Theoretical interpretation of interphase partition of the series of polychlorinated biphenyls

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Dedicated to Professor L. Valko, DrSc., in honour of his 60th birthday

For the series of 15 derivatives of polychlorinated biphenyls the Gibbs energies of solvation ΔG in water and octanol were calculated using the polarizable continuum method. Using these values the Gibbs energies of interphase partition ΔG_{part} were expressed which then were correlated with experimental constants of $\log P$. The statistically significant correlation equations between the calculated and experimental data have been obtained indicating that the used method describes qualitatively correctly the physical nature of the studied properties of substances. On the basis of ΔG_{part} calculations, by this procedure it is at the same time possible to predict the $\log P$ values for those PCB derivatives for which these values are not known.

Провелись расчеты сольватационных Гиббсовых энергий ΔG для серии 15-ти производных полихлорированных бифенилов в воде и октаноле методом поляризованной непрерывности. Из этих данных получились величины Гиббсовых энергий для межфазового распределения ΔG_{part}, которые сопоставлялись с экспериментальными величинами $\log P$. Получились статистически значительные корреляционные уравнения между вычисленными и экспериментальными данными, которые показывают, что применен метод качественно правильно улавливает физическую основу изученных свойств веществ. Этим ходом можно одновременно на основании расчетов ΔG_{part} предсказать величины $\log P$ для этих производных ПХБ, для которых эти величины неизвестные.

Many studies in the field of quantitative relationships between structure and biological activity (QSAR) prove that one of the most significant physical properties of compounds which influences their biological activity is the lipophilicity. In the QSAR studies the lipophilicity is largely expressed in terms of the logarithm of the partition coefficient ($\log P$) in the 1-octanol—water system which is the most suitable reference system for organic and aqueous biophase. Experimentally the partition coefficient is most frequently expressed spectrophotometrically. To determine $\log P$ the retention characteristics are also used measured by chromatographic methods mainly by the high-performance liquid

chromatography on the reversed phases (RPLC) [1] but also by thin-layer and gas chromatographies, respectively.

Between the logarithm of the capacity factor of organic substances and the partition coefficient $\log P$ there exists the relationship [2, 3]

$$\log k' = \log P + \log (V_s/V_m) \tag{1}$$

where k' is the capacity factor expressed from the retention time t_R and dead time t_M $(k' = (t_R - t_M)/t_M)$, P is the partition coefficient of the substance in the given chromatographic distribution system and V_s/V_m is the ratio of volumes of the stationary and mobile phases. Under the assumption that eqn (1) is valid $\log P$ can be expressed [2, 3]

$$\log P^{o/w} = a \log k' + b \tag{2}$$

In many cases there was really found the linear relationship between $\log P$ and the capacity factor k', which was used to determine the $\log P$ values [4, 5]. The determination of $\log P$ especially on the C_{18} chemically bonded phases (RPLC) is at present the object of intensive studies of several authors [1, 6—9].

In the experimental determination of the partition coefficients certain difficulties may occur in some cases mainly with the reactive or unstable compounds, respectively. Moreover, for the applications in QSAR and in other fields it is necessary to know $\log P$ for hypothetical (not yet synthesized) compounds. Due to these as well as other reasons the endeavour is parallelly developed to express the partition coefficients in terms of theoretical or empirical approaches, respectively.

At present two empirical approaches are used how to express $\log P^{o/w}$ or lipophilicity, respectively, in terms of empirical constants:

a) the original Hansch system [10—12] according to which the lipophilic parameter π is defined as follows

$$\pi = \log P_X - \log P_H \tag{3}$$

where P_X and P_H are the partition coefficients of the substituted and nonsubstituted molecule, respectively. The problem of the $\log P$ calculation is then reduced to the determination of some additive values in the equation

$$\log P = \sum_i^n \pi_i \tag{4}$$

Within the framework of this approach the molecule is divided into n parts the substituting effects of which in a group of related compounds are evaluated by π_i constants.

b) the fragment method by *Nyss* and *Rekker* [12, 13] where the so-called fragment constants f are defined by the equation

$$\log P = \sum_n a_n f_n \tag{5}$$

where f_n is the n-th fragment contribution to the $\log P$ value, a_n is the multiplicity of the fragment in molecule. The fragment approach was then precised by *Hansch* [14, 15] where besides the fragment constants also fragment factors F have been introduced so that $\log P$ is expressed by the sum a_i of fragment constants f_i and b_j of the fragment factors F_j in this case

$$\log P = \sum_i^n a_i f_i + \sum_j^m b_j F_j \tag{6}$$

Chou and *Jurs* [16] automated the fragment approach considering all accessible fragment constants and fragment factors. In the practical use of these methods some difficulties have occurred. For certain functional groups these approaches are unreliable, further in certain cases the division of the molecule into the fragments is not unambiguous, which causes different values of $\log P$. Serious lack in some cases may be the fact that different kinds of intramolecular interactions (*e.g.* the dipole ones, redistribution of electron density, *etc.*) cannot be considered here.

Klopman and *Iroff* [17, 18] have proposed another approximation where the specificity of the given molecular structure is considered by the help of charge densities on the atoms in the $\log P$ calculation. In this method the simple solvation model is used to obtain the semiempirical equation for $\log P$ in the form

$$\log P = \sum_i p_i + \sum_i p_i' q_i + \sum_i p_i'' q_i^2 \tag{7}$$

where p_i, p_i', p_i'' are the empirical parameters characterizing the given i-th atom and q_i are the charge densities corresponding with the given state of the atom in the molecule.

Moriguchi [19] parametrized the lipophilicity by the help of constants which are connected with the molecule volume (*e.g.* with the Exner and van der Waals molar volume, molar refractivity, *etc.*). Also high linear correlation of the connectivity index [20] with $\log P$ especially in the homogeneous series of substances was found. *Dunn et al.* [21] assume that the molecule size represented

by its isotropic surface area is the main factor influencing $\log P$ (about 80 %).

The physically well-founded theoretical procedure how to express $\log P$ must start from the knowledge of the Gibbs energy of partition $\Delta G_{part}^{1/2}$ between the phases 1 and 2

$$\log P^{1/2} = -\frac{1}{2.303\,RT}(\Delta G^1 - \Delta G^2) = -\frac{1}{2.303\,RT}\Delta G_{part}^{1/2} \qquad (8)$$

The values ΔG^1 and ΔG^2 are, actually, the Gibbs energies of solvation in the solvent 1 and 2, respectively.

Cammarata and *Rogers* [22] attempted as the first such theoretical estimation of $\log P$. For the calculation of changes of Gibbs energy of the distribution process they have used the quantum-chemical procedure. They, however, have used very approximative estimation of the solvation energy. Within the perturbation theory they expressed the difference between the electrostatic contributions of the solvation energy without considering the dispersion-repulsion and cavitation contribution. Similar approach was used also by *Hopfinger* and *Battershell* [23] who have used the so-called solvent conformational analysis for the estimation of solvation energy.

Záhradník et al. [24] have made the direct calculation of the partition coefficient by the help of discrete model for methane in the water—CCl_4 system where the enthalpic changes were expressed quantum-chemically as the interaction and cavitation energies, respectively. For the determination of entropic changes the statistical thermodynamics was used. In the discrete models the problem remains where and how many solvent molecules are to be located in the solvation calculation. In the case of large solvent molecules the enormous computer demands prevent practical applications.

In expressing the individual contributions of the Gibbs energy of solvation there were used different simplifications. For this reason it is necessary to elaborate a more precise method of the $\log P$ calculation, which is the aim of the present work. The proposed method is based on the as precise expression of all contributions of the Gibbs energy of solvation in both phases within the framework of continuum model as possible.

The calculated energetic contributions in both phases are further correlated by the method of regression analysis with the experimental $\log P^{o/w}$ values. The obtained correlation equations may be used to predict the $\log P^{o/w}$ values. We have studied the series of 15 polychlorinated biphenyls (PCB). The experimental data of the partition coefficients $\log P$ in the octanol—water system were taken from the review article by *Shiu* and *Mackay* [25]. On the basis of the obtained correlations we further want to assess the ability of the prediction of $\log P$ by

our method for further chosen, till now unmeasured $\log P$ of the PCB derivatives.

Method and calculations

The partition coefficient $\log P$ characterizing the partition between both phases may be referred to the Gibbs energy of partition according to eqn (9). The Gibbs energy may be determined as the difference between the Gibbs energies of solvation in the solvent 1 (octanol) and solvent 2 (water)

$$\Delta G_{\text{part}}^{1/2} = \Delta G_{\text{solv}}^1 - \Delta G_{\text{solv}}^2 \tag{9}$$

There exist different approaches to the calculation of the Gibbs energies of solvation [26, 27]. Recently we have proposed the method for the calculation of the Gibbs energy of solvation [28—32] based on the polarizable continuum model.

In the continuum model the Gibbs energy of solvation may be generally expressed as the sum of electrostatic dispersion-repulsion and cavitation contributions

$$\Delta G = \Delta G_{\text{elst}} + \Delta G_{\text{dr}} + \Delta G_{\text{cav}} \tag{10}$$

The final form of the Gibbs energy of distribution between two phases (1 and 2) is thus as follows

$$\Delta G_{\text{part}}^{1/2} = (\Delta G_{\text{elst}}^1 - \Delta G_{\text{elst}}^2) + (\Delta G_{\text{dr}}^1 - \Delta G_{\text{dr}}^2) + (\Delta G_{\text{cav}}^1 - \Delta G_{\text{cav}}^2) \tag{11}$$

Details relating to the individual contributions may be found in Ref. [31].

For the calculation of the electrostatic contribution we have used two modifications:

a) Coulombic part of the electrostatic contribution ($\Delta G_{\text{elst}} \approx \Delta G_{\text{coul}}$) was expressed according to the equation by Jano modified in Ref. [33]. For the calculation of charges on the individual atoms the CNDO/2 method was used.

b) The more exact way how to express ΔG_{elst} is offered by the method of the polarizable continuum. The details on the calculation are presented in Refs. [28—32]. In our present work the modification of the method denoted as CNDO/2 GP III and described in Ref. [34] was used for the ΔG_{elst} calculation.

The dispersion and repulsion contribution ΔG_{dr} was expressed by the method reported in Ref. [31]. The cavitation contribution may be expressed by the help of two methods, i.e. by those of Sinanoglu [35] and Pierotti [36, 37].

In the present work both methods are used (the values are denoted by the indices S and P, respectively). Details on the modification of the Pierotti method are presented in Ref. [31].

For the calculations in water and octanol we used the following parameters: relative permittivity $\varepsilon_{r,w} = 80.0$, $\varepsilon_{r,oct} = 10.3$; polarizability $\alpha_w = 1.49\,\text{Å}^3$, $\alpha_{oct} = 16.2\,\text{Å}^3$. The atomic polarizabilities were taken from Ref. [38]. The standard geometries of PCB molecules were taken from the data of the paper [39]. For the series of all 15 PCB's a uniform torsion angle $\Theta = 60°$ was chosen since the results for optimum angles are very similar.

Results and discussion

We have calculated the individual contributions of the solvation energy for the series of 15 PCB's in water and octanol, respectively. The values of the individual contributions of the Gibbs energy of solvation in water and octanol are presented in Tables 1—3. At the same time, the $\Delta G_{elst,G}$ values were calculated from the model of a polarizable continuum. The values are greater in comparison with those of ΔG_{elst} (in the absolute value), which is natural because besides the coulombic also the polarization contribution is included into these values. These values are presented in Table 1.

Table 1

Calculated values of electrostatic contributions of the Gibbs energy of solvation (kJ mol^{-1}) of PCB derivatives

Compound	Position of substituent	ΔG_{elst}^w	ΔG_{elst}^o	$\Delta G_{elst,G}^w$	$\Delta G_{elst,G}^o$
I	—	− 1.21	− 1.10	− 93.78	− 72.73
II	2	− 10.55	− 9.64	− 129.14	− 109.88
III	2.2'	− 19.72	− 18.04	− 158.61	− 134.69
IV	2.3'	− 19.89	− 18.19	− 165.82	− 140.97
V	2.6	− 18.55	− 16.96	− 156.29	− 131.63
VI	2.5.4'	− 27.43	− 25.08	− 189.62	− 161.46
VII	2.4.4'	− 27.61	− 25.25	− 190.34	− 162.06
VIII	2.3.2'.3'	− 32.61	− 29.82	− 231.99	− 195.13
IX	2.3.2'.5'	− 33.76	− 30.87	− 229.31	− 193.14
X	3.4.3'.4'	− 32.59	− 29.80	− 257.99	− 219.13
XI	2.5.2'.5'	− 34.96	− 31.96	− 226.67	− 191.56
XII	2.5.3'.4'	− 31.65	− 28.94	− 231.87	− 196.45
XIII	2.4.2'.5'	− 35.21	− 32.19	− 228.11	− 192.27
XIV	2.4.2'.4'	− 35.28	− 32.26	− 223.53	− 188.80
XV	2.3.4.2'.5'	− 39.63	− 36.23	− 272.77	− 227.97

Table 2

Calculated values of the dispersion-repulsion and cavitation contributions of the Gibbs energies of solvation (kJ mol^{-1}) of PCB derivatives

Compound	ΔG_{dr}^w	ΔG_{dr}^o	$\Delta G_{cav,S}^w$	$\Delta G_{cav,S}^o$	$\Delta G_{cav,P}^w$	$\Delta G_{cav,P}^o$
I	− 97.23	− 91.62	89.13	33.35	176.57	101.72
II	−116.71	−113.84	94.90	35.11	183.97	106.18
III	−135.86	−135.00	100.56	36.83	191.94	111.00
IV	−140.65	−140.38	102.03	37.28	193.86	112.22
V	−137.92	−137.53	100.65	36.86	191.33	110.64
VI	−162.57	−165.18	109.41	39.53	204.24	118.31
VII	−162.03	−164.69	109.41	39.53	204.24	118.31
VIII	−187.71	−190.99	112.10	40.35	206.40	119.95
IX	−178.86	−183.38	112.92	40.60	207.81	120.79
X	−184.55	−189.57	116.28	41.62	213.87	124.23
XI	−181.46	−186.15	113.87	40.89	209.45	121.66
XII	−184.18	—189.25	115.69	41.44	212.67	123.49
XIII	−180.64	−185.40	113.87	40.89	209.45	121.66
XIV	−179.98	−184.82	113.94	40.91	209.60	121.68
XV	−200.12	−207.17	119.29	42.54	216.41	125.99

Table 3

Calculated values of Gibbs energies of partition (kJ mol^{-1}) between octanol and water and experimental values of log P for the PCB derivatives

Compound	$\Delta G_{part,S}^{o/w}$	$\Delta G_{part,P}^{o/w}$	log $P_{exp}^{o,w}$ [25]
I	− 50.07	− 69.16	3.9 ± 0.2
II	− 56.01	− 74.01	4.3 ± 0.5
III	− 61.18	− 78.38	4.9 ± 0.5
IV	− 62.78	− 79.67	4.8 ± 0.3
V	− 61.82	− 78.72	5.0 ± 0.2
VI	− 70.14	− 84.90	5.7 ± 0.2
VII	− 70.17	− 86.23	5.8 ± 0.2
VIII	− 72.24	− 86.94	5.6 ± 0.3
IX	− 73.95	− 88.64	6.0 ± 0.3
X	− 76.90	− 91.88	6.1 ± 0.4
XI	− 74.68	− 89.49	6.1 ± 0.2
XII	− 76.60	− 91.53	5.9 ± 0.3
XIII	− 74.73	− 89.54	6.1 ± 0.2
XIV	− 74.85	− 89.73	5.9 ± 0.3
XV	− 80.40	− 94.08	6.5 ± 0.4

The polarization contribution may seem to be too great against the coulombic one. This is, however, caused by the fact that in the calculation of $\Delta G_{elst.G}$ the GIPE III version was used which represents the more exact procedure not neglecting the integrals of the CNDO type. (The details see in Ref. [34].)

From the presented values it follows that the individual components are of considerably different size. Similar results were obtained also in the calculation of the contributions of solvation energies for small molecules [31]. However, the values of the electrostatic contribution ΔG_{elst} (in the absolute value) are much less than those of the dispersion-repulsion one. This is associated with small PCB polarity and with the predominance of hydrophobic interactions. As for the dispersion-repulsion contribution ΔG_{dr} we may notice that for PCB with the order number I up to V this is greater in water than in octanol (in the absolute value). On the contrary, for the PCB VI up to XV this is greater in octanol than in water. It means that with the increasing number of chlorine atoms the "hydrophobicity" of molecules increases, herewith the value of the dispersion-repulsion contribution in octanol increases (Table 2).

It is more problematical to express the cavitation contribution. As seen from Table 2 two different approaches offer different values of the cavitation energies. Also other authors [40] have drawn attention to this shortcoming. At the transition from water to octanol the cavitation energy of biphenyl in the Sinanoglu method decreases by $55.78 \text{ kJ mol}^{-1}$ and in the Pierotti one by $74.85 \text{ kJ mol}^{-1}$. With the increasing number of chlorine atoms also the cavitation contribution increases both in water and octanol in both methods. Using the Sinanoglu method the difference in cavitation contribution in water between biphenyl (I) and pentachloro derivative (XV) makes $30.16 \text{ kJ mol}^{-1}$ and that of cavitation contribution in octanol makes 9.19 kJ mol^{-1} (Table 2). Using the Pierotti method the differences in the cavitation contribution are greater, they make for water $39.84 \text{ kJ mol}^{-1}$ and for octanol $24.27 \text{ kJ mol}^{-1}$, respectively. In the final consequence all these effects are qualitatively similar and lead to the better PCB solvation in octanol. At present it is difficult to decide clearly which of the presented methods of the cavitation contribution calculation is accurate in the absolute expression. The decrease in the $\Delta G_{cav.P}$ values according to Pierotti when passing from water to octanol seems to be too great. Moreover this causes that the ΔG_{solv} values are negative both in water and in octanol and are greater (in the absolute value) in octanol. Therefore, it is more important to evaluate relative trends in the change of the Gibbs energy of solvation as well as of its individual contributions.

The differences in the Gibbs energies of solvation $\Delta G_{part.S}^{o,w}$ and $\Delta G_{part.P}^{o,w}$, respectively (Table 3) are both of the same sign (they are negative) and trend. The negative values of the differences in the Gibbs energies of solvation are in accordance with the positive values of $\log P^{o,w}$ of PCB [25]. With the increasing

Table 4

Experimental and theoretically calculated values of log P of PCB derivatives

Compound	log P_{exp} [25]	log P_{calc} (eqn (13))
I	3.9 ± 0.2	3.90
II	4.3 ± 0.5	4.40
III	4.9 ± 0.5	4.84
IV	4.8 ± 0.3	4.97
V	5.0 ± 0.2	4.90
VI	5.7 ± 0.2	5.60
VII	5.8 ± 0.2	5.61
VIII	5.6 ± 0.3	5.76
IX	6.0 ± 0.3	5.93
X	6.1 ± 0.4	6.17
XI	6.1 ± 0.2	6.00
XII	5.9 ± 0.3	6.12
XIII	6.1 ± 0.2	5.85
XIV	5.9 ± 0.3	6.00
XV	6.5 ± 0.4	6.48

Table 5

Prediction of log P values for further PCB derivatives

Position of substituent	$\Delta G^{o/w}_{part,S}$	log P_{exp} [25]	log P_{calc} (eqn (13))
2,4,5	−70.086	5.6 ± 0.3	5.60
2,2′,3,4	−73.853	6.0 ± 0.3	5.92
2,2′,4,5,5	−81.559	6.4 ± 0.5	6.57
2,3′,4,4′,5	−83.192	6.4 ± 0.3	6.71
2,6,3′	−69.182		5.52
2,3,5	−69.285		5.53
2,5,3′	−69.992		5.59
2,3′,4	−70.465		5.63
2,2′,3,6′	−73.161		5.86
2,2′,4,6	−74.086		5.94
2,2′,3,5′	−74.464		5.97
2,2′,4,5	−74.633		5.99
2,2′,3,4′	−74.721		5.99
2,3,3′,4′	−76.071		6.11
2,2′,3,3′,5	−80.794		6.51

number of chlorine atoms in PCB the stabilization in the nonpolar phase increases, which corresponds with the experimental trend of the increase in the log $P^{o/w}$ values.

The relative trends may be assessed best by using linear regression. Thus we have compared theoretically calculated ΔG values of components with the experimental log P values taken from Ref. [25]. For the series of 15 PCB derivatives the following correlations are obtained

$$\log P = -0.085 \, \Delta G^{o/w}_{\text{part,S}} - 0.3574 \qquad (12)$$

$$r = 0.980 \quad n = 15 \quad \text{S.R.} = 328.91 \quad 1 - \alpha > 99.99 \, \%$$

$$\log P = -0.1017 \, \Delta G^{o/w}_{\text{part,P}} - 3.1230 \qquad (13)$$

$$r = 0.983 \quad n = 15 \quad \text{S.R.} = 378.80 \quad 1 - \alpha > 99.99 \, \%$$

It is interesting that somewhat better correlation is obtained when the Pierotti method is used to express the cavitation contribution. The high quality of correlation (represented by the correlation coefficient, regression significance S.R. as well as by the level of statistical significance α) indicates that the formulated theory rightly assesses the reality of experimental conditions. In the case of both correlation eqns (12, 13) the signs in accordance with physical sense of eqn (8) have been obtained.

By using the presented correlation eqns (12, 13) the log $P^{o/w}$ values of the given series of 15 PCB's may be calculated. The calculated log $P^{o/w}_{\text{calc}}$ values are, as a whole, in good accordance with the experimental log $P^{o/w}_{\text{exp}}$ ones within the framework of experimental error of measurement (Table 4).

The obtained equations, however, may also be used for the prediction of the log $P^{o/w}$ partition coefficients for further PCB derivatives which do not belong to the above studied 15 derivatives of PCB. These are the PCB derivatives for which, e.g. the standards are not synthesized or those for which the log $P^{o/w}$ values are not known till now. In principle it would be possible to calculate the log $P^{o/w}$ values for all 209 PCB derivatives.

In Table 5 the predicted log $P^{o/w}$ values of those PCB are presented for which the experimental log $P^{o/w}$ are known as well as the predicted log $P^{o/w}$ ones of those PCB for which the experimental log $P^{o/w}$ values are not known up to now. It would be interesting to measure the log $P^{o/w}$ values of those derivatives and thus to verify the prediction.

Conclusion

In this paper the method of calculation of the interphase partition based on the continuum model of the influence of environment is presented. From the results obtained for the series of 15 PCB's we can conclude that our model may be successfully used for the prediction of logarithms of the partition coefficients log P of further PCB derivatives the total number of which is 209. The advantage of the presented procedure is that it can be used for any hypothetical structures (*e.g.* that of metabolites).

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Translated by S. Miertuš