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Research article

A NEW METHOD FOR THE ESTIMATION OF OCTANOL/WATER PARTITION COEFFICIENT OF SUBSTITUTED FERROCENE USING THE ATOM-ADDITIVE METHOD

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ABSTRACT

Octanol/water partition coefficients P of selected substituted ferrocene were determined for the first time using the atom-additive method. We have investigated the accuracy of obtained theoretical partition coefficients values of logP for all studied substituted ferrocene with known experimental values obtained from the literature. It was shown that calculated partition coefficients were in good agreement with experimental values. For estimation of the octanol/water partition coefficients of the selected compounds, the average absolute error of log P is 0.14, and the average relative error is 33 %.

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

INTRODUCTION

The n-octanol water partition coefficients of a substance between an organic phase and water, usually expressed as logP values, are used as a measure of lipophilicity of this substance. Lipophilicity of a substance is one of the parameters, which influence its biological activity[1-9]. It can be determined experimentally by a classical method[10] or it can be determined by theoretical calculations. The importance of the use of partition coefficients in quantitative structure activity relationships (QSAR) is well established for prediction of biological or pharmacological activity of compounds[11-14]. Hansch et al. initiated the study of QSAR in 1962, with a publication on plant growth regulation in which bioactivity was successfully coupled with lipophilicities and electronic character of the phenyl substituents[10, 15]. The possibility to predict drugs biological properties due to their lipophilicity allows the optimization of new drugs structure designs.

In previous work we presented the calculation of logP of ferrocene derivatives using the Rekker method[16]. We herein present a new and simple

method for the calculation of this very important parameter that quantifies the lipophilicity of substituted ferrocene. The method used for obtaining logP of substituted ferrocene is based upon the adaptation of atom-additive xlogP method used for organic molecules[17].

RESULTS AND DISCUSSION

We describe in this section the generation of our method for logP calculation of substituted ferrocene. This calculation is based upon the adaptation of the exciting atom-additive xlogP method, which considers the partition molecular species between an aqueous phase and an organic phase (octanol).

Principle of the xlogp approach

Atom-additive xlogP method gives logP values by summing the contributions of component atoms and correction factors. The contributions of each atom type and correction factor are derived by multivariate regression analysis of 1853 organic compounds with known experimental logP values[17].

$$\log P = \sum a_i A_i + \sum b_j B_j \quad (1)$$

where a_i and b_j are regression coefficients, A_i is the number of occurrences of the *i*th atom type, and B_j is the number of occurrences of the jth correction factor.

The method is based on additive atomic contribution of logP parameters which can be obtained by classifying atoms into different atom types according to their hybridization states and their neighboring atoms; we also include correction factors to accounts for some intramolecular interaction.

Adaptation and simulation of the xlogp approach

Since the theoretical value of the octanol/water partition coefficient logP of ferrocene itself is not known and is not described in the literature, we consider that the octanol/water partition coefficient logP value of ferrocene, calculated by the xlogP method, is equal to the experimental value of logP, which is equal to 2.66[18].

According to xlogP method, the contribution of an aromatic carbon atom attached to any type of carbon $a_{C_{ar-C}}$ is greater than the contribution of an aromatic carbon atom attached to hydrogen atom $a_{C_{ar-H}}$, the difference can be calculated as follows:

$$a_{C_{ar-C}} - a_{C_{ar-H}} = 0.302 - 0.281 = 0.021 \quad (2)$$

The contribution of an aromatic carbon atom attached to an atom X (O, N, S, P,…) $a_{C_{ar-X}}$ is less than the contribution of an aromatic carbon atom attached to hydrogen atom $a_{C_{ar-H}}$, the difference can also be calculated from the following equation 3,

$a_{C_{ar}-X} - a_{C_{ar}-H} = -0.064 - 0.281 = -0.345$ (3)

To calculate the contribution of a ferrocenyl group attached to a carbon atom or an atom of type X, these values 0.021 and -0.345 should be added to a logP value of ferrocene and the contributions of the hydrogen atoms a_H should be subtracted

$a_{Fc} = \log P_{Fc} - n_1(a_H - 0.021) - n_2(a_H + 0.345)$ (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, and $0 \le n_1 + n_2 \le 10$.

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 zero.

$$a_{Fc} = \log P_{Fc} - a_H - 0.345 = 2.66 - 0.046 - 0.345 = 2.269 \quad (5)$$

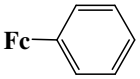
If a ferrocenyl group is attached to a carbon atom, its contribution is calculated from the same equation 4; with n_2 in this case is equal zero.

$$a_{Fc} = \log P_{Fc} - a_H - 0.345 = 2.66 - 0.046 + 0.021 = 2.635 \quad (6)$$

CALCULATION AND VALIDATION OF THE METHOD

We validated our method for the calculation of logP with ten different substituted ferrocene (mainly selected from literature sources)[19]. We recommend carrying out the calculations in three decimals, with the final result rounded to two decimals.

1. Phenylferrocene (1)



logP for this compound is calculated, according to equation 1, as follows:

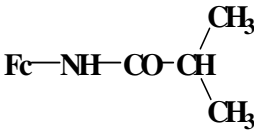
$\log P = a_{Fc} + a_C(29) + 5a_C(26) + 5a_H(37)$

The number between brackets is the atom type in xlogP.

$\log P = 2.635 + 0.302 + 5 \times 0.281 + 5 \times 0.046$

$\log P = 4.57$

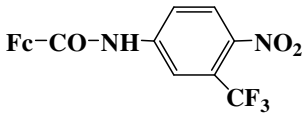
2. N-(ferrocenyl)-isobutyamide (2)



$\log P = a_{Fc} + 2a_{CH_3}(1) + a_{RNH}(64) + a_{R_3CH}(9) + 8a_H(37) + a_{XRC=X}(24)$

$\log P = 2.269 + 2 \times 0.484 + (-0.212) + (-0.138) + (-2.057) + 8 \times 0.046 + 1.637,\ \log P = 2.83$

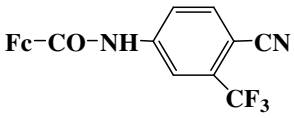
3. N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide (3)



$\log P = a_{Fc} + 3a_C(28) + a_C(29) + 2a_C(30) + a_{RNH}(64) + a_{R=O}(44) + 4a_H(37) + a_{XRC=X}(24) + a_C(16) + 3a_F(72) + a_{NO_2}(80)$

$\log P = 2.635 + 3 \times 0.281 + 0.302 + 2 \times (-0.064) + (-0.212) + (-2.057) + 4 \times 0.046 + 1.637 + (-0.699) + 3 \times 0.493 + 0.264,\ \log P = 4.25$

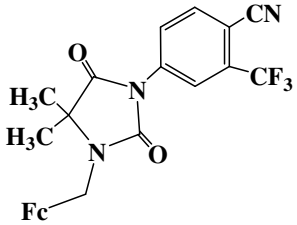
4. N-[4-cyano-3-trifluoromethyl-phenyl]-ferrocenecarboxamide (4)



$$\log P = a_{Fc} + 3a_C(28) + 2a_C(29) + a_C(30) + a_{RNH}(64) + a_{R=O}(44) + 4a_H(37) + a_{XRC=X}(24) + a_C(16) + 3a_F(72) + a_{CN}(77)$$

$$\text{logP} = 2.635 + 3\times0.281 + 2\times0.302 + 2\times(-0.064) + (-0.212) + (-2.057) + 4\times0.046 + 1.637 + (-0.699) + 3\times0.493 + (-0.256),\ \ \text{logP} = 4.09$$

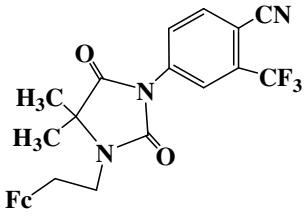
5. 4-(4',4'-dimethyl-2',5'-dioxo-3'-ferrocenylmethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile (5)



$$\log P = a_{Fc} + 3a_C(28) + 2a_C(29) + a_C(30) + 2a_{R_2N}(51) + 2a_{R=O}(44) + 11a_H(37) + 2a_{XRC=X}(24) + a_C(16) + a_{CH_3}(1) + a_C(14) + a_{CH_2}(6) + 3a_F(72) + a_{CN}(77)$$

$$\log P = 2.635 + 3\times0.281 + 2\times0.302 + (-0.064) + 2(0.443) + 2(-2.057) + 11\times0.046 + 2\times1.637 + (-0.699) + 2\times0.484 + (-0.598) + (-0.344) + 3\times0.493 + (-0.256),\ \log P = 5.12$$

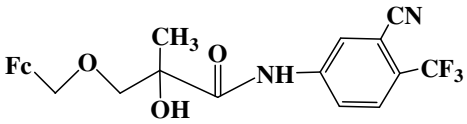
6. 4-(4',4'-dimethyl-2',5'-dioxo-3'-ferrocenylethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile (6)



$$\log P = a_{Fc} + 3a_C(28) + 2a_C(29) + a_C(30) + 2a_{R_2N}(51) + 2a_{R=O}(44) + 13a_H(37) + 2a_{XRC=X}(24) + a_C(16) + 2a_{CH_3}(1) + a_C(14) + a_{CH_2}(5) + a_{CH_2}(6) + 3a_F(72) + a_{CN}(77)$$

$$\log P = 2.635 + 3\times0.281 + 2\times0.302 + (-0.064) + 2(0.443) + 2(-2.057) + 13\times0.046 + 2\times1.637 + (-0.699) + 2\times0.484 + (-0.598) + 0.009 + (-0.344) + 3\times0.493 + (-0.256)$$
$$\log P = 5.22$$

7. N-(4-cyano-3-trifluoro methylphenyl) -3-ferrocenylmethoxy-2-hydroxy-2-methyl-propanamide (7)

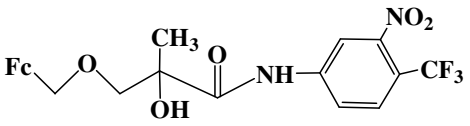


$$\log P = a_{Fc} + 3a_C(28) + 2a_C(29) + a_C(30) + a_{RNH}(64) + 2a_O(41) + a_{OH}(38) + a_C(14) + 2a_{CH_2}(6) + 2a_{CH_3}(1) + a_{R=O}(44) + 12a_H(37) + a_{XRC=X}(24) + a_C(16) + 3a_F(72) + a_{CN}(77) + 2I_H$$

I_H: Correction for Intermolecular hydrogen bond

$$\log P = 2.635 + 3\times0.281 + 2\times0.302 + (-0.064) + (-0.212) + 0.397 + (-0.399) + (-0.598) + 2(-0.344) + 0.484 + (-2.057) + 12\times0.046 + 1.637 + (-0.699) + 3\times0.493 + (-0.256) + 2\times0.6, \log P = 4.86$$

8. 3-ferrocenylmethoxy-2-hydroxy-2-methyl-N-(4-nitro-3-trifluoromethyl-phenyl)-propanamide (8)

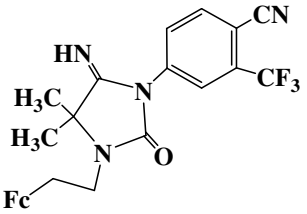


$$\log P = a_{Fc} + 3a_C(28) + a_C(29) + 2a_C(30) + a_{RNH}(64) + a_O(41) + a_{OH}(38) + a_C(14) + 2a_{CH_2}(6) + a_{CH_3}(1) + a_{R=O}(44) + 12a_H(37) + a_{XRC=X}(24) + a_C(16) + 3a_F(72) + a_{NO_2}(80) + 2I_H$$

I_H: Correction for Intermolecular hydrogen bond

$$\log P = 2.635 + 3\times0.281 + 0.302 + 2\times(-0.064) + (-0.212) + 0.397 + (-0.399) + (-0.598) + 2(-0.344) + 0.484 + (-2.057) + 12\times0.046 + 1.637 + (-0.699) + 3\times0.493 + 0.264 + 2\times0.6,\ \log P = 5.01$$

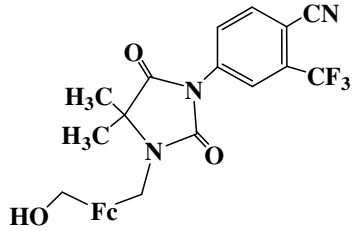
9. 4-(4',4'-dimethyl-3'-ferrocenylethyl-5'-imino-2'-oxo-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile (9)



$$\log P = a_{Fc} + 3a_C(28) + 2a_C(29) + a_C(30) + 2a_{R_2N}(51) + a_{R=O}(44) + a_{H-N=C}(53) + 14a_H(37) + 2a_{XRC=X}(24) + a_C(16) + 2a_{CH_3}(1) + a_C(14) + a_{CH_2}(5) + a_{CH_2}(6) + 3a_F(72) + a_{CN}(77)$$

$$\log P = 2.635 + 3\times0.281 + 2\times0.302 + (-0.064) + 2(0.443) + (-2.057) + (-2.052) + 14\times0.046 + 2\times1.637 + (-0.699) + 2\times0.484 + (-0.598) + 0.009 + (-0.344) + 3\times0.493 + (-0.256)$$
$$\log P = 5.27$$

10. 4-(4',4'-dimethyl-2',5'-dioxo-3'-ferrocenylmethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile (10)

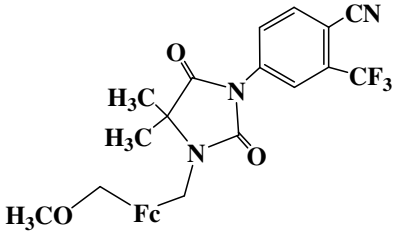


$$\log P = a_{Fc} + 3a_C(28) + 2a_C(29) + a_C(30) + 2a_{R_2N}(51) + a_{R=O}(44) + 14a_H(37) + 2a_{XRC=X}(24) + a_C(16) + 2a_{CH_3}(1) + a_C(14) + a_{CH_2}(6) + a_{OH}(38) + 3a_F(72) + a_{CN}(77)$$

The ferrocenyl group in this derivative is attached to two carbon atoms, its contribution is calculated from equation 4 where $n_1 = 2$ and $n_2 = 0$

$$\log P = 2.610 + 3\times0.281 + 2\times0.302 + (-0.064) + 2(0.443) + 2(-2.057) + 14\times0.046 + 2\times1.637(-0.699) + 2\times0.484 + (-0.598) + 2(-0.344) + (-0.399) + 3\times0.493 + (-0.256)$$
$$\log P = 4.49$$

11. 4-[4',4'-dimethyl-2',5'-dioxo-1'-imidazolidinyl-(3'-ortho-methoxy-methyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile (11)



$$\log P = a_{Fc} + 3a_C(28) + 2a_C(29) + a_C(30) + 2a_{R_2N}(51) + a_{R=O}(44) + 16a_H(37) + 2a_{XRC=X}(24) + a_C(16) + 2a_{CH_3}(1) + a_C(14) + a_{CH_3}(3) + 2a_{CH_2}(6) + a_O(41) + 3a_F(72) + a_{CN}(77)$$

$$\log P = 2.610 + 3\times0.281 + 2\times0.302 + (-0.064) + 2(0.443) + 2(-2.057) + 16\times0.046 + 2\times1.637 + (-0.699) + 2\times0.484 + (-0.598) + (-0.181) + 2(-0.344) + 0.397 + 3\times0.493 + (-0.256)$$

$$\log P = 5.20$$

Table 1 : Estimation results

compound	$\log P_{calc.}$	$\log P_{exp.}$[19]	AE	RE
1	4.57	4.59	0.02	04.50
2	2.83	2.64	0.19	54.90
3	4.25	4.42	0.17	32.40
4	4.09	4.10	0.01	02.28
5	5.12	5.23	0.11	22.30
6	5.22	5.62	0.40	60.10
7	4.86	4.63	0.23	69.80
8	5.01	5.01	0.00	00.00
9	5.27	5.04	0.23	69.80
10	4.49	4.44	0.05	12.20
11	5.20	5.08	0.12	31.80

To analyze the error of the results, the absolute error of logP, AE, is calculated by formula 7, and the related error of P, RE, is calculated by formula 8. The results are shown in Table 1.

$$\Delta \log P = \left| \log P_{calc.} - \log P_{\text{exp.}} \right| \quad (7)$$

$$RE = \left| \frac{P_{calc.} - P_{\text{exp.}}}{P_{\text{exp.}}} \right| \times 100 \quad (8)$$

CONCLUSION

In this study we successfully find a theoretical method for the estimation of the octanol/water partition coefficients of substituted ferrocene. The calculations are based on the atom-additive method starting from ferrocene compound. After having adapted this method for the calculation of partition coefficient, we became able, for the first time, to apply the xlogP method for calculations of the partition coefficient of substituted ferrocene. Values of experimental and calculated logP for a series of substituted ferrocene are in good agreement. This approves the process of adaptation. The results obtained for logP enable us to consider that the process is a solution for calculating partition coefficient for ferrocene derivatives and generalizing it to include all analogous complex compounds.

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