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Calculation of Octanol/Water Partition Coefficients of Ferrocene Derivatives

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Octanol/water partition coefficients, log P, of ferrocene derivatives were determined by theoretical calculations and predictions from literature methods. The calculations were developed on the basis of the adaptation of the existing Rekker approach. The prediction ability of the developed approach was estimated by the comparison of the calculated log P values with the experimental values. Although the log P values determined by the proposed methods are close to the experimental values. The calculated and experimental log Ps of ferrocene derivatives lacking a bulky group are significantly closer than those obtained for ferrocenes containing a bulky group.

Key Words: Partition coefficient, Ferrocene derivatives, Liquid-Liquid extraction.

INTRODUCTION

In recent years, the octanol/water partition coefficient, log P, 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, log P considered a required property in studies of new or undesired chemicals. Although, there has been a lot of interest in octanol/water partition coefficient measurements over the past 90 years, no comprehensive articles on the partition coefficient of ferrocene derivatives have been published. In fact, despite the value of log P of ferrocene itself, no value of partition coefficients of ferrocene derivatives has appeared in the literature.

Among the many published methods for the calculation of log P of several simple aliphatic and aromatic compounds[1-4] none of these methods can be applied to organometallic compounds, such as ferrocene derivatives. The rapid advancement 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 octanol/water partition coefficient of ferrocene derivatives. We herein present a new and simple approach for the calculation of log P that quantifies the lipophilicity of these derivatives and shows relationship between their structure and biological activity. The method used for obtaining log P of ferrocene derivatives is based upon the adaptation of the Rekker approach used for organic molecules[1,12,13].

RESULTS AND DISCUSSION

In this section, the generation of our approach for log P calculation for ferrocene derivatives is described. This calculation is based upon the adaptation of the Rekker approach, which considers the partition molecular species between an aqueous phase and an organic phase (octanol).

Principle of the Rekker approach: The calculation of log P, according to this approach, is based upon the decomposition of the molecule into small suitable substructures which are attributed theoretical hydrophobic values. The summing of these values together with the correction terms for intramolecular interactions, Cm, gives the partition coefficient of the considered molecule as expressed by the following equation:

$$\log P = \sum a_i f_i + \sum Cm \quad (1)$$

where a_i is the number of a given fragment present in the molecule and f_i is the log P increment of the fragment. The interaction terms can be expressed as an integral multiple of one single constant Cm (so-called 'magic constant')[1].

Adaptation and simulation of the Rekker approach: We describe in this section the adaptation of the Rekker approach to ferrocene derivatives. Since the theoretical value of the octanol/water partition coefficient log P of the ferrocene molecule is not known and is not described in the literature and since the ferrocene molecule does not contain any hydrogen bonding or any interaction which can affect this value, we are going to consider that this theoretical value is equal to the experimental value of log P which is equal to 2.66[14].

A ferrocene derivative FcX is obtained by the substitution of a hydrogen atom of the ferrocene molecule, FcH, by the substituent X. Thus the contribution of the ferrocenyl group, Fc, is obtained by subtracting the contribution of the hydrogen atom as follows:

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

where $\log P_{Fc-H}$ is the logarithm of the partition coefficient of ferrocene between *n*-octanol and water, 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:

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

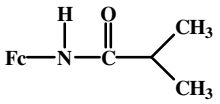
The logarithm of the partition coefficient between *n*-octanol and water, log P, for any ferrocene derivatives, FcX, is therefore calculated by substituting f_H in the previous relation by fx and adding the corrective term Cm as given by eqn. 4.

$$\log P_{Fc-X} = f_{Fc} + fx + \sum Cm = 2.456 + fx + \sum Cm \quad (4)$$

The values of fx are obtained from literature[12]; Cm is equal to 0.219.

Calculation and validation of the model: We validated our approach with 10 different ferrocene derivatives (selected from literature sources[15]). We recommend carrying out the calculations in three decimals, with the final result rounded to two decimals.

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



1

No correction is needed for this type of compounds; log P is obtained by the summation of the value of the fragmental constant of the four groups in the molecule (ferrocenyl, amide, CH and CH_3).

$$\log P = f_{Fc} + f_{NHCO} + f_{CH} + 2f_{CH_3} = 2.456 - 1.559 + 0.315 + 2 \times 0.724 = 2.66$$

$$\log P_{exp.} = 2.64$$

Ferrocenes with ferrocenyl-aryl conjugation as exemplified by phenylferrocene (**2**) requires a correction of 1 Cm.

FcPh

2

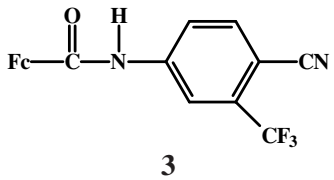
The conjugation require in general the application of 1 Cm, thus log P for phenylferrocene (**2**) can be obtained by the summation of the fragmental constant of the ferrocenyl and the phenyl groups which are equal to 2.456 and 1.902, respectively a correction of 1 Cm = 0.219 should be added which correspond to ferrocenyl-aryl conjugation, this gives a value of 4.58 for log P.

$$\log P = f_{Fc} + f_{Ph} + 1\text{Cm} = 2.456 + 1.902 + 0.219 = 4.58$$

$$\log P_{exp.} = 4.59$$

The correction of 1 Cm is for ferrocenyl-aryl conjugation.

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 (**3**).



3

In addition to the summing of each fragmental constant in the molecule (ferrocenyl, amide, phenyl with three substituents, nitrile and trifluoromethyl) a correction of 1 Cm should be added which correspond to the basic fragment (amide group) linked to two aromatic rings (ferrocenyl and phenyl).

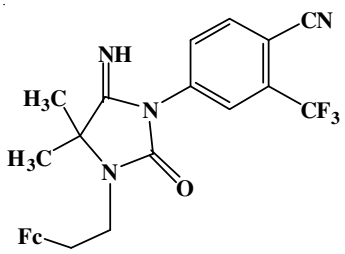
$$\log P = f_{Fc} + f_{NHCO} + f_{C_6H_3} + f_{CN} + f_{CF} + 1\text{ Cm} =$$

$$2.456 - 1.559 + 1.494 - 0.155 + 1.223 + 0.219 = 3.68$$

$$\log P_{exp.} = 4.10$$

The correction of 1 Cm is for the basic fragment NHC=O 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 in compound 4-(4',4'-dimethyl-3'-ferrocenylethyl-5'-imino-2'-oxo-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile (**4**).



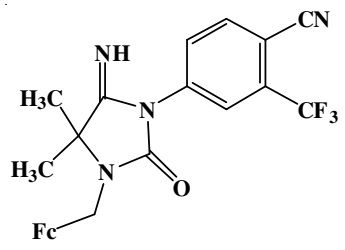
4

log P is calculated as mentioned before, the correction of the basic fragment is replaced by the heterocyclic ring.

$$\log P = f_{Fc} + f_{NH-C} + f_{C_6H_3} + (f_{NH(CO)NH_2} - 3f_H) + 2f_{CH_3} + 2f_{CH_2} + f_{CN} + f_C + f_{CF_3} + 3Cm =$$
$$2.456 - 1.500 + 1.494 + (-0.984 - 3\times 0.204) + 2\times 0.724 + 2\times 0.519 - 0.155 +$$
$$0.11 + 1.223 + 3\times 0.219 = 5.17$$
$$\log P_{exp.} = 5.04$$

The correction of 3 Cm is for the heterocyclic ring.

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



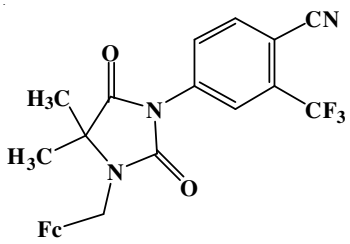
5

The NCON group in this molecule can be regarded as $HNCONH_2$ minus 3H, to obtain the fragmental constant for this group. We have subtracted 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 gave the value of 4.66 for log P.

$$\log P = f_{Fc} + f_{NH-C} + f_{C_6H_3} + (f_{NH(CO)NH_2} - 3f_H) + 2f_{CH_3} + f_{CH_2} + f_{CN} + f_C + f_{CF_3} + 3Cm =$$
$$2.456 - 1.500 + 1.494 + (-0.984 - 3\times 0.204) + 2\times 0.724 + 0.519 - 0.155 +$$
$$0.111 + 1.223 + 3\times 0.219 = 4.66$$
$$\log P_{exp.} = 4.68$$

The correction of 3 Cm is for the heterocyclic ring.

4-(4',4'-Dimethyl-2',5'-dioxo-3'-ferrocenylmethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile (**6**).



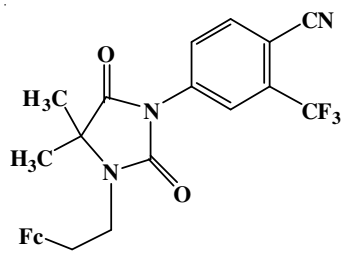
6

log P is calculated as mentioned before.

$$\log P = f_{Fc} + f_{C=O} + f_{C_6H_3} + (f_{NH(CO)NH_2} - 3f_H) + 2f_{CH_3} + f_{CH_2} + f_{CN} + f_C + f_{CF_3} + 3Cm =$$
$$2.456 - 0.976 + 1.494 + (-0.984 - 3\times 0.204) + 2\times 0.724 + 0.519 - 0.155 +$$
$$0.111 + 1.223 + 3\times 0.219 = 5.18$$
$$\log P_{exp.} = 5.23$$

The correction of 3 Cm is for the heterocyclic ring.

4-(4',4'-Dimethyl-2',5'-dioxo-3'-ferrocenylethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile (**7**).



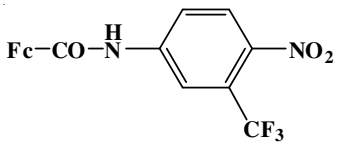
7

log P is calculated as mentioned before.

$$\log P = f_{Fc} + f_{C=O} + f_{C_6H_3} + (f_{NH(CO)NH_2} - 3f_H) + 2f_{CH_3} + 2f_{CH_2} + f_{CN} + f_C + f_{CF_3} + 3Cm =$$
$$2.456 - 0.976 + 1.494 + (-0.984 - 3\times 0.204) + 2\times 0.724 + 2\times 0.519 - 0.155 +$$
$$0.11 + 1.223 + 3\times 0.219 = 5.69$$
$$\log P_{exp.} = 5.62$$

The correction of 3 Cm is for the heterocyclic ring.

Ferrocenes with a basic fragment linked to two aromatic rings and resonance interaction as shown in compound N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide (**8**), which needs two corrections, the first is 3 Cm for the basic fragment and the second is 1 Cm for the resonance interaction.



8

After summing the fragmental constant of each group in the molecule (ferrocenyl, amide, phenyl with three substituents, nitro and trifluoromethyl), 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.

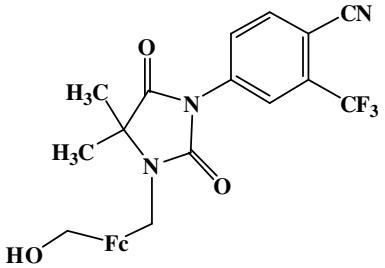
$$\log P = f_{Fc} + f_{NHC=O} + f_{C_6H_3} + f_{NO_2} + f_{CF_3} + 4\,Cm =$$

$$2.456 - 1.559 + 1.494 - 0.039 + 1.223 + 4 \times 0.219 = 4.45$$

$$\log P_{exp.} = 4.42$$

4 Cm is the correction of the basic fragment NHC=O linked to two aromatic rings (1 Cm) and for resonance interaction (3 Cm).

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 (**9**).



9

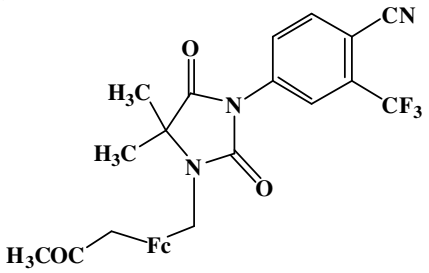
log P is calculated with the same method as before. In addition to the correction of 3 Cm for the heterocyclic ring, a correction of 2 Cm should be added for the hydrogen bond between the hydrogen of the hydroxyl group and the oxygen of the

carbonyl group, as confirmed by X-ray study[14], the effect of the two substuents on the ferrocenyl group is not considered when there is a hydrogen bond in the molecule.

$$\log P = (f_{Fc} - f_H) + f_{C=O} + f_{C_6H_3} + (f_{NH(CO)NH_2} - 3f_H) + 2f_{CH_3} + 2f_{CH_2} + f_{CN} +$$
$$f_{OH} + f_C + f_{CF_3} + 5Cm = (2.456 - 0.204) - 0.976 + 1.494 + (-0.984 - 3\times 0.204) +$$
$$2\times 0.724 + 2\times 0.519 - 0.155 - 1.448 + 0.11 + 1.223 + 5\times 0.219 = 4.48$$
$$\log P_{exp.} = 4.44$$

5 Cm is the correction of the hydrogen bond (2 Cm) and the heterocyclic ring (3 Cm).

Ferrocenes with electronic effect needs the application of a correction of 2 Cm as illustrated in compound 4-[4',4'-dimethyl-2',5'-dioxo-1'-imidazolidinyl-(3'-*ortho*-methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile (**10**).



10

log P is calculated as mentioned before. We add 2 Cm for electronic effect of two substituents CH_2OCH_3 and CH_2N- on the same ring (cyclopentadienyl ring).

$$\log P = (f_{Fc} - f_H) + f_{C=O} + f_{C_6H_3} + (f_{NH(CO)NH_2} - 3f_H) + 2f_{CH_3} + 2f_{CH_2} + f_{CN} +$$
$$f_{OCH_3} + f_C + f_{CF_3} + 5Cm = (2.456 - 0.204) - 0.976 + 1.494 + (-0.984 - 3\times 0.204) +$$
$$2\times 0.724 + 2\times 0.519 - 0.155 - 0.821 + 0.11 + 1.223 + 5\times 0.219 = 5.11$$
$$\log P_{exp.} = 5.08$$

5 Cm is the correction of the electronic effect (2 Cm) and the heterocyclic ring (3 Cm).

Fig. 1 shows the correlation between experimental log P and calculated log P from equation 5 for 10 ferrocene derivatives. Value for r^2 of 0.976 was found for eqn. 4.

Conclusion

In light of the major importance of partition coefficients in chemistry, a theoretical method for calculating the octanol/water partition coefficients of ferrocene derivatives is successfully developed. Adapting the Rekker method for the calculation

of partition coefficient, we were able to calculate, for the first time, the partition coefficient of ferrocene derivatives. Values of experimental and calculated log P for a series of ferrocene derivatives are in good agreement. This validates the process of adaptation. Present method nicely provides a solution for calculating the partition coefficient of ferrocene derivatives and potentially all analogous complex compounds.

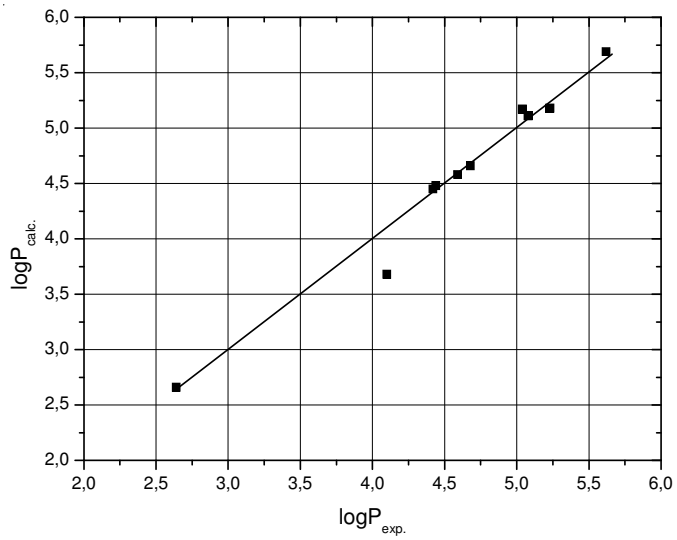


Fig. 1. Correlation between experimental log P and calculated log P from eqn. 4 for 10 ferrocene derivatives

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