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PREDICTION OF OCTANOL/WATER PARTITION COEFFICIENT OF SELECTED FERROCENE DERIVATIVES USING REKKER METHOD

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ABSTRACT

In this work we present a theoretical approach for the determination of octanol/water partition coefficient of selected ferrocenes bearing different substituents, the calculation is based on the adaptation of the Rekker method. Our prediction of obtained theoretical partition coefficients values of logP for all studied substituted ferrocene was confirmed by comparison with known experimental values obtained mainly from literature. The results obtained show that calculated partition coefficients are 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 0.13, and The correlation coefficient is $R^2 = 0.966$.

Key words: experimental logP, theoretical partition coefficient, substituted ferrocene, lipophilicity, QSAR.

1. INTRODUCTION

In recent years the octanol/water partition coefficient logP has become a key parameter in studies of the environmental fate of organic chemicals. Because of its increasing use in the estimation of many other properties, logP is considered a required property in studies of new or problematic chemicals. Although this surmounting interest in octanol/water partition coefficient measurements lays out over the past 90 years, no comprehensive articles of the partition coefficient of ferrocene derivatives have ever been published.

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In fact, despite the ferrocene itself, no value of partition coefficients has appeared in the literature. Among the many different theoretical methods for the calculation of logP of several simple aliphatic and aromatic compounds, which is described in literature,[1-4] no one of these arithmetic methods can be applied to organometallic compounds, such as ferrocene derivatives. The very rapid expansion of ferrocene chemistry during the last 50 years, notably in areas related to biology, medicine, catalysis and materials [5-9], led us to turn our attention to the octanol/water partition coefficient of ferrocene derivatives, the aim of the present paper is to present a new and simple method for the calculation of this very important parameter that quantifies the lipophilicity of these derivatives and connects between their structure and their biological activities. The calculation used for obtaining logP of ferrocene derivatives is based upon the adaptation of the Rekker method used for organic molecules [1-10].

We herein present a 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 Rekker method used for organic molecules.

2. RESULTS AND DISCUSSION

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

3. PRINCIPLE OF THE REKKER APPROACH

The calculation of logP according to Rekker method, which is a fragmental approach, is based on the decomposition of the molecule into small suitable substructures to which are attributed theoretical hydrophobic values. The contribution of a fragment is represented by a fragmental constant noted f_i the summing of these values together, taking into account corrections needed for certain intramolecular interactions should give the theoretical value of logP. All type of corrections like resonance, hydrogen bonding, ring fusion, and others requires the addition of a multiple of a constant noted C_M, which Rekker called the “magic constant”, the partition coefficient of the considered molecule is given by the following equation:

$$\log P = \sum_{i=1}^{n} a_i \times f_i + \sum_{i=1}^{m} k_i \times C_M \quad (1)$$

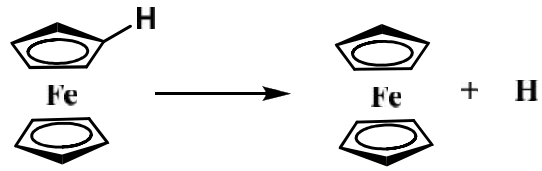
Where f_i is the fragmental constant, and a_i its number, C_M is the correction factor, and k_i the frequency of C_M that varies with the type of intramolecular interactions and always is an integer not a fraction.

In the following article, calculated partition coefficients using this method are symbolized as $\log P_{cal.}$, while experimental partition coefficient are symbolized as $\log P_{exp}$.

3.1. Adaptation of the Rekker approach:

Since the theoretical value of the octanol/water partition coefficient logP of the ferrocene molecule is not known and is not so far described in the literature and since the ferrocene molecule does not contain any hydrogen bonding or any interaction which can affect its value of logP, we consider the theoretical value of logP of the ferrocene molecule is equal to the experimental value which is 2.66[11].

A ferrocenyl group is regarded as a ferrocene molecule minus an atom of hydrogen as demonstrated by the following scheme 1:



ferrocene ferrocenyl

Scheme 1 *obtaining of a ferrocenyl group*

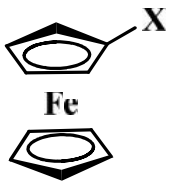
The contribution of a ferrocenyl group is therefore obtained by the subtraction of a contribution of a hydrogen atom from the ferrocene molecule as indicated by the following relation.

$$f_{F_C} = \log P_{F_C-H} - f_H \quad (2)$$

Where $\log P_{F_C-H}$ is the logarithm of the n-octanol/water of ferrocene, f_{Fc} and f_H are the contributions of the theoretical hydrophobic values of the ferrocenyl group and the hydrogen atom, respectively, the numerical application gives:

$$f_{FC} = 2.660 - 0.204 = 2.456 \quad (3)$$

The logP, for any ferrocene derivatives F_C-X, of formula



Ferrocene derivative

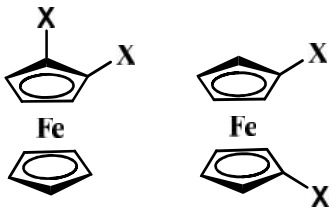
is therefore can be calculated by summing the contribution of a substituent X, to the contribution of a ferrocenyl group and adding the corrective term C_M as given by equation 4

$$\log P = 2.456 + f_X + \sum C_M \quad (4)$$

C_M is equal to 0.219.

f_X can be obtained from[1], F_C refers to ferrocenyl group

When two substituents are introduced to the ferrocene, the contribution of a ferrocenyl group is calculated in this case as follows:



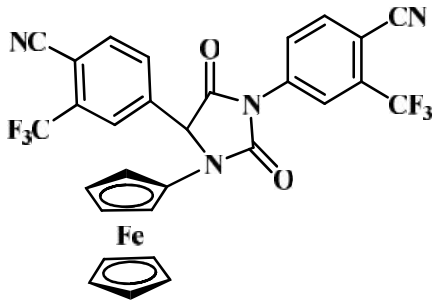
$$f_{FC} = 2.660 - 2 \times 0.204 = 2.252 \quad (5)$$

3.2. Calculation and validation of the model

We validated our approach with 10 different ferrocene derivatives (selected from literature sources [12-14]). We recommend carrying out the calculations in three decimals, with the final result rounded to two decimals.

4’-ferrocényl-1’,4’-[bis-(2-trifluorométhyl-1-cyano-phényl)]-2’,5’-imidazolidinedione

This compound (1) is an example of ferrocene linked to a direct heterocyclic ring , we propose for these type of molecules a correction factor of 6 C_M, 3 C_M for the proximity effects and 3 C_M for hydrogen band, logP is obtained by the summation of the value of the fragmental constant of the all of fragments in the molecule and the addition of a corrective term ,the method of calculating of logP is illustrated in table I-1.



(1)

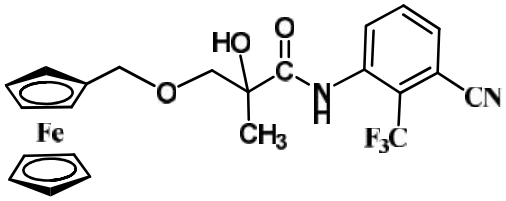
4’-ferrocényl-1’,4’-[*bis*-(2-trifluorométhyl-1-cyano-phényl)]-2’,5’-imidazolidinedione

Table I-1. Calculation of logP for compound (1)

fragment	a_i	f_i	$a_i \times f_i$
Fc	1	2.456	2.456
C=O	1	-0.976	-0.976
$NHCONH_2$	1	-1.596	-1.596
C_6H_3	2	1.494	2.988
C	1	0.110	0.110
CN	2	-0.155	-0.31
CF_3	2	1.223	2.446
$k_i \times C_M$		6×0.219	1.314
$logP_{cal.}$			6.64

1. N-(4-cyano-3-trifluoromethylphenyl)-3-ferrocenylmethoxy-2-hydroxy-2-methyl-propanamide

This following compound receives a correction of C_M value +9 because it has a proximity effects over two carbons between O and OH +2C_M, the proximity effect over one carbon between NHCO and OH+3 C_M, the branching effect with a quaternary C ($CCH_2(CH_3)$-OH),-2C_M , two intermolecular hydrogen bond +3C_M for each one.



(2)

N-(4-cyano-3-trifluoromethylphenyl)-3-ferrocenylmethoxy-2-hydroxy-2-methyl-propanamide

Table I-2. *Calculation method of logP for compound (2)*

fragment	a_i	f_i	$a_i \times f_i$
Fc	1	2.456	2.456
OH	1	-1.448	-1.448
CONH	1	-1.596	-1.596
C_6H_3	1	1.494	1.494
CH_3	1	0.724	0.724
CH_2	2	0.519	1.038
CN	1	-0.155	-0.155
C	1	0.110	0.110
O	1	-1.545	-1.545
CF_3	1	1.223	1.223
$k_i \times C_M$		9×0.219	1. 971
$logP_{cal.}$			4.40

2. 3-ferrocenylmethoxy-2-hydroxy-2-methyl-N-(4-nitro-3-trifluoromethylphenyl)-propanamide

The compound needed a correction factor of +12 C_M which can be distributed as follows:

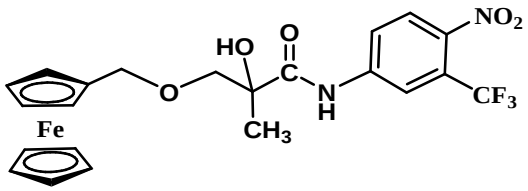
+2 C_M for the proximity effect over two carbons between O and OH.

+3 C_M for the proximity effect over one carbon between NHCO and OH.

-2 C_M for the branching effect with a quaternary C ($CCH_2(CH_3)$-OH).

+6 C_M for the two intermolecular hydrogen bond +3C_M for each one.

+3 C_M for the resonance between NHC(O) and NO_2.



(3)

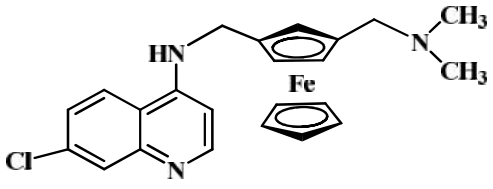
3-ferrocenylmethoxy-2-hydroxy-2-methyl-N-(4-nitro-3-trifluoromethylphenyl)-Propanamide

Table I-3. *Calculation of logP for compound (3)*

fragment	a_i	f_i	$a_i \times f_i$
Fc	1	2.456	2.456
OH	1	-1.448	-1.448
CONH	1	-1.596	-1.596
C_6H_3	1	1.494	1.494
CH_3	1	0.724	0.724
CH_2	2	0.519	1.038
NO_2	1	-0.039	-0.039
C	1	0.110	0.110
O	1	-1.545	-1.545
CF_3	1	1.223	1.223
$k_i \times C_M$		12×0.219	2. 628
$logP_{cal.}$			5.17

3. N-(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-amine

We propose as correction factor for this type of compounds the value of 3 C_M for the hydrogen bond .



(4)

N-(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-amine

Table I-4. *Calculation of logP for compound (4)*

fragment	a_i	f_i	$a_i \times f_i$
Fc	1	2.456-0.204	2.252
arNH	1	-0.938	-0.938
Quinolinyl	1	1.821-0.204	1.617
CH_3	2	0.724	1.448
CH_2	2	0.519	1.038
N	1	-2.074	-2.074
Cl	1	0.933	0.933
$k_i \times C_M$		3×0.219	0.657
$logP_{cal.}$			4.93

4. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-methylamine

We propose no correction for these type of compounds, logP is calculated as mentioned before, $logP_{cal.}$ = 4.96.

5. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-butylamine

We propose no correction for these types of compounds, logP is calculated as mentioned before, $P_{cal.} = 6.52$.

6. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-isobutylamine

We propose no correction for these types of compounds, logP is calculated as mentioned before, $logP_{cal.} = 6.52$.

7. 4-(-2-(ferrocenyl)-1-phenylbut-1-enyl)benzonitrile

Ferrocenes with two quaternary carbons bulk arises from thus carbon needs corrector factor (-2C_M for each), logP is calculated as mentioned before, $logP_{cal.} = 6.49$.

8. 1-(-1-(-4-amino phenyl)-1-phenylbut-1-en-2-yl)ferrocene

Ferrocenes with two quaternary carbons bulk arises from thus carbon needs corrector factor (-2C_M for each carbon), logP is calculated as mentioned before, $logP_{cal.} = 5.74$.

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

Ferrocenes with two quaternary carbons bulk arises from thus carbon needs corrector factor (-2C_M for each), logP is calculated as mentioned before, $logP_{cal.} = 5.80$.

In order to analyze the errors of our results for calculated partition coefficient $logP_{cal.}$, the absolute error AE of logP is calculated according to the following relation.

$$\Delta logP = \left| logP_{calc.} - logP_{exp.} \right| \quad (6)$$

The results are summarized in table II-5.

Table I-5. Estimation and absolute error results for ferrocene derivatives

compound	$logP_{calc.}$	$logP_{exp.}$[12-14]	AE
1	6.47	6.64	0.17
2	4.40	4.63	0.23
3	5.17	5.01	0.16
4	4.93	5.10	0.17
5	4.96	4.89	0.07
6	6.52	6.70	0.18
7	6.52	6.60	0.08
8	6.49	6.37	0.12
9	5.74	5.75	0.01
10	5.80	5.92	0.12

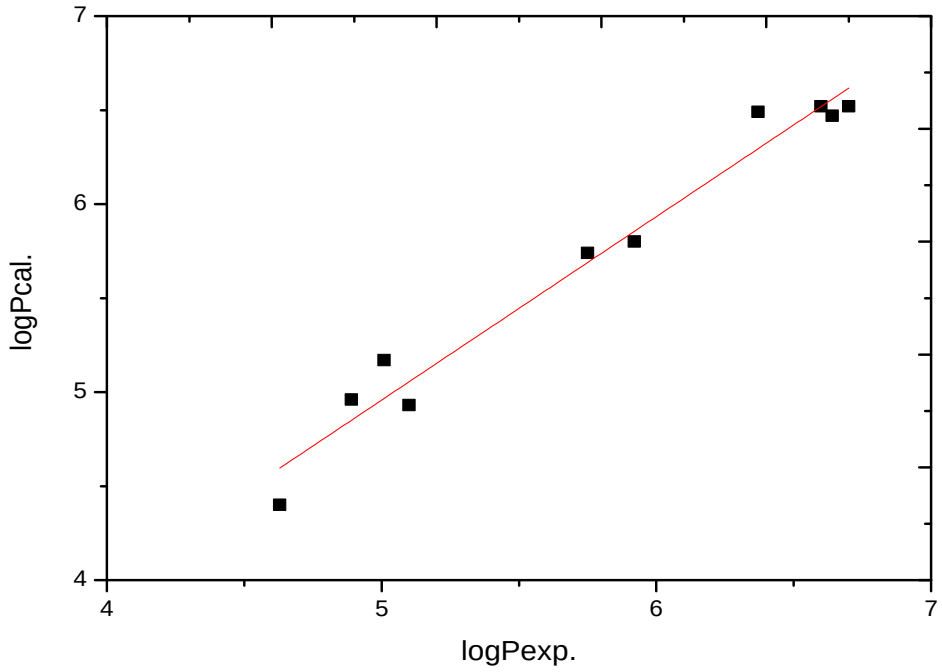


Fig.1. correlation between experimental logP and calculated logP for substituted ferrocenes

4. 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 Rekker 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 this 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.

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