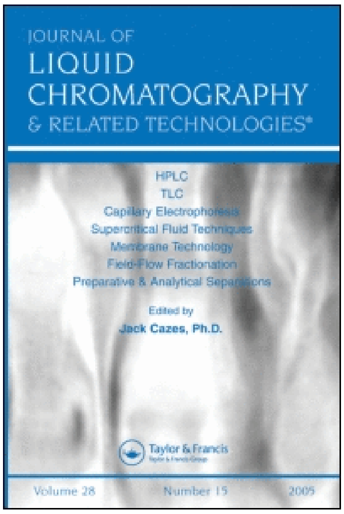

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QUANTITATIVE CORRELATIONS BETWEEN REVERSED-PHASE LC DATA AND MOLECULAR PARAMETERS FOR SOME WEAKLY RELATED PESTICIDES

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☐ *Retention in reversed-phase liquid chromatography for some polar and weakly related pesticides (urea derivatives or containing the thiophosphate group), using two types of stationary phases (C8 and C18), was studied for different compositions of mobile phase in order to estimate extrapolated values of capacity factor for entirely aqueous content of mobile phase. Two organic modifiers were used in composition of mobile phase: methanol or acetonitrile. The inter-correlations between extrapolated values for the two types of stationary phase were very high. The extrapolated values for studied pesticides were correlated by linear and multilinear regressions with molecular parameters, computed by means of different theoretical approaches (PM3 quantum chemical model, and DFT computational scheme). The best correlations were obtained for extrapolated values from retention study using acetonitrile as organic modifier in mobile phase composition.*

Keywords hydrophobicity, linear and multilinear regressions, molecular parameters, pesticides, retention behavior, reversed-phase LC

INTRODUCTION

Reversed-phase liquid chromatography (RP-LC) is still one of the most used mechanisms in separation of multi-component samples, with large applications in environmental monitoring, e.g.,[1–3] Retention in RP-LC depends on a large number of parameters characterizing the structure of analytes (molecular descriptors), stationary, and mobile phases. So far, a

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large number of papers have been focused on retention modeling taking into account experimental parameters assigned to the mobile phase or to the stationary phase.[4] Retention modeling via molecular descriptors is very popular in many applications and known as quantitative retention-structure relationships (QSRR), which may offer useful information in developing analytical procedures based on RP-LC.[5–7] This theoretical approach (QSRR) was already used in data analysis of RP-LC for related compounds,[8–10] but the only in rare cases quantitative correlations have been studied for weakly related pesticides. Therefore, it is the aim of this paper to study the retention behavior of several weakly related pesticides, given by urea derivatives or containing the (thio)phosphate group, on different stationary phases and two organic modifiers in mobile phase composition. The extrapolated values of capacity factor resulted from these retention studies were quantitatively correlated to some molecular descriptors estimated by quantum methods (PM3 quantum chemical model, and DFT computational scheme). The results can be useful in interpreting experimental conditions as well as in predicting the chromatographic behavior of similar compounds, such as degradation products of these pesticides under environmental conditions.

EXPERIMENTAL

Solvents and Chemicals

All pesticides in this study (diuron 99.5%; isoproturon 99.8%; linuron 99.7%; monolinuron 99.9%; propanil 99.7%; dichlorvos 98.8%; fenitrothion 95.4%; coumaphos 99.7%; phoxim 98.8%) were supplied by Riedel-de-Haën (Seelze, Germany) and were used without further purification. Individual stock solutions (500 μg/mL) were prepared by dissolving 25 mg of each compound in 50 mL methanol and were stored at 4°C.

The HPLC-grade methanol (MeOH), acetonitrile (ACN) and water obtained from Merck (Darmstadt, Germany) were used for the preparation of the mobile phases. All the solvents were filtered through a 0.45 μm cellulose filter from Scharlau (Barcelona, Spain) before use.

Uracil (2,4-dihydroxypyrimidine) used to estimate the dead time (t_0) was purchased from Fluka Chemie (Buchs, Switzerland).

Instrumentation

Retention of the selected pesticides was investigated by using an Agilent 1100 LC system equipped with a degasser, quaternary pump, autosampler, column thermostat, and multiple wavelength detector (MWD).

The elutions were performed on two analytical columns: Zorbax Eclipse XDB-C18 (150 mm × 4.6 mm i.d.; 5 µm particle size; double endcapped) and Zorbax Eclipse XDB-C8 (150 mm × 4.6 mm i.d.; 5 µm particle size; double endcapped). The constructive data calculated for these columns are following: volume of mobile phase (V_{mp}), calculated from averaged dead time, is 1.587 mL, while the value of stationary phase (V_{sp}) resulted from difference between geometric column volume and V_{mp}.

System control and data acquisition were achieved by means of a computer equipped with an Agilent ChemStation program. The chromatographic system was operationally qualified before performing this study.

Determination of Retention Parameters

HPLC experiments for estimating dependences of capacity factor for each analyte on mobile phase composition were carried out at 25°C, with a flow-rate of 1 mL/min, under isocratic conditions. The injection volume was 1 µL. Retention data were collected by injecting methanol solutions of single pesticide (50 µg/mL), in duplicate. Detection was achieved at 254 nm. The retention behavior of each analyte was investigated as a function of mobile phase composition, ranging from 30 to 70% (v/v) acetonitrile, and from 50 to 80% (v/v) methanol, respectively, by steps of 2.5%. The dead time (t_0) of the column was determined by injection of uracil-containing solution. Calculation of the capacity factor (k) for each analyte was made according to the relation $k = (t_r - t_0)/t_0$, where t_r represents the absolute retention time of studied analyte.

Computational Methods

Both semiempirical PM3 and a DFT computational scheme were applied in this study. To the PM3 quantum chemical model[11] a SM5.42 solvation model was added,[12] which were also parameterized for P in the frame of the AMSOL program. The DFT calculations were performed in Gaussian 03. After a preliminary conformational search, the complete optimization of the equilibrium geometry was performed for the most stable conformer. Although the widely used PCM solvation model[13] usually gives very good results for the hydration energy,[14] the main problem encountered with the *ab initio* procedure was given by the lack of parameterization for octanol as solvent in Gaussian 03. Octanol can be used with the Onsager model,[15,16] via the dielectric constant, but this model takes into account only the electrostatic component of the solvation energy, entirely neglecting the solute polarization and cavity formation. An alternative was to externally parameterise PCM for octanol, via the dielectric constant (9.86), infinite dielectric constant (3.03), density ($0.823\,\mathrm{g/cm^3}$), and molar volume ($160.8\,\mathrm{cm^3/mol}$). This type of hybrid parameterisation of a solvent has some drawbacks, as it uses some of the internally stored parameters for other solvent.

RESULTS AND DISCUSSIONS

Chromatographic Data Correlations

The dependence of capacity factor (as ten-base logarithm of k) on concentration of organic modifier in mobile phase (C_m) is generally described by the following equation, e.g.,[4–7,10]:

$$\lg k = \sum_{i=0}^{n} \alpha_i C_m^i, \tag{1}$$

which may be of the first order ($i = 1$) or upper orders, mainly of the second order ($i = 2$). This equation allows to determine the parameter α_0, which represents the decimal logarithm of extrapolated value of capacity factor ($\lg k_w$) for a mobile phase consisting in only water ($\alpha_0 = \lg k_w$, for $C_m = 0$). At its turn, this parameter is related to the partition constant of solute between mobile (aqueous phase) and stationary phase (hydrocarbonaceous layer), which is taken in a very good approximation as octanol/water partition coefficient (K_{ow}). The relationship between k_w and K_{ow} is well-known: $K_{ow} = k \cdot V_{mp}/V_{sp}$.

Linear regression ($n = 1$) were applied for the experimental dependences between k and C_m, for both types of stationary phase, and the two organic modifiers used in this study (acetonitrile, and methanol). The regression parameters are given in Table 1, which are characterized by very good correlation coefficients ($r^2 > 0.9900$).

The calculated values for $\lg K_{ow}$ for studied compounds and all experimental sets are given in Table 2 and compared to the values obtained from shake-flask experiments.[17]

Correlations between octanol/water partition coefficients determined from study on C8, denoted by $\lg K_{ow}^{C8}$, and octanol/water partition coefficients determined from study on C18, denoted by $\lg K_{ow}^{C18}$, using acetonitrile as organic modifier, were given by the following equation:

$$\lg K_{ow}^{C18} = 0.9315 \cdot \lg K_{ow}^{C8} + 0.1954 \; (r^2 = 0.9665) \tag{2}$$

In case of methanol as organic modifier, the regression equation for these partition coefficients is following:

$$\lg K_{ow}^{C18} = 1.066 \cdot \lg K_{ow}^{C8} - 0.1607 \; (r^2 = 0.9968) \tag{3}$$

TABLE 1 Linear Regression Parameters for the Dependence lg $k = \alpha_0 + \alpha_1 \cdot C_m$ for C8 and C18 Stationary Phases

	m – ACN			m – MeOH		
Analyte	α_0	α_1	r^2	α_0	α_1	r^2
C8 stationary phase						
Dichlorvos	1.515	−0.029	0.9975	2.359	−0.038	0.9985
Isoproturon	2.103	−0.036	0.9921	2.513	−0.036	0.9986
Diuron	2.114	−0.037	0.9924	2.893	−0.040	0.9988
Monolinuron	2.073	−0.035	0.9942	2.935	−0.040	0.9985
Propanil	2.508	−0.040	0.9932	3.302	−0.043	0.9985
Linuron	2.719	−0.043	0.9936	3.338	−0.043	0.9984
Fenitrothion	2.711	−0.037	0.9957	3.563	−0.047	0.9995
Coumaphos	2.952	−0.037	0.9980	4.481	−0.056	0.9987
Phoxim	3.365	−0.042	0.9945	4.593	−0.057	0.9995
C18 stationary phase						
Dichlorvos	1.615	−0.031	0.9956	2.331	−0.037	0.9962
Isoproturon	2.138	−0.037	0.9926	2.536	−0.036	0.9989
Diuron	2.162	−0.037	0.9930	2.911	−0.040	0.9987
Monolinuron	2.118	−0.035	0.9932	2.963	−0.040	0.9988
Propanil	2.603	−0.042	0.9932	3.320	−0.043	0.9987
Linuron	2.798	−0.043	0.9906	3.325	−0.043	0.9988
Fenitrothion	2.673	−0.034	0.9990	3.649	−0.046	0.9996
Coumaphos	3.145	−0.038	0.9960	4.536	−0.054	0.9994
Phoxim	3.207	−0.040	0.9980	4.794	−0.057	0.9995

In what concerns the correlations between shake-flask experimental values of octanol/water partition coefficients (denoted by $\log K_{ow}^{sh\text{-}fl}$), the following regression equations were obtained:

For acetonitrile:

$$\lg K_{ow}^{C8} = 0.5088 \cdot \lg K_{ow}^{sh\text{-}fl} + 0.739 \ (r^2 = 0.9203) \tag{4}$$

TABLE 2 lg K_{ow} Values Obtained from Extrapolations of Linear Regression Parameters for the Dependence lg $k = \alpha_0 + \alpha_1 \cdot C_m$ for Two Types of Stationary Phase, in Comparison with Experimental Shake-Flasks

		ACN		MeOH	
Analyte	Shake-Flask Values	lg K_{ow} from C8	lg K_{ow} from C18	lg K_{ow} from C8	lg K_{ow} from C18
Dichlorvos	0.706	1.270	1.370	2.114	2.086
Isoproturon	2.319	1.858	1.893	2.268	2.291
Diuron	2.784	1.869	1.917	2.648	2.666
Monolinuron	2.300	1.828	1.873	2.690	2.718
Propanil	3.179	2.263	2.358	3.057	3.075
Linuron	3.201	2.474	2.553	3.093	3.080
Fenitrothion	3.204	2.466	2.428	3.318	3.404
Coumaphos	3.857	2.707	2.900	4.236	4.291
Phoxim	4.390	3.120	2.962	4.348	4.549

$$\lg K_{ow}^{C18} = 0.8733 \cdot \lg K_{ow}^{sh\text{-}fl} + 0.478 \ (r^2 = 0.9056) \qquad (5)$$

For methanol:

$$\lg K_{ow}^{C8} = 1.1656 \cdot \lg K_{ow}^{sh\text{-}fl} + 0.667 \ (r^2 = 0.7743) \qquad (6)$$

$$\lg K_{ow}^{C18} = 1.0745 \cdot \lg K_{ow}^{sh\text{-}fl} + 0.713 \ (r^2 = 0.7785) \qquad (7)$$

Excepting methanol used as organic modifier in our retention study for these pesticide compounds, all cross-correlations between experimental data were very good ($r^2 > 0.9$).

Quantum Computations and Correlations with Extrapolated Chromatographic Data

Linear and multilinear regressions were made to correlate the experimental α_0 parameter with some calculated molecular parameters. For the sake of comparison, the calculated partition coefficient, $\lg K_{ow}$, was also considered. Although it is extensively used and with good results, $\lg K_{ow}$ is a fragment mediated parameter derived from experimental data that does not take into account quantum or conformational effects on the molecule. Only quantum mechanics completely describes the structure of a molecule, characterizing its geometric and electron structure. The idea behind the theoretical part of the present study is to find quantum chemical relevant parameters that can quantitatively describe the retention process and the possibility to correlate theoretical-based results with experimental data. It must be stressed here that the molecules in the studied set are pesticides that belong to different classes of organic compounds, urea derivatives or containing the (thio)phosphate group.

For this reason, the solvation free energy in octanol, $(\Delta G_{sol})_o$, and water, $(\Delta G_{sol})_w$, were calculated by means of computational methods as kcal/mol. The computed parameter

$$\Delta(\Delta G_{sol}) = (\Delta G_{sol})_o - (\Delta G_{sol})_w \qquad (8)$$

having the signification in schema from Fig. 1. The difference of solvation energy, $\Delta(\Delta G_{sol})$, characterises the octanol/water solvation equilibrium and can be linearly correlated with the experimentally determined extrapolated parameter k_w, due to the relationship:

$$\ln K_{ow} = -\Delta(\Delta G_{sol})/RT \qquad (9)$$

In a previous paper, we succeeded to apply a similar equation to correlate ln t_R with the same parameter in the case of compounds from the verapamil class known for their multidrug resistant reversal activity.[18]

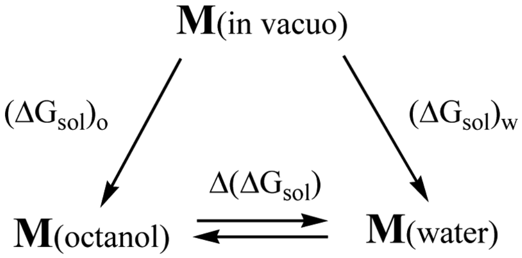


FIGURE 1 Thermodynamic cycle of the solvation processes in octanol (o) and water (w) of the solute molecule (M).

In another paper, a correlation between the experimental log K_{ow} and a theoretical estimate based on $\Delta(HG_{sol})$ was found.[19] Specific interaction through H bond formation with the medium is also implied in the retention process, but continuum solvation models do not take into account the H bond formation tendency of the solvent. We aimed at using a parameter to address this problem. The electrostatic potential, ESP (a.u.), is considered a well suited measure of the H bond acceptor ability of a molecule. Comparing to the atomic charge on the respective heteroatom, it has the advantage that it effectively describes the electrical field with which the H atom interacts in the region in which the interaction occurs. In the recent years, several models that describe the H bond formation ability in terms of the ESP were published.[20–23] Linear correlations between the calculated H bond energy and ESP were found in the literature,[22,23] so there are evidences of proportionality between the tendency of H bond formation and ESP.

Some other parameters were considered too, such as solvent accessible aria ($Å^2$), molecular volume ($Å^3$). The solvent accessible aria is the molecular van der Waals aria spanned by a sphere which represents the solvent molecule. The polar surface ($Å^2$) and polarizability ($Å^3$) were taken from the Chemspider database.[24] The polar surface of a molecule is defined as the surface sum over all polar atoms. Multilinear regressions were checked for intercorrelated parameters and only the uncorrelated ones were considered. The best correlations were obtained for k_w from retentions using acetonitrile as organic modifier, so only these values are further considered.

Figure 2 presents the plot of lg k_w versus lg K_{ow}. A correlation coefficient of 0.8741 is obtained. The value of lg K_{ow} being based on fragment mediated experimental data it describes, apart from the dipolar interactions, some of the H bond interaction. That insures a good correlation with experimental data related to the retention process even for molecules in weakly related classes, as chosen in this study.

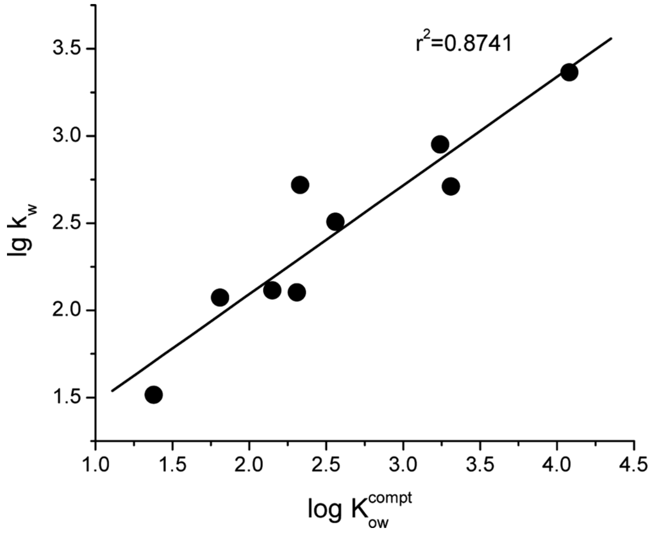


FIGURE 2 Correlation between extrapolated value lg k$_w$ and the calculated partition coefficient ($\log K_{ow}^{compt}$).

The DFT parameters calculated are presented in Table 3. A straightforward correlation between a theoretical parameter and the experimental measured lg k$_w$ can be made on grounds of Eq. (9). It was found that the Onsager model cannot describe properly the partition process (data not shown), meaning that the cavitation-dispersion energy are important terms that cannot be neglected when using solvation data in two different solvents. The linear regression lg $k_w = f(\Delta(\Delta G_{sol}))$ gives a very low correlation coefficient (0.258) for the semiempirical data. For DFT/PCM, r^2 is improved to 0.4762, but if we exclude dichlorvos from correlation, the value of $r^2 = 0.7372$ is obtained (Fig. 3). Obviously, the semiempirical PM3/SM5.42 model does not describe the solvation process in octanol and water properly. First of all, in all the optimized geometries the amide group was non-planar

TABLE 3 DFT Calculated Parameter $\Delta(\Delta G_{sol})$ [kcal/mol], Most Negative ESP [a.u.] and the Group on which it is Located

Pesticide Name	$\Delta(\Delta G_{sol})$	ESP$_1$	Group
Dichlorvos	−9.36	−0.068	P=O
Isoproturon	−6.56	−0.083	C=O
Diuron	−7.52	−0.074	C=O
Monolinuron	−7.72	−0.072	C=O
Propanil	−7.27	−0.073	C=O
Linuron	−8.65	−0.068	C=O
Fenitrothion	−11.62	−0.068	NO$_2$
Coumaphos	−14.56	−0.079	P=S
Phoxim	−13.60	−0.069	CN

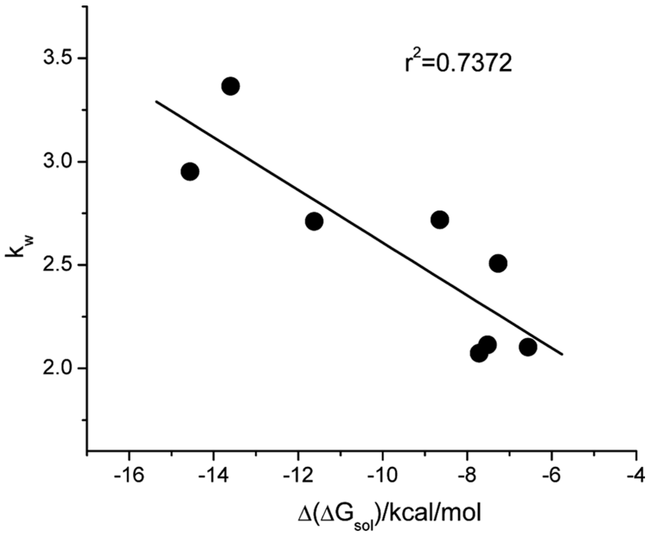


FIGURE 3 Correlation of lg k_w with the calculated $\Delta(\Delta G_{sol})$ with multilinear regressions.

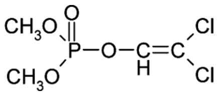
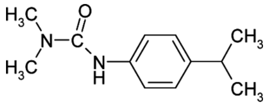
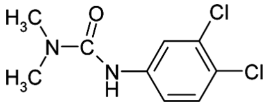
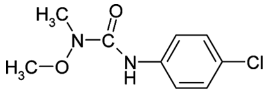
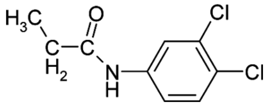
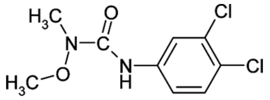
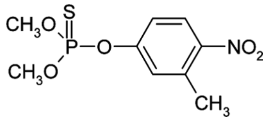
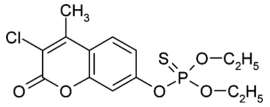
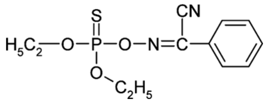
(C-N-C-O dihedral of around 20°), which is not the case for the DFT calculations. Our DFT results are in agreement with HF and MP2 literature data on diuron, which indicate that the most stable isomer is planar.[25] Secondly, the semiempirical methods are known to give large errors in what concerns the net atomic charges, which are very important in the treatment of solvation, especially in the polarisable continuum scheme. Furthermore, the specific interactions are not taken into account. The DFT/PCM model improves the correlation coefficient, but here also the specific interactions are neglected, which can explain the poor correlation.

In order to account for the specific interactions, the calculated ESP was considered, along with $\Delta(\Delta G_{sol})$, in multilinear regressions. As ESP is proportional to the tendency for H bond formation, we focused on the most negative value of the ESP, which indicates the strongest H bond accepting center. In most of the considered molecules, there are more than one negative ESP regions, on other heteroatomic groups such as P=S, Cl, ether groups (see the molecular structure given in Table 4). That means the possibility of more than one H bonds to form. We only took into account the first two most negative ESPs, noted as ESP_1 and ESP_2.

As regards the multilinear regressions with two or three calculated parameters, they give r^2 in the range 0.5–0.9. The best fit of semiempirical data comprises $\Delta(\Delta G_{sol})$, polar surface (S), and the most negative ESP and follows the equation:

$$\lg k_w = 4.993 + 0.0081 \cdot S^{-0.13} \cdot \Delta(\Delta G_{sol}) + 21.348 \cdot ESP_1,\ r^2 = 0.8742 \quad (10)$$

TABLE 4 Identification Data on the Studied Pesticides

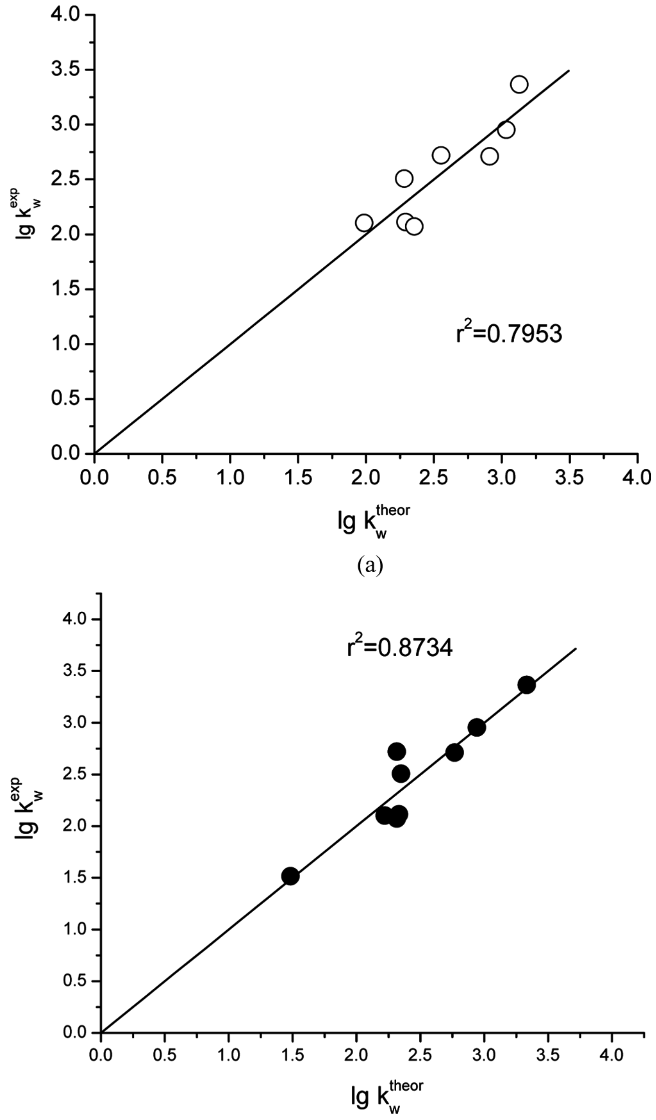
Commercial Name	IUPAC Name and CAS Number	Structure
Dichlorvos	1,1-dichloro-2-dimethoxyphosphoryloxyethene (000062–73-7)	
Isoproturon	3-(4-isopropylphenyl)-1,1-dimethylurea (034123–59-6)	
Diuron	3-(3,4-dichlorophenyl)-1,1-dimethylurea (000330-54-1)	
Monolinuron	3-(4-chlorophenyl)-1-methoxy-1-methylurea (1746-81-2)	
Propanil	3′4′-dichloropropionanilide (000709-98-8)	
Linuron	3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea (000330-55-2)	
Fenitrothion	Dimethoxy-(3-methyl-4-nitro-phenoxy)-sulfanylidene-phosphorane (000122-14-5)	
Coumaphos	3-chloro-7-diethoxyphosphinothioyloxy-4-methyl-chromen-2-one (000056-72-4)	
Phoxim	2(E)-2-diethoxyphosphinothioyloxyimino-2-phenyl-acetonitrile (014816-18-3)	

For DFT data, as S and $\Delta(\Delta G_{sol})$ were found to be inter-correlated, the aforementioned equation could not be considered. The following equations are obtained, but only when dichlorvos is excluded from the data set:

$$\lg k_w = 2.938 - 0.12 \cdot \Delta(\Delta G_{solv}) + 20.98 \cdot ESP_1,\ r^2 = 0.7953 \tag{11}$$

$$\lg k_w = 3.733 - 0.141 \cdot \Delta(\Delta G_{sol}) + 31.105 \cdot ESP_1 + 7.246 \cdot ESP_2,\ r^2 = 0.8734 \tag{12}$$

As it can be seen from the last two equations, the second most negative ESP does not improve the correlation coefficient to a great extent, so it can be concluded that only the stronger of the H bonds plays an important role



(a)

(b)

FIGURE 4 Correlations between the calculated ($\lg k_w^{theor}$) and experimental values ($\lg k_w^{\exp}$) for regressions: (a) using Eq. (11); and (b) using Eq. (12).

in the retention process. In Fig. 4 the correlation between the theoretical and experimental values of parameter lg k_w for Eqs. (11) and (12) are presented.

CONCLUSIONS

The liquid chromatographic behavior of several pesticides belonging to urea derivative class or containing the thiophosphate group was studied under reversed-phase mechanism, using octyl or octadecyl based silica stationary phases. Extrapolated values of capacity factor for mobile phase containing only aqueous component (so-called k_w parameter) were correlated between them or with molecular parameters computed by quantum methods. However, the extrapolated parameter lg k_w was proven to depend on organic modifier added in mobile phase. The best data correlations were obtained when acetonitrile was used as organic modifier in mobile phase composition. To sum up the theoretical part, from a quantum mechanical point of view, the retention process can be described by a parameter that takes into account an implicit manner the different solvation effect in octanol and water and another one that is correlated with the tendency for H bond formation. Thus, both nonspecific and specific interactions are described by the multilinear correlation experimental lg k_w *vs.* the free energy for the octanol-water partition process and the electrostatic potential on H bond acceptor centers in the solute. A way of improving the model is, no doubt, the use of internal parameterization of octanol for PCM, which is not available in Gaussian 03.

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