Composition of Partition Coefficients of Polychlorinated Hydrocarbons

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Partition coefficients (P) of tri-, tetra-, penta-, and hexa-chlorocyclohexene isomers were measured in an octanol/water system. These log P values and values previously determined for polychlorocyclohexane isomers and some polychlorinated acyclic alkenes were analyzed by the summation of the hydrophobic fragment constants of their structural units and features. The introduction of new fragment constants, including interactive and conformational factors, brought calculated values into good agreement with observed values. The additive and constitutive character of the log P value was shown to hold in this series of vicinally substituted polyhalogenated (cyclo)-alkanes and -alkenes.

INTRODUCTION

The versatility of the hydrophobic parameter, log P (P is the octanol/water partition coefficient), in understanding the way various bioactive molecules interact with biomacromolecules and biomembranes[1] as well as their accumulation in the environment[2] has been well established. Preferably the log P value determined experimentally should be used as the parameter whenever possible. It is not always accessible, however, for determining the partition coefficients of a vast number of organic compounds. Thus, there is the need for a reliable method by which to estimate the P value without performing experimental determinations.[3]

By use of its additive and constitutive nature,[1] a log P value can be estimated by summation of the hydrophobic constants of substructural fragment (f) and factors (F) for structural features such as double bonds and branching. The situation is expressed in Eq. 1 as

$$\log P = \Sigma f + \Sigma F \tag{1}$$

The principal f and F values have already been proposed and published,[3] but for polyfunctional and polysubstituted molecules these values do not always give accurate predictions of the log P values. In these molecules, the simple additivity principle does not always hold because of interactive factors between substituents.

We here report the partition coefficient values for polychlorocyclo-hexenes and -hexanes that are related structurally to an insecticide, lindane (γ-BHC). By analyzing

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Table I. Structure and log P value of polychlorinated hydrocarbons

| Compound | | Hydrophobic fragment constants and factor values | | | | | | | | | | Calc'd log P with constants in | | Obs'd log |
| | | Fundamental values in Table II | | | | | | Newly derived values in Tables IIIA[b] and IIIB | | | | | | |
Fundamental Structure	Conformation of Isomer[a]	f_C	f_H	f_{Cl}	F_b	F_{mhVn}	F_{mhG_2}	f_{Cl}^v	$F_{(=)}$	F_{axCl}	F_{a-a-Cl}	Table IIIA	Table IIIB	
BHC	α aaeeee									0.11×2	−0.22	3.89	3.89	3.82
	β eeeeee	0.20×6	0.23×6	0.06×6	−0.09×5	0.28×5	—	—	—	—	—	3.89	3.89	3.80
	γ aaaeee									0.11×3	−0.22×2	3.89	3.78	3.72
	δ aeeeee									0.11	—	3.89	4.00	4.14
HCCHE	(36/45) vvaaee									0.11	—	4.27	4.40	4.34
	(34/56) vvaeea	0.20×6	0.23×6	0.06×4	−0.09×5	0.28×4	—	0.39×2	—	—	—	4.27	4.29	4.12
	(346/5) vvaeee							(0.40×2)	—	—	—	4.27	4.29	4.31
	(35/46) vveeee									—	—	4.27	4.29	4.56
PCCHE	(36/45) vH̄eeaa									0.11	—	3.83	3.95	3.95
	(34/56) vH̄aeea									—	—	3.83	3.84	3.60
	(346/5) vH̄aeee	0.20×6	0.23×7	0.06×4	−0.09×5	0.28×3	—	0.39	—	—	—	3.83	3.84	3.85
	(356/4) vH̄eeea							(0.40)		—	—	3.83	3.84	3.80
	(35/46) vH̄eeee									—	—	3.83	3.84	3.61
BTC	(36/45) H̄H̄aaee									0.11	—	3.13	3.25	3.40
	(34/56) H̄H̄aeea									—	—	3.13	3.14	3.08
	(346/5) H̄H̄aeee	0.20×6	0.23×8	0.06×4	−0.09×5	0.28×2	—	—	−0.26	—	—	3.13	3.14	3.15
	(35/46) H̄H̄eeee								(−0.25)	—	—	3.13	3.14	3.08
	(345/6) H̄H̄eaee									0.11	—	3.13	3.25	3.74[c]

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Compound		Conf.													
TCCHE	(35/4)	vH̄eeeH								—		—	3.44	3.45	3.72
	(34/5)	vH̄aeeH	0.20×6	0.23×8	0.06×3	−0.09×5	0.28	—	0.39 (0.40)	—		—	3.44	3.45	3.52
	(3/45)	vH̄aaeH								0.11		—	3.44	3.56	3.65
TriCCHE	(34/5)	H̄H̄aeeH	0.20×6	0.23×9	0.06×3	−0.09×5	0.28	—	—	−0.26 (−0.25)		—	3.02	3.03	2.84
PCCHA	(1245/3)	eaaaeH	0.20×6	0.23×7	0.06×5	−0.09×5	0.28×3	—	—	0.11×3	−0.22×2		3.50	3.39	3.37
	(134/25)	aaeeeH								0.11×2	−0.22		3.50	3.50	3.53
TCCHA	(1245/0)	aeHeaH	0.20×6	0.23×8	0.06×4	−0.09×5	—	—	—	0.11×2	—		2.83	3.05	2.82
DCCHA	cis	aeHHHH								0.11	—		3.17	3.28	3.18
	trans { eeHHHH (0.75) / aaHHHH (0.25) }	d) 0.20×6	0.23×10	0.06×2	−0.09×5	—	—	—	—	0.11×0.5e)	−0.22×0.25e)		3.17	3.17	3.21
Hexachlorobutadiene			0.20×4	0.23×4	—	−0.12×8	0.28	0.30×4	0.39×6 (0.40×6)	—	—	—	4.58	4.64	4.74
Tetrachloroethylene			0.20×2	0.23×2	—	−0.12×4	—	0.30×4	0.39×4 (0.40×4)	—	—	—	3.14	3.18	2.88
Trichloroethylene			0.20×2	0.23×3	—	−0.12×3	—	0.30×2	0.39×3 (0.40×3)	—	—	—	2.50	2.53	2.42
1, 2-Dichloroethylene cis			0.20×2	0.23×4	—	−0.12×2	—	—	0.39×2 (0.40×2)	—	—	—	1.86	1.88	1.86
trans													1.86	1.88	2.09
1, 1-Dichloroethylene			0.20×2	0.23×4	—	−0.12×2	—	0.30×2	0.39×2 (0.40×2)	—	—	—	2.46	2.48	2.13

a) Conformations were determined by PMR: a=axial, e=equatorial, a̲=pseudo-axial, e̲=pseudo-equatorial, v=vinylic chlorine. H=no substituents. H̄=no substituents on the vinylic position.   b) In parentheses, calculations with constants in Table IIIB.

c) Not included in the regression analyses. The factor due to ea (pseudoequatorial-axial) interaction should be included, but it appears only once in the series of compounds.   d) Approximate ratio of conformers ee and aa was estimated by PMR analysis, and was 0.75: 0.25.

e) Contributions from the aa conformer are listed.

the composition of their log P values and values published for polychloroalkenes by means of Eq. 1, with newly introduced constants for interactive and conformational factors, we have improved the procedure for estimating log P values by use of their additive-constitutive nature.

EXPERIMENTAL

Compounds: The partition coefficients were measured for isomers of 3, 4, 5-tri-(TriCCHE); 1, 3, 4, 5-tetra- (TCCHE); 3, 4, 5, 6-tetra- (BTC); 1, 3, 4, 5, 6-penta-(PCCHE); 1, 2, 3, 4, 5, 6-hexa-chlorocyclohexene(HCCHE); 1, 2-di- (DCCHA); 1, 2, 4, 5-tetra- (TCCHA); 1, 2, 3, 4, 5-penta- (PCCHA) and 1, 2, 3, 4, 5, 6-hexa-chlorocyclohexane(BHC) (Table I). Preparation of these compounds has been described previously.[4] For some, the log P values already have been published.[5,6] The reported log P values of some polychlorinated alkenes[3] also have been included.

Measurement of Partition Coefficient: Each compound (1–5 mg) was dissolved in octanol (2 to 3 ml) saturated with water, then the bottle was shaken vigorously for at least 30 min at 28°C on the addition of water (5 to 7 ml) saturated with octanol. After centrifugal separation of the two layers and their dilution or treatment with hexane, the concentration of the compound in each layer was analyzed by gas chromatography. The solute concentration in the organic layer was between 4 and 20 mM.

Calculation of the Log P Value by the Fragment Method: The log P value of each compound is supposed to be calculable in the form of Eq. 2, in which f_i is the fragment constant of the *i*-th substructure and F_j the factor value of the *j*-th structural feature.

$$\log P = \Sigma f_i X_i + \Sigma F_j Y_j + c \tag{2}$$

Table II. Fragment constants and factor values used in the primary calculation of log P

Fragment	f-value	Factor	F-value	Multiplier
$-\overset{\mid}{\underset{\mid}{C}}-$	f_C: 0.20	Chain Bond	F_b: − 0.12	$n-1$[a]
$-H$	f_H: 0.23	Ring Bond	F_b: − 0.09	$n-1$[a]
$-Cl$	f_{Cl}: 0.06	MH^b on		
		adjacent C	F_{mhV}: 0.28	$n-1$[c]
		same C	F_{mhG_2}: 0.30	n[d]

a) "n" is the number of "bond" in a molecule. For example, n in C–C–C–C equals 3; the total contribution from this bond factor is calculated as $-0.12 \times (3-1) = -0.24$. For cyclohexane, the value of -0.09 is used; thus, $-0.09 \times (6-1)$ is the total bond factor value.

b) Multiple halogenation.

c) "n" is the number of pairs of vicinal Cl atoms (see text). A "vicinal" pair separated by a double bond is not counted (see ref. 3).

d) When the number of geminal Cl atoms is 2, $2 \times F_{mhG_2} = 2 \times 0.30$ is the total value. In hexachlorobutadiene, it is $4 \times F_{mhG_2} = 4 \times 0.30$.

X_i and Y_j are indicator variables that take values of 0, 1, 2, 3 or any integer according to the number of i-th or j-th structural units involved in a molecule; c is a constant. f and F values for the fundamental structural units listed in Table II are from the compilation of Hansch and Leo.[3]

For some fragments and features, values from the same compilation were not always suitable. For instance, multiple halogenation on the same or adjacent carbon atoms produces a higher log P than that predicted by simple additivity because of interactive factors. To account for these factors, Hansch and Leo introduced the F_{mhV} (multiple halogenation, vicinal) and F_{mhG} (multiple halogenation, geminal) values listed in Table II. We reexamined the procedure used to estimate the multiple halogenation factors and found that use of the number of pairs of vicinal Cl atoms (n), instead of the originally proposed number of vicinal Cl atoms, to multiply the F_{mhV} value (by n–1) gives a much better prediction of the log P values of the present set of compounds.

Factors caused by conformational effects and the relative orientation of Cl substituents have not been reported. Therefore, we first summed up the fragment and factor values that are listed in Table II for the compounds, including alkenes, given in Table I. Then, using Eq. 2, we analyzed the composition of the differences from experimentally determined log P values in terms of the f and F values of structural units that had not been examined accurately. The newly examined values are the f value for the Cl atom attached to a double bond, the F values for three types of double bond: $H>=<H$, $H>=<Cl$ and $Cl>=<Cl$, and conformational factors.

The effect of conformational variations on log P values could be rationalized by possible variations in the entropy value of water molecules in the iceberg structure surrounding the envelope of an organic molecule in the aqueous phase. The conformation of a single Cl atom, as well as conformational relationships among vicinally situated Cl atoms, are considered to affect the molecular envelope. Since the log P value of β–BHC, in which all the Cl substituents are equatorial, is almost equivalent to that calculated without considering conformational factors, equatorial Cl was the point of reference. We examined conformational factors caused by change from an equatorial to an axial or pseudo-axial conformation. Cyclohexane derivatives exist as chair forms and cyclohexene derivatives as half-chair forms. Although they undergo ring conversion, the conformational features were assigned on the basis of the favored conformation determined from the PMR spectra shown in Table I.

Each of the f_i and F_j values were determined as a coefficient of each of the X_i and Y_j terms by regression analysis. The procedure used is essentially the same as that in the modified Free-Wilson analysis.[7]

RESULTS AND DISCUSSION

Composition of Log P Values: We first analyzed the log P values without considering the conformational factors and derived values shown in Table III. For the f value of the Cl atom attached to an unsaturated carbon atom, Hansch and Leo gave the average of values for the aromatic and aliphatic Cl, $f_{Cl}^{b/2}$ (0.50), on the assumption that the

Table III.   Newly derived fragment constants and factor values

A: Without consideration of conformational factors	B: With consideration of conformational factors
$F_{(=)}$: -0.26 (>0.995)[a] f^v_{Cl} : $+0.39$ (>0.995)	$F_{(=)}$: -0.25 (>0.990) f^v_{Cl} : $+0.40$ (>0.995) F_{axCl} : $+0.11$ (>0.900) F_{a-a-Cl}: -0.22 (>0.950)
$n=32$, SD$=0.172$, r$=0.961$[b]	$n=32$, SD$=0.163$, r$=0.968$

a) In parentheses, the level of significance.
b) n$=$number of compounds, SD$=$standard deviation, and r$=$correlation coefficient.

vinylic Cl fragment constant lies halfway between the aromatic and aliphatic values. This value was not applicable to our compounds; therefore, we estimated the value of the vinylic Cl, f^v_{Cl} by regression analysis.   The value obtained, 0.39, is somewhat smaller than the published value for $f^\phi_{Cl}/2$.

F values proposed for various types of double bonds also were not applicable to the types of double bonds with and without vinylic Cl atom(s) [$F^{Cl}_{(=)}$ and $F_{(=)}$] that were present in our compounds.   The newly derived value for a double bond, $F_{(=)}$, with no substituent (-0.26) differs considerably from that reported by Hansch and Leo (-0.55).   The factor due to a double bond, which conjugates with one or two Cl substituents, does not seem to contribute significantly to the total hydrophobicity. That is, $F^{Cl}_{(=)}$ does not differ significantly from 0.   For a conjugate double bond, Hansch and Leo gave a value of -0.42.   In general, in our polychlorinated compounds, the double bond, which otherwise acts to lower the log P value, seems to be insulated by surrounding Cl atoms.

The log P values for each compound calculated with the f and F values given in Table III are listed in Table I.

Conformational Factors: The entropy value of the water molecules that surround an all-equatorial reference compound would decrease on the change of the conformation of one of the Cl atoms from equatorial to axial because the molecular envelope is more "irregular" than the "disk" type and requires more water molecules to surround it. The decrease in the entropy value may be compensated for by the 1, 2-diaxial coplanar arrangement.

We introduced terms into the regression analysis that account for factors for the single axial Cl as well as the 1, 2-axial-axial and 1, 2-axial-psudoaxial orientations. We derived F_{axCl} value for the axial Cl arrangement and F_{a-a-Cl} value for the 1, 2-diaxial arrangement, together with slightly modified f^v_{Cl} and $F_{(=)}$ values.   These are listed in Table IIIB.   F values produced by pseudoaxial Cl substituents were either statistically insignificant or physicochemically unreasonable.

Calculation with these values gives a slightly better correlation (Table IIIB) with a lower standard deviation (SD) and a higher correlation coefficient(r) although the F_{axCl} value is justified at better than the 90% confidence level.   Log P values calculated from conformational factor values and modified f^v_{Cl} and $F_{(=)}$ values are listed

in Table I. Obviously, they fit both cyclic and acyclic polychlorinated hydrocarbons fairly well.

The additive-constitutive nature of the log P value was shown to hold even in vicinally substituted polychloro-hydrocarbons. Each of the interactive and conformaional factors involved in the log P value was separated fairly well. We hope that these newly derived f and F values together with the values already published will contribute to better calculation procedures for estimating the hydrophobicity of polyhalogenated hydrocarbons that might constitute environmental pollutants.

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