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AlogP calculation of octanol/water partition coefficient of ferrocene derivatives

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Abstract: The aim of this work is to calculate octanol/water partition coefficients, logP of a series of twelve ferrocene derivatives, using theoretical calculations on the basis of the adaptation of the existing AlogP approach. The accuracy of calculated theoretical partition coefficients values of all studied ferrocene derivatives has been investigated and compared with known experimental values mainly obtained from literature sources. It was shown that calculated partition coefficients were in good agreement with experimental values. The average of absolute error is 0.18, and the obtained correlation coefficient value R^2 for the linear dependencies between experimental and calculated partitions coefficients is 0.95.

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

Introduction

Octanol/water partition coefficient of a substance can be defined as its concentration in the octanol phase to its concentration in the aqueous phase at equilibrium. It is a physical property that describes the lipophilic and hydrophobic characteristics of the substance. Pioneering work by Hansch and Leo[1] has led to use logP parameterin many quantitative structure–activity relationships (QSAR) developed for the pharmaceutical, biochemical and toxicological sciences[2-6]. Many studies have shown that these physical properties are useful for correlating a drug's transport processes, its interactions with receptor molecules, and tendency to cross biological membranes. With the increasing use of combinatorial chemistry and QSAR evaluation, logP is considered necessary data in evaluating new compounds during drug discovery and design. It can be determined experimentally by a classical method or it can also be determined by theoretical calculations[7].

In a previous work, the calculation of logP of ferrocene derivatives using two different methods, Rekker and XlogP has been reported[8,9].

In this work a new and simple method is developed for the calculation of n-octanol/water partition coefficients of a series of twelve ferrocene derivatives using theoretical calculations on the basis of the adaptation of the existing AlogP approach.

Materials and methods

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

Principle of the AlogP approach

Generally AlogP method gives $logP$values by summing the contributions of component atoms. The total numbers of occurrences of each atom type in the database were obtained from a regression model based on 8364 molecules, covering a large variety of organic structures, equation (1).

$$\log P_{Fc} = \sum n_i a_i \qquad (1)$$

Where $n_i$is the number of atoms of type $i$and $a_i$is the atomic$\log P$ contribution. The method is based on additive atomic contribution of $\log P$ parameters which can be obtained by classifying atoms into different atom types according to their hybridization states and their neighbouring atoms.

Adaptation and simulation of the $AlogP$ approach

In order to adapt $\mathrm{Alog_P}$ approach to n-octanol/water partition coefficient of ferrocene derivatives, the following approximation should be made, $\log P$ value of ferrocene calculated by $\mathrm{Alog P}$ method should be equal to the experimental value of $\log P$ of ferrocene itself, which is equal to 2.66[11]. The calculation can be carried out as follows, according to $\mathrm{Alog P}$ method, the contribution of an aromatic carbon atom attached to any type of carbon symbolised by $a_{c_{ar}-c}$is greater than the contribution of an aromatic carbon atom attached to a hydrogen atom $a_{c_{ar}-H}$, the difference can be calculated as follows:

$$a_{c_{ar}-c} - a_{c_{ar}-H} = 0.1492 - (-0.3251) = 0.4743 \qquad (2)$$

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

$$a_{c_{ar}-X} - a_{c_{ar}-H} = 0.1539 - (-0.3251) = 0.4790 \qquad (3)$$

To calculate the contribution of a ferrocenyl group attached to a carbon atom or an atom of type X, the obtained values of 0.4743and 0.4790should be added to $\log P$ value of ferrocene and the contributions of the hydrogen atoms $a_H(67)$should be subtracted as indicated by equation (4).

$$\mathrm{a}_{Fc} = \log P_{Fc} - n_1(a_H - 0.4743) - n_2(a_H - 0.4790) \qquad (4)$$

$n_1$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.

$$\mathrm{a}_{Fc} = \log P_{Fc} - a_H + 0.4790 \qquad (5)$$

$$2.66 - 0.6301 + 0.4790 = 2.5089$$

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.

$$\mathrm{a}_{Fc} = \log P_{Fc} - a_H + 0.4743 \qquad (6)$$

$$2.66 - 0.6301 + 0.4743 = 2.5042$$

$\log P$, for any ferrocene derivatives of type $Fc - X'$, is therefore can be calculated by summing the contributions of a substituentX' atom type to the contribution of a ferrocenyl group as given by the following equation:

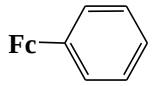
$$\log P = a_{Fc} + \mathrm{a}_{X'} \qquad (7)$$

Results and Discussion

Calculation and validation of the method

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

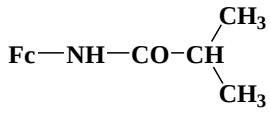
1. Phenylferrocene (1)



$\log P$ of this ferrocene derivatives is calculated according to equation 7 as follows:

$$logP = a_{Fc} + a_c\,(25) + 5a_c\,(24) + 5a_H\,(47)$$
$$= 2.5042 + 0.1492 + 5 \times (-0.3251) + 5 \times (0.6301)$$
$$logP = 4.18$$

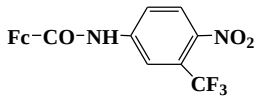
2. N-(ferrocenyl)-isobutyamide (2)



Using the same equation 7, $\log P$ of this compound is calculated as follows,

$$logP = a_{Fc} + a_N\,(72) + a_c\,(40) + a_O\,(58) + a_c\,(3) + 2 \times a_c\,(1) + a_H\,(50)$$
$$+6 \times a_H\,(46) + a_H(51)$$
$$= 2.5089 - 0.5113 - 0.1002 - 0.0233 - 0.6681 - 2 \times 1.5603 - 0.1036$$
$$+6 \times 0.7341 + 0.5234$$
$$logP = 2.90$$

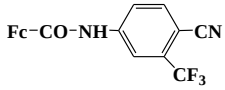
3. N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide (3)



Ferrocene with a basic fragment linked to two aromatic rings is described in this compound, $\log P$ is obtained by summing the atom types of each group in the molecule, ferrocenyl, amidephenyl with three substituents, nitro and trifluoromethyl,

$$logP = a_{Fc} + a_N(72) + a_c(40) + a_O(58) + 2 \times a_c(26) + 3 \times a_c(24)_+ a_c(25)$$
$$+a_H(50) + 3 \times a_H(47) + a_c(13) + 3\,a_F(83)_+ a_N(76) + 2 \times a_O(61)$$
$$logP = 2.5042 - 0.5113 - 0.1002 - 0.0233 + 0.1492 - 3 \times 0.3251 + 2 \times 0.1539$$
$$-0.1036 + 3 \times 0.6301 + 0.7894 + 3 \times 0.1029 - 2.0585 + 2 \times 1.052$$
$$logP = 4.28$$

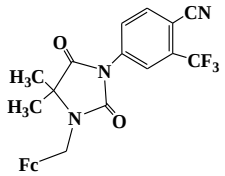
4. N-[4-cyano-3-trifluoromethylphenyl]-ferrocenecarboxamide (4)



$\log P$ of this ferrocene derivatives which contains a basic fragment linked to aromatic ring, is obtained by summing the contribution of each atom types of constituent of the molecule (i.e. ferrocenyl, carbons, nitrogen, oxygen, fluoride and hydrogen),these contribution can be obtained as follows :

$$log\ \text{ıı} = a_{Fc} + a_N(72) + a_c(40) + a_O(58) + 2 \times a_c(25) + 3 \times a_c(24) + a_c(26)$$
$$+ a_H(50) + 3 \times a_H(47) + a_c(13) + 3\ a_F(83) + a_N(74) + a_C(40)$$
$$logP = 2.5042 - 0.5113 - 0.1002 - 0.0233 + 2 \times 0.1492 - 3 \times 0.3251 + 0.1539$$
$$-0.1036 + 3 \times 0.6301 + 0.7894 + 3 \times 0.1029 + 0.1349 - 0.1002$$
$$logP = 4.26$$

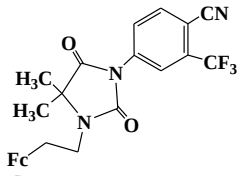
5. 4-(4',4'-dimethyl-2',5'-dioxo-3'-ferrocenylmethyl-1'-imidazolidinyl)-2-trifluoromethylbenzonitrile(5)



logPfor this derivatives is calculated using equation 7, as follows,

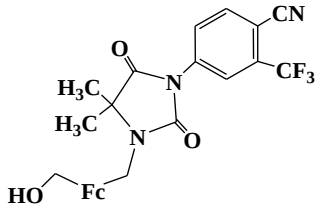
$$logP = a_{Fc} + a_N(68) + a_c(6) + a_c(41) + 2 \times a_O(58) + a_N(72) + 2 \times a_c(25) +$$
$$3 \times a_c(24) + a_c(26) + 6 \times a_H(52) + 5 \times a_H(47) + a_c(13) + 3\ a_F(83) + a_N(74)$$
$$+ 2 \times a_c(24) + 2 \times a_c(1) + a_c(11)$$
$$logP = 2.5042 - 1.2486 + 0.0132 + 0.4182 - 2 \times 0.0233 - 0.5113 + 2 \times 0.1492$$
$$-3 \times 0.3251 + 0.1539 + 6 \times 0.6666 + 5 \times 0.6301 + 0.7894 + 3 \times 0.1029 +$$
$$0.1349 - 2 \times 0.1002 - 2 \times 1.5603 - 0.2849 = 5.38$$
$$logP = 5.38$$

6.4-(4',4'-dimethyl-2',5'-dioxo-3'-ferrocenylethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile (6)



$$logP = a_{Fc} + a_c(2) + a_N(68) + a_c(6) + a_c(41) + 2 \times a_O(58) + a_N(72)$$
$$+ 2 \times a_c(25) + 3 \times a_c(24) + a_c(26) + 8 \times a_H(52) + 5 \times a_H(47)$$
$$+ a_c(13) + 3\ a_F(83) + a_N(74) + 2 \times a_c(40) + 2 \times a_c(1) + a_c(11)$$
$$logP = 2.5042 - 1.0120 - 1.2486 + 0.0132 + 0.4182 - 2 \times 0.0233 - 0.5113$$
$$2 \times 0.1492 - 3 \times 0.3251 + 0.1539 + 8 \times 0.6666 + 5 \times 0.6301 + 0.7894 + 0.1349$$
$$3 \times 0.1029 - 2 \times 0.1002 - 2 \times 1.5603 - 0.2849 = 5.7045$$
$$logP = 5.70$$

7. 4-(4',4'-dimethyl-2',5'-dioxo-3'-ferrocenylmethyl-1'-imidazolidinyl)-2-trifluoromethyl- benzonitrile (7)

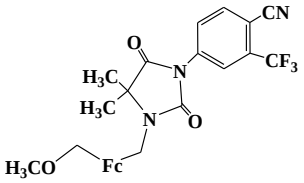


The ferrocenyl group in this derivative is attached to two carbon atoms, its contribution is calculated from equation4 where n_1 is equal to2and $n_2$is equal to 0.

$$logP = a_{Fc} + 2 \times a_c(6) + a_O(56) + a_N(68) + a_c(41) + 2 \times a_O(58) + a_N(72)$$
$$+ 2 \times a_c(25) + a_c(26) + 3 \times a_c(24) + a_H(50) + 6 \times a_H(52) + 7 \times a_H(47)$$
$$+ a_c(13) + 3\ a_F(83) + a_N(74) + 2 \times a_c(40) + 2 \times a_c(1) + a_c(11)$$
$$logP = 2.3484 - 2 \times 1.2486 - 0.3567 + 0.0132 + 0.4182 - 2 \times 0.0233 - 0.5113$$
$$2 \times 0.1492 - 3 \times 0.3251 + 0.1539 + 6 \times 0.6666 + 7 \times 0.6301 + 0.7894 + 0.1349$$
$$3 \times 0.1029 - 2 \times 0.1002 - 2 \times 1.5603 - 0.2849 - 0.1036 = 4.77$$
$$l\ gP = 4.77$$

8. 4-[4',4'-dimethyl-2',5'-dioxo-1'-imidazolidinyl-(3'-ortho-methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile (8)

This compound is an example of ferrocene with electronic effect $\log P$ is calculated by summing the different atom types that form the molecule in a similar manner as the above calculation.

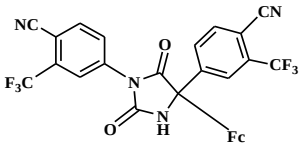


$$logP = a_{Fc} + 2 \times a_c(6) + a_O(59) + a_c(5) + a_N(68) + a_c(41) + 2 \times a_O(58) + + a_N(72) + 2 \times a_c(25) + 3 \times a_c(24) + a_c(26) + 6 \times a_H(52) + 10 \times a_H(47) + a_c(13) + 3\, a_F(83) + a_N(74) + 2 \times a_c(40) + 2 \times a_c(1) + a_c(11)$$

$$logP = 2.3484 - 2 \times 1.2486 - 0.1541 - 1.788 + 0.0132 + 0.4182 - 2 \times 0.0233 - 0.5113 + 2 \times 0.1492 - 3 \times 0.3251 + 0.1539 + 6 \times 0.6666 + 10 \times 0.6301 + 0.7894 + 0.1349 + 3 \times 0.1029 - 2 \times 0.1002 - 2 \times 1.5603 - 0.2849 = 5.187$$

$$logP = 5.18$$

9.4'-ferrocényl-1',4'-[*bis*-(2-trifluorométhyl-1-cyano-phényl)]-2',5'-imidazolidinedione(10)

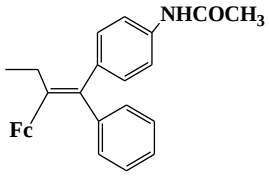


$$logP = a_{Fc} + a_c(11) + 3 \times a_c(40) + a_c(41) + 2 \times a_O(58) + a_N(72) + a_N(67) + 5 \times a_c(25) + 6 \times a_c(24) + a_c(26) + a_H(50) + 6 \times a_H(47) + 2 \times a_c(13) + 6\, a_F(83) + 2 \times a_N(74).$$

$$logP = 2.5042 - 0.2849 - 3 \times 0.1002 + 0.4182 - 2 \times 0.0233 - 0.5113 - 0.3168 + 5 \times 0.1492 - 6 \times 0.3251 + 0.1539 - 0.1036 + 6 \times 0.6301 + 2 \times 0.7894 + 6 \times 0.1029 + 2 \times 0.1349 = 6.55$$

$$logP = 6.55$$

10. N-(4-(-2-(ferrocenyl)-1- phenylbut-1- enyl) phenyl)acetamide

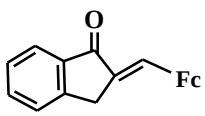


$$logP = a_{Fc} + 2 \times a_C(1) + a_c(2) + 2 \times a_C(17) + 9 \times a_c(24) + 2 \times a_c(25) + a_c(26) + a_0(58) + a_C(40) + a_N(72) + 3 \times a_H(51) + a_H(50) + 9 \times a_H(47) + 5 \times a_H(46)$$

$$logP = 2.5042 - 2 \times 1.5603 - 1.012 + 2 \times 0.0383 - 9 \times 0.3251 + 2 \times 1492 + 0.1539 - 0.0233 - 0.1002 - 0.5113 + 3 \times 5234 - 0.1036 + 9 \times 06301 + 5 \times 7341$$

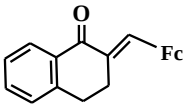
$$logP = 6.15$$

11. (E)-2-ferrocenylmethylene -2,3-dihydroinden-1-one



$$logP = a_{Fc} + 4 \times a_C\,(24) + 2 \times a_C\,(25) + a_c\,(2) + a_C\,(39) + a_c\,(16) + a_c\,(17)_+$$
$$+a_0\,(58) + 2 \times a_H(46) + 5 \times a_H\,(47)$$
$$logP = 2.5042 - 4 \times 0.3251 + 0.1492 - 0.0909 - 0.3962 + 0.0383 - 0.0233 + 2 \times 0.7341 + 5 \times 0.6301$$
$$logP = 4.64$$

12. (E)-2-ferrocenylmethylene -3,4-dihydronaphthalen(2H)-1-one



$$logP = a_{Fc} + 4 \times a_C\,(24) + 2 \times a_C\,(25) + 2 \times a_c\,(2) + a_C\,(39) + a_c\,(16) + a_c\,(17)_+$$
$$+a_0\,(58) + 4 \times a_H(46) + 5 \times a_H\,(47)$$
$$logP = 2.5042 - 4 \times 0.3251 + 2 \times 0.1492 - 2 \times 0.0909 - 0.3962 + 0.0383 - 0.0233 + 4 \times 0.7341 + 5 \times 0.6301$$
$$logP = 5.09$$

Obtained values of $\log P$ for the twelve ferrocene derivatives are summarised in table 1.

Table1.Calculated $\log P$ and absolute error results for examined ferrocene derivatives

compound	Calculated $logP_{cal.}$	Experimental $logP_{exp.}$*	absolute error AE**
1	4.18	4.59	0.41
2	2.90	2.64	0.26
3	4.28	4.42	0.14
4	4.26	4.10	0.16
5	5.38	5.23	0.15
6	5.70	5.62	0.08
7	4.77	4.44	0.33
8	5.18	5.08	0.10
9	6.55	6.47	0.08
10	6.15	5.92	0.23
11	4.64	4.77	0.13
12	5.09	5.27	0.18

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

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 0.95.

In this work, we have successfully developed a theoretical method for the prediction of octanol/water partition coefficients of ferrocene derivatives. Predictions are based on the adaptation of the existing AlogP approach. For the first time, we have become able to calculate the partition coefficient of ferrocene derivatives. Values of experimental and calculated logP for a series of twelve ferrocene derivatives are in good agreement.

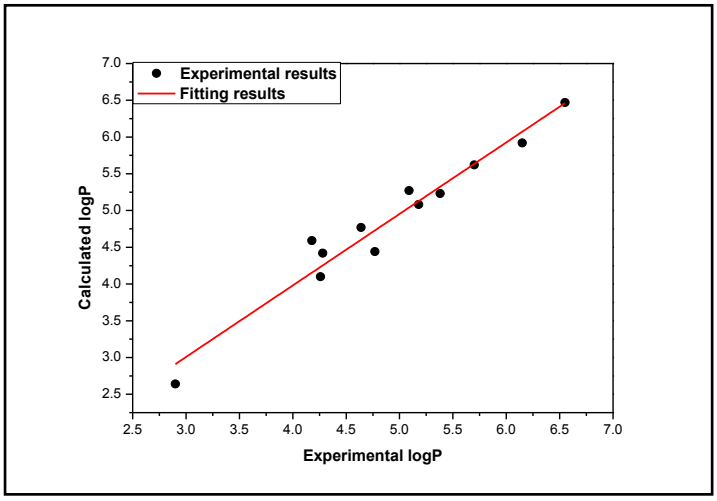


Figure 1. Correlation between experimental and calculated $logP$ of substituted ferrocene

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