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

Iván P. Román[1,a], Anna Mastromichali[2,a], Konstantina Tyrovola[2], Antonio Canals[1], Elefteria Psillakis[2*]

[1]*Departamento de Química Analítica, Nutrición y Bromatología e Instituto Universitario de Materiales, Facultad de Ciencias, Universidad de Alicante, P.O. Box 99, E-03080 Alicante, Spain.*

[2]*Laboratory of Aquatic Chemistry, School of Environmental Engineering, Technical University of Crete, Polytechneioupolis, GR-73100 Chania, Greece*

[a]These authors equally contributed to the present work

*Corresponding author. Tel.: +302821037810; Fax: +302821037846

E-mail address: elia@enveng.tuc.gr

ABSTRACT

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

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

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

2. EXPERIMENTAL

2.1. Chemicals and solutions

The six compounds investigated here and some of their physicochemical properties are provided in Table 1. Hydroquinone (≥99%) and naphthalene (99%) were purchased from Sigma-Aldrich (Steinheim, Germany). Simazine, 2,6-dichlorophenol and dichlorvos (all Pestanal$^{\circledR}$ grade) were 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 μL 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-µL 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 μm particles size) purchased form 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 μL 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 μL 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 $\mathrm{p}K_a$ 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]

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

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.

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

3. RESULTS AND DISCUSSION

3.1. Determination of equilibrium time

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

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

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

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

During the present investigations, the time needed to attain equilibrium with VALLME was determined for each model compound. Fig. 1 depicts two typical peak area time profiles obtained so as to visualize the kinetics of analyte transfer in the octanol phase as a function of vortex time. For 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 solutes with higher log K_{ow} values, proper phase volume choices should be made. However, the use of larger aqueous volumes or smaller octanolic phase volumes is impractical when using the VALLME procedure. Overall, the proposed procedure is a friendly, fast and low cost miniaturized platform for measuring log K_{ow} values within the realistic measurable range as reported in the past [4].

Conclusions

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

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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	$C_6H_6O_2$	110.11	72000 (25 ^{0}C)	10.9
Dichlorvos	62-73-7	$C_4H_7Cl_2O_4P$	220.98	8000 (20 ^{0}C)	
Simazine	122-34-9	$C_7H_{12}ClN_5$	201.66	6.2 (22 ^{0}C)	1.62
2,6-Dichlorophenol	87-65-0	$C_6H_4Cl_2O$	163.00	1900 (25 ^{0}C)	6.79
2,4-Dichlorophenol	120-83-2	$C_6H_4Cl_2O$	163.00	5550 (25 ^{0}C)	7.89
Naphthalene	91-20-3	$C_{10}H_8$	128.18	31 (25 ^{0}C)	

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

Table 2. External calibration curves: concentration ranges of the octanolic standard solutions and calibration parameters obtained for the six model compounds.

Compound	**Conc. Range (µM)**	**Coefficient of determination (r^2)**	**Intercept**	**Slope**
Hydroquinone	200-2000	0.9996	53667	6236

Dichlorvos	100-1000	0.9993	19735	1616314
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

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

Compound	**Conc. Range**$^{(c)}$ **(μM)**	**log** K_{ow} $^{(a)}$	**Literature values**	**Reference**
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]
2,6-Dichlorophenol	0.5-10	2.82 (±0.14)$^{(b)}$	2.84-2.92	[29]
2,4-Dichlorophenol	0.5-10	3.22 (±0.21) $^{(b)}$	3.08-3.23	[9,12,27,29]
Naphthalene	0.25-1.4	3.51 (±0.08)	3.01-3.59	[8,9,10,12,15,27,28]

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

(b) value corrected for ionization

(c) concentration range in aqueous solution

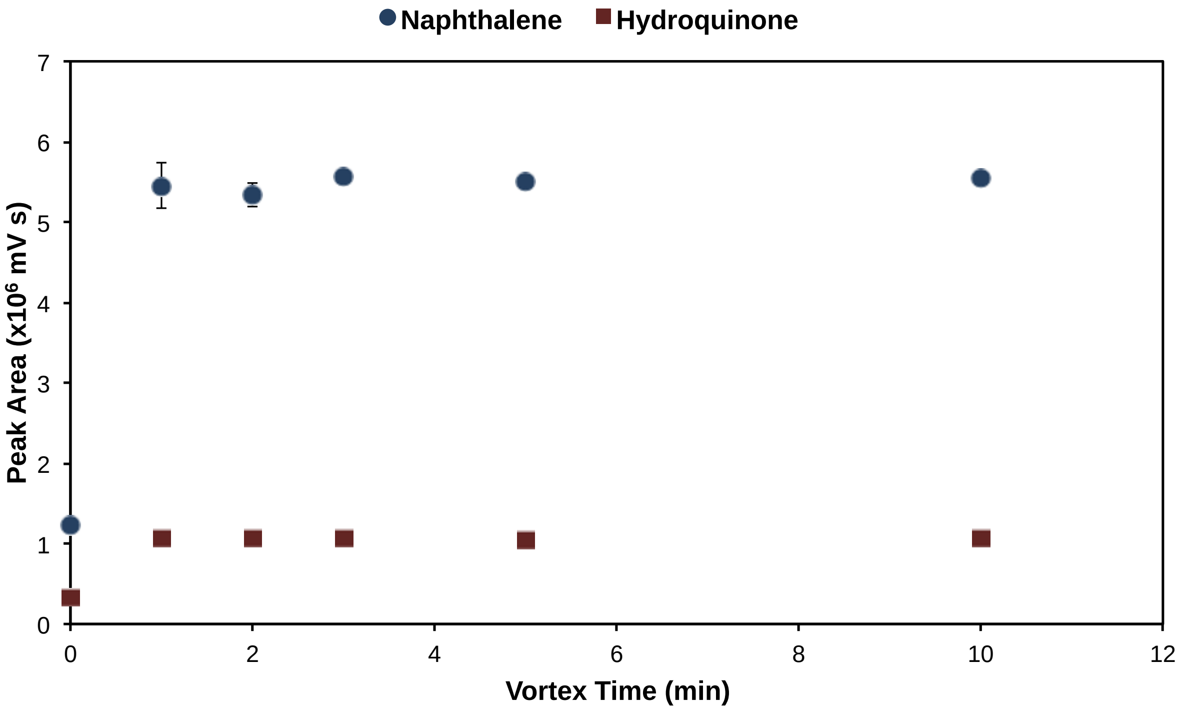
● Naphthalene
■ Hydroquinone
Peak Area (x10⁶ mV s)
0
1
2
3
4
5
6
7
0
2
4
6
8
10
12
Vortex Time (min)

Fig. 1.

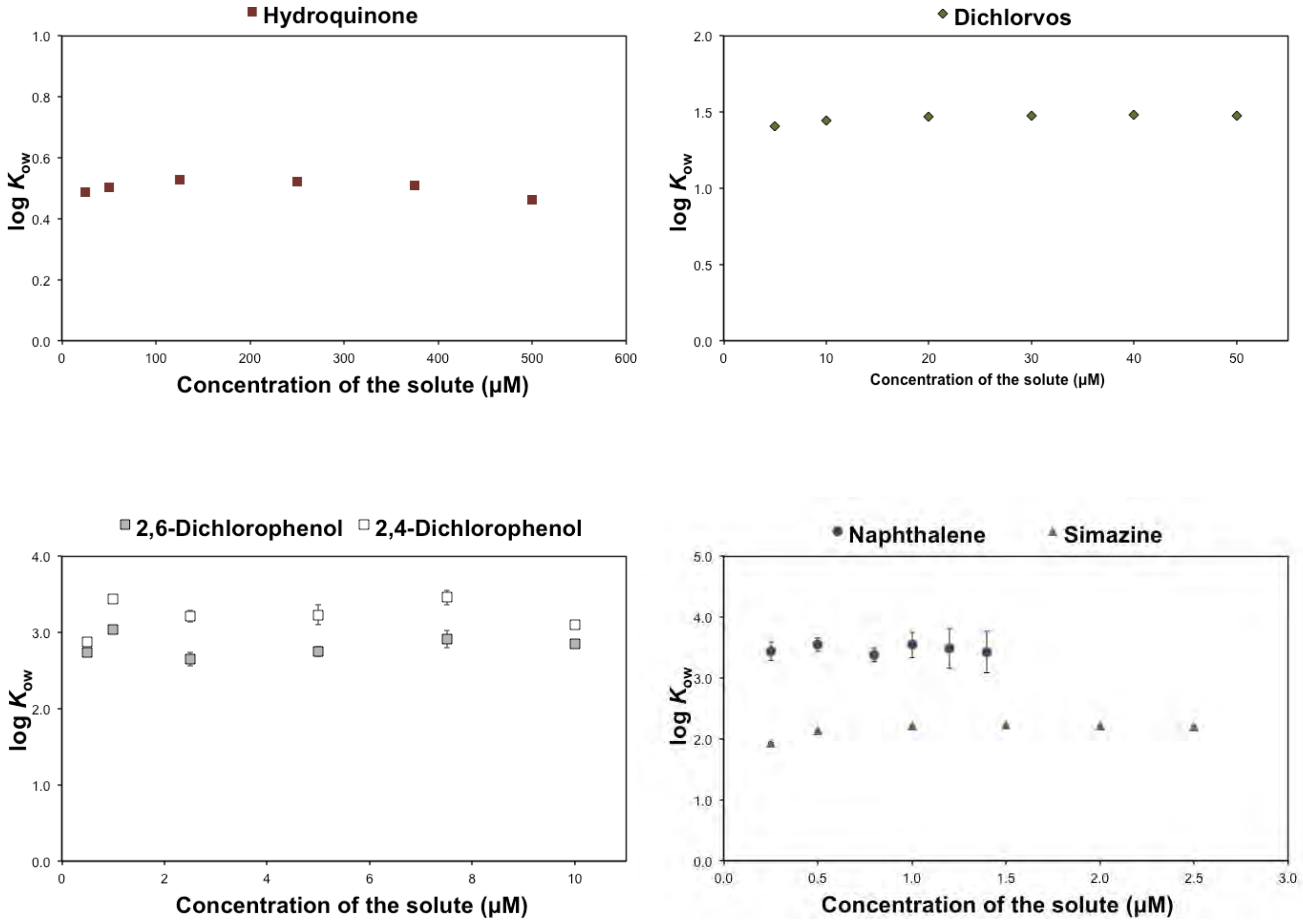
■ Hydroquinone
log K_{ow}
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
Concentration of the solute (μM)
◆ Dichlorvos
log K_{ow}
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
Concentration of the solute (μM)
▨ 2,6-Dichlorophenol
☐ 2,4-Dichlorophenol
log K_{ow}
4.0
3.0
2.0
1.0
0.0
0
2
4
6
8
10
Concentration of the solute (μM)
● Naphthalene
▲ Simazine
log K_{ow}
5.0
4.0
3.0
2.0
1.0
0.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Concentration of the solute (μM)

Fig. 2.

Figure Captions

Fig. 1. Uptake profiles of naphthalene and hydroquinone in the octanol phase as a function of time. Some error bars are too small to be visible as compared to the physical sizes of the symbols.

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