

**CALCULATION OF OCTANOL/WATER PARTITION COEFFICIENTS  
USING A QUANTUM MECHANICAL – CONTINUUM SOLVENT  
MODEL FOR SOLVATION**

Valentin Gogonea\*

152 Davey Laboratory, Department of Chemistry, Penn State University, University Park, PA  
16802, USA

Dan Ciubotariu\*

Department of Organic Chemistry, Faculty of Pharmacy, University of Medicine and  
Pharmacy, P-ta Eftimie Murgu No. 2, 1900 Timisoara, ROMANIA

Camelia Baleanu–Gogonea

Department of Biochemistry and Molecular Biology, South-Frear Lab, Pennsylvania State  
University, University Park, PA 16802, USA

Ciprian Ciubotariu

Department of Computer Sciences, Faculty of Automation and Computer Sciences, Technical  
University "Politehnica", Str. V. Parvan No. 2, 1900 Timisoara, ROMANIA

## ABSTRACT

The partition of a chemical compound between lipophilic membranes or tissues and aqueous phase of living organisms is often modeled by the 1-octanol/water partition coefficient ( $\log K_{ow}$ ). However, due to experimental difficulties, some theoretical methods for estimation of  $\log K_{ow}$  on the basis of molecular structure have been developed.

In this paper we present a new method for prediction of octanol/water partition coefficients from calculated solvation free energy in octanol and water, taking into account the fine details of molecular structure. A program that combines the semi-empirical quantum method AM1 with the Poisson – Boltzmann equation, performs the calculation. This methodology was applied to the calculation of  $\log K_{ow}$  for a set of twelve chlorinated benzene derivatives. The obtained results are in good agreement with the experimental values. Hence, the method can be used to evaluate the  $\log K_{ow}$  values with higher accuracy for both known and novel compounds.

## INTRODUCTION

The biochemical interactions in the living cell occur in both aqueous and hydrophobic media (e.g. coupling to an active site of an enzyme, transport through a biomembrane).<sup>1</sup> In addition, other pharmaco-kinetic properties are related to the difference in solubility of bioactive molecules in aqueous and organic solvents.<sup>2,3</sup> Hence, it is important to properly account for the solute interactions with both aqueous and organic media. The partition of chemical compounds between organic and aqueous phases is often modeled by the octanol/water partition coefficient ( $\log K_{ow}$ ),<sup>4</sup> because it is assumed that octanol may reflect lipid tissues in living organisms.  $K_{ow}$  has been successfully related to bioconcentration factors, soil and sediment sorption partition coefficients and to toxicity of organic chemicals towards several aquatic organisms.<sup>5-10</sup> Direct measurement of  $K_{ow}$  through means of the shake-flask procedure yields only reliable data for chemicals with  $\log K_{ow}$  less than 4-5.<sup>11,12</sup>  $K_{ow}$  of more hydrophobic substances can be measured by either the generator-column method<sup>13-15</sup> or by slow-stirring technique.<sup>12,16,17</sup> In addition, to these direct approaches to the determination of  $K_{ow}$ , several other methods were employed: (a) calculation based on molecular fragments additivity,<sup>18,19</sup> (b) correlation with capacity factors on reversed-phase HPLC,<sup>20-22</sup> (c) correlation with molecular descriptors (volume, surface area, molar refraction, parachor, molecular weight),<sup>23-26</sup> and (d) correlation with molar volume and solvatochromic parameters.<sup>27-29</sup>

The partitioning of a hydrophobic solute between octanol and water is due to the difference between the interactions that solute is experiencing in water versus octanol.<sup>30</sup> Hence, the relationship between water solubility and  $K_{ow}$  (Hansch et al.<sup>31</sup>) has been studied extensively over the last two decades.<sup>23,30</sup> Examples of such correlation have been published for halogenated benzene,<sup>32</sup> aromatic hydrocarbons,<sup>32</sup> aldehydes, esters and alcohols.<sup>15</sup> However, due to experimental difficulties, few accurate data for compounds with  $\log K_{ow}$  greater than 6 have been reported, which limits the use of such correlation for prediction purposes. The correlation between  $\log K_{ow}$  and molecular volume or surface area is based on the idea that the partitioning of a hydrophobic solute between water and octanol is determined by the difference in solvation free energy in the two media.<sup>25,26</sup> A large part of the solvation free energy is the free energy of cavity formation, which is related with the size (volume, surface area) and the shape of the molecule,<sup>34</sup> hence for non-polar molecules a relationship between size descriptors and solvation free energy seems to be adequate and these kind of relationships were used extensively.<sup>23,30</sup> For polar compounds the solvation free energy depends strongly also on solute-solvent electrostatic interactions. Taft and coworkers have shown that aqueous solubility and octanol/water partition coefficient can be well described by linear correlation with three types of terms which measure cavity size, solute polarity/polarizability and hydrogen bond donor/acceptor character.<sup>27,28</sup>

## METHOD

The novelty in our method is in the use of a quantum mechanical (semiempirical) continuum solvation approach for calculating octanol/water partition coefficients as opposed to traditional methods that use group increments. The continuum description of the solvent (water or octanol) is achieved by the use of the Poisson-Boltzmann equation for calculating the electrostatic potential.

The octanol/water partition coefficient of a solute is related with the free energy of transfer,  $G_{tr}$ , from water to octanol as follows:<sup>35</sup>

$$\Delta G_{tr} = G_{so} - G_{sw} = -RT \ln K_{ow} \quad (1)$$

where  $G_{so}$  and  $G_{sw}$  are the solvation free energies of the solute in octanol and water, respectively.  $R$  is the gas constant and  $T$  the absolute temperature.

The solvation free energy  $G_s$  of a solute in an arbitrary solvent can be written as a sum of three terms:<sup>36</sup>

$$G_s = G_c + G_{vdw} + G_{el} \quad (2)$$

$G_c$  is the free energy required to build a cavity in solvent, of appropriate size to accommodate the solute, and  $G_{vdw}$  and  $G_{el}$  are the free energies due to solvent-solute van der Waals and electrostatic interactions.<sup>36</sup> The solvent-solute electrostatic interaction free energy contains contributions from solvent polarization due to the electric field generated by solute electronic structure (the reaction field<sup>37</sup>), and solute polarization,<sup>38</sup> i.e. the change in solute electronic structure due to solvent polarization. Solvent polarization is usually accounted for by means of the Poisson-Boltzmann equation (the linear form):<sup>39</sup>

$$\nabla \cdot [\epsilon(\mathbf{r})\nabla\phi(\mathbf{r})] - \kappa^2(\mathbf{r})\phi(\mathbf{r}) = -4\pi\rho(\mathbf{r}) \quad (3)$$

where  $\phi$  is the electrostatic potential (due to solute charge density and solvent reaction field) at position  $\mathbf{r}$ ,  $\epsilon$  solvent dielectric constant,  $\kappa$  the Debye-Hückel (ionic) parameter and  $\rho$  solute charge density. Poisson-Boltzmann equation is obtained from the Poisson equation for a charge distribution in vacuum by the addition of a linear term in the electrostatic potential coming from Debye-Hückel theory of ionic solutions. Thus, Poisson-Boltzmann equation relates the electrostatic potential with its sources: the solute charge density  $\rho$  and the ionic strength (included in  $\kappa$ ). This differential equation is solved for charge distributions embedded in cavities with irregular shapes (molecules) using numerical methods (e.g. the finite difference<sup>47</sup> or boundary element methods<sup>48</sup>). We used in these calculations our implementation of the boundary element method.<sup>49</sup> The solvation free energy part due to solvent polarization is obtained from solute electrostatic potential as follows:

$$G_{RF} = \frac{1}{2} \int_V \rho(\mathbf{r})\phi(\mathbf{r})d\mathbf{r} \quad (4)$$

In the case of polar solvents, solvent dipoles orient themselves in the electric field generated by solute charge density and this creates a reaction field, which acts back on the solute.  $G_{RF}$  is the free energy due to the interaction between the reaction field and solute charge density.

When solvent is described as a dielectric continuum,  $G_{dij}$  in eq. 2 is  $G_{RF}$ .  $V$  is the volume filled by solute charge density  $\rho$ . Alternatively,  $G_{RF}$  can be calculated by using a surface charge density located at the dielectric interface, instead of the electrostatic potential  $\phi$ . In this case the volume integral in eq. 4 reduces to a surface integral (over the dielectric interface). The surface charge density can be obtained either from the normal component of the electric field ( $-\nabla\phi$ ) or directly by using the boundary element method.<sup>48</sup> Solute polarization can be taken into account only if the solute is described quantum mechanically. In this case, solute polarization free energy is obtained as the difference in solute free energies in gas phase with and without the effect of the reaction field.<sup>40</sup>

The free energies due to cavity formation,  $G_c$ , and solvent-solute dispersion interactions,  $G_{vdw}$ , can be in principle calculated separately, but it is customary to evaluate their sum (called the non-polar term  $G_{np}$ ) as a function of solvent-accessible surface area:<sup>41</sup>

$$G_{np} = G_c + G_{vdw} = \sum_i \tau_i A_i \quad (5)$$

where  $A_i$  is the solvent-accessible surface area, and  $\tau_i$  the surface tension parameter of atom  $i$ .  $A_i$  was obtained using Connolly's program for calculating surface area.<sup>50</sup> For the evaluation of solvation free energies in water and octanol we used only one surface tension parameter per solvent. The surface tension parameter for water was obtained by linear regression. The regression line was obtained by using the solvent-accessible surface area and the water solubility of a set of 34 alkanes.<sup>40</sup> The surface tension parameter for octanol was obtained from the correlation of solvent-accessible surface area of polychlorinated benzenes (Table 1) with their 'experimental' non-polar free energies (obtained from their solvation free energies in octanol). We use eq. 4 to calculate the solute-octanol electrostatic interaction (with octanol dielectric constant in eq. 3) for the set of polychlorinated benzenes and extracted this quantity from the solvation free energy in octanol. Thus we were left with the nonpolar part (eq. 2). The nonpolar interaction free energies obtained in this way were used to obtain by linear regression the surface tension for octanol. The quotation marks on experimental non-polar free energies refers to the way these quantities were obtained, i.e. by combining experimental and calculated quantities.

The polarization of solute under the reaction field of solvent is taken into account by using a quantum mechanical description of the solute. We use a semiempirical Hamiltonian (AM1) because it was shown previously that this Hamiltonian in combination with CM1<sup>43</sup> charges gives good solvation free energies.<sup>42</sup> The AM1 semiempirical Hamiltonian<sup>45</sup> is of MNDO type<sup>46</sup> (modified neglect of the differential overlap) and can be found in popular quantum mechanical programs as Gaussian and MOPAC.

## RESULTS AND DISCUSSION

We exemplify further the calculation of octanol/water partition coefficient by applying the methodology described above to the calculation of  $\log K_{ow}$  for a set of twelve chlorinated benzene derivatives. The calculations were performed with a program which combines the semi-empirical quantum mechanical Hamiltonian AM1 with the Poisson-Boltzmann equation.<sup>42</sup>

**Table 1.** Octanol/Water Partition Coefficients for Polychlorinated Benzene Derivatives Calculated by a Combined Semi-empirical Poisson-Boltzmann Equation Method.

Compound <sup>1</sup>	Water			Octanol			Log $K_{ow}$	
	$G_{el}$	$G_{sp}$	$G_s$	$G_{el}$	$G_{sp}^2$	$G_s$	Calc. <sup>3</sup>	Exp. <sup>4</sup>
benzene	-4.27	2.27	-2.00	-3.49	-1.45	-4.94	2.154	2.186
chlorobenzene	-4.30	2.41	-1.89	-3.46	-2.17	-5.63	2.745	2.898
1,2-dichlorobenzene	-4.28	2.53	-1.76	-3.44	-2.80	-6.24	3.288	3.433
1,3-dichlorobenzene	-3.78	2.55	-1.23	-3.03	-2.89	-5.92	3.439	3.525
1,4-dichlorobenzene	-3.80	2.55	-1.25	-3.05	-2.89	-5.94	3.440	3.444
1,2,3-trichlorobenzene	-3.73	2.65	-1.08	-2.97	-3.42	-6.39	3.895	4.139
1,2,4-trichlorobenzene	-3.29	2.67	-0.63	-2.64	-3.52	-6.16	4.057	4.050
1,3,5-trichlorobenzene	-2.63	2.68	0.05	-2.10	-3.61	-5.71	4.222	4.189
1,2,3,4-tetrahalorobenzene	-2.83	2.77	-0.06	-2.26	-4.05	-6.31	4.583	4.635
1,2,3,5-tetrahalorobenzene	-2.22	2.79	0.57	-1.76	-4.14	-5.90	4.746	4.658
1,2,4,5-tetrahalorobenzene	-2.33	2.79	0.46	-1.86	-4.15	-6.01	4.746	4.604
pentachlorobenzene	-1.42	2.89	1.47	-1.12	-4.66	-5.78	5.322	5.183
hexachlorobenzene	-0.23	2.99	2.76	-0.18	-5.18	-5.36	5.960	5.731

<sup>1</sup> The geometry was optimized at semi-empirical level (AM1) in gas phase. The free energy entries are in Kcal/mol.

<sup>2</sup> Calculated from the correlation of solvent-accessible surface area and the difference between experimental solvation free energy in octanol and the electrostatic free energy evaluated as described in text.

<sup>3</sup> Using eq. 1 (see text).

<sup>4</sup> Low stirring data from Brujin et al.<sup>12</sup>

Table 1 shows both experimental (obtained from low stirring data<sup>12</sup>) and calculated octanol/water partition coefficients for chlorinated benzene derivatives. The considered temperature is 298K, which makes the RT factor about 0.59 Kcal/mol. This together with the conversion factor from natural logarithm to the logarithm to base ten should give the values for  $\log K_{ow}$  listed in Table 1. The comparison of the two sets of partition coefficients (calculated and experimental) indicates a good agreement between theory and experiment. The largest deviation from experimental values were found for 1,2,3-trichlorobenzene (0.244) and hexachlorobenzene (-0.229), which corresponds to a difference in solvation free energy of about 0.3 Kcal/mol. This difference is in the range of the average error in calculating solvation free energies for the nowadays state of the art programs,<sup>43</sup> and indicates the accuracy that can be achieved in evaluating partition coefficients too.

Thus, it is possible to evaluate with good accuracy the partition coefficients of some compounds from calculated solvation free energies in octanol and water.

## CONCLUSIONS

This 'computational direct' method for the calculation of octanol/water partition coefficients can be refined systematically by improving the methods used to evaluate each term in solvation free energy and extending the set of compounds used in derivation the surface tension parameter for octanol. The method may be expected to obtain higher accuracy in calculating partition coefficients for already know chemical, and might be used also in predicting partition coefficients for novel compounds. Its strength stems from the fact that it takes into account the fine details of molecular structure including the quantum mechanical description of the solute.

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