Prediction of RP-HPLC Log *P* from Semiempirical Molecular Properties of Diphenyl Ether and Phenopylate Herbicides

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The relationships between octanol/water partition coefficients (log *P*) estimated by reversed-phase high-performance liquid chromatography (RP-HPLC) and various bulk and electronic properties, calculated by molecular and quantum mechanics methods, of diphenyl ether (DPE) and phenopylate herbicides were examined. The three molecular parameters, van der Waals volume, dipole moment, and energy of the highest occupied molecular orbital, together accounted for 78–83% of the variation in the log *P* data. On the average, the predicted values using regression equations deviated from the observed values by only 0.13 and 0.19 log unit in DPE and phenopylate classes, respectively. The same three molecular parameters appeared in the model when the structures of two classes of herbicides were included in the regression analysis. This research suggests that one can successfully predict the RP-HPLC partition coefficients from the semiempirical molecular properties calculated from molecular and quantum mechanical techniques. In addition, the RP-HPLC estimated log *P* values and those calculated from the fragment additivity method using the CLOGP computer program were highly correlated (r = 0.91).

INTRODUCTION

The lipophilicity of a bioactive molecule is one of the most important physicochemical properties which influences its capacity to move through biological compartments. The path between the point of application of a xenobiotic molecule to its actual site of action inside the cell involves both aqueous and nonaqueous phases. Highly nonpolar molecules tend to be trapped in the membrane layers, while highly polar structures are repelled by these membranes, thus preventing their entry into them. Therefore, for a successful transport across cellular components the compound must have an optimum lipophilicity.

Lipophilicity is generally defined as the tendency of a chemical to distribute between an immiscible nonpolar solvent and water and is expressed as a logarithm of partition coefficients ($\log_{10} P$). Direct measurement of partition coefficients has been accomplished by means of shake-flask (Leo et al., 1971), generator-column (Woodburn et al., 1984), slow-stirring (Bruijn et al., 1989), and differential scanning calorimetry (Redman-Furey and Antinore, 1991) techniques. These methods are labor intensive and time-consuming. Apart from these direct techniques, several indirect methods have been attempted: estimation by reversed-phase high-performance liquid chromatography (RP-HPLC) (Garst and Wilson, 1984; Lipinski et al., 1991; Demotes-Mainard et al., 1991; Calvino et al., 1991; Galushko et al., 1991), calculation from computer program (CLOGP and CHEMICALC) based on fragment or group additivity models (Hansch and Leo, 1979; Suzuki and Kudo, 1990), and correlations with various molecular parameters such as molar volume and solvatochromatic parameters (Leahy, 1986; Kamlet et al., 1984), aqueous solubility (Miller et al., 1985), molecular surface area, volumes, and weight (Bruijn and Hermens, 1990; Doucette and Andren, 1987; Bodor et al., 1989), solvent-accessible surface area (Dunn et al., 1987), molar polarizability (Lewis, 1989), charge densities (Klopman et al., 1985), and molecular electrostatic potentials (Sasaki et al., 1991).

In RP-HPLC, the stationary phase consists of a nonpolar organic surface layer such as a C_{18} alkyl chain covalently bound to silica particles, whereas the mobile phase consists of water with an organic solvent added as a modifier. Because of the lipophilic nature of the stationary phase, the least polar solutes are retained longer on the column than the polar solutes. Braumann (1986) has drawn an excellent parallel between the mobile phase–stationary phase interface in RP-HPLC and the membrane–water interface in biological systems. The chemically bonded phase in RP-HPLC resembles the ordered array of the membranous hydrocarbon chains of biological systems. Similarly, the residual silanol groups and the adsorbed layer of hydrogen-bonding organic modifiers (e.g., methanol) and water molecules resemble the polar, outer membrane regions. Furthermore, both RP-HPLC and biological systems are dynamic. Thus, the partition coefficient (*P*) determined by the RP-HPLC method may more accurately represent a chemical's true biotransport capability than the *P* measured by octanol/water partitioning methods.

In this paper, we have analyzed the relationships between log *P*, as estimated by the capacity factors (k') on reversed-phase HPLC, of diphenyl ether and phenopylate compounds and their semiempirical molecular properties as calculated from molecular and quantum mechanics computer programs. We have also compared the log *P* values estimated by the RP-HPLC method with those based on the fragment constant model using CLOGP computer software.

MATERIALS AND METHODS

RP-HPLC Log *P*. The RP-HPLC procedure of Ellgehasen et al. (1981) was used for the estimation of partition coefficients of 34 nonionic herbicides (Tables I and II). The RP-HPLC

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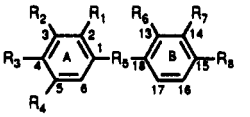
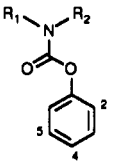
Table I. Structures of Diphenyl Ether Herbicides



compd	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
acifluorfen-Me	Cl	H	CF_3	H	O	H	$COOCH_3$	NO_2
aclonifen	H	H	H	H	O	Cl	NH_2	NO_2
benzofluorfen	Cl	H	CF_3	H	O	H	$COOCH_2COOH$	NO_2
bifenox	Cl	H	Cl	H	O	H	$COOCH_3$	NO_2
fluorodifen	NO_2	H	CF_3	H	O	H	H	NO_2
lactofen	Cl	H	CF_3	H	O	H	$COOCHCH_3COOC_2H_5$	NO_2
MC-15608	Cl	H	CF_3	H	O	H	$COOCH_3$	Cl
MT-124	Cl	H	CF_3	H	O	H		NO_2
nitrofen	Cl	H	Cl	H	O	H	H	NO_2
nitrofluorfen	Cl	H	CF_3	H	O	H	H	NO_2
oxyfluorfen	Cl	H	CF_3	H	O	H	OC_2H_5	NO_2
PPG-1013	Cl	H	CF_3	H	O	H	$CCH_3NOCH_2COOCH_3$	NO_2
RH-0211	H	H	H	H	O	H	H	NO_2
RH-1460	Cl	H	CF_3	H	S	H	$COOCH_3$	NO_2
RH-4638 (*R*)	Cl	H	CF_3	H	O	H	$OCHCH_3COOC_2H_3$	NO_2
RH-4639 (*S*)	Cl	H	CF_3	H	O	H	$OCHCH_3COOC_2H_5$	NO_2
RH-5348	Cl	H	H	CF_3	O	H	$COOCH_3$	NO_2
RH-8378	H	CH_3	H	H	O	H	H	NO_2
RH-8826	Cl	H	CF_3	H	SO_2	H	$COOCH_3$	NO_2
RH-8827	Cl	H	CF_3	H	SO	H	$COOCH_3$	NO_2

Table II. Structures of Phenopylate Herbicides



compd	2	4	5	R_1	R_2
phenopylate	Cl	Cl	H	$-(CH_2)_4-$	
RH 0710	Cl	$-OCH_2CO(CH_2C{\equiv}CH)N-$		$-(CH_2)_4-$	
RH 0978	Cl	Cl	$OCH_2C{\equiv}CH$	$-(CH_2)_2CF_2CH_2-$	
RH 1224	Cl	Cl	$OCH_2C{\equiv}CH$	$-(CH_2)_2CF_2(CH_2)_2-$	
RH 1422	F	Cl	CO_2i-Pr	$-(CH_2)_4-$	
RH 1908	H	H	H	$-(CH_2)_4-$	
RH 1909	Cl	H	H	$-(CH_2)_4-$	
RH 1911	H	Cl	H	$-(CH_2)_4-$	
RH 1964	Cl	Cl	CO_2i-Pr	$-(CH_2)_4-$	
RH 1965	Cl	Cl	CO_2CH_3	$-(CH_2)_4-$	
RH 4663	Cl	Cl	$OCH_2C{\equiv}CH$	$-(CH_2)_4-$	
RH 6251	Cl	Cl	$OCH_2C{\equiv}CH$	$-(CH_2)_5-$	
RH 7160	Cl	Cl	$OCH_2C{\equiv}CH$	C_2H_5	C_2H_5
RH 9611	Cl	Cl	OH	$-(CH_2)_4-$	

technique involved determination of capacity factors (k') for a set of standard compounds with a wide range of known experimental partition coefficients (Table I). The k' values were calculated from

$$k' = (t_R - t_0)/t_0$$

where t_R is retention time of the compound and t_0 is the retention time of the nonsorbed compound (acetone). A standard curve of log P vs log K' was constructed. Using the same HPLC conditions as in the standard curve, the capacity factors for the herbicides were determined. The log P of herbicides was calculated using the linear regression equations of the form log $P = a + b$ (log k').

The HPLC system was composed of Waters Associates components which included Model 510 pumps, a Model 712 autosampler, a Maxima 820 controller, and a Model 490 multiwavelength detector. The column was a 250 × 4.6 mm (i.d.) Spherisorb 5 μm ODS-1, C_{18} reversed-phase column. The mobile phase was methanol/water (75:25 v/v). The HPLC analyses of the two classes of herbicides were performed at different times, each time with a slightly different method. In method 1 (Figure 1), used for DPE herbicides, a flow rate of 1.0 mL/min and room temperature of 24 ± 2 °C were used. In method 2 (Figure 1), used for phenopylates, a flow rate of 1.4 mL/min was used and

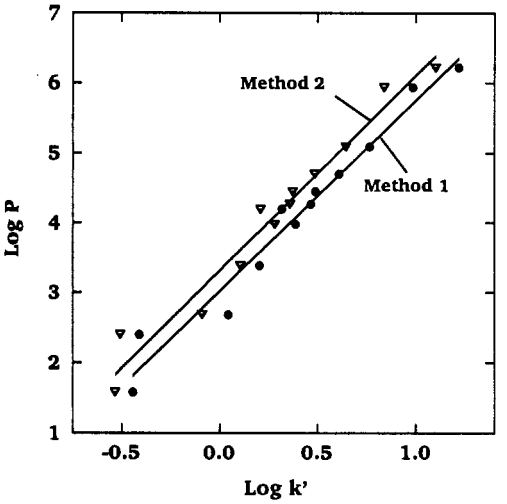


Figure 1. Relationships between capacity factors (log k') and octanol/water partition coefficients (log P) for 12 compounds listed in Table IV. The regression lines labeled methods 1 and 2 were used for estimating RP-HPLC log P values of diphenyl ether and phenopylate herbicides, respectively.

a column temperature of 28 °C was maintained by a Waters temperature control and column heater module. The injection volume was 5 μL. The herbicides and standard compounds were dissolved in methanol at 1 mg/mL concentration. The detector was set at 254 nm. In both methods, there were three replicate determinations for each compound.

Calculated Log *P*. The calculated log P values based on the fragment constant model were obtained from the MedChem CLOGP computer program (Pomona College Medicinal Chemistry Project, MedChem Software, Version 3.53, Claremont, CA). The general form of the fragment constant model is given as

$$\log_{10}P = \sum_i n_i F_i + \sum_j C_j$$

where F_i is the fragment constant for the ith fragment which occurs n_i times in a molecule and C_j is the jth correction term.

The CLOGP computer program builds the structures from SMILES notation, and the built-in algorithm breaks down the structure into fragments. The fragment values and associated

Table III. List of Semiempirical Molecular Descriptors Used in Regression Analysis

type	descriptor
whole molecule properties	
bulk descriptors	van der Waals volume (VDW_{volume})
	van der Waals area (VDW_{area})
shape descriptors	maximum lengths of x, y, and z axes
electronic descriptors	dipole moment
	molecular electrostatic potentials + and − volumes and areas ($+MEP_{volume}$, $-MEP_{volume}$, $+MEP_{area}$, and $-MEP_{area}$)
	superdelocalizability (S) S_{HOMO}, S_{LUMO}, electrophilic S (S_E), and nucleophilic S (S_N)
energy descriptors	energy of HOMO (ϵ_{HOMO}) and LUMO (ϵ_{LUMO})
atom-centered electronic properties	partial charge, S_E, and S_N of common atoms of analogues

correction factors stored in the database are then used for computing log P of the compounds.

Molecular Properties. The semiempirical molecular properties (Table III) of herbicides were computed using Chem-X (Chemical Design, Inc., Oxford, U.K.) molecular modeling software described in detail in our previous publications (Nandihalli et al., 1992a,b). The starting geometries were obtained either from crystal structure data or from the parameter file of Chem-X software. The structures were optimized by MOPAC (Quantum Chemistry Program Exchange, No. 560, Version 6.0, Department of Chemistry, Indiana University, Bloomington, IN) using modified neglect of diatomic overlap (MNDO) parameterization.

The van der Waals (VDW) volume maps were calculated using Chem-X, which displays the surface of the molecule at the VDW radius. To map VDW volume (VDW_{volume}) using contour, Chem-X uses a continuous function, instead of a step function, for describing the transition across the molecular surface. The volume enclosed by a contour level of 1 was computed by multiplying the total number of grid points in the display lattice which lay inside the contour by the separation between the grid points along each axis of the lattice.

Chem-X treats the charge on each atom in a molecule as a point charge positioned at the center of the atom. For calculating MEP, positive unit charge equivalent to that of a proton is placed at each grid point, and the electrostatic interaction between the atoms of the structure and the unit charge is then calculated. When calculations are completed, a map showing positive and negative isopotential contour lines is drawn. The number of grid points chosen was 15 per molecule. The levels of potential energy as defined by contour levels were +10 and −10 kcal/mol for positive and negative energy potentials, respectively.

The superdelocalizability (S) of an atom is a measure of its available electron density. It is the ratio of orbital density to orbital energy summed over all orbitals. S is calculated from the expression (Brown and Simas, 1982; *Chem-X Reference Guide*, 1991, Vol. II, pp 14–26)

$$S = \sum_j n_j \sum_m (C_{jm}^2/\epsilon_j)$$

where n_j is the number of electrons in molecular orbital j, C_{jm} is the eigenvector of atomic orbital m in molecular orbital j, and ϵ_j is the eigenvalue (energy) of molecular orbital j.

RESULTS

Standard Curves. The relationship between log k', derived from retention times (Table IV), and log P of standard compounds was linear (Figure 1). The equation derived from method 1 which was used for estimating DPE log P values is

$$\log P = 3.22 + 2.48(\log k') \quad r^2 = 0.98 \qquad (1)$$

Similarly, the equation derived from method 2 which was used for estimating log P values of phenopylate analogues is

$$\log P - 3.32 + 2.79(\log k') \quad r^2 = 0.97 \qquad (2)$$

The standard curves covered the log P range of herbicides of both classes.

Table IV. Experimental Log P Values and RP-HPLC Retention Times (Means of Three Replicates) of Compounds Used in the Development of Standard Curves

compd	exptl log P[a]	retention time, min	
		method 1	method 2
acetone		3.21	2.30
acetophenone	1.58	4.43	2.98
diphenyl sulfone	2.40	4.53	3.02
toluene	2.69	6.64	4.17
1,2-dichlorobenzene	3.38	8.46	5.23
biphenyl	3.98	11.21	6.69
diphenyl ether	4.20	10.02	6.03
1,2,4-trichlorobenzene	4.27[c]	12.80	7.56
diphenyl sulfide	4.45	13.33	7.74
bibenzyl	4.70	16.54	9.35
dimethylbiphenyl	5.09	22.27	12.46
DDT	5.94	34.94	18.17
hexachlorobenzene	6.22[b]	57.38	31.41

[a] Experimental log P values taken from Hansch and Leo (1979). [b] Taken from McDuffie (1981). [c] Obtained from Sandoz Crop Protection, Palo Alto, CA.

Table V. Observed (Means of Three Replicates) and Predicted Log P Values and the Descriptors Used in the Regression Equations 3 and 4

compd	log P			descriptors		
	obsd	pred	change	VDW_{volume}, Å^3	ϵ_{HOMO}, eV	μ, D
diphenyl ethers						
acifluorfen-Me	4.26	4.20	−0.04	245.5	−10.40	4.597
aclonifen	4.04	4.15	+0.11	185.4	−9.71	5.031
benzofluorfen	4.27	4.16	−0.11	262.0	−10.46	5.372
bifenox	4.34	4.34	0	222.1	−10.19	5.589
fluorodifen	3.60	4.02	+0.42	209.2	−10.39	5.088
lactofen	4.81	4.69	−0.12	304.4	−10.33	3.919
MC-15608	5.04	5.07	−0.03	239.4	−9.78	2.982
MT-124	4.33	4.54	+0.21	260.0	−9.70	4.332
nitrofen	4.64	4.24	−0.40	192.3	−9.99	4.875
nitrofluorfen	4.54	4.64	+0.10	208.4	−10.19	3.401
oxyfluorfen	4.73	4.55	−0.18	238.6	−9.86	4.198
PPG-1013	4.54	4.46	+0.08	277.8	−10.30	4.477
RH-0211	3.92	4.12	+0.20	159.7	−9.74	5.759
RH-1460	4.76	4.51	−0.25	250.3	−10.03	4.544
RH-4638	4.54	4.76	+0.22	288.8	−9.98	4.160
RH-4639	4.53	4.61	+0.08	281.9	−10.19	4.283
RH-5348	4.21	4.25	+0.04	240.9	−10.37	4.412
RH-8378	4.40	4.16	−0.24	170.7	−9.69	5.838
RH-8826	3.57	3.50	−0.07	265.4	−11.08	2.922
RH-8827	3.65	3.73	+0.08	255.9	−10.70	5.504
phenopylates						
phenopylate	3.94	3.66	−0.28	180.8	−9.79	4.594
RH-0710	2.93	2.88	−0.05	248.3	−9.01	4.254
RH-0978	3.42	3.81	+0.39	238.9	−9.84	3.213
RH-1224	3.57	3.47	−0.10	249.1	−9.84	2.536
RH-1422	4.20	4.31	+0.11	238.4	−10.04	4.602
RH-1908	2.73	2.73	0.0	151.3	−9.42	3.518
RH-1909	3.13	3.26	+0.13	161.6	−9.60	5.036
RH-1911	3.38	3.11	−0.27	172.8	−9.62	3.342
RH-1964	4.67	4.38	−0.29	250.4	−10.02	4.324
RH-1965	3.95	4.14	−0.19	225.8	−10.04	4.017
RH-4663	3.82	3.95	+0.13	228.4	−9.71	4.854
RH-6251	4.25	4.00	−0.25	239.8	−9.68	4.436
RH-7160	3.95	3.87	−0.08	225.8	−9.68	4.196
RH-9611	2.98	3.36	+0.38	195.2	−9.49	4.159

Correlations between RP-HPLC Log P and Molecular Properties. In both herbicide classes, the van der Waals molecular volume (VDW_{volume}), total dipole moment (μ), and energy of the highest occupied molecular orbital (ϵ_{HOMO}) (Table V) significantly ($\alpha = 0.0001$) accounted for the variation in the log P of compounds. The

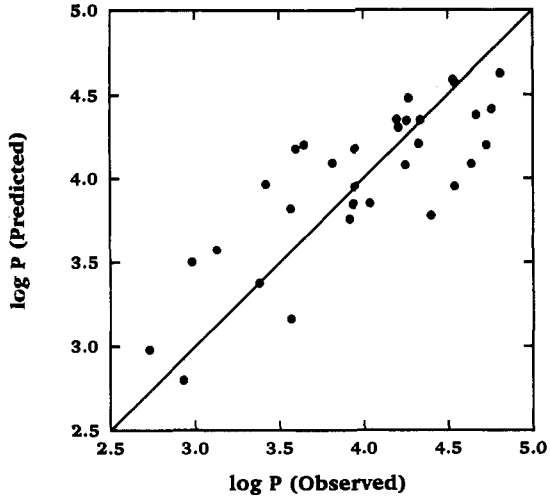


Figure 2. Plot of observed vs predicted log P values calculated using eq 5.

other molecular parameters (Table III) such as electrostatic potentials, various superdelocalizabilities, energy of the lowest unoccupied molecular orbital, and shape parameters did not contribute significantly to the regression models. The multiple regression equation for the DPE family is

$$\log P = -120 + 0.0041(\mathrm{VDW}_{\mathrm{volume}}) - 25.7(\epsilon_{\mathrm{HOMO}}) - 1.3(\epsilon_{\mathrm{HOMO}})^2 - 1.48(\mu) + 0.144(\mu)^2 \quad (3)$$

$$n = 20 \quad F = 9.8 \quad r^2 = 0.78$$

The multiple linear regression equation for the phenopylate family of herbicides is

$$\log P = -93.53 + 0.0079(\mathrm{VDW}_{\mathrm{volume}}) - 17.79(\epsilon_{\mathrm{HOMO}}) - 0.858(\epsilon_{\mathrm{HOMO}})^2 + 1.66(\mu) - 0.179(\mu)^2 \quad (4)$$

$$n = 14 \quad F = 8.03 \quad r^2 = 0.83$$

The slopes of eqs 3 and 4 were found to differ significantly ($p \leq 0.05$) on the basis of the 5 df F-test for homogeneity of slope. In other words, the three molecular properties did not influence the log P data the same way in each chemical class, and therefore different coefficients were apparent in eqs 3 and 4.

The predicted log P values using eqs 3 and 4 are presented in Table V. On the average the estimated log P values deviated from the predicted values by 0.13 and 0.19 log unit in DPE and phenopylate classes, respectively, with ranges between −0.40 and +0.42 log unit.

Next, we performed a regression analysis on a set comprising all 34 herbicides to determine if the molecular parameters of eqs 3 and 4 could still be able to predict RP-HPLC log P of a set of analogues belonging to two different chemical classes. It was found that the same three molecular parameters as in eqs 3 and 4 contributed significantly to the variation in the log P data as shown:

$$\log P = -122.09 + 0.0061(\mathrm{VDW}_{\mathrm{volume}}) - 24.27(\epsilon_{\mathrm{HOMO}}) - 1.194\,(\epsilon_{\mathrm{HOMO}})^2 + 0.604(\mu) - 0.051(\mu)^2 \quad (5)$$

$$n = 34 \quad F = 10.17 \quad r^2 = 0.65$$

From the plot of observed vs predicted values, clearly these parameters were able to predict log P values with reasonable accuracy for chemicals of such wide structural diversity (Figure 2). On the average, the estimated log P values deviated from the true values by 0.26 log unit, with the ranges between −0.58 and +0.59 log unit.

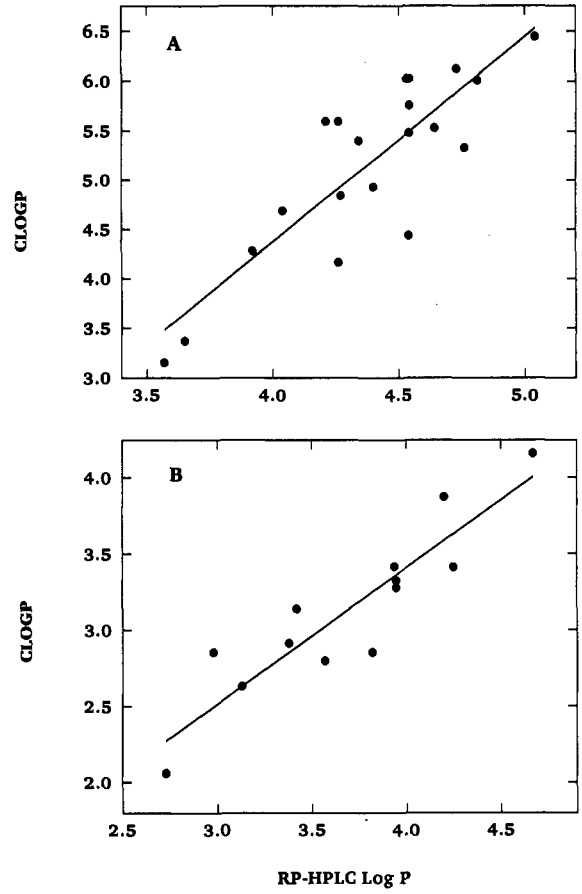


Figure 3. Relationships between RP-HPLC log P and log P calculated using CLOGP program of diphenyl ether (A) and phenopylate (B) herbicides.

Correlation between RP-HPLC Log *P* and CLOGP. High correlations were found between log P values estimated from RP-HPLC and those calculated from the CLOGP program in both DPE ($r = 0.91$) and phenopylate ($r = 0.91$) classes (Figure 3). On the average, the CLOGP values were 0.56 log unit lower than the RP-HPLC values in the phenopylate set, with a deviation ranging from 0.125 to 0.966 log unit. In contrast, the CLOGP values were 0.90 log unit higher than the RP-HPLC values with DPE analogues. The range of deviation varied from −0.415 to +1.49 log units. For two compounds belonging to the DPE set which had either sulfoxide or sulfone linkages between phenyl rings, the CLOGP procedure produced lower log P values than did the RP-HPLC method. This discrepancy arises because in the CLOGP method the calculated log P value is dependent upon which way the particular structure is fragmented.

DISCUSSION

The RP-HPLC method involves the determination of retention times for molecules, followed by calculation of capacity factors (k'). In this study, the log P values of herbicides were calculated by substituting their k' values in regression eq 1 or 2. As expected, we found very high positive correlations between the retention times and log P values in both classes of compounds ($r = 0.98$ for DPE and $r = 0.97$ for phenopylates). We chose the use of log P, rather than retention times, for the discussion of results because of (a) high correlations found between retention times and log P and (b) universal use of log P as an index of lipophilicity.

It has been suggested that the partition coefficient determined by the RP-HPLC method represents a true and reliable lipophilicity factor for use in QSAR studies because the mobile and stationary phases of RP-HPLC closely resemble the aqueous and nonaqueous phases of biological systems (Braumann, 1986), in contrast to the octanol/water partitioning method. Octanol is an isotropic liquid in which the size and shape of solute molecules are not the determinants of the partition process. On the contrary, biomembranes are anisotropic, and the molecular size and shape and the orientation of functional groups will play a role in the partition process. Furthermore, the former is a static system, while the latter is a dynamic system. The RP-HPLC system is both anisotropic and dynamic.

To our knowledge, there are no published studies which have examined the relationships between RP-HPLC log P and bulk and electronic properties of structures calculated by molecular orbital methods. However, there are several papers in which correlations between molecular properties and directly measured octanol/water partition coefficients have been carried out. With chlorobenzene analogues, Bruijn and Hermens (1990) found a very high linear relationship (r^2 = 0.997) between van der Waals surface area and octanol/water partition coefficients determined by the slow-stirring method. Similarly, Doucette and Andren (1987) found a linear relationship (r^2 = 0.924) between log P values as determined by generator-column method and van der Waals surface area of 32 polychlorinated and polybrominated biphenyls and furans. Taft et al. (1985), using 102 aliphatic and polychloroaliphatic compounds, showed that log P can be accurately described by an equation (r^2 = 0.99) comprising three terms: molecular cavity, molecular polarity (π^*), and hydrogen bond donor or acceptor abilities. Log P values of gases and solids were best predicted from a multiple linear regression equation comprised of van der Waals volume, dipole moment, and hydrogen bond acceptor basicity (Leahy, 1986).

In this paper, we have attempted to identify the molecular properties of chemicals belonging to two herbicide classes which influence RP-HPLC partition coefficients. It was found that the three properties, VDW_{volume}, μ, and ϵ_{HOMO}, influenced the interaction of herbicide molecules with the RP-HPLC stationary–mobile phases. Each of these three parameters corresponded to three terms, molecular cavity, molecular polarity, and hydrogen bond basicity, which are known to affect the octanol/water partitioning process (Taft et al., 1985). VDW_{volume}, μ, and ϵ_{HOMO} represent molecular bulk, molecular polarity, and reactivity (hydrogen bond basicity) parameters, respectively. The molecular cavity is represented by molar volume (molecular weight divided by density at 25 °C), but Leahy (1986) reported that molar volume could be replaced by an intrinsic molar volume represented by van der Waals volume as a measure of the cavity term in the linear solvation energy relationships. Lewis (1989) found that the expression involving three parameters, molar polarizability, dipole moment, and ϵ_{HOMO}, derived from CNDO/2 molecular orbital calculations best predicted log P. The ϵ_{HOMO} represents the electron-donating power of the molecule and thus is related to the hydrogen bond basicity of Taft et al. (1985). Furthermore, polarizability relates to molar volume and π^* relates to dipole moment.

In RP-HPLC the "driving force" for retention is the unfavorable interaction of a solute with the surrounding water molecules present in the mobile phase (Horvath et al., 1976). This leads to a net free-energy change on exclusion of the solute molecule from the mobile phase (aqueous phase) to the nonpolar ligands of the stationary phase (organic phase). In other words, the partition coefficient between two immiscible phases is dependent on the solvation energy differences of the solute between the organic and aqueous phases. The two most important components of solvation energy are electrostatic and polarization energy changes, and therefore it is assumed that log P is comprised of polarization, electrostatic, and electronic terms (Lewis, 1989). Therefore, it was not unexpected that molecular size (VDW_{volume}), polarity (μ), and energy (ϵ_{HOMO}) parameters were found to be the determinants of solute retention in RP-HPLC.

The conformation of a molecule will affect its VDW_{volume} and μ values. The differences in these values between the two compounds of the chiral pair, RH4638 and RH4639, are in part due to conformational differences. When a molecule is highly flexible, as some of the herbicides in this study are, use of a single low-energy conformer for calculation of these values is an oversimplification. However, for practical purposes, the conformer with the lowest free energy should provide a reasonable estimate of these values for further estimation of log P.

The dependence of log P on μ in both classes of herbicides was parabolic in that, in general, log P increased with increase in μ up to about 4 D; further increase in μ decreased the log P (Table V). With chlorobenzenes, a relatively high polarity term led to a decrease in the octanol/water P (Kamlet et al., 1984). Similarly, a parabolic relationship existed between log P and ϵ_{HOMO}. In both herbicide classes, the VDW_{volume} was related to log P in a linear fashion. We predict that the VDW_{volume} data which conformed between 151.3 and 304.4 Å^3 (Table II) were within the range where linear kinetics was still operative. Doucette and Andren (1987) and Bruijn and Hermens (1990) showed that octanol/water log P was related linearly to the total surface area between 100 and 400 Å^2. The molecular volumes and surface areas calculated on the van der Waals radius using semiempirical methods are highly correlated. For example, the r values for correlation between VDW volume and surface areas were >0.99 in both DPE and phenopylate herbicide groups.

In summary, it is possible to predict RP-HPLC log P from molecular properties calculated from semiempirical molecular and quantum mechanical approaches. This technique is simple and provides reliable partition coefficients for use in structure–activity studies of xenobiotics. The partition coefficients estimated from RP-HPLC and those calculated from fragment constant method were highly correlated.

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