

Original article

Air to brain, blood to brain and plasma to brain distribution of volatile organic compounds: linear free energy analyses

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Received 15 September 2005; received in revised form 3 January 2006; accepted 11 January 2006

Available online 03 March 2006

Abstract

Partition coefficients, K_{brain} , for volatile organic compounds, VOCs, from air to brain have been collected for 81 compounds (air to human brain and air to rat brain). For the 81 VOCs a linear free energy equation (LFER) correlates $\log K_{\text{brain}}$ with $R^2 = 0.923$ and S.D. = 0.346 log units. Use of training and test sets gives a predictive assessment of 0.35–0.40 log units. Combination of $\log K_{\text{brain}}$ with our previously listed values of $\log K_{\text{blood}}$ enables blood to brain partition, as $\log P_{\text{b-brain}}$, to be obtained for 78 VOCs. These values can be correlated with $R^2 = 0.725$ and S.D. = 0.203 log units; use of training and test sets allows a predictive assessment for $\log P_{\text{b-brain}}$ of 0.16–0.20 log units. Values for air to plasma were available for 21 VOCs. When these data were combined with the data on air to blood and air to brain, values for partition between (blood or plasma) to brain, $P_{\text{bp-brain}}$, were available for 99 VOCs. A LFER correlates this data with $R^2 = 0.703$ and S.D. = 0.197 log units; use of training and test sets allows a predictive assessment for $\log P_{\text{bp-brain}}$ of 0.15–0.20 log units.

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Keywords: Air–blood; Air–brain; Blood–brain; Plasma–brain; Volatile organic compounds; Linear free energy relationship

1. Introduction

The distribution of organic compounds between blood and tissues is of crucial importance in the understanding of potential toxic effects. For volatile organic compounds, VOCs, the usual method of determination of blood to tissue partition coefficients is separately to obtain the corresponding air to blood and air to tissue partition coefficients. The importance of the subject is illustrated by the very large number of published investigations, especially of blood to brain partition. We have previously [1] studied the air to blood partition coefficients of VOCs, with respect to human blood, $\log K_{\text{blood}}$ (human), and to rat blood, $\log K_{\text{blood}}$ (rat). Note that in these studies [1] and in the present work, the set of compounds includes a number of inorganic gases. However, we shall use the term VOCs to cov-

er both volatile inorganic and volatile organic compounds. The defining equation for air to blood partition, at 37 °C, is:

$$K_{\text{blood}} = \frac{[\text{conc. of compound in blood}]}{[\text{conc. of compound in air}]} \quad (1)$$

Concentrations of VOCs are expressed as mol dm^{-3} in blood and in air, so that K_{blood} has no units, and is equivalent to the Ostwald solubility coefficient.

It has been suggested that K_{blood} (human), and K_{blood} (rat) are not quite the same, and ratios of K_{blood} (rat)/ K_{blood} (human) of 1.5–2.0 have been observed [2]. Other workers [3] found ratios between 1.3 and 1.7 and ratios as low as 1.08 for esters have been observed [4]. We have found previously [1] that for 86 common VOCs the average error, AE, between the two sets of $\log K_{\text{blood}}$ values is only 0.12 log units, corresponding to a ratio of 1.3 and smaller than our estimated experimental error between laboratories. We therefore suggested [1] that values of

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log K_{blood} (human), and log K_{blood} (rat) could be taken together in order to obtain relationships that could be used to predict further values of log K_{blood} .

We were able to collect values of log K_{blood} (human) for 155 VOCs and of log K_{blood} (rat) for 127 VOCs, giving values for a total of 196 individual VOCs. The aims of the present work are to collect data on log K_{brain} for VOCs, to devise a predictive equation for log K_{brain} , and then to combine the two sets of data for log K_{blood} and log K_{brain} to yield values for partition from blood to brain, log $P_{\text{b-brain}}$, and finally to obtain a predictive equation for log $P_{\text{b-brain}}$. We note at the outset, that values of log K_{brain} or log $P_{\text{b-brain}}$ obtained from some particular equation are often referred to as ‘predicted values’. We shall refer to these only as ‘calculated values’ and reserve the term ‘predicted values’ for true predictions obtained from an independent set of values, the ‘test set’, that has not been used to construct a particular equation.

Although there has been much interest in air to brain partition of VOCs, there have been few correlations of log K_{brain} reported. An early attempt used a correlation against air to water and air to oil partitions, but only for 17 compounds [5]. A version of the methodology used in the present paper was applied to 41 compounds [6] and a double regression method was used to correlate values of log K_{brain} for 35 VOCs [3]. Details of the latter two analyses are presented in Table 1. No independent test sets of compounds were used, and so the predictive capability of the equations is unknown. The average error is denoted as AE, the absolute average error as AAE, and the standard deviation as S.D. In addition to these correlations, Krishnan and co-workers (Beliveau et al. [7,8]) have set out a physiologically based method for air to tissue partition coefficients, based on partition coefficients for air to water, air to vegetable oil and air to protein, the latter, in turn, being estimated by a fragmentation method. They studied 48 VOCs that formed a restricted chemical set of hydrocarbons and halogenated hydrocarbons. Since air to brain partitions were not considered, we can make no comparison with our results.

The situation with respect to the correlation and prediction of blood to brain partition coefficients, as log $P_{\text{b-brain}}$, for VOCs is almost as unsatisfactory. A connection between blood to brain and blood to fat partitions has been noted for 35 VOCs

Table 1
Statistics for the correlation and prediction of log K_{brain} for VOCs from Eqs. (4), (5) and (6). Comparison with previous work

Reference	^a	Training set			Test set			
		<i>N</i>	<i>R</i> ²	S.D.	<i>N</i>	S.D.	AAE	AE
[6]	H	41	0.97	0.24				
[3]	H	35	0.98					
[3]	R	19	0.90					
Eq. (4) ^d	HR	41	0.93	0.34	40	0.41	0.35	−0.14
Eq. (5) ^d	HR	40	0.93	0.33	41	0.42	0.31	0.08
Eq. (6) ^d	HR	81	0.92	0.35				

^a H human blood, R rat blood.

^d This work. HR indicates human and rat data averaged. *N* is the number of data points, *R* is the correlation coefficient, S.D. is the standard deviation, AAE is the average absolute error, and AE is the average error.

Table 2
Statistics for the correlation and prediction of log $P_{\text{b-brain}}$ for VOCs from Eqs. (7), (8), (9), (13) and (14). Comparison with previous work

Reference	^a	Training set			Test set			
		<i>N</i>	<i>R</i> ²	S.D.	<i>N</i>	S.D.	AAE	AE
[6]	H	39	0.87	0.15				
[10]	H	35	0.96	0.08				
[11]	H	35	0.92	0.12				
Eq. (7) ^c	HR	39	0.66	0.22	39	0.20	0.15	0.03
Eq. (8) ^c	HR	39	0.78	0.20	39	0.21	0.16	0.02
Eq. (9) ^c	HR	78	0.72	0.20				
Eq. (13) ^f	HR	50	0.70	0.21	49	0.20	0.15	0.00
Eq. (14) ^f	HR	99	0.69	0.20				

^a H human blood, R rat blood.

^c This work. HR indicates human and rat data averaged.

^f This work, for partition from blood or plasma to brain. *N* is the number of data points, *R* is the correlation coefficient, S.D. is the standard deviation, AAE is the average absolute error, and AE is the average error.

[9], but this is not very useful as a predictive method. A version of the present method was used to correlate log $P_{\text{b-brain}}$ for 39 VOCs [6], and a rather complicated expression involving water to octanol partition coefficients, P_{oct} , was applied to 35 VOCs [10]. Various descriptors have been used in a nonlinear expression to correlate values of log $P_{\text{b-brain}}$ for 35 VOCs [11]. In none of these cases was any test set used, and so the predictive capability of the equations cannot be assessed. Details are presented in Table 2.

2. Methods

Our method is based on the following two linear free energy relationships, LFERs:

$$\text{SP} = c + e.E + s.S + a.A + b.B + l.L \quad (2)$$

$$\text{SP} = c + e.E + s.S + a.A + b.B + v.V \quad (3)$$

In these equations, SP is the dependent variable. Eq. (2) is used to correlate air to tissue or air to solvent partitions, and SP is then log K_{blood} or log K_{brain} . Eq. (3) is used to correlate partition from one condensed phase to another, for example SP is then log $P_{\text{b-brain}}$. The dependent variables in Eqs. (2) and (3) are VOC properties, as discussed several times [12, 13]. **E** is the solute excess molar refractivity in units of (dm³ 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 25 °C, and **V** is the McGowan volume in units of (dm³ mol^{−1})/100. We chose to use Eqs. (2) and (3) because these are well-known general equations that have been used many times to correlate gas to solvent and water to solvent partition coefficients [12–14]. Furthermore, the descriptors in Eqs. (2) and (3) are available for some 3000 compounds, and can be predicted just from structure, if required [14], so that application of Eqs. (2) and (3) to the prediction of further values of the dependent variables is extremely easy and straightforward.

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