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Research Article

ESTIMATING OCTANOL/WATER PARTITION COEFFICIENT FOR SELECTED FERROCENE DERIVATIVES USING XLOGPV2.0 APPROACH

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ABSTRACT

Octanol/water partition coefficients P of several substituted ferrocene were calculated on the basis of the adaptation of the existing XlogPv2.0 approach. The predicted of calculated partition coefficients values of logP for selected ferrocene derivatives was compared with known experimental values taken from literature.The shown Results confirmed that the calculated partition coefficients were in good accord with experimental values. The average of absolute error is 0.12, and the obtained correlation coefficient value R^2 for the linear dependencies between experimental and calculated partitions coefficients is 0.977.

Keywords: Experimental logP, theoretical partition coefficient, ferrocene derivatives, lipophilicity, QSAR.

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1. INTRODUCTION

Octanol-water partition coefficient P generally expressed as logP is fundamental physicochemical phenomenon, that extensively describe a chemical lipophilic or hydrophobic properties, is defined as the rapport of the molar concentration of a chemical dissolved at

equilibrium in octanol phase to its molar concentration in aqueous phase [1],it's used in many scientific area such as analytical chemistry, environmental science, in the assessment of environmental fate and transport of organic chemicals, pharmaceutical research such as drug design and toxicological sciences [2-5], successful applications in quantitative structure activity relationships (QSAR), it is considered a required property in studies of new or undesired chemicals.

Previously, the estimation of logP of several substituted ferrocene using three different methods, Rekker, XlogPand AlogP has been reported[6-9].

We herein present a simple approach for the predition of n-octanol/water partition coefficients of a series of eleven ferrocene derivatives using theoretical calculations on the basis of the adaptation of the existing XlogPv2.0 approach, the XlogP's improved method.

2. MATERIALS AND METHODS

This section explains the generation of our model of calculation of logP of substituted ferrocene. This calculation is based upon the adaptation of the exciting atom-additive XlogPv2.0 method, which considers the partition molecular species between an aqueous phase and an organic phase, in our case is octanol.

2.1. Principle of the xlogpv2.0 approach

Atom-additive XlogPv2.0 method gives logP values by summing the contributions of component atoms and correction factors [10] equation (1).

$$\log P = \sum C_i a_i + \sum d_j D_j \qquad (1)$$

Where ci and dj are regression coefficients, Ci is the number of occurrences of the ith atom type, and Dj is the number of occurrences of the jth correction, there are 100 terms in this equation (90 atom types plus 10 correction factors). The atom type can be obtained by classifying atoms according to their number of attached hydrogen atoms, hybridization states and their neighbouring atoms.

2.2. Adaptation and simulation of the xlogpv2.0 approach

In order to adapt XlogPv2.0 approach to n-octanol/water partition coefficient of ferrocene derivatives, the following approximation should be made; firstly the ferrocene molecule does

not contain any hydrogen bonding or any interaction which can affect its value. LogP value of ferrocene by XlogPv2.0 method should be equal to the measured value of logP of ferrocene itself, which is equal to 2.66 [11]. The calculation can be carried out as follows, according to XlogPv2.0 method, the contribution of an aromatic carbon atom attached to any type of carbon symbolised by $c_{c_{ar}-c}$ is less than the contribution of an aromatic carbon atom attached to a hydrogen atom $a_{c_{ar}-H}$, and the difference can be calculated as follows:

$$c_{c_{ar}-c} - c_{c_{ar}-H} = 0.296 - 0.337 = -0.041 \qquad (2)$$

The contribution of an aromatic carbon atom attached to an atom of type X (O, N, S, P,…) symbolised as $c_{c_{ar}-X}$ is less than the contribution of an aromatic carbon atom attached to a hydrogen atom symbolised as $c_{c_{ar}-H}$, the difference can also be calculated as indicated by the following equation (3),

$$c_{c_{ar}-X} - c_{c_{ar}-H} = -0.151 - 0.337 = -0.488 \qquad (3)$$

To calculate the contribution of a ferrocenyl group attached to a carbon atom or an atom of type X, the obtained values of -0.041 and -0.488 should be subtracted to logP value of ferrocene and the contributions of the attached hydrogen atoms are included in atom type, were subtracted as indicated by equations (2)and(3), as follows

$$\mathrm{c}_{Fc} = \log P_{Fc} - n_1(0.041) - n_2(0.488) \qquad (4)$$

$n_1$number of substituents attached to the ferrocenyl group via a carbon atom, n_2 number of substituents attached to the ferrocenyl group via an heteroatom, with$0 \leq n_1 + n_2 \leq 10$, the contribution of a ferrocenyl group attached to an atom of type X is calculated from equation 4, n_1 in this case is equal to zero and $n_2$is equal to 1.

$$\mathrm{c}_{Fc} = \log P_{Fc} - 0.488 \qquad (5)$$

$$2.66 - 0.488 = 2.172$$

If a ferrocenyl group is attached to a carbon atom, its contribution is calculated from the same equation 4; with n_2 in this case is equal to zero.

$$\mathrm{c}_{Fc} = \log P_{Fc} - 0.041 \qquad (6)$$

$$2.66 - 0.041 = 2.619$$

logP, for any ferrocene derivatives of type $Fc - X'$, is therefore can be calculated by summing the contributions of a substituent X'atom type to the contribution of a ferrocenyl group plus the constitutive (correction factors) terms: as given by the following equation:

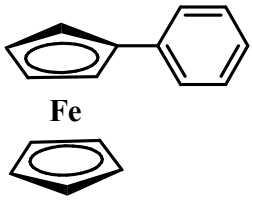
$$\log P_{Fc-X'} = c_{Fc} + c_{X'} + \sum d_j D_j \qquad (7)$$

3. RESULTS AND DISCUSSION

3.1. Calculation and validation of the method

Our method for the prediction of logP for substituted ferrocene is validated using eleven different ferrocene derivatives (mainly selected from literature sources) [12-15]. Calculations were carried out in three decimals, with the final result rounded to two decimals.

1. Phenylferrocene (1)



logP of this ferrocene derivatives is calculated according to equation 7 as follows:

Table1. Calculation method of logP for compound (1)

Atom type	C_i	c_i	$c_i \times C_i$
c_{Fc}	1	2.619	2.619
c_C (34)	1	0.296	0.296
c_C (32)	5	0.337	1.685
$d_j \times D_j$		-	-
$logP_{cal.}$			4.60

2. N-(ferrocenyl)-isobutyamide (2)

Ferrocene derivatives with saturated aliphatic hydrocarbon chains carrying functionalized group, we propose no correction for these types of compounds. LogP is calculated using the same equation 7, logP of this compound is calculated as follows,

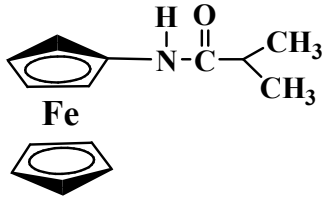
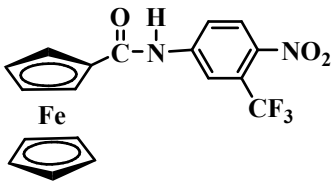


Table2. Calculation method of logP for compound (2)

Atom type	C_i	c_i	$c_i \times C_i$
c_{Fc}	1	2.172	2.172
c_C (1)	2	0.528	1.056
c_N (55)	1	-0.096	-0.096
c_C (11)	1	-0.243	-0.243
c_O (75)	1	-0.399	-0.399
c_C (29)	1	-0.027	-0.027
$d_j \times D_j$		-	-
$logP_{cal.}$			2.46

3. N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide (3)

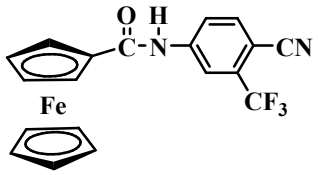


Ferrocene with a basic fragment linked to two aromatic rings is described in this compound, logP is obtained by summing the atom types of each group in the molecule and the correction factor for halogen 1–3 pair I_{Hal}.

Table3. Calculation method of logP for compound (3)

Atom type	C_i	c_i	$c_i \times C_i$
c_{Fc}	1	2.619	2.619
c_N (55)	1	-0.096	-0.096
c_C (29)	1	-0.030	-0.030
c_O (75)	1	-0.399	-0.399
c_C (32)	3	0.337	1.011
c_C (34)	1	0.296	0.296
c_C (35)	2	-0.151	-0.302
c_C (20)	1	-0.723	-0.723
c_F (83)	3	0.375	1.125
c_{NO_2}(66)	1	1.178	1.178
$d_j \times D_j$		0.137× 3	0.411
$logP_{cal.}$			4.29

4. N-[4-cyano-3-trifluoromethylphenyl]-ferrocenecarboxamide (4)

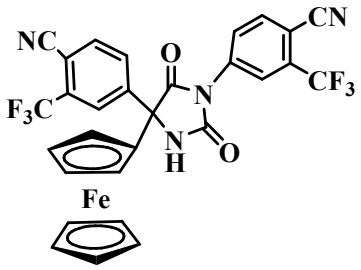


LogP of this ferrocene derivative can be obtained as follows:

Table4. Calculation method of logP for compound (4)

Atom type	C_i	c_i	$c_i \times C_i$
c_{Fc}	1	2.619	2.619
c_N (55)	1	-0.096	-0.096
c_C (29)	1	-0.027	-0.027
c_O (75)	1	-0.399	-0.399
c_C (32)	3	0.337	0.337
c_C (34)	2	0.296	0.592
c_C (35)	1	-0.151	-0.151
c_C (20)	1	-0.723	-0.723
c_F (83)	3	0.375	1.125
c_{CN} (68)	1	-0.566	-0.566
c_C (39)	1	0.330	0.330
$d_j \times D_j$		0.137× 3	0.411
$logP_{cal.}$			4.13

5.4'-ferrocényl-1',4'-[*bis*-(2-trifluorométhyl-1-cyano-phényl)]-2',5'-imidazolidinedione (9)



Ferrocene linked to a direct heterocyclic ring ,we propose for these type of molecules a correction factor of 0.580 correction factor for the sp^2 oxygen 1–5 pair (I_O) and 0.137 correction factor for each halogen 1–3 pair(I_{Hal}),logP is illustrated in table 5.

Table5. Calculation method of logP for compound (5)

Atom type	C_i	c_i	$c_i \times C_i$
c_{Fc}	1	2.619	2.619
c_C (20)	1	-0.723	-0.723
c_N (45)	1	0.545	0.545
c_C (29)	2	-0.030	-0.060
c_N (50)	1	0.761	0.761
c_O (75)	2	-0.399	-0.798
c_C (32)	6	0.337	2.022
c_C (31)	1	-0.315	-0.315
c_C (39)	1	0.330	0.330
c_C (34)	5	0.296	1.48
c_C (35)	1	-0.151	-0.151
c_C (20)	2	-0.723	-1.446
c_F (83)	6	0.375	2.250
c_{CN} (68)	2	-0.566	-1.132
$d_j \times D_j$		0.137x6	0.822
$d_j \times D_j$		0.580	0.580
$logP_{cal.}$			6.14

Simillarly as the above logP for six ferrocene derivatives *(*ferrocene in each of those molecule is linked to a direct heterocyclic ring via one or two methylene groups), were calculated from the same equation 7. The results are illustrated in table 6.

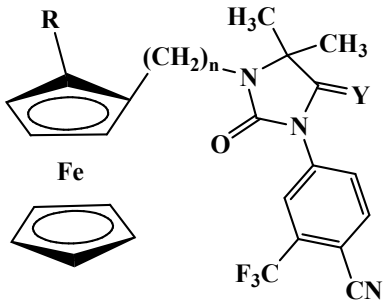


Table6. Calculation method of logP for six ferrocene derivatives compounds

N °	Ferrocene derivatives	R	n	Y	$logP_{cal.}$
6	4-(4’,4’-dimethyl-2’,5’-dioxo-3’-ferrocenylmethyl-1’-imidazolidinyl)-2-tri fluoromethyl benzonitrile	H	1	O	5.13
7	4-(4’,4’-dimethyl-2’,5’-dioxo-3’-ferrocenylethyl-1’-imidazolidinyl)-2-tri fluoromethyl-benzonitrile	H	2	O	5.63
8	(4’,4’-Dimethyl-3’-ferrocenylmethyl-5’-imino-2’-oxo-1’ imidazolidinyl) -2- trifluoromethyl-benzonitrile (10)	H	1	NH	4.67
9	4',4'-dimethyl-3'-ferrocenylethyl-5'-imino-2'-oxo-1'-imidazolidinyl)-2- trifluoromethylbenzonitrile (11)	H	2	NH	5.18
10	-(4’,4’-dimethyl-2’,5’-dioxo-3’-ferrocenylmethyl-1’-imidazolidinyl)-2-trifluoromethyl- benzonitrile (7)	CH_2OH	1	O	4.32
11	4-[4’,4’-dimethyl-2’,5’-dioxo-1’-imidazolidinyl-(3’-ortho-methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile (8)	CH_2OCH_3	1	O	4.84

Obtained values of logP for the eleven ferrocene derivatives are summarised in table 7.

Table7. Calculated logP and absolute error results for examined ferrocene derivatives

compound	Calculated $logP_{cal.}$	Experimental $logP_{exp.}$*	absolute error AE**
1	4.60	4.59	0.01
2	2.46	2.64	0.18
3	4.29	4.42	0.13
4	4.13	4.10	0.03
5	6.14	6.47	0.33
6	5.13	5.23	0.10
7	5.63	5.62	0.01
8	4.67	4.68	0.01
9	5.18	5.04	0.14
10	4.32	4.44	0.12
11	4.84	5.08	0.24

*references [12-15], **$AE = \left|\log P_{cal} - \log P_{exp}\right|$

The linear dependencies were received between experimental n-octanol/water partition coefficients and theoretical partition coefficients (Figure.1). The obtained correlation coefficient value for the linear dependencies between partitions coefficients is 0.977.

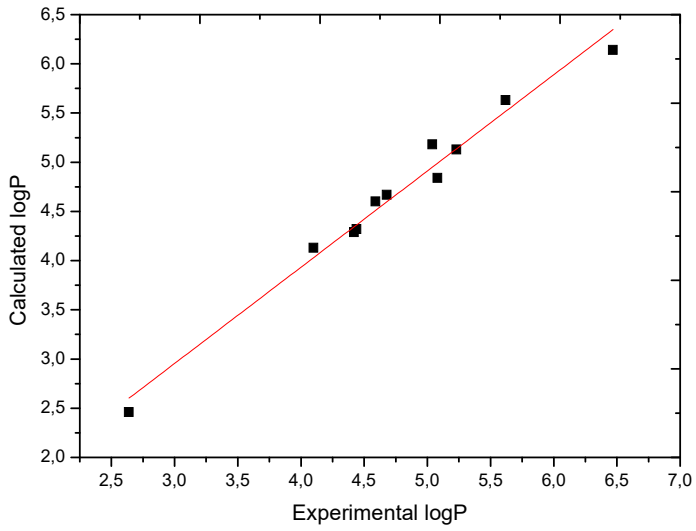


Fig.1. Correlation between experimental and calculated logP of substituted ferrocene

4. CONCLUSION

In this study, we successfully find a theoretical approach for the estimation of the octanol/water partition coefficients of substituted derivatives. Predictions are based on the expansion of the

existing XlogPv2.0 approach, we have become able to estimate the partition coefficient of ferrocene derivatives. Values of mesured and theoretical logP for several of ferrocene derivatives are in good accord. This approves the process of adaptation.

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