phase system represented by the octanol-water partition coefficient.[9,10,34,38,58] Like the current practice, it uses volume fractions as composition variable and volume fraction activity coefficients. This convention, when used in conjunction with the (volume-based) partition coefficient, simplifies the thermodynamic argument. An equivalent though incomplete, analysis using mole fractions is given elsewhere.[33,39] If a liquid substance X is distributed between organic and aqueous phases at equilibrium, we can write for each phase[9]

$$\mu_x = \mu_x^0 + RT \ln a_x \qquad (2)$$

$$= \mu_x^0 + RT \ln(\gamma_x \varphi_x), \qquad (3)$$

where μ_x is the chemical potential of X in solution, μ_x^0 is the chemical potential of pure liquid X, a_x is its activity in solution, γ_x is the volume-fraction activity coefficient and φ_x is the volume fraction of X in the solution. From the defining Eqs. (2) and (3), the activity coefficient is normalized by $\gamma_x \to 1$ as $\varphi_x \to 1$.

By definition, in each phase we have

$$[X]V_x = \varphi_x, \qquad (4)$$

where V_x is the (partial) molar volume of X in solution. (For dilute solutions of liquid nonelectrolytes in water or octanol, partial molar volume can be replaced by pure liquid molar volume without appreciable error.) At equilibrium, $\mu_x^{org} = \mu_x^{aq}$. Combining this equality with Eqs. (1), (3), and (4) yields[9]

$$\log P = \log(\gamma_x^{aq}/\gamma_x^{org}), \qquad (5)$$

i.e., P is equivalent to the ratio of the Henrian activity coefficients of the solute in the phases. Equation (5) has been derived using the assumption that $V_x^{aq} = V_x^{org}$.

1.2.b. Temperature dependence

The variation of $\log P$ with temperature[1] is small, approximately $\pm 0.01 \ K^{-1}$. Table 1 presents experimental data of $d(\log P)/dT$ for some specific compounds.

The thermodynamic transfer functions are closely related to $\log P$:

$$\Delta_{tr} G = -RT \ln P \qquad (6)$$

$$d(\Delta_{tr} G)/dt = -\Delta_{tr} S \qquad (7)$$

$$\Delta_{tr} G = \Delta_{tr} H - T \Delta_{tr} S \qquad (8)$$

As a consequence of the definition of P, these transfer quantities are independent of concentration and refer to the difference: (function for solute in water-saturated octanol)— (function for solute in octanol-saturated water).

The temperature dependence of $\Delta_{tr} G$ and hence of $\log P$ can be represented by $\Delta_{tr} H$ and $\Delta_{tr} S$ through Eqs. (6), (7), and (8). A van't Hoff plot of $\ln P$ may be used to obtain

TABLE 1. Temperature dependence of Log P of some compounds at room temperature

Substances	Temperature range, °C	1000 $d(\text{Log } P)/dT$ K^{-1}	Ref.
n-propylbenzene	10–35	≈ 0	10,11
chlorinated benzenes	13–33	-29 to -5	12
phenol	10–60	-3.4	16
phenol	20–50	-4.9	17
p-cresol	15–35	-7.5	18
phenol	15–35	-16	18
m-alkoxyphenols	15–35	-5 to -3	19
resorcinol	15–35	-8.8	19
substituted phenols	10–60	-8 to -1	16
substituted phenols	20–50	-3 to $+10$	17
chlorophenols	···	-8.6 (mean)	20
hydroxybenzoic acids	···	-14 (mean)	20
methyl nicotinate	5–25	7.4	14
ephedrine	15–40	8.1	15
methamphetamine	15–40	0.4	15
alkyl amidylpyridines	20–40	2 to 6	13
methyl acetanilides	···	≈ 0 (mean)	20

enthalpy and entropy of transfer.[17-20] However, P is a Gibbs energy function—as are solubility and vapor-liquid equilibrium—and these functions are usually found to be relatively insensitive to temperature. The enthalpy of transfer may be more precisely determined[21] either by direct experimental measurement in an isoperibol flow calorimeter[22,23] (in which two immiscible phases are brought into direct contact) or indirectly from the calorimetric limiting enthalpies of solution in the two solvents separately.

As will be discussed in greater detail in the next section, both $\Delta_{tr}G$ and $\Delta_{tr}H$ may be determined from measurements on solutions based on the two solvents separately. This is a possible route, provided it is realized that solute thermodynamic functions in pure water or pure octanol may be significantly different from those in mutually saturated solvents.

1.2.c. Specific thermodynamic relations

Mutually saturated solvents.

From liquid–liquid equilibrium data[2,4] the equilibrium mole fractions of octanol in the two-phase system water/n-octanol at 25 °C are 7.03×10^{-5} and 0.793. Saturated octanol thus contains an appreciable amount of water; the molar volume of wet octanol[25] is 126.6 cm^3, and the water content is equivalent to 1.64 mol L^{-1}. The two phases in a shake-flask determination of P are ternary. The question whether or not the presence of the other solvent in a phase significantly alters the thermodynamic properties of the solute becomes important in considering recently elaborated "activity coefficient" methods of determining the partition coefficient.

For example, Berti *et al.*[22] compared the transfer Gibbs energies from shake-flask log P values of some common solutes to those found from the directly measured Henrian activity coefficients of the same solutes in pure octanol and pure water. The differences in $\Delta_{tr}G$, 1 to 2 kJ mol^{-1}, is equivalent to differences of as much as $\pm$ 0.4 in log P, being negative or positive or zero, depending on the solute. Calorimetrically determined enthalpies of transfer of m-alkoxy phenols[26] in neat and mutually saturated solvents differed by up to 1.6 kJ mol^{-1}; the same effect is found in the corresponding enthalpies of solution[22,26] from which the transfer enthalpies are derived. Again, the magnitude of the effect depends on the solute; the transfer enthalpies of n-alkanols[27] for example, are much less sensitive in this respect.

Platford[28,29] used the isopiestic method to measure the limiting activity coefficients of CCl$_4$ and benzene in neat and mutually saturated solvents, and found no detectable difference in the results. Henrian activity coefficients in octanol for 22 monofunctional compounds were measured by gas chromatography[58]; within experimental error the relation

$$P = \gamma_X^w / \gamma_X^{oct}, \tag{9}$$

was valid.

Relationship with aqueous solubility.

Thermodynamic considerations have also elucidated the relation between log P and aqueous solubility, ζ, early proposed by Hansch et al.[30] Since both log P and ζ may be regarded as Gibbs energy transfer functions, an equation of the type

$$\log P = m \log \zeta + n, \tag{10}$$

might be expected to be valid, where m and n are correlation coefficients. A relation like Eq. (10), if true, would greatly reduce the experimental effort necessary to obtain P. The search for refinement and rationalization of Eq. (10) has been lively, giving rise to at least one polemic exchange in the literature.[31,32]

A relation of the form of Eq. (10) can be derived from thermodynamic first principles.[33,34] The case for a liquid solute will be given first, as a solid solute introduces a complication into the argument. For a liquid solute distributed at equilibrium between organic and aqueous solvents (The solvents are assumed to be mutually saturated, in order to keep the analysis as close as possible to the conditions in a real shake-flask situation.) Eq. (3) can be applied to both phases to give

$$(\gamma_X \varphi_X)^{org} = (\gamma_X \varphi_X)^{aq} \tag{11}$$

which, by Eq. (4) becomes

$$(\gamma_X [X])^{org} = (\gamma_X [X])^{aq}. \tag{12}$$

Consider now, as a separate system, the solute in saturation equilibrium in the aqueous solvent. On the assumption that the equilibrium free solute contains no solvent, Eq. (3) under these conditions becomes

$$\mu_X = \mu_X^0 = \mu_X^0 + RT \ln(\gamma_X \varphi_X)^{sat} \tag{13}$$

or

$$(\gamma_X \varphi_X)^{sat} = 1. \tag{14}$$

Combined with Eq. (4), this becomes

$$(\gamma_X c_X V_X)^{sat} = 1, \tag{15}$$

where c_X has units inverse to that of V_X. Recalling Eqs. (1) and (5),

$$P = [X]^{org} / [X]^{aq} = \gamma_X^{aq} / \gamma_X^{org}. \tag{16}$$

Introducing Eq. (15),

$$P = 1/(\gamma_X^{org} \zeta_X^{aq} V_X) \tag{17}$$

$$\log P = -\log \zeta_X - \log(\gamma_X V_X)^{org}, \tag{18}$$

Eq. (18) has the same form of Eq. (10). Clearly, data for liquid solutes would all fall on a common linear plot of log P vs log ζ, with the following provisos:

ASSUMPTION 1: γ_X^{org}, the Henrian activity coefficient for liquid solutes in organic solvent, is the same for all solutes.

ASSUMPTION 2: ζ_X refers to water saturated with octanol.

ASSUMPTION 3: the solute obeys Henry's law for concentrations up to saturation in the aqueous solvent.

ASSUMPTION 4: the free liquid solute, as an equilibrium phase, contains no solvent (i.e., its activity is unity).

For solutes which are solid at temperature of measurement, fundamental equations such as Eq. (2) are valid. In this case, however, the reference state for μ_X^0 cannot be the pure solid, since it is desirable to keep the same Raoult's law convention for the activity coefficients. The approach is then

through solid–liquid equilibrium. For a component in equilibrium between solid and liquid phases,

$$\mu_X(s) = \mu_X(1), \tag{19}$$

$$\mu_X^0(s) + RT \ln a_X(s) = \mu_X^0(1) + RT \ln a_X(1), \tag{20}$$

$$\mu_X^0(1) - \mu_X^0(s) = RT \ln a_X(s)/a_X(1). \tag{21}$$

The quantity on the left-hand side of Eq. (21) is the Gibbs energy of fusion of the solute at temperature T, $\Delta_{\mathrm{fus}}G_T^0$. If the equilibrium solid phase is pure solid, then

$$\Delta_{\mathrm{fus}}G_T^0 = -RT \ln a_X(1). \tag{22}$$

For temperatures below the normal melting point of the solute, $\Delta_{\mathrm{fus}}G_T^0$ refers to the process (solid→supercooled liquid).[34,35] Since the solution is saturated,

$$\Delta_{\mathrm{fus}}G_T^0 = -RT \ln(\gamma_X \varphi_X)^{\mathrm{sat}}. \tag{23}$$

The thermodynamic argument represented by Eqs. (12)–(18) can be repeated again, with Eq. (23). The result is

$$\log P = -\Delta_{\mathrm{fus}}G_T^0/2.303RT - \log\zeta_X$$
$$- \log(\gamma_X V_X)^{\mathrm{org}}, \tag{24}$$

Eq. (24) is the same as Eq. (18), with the addition of the Gibbs energy of fusion term. The validity of Eq. (24) is of course subject to the same assumptions attached to Eq. (18).

For correlation purposes, the Gibbs energy of fusion to the supercooled liquid state may be expressed in terms of the usual fusion quantities:

$$-\Delta_{\mathrm{fus}}G_T^0/RT$$
$$= (\Delta_{\mathrm{fus}}H^0/2.303R)(T - T_{\mathrm{fus}})/TT_{\mathrm{fus}}$$
$$+ (\Delta_{\mathrm{fus}}C_p^0)(\ln(T/T_{\mathrm{fus}}) + (T_{\mathrm{fus}} - T)/T). \tag{25}$$

In Eq. (25), the enthalpy and heat capacity quantities refer to corresponding changes at the normal melting point (T_{fus}). [The heat capacities of solid and liquid solute have been assumed to be independent of temperature. They are not so in general, and Eq. (25) could be modified to take this into account.] Eqs. (24) and (25) together are identical to Eq. (14) of Miller *et al.*[34] Eq. (25) may be simplified by putting $\Delta_{\mathrm{fus}}C_p^0 = 0$ and[36] $\Delta_{\mathrm{fus}}H^0 = T_{\mathrm{fus}} \Delta_{\mathrm{fus}}S^0 = 56.5T_{\mathrm{fus}}$ J mol^{-1}. The result is an expression equivalent to Eq. (26) of Mackay *et al.*[33]

Apart from these simplifications, the four assumptions quoted above are of varying importance. The Henrian activity coefficient in octanol, γ_X^{oct}, has been estimated by indirect[33] and direct[37,38] methods. It is clear, particularly for hydrophobic compounds, that this activity coefficient increases with molecular weight (or molar volume). The water solubility ζ_X is usually taken as that in pure water. The solubilities of organic compounds in octanol-saturated water are measurably different.[26,38,39] The difference increases with molecular weight. It is difficult at present (if not impossible) to define precisely the individual errors introduced into Eqs. (18) and (24) by these assumptions and simplifications.[33,38,39]

Ratio of solubilities.

It has been stated that P is equivalent to the ratio of solute solubilities in the two solvents,[40] or is well approximated by this ratio.[37] The thermodynamic justification for liquid and solid solutes is derived from Eqs. (1), (15), and (22) for the case of two phases saturated with solute. The result is

$$P = \zeta_X^{\mathrm{org}}/\zeta_X^{\mathrm{aq}} \approx \zeta_X^{\mathrm{oct}}/\zeta_X^w \tag{26}$$

As before, the important qualifying assumptions apply here also. There may be some fortuitous cancellation of effects. Yalkowsky *et al.*[37] have tested Eq. (26) using solubilities in neat solvents for 36 solid compounds and found reasonable, though not exact, correlation.

Henry's law.

The Henry's law constant, like log P, is a limiting Gibbs energy quantity and its usefulness overlaps that of log P.[41] Henry's constant for a solute on the mole fraction scale, H_M, may be defined as[41] (where x is the mole fraction of solute)

$$\lim_{x \to 0}(p/x) = H_M, \tag{27}$$

where p is the partial pressure of solute above the solution. Henrian behavior of solutes has been exploited[42] in the "head-space gas chromatographic method" for measuring P. The principal feature of this method[43] is the sampling and quantitative analysis, by gas chromatography, of the vapor mixture above a liquid solution. In a measurement of P, the vapor above an unsaturated aqueous solution (volume v_1) of the solute is sampled and the gas chromatographic peak height (h_1) of the solute is obtained. A volume v_2 of octanol is added, and after equilibration the vapor is sampled and analyzed as before (h_2). The partition coefficient is then

$$P = v_1(h_1/h_2 - 1)/v_2. \tag{28}$$

Equation (28) assumes that Henry's law is obeyed by the solute in the aqueous phase; that H_M is independent of the presence of co-solvent; that there is a strict mass balance for the solute; and the vapor behaves ideally.

1.3. The case of ionizable solutes

In the present work, two types of organic compounds may ionize in aqueous solution, viz., acids (HA) and amines (B):

$$\mathrm{HA} \rightleftharpoons \mathrm{H}^+ + \mathrm{A}^-, \tag{29}$$

$$\mathrm{BH}^+ \rightleftharpoons \mathrm{B} + \mathrm{H}^+, \tag{30}$$

where A^- is the acid anion. [Water should appear on both sides of Eqs. (29) and (30), but since in dilute solution its activity is practically unity and does not change, it may be omitted from the thermodynamic analysis.] The thermodynamic dissociation constant is defined as

$$K_a = a(\mathrm{H}^+)a(\mathrm{A}^-)/a(\mathrm{HA}) \tag{31}$$

after Eq. (29), and

$$K_a = a(\mathrm{H}^+)a(\mathrm{B})/a(\mathrm{BH}^+) \tag{32}$$

after Eq. (30). Since P is defined only for the same (undissociated) species in both phases, the *apparent* partition coefficient P_{app} (sometimes called distribution coefficient) measured in the presence of appreciable ionization according to Eqs. (29) and (30) will differ from P. It can be shown[44] that P_{app} and P for an acid are related by

$$P = P_{\mathrm{app}}[1 + 10^{(pH - pK_a)}] \tag{33}$$

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