Rapid Determination of Octanol-Water Partition Coefficient using Vortex-Assisted Liquid-Liquid Microextraction

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17 **ABSTRACT**

18 Vortex-assisted liquid-liquid microextraction (VALLME) coupled with high-performance liquid
19 chromatography (HPLC) is proposed here for the rapid determination of octanol-water partitioning
20 coefficients (K_{ow}). VALLME uses vortex agitation, a mild emulsification procedure, to disperse
21 microvolumes of octanol in the aqueous phase thus increasing the interfacial contact area and
22 ensuring faster partitioning rates. With VALLME, 2 min were enough to achieve equilibrium
23 conditions between the octanolic and aqueous phases. Upon equilibration, separation was achieved
24 using centrifugation and the octanolic microdrop was collected and analyzed in a HPLC system. Six
25 model compounds with log K_{ow} values ranging between ~0.5 and 3.5 were used during the present
26 investigations. The proposed method produced log K_{ow} values that were consistent with previously
27 published values and the recorded uncertainty was well within the acceptable log unit range. Overall,
28 the key features of the proposed K_{ow} determination procedure comprised speed, reliability,
29 simplicity, low cost and minimal solvent consumption.

30 **Keywords:** octanol-water partition coefficient; organic compounds; liquid-liquid microextraction;
31 vortex agitation.

1. INTRODUCTION

The octanol-water partition coefficient (K_{ow}) and water solubility play an important role in determining the partitioning behavior of chemicals in the environment [1-3]. In particular, K_{ow} serves not only as a general indicator of a compound's tendency to partition into an organic phase, but furthermore, this coefficient is practically the same as the compound's lipid (triolein)-water partition coefficient (K_{tw}), the latter accounting directly for the fish bioconcentration factor on a lipid-weight basis [2].

In general, accurate K_{ow} values are obtained by taking particular steps to minimize measurement errors, such as those caused by the impurities of test compounds and solvents, the equilibration and separation methods, as well the equipment sensitivity for detecting target compounds [2,4]. Currently, the most consistent and reliable direct experimental methods used for the determination of K_{ow} values are the shake-flask (usually coupled with centrifugation), the slow stirring method and the generator-column equilibration techniques. The main drawbacks of these methods are that they are time-consuming, labor intensive and that they consume large amounts of solvent per sample [2,5]. Indirect experimental methods (e.g. those using high-performance liquid chromatography) seem to circumvent these problems, though their uses are usually confined to relatively simple molecules or those within a homologous series [2,5]. Regardless of the experimental method used, the accurate and reproducible determination of K_{ow} may be a challenging task with seemingly identical replicate samples, thus giving rise to markedly different results and frequent inconsistencies between K_{ow} values which were previously reported by different laboratories or by different analytical methods [6].

Recently, microextraction methods were proposed as an effective alternative for the determination of K_{ow} values. Previous reports included procedures based on hollow fiber liquid-phase microextraction whereby target solutes are sampled from an aqueous phase into microliters of 1-octanol immobilized

56 in the pores and lumen of a porous polypropylene fiber [7-9]. The resulting methods were simple,
57 however long periods of extraction (from 1 to 24 hours) were necessary to reach equilibrium
58 conditions. In other published reports, liquid-liquid microextraction coupled with magnetic
59 nanoparticles predispersed in the octanol phase were reported to result in faster, yet multi-step, K_{ow}
60 determination procedures [10,11]. In the past, K_{ow} values were also correlated with distribution
61 coefficient data obtained through the solid-phase microextraction approach [12].

62 The aim of the present study was to investigate the possibility of using our recently introduced
63 equilibrium-based microextraction method, termed vortex-assisted liquid-liquid microextraction
64 (VALLME) [13,14], for the direct determination of K_{ow} values. According to VALLME,
65 microvolumes of octanol (a low-density extractant organic solvent) are dispersed into an aqueous
66 sample using vortex mixing, a mild emulsification procedure. The fine microdroplets formed ensure
67 fast partitioning rates, i.e. short equilibration times, due to the shorter diffusion distance and larger
68 specific surface area. Upon centrifugation the octanolic phase restores its initial single microdrop
69 shape and can be used for high-performance liquid chromatography (HPLC) analysis once collected.
70 Six model compounds, with reported log K_{ow} values ranging between ~0.5 and 3.5, were used during
71 the present investigations and the results revealed that VALLME is a rapid, efficient, facile and low
72 cost experimental method for the direct determination of K_{ow} values.

73

74 **2. EXPERIMENTAL**

75 *2.1. Chemicals and solutions*

76 The six compounds investigated here and some of their physicochemical properties are provided in
77 Table 1. Hydroquinone ($\geq 99\%$) and naphthalene (99%) were purchased from Sigma-Aldrich
78 (Steinheim, Germany). Simazine, 2,6-dichlorophenol and dichlorvos (all Pestanal[®] grade) were
79 purchased from Riedel-de Haën (Seelze, Germany) and 2,4-dichlorophenol from Fluka (Steinheim,

Germany). 1-octanol and methanol (Chromasolv) were obtained from Riedel-de Haën (Seelze, Germany). Throughout this text 1-octanol is referred as octanol. Purified water was prepared from an EASYpure RF system (Barnstead/Thermolyne, IA, USA). Octanol and water were mutually saturated in a 1000 mL separation funnel. The mixture of the two solvents was initially shaken for several minutes and then left undisturbed for 24 hours. A 100 μ L Hamilton (Bellefonte, PA, USA) HPLC 710 SNR model microsyringe was used to inject octanol into the aqueous solution and then collect it for HPLC analysis.

Individual stock standard solutions of each model analyte were prepared in methanol and in octanol saturated with water. All stock solutions were stored at 4 °C, in the dark when not in use. Aqueous working solutions were prepared daily using an appropriate dilution of the individual methanolic stock solution. Octanolic stock standard solutions were used for preparing calibration standard solutions by further diluting them in octanol saturated with water. The resulting calibration curves were used for determining the concentration of model analytes in the octanol phase after VALLME. The concentration ranges of the octanolic solutions and the resulting calibration parameters for the model compounds investigated here are provided in Table 2.

2.2. HPLC analysis

Quantification was performed on an HPLC (Shimadzu Corporation, Kyoto, Japan), equipped with a SPD-M10A diode array detector and two solvent delivery pumps (LC 10AD). The HPLC system was also equipped with a Rheodyne manual sample injector valve with a 10- μ L loop (Chrom Tech Inc., MN, USA) and an Agilent Zorbax Eclipse XDB C-18 column (150 mm x 4.6 mm i.d., with 5 μ m particles size) purchased from Agilent Technologies Inc. (Palo Alto, CA, USA) and thermostated at 27 °C. The mobile phase was a mixture of methanol:water (85:15) at a flow rate of 0.8 mL min⁻¹. The total analysis time was 5 minutes.

2.3. VALLME procedure and K_{ow} calculation

The experimental procedure used for VALLME was as follows: A 10 mL solution of water, saturated in octanol and spiked with a model analyte at a preset concentration was placed in a conical-bottom centrifuge glass tube. With the help of a microsyringe, 50 μ L of octanol saturated in water was slowly introduced and the mixture was then vigorously shaken using a vortex agitator (Reax Control, Heidolph, Germany) for 2 min at 2500 rpm (maximum setting) leading to the formation of fine octanol droplets. The two phases were subsequently separated by centrifugation (Labofuge 400 Heraeus, Kendro Laboratory Products, Germany) at 3500 rpm (maximum setting) for 2 min. After centrifugation, the octanol phase restored its initial single microdrop shape on the upper surface of the sample solution and 30 μ L of octanol could be collected with the help of a microsyringe and used for HPLC analysis. All log K_{ow} values were reported for room-temperature where partitioning systems show temperature dependence of about 0.01 log unit/deg [15]. Buffers were not used here since they may affect partitioning [4]. Based on the physicochemical properties of hydroquinone and simazine (Table 1) and the pH of the aqueous solutions, the neutral forms of hydroquinone (protonated) and simazine (dissociated) dominated. Thus, it was presumed that for these two compounds, the ratio of the total concentrations, (dissociated and associated species), termed distribution coefficient or apparent partition coefficient (D_{ow}), was essentially the same as the true partition coefficient (K_{ow}), which relates to the same molecular species in each phase [4]. Based on the pK_a values of 2,4- and 2,6-dichlorophenol, the apparent partition coefficients (D_{ow}) for these two compounds were corrected for ionization using [6,16]

$$K_{ow} = D_{ow} [1 + 10^{(pH - pK_a)}] \quad (1)$$

The true partition coefficients are reported in the text, tables and figures. The pH of the sample solution was measured before and after extraction, and the pH value after extraction was used for data process.

129 The equilibrium concentration of the target analyte in the octanol phase was calculated each time
130 using the external calibration curves (Table 2) constructed from spiked octanol (saturated with
131 water) solutions. Measuring the exact volume of the octanol drop restored after centrifugation was
132 unnecessary as the analyte concentration in the octanol phase was determined by HPLC using
133 external calibration [9]. The corresponding equilibrium concentration in the aqueous phase was
134 calculated using the mass balance equation [6]. The value of K_{ow} was then calculated as the ratio of
135 equilibrium concentrations in the octanol and water phases. The $\log K_{ow}$ values were calculated for
136 each concentration level of a six-point concentration range. Every experiment was run in duplicate
137 (from different vials from the same stock solutions) and the average values are given in figures. The
138 values given in Table 3 are the mean values of the $\log K_{ow}$ values calculated at each concentration
139 level.

140

141 **3. RESULTS AND DISCUSSION**

142 *3.1. Determination of equilibrium time*

143 For accurate partition coefficient determination, it is generally recommended to allow adequate time
144 for the system to reach equilibrium conditions. The time needed to attain steady state conditions
145 varies enormously and partitioning rates may be fast or slow depending on the partition coefficient
146 of the analyte and the degree of agitation applied. For example, Leo, Hansch and Elkins [15]
147 recommended about 100 inversions in 5 minutes of a stoppered test-tube containing the two phases
148 for consistent K_{ow} measurements. At the other extreme, Brooke, Dobbs and Williams [17] reported
149 that 2 to 3 days were necessary to reach steady state conditions without emulsification whilst using
150 the slow stirring method. Previously published microextraction-based procedures concluded that
151 times ranging from 1 to 24 h were necessary to ensure equilibrium between the octanol and water
152 phases [7-9]. Ensuring fast mass transfer kinetics of the solute will result into short equilibration

153 times and as such rapid K_{ow} measurements. The benefits of measuring octanol water partition
154 coefficients in a rapid and economical manner are readily apparent.

155 Based on the relevant rate equation described in the past for liquid-liquid microextraction [18], key
156 experimental variables to control for achieving rapid equilibrium between the two immiscible phases
157 include maximization of (i) the interfacial contact area between the two immiscible liquid phases (A_i)
158 and/or (ii) the overall mass transfer coefficient with respect to the organic phase ($\overline{\beta_o}$). Assuming
159 rapid mass transfer across the liquid-liquid interface, $\overline{\beta_o}$ can be expressed as

160
$$\frac{1}{\overline{\beta_o}} = \frac{1}{\beta_o} + \frac{1}{\beta_{aq}} \quad (2)$$

161 where β_o and β_{aq} are the individual mass transfer coefficients for the organic and aqueous phases.

162 During VALLME, the octanol phase is subjected to mechanical stress due to vortex agitation and
163 bursts into several smaller droplets. This is a net advantage over other agitation methods such as
164 magnetic stirring given that this process markedly increases the interfacial contact area (A_i) and
165 reduces the thickness of the stagnant aqueous film (δ_{aq}) adjacent to the octanol-water interface, as
166 described in the two-film theory [19,20]. Since δ_{aq} is inversely related to β_{aq} [20], reducing the
167 thickness of the aqueous film will also increase the mass transfer coefficient for the aqueous phase
168 and consequently, the overall mass transfer coefficient with respect to the organic phase ($\overline{\beta_o}$). This
169 means that, according to the theory, the time needed to reach equilibrium is expected to be faster
170 when using the VALLME approach. Indeed, the above theoretical consideration has been
171 experimentally proven on several occasions in the past and short equilibration times have always
172 been reported for VALLME [13,14,21,22].

173 During the present investigations, the time needed to attain equilibrium with VALLME was
174 determined for each model compound. Fig. 1 depicts two typical peak area time profiles obtained so
175 as to visualize the kinetics of analyte transfer in the octanol phase as a function of vortex time. For
176 reasons of clarity, the profiles of naphthalene and hydroquinone (having the highest and lowest

reported log K_{ow} values respectively) are only given. The experimental point “0 min” corresponded to experiments where the octanol-water mixtures were only centrifuged (2 min at 3500 rpm) resulting in analyte transfer solely due to diffusion during the centrifugation step [13]. As can be seen, with VALLME, analytes reach equilibrium quickly and 2 min of vortex agitation are sufficient to achieve equilibrium conditions. The rapid partitioning rate (i.e. short equilibration time) achieved with VALLME is one of the key features of the proposed K_{ow} determination method.

3.2 Determination of log K_{ow} values with VALLME: Effect of model compound concentration on log K_{ow}

It is generally recommended that partition coefficients are to be determined using as low solute concentration as gives acceptable accuracy. There are three main reasons for using low concentrations of solute: (i) maintenance of activity coefficient (γ) at or very close to unity, (ii) prevention of solute self-association and (iii) maintenance of constant phase composition [6]. Table 3 shows the mean log K_{ow} values obtained for each model compound and the concentration ranges used. The results revealed that consistency exists between the mean log K_{ow} values obtained with the VALLME approach and those reported in the literature (also shown in Table 3). The small differences observed between log K_{ow} , as determined by VALLME, are not uncommon when considered in terms of the reported variability for log K_{ow} values [12]. For example, the diversity of the previously reported log K_{ow} values for simazine (Table 3), commonly observed in the case of ionizable compounds [6], highlights the experimental difficulty in determining accurate and precise log K_{ow} values.

Based on previous knowledge, partition coefficients were expected to be independent of the variation of the solute concentration. If K_{ow} differs significantly (more than one standard deviation for replicate determinations) at two solute levels, an intraphase interfering equilibrium (solute association or dissociation) is suggested [30]. During the present investigations, log K_{ow} values were

determined by VALLME for different solute concentrations and the effect of solute concentration on $\log K_{ow}$ is provided in Fig. 2. The results confirmed that within the concentration range tested, measured $\log K_{ow}$ values were found to be independent of the chemical concentration of the solute.

The difficulties commonly besetting experimental procedures have been repeatedly reported in the past with seemingly identical replicate samples providing different results, and determinations by different workers producing marked variations [6]. Nevertheless, many compounds have replicate values within a very narrow range, and it is generally considered that values with an uncertainty range of 0.3 log units are acceptable [6,31]. During the present investigations, the recorded uncertainty for the replicates at each concentration level was recorded below ~0.01 log units for hydroquinone and dichlorvos and ~0.02 log units for simazine. In the case of 2,6- and 2,4-dichlorophenol, uncertainty was recorded as <0.1 log units whereas for naphthalene standard deviation was found to increase with increased solute concentration, though below ~0.3 log units throughout the concentration range tested. Furthermore, the standard deviation of the mean $\log K_{ow}$ value calculated from the six-point concentration range used for each compound was below 0.2 log units (Table 3). Based on the above observations, the uncertainties found here were proved to be acceptable for the hazard and fate assessments of xenobiotic chemicals in the environment.

3.3. Range of $\log K_{ow}$ values

A high partition coefficient corresponds to a high ratio of concentrations. This will result, in a very low (and probably inaccurately measured) concentration in the aqueous phase [5,6]. Clearly the higher the partition coefficient, the greater the water to octanol phase volume ratio should be. With very lipophilic molecules, it is evident, that small volumes of octanol must be used, otherwise there will be insufficient material left in the aqueous phase for analysis or that the remaining amount of solute will be inaccurately calculated. During the present investigations the $\log K_{ow}$ values of the tested compounds ranged from ~ 0.5 to 3.5. To extend the applicability of VALLME and cover

227 solutes with higher $\log K_{ow}$ values, proper phase volume choices should be made. However, the use
228 of larger aqueous volumes or smaller octanolic phase volumes is impractical when using the
229 VALLME procedure. Overall, the proposed procedure is a friendly, fast and low cost miniaturized
230 platform for measuring $\log K_{ow}$ values within the realistic measurable range as reported in the past
231 [4].

232

233 **Conclusions**

234 The use of VALLME for determining octanol-water partition coefficient values for a range of
235 solutes has been reported. The experimentally determined $\log K_{ow}$ values found here were consistent
236 with previously published octanol-water partition coefficient data having $\log K_{ow}$ values below ~ 3.5 .
237 Apart from its simplicity and environmentally friendly character, the main advantage of the proposed
238 method is the short equilibration time, making VALLME a rapid tool to determine accurate K_{ow}
239 values.

240

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Compound	CAS No	Molecular Formula	Molecular Weight (g mol ⁻¹)	Water Solubility (mg L ⁻¹)	pK _a
Hydroquinone	123-31-9	C ₆ H ₆ O ₂	110.11	72000 (25 °C)	10.9
Dichlorvos	62-73-7	C ₄ H ₇ Cl ₂ O ₄ P	220.98	8000 (20 °C)	
Simazine	122-34-9	C ₇ H ₁₂ ClN ₅	201.66	6.2 (22 °C)	1.62
<u>2,6-Dichlorophenol</u>	<u>87-65-0</u>	<u>C₆H₄Cl₂O</u>	<u>163.00</u>	<u>1900 (25 °C)</u>	<u>6.79</u>
<u>2,4-Dichlorophenol</u>	<u>120-83-2</u>	<u>C₆H₄Cl₂O</u>	<u>163.00</u>	<u>5550 (25 °C)</u>	<u>7.89</u>
Naphthalene	91-20-3	C ₁₀ H ₈	128.18	31 (25 °C)	

Table 1. Some of the physicochemical properties of the six model compounds.

293 **Table 2.** External calibration curves: concentration ranges of the octanolic standard solutions and

p@95 ratio

36297 para

298 mete299 rs300 obta301 ined302 for

303 the six model compounds.

Dichlorvos	100-1000	0.9993	19735	161614
Simazine	5-500	0.9913	455076	30456
2,6-Dichlorophenol	50-500	0.9980	-28205	8347
2,4-Dichlorophenol	20-300	0.9994	709735	8855
Naphthalene	10-300	0.9953	1111618	118957

315

316 **Table 3.** The mean $\log K_{ow}$ values obtained by VALLME, the concentration range tested and
 317 experimental $\log K_{ow}$ values found in the literature.

318

Compound	Conc.	$\log K_{ow}^{(a)}$	Literature values	Reference
	Range ^(c) (μ M)			
Hydroquinone	25-500	0.50 (± 0.02)	0.54-0.59	[23-26]
Dichlorvos	5-50	1.46 (± 0.03)	1.16-1.73	[23,27]
Simazine	0.25-2.5	2.16 (± 0.11)	1.51-2.26	[23,27,28]
<u>2,6-Dichlorophenol</u>	<u>0.5-10</u>	<u>2.82 (± 0.14)^(b)</u>	<u>2.84-2.92</u>	<u>[29]</u>
<u>2,4-Dichlorophenol</u>	<u>0.5-10</u>	<u>3.22 (± 0.21)^(b)</u>	<u>3.08-3.23</u>	<u>[9,12,27,29]</u>
Naphthalene	0.25-1.4	3.51 (± 0.08)	3.01-3.59	[8,9,10,12,15,27,28]

319

320 ^(a) mean $\log K_{ow}$ calculated from a six-point concentration range (each point run in duplicate);
 321 standard deviation is given in parentheses

322 ^(b) value corrected for ionization

323 ^(c) concentration range in aqueous solution

324

325

326

327

328

329

Fig. 1.

Fig. 2.

350

351 **Figure Captions**

352

353 **Fig. 1.** Uptake profiles of naphthalene and hydroquinone in the octanol phase as a function of time.

354 Some error bars are too small to be visible as compared to the physical sizes of the symbols.

355

356

357 **Fig. 2.** The log K_{ow} -concentration profiles obtained for each model compound with VALLME. Some
358 error bars are too small to be visible as compared to the physical sizes of the symbols.

359