

Partition of compounds from gas to water and from gas to physiological saline at 310 K: Linear free energy relationships

Michael H. Abraham^{a,*}, Adam Ibrahim^a, William E. Acree Jr.^b

^a Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

^b Department of Chemistry, P.O. Box 305070, University of North Texas, Denton, TX 76203-5070, USA

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Abstract

Data have been assembled on gas to water partition coefficients for 374 compounds at 310 K. It is shown that an Abraham solvation equation with five descriptors can be used to correlate 350 such values, as $\log K_W(310)$, with $R^2 = 0.994$ and S.D. = 0.154 log units. Division into a training set and a test set shows that there is no bias in predictions and that predictive capability of the equation is 0.16 log units. Use of indicator variables allows the inclusion of polyaromatic hydrocarbons and polychlorobiphenyls, and for a total data set of 374 compounds $R^2 = 0.993$ and S.D. = 0.163 log units. For partition from the gas phase into physiological saline (0.9% sodium chloride) at 310 K, a similar equation with five descriptors correlates values for 257 compounds with $R^2 = 0.989$ and S.D. = 0.180 log units. For 135 overlapping compounds for which both $\log K_W(310)$ and $\log K_W(\text{saline})$ are known, the average error is only 0.032 log unit, suggesting that the two data sets can be combined. For the total of 631 data points, an equation with five descriptors plus indicator variables for polyaromatic hydrocarbons and polychlorobiphenyls has $R^2 = 0.992$ and S.D. = 0.177 log units.

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1. Introduction

There have been numerous reports of methods for the correlation and prediction of Henry’s Law constants, or the equivalent gas to water partition coefficients, in water at 298 K. Although this is a standard temperature for physicochemical measurements, it has no physiological significance. Hence measurements of the partition of compounds between the gas phase and biological tissues, and anaesthetic measurements are invariably carried out at 310 K, see for example [1–5]. The temperature dependence of Henry’s Law constants in water is of increasing concern [6–8], and measurements of environmentally important chemicals such as aroma chemicals [9] and terpenes [10] are often carried out at 310 K. A number of algorithms for the prediction of distribution between the gas phase and biological tissues involve the gas to water distribution at 310 K as a descriptor [11,12], and so

it is of importance to be able to predict the latter in cases where experimental values are not available.

Unfortunately, the only predictive methods for gas to water partition that refer specifically to 310 K are an LFER equation of Abraham and Weathersby [13] for 75 compounds, and a fragmentation method of Beliveau et al. [14] who used 46 compounds of rather restricted chemical type. Of course, a prediction of the Henry’s Law constant, or gas to water partition coefficient, at 310 K can be made from a known partition value at 298 K together with a known enthalpy of hydration; valuable compilations of enthalpies of hydration have been given by Cabani et al. [15] and by Kuhne et al. [16]. The latter have combined a predictive method for enthalpies of hydration with known partition coefficients at 298 K to obtain a general algorithm for Henry’s Law constants at various temperatures between 273 K and 298 K. More recently, Goss [17] has used a similar method but this time for a number of specific temperatures between 273 K and 318 K, although not at 310 K. Although this is clearly a valuable method for the calculation of gas to water partition coefficients at various temperatures, the 217 compound data set

* Corresponding author. Tel.: +44 2076794639; fax: +44 2076797463.
E-mail address: m.h.abraham@ucl.ac.uk (M.H. Abraham).

used by Goss is somewhat restricted in chemical type. For example, there is only one compound that contains a fluorine atom (2,2,2-trifluoroethanol) and so these compounds are not well represented at all.

Another physicochemical property that is often measured [1,4,5,18] is the partition coefficient between the gas phase and physiological saline (0.9%) at 310 K; the work of Eger et al. [19–23] in the field of anesthetics is especially notable. Gargas et al. [18] have correlated such partition coefficients, as $\log K_W(\text{saline})$, against connectivity indices, but only for 27 compounds.

The aim of the present work was to compile a list of gas to water partition coefficients and gas to saline partition coefficients at 310 K for as large a number of compounds as possible, and then to construct linear free energy relationships, LFERs, for the prediction of further values.

2. Methods

We give data in the form of the gas to water (or saline) partition coefficient, K_W , defined through Eq. (1) where the concentrations are those at equilibrium and K_W is either extrapolated to zero concentration or is determined at very low solute concentration. If concentrations in water (or saline) and the gas phase are expressed in the same units, then K_W is dimensionless, and is equivalent to the Ostwald solubility coefficient, L_W :

$$K_W = \frac{[\text{concentration of solute in water (or saline), mol dm}^{-3}]}{[\text{concentration of solute in the gas phase, mol dm}^{-3}]} \quad (1)$$

K_W and the corresponding Henry's Law constant, H , are easily converted into each other since $K = H/RT$ with due regard to units. Some of the values of gas to water partition that we list in Table 1, as $\log K_W(310)$, have been measured directly at 310 K, for example those of Batterman et al. [24] and of Maaßen et al. [25] or those listed by Weathersby and Homer [2] and by Abraham and Weathersby [13]. Wilhelm et al. [26] give a list of equations that can be used for the calculation of K at 310 K, and Plyasunov et al. [27–32] give valuable compilations of Gibbs energies and enthalpies of hydration at 298 K and heat capacities of hydration from which K_W at 310 K may be calculated. Numerous workers list Henry's Law constants at various temperatures from which we have interpolated, or sometimes slightly extrapolated, values at 310 K and then converted them into $\log K_W(310)$ values. Similarly, infinite dilution activity coefficients at various temperatures have been used to obtain values at 310 K and the latter combined with vapour pressures to obtain Henry's Law constants and then the corresponding $\log K_W(310)$ values. Where vapour pressure equations were given, we used them to obtain vapour pressures at 310 K, otherwise we took vapour pressure equations from the literature, most equations were from Refs. [33–35]. We also calculated $\log K_W(310)$ values from literature data on the solubility of sparingly soluble compounds and vapour pressures after the latter were converted to gas phase concentrations. The list of all the $\log K_W(310)$ values we thus obtained is in Table 1, together

with the compound descriptors that we used in the subsequent analysis.

For the analysis of the data, we used the two linear free energy equations of Abraham et al. [36,37], Eqs. (2) and (3). In brief, the two equations are used in multiple linear regression analyses of the independent variable, SP. Eq. (2) is used for gas to condensed phase processes; in the present work SP is $\log K_W$. Eq. (3) is normally used for processes within condensed phases, but an exception [38] is the gas to water partition where SP can also be $\log K_W$. This is due to both the l -coefficient and the v -coefficient being numerically very small for the gas to water transfer.

$$SP = c + eE + sS + aA + bB + lL \quad (2)$$

$$SP = c + eE + sS + aA + bB + vV \quad (3)$$

The dependent variables in Eqs. (2) and (3) are solute properties, as discussed before [36,37]. E is the solute excess molar refractivity in units of $(\text{dm}^3 \text{mol}^{-1})/10$; S is the solute dipolarity/polarizability; A and B are the overall or summation hydrogen bond acidity and basicity; L is the logarithm of the gas-hexadecane partition coefficient at 298 K; V is the McGowan volume in units of $(\text{dm}^3 \text{mol}^{-1})/100$. E is obtained from the refractive index of the pure liquid compound at 293 K; if the compound is a gas or solid the refractive index can be estimated or E itself can be calculated quite easily [36]. The descriptors S , A , B and L are obtained from gas liquid chromatographic measurements and water to solvent partition measurements, as described in detail [37]; they can also be calculated just from structure [39]. The important V descriptor is trivially calculated from the number and type of atoms, and the number of rings in a molecule [37].

Both Eqs. (2) and (3) have been applied to gas to water partition coefficients at 298 K, yielding Eqs. (4) and (5), respectively [38].

$$\begin{aligned} \log K_W(298) &= -1.271 + 0.822E + 2.743S \\ &\quad + 3.904A + 4.814B - 0.213L, \\ N &= 392, \text{ S.D.} = 0.185, R^2 = 0.992, F = 10, 229 \end{aligned} \quad (4)$$

$$\begin{aligned} \log K_W(298) &= -0.994 + 0.577E + 2.549S \\ &\quad + 3.813A + 4.841B - 0.869V, \\ N &= 408, \text{ S.D.} = 0.151, R^2 = 0.995, F = 16, 810 \end{aligned} \quad (5)$$

In these equations, N is the number of compounds, S.D. is the regression standard deviation, R is the correlation coefficient and F is the F -statistic. Goss [40] has suggested an amended equation in which the descriptor E is left out, and S , A , B , L , and V are used, but Flanagan et al. [41] have shown that results are not substantially different to those using Eqs. (4) and (5).

3. Results

3.1. Gas to water partition coefficients at 310 K

In Table 1 are listed $\log K_W(310)$ values for solutes [13,24–26,28,31–33,38,42–85] including those for 12 polychlorobiphenyls, PCBs, and 12 polyaromatic hydrocarbons,

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