

EXTENSION OF REKKER METHOD FOR THE PREDICTION OF N-OCTANOL / WATER COEFFICIENT OF FERROCENE DERIVATIVES

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ABSTRACT

Octanol/water partition coefficients logP of many selected substituted ferrocenes were predicted by calculation for the first time using the fragmental Rekker method. The calculated values of logP were compared with the experimental values. For estimation of the logP of the selected substituted ferrocenes, the average absolute error of logP is 0.08. Although the obtained values of logP by the proposed method are all very close to the experimental values, the values of logP obtained for ferrocene derivatives that do not contain a bulky group in their structure were significantly better than the results obtained for those containing a bulky group.

KEYWORDS: logP, partition coefficient, ferrocene derivatives, liquid /liquid extraction,

RESUME

Le coefficient de partage octanol/eau de quelques ferrocènes substitués a été prédit pour la première fois par l'adaptation de la méthode de Rekker. Les valeurs calculées de logP ont été comparées avec les valeurs expérimentales. La moyenne de l'erreur absolue de logP pour les dérivés ferrocéniques étudiés est de 0.08. Malgré que les valeurs obtenues de logP sont très voisines aux valeurs expérimentales, les valeurs de logP pour les ferrocènes non porteurs des groupements volumineux sont mieux que ceux porteurs des groupements volumineux.

MOTS CLES : logP, coefficient de partage, dérivés ferrocéniques, extraction liquid /liquid.

1. Introduction

In recent years the n-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. 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 estimation 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 [5-11], led us to turn our attention to the n-octanol/water partition coefficient of ferrocene derivatives, the aim of the present paper is to present an extension of the Rekker 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 extension of the Rekker method used for organic molecules [1, 12].

2. Theoretical aspect

The partition coefficient "P" of a molecular specie between two phases is defined as:

$$P = \frac{C_{S_1}}{C_{S_2}} \quad (1)$$

in which C_{S_1} and C_{S_2} are the concentrations, in mol/l, of the species in the two phases S_1 and S_2 respectively [13]. In the most general terms, then, the concentrations of any singular molecular species in two phases which are in equilibrium with one another will bear a constant ratio to each other as long as the activity coefficients remain relatively constant.

Equation 1 can be regarded as an extension of Henry's law which describes the equilibrium of a gas with its solution in some solvent, so we can write:

$$K = \frac{m}{p} \quad (2)$$

where m is the mass of gas dissolved per unit volume and p is the pressure at constant temperature. The fact that the concentration of molecules in the gaseous phase is proportional to its pressure; the latter can be replaced by C_{S_1} and the mass/unit volume of gas in solution designated by C_{S_2} . Equation 2 can then be restated as Equation 1.

In the case of ionization of the molecular spices in both phases, then the partition coefficient is replaced by the distribution coefficient D which can be defined as:

$$D = \frac{C_{S_1} + C_{S_1}^+}{C_{S_2} + C_{S_2}^+} \quad (3)$$

In which C_{S_1} and C_{S_2} are the concentration of the ionized molecular species in the both phases S_1 and S_2 respectively. For purpose of simplification of calculation we assume that there are no significant solute-solute interactions as well as no strong specific solute-solvent interactions. We also assume that there is no ionization in both phases.

3. Principle of the Rekker method

The calculation of logP, according to this method, is based upon the decomposition of the molecule into small suitable fragments to which is attributed a theoretical hydrophobic value. The summing of these theoretical hydrophobic values together with the correction terms for intramolecular interactions C_m gives the partition coefficient of the considered molecule as given by the following equation:

$$\log P = \sum a_i f_i + \sum K_j C_m \quad (4)$$

where a_i is the number of a given fragment present in the molecule and f_i is the logP increment of the fragment. The interaction terms can be expressed as an integral multiple of one single constant C_m (so-called "magic constant"). The fragment constants f_i and C_m have been determined from a list of 1054 experimental partition coefficient values of 825 compounds using multiple regression analysis[1].

4. Results and discussion

In this section we describe the generation of our model for logP calculation for ferrocene derivatives, this calculation is based upon the extension of the Rekker method which consider the partition of a molecular spice between an aqueous phase and an organic phase.

5. Extension of the Rekker method:

We describe in this section the adaptation of the Rekker method to ferrocene derivatives. Since the theoretical value of the n-octanol/water partition coefficient $\log P$ of the ferrocene molecule is not known and is not described in literature, and since the ferrocene molecule does not contain any hydrogen bonding which can affect this value, we are going to consider, in first approximation, that this theoretical value is equal to the experimental value of $\log P$ which is equal to 2.66[14].

$$\log P_{\text{theor}} = \log P_{\text{exp}} \quad (5)$$

A ferrocene derivative FcX can be either regarded as the insertion of the substituent H-X to the ferrocenyl substructure Fc or the substitution of a hydrogen atom in the ferrocene molecule by the substituent X. In this work we consider the second case, and then all we need to calculate the n-octanol/water partition coefficient $\log P$ of the ferrocenyl group is to subtract the contribution of the hydrogen atom in the molecule as follows:

$$\log P_{\text{Fc-H}} = f_{\text{Fc}} + f_{\text{H}} \quad (6)$$

where $\log P_{\text{Fc-H}}$ is the logarithm of the partition coefficient of ferrocene, f_{Fc} and f_{H} is the contribution of the theoretical hydrophobic value of the ferrocenyl group and the hydrogen atom, respectively. The numerical application gives:

$$f_{\text{Fc}} = 2.660 - 0.2045 = 2.4555 \quad (7)$$

The logarithm of the partition coefficient between n-octanol and water, $\log P$, for any ferrocene derivative FcX, is therefore calculated by substituting f_{H} in the previous relation by f_{X} and adding the corrective term C_m as given by equation 8.

$$\log P_{\text{Fc-X}} = f_{\text{Fc}} + \sum f_{\text{X}} + \sum R_f C_m = 2.4555 + \sum f_{\text{X}} + \sum R_f C_m \quad (8)$$

The values of f_{X} are obtained from literature tables[12], C_m is equal to 0.219.

If a ferrocene derivative contains a heterocyclic ring or a combination of two groups like nitro, carboxyl or carbonamide on a phenyl ring in para or meta position gives rise to a resonance interaction resulting in an increase of 3 C_m [1].

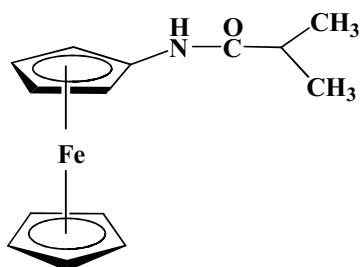
Table 1: The values of f_{al} and f_{ar}

fragment	f_{al}	f_{ar}
H	0.2045	
C	0.110	
CH	0.315	
CH ₂	0.519	
CH ₃	0.724	
C ₆ H ₅	—	1.903
N	-2.074	-0.979
O	-1.545	-0.450
S	-0.558	0.099
F	-0.213	0.444
Cl	0.057	0.933
Br	0.258	1.134
I	0.570	1.446
NO ₂	-0.915	-0.039
OH	-1.448	-0.353
SH	-0.046	0.611
NH ₂	-1.340	-0.902
NH	-1.814	-0.938
CO	-1.633	-0.976
CH=O	-0.991	-0.334
CO-O	-1.200	-0.543
O-CO	—	-0.981
COOH	-0.942	-0.066
CONH ₂	-2.011	-1.135
CONH	-2.435	-1.559
NHC=O	-2.435	-1.559
NC=O	-2.859	-1.544
CON	-2.859	-1.983
OCONH ₂	-1.405	-0.967
CONHNH	-3.348	-2.253
OCH ₃	-0.821	0.274
SCH ₃	0.166	0.823
CN	-1.031	-0.155

6. Calculation and validation of our model

We validated our model with ten different ferrocene derivatives (mainly selected from literature sources [15]) and we recommend carrying out the calculations in three decimals, with the final result rounded to two decimals.

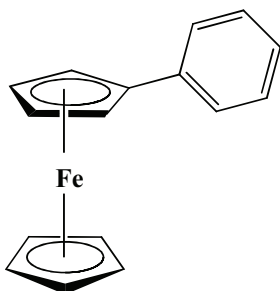
1. Ferrocenes with saturated aliphatic hydrocarbon chains or functionalized aliphatic saturated chains as exemplified by N-(ferrocenyl)-isobutyramide



Fragmental constant	contribution
Fc	2.456
arNHC=O	-1.559
CH	0.315
2xCH ₃	2x0.724
logP	2.66

No correction is needed for this type of compounds; logP is obtained by the summation of the value of the fragmental constant of the four groups in the molecule (ferrocenyl, amide, CH and CH₃).

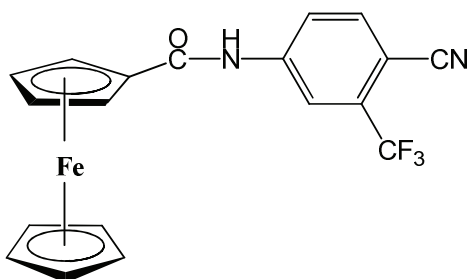
2. Ferrocenes with ferrocenyl-aryl conjugation as exemplified by Phenylferrocene requires a correction of 1 Cm.



Fragmental constant	Contribution
Fc	2.456
Ph	1.903
Aryl-aryl conjugation	0.219
logP	4.58

The conjugation require in general the application of 1 Cm, thus logP for Phenylferrocene can be obtained by the summation of the fragmental constant of the ferrocenyl and the phenyl groups which equal respectively to 2.456 and 1.902, a correction of 1 Cm = 0.219 should be added which correspond to ferrocenyl-aryl conjugation this gives a value of 4.58 for logP.

3. Ferrocenes with a basic fragment linked to two aromatic rings requires a correction of 1 Cm, example of this type of compound is N-[4-cyano-3-trifluoromethyl-phenyl]-ferrocenecarboxamide,



Fragmental constant	contribution
Fc	2.456
NHC=Oar	- 1.559
C ₆ H ₃	1.494
CN	- 0.155
CF ₃	1.223
Basic fragment NHC=O	0.219
logP	3.68

In addition to the summing of each fragmental constant in the molecule a correction of 1 Cm should be added which correspond to the basic fragment linked to two aromatic rings. Ferrocenes linked to a direct heterocyclic ring or separated by one or more methylene groups requires a correction of 3 Cm; as shown for 4-(4',4'-dimethyl-3'-ferrocenylethyl-5'-imino-2'-oxo-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile

logP is calculated as mentioned before, the correction of the basic fragment is replaced by the heterocyclic ring. logP = 5.17

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

The NCON group in this molecule can be regarded as HNCONH_2 minus 3H, to obtain the fragmental constant for this group we subtract three fragmental constants of a hydrogen atom from the value of the fragmental constant of HNCONH_2 , the summing of the fragmental constant of all groups in the molecule and the addition of a corrective term of 3 cm which correspond to the existence of a heterocyclic ring in the molecule gives the value of 4.66 for logP.

5. 4-(4',4'-dimethyl-2',5'-dioxo-3'-ferrocenylmethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile, logP is calculated as mentioned before. logP = 5.18
6. 4-(4',4'-dimethyl-2',5'-dioxo-3'-ferrocenylethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile, logP is calculated as mentioned before. logP = 5.69
7. Ferrocenes with a basic fragment linked to two aromatic rings and resonance interaction as shown for N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide, this needs two corrections, the first is 3 Cm for the basic fragment and the second is 1 Cm for the resonance interaction.

After summing the fragmental constant of each group in the molecule, two corrections should be added, the first which equal to 1 Cm is for basic fragment (amide group) linked to two aromatic rings (ferrocenyl and phenyl), the second is equal to 3 Cm for the combination of two groups (nitro and amide) on a phenyl ring in para position which gives rise to a resonance interaction resulting in increased log P. logP = 4.45.

8. Ferrocenes with Hydrogen bonding requires a correction of 2 Cm as exemplified by 4-[4',4'-dimethyl-2',5'-dioxo-3'-ortho-hydroxymethyl-ferrocenylmethyl-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile.

In addition to the correction of 3 Cm for the heterocyclic ring, a correction of 2 Cm should be added for the hydrogen bond between the hydrogen of the hydroxyl group and the oxygen of the carbonyl group, as confirmed by X ray study[14], the effect of the two substituents on the ferrocenyl group is not considered when there is a hydrogen bond in the molecule. logP = 4.48.

9. Ferrocenes with electronic effect needs the application of a correction of 2 Cm as illustrated in 4-[4',4'-dimethyl-2',5'-dioxo-1'-imidazolidinyl-(3'-ortho-methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile

We add 2 Cm for electronic effect of two substituents CH_2OCH_3 and $\text{CH}_2\text{N}^+\text{CH}_3$ on the same ring (cyclopentadienyl ring), logP = 5.11.

The experimental and calculated logP values for the ten ferrocene derivatives are presented in table2. These values are in good agreement between them.

Tableau 2 : calculated and experimental logP values

Compound	logP _{calc}	logP _{exp} [15]
N-(ferrocenyl)-isobutyamide	2.66	2.64
Phenylferrocene	4.58	4.59
N-[4-cyano-3-trifluoromethyl-phenyl]-ferrocenecarboxamide	3.68	4.10
4-(4',4'-dimethyl-3'-ferrocenylmethyl-5'-imino-2'-oxo-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile	4.66	4.68
4-(4',4'-dimethyl-2',5'-dioxo-3'-ferrocenylmethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile	5.18	5,23
4-(4',4'-dimethyl-2',5'-dioxo-3'-ferrocenylethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile	5.69	5,62
N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide	4.45	4.42
4-[4',4'-dimethyl-2',5'-dioxo-3'-ortho-hydroxymethyl-ferrocenylmethyl-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile	4.48	4.44
4-[4',4'-dimethyl-2',5'-dioxo-1'-imidazolidinyl-(3'-ortho-methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile	5.11	5.08
4-(4',4'-dimethyl-3'-ferrocenylethyl-5'-imino-2'-oxo-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile	5.17	5,04

Value for r^2 of 0.976 was found for equation 8.

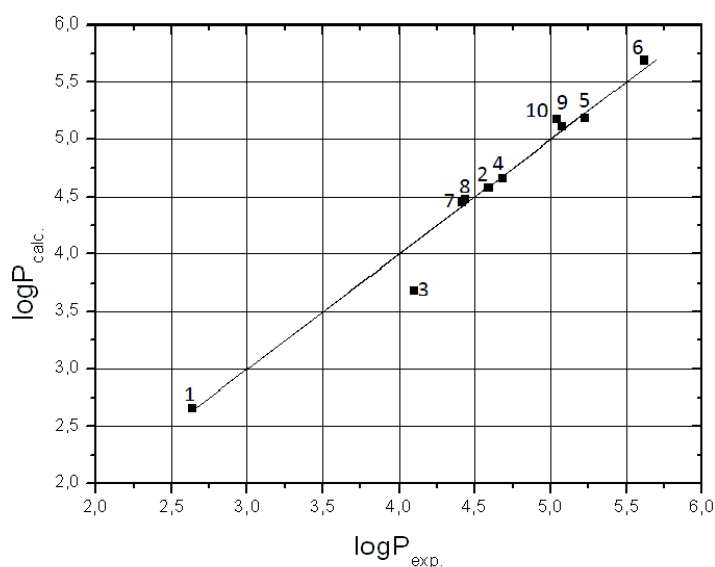


Fig.1. correlation between experimental logP and calculated logP from equation 8 for substituted ferrocenes

7. Conclusion

Due to the major importance of partition coefficients in related study in chemistry, we try successfully in this study to extend the rekker method for calculating octanol/water partition coefficients of ferrocene derivatives starting from characteristics of ferrocene compound. After having adapted the Rekker method for the calculation of partition coefficient, we became able, for the first time, to calculate the partition coefficient of ferrocene derivatives. Values of experimental and calculated logP for a series of ferrocene derivatives are in good agreement. The results obtained for logP enable us to consider the process a solution for calculating partition coefficient for ferrocene derivatives and generalizing it to include all analogous complex compounds.

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