Experimental and Computational Study of Membrane Affinity for Selected Energetic Compounds

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ABSTRACT - The affinity of various energetic compounds for a biological membrane was investigated using experimental and computational techniques. We measured octanol-water ($\log(K_{ow})$) and liposome-water ($\log(K_{lipw})$) partition coefficients for the following chemicals: trinitrotoluene (TNT), 2,4-dinitrotoluene (2,4-DNT), 2,6-dinitrotoluene (2,6-DNT), 2,4-dinitroanisole (DNAN), 2methoxy-5-nitrophenol (2M5NP), 2,4,6-trinitrobenzene (TNB), and 2,4-dinitrophenol (2,4-DNP). In order to determine $\log(K_{lipw})$ experimentally, we used artificial solid supported lipid liposomes produced under trade mark TRANSIL. $\log(K_{ow})$ value were predicted with several program packages including the COSMOthermX software. $\log(K_{lipw})$ were estimated with COSMOmic as implemented in the COSMOthermX program package. In order to verify accuracy of our experimentally obtained results, we performed basic statistical analysis of data taken from the literature. We concluded that compounds considered in this study possess a moderate ability to penetrate into membranes. Comparison of both coefficients has shown that in general, the $\log(K_{ow})$ values are slightly smaller than $\log(K_{lipw})$.

1.Introduction

The penetration of chemicals through biological membranes is a key factor in the determination of the possible effects of substances such as toxicants and drugs interacting with biological systems.(Endo et al., 2011) The simplest way to characterize the ability of a substance to bioaccumulate is to consider the partition coefficient between water and a lipid pool i.e. biological membrane. In its simplest form, bioconcentration has been characterized as the ratio of the equilibrium concentrations of a chemical (solute) that partitions between n-octanol (representing the lipid fraction) and water:

$$K_{ow} = \frac{[C_o]}{[C_w]} \quad (1)$$

where C_o and C_w are the molar equilibrium concentration of the solute in octanol and water at a specified temperature, correspondingly. General formula for partitioning coefficient was described by (Nernst, 1891).

However, to obtain an accurate estimate of this partition in a realistic lipid system, factors relating to membrane specifics such as type of lipid,(Kramer, 2001; Avdeef, 2012) chemical structure of the lipids that comprise the membrane,(Poulin and Theil, 2002; Rodgers and Rowland, 2006; Schmitt, 2008) external conditions, (Poulin and Theil, 2002; Rodgers and Rowland, 2006; Schmitt, 2008) etc.) need to be taking into account.

Despite the fact that the traditional definition of K_{ow} actually characterizes hydrophobicity of a substance, numerous studies have shown (Jonker and Van Der Heijden, 2007; Endo et al., 2011) that in many cases also bioconcentration can be described by this parameter quite efficiently. The exceptions are among highly hydrophobic ($\log(K_{ow})$ greater than 5 - 6) and ionic compound. Experimental measurement of K_{ow} is often times complicated and time consuming since partition

equilibrium is difficult to determine. Given the difficulties in measuring partitioning of organic substances across a biological membrane, many researchers substitute octanol-water partition coefficients as a measure of the partitioning across lipid bilayer.

To improve the ease and repeatability of bioconcentration measurements, recently test membranes comprised of a class of artificial membrane vesicles made up from phospholipids (liposomes) were synthesized and made commercially available. Such model systems support the investigation of numerous biological processes (ligand-receptor interaction,(Plant et al., 1995; Pum et al., 1997; Yang et al., 2001; Yang et al., 2003) viral attack,(Ono and Freed, 2001; Xu et al., 2002) cellular signaling events(Kasahara and Sanai, 2001; Qi et al., 2001; Stoddart et al., 2002)) including measuring partition between water and liposome. Similar to eq. (1) such partition will be defined as

$$K_{lipw} = \frac{[C_{lip}]}{[C_w]} \quad (2)$$

where C_{lip} and C_w are the molar equilibrium concentration of the solute in liposome and water respectively.

There exist several experimental techniques to measure K_{lipw} .(Castellana and Cremer, 2006) One of these techniques is based on the solid supported lipid membranes application, which is commercially available under the trade mark TRANSIL.(Loidl-Stahlhofen et al., 2001a; Loidl-Stahlhofen et al., 2001b) In these systems, porous silica beads are covered by a unilamellar liposomal membrane that is noncovalently bounded to the bead. The main advantage of these systems is the very short time (c.a. 2 min) needed to reach equilibrium. This is in contrast to other liposomal-based approaches where in some cases up to 12 hours is required to reach equilibrium.(Loidl-Stahlhofen et al., 2001a) Experimental measurements of K_{ow} are often similarly time-consuming.

The existence of two sets of parameters that characterize related chemical behavior, hydrophobicity (K_{ow}) and bioconcentration (K_{lipw}), raises the question on the comparison and relative importance of them. On one hand it has been stated that K_{lipw} is a more accurate descriptor to estimate membrane affinity of chemicals (Jonker and Van Der Heijden, 2007; van der Heijden and Jonker, 2009). Several publications indicate not only the difference between K_{ow} and K_{lipw} but also the absence of the correlation between the corresponding values. (Jabusch and Swackhamer, 2005; Jonker and Van Der Heijden, 2007) It is also expected that penetration of neutral compounds from water solution into membrane is higher than from water to octanol ($K_{lipw} > K_{ow}$). (Gobas et al., 1988; Dulfer and Govers, 1995; Endo et al., 2011)

Conversely, it is also noted that K_{ow} is still a fundamental parameter that is used in most bioaccumulation models. Several publications show that even if a difference between K_{ow} and K_{lipw} exists, their values have the same trend. (Endo et al., 2011) In addition K_{ow} values are available for a large number of chemicals, while the currently available amount of K_{lipw} values is significantly less.

A third approach to estimate both K_{ow} and K_{lipw} values is based on computational methods. Currently among the most efficient tools for such predictions are Quantitative Structure - Activity (Property) Relationships (QSAR/QSPR) techniques. These approaches have been successfully used for over forty years (Jonker and Van Der Heijden, 2007) especially in the environmental science and pharmaceutical industries to predict K_{ow} values. Another group of computational techniques is based on combination of quantum-mechanical and statistical approaches. (Klamt, 1995; Gurtovenko et al., 2004; Patra et al., 2004; Klamt et al., 2008; Sapay and Tieleman, 2011) This approach allows both K_{ow} and K_{lipw} to be estimated. In addition, quantum-chemistry based techniques do not need a training set of compounds since they directly

calculate K_{ow} and K_{lipw} . Both approaches have been shown to predict these values with near experimental accuracy, and are also cost effective. Another computational way to predict K_{ow} and K_{lipw} is based on classical molecular dynamics. However, this approach is very time consuming because one needs to get very long trajectories (hundred nanoseconds or even microsecond). (Lange et al., 2006; Zhang and Voth, 2011; Paloncýová et al., 2014) Therefore, selected computational studies can be used to supplement more extensive and costly experimental evaluations. (Endo et al., 2011)

In this work, measurements and verifications of the K_{lipw} values for the following chemicals was undertaken: trinitrotoluene (TNT), 2,4-dinitrotoluene (2,4-DNT), 2,6-dinitro-toluene (2,6-DNT), 2,4-dinitroanisole (DNAN), 2-methoxy-5-nitrophenol (2M5NP), 2,4,6-trinitrobenzene (TNB), and 2,4-dinitrophenol (2,4-DNP). These compounds are energetic compounds that may be potential environmental contaminants. Since experimentally obtained values of K_{ow} and K_{lip} cover the interval in several order of magnitude, in practice the $\log(K_{ow})$ and $\log(K_{lip})$ are used. While there are numerous publications on predictions of the $\log(K_{ow})$ values for these compounds (Hansch and Leo, 1979; Jenkins, 1989; Hansch et al., 1995; Boddu and Redner, 2010), to the best of our knowledge, neither experimental nor computational values of $\log(K_{lipw})$ have been published. Thus, this study also includes comparison and analysis of $\log(K_{lipw})$ obtained experimentally and computationally.

2. Materials and Methods

2.1. Experimental approach

TNT and 2,4-DNT are from ChemService (Westchester, PA, USA), 2,6-DNT from SRI International (Menlo Park, CA, USA), TNB, DNAN, 2M5NP, from Sigma-Aldrich (St. Louis,

MO, USA). 2,4-DNP is from Fischer Scientific (Pittsburgh, PA, USA). Compound stock solutions (100,00 ppm in dimethyl sulfoxide (DMSO)) were created for each compound and were stored at -80 °C until usage. Prior to experimentation, each energetic compound (EC) was diluted to 1000 ppm in DMSO and was then diluted using phosphate buffered saline (PBS) at pH 7.4 to create a 10X stock solution: 10 ppm (mg/L) for MCs, 10 ppm for 2,4 DNP in 90% PBS 10% DMSO. Biolipid assay requires a final 1:10 dilution with ultimate concentration 1 ppm for MCs and 2,4-DNP, all in 99% PBS 1% DMSO employed.

Solid supported egg phosphatidylcholine (egg-PC) liposome beads, i.e. biolipid beads, were obtained from manufacturer (TRANSILXL Intestinal Absorption kit, Sovicell, Leipzig, Germany) via their American distributor (ADMEcell, Alameda, USA).

Solid supported lipid has a greater density than water allowing rapid separation of lipid phase from the supernatant without the need for ultracentrifugation. 6 kits consisting of 12 stripes of 8 wells each were purchased from the same lot. TRANSIL® kit Certificates of Analyses reported Lot No: BHNO, Expiration: Feb, 2013, Surface: Egg-PC, Buffer: Dulbecco's PBS 1X pH 7.4: required compound volume: 18 µL. Assay Parameters are Assay Volume: 168.7 µL, Lipid Content: six logarithmically spaced (factor 1.585) lipid concentrations ranging from 0.73 to 7.23 µL lipid/ml assay buffer. Compounds were incubated with the lipid beads following this protocol: 18 µL addition of 10X stock solution to each well of a stripe per compound, 12 min equilibration time at ambient temperature 25 ± 3 °C with vortexing of wells every 2 minutes, spinning down of stripe for 10 min at 750 RCF, harvesting of 75-100 µL supernatant for analytical analysis using either gas chromatography mass spectroscopy (GC-MS) or high performance liquid chromatography (HPLC) chemical analysis.

2M5NP, TNT, 2,4-DNP and the metabolites of TNT were analyzed using a modified EPA method 8330B. The method utilized an Agilent (Palo Alto, CA) 1200 HPLC equipped with Phenomenex Synergi 4 μ m hydroRP (80A 250x4.6 mm) column. The operational conditions for the HPLC were as follows; injection volume 50 μ L, isocratic elution at 0.9 mL/min utilizing 45:51:4 methanol:water:acetonitrile as the mobile phase, UV absorbance 254 nm, and autosampler and column temperatures at 10°C and 35°C, respectively.

Aqueous concentration (ppm) from chemical analysis was entered into the assay provided TRANSIL® statistical spreadsheet with assay plate parameters. K_{lipw} is determined for every lipid containing well (6/8).

2.2. Computational approach

$\text{Log}(K_{ow})$ values were predicted using the following publically available software that utilizes different variants of Qualitative Structure-Properties Relationships (QSPR: EPI Suite™(Agency, 2012) subroutine KOWWIN, ACD labs, (Advanced Chemistry Development, 2012) and ChemAxon (Ltd., 2010)).

A COSMOthermX (version C30_1201)(F. Eckert, 2012) package has been used to predict $\text{log}(K_{ow})$ at the quantum-chemical level with the COSMO-RS (Klamt and Eckert, 2000) based approach. Quantum-chemical calculations for COSMOthermX were performed with the TURBOMOLE suit (version 6.4) (Ahlich et al., 1989) using the BP-DFT functional (Treutler and Ahlich, 1995) and def2-TZVPD (Rappoport and Furche, 2010) basis set. The optimized geometries, energies and surface screening charge densities obtained at BP/def2-TZVPD level are used as the input for application of statistical thermodynamics. COSMO-RS treats the solvent S as an ensemble of pair-wise interacting surface segments. The interaction energies of

the surface pairs are defined in terms of the screening charge densities and the respective surface segments.

The COSMO-RS methodology operates by pseudo-chemical potentials of liquid or mixed liquids. Those pseudo-chemical potential is calculated as follows:

$$\mu_s^x = \mu_{C,S}^x + \int \rho^x(\sigma) \mu_s(\sigma) d\sigma \quad (3)$$

where

$$\mu_s(\sigma) = \frac{RT}{\alpha_{eff}} \ln \left[\rho_s(\sigma') \exp \left(\frac{1}{RT} (\alpha_{eff} \mu_s(\sigma') - E_{misfit}(\sigma, \sigma') - E_{HB}(\sigma, \sigma')) \right) d\sigma' \right]$$

(4)

and $\mu_{C,S}^x$ is special combinatorial term that takes into account size and shape differences of the molecules in the system.

Since, pseudo-chemical potential of a substance is defined for any solvent with given charge densities an octanol/water partition coefficients is calculated as follows:

$$\log(K_{ow}) = \log[\exp((\mu_{oct} - \mu_{water}) / RT) V_1 / V_2] \quad (5)$$

Log(K_{lipw}) were estimated using the COSMOmic (Klamt et al., 2008) model, which is an extension of the COSMO-RS model, where the lipid bilayer is treated as inhomogeneous liquid layers. The number of layers has to be chosen based on the system size and must be small enough to capture all structural details. (Jakobtorweihen et al., 2013) A layer size of 0.1 nm is sufficient and therefore we split the system into 40 layers. The lipid bilayer (including water molecules) model consist of 128 lipids in total was constructed using the publically-available PDB structure for POPC (2-oleoyl-1-pamlitoyl-sn-glycero-3-phosphocholine) lipid.(Tieleman et al., 1999) Quantum chemical calculations for all components of studied systems were performed

using the same procedure as for predictions of $\log(K_{ow})$ with the def-TZVP basis set. All calculations were performed for 25 C temperature.

In case of energetic compounds successive application of COSMO-RS has been already shown in the following publications (Qasim et al., 2007; Kholod et al., 2009; Kholod et al., 2011).

There is also a number of publications devoted to successive application of COSMO-RS and COSMO-mic to another classes of chemical compounds. (Schröder et al., 2010; Bittermann et al., 2014; Paloncýová et al., 2014)

3. Results and Discussion

There are two the most important issues that we would like to discuss below. First, we will discuss very simplified case of interactions that take place during partitioning of some idealized substance in the case of the water-octanol and water - liposome systems. Secondly, we will verify whether conclusions that follow from these simplified comparisons are correct in the case of large database of chemicals of different classes available in literature.(Endo et al., 2011) In the next step, we will apply obtained results from both steps to verify K_{lipw} for chemicals of interest.

A comparison of the water-octanol and water – biological membrane systems is presented in Figure 1. One may see that from the point of structural chemistry, the common feature between octanol and POPC is that both molecules consist of polar (-OH in case of octanol and phosphatidylcholine one in case of POPC) and nonpolar (octanic radical in case of octanol and palmitoyl and oleyl fragments in case of POPC) parts. Therefore, the partition of a chemical in both cases could be considered as the result of a diffusion from a bulk water hydrated state to the state when a chemical will interact with a media of relatively similar chemical structure. At this very simplified level of consideration, the most important difference between octanol and POPC

is the internal structure of octanol and POPC media. In case of octanol this is typical liquid, in case of POPC this is a gel or liquid crystalline (Dulfer and Govers, 1995; Endo et al., 2011) depending on the ambient conditions during chemical partition. Thus, the Gibbs free energy of a substance in both media can be expressed as the sum of two components. The first component originates from the interaction between a chemical and media (water, octanol, POPC) and the second one is Gibbs free energy to form a cavity inside of water, octanol or POPC medium.

$$\Delta G_{subst}^o = \Delta G_{int} + \Delta G_{cav} \quad (6)$$

Thus, the Gibbs free energy of partitioning is just a difference of the Gibbs free energy of a substance in corresponding media (octanol, or lipid)

$$\Delta G_{part}^o = \Delta G_{subst}^{oct(lip)} - \Delta G_{subst}^w \quad (7)$$

Due to the reasons described above we expect that both components of equation 6 will be only insignificantly different in the case of water-octanol and water - liposome partition. This means that the driving force (see eq. 7) that characterizes octanol-water partition will be of the same order of magnitude as the one which characterizes partitioning between water and liposome.

To illustrate the statement pointed out in a previous paragraph, data of the most systematic study performed to date (Endo et al., 2011) were analyzed. The authors provide the $\log(K_{ow})$ and $\log(K_{lipw})$ values for 155 compounds of differing chemistries. These data are publically available as supplementary materials to (Endo et al., 2011). Selected compounds with partitioning coefficients can be found in the supporting information Tables S1-S5. All of the $\log(K_{lipw})$ values are measured for phosphatidylcholine liposome at a temperature range of 20-40 °C. The results of their statistical treatment are collected in the Table 1. In general, these results are in

agreement with published values(Endo et al., 2011), where they have been treated in slightly different way.

As one may see from the data presented in Table 1, strong linear correlation between $\log(K_{ow})$ and $\log(K_{lipw})$ takes place only in case when all 155 compounds of both hydrophobic and hydrophilic types are included. This correlation is characterized by a moderate value of mean absolute error and moderate standard deviation. The correlation was reduced for any situation which decreases amount of chemicals. All considered cases are characterized by c.a. the same values of MAE and standard deviation.

As stated previously, some studies suggest (Gobas et al., 1988; Dulfer and Govers, 1995; Escher et al., 2000a, b; Endo et al., 2011) that penetration into liposome is higher than into octanol. The data presented in Table 1 agree with this point in principle: NN1 is systematically c.a. twice greater than NN2 for hydrophobic compounds. However, the values of MAE and SD show that differences between $\log(K_{ow})$ and $\log(K_{lipw})$ on average do not exceed 0.5 log. unit (corresponding $\Delta G_{part}=0.68\text{kcal/mol}$). For nearly one third of the chemicals in the study, the differences between $\log(K_{lipw})$ and $\log(K_{ow})$ does exceed SD and MAE (the value NN3). Among those NN3 there are just 6 compounds for which the difference is greater than 1 log unit. All these observations support our point that the values of ΔG_{part} for the case of octanol-water and liposome – water systems are not significantly different.

Data presented in Table 2 suggest that in accordance with the above discussion, experimentally measured $\log(K_{lipw})$ values are slightly larger than experimentally measured $\log(K_{ow})$. The same situation is observed for the “energetic-like” compounds which have similar chemical structure among hydrophobic and relatively hydrophobic compounds (Tables S5) as investigated in the current work and analyzed in Table 1. Experimentally measured and computationally predicted

log(K_{lipw}) are in quite satisfactory agreement (Table 2). The largest deviation is observed for TNB (0.83 log. unit) and 2,4-DNP (0.67 log.unit). Based on these findings, it appears that TNT, 2,4DNT, 2,6DNT, DNAN, 2M5NP, TNB, 2,4-DNP belong to a class of hydrophobic like substances with a moderate ability to penetrate into a biological membrane. Moreover, such penetration ability into a biological membrane will be slightly larger than into octanol.

It is always tempting to apply Van't Hoff equation to computationally obtained set of log(K_{ow}) and log(K_{lipw}) values calculated at different temperatures. Such analysis has been performed and described in the section "Application of Van't Hoff equation" of supplementary materials. According to that analysis we expect that COSMO-RS level computed values of enthalpy and entropy that characterize the partition between phases are less accurate than the resulted Gibbs free energies of partition. Therefore, only quantitative conclusions are possible. In case of water–octanol partition we believe, that both enthalpy and entropic terms contribute to the values of Gibbs free energy of partition. In contrast, the penetration of considered energetic compounds into POPC phase is governed mostly by enthalpy contributions (see section "Application of Van't Hoff equation" in supplementary materials).

4. Conclusion

We have presented thermodynamic analysis of the nature of driving forces in water-octanol and water–liposome systems. Based on performed analysis and a statistical treatment of data available from literature we were able to reveal distinctions in character of driving forces that govern penetration of considered environmental contaminants from water bulk into octanol and from water bulk into liposome. In spite of those distinctions, it was concluded that driving force

that characterizes octanol-water partition is of the same order of magnitude as the one that characterizes partitioning between water and liposome. This means also that the values of $\log(K_{ow})$ and $\log(K_{lipw})$ are of the same order of magnitude. This finding has been confirmed by the comparison of computationally and experimentally obtained values of $\log(K_{ow})$ with the values of $\log(K_{lipw})$, also obtained computationally and experimentally. Based on the analysis one may conclude that trinitrotoluene, 2,4-dinitrotoluene, 2,6-dinitrotoluene, 2,4-dinitroanisole, 2-methoxy-5-nitrophenol, 2,4,6-trinitrobenzene, and 2,4-dinitrophenol belong to a class of hydrophobic chemicals with a moderate ability to penetrate into biological membrane and such penetration is greater into a biological membrane than into octanol.

Figure 1. Schematic representation of structural differences between octanol/water and liposome/water phases

TABLES

Table 1. Selected statistical parameters for treatment of data based on available from (Endo et al., 2011)

Type of compounds	N ^a	R ^{2b}	MAE ^c	SD ^d	NN1 ^e	NN2 ^f	NN3 ^g
All	155	0.95	0.36	0.43	100	55	50
Hydrophilic -3 <K _{ow} < 1	18	0.75	0.37	0.27	9	9	7
Hydrophobic(all) 1 <K _{ow} < 7	137	0.77	0.37	0.43	91	46	45
Relatively hydrophobic 1 <K _{ow} < 4	93	0.74	0.33	0.39	62	31	30
Strongly hydrophobic 4 <K _{ow} < 7	44	0.82	0.43	0.48	29	15	18
Energetic-like x <K _{ow} < y	10	0.27	0.51	0.28	9	1	7

^aN - total amount of the chemicals

^bR² - correlation coefficient of the regression equation $K_{lipw} = aK_{ow} + b$

^cMAE - Mean Absolute Error

^dSD – standard deviation

^eNN1 - amount of the compounds with log(K_{lipw}) greater than log(K_{ow})

^fNN2 - amount of the compounds with log(K_{ow}) greater than log(K_{lipw})

^gNN3 – amount of the compounds with NN1 and NN2 greater than SD

Table 2. Experimentally measured and computationally predicted log(K_{lipw}) and log(K_{ow}) partition coefficients values for compounds in the study

Compound	Log(K _{lipw})		Log(K _{ow})				
	Exper.	COSMO-mic	Exper.	EPI Suite ^{a[28]}	ACD ^{a[29]}	ChemAxon ^{a[30]}	COSMO-RS
TNT	2.18	2.79	1.6 - 2.2 ^a	1.99	1.59	2.31	2.10
2,4-DNT	2.41	2.38	1.85 - 2.0 ^b	2.18	2.08	2.37	1.71
2,6-DNT	2.64	2.26	1.83 - 2.1 ^c	2.18	1.98	2.37	1.70
DNAN	2.17	2.03	1.60 ^d	1.71	1.65	1.7	1.12
2M5NP	2.3	2.03	n/a	2.46	1.91	1.45	1.37
TNB	1.73	2.56	1.18 ^e	1.45	1.22	1.79	1.62
2,4-DNP	1.6	2.27	1.67 ^f	1.73	1.74	1.55	1.67

^a (Jenkins, 1989)

^b (Hansch and Leo, 1979)

^c (Jenkins, 1989)

^d (Boddu and Redner, 2010)

^e (Hansch and Leo, 1979)

315 ^f(Hansch et al., 1995)
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