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1  A simple method for estimating in vitro air-tissue and in vivo blood-tissue

2  partition coefficients**.**

3  Michael H. Abraham, [*a] Joelle M. R. Gola, [a] Adam Ibrahim, [a]William E Acree, Jr., [b] and

4  Xiangli Liu [c]

5  [a] *Department of Chemistry, University College London, 20 Gordon Street, London WC1H*

6  *0AJ, UK*

7  [b] *Department of Chemistry, 1155 Union Circle Drive #305070, University of North*

8  *Texas, Denton, TX   76203-5017, USA*

9  [c] *School of Pharmacy, University of Bradford, Bradford, BD7 1DP, UK*

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11  * Corresponding author. E-mail address ucca16a@ucl.ac.uk (M. H. Abraham)

12

13  **Abstract**

14  A simple method is reported for the estimation of *in vivo* air-tissue partition coefficients
15  of VOCs and of *in vitro* blood-tissue partition coefficients for volatile organic compounds
16  and other compounds. Linear free energy relationships for tissues such as brain, muscle,
17  liver, lung, kidney, heart, skin and fat are available and once the Abraham descriptors are
18  known for a compound, no more than simple arithmetic is required to estimate air-tissue
19  and blood-tissue partitions.

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## 1. Introduction

Air-tissue and blood-tissue partition coefficients are of considerable environmental importance. They enable the fate of pollutants in the body to be established, and are a pre-requisite of any pharmacokinetic (PBPK) analysis. The PBPK models themselves are used to assess the risk from exposure to chemicals.

A method for the prediction of *in vivo* air-tissue partition coefficients for volatile organic compounds, VOCs, has been proposed (Endo et al., 2013) based on the key equation

$$K_{tissue/w} = f_{lipid} K_{lipid/w} + f_{membrane} K_{membrane/w} + f_{albumin} K_{albumin/w}$$
$$+ f_{protein} K_{protein/w} + f_w \tag{1}$$

In eq 1, $f_{lipid}$, $f_{membrane}$, $f_{albumin}$, $f_{protein}$ and $f_w$ are the volume fractions of storage lipid, phospholipid membrane, serum albumin and other proteins in a given biological tissue, $K_{tissue/w}$ is the water to tissue partition coefficient for the given biological tissue, and $K_{lipid/w}$, $K_{membrane/w}$, $K_{albumin/w}$ and $K_{protein/w}$, are water to phase partition coefficients. These four partition coefficients can be predicted for VOCs through a series of LFERs based on the Abraham equation (Abraham, 1993; Abraham and Acree, 2013a, 2013b; Abraham et al., 2004, 2007, 2010, 2014) eq 2, with the equation coefficients shown in Table 1. The symbol $K$ has been used (Endo et al., 2013) for the water-phase partition coefficient, but the usual symbol is $P$.

$$\log K (P) = c + eE + sS + aA + bB + vV \tag{2}$$

In order to convert the values of $K_{tissue/w}$ found using eq 1 to the required values of the air to tissue partition coefficient, $K_{tissue/air}$, the air-to-water partition coefficient, $K_{w/air}$, was then calculated through eq 3 (Endo et al., 2013) using the coefficients in Table 1.

$$K_{tissue/air} = K_{tissue/w} / K_{w/air} \tag{3}$$

56    Table 1.

57    Coefficients in the LFER , eq 2, at $37^{o}C$

| Process | $c$ | $e$ | $s$ | $a$ | $b$ | $v$ | Ref |
|---|---|---|---|---|---|---|---|
| water – lipid | -0.07 | 0.70 | -1.08 | -1.72 | -4.14 | 4.11 | a |
| water–membrane | 0.29 | 0.74 | -0.72 | 0.11 | -3.63 | 3.30 | a |
| water-albumin | 0.29 | 0.36 | -0.26 | 0.37 | -3.23 | 2.82 | a |
| water-protein | -0.65 | 0.51 | -0.51 | 0.26 | -2.98 | 3.01 | a |
| air-water | -1.06 | 0.59 | 2.57 | 3.59 | 4.24 | -0.97 | b |

58    [a] (Endo et al., 2013). [b] (Abraham et al., 2007)

59

60    Although the above method yields reasonable predictions of $K_{tissue/air}$ values, there

61    are a number of difficulties with the method. First of all, eq 1 has no physicochemical

62    basis at all. The idea that partition into a composite phase can be obtained by simply

63    adding up contributions through eq 1 is completely contrary to all known conventional

64    theories of solution. Indeed, if eq 1 was in any way valid, there would be no need for any

65    complicated theories of solution at all. Furthermore, eq 1 is contrary to known

66    experimental data for partition from water into composite phases. A great deal of work on

67    solubility in water-ethanol phases (equivalent to partition from water to water-ethanol

68    mixtures) has been carried out (Li and Yalkowsky, 1992; Millard et al., 2002; Machatha

69    et al. 2004) and the situation is much more complicated than indicated by eq 1. For the

70    two-component phase water-ethanol, eq.1 (we use $P$ instead of $K$) leads to

71

72    $P_{EtOH/w/mixture} = f_{EtOH}*P_{EtOH} + f_w$          (4)

73

74    Then since $f_{EtOH} + f_w = 1$          (5)

75

76    $P_{EtOH/w/mixture} = 1.00 + f_{EtOH}*[P_{EtOH} -1]$          (6)

77

78    That is, according to eq 1, the partition coefficient of a compound into water-ethanol

79    mixtures is a linear function of the volume fraction ethanol, $f_{EtOH}$. The partition

80    coefficient of an unionized compound from water into any phase is given by the ratio of

81    solubilities, $S$, in mol dm$^{-3}$, so that for water-ethanol mixtures,

82

83     $P_{EtOH/w/mixture} \; = \; S_{EtOH/w/mixture} \; / \; S_w$            (7)

84

85     Then the solubility of an unionized compound into water-ethanol mixtures must also be a

86     linear function of $f_{EtOH}$. On the contrary, the recent equation of Yalkowsky is eq 8, where

87     $a$, $b$ and $c$ are constants (Machatha et al., 2004)

88

89     $\text{Log } S_{EtOH/w/mixture} \; = \; \log \; S_w \; + a^* f_{EtOH} \; /(1 + b^* \, f_{EtOH} \; + c[f_{EtOH}]^2)$       (8)

90

91     Plots of the solubility of salicylic acid and caffeine are also quite contrary to eq 1.

92     (Williams and Amidon, 1988) It is not just drugs or complicated molecules that do not

93     obey eq 1. In Fig 1 and Fig 2 we give partition coefficients for methane and ethane from

94     water to water-ethanol mixtures against the volume fraction ethanol using literature data

95     (Yaacobi and Ben-Naim, 1973). The predicted values are shown by the straight line.

96     Quite clearly eq 1 is not valid for these very simple VOCs.

97        An equivalent equation to eq 8 follows from eq 1 for partition into any two-

98     component phase, where the partition coefficient of a solute must be linear in volume

99     fraction of one of the components. Such a linear form would not be mathematically

100    capable of describing solute partitioning in water-to-binary solvent systems exhibiting

101    either a maximum or minimum in the partition coefficient versus volume fraction curve.

102    Partition coefficients of phenol from water to a number of nonaqueous binary mixtures

103    (two-component phases) have been determined (Korenman, 1973). None of the data

104    conform to eq 1, as shown in Fig 3 where the binary mixture is nonanol-nitrobenzene.

105    This system does show a maximum in the observed partition coefficient near a volume

106    fraction composition of nonanol of 0.60. Hence the compartmental eq 1 does not hold for

107    a variety of systems including partition from water into aqueous mixtures and partition

108    from water into nonaqueous mixtures, with solutes as varied as methane, ethane, phenol,

109    salicylic acid and caffeine. There appears to be no reason at all why eq 1 should hold for

110    partition from water into biological tissues.

111

112 **2. Methods and Results**

113 Our method is very much simpler than that used before (Endo et al., 2013) and is based

114 on the two LFERs eq 2 and eq 9 (Abraham, 1993; Abraham and Acree, 2013a, 2013b;

115 Abraham et al., 2004, 2007, 2010, 2014).

116

117 $\log P = c + eE + sS + aA + bB + vV$ (2)

118

119 $\log K = c + eE + sS + aA + bB + lL$ (9)

120

121 The descriptors in eq 2 and eq 9, $E$, $S$, $A$, $B$, $V$ and $L$ are properties of solutes as follows.

122 $E$ is the solute excess molar refractivity in units of $(cm^3 \ mol^{-1})/10$, $S$ is the solute

123 dipolarity / polarizability, $A$ and $B$ are the overall or summation hydrogen bond acidity

124 and basicity, and $V$ is the McGowan characteristic volume in units of $(cm^3 \ mol^{-1})/100$. $L$

125 is the gas-hexadecane partition coefficient at $25^O C$. The solute descriptors are obtained

126 from a variety of experimental data, including water-solvent partition coefficients,

127 solubilities in organic solvents, and chromatographic data, as detailed by us previously

128 (Abraham, 1993; Abraham and Acree, 2013a, 2013b; Abraham et al., 2004, 2007, 2010,

129 2014). Detailed accounts of our entire method are available (Clarke and Mallon, 2013;

130 Poooe et al., 2013) including the determination of the Abraham solute descriptors (Clarke

131 and Mallon, 2013). The coefficients in eq. 2 and eq 9 are obtained by multiple linear

132 regression. Thus once the descriptors in eq 2 and eq 9 have been determined for a given

133 compound, partition coefficients in condensed phases can be predicted through eq 2 and

134 air-phase partition coefficients can be predicted through through eq 9. The coefficients

135 required for condensed phase partitions in biological systems are in Table 1 and Table 2.

136 The important *in vivo* blood-tissue partitions can simply be predicted through eq 2,

137 using the equation coefficients listed in Table 2 for drugs and other molecules (Abraham

138 et al., 2014) as we have recently shown for artemisinin and some of its derivatives

139 (Abraham et al., 2013a) and for a number of agrochemicals (Abraham et al., 2014). Quite

140 recently an extensive list of blood-tissue partition coefficients has been reported (Yun et

141 al., 2014) and we have used this extra data to update our equations for blood-kidney and

142 blood-heart that were reported earlier (Abraham et al., 2014). The revised coefficients are

143 in Table 2 and now refer to 125 drugs (blood-kidney) and 107 drugs (blood-heart).

144     Of course, water-solvent partitions can also be predicted for a very large number of

145 partitions for which we have the required coefficients (Abraham et al., 2010, 2013a,

146 2013b, 2014). The *in vitro* partition coefficients for VOCs can be predicted from eq 9

147 using the necessary descriptors and the coefficients given in Table 3.

148

149

150 Table 2.

151 Coefficients in the LFER eq 2 for *in vivo* processes, as log *P,* at 37$^{o}$C [a]

| Process | $c$ | $e$ | $s$ | $a$ | $b$ | $v$ | $Ic$ [b] |
|---|---|---|---|---|---|---|---|
| Blood-brain | 0.547 | 0.221 | -0.604 | -0.641 | -0.681 | 0.635 | -1.216 |
| Blood-muscle | 0.082 | -0.059 | 0.010 | -0.248 | 0.028 | 0.110 | -1.022 |
| Blood-liver | 0.292 | 0.000 | -0.296 | -0.334 | 0.181 | 0.337 | -0.597 |
| Blood-lung | 0.269 | 0.000 | -0.523 | -0.723 | 0.000 | 0.720 | -0.988 |
| Blood-kidney | 0.487 | -0.072 | -0.390 | -0.310 | 0.188 | 0.412 | -0.513 |
| Blood-heart | 0.195 | -0.063 | -0.311 | -0.322 | 0.017 | 0.448 | -0.575 |
| Blood-skin | -0.105 | -0.117 | 0.034 | 0.000 | -0.681 | 0.756 | -0.816 |
| Blood-fat | 0.077 | 0.249 | -0.215 | -0.902 | -1.523 | 1.234 | -1.013 |
| Water-skin | 0.523 | 0.101 | -0.076 | -0.022 | -1.951 | 1.652 | |
| Water-wet octanol [c] | 0.088 | 0.562 | -1.054 | 0.034 | -3.460 | 3.814 | |
| Water-dry octanol [c] | -0.034 | 0.489 | -1.044 | -0.024 | -4.235 | 4.218 | |
| Skin permeation [d] | -5.420 | -0.102 | -0.457 | -0.324 | -2.608 | 2.066 | |

152 [a] (Abraham and Acree, 2013a; Abraham et al., 2014). [b]An indicator variable for

153 carboxylic acids. [c] Water-solvent partitions at 25$^{o}$C [d] *In vitro* permeation with log *Kp* in

154 cm s$^{-1}$,

155

156 Table 3.

157 Coefficients in the LFER eq 9 for *in vitro* processes, as log *K,* at 37$^{o}$C, and for some

158 physicochemical processes at 25$^{o}$C [a]

| Process | $c$ | $e$ | $s$ | $a$ | $b$ | $l$ |
|---|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| air-blood | -1.062 | 0.460 | 1.067 | 3.777 | 2.558 | 0.375 |
| air-brain | -0.987 | 0.263 | 0.411 | 3.358 | 2.025 | 0.591 |
| air-muscle | -1.039 | 0.207 | 0.723 | 3.242 | 2.469 | 0.463 |
| air-liver | -0.943 | 0.000 | 0.836 | 2.836 | 2.081 | 0.564 |
| air-lung | -1.250 | 0.639 | 1.038 | 3.661 | 3.043 | 0.420 |
| air-kidney | -1.005 | 0.489 | 0.774 | 3.000 | 2.719 | 0.497 |
| air-heart | -1.199 | 0.185 | 0.596 | 2.951 | 2.450 | 0.589 |
| air-fat (lipid) | -0.052 | 0.051 | 0.728 | 1.783 | 0.332 | 0.743 |
| air-olive oil | -0.188 | -0.095 | 0.851 | 1.468 | 0.000 | 0.873 |
| air-skin | -0.254 | 0.311 | 2.230 | 3.705 | 2.925 | 0.243 |
| air-wet octanol [b] | -0.198 | 0.002 | 0.709 | 3.519 | 1.429 | 0.858 |
| air-dry octanol [b] | -0.147 | -0.214 | 0.561 | 3.507 | 0.749 | 0.943 |

159    [a] (Abraham and Acree, 2013a; Abraham et al., 2014). [b]Air solvent partitions at 25$^{o}$C

160

161        In order to apply eq 1 to a 'new' compound for which no air-tissue partition
162    coefficients are available, the water-tissue LFERs given in Table 1 were used to obtain
163    the four water-tissue distributions in eq 1, and then knowing the *f*-values for other tissues,
164    the water-tissue distributions for these other tissues were calculated (Endo et al., 2013)..
165    Finally, the LFER for air-water was used convert the water-tissue values to air-tissue. All
166    this requires a knowledge of the Abraham descriptors for the 'new' compound. But if
167    these descriptors for the 'new' compound are known, they can be used in the equations
168    listed in Table 3 to give the air-tissue values straight away through the LFER, eq 9
169    ((Abraham, 1993; Abraham and Acree, 2013a, 2013b; Abraham et al., 2004, 2007, 2010,
170    2014).There is no need at all to use eq 1 and no need to use the air-water LFER for any
171    conversion. An additional advantage of using the LFER, eq 9, is that it can be used to
172    predict log *K* values not only from air to biological phases, but from air to a very large
173    number of solvents; coefficients in eq 9 are known for some 90 wet or dry solvents
174    (Abraham and Acree, 2013b). The complicated method (Endo et al., 2013) yields
175    predictions of air-tissue partitions that cannot be better than our very simple method, and
176    there seems little point in using such a method.
177        It has been claimed (Endo et al., 2013) that the tissue specific LFERs, Tables 2 and
178    3, cannot be used to deal with composite materials if the studied chemicals (solutes)
179    cover a wide range of size and polarity. This is completely incorrect. Partition from water

180      to wet octanol involves partition into a composite material (wet octanol contains about

181      0.27 mol fraction water) and our LFER has been used for the water-wet octanol system,

182      not only by us, but by Endo et al. themselves (Endo et al., 2013). Our LFER model has

183      been used (Qian and Poole, 2007) to describe the Folch partitioning (chloroform-

184      methanol-water partitioning system; 8:4:3 v/v) of 86 different organic solutes.  The Folch

185      system is often employed in the extraction of neutral lipids from animal tissues (Folch et

186      al., 1957).  Gas-to-liquid partition coefficients of a series of diverse organic solutes on

187      chromatographic stationary phases coated with binary mixtures of two ionic liquids (a

188      composite material) have been correlated in terms of our LFER model eq  9 (Baltazar et

189      al., 2008). Our recent analysis of retention of solutes on cerasome (a composite material)

190      includes compounds as large as digitoxin ($V = 5.694$) and anions and cations with

191      extraordinary large polarities such as the ketoprofen anion with $S = 5.49$ and $B = 3.39$,

192      and the 4-MeC$_6$H$_4$CH$_2$NMeH$^+$ cation with $S = 2.64$ and $A = 1.47$ (Zhang et al., 2011).

193      Quite contrary to the previous claim (Endo et al., 2013), our LFERs have been shown to

194      apply to all kinds of composite materials with almost no restriction as to the kind or type

195      of chemical. This is one great advantage of the LFERs, eq 2 and eq 9.

196      In conclusion, use of the LFERs based on eq 9 together with the coefficients listed in

197      Table 3 is a very simple method of predicting *in vivo* air-tissue partition coefficients for

198      any compound for which the Abraham descriptors are available. LFERs based on eq 2

199      can be used to estimate blood-tissue partitions, partitions between water and numerous

200      organic solvents (Abraham et al., 2010), permeation from water through human skin

201      (Zhang et al., 2012) and the solubility of gases and vapors in water from 273 to 573 K

202      (Abraham and Acree, 2012). Eq 2 and eq 9 have been used to set up equations for the

203      sorption of compounds from air to soil and from water to soil (Poole and Poole, 1999)

204      and later workers have also used eq 2 for the water to soil sorption (Nguyen et al., 2005).

205      These equations refer to rather high concentrations of solute, and so equations were set

206      out based on the LFER eq 2 for sorption from water to a number of specific soils at solute

207      concentrations that were nearer environmental significance (Endo et al., 2009) and it is

208      these LFERs that are recommended.

209      Application of the LFERs, eq 2 and eq 9, requires a knowledge of the descriptors for

210      compounds. Although there is an extensive data base of compound descriptors (Absolv,

211  version 5.0, 2013), there may be no determined descriptors for a given compound. In this

212  case, descriptors can be calculated using the ACD 'Absolv' software (Absolv, version

213  5.0, 2013). For compounds that have not even been synthesized and for which estimates

214  of air-phase and condensed phase partition coefficients are required, for example for

215  candidate anesthetics or candidate drugs or candidate agrochemicals, descriptors can

216  again be calculated using the ACD 'Absolv' software (Absolv, version 5.0, 2013).
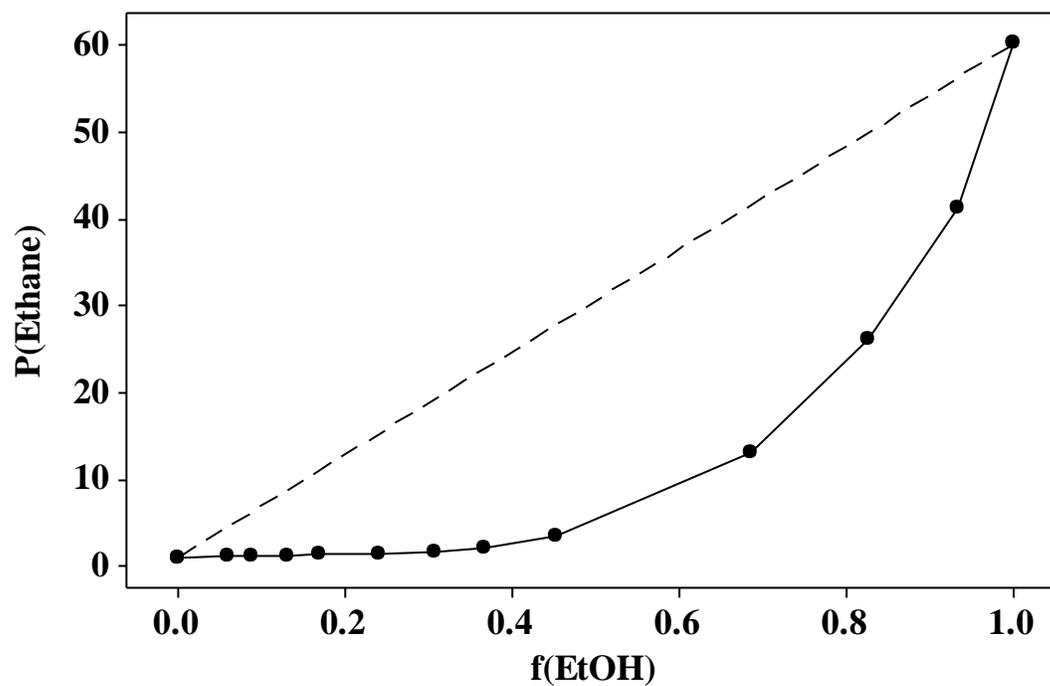
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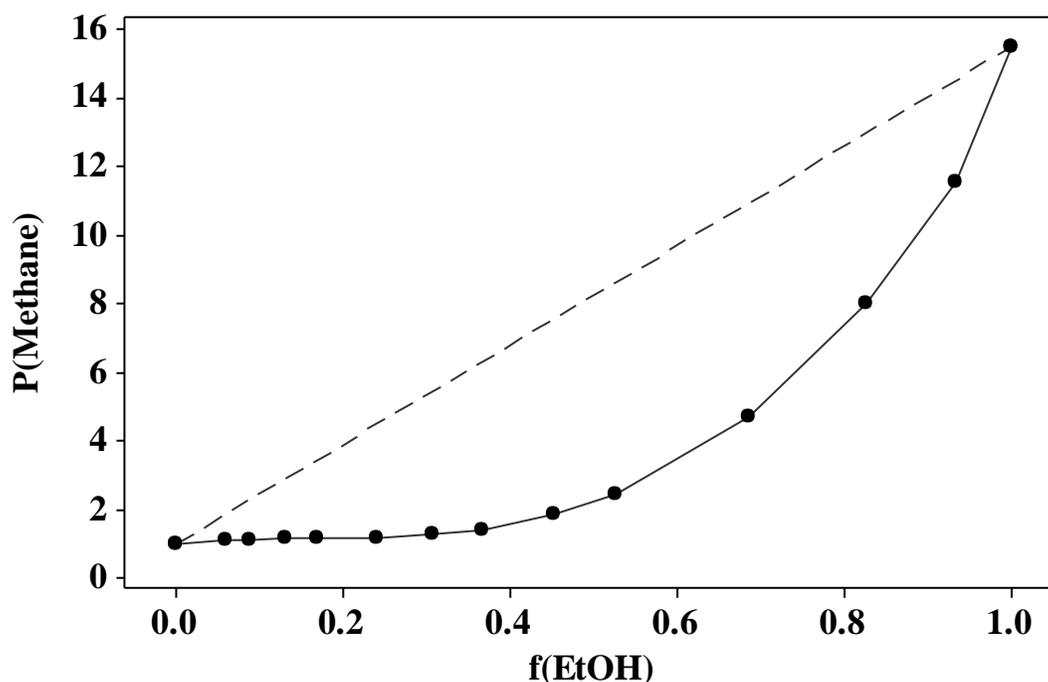


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220  Figure 1. Plot of the water to solvent partition coefficient, $P$, for methane, against volume

221  fraction ethanol in water-ethanol mixtures. ● Experimental values; ----- calculated values
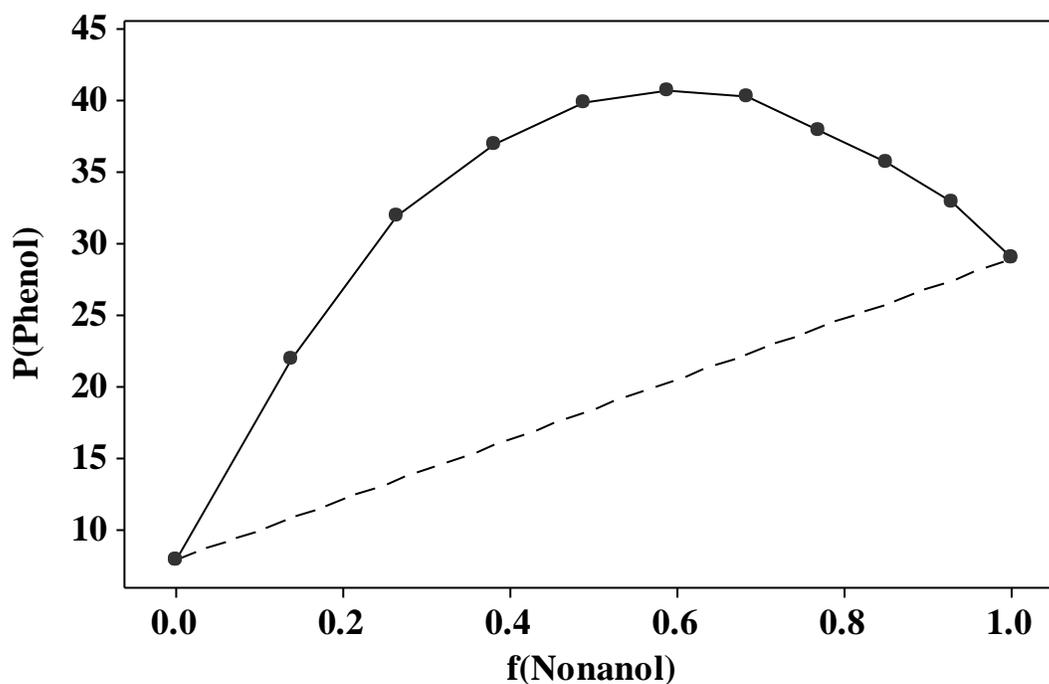
222  through eq 1.

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Figure 2. Plot of the water to solvent partition coefficient, *P*, for ethane, against volume
fraction ethanol in water-ethanol mixtures. ● Experimental values; ----- calculated values
through eq 1.

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231 Figure 3. Plot of the water to solvent partition coefficient, *P*, for phenol, against volume
232 fraction nonanol in nonanol-nitrobenzene mixtures. ● Experimental values; -----
233 calculated values through eq 1.

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<table>
<tr><td colspan="2" align="center"><strong>Compounds in the gas phase</strong></td></tr>
<tr><td>Partition ↓</td><td>E, S, A, B, L descriptors</td></tr>
<tr><td colspan="2" align="center"><strong>brain, muscle, liver, lung, kidney, heart, fat</strong></td></tr>
<tr><td>Partition ↑</td><td>E, S, A, B, V descriptors</td></tr>
<tr><td colspan="2" align="center"><strong>Compounds in blood</strong></td></tr>
</table>