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Estimation de logP de quelques dérivés ferrocèniques basée sur le concept de contributions des fragmentations du soluté

LogP estimation of some ferrocene derivatives based on the concept of the contributions of fragmentations of solute

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Dedication

This work is lovingly dedicated to my mother, her support, encouragement, and constant love sustained throughout my life.

Abstract:

Octanol–water partition coefficient, P, is a key physicochemical property for many filed of sciences such as pharmaceutical drugs, analytical chemistry, environmental science in the assessment of environmental fate, transport of organic chemicals and agrochemicals. This work describes new methods for determining logP values for a large number of ferrocene derivatives with widely varying structure, size and function using theoretical calculation and prediction from literature. Calculations are based on the adaptation of some existing methods such as Rekker, XLogP and ALogP.

In order to validate our proposed theoretical method partition coefficients of a numerous ferrocene derivatives were also successfully determined, using for the first time square wave voltammetry techniques.Values of experimental and calculated logP of substituted ferrocene are in good agreement.

Key words: Partition coefficient, logP, lipophilicity, ferrocene derivatives, liquid-liquid extraction, hydrophilicity.

الملخص :

يعتبر معامل التوزيع P في نظام أوكتانول – ماء ، من أهم الخصائص الفيزيو- كيميائية في العديد من العلوم ، كالصيدلة, الكيمياء الزراعية, الكيمياء التحليلية و البيئة . يصف هذا العمل طرق نظرية جديدة لتحديد قيم LogP للعديد من مشتقات الفيروسان والتنبؤ بها حسابيا . نعتمد في الحساب على تكييف الطرق النظرية Rekker , XLogP و ALogP من أجل التاكد من نجاعة التنبؤ ات بالطرق النظرية قمنا بقياسlogP لعدد من مشتقات الفيروسان مخبريا باستعمال تقنية فولطامتري الموجة المربعة. قيم LogP لمشتقات الفيروسان المتحصل عليها حسابيا بمختلف هذه الطرق متقاربة في ما بينها ومتوافقة مع القيم التجريبية.

الكلمات الدالة :معامل التوزيع ,logP , محب للدهون, مشتقات الفيروسان، استخلاص سائل- سائل, محب للماء

Résumé :

Le coefficient de partage dans le système octanol-eau, exprimée par P, est une propriété physico-chimique principale, basées sur laquelle plusieurs domaines scientifique telles que Pharmacologie et chimie agricole. Ce travail décrit une nouvelle et simple méthode pour déterminer des valeurs de LogP pour un grand nombre de dérivés de ferrocène en utilisant le calcul théorique et la prévision de la littérature. Les calculs sont basés sur l'adaptation de certaines méthodes existantes telles que Rekker, XLogP, AFC, et ALogP. Pour valider les méthodes de calcul proposées, logP d'un nombre des drivées ferrocéniques ont été mesurés en utilisant la voltammetrie à onde carrée. Toutes les valeurs de logP des dérivés de ferrocène obtenues par les différentes méthodes proposées sont très proches l'une de l'autre et en bon accord avec les valeurs expérimentales.

Mots clés : Coefficient de partage, logP, lipophilicité, dérivés de ferrocène, l'extraction liquide - liquide, hydrophilicité.

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List of abbreviations

A	Ampere
AE	Auxiliary electrode
AFC	Atom/fragment contribution
aq	Aqueous phase
app pKa	Logarithm of the apparent acid dissociation constant
C	Concentration
CASE	Computer automated structure evaluation
C_P	Cyclopentadienyl
C_M	Magic constant
D	Diffusion coefficient
DMF	Dimethylformamide
di_p	Peak current
E	Potential
Enk	Enkephalin
Eq	Equation
F	Faraday constant
Fc	Ferrocenyl group
f_i	Fragmental constant
g	Gram
HPLC	High-performance liquid chromatography
H-bond	Hydrogen bond
I	Current
L	Liter
logP	Logarithm of n-octanol-water partition coefficient.
$\log P_{cal.}$	Calculated logarithm of octanol-water partition coefficient
$\log P_{exp.}$	Measured logarithm of n- octanol-water partition coefficient
$\log P^{BH^+}$	Logarithm of the partition coefficient of the ionic form in n-octanol-water
$\log P^{B}$	Logarithm of the partition coefficient of the neutral form in n-octanol-water
m	Mass
M	Molarity

mM	Millimolar
MLP	Molecular lipophilicity potential
mL	Milliliter
mV	Millivolts
nm	Nanometer
n	Number of charge
P	Octanol-water partition coefficient
pKa	Logarithm of acid dissociation constant
Ph	Phenyl group
QSAR	Quantitative structure-activity relationships
R	Gas constant (8.31 $J{\cdot}K^{-1}{\cdot}mol^{-1}$)
RE	Reference electrode
$\mathbf{R^2}$	Square correlation coefficient
r	Phase volume ratio
s	Time second
SWV	Square-wave voltammetry
T	Staircase period
$\boldsymbol{t_r}$	Retention time of the substance
$\boldsymbol{t_o}$	Elution time of the solvent
UV–vis	Ultraviolet–visible spectroscopy
V	Volts
$\mathbf{V_X}$	Molecular volume
WE	Working electrode
$\mathbf{z_i}$	Ionic charge

Key to symbols

$\boldsymbol{\mu}$	Chemical potential
$\boldsymbol{\beta_2^H}$	Parameter of strength of hydrogen bond
$\boldsymbol{\lambda_{max}}$	Maximum wavelength
$\Delta G_{w\to o}^{o}$	Standard free-energy of transfer between water and ocatnol solvents
$\boldsymbol{\Delta S_{w\to o}^{o}}$	Standard entropy of transfer between water and ocatnol solvents

Summary

Octanol-water partition coefficient P generally expressed as logP is fundamental physicochemical parameter that extensively describe a chemical lipophilic or hydrophobic properties, is used in many scientific area such as analytical chemistry, environmental science, in the assessment of environmental fate and transport of organic chemicals, pharmaceutical research such as drug design, successful applications in quantitative structure activity relationships, it is considered a required property in studies of new or undesired chemicals.

Octanol-water partition coefficient is defined as the ratio of the molar concentration of a chemical dissolved at equilibrium in octanol phase to its molar concentration in aqueous phase.

There are several methods for predict partition coefficient logP such as Rekker fragment method, atom additive XlogP and AlogP methods all those approach are described for simple aliphatic and organic compounds, also numerous of methods were reported for the measurement of octanol–water partition coefficient, all of them are based on the measurement of the concentrations at equilibrium in both octanol and aqueous phases.

Among all reported theoretical methods for the calculation of logP for organic and aliphatic compounds, no one can be calculate logP of ferrocene or its derivatives, this may due to the nature of bonding between carbon and iron atom in the ferrocene molecule.

In this research work we present new approaches for the calculation of partition coefficient of ferrocene and its derivatives based on the adaptation of some existing methods such as Rekker, XlogP, AlogP approaches.

The proposed approaches were validated using logP experimental values of ferrocene and its derivatives. Experimental logP values were measured using electrochemical and spectrometric methods based on square wave valtametry and UV-visible respectively.

This thesis is divided in to three chapters as follows:

The first chapter is a bibliographic overview contains definition, background of partition coefficient and different methods of calculation and measurement of patition coefficient.

The second chapter, is devoted to describe the Rekker, XlogP, AlogP approaches for calculation of partition coefficient for simple organic and aliphatic compounds which will be adapted to calculate logP of ferrocene derivatives, also in this chapter we depicts the different experimental

methods for the determination of octanol–water partition coefficient touching the appropriate method used to measure logP for ferrocene derivatives, which consider the partition of a molecular spice between an aqueous phase and an organic phase (octanol).

The third chapter dealt with the generation of our approaches for partition coefficient calculation for ferrocene derivatives, the calculation is based upon the adaptation of the Rekker, XlogP, AlogP approaches, in the end of the chapter describes the measurement of logP values using the shake flask method, the octanol phase concentration is determined using the peak current of square wave voltammograms.

Finally, general conclusion summarizes the research described in this work which concludes the important results based on accuracy and efficiency of the adapted methods, and future prospects research in organometallic chemistry.

CHAPTER I

Bibliographic overview

I-1 - Octanol – water partition coefficient

Octanol-water partition coefficient, *P*, is prime physicochemical property that describes a chemical's lipophilic and hydrophobic characteristics, it has become a key parameter in studies of the environmental fate and transport of organic chemicals. Because of its increasing use in the estimation of many other properties, this parameter plays a significant role in various areas of pharmaceutical research such as drug design. Successful applications in quantitative structure activity relationships it is considered a required property in studies of new or undesired chemicals; the partition coefficient P, defined as the ratio of molar concentration of a chemical dissolved at equilibrium in octanol phase $\mathrm{C_{oct}}$ to its molar concentration in aqueous phase $\mathrm{C_{aq}}$ [1-3],figure I-1, and is given by the equation:

$$\mathrm{P} = \left(\frac{\mathrm{C_{oct}}}{\mathrm{C_{aq}}}\right)_{\mathrm{equilibrium}} \qquad \mathrm{I-1}$$

Always represented as logP logarithm is employed because of the wide range to be covered, often close to 8-10 orders of magnitude.

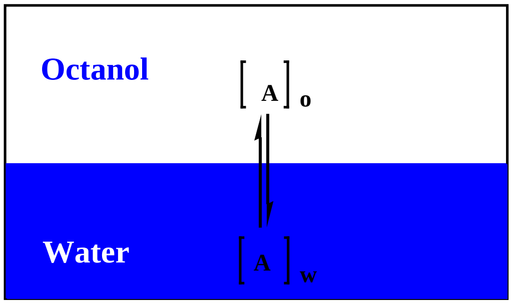


Figure -I-1: *Schematic depictions of the partition of species between octanol and water*

Which $[A]_o$ and $[A]_w$ are the concentrations of the compound A in organic and aqueous phases, respectively.

I-2- Thermodynamics aspects of partition coefficient

As equilibrium constant for two phase system, logP is determined by the difference between the salvation free energies of the solute in each phase. This difference is represented by the partial molar standard free energy of transfer or by the chemical potential [4].

the chemical potential μ given according to the equation:

$$\mu = \mu^{\theta} + \mathrm{RTlnC} \qquad \mathrm{I}-2$$

Where C is the solute's molarity in the solvent and μ^{θ} the chemical potential of 1 M solution under standard conditions.

When a solute is in equilbrium between two solvents, the chemical potential of this solute becomes equal in both phases. With the octanol-water system and for a given compound:

$$\mu_{\mathrm{w}} = \mu_{\mathrm{o}} \qquad \mathrm{I}-3$$

μ_{w} is the chemical potential in water phase, μ_{o} is the chemical potential in ocanol phase.

$$\mu_{\mathrm{o}}^{\theta} + \mathrm{RTlnC_o} = \mu_{\mathrm{w}}^{\theta} + +\mathrm{RTlnC_w} \qquad \mathrm{I}-4$$

$\mu_{\mathrm{o}}^{\theta} and\ \mu_{\mathrm{w}}^{\theta}$ are the chemical potential under standard conditions this relation leads to:

$$\mu_{\mathrm{o}}^{\theta} - \mu_{\mathrm{w}}^{\theta} = \mathrm{RTlnC_w} - \mathrm{RTlnC_o} \qquad \mathrm{I}-5$$

$$= \mathrm{RTln}\frac{\mathrm{C_w}}{\mathrm{C_o}} = -\mathrm{RTlnP} \qquad \mathrm{I}-6$$

P: is partition coefficient

The quantity $\mu_{\mathrm{o}}^{\theta} - \mu_{\mathrm{w}}^{\theta}$ corresponds to the standard free-energy change accompanying the transfer of one mole of solute from one solvent to another.

$$\Delta G^{o}_{w\rightarrow o} = -2.3RTlogP \qquad \text{I} - 7$$

The quantity of the logarithm of the partition coefficient, logP is related linearly to the molar standard free energy $\Delta G^{o}_{w\rightarrow o}$ of transfer from the aqueous phase to octanol phase.

$$\text{logP} = -\frac{\Delta G^{o}_{w\rightarrow o}}{2.3\text{RT}} \qquad \text{I} - 8$$

Lipophilicity is then represented in terms of the partition coefficient logP. If a compound is strongly hydrophilic (water-lover), its concentration in the water phase is higher than in octanol phase, otherwise a strong lipophilic compound has positive partition coefficient (logP).

Transfer-free energy can be deconstructed into two components, enthalpy of transfer, and entropy of transfer.

$$\Delta G^{o}_{w\rightarrow o} = \Delta H^{o}_{w\rightarrow o} - T\Delta S^{o}_{w\rightarrow o} \qquad \text{I} - 9$$

At constant pressure and temperature, a negative $\Delta G^{o}_{w\rightarrow o}$value promotes the transfer towards octanol. The partition coefficient therefore represents the result of these two effects $\Delta H^{o}_{w\rightarrow o}$and $\Delta S^{o}_{w\rightarrow o}$.

I-2-1-The influence of thermodynamic factors on solute transfer

In generaly, study of the partition coefficient of a substance between solvents requires a comparison in each medium of the solvent-solvent and solvent-solute association forces (which influences the enthalpic term) as well as the respective molecular arrangements (entropic term).

I-2-1-1-The influence of the transfer enthalpy $\Delta H^{o}_{w\rightarrow o}$

We noted for the majority of a change in the transfer enthalpy

$$\Delta H^{o}_{w\rightarrow o} > 0$$

When a substance dissolves in water, the forces maintaining the cohesion of water molecule to each other are ruptured and these are replaced by interaction forces between water and solute. These phenomenons do not favours the transfer towards octanol.

The hydrophilic interaction is an enthalpic controlled phenomenon, this due to the interaction forces as hydrogen and vander waals bonds between the molecule of solute and the molecule of solvents were weaker in the organic phase than into the aqueous phase.

Since the cohesive forces between water and organic solute are generally weak compared to those existing between water molecules, the aqueous medium has a tendency to expel the organic molecules towards the exterior.

I-2-1-2-The influence of the transfer entropy $\Delta \boldsymbol{S}^{\boldsymbol{o}}_{\boldsymbol{w\rightarrow o}}$

We noted for the majority of the transfer entropy

$$\Delta S^{o}_{w\rightarrow o} > 0$$

Entropy measures the tendency of a system to reach maximum disorder. Lipophilic interaction is an entropic controlled phenomenon, this due to the molecules acquire supplementary degrees of freedom which as result of the weakening bonds between the solute –solvent, which promotes the transfer towards octanol.

I-3- Partition coefficient history

It was well over 100 years ago that Crum Brown and Fraser [5] first suggested that biological activity could depend on a physiochemical property, namely aqueous solubility. At the same time in1869, Richardson [6] showed that the narcotic effect of primary aliphatic alcohols varied with their molecular weight. In 1893 Richet [7] confirmed Crum Brown and Fraser's prediction by showing that the toxicities of a variety of simple polar compounds such as ethers, alcohols and ketones were inversely related to their aqueous solubilities. Just before the turn of the century, Overton [8] and Meyer [9] independently extended Richet's work and found that the narcotic potency of compounds of various classes tends of increase as the oil-water partition coefficient increase. There is a strong correlation between an oil-water partition coefficient and anesthetic effect. There has been more continuous interest in defining lipophilicity and it role in environmental and biological activity processes.

Partition coefficient, first defined by Berthelot and Jungfleisch [10] is, in practical terms, the ratio of concentrations at equilibrium of a solute distributed between two immiscible phases. The term "immiscible" does not preclude the two phases having partial miscibility.

Water in other common solvents is given by Leo [11]. The term "partition coefficient" is restricted to defining the concentration ratio of the same molecular species, as was first pointed out by Nernst [12]. The terms "distribution coefficient" or "apparent partition coefficient" apply to the ratio of total concentrations, including ionized and associated species. Partition coefficients quoted in this review are measured in the 1-octanol-water system unless otherwise stated.

The work of Meyer and Overton [8,9] implied that the more lipophilic a compound, the better could it penetrate lipid membranes. The scene was thus set for further work on the relationship between lipophilicity and biological activity.

In the sixty‘s the work in this field expanded following the work of Hansch et al., in1962 and Fujita in 1964[13], and the first review devoted entirely to partition coefficients was published only in 1971[14] by Leo et al,. Since its first use by Collander in 1951, and especially during the last three decades, logP has become the standard lipophilicity parameter used in such QSAR and other relationships.

Selection of the octanol-water system as reference is usually rationalized as modeling partition coefficient between aqueous and biophases [15].

This system is widely used to measure the lipophilicity of biological systems, the validity of the model is generally demonstrated by a significant correlation observed between the biological properties of a substance and its partition coefficient logP measured in this system, to be a representative model of biological systems.

While the proper choice of model of other required solvent systems, is now again quite open.

The systems can be broadly classified into four groups according to the nature of the organic phase as follows:

- Inerts: alkane-water (mainly cyclohexane, heptane) and aromatic-water (benzene ,xylene, toluene).
- Amphiprotic : octanol-water, pentanol-water, butanol-water, oleic alcohol-water.
- Proton donors : $CHCl_3$-water.
- Proton acceptors : propylene glycol dipelargonate, 2-butanone- water.

The octanol - water system is the favored as the main reasons as follows:

- Franks and Lieb works [16] found for the anesthetic potency plotted against solvent-water Partition coefficient, octanol gave an excellent correlation for all compounds and all animals over an extremely wide range. Correlation were much better than for oil -water, hexadecane - water, or benzene - water systems
- Large values of experimental octanol-water system partition coefficient logP data in the literature are the majority of data, are already available [17**,**18].
- Most compounds of interest have logP values in octanol-water system, where experimental determinations using standard methods for example (shake – flask) are relatively simple is this a consequence of the fact that octanol still retains some hydrogen bonding ability of water in very nonpolar solvents, like hexadecane, structural variations tend to cause large variations and solute association can easily become a problem, however even with octanol.
- Octanol has low vapor pressure at room temperature and is well suited for simple concentration measurement.
- Several approaches for logP estimation in octanol-water system have al ready been developed.

I-4-Partition coefficient prediction methods

There are several methods for the prediction of the partition coefficient logP, the basic idea behind all these methods, based in two principles as follows:

The first principle based to cut molecules into fragments or down to the single atom level and apply correction factors in order to compensate for intramolecular interactions summing the substructure contributions and the corrector factor gives the final logP.

The second principle based into utilize descriptions of the entire molecule including molecular lipophilicity potentials (MLP), topological indices or molecular properties like charge densities, volume and electrostatic potential to quantify logP.

Some of these predictive methods are as follows:

- Atomic or group contribution methods:

- Fujita and Hansch in 1964 [11,19] developed a method of constitutive and additive calculation of the partition coefficient, for which the overall partition coefficient of a molecule is equal to the sum of the elementary contributions from each constitutive element of the structure evaluation of the overall logP of substituted benzene.
- An attractive objective in the domain of prediction is the evaluation of logP only from knowledge of the molecular structure, such an approach involves the summation of the contribution to the partition coefficient of all the different component 'fragments' of a molecule. The procedure put forward by Rekker et al [20-25].

  Rekker's pioneering fragmental constants method, it's widely used, this method was developed using a "reductionist approach", where, after defining a set of fragments, their fragmental contribution were obtained by multiple linear regression using sets of available logP data, and apply correction factors in order to compensate for intramolecular interactions, it is relatively simple and straightforward method. Corrections factors in an interesting manner, correction factor are considered to be quantified, they can be only integer multiples of so-colled "magic constant C_M [26,27].
- The used similar method of Hansch and leo in 1979 [28–30] developed using a constructionist approach that starts with the fragment value of H and each fragment's contribution is determined based on one corresponding well determined experimental value. This method has been adapted for computational use by Chou and Jurs in1979 [31] and is continuously improved by introduction of new correction factors [32,33] by Leo in1983, and by Calvino et al in1992.
- The atomic approach [34] of Broto et al., in 1984 using 222 descriptors was among the firsts, following by that a classical atomic approach was developed by Ghose and Crippen using 110 descriptors, and this atom additive method AlogP extended later by Viswanadhan [35,36] to include 120 descriptors. It is illustrative that this method contains 44 atom type devoted to carbon, and 10 different hydrogen atom contributions, AlogP [37] method will be discuss and explain in detail in the following chapter.

- Recently by that of wang and coworkers XlogP [38] method is a further atom-additive method as expressed by its almost exclusive use of atomic contributions, is quit similar to these previous methods but reduce the number of descriptors to 80 this method used correction factors to compensate for intramolecular interactions. This model for logP calculation includes additive atom types contribution and correction factors as well.
- the atom/fragment contribution method (AFC, LOGPKOW) of Meylan and Howard in1995 [39-41] was devloped more recently, this method also employs a reductionist approach, using a quite large database of exprimental values.
- The logP evaluation method of Klopman et al., [42,43] using their computer automated structure evaluation (CASE) approach KLOGP-Klopman and Wang in1991; and klopman et al., in 1994.
- The computerized ACD/logP approach is based on logP contributions of separate atoms that uses over 1200 different fragment contribution and over 2400 different intermolecular interaction contribution in its present version [44].
- Solvatochromic model[45-49] developed by Taft, Kamlet Abraham, and coworkers in 1983, 1988 to 1996, that uses a more rigorous physicochemical basis to describe such properties, but the parameters are either derived from solvent effects or calculated by rather complex set of (apparently empirical) rules with values “ settled down” after a series of successive approximations.
- A recent model based on ab initio quantum chemical calculations of the electrostatic potential of molecules at the Hartree –Fock/6-31G* level using GAUSSIAN 94, Haeberlein and Brinck in1997 developed into a new logP model who uses three parameters that could be interpreted as representing a cavity term, dipolarity/polarizability term, and a hydrogen bonding term [50-51].

I-5-Partition coefficient determination methods

Different method were reported for the determination of octanol–water partition coefficient, all of them are based on the measurement of the concentrations at equilibrium in both octanol and aqueous phases [1], these concentrations are usually calculated from the HPLC retention time

[52], using a potentiometric titration technique [53], or using electrochemical methods based on electrochemistry at liquid/liquid interfaces [54,55], all those methods will be described in third chapter.

Although as stated in the introduction of this thesis there are many methods for the determination of partition coefficient logP, no one can be applied to ferrocene derivative. This work is contribution to extend the existing methods to the ferrocene and its derivatives.

In other side, despite there has been a lot of interest in octanol-water partition coefficient measurements over the past 90 years, although the rapid advancement of ferrocene chemistry only there are very few LogP values reported for ferrocene derivatives, that led us to turn our attention to the octanol-water partition coefficient of ferrocene derivatives. We contribute in this work, experimental determination of this very important parameter that quantifies the lipophilicity of these derivatives and shows relationship between their structure and biological activity. logP values of ten ferrocene derivatives, for which a few experimental data are available, is determined using the shake flask method. The octanol phase concentration is determined using the peak current of square wave voltammograms.

Over sixty years since the discovery of this sandwich complex in 1951[56], ferrocene remains one of the most important and intensely studied organometallic compounds[57], because the verssality of its applications in bioorganometallic chemistry[58-68], petrochemistry[69], catalysis and materials science [70], mainly due to its unique properties such as stability, aromaticity, low toxicity and redox activity.

The unique sandwich structure of the ferrocene has routed to enormous interest in the compounds of the transition metals with the hydrocarbons and also played a great role in the development of the flourishing study of organometallic chemistry. The applications of ferrocene compounds are not only a subject of increasing interest in academia, but also in industry.

I-6-Chemical structure and properties of ferrocene

Ferrocene is a sandwich organometallic compound [71,72] with the chemical formula Fe $(C_5H_5)_2$. It is a prototypical metallocene that consists of two cyclo-pentadienyl rings that are bound on the opposite sides of the central Iron Fe atom. The chemical structure of ferrocene is illustrated in figure I– 2.

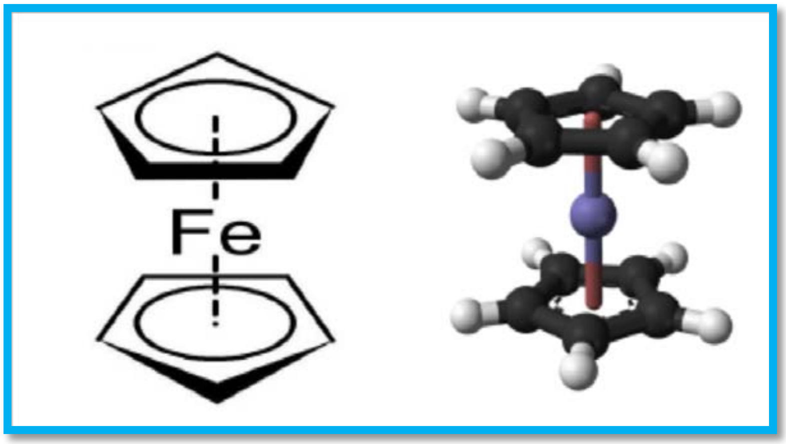


Figure I-2: *The chemical structure of ferrocene*

Ferrocene occurs as highly stable orange crystals with a melting point of 174°C chemically ferrocene behaves like benzene and other aromatic compounds in that it undergoes substitution reactions, ferrocene is undergoes 18-electron rule, consisting of a Fe^{2+} (d^6) and two 6e- aromatic rings ($C_5H_5^-$).

The removal of one electron from the molecule raises the iron atom to the next-higher oxidation state +2 to +3, leading to the formation of salts containing the ferrocinium cation, $(C_5H_5)_2Fe^+$,this cation is rather stable and the redox reaction is reversible for most ferrocene derivatives [73-75].

The redox chemistry of the iron centre and its unique structure is of the particular importance in the study of the chemistry of the ferrocenes. Because of the unique geometry, electronic properties [76-78], and the reactivity that the ferrocene provides. The ferrocene moiety has played a very significant role as the backbone of many reactions, a plethora of its derivatives has been synthesized and characterized following classical methods of organic chemistry.

Generally ferrocenes have many ideal properties besides their unique structure like the stability to the temperatures, and very high tolerance to oxygen, moisture, and various types of the reagents.The ferrocene-based ligands have gained a lot of organometallic importance in the asymmetric catalysis due to their unique aspects of stereochemistry, availability, and the wide range of possibility for fine-tuning of various electronic and steric properties.

CHAPTER II

Octanol- water partition coefficients prediction and measurement methods

II-1-Rekker method

II-1-1-Introduction

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 or its derivatives have been published. In fact, despite the value of logP 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 logP of several simple aliphatic and aromatic compounds [26,27] [37-41] 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 [70], led us to turn our attention to the octanol-water partition coefficient of ferrocene derivatives. In this subchapter we present Rekker approach for the calculation of logP for organic molecules that quantifies their lipophilicity and shows relationship between their structure and biological activity. Rekker's approach [26,27], will be adapted for obtaining logP of ferrocene derivatives .

II-1-2-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:

$$\log P = \sum_{i=1}^{n} a_i \times f_i + \sum_{i=1}^{m} k_i \times C_M \qquad \text{II} - 1 - 1$$

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.

Fragments receive a value of 0 to 1 or a multiple of 1 depending on the number of times the fragment is present in the molecule, the correction factor is included in the equation as an independent variable.

The Rekker's fragmental constant approach is known as a reductionistic approach because it uses a large database of aromatic (ar) and aliphatic (al) fragments to determine the fragmental constants such as aromatic fragments like C, H, ar-O-, ar-CO, ar-CN, ar-NO_2, ar-OH, ar-NH_2, and aliphatic fragments such as al-O, al-F, al-Cl, al-Br al-C(O), al-NH, al-CN, al-NO_2, al-OH, al-NH_2, al-COO, al-CHO al-OCO, there is a difference between the aromatic ‘’ar-fragmental’’ constants and the aliphatic ‘’al-aliphatic’’ ones, but there is no difference between an aromatic and aliphatic carbon C or hydrogen H, table II-1 summarizes most used fragmental constants of different fragment.

II-1-3-Development of Rekker method

The initial fragmental constants of the Rekker method were firstly derived from experimental logP values for about hundred simple organic compounds by regression analyses [20-23] and the data set were enlarged to other complicated organic compounds. Where resulted in a valuable system for logP calculation based on 126 fragment values. The fragmentation procedure leaves functional groups with direct resonance interaction intact and generates fragments ranging from atoms to complicated substituents, in particular heterocyclic rings, all fragments are differentiated according to their aliphatic or aromatic attachment, the differences between measurement and calculation could be attributed to chemical characteristics of the molecules, which in turn allowed the definition of correction rules such as chain conjugation, electronegativity facing bulk or the proximity effect, which describes the presence of electronegative centers in a molecule separated by one or two carbons. Correction values needed for logP calculation were shown to represent multiples of a constant value of 0.289, which is called the magic constant (C_M). It proves to be of great importance in restoring imbalances between experimental and calculated logP.

Latter there was a revision [24], of this method which is focused on the correction term C_M, it was given a value of 0.219 instead 0.289, this new value was adequate to treat the following anomalous points:

1)- the bad fit of aliphatic hydrocarbon logP to this method.

2)- the irregular fit of logP for simple halo-alkanes with calculated data.

3)- the impossibility of connecting the correction factor for structures with electronegativity facing alkyl bulk with multiples of C_M.

In the last step the system required to be updated to solve the problems raised in the calculation of multihalogenation in aliphatic hydrocarbon structures. To update the system a series of logP data from the available literature were assembled and elaborated the following updating [25,27], up-corrections of 0.219 were undertaken for Cl, Br and I, leaving F unchanged. The presence of two halogens on the same carbon requires an extra C_M to be added in the calculation, a halogenation pattern with three geminal halogens demands four extra C_M, for per-halogenated compounds no correction factor is needed.

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

Table II-1 : *Fragmental constants*

Fragment	f_{ar}	f_{al}
H	0.2045	0.2045
C	0.1102	0.1102
F	0.444	-0.2130
Br	1.134	0.477
Cl	0.933	0.276
I	1.446	0.789
O	-0.450	-1.545
N	-0.979	-2.074
S	0.099	-0.558
CH	0.315	0.315
OH	-0.353	-1.448
NH	-0.938	-1.814
SH	0.611	-0.046
CO	-0.976	-1.633
CN	-0.155	-1.031
SO	-2.13	-2.79
CH_2	0.519	0.519
NH_2	-0.902	-1.340
NO_2	-0.039	-0.915
SO_2	-2.07	-2.83
COO	-0.543	-1.200
CON	-1.983	-2.859
NCO	-1.544	
C=NH	-1.500	
COH	-0.334	-0.991
CH_3	0.724	0.724
CF_3	1.223	0.566
COOH	-0.066	-0.942
CONH	-1.559	-2.435

Table II-1: *Fragmental constants (continued)*

fragment	f_{ar}	f_{al}
NHCO	-1.559	
OCH_3	0.274	-0.821
$CONH_2$	-1.135	-2.011
NCONH		-3.132
OOCNH	-1.391	-1.829
NHCOO	-0.734	
SCH_3	0.823	0.166
SO_2NH	-1.864	
$NHSO_2$	-1.645	
$OOCNH_2$	-0.927	-1.405
CONHNH	-2.253	-3.348
NHCONH	-1.408	-2.284
$NCONH_2$		-2.708
CH=N-NOH	-0.141	-0.798
CH=CH-CO	-0.565	
$NHCONH_2$	-0.984	-1.860
NHCSNH	-1.614	-1.833
C_6H	1.085	
C_6H_2	1.289	
$NHCSNH_2$	-1.190	-1.409
$CH=CH-NO_2$	0.153	
$O-CH_2.COOH$	-0.606	-1.044
CH=CH-CONH	-1.367	
C_6H_3	1.494	
$CONHCONH_2$		-1.602
$NHNHCONH_2$		-2.850
$NH-C(NH_2)=N-C\equiv N$	-0.916	-1.573
C_6H_4	1.698	
C_6H_5	1.902	
Imidazolyl	-0.046	

Table II-1: *Fragmental constants (continued)*

Fragment	f_{ar}
Pyrrolyl	0.615
Pyridinyl	0.534
1,2,4-Triazolyl	-0.937
1,2,3-Triazolyl	-0.499
Tetrazolyl	-0.917
Benzimidazolyl	1.2410
Uracilyl	-1.297
Barbituryl	-1.500
Indolyl	1.902
Carbazolyl	3.570
Quinolinyl	1.821
Isoquinolinyl	1.821
Acridinyl	3.110
Benzotriazolyl	1.227
Pyrimidinyl	-0.683
Pyrazinyl	-0.464
Pyridazinyl	-0.902
Furyl	1.086
Phenothiazinyl	3.665
Phenyloxyphenyl	4.026

II-1-4-Examples of calculation of logP according to Rekker method

- ✓ **Molecules without interactions treatment**

This type of molecules do not require any correction, means that there is no need to add the magic constant.

Examples

1. Acetone

$$(CH_3)_2C{=}O$$

This molecule can be cut into two methyl fragments CH_3 and one carbonyl fragment $C = O$ then we search for the values of the contribution of these fragments from table II-1 the partition coefficient is then calculated from relation II-1-1 as follows:

$$\log P_{cal.} = 2 \times \mathrm{f}(\mathrm{CH_3}) + \mathrm{f}(\mathrm{C=O}) = 2 \times 0.724 - 1.633 = -0.19$$

$$\log \mathrm{P_{exp.}} = -0.24$$

Fragments can also be cut into its constituent atoms, if there is no internal resonance, in this case the fragment CH_3 can be decomposed into one carbon atom and three hydrogen atoms:

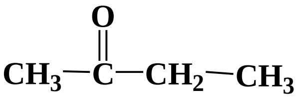
$$\mathrm{f}(CH_3) = \mathrm{f(C)} + 3 \times \mathrm{f(H)} = 0.11 + 3 \times 0.204 = 0.722$$

In contrast the fragment $C = O$ can not be decomposed into its constituent atoms because of the internal resonance between the carbon and oxygen,

$$f(\mathrm{C\,O}) \neq \mathrm{f(C)} + \mathrm{f(O)} = 0.11 - 1.545 = -1.435 > f(\mathrm{CO}) = -1.633$$

As it can be seen the polarization of the fragment $C = O$ increase its hydrophilicity.

2. Butanone



$$\mathrm{CH_3{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_2{-}CH_3}$$

This molecule can be divided according to Rekker method into two methyl fragments CH_3 , one mthylene fragment CH_2 and one carbonyl fragment $C = O$; the adequate fragmental constants values is then attributed from table II-1, the summing of the substructure contributions gives the value of partition coefficient as follows:

$$\begin{aligned}\log P_{cal.} &= 2 \times \mathrm{f}(\mathrm{CH_3}) + \mathrm{f}(\mathrm{CH_2}) + \mathrm{f}(\mathrm{C=O}) \\ &= 2 \times 0.724 + 0.519 - 1.633 = 0.33\end{aligned}$$

$$\log \mathrm{P_{exp.}} = 0.29$$

- ✓ **Molecules with interactions treatment**

The following sections provide detailed explanation of the various correction rules used in the Rekker's model for calculating logP. Various molecular effects such as saturated aliphatic hydrocarbon, unsaturated aliphatic hydrocarbon chains, saturated aliphatic hydrocarbon rings aromatic hydrocarbon rings, basic fragment linked to aromatic ring, basic fragment linked between two aromatic rings, extended chain conjugation, electronic effects between polar fragments or proximity effects, branching to a carbon bearing a polar fragment, hydrogen bonding, hydrogen attached to electronegative fragment groups, decoupling of resonance interaction, electronegativity facing alkyl bulk, oxygen bounded to a phenyl ring through one aliphatic carbon.

The concept of the "magic constant" C_M, is introduced in the calculation of logP, the value of C_M as determined by Rekker is equal to 0.219, though the "magic constant" does not have a meaningful physic-chemical foundation, it accounts for real intramolecular interactions and effects. Without the "magic constant," each of these molecular phenomena would require different degrees of correction, rather than a simple multiple of a constant. However, accounting for each effect individually would make the model more complicated.

II-1-5- Interactions rules

II-1-5-1-Saturated aliphatic hydrocarbon chains

Saturated hydrocarbons in general need the addition of 2 C_M. However there was only one exception to this rule for methane, which needs a positive correction of only +1 C_M.

Example:

Butane

$$\mathbf{CH_3{-}CH_2{-}CH_2{-}CH_3}$$

This molecule composed of two methylene fragments $CH_2$and two methyl fragments CH_3, we can divided it into two fragments CH_2 and two fragments CH_3 and added the correction factor this molecule has total C_M of 2 because it is a saturated alkane, summing the substructure contributions and the correction factor gives the final log $P_{cal.}$ as follows :

$$\log P_{cal.} = 2 \times \mathrm{f(CH_3)} + 2 \times \mathrm{f(CH_2)} + 2 \times \mathrm{C_M}$$

$$= 2 \times 0.724 + 2 \times 0.519 + 2 \times 0.219 = 2.92$$

$$\log P_{exp.} = 2.89$$

II-1-5-2-Unsaturated aliphatic hydrocarbon chains

A double bond needs no correction, while a triple bond requires -1C_M the decrease of lipophilicity due to the greater polarizability of π electrons over σ electrons.

Examples

1. 1,4-Pentadiene

$$H_2C{=}CH{-}CH_2{-}CH{=}CH_2$$

This molecule should be cut into in to three methylene fragments CH_2 and two CH fragments, no corrector factor is needed for a double bond, summing the substructure contributions of fragments from table II-1 gives the final $\log P_{cal.}$ as follows.

$$\log P_{cal.} = 3 \times f(CH_2) + 2 \times f(CH)$$
$$= 3 \times 0.519 + 2 \times 0.315 = 2.19$$
$$\log P_{exp.} = 2.47$$

2. Pentyne

$$CH_3{-}(CH_2)_2{-}C{\equiv}CH$$

The calculation of logP of this compound describes how to apply correction factors in alcynes, we can cut the above molecule into four fragments one methyl fragment CH_3 two methylene fragments CH_2, one fragment CH and one carbon fragment C, the summing of fit fragmental constants values of these fragments from Table II-1 and the correction factor, of triple bond which needs -1C_M, give $\log P_{cal.}$ as follows:

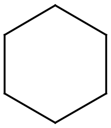
$$\log P_{cal.} = f(CH_3) + 2 \times f(CH_2) + f(C) + f(CH) - C_M$$
$$= 0.724 + 2 \times 0.519 + 0.110 + 0.315 - 0.219 = 1.97$$
$$\log P_{exp.} = 1.98$$

II-1-5-3-Saturated aliphatic hydrocarbon rings

Saturated aliphatic hydrocarbon rings need 2 C_M for correction exception cyclopropane which needs a correction of 1 C_M.

Examples

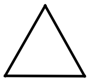
1. Cyclohexane



This molecule contains six methylene groups, so it can be cut into six methylene fragments CH_2 the correction factor needed is 2C_M, summing the substructure contributions and the correction factor gives the final $\log P_{cal.}$

$$\log P_{cal.} = 6 \times \mathrm{f(CH_2)} + 2 \times \mathrm{C_M}$$
$$= 6 \times 0.519 + 2 \times 0.219 = 3.55$$
$$\mathrm{logP_{exp.}} = 3.44$$

2. Cyclopropane



Cyclopropane present the exception to the rule correction of Rekker's method for saturated aliphatic hydrocarbon rings, to calculate logP the molecule should be cut into three methylene fragments CH_2, then we search the adequate fragmental constant of these fragments, the corrector factor in this case is $1C_M$ because this molecule is an exception to the rule for cycloalkanes, $\mathrm{logP_{cal.}}$ is calculated according to relation II − 1 − 1 as follows:

$$\log P_{cal.} = 3 \times \mathrm{f(CH_2)} + 1 \times \mathrm{C_M}$$
$$= 3 \times 0.519 + 1 \times 0.219 = 1.77$$
$$\mathrm{logP_{exp.}} = 172$$

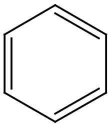
II-1-5-4-Aromatic hydrocarbons ring

There are two ways to calculate partition coefficient of aromatic rings using relation II-1-1.

1. If we calculate partition coefficient from aliphatic fragmental constant i.e f(C) and f(H), in this case required a positive a correction of 1 C_M per cycle is needed, which included all forms of C_6Hn such as C_6H_5-, C_6H_4-, C_6H_3- .
2. if we use the aromatic fragmental constant f_{ar} no correction is needed .

Example

Benzene: C_6H_6



1. We can cut this molecule into six carbon fragments C and six hydrogen fragments H, and we added the correction factor needed $1C_M$ for the aromatic ring, summing the substructure contributions and the correction factor gives the final log*P* value from relation II-1-1.

$$\mathrm{logP_{cal.}} = 6 \times \mathrm{f_C} + 6 \times \mathrm{f_H} + \mathrm{C_M}$$
$$= 6 \times 0.110 + 6 \times 0.204 + 0.219 = 2.10$$

$$\log P_{exp.} = 2.13$$

2. We can cut benzene into one phenyl fragment C_6H_5 and one hydrogen fragment H, in this case no correction factor is required final logP is calculated using relation II-1-1.

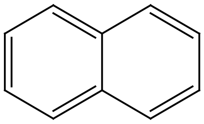
$$\log P_{cal.} = f_{ar}(C_6H_5) + f(H)$$
$$= 1.902 + 0.204 = 2.11$$
$$\log P_{exp.} = 2.13$$

II-1-5-5-Fused rings in aromatic compounds

If rings are fused aromatic compounds, a correction of $+1C_M$ per common summits shouled be added. As illustrated by the following example:

Examples

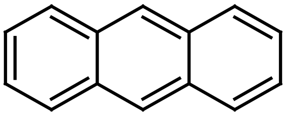
1. **Naphthalene : $C_{10}H_8$**



To calculate logP of this compound with we can divide it into ten carbon fragments C and eight hydrogen H fragments, than we attribute the adequate fragmental constants values for those fragment from table II-1, and we add the correction factor of $+3\ C_M$, $+2\ C_M$ for the rings fusion and $+1\ C_M$ for common summits, summing the substructure contributions and the correction factors we obtain $\log P_{cal.}$ value.

$$\log P_{cal.} = 10 \times f_C + 8 \times f_H + 3 \times C_M$$
$$= 10\ \times\ 0.1102\ + 8\ \times\ 0.204\ +\ 3 \times\ 0.219\ \ = 3.90$$
$$\log P_{exp.} = 3.87$$

2. **Anthracene** : **$C_{14}H_{10}$**



This compound contains three fused aromatic rings, to calculate logP we can cut molecule into fourteen carbon fragments C and ten hydrogen fragments H, then we attribute the adequate fragmental constants values for these fragment from the table II-1, and we added the correction factors of +5 C_M , +1 C_M for each aromatic ring , +1C_M for each common summits, summing the substructure contributions and the correction factors gives the final logP via the application of relation II-1-1.

$$\log P_{cal.} = 14f_C + 10f_H + 5 \times C_M$$

$$= 14 \times 0.110 + 10 \times 0.204 + 5 \times 0.219 = 4.67$$

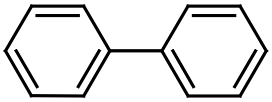
$$\log P_{exp.} = 4.45$$

II-1-5-6- Jointed rings in aromatic compounds

The correction factor for Jointed ring needed 1C_M for the occurrence of two aromatic rings joined by simple sigma bond.

Example

Phenylbenzene : $C_{12}H_{10}$



This molecule can be cut into two C_6H_5 fragments, the correction factor required is 1C_M, for the junction of the two rings, logP is obtained as follows :

$$\log P_{cal.} = 2 \times f_{ar}(C_6H_5) + C_M$$

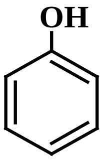
$$= 2 \times 1.902 + 0.219 = 4.02$$

$$\log P_{exp.} = 4.01$$

II-1-5-7- Basic fragment linked to aromatic ring

Example

Phenol : C_6H_5-OH



This molecule can be cut into one phenyl fragment C_6H_5 and one hydroxyl fragment OH, and the we search for the adequate fragmental constants values for fragments from table II-1, no correction in this case is needed.

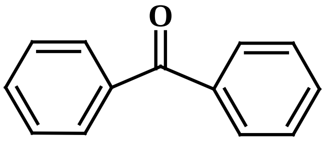
$$\log P_{cal.} = f_{ar}(C_6H_5) + f_{ar}(OH)$$
$$= 1.902 - 0.353 = 1.55$$
$$\log P_{exp.} = 1.47$$

II-1-5-8- Basic fragment linking two aromatic rings or cross-conjugation

When a basic fragment linking two aromatic rings, $1C_M$ should be added as corrector factor, this correction is due to resonance between the two aromatic rings, which according to Rekker's method increases partitioning.

Example

Benzophenone : $C_{13}H_{10}O$



This structure presents two phenyl fragments C_6H_5 and one carbonyl fragment CO, the correction factor in this case requires $1C_{M.}$

$$\log P_{cal.} = 2 \times f_{ar}(C_6H_5) + f_{ar}(CO) + C_M$$
$$= 2 \times 1.902 - 0.976 + 0.219 = 3.05$$
$$\log P_{exp.} = 3.18$$

II-1-5-9-Conjugated bonds

In conjugated compound the extended chain conjugation occurs when two double bonds are separated by one sigma bond. We need to add in this case 2 C_M as a corrector factor per pair of double or triple conjugated bonds for extended chain conjugation.

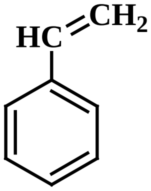
Examples

1. 1,3-Butadiene : C_4H_6

logP of this molecule is obtained by summing the two methylene fragments, the two CH fragments and the correction factor for the pair of double conjugated bonds which requires $2C_M$

$$\log P_{cal.} = 2 \times f(CH_2) + 2 \times f(CH) + 2 \times C_M$$
$$= 2 \times 0.519 + 2 \times 0.315 + 2 \times 0.219 = 2.11$$
$$\log P_{exp.} = 1.99$$

2. Styrene: C_8H_8



The fragments in this molecule are phenyl C_6H_5, CH and methylene CH_2, logP is obtained by adding their fragmental constants values together with correction factor of $2C_M$ for conjugated bonds.

$$\log P_{cal.} = f_{ar}(C_6H_5) + f(CH) + f(CH_2) + 2 \times C_M$$
$$= 1.902 + 0.315 + 0.519 + 2 \times 0.219 = 3.17$$
$$\log P_{exp.} = 2.95$$

II-1-5-10-Electronic effects between polar fragment or Proximity effects

The electronic effects are manifested in compounds of structure type X-$(CH_2)_n$-Y where X and Y are either electron-donating or electron-withdrawing groups. The correction depends on the proximity of the two groups, means the value of n:

1. for n = 1, should be added 3 C_M
2. for n = 2, should be added 2 C_M
3. for n > 2, no correction is required

Examples

1. Dichloromethane

$$Cl—CH_2—Cl$$

In this compound n is equal to 1, logP is calculated as follows:

$$\log P_{cal.} = f(CH_2) + 2 \times f_{al}(Cl) + 3 \times C_M$$
$$= 0.519 + 2 \times 0.276 + 3 \times 0.219 = 1.73$$
$$\log P_{exp.} = 1.25$$

2. Ethylene-glycol

$$\mathbf{HO—(CH_2)_2—OH}$$

The molecule can be divided into two methylene fragments CH_2 and two hydroxyl fragments OH, then we search the fit fragmental constants values for these fragments from table II-1and add the correction factor of $2C_M$, the value of n in this case is equal to 2.

$$\log P_{cal.} = 2 \times f(CH_2) + 2 \times f_{al}(OH) + 2 \times C_M$$

$$= 2 \times 0.519 - 2 \times 1.448 + 2 \times 0.219 = -1.42$$

$$\log P_{exp.} = -1.36$$

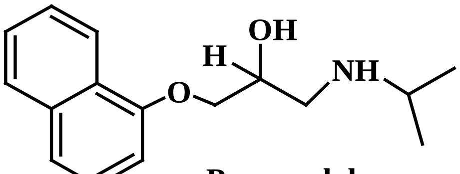
II-1-5-11-Branching to a carbon bearing a polar fragment

When an aliphatic substituent R is placed on a carbon already carrying a polar group X, the inductive effect increases the basicity, the latter resulting in a decrease in lipophilicity electronegativity facing alkyl bulk requires a negative correction factor depending on whether the bulk arises from a quaternary or a tertiary carbon centre. This rule does not hold for functional groups like -COO-; the oxygen is far enough from the alkyl bulk to avoid this effect, the correction factor is proposed as follows:

-1 C_M for one substituted $\mathbf{—CH(R)—X}$

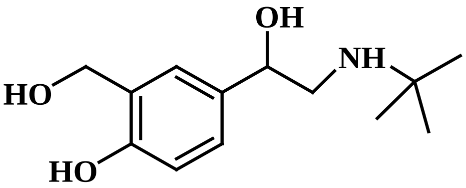
-2 C_M for two substituted $\mathbf{—C(R)_2—X}$

1. Electronegativity facing tertiary carbon



Propanolol

2. Electronegativity facing quaternary carbon



Salbutamol

Examples

1. **Butanol : $C_6H_{10}O$**

$$CH_3-CH_2-CH_2-CH_2-OH$$

The compound does not require any corrections

$$\log P_{cal.} = f(CH_3) + 3 \times f(CH_2) + f_{al}(OH)$$
$$= 0.724 + 3 \times\ 0,519\ - 1.448 = 0.83$$
$$\log P_{exp.} = 0.88$$

2. **2- Butanol : $C_6H_{10}O$**

$$CH_3-CH_2-CH(CH_3)^{-}OH$$

This compound requires a correction factor of -1 C_M.

$$\log P_{cal.} = 2 \times f(CH_3) + f(CH_2) + f(CH) + f_{al}(OH) - C_M$$
$$= 2\ \times\ 0.724\ +\ 0.519 +\ 0.315 - 1.448 -\ 0.219 = 0.61$$
$$\log P_{exp.} = 0.61$$

3. **2-Methyl-2-propanol** :

$$CH_3-C(CH_3)_2-OH$$

This example shows two substituents CH_3 are placed on a carbon carrying a polar group hydroxyl OH, we cut the molecule into three methyl fragments CH_3, one carbon fragment C, and one hydroxyl fragment OH, then we search the adequate fragmental constants values for these fragments from table II-1, the correction factor in this case requires a negative correction of - $2C_M$.

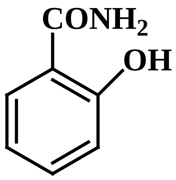
$$\log P_{cal.} = 3 \times f(CH_3) + f(C) + f_{al}(OH) - 2 \times C_M$$
$$= 3\ \times\ 0.724\ +\ 0.11\ - 1.448 - 2 \times 0.219 = 0.40$$
$$\log P_{exp.} = 0.35$$

II-1-5-12- Hydrogen bonding

Intramolecular hydrogen bonding increases lipophilicity with 3 C_M as exemplified as follows:

Example

Salicylamide



The fragments in this molecule are phenyl C_6H_4, hydroxyl OH and amide $CONH_{2,}$ logP is obtained by adding their fragmental constants values together with the correction factor of + $3C_M$ for hydrogen bond.

$$\log P_{cal.} = f_{ar}(C_6H_4) + f(CONH_2) + f(OH) + 3C_M$$
$$= 1.698 - 0.353 - 1.135 + 3 \times 0.219 = 0.87$$
$$\log P_{exp.} = 0.89$$

II-1-5-13-Hydrogen attached to electronegative fragments groups

Hydrogen gains in lipophilicity a correction of 1 C_M

Example

Methanoic acid

H-COOH

The molecule is cut into hydrogen fragment H and carboxylic fragment COOH the corrector factor requires $1C_{M,}$ logP is calculated as follows:

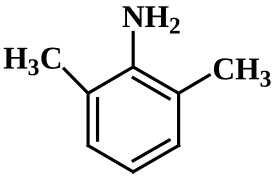
$$\log P_{cal.} = f(H) + f_{al}(COOH) + C_M$$
$$= 0.204 - 0.942 + 0.219 = -0.52$$
$$\log P_{exp.} = -0.54$$

II-1-5-14-Decoupling of resonance

In aromatic rings, neutral group example alkyl in an ortho position to another function group substituent that can undergo resonance interaction may perform a decoupling of resonance with regard to the aromatic system, because in order for resonance to occur, the π electrons on the aromatic ring and those associated with the resonating functional group must overlap. The bulkiness of an ortho- substituent causes the resonating functional group to be pushed out of plane. This decreases orbital overlap between the lone pair of electrons of the resonating functional group and the π electrons of the phenyl ring, this will convert the lipophilicity contribution of the aromatic substituent to a more aliphatic value the difference between aliphatic and aromatic fragmental constants values is connected with down multiples of C_M depending on the resonance power of the substituent: OCH_3: $-5C_M$; COOH, $CONH_2$: $-4C_M$; C=O, CONH, NHCO: $-3C_M$; NH_2: $-2C_M$.

Example

2,6-dimethylaniline



This molecule can be cut into one phenyl fragment C_6H_3, two methyl fragments CH_3 and one amine fragment NH_2, logP is obtained by adding their fragmental constants values together with correction factor of $-2C_M$ for decoupling of resonance in this case of amine substituent.

$$\log P_{cal.} = f_{ar}(C_6H_3) + f(NH_2) + 2f(CH_3) - 2C_M$$

$$= 1.494 - 0.902 + 2 \times 0.724 - 2 \times 0.219 = 1.60$$

$$\log P_{exp.} = 1.84$$

II-1-5-15-Resonance interaction

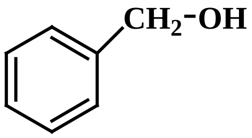
The combination of two groups like nitro, carboxyl or carbonamide on a phenyl ring in para or meta position gives rise to a resonance interaction resulting in increased logP between 1 to $3C_M$, subrules have not been developed so far; for a practical approach they propose an averaged correction of $2C_M$.

II-1-5-16-Oxygen connected to an aromatic ring via one carbon

When an oxygen atom from the –OH functional group connected to aromatic rings via one carbon C should be added a positive correction of $1C_M$, because the electrons associated with -O- overlapped with the π electrons of the phenyl ring and thereby increased partitioning, that created a pseudo-ring arose from a spatial orbital-overlap. A conjugative absorption band was noticed while studying benzyl alcohol with UV absorption spectroscopy this conjugation in pseudo-ring, like conjugation in naphthalene.

Example

Phenylmethanol



This molecule can be cut into one phenyl fragment C_6H_5, one methylene fragment CH_2, and one hydroxyl fragment OH, we then search the adequate fragmental constants values for these fragments from table II-1, and we should add the correction factor for benzyl alcohol which requires in this case $1C_M$ because it has a phenyl ring connected to an OH that is separated from the phenyl ring by one carbon for conjugated bonds, summing the substructure contributions and the correction factor gives the final logP..

$$\log P_{cal.} = f_{ar}(C_6H_5) + f(CH_2) + f(OH) + C_M$$

$$= 1.902 + 0.519 - 1.448 + 0.219 = 1.19$$

$$\log P_{exp.} = 1.10$$

II -2-XlogP method

II-2-1-Introduction

In this section we present a new and simple approach for the calculation of logP that quantifies the lipophilicity of these derivatives and shows relationship between their structure and biological activity. The method used for obtaining logP of ferrocene derivatives is based upon the adaptation of the XlogP‘s[79] approach used for organic molecules.

II-2-2-Principle of the XlogP method

Atom-additive XlogP[38] method based on additive atomic contribution of logP parameters which can be obtained by classifying atoms carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus and halogens in neutral organic compounds into 76 different atom types, besides thus basic atom types, four functional groups, i.e, cyano, isothiocyano, nitroso and nitro groups were defined as pseudoatom types since these groups are all “terminal” groups and can be treated as a whole. Thus, we used a total of 80 descriptors in atom classification according to their hybridization states, their neighboring atoms and the number of attached hydrogen atoms, the atoms belonging to the same atom type were assumed to have similar values, in the table II-2. logP values gives by summing of the contributions of each atom type as described as the following equation:

$$\mathrm{logP} = \sum_{\mathrm{i}} a_i \, A_i \qquad II-2-1$$

Where a_i is the contribution coefficient and A_i is the number of occurrences of the *i* atom type

Table II-2: Atom types in XlogP

N^o	**Atom type**	**Contribution**	**no**	**Atom type**	**Contribution**
At	**SP^3 Carbon**		26	R…C(H)…R	0.281
01	CH_3 R ($\pi = 0$)^b	0.484	27	R…C(H)…X	0.142
02	CH_3 R ($\pi \neq 0$)^b	0.168	28	X…C(H)…X	0.715
03	CH_3 X	-0.181	29	R…C(R)…R	0.302
04	CH_2 R_2 ($\pi = 0$)	0.358	30	R…C(X)…R	-0.064
05	CH_2 R_2 ($\pi \neq 0$)	0.009	31	R…C(R)…X	0.079
06	CH_2 RX	-0.344	32	R…C(X)…X	0.200
07	CH_2 X_2	-0.439	33	X…C(H)…X	0.869
08	CHR_3 ($\pi = 0$)	0.051	34	A…C (..A)…A^c	0.316
09	CHR_3 ($\pi \neq 0$)	-0.138	At	**SP Carbon**	
10	CHR_2 X	-0.417	35	R≡CH	0.054
11	$CHRX_2$, CHX_3	-0.454	36	R≡CR , R≡CX , R=C=R	0.347
12	CR_4 ($\pi = 0$)	-0.378	37	**Hydrogen** H	0.046
13	CR_4 ($\pi \neq 0$)	0.223	At	**SP^3 Oxygen**	
14	CR_3 X	-0.598	38	R-OH ($\pi = 0$)	-0.399
15	CR_2X_2	-0.396	39	R-OH ($\pi \neq 0$)	-0.029
16	CRX_3	-0.699	40	X-OH	-0.330
17	CX_4	-0.362	41	R-O-R	0.397
At	**SP^2 Carbon**		42	R-O-X , X-O-X	0.068
18	R=CH_2	0.395	43	Π-O- Π (ring)^d	0.327
19	R=CHR	0.236	At	**SP^2 Oxygen**	
20	R=CHX	- 0.166	44	O =R	-2.057
21	X=CHR , X=CHX	1.726	45	O=X	0.218
22	R=CR_2	0.098	At	**SP^3 Nitrogen**	
23	R=CRX, R=CX_2	- 0.108	46	R-NH_2($\pi = 0$)	-0.582
24	X=CR_2 , X=CXR	1.637	47	R-NH_2($\pi \neq 0$)	-0.449
25	X=CX_2	1.774	48	X-NH_2	-0.774
At	**Aromatic Carbon**		49	R-NH-R	0.040

Table II-2: Atom types in XlogP (continued)

N°	Atom type	Contribution	N°	Atom type	Contribution
50	R-NH-X , X-NH-X	-0.381	67	R-S-R , R-S-X	1.071
51	NR_3	0.443	68	Π-S- Π (in ring)[g]	0.964
52	NR_2X , NRX_2 , NX_3	-0.117	At	**SP^2 sulfur**	
At	**SP^2 Nitrogen**		69	S=R	-1.817
53	R=NH , R=NR	-2.052	At	**Sulfoxide sulfur**	
54	R=NX	-1.716	70	A-SO-A	-1.214
55	X=NR	0.321	At	**Sulfone sulfur**	
56	X=NX	-0.924	71	$A-SO_2-A$	-0.778
At	**Aromatic nitrogen**		72	Florine F	0.493
57	A…N….A[e]	-0.704	73	Chlorine Cl	1.010
At	**Trigonal planar (N)**		74	Bromine Br	1.187
58	R-NH-R	0.119	75	Iodine I	1.489
59	R-NH-X , X-NH-X	1.192	At	**Phosphorus**	
60	A-NH-A (in ring)[f]	0.434	76	A-PO(A)-A	-0.802
61	NA_3	0.587	At	**Terminal groups**	
62	NA_3 (in ring)	0.668	77	-CN	-0.256
At	**Amide nitrogen**		78	NCS	1.626
63	$-NH_2$	-0.791	79	-NO	0.077
64	-NHR , -NHX	-0.212	80	$-NO_2$	0.264
65	$-NR_2$, -NRX	0.016			
At	**SP^3 sulfur**				
66	A-SH	0.752			

[a] Definitions: − single bond; = double bond; ≡ triple bond; …., aromatic bond; R, any group linked through carbon; X, any heteroatom (O,N, S, P, and halogens); A, any atom except hydrogen, i.e., R or X; π, any atom involved in a conjugated system, such as sp^3- and sp^2-hybridized atoms and aromatic atoms. $\pi^b = 0$ represents that no π atom is a neighboring atom, while $\pi \neq 0$ represents that this atom is connected to a conjugated system. [c] The joint aromatic carbon in polycyclic aromatic systems. [d] As in a furan ring. [e] This only represents the nitrogen

atom in a six-membered aromatic ring, such as in a pyridine ring. [f] This is a special atom type adopted by the Tripos force field. When a nitrogen is connected with two or three π atoms, i.e., π -NH-π or π -N(A)-π , it adopts a trigonal planar geometric structure instead of a tetrahedron. [g] As in a pyrrole ring or some other five-membered ring. [h] As in a thiophene ring.

The difference between experimental logP and calculation be attributed to the chemical characteristics of the molecules witch affect an intramolecular interaction, to treat these interaction in restoring imbalances between experimental logP and calculation a correction factors be accounted and included, has introduced, these corrections factors are derived to correctly handle hydrophobic carbon, internal hydrogen bonding, amino acid and halogen 1 – 3 pair.

The model for XlogP calculation includes additive (atom types) and constitutive (correction factors) terms, the final logP is described as follows:

$$\mathrm{logP} = \sum_{\mathrm{i}} a_i\, A_i + \sum_{\mathrm{j}} b_j\, B_j \qquad II-2-2$$

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 j th correction factor.

In the following sections, the calculate partition coefficient that were calculated using this method are symbolized as $\log P_{\mathrm{cal.}}$ while the experimental partition coefficient are written as $\log P_{\mathrm{exp.}}$.

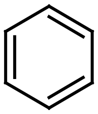
II-2-3-Examples of calculation of logP according to XlogP method

- ✓ **Molecules without interactions treatment**

This type of molecules does not need any correction.

Examples

1. **Benzene**



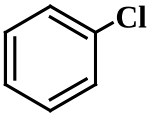
This molecule can be devided according to XlogP method into six aromatic carbon atoms C, type (26), and six hydrogen atoms, H type (37), then we search the adequate contribution from these atoms type from tableII-2, summing the atom types contributions gives the value of partition coefficient $\log P_{cal.}$, according to relation II-2-1 as follows :

$$\log P_{cal.} = 6 \times a_C(26) + 6 \times\ a_H(37)$$

$$= 6 \times 0.281 + 6 \times 0.046 = 1.96$$

$$\log P_{exp.} = 2.13$$

2. Chlorobenzene



To calculate logP of this compound we can divide it into five aromatic carbon atoms C, type (26), one atom aromatic carbon C type (30),five hydrogen atoms, H type (37) and one atom chloride Cl type (73) then we attribute the adequate contribution from these atoms types from table II-2, summing the atom types contributions we obtain $\log P_{cal.}$ value.

$$\log P_{cal.} = 5 \times a_C(26) + 5 \times a_H(37) +\ a_C(30) + a_{Cl}\,(73)$$

$$= 5 \times 0.281 + 5 \times 0.046 - 0.064 + 1.01 = 2.58$$

$$\log P_{exp.} = 2.89$$

- ✓ **Molecules with interactions treatment**

In this section we present various correction rules used in the XlogP's model for calculating logP, differing intramolecular interactions such as hydrophobic carbon, internal hydrogen bonding, amino acid and halogen 1 – 3 pair, as explained in detail below:

II-2-4- Interactions rules

II-2-4-1-Hydrophobic carbon

The hydrophobicity of compounds having hydrocarbon chains is generally underestimated from the summation of atomic contributions alone because of chain flexibility. Thus, certain compensations are required to account for these factors. We defined sp^3 and sp^2 hybridized carbons without any attached heteroatoms, i.e., atom types 1, 2, 4, 5, 8, 9, 12, 13, 18, 19 and 22 to be “hydrophobic carbons”. The number of hydrophobic carbons is used as a correction factor for only hydrocarbons, hydrophobic carbon needs correction factor is equal to 0.19.

Example

1,4 - Pentadiene

$$\mathbf{H_2C{=}CH{-}CH_2{-}CH{=}CH_2}$$

The calculation of logP of this compound describes how to apply hydrophobic carbon correction factor in aliphatic hydrocarbon chains, This molecule should be cut into two aliphatic atoms carbons C type (18), two aliphatic atoms carbons C type (19), one aliphatic atom carbon C type (4) and eight hydrogen atoms H type (37) and added the correction factor, of hydrophobic carbon which needs 0.19, summing the atom types contributions and the correction factor gives the final log $P_{cal.}$ as follows:

$$\log P_{cal.} = 2 \times a_C(18) + 2 \times a_C(19) + a_C(4) + 8 \times a_H(37) + 0.19$$

$$= 2 \times 0.395 + 2 \times 0.236 + 0.358 + 8 \times 0.046 + 0.19 = 2.18$$

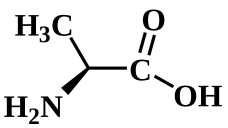
$$\log P_{exp.} = 2.89$$

II-2-4-2- Amino acid

log P values of amino acids have been largely overestimated by the summation of simple atomic contributions because amino acids do not contain free amino and carboxylic acid groups but rather exist as zwitterions, which amino acid requires correction factor of -2.27.

Example

Alanine



This molecule should be cut into in one carbon atom C type (1), one carbon atom C type(10), one oxygen atom O type (39), one nitrogen atom N type(46), one oxygen atom O type (44), one carbon atom C type (24) and seven hydrogen atoms H type (37) and added the correction factor of amino acid requires-2.27, summing the atom types contributions from table II-2 and the correction factor gives the final log $P_{cal.}$ as follows:

$$\log P_{cal.} = a_C(1) + a_C(10) + a_O(39) + a_N(46) + a_O(44) + a_c(24) + 7 \times a_H(37) - 2.27$$

$$= 0.484 - 0.417 - 0.029 - 0.582 - 2.057 + 1.637 + 7 \times 0.046 - 2.27 = -294$$

$$\log P_{exp.} = -2.94$$

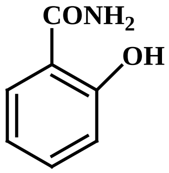
II-2-4-3- Intramolecular Hydrogen Bond

Intermolecular hydrogen bonds can increase the hydrophobicity of a molecule, hydrogen bonding requires value equal to 0.60 but identifying the existence of hydrogen bonds within a compound from its chemical structure, to define an intermolecular hydrogen bond:

1. The hydrogen donor could be a heteroatom attached to one or two hydrogens.
2. The hydrogen acceptor could be a sp^2 hybridized oxygen, fluorine, or hydrogen donor atom defined above.
3. The distance between the donor and the acceptor should be within a proper range.
4. The intramolecular hydrogen bond could form a six-membered ring in the molecule. Only when all four conditions are met do we assign an intramolecular hydrogen bond to a given molecule.

Example

Salicylamide



We can cut this compound with above structural formula into one atom aromatic carbon C type (30), four aromatic carbon atoms C type (26), aromatic carbon atom C type (29), one carbon atom C type (24), two different oxygen atoms has types (44) and type (39), nitrogen atom N type (63), and seven hydrogen atoms type (37) we search the adequate contribution from these atom types in the table II-2, and added the corrector factor, in this case a corrector factor for intramolecular Hydrogen bond requires 0.6, summing the atom types contributions and the corrector factor gives the final log $P_{cal.}$ as follows:

$$\log P_{cal.} = a_C(30) + 4 \times a_C(26) + a_C(29) + a_C(24) + a_O(44) + a_N(63) + a_C(24) + 7 \times a_H(37) + a_O(39) + 7 \times a_H(37) + 0.6$$

$$= -0.064 + 4 \times 0.281 + 1.637 - 2.057 - 0.791 - 0.029 + 7 \times 0.046 + 0.60 = 1.04$$

$$\log P_{exp.} = 0.89$$

II-2-4-4- Halogen-Halogen 1-3 (Geminal) Interaction

When two or more halogen atoms are attached to the same atom, some relatively changes occur because of dipole shielding. In our model, we have found that whether fluorine is involved or not determines the extent of the change. This is because fluorine is much smaller than the other halogens and is extremely electronegative. Thus, we have used two different parameters to account for halogen-halogen 1-3 (geminal) interaction .In general, the correction factor is positive when fluorine is involved and negative when fluorine is not involved, the contribution corrections factor for halogen 1-3 pair (F-F, F-X) correction factor Negligible nearly devolve to zero required 0.08, but for halogen 1-3 pair (X-X) correction factor requires -0.26, X represents Cl, Br, and I.

Example

Dichloromethane

$$\mathbf{Cl{-}CH_2{-}Cl}$$

This structure presents two chloride atoms Cl type (73), one carbon atom C type (7) and two hydrogen atoms type (37), logP is obtained by adding their contribution atom types values together with the correction factor value of -0.26 for halogen (Cl-Cl), 1-3 pair.

$$\log P_{cal.} = a_C(7) + 2 \times a_{Cl}(73) + 2 \times a_H(37) - 0.26$$

$$= -0.439 + 2 \times 1.01 + 2 \times 0.046 - 0.26 = 1.32$$

$$\log P_{exp.} = 1.25$$

II-3- AlogP method

II-3- 1-Introduction

In previous subchapters we described two different methods for calculation of partition coefficient of simple organic compounds Rekker and XlogP methods.

We present in this subchapter an other simple atom-additive approach AlogP [79] for the calculation of octanol-water partition coefficient that quantifies the lipophilicity. This method used for obtaining logP of various classes of simple organic molecules.

II-3- 2- Principle of the AlogP approach

Atom-additive AlogP method[37] gives logP values by summing the contributions of component atoms, this method is based on additive atomic contribution of logP parameters which can be obtained by classifying carbon, oxygen, nitrogen, sulfur, boron, silicon and selenium into 120 atom types according to their hybridization states and the chemical nature of their neighboring atoms, the complexity of classification is attested by a total of 44 carbon types alone, hydrogen and halogens are classified by the hybridization and oxidation state of the carbon they are bonded to. The total number 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. The logP of a molecule is assumed to be the summation of the contributions of each atom type in the table II-3 as the following equation:

$$\log P = \sum n_i a_i \qquad II-3-1$$

Where n_i is the number of atoms of type i and a_i is the atomic log P contribution, this method does not require correction factors.

Table II-3: Atom types in AlogP

N°	Atom type	Contribution	N°	Atom type	Contribution
	C				
01	:CH_3R[a], CH_4	- 1.5603	26	:R- -CX- -R	0.1539
02	:CH_2R_2	-1.0120	27	:R- -CH- -X	0.0005
03	:CHR_3	-0.6681	28	:R- -CR- -X	0.2361
04	:CR_4	-0.3698	29	:R- -CX- -X	0.3514
05	:CH_3X	-1.7880	30	:X- -CH- -X	0.1814
06	:CH_2RX	-1.2486	31	:X- -CR- -X	0.0901
07	:CH_2X_2	-1.0305	32	:X- -CX- -X	0.5142
08	:CHR_2X	-0.6805	33	:R- -CH…X	-0.3723
09	:$CHRX_2$	-0.3858	34	:R- -CR…X	0.2813
10	:CHX_3	0.7555	35	:R- -CX…X	0.1191
11	:CR_3X	-0.2849	36	:Al-CH=X	-0.1320
12	:CR_2X_2	0.0200	37	:Ar-CH=X	-0.0244
13	:CRX_3	0.7894	38	:Al-C(=X)-Al	-0.2405
14	:CX_4	1.6422	39	:Ar-C(=X)-R	-0.0909
15	=:CH_2	-0.7866	40	:R-C(=X)-X. R-C:≡X, X=C=X	-0.1002
16	=CHR	-0.3962	41	:X-C(=X)-X	0.4182
17	=CR_2	0.0383	42	:X- -CH…X	-0.2147
18	=CHX	-0.8051	43	:X- -CR…X	-0.0009
19	:=CRX	-0.2129	44	:X- -CX….X	01388
20	=CX_2	0.2432		**H** attached to[c]	
21	=CH	0.4697	45	-	-
22	:≡CR, R=C=R	0.2952	46	C^0sp^3	0.7341
23	:≡CX	-	47	C^1sp^3 ,C^0sp^2	0.6301
24	:R- -CH- -R	-0.3251	48	C^2sp^3 , C^1sp^2 ,C^0sp	0.5180
25	:R- -CR- -R	0.1492	49	C^3sp^3 , $C^{2-3}sp^2$, $C^{1-3}sp$	-0.0371

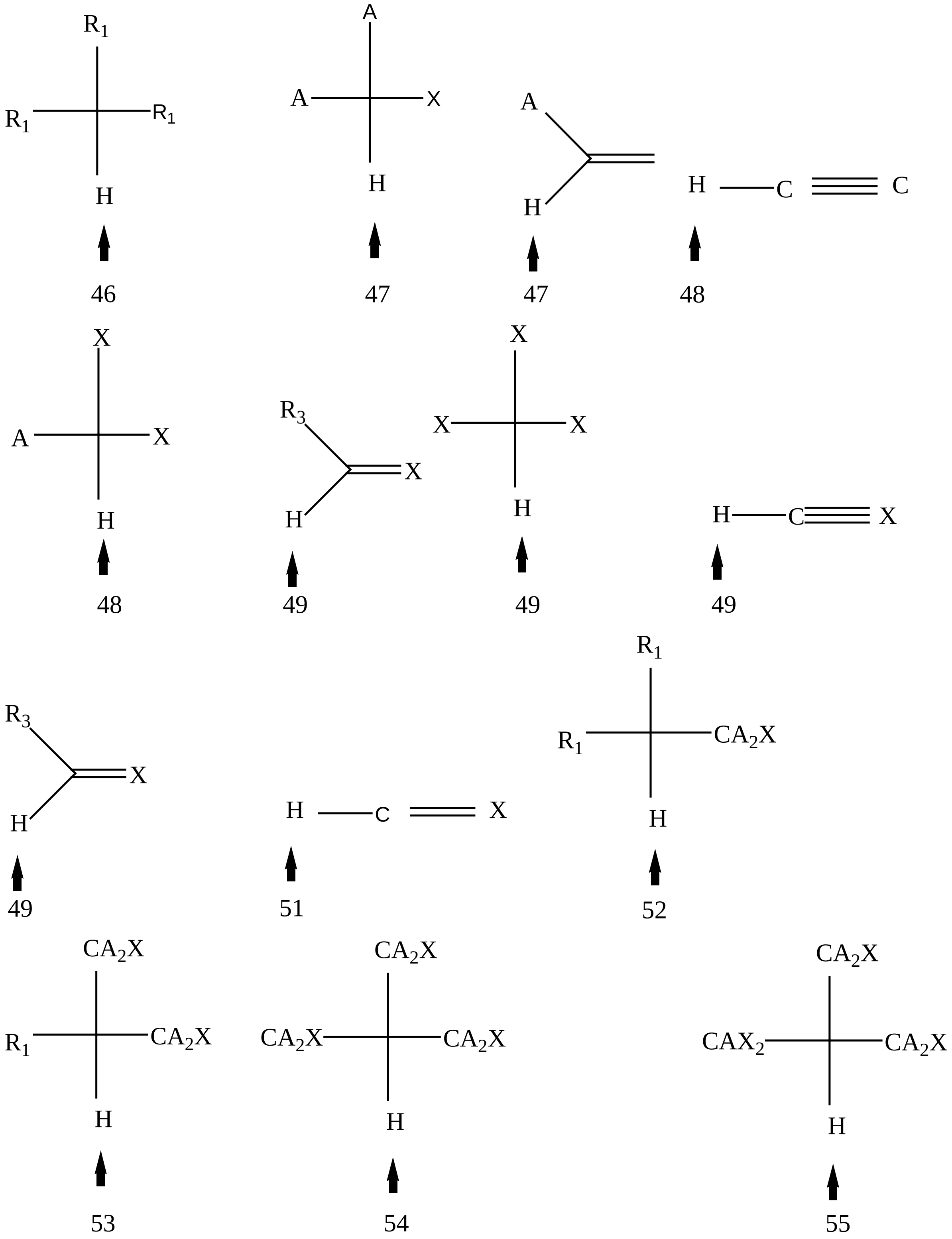
Table II-3: Atom types in AlogP (continued)

N°	Atom type	Contribution
50	**heteroatom**	-0.1036
51	α- C^{d}	0.5234
52	$C^{0}_{sp^{3}}$ 1 X attached to next c	0.6666
53	$C^{0}_{sp^{3}}$ 2 X attached to next c	0.5372
54	$C^{0}_{sp^{3}}$ 3 X attached to next c	0.6338
55	$C^{0}_{sp^{3}}$ 4 ≥ X attached to next c	0.3620
	O in	
56	:alcohol	-0.3567
57	phenol, enol, carboxyl OH	-0.0127
58	:=O	-0.0233
59	:Al-O-Al	-0.1541
60	:Al-O-Ar, Ar_2O	0.0324
	:R...O...R, R-O-C=X	
61[e]	:- -O	1.0520
62	:O- (negatively charged)	-0.7941
63	:R-O-O-R	0.4165
	Se in	
64	:Any-Se-Any	0.6601
65	:=Se	-
	N in	
66	:Al-NH_2	-0.5427
67	:Al_2NH	-0.3168
68	:Al_3N	0.0132
69	:Ar-NH_2, X-NH_2	-0.3883
70	:Ar-NH-Al	0.0389
71	:Ar-NAl_2	0.1087
72	:RCO-N<, >N-X=X	-0.5113
73	:Ar_2NH, Ar_3N :Ar_2N-Al, R…N….R[f]	0.1259
74	:R≡N,R=N-	0.1349
75	:R- -N- -R, [g]R- -N- -X	-0.1624
76	:Ar-NO_2, R- -N(- -R)- -O[h] RO-NO,	-2.0585
77	:Al-NO_2	-1.9150
78	:Ar-N=X, X-N=X	0.4208
79	:N+ (positively charged)	-1.4439
80	-	-
	F attached to	
81	$C^{1}_{sp^{3}}$	0.4797
82	$C^{2}_{sp^{3}}$	0.2358
83	$C^{3}_{sp^{3}}$	0.1029
84	$C^{1}_{SP^{2}}$	0.3566
85	$C^{2-4}sp^{2}$,$C^{1}sp$,$C^{4}sp^{3}$, X	0.1988
	Cl attached to	
86	$C^{1}_{sp^{3}}$	0.7443
87	$C^{2}_{sp^{3}}$	0.5337
88	$C^{3}_{sp^{3}}$	0.2996
89	$C^{1}_{SP^{2}}$	0.8155
90	$C^{2-4}sp^{2}$, $C^{1}sp$, $C^{4}sp^{3}$, X	0.4856
	Br attached to	
91	$C^{1}_{sp^{3}}$	0.8888
92	$C^{2}_{sp^{3}}$	0.7452
93	$C^{3}_{sp^{3}}$	0.5034
94	$C^{1}_{SP^{2}}$	0.8995

Table II-3: Atom types in AlogP (continued)

N°	Atom type	Contribution	N°	Atom type	Contribution
95	$C^{2-4}sp^{2}$, $C^{1}sp$,$C^{4}sp^{3}$, X	0.5946	108	:R=S	0.8758
	I attached to		109	:R-SO-R	-0.4979
96	$C^{1}{}_{sp}{}^{3}$	1.4201	110	:R-SO_2-R	-0.3786
97	$C^{2}{}_{sp}{}^{3}$	1.1472		**Si** in	
98	$C^{3}{}_{sp}{}^{3}$	-	111	:>Si< as in silicones	1.5188
99	$C^{1}{}_{SP}{}^{2}$	0.7293		**B** in	
100	$C^{2-4}sp^{2}$, $C^{1}sp$,$C^{4}sp^{3}$, X	0.7173	112	:>B^- as in boranes	1.0255
	halide ions			**P** in	
101	:fluoride ion	-	115	**:ylids**	-
102	:chloride ion	-2.6737	116	:R_3-P=X	-0.9359
103	:bromide ion	2.4178	117	:X_3-P=X (phosphate)	-0.1726
104	:iodide ion	-3.1121	118	:PX_3 (phosphite)	-0.7966
	S in		119	:PR_3 (phosphine)	0.6705
106	:R-SH	0.6146	120	:C-P$(X)_2$=X (phosphonate)	-0.4801
107	:R_2S, RS-SR	0.5906			

[a]R represents any group linked through carbon; X represents any heteroatom (O, N, S, P, Se, and halogens); Al and Ar represent aliphatic and aromatic groups, respectively; = represents a double bond;≡ represents a triple bond; - - represents a aromatic bonds as in benzene or delocalized bonds such as the N-O bond in a nitro group; … represents aromatic single bonds as the C-N bond in pyrrole. [c] represents the hybridization and its formal oxidation number. [d] An α-C may be defined as a C attached through a single bond with –C=X, -C≡X, -C- -X. [e] As in nitro, *N*-oxides. [f] Pyrrole-type structure. [g] *p*yridine type structure. [h] Pyridine *N*-oxide type structure.



FigureII-3: *Description of various types of hydrogen*

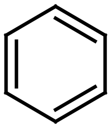
R_1 = H or CA_3 where A = C or H, X any electronegative atom, R_3 = C or H or X. For atom types 53-55, the electronegative atom may be attached to the same or different carbon atom as shown above.

II-3- 3- Examples of calculation of logP according to AlogP method

- ✓ **Aromatic molecules**

Examples

1. Benzene: C_6H_6



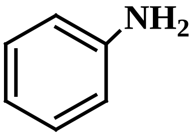
This molecule can be divided according to AlogP method into six aromatic carbon atoms C type (24), and six hydrogen atoms, H type (47), then we search the adequate contribution from these atoms types from table II-3, summing the atoms types contributions gives the value of partition coefficient $\log P_{cal.}$, according to relation $II-3-1$ as follows :

$$\mathrm{logP_{cal.}} = 6 \times \mathrm{a_C}(24) + 6 \times \mathrm{a_H}(47)$$

$$= -6 \times 0.3251 + 6 \times 0.6301 = 1.83$$

$$\mathrm{logP_{exp.}} = 2.13$$

2. Aniline : C_6H_5-NH_2



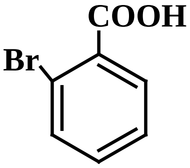
This molecule can be cut into five aromatic carbon atoms C, type (24), one aromatic carbon atoms C type (26), five hydrogen atoms, H type (47), two hydrogen atoms, H type (50) and one nitrogen atom N type (69), then we attribute the adequate contribution for these atom types from table II-3, summing the atom types contributions we obtain $\log P_{cal.}$ value.

$$\mathrm{logP_{cal.}} = 5 \times \mathrm{a_C}(24) + 5 \times \mathrm{a_H}(47) + 2 \times \mathrm{a_H}(50) + \mathrm{a_C}(26) + \mathrm{a_N}(69)$$

$$= -5 \times 0.3251 + 5 \times 0.6301 - 2 \times 0.1036 + 0.1539 - 0.3883 = 1.08$$

$$\log P_{exp.} = 0.94$$

3. 2-Bromobenzoic acid : $C_6H_4BrCOOH$



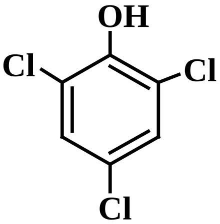
logP value of this molecule is obtained by summing the contribution from four aromatic carbon atoms C, type (24), one aromatic carbon atom C type (25), one aromatic carbon atom C type (26), one carbon atom C type (40), four hydrogen atoms H type (47), one hydrogen atom, H type (50), one oxygen atom O type (57) one bromide atom Br type (94), and one oxygen atom O type (58).

$$\log P_{cal.} = 4 \times a_C(24) + 4 \times a_H(47) + a_H(50) + a_C(25) + a_C(26) + a_C(40) + a_{OH}(57) + a_O(58) + a_{Br}(94)$$

$$= -4 \times 0.3251 + 4 \times 0.6301 - 0.1036 + 0.1492 + 0.1539 - 0.1002 - 0.0127 - 0.0233 + 0.8995 = 2.18$$

$$\log P_{exp.} = 2.20$$

4. 2, 4,6-Trichlorophenol : $C_6H_3Cl_3O$



logP value of this molecule is obtained by summing the contribution from two aromatic carbon atoms C type (24), four aromatic carbon atoms C type (26), two hydrogen atoms H type (47), one hydrogen atom H type (50), one oxygen atom O type (57) and three chloride atoms Cl type (89).

$$\log P_{cal.} = 2 \times a_C(24) + 2 \times a_H(47) + a_H(50) + 4 \times a_C(26) + a_{OH}(57) + 3 \times a_{Cl}(89)$$

$$= -2 \times 0.3251 + 2 \times 0.6301 - 0.1036 + 4 \times 0.1539 - 0.0127 + 3 \times 0.8155 = 3.55$$

$$\log P_{exp.} = 3.69$$

✓ **Aliphatic molecules**

Examples

1. **Butane : C_4H_{10}**

$$\mathbf{CH_3{-}CH_2{-}CH_2{-}CH_3}$$

This molecule should be cut into two carbon atoms C type (1), two carbon atoms C type (2), and ten hydrogen atoms H type (46), summing the atom types contributions from table II-3 gives the final log $P_{cal.}$ as follows:

$$logP_{cal.} = 2 \times a_C(1) + 2 \times a_C(2) + 10 \times a_H(46)$$
$$= -2 \times 1.5603 - 2 \times 1.012 + 10 \times 0.7341 = 2.20$$
$$\log P_{exp.} = 2.89$$

The difference between the experimental logP value and calculated value equal to 0.69 this underestimation due to flexibility of chain of aliphatic hydrocarbon, to compensate that deviation, this calculated method required a correction to account for these factors.

2. **1,4-Pentadiene : C_5H_8**

$$\mathbf{H_2C{=}CH{-}CH_2{-}CH{=}CH_2}$$

This unsaturated molecule should be cut into two carbon atoms C type (15), two carbon atoms C type (16), one carbon atom C type (2) two hydrogen atoms H type (46) and six hydrogen atoms H type (47), summing the atom types contributions from table II-3 gives the final log $P_{cal.}$ as follows:

$$\log P_{cal.} = 2 \times a_C(15) + 2 \times a_C(16) + a_C(2) + 2 \times a_H(46) + 6 \times a_H(47)$$
$$= -2 \times 0.7866 - 2 \times 0.3962 - 1.012 + 2 \times 0.7341 + 6 \times 0.6301 = 1.87$$
$$\log P_{exp.} = 2.47$$

3. **Butanol : $C_4H_{10}O$**

$$\mathbf{CH_3{-}CH_2{-}CH_2{-}CH_2{-}OH}$$

logP for this molecule which contains an alcohol function we can be calculated by summing the contribution from two carbon atoms C type (2), one carbon atom C type (1), one carbon atom C type (6), one oxygen atom O type (56), five hydrogen atoms H type (46), one hydrogen atom H type (50), two hydrogen atoms H type (47) and two hydrogen atoms H type (52) as follows:

$$\begin{aligned}\mathrm{logP_{cal.}} &= a_C(1) + 2 \times a_C(2) + a_C(6) + a_O(56) + 5 \times a_H(46) + 2 \times a_H(52) + \\ &\quad a_H(50) + 2 \times a_H(47) \\ &= -1.5603 - 2 \times 1.012 - 1.2486 - 0.3567 + 5 \times 0.7341 + 2 \times 0.6666 - \\ &\quad 0.1036 + 2 \times 0.6301 = 0.97\end{aligned}$$

$$logP_{exp.} = 0.88$$

4. Dichloromethane

$$\mathbf{Cl{-}CH_2{-}Cl}$$

This example shows two chloride Cl atoms are placed on a carbon atom, This molecule can be divided according to AlogP method into one carbon atom C type (7) , two chloride atoms Cl type (86) and two hydrogen atoms H type (48), the adequate contributions values of atoms types is then attributed from table II-3, the summing of the atom types contributions values gives the value of partition coefficient as follows:

$$\begin{aligned}logP_{cal.} &= a_C(7) + 2 \times a_H(48) + 2 \times a_{Cl}(86) \\ &= -1 \times 1.0305 + 2 \times 0.5180 + 2 \times 0.7443 = 1.49\end{aligned}$$

$$logP_{exp.} = 1.25$$

5. 4-Chlorobutanol : $C_4H_{10}ClO$

$$\mathbf{Cl{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}OH}$$

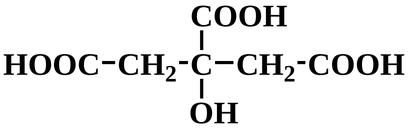
logP for this molecule which contains an alcohol function we can be calculated by summing the contribution from two carbon atoms C type (2), two carbon atoms C type (6), one oxygen atom O type (56), one chloride atom Cl type (86), one hydrogen atom H type (50), for hydrogen atoms H type (47) , and for hydrogen atoms H type (52) as follows:

$$\begin{aligned}\mathrm{logP_{cal.}} &= 2 \times a_C(2) + 2 \times a_C(6) + a_O(56) + a_{Cl}(86) + 4 \times a_H(52) + a_H(50) + \\ &\quad 4 \times a_H(47)\end{aligned}$$

$$= -2 \times 1.012 - 2 \times 1.2486 - 0.3567 + 0.7443 + 4 \times 0.6666 - 0.1036 + 4 \times 0.6301 = 0.95$$

$$logP_{exp.} = 0.85$$

6. Citric acid: $C_6H_8O_7$



$$HOOC-CH_2-\underset{\displaystyle OH}{\overset{\displaystyle COOH}{C}}-CH_2-COOH$$

The atom types in this molecule which contains carboxyl function are a two carbon atoms C type (2), one carbon atom C type (13), three carbon atoms C type (40), four hydrogen atoms H type (50), one oxygen atom O type (56), three oxygen atoms O type (57), three oxygen atoms O type (58) and four hydrogen atoms H type (53), summing the atom types contributions values from table II-3, gives the final log $P_{cal.}$ as follows:

$$logP_{cal.} = 2 \times a_C(2) + a_C(13) + 3 \times a_C(40) + 4 \times a_H(50) + a_{OH}(56) + 3 \times a_{OH}(57) + 3 \times a_O(58) + 4 \times a_H(53)$$

$$= -2 \times 1.012 - 0.2849 - 3 \times 0.1002 - 4 \times 0.1036 - 0.3567 - 3 \times 0.0127 - 3 \times 0.0233 + 4 \times 0.5372 = -1.34$$

$$\mathrm{logP_{exp.}} = -1.72$$

II-4- LogP measurement methods

II-4-1- Introduction

There are different methods for the measurement of octanol – water partition coefficient, numerous of those methods are based on the measurement of the concentrations at equilibrium in both octanol and aqueous phases.

In this subchapter we present an overview covered the important methods to determine partition coefficients explaining its different stages, and giving literature review and studies for the electrochemical method to be used in the first time in this research work based on square wave voltammetry technique.

II-4-1-1- Shake flask method

The shake flask method is the oldest and most tedious way of measuring logP values. In order to determine a partition coefficient, equilibrium between all interacting components of the system must be achieved, and the concentrations of the substances dissolved in the two phases must be determined. Octanol and water are standard solvents for the equilibrium experiments. They are readily available and allow equilibrium experiments with good repeatability and reproducibility.

Two large stock bottles of high purity analytical grade n-octanol or water are saturated with a sufficient quantity of the other solvent. Both solvents are shaken for 24 hours on a mechanical shaker. They are allowed to stand for two days to permit the phases to separate. In order to determine logP, it is necessary to determine the concentrations of the test substance in both phases. The total quantity of substance present in both phases should be calculated and compared with the quantity of the substance originally introduced. The logP value is calculated from the ratio of their presence in the two components is given by the equation I − 1 [80-83].

II-4-1-2- Stir-flask method

The shake-flask method was further developed into the stir-flask method by Brooke et al[84]. In this procedure, water is brought into a vessel together with a Teflon-coated magnetic stirring bar. When the aqueous phase has reached the desired temperature the n-octanol phase containing the test substance is poured very carefully on top of the aqueous phase in order to avoid emulsion formation as far as possible. The vessel is not shaken; instead the system is stirred for an extended period of time at least 36 h allowing equilibrium to be reached. Samples from both phases are taken for analysis. Results obtained using the stir-flask method were reported [85-86] and shown to be very reproducible and also in good agreement with P values measured by other techniques. The method removes the risk for gross contamination of one phase by the other as a result of emulsification. Close temperature control is however necessary to avoid precipitation and the formation of micelles and emulsions caused by temperature cycling during the equilibration period.

II-4-1-3- Chromatography method

Chromatography [4] [86] is one of the major methods used to determine lipophilicity data, and it is readily available and easy to use.

In chromatographic HPLC method the partition of the compound between stationary phase and mobile phase is used as surrogate parameter for lipophilicity. The retention time of the analyte correlates with the lipophilicity of the compound. In order to get direct octanol-water partitioning, it is essential to immobilize octanol at the stationary phase, logP of a solute can be determined by correlating with its retention time, the equation giving the partition coefficient is written as:

$$logP = loga + logk' \qquad II-4-1$$

With $$k' = \frac{t_r - t_o}{t_o} \qquad II-4-2$$

Where t_r is the retention time of the substance, t_o the elution time of the solvent and a *is* a constant.

II-4-1-4- Potentiometric method

Potentiometric [87-101] measurements provide a highly selective method for the quantitative determination of numerous cations and anions. This technique allows measurement of the logP values of ionizable solutes exclusively. This method is based on the observation that when an ionizable compound in aqueous solution is titrated in the presence of an organic phase, the titration curve shifts to the right for acids and to the left for bases. This shift is related to the phase ratio and to the lipophilicity of both electrical species of the solute.

In the simple case of a monobasic drug B, the apparent pKa (app pKa) of the substance measured in the presence of the organic phase is given by Equation.

$$\mathrm{PK_a^{app}} = \mathrm{pK_a} - \log\left[\frac{\mathrm{r.P^{B}} + 1}{\mathrm{r.P^{BH^+}} + 1}\right] \qquad II - 4 - 3$$

Where $\mathrm{P^B}$ and $\mathrm{P^{BH^+}}$ are the partition coefficients of the neutral and protonated drug, respectively, and r is the phase volume ratio. Thus the determination of the logP values of a monobasic or monoacid compound requires knowledge of its pKa and a minimum of two titrations in the presence of two different phase volume ratios, yielding two app pKa values. The resolution of the system given by equations II-4-4 and II-4-5 yields $\log\mathrm{P^B}$ and $\log\mathrm{P^{BH^+}}$ values.

$$\mathrm{pK_a^{app1}} = \mathrm{pK_a} - \log\left[\frac{\mathrm{r_1.P^{B}} + 1}{\mathrm{r_1.P^{BH^+}} + 1}\right] \qquad II - 4 - 4$$

$$\mathrm{pK_a^{app2}} = \mathrm{pK_a} - \log\left[\frac{\mathrm{r_2.P^{B}} + 1}{\mathrm{r_2.P^{BH^+}} + 1}\right] \qquad II - 4 - 5$$

The advantage of the potentiometry method is the possibility to use a large set of solvents and to measure a large range of logP values [102].

II-4-1-5- Voltammetric methods:

Cyclic voltammetry at the interface between two immiscible electrolyte solutions is an electrochemical method to determine the lipophilicity of ions and to study their mechanism of transfer at the liquid-liquid interface [103-107]. This technique requires the use of a polarizable interface which is available with a solvent system. The main advantage of cyclic voltammetry is to provide standard log P values for ions, independent on the experimental conditions (except on temperature and solvents) [108], the partition coefficient is given by the following relation:

$$logP = -\frac{z_i.F}{R.T2.3}\Delta_\beta^\alpha\phi_i^0 \qquad II-4-6$$

Where $\Delta_\beta^\alpha\phi_i^0$ is the standard transfer potential of ion between phases α and β, R is the gas constant ($8.31\ J\cdot K^{-1}\cdot mol^{-1}$), F is the Faraday constant ($9.65\cdot 10^4\ C\cdot mol^{-1}$), T is the temperature in Kelvin and z_i is the charge of ion.

Although, the rapid advancement of ferrocene chemistry, notably in areas related to biology, medicine[109-114], catalysis and materials [115], there are only very few experimental values of interest fundamental physicochemical parameter octanol-water partition coefficient logP reported for ferrocene derivatives[116]. This work in is contribution to determine partition coefficient logP for ten ferrocene derivatives based on the electrochemical properties of ferrocenes using square-wave voltammetry technique.

II-4-2- Literature review:

II-4-2-1- Electrochemical properties of ferrocene

Ferrocene $Fe(C_5H_5)_2$ is a molecule with a sandwich-type structure in which the iron atom is sandwiched between two five-membered carbon rings [117], the oxidation of ferrocene to the ferrocenium cation $Fe(C_2H_5)^+_2$ figureII-4-1, is a standard one-electron transfer reversible process because the rate of electron transfer is extremely fast [118-119]. During the last three decades, ferrocene has been employed for evaluating both kinetic and thermodynamic parameters in numerous electrochemical studies, as an electron-donor unit having chemical versatility, ferrocene and its derivatives have received considerable attention since they have found potential applications in bioorganometallic chemistry, particularly in materials science.

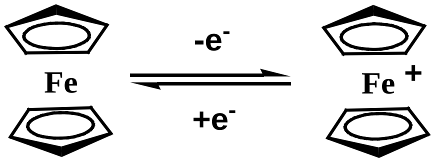


Figure II-4-1: *One electron oxidation of ferrocene to yield the ferricenium ion and reverse reduction reaction.*

II-4-2-2- Electroanalytical chemistry

Electroanalytical chemistry is concerned with the analysis of chemical reactions in relationship to their electrical quantities (i.e. current, potential and charge). It involves the reactions that take place at the electrode solution interface. That are a group of quantitative analytical methods are based on the electrical properties of a solution containing an analyte (an electroactive chemical species) when it is made part of an electrochemical cell (Skoog and Leary, 1998). Electroanalytical methods can have low detection limits and have several advantages over other analytical techniques, they are specific for particular oxidation states of an element, the equipment needed is relatively inexpensive, and they can provide activities rather than concentrations of chemical species.

The Principle of electroanalytical chemistry is related to the measure of a current response related to the concentration of an analyte. This response is related to the transfer of electrons between the electrode-solution interface of a redox reaction. Several electrochemical methods including voltammetric technique.

II-4-2-3- Voltammetric methods

Voltammetry is comprised of a group of electrochemical methods that provide information about an analyte by measuring the current as a function of applied potential and is obtained under conditions that promote polarization of the working electrode (Skoog and Leary, 1998). Polarization is defined as the change of potential of an electrode from its equilibrium potential upon the application of a current (Electrochemistry Dictonary, 2006). Techniques that vary the potential being applied yield several voltammetric methods including, square wave voltammetry, cyclic voltammetry, These techniques are used to measure the concentration of electroactive species in solution; where one technique may be more effective than another at detecting a certain chemical species because of the method differences in sensitivity and signal to noise ratios (Rubinson, 2000).

Voltammetry technique makes use of a three-electrode system such as working electrode (WE), reference electrode (RE) and auxiliary electrode (AE). The whole system consists of a voltammetric cell with a various volume capacity.

II-4-2-4- Current in voltammetry

When an analyte is oxidized at the working electrode, a current passes electrons through the external electric circuitry to the auxiliary electrode, where reduction of the solvent or other components of the solution matrix occurs. Reducing an analyte at the working electrode requires a source of electrons, generating a current that flows from the auxiliary electrode to the cathode. In either case, a current resulting from redox reaction at the working electrode and auxiliary electrode is called a faradaic current. A current due to the analyte’s reduction is called a cathodic current. Anodic currents are due to oxidation reaction. The magnitude of the faradaic current is determined by the rate of the resulting oxidation or reduction reaction at the electrode surface. Two factors contribute to the rate of the electrochemical reaction which are the rate at which the reactants and products are transported to and from the electrode, and the rate at which electron pass between the electrode and the reactants and products in solution.

II-4-2-5- Square-wave voltammetry

Square-wave voltammetry (SWV) is a powerful electrochemical technique that can be applied in both electrokinetic and analytic measurements [120-123], provided by modern computer-controlled electroanalytical instruments, such as Autolab, The technique originates from the Kalousek commutator and Barker’s. Square-wave voltammetry developed by Dr. Osteryoung and thus commonly referred to as the Osteryoung SWV technique. This technique consists of the application of a square-wave of constant amplitude superimposed on a staircase wave form . The current is sampled twice in each pulse period, at the reverse half cycle and the forward half cycle. The resulting peak current is proportional to the concentration of the chemical species is the difference between the two currents is given by the equation II-4-7, which is displayed as a function of the resultant potential. This allows the effect of charging current to be minimized, as any residual charging current is subtracted and high sensitivity is achieved. Figure II-4-2 shows the potential–time waveform of modern SWV. Figure II-4-3 shows the square wave voltammograms.

The difference between these two currents is the peak current which is proportional to the chemical species concentration over a given concentration range, and is given [124] by the equation $II-4-7$.

$$di_p = \frac{2n^2F^2rDCE}{RT} \qquad II-4-7$$

Where di_p is the peak current, n is the charge, F is the Faraday constant, r is the electrode radius, D the diffusion coefficient of the electroactive species in solution, C is the bulk concentration of the electroactive species, E step potential, R is the gas constant, and T is the temperature. The diffusion coefficient of analyte in solution is constant at the low concentration.

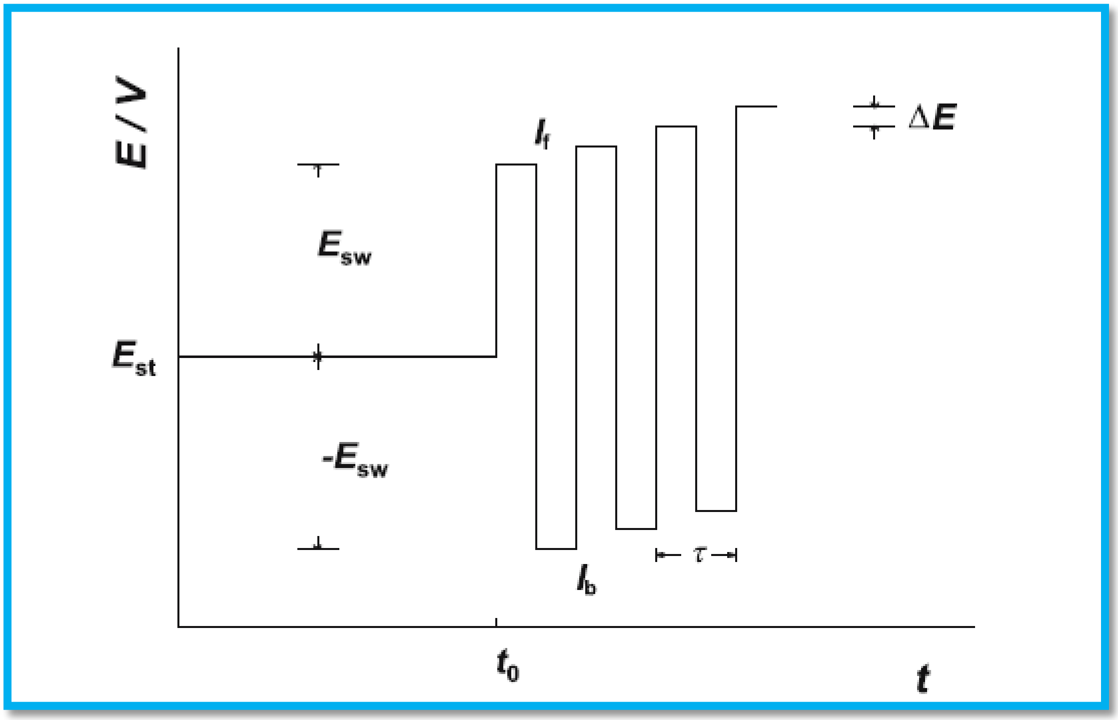


Figure II-4-2: *Scheme of the square-wave voltammetric wave form*

Where E_{st} starting potential, E_{sw} square wave amplitude, ΔE scan increment, τ staircase period, t_0 delay time and I_f and I_b denote the points where the forward and backward currents are sampled respectively.

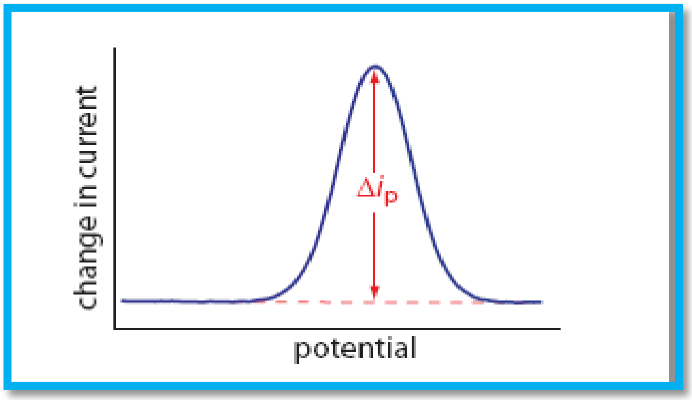


Figure II-4-3: Square wave voltammogram

II-4-2-6- Devloppement of square wave voltammetry

Square wave voltammetry technique originates from the Kalousek commutator [125] and Barker's square-wave polarography [126]. Kalousek constructed an instrument with a rotating commutator that switched the potential of the dropping mercury electrode between two voltage levels with the frequency of five cycles per second [127,128].The method was improved by Ishibashi and Fujinaga, who introduced the differential polarography by measuring the difference in current between successive half-cycles of the square-wave signal [129–131].

Barker and Jenkins introduced important innovations to minimize the influence of capacity current, i.e., to discriminate that current with respect to the faradaic current. During each half cycle, the double layer charging current decreases exponentially with time, while the faradaic current is inversely proportional to the square-root of time. Under certain conditions, the charging current at the end of half-cycle may be smaller than the faradaic current.

This method was developed further by superimposing the square-wave signal onto a staircase signal [132,133]. Some of the possible potential-time waveforms was shown in figure II-4-2, usually each square-wave cycle occurs during one stair- case period, which is sometimes called Osteryoung SWV [134-137].

In this experimental research work we present the experimental determination of partition coefficient of ten ferrocene derivatives with using shake flask method, this simplest method consists of distributing a known quantity of the substance between octanol and water mutually saturated beforehand, which involves shaking the two solvents together until the partition equilibrium of the solute is reached, so they left to stand until phase separation, about 2-3 days.

For the determination of the partition coefficient, it is necessary to determine the concentrations of the substance in both phases, the octanol phase concentration of ferrocene derivatives is determined using electrochemical methods for the first time carried out by square-wave voltammetry technique, and the aqueous phase concentration of ferrocene derivative is calculated base on a mass balance. The partition coefficient was calculated as the ratio of the concentration of each ferrocene derivatives in the octanol phase to its concentration in the aqueous phase.

The quantitative information using electrochemical methods is obtained by relating current peak of square wave voltammograms to the concentration of ferrocene derivatives in the solution.

Electrochemical measurements are commonly carried out in a medium which consists of solvent has as electrochemical activity and chemical reactivity, the choice of the solvent is primarily by the solubility of the analyte and the solvent should not react with it.

Octanol is bed electrochemical solvent when SWV technique is applied to measure the octanol phase concentration under this solvent based conditions there is no current is recorded.

To solve this problem we required to mix other appropriate solvents with octanol simultaneously have best electrochemical properties such as ethanol, acetone, DMF, the obtained mixtures should be respect the volume proportion between their consists solvents, which depends of the diffusion coefficient.

The choice of the supporting electrolyte is mainly by the solubility in the mixture to make solution conductive, should be taken into account the nature of the function of the ferrocene derivatives, the supporting electrolyte should not react with it.

These studies were carried out by a series of experiments according to the procedures elaborated below.

To validate our method, similarly studies carried out using spectroscopic method to determinate the partition coefficient of ferrocene and 1-ferrocenylethanol, based on the a linear relationship between the concentration of the ferrocene derivatives and the amount of energy that it absorbed that can be defined by the Beer-Lambert Law, the aqueous phase concentration of ferrocene 1-ferrocenylethanol are determined using UV-vis spectrophotometer instrument, the octanol phase concentration of ferrocene 1-ferrocenylethanol are calculated base on a mass balance, then the values of logP determined by this method are compared with those obtained by SWV method.

The objectives of this experimental work are:

- Determination of partition coefficient of ten of ferrocene derivatives using electrochemical methods for the first time carried out by square-wave voltammetry technique.
- Developing and improving the electrochemical medium to obtain medium has best electrochemical properties able to apply in SWV technique with optimum conditions.
- Validation of this method by comparing the obtained results with the values obtained by using spectroscopic method.

CHAPTER III

Calculation and measurement of octanol-water partition coefficients of ferrocene derivatives

III-1-Rekker method for octanol-water partition coefficients determination

III-1-1- Introduction

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

III-1-2- Determination procedure

III-1-2-1- 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.

A ferrocenyl group is regarded as a ferrocene molecule minus an atom of hydrogen as demonstrated by the following figure III- 1-1.

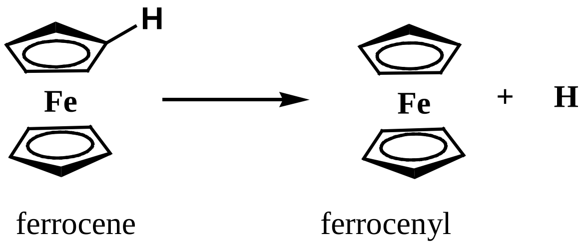


Figure III- 1-1: *Obtaining of a ferrocenyl group*

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 relation III-1-1.

$$f_{F_C} = \log P_{F_C-H} - f_H \qquad \text{III- 1-1}$$

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:

$$f_{FC} = 2.660 - 0.204 = 2.456$$

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

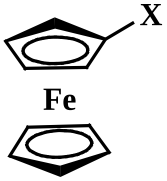


Figure III- 1-2: *Ferrocene derivative mono substituted*

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 III-1-2.

$$\log P = 2.456 + f_X + \sum C_M \qquad \text{III} - 1 - 2$$

C_M is equal to 0.219.

f_X can be obtained from table II-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:

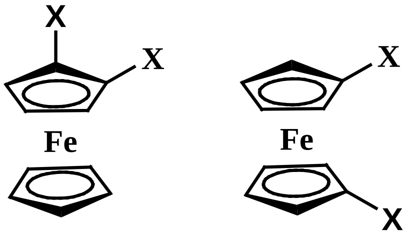


Figure III- 1-3: *Ferrocene derivative bi- substituted*

$$f_{FC} = 2.660 - 2 \times 0.204 = 2.252 \qquad \text{III} - 1 - 3$$

III-1-2-2- Specific correction factor rule for ferrocenyl ring

III-1-2-2-1-Structural bonding of ferrocene

The iron atom in ferrocene is normally assigned to the +2 oxidation state, as can be shown using Mössbauer spectroscopy. Each cyclopentadienyl ring (Cp) is then allocated a single negative charge, bringing the number of π-electrons on each ring to six, and thus making them aromatic. [138]These twelve electrons (six from each ring) are then shared with the metal via hapticcovalent bonding, which, when combined with the six d-electrons of Fe^{2+}, results in the complex having an 18-electron configuration, the aromaticity of this molecule is three dimensional in nature, and is mediated by the d orbitals of the iron atom. The π molecular orbitals in ferrocene can be considered as combinations of the π orbitals of a cyclopentadienyl dimer and the valence orbitals of the iron atom, the stability of this transition-metal compound explained by the 18-electron principle [139]. The current-density maps for ferrocene are given in figure III-1-4.

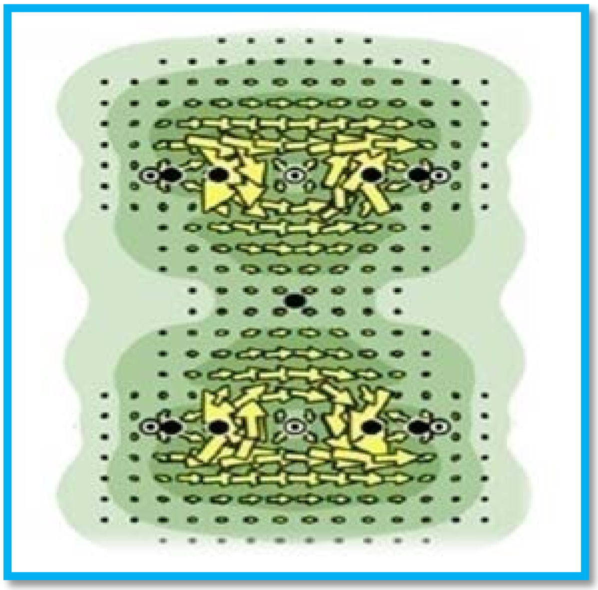


Figure III- 1-4: *The current-density map for ferrocene*

III-1-2-2-2- Correction rule for ferrocenyl ring connected to hydroxyl via carbons

When an oxygen atom from the OH functional group is attached to a ferrocenyl group means Cp ring through one to four carbons as in ferrocenylalcohol, the electrons associated with -O- in this kind of compounds does not overlapped with the π electrons of the ferrocenyl group, which does not allow the creation of pseudo-ring, that turn to the structure of ferrocene compound, so the π molecular orbitals in ferrocene considered as combinations of the π orbitals of a cyclopentadienyl dimer and the valence orbitals of the iron atom. In this case ferrocenyl alcohol FigIII-1-5, [140] undergoes to intramolecular interaction Fe…H-O the metal atom to be the site of a substantially strong intrarnolecular hydrogen bond involving the electrons of the metal atom acting as proton acceptor, thus producing a bent structure, followed by conformer undergoes to an other intramolecular interaction sited in π−ring •••H-O is stabilized by weak electrostatic interactions, we propose correction factor $+1C_M$. When an other H-bond acceptors as intramolecular hydrogen band are present, the intramolecular OH•••Fe or π−ring •••H-O interactions were vanished.

Intramolecular hydrogen band was noticed while studying 4- [4’,4’-dimethyl-2’,5’-dioxo-3’-ortho-hydroxymethyl-ferrocenylmethyl-1’-imidazolidinyl]-2-trifluoromethyl-benzonitrile (a)with X ray(b), but not a pseudo-ring between oxygen and a cyclopentadienyl ring figure III-1-6 shows the hydrogen band between hydrogen and oxygen in compound of the following structure according to that, ferrocene derivatives containing intramolecular hydrogen bands require a correction factor and we consider also that is correction when ferrocenyl ring connected to an oxygen atom via carbon.

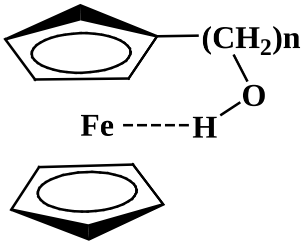
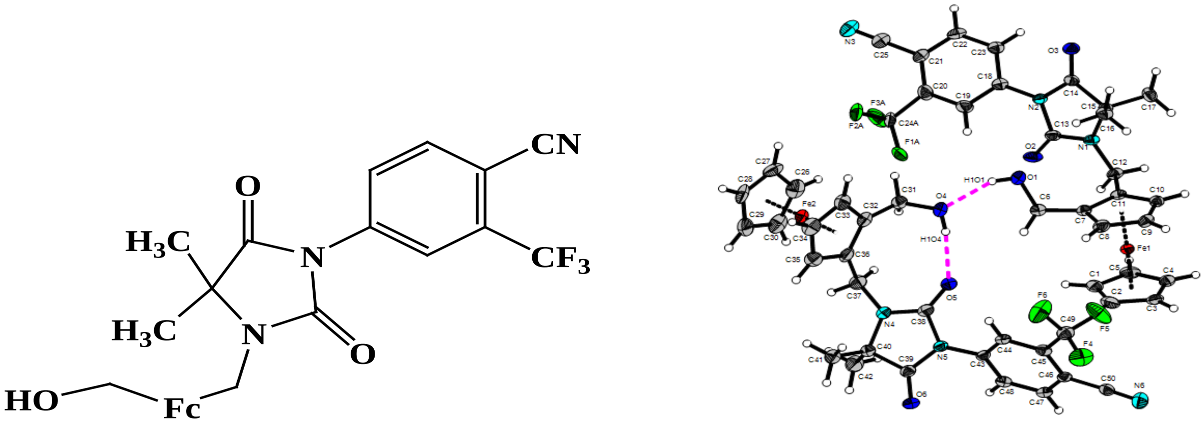


Figure III-1-5: *Ferrocenyl alcohol OH···Fe interaction*



(a) (b)

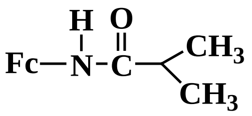
FigureIII-1-6: *General structure (a) and X–ray (b) of 4-[4’,4’-dimethyl-2’,5’-dioxo-3’-ortho-hydroxymethyl –ferrocenylmethyl- 1’-imidazolidinyl]-2-trifluoromethyl-benzonitrile structure*[141]

According to that, ferrocene derivatives containing hydrogen bands require a correction factor and we consider also that is correction when ferrocenyl ring connected to a hydroxyl atom via carbon with out of an other H-bond acceptors.

III-1-3- Calculation and validation of our model

Our model for the calculation of logP of ferrocene derivatives is validated using a series of values of $\log P_{exp.}$ of different ferrocene derivatives selected mainly from literature sources .All the calculation of logP is carried out in three decimals but the final value is rounded to two decimals.

1. N-(ferrocenyl)isobutylamide



(1)

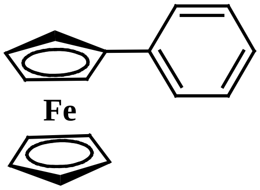
N-(ferrocenyl)isobutylamide

This compound (1) is an example of ferrocene derivatives with saturated aliphatic hydrocarbon chains carrying functionalized group, in this case no corrections are required, logP is obtained by simple summation of the fragmental constant values of the four constituent groups of the molecule, this being: ferrocenyl, amide, CH and CH_3, table III-1-1.

Table III-1-1: *Calculation of logP for compound (1)*

<table>
<tr><th>fragment</th><th>a_i</th><th>f_i</th><th>$a_i \times f_i$</th><th></th></tr>
<tr><td>Fc</td><td>1</td><td>2.456</td><td>2.456</td><td></td></tr>
<tr><td>NHCO</td><td>1</td><td>-1.559</td><td>-1.559</td><td></td></tr>
<tr><td>CH</td><td>1</td><td>0.315</td><td>0.315</td><td></td></tr>
<tr><td>CH_3</td><td>2</td><td>0.724</td><td>1.448</td><td></td></tr>
<tr><td colspan="2">$k_i \times C_M$</td><td>-</td><td>-</td><td></td></tr>
<tr><td colspan="3">$logP_{cal.}$</td><td>2.66</td><td rowspan="2">$\Delta \log P = 0.02$</td></tr>
<tr><td colspan="3">$logP_{exp.}$ [141] [142]</td><td>2.64</td></tr>
</table>

2. Phenylferrocene



(2)

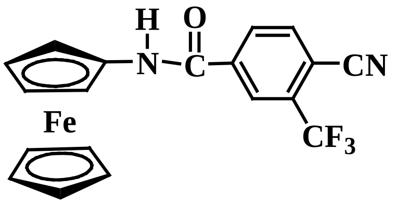
Phenylferrocene

In this type of molecule we propose a correction factor of 1C_M for the ferrocenyl-phenyl (F_C — Ph) conjugation, the value of logP for this ferrocene derivative (2) can be estimated by summing the fragmental constant of the ferrocenyl and the phenyl groups which are equal respectively to 2.456 and 1.902, a correction factor of 1 C_M should be added which correspond to the ferrocenyl-phenyl conjugation, this gives a value of 4.58 for logP table III-1-2.

Table III-1-2: *Calculation of logP for compound (2)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
Ph	1	1.902	1.902	
$k_i \times C_M$		0.219	0.219	
$logP_{cal.}$			4.58	$\Delta\text{logP} = 0.01$
$logP_{exp.}$[143]			4.59	

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



(3)

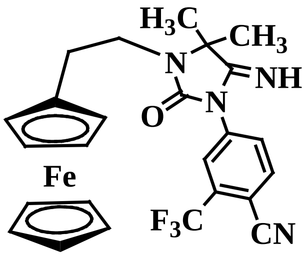
N-[4-cyano-3-trifluoromethylphenyl]- ferrocenecarboxamide

This type of compound is an example of ferrocene derivatives containing a basic fragment linked to aromatic ring, for this kind of compound we propose a corrections factor of +3C_M which the first correspond to the basic fragment (in this case is the amide group) linked to two aromatic rings (cyclopentadienyl ring of the ferrocenyl group and the phenyl ring) is equal to 1, the second is equal to 2 C_M for the combination of two groups (cyano and amide) on a phenyl ring in para position which gives rise to a resonance interaction. logP is obtained by summing the contribution of each fragmental constituent of the molecule (i.e. ferrocenyl, amide, phenyl, nitrile and trifluoromethyl).

Table III-1-3: *Calculation of logP for compound (3)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
NHCO	1	-1.559	-1.559	
C_6H_3	1	1.494	1.494	
CN	1	-0.155	-0.155	
CF_3	1	1.223	1.223	
$k_i \times C_M$		3×0.219	0.657	
$logP_{cal.}$			4.12	ΔlogP = 0.02
$logP_{exp.}$[141]			4.10	

4. 4-(4’,4’-dimethyl-3’-ferrocenylethyl-5’-imino-2’-oxo-1’-imidazolidinyl)-2-trifluoromethylbenzonitrile



(4)

4-(4',4'-dimethyl-3'-ferrocenylethyl-5'-imino-2'-oxo-1'- imidazolidinyl)-2-trifluoromethylbenzonitrile

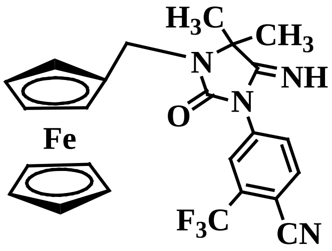
Ferrocene in this molecule is linked to a direct heterocyclic ring via two methylene groups, we define the interaction in this case as: ‘’proximity effects’’ and we propose a correction factor of

$3C_M$, logP is calculated by the same manner as in the exemple above compound (3) except that the correction for the basic fragment is replaced by the heterocyclic ring or ‘’proximity effects’’.

Table III-1-4: *Calculation of logP for compound (4)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
NH=C	1	-1.500	-1.500	
$NHCONH_2$	1	-1.596	-1.596	
C_6H_3	1	1.494	1.494	
CH_3	2	0.724	1.448	
CH_2	2	0.519	1.038	
C	1	0.110	0.110	
CN	1	-0.155	-0.155	
CF_3	1	1.223	1.223	
$k_i \times C_M$		3×0.219	0.657	
$logP_{cal.}$			5.17	$\Delta logP = 0.13$
$logP_{exp.}$[141]			5.04	

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



(5)

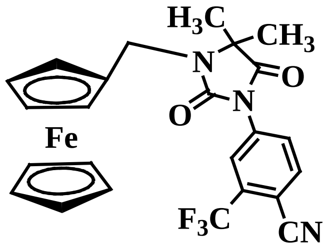
4-(4’,4’-Dimethyl-3’-ferrocenylmethyl-5’-imino-2’-oxo-1’-imidazolidinyl)-2- trifluoromethyl-benzonitrile

The NCON group in this molecule can be regarded as $HNCONH_2$ minus 3H, to obtain the fragmental constant for this group, we 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 C_M which correspond to the existence of a heterocyclic ring in the molecule gives the value of 4.66 for logP.

Table III-1-5: *Calculation of $logP$ for compound (5)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
NH=C	1	-1.500	-1.500	
$NHCONH_2$	1	-1.596	-1.596	
C_6H_3	1	1.494	1.494	
CH_3	2	0.724	1.448	
CH_2	1	0.519	0.519	
C	1	0.110	0.110	
CN	1	-0.155	-0.155	
CF_3	1	1.223	1.223	
$k_i \times C_M$		3×0.219	0.657	
$logP_{cal.}$			4.66	$\Delta logP = 0.02$
$logP_{exp.}$[141]			4.68	

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



(6)

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

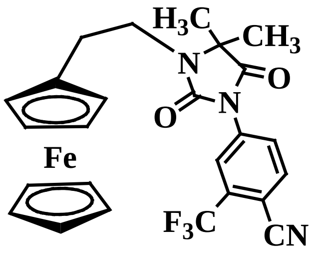
We propose as a correction factor this type of molecules a value of $3C_M$ which can be attributed to heterocyclic ring or the proximity effects. logP is calculated by summing the different contribution of all fragments in the molecule which can be obtained from table II-1, the addition of the correction factor as shown in table III-1-6.

Table III-1-6: *Calculation of logP for compound (6)*

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	1	1.494	1.494	
CH_3	2	0.724	1.448	
CH_2	1	0.519	0.519	
C	1	0.110	0.110	
CN	1	-0.155	-0.155	
CF_3	1	1.223	1.223	
$k_i \times C_M$		3×0.219	0.657	
$logP_{cal.}$			5.18	$\Delta \log P = 0.05$
$logP_{exp.}$[141]			5.23	

The fragmental constant value of heterocyclic ring can be confirmed in this molecule as the value of partition coefficient of nilutamide minus the fragmental constants of phenyl, trifluorométhyl, cyano and subtracting the electronic effect.

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



(7)

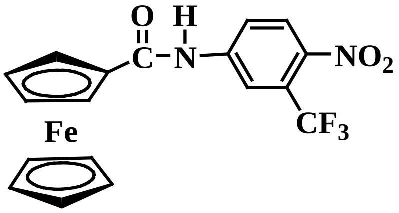
4-(4’,4’-dimethyl-2’,5’-dioxo-3’-ferrocenylethyl-1’-imidazolidinyl)-2-trifluoromethyl-benzonitrile

We propose as a correction factor this type of molecules a value of $3C_M$ which can be attributed to heterocyclic ring or the proximity effects.

Table III-1-7: *Calculation of logP for compound (7)*

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	1	1.494	1.494	
CH_3	2	0.724	1.448	
CH_2	2	0.519	1.038	
C	1	0.110	0.110	
CN	1	-0.155	-0.155	
CF_3	1	1.223	1.223	
$k_i \times C_M$		3×0.219	0.657	
$logP_{cal.}$			5.70	$\Delta logP = 0.08$
$logP_{exp.}$[141]			5.62	

8. N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide



(8)

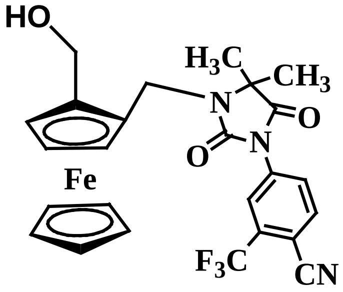
N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide

This example describe ferrocenes with a basic fragment linked to two aromatic rings and resonance interaction, 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 C_M is for basic fragment (amide group) linked to two aromatic rings (ferrocenyl and phenyl), the second is equal to 3 C_M 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 logP.

Table III-1-8: *Calculation of logP for compound (8)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
NHCO	1	-1.559	-1.559	
C_6H_3	1	1.494	1.494	
NO_2	1	-0.039	-0.039	
CF_3	1	1.223	1.223	
$k_i \times C_M$		1×0.219 3×0.219	0. 876	
$logP_{cal.}$			4.45	$\Delta \log P = 0.03$
$logP_{exp.}$[141]			4.42	

9. 4-[4’,4’-dimethyl-2’,5’-dioxo-3’-ortho-hydroxymethyl-ferrocenylmethyl-1’-imidazolidinyl]-2-trifluoromethyl-benzonitrile



(9)

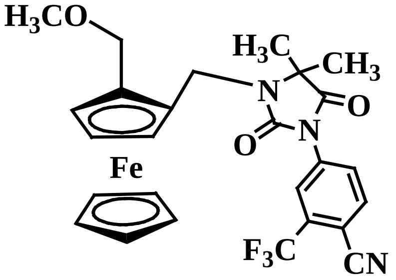
4-[4’,4’-dimethyl-2’,5’-dioxo-3’-ortho-hydroxymethyl-ferrocenylmethyl 1’- imidazolidinyl]-2-trifluoromethyl-benzonitrile

logP is calculated by the same manner as before . In addition to the correction of 3 C_M for the heterocyclic ring, a correction of 2 C_M 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 [141], the effect of the two substuents on the ferrocenyl group is not considered when there is a hydrogen bond in the molecule.

Table III-1-9: *Calculation of logP for compound (9)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456-0.204	2.252	
C=O	1	-0.976	-0.976	
$NHCONH_2$	1	-1.596	-1.596	
C_6H_3	1	1.494	1.494	
CH_3	2	0.724	1.448	
CH_2	2	0.519	1.038	
C	1	0.110	0.110	
CN	1	-0.155	-0.155	
CF_3	1	1.223	1.223	
OH	1	-1.448	-1.448	
$k_i \times C_M$		5×0.219	1.095	
$logP_{cal.}$			4.48	$\Delta \log P = 0.04$
$logP_{exp.}$[141]			4.44	

10. 4-[4’,4’-dimethyl-2’,5’-dioxo-1’-imidazolidinyl-(3’-ortho-methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile



(10)

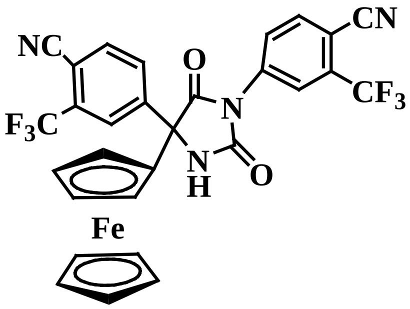
4-[4’,4’-dimethyl-2’,5’-dioxo-1’-imidazolidinyl-(3’-ortho- methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile

This compound is an example of ferrocenes with electronic effect, we propose in this case a correction of $5C_M$, $3\ C_M$ for the proximity effects and $2\ C_M$ for the electronic effect.

Table III-1-10: *Calculation of logP for compound (10)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456-0.204	2.252	
C=O	1	-0.976	-0.976	
$NHCONH_2$	1	-1.596	-1.596	
C_6H_3	1	1.494	1.494	
CH_3	2	0.724	1.448	
CH_2	2	0.519	1.038	
C	1	0.110	0.110	
CN	1	-0.155	-0.155	
CF_3	1	1.223	1.223	
OCH_3	1	-0.821	-0.821	
$k_i \times C_M$		5×0.219	1.095	
$logP_{cal.}$			5.11	$\Delta logP = 0.03$
$logP_{exp.}$[141]			5.08	

11. 4’-ferrocenyl-1’,4’-[bis-(2-trifluoromethyl-1-cyano-phenyl)] -2’,5’-imidazolidinedione



(11)

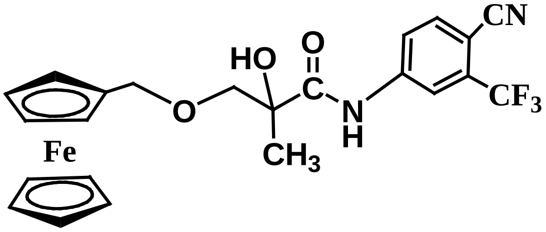
4’-ferrocenyl-1’,4’-[*bis*-(2-trifluoromethyl-1-cyano-phenyl)]
-2’,5’-imidazolidinedione

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, the method of calculating of logP is illustrated in table III-1-11.

Table III-1-11: *Calculation of logP for compound (11)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C=O	1	-0.976	-0.976	
NHCON	1	-1.612	-1. 612	
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	
$logP_{cal.}$			6.42	$\Delta \log P = 0.05$
$logP_{exp.}$[141]			6.47	

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



(12)

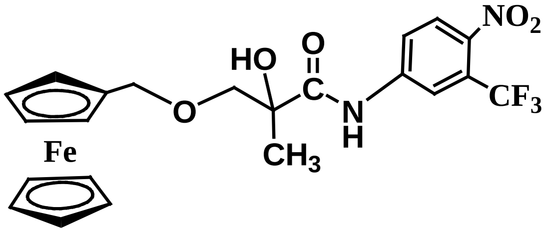
N-(4-cyano-3-trifluoro methylphenyl) -3-ferrocenylmethoxy-2-hydroxy- 2-methyl-propanamide

This following compound receives a correction of C_M value +11 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 C_M for the resonance between NHC(O) and CN.

Table III-1-12: *Calculation method of logP for compound (12)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
OH	1	-1.448	-1.448	
CONH	1	-1.559	-1.559	
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	
$k_i \times C_M$		11×0.219	2.409	
$logP_{cal.}$			4.75	$\Delta \text{logP} = 0.12$
$logP_{exp.}$[141][142]			4.63	

13. 3-ferrocenylmethoxy-2-hydroxy-2- methyl-N-(4-nitro-3-trifluoromethylphenyl)-propanamide



(13)

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).

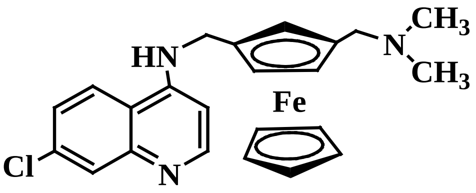
+6 C_M for the two intermolecular hydrogen bond +3C_M for each one.

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

Table III-1-13: *Calculation of logP for compound (13)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
OH	1	-1.448	-1.448	
CONH	1	-1.559	-1.559	
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	
$logP_{cal.}$			5.08	$\Delta \text{logP} = 0.07$
$logP_{exp.}$[141] [142]			5.01	

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



(14)

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.This compound contains a hydrogen bond as indicated by X-ray diffraction study [144] figure III-1-7.

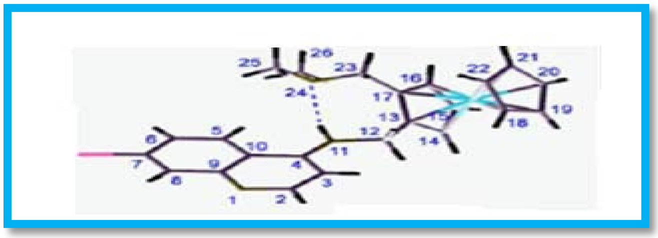
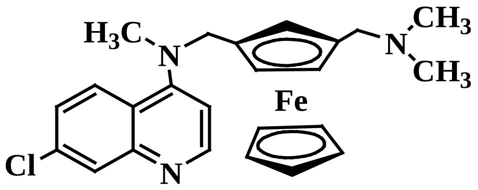


Figure III-1-7: X-ray of N-(7-Chloro-quinolin-4-yl)-(2- dimethylaminomethylferrocenyl)-amine structure

Table III-1-14: *Calculation of logP for compound (14)*

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	$\Delta logP = 0.17$
$logP_{exp.}$[145]			5.10	

15. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- methylamine



(15)

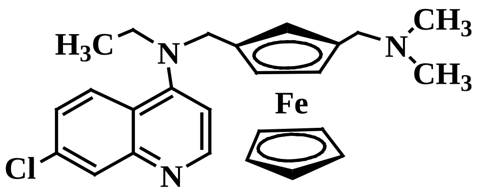
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- methylamine

We propose no correction for these type of compounds.

Table III-1-15: *Calculation of logP for compound (15)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.252	2.252	
arN	1	-0.979	-0.979	
Quinolinyl	1	1.821-0.204	1.617	
CH_3	3	0.724	2.172	
CH_2	2	0.519	1.038	
N	1	-2.074	-2.074	
Cl	1	0.933	0.933	
$k_i \times C_M$		-	-	
$logP_{cal.}$			4.96	$\Delta logP = 0.07$
$logP_{exp.}$[145]			4.89	

16. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-ethylamine



(16)

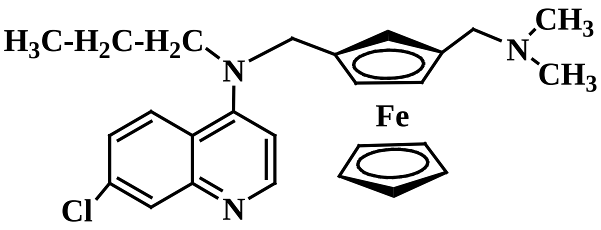
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-ethylamine

We propose no correction for these types of compounds.

Table III-1-16: *Calculation of logP for compound (16)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.252	2.252	
arN	1	-0.979	-0.979	
Quinolinyl	1	1.821-0.204	1.617	
CH_3	3	0.724	2.172	
CH_2	3	0.519	1.557	
N	1	-2.074	-2.074	
Cl	1	0.933	0.933	
$k_i \times C_M$		-	-	
$logP_{cal.}$			5.48	$\Delta \log P = 0.41$
$logP_{exp.}$[145]			5.89	

17. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-propylamine



(17)

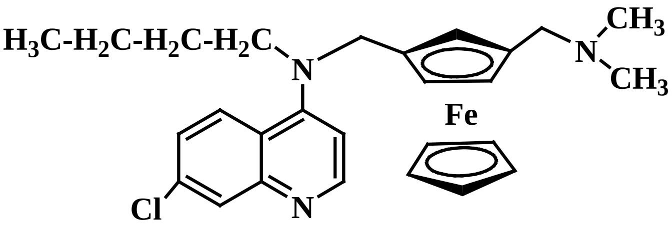
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-propylamine

We propose no correction for these type of compounds.

Table III-1-17: *Calculation of logP for compound (17)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.252	2.252	
arN	1	-0.979	-0.979	
Quinolinyl	1	1.821-0.204	1.617	
CH_3	3	0.724	2.172	
CH_2	4	0.519	2.076	
N	1	-2.074	-2.074	
Cl	1	0.933	0.933	
$k_i \times C_M$		-	-	
$logP_{cal.}$			6.00	$\Delta\log P = 0.33$
$logP_{exp.}$[145]			6.33	

18. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- butylamine



(18)

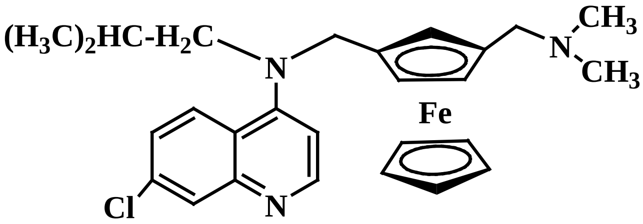
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethyl ferrocenyl)-butylamine

We propose no correction for these types of compounds.

Table III-1-18: *Calculation of logP for compound (18)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.252	2.252	
arN	1	-0.979	-0.979	
Quinolinyl	1	1.821-0.204	1.617	
CH_3	3	0.724	2.172	
CH_2	5	0.519	2.595	
N	1	-2.074	-2.074	
Cl	1	0.933	0.933	
$k_i \times C_M$		-	-	
$logP_{cal.}$			6.52	$\Delta\log P = 0.18$
$logP_{exp.}$[145]			6.70	

19. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- isobutylamine



(19)

(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethyl ferrocenyl)- isobutylamine

We propose no correction for these types of compounds.

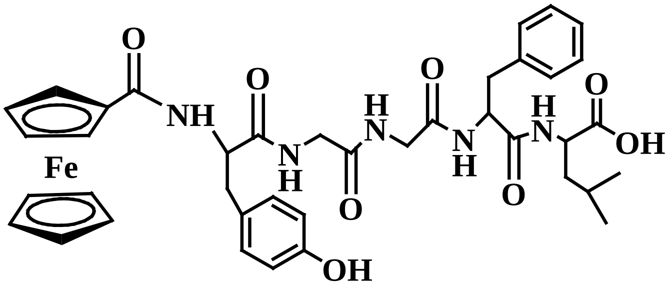
Table III-1-19: *Calculation of logP for compound (19)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.252	2.252	
arN	1	-0.979	-0.979	
Quinolinyl	1	1.821-0.204	1.617	
CH_3	4	0.724	2.896	
CH_2	3	0.519	1. 557	
CH	1	0.315	0.315	
N	1	-2.074	-2.074	
Cl	1	0.933	0.933	
$k_i \times C_M$		-	-	
$logP_{cal.}$			6.52	$\Delta \log P = 0.08$
$logP_{exp.}$[145]			6.60	

We propose for the following compounds with complicated structure which contain enkephalin derivatives extra correction factors compound to those studied previously.

20. Fc-CO-Enk-OH

Enkephalin: 2-amino-3- (4- hydroxyphenyl)propanoyl]amino]acetyl] amino]acetyl]amino]-3-phenylpropanoyl] amino]-4-methylpentanoic acid.



(20)

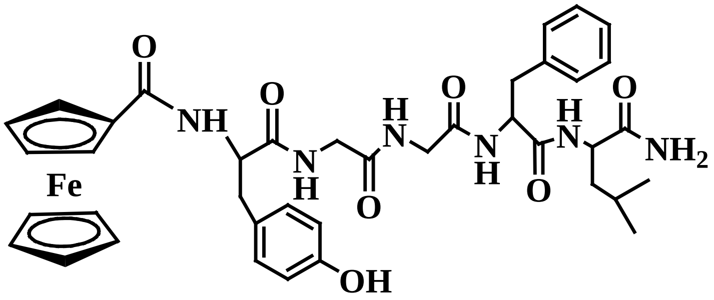
Fc-CO-Enk-OH

The correction factor in this compound is equal to 30 C_M because it has four a proximity effect over one carbon between NHCO and NHCO +3C_M for each, the proximity effect over one carbon between NHCO and COOH+3C_M, the five occurrences hydrogen bond +3C_M for each.

Table III-1-20: *Calculation of logP for compound (20)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
arNHCO	1	-1.559	- 1.559	
NHCO	4	- 2.435	- 9.740	
C_6H_5	1	1.902	1.902	
C_6H_4	1	1.698	1.698	
CH_3	2	0.724	1.448	
CH_2	5	0.519	2.595	
CH	4	0.315	1.260	
COOH	1	- 0.942	- 0.942	
OH	1	- 0.353	- 0.353	
$k_i \times C_M$		30×0.219	6.57	
$logP_{cal.}$			5.33	$\Delta \log P = 0.46$
$logP_{exp.}$[146]			5.79	

21. Fc-CO-Enk-NH$_2$



(21)

Fc-CO-Enk-NH$_2$

We propose a total of +27 C_M as a correction factor for these type of compounds as follows:

+ 4×3 = 12 C_M for the proximity effect over one carbon between NHCO and NHCO.

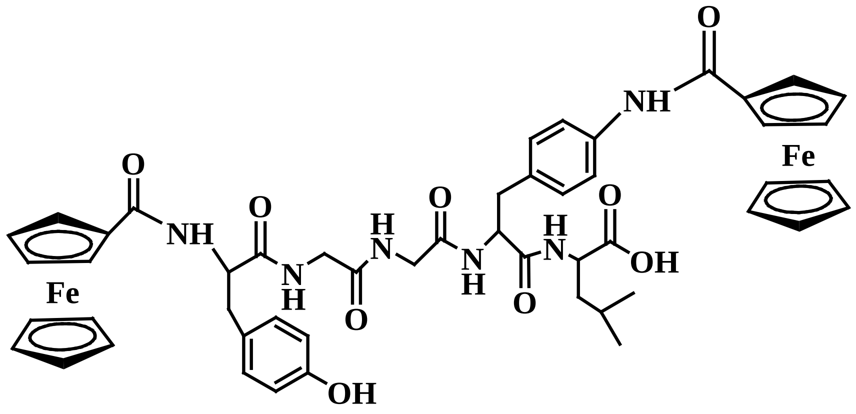
+ 1×3 = 3 C_M for the proximity effect over one carbon between NHCO and CONH$_2$.

+ 4×3 = 12 C_M for the five occurrences hydrogen bond.

Table III-1-21: *Calculation of logP for compound (21)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
arNHCO	1	-1.559	-1.559	
NHCO	4	-2.435	-9.740	
C_6H_5	1	1.902	1.902	
C_6H_4	1	1.698	1.698	
CH_3	2	0.724	1.448	
CH_2	5	0.519	2.595	
CH	4	0.315	1.260	
$CONH_2$	1	-2.011	-2.011	
OH	1	-0.353	-0.353	
$k_i \times C_M$		27×0.219	5.913	
$logP_{cal.}$			3.61	$\Delta \log P = 0.39$
$logP_{exp.}$[146]			4.00	

22. Fc-CO-Enk[Phe (NH-CO-Fc)]-OH



(22)

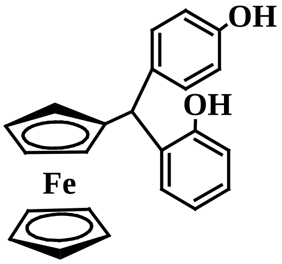
Fc-CO-Enk[Phe (NH-CO-Fc)]-OH

This compound requires +31 C_M as a correction factor because it has four a proximity effect over one carbon between NHCO and NHCO (+3C_M for each), the proximity effect over one carbon between NHCO and COOH(3C_M), five occurrences hydrogen bond (+3C_M for each bond), and +1 C_M is for basic fragment (amide group) linked to two aromatic rings ferrocenyl and phenyl.

Table III-1-22: *Calculation of logP for compound (22)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	2	2.456	4.912	
arNHCO	2	-1.559	-3.118	
NHCO	4	-2.435	-9.740	
C_6H_4	2	1.698	3.396	
CH_3	2	0.724	1.448	
CH_2	5	0.519	2.595	
CH	4	0.315	1.260	
COOH	1	- 0.942	- 0.942	
arOH	1	- 0.353	- 0.353	
$k_i \times C_M$		31×0.219	6.789	
$logP_{cal.}$			6.25	$\Delta \log P = 0.24$
$logP_{exp.}$[146]			6.49	

23. 1-((2-hydroxyphenyl)(4-hydroxyphenyl)methyl) ferrocene



(23)

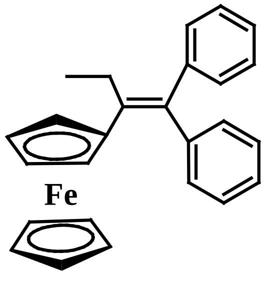
1-((2-hydroxyphenyl)(4-hydroxyphenyl)methyl) ferrocene

Ferrocenes with a tertiary carbon bulk needs corrector factor -1C_M.

Table III-1-23: *Calculation of logP for compound (23)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_4	2	1.698	3.396	
CH	1	0.315	0.315	
OH	2	- 0.353	- 0.706	
$k_i \times C_M$		- 0.219	- 0.219	
$logP_{cal.}$			5.24	ΔlogP = 0.34
$logP_{exp.}$[147]			4.90	

24. 1-(1,1-diphenylbut-1-en-2-yl) ferrocene



(24)

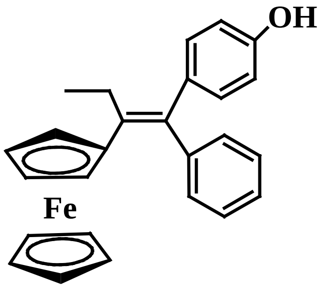
1-(1,1-diphenylbut-1-en-2-yl) ferrocene

Bulky ferrocenes with propeller [148,149]structure type is described in this example, the four carbons atoms connecting to the double bond of vinyl in this compound are not strictly coplanar that due to the aryl group are twisted, that occurs steric hinderance of resonance, arises from thus carbon needs corrector factor (-2C_M for each carbon of ethylene).

Table III-1-24: *Calculation of logP for compound (24)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_5	2	1.902	3.804	
C	2	0.1102	0.2204	
CH_2	1	0.519	0.519	
CH_3	1	0.724	0.724	
$k_i \times C_M$		- 4×0.219	- 0.876	
$logP_{cal.}$			6.85	$\Delta logP = 0.42$
$logP_{exp.}$[150]			6.43	

25. 1-(1-(- 4-hydroxy phenyl)-1-phenylbut-1-en-2-yl) ferrocene



(25)

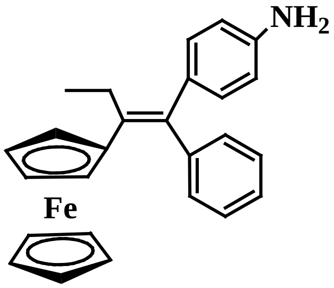
1-(1-(- 4-hydroxy phenyl)-1-phenylbut-1-en-2-yl) ferrocene

Ferrocenes with two carbons bulk arises from thus steric carbon needs corrector factor (-2C_M for each).

Table III-1-25: *Calculation of logP for compound (25)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_5	1	1.902	1.902	
C_6H_4	1	1.698	1.698	
C	2	0.1102	0.2204	
CH_2	1	0.519	0.519	
CH_3	1	0.724	0.724	
OH	1	- 0.353	- 0.353	
$k_i \times C_M$		- 4×0.219	- 0.876	
$logP_{cal.}$			6.29	$\Delta logP = 0.12$
$logP_{exp.}$[150]			6.17	

26. 1-(-1-(- 4-amino phenyl)-1-phenylbut-1-en-2-yl) ferrocene



(26)

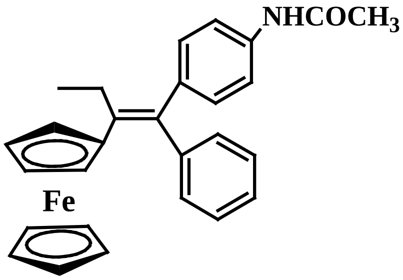
1-(-1-(- 4-amino phenyl)-1-phenylbut-1-en-2-yl) ferrocene

Ferrocenes with two carbons bulk arises from thus carbons needs correction -2C_M for each).

Table III-1-26: *Calculation of logP for compound (26)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_5	1	1.902	1.902	
C_6H_4	1	1.698	1.698	
C	2	0.1102	0.2204	
CH_2	1	0.519	0.519	
CH_3	1	0.724	0.724	
NH_2	1	- 0.902	- 0.902	
$k_i \times C_M$		- 4×0.219	- 0.876	
$logP_{cal.}$			5.74	$\Delta logP = 0.01$
$logP_{exp.}$[150]			5.75	

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



(27)

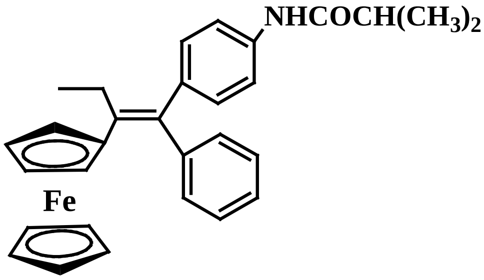
N-(4-(-2-(ferrocenyl)-1- phenylbut-1- enyl)phenyl)acetamide

Ferrocenes with two carbons bulk arises from thus carbon needs corrector factor (-2C_M for each).

Table III-1-27: *Calculation of logP for compound (27)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_5	1	1.902	1.902	
C_6H_4	1	1.698	1.698	
C	2	0.1102	0.2204	
CH_2	1	0.519	0.519	
CH_3	2	0.724	1.448	
NHCO	1	- 1.559	- 1.559	
$k_i \times C_M$		- 4×0.219	- 0.876	
$logP_{cal.}$			5.81	$\Delta logP = 0.11$
$logP_{exp.}$[150]			5.92	

28. N-(4-(-2-(ferrocenyl)-1- phenylbut-1- enyl)phenyl)isobutyramide



(28)

N-(4-(-2-(ferrocenyl)-1- phenylbut-1- enyl)phenyl)isobutyramide

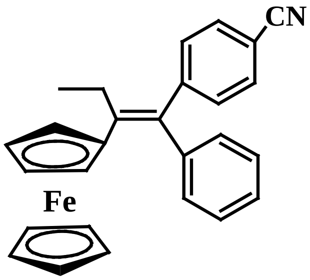
Ferrocenes with two carbons bulk arises from thus carbon needs corrector factor (-2C_M for each).

The existence of isopropyl group causes the resonating functional group to be pushed out of plane this decreases orbital overlap between the lone pair of electrons of the resonating functional group and the π electrons of the phenyl ring requires -3$C_{M.}$

Table III-1-28: *Calculation of logP for compound (28)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_5	1	1.902	1.902	
C_6H_4	1	1.698	1.698	
C	2	0.1102	0.2204	
CH	1	0.315	0.315	
CH_2	1	0.519	0.519	
CH_3	3	0.724	2.172	
NHCO	1	- 1.559	- 1.559	
$k_i \times C_M$		- 7×0.219	- 1.533	
$logP_{cal.}$			6.19	$\Delta logP = 0.06$
$logP_{exp.}$[150]			6.13	

29. 4-(-2-(ferrocenyl)-1- phenylbut-1- enyl)benzonitrile



(29)

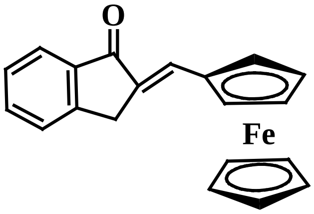
4-(-2-(ferrocenyl)-1- phenylbut-1- enyl) benzonitrile

Ferrocenes with two carbons bulk arises from thus carbon needs corrector factor (-2C_M for each).

Table III-1-29: *Calculation of logP for compound (29)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_5	1	1.902	1.902	
C_6H_4	1	1.698	1.698	
C	2	0.1102	0.2204	
CH_2	1	0.519	0.519	
CH_3	1	0.724	0.724	
CN	1	- 0.155	- 0.155	
$k_i \times C_M$		- 4×0.219	- 0.876	
$logP_{cal.}$			6.49	$\Delta logP = 0.12$
$logP_{exp.}$[150]			6.37	

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



(30)

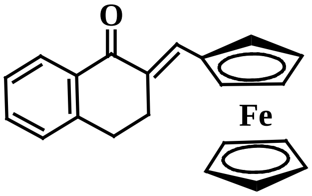
(E)-2-ferrocenylmethylene -2,3-dihydroinden-1-one

This following compound receives a correction of C_M value +3 because it has conjugation(+2C_M) and +1 C_M is for cross conjugation.

Table III-1-30: *Calculation of logP for compound (30)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_4	1	1.698	1.698	
C		0.1102	0.1102	
CH_2	1	0.519	0.519	
CO	1	-0.976	-0.976	
CH	1	0.315	0.315	
$k_i \times C_M$		3×0.219	0.657	
$logP_{cal.}$			4.78	$\Delta logP = 0.01$
$logP_{exp.}$[151]			4.77	

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



(31)

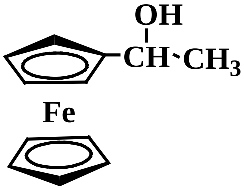
(E)-2-ferrocenylmethylene -3,4-dihydronaphthalen(2H)-1-one

This compound receives a correction of C_M value +3 because it has conjugation(+2C_M) and +1 C_M is for cross conjugation.

Table III-1-31: *Calculation of logP for compound (31)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_4	1	1.698	1.698	
C	1	0.1102	0.1102	
CH_2	2	0.519	1.038	
CO	1	-0.976	-0.976	
CH	1	0.315	0.315	
$k_i \times C_M$		3×0.219	0.657	
$logP_{cal.}$			5.30	$\Delta \log P = 0.03$
$logP_{exp.}$[151]			5.27	

32. 1-ferrocenylethanol



(32)

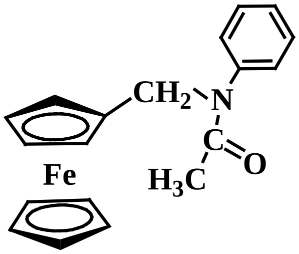
1-ferrocenylethanol

logP for this ferrocene carrying functionalized alcohol group is calculated in table III-1-32.This compound receives a correction of C_M value 0 because it has branching effect with a tertiary C (FcCH (CH_3)-OH), (-1C_M) and +1 C_M is for ferrocenyl ring connected to a hydroxyl sums to total of 0 C_M.

Table III-1-32: *Calculation of logP for compound (32)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
OH	1	-1.448	-1.448	
CH	1	0.315	0.315	
CH_3	2	0.724	0.724	
$k_i \times C_M$		0	0	
$logP_{cal.}$			2.05	$\Delta \log P = 0.13$
$logP_{exp.}$			2.18	

33. N-ferrocenymethyl-N-phenylacetamide



(33)

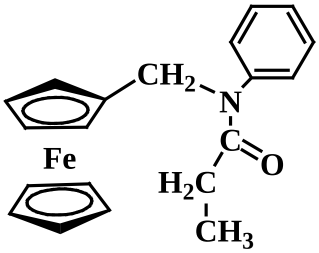
N-ferrocenymethyl-N-phenylacetamide

logP for this ferrocene carrying functionalized amide group is calculated in table III-1-33.

Table III-1-33: *Calculation of logP for compound (33)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
NCO	1	-1.544	-1.544	
C_6H_5	1	1.902	1.902	
CH_3	1	0.724	0.724	
CH_2	1	0.519	0.519	
$k_i \times C_M$		-	-	
$logP_{cal.}$			4.06	$\Delta \text{logP} = 0.11$
$logP_{exp.}$			3.95	

34. N-ferrocenymethyl-N-phenylpropionamide



(34)

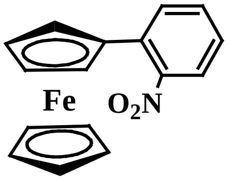
N-ferrocenymethyl-N-phenylpropionamide

logP for this ferrocene derivatives is calculated in table III-1-34.

Table III-1-34: *Calculation of logP for compound (34)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
NCO	1	-1.544	-1.544	
C_6H_5	1	1.902	1.902	
CH_3	1	0.724	0.724	
CH_2	2	0.519	1.038	
$k_i \times C_M$		-	-	
$logP_{cal.}$			4.58	$\Delta logP = 0.20$
$logP_{exp.}$			4.38	

35. Ferrocenyl-2-nitrophenyl



(35)

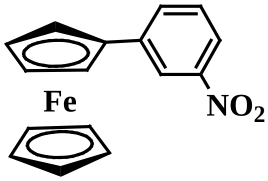
ferrocenyl-2-nitrophenyl

We propose no correction factor for this ferrocene carrying functionalized nitro group to the position ortho [152] in this case the conjugation interaction vanishes and the extra C_M can be ignored, logP is calculated in table III-1-35.

Table III-1-35: *Calculation of logP for compound (35)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_4	1	1.698	1.698	
NO_2	1	-0.039	-0.039	
$k_i \times C_M$			-	
$logP_{cal.}$			4.11	$\Delta logP = 0.23$
$logP_{exp.}$			3.88	

36. Ferrocenyl-3-nitrophenyl



(36)

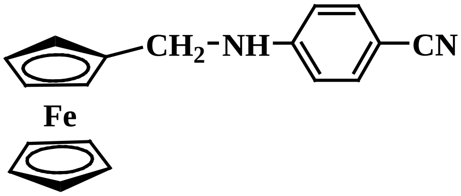
Ferrocenyl-3-nitrophenyl

We propose a correction factor of 1C_M for the ferrocenyl-phenyl conjugation for this ferrocene carrying functionalized nitro group, logP for this ferrocene is calculated in table III-1-36.

Table III-1-36: *Calculation of logP for compound (36)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
C_6H_4	1	1.698	1.698	
NO_2	1	-0.039	-0.039	
$k_i \times C_M$		0.219	0.219	
$logP_{cal.}$			4.33	$\Delta logP = 0.34$
$logP_{exp.}$			3.99	

37. 4-(ferrocenylmethylamino)benzonitrile



(37)

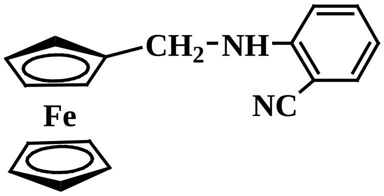
4-(ferrocenylmethylamino)benzonitrile

The compound needed a correction factor of +2 C_M for the resonance between NH and CN logP for this ferrocene is calculated in table III-1-37.

Table III-1-37: *Calculation of logP for compound (37)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
NH	1	-0.938	-0.938	
C_6H_4	1	1.698	1.698	
CH_2	1	0.519	0.519	
CN	1	-0.155	-0.155	
$k_i \times C_M$		2×219	0.438	
$logP_{cal.}$			4.02	$\Delta logP = 0.51$
$logP_{exp.}$			3.51	

38. N-ferrocenylmethyl-2-cyanoaniline



(38)

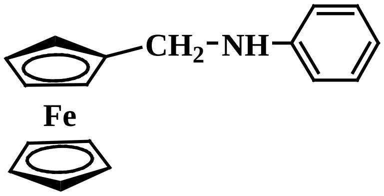
N-ferrocenylmethyl-2-cyanoaniline

For this ferrocene is calculated in table III-1-38.

Table III-1-38: *Calculation of logP for compound (38)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
NH	1	-0.938	-0.938	
C_6H_4	1	1.698	1.698	
CH_2	1	0.519	0.519	
CN	1	-0.155	-0.155	
$k_i \times C_M$		-	-	
$logP_{cal.}$			3.58	$\Delta logP = 0.06$
$logP_{exp.}$			3.64	

39. N-ferrocenylmethylaniline



(39)

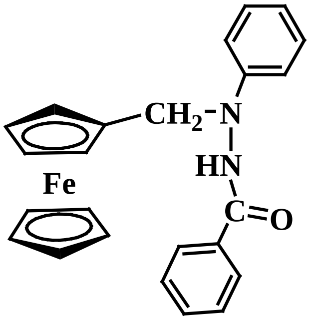
N-ferrocenylmethylaniline

logP for this ferrocene linked to aniline via methylene group is calculated as follows**:**

Table III-1-39: C*alculation of logP for compound (39)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
NH	1	-0.938	-0.938	
C_6H_5	1	1.902	1.902	
CH_2	1	0.519	0.519	
$k_i \times C_M$		-	-	
$logP_{cal.}$			3.94	$\Delta logP = 0.12$
$logP_{exp.}$			3.82	

40. N’- ferrocenylmethyl-N’-phenylbenzohydrazide



(40)

N’-ferrocenylmethyl-N’-phenylbenzohydrazide logP for this ferrocene derivative carrying functionalized hydrazide group is calculated as the following table III-1-40.

Table III-1-40: *Calculation of logP for compound (40)*

fragment	a_i	f_i	$a_i \times f_i$	
Fc	1	2.456	2.456	
-NNHCO	1	-2.253-0.2045	-2.4575	
C_6H_5	2	1.902	3.804	
CH_2	1	0.519	0.519	
$k_i \times C_M$		-	-	
$logP_{cal.}$			4.32	$\Delta \text{logP} = 0.13$
$logP_{exp.}$			4.19	

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.

$$\text{AE} = \Delta logP = \left| logP_{cal.} - logP_{exp.} \right|$$

The results are summarized in table III-1-41.

Table III-1-41: *Estimation and absolute error results for ferrocene derivatives*

Compound	$\text{logP}_{\text{cal.}}$	$\text{logP}_{\text{exp.}}$	AE	Compound	$\text{logP}_{\text{cal.}}$	$\text{logP}_{\text{exp.}}$	AE
1	2.66	2.64	0.02	21	3.61	4.00	0.39
2	4.58	4.59	0.01	22	6.25	6.49	0.24
3	4.12	4.10	0.02	23	5.24	4.90	0.34
4	5.17	5.04	0.13	24	6.85	6.43	0.42
5	4.66	4.68	0.02	25	6.29	6.17	0.12
6	5.18	5.23	0.05	26	5.74	5.75	0.01
7	5.70	5.62	0.08	27	5.81	5.92	0.11
8	4.45	4.42	0.03	28	6.19	6.13	0.06
9	4.48	4.44	0.04	29	6.49	6.37	0.12
10	5.11	5.08	0.03	30	4.78	4.77	0.01
11	6.42	6.47	0.05	31	5.30	5.27	0.03
12	4.75	4.63	0.12	32	2.05	2.18	0.13
13	5.08	5.01	0.07	33	4.06	3.95	0.11
14	4.93	5.10	0.17	34	4.58	4.38	0.20
15	4.96	4.89	0.07	35	4.11	3.88	0.23
16	5.48	5.89	0.41	36	4.33	3.99	0.34
17	6.00	6.33	0.33	37	4.02	3.51	0.51
18	6.52	6.70	0.18	38	3.58	3.64	0.06
19	6.52	6.60	0.08	39	3.94	3.82	0.12
20	5.33	5.79	0.46	40	4.32	4.19	0.13

III-1-4-Results and Discussion

Table III-1-41shows those values of logP for ferrocene derivatives calculated by our model are in good agreement with the values of experimental logP.

However when enkephalin derivatives are introduced to ferrocene, compounds 20 and 22 the value of calculated logP resulting ferrocene derivatives is remarkably smaller than $\log P_{exp..}$, this may be due to he multifunction groups Existing in the molecule which introduce extra interactions that can not be taken in consideration according to Rekker method which we try to adapt to ferrocene derivatives.

The correction rules assume that all resonance interactions between functional groups on an aromatic ring have the same level of interaction receive a +2 C_M is slightly flawed, this is most assuredly not true because a functional group such as NO_2 can withdrawal electrons more effectively than CN or CO, who may be explains the different between observed and calculated logP value for the compound 37 the deference is about 0.51.

This indicates update via up-corrections factor is needed to compensate for irregularities in predicted partition coefficients caused by intramolecular effects, also specific correction for ferrocene and its derivatives are requested for restoring the imbalances between calculated and measured logP values for those complicated compounds, in this trend a specific correction were proposed when ferrocenyl ring connected to a hydroxyl atom via carbon with out of an other H-bond acceptors.

The correlation between experimental logP and calculated logP from equation III-1-2 for 40ferrocene derivatives were shown in figure III-1-8**,** value for R^2 of 0.964 was found.

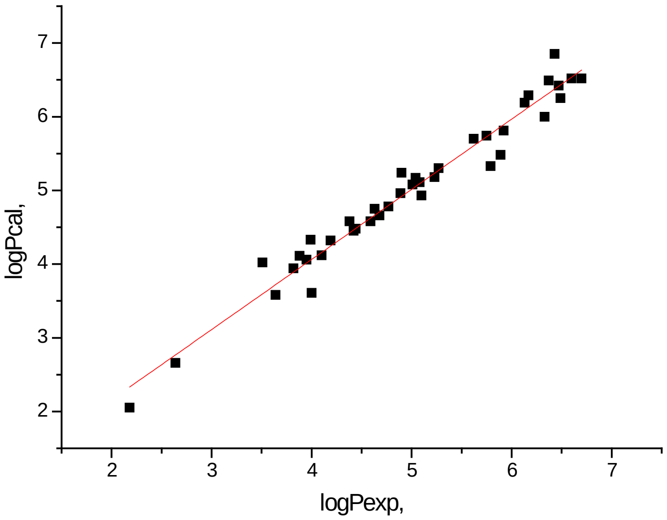


Figure III-1-8: *Correlation between experimental logP and calculated logP from eqn. III-1-2 for 40 ferrocene derivatives*

III-1-5- Conclusion

In the light of the results obtained for the calculation of partition coefficient logP of ferrocene derivatives based on the adaptation of the Rekker method, we successfully developed theoretical model for calculating the octanol-water partition coefficients of ferrocene derivatives.

Our model for the calculation of logP is deduced from the Rekker approach for the calculation of octanol-water partition coefficients.

Our model able us to calculate for the first time, the partition coefficient logP of ferrocene derivatives, values of calculated logP are in good agreement with experimental logP, this indicates the reliability of our model.

III-2-XlogP method for octanol-water partition coefficients determination

III-2-1-Introduction

In this section, we describe the generation of our approach for logP calculation for ferrocene derivatives. This calculation is based upon the adaptation of the XlogP approach, which considers the partition molecular species between an aqueous phase and an organic phase in our case is octanol.

III-2-2-Determination procedure

III-2-2-1- Adaptation of XlogP approach

As far we know, the theoretical value of the octanol-water partition coefficient logP of ferrocene itself is not known and is not described in the literature, the reason why we consider that the octanol-water partition coefficient logP value of ferrocene, calculated form the XlogP method, is equal to the experimental value of logP, which is equal to 2.66[116].

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

$$a_{Car-C} - a_{Car-H} = 0.302 - 0.281 = 0.021 \qquad \text{III-2-1}$$

The contribution of an aromatic carbon atom attached to an atom X (O, N, S, P,….) a_{Car-X} is less than the contribution of an aromatic carbon atom attached to hydrogen atom a_{Car-H} , the difference can also be calculated from the following equation III-2-2 as follows:

$$\mathrm{a}_{\mathrm{Car-X}} - \mathrm{a}_{\mathrm{Car-H}} = -0.064 - 0.281 = -0.345 \qquad \text{III-2-2}$$

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 $a_H(37)$ should be subtracted.

$$a_{F_C} = logP_{Fc} - n_1(\, a_H - 0.021) - n_2(\, a_H + 0.345) \qquad \text{III-2-3}$$

n_1 number of substituents attached to ferrocenyl group via a carbon atom, n_2 number of substituents attached to ferrocenyl group via heteroatom, $0 \leq n_1 + n_2 \leq 10$

The contribution of a ferrocenyl group attached to an atom of type X is calculated from equation III-2-3, n_1 in this case is equal to zero.

$$a_{F_C} = logP_{Fc} - \ a_H - 0.345 = 2.66 - 0.046 - 0.345 = 2.269 \qquad \text{III-2-4}$$

This value 2.269 represent the contribution of the Fc group when attached to an atom of type X. If a ferrocenyl group is attached to a carbon atom, its contribution is calculated from the same equation III-2-3; with n_2 in this case is equal to zero.

$$a_{F_C} = logP_{Fc} - \ a_H + 0.021 = 2.66 - 0.046 + 0.021 = 2.635 \qquad \text{III-2-5}$$

This value 2.635 represent the contribution of the Fc group when attached to a carbon atom.

LogP, for any ferrocene derivatives F_C-X', of formula represented in figure III-2-1

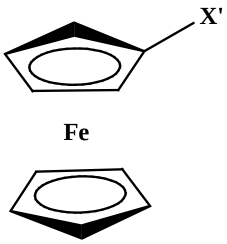


***Figure* III-2-1**: *Ferrocene derivative*

is therefore can be calculated by summing the contribution of atom type of a substituent X', to the contribution of a ferrocenyl group with the addition of the corrective term as illustrated by the following equation:

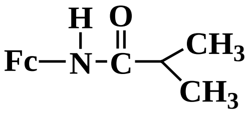
$$logP_{Fc-X'} = a_{Fc} + a_{X'} + \sum_j b_j \, B_j \qquad \text{III-2-6}$$

$a_{X'}$ can be obtained from table II-2, F_C refers to ferrocenyl group, and B_j is the number of occurrences of the j^{th} correction factor b_j.

III-2-2-2- Calculation and validation of the method

We validated our method for the calculation of logP of ferrocene derivatives using different substituted ferrocene mainly selected from scientific literature sources and several of ferrocene derivatives partition coefficient are determined in laboratory. We recommend carrying out the calculations in three decimals with the final value of logP is rounded to two decimals.

1. N-(ferrocenyl)isobutylamide



(1)

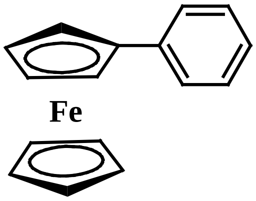
N-(ferrocenyl)isobutylamide

This compound is an example of ferrocenes with saturated aliphatic hydrocarbon chains carrying functionalized aliphatic saturated chains, logP of this compound according to XlogP method is calculated by summation of the value of atom types contributions in this molecule, ferrocenyl group is obtained from equation III-2-4,the contribution of each atom can be attained from table II-2 which being one nitrogen atom N type (64), one aromatic carbon atom C type (9), one aromatic carbon atom C type (24), two aliphatic carbons atoms C type (1), one oxygen atom O type (44) and eight hydrogen atoms H type (37), no correction factor is required in this case, final logP is calculated using the relation III-2-6. The number between brackets is the atom type in XlogP method.

Table III-2-1: *calculation of logP for compound (1)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.269	2.269	
a_C (1)	2	0.484	0.968	
a_N (64)	1	-0.212	-0.212	
a_C (9)	1	-0.138	-0.138	
a_O (44)	1	-2.057	-2.057	
a_C (24)	1	1.637	1.637	
a_H (37)	8	0.046	0.368	
$b_i \times B_j$		-	-	
$logP_{cal.}$			2.83	$\Delta \text{logP} = 0.19$
$logP_{exp.}$[141] [142]			2.64	

2. Phenylferrocene



(2)

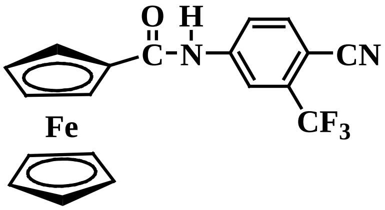
Phenylferrocene

This compound is an example of ferrocenes with aromatic hydrocarbon rings, logP for phenylferrocene is obtained by summing the different contribution of all atom types which constitued in the molecule and can be obtained from table II-2, in this case no corrections are required, logP for this compound is calculated, according to equation III-2-6, this gives a value of 4.57 for logP, are summarized in table III-2-2.

Table III-2-2: *calculation of logP for compound (2)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (29)	1	0.302	0.302	
a_C (26)	5	0.281	1.405	
a_H (37)	5	0.046	0.230	
$b_i \times B_j$		-	-	
$logP_{cal.}$			4.57	ΔlogP = 0.02
$logP_{exp.}$[143]			4.59	

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



(3)

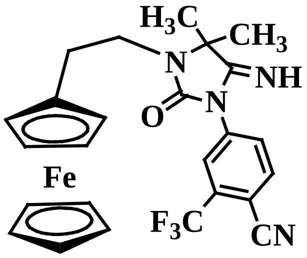
N-[4-cyano-3-trifluoromethylphenyl]- ferrocenecarboxamide

This compound illustrated an example of ferrocene with basic fragment linked to aromatic ring. logP is obtained by summing the contribution of each atom types constituent of this molecule, these being ferrocenyl group, one nitrogen atom N type (64), five atoms types of carbons C, (16), (24), (26), (29), and (30), one fluorine atom F type (72), one oxygen atom O type (44), one hydrogen atom H type(37), finally CN terminal group (77), no corrections factor are required in this case, logP for this compound is obtained according to relation III-2-6, as follows :

Table III-2-3: *Calculation of logP for compound (3)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_N (64)	1	-0.212	-0.212	
a_C (24)	1	1.637	1.637	
a_O (44)	1	-2.057	-2.057	
a_C (26)	3	0.281	0.843	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_H (37)	4	0.046	0.184	
a_C (16)	1	-0.699	-0.699	
a_F (72)	3	0.493	1.479	
a_{CN} (77)	1	-0.256	-0.256	
$b_i \times B_j$		-	-	
$logP_{cal.}$			4.09	$\Delta\text{logP} = 0.01$
$logP_{exp.}$[141]			4.10	

4. 4-(4’,4’-Dimethyl-3’-ferrocenylethyl-5’-imino-2’-oxo-1’-imidazolidinyl)-2-Trifluoromethylbenzonitrile



(4)

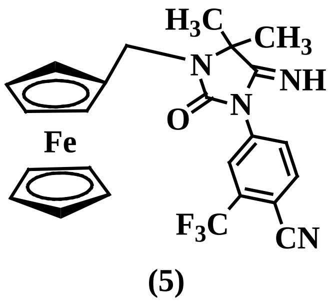
4-(4',4'-dimethyl-3'-ferrocenylethyl-5'-imino-2'-oxo-1'- imidazolidinyl)-2-trifluoromethylbenzonitrile

In this molecule we describe ferrocene linked to a direct heterocyclic ring via two methylene groups, after summing the atom types in the molecule as illustrated in table III-2-4, we propose no correction for these type of compounds, logP is calculated by the same manner of compound (3) which gives the value of 5.27.

Table III-2-4: *Calculation of logP for compound (4)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (6)	1	-0.344	-0.344	
a_C (5)	1	0.009	0.009	
a_N (51)	2	0.443	0.886	
a_N (53)	1	-2.052	-2.052	
a_C (1)	2	0.484	0.968	
a_C (14)	1	-0.598	-0.598	
a_C (24)	2	1.637	3.274	
a_O (44)	1	-2.057	-2.057	
a_C (26)	3	0.281	0.843	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_H (37)	14	0.046	0.644	
a_C (16)	1	-0.699	-0.699	
a_F (72)	3	0.493	1.479	
a_{CN} (77)	1	-0.256	-0.256	
$b_i \times B_j$		-	-	
$logP_{cal.}$			5.27	$\Delta \text{logP} = 0.23$
$logP_{exp.}$[141]			5.04	

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



(5)

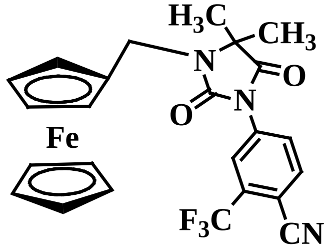
4-(4’,4’-Dimethyl-3’-ferrocenylmethyl-5’-imino-2’-oxo-1’-imidazolidinyl)-2- trifluoromethyl-benzonitrile

No correction factor is proposed for this type of molecules, logP is calculated according to equation III-2-6 by summing the contribution of all atom types in the molecule, as shown in table III-2-5.

Table III-2-5: *Calculation of logP for compound (5)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (6)	1	-0.344	-0.344	
a_N (51)	2	0.443	0.886	
a_N (53)	1	-2.052	-2.052	
a_C (1)	2	0.484	0.968	
a_C (14)	1	-0.598	-0.598	
a_C (24)	2	1.637	3.274	
a_O (44)	1	-2.057	-2.057	
a_C (26)	3	0.281	0.843	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_H (37)	12	0.046	0.552	
a_C (16)	1	-0.699	-0.699	
a_F (72)	3	0.493	1.479	
a_{CN} (77)	1	-0.256	-0.256	
$b_i \times B_j$		-	-	
$logP_{cal.}$			5.17	ΔlogP = 0.49
$logP_{exp.}$[141]			4.68	

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



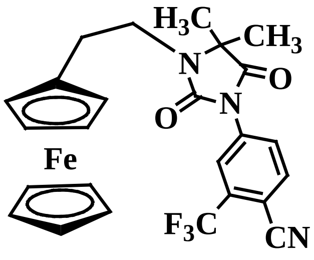
(6)

4-(4',4'-Dimethyl-2',5'-dioxo-3'-ferrocenylmethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile logP is calculated by summing the different atom types contribution of all atoms and the contribution of terminal group CN in the molecule, no correction are required, gives the value of 5.12 for logP.

Table III-2-6: *Calculation of logP for compound (6)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (6)	1	-0.344	-0.344	
a_N (51)	2	0.443	0.886	
a_C (1)	2	0.484	0.968	
a_C (14)	1	-0.598	-0.598	
a_C (24)	2	1.637	3.274	
a_O (44)	2	-2.057	-4.114	
a_C (26)	3	0.281	0.843	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_H (37)	11	0.046	0.506	
a_C (16)	1	-0.699	-0.699	
a_F (72)	3	0.493	1.479	
a_{CN} (77)	1	-0.256	-0.256	
$b_i \times B_j$		-	-	
$logP_{cal.}$			5.12	$\Delta \log P = 0.11$
$logP_{exp.}$[141]			5.23	

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



(7)

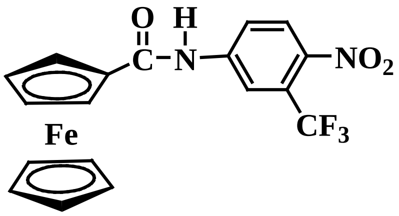
4-(4’,4’-dimethyl-2’,5’-dioxo-3’-ferrocenylethyl-1’-imidazolidinyl)-2-trifluoromethyl-benzonitrile

By the same manner logP for this compound is obtained according to equation III-2-6, as illustrated in table III-2-7 as follows:

Table III-2-7: *Calculation of logP for compound (7)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (6)	1	-0.344	-0.344	
a_C (5)	1	0.009	0.009	
a_N (51)	2	0.443	0.886	
a_C (1)	2	0.484	0.968	
a_C (14)	1	-0.598	-0.598	
a_C (24)	2	1.637	3.274	
a_O (44)	2	-2.057	-4.114	
a_C (26)	3	0.281	0.843	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_H (37)	13	0.046	0.598	
a_C (16)	1	-0.699	-0.699	
a_F (72)	3	0.493	1.479	
a_{CN} (77)	1	-0.256	-0.256	
$b_i \times B_j$		-	-	
$logP_{cal.}$			5.22	$\Delta \text{logP} = 0.40$
$logP_{exp.}$[141]			5.62	

8. N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide



(8)

N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide

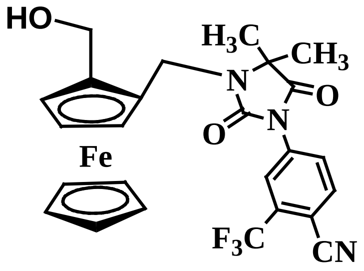
This compound is an example describing ferrocenes with a basic fragment linked to two aromatic rings with resonance, logP is calculated by summing ferrocenyl contribution with the different atom types contribution of each atom in this molecule. The kind of all atom types are five carbons atom types,(16),(24),(26),(29),(30), one nitrogen atom N type (64), one fluorine atom F type (72), oxygen O atom type (44), and the contribution of the terminal group nitro

NO_2 type (80), no corrections factor are required, logP is obtained via applying the relation III-2-6.

Table III-2-8: *Calculation of logP for compound (8)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_N (64)	1	-0.212	-0.212	
a_C (24)	1	1.637	1.637	
a_O (44)	1	-2.057	-2.057	
a_C (26)	3	0.281	0.843	
a_C (29)	1	0.302	0.302	
a_C (30)	2	-0.064	-0.128	
a_H (37)	4	0.046	0.184	
a_C (16)	1	-0.699	-0.699	
a_F (72)	3	0.493	1.479	
a_{NO_2}(80)	1	0.264	0.264	
$b_i \times B_j$		-	-	
$logP_{cal.}$			4.25	$\Delta \text{logP} = 0.17$
$logP_{exp.}$[141]			4.42	

9. 4-[4',4'-dimethyl-2',5'-dioxo-3'-ortho-hydroxymethyl-ferrocenylmethyl-1'-imidazolidinyl]-2-trifluoromethyl-benzonitrile



(9)

4-[4',4'-dimethyl-2',5'-dioxo-3'-ortho-hydroxymethyl-ferrocenylmethyl 1'- imidazolidinyl]-2-trifluoromethyl-benzonitrile

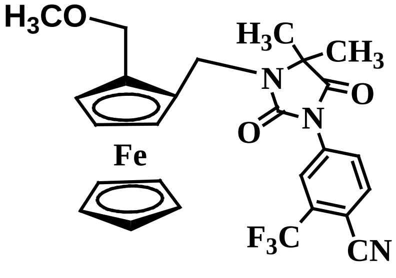
In thin type of compound, ferrocene is linked on one side to a direct heterocyclic ring via a methylene group and with hydroxyl group via a methylene on the other side, in this case the ferrocenyl group is attached to two carbon atoms, its contribution is calculated from equation

III-2-3 where $n_1 = 2$ and $n_2 = 0$. logP is calculated by the same manner as in the example above compound (8) gives the value of 4.49 as follows:

Table III-2-9: *Calculation of logP for compound (9)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.610	2.610	
a_C (6)	2	-0.344	-0.688	
a_{OH} (38)	1	-0.399	-0.399	
a_N (51)	2	0.443	0.886	
a_C (1)	2	0.484	0.968	
a_C (14)	1	-0.598	-0.598	
a_C (24)	2	1.637	3.274	
a_O (44)	2	-2.057	-4.114	
a_C (26)	3	0.281	0.843	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_H (37)	14	0.046	0.644	
a_C (16)	1	-0.699	-0.699	
a_F (72)	3	0.493	1.479	
a_{CN} (77)	1	-0.256	-0.256	
$b_i \times B_j$		-	-	
$logP_{cal.}$			4.49	$\Delta\text{logP} = 0.05$
$logP_{exp.}$[141]			4.44	

10. 4-[4’,4’-dimethyl-2’,5’-dioxo-1’-imidazolidinyl-(3’-ortho-methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile



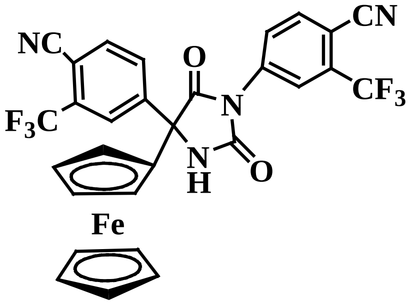
(10)

4-[4’,4’-dimethyl-2’,5’-dioxo-1’-imidazolidinyl-(3’-ortho- methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile logP for this compound is obtained according to equation III-2-6, by the same manner of the example above compound (9) as follows:

Table III-2-10: *Calculation of logP for compound (10)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.610	2.610	
a_C (6)	2	-0.344	-0.688	
a_C (3)	1	-0.181	-0.181	
a_O (41)	1	0.397	0.397	
a_N (51)	2	0.443	0.886	
a_C (1)	2	0.484	0.968	
a_C (14)	1	-0.598	-0.598	
a_C (24)	2	1.637	3.274	
a_O (44)	2	-2.057	-4.114	
a_C (26)	3	0.281	0.843	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_H (37)	16	0.046	0.736	
a_C (16)	1	-0.699	-0.699	
a_F (72)	3	0.493	1.479	
a_{CN} (77)	1	-0.256	-0.256	
$b_i \times B_j$		-	-	
$logP_{cal.}$			5.20	$\Delta \text{logP} = 0.12$
$logP_{exp.}$[141]			5.08	

11. 4’-ferrocenyl-1’,4’-[bis-(2-trifluorométhyl-1-cyano-phenyl)] -2’,5’-imidazolidinedione



(11)

4’-ferrocenyl-1’,4’-[*bis*-(2-trifluoromethyl-1-cyano-phenyl)]

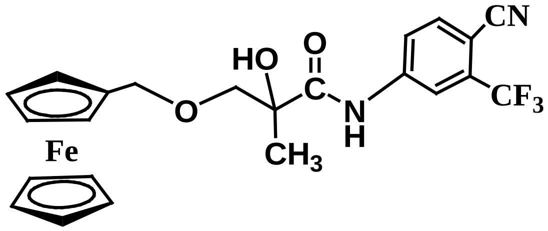
-2’,5’-imidazolidinedione

This compound describes ferrocene linked to two aromatic rings, logP is obtained according to relation III-2-6 as summarized in the following table III-2-11.

Table III-2-11: *Calculation of logP for compound (11)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (14)	1	-0.598	-0.598	
a_N (60)	1	0.434	0.434	
a_C (24)	2	1.637	3.274	
a_N (51)	1	0.443	0.443	
a_O (44)	2	-2.057	-4.114	
a_C (26)	6	0.281	1.686	
a_C (29)	5	0.302	1.510	
a_C (30)	1	-0.064	-0.064	
a_H (37)	7	0.046	0.322	
a_C (16)	2	-0.699	-1.398	
a_F (72)	6	0.493	2.958	
a_{CN} (77)	2	-0.256	-0.512	
$b_i \times B_j$		-	-	
$logP_{cal.}$			6.58	$\Delta \log P = 0.11$
$logP_{exp.}$[141]			6.47	

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



(12)

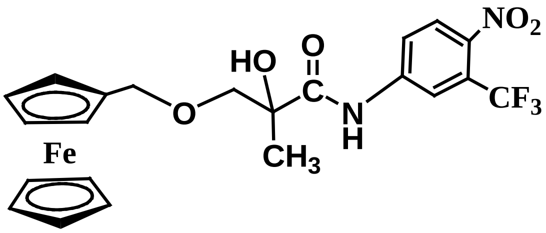
N-(4-cyano-3-trifluoro methylphenyl) -3-ferrocenylmethoxy-2-hydroxy- 2-methyl-propanamide

This following compound receives a correction factor value of 1.20 for the two intermolecular hydrogen bond 0.6 for each one, logP is illustrated in table III-2-12.

Table III-2-12: *Calculation of logP for compound (12)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (6)	2	-0.344	-0.688	
a_C (14)	1	-0.598	-0.598	
a_O (41)	1	0.397	0.397	
a_C (1)	1	0.484	0.484	
a_{OH} (38)	1	-0.399	-0.399	
a_C (24)	1	1.637	1.637	
a_O (44)	1	-2.057	-2.057	
a_N (64)	1	-0.212	-0.212	
a_C (16)	1	-0.699	-0.699	
a_C (26)	3	0.281	0.843	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_H (37)	12	0.046	0.552	
a_F (72)	3	0.493	1.479	
a_{CN} (77)	1	-0.256	-0.256	
$b_i \times B_j$		2×0.6	1.20	
$logP_{cal.}$			4.86	ΔlogP = 0.23
$logP_{exp.}$[141][142]			4.63	

13. 3-ferrocenylmethoxy-2-hydroxy-2- methyl-N-(4-nitro-3- trifluoromethylphenyl)-propanamide



(13)

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

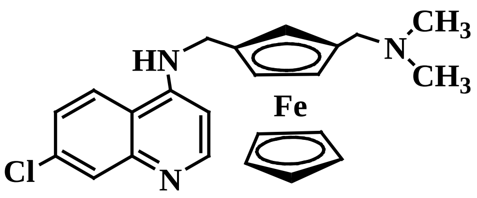
Propanamide

This compound needed a correction factor of +1,20 because it has two intermolecular hydrogen bond +0.6 for each one, logP for this compound is calculated by the same manner of the example above compound (12) as shown table III-2-13.

Table III-2-13: *Calculation of logP for compound (13)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (6)	2	-0.344	-0.688	
a_C (14)	1	-0.598	-0.598	
a_O (41)	1	0.397	0.397	
a_C (1)	1	0.484	0.484	
a_{OH} (38)	1	-0.399	-0.399	
a_C (24)	1	1.637	1.637	
a_O (44)	1	-2.057	-2.057	
a_N (64)	1	-0.212	-0.212	
a_C (16)	1	-0.699	-0.699	
a_C (26)	3	0.281	0.843	
a_C (29)	1	0.302	0.302	
a_C (30)	2	-0.064	-0.128	
a_H (37)	12	0.046	0.552	
a_F (72)	3	0.493	1.479	
a_{NO_2} (80)	1	0.264	0.264	
$b_i \times B_j$		2×0.6	1.20	
$logP_{cal.}$			5.01	ΔlogP = 0.00
$logP_{exp.}$[141][142]			5.01	

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



(14)

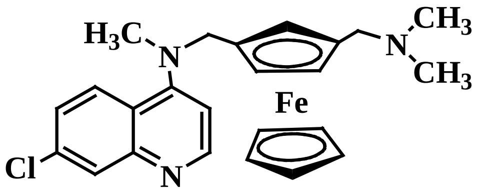
N-(7-Chloro-quinolin-4-yl)-(2- dimethylaminomethylferrocenyl)-amine

This ferrocene derivatives is attached to two carbons atoms, its contribution is calculated from equation III-2-6 where $n_1 = 2$ and $n_2 = 0$, we propose for these type of molecules a correction factor of 0.6 for hydrogen band [144] figure III-1-7, the method of calculating of logP is illustrated in table III-2-14.

Table III-2-14: *Calculation of logP for compound (14)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.610	2.610	
a_C (6)	2	-0.344	-0.688	
a_N (51)	1	0.443	0.443	
a_C (3)	2	-0.181	-0.362	
a_N (49)	1	0.040	0.040	
a_N (57)	1	-0.704	-0.704	
a_C (26)	4	0.281	1.124	
a_C (29)	1	0.302	0.302	
a_C (30)	2	-0.064	-0.128	
a_C (27)	1	0.142	0.142	
a_C (31)	1	0.079	0.079	
a_H (37)	16	0.046	0.736	
a_{Cl} (73)	1	1.010	1.010	
$b_i \times B_j$		1×0.6	0.6	
$logP_{cal.}$			5.20	$\Delta \text{logP} = 0.10$
$logP_{exp.}$[145]			5.10	

15. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- methylamine



(15)

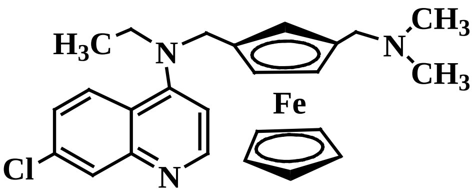
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- methylamine

No correction was proposed for these type of compounds.

Table III-2-15: *Calculation of logP for compound (15)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.610	2.610	
a_C (6)	2	-0.344	-0.688	
a_N (51)	2	0.443	0.886	
a_C (3)	3	-0.181	-0.543	
a_N (57)	1	-0.704	-0.704	
a_C (26)	4	0.281	1.124	
a_C (29)	1	0.302	0.302	
a_C (30)	2	-0.064	-0.128	
a_C (27)	1	0.142	0.142	
a_C (31)	1	0.079	0.079	
a_H (37)	18	0.046	0.828	
a_{Cl} (73)	1	1.010	1.010	
$b_i \times B_j$		-	-	
$logP_{cal.}$			4.92	$\Delta logP = 0.03$
$logP_{exp.}$[145]			4.89	

16. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-ethylamine



(16)

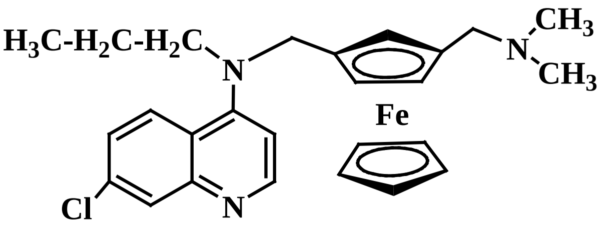
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-ethylamine

According to XlogP method we propose no correction for these type of compounds.

Table III-2-16: *Calculation of logP for compound (16)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.610	2.610	
a_C (6)	3	-0.344	-1.032	
a_N (51)	2	0.443	0.886	
a_C (3)	2	-0.181	-0.362	
a_C (1)	1	0.484	0.484	
a_N (57)	1	-0.704	-0.704	
a_C (26)	4	0.281	1.124	
a_C (29)	1	0.302	0.302	
a_C (30)	2	-0.064	-0.128	
a_C (27)	1	0.142	0.142	
a_C (31)	1	0.079	0.079	
a_H (37)	20	0.046	0.920	
a_{Cl} (73)	1	1.010	1.010	
$b_i \times B_j$		-	-	
$logP_{cal.}$			5.33	$\Delta \log P = 0.56$
$logP_{exp.}$[145]			5.89	

17. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-propylamine



(17)

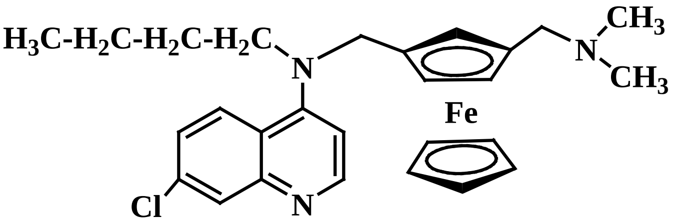
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-propylamine

No correction factor is needed for these type of compounds.

Table III-2-17: *Calculation of logP for compound (17)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.610	2.610	
a_C (6)	3	-0.344	-1.032	
a_N (51)	2	0.443	0.886	
a_C (3)	2	-0.181	-0.362	
a_C (1)	1	0.484	0.484	
a_C (4)	1	0.358	0.358	
a_N (57)	1	-0.704	-0.704	
a_C (26)	4	0.281	1.124	
a_C (29)	1	0.302	0.302	
a_C (30)	2	-0.064	-0.128	
a_C (27)	1	0.142	0.142	
a_C (31)	1	0.079	0.079	
a_H (37)	22	0.046	1.012	
a_{Cl} (73)	1	1.010	1.010	
$b_i \times B_j$		-	-	
$logP_{cal.}$			5.78	ΔlogP = 0.55
$logP_{exp.}$[145]			6.33	

18. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- butylamine



(18)

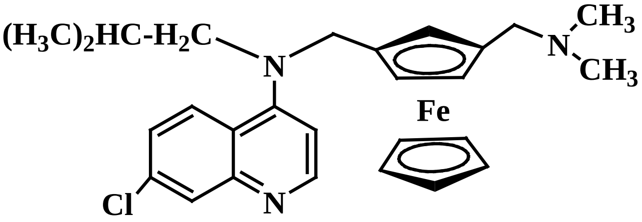
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethyl ferrocenyl)-butylamine

We propose no correction for these types of compounds.

Table III-2-18: *Calculation of logP for compound (18)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.610	2.610	
a_C (6)	3	-0.344	-1.032	
a_N (51)	2	0.443	0.886	
a_C (3)	2	-0.181	-0.362	
a_C (1)	1	0.484	0.484	
a_C (4)	2	0.358	0.716	
a_N (57)	1	-0.704	-0.704	
a_C (26)	4	0.281	1.124	
a_C (29)	1	0.302	0.302	
a_C (30)	2	-0.064	-0.128	
a_C (27)	1	0.142	0.142	
a_C (31)	1	0.079	0.079	
a_H (37)	24	0.046	1.104	
a_{Cl} (73)	1	1.010	1.010	
$b_i \times B_j$		-	-	
$logP_{cal.}$			6.23	$\Delta \text{logP} = 0.47$
$logP_{exp.}$[145]			6.70	

19. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- isobutylamine



(19)

(7-Chloro-quinolin-4-yl)- (2-dimethylaminomethyl ferrocenyl)- isobutylamine

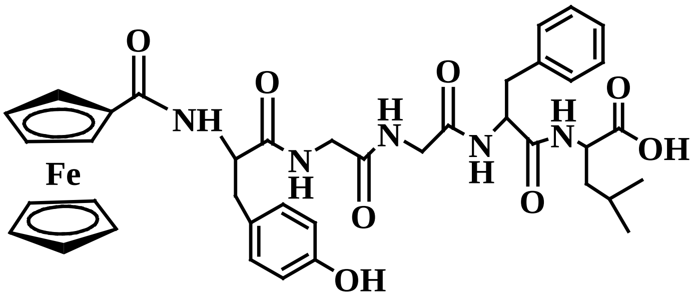
No corrections factor are needed for these type of compounds.

Table III-2-19: *Calculation of logP for compound (19)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.610	2.610	
a_C (6)	3	-0.344	-1.032	
a_N (51)	2	0.443	0.886	
a_C (3)	2	-0.181	-0.362	
a_C (1)	2	0.484	0.968	
a_C (8)	1	0.051	0.051	
a_N (57)	1	-0.704	-0.704	
a_C (26)	4	0.281	1.124	
a_C (29)	1	0.302	0.302	
a_C (30)	2	-0.064	-0.128	
a_C (27)	1	0.142	0.142	
a_C (31)	1	0.079	0.079	
a_H (37)	24	0.046	1.104	
a_{Cl} (73)	1	1.010	1.010	
$b_i \times B_j$		-	-	
$logP_{cal.}$			6.05	$\Delta\text{logP} = 0.55$
$logP_{exp.}$[145]			6.60	

20. Fc-CO-Enk-OH

Enkephalin: 2-amino-3- (4- hydroxyphenyl)propanoyl]amino]acetyl] amino]acetyl]amino]-3-phenylpropanoyl] amino]-4-methylpentanoic acid.



(20)

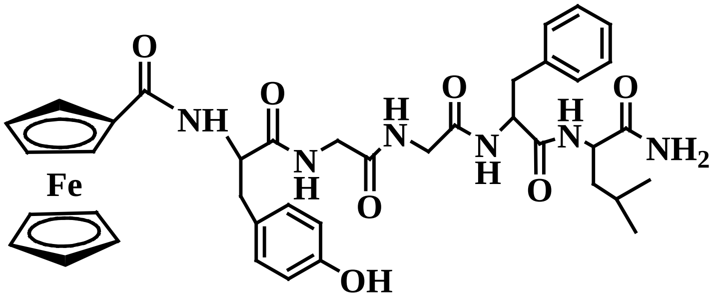
Fc-CO-Enk-OH

For this complicated compounds ferrocene containing enkephalin needed corrections factor of value 3 because it has five occurrences hydrogen bond +0.6 for each, logP is calculated as follows:

Table III-2-20: *Calculation of logP for compound (20)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (6)	2	-0.344	-0.688	
a_N (64)	5	-0.212	-1.060	
a_C (5)	2	0.009	0.018	
a_C (8)	1	0.051	0.051	
a_C (10)	3	-0.417	-1.251	
a_C (4)	1	0.358	0.358	
a_C (1)	2	0.484	0.968	
a_O (38)	1	-0.399	-0.399	
a_O (39)	1	-0.029	-0.029	
a_O (44)	6	-2.057	-12.342	
a_C (24)	6	1.637	9.822	
a_C (26)	9	0.281	2.529	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_H (37)	35	0.046	1.610	
$b_i \times B_j$		5×0.6	3	
$logP_{cal.}$			5.76	ΔlogP = 0.03
$logP_{exp.}$[146]			5.79	

21. Fc-CO-Enk-NH$_2$



(21)

Fc-CO-Enk-NH$_2$

We propose a total of +2.4 as a correction factor for these type of compounds because it has four occurrences hydrogen bond +0.6 for each, logP is calculated as follows:

Table III-2-21: *Calculation of logP for compound (21)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (6)	2	-0.344	-0.688	
a_N (64)	5	-0.212	-1.060	
a_N (63)	1	-0791	-0.791	
a_C (5)	2	0.009	0.018	
a_C (8)	1	0.051	0.051	
a_C (10)	3	-0.417	-1.251	
a_C (4)	1	0.358	0.358	
a_C (1)	2	0.484	0.968	
a_O (39)	1	-0.029	-0.029	
a_O (44)	6	-2.057	-12.342	
a_C (24)	6	1.637	9.822	
a_C (26)	9	0.281	2.529	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_H (37)	36	0.046	1.656	
$b_i \times B_j$		4×0.6	2.4	
$logP_{cal.}$			4.82	$\Delta \text{logP} = 0.82$
$logP_{exp.}$[146]			4.00	

The difference between the experimental logP value and calculated value is equal to 0.82 this rather great deviation may be due the accessible surface area which is defined as the surface area of a molecule that is accessible to a solvent, in this molecule the hydrophilic areas dominate the solvent accessibility surface. Figure III-2-2 shows the molecule envelope which is accessible to and attracts water molecules that due to structure or conformation of compound in space, where the amide and generally the peptide can be identified as locations of elevated hydrophilicity. The XlogP method had not sensitivity to conformational effects.

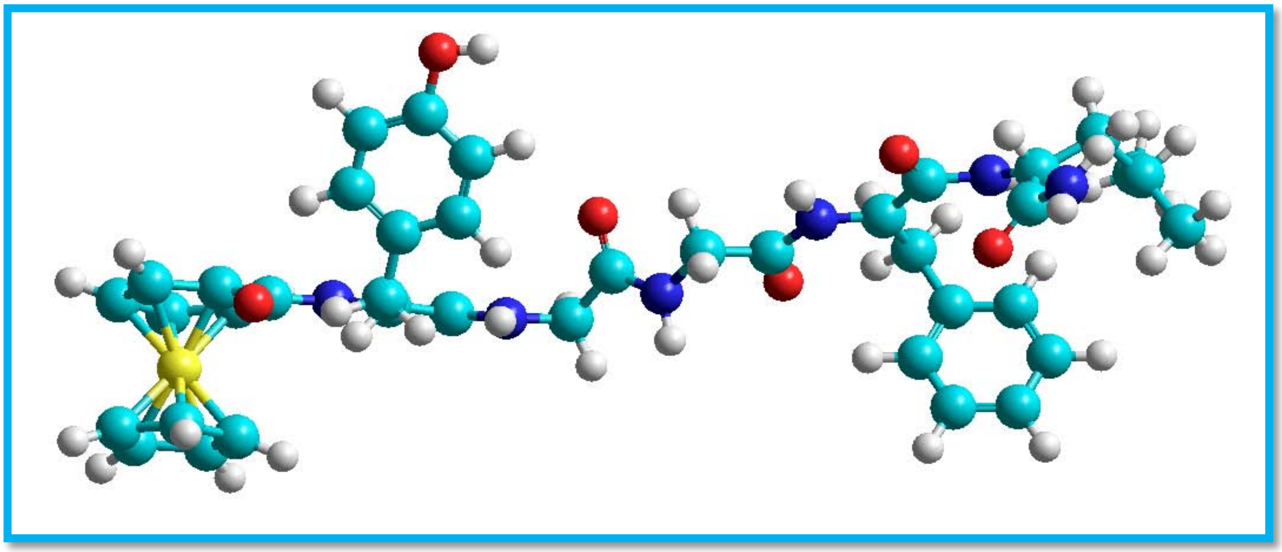
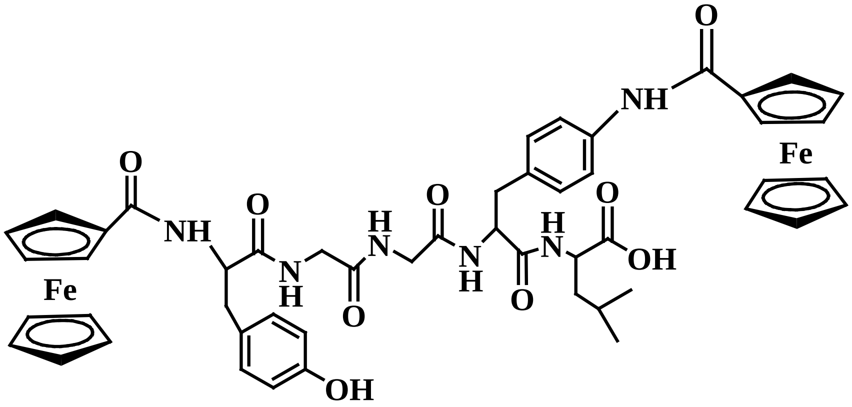


Figure III-2-2: *Structure of Fc-CO-Enk-NH_2 were drawn using HyperChem8.03 optimized by (MM+)*

22. Fc-CO-Enk[Phe (NH-CO-Fc)]-OH



(22)

Fc-CO-Enk[Phe (NH-CO-Fc)]-OH

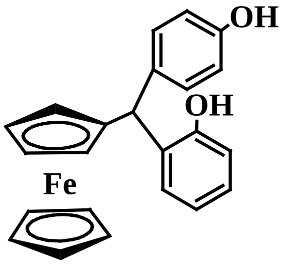
Our proposition for the correction factors for these type of compounds is equal to +3 for the five occurrences hydrogen bond, logP is calculated as follows:

Table III-2-22: *Calculation of logP for compound (22)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	2	2.635	5.270	
a_C (6)	2	-0.344	-0.688	
a_N (64)	6	-0.212	-1.272	
a_C (5)	2	0.009	0.018	
a_C (8)	1	0.051	0.051	
a_C (10)	3	-0.417	-1.251	
a_C (4)	1	0.358	0.358	
a_C (1)	2	0.484	0.968	
a_O (38)	1	-0.399	-0.399	
a_O (39)	1	-0.029	-0.029	
a_O (44)	7	-2.057	-14.399	
a_C (24)	7	1.637	11.459	
a_C (26)	8	0.281	2.248	
a_C (29)	2	0.302	0.604	
a_C (30)	2	-0.064	-0.128	
a_H (37)	36	0.046	1.656	
$b_i \times B_j$		5×0.6	3	
$logP_{cal.}$			7.47	$\Delta \text{logP} = 0.98$
$logP_{exp.}$[146]			6.49	

The difference between the experimental logP value and calculated value equal to 0.98 this deviation may be due to the conformational effects as in compound (21) cited before.

23. 1-((2-hydroxyphenyl)(4-hydroxyphenyl)methyl) ferrocene



(23)

1-((2-hydroxyphenyl)(4-hydroxyphenyl)methyl) ferrocene

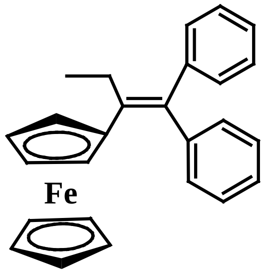
This compound is an example of ferrocene with a tertiary carbon, in this case no corrections are required, gives a value of 5.67 for logP table III-2-23.

Table III-2-23: *Calculation of logP for compound (23)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	8	0.281	2.248	
a_C (29)	2	0.302	0.604	
a_C (30)	2	-0.064	-0.128	
a_O (39)	2	-0.029	-0.058	
a_C (9)	1	-0.138	-0.138	
a_H (37)	11	0.046	0.506	
$b_i \times B_j$		-	-	
$logP_{cal.}$			5.67	ΔlogP = 0.77
$logP_{exp.}$[147]			4.90	

The difference between the experimental logP value and calculated value equal to 0.77 that may be due to the bulky groups which this compound carry.

24. 1-(1,1-diphenylbut-1-en-2-yl) ferrocene



(24)

1-(1,1-diphenylbut-1-en-2-yl) ferrocene

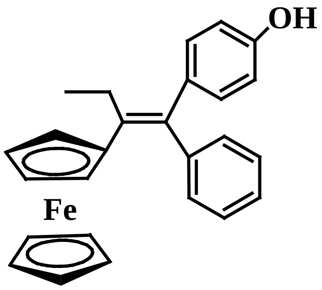
logP for this ferrocene derivative is calculated as shown in table III-2-24.

Table III-2-24: *Calculation of logP for compound (24)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	10	0.281	2.810	
a_C (29)	2	0.302	0.604	
a_C (22)	2	0.098	0. 196	
a_C (5)	1	0.009	0.009	
a_C (1)	1	0.484	0.484	
a_H (37)	15	0.046	0.690	
$b_i \times B_j$		-	-	
$logP_{cal.}$			7.43	$\Delta \text{logP} = 1.00$
$logP_{exp.}$[150]			6.43	

The difference between the experimental logP value and calculated value equal to 1, that may be due to the bulky groups which this compound carry.

25. (1-(- 4-hydroxy phenyl)-1-phenylbut-1-en-2-yl) ferrocene



(25)

1-(1-(- 4-hydroxy phenyl)-1-phenylbut-1-en-2-yl) ferrocene

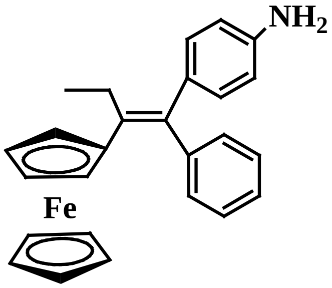
logP for this ferrocene derivative is calculated as the following table III-2-25.

Table III-2-25: *Calculation of logP for compound (25)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{Fc}	1	2.635	2.635	
a_C (26)	9	0.281	2.529	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_C (22)	2	0.098	0. 196	
a_O (39)	1	-0.029	-0.029	
a_C (5)	1	0.009	0.009	
a_C (1)	1	0.484	0.484	
a_H (37)	15	0.046	0.690	
$b_i \times B_j$		-	-	
$logP_{cal.}$			7.05	ΔlogP = 0.88
$logP_{exp.}$[150]			6.17	

The difference between the experimental logP value and calculated value is equal to 0.88 this deviation may be due to volume that occupy this molecule in space.

26. (1-(- 4-amino phenyl)-1-phenylbut-1-en-2-yl) ferrocene



(26)

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

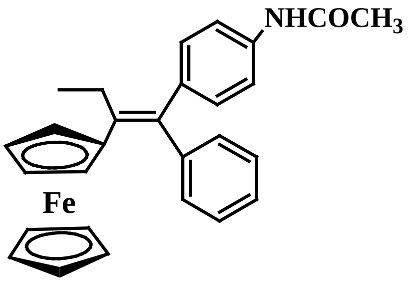
For this type of compounds no correction are needed, gives a value of 6.68 for logP table III-2-26.

Table III-2-26: *Calculation of logP for compound (26)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	9	0.281	2.529	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_C (22)	2	0.098	0. 196	
a_N (47)	1	-0.447	-0.447	
a_C (5)	1	0.009	0.009	
a_C (1)	1	0.484	0.484	
a_H (37)	16	0.046	0. 736	
$b_i \times B_j$		-	-	
$logP_{cal.}$			6.68	$\Delta\text{logP} = 0.93$
$logP_{exp.}$[150]			5.75	

The deviation between the experimental logP value and calculated value equal to 0.93, this deviation may be due to volume that occupies this molecule in space.

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



(27)

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

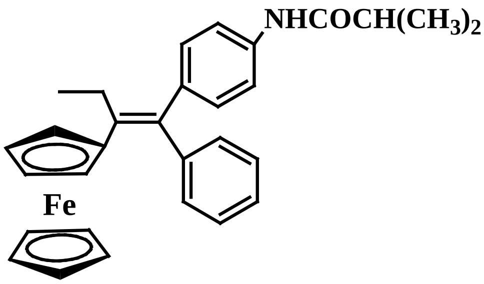
For this type of compounds no corrections factor are needed, logP is calculated as illustrated in table III-2-27.

Table III-2-27: *Calculation of logP for compound (27)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	9	0.281	2.529	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_C (22)	2	0.098	0. 196	
a_N (64)	1	-0.212	-0.212	
a_C (24)	1	1.637	1.637	
a_O (44)	1	-2.057	-2.057	
a_C (5)	1	0.009	0.009	
a_C (2)	1	0.168	0.168	
a_C (1)	1	0.484	0.484	
a_H (37)	18	0.046	0. 828	
$b_i \times B_j$		-	-	
$logP_{cal.}$			6.76	$\Delta \text{logP} = 0.84$
$logP_{exp.}$[150]			5.92	

The difference between the experimental logP value and calculated value equal to 0.84 this deviation may be due to volume that occupies this molecule in space.

28. N-(4-(-2-(ferrocenyl)-1- phenylbut-1- enyl)phenyl)isobutyramide



(28)

N-(4-(-2-(ferrocenyl)-1- phenylbut-1- enyl) phenyl)isobutyramide

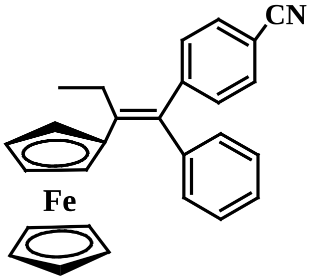
logP for this ferrocene is calculated in table III-2-28**.**

Table III-2-28: *Calculation of logP for compound (28)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	9	0.281	2.529	
a_C (29)	2	0.302	0.604	
a_C (30)	1	-0.064	-0.064	
a_C (22)	2	0.098	0. 196	
a_N (64)	1	-0.212	-0.212	
a_C (24)	1	1.637	1.637	
a_O (44)	1	-2.057	-2.057	
a_C (9)	1	-0.138	-0.138	
a_C (5)	1	0.009	0.009	
a_C (1)	3	0.484	1.452	
a_H (37)	22	0.046	1.012	
$b_i \times B_j$		-	-	
$logP_{cal.}$			7.60	$\Delta \text{logP} = 1.47$
$logP_{exp.}$[150]			6.13	

The difference between the experimental logP value and calculated value equal to 1.47 this deviation may be due to volume that occupies this molecule in space.

29. 4-(-2-(ferrocenyl)-1- phenylbut-1- enyl)benzonitrile



(29)

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

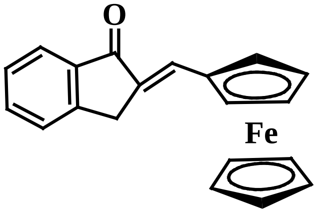
This type of compounds no corrections are needed, logP is calculated in table III-2-29.

Table III-2-29: *Calculation of logP for compound (29)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	9	0.281	2.529	
a_C (29)	3	0.302	0.906	
a_C (22)	2	0.098	0. 196	
a_C (5)	1	0.009	0.009	
a_{CN} (77)	1	-0.256	-0.256	
a_C (1)	1	0.484	0.484	
a_H (37)	14	0.046	0. 644	
$b_i \times B_j$		-	-	
$logP_{cal.}$			7.15	$\Delta logP = 0.78$
$logP_{exp.}$[150]			6.37	

The difference between the experimental logP value and calculated value equal to 0.78 this deviation may be due to the same factors of the compound (28), because they have almost the same structure.

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



(30)

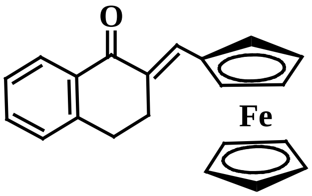
(E)-2-ferrocenylmethylene -2,3-dihydroinden-1-one

We propose no correction for these types of compounds. logP for this ferrocene derivative is calculated in table III-2-30.

Table III-2-30: *Calculation of logP for compound (30)*

Atom type	$\mathrm{A_i}$	$\mathrm{a_i}$	$\mathrm{a_i \times A_i}$	
a_{F_c}	1	2.635	2.635	
a_C (24)	1	1.637	1.637	
a_O (44)	1	-2.057	-2.057	
a_C (26)	4	0.281	1.124	
a_C (29)	2	0.302	0.604	
a_C (5)	1	0.009	0.009	
a_C (19)	1	0.236	0.236	
a_C (22)	1	0.098	0.098	
a_H (37)	7	0.046	0.322	
$\mathrm{b_i \times B_j}$		-	-	
$logP_{cal.}$			4.61	$\Delta\mathrm{logP} = 0.16$
$logP_{exp.}$[151]			4.77	

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



(31)

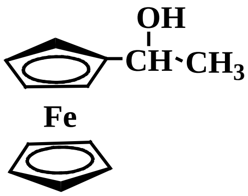
(E)-2-ferrocenylmethylene -3,4-dihydronaphthalen(2H)-1-one

We propose no correction for these types of compounds. logP for this ferrocene derivative is calculated in table III-2-31.

Table III-2-31: *Calculation of logP for compound (31)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (24)	1	1.637	1.637	
a_O (44)	1	-2.057	-2.057	
a_C (26)	4	0.281	1.124	
a_C (29)	2	0.302	0.604	
a_C (4)	1	0.358	0.358	
a_C (5)	1	0.009	0.009	
a_C (19)	1	0.236	0.236	
a_C (22)	1	0.098	0.098	
a_H (37)	9	0.046	0.322	
$b_i \times B_j$		-	-	
$logP_{cal.}$			4.97	$\Delta \text{logP} = 0.30$
$logP_{exp.}$[151]			5.27	

32. 1-ferrocenylethanol



(32)

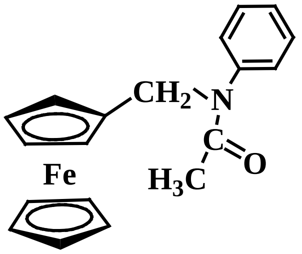
1-ferrocenylethanol

This type of compound appears to have a sample structure and few groups, that's why no correction are needed when calculation logP of this type of compounds. The calculations are illustrated in table III-2-32.

Table III-2-32: *Calculation of logP for compound (32)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (1)	1	0.484	0.484	
a_O (38)	1	-0.399	-0.399	
a_C (10)	1	-0.417	-0.417	
a_H (37)	5	0.046	0.23	
$b_i \times B_j$		-	-	
$logP_{cal.}$			2.53	$\Delta \text{logP} = 0.35$
$logP_{exp.}$			2.18	

33. N-ferrocenymethyl-N-phenylacetamide



(33)

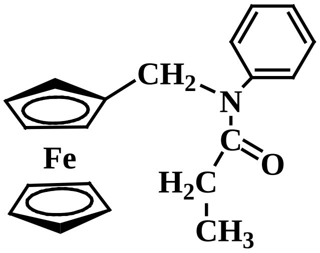
N-ferrocenymethyl-N-phenylacetamide

Athougt this compound is carring a phenyl group and an amide function, no corrections are needed for the calculation of logP of this type of molecule as shown in table III-2-33.

Table III-2-33: *Calculation of logP for compound (33)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (6)	1	-0.344	-0.344	
a_C (26)	5	0.281	1.405	
a_C (30)	1	-0.064	-0.064	
a_C (2)	1	0.168	0.168	
a_N (65)	1	0.016	0.016	
a_C (24)	1	1.637	1.637	
a_H (37)	10	0.046	0.46	
a_O (44)	1	-2.057	-2.057	
$b_i \times B_j$		-	-	
$logP_{cal.}$			3.86	$\Delta\text{logP} = 0.09$
$logP_{exp.}$			3.95	

34. N-ferrocenymethyl-N-phenylpropionamide



(34)

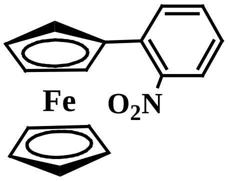
N-ferrocenymethyl-N-phenylpropionamide

This compound does not differ from that presented in example (33), the only difference is methylene group, that the reason why logP for this compound is calculated by the same manner as before (example33).

Table III-2-34: *Calculation of logP for compound (34)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (6)	1	-0.344	-0.344	
a_C (26)	5	0.281	1.405	
a_C (30)	1	-0.064	-0.064	
a_C (5)	1	0.009	0.009	
a_C (1)	1	0.484	0.484	
a_N (65)	1	0.016	0.016	
a_C (24)	1	1.637	1.637	
a_H (37)	12	0.046	0.552	
a_O (44)	1	-2.057	-2.057	
$b_i \times B_j$		-	-	
$logP_{cal.}$			4.27	$\Delta \text{logP} = 0.11$
$logP_{exp.}$			4.38	

35. Ferrocenyl-2-nitrophenyl



(35)

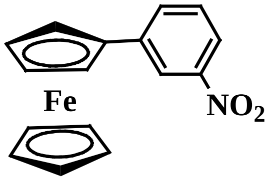
ferrocenyl-2-nitrophenyl

Due to the simple structure of this compound, no corrections are needed for the calculation of logP as the following table III-2-35.

Table III-2-35: *Calculation of logP for compound (35)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	4	0.281	1.124	
a_C (29)	1	0.302	0.302	
a_C (30)	1	-0.064	-0.064	
a_N (80)	1	0.264	0.264	
a_H (37)	4	0.046	0.184	
$b_i \times B_j$		-	-	
$logP_{cal.}$			4.44	ΔlogP = 0.56
$logP_{exp.}$			3.88	

36. Ferrocenyl-3-nitrophenyl



(36)

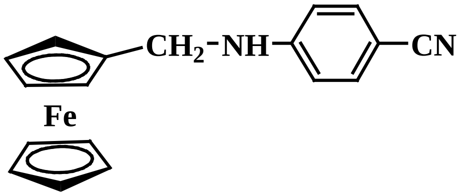
Ferrocenyl-3-nitrophenyl

Table III-2-36: *Calculation of logP for compound (36)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	4	0.281	1.124	
a_C (29)	1	0.302	0.302	
a_C (30)	1	-0.064	-0.064	
a_N (80)	1	0.264	0.264	
a_H (37)	4	0.046	0.184	
$b_i \times B_j$		-	-	
$logP_{cal.}$			4.44	ΔlogP = 0.45
$logP_{exp.}$			3.99	

This example illustrates the influence of the position of a function(ortho and meta) according to ferrocene position. As expected there is no difference in logP, |ΔlogP|= |4.44-4.44| =0.

37. 4-(ferrocenylmethylamino)benzonitrile



(37)

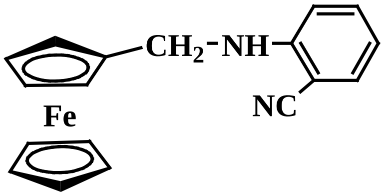
4-(ferrocenylmethylamino)benzonitrile

This example illustrated the influence of nitrile group as compared with compound 34 and also illustrated the influence of its position (ortho and para) as compared with compound 38, logP for this compound is calculated in table III-2-37.

Table III-2-37: *Calculation of logP for compound (37)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	4	0.281	1.124	
a_C (29)	1	0.302	0.302	
a_C (30)	1	-0.064	-0.064	
a_C (6)	1	-0.344	-0.344	
a_N (49)	1	0.040	0.040	
a_{CN} (77)	1	-0.256	-0.256	
a_H (37)	7	0.046	0.322	
$b_i \times B_j$		-	-	
$logP_{cal.}$			3.76	ΔlogP = 0.25
$logP_{exp.}$			3.51	

38. N-ferrocenylmethyl-2-cyanoaniline



(38)

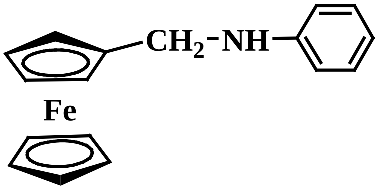
N-ferrocenylmethyl-2-cyanoaniline

For this ferrocene is calculated in table III-2-38.

Table III-2-38: *Calculation of logP for compound (38)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	4	0.281	1.124	
a_C (29)	1	0.302	0.302	
a_C (30)	1	-0.064	-0.064	
a_C (6)	1	-0.344	-0.344	
a_N (49)	1	0.040	0.040	
a_{CN} (77)	1	-0.256	-0.256	
a_H (37)	7	0.046	0.322	
$b_i \times B_j$		-	-	
$logP_{cal.}$			3.76	ΔlogP = 0.12
$logP_{exp.}$			3.64	

39. N-ferrocenylmethylaniline



(39)

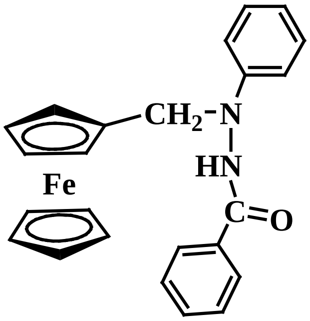
N-ferrocenylmethylaniline

logP for this ferrocene linked to aniline via methylene group is calculated as follows**:**

Table III-2-39: *Calculation of logP for compound (39)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	5	0.281	1.405	
a_C (30)	1	-0.064	-0.064	
a_C (6)	1	-0.344	-0.344	
a_N (49)	1	0.040	0.040	
a_H (37)	8	0.046	0.368	
$b_i \times B_j$		-	-	
$logP_{cal.}$			4.04	ΔlogP = 0.22
$logP_{exp.}$			3.82	

40. N’-ferrocenylmethyl-N’-phenylbenzohydrazide



(40)

N’-ferrocenylmethyl-N’-phenylbenzohydrazide

logP for this ferrocene derivative carrying functionalized hydrazide group is calculated as the following table III-2-40.

Table III-2-40: *Calculation of logP for compound (40)*

Atom type	A_i	a_i	$a_i \times A_i$	
a_{F_c}	1	2.635	2.635	
a_C (26)	10	0.281	2.81	
a_C (30)	1	-0.064	-0.064	
a_C (29)	1	0.302	0.302	
a_C (24)	1	1.637	1.637	
a_O (44)	1	-2.057	-2.057	
a_C (6)	1	-0.344	-0.344	
a_N (52)	1	-0.117	-0.117	
a_N (64)	1	-0.212	-0.212	
a_H (37)	13	0.046	0.598	
$b_i \times B_j$		-	-	
$logP_{cal.}$			5.19	ΔlogP = 1
$logP_{exp.}$			4.19	

The difference between the experimental logP value and calculated value is equal to 1, this difference may be due to atom type of $(R)_2N-NHCOR$ which has no contribution in XlogP calculation method.

Different values of experimental and calculated partition coefficients according to XlogP are summarized in table III-2-41.The absolute error AE of logP varies from 0.00 for compound 13 to 1 for compounds24 and40. In exception the AE for compound 28 is equal to 1.47, these value of AE may due to the fact this ferrocene derivative is bulky.

Table III-2-41: Estimation and absolute error results for ferrocene derivatives

Compound	$logP_{cal.}$	$logP_{exp.}$	AE		Compound	$logP_{cal.}$	$logP_{exp.}$	AE
1	2.83	2.64	0.19		21	4.82	4.00	0.82
2	4.57	4.59	0.02		22	7.47	6.49	0.98
3	4.09	4.10	0.01		23	5.67	4.90	0.77
4	5.27	5.04	0.23		24	7.43	6.43	1.00
5	5.17	4.68	0.49		25	7.05	6.17	0.88
6	5.12	5.23	0.11		26	6.68	5.75	0.93
7	5.22	5.62	0.40		27	6.76	5.92	0.84
8	4.25	4.42	0.17		28	7.60	6.13	1.47
9	4.49	4.44	0.05		29	7.15	6.37	0.78
10	5.20	5.08	0.12		30	4.61	4.77	0.16
11	6.58	6.47	0.11		31	4.97	5.27	0.30
12	4.86	4.63	0.23		32	2.53	2.18	0.35
13	5.01	5.01	00		33	3.86	3.95	0.09
14	5.20	5.10	0.10		34	4.27	4.38	0.11
15	4.92	4.89	0.03		35	4.44	3.88	0.56
16	5.33	5.89	0.56		36	4.44	3.99	0.45
17	5.78	6.33	0.55		37	3.76	3.51	0.25
18	6.23	6.70	0.47		38	3.76	3.64	0.12
19	6.05	6.60	0.55		39	4.04	3.82	0.22
20	5.76	5.79	0.03		40	5.19	4.19	1

$$\mathrm{AE} = \left| logP_{cal.} - logP_{exp.} \right|$$

III-2-3- Discussion of results

Table III-2-41 shows that values of logP for ferrocene derivatives containing various organic functions calculated by our model are in good agreement with experimental values.

Although this model gave reasonably good results, there are deviations between experimental logP and calculated for ferrocene derivatives 21 to29 and 40.

The deviation in logP values for compounds 21 and 22 may be due to the conformational effects which are not taken account in XlogP calculation method.

The values of calculated logP for ferrocene derivatives 23 to 29 have deviation can explained by the fact that these compounds have a complex structure and are bulky, which increase their lipophilicity the deviation in the compound40 can be attributed to the fact that XlogP method does not take in account atom type of $(R)_2N$-NHCOR.

Figure III-2-3 shows the correlation between experimental and calculated logP from equation III-2-6 for 40 ferrocene derivatives, value of R^2 of 0.827 was found this value of R^2 can reach 0.880 if 22, 24 to 28 and40 which required great corrections are ignored, figure III-2-4 shows the correlation between experimental logP and calculated logP from equation III-2-6 for 33 ferrocene derivatives.

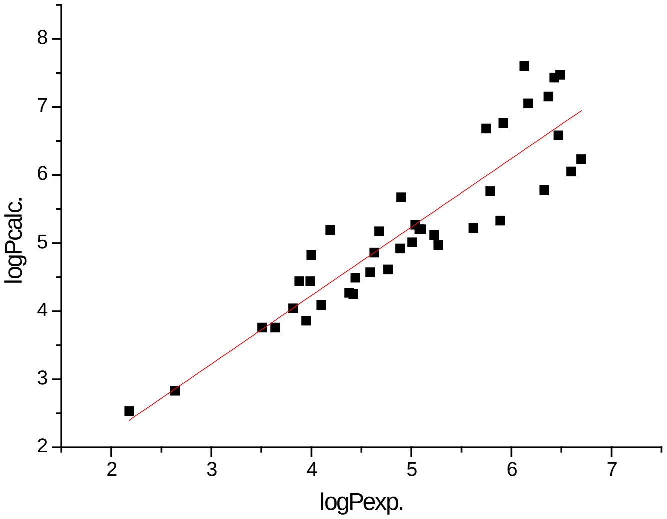


Figure III-2-3: *Correlation between experimental log P and calculated log P from eqn.III-2-6 for 40 ferrocene derivatives*

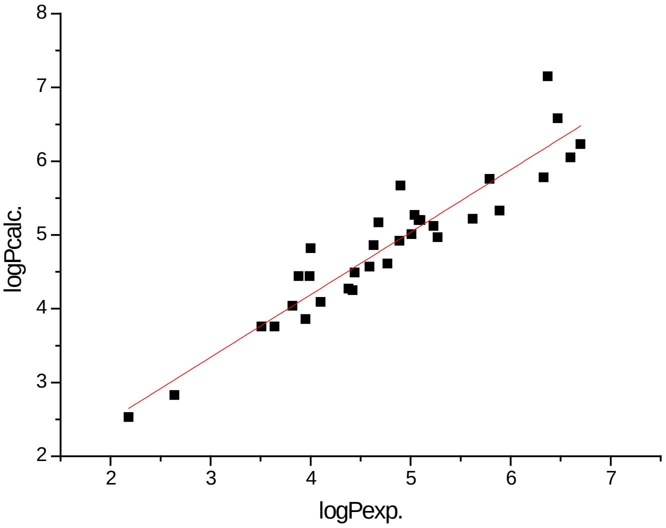


Figure III-2-4: *Correlation between experimental logP and calculated logP from eqn.III-2-6 for 33 ferrocene derivatives*

III-2- 4- Conclusion

In this study we successfully developed theoretical approach 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. As a result of this adaptation, 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 40 substituted ferrocene are in good agreement, this approve 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 complexes.

III-3- AlogP method for octanol-water partition coefficients determination

III-3-1- Introduction

We describe in this section the generation of our modified AlogP method for logP calculation of substituted ferrocene. This calculation is based upon the adaptation of the existing atom-additive AlogP method, which considers the partition of ferrocene derivatives between a water phase and a octanol phase.

III-3- 2- Determination procedure

III-3- 2-1-Adaptation of the AlogP approach

Since the theoretical value of the octanol - water partition coefficient logP of ferrocene itself is not known and is not described in the scientific literature, we consider that the octanol-water partition coefficient logP value of ferrocene, calculated by the AlogP method, is the same as the experimental value of logP for ferrocene, which is equal to 2.66. According to AlogP 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:

$$a_{c_{ar}-c} - a_{c_{ar}-H} = 0.1492 - (-0.3251) = 0.4743 \qquad \text{III} - 3 - 1$$

The contribution of an aromatic carbon atom attached to an atom X (O, N, S, P,…) $a_{c_{ar}-X}$ is greater 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 III – 3 – 2 as follows:

$$a_{c_{ar}-X} - a_{c_{ar}-H} = 0.1539 - (-0.3251) = 0.4790 \qquad \text{III} - 3 - 2$$

To calculate the contribution of a ferrocenyl group attached to a carbon atom or an atom of type X, these values 0.4743 and 0.4790 should be added to a logP value of ferrocene and the contributions of the hydrogen atoms a_{H} *(47)* should be subtracted.

$$a_{Fc} = \log P_{Fc} - n_1(a_H - 0.4743) - n_2(a_H - 0.4790) \qquad \text{III} - 3 - 3$$

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 $0 \leq n_1 + n_2 \leq 10$ the contribution of a ferrocenyl group attached to an atom of type X is calculated from equation III – 3 – 4, n_1 in this case is equal to zero n_2 is equal to1.

$$a_{Fc} = \log P_{Fc} - a_H + 0.4790 \qquad \text{III} - 3 - 4$$

$$2.66 - 0.6301 + 0.4790 = 2.5089$$

This value 2.5089 represent the contribution of the Fc group when attached to an atom of type X.

If a ferrocenyl group is attached to a carbon atom, its contribution is calculated from the same equation III − 3 − 3; with n_2 in this case is equal to zero.

$$a_{Fc} = \log P_{Fc} - a_H + 0.4743 \qquad \text{III} - 3 - 5$$

$$2.66 - 0.6301 + 0.4743 = 2.5042$$

This value 2.5042 represent the contribution of the Fc group when attached to a carbon atom LogP, for any ferrocene derivatives F_C-X', is therefore can be calculated by summing the contributions of a substituent X' atom type to the contribution of a ferrocenyl group as given by the following equation:

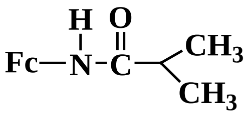
$$\log\mathrm{P} = a_{Fc} + \mathrm{a}_{\mathrm{X}'} \qquad III - 3 - 6$$

$\mathrm{a}_{\mathrm{X}'}$ can be obtained from table II-3-1, F_{C} refers to ferrocenyl group.

III- 3- 2-2- Calculation and validation of the model

Our model for the calculation of logP of ferrocene derivatives is validated using a series of values of $\log P_{exp.}$ of different ferrocene derivatives selected mainly either from scientific literature sources or determined experimentally in laboratory. All the calculation of logP is carried out in three decimals but the final value is rounded to two decimals.

1. N-(ferrocenyl)isobutylamide



$$\mathrm{Fc{-}N(H){-}C({=}O){-}CH(CH_3)_2}$$

(1)

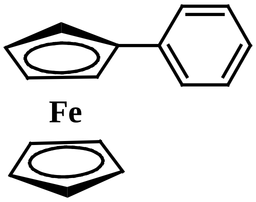
N-(ferrocenyl)isobutylamide

To calculate logP of this ferrocene derivatives (1) with saturated aliphatic hydrocarbon chains carrying amide group, according to AlogP method we can divide the molecule into two carbon atoms C, type (1), one carbon atom C type (3), one carbon atom C type (40), one nitrogen atom N type (72), one oxygen atom O type (58), one hydrogen atom, H type (51), six hydrogen atoms, H type (46), one hydrogen atom, H type (50) and a ferrocenyl group then we attribute the adequate contribution for these atom types from table II-3, summing the atom type contributions with that of the ferrocenyl type we obtain $\log P_{cal.}$ value.

Table III-3-1: *Calculation of logP for compound (1)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (1)	2	-1.5603	-3.1206	
a_C (3)	1	-0.6681	-0.6681	
a_C (40)	1	-0.1002	-0.1002	
a_N (72)	1	-0.5113	-0.5113	
a_O (58)	1	-0.0233	-0.0233	
a_H (51)	1	0.5234	0.5234	
a_H (46)	6	0.7341	4. 4046	
a_H (50)	1	-0.1036	-0.1036	
$logP_{cal.}$			2.90	$\Delta \log P = 0.26$
$logP_{exp.}$[141] [142]			2.64	

2. Phenylferrocene



(2)

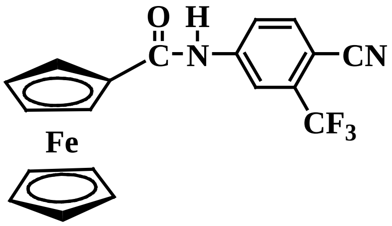
Phenylferrocene

The value of logP for this ferrocene derivative (2) can be estimated according to modified AlogP by summing the contribution of one carbon atom C type (24), one carbon atom, C type (25), five hydrogen atoms, H type (47) and the contribution of ferrocenyl group, this gives a value of 4.18 for logP table III-3-2.

Table III-3-2: *Calculation of logP for compound (2)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	5	-0.3251	-1.6255	
a_C (25)	1	0.1492	0.1492	
a_H (47)	5	0.6301	3.1505	
$logP_{cal.}$			4.18	ΔlogP = 0.41
$logP_{exp.}$[143]			4.59	

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



(3)

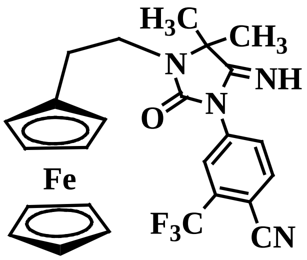
N-[4-cyano-3-trifluoromethylphenyl]- ferrocenecarboxamide

logP of This ferrocene derivatives which containing 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, nitrogens, oxygens, fluoride and hydrogens), these contribution can be obtained from table II-3.

Table III-3-3: *Calculation of logP for compound (3)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_N (74)	1	0.1349	0.1349	
a_F (83)	3	0.1029	0.3087	
a_C (13)	1	0.7894	0.7894	
a_C (24)	3	-0.3251	-0.9753	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_C (40)	2	-0.1002	-0.2004	
a_N (72)	1	-0.5113	-0.5113	
a_O (58)	1	-0.0233	-0.0233	
a_H (50)	1	-0.1036	-0.1036	
a_H (47)	3	0.6301	1.8903	
$logP_{cal.}$			4.26	ΔlogP = 0.16
$logP_{exp.}$[141]			4.10	

4. 4-(4’,4’-dimethyl-3’-ferrocenylethyl-5’-imino-2’-oxo-1’-imidazolidinyl)-2-Trifluoromethylbenzonitrile



(4)

4-(4',4'-dimethyl-3'-ferrocenylethyl-5'-imino-2'-oxo-1'- imidazolidinyl)-2-trifluoromethylbenzonitrile

In this molecule ferrocene is linked to a direct heterocyclic ring via two methylene groups, logP is calculated by the same manner as in the above example compound (3),

This molecule contain a nitrogen atom type R(C=N-H)-N which can not be found in the AlogP approach, this let encourage us to propose the replace of this type of atom by type (72) in table II-3. The reason behind this replacement is as follows:

- Generally oxygen and nitrogen decreases the hydrophobicity.
- Both oxygen and nitrogen have the same hybridization state.
- Establishing from the equation $III-3-7$ which relating the partition coefficient to the strength of hydrogen bond, where this strength depends first on the nature of the hydrogen bond acceptor atom, due to oxygen and nitrogen have nearly strength of hydrogen bond [153] and according to the following equation $III-3-7$ we can replace it.

$$logP = 0.24 + 0.0367\, V_X - 0.04\mu^2 - 3.00 \sum \beta_2^H \qquad III-3-7$$

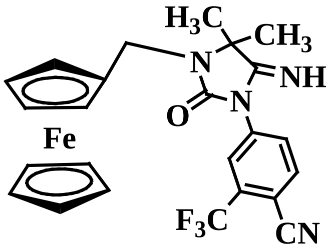
Which V_X represent the molecular volume, μ represent the molecule dipole moment, β_2^H the parameter of strength of hydrogen bond.

Table III-3-4: *Calculation of logP for compound (4)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_N (74)	1	0.1349	0.1349	
a_N (68)	1	0.0132	0.0132	
a_N (71)	1	0.1087	0.1087	
a_C (6)	1	-1.2486	-1.2486	
a_C (2)	1	-1.0120	-1.0120	
a_C (1)	2	-1.5603	-3.1206	
a_C (41)	1	0.4182	0.4182	
a_C (40)	2	-0.1002	-0.2004	
a_F (83)	3	0.1029	0.3087	
a_C (13)	1	0.7894	0.7894	
a_C (24)	3	-0.3251	-0.9753	
a_C (25)	2	0.1492	0.2984	
a_N (72)	1	-0.5113	-0.5113	
a_C (26)	1	0.1539	0.1539	
a_H (52)	8	0.6666	5.3328	
a_H (50)	1	-0.1036	-0.1036	
a_O (58)	1	-0.0233	-0.0233	
a_C (11)	1	-0.2849	-0.2849	
a_H (47)	5	0.6301	3.1505	
$logP_{cal.}$			5.73	$\Delta \text{logP} = 0.69$
$logP_{exp.}$[141]			5.04	

The difference between the experimental logP value and calculated value is equal to 0.69, this may be due to atom type of R(C=N-H)-N which have not the contribution exact in AlogP calculation.

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



(5)

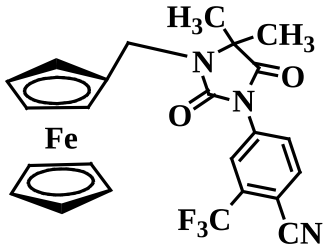
4-(4’,4’-Dimethyl-3’-ferrocenylmethyl-5’-imino-2’-oxo-1’-imidazolidinyl)-2- trifluoromethyl-benzonitrile

The summing of the contribution of atoms types of all groups in this molecule corresponding to the existing of a ferrocenyl, methylene, heterocyclic ring, phenyl, nitrile and trifluoromethyl in the molecule gives the value of 5.41for logP, as summarized in table III-3-5.

Table III-3-5: *Calculation of logP for compound (5)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_N (74)	1	0.1349	0.1349	
a_N (68)	1	0.0132	0.0132	
a_N (71)	1	0.1087	0.1087	
a_C (6)	1	-1.2486	-1.2486	
a_C (1)	2	-1.5603	-3.1206	
a_C (41)	1	0.4182	0.4182	
a_C (40)	2	-0.1002	-0.2004	
a_F (83)	3	0.1029	0.3087	
a_C (13)	1	0.7894	0.7894	
a_C (24)	3	-0.3251	-0.9753	
a_C (25)	2	0.1492	0.2984	
a_N (72)	1	-0.5113	-0.5113	
a_C (26)	1	0.1539	0.1539	
a_H (52)	6	0.6666	3.9996	
a_H (50)	1	-0.1036	-0.1036	
a_O (58)	1	-0.0233	-0.0233	
a_C (11)	1	-0.2849	-0.2849	
a_H (47)	5	0.6301	3.1505	
$logP_{cal.}$			5.41	ΔlogP = 0.73
$logP_{exp.}$[141]			4.68	

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



(6)

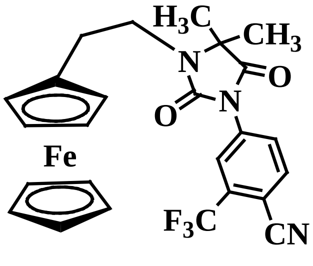
4-(4',4'-Dimethyl-2',5'-dioxo-3'-ferrocenylmethyl-1'-imidazolidinyl)-2-trifluoromethyl-benzonitrile

For this ferrocene derivative logP is calculated by summing the different contribution of all atom types in the molecule which can be obtained from table II-3, the needed atom types for calculation are summarized in table III-3-6.

Table III-3-6: *Calculation of logP for compound (6)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_N (74)	1	0.1349	0.1349	
a_N (68)	1	0.0132	0.0132	
a_C (6)	1	-1.2486	-1.2486	
a_C (1)	2	-1.5603	-3.1206	
a_C (41)	1	0.4182	0.4182	
a_C (40)	2	-0.1002	-0.2004	
a_F (83)	3	0.1029	0.3087	
a_C (13)	1	0.7894	0.7894	
a_C (24)	3	-0.3251	-0.9753	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_H (52)	6	0.6666	3.9996	
a_N (72)	1	-0.5113	-0.5113	
a_O (58)	2	-0.0233	-0.0466	
a_C (11)	1	-0.2849	-0.2849	
a_H (47)	5	0.6301	3.1505	
$logP_{cal.}$			5.38	$\Delta \log P = 0.15$
$logP_{exp.}$[141]			5.23	

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



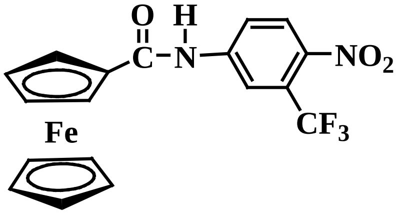
(7)

4-(4’,4’-dimethyl-2’,5’-dioxo-3’-ferrocenylethyl-1’-imidazolidinyl)-2-trifluoromethyl-benzonitrile logP for this type of compound is calculated in the same manner as described for the previous of compound 6.

Table III-3-7: *Calculation of logP for compound (7)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_N (74)	1	0.1349	0.1349	
a_N (68)	1	0.0132	0.0132	
a_C (6)	1	-1.2486	-1.2486	
a_C (1)	2	-1.5603	-3.1206	
a_C (2)	1	-1.0120	-1.0120	
a_C (41)	1	0.4182	0.4182	
a_C (40)	2	-0.1002	-0.2004	
a_F (83)	3	0.1029	0.3087	
a_C (13)	1	0.7894	0.7894	
a_C (24)	3	-0.3251	-0.9753	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_H (52)	8	0.6666	5.3328	
a_N (72)	1	-0.5113	-0.5113	
a_O (58)	2	-0.0233	-0.0466	
a_C (11)	1	-0.2849	-0.2849	
a_H (47)	5	0.6301	3.1505	
$logP_{cal.}$			5.70	$\Delta\text{logP} = 0.08$
$logP_{exp.}$[141]			5.62	

8. N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide



(8)

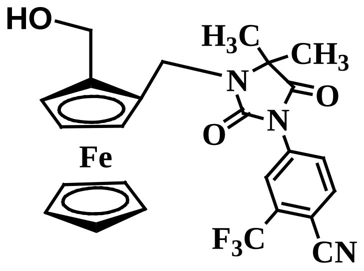
N-[4-nitro-3-trifluoromethyl-phenyl]-ferrocenecarboxamide

This compound describe ferrocenes with a basic fragment linked to two aromatic rings, logP is obtained by summing the atom types of each group in the molecule, ferrocenyl, amide, phenyl with three substituents, nitro and trifluoromethyl, resulting the value of 4.28 for logP.

Table III-3-8: *Calculation of* $logP$ *for compound (8)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_N (76)	1	-2.0585	-2.0585	
a_O (61)	2	1.0520	2.104	
a_F (83)	3	0.1029	0.3087	
a_C (13)	1	0.7894	0.7894	
a_C (24)	3	-0.3251	-0.9753	
a_C (25)	1	0.1492	0.1492	
a_C (26)	2	0.1539	0.3078	
a_C (40)	1	-0.1002	-0.1002	
a_N (72)	1	-0.5113	-0.5113	
a_O (58)	1	-0.0233	-0.0233	
a_H (50)	1	-0.1036	-0.1036	
a_H (47)	3	0.6301	1.8903	
$logP_{cal.}$			4.28	$\Delta \mathrm{logP} = 0.14$
$logP_{exp.}$[141]			4.42	

9. 4-[4’,4’-dimethyl-2’,5’-dioxo-3’-ortho-hydroxymethyl-ferrocenylmethyl-1’-imidazolidinyl]-2-trifluoromethyl-benzonitrile



(9)

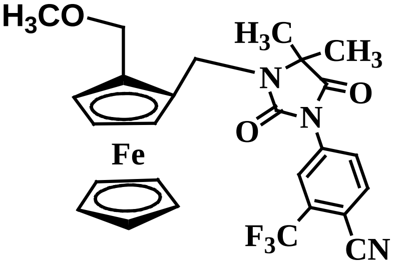
4-[4’,4’-dimethyl-2’,5’-dioxo-3’-ortho-hydroxymethyl-ferrocenylmethyl 1’- imidazolidinyl]-2-trifluoromethyl-benzonitrile

logP is calculated for this ferrocene derivative by the same manner as stated before.

Table III-3-9: *Calculation of logP for compound (9)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.3484	2.3484	
a_N (74)	1	0.1349	0.1349	
a_N (68)	1	0.0132	0.0132	
a_C (6)	2	-1.2486	-2.4972	
a_C (1)	2	-1.5603	-3.1206	
a_C (41)	1	0.4182	0.4182	
a_C (40)	2	-0.1002	-0.2004	
a_F (83)	3	0.1029	0.3087	
a_C (13)	1	0.7894	0.7894	
a_C (24)	3	-0.3251	-0.9753	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_H (50)	1	-0.1036	-0.1036	
a_H (52)	6	0.6666	3.9996	
a_N (72)	1	-0.5113	-0.5113	
a_O (56)	1	-0.3567	-0.3567	
a_O (58)	2	-0.0233	-0.0466	
a_C (11)	1	-0.2849	-0.2849	
a_H (47)	7	0.6301	4.4107	
$logP_{cal.}$			4.78	$\Delta \text{logP} = 0.34$
$logP_{exp.}$[141]			4.44	

10. 4-[4’,4’-dimethyl-2’,5’-dioxo-1’-imidazolidinyl-(3’-ortho-methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile



(10)

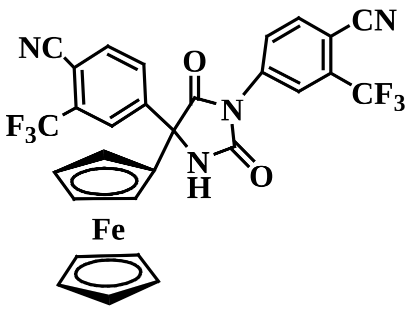
4-[4’,4’-dimethyl-2’,5’-dioxo-1’-imidazolidinyl-(3’-ortho- methoxymethyl-ferrocenylmethyl)]-2-trifluoromethyl-benzonitrile

This compound is an example of ferrocene with electronic effect logP is calculated by summing the different atom types that forming the molecule in a manner that does not differ from the above calculation.

Table III-3-10: *Calculation of logP for compound (10)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.3484	2.3484	
a_N (74)	1	0.1349	0.1349	
a_N (68)	1	0.0132	0.0132	
a_C (5)	1	-1.7880	-1.7880	
a_C (6)	2	-1.2486	-2.4972	
a_C (1)	2	-1.5603	-3.1206	
a_C (41)	1	0.4182	0.4182	
a_C (40)	2	-0.1002	-0.2004	
a_F (83)	3	0.1029	0.3087	
a_C (13)	1	0.7894	0.7894	
a_C (24)	3	-0.3251	-0.9753	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_H (52)	6	0.6666	3.9996	
a_N (72)	1	-0.5113	-0.5113	
a_O (59)	1	-0.1541	-0.1541	
a_O (58)	2	-0.0233	-0.0466	
a_C (11)	1	-0.2849	-0.2849	
a_H (47)	10	0.6301	6.3010	
$logP_{cal.}$			5.19	$\Delta\text{logP} = 0.11$
$logP_{exp.}$[141]			5.08	

11. 4’-ferrocenyl-1’,4’-[bis-(2-trifluoromethyl-1-cyano-phenyl)] -2’,5’-imidazolidinedione



(11)

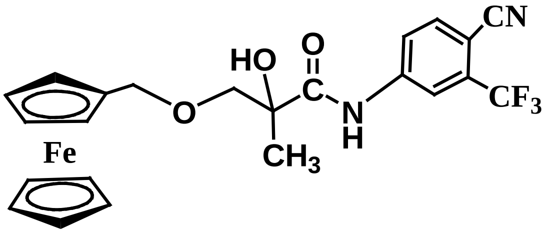
4’-ferrocenyl-1’,4’-[*bis*-(2-trifluoromethyl-1-cyano-phenyl)]
-2’,5’-imidazolidinedione

For these type of molecules the method of calculating of logP is illustrated in table III-3-11

Table III-3-11: *Calculation of logP for compound (11)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_N (74)	2	0.1349	0.2698	
a_N (67)	1	-0.3168	-0.3168	
a_C (41)	1	0.4182	0.4182	
a_C (40)	3	-0.1002	-0.3006	
a_F (83)	6	0.1029	0.6174	
a_C (13)	2	0.7894	1.5788	
a_C (24)	6	-0.3251	-1.9506	
a_C (25)	5	0.1492	0.746	
a_C (26)	1	0.1539	0.1539	
a_H (50)	1	-0.1036	-0.1036	
a_N (72)	1	-0.5113	-0.5113	
a_O (58)	2	-0.0233	-0.0466	
a_C (11)	1	-0.2849	-0.2849	
a_H (47)	6	0.6301	3.7805	
$logP_{cal.}$			6.55	ΔlogP = 0.08
$logP_{exp.}$[141]			6.47	

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



(12)

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

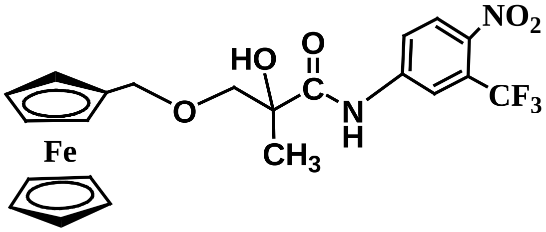
For the above compound logP is calculated as indicated in table III-3-12.

Table III-3-12: *Calculation method of logP for compound (12)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (1)	1	-1.5603	-1.5603	
a_C (6)	2	-1.2486	-2.4972	
a_C (26)	1	0.1539	0.1539	
a_C (24)	3	-0.3251	-0.9753	
a_C (25)	2	0.1492	0.2984	
a_C (13)	1	0.7894	0.7894	
a_F (83)	3	0.1029	0.3087	
a_O (59)	1	-0.1541	-0.1541	
a_O (58)	1	-0.0233	-0.0233	
a_O (56)	1	-0.3567	-0.3567	
a_C (11)	1	-0.2849	-0.2849	
a_C (40)	2	-0.1002	-0.2004	
a_N (72)	1	-0.5113	-0.5113	
a_N (74)	1	0.1349	0.1349	
a_H (52)	3	0.6666	1.9998	
a_H (47)	7	0.6301	4.4107	
a_H (50)	2	-0.1036	-0.2072	
$logP_{cal.}$3.83			3.83	$\Delta \log P = 0.80$
$logP_{exp.}$[141][142]			4.63	

The difference between the experimental and calculated logP values is equal to 0.80, this underestimation may be due to several factors, among which is the two intermolecular hydrogen bond.

13. 3-ferrocenylmethoxy-2-hydroxy-2- methyl-N-(4-nitro-3-trifluoromethylphenyl)-propanamide



(13)

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

Propanamide

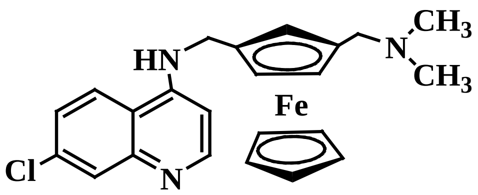
Details of calculation of logP of this ferrocene derivative are illustrated in table III-3-13.

Table III-3-13: *Calculation of logP for compound (13)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (1)	1	-1.5603	-1.5603	
a_C (6)	2	-1.2486	-2.4972	
a_C (26)	2	0.1539	0.3078	
a_C (24)	3	-0.3251	-0.9753	
a_C (25)	1	0.1492	0.1492	
a_C (13)	1	0.7894	0.7894	
a_F (83)	3	0.1029	0.3087	
a_O (59)	1	-0.1541	-0.1541	
a_O (58)	1	-0.0233	-0.0233	
a_O (56)	1	-0.3567	-0.3567	
a_C (11)	1	-0.2849	-0.2849	
a_C (40)	1	-0.1002	-0.1002	
a_N (72)	1	-0.5113	-0.5113	
a_N (76)	1	-2.0585	-2.0585	
a_O (61)	2	1.0520	2.104	
a_H (52)	3	0.6666	1.9998	
a_H (47)	7	0.6301	4.4107	
a_H (50)	2	-0.1036	-0.2072	
$logP_{cal.}$			3.84	ΔlogP = 1.17
$logP_{exp.}$[141][142]			5.01	

The difference between the experimental and calculated logP values is equal to 1.17, this difference may dueattributed to the same factors as in compound 12.

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



(14)

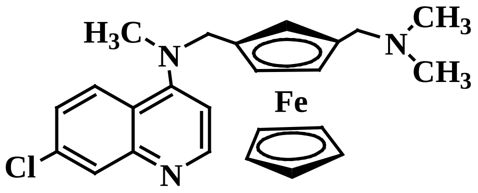
N-(7-Chloro-quinolin-4-yl)-(2- dimethylaminomethylferrocenyl)-amine

For these type of compounds calculation of logP is illustrated in the table III-3-14.

Table III-3-14: *Calculation of logP for compound (14)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.3484	2.3484	
a_C (24)	4	-0.3251	-1.3004	
a_C (26)	2	0.1539	0.3078	
a_C (25)	1	0.1492	0.1492	
a_C (28)	1	0.2361	0.2361	
a_C (27)	1	0.0005	0.0005	
a_N (75)	1	-0.1624	-0.1624	
a_C (6)	2	-1.2486	-2.4972	
a_N (68)	1	0.0132	0.0132	
a_C (5)	2	-1.788	-3.576	
a_H (50)	1	-0.1036	-0.1036	
a_N (70)	1	-0. 0389	-0.0389	
a_{Cl} (89)	1	0.8155	0.8155	
a_H (48)	1	0.5180	0.5180	
a_H (47)	14	0.6301	8.8214	
$logP_{cal.}$			5.53	$\Delta \mathrm{logP} = 0.43$
$logP_{exp.}$[145]			5.10	

15. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- methylamine



(15)

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

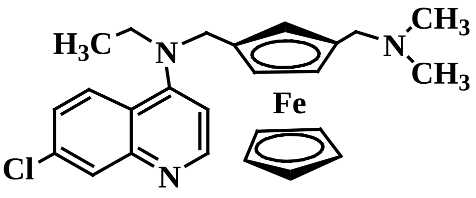
For these type of compounds logP is calculated by the same manner as in the previous example compound (14).

Table III-3-15: *Calculation of logP for compound (15)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.3484	2.3484	
a_C (24)	4	-0.3251	-1.3004	
a_C (26)	2	0.1539	0.3078	
a_C (25)	1	0.1492	0.1492	
a_C (28)	1	0.2361	0.2361	
a_C (27)	1	0.0005	0.0005	
a_N (75)	1	-0.1624	-0.1624	
a_C (6)	2	-1.2486	-2.4972	
a_N (68)	1	0.0132	0.0132	
a_C (5)	3	-1.788	-5.364	
a_N (71)	1	0.1087	0.1087	
a_{Cl} (89)	1	0.8155	0.8155	
a_H (48)	1	0.5180	0.5180	
a_H (47)	17	0.6301	10.7117	
$logP_{cal.}$			5.88	$\Delta \log P = 0.99$
$logP_{exp.}$[145]			4.89	

The difference between the experimental and calculated logP values is equal to 0.99, this rather great difference may be to the larger structure of this compound.

16. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-ethylamine



(16)

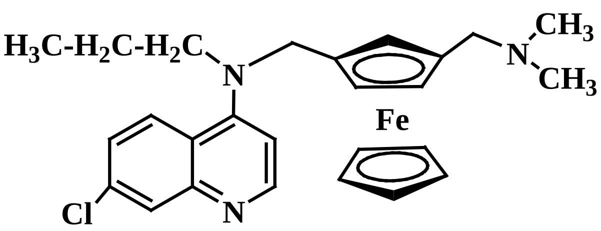
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-ethylamine

For this compound logP is calculated as follows:

Table III-3-16: *Calculation of logP for compound (16)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.3484	2.3484	
a_C (24)	4	-0.3251	-1.3004	
a_C (26)	2	0.1539	0.3078	
a_C (25)	1	0.1492	0.1492	
a_C (28)	1	0.2361	0.2361	
a_C (27)	1	0.0005	0.0005	
a_N (75)	1	-0.1624	-0.1624	
a_C (6)	3	-1.2486	-3.7458	
a_C (14)	1	-1.5603	-1.5603	
a_N (68)	1	0.0132	0.0132	
a_C (5)	2	-1.788	-3.576	
a_N (71)	1	0.1087	0.1087	
a_{Cl} (89)	1	0.8155	0.8155	
a_H (48)	1	0.5180	0.5180	
a_H (52)	3	0.6666	1.9998	
a_H (47)	16	0.6301	10.0816	
$logP_{cal.}$			6.23	$\Delta\text{logP} = 0.34$
$logP_{exp.}$[145]			5.89	

17. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-propylamine



(17)

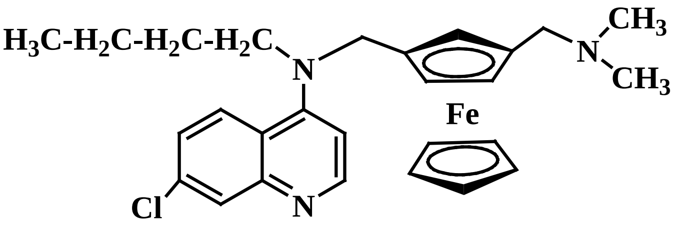
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)-propylamine

Table III-3-17 shows the atom types that contributed for the calculation of logP of this derivatives to gather with the $\text{logP}_{\text{cal.}}$ and $\text{logP}_{\text{exp.}}$.

Table III-3-17: *Calculation of logP for compound (17)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.3484	2.3484	
a_C (24)	4	-0.3251	-1.3004	
a_C (26)	2	0.1539	0.3078	
a_C (25)	1	0.1492	0.1492	
a_C (28)	1	0.2361	0.2361	
a_C (27)	1	0.0005	0.0005	
a_N (75)	1	-0.1624	-0.1624	
a_C (6)	3	-1.2486	-3.7458	
a_C (1)	1	-1.5603	-1.5603	
a_C (2)	1	-1.012	-1.012	
a_N (68)	1	0.0132	0.0132	
a_C (5)	2	-1.788	-3.576	
a_N (71)	1	0.1087	0.1087	
a_{Cl} (89)	1	0.8155	0.8155	
a_H (48)	1	0.5180	0.5180	
a_H (52)	2	0.6666	1.3332	
a_H (46)	3	0.7341	2.2023	
a_H (47)	16	0.6301	10.0816	
$logP_{cal.}$			6.76	ΔlogP = 0.43
$logP_{exp.}$[145]			6.33	

18. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- butylamine



(18)

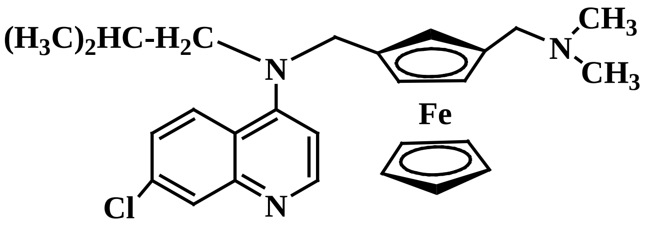
(7-Chloro-quinolin-4-yl)-(2-dimethylaminomethyl ferrocenyl)-butylamine

The contribution of atom types that can participate for the calculation of logP for this molecule are summarized in table III-3-18, the calculation does not differ from that of others molecules.

Table III-3-18: *Calculation of logP for compound (18)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.3484	2.3484	
a_C (24)	4	-0.3251	-1.3004	
a_C (26)	2	0.1539	0.3078	
a_C (25)	1	0.1492	0.1492	
a_C (28)	1	0.2361	0.2361	
a_C (27)	1	0.0005	0.0005	
a_N (75)	1	-0.1624	-0.1624	
a_C (6)	3	-1.2486	-3.7458	
a_C (1)	1	-1.5603	-1.5603	
a_C (2)	2	-1.012	-2.024	
a_N (68)	1	0.0132	0.0132	
a_C (5)	2	-1.788	-3.576	
a_N (71)	1	0.1087	0.1087	
a_{Cl} (89)	1	0.8155	0.8155	
a_H (48)	1	0.5180	0.5180	
a_H (52)	2	0.6666	1.3332	
a_H (46)	5	0.7341	3.6705	
a_H (47)	16	0.6301	10.0816	
$logP_{cal.}$			7.21	ΔlogP = 0.51
$logP_{exp.}$[145]			6.70	

19. (7-Chloro-quinolin-4-yl)-(2-dimethylaminomethylferrocenyl)- isobutylamine



(19)

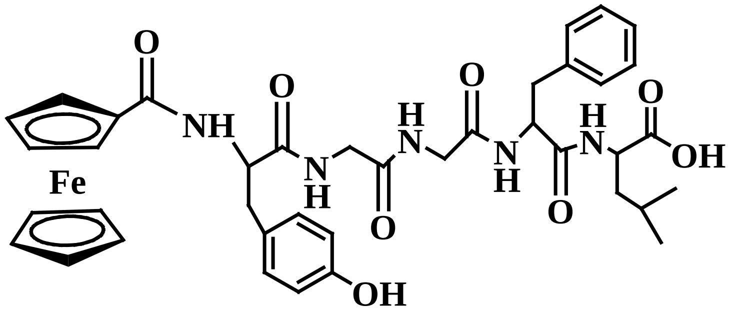
(7-Chloro-quinolin-4-yl)- (2-dimethylaminomethyl ferrocenyl)- isobutylamine

Table III-3-19 shows the summering the contribution of all atom types that gives $logP_{cal.}$

Table III-3-19: *Calculation of logP for compound (19)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.3484	2.3484	
a_C (24)	4	-0.3251	-1.3004	
a_C (26)	2	0.1539	0.3078	
a_C (25)	1	0.1492	0.1492	
a_C (28)	1	0.2361	0.2361	
a_C (27)	1	0.0005	0.0005	
a_N (75)	1	-0.1624	-0.1624	
a_C (6)	3	-1.2486	-3.7458	
a_C (1)	2	-1.5603	-3.1206	
a_C (3)	1	-0.6681	-0.6681	
a_N (68)	1	0.0132	0.0132	
a_C (5)	2	-1.788	-3.576	
a_N (71)	1	0.1087	0.1087	
a_{Cl} (89)	1	0.8155	0.8155	
a_H (48)	1	0.5180	0.5180	
a_H (52)	1	0.6666	0.6666	
a_H (46)	6	0.7341	4.4046	
a_H (47)	16	0.6301	10.0816	
$logP_{cal.}$			7.08	$\Delta \log P = 0.48$
$logP_{exp.}$[145]			6.60	

20. Fc-CO-Enk-OH



(20)

Fc-CO-Enk-OH

Enkephalin : 2-amino-3- (4- hydroxyphenyl)propanoyl]amino]acetyl] amino]acetyl]amino]-3-phenylpropanoyl] amino]-4-methylpentanoic acid.

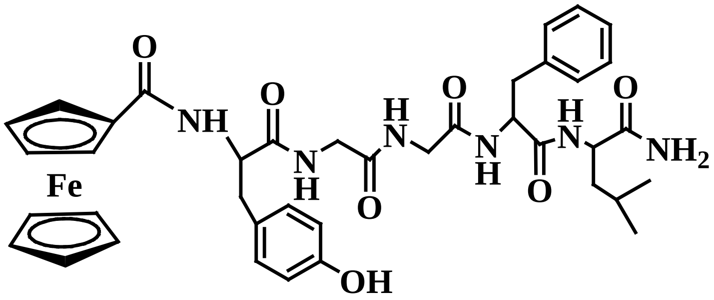
For the above compound with complicated structure which containing enkephalin derivatives logP is calculated as follows:

Table III-3-20: *Calculation of logP for compound (20)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (40)	6	-0.1002	-0.6012	
a_O (58)	6	-0.0233	-0.1398	
a_O (57)	2	-0.0127	-0.0254	
a_N (72)	5	-0.5113	-2.5565	
a_C (8)	3	-0.6805	-2.0415	
a_C (6)	2	-1.2486	-2.4972	
a_C (2)	3	-1.012	-3.036	
a_C (3)	1	-0.6681	-0.6681	
a_C (1)	2	-1.5603	-3.1206	
a_C (24)	9	-0.3251	-2.9259	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_H (50)	7	-0.1036	-0.7252	
a_H (46)	7	0.7341	5.1107	
a_H (52)	6	0.6666	3.9996	
a_H (47)	16	0.6301	10.0816	
$logP_{cal.}$			3.81	$\Delta \log P = 1.98$
$logP_{exp.}$[146]			5.79	

The difference between the experimental logP value and calculated value is equal to 1.98, this underestimation may be due to the existence intramolecular hydrogen bonds which increase the hydrophobicity of this molecule and then the predictive R^2 for peptides compounds using AlogP method before the adaptation was equal to 0.58 this method has problem to calculate the peptides compounds.

21. Fc-CO-Enk-NH_2



(21)

Fc-CO-Enk-NH_2

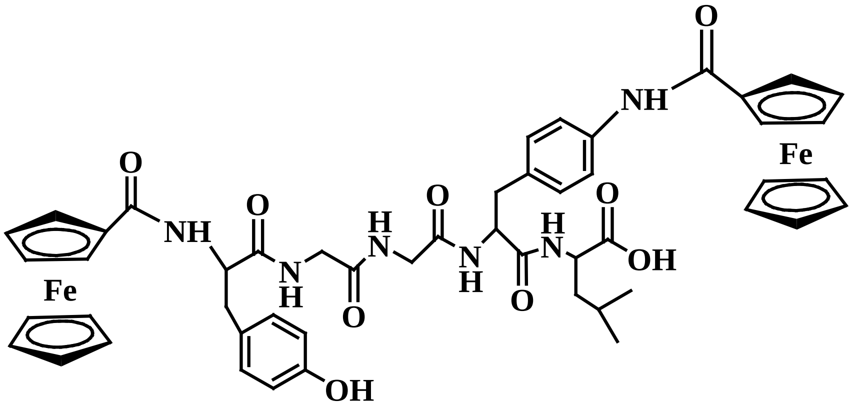
This molecule does not differ a lot from the structure of the previous compound (20) except that is smaller in side, logP for this ferrocene derivatives is calculated based on contribution of atom type from table III-3-21.

Table III-3-21: *Calculation of logP for compound (21)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (40)	6	-0.1002	-0.6012	
a_O (58)	6	-0.0233	-0.1398	
a_O (57)	1	-0.0127	-0.0127	
a_N (72)	6	-0.5113	-3.0678	
a_C (8)	3	-0.6805	-2.0415	
a_C (6)	2	-1.2486	-2.4972	
a_C (2)	3	-1.012	-3.036	
a_C (3)	1	-0.6681	-0.6681	
a_C (1)	2	-1.5603	-3.1206	
a_C (24)	9	-0.3251	-2.9259	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_H (50)	8	-0.1036	-0.8288	
a_H (46)	7	0.7341	5.1107	
a_H (52)	6	0.6666	3.9996	
a_H (47)	16	0.6301	10.0816	
$logP_{cal.}$			3.21	$\Delta \log P = 0.79$
$logP_{exp.}$[146]			4.00	

The deviation between the experimental logP value and calculated value is equal to 0.79, this underestimation may be due to same cause of that of compound(20), the difference only in the number of intramolecular hydrogen bond.

22. Fc-CO-Enk[Phe (NH-CO-Fc)]-OH



(22)

Fc-CO-Enk[Phe (NH-CO-Fc)]-OH

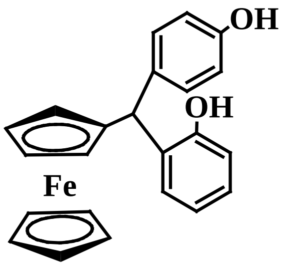
This compound describe basic fragment (amide group) linked to two aromatic rings, these being ferrocenyl and phenyl groups, logP for this molecule is calculated as the follows table III-3-22.

Table III-3-22: *Calculation of logP for compound (22)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	2	2.5042	5.0084	
a_C (40)	7	-0.1002	-0.7014	
a_O (58)	7	-0.0233	-0.1631	
a_O (57)	2	-0.0127	-0.0254	
a_N (72)	6	-0.5113	-3.0678	
a_N (69)	1	-0.3883	-0.3883	
a_C (8)	3	-0.6805	-2.0415	
a_C (6)	2	-1.2486	-2.4972	
a_C (2)	3	-1.012	-3.036	
a_C (3)	1	-0.6681	-0.6681	
a_C (1)	2	-1.5603	-3.1206	
a_C (24)	8	-0.3251	-2.6008	
a_C (25)	2	0.1492	0.2984	
a_C (26)	2	0.1539	0.3078	
a_H (50)	8	-0.1036	-0.8288	
a_H (46)	7	0.7341	5.1107	
a_H (52)	6	0.6666	3.9996	
a_H (47)	15	0.6301	9.4515	
$logP_{cal.}$			5.05	$\Delta \text{logP} = 1.44$
$logP_{exp.}$[146]			6.49	

The difference between the experimental and calculated logP values is equal to 1.44, this underestimation may be due to same cause of that of compound 21.

23. 1-((2-hydroxyphenyl)(4-hydroxyphenyl)methyl) ferrocene



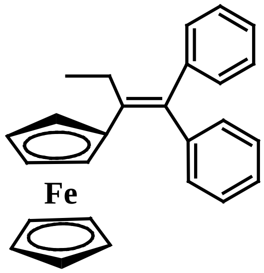
(23)

1-((2-hydroxyphenyl)(4-hydroxyphenyl)methyl) ferrocene logP for this ferrocene with a tertiary carbon is calculated as follows.

Table III-3-23: *Calculation of logP for compound (23)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (3)	1	-0.6681	-0.6681	
a_C (24)	8	-0.3251	-2.6008	
a_C (25)	2	0.1492	0.2984	
a_C (26)	2	0.1539	0.3078	
a_O (58)	2	-0.0127	-0.0254	
a_H (50)	2	-0.1036	-0.2072	
a_H (47)	8	0.6301	5.0408	
a_H (46)	1	0.7341	0.7341	
$logP_{cal.}$			5.38	ΔlogP = 0.48
$logP_{exp.}$[147]			4.90	

24. 1-(1,1-diphenylbut-1-en-2-yl) ferrocene



(24)

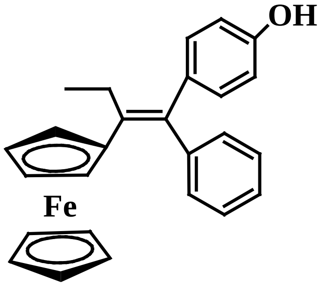
1-(1,1-diphenylbut-1-en-2-yl) ferrocene

logP for this ferrocene derivative is calculated as indicated in table III-3-24**.**

Table III-3-24: *Calculation of logP for compound (24)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (1)	1	-1.5603	-1.5603	
a_C (2)	1	-1.0120	-1.0120	
a_C (17)	2	0.0383	0.0766	
a_C (24)	10	-0.3251	-3.251	
a_C (25)	2	0.1492	0.2984	
a_H (47)	10	0.6301	6.301	
a_H (46)	5	0.7341	3.6705	
$logP_{cal.}$			7.03	ΔlogP = 0.60
$logP_{exp.}$[150]			6.43	

25. 1-(1-(- 4-hydroxy phenyl)-1-phenylbut-1-en-2-yl) ferrocene



(25)

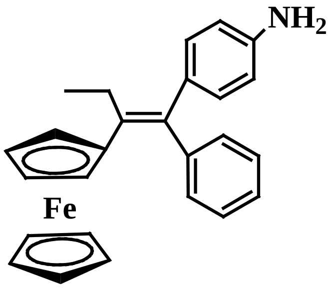
1-(1-(- 4-hydroxy phenyl)-1-phenylbut-1-en-2-yl) ferrocene

Calculation of logP for this molecule is described in table III-3-25.

Table III-3-25: *Calculation of logP for compound (25)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (1)	1	-1.5603	-1.5603	
a_C (2)	1	-1.0120	-1.0120	
a_C (17)	2	0.0383	0.0766	
a_C (24)	9	-0.3251	-2.9259	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_O (57)	1	-0.0127	-0.0127	
a_H (50)	1	-0.1036	-0.1036	
a_H (47)	9	0.6301	5.6709	
a_H (46)	5	0.7341	3.6705	
$logP_{cal.}$			6.76	ΔlogP = 0.59
$logP_{exp.}$[150]			6.17	

26. 1-(1-(- 4-amino phenyl)-1-phenylbut-1-en-2-yl) ferrocene



(26)

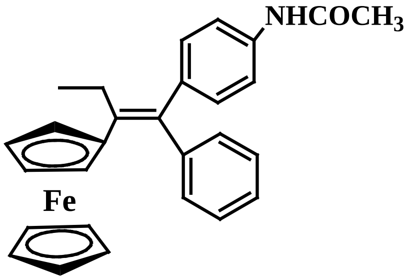
1-(-1-(- 4-amino phenyl)-1-phenylbut-1-en-2-yl) ferrocene

logP for this ferrocene derivative is calculated as follows table III-3-26**.**

Table III-3-26: *Calculation of logP for compound (26)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (1)	1	-1.5603	-1.5603	
a_C (2)	1	-1.0120	-1.0120	
a_C (17)	2	0.0383	0.0766	
a_C (24)	9	-0.3251	-2.9259	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_N (69)	1	-0.3883	-0.3883	
a_H (50)	2	-0.1036	-0.2072	
a_H (47)	9	0.6301	5.6709	
a_H (46)	5	0.7341	3.6705	
$logP_{cal.}$			6.28	ΔlogP = 0.53
$logP_{exp.}$[150]			5.75	

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



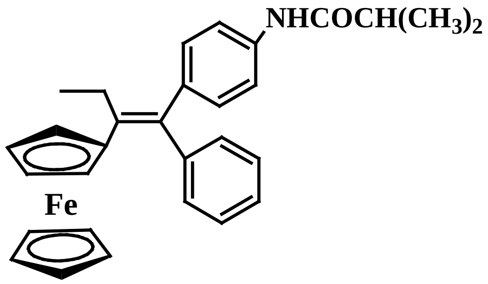
(27)

N-(4-(-2-(ferrocenyl)-1- phenylbut-1- enyl)phenyl)acetamide logP for this ferrocene with two bulky carbons can be calculated as explained in table III-3-27.

Table III-3-27: *Calculation of logP for compound (27)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (1)	2	-1.5603	-3.1206	
a_C (2)	1	-1.0120	-1.0120	
a_C (17)	2	0.0383	0.0766	
a_C (24)	9	-0.3251	-2.9259	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_O (58)	1	-0.0233	-0.0233	
a_C (40)	1	-0.1002	-0.1002	
a_N (72)	1	-0.5113	-0.5113	
a_H (51)	3	0.5234	1.5702	
a_H (50)	1	-0.1036	-0.1036	
a_H (47)	9	0.6301	5.6709	
a_H (46)	5	0.7341	3.6705	
$logP_{cal.}$			6.15	ΔlogP = 0.23
$logP_{exp.}$[150]			5.92	

28. N-(4-(-2-(ferrocenyl)-1- phenylbut-1- enyl)phenyl)isobutyramide



(28)

N-(4-(-2-(ferrocenyl)-1- phenylbut-1- enyl)phenyl)isobutyramide

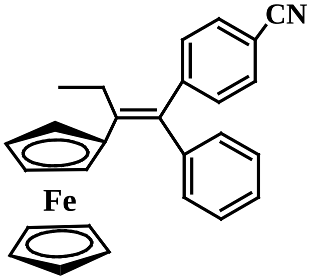
Details of calculation of logP of this molecule are summarized in table III-3-28**.**

Table III-3-28: *Calculation of logP for compound (28)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (1)	3	-1.5603	-4.6809	
a_C (2)	1	-1.0120	-1.0120	
a_C (17)	2	0.0383	0.0766	
a_C (24)	9	-0.3251	-2.9259	
a_C (25)	2	0.1492	0.2984	
a_C (26)	1	0.1539	0.1539	
a_N (72)	1	-0.5113	-0.5113	
a_C (3)	1	-0.6681	-0.6681	
a_C (40)	1	-0.1002	-0.1002	
a_O (58)	1	-0.0233	-0.0233	
a_H (50)	1	-0.1036	-0.1036	
a_H (47)	9	0.6301	5.6709	
a_H (51)	1	0.5234	0.5234	
a_H (46)	11	0.7341	8.0751	
$logP_{cal.}$			7.28	$\Delta \text{logP} = 1.15$
$logP_{exp.}$[150]			6.13	

The difference between the experimental and calculated logP values is equal to 1.15, this difference may be due to this compound was bulky.

29. 4-(-2-(ferrocenyl)-1- phenylbut-1- enyl)benzonitrile



(29)

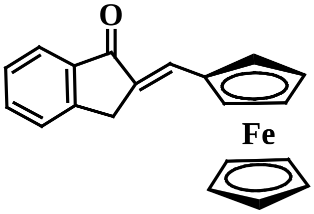
4-(-2-(ferrocenyl)-1- phenylbut-1- enyl) benzonitrile

logP for this ferrocene derivative is calculated as described in table III-3-29**.**

Table III-3-29: *Calculation of logP for compound (29)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (1)	1	-1.5603	-1.5603	
a_C (2)	1	-1.0120	-1.0120	
a_C (17)	2	0.0383	0.0766	
a_C (24)	9	-0.3251	-2.9259	
a_C (25)	3	0.1492	0.4476	
a_C (40)	1	-0.1002	-0.1002	
a_N (74)	1	0.1349	0.1349	
a_H (47)	9	0.6301	5.6709	
a_H (46)	5	0.7341	3.6705	
$logP_{cal.}$			6.91	ΔlogP = 0.54
$logP_{exp.}$[150]			6.37	

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



(30)

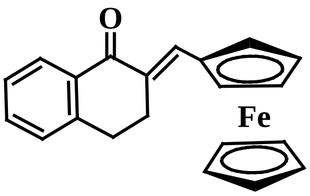
(E)-2-ferrocenylmethylene -2,3-dihydroinden-1-one

logP for this ferrocene derivatives is calculated as indicated in table III-3-30.

Table III-3-31: *Calculation of logP for compound (30)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	4	-0.3251	-1.3004	
a_C (25)	2	0.1492	0.2984	
a_C (2)	1	-1.0120	-1.0120	
a_C (39)	1	-0.0909	-0.0 909	
a_C (16)	1	-0.3962	-0.3962	
a_C (17)	1	0.0383	0.0383	
a_O (58)	1	-0.0233	-0.0233	
a_H (46)	2	0.7341	1.4682	
a_H (47)	5	0.6301	3.1505	
$logP_{cal.}$			4.64	ΔlogP = 0.13
$logP_{exp.}$[151]			4.77	

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



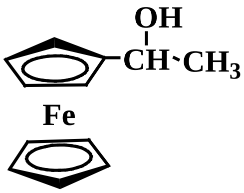
(31)

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

Table III-3-31: *Calculation of logP for compound (31)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	4	-0.3251	-1.3004	
a_C (25)	2	0.1492	0.2984	
a_C (2)	2	-1.0120	-2.024	
a_C (39)	1	-0.0909	-0.0 909	
a_C (16)	1	-0.3962	-0.3962	
a_C (17)	1	0.0383	0.0383	
a_O (58)	1	-0.0233	-0.0233	
a_H (46)	4	0.7341	2.9364	
a_H (47)	5	0.6301	3.1505	
$logP_{cal.}$			5.09	ΔlogP = 0.18
$logP_{exp.}$[151]			5.27	

32. 1-ferrocenylethanol



(32)

1-ferrocenylethanol

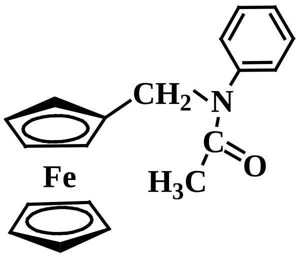
logP for this ferrocene containing alcohol function is calculated according to contribution regrouped in table III-3-32.the simple structure of this derivatives and its small size lead to a slight difference between experimental and calculated logP values

.

Table III-3-32: *Calculation of logP for compound (32)*

tom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (1)	1	-1.5603	-1.5603	
a_C (8)	1	-0.6805	-0.6805	
a_O (56)	1	-0.3567	-0.3567	
a_H (50)	1	- 0.1036	- 0.1036	
a_H (47)	1	0.6301	0.6301	
a_H (51)	3	0.5234	1.5702	
$logP_{cal.}$			2.00	ΔlogP = 0.18
$logP_{exp.}$			2.18	

33. N-ferrocenymethyl-N-phenylacetamide



(33)

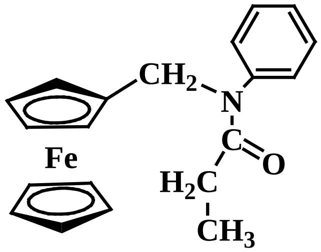
N-ferrocenymethyl-N-phenylacetamide

logP for this ferrocene containing amide function is calculated as illustrated in table III-3-33.

Table III-3-33: *Calculation of logP for compound (33)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	5	-0.3251	-1.6255	
a_C (26)	1	0.1539	0.1539	
a_N (74)	1	-0.5113	-0.5113	
a_C (6)	1	-1.2486	-1.2486	
a_C (1)	1	-1.5603	-1.5603	
a_C (40)	1	-0.1002	-0.1002	
a_O (58)	1	-0.0233	-0.0233	
a_H (51)	3	0.5234	1.5702	
a_H (47)	7	0.6301	4.4107	
$logP_{cal.}$			3.57	ΔlogP = 0.38
$logP_{exp.}$			3.95	

34. N-ferrocenymethyl-N-phenylpropionamide



(34)

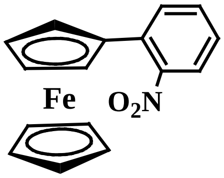
N-ferrocenymethyl-N-phenylpropionamide

logP for this ferrocene derivatives is calculated as explained in table III-3-34.

Table III-3-34: *Calculation of logP for compound (34)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	5	-0.3251	-1.6255	
a_C (26)	1	0.1539	0.1539	
a_N (74)	1	-0.5113	-0.5113	
a_C (6)	1	-1.2486	-1.2486	
a_C (1)	1	-1.5603	-1.5603	
a_C (40)	1	-0.1002	-0.1002	
a_O (58)	1	-0.0233	-0.0233	
a_H (51)	2	0.5234	1.0468	
a_C (2)	1	-1.012	-1.012	
a_H (46)	3	0.7341	2.2023	
a_H (47)	7	0.6301	4.4107	
$logP_{cal.}$			4.24	ΔlogP = 0.14
$logP_{exp.}$			4.38	

35. Ferrocenyl-2-nitrophenyl



(35)

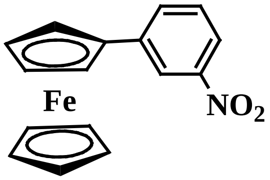
ferrocenyl-2-nitrophenyl

logP for this ferrocene containing nitro function is calculated according to table III-3-35**.**

Table III-3-35: *Calculation of logP for compound (35)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	4	-0.3251	-1.3004	
a_C (25)	1	0.1492	0.1492	
a_C (26)	1	0.1539	0.1539	
a_O (61)	2	1.0520	2.1040	
a_N (76)	1	-2. 0585	-2.0585	
a_H (47)	4	0.6301	2.5204	
$logP_{cal.}$			4.07	ΔlogP = 0.19
$logP_{exp.}$			3.88	

36. Ferrocenyl-3-nitrophenyl



(36)

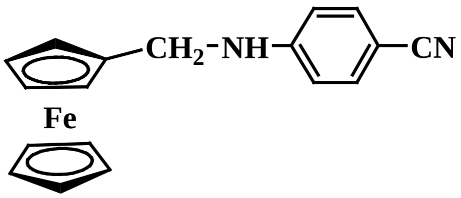
Ferrocenyl-3-nitrophenyl

logP for this ferrocene is calculated as detailed in table III-3-36.

Table III-3-36: *Calculation of logP for compound (36)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	4	-0.3251	-1.3004	
a_C (25)	1	0.1492	0.1492	
a_C (26)	1	0.1539	0.1539	
a_O (61)	2	1.0520	2.1040	
a_N (76)	1	-2. 0585	-2.0585	
a_H (47)	4	0.6301	2.5204	
$logP_{cal.}$			4.07	ΔlogP = 0.08
$logP_{exp.}$			3.99	

37. 4-(ferrocenylmethylamino)benzonitrile



(37)

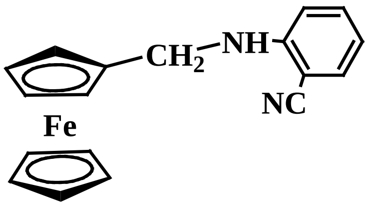
4-(ferrocenylmethylamino)benzonitrile

When a ferrocene group bears a nitrile function as in this molecule, logP can be calculated as indicated in table III-3-37 as follows:

Table III-3-37: *Calculation of logP for compound (37)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	4	-0.3251	-1.3004	
a_C (25)	1	0.1492	0.1492	
a_C (26)	1	0.1539	0.1539	
a_N (70)	1	-0.0389	-0.0389	
a_N (74)	1	0.1349	0.1349	
a_C (40)	1	-0.1002	-0.1002	
a_C (6)	1	-1.2486	-1.2486	
a_H (50)	1	-0.1036	-0.1036	
a_H (47)	6	0.6301	3.7806	
$logP_{cal.}$			3.93	$\Delta logP = 0.42$
$logP_{exp.}$			3.51	

38. N-ferrocenylmethyl-2-cyanoaniline



(38)

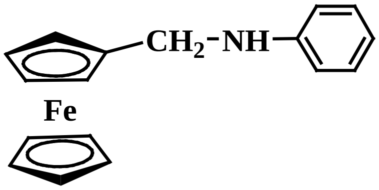
N-ferrocenylmethyl-2-cyanoaniline

In addition to the amine function, this derivative carries a nitrile function. The presences of these contribute to the final value of logP, calculating is summarized in table III-3-38.

Table III-3-38: *Calculation of logP for compound (38)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	4	-0.3251	-1.3004	
a_C (25)	1	0.1492	0.1492	
a_C (26)	1	0.1539	0.1539	
a_N (70)	1	-0.0389	-0.0389	
a_N (74)	1	0.1349	0.1349	
a_C (40)	1	-0.1002	-0.1002	
a_C (6)	1	-1.2486	-1.2486	
a_H (50)	1	-0.1036	-0.1036	
a_H (47)	6	0.6301	3.7806	
$logP_{cal.}$			3.93	$\Delta\text{logP} = 0.29$
$logP_{exp.}$			3.64	

39. N-ferrocenylmethylaniline



(39)

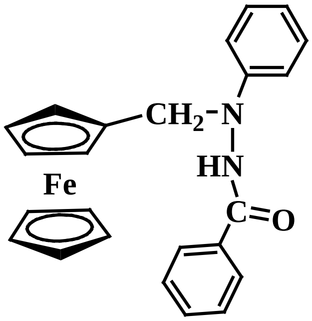
N-ferrocenylmethylaniline

This molecule contain only one function which is the amine group, the contribution of this function is of type (70) summing the contribution of the amine function with other contribution of atoms that forming the molecule gives $\text{logP}_{cal.}$ as regrouped in table III-3-39.

Table III-3-39: *Calculation of logP for compound (39)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	5	-0.3251	-1.6255	
a_C (26)	1	0.1539	0.1539	
a_N (70)	1	-0.0389	-0.0389	
a_C (6)	1	-1.2486	-1.2486	
a_H (50)	1	-0.1036	-0.1036	
a_H (47)	7	0.6301	4.4107	
$logP_{cal.}$			4.05	ΔlogP = 0.23
$logP_{exp.}$			3.82	

40. N'-ferrocenylmethyl-N'-phenylbenzohydrazide



(40)

N'-ferrocenylmethyl-N'-phenylbenzohydrazide

logP for this ferrocene derivative containing hydrazide function is calculated as follows:

Table III-3-40: *Calculation of logP for compound (40)*

Atom type	n_i	a_i	$a_i \times n_i$	
a_{F_c}	1	2.5042	2.5042	
a_C (24)	10	-0.3251	-3.251	
a_C (26)	1	0.1539	0.1539	
a_C (25)	1	0.1492	0.1492	
a_N (74)	1	-0.5113	-0.5113	
a_C (6)	1	-1.2486	-1.2486	
a_N (69)	1	-0.3883	-0.3883	
a_C (40)	1	-0.1002	-0.1002	
a_O (58)	1	-0.0233	-0.0233	
a_H (50)	1	-0.1036	-0.1036	
a_H (47)	12	0.6301	7.5612	
$logP_{cal.}$			4.74	ΔlogP = 0.55
$logP_{exp.}$			4.19	

Different experimental and calculated partition coefficients according to AlogP are summarized in table III-3-41.The absolute error AE of logP varies from 0.08 for compound 7 and 11 to 1.44 for compound 22. In exception the AE for compound 20 is equal to 1.98, this hight AE may due to the existence intramolecular hydrogen bonds in this molecule.

Table III-3-41: Estimation and absolute error results for ferrocene derivatives

Compound	logP$_{\text{cal.}}$	logP$_{\text{exp.}}$	AE	Compound	logP$_{\text{cal.}}$	logP$_{\text{exp.}}$	AE
1	2.90	2.64	0.26	21	3.21	4.00	0.79
2	4.18	4.59	0.41	22	5.05	6.49	1.44
3	4.26	4.10	0.16	23	5.38	4.90	0.48
4	5.73	5.04	0.69	24	7.03	6.43	0.60
5	5.41	4.68	0.73	25	6.76	6.17	0.59
6	5.38	5.23	0.15	26	6.28	5.75	0.53
7	5.70	5.62	0.08	27	6.15	5.92	0.23
8	4.28	4.42	0.14	28	7.28	6.13	1.15
9	4.78	4.44	0.34	29	6.91	6.37	0.54
10	5.19	5.08	0.11	30	4.64	4.77	0.13
11	6.55	6.47	0.08	31	5.09	5.27	0.18
12	3.83	4.63	0.80	32	2.00	2.18	0.18
13	3.84	5.01	1.17	33	3.57	3.95	0.38
14	5.53	5.10	0.43	34	4.24	4.38	0.14
15	5.88	4.89	0.99	35	4.07	3.88	0.19
16	6.23	5.89	0.34	36	4.07	3.99	0.08
17	6.76	6.33	0.43	37	3.93	3.51	0.42
18	7.21	6.70	0.51	38	3.93	3.64	0.29
19	7.08	6.60	0.48	39	4.05	3.82	0.23
20	3.81	5.79	1.98	40	4.74	4.19	0.55

$$\mathrm{AE} = \left| logP_{cal.} - logP_{exp.} \right|$$

III-3-3- Discussion of results

Table III-3-41 shows that values of logP for ferrocene derivatives containing various organic functions calculated by our model are in good agreement of experimental values.

Although this model gave reasonably good results, there are deviations between experimental logP and calculated for ferrocene derivatives 4, 5, 12, 13, 15, 20 to 22 and 28.

The deviation in logP values for compounds 4 and 5 may be due to the atom of type R(C=N-H)-N which does not have contribution in AlogP calculation, the error is as result of the replacement of this type of atom in our calculation by type (72).

The values of calculated logP for ferrocene derivatives 12, 13, 20 to 22 are underestimated this may be due to the existence intramolecular hydrogen bonds, which increase their hydrophobicity.

The fact that AlogP approach does not required any correction for H-bond, stands behind the observed deviation between $\log P_{cal.}$ and $\log P_{exp.}$.

For the complicated compounds15 there is a great deviation that may be due to this compound is bulky.

For the complicated compound 28 the different between the measured values and calculated ones may be due to the interactions in those bulky ferrocene derivative with diphenyl butene.

Figure III-3-1 shows the correlation between experimental and calculated logP values from equation III-3-6 for 40 ferrocene derivatives, value for R^2 of 0.766 was found, if logP compounds 4,5,12,13,20 to 22 are neglected from calculation, then the value of R^2 becomes 0.943,the reason of removing these compounds from calculation is that they require correction to compensate the deviation between the measured values and calculated ones, the correlation between experimental and calculated logP values from equation III-3-6 for 33 ferrocene derivatives were shown in figure III-3-2.

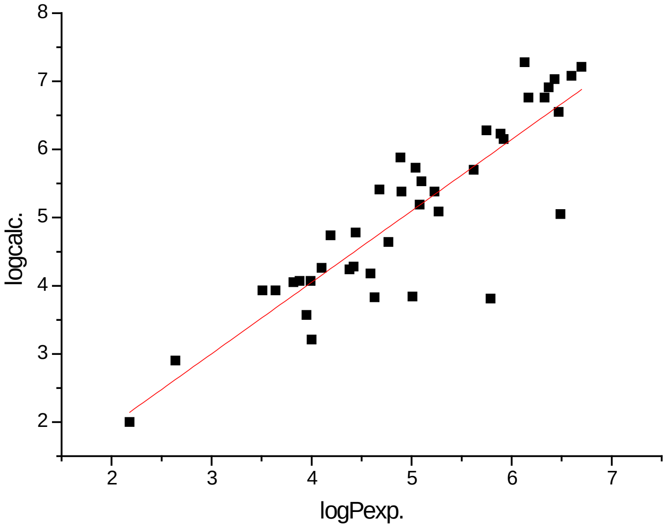


Figure III-3-1: *Correlation between experimental logP and calculated logP from eqn.* $III - 3 - 6$ *for 40 ferrocene derivatives.*

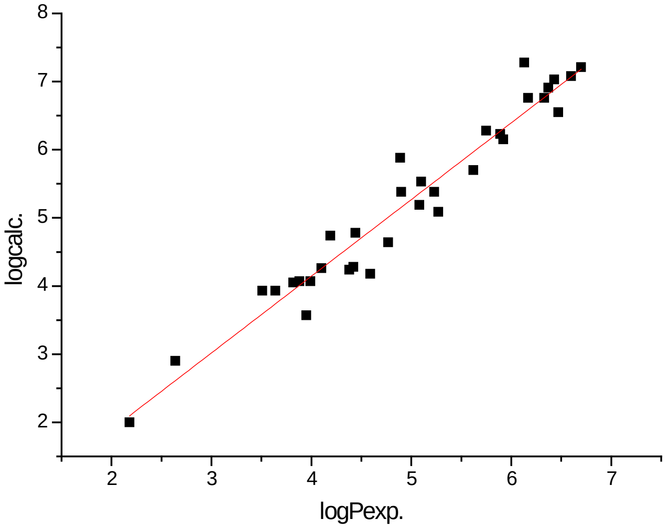


Figure III-3-2: *Correlation between experimental log P and calculated log P from eqn.* $III-3-6$ *for 33 ferrocene derivatives.*

III-3- 4- Conclusion

In this study we successfully developed theoretical approach 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. As result of this adaptation for the calculation of partition coefficient, we became able, for the first time, to apply the AlogP method for calculations of the partition coefficient of substituted ferrocene. Values of experimental and calculated logP for a series of 40 substituted ferrocene are in good agreement, this approve 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 complexes.

III-4-Square wave method for octanol-water partition coefficients determination

III-4-1- Material and instrumentation

III-4-1-1-Material

HPLC grade 1-octanol was purchased from AppliChem, water used was purified through a Milli-Q Gradient A10 from Millipore (Billerica,MA), all other reagents used were of analytical grade, Ferrocene. N-ferrocenylmethylaniline, ferrocenyl-2-nitrophenyl, N-ferrocenymethyl-N-phenylpropionamide, N'-ferrocenylmethyl-N'-phenylbenzohydrazide, ferrocenyl-3-nitrophenyl, N-ferrocenymethyl-N-phenylacetamide, 1-ferrocenylethanol, N-Ferrocénylmethyl(2-cyano) aniline, 4-(ferrocenylmethylamino)benzonitrile, were obtained using procedures which will be described latter in detail.

III-4-1-2-Instrumentation and software

Square wave voltammetry measurements were performed using PGZ301 potentiostat (radiometer analytical SAS) and a voltammetric cell with a volumetric capacity of 50 mL containing a glassy carbon working electrode (radiometer analytical SAS), a Pt wire counter electrode, and an Hg/Hg_2Cl_2 reference electrode (3.0 M KCl). Solutions were deoxygenated with high purity nitrogen for 3 min prior to each experiment. Data acquisitions were accomplished with a Pentium IV (CPU 3.0 GHz and RAM 1 Gb) microcomputer using VoltaMaster4 software version 7.08 (radiometer analytical SAS). Graphs plot were carried out using OriginLab software version 2.0 (Integral Software, France).

Figure III-4-1: *VoltaLab PGZ301 potentiostat*

III-4-2- Measurement procedure

III-4-2-1- General procedure for square wave voltammetry

The procedure used to obtain SW voltammograms was according to the following steps, glassy carbon electrode was polished and inserted into the cell, the mixture was placed in a voltammographic cell, the solution was purged with a stream of nitrogen gas which was continuously bulbed through the cell for 3 minutes, all the outlets to cell were closed so no air oxygen returned to the cell during the experiment was quiet with no vibration and no disturbance from the stream of nitrogen so when the solution become quiescent the going potential was initiated, the potential range used was 150 mV to 700 mV versus saturated calomel reference electrode, all the experiments were performed at room temperature (26 ± 2 °C). The square wave voltammograms conditions were as follows, the potential step was 15 mV, the square wave amplitude was 15 mV, the pulse 50 mV, and the scan rate was 15 mV/s.

III-4-2-2- General procedure for the preparation of calibration curve

The stock solution of each ferrocene derivative was prepared by dissolving a known mass (m) of the corresponding derivative in a volume V_{oct} of octanol presaturated with water. The standard solutions were then prepared by diluting, with octanol presaturated with water, an accurately volume V of the stock solution to a volume V_T. To each diluted solution was added 20 ml of ethanol, 6 mL of acetone and 0.5 mL of concentrated sulphuric acid as supporting electrolyte. The acetone is replaced by 5 to 6 mL of dimethylformamide (DMF) and the sulphuric acid is replaced by 0.25 g of tetrabutylammonium hexafluorophosphate ($C_{16}H_{36}F_6NP$) in the case when ferrocene derivatives carry an amine function.

Calibration curves were prepared by plotting different concentrations of ferrocene derivatives in a volume V_T of the mixture versus the peaks current obtained from square wave voltammograms. The equation obtained from the linear calibration graph in the studied concentration range for each ferrocene derivative standard solutions is, $y = Ax + B$ (where y represents the value of the peak current and x, the value of concentration of standard ferrocene derivatives solutions, expressed as mol/L)

III-4-2-3- General procedure for the preparation of real simple voltammogram

A known mass (m) of ferrocene derivatives was dissolved in a volume V_{oct} of octanol presaturated with water and a volume V_{aq} of water presaturated with octanol was then added, the obtained two phases were then shaken for 10-15 minutes. They were then left to stand until phase separation, about 2-3 days. After separation of the two layers, a volume V of the octanol layer was taken, and 6 mL of acetone, 20 mL of ethanol and 0.5 mL of concentrated sulphuric acid were added to it. The solution was then introduced into the electrochemical cell and the oxidation peak current of the voltammogram was recorded. The acetone is replaced by 5 to 6 mL of DMF and the sulphuric acid is replaced by 0.25 g of $C_{16}H_{36}F_6NP$ in the case when the ferrocene derivatives carry an amine function.

III-4-2-4- Determination of partition coefficient of ferrocene derivatives

III-4-2-4-1- Determination of partition coefficient of ferrocene

Ferrocene (99%) was purchased from Alfa Aesar and was used without any further purification.

- **Preparation of calibration curve**

Calibration curves were prepared as follows, first we prepared a stock solution by dissolving 0.004 g of ferrocene in 8 mL of octanol saturated water then a series of five standard solutions of ferrocene were prepared, as indicated in table III-4-1, by successive dilution of a volume V_1 of the stock solution prepared as described previously with a volume V_2 of octanol presaturated with water, 20 mL of ethanol, 6 mL of acetone and 0.5 mL of conc.H_2SO_4 were then added to standard solution, the concentration range is from 0.188603 mM to 0.028290 mM.

Table III-4-1: *Peak current of ferrocene standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	di (µA)
S_1	2	0	0.188603	3 .09375
S_2	1.5	0.5	0.141452	2.34375
S_3	1	1	0.094301	1.62500
S_4	0.5	1.5	0.047150	1.09375
S_5	0.1	1.9	0.028290	0.81250

Each standard solution is introduced into the electrochemical cell and the voltammogram is recorded, figure III-4-2shows the obtained voltammograms at different ferrocene concentrations. Figure III-4-3 shows the calibration curve obtained by plotting different concentrations of ferrocene derivatives versus the peaks current.

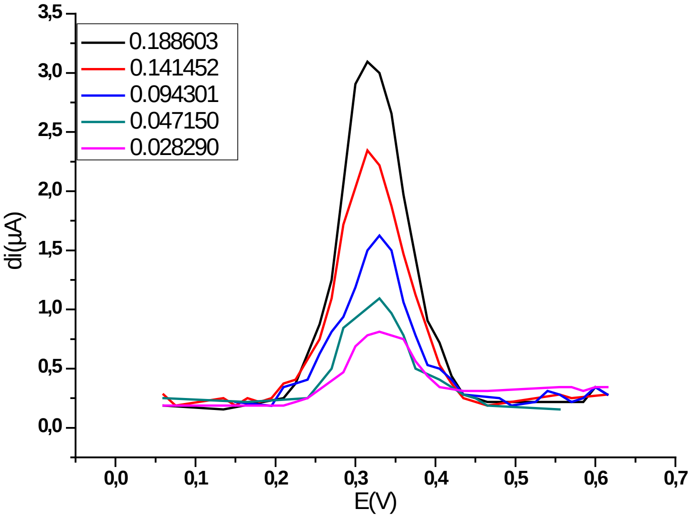


Figure III-4-2: *Square wave voltammograms referring to different ferrocene concentrations in octanol.*

The equation obtained from the linear calibration graph in the studied concentration range for ferrocene standard solutions is, $y = 1.404x + 0.389$ with a correlation coefficient of $R^2 = 0.995$.

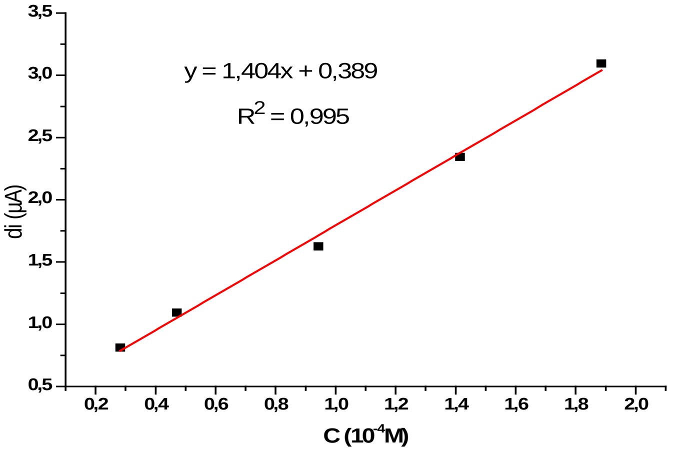


Figure III-4-3: *Calibration curve obtained from SWV for different ferrocene concentrations in octanol.*

- **Preparation of voltammogram of the real sample of ferrocene**

Voltammogram of the real sample ferrocene was measured by dissolving 0.01g of ferrocene in 20 mL of octanol presaturated with water, thus the initial concentration is equal to 2.687594 mM, to this solution was added 20 mL of water presaturated with octanol and the mixture shaken 15-20min and then was left to stand until phase separation (2 days). The octanol layer was separated, and 2 mL of this layer was then taken and was added to it 6 mL of acetone, 20 mL of ethanol, and 0.5 mL of concentrated sulphuric acid, the resulting solution was then introduced into the electrochemical cell and the voltammogram was recorded, figure III-4-4.

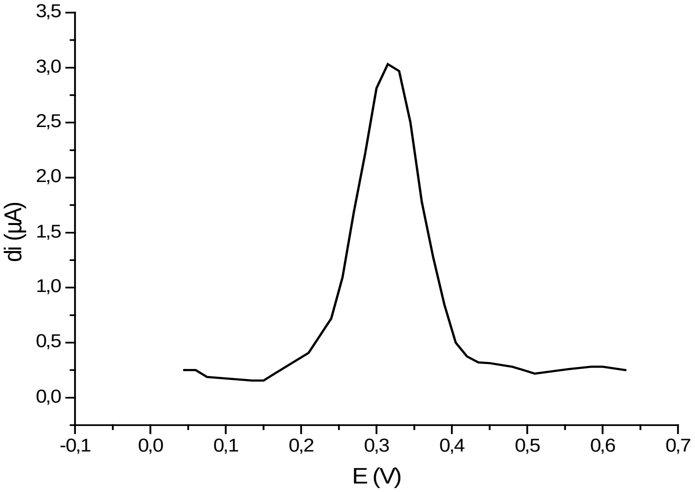


Figure III-4-4: *SWV of the real sample of ferrocene in octanol*

- **LogP determination**

Partition coefficient of ferrocene was measured as follows with literature.

The concentration of ferrocene in octanol phase C_{oct} was obtained by replacing the density of the peak current 3.03125 µA obtained from the voltammogram of figure III-4-4, in the equation $y = 1.404x + 0.389$ obtained from the linear calibration graph of figure III-4-3, this gives,

$$x = 0.1881944\ mM$$

Thus the number of moles in 28.5 mL is,

$$n = 0.1881944.10^{-3} \times 28.5 \times 10^{-3} = 5.363540 \times 10^{-6}\ mol$$

n, is also equal to the number of moles in 2 mL taken from the octanol phase, so in 20 mL of the octanol phase the number of moles is

$$5.363540 \times 10^{-6} \times 10 = 5.363540 \times 10^{-5} \quad mol$$

Therefore the concentration of ferrocene in the octanol phase is

$$C_{oct} = \frac{5.363540 \times 10^{-5}}{20 \times 10^{-3}} = 2.681770\,mM$$

The concentration of ferrocene in the aqueous phase C_{aq} can be calculated based on a mass balance using equation (III − 4 − 1)

$$V_{oct}C_{initial} = V_{oct}C_{oct} + V_{aq}C_{aq} \qquad (\mathrm{III}-4-1) \qquad \text{with} \qquad V_{oct} = V_{aq}$$

Thus,

$$C_{aq} = 2.687594 - 2.681770 = 0.005824\,mM$$

The partition coefficient is calculated using the following equation (I − 1)

$$\mathrm{P} = \left(\frac{\mathrm{C_{oct}}}{\mathrm{C_{aq}}}\right)_{\mathrm{equilibrium}}$$

This gives

$$P = \frac{2.681770}{0.005824} = 459.21, \quad and \quad logP = 2.66$$

III-4-2-4-2- Determination of partition coefficient of 1-ferrocenylethanol

- **Synthesis**

To a three necked round bottom flask was introduced a solution of ferrocenyl acetone (3,66 g, 0,016 mol) in ether (100 ml) and suspension of lithium aluminum hydride (0.54 g, 0.014 mol) in ether (125 mL). The reaction mixture was heated under reflux for two hours; it was then allowed to cool to room temperature, the excess of lithium aluminum hydride was destroyed by careful addition of ethyl acetate and water. The obtained white precipitate was filtered, the filtrate was dried over magnesium sulphate and evaporated to give a yellow solid (3.25 g, 88%) which was identified as 1-ferrocenylethanol

RMN ^{1}H (300 MHz, $CDCl_3$)

δ 1,45 (d, 3H, *J*= 6.4 Hz, CH_3) ; 1.85 (sl, 1H, OH); 4.21 (s, 5H, Cp); 4.15-4.25 (m, 4H, Cp) ; 4.56 (q, 1H, *J*= 6.4 Hz, C*H*(Me)).

- **Preparation of calibration curve**

Following the same procedure as described for ferrocene, The stock solution of 1-ferrocenylethanol was prepared by dissolving 0.007 g of 1-ferrocenylethanol in 16 mL of octanol saturated water, then a series of four standard solutions were prepared, as summarised in table III-4-2, by successive dilution of a volume V_1 of the sock solution prepared as describe previously with a volume V_2 of octanol presaturated with water, 20 mL of ethanol, 6 mL of acetone and 0.5 mL of conc.H_2SO_4 to each standard solution were then added. The concentration ranges from 0.249365 mM to 0.062341 mM.

Table III-4-2: *Peak current of 1-ferrocenylethanol standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	di (µA)
S_1	4	0	0.249365	2.46875
S_2	3	1	0.187024	1.88750
S_3	2	2	0.124682	1.32812
S_4	1	3	0.062341	0.70625

Each standard solution is introduced into the electrochemical cell and the voltammogram is recorded, figure III-4-5 shows the obtained voltammograms at different 1-ferrocenylethanol concentrations. Figure III-4-6 shows the calibration curve obtained by plotting different concentrations of 1-ferrocenylethanol versus its peaks current.

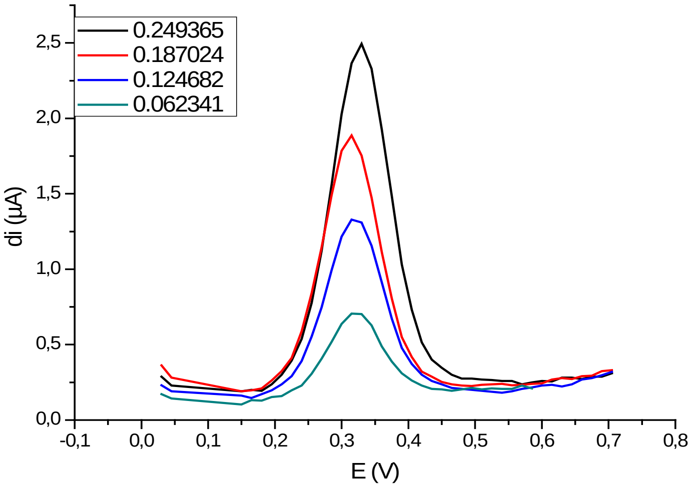


Figure III-4-5: *Square wave voltammograms referring to different 1-ferrocenylethanol concentrations in octanol.*

The equation obtained from the linear calibration graph in the studied concentration range for ferrocene standard solutions is, $y = 0.937x + 0.135$ with a correlation coefficient of $R^2 = 0.999$.

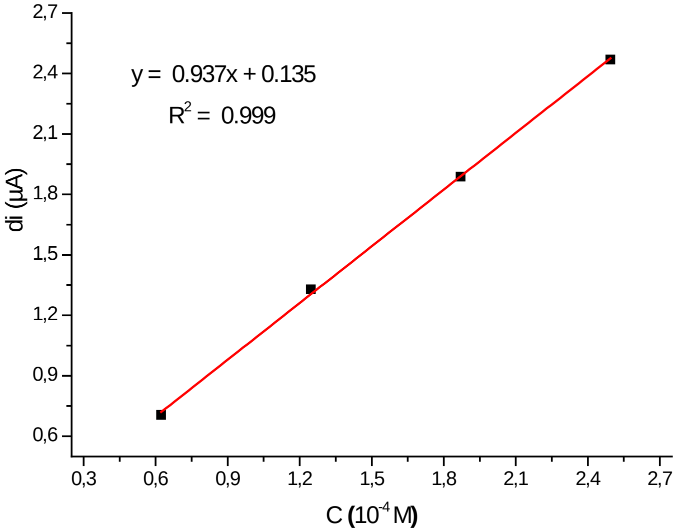


Figure III-4-6: *Calibration curve obtained from SWV for different 1-ferrocenylethanol concentrations in octanol.*

- **Preparation of voltammogram of the real sample of 1-ferrocenylethanol**

Voltammogram of 1-ferrocenylethanol was measured by dissolving 0.007g of this compound in 16 mL of octanol presaturated with water, thus the initial concentration is equal to 1.901409 mM, to this solution was added 16 mL of water and the mixture is allowed to equilibrate, after phases separation (2 days). The organic layer was separated, and to 4 mL of this layer was added 6 mL of acetone, 20 mL of ethanol, and 0.5 mL of concentrated sulphuric acid. The obtained solution was then introduced into the electrochemical cell and the voltammogram was recorded, figure III-4-7.

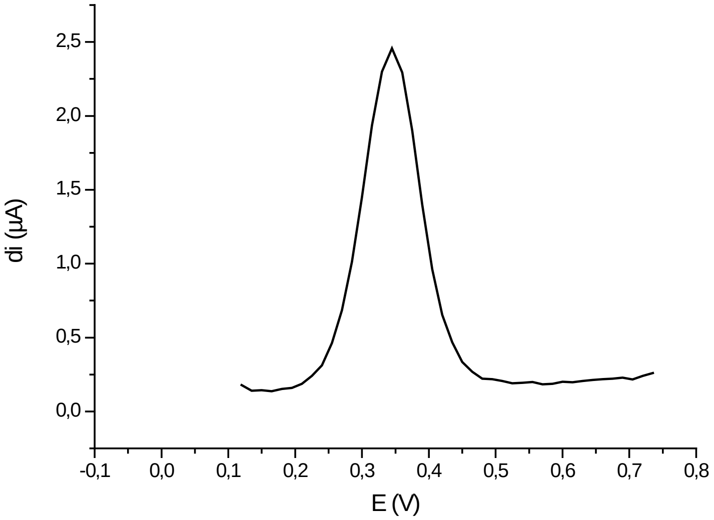


Figure III-4-7: *SWV of the real sample of 1-ferrocenylethanol in octanol*

- **LogP determination**

The concentration of 1-ferrocenylethanol in octanol phase C_{oct} is obtained by replacing the density of the peak current 2.45625µA obtained from the voltammogram of figure III-4-7 in the equation obtained from the linear calibration graph of figure III-4-6, this gives,

$$x = 0.2477321\ mM$$

Thus the number of moles in 30.5 mL, is

$$n = 0.2477321.10^{-3} \times 30.5 \times 10^{-3} = 7.555830 \times 10^{-6}\ mol$$

n, is also equal to the number of moles in 4 mL taken from the octanol phase, so in 16 mL of the octanol phase the number of moles is

$$7.555830 \times 10^{-6} \times 4 = 30.22332 \times 10^{-6}\ mol$$

The concentration of 1-ferrocenylethanol in the octanol phase is

$$C_{oct} = \frac{30.22332 \times 10^{-6}}{16 \times 10^{-3}} = 1.888957\ mM$$

The concentration of 1-ferrocenylethanol in the aqueous phase C_{aq} is calculated based on a mass balance using equation (III-4-1)

$$C_{aq} = 1.901409 - 1.888957 = 0.012452\ mM$$

The partition coefficient is given using equation $(\mathrm{I}-1)$

$$P = \frac{1.888957}{0.012452} = 151.70 \quad and \quad logP = 2.18$$

III-4-2-4-3- Determination of partition coefficient of N-Ferrocenymethyl-N-phenylpropionamide

- **Synthesis**

To a round bottom flask equipped with a reflux condenser and a magnetic stirrer was added under a nitrogen atmosphere a portion of N-Ferrocenylmethylaniline (6 g, 20 mmol) in 50 ml of anhydride toluene. The resulting suspension was heated at 65°C until total dissolution. 10 ml of propenoic acid was then added and the resulting mixture was vigorously stirred under reflux for 25 min. The reaction mixture was then allowed to cool to room temperature and washed twice with water. The organic layer was then dried and evaporated. The residue was recrystallized from a mixture of ethanol–water to yield N-Ferrocenymethyl-N-phenylpropionamide as yellow-orange needles (yield: 5.85 g, 84%). m.p. 121–122°C. The compounds gave clean ^{1}H and ^{13}C NMR spectra in $CDCl_3$.

RMN ^{1}H (300 MHz, $CDCl_3$)

δ 1.00 (t, 3H, H12), 1.95 (m, 2H, H11), 4.04 (s, 4H, H2 et H3), 4.08 (s, 5H, H4), 4.61 (s, 2H, H5), 6.95 (d, 2H, H7), 7.28-7.36 (m, 3H, H8 et H9)

RMN ^{13}C (75 MHz, $CDCl_3$)

δ 9.67 (1C, C_{12}), 27.87 (1C, C_{11}), 48.65 (1C, C_5), 68.13 (2C, C_2 ou C3), 8,57 (5C, C_4), 69.95 (2C, C_3 ou C2), 83.33 (1C, C_1), 127.86 (1C, C_9), 128.77 (2C, C_7), 129.46 (2C, C_8), 142.50 (1C, C_6), 173.17 (1C, C10)

- **Preparation of calibration curve**

Following the same procedure as described for ferrocene, The stock solution of N-Ferrocenymethyl-N-phenylpropionamide was prepared by dissolving a by dissolving 0.007 g of N-Ferrocenymethyl-N-phenylpropionamide in 14 mL of octanol saturated water then a series of five standard solutions were prepared, as summarised in table III-4-3, by successive dilution of a volume V_1 of the sock solution prepared as describe previously with a volume V_2 of octanol presaturated with water, 20 mL of ethanol, 6 mL of acetone and 0.5 mL of conc.H_2SO_4 as the supporting electrolyte, for each standard solution were then added. The concentration ranges from 0,101047 mM to 0,015157 mM.

Table III-4-3: *Peak current of N- Ferrocenymethyl-N-phenylpropionamide standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	di (µA)
S_1	2	0	0,101047	1,27500
S_2	1.5	0.5	0,075785	0,97501
S_3	1	1	0,050523	0,75101
S_4	0.5	1.5	0,025269	0,50000
S_5	0.3	1.7	0,015157	0,43750

Each standard solution is introduced into the electrochemical cell and the voltammogram is recorded, figure III-4-8 shows the obtained voltammograms at different N- Ferrocenymethyl-N-phenylpropionamide concentrations. Figure III-4-9 shows the calibration curve obtained by plotting different concentrations of N- Ferrocenymethyl-N-phenylpropionamide versus its peaks current.

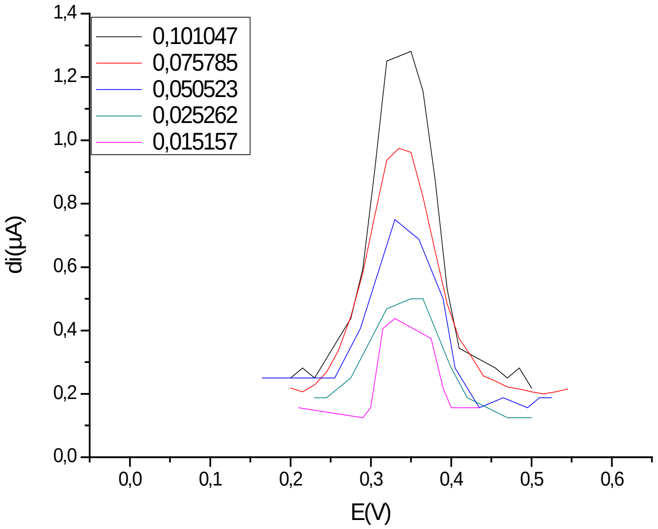


Figure III-4-8: *Square wave voltammograms referring to different N-Ferrocenymethyl-N-phenylpropionamide concentrations in octanol.*

The equation obtained from the linear calibration graph in the studied concentration range for ferrocene standard solutions is, $y = 0.973x + 0.266$ with a correlation coefficient of $R^2 = 0.995$.

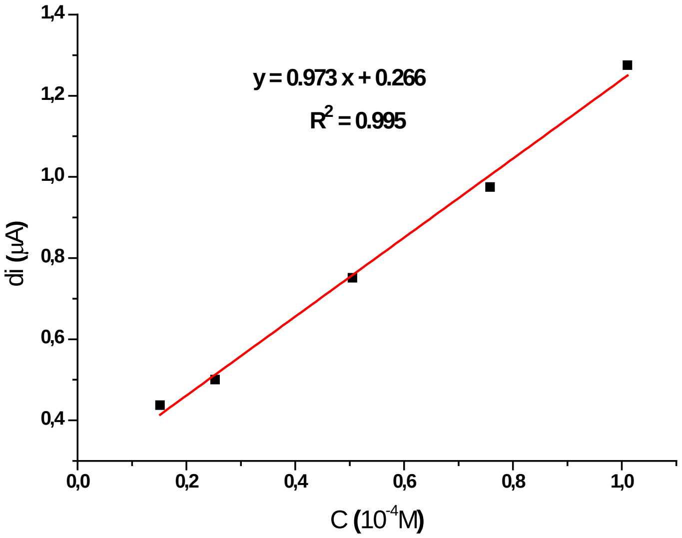


Figure III-4-9: *SWV of the real sample of N- Ferrocenymethyl-N-phenylpropionamide in octanol*

- **Preparation of voltammogram of the real sample of N-Ferrocenymethyl-N-phenylpropionamide**

Voltammogram of N-Ferrocenymethyl-N-phenylpropionamide was measured by dissolving 0.01g of this compound in 20 mL of octanol presaturated with water, thus the initial concentration is equal to 1.439924 mM, to this solution was added 20 mL of water and the mixture is allowed to equilibrate, after phases separation (3 days). The organic layer was separated, and to 2 mL of this layer was added 6 mL of acetone, 20 mL of ethanol, and 0.5 mL of concentrated sulphuric acid. The obtained solution was then introduced into the electrochemical cell and the voltammogram was recorded, figure III-4-10.

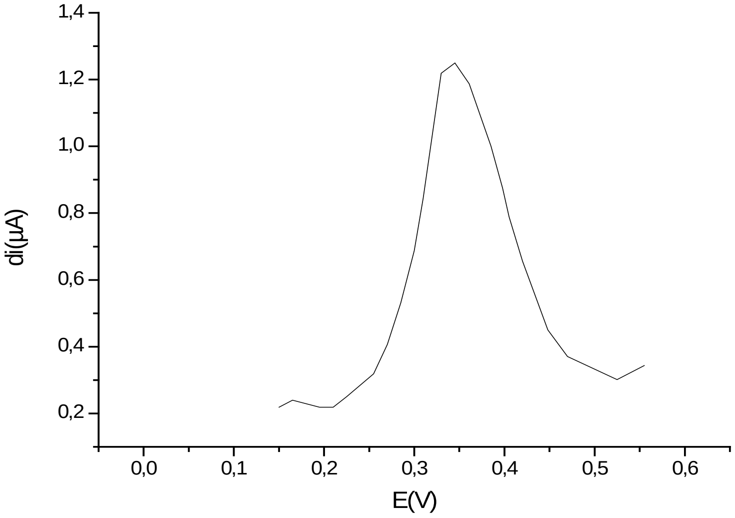


Figure III-4-10: *SWV of the real sample of N-Ferrocenymethyl-N-phenylpropionamide in octanol*

- **LogP determination**

The concentration of N-Ferrocenymethyl-N-phenylpropionamide in octanol phase C_{oct} is obtained by replacing the density of the peak current 1.24915µA obtained from the voltammogram of figure III-4-10 in the equation obtained from the linear calibration graph of figure III-4-9, this gives,

$$x = 0.1010432\ mM$$

Thus the number of moles in 28.5 mL, is

$$n = 0.1010432.10^{-3} \times 28.5 \times 10^{-3} = 2.879731 \times 10^{-6}\ mol$$

n, is also equal to the number of moles in 2 mL taken from the octanol phase, so in 20 mL of the octanol phase the number of moles is

$$2.879731 \times 10^{-6} \times 10 = 2.879731\ \times 10^{-5}\ mol$$

The concentration of N-Ferrocenymethyl-N-phenylpropionamide in the octanol phase is

$$C_{oct} = \frac{2.879731\ \times 10^{-5}}{20 \times 10^{-3}} = 1.439865\ mM$$

The concentration of N-Ferrocenymethyl-N-phenylpropionamide in the aqueous phase C_{aq} is calculated based on a mass balance using equation(III-4-1)

$$C_{aq} = 1.439924 \times 10^{-3} - 1.439865\ \times 10^{-3}\ = 5.9 \times 10^{-5}\ mM$$

The partition coefficient is given using equation (I-1)

$$P = \frac{1.439865 \times 10^{-3}}{5.9 \times 10^{-5}} = 24404.49 \quad and \quad logP = 4.38$$

III-4-2-4-4- Determination of partition coefficient of N-Ferrocenymethyl-N-phenylacetamide

- **Synthesis**

To a 250 ml round bottom flask equipped with a reflux condenser and a magnetic stirrer was added under a nitrogen atmosphere a portion of N- ferrocenylmethylaniline (6 g, 20 mmol) in 50 ml of anhydride toluene. The resulting suspension was heated at 65°C until total dissolution. 10 ml of anhydride acetic acid was then added and the resulting mixture was vigorously stirred under reflux for 25 min. The reaction mixture was then allowed to cool to room temperature and was poured onto water. The organic layer was separated, dried over anhydrous magnesium sulphate and evaporated. The residue was recrystallized from a mixture of ethanol–water to yield 5.6 g N-Ferrocenymethyl-N-phenylacetamide as orange needles yield g, 81%. m.p. 116–117°C. The is yield, 81%.

RMN ^{1}H (300 MHz, $CDCl_3$)

δ 1.75 (s, 3H, H11), 4.03 (s, 4H, H2 et H3), 4.08 (s, 5H, H4), 4.61 (s, 2H, H5), 6.99 (d, 2H, H7), 7.28-7.35 (m, 3H, H8 et H9)

RMN ^{13}C (75 MHz, $CDCl_3$)

δ 22.83 (1C, C11), 48.40 (1C, C5), 68.13 (2C, C2 ou C3), 68.55 (5C, C4), 69.89 (2C, C3 ou C2), 83.13 ((1C, C1), 127.87, 128.55, 129.43 (5C, C9, C7 et C8), 142.84 (1C, C6), 169.74 (1C, C10)

- **Preparation of calibration curve**

Following the same procedure as described for ferrocene, The stock solution of N-Ferrocenymethyl-N-phenylacetamide was prepared by dissolving a by dissolving 0.006 g of N-Ferrocenymethyl-N-phenylacetamide in 12 mL of octanol saturated water then a series of four standard solutions were prepared, as summarised in table III-4-4, by successive dilution of a volume V_1 of the sock solution prepared as describe previously with a volume V_2 of octanol presaturated with water, 20 mL of ethanol, 6 mL of acetone and 0.5 mL of conc.H_2SO_4 as the supporting electrolyte, for each standard solution were then added. The concentration ranges from 0,105302 mM to 0,034223mM.

Table III-4-4: *Peak current of N-Ferrocenymethyl-N-phenylacetamide standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	di (µA)
S_1	2	0	0,105302	1,03125
S_2	1.5	0.5	0,078976	0,81249
S_3	1	1	0,052651	0,62500
S_4	0.65	1.35	0,034223	0.4600

Each standard solution is introduced into the electrochemical cell and the voltammogram is recorded, figure III-4-11 shows the obtained voltammograms at different N-Ferrocenymethyl-N-phenylacetamide concentrations. Figure III-4-12 shows the calibration curve obtained by plotting different concentrations of N-Ferrocenymethyl-N-phenylacetamide versus its peaks current.

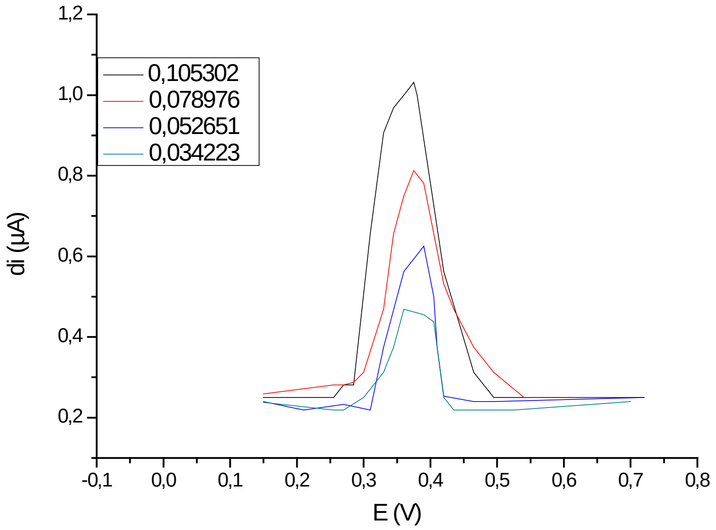


Figure III-4-11: *Square wave voltammograms referring to different N-Ferrocenymethyl-N-phenylacetamide concentrations in octanol.*

The equation obtained from the linear calibration graph in the studied concentration range for N-Ferrocenymethyl-N-phenylacetamide standard solutions is, $y = 0.792x + 0.195$ with a correlation coefficient of $R^2 = 0.998$.

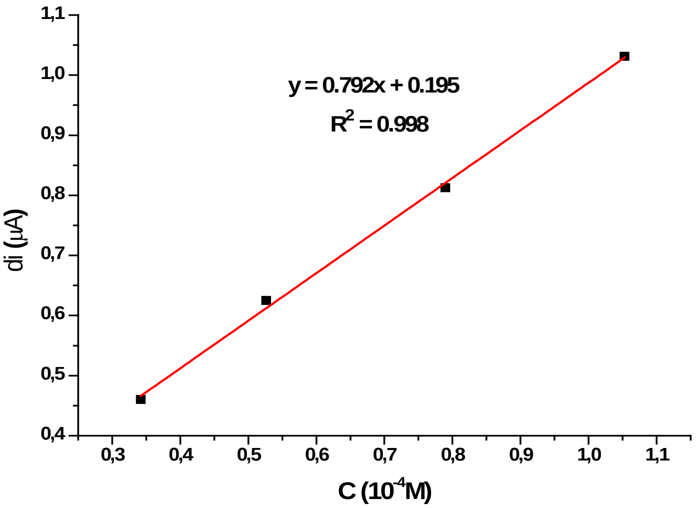


Figure III-4-12: *Calibration curve obtained from SWV for different N-Ferrocenymethyl-N-phenylacetamide concentrations in octanol.*

- **Preparation of voltammogram of the real sample of N-Ferrocenymethyl-N-phenylacetamide**

Voltammogram of N-Ferrocenymethyl-N-phenylacetamide was measured by dissolving 0.01g of this compound in 20 mL of octanol presaturated with water, thus the initial concentration is equal to 1.500555mM, to this solution was added 20 mL of water and the mixture is allowed to equilibrate, after phases separation (2 days). The organic layer was separated, and to 2 mL of this layer was added 6 mL of acetone, 20 mL of ethanol, and 0.5 mL of concentrated sulphuric acid. The obtained solution was then introduced into the electrochemical cell and the voltammogram was recorded, figure III-4-13.

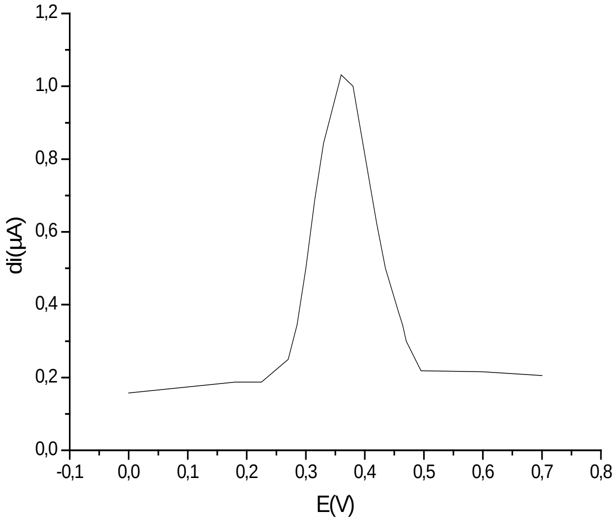


Figure III-4-13: *SWV of the real sample of N-Ferrocenymethyl-N-phenylacetamide in octanol*

- **LogP determination**

The concentration of N-Ferrocenymethyl-N-phenylacetamide in octanol phase C_{oct} is obtained by replacing the density of the peak current 1.0289µA obtained from the voltammogram of figure III-4-13 in the equation obtained from the linear calibration graph of figure III-4-12, this gives,

$$x = 0.1052904\, mM$$

Thus the number of moles in 28.5 mL, is

$$n = 0.1052904.10^{-3} \times 28.5 \times 10^{-3} = 3.000776 \times 10^{-6}\, mol$$

n, is also equal to the number of moles in 2 mL taken from the octanol phase, so in 20 mL of the octanol phase the number of moles is

$$3.000776 \times 10^{-6} \times 10 = 3.000765 \times 10^{-5}\ mol$$

The concentration of N- N-Ferrocenymethyl-N-phenylacetamide in the octanol phase is

$$C_{oct} = \frac{3.000776 \times 10^{-5}}{20 \times 10^{-3}} = 1.500388\, mM$$

The concentration of N-Ferrocenymethyl-N-phenylacetamide in the aqueous phase C_{aq} is calculated based on a mass balance using equation (III-4-1)

$$C_{aq} = 1.500555 \times 10^{-3} - 1.500388 \times 10^{-3} = 1.67 \times 10^{-4}\ mM$$

The partition coefficient is given using equation (I-1)

$$P = \frac{1.500388 \times 10^{-3}}{1.67 \times 10^{-7}} = 8984.36 \quad and \quad logP = 3.95$$

III-4-2-4-5- Determination of partition coefficient of ferrocenyl-2-nitrophenyl

- **Synthesis**

To a solution of ferrocene (18.6, 0.10mol) in ether (450 cm^3) was at once run a filtered aqueous solution of o-nitrobenzenediazonium chloride prepared from 2-nitroaniline (15.2g, 0.11 mol) and sodium nitrite (8g ,0.11 mol). The mixture was then left to stir at room temperature until evolution of nitrogen ceased (approx. 3 hours).The ether was separated, washed with water, dried, and evaporated the residue was chomatographed on alumina using light petrolum / ether (2:3) to elute o-nitrophenylferrocene (18.4g,60%) witch was recrystallized from methanol to produce purple crystals.

RMN ^{1}H (300 MHz, CDCl$_3$):

δ = 4,06 (5H, s, C_5H_5), 4,41 (2H, t, C_5H_4, Hβ, J = 1,8 Hz), 4,72 (2H, t, C_5H_4, Hα , J = 1,8 Hz), 7,44 (1H, t, H5, ^{3}J = 8,1 Hz), 7,76 (1H, dt, H6, ^{3}J = 8,1 Hz, ^{4}J = 1,8 Hz), 8,03 (1H, dt, H4, ^{3}J = 8,1 Hz, ^{4}J = 1,8 Hz), 8,28 (1H, t, H2, ^{4}J = 1,8 Hz).

RMN ^{13}C (75 MHz, CDCl$_3$):

δ = 66,9 (2C, C_5H_4); 69,9 (C_5H_5); 70,0 (2C, C_5H_4); 82,6 (C_{ipso}, C_5H_4); 120,5 (C4); 120,6 (C2); 129,4 (C5); 131,8 (C6); 142,3 (C1); 149,0 (C3).

- **Preparation of calibration curve**

Following the same procedure as described for ferrocene, the stock solution of N ferrocenyl-2-nitrophenyl was prepared by dissolving a by dissolving 0.0035 g of ferrocenyl-2-nitrophenyl in 10 mL of octanol saturated water then a series of four standard solutions were prepared, as summarised in table III-4-5, by successive dilution of a volume V_1 of the sock solution prepared as describe previously with a volume V_2 of octanol presaturated with water, 20 mL of ethanol, 6 mL of acetone and 0.5 mL of conc.H_2SO_4 as the supporting electrolyte, for each standard solution were then added. The concentration ranges from 0, 079970 mM to 0,031988 mM.

Table III-4-5: *Peak current of ferrocenyl-2-nitrophenyl standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	di (µA)
S_1	2	0	0.079970	1,09900
S_2	1.5	0.5	0.059977	0,84370
S_3	1	1	0.039985	0,62187
S_4	0.8	1.2	0.031988	0,49063

Each standard solution is introduced into the electrochemical cell and the voltammogram is recorded, figure III-4-14 shows the obtained voltammograms at different ferrocenyl-2-nitrophenyl concentrations. Figure III-4-15 shows the calibration curve obtained by plotting different concentrations of ferrocenyl-2-nitrophenyl versus its peaks current.

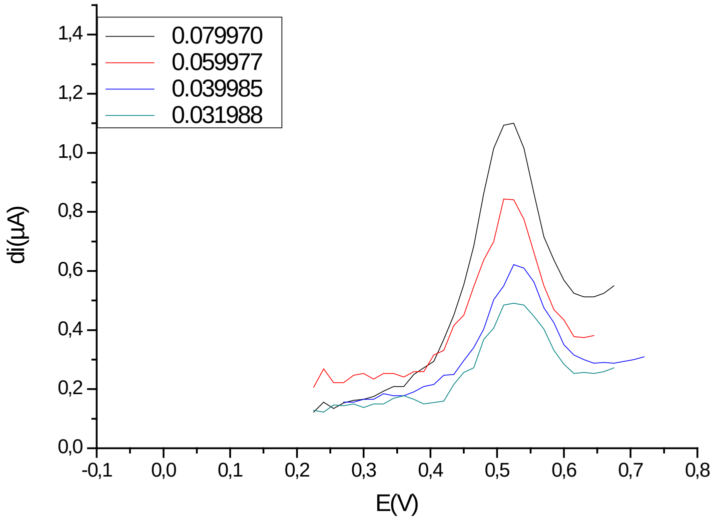


Figure III-4-14: *Square wave voltammograms referring to different ferrocenyl-2-nitrophenyl concentrations in octanol.*

The equation obtained from the linear calibration graph in the studied concentration range for ferrocenyl-2-nitrophenyl standard solutions is, $y = 0.123x + 0.107$ with a correlation coefficient of $R^2 = 0.997$.

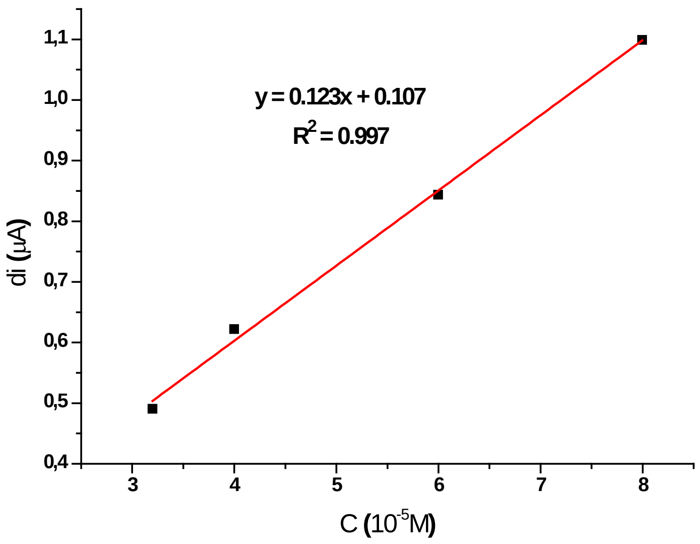


Figure III-4-15: *Calibration curve obtained from SWV for different ferrocenyl-2-nitrophenyl concentrations in octanol.*

- **Preparation of voltammogram of the real sample of ferrocenyl-2-nitrophenyl**

Voltammogram of ferrocenyl-2-nitrophenyl was measured by dissolving 0.007g of this compound in 20 mL of octanol presaturated with water, thus the initial concentration is equal to 1.139571mM, to this solution was added 20 mL of water and the mixture is allowed to equilibrate, after phases separation (2 days). The organic layer was separated, and to 2 mL of this layer was added 6 mL of acetone, 20 mL of ethanol, and 0.5 mL of concentrated sulphuric acid.The obtained solution was then introduced into the electrochemical cell and the voltammogram was recorded, figure III-4-16.

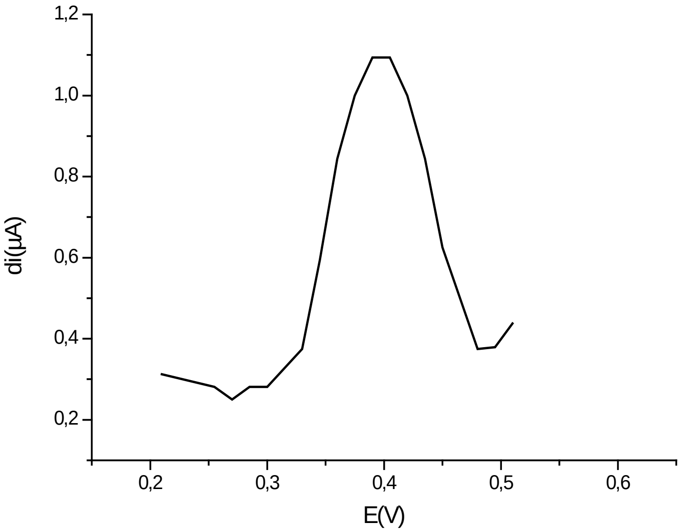


Figure III-4-16: *SWV of the real sample of ferrocenyl-2-nitrophenyl in octanol.*

- **LogP determination**

The concentration of ferrocenyl-2-nitrophenyl in octanol phase C_{oct} is obtained by replacing the density of the peak current 1.0905µA obtained from the voltammogram of figure III-4-16 in the equation obtained from the linear calibration graph of figure III-4-15, this gives,

$$x = 0.0799593mM$$

Thus the number of moles in 28.5 mL, is

$$n = \ 0.0799593.10^{-3} \times 28.5 \times 10^{-3} = 2.278840 \times 10^{-6}\ mol$$

n, is also equal to the number of moles in 2 mL taken from the octanol phase, so in 20 mL of the octanol phase the number of moles is

$$2.278840 \times 10^{-6} \times 10 = 2.278840\ \times 10^{-5}\ \ mol$$

The concentration of ferrocenyl-2-nitrophenyl in the octanol phase is

$$C_{oct} = \frac{2.278840\ \ \times 10^{-5}}{20 \times 10^{-3}} = 1.139420\ mM$$

The concentration of ferrocenyl-2-nitrophenyl in the aqueous phase C_{aq} is calculated based on a mass balance using equation (III-4-1)

$$C_{aq} = 1.139571\ \times 10^{-3} - 1.139420\ \times 10^{-3}\ = 1.51 \times 10^{-4}\ \ mM$$

The partition coefficient is given using equation (I-1)

$$P = \frac{1.139420 \times 10^{-3}}{1.51 \times 10^{-7}} = 7545.83 \quad and \quad logP = 3.88$$

III-4-2-4-6- Determination of partition coefficient of ferrocenyl-3-nitrophenyl

- **Synthesis**

To a solution of ferrocene (18.6, 0.10mol) in ether (450 cm^3) was at once run a filtered aqueous solution of m-nitrobenzenediazonium chloride prepared from 3-nitroaniline (15.2g, 0.11 mol) and sodium nitrite (8g ,0.11 mol). The mixture was then left to stir at room temperature until evolution of nitrogen ceased (approx. 3 hours).The ether was separated, washed with water, dried, and evaporated the residue was chomatographed on alumina using light petrolum / ether (2:3) to elute m-nitrophenylferrocene (18.4g,60%) witch was recrystallized from methanol to produce purple crystals.

RMN ^{1}H (300 MHz, CDCl$_3$):

δ = 4,06 (5H, s, C_5H_5), 4,41 (2H, t, C_5H_4, Hβ, J = 1,8 Hz), 4,72 (2H, t, C_5H_4, Hα , J = 1,8 Hz), 7,44 (1H, t, H5, ^{3}J = 8,1 Hz), 7,76 (1H, dt, H6, ^{3}J = 8,1 Hz, ^{4}J = 1,8 Hz), 8,03 (1H, dt, H4, ^{3}J = 8,1 Hz, ^{4}J = 1,8 Hz), 8,28 (1H, t, H2, ^{4}J = 1,8 Hz).

RMN ^{13}C (75 MHz, CDCl$_3$): δ = 66,9 (2C, C_5H_4); 69,9 (C_5H_5); 70,0 (2C, C_5H_4); 82,6 (C_{ipso}, C_5H_4); 120,5 (C4); 120,6 (C2); 129,4 (C5); 131,8 (C6); 142,3 (C1); 149,0 (C3).

- **Preparation of calibration curve**

Following the same procedure as described for ferrocene, The stock solution of ferrocenyl-3-nitrophenyl was prepared by dissolving a by dissolving 0.0070 g of ferrocenyl-3-nitrophenyl in 14 mL of octanol saturated water then a series of three standard solutions were prepared, as summarised in table III-4-6, by successive dilution of a volume V_1 of the sock solution prepared as describe previously with a volume V_2 of octanol presaturated with water, 20 mL of ethanol, 6 mL of acetone and 0.5 mL of conc.H_2SO_4 as the supporting electrolyte, for each standard solution were then added. The concentration ranges from 0,114243 mM to 0,028561 mM.

Table III-4-6: *Peak current of ferrocenyl-3-nitrophenyl solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	di (μA)
S_1	2	0	0,114243	1,33125
S_2	1.5	0.5	0,057121	0,78750
S_3	0.5	1.5	0,028561	0,53750

Each standard solution is introduced into the electrochemical cell and the voltammogram is recorded, figure III-4-17 shows the obtained voltammograms at different ferrocenyl-3-nitrophenyl concentrations. Figure III-4-18 shows the calibration curve obtained by plotting different concentrations of ferrocenyl-3-nitrophenyl versus its peaks current.

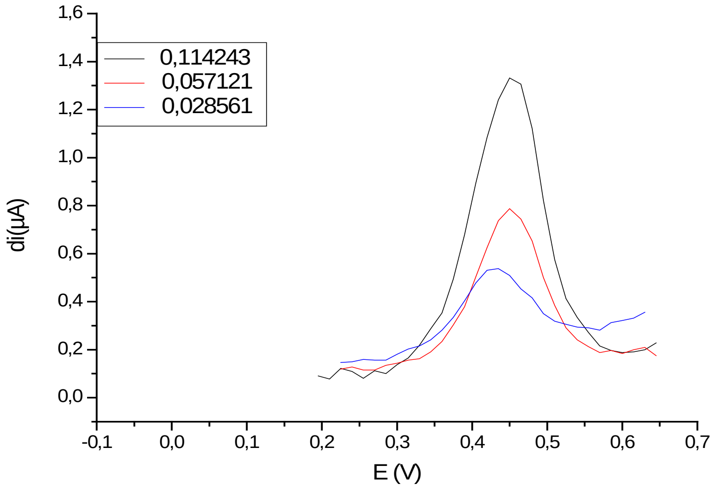


Figure III-4-17: *Square wave voltammograms referring to different ferrocenyl-3-nitrophenyl concentrations in octanol.*

The equation obtained from the linear calibration graph in the studied concentration range for ferrocenyl-3-nitrophenyl standard solutions is, $y = 0.93x + 0.265$, R^2 = 0.999.

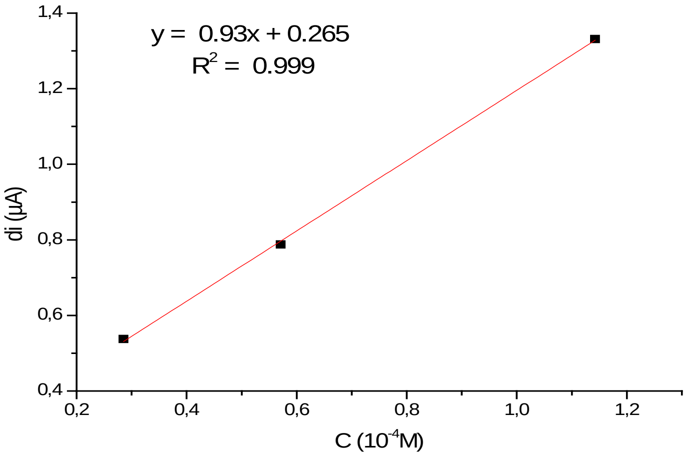


Figure III-4-18: Calibration curve obtained from SWV for different ferrocenyl-3-nitrophenyl concentrations in octanol.

- **Preparation of voltammogram of the real sample of ferrocenyl-3-nitrophenyl**

Voltammogram of ferrocenyl-3-nitrophenyl was measured by dissolving 0.010g of this compound in 20 mL of octanol presaturated with water, thus the initial concentration is equal to 1.627959mM, to this solution was added 20 mL of water and the mixture is allowed to equilibrate, after phases separation (2 days). The organic layer was separated, and to 2 mL of this layer was added 6 mL of acetone, 20 mL of ethanol, and 0.5 mL of concentrated sulphuric acid. The obtained solution was then introduced into the electrochemical cell and the voltammogram was recorded, figure III-4-19.

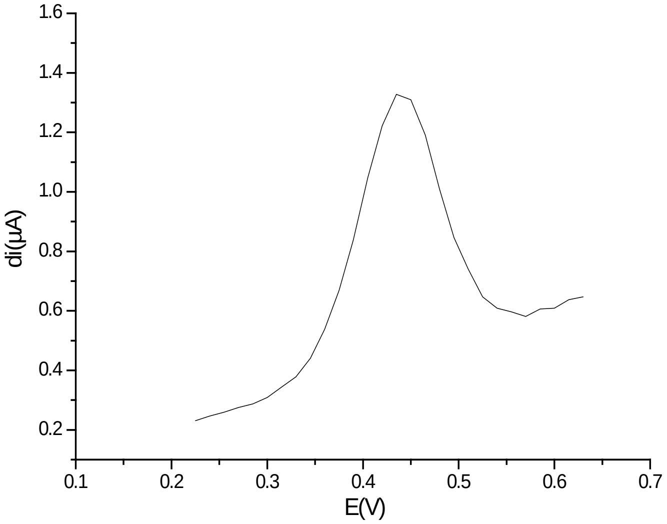


Figure III-4-19: *SWV of the real sample of ferrocenyl-3-nitrophenyl in octanol.*

- **LogP determination**

The concentration of ferrocenyl-3-nitrophenyl in octanol phase C_{oct} is obtained by replacing the density of the peak current 1.32735µA obtained from the voltammogram of figure III-4-19 in the equation obtained from the linear calibration graph of figure III-4-18, this gives,

$$x = 0.1142311mM$$

Thus the number of moles in 28.5 mL, is

$$n = 0.114231.10^{-3} \times 28.5 \times 10^{-3} = 3.255583 \times 10^{-6}\, mol$$

n, is also equal to the number of moles in 2 mL taken from the octanol phase, so in 20 mL of the octanol phase the number of moles is

$$3.255583 \times 10^{-6} \times 10 = 3.255583 \times 10^{-5}\ mol$$

The concentration of ferrocenyl-3-nitrophenyl in the octanol phase is

$$C_{oct} = \frac{3.255583 \times 10^{-5}}{20 \times 10^{-3}} = 1.627791\ mM$$

The concentration of ferrocenyl-3-nitrophenyl in the aqueous phase C_{aq} is calculated based on a mass balance using equation (III-4-1)

$$C_{aq} = 1.627959 \times 10^{-3} - 1.627791 \times 10^{-3} = 1.68 \times 10^{-4}\ mM$$

The partition coefficient is given using equation(I-1)

$$P = \frac{1.627791 \times 10^{-3}}{1.51 \times 10^{-7}} = 9689.23 \quad and \quad logP = 3.99$$

III-4-2-4-7- Determination of partition coefficient of N-ferrocenylmethylaniline

- **Synthesis**

To a three necked round bottom flask was introduced a solution was added under a slow stream of nitrogen a solution of aniline (55.6g, 0.597mol) in water (600 ml) and (ferrocenylmethy)trimethylammonium iodide (40 g, 0.104 mol). The resulting mixture was heated for two hours under continuous string; it was then allowed to cool to room temperature and extracted with toluene. The organic layer was separated, dried over magnesium sulphate and evaporated under reduced pressure to produce an orange brownish precipitate. It was recrystallised from aqueous ethanol to yield (20.09 g, 66 %) of yellow crystals of N-ferrocenylmethylaniline, m.p. 85-86 °C

RMN ^{1}H (300 MHz, CDCl$_3$)

δ 4.01 (s, 2H, H5), 4.20 (s, 2H, H2 ou H3), 4.24 (s, 5H, H4), 4.33 (s, 2H, H3 ou H2), 6.72 (d, 2H, H7), 6.78 (t, 1H, H9), 7.255 (t, 2H, H8), 7.31(s, 1H, H-N)

RMN ^{13}C (75 MHz, CDCl$_3$)

δ 43.52 (1C, C5), 68.04 (2C, C2 ou C3), 68.25 (2C, C3 ou C2), 68.63 (5C, C4), 86.60 (1C, C1), 112.97 (2C, C7), 117.68 (1C, C9), 129.44 (2C, C8), 148.42 (1C, C6)

- **Preparation of calibration curve**

When we applied the same experimental condition to those used for five listed previously ferrocene derivatives ,we did not obtain a SW voltmmogram,this may due the protonation of the NH function carried by the N-ferrocenylmethylaniline in this acidic medium. This obliged us to avoid the acidic midum by use of tetrabutylammonium hexflorophospatate ($C_{16}H_{36}F_6NP$) in DMF.Calibration curves were prepared as follows, first we prepared a stock solution by dissolving 0.007 g of N-ferrocenylmethylaniline in 14 mL of octanol saturated water then a series of three standard solutions of N-ferrocenylmethylaniline were prepared, as indicated in table III-4-7, by successive dilution of a volume V_1 of the stock solution prepared as described previously with a volume V_2 of octanol presaturated with water, 20 mL of ethanol, 5 mL of N, N demethylformamide and 0.25 mg of tetrabutylammonium hexafluorophosphate ($C_{16}H_{36}F_6NP$) as the supporting electrolyte, for each standard solution were then added, the concentration range is from 0. 236856 to 0.059210mM.

Table III-4-7: *Peak current of N-ferrocenylmethylaniline standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	di (µA)
S_1	4	0	0.236856	1.0622
S_2	1.5	2.5	0.088820	0.5062
S_3	1	3	0.0 59210	0.4125

Each standard solution is introduced into the electrochemical cell and the voltammogram is recorded, figure III-4-20 shows the obtained voltammograms at different N-ferrocenylmethylaniline concentrations. Figure III-4-21 shows the calibration curve obtained by plotting different concentrations of N-ferrocenylmethylaniline versus the peaks current.

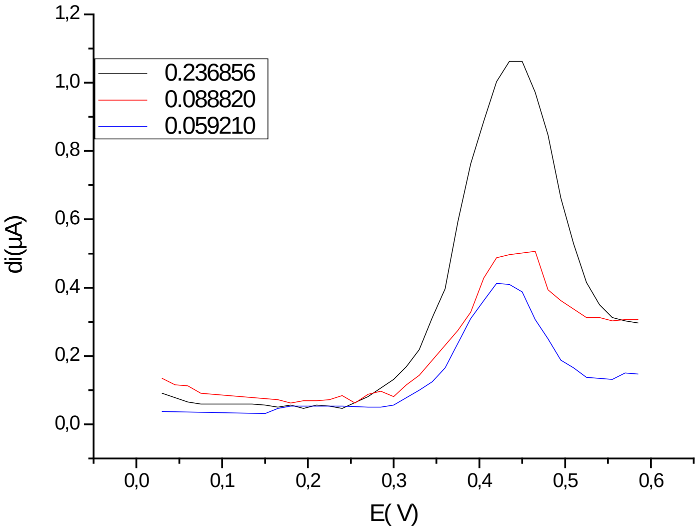


Figure III-4-20: *Square wave voltammograms referring to different N-ferrocenylmethylaniline concentrations in octanol.*

The equation obtained from the linear calibration graph in the studied concentration range for N-ferrocenylmethylaniline standard solutions is, $y = 0.369x + 0.187$ with a correlation coefficient of $R^2 = 0.999$.

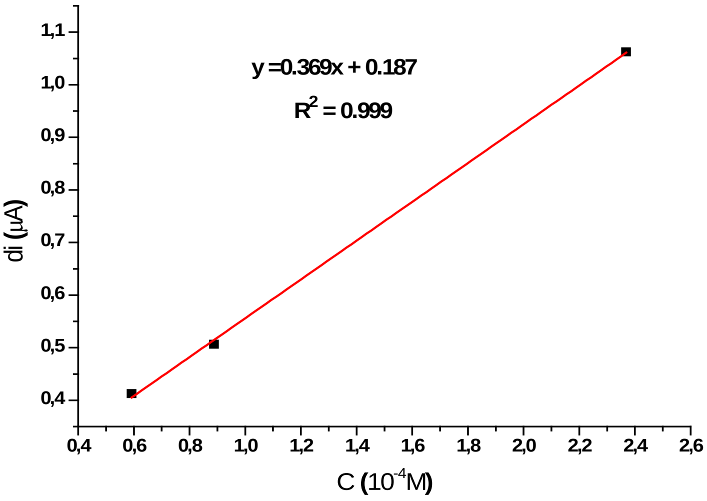


Figure III-4-21: *Calibration curve obtained from SWV for different N-ferrocenylmethylaniline concentrations in octanol.*

- **Preparation of voltammogram of the real sample of N-ferrocenylmethylaniline**

Voltammogram of N-ferrocenylmethylaniline was measured by dissolving 0.01g of this compound in 20 mL of octanol presaturated with water, thus the initial concentration is equal to 1. 717210mM, to this solution was added 20 mL of water and the mixture is allowed to equilibrate, after phases separation (2 days). The organic layer was separated, and to 4 mL of this layer was added 5 mL of acetone, 20 mL of ethanol, and 0.25 mg of tetrabutylammonium hexafluorophosphate ($C_{16}H_{36}F_6NP$) as the supporting electrolyte. The obtained solution was then introduced into the electrochemical cell and the voltammogram was recorded, figure III-4-22.

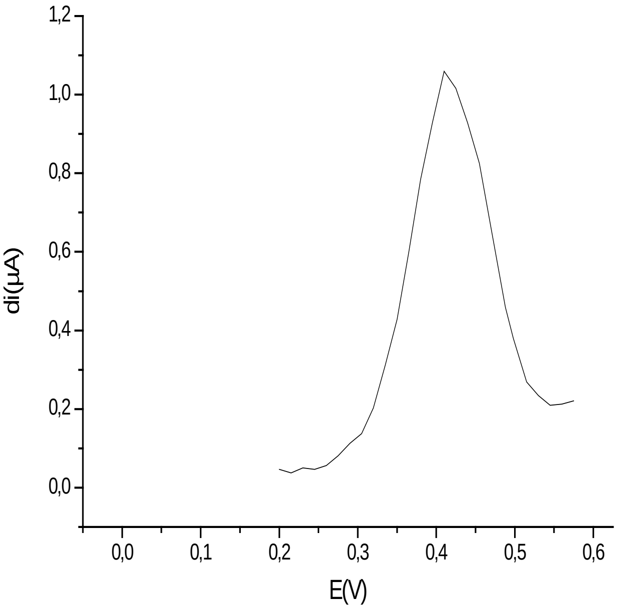


Figure III-4-22: *SWV of the real sample of N-ferrocenylmethylaniline in octanol*

- **LogP determination**

The concentration of N-ferrocenylmethylaniline in octanol phase C_{oct} is obtained by replacing the density of the peak current 1.0585 µA obtained from the voltammogram of figure III-4-22 in the equation obtained from the linear calibration graph of figure III-4-21, this gives,

$$x = 0.2368206\ mM$$

Thus the number of moles in 29 mL, is

$$n = 0.2368206.10^{-3} \times 29 \times 10^{-3} = 6.867797 \times 10^{-6}\ mol$$

n, is also equal to the number of moles in 4 mL taken from the octanol phase, so in 20 mL of the octanol phase the number of moles is

$$6.867797 \times 10^{-6} \times 5 = 34.338985 \times 10^{-6}\ mol$$

The concentration of N-ferrocenylmethylaniline in the octanol phase is

$$C_{oct} = \frac{34.338985 \times 10^{-6}}{20 \times 10^{-3}} = 1.716949\ mM$$

The concentration of N-ferrocenylmethylaniline in the aqueous phase C_{aq} is calculated based on a mass balance using equation (III-4-1)

$$C_{aq} = 1.717210 \times 10^{-3} - 1.716949 \times 10^{-3} = 2.61.10^{-4} mM$$

The partition coefficient is given using equation (I-1).

$$P = \frac{1.716949 \times 10^{-3}}{2.61.10^{-7}} = 6578.34 \quad and \quad logP = 3.82$$

III-4-2-4-8- Determination of partition coefficient of N’-Ferrocenylmethyl-N’-phenyl benzohydrazide

- **Synthesis**

N’-Phenylbenzohydrazide (4.67 g, 22 mmol) was added to a well stirred solution of (ferrocenylmethy)trimethylammonium iodide (7.70 g, 20 mmol) in sodium-dried toluene (55 cm^3). The resulting suspension was heated under reflux for 6 hours. It was then allowed to cool to room temperature and filtered. The filtrate was washed with water to remove any trace of unchanged quaternary ammonium salt. It was then dried and evaporated. The residue was recrystallised from ethanol to give N’-ferrocenylmethyl-N’-phenylbenzohydrazide (6.7 g, 82 %) as yellow-orange needles, m.p. 169°C (decomp.).

RMN ^{1}H (300 MHz, $CDCl_3$)

δ 4.14 (s, 2H, H2 ou H3), 4.18 (s, 5H , H4), 4.21 (s, 2H, H3 ou H2), 4.60 (s , 2H , H5), 6.86 (t, 1H, H9), 6.97(d, 2H, H7), 7.27 (t, 2H, H8), 7.44(t, 2H, C13), 7.54 (t, H, C14), 7.73(d, 2H, C12), 7.59(s, H, N-H).

RMN ^{13}C (75 MHz, $CDCl_3$)

δ 51.17 (1C, C5), 68.82 (2C, C2 ou C3), 68.92 (5C, C4), 70.05 (2C, C3 ou C2), 81.41(1C, C1), 113.62 (2C, C7), 120.03 (1C, C9), 127.26 (2C, C12) 128.90 (2C, C13), 129.34 (2C, C8), 132.16 (C, C14), 133.08 (C, C11), 148.43 (1C, C6), 166.57 (1C, C10).

MS m/z M^+ 410.010 ($C_{24}H_{22}FeN_2O$ calcd. 410.290) and major fragment ions at m/z 121(16), 199(100).

- **Preparation of calibration curve**

This compound within also an NH function which may be protonated in acidic medum, so we applied the same procedure as described for the previous compound.

The stock solution of N'-Ferrocenylmethyl-N'-phenylbenzohydrazide was prepared by dissolving a by dissolving 0.007 g of N'-Ferrocenylmethyl-N'-phenylbenzohydrazide in 14 mL of octanol saturated water then a series of three standard solutions were prepared, as summarised in table III-4-8, by successive dilution of a volume V_1 of the sock solution prepared as describe previously with a volume V_2 of octanol presaturated with water, 20 mL of ethanol, 6 mL of acetone and 5 mL of N, N demethylformamide and 0.25 mg of tetrabutylammonium hexafluorophosphate ($C_{16}H_{36}F_6NP$) as the supporting electrolyte, for each standard solution were then added, the concentration range is from 0, 168086 mM to 0,084043mM.

Table III-4-8:*Peak current of N'-Ferrocenylmethyl-N'-phenylbenzohydrazide standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	di (µA)
S_1	4	0	0,168086	0,96830
S_2	3	1	0,126065	0,75000
S_3	2	2	0,084043	0,58438

Each standard solution is introduced into the electrochemical cell and the voltammogram is recorded, figure III-4-23 shows the obtained voltammograms at different N'-Ferrocenylmethyl-N'-phenylbenzohydrazide concentrations. Figure III-4-24 shows the calibration curve obtained by plotting different concentrations of N'-Ferrocenylmethyl-N'-phenylbenzohydrazide versus the peaks current.

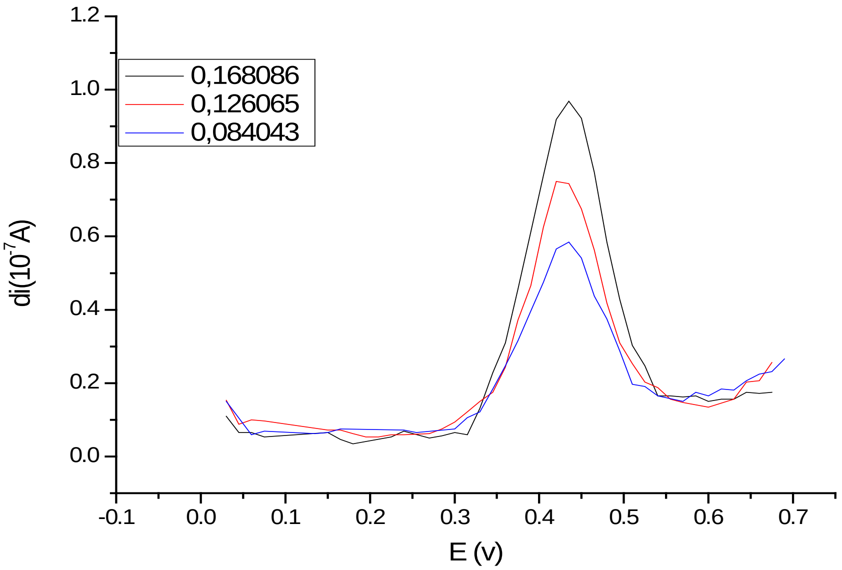


Figure III-4-23: *Square wave voltammograms referring to different N'-Ferrocenylmethyl-N'-phenylbenzohydrazide concentrations in octanol.*

The equation obtained from the linear calibration graph in the studied concentration range for N'-Ferrocenylmethyl-N'-phenylbenzohydrazide standard solutions is, $y = 4.568x + 1.916$ with a correlation coefficient of $R^2 = 0.993$.

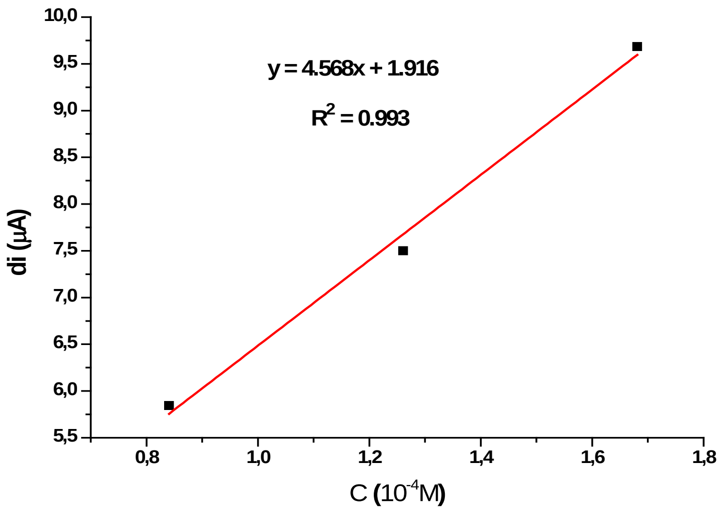


Figure III-4-24: *Calibration curve obtained from SWV for different N'-Ferrocenylmethyl-N'-phenylbenzohydrazide concentrations in octanol.*

- **Preparation of voltammogram of the real sample of N'-ferrocenylmethyl-N'-phenylbenzohydrazide**

Voltammogram of N'-ferrocenylmethyl-N'-phenylbenzohydrazide was measured by dissolving 0.01g of this compound in 20 mL of octanol presaturated with water, thus the initial concentration is equal to 1,218627 mM, to this solution was added 20 mL of water and the mixture is allowed to equilibrate, after phases separation (3 days). The organic layer was separated, and to 4 mL of this layer was added 5 mL of N, N demethylformamide, 20 mL of ethanol, and 0.25 mg of tetrabutylammonium hexflorophospatate ($C_{16}H_{36}F_6NP$) as the supporting electrolyte. The obtained solution was then introduced into the electrochemical cell and the voltammogram was recorded, figure III-4-25.

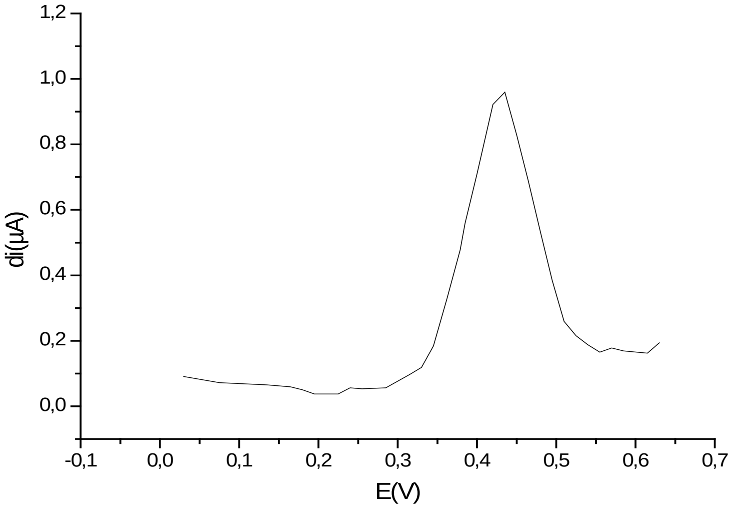


Figure III-4-25: *SWV of the real sample of N'-Ferrocenylmethyl-N'-phenylbenzohydrazide in octanol.*

- **LogP determination**

The concentration of N'-Ferrocenylmethyl-N'-phenylbenzohydrazide in octanol phase C_{Oct} is obtained by replacing the density of the peak current 0.95937 µA obtained from the voltammogram of figure III-4-25 in the equation obtained from the linear calibration graph of figure III-4-24, this gives,

$$x = 0{,}1680757.mM$$

Thus the number of moles in 29 mL, is

$$n = 0{,}1680757.10^{-3} \times 29 \times 10^{-3} = 4.874195 \times 10^{-6}\, mol$$

n, is also equal to the number of moles in 4 mL taken from the octanol phase, so in 20 mL of the octanol phase the number of moles is

$$4.874195 \times 10^{-6} \times 5 = 24.370976 \times 10^{-6}\ mol$$

The concentration of N'-Ferrocenylmethyl-N'-phenylbenzohydrazide in the octanol phase $C_{Oct}$is

$$C_{Oct} = \frac{24.370976 \times 10^{-6}}{20 \times 10^{-3}} = 1.218549\, mM$$

The concentration of N'-Ferrocenylmethyl-N'-phenylbenzohydrazide in the aqueous phase C_{aq} is calculated based on a mass balance using equation (III-4-1).

$$C_{aq} = 1{,}218627 \times 10^{-3} - 1{,}218549 \times 10^{-3} = 7{,}8.\,10^{-5} mM$$

The partition coefficient is given using equation (I-1)

$$P = \frac{1{,}218549 \times 10^{-3}}{7{,}8.\,10^{-8}} = 15622{,}42 \quad and \quad logP = 4.19$$

III-4-2-4-9- Determination of partition coefficient of 2-(ferrocenylmethylamino) benzonitrile

- **Synthesis**

2- aminobenzonitrile (1.83g, 15.48 mmol) was added in small portions to well-stirred solution of (ferrocenylmethy)trimethylammonium iodide (6 g, 15.48 mmol) in water (120 cm^3). The resulting mixture was then heated at 110-115°C for 6 hours. It was then allowed to cool to room temperature. The resulting precipitate was separated by filtration, washed with water to remove any trace of unchanged quaternary ammonium salt and finally recrystallized to produce 2-(ferrocenylmethylamino)benzonitrile (4.68g, 95.5%). The product was recrystallized from aqueous ethanol 95% (1: 2) to give buttercup yellow pellets, m.p. 128°C.

ν_{max}(KBr disc) 1605; 2208 cm^{-1};

RMN ^{1}H (300 MHz, CDCl$_3$)

δ 4.02(d, 2H, J = 4.72 Hz, CH$_2$Fc); 4.20(t, 2H, J = 1.70 Hz, η^5-C$_5$H$_4$ ortho); 4.27(s, 2H, η^5-C$_5$H$_4$ meta); 4.27(s, 5H, η^5-C$_5$H$_5$); 4.99(s, 1H, NH); 6.70(t, 1H, J = 7.75 Hz, ArH); 6.74(d, 1H, ArH); 7.42(d, 1H, ArH); 7.44(t, 1H, ArH);

RMN ^{13}C (75 MHz, $CDCl_3$)

δ 42.6(-ve DEPT)(1C, CH_2Fc); 67.9(2C, η^5-C_5H_4 meta); 68.5(2C, η^5-C_5H_4 ortho); 69.1(5C, η^5-C_5H_5); 85.6(1C, η^5-C_5H_4); 96.0(1C, C_6H_4); 111.0(1C, C_6H_4); 116.9(1C, C_6H_4); 118.4(1C, CN); 133.1(1C, C_6H_4); 134.7(1C, C_6H_4); 150.4(1C, C_6H_4).

- **Preparation of calibration curve**

This compound within also an NH function which may be protonated in acidic medum, so we applied the same procedure as described for the previous compound.

The stock solution of 2-(ferrocenylmethylamino)benzonitrile was prepared by dissolving a by dissolving 0.008 g of 2-(ferrocenylmethylamino)benzonitrile in 16 mL of octanol saturated water then a series of four standard solutions were prepared, as summarised in table III-4-9, by successive dilution of a volume V_1 of the sock solution prepared as describe previously with a volume V_2 of octanol presaturated with water, 20 mL of ethanol, 6 mL of N, N demethylformamide and 0.25 mg of tetrabutylammonium hexafluorophosphate ($C_{16}H_{36}F_6NP$) as the supporting electrolyte, for each standard solution were then added, the concentration range is from 0.210846mM to 0,026355mM.

Table III-4-9:*Peak current 2-(ferrocenylmethylamino)benzonitrile standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	di (µA)
S_1	4	0	0,210846	1,02080
S_2	3	1	0,158134	0,77813
S_3	2	2	0,052711	0,34374
S_4	1	3	0,026355	0,22500

Each standard solution is introduced into the electrochemical cell and the voltammogram is recorded, figure III-4-26 shows the obtained voltammograms at different 2-(ferrocenylmethylamino)benzonitrile concentrations. Figure III-4-27 shows the calibration curve obtained by plotting different concentrations of 2-(ferrocenylmethylamino)benzonitrile versus the peaks current.

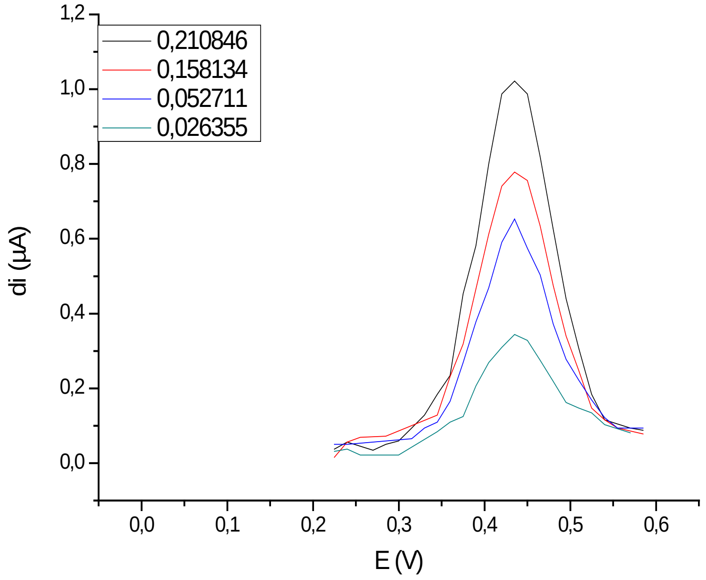


Figure III-4-26: Square wave voltammograms referring to different 2-(ferrocenyl methylamino)benzonitrile concentrations in octanol.

The equation obtained from the linear calibration graph in the studied concentration range for 2-(ferrocenylmethylamino)benzonitrile standard solutions is, $y = 0.426x + 0.113$ with a correlation coefficient of $R^2 = 0.999$.

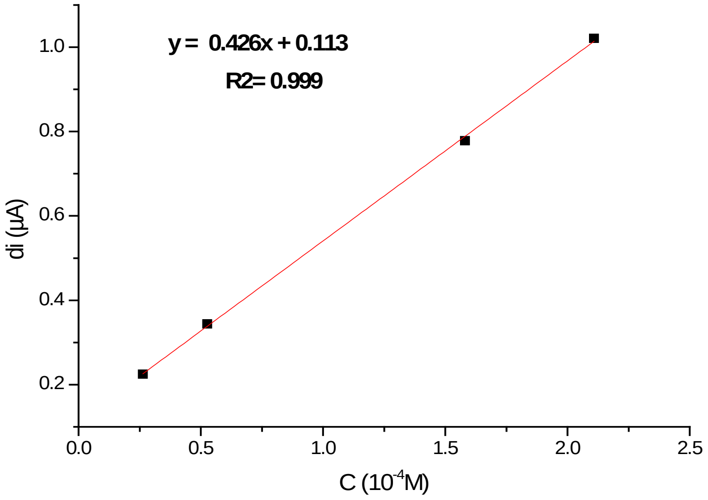


Figure III-4-27: Calibration curve obtained from SWV for different 2-(ferrocenyl methylamino)benzonitrile concentrations in octanol.

- **Preparation of voltammogram of the real sample of 2-(ferrocenylmethylamino) benzonitrile**

Voltammogram of 2-(ferrocenylmethylamino)benzonitrile was measured by dissolving 0.008g of this compound in 16 mL of octanol presaturated with water, thus the initial concentration is equal to 1.581344mM, to this solution was added 20 mL of water and the mixture is allowed to equilibrate, after phases separation (2 days). The organic layer was separated, and to 4 mL of this layer was added 6 mL of N, N demethylformamide, 20 mL of ethanol, and 0.25 mg of tetrabutylammonium hexflorophospatate ($C_{16}H_{36}F_6NP$) as the supporting electrolyte. The obtained solution was then introduced into the electrochemical cell and the voltammogram was recorded, figure III-4-28.

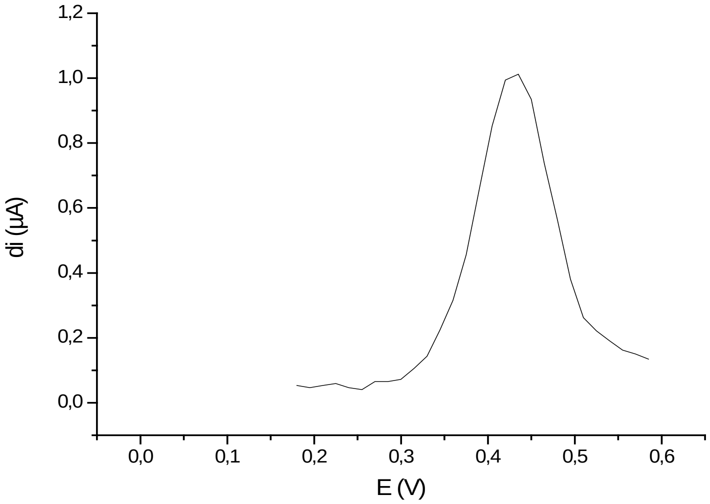


Figure III-4-28: SWV of the real sample of of 2-(ferrocenylmethylamino)benzonitrile in octanol

- **LogP determination**

The concentration of 2-(ferrocenylmethylamino)benzonitrile in octanol phase C_{oct} is obtained by replacing the density of the peak current 1.010 µA obtained from the voltammogram of figure III-4-28 in the equation obtained from the linear calibration graph of figure III-4-27 , this gives,

$$x = 0.2107981\ mM$$

Thus the number of moles in 30 mL, is

$$n = 0.2107981.10^{-3} \times 30 \times 10^{-3} = 6.323943 \times 10^{-6}\ mol$$

n, is also equal to the number of moles in 4 mL taken from the octanol phase, so in 20 mL of the octanol phase the number of moles is

$$6.323943 \times 10^{-6} \times 5 = 31.619715 \times 10^{-6}\ mol$$

The concentration of 2-(ferrocenylmethylamino)benzonitrile in the octanol phase is

$$C_{oct} = \frac{31.619715 \times 10^{-6}}{20 \times 10^{-3}} = 1.580986\, mM$$

The concentration of 2-(ferrocenylmethylamino)benzonitrile in the aqueous phase C_{aq}

is calculated based on a mass balance using equation (III-4-1)

$$C_{aq} = 1.581344 \times 10^{-3} - 1.580986 \times 10^{-3} = 3{,}58.\,10^{-4} mM$$

The partition coefficient is given using equation (I-1)

$$P = \frac{1.580986 \times 10^{-3}}{3{,}58.\,10^{-7}} = 4416.16 \quad and \quad logP = 3.64$$

III-4-2-4-10- Determination of partition coefficient of 4-(ferrocenylmethylamino) benzonitrile

- **Synthesis**

4-(ferrocenylmethylamino)benzonitrile (4.54g, 92.7%) was obtained from (ferrocenylmethy)trimethylammonium iodide (6 g , 15.48 mmol) and 4-aminobenzonitrile (1.83g, 15.48 mmol) following the same procedure as described for 2-(ferrocenylmethylamino)benzonitrile . The product was recrystallized from aqueous ethanol 95%-acetone (1:1:1) to furnish golden yellow crystals, m.p. 132°C.

ν_{max}(KBr disc) 2208; 1603 cm^{-1};

RMN ^{1}H (300 MHz, $CDCl_3$)

δ 4.00(d, 2H, J = 5.09 Hz, CH_2Fc); 4.18(t, 2H, J = 1.70 Hz, η^5-C_5H_4 ortho); 4.19(s, 5H, η^5-C_5H_5); 4.23(t, 2H, J = 1.70 Hz, η^5-C_5H_4 meta); 4.45(s, 1H, NH); 6.58-6.61(d, 2H, ArH); 7.42-7.45(d, 2H, ArH);

RMN ^{13}C (75 MHz, $CDCl_3$)

δ 43.0(-ve DEPT)(1C, CH_2Fc); 68.5(2C, η^5-C_5H_4 meta); 68.6(2C, η^5-C_5H_4 ortho); 70.0(5C, η^5-C_5H_5 C_4); 85.2(1C, η^5-C_5H_4); 99.1(1C, C_6H_4); 112.5(2C, C_6H_4); 120.8(1C, CN); 134.1(2C, C_6H_4 and η^5-C_5H_4); 151.3(1C, C_6H_4).

- **Preparation of calibration curve**

This compound within also an NH function which may be protonated in acidic medum, so we applied the same procedure as described for the previous compound.

The stock solution of 4-(ferrocenylmethylamino)benzonitrile was prepared by dissolving a by dissolving 0.005 g of 4-(ferrocenylmethylamino)benzonitrile in 10 mL of octanol saturated water then a series of four standard solutions were prepared, as summarised in table III-4-10, by successive dilution of a volume V_1 of the sock solution prepared as describe previously with a volume V_2 of octanol presaturated with water, 20 mL of ethanol, 5 mL of N, N demethylformamide and 0.25 mg of tetrabutylammonium hexafluorophosphate ($C_{16}H_{36}F_6NP$) as the supporting electrolyte, for each standard solution were then added, the concentration range is from 0, 169430mM to 0,028238 mM.

Table III-4-10: *Peak current of 4-(ferrocenylmethylamino)benzonitrile standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	di (µA)
S_1	3	0	0,169430	1,16100
S_2	2	1	0,112953	0,86251
S_3	1	2	0,056476	0,506251
S_4	0.5	2.5	0,028238	0,428121

Each standard solution is introduced into the electrochemical cell and the voltammogram is recorded, figure III-4-29 shows the obtained voltammograms at different 4-(ferrocenylmethylamino) benzonitrile concentrations. Figure III-4-30 shows the calibration curve obtained by plotting different concentrations of 4-(ferrocenylmethylamino)benzonitrile versus the peaks current.

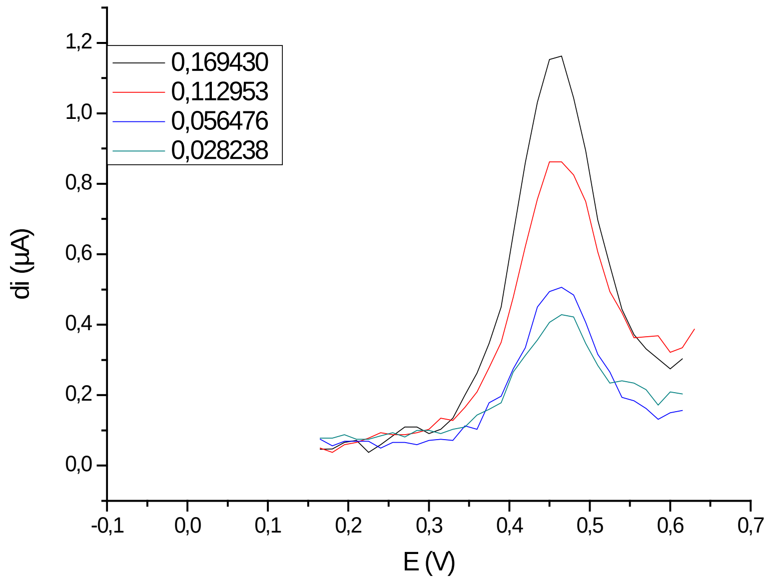


Figure III-4-29: *Square wave voltammograms referring to different 4- (ferrocenyl methylamino)benzonitrile concentrations in octanol.*

The equation obtained from the linear calibration graph in the studied concentration range for 4-(ferrocenylmethylamino)benzonitrile standard solutions is, $y = 0.538x + 0.245$ with a correlation coefficient of $R^2 = 0.991$.

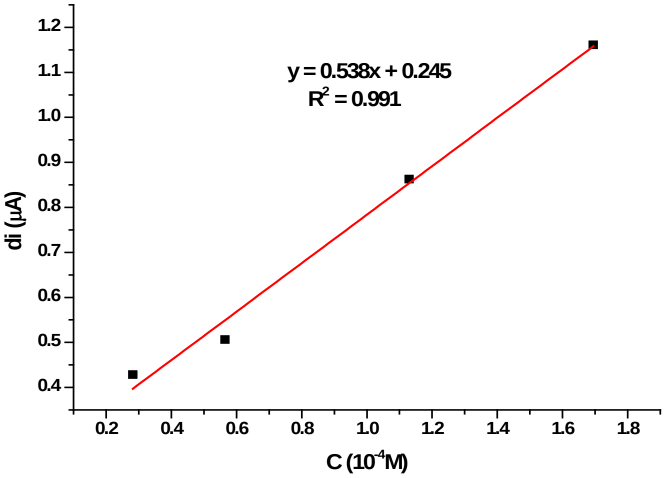


Figure III-4-30: Calibration curve obtained from SWV for different 4-(ferrocenyl methylamino)benzonitrile concentrations in octanol.

- **Preparation of voltammogram of the real sample4-(ferrocenylmethylamino) benzonitrile**

Voltammogram of 4-(ferrocenylmethylamino)benzonitrile was measured by dissolving 0.01g of this compound in 20 mL of octanol presaturated with water, thus the initial concentration is equal to 1.581344mM, to this solution was added 20 mL of water and the mixture is allowed to equilibrate, after phases separation (2 days). The organic layer was separated, and to 3 mL of this layer was added 6 mL of N, N demethylformamide, 20 mL of ethanol, and 0.25 mg of tetrabutylammonium hexafluorophosphate ($C_{16}H_{36}F_6NP$) as the supporting electrolyte. The obtained solution was then introduced into the electrochemical cell and the voltammogram was recorded, figure III-4-31.

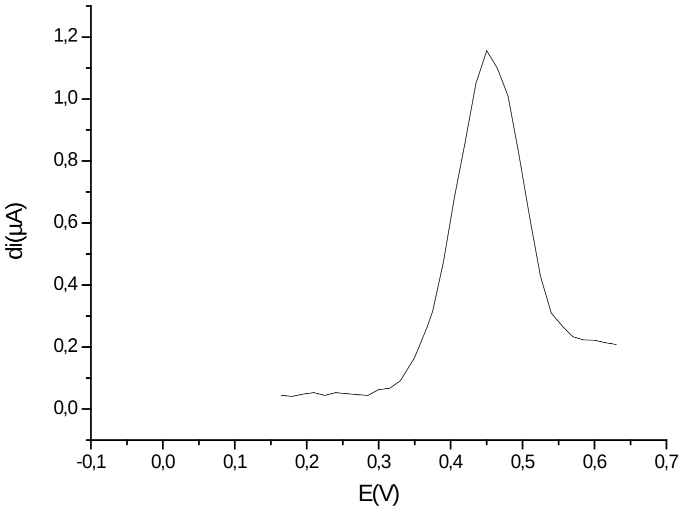


Figure III-4-31: *SWV of the real sample of 4-(ferrocenylmethylamino)benzonitrile in octanol*

- **LogP determination**

The concentration of 4-(ferrocenylmethylamino)benzonitrile in octanol phase C_{Oct} is obtained by replacing the density of the peak current 1.15625 µA obtained from the voltammogram of figure III-4-31 in the equation obtained from the linear calibration graph of figure III-4-30, this gives,

$$x = 0.169377\ mM$$

Thus the number of moles in 28 mL, is

$$n = 0.2107981.10^{-3} \times 28 \times 10^{-3} = 4.742564 \times 10^{-6}\ mol$$

n, is also equal to the number of moles in 3 mL taken from the octanol phase, so in 20 mL of the octanol phase the number of moles is

$$\frac{6.323943 \times 20 \times 10^{-6}}{3} = 31.617093 \times 10^{-6}\, mol$$

The concentration of 4-(ferrocenylmethylamino)benzonitrile in the octanol phase is

$$C_{oct} = \frac{31.617093 \times 10^{-6}}{20 \times 10^{-3}} = 1.580855\, mM$$

The concentration of 4-(ferrocenylmethylamino)benzonitrile in the aqueous phase C_{aq} is calculated based on a mass balance using equation (III-4-1)

$$C_{aq} = 1.581344 \times 10^{-3} - 1.580855 \times 10^{-3} = 4.89.\, 10^{-4} mM$$

The partition coefficient is given using equation (I-1)

$$P = \frac{1.580855 \times 10^{-3}}{4.89.\, 10^{-7}} = 3232.83 \quad and \quad logP = 3.51$$

III-4-3-Validation of electrochemical method

To validate our method, Partition coefficient of ferrocene and 1-ferrocenylethanol were measured by UV–vis Spectrophotometer, and comparing those with the obtained values by the SW method.

The determination partition coefficient of ferrocene derivatives based on the linear relationship between the concentration of the ferrocene derivatives and the amount of energy that it absorbed that can be defined by the Beer-Lambert Law.

In this procedure the aqueous phase concentration of ferrocene derivatives is determined using UV-vis spectrophotometer (UV-1800, SHIMADZU Co., Japan) within the range of 190 nm to 500 nm. Experiments were performed in 1 cm path length quartz cuvette, the absorbtion were recorded using a double beam, the octanol phase concentration of ferrocene derivative is calculated base on a mass balance, in the two phases using the equation (I-1).

III-4-3-1-Determination of partition coefficient of ferrocene

- **Preparation of calibration curve**

Calibration curves were prepared as follows, first we prepared a stock solution by dissolving 0. 5 mg of ferrocene in 50 mL of water saturated with octanol then a series of four standard solutions of ferrocene were prepared, as indicated in table III-4-11, by successive dilution of a volume V_1 of the stock solution prepared as described previously with a volume V_2 of water presaturated with octanol the concentration range is from 0.05375 mM to 0.01612mM.

Table III-4-11: *absorbance of ferrocene standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration(mM)	Absorption (at λ_{248nm})
S_1	5	0	0.05375	0.065
S_2	4	1	0.04300	0.060
S_3	2.5	2.5	0.02687	0.046
S_4	1.5	3.5	0.01612	0.035

The ultraviolet absorption spectrum of ferrocene solved in water were examined in λ_{max} (248 nm) using UV-1800, Shimadzu. Each standard solution is introduced into the UV-vis spectrophotometer cell and the absorbance is recorded. Figure III-4-32 shows the calibration curve obtained by plotting different concentrations of ferrocene derivatives versus the absorbance.

The equation obtained from the linear calibration graph in the studied concentration range for ferrocene standard solutions is, $y = 0.0079x + 0.002385$ with a correlation coefficient of R^2 = 0.985.

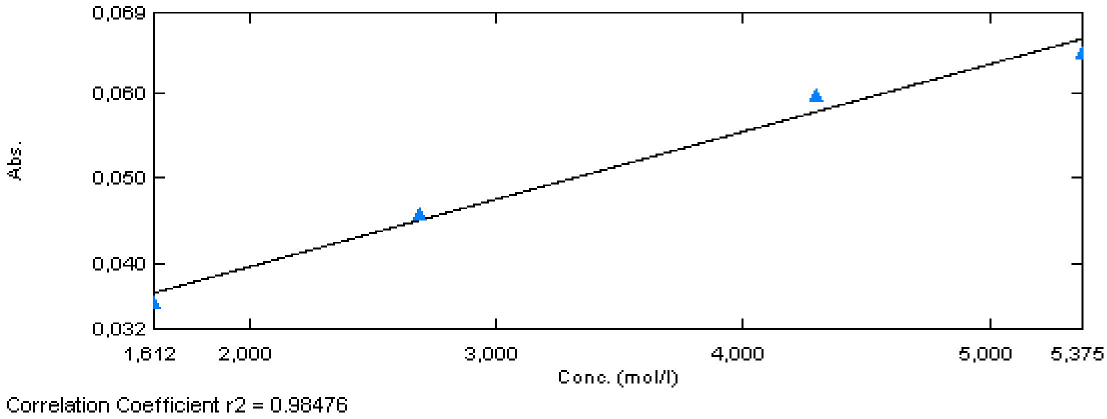


Figure III-4-32: *Calibration curve obtained from UV-visible1800 for different ferrocene concentrations in aqueous at λ_{248nm} wavelength.*

- **Preparation of the real sample of ferrocene**

the same real sample of ferrocene, was used in this method , was prepared previously, after the water layer was separated, 3 mL of this layer was then introduced into the into the UV-vis spectrophotometer cell, the absorbance and the concentration of the real sample of ferrocene were recorded.

- **LogP determination:**

The concentration of ferrocene in water phase was obtained by replacing the absorbance of ferrocene sample 0.028 obtained from UV-vis spectrophotometer, in the equation $y = 0.0079x + 0.002385$ obtained from the linear calibration graph of figure III-4-32, this gives,

$$x = 0.00545\, mM$$

Therefore the concentration of ferrocene in the aqueous phase is

$$C_{aq} = 0.0545\, mM$$

The value of concentration measured with maximum precision may be found in the following way:

Obtaining the relative error is gives as,

$$\frac{\Delta A}{A} = \frac{\Delta C_{aq}}{C_{aq}}$$

Thus gives,

$$\Delta C_{aq} = \frac{\Delta A . C_{aq}}{A}$$

$$\Delta C_{aq} = \frac{0.002 \times 0.545 \times 10^{-5}}{0.028} = 0.000389 mM$$

Then the concentration of ferrocene in the aqueous phase is

$$\Delta C_{aq} + C_{aq} = 0.00545 + 0.000389 = 0.005839\, mM$$

The concentration of ferrocene in the octanol phase $\mathrm{C_{oct}}$ can be calculated based on a mass balance as gives, using equation(III-4-1)

Thus,

$$C_{oct} = 2.687594 - 0.005839 = 2.681755\, mM$$

The partition coefficient is calculated using the following equation (I-1)

This gives

$$P = \frac{2.681755}{0.005839} = 4.59.28, \quad and \quad logP = 2.66$$

Or the concentration of ferrocene value in the octanol phase was obtained by electrochemical Thus,

$$P = \frac{2.681770}{0.005839} = 459.28, \quad and \quad logP = 2.66$$

III-4-3-2- Determination of partition coefficient of 1-ferrocenylethanol

- **Preparation of calibration curve**

Following the same procedure as described for ferrocenylethanol, The stock solution of 1-ferrocenylethanol was prepared by dissolving 0. 9 mg of ferrocenylethanol in 50 mL of water saturated with octanol then a series of four standard solutions of ferrocenylethanol were prepared, as indicated in table III-4-12, by successive dilution of a volume V_1 of the stock solution prepared as described previously with a volume V_2 of water presaturated with octanol the concentration range is from 0.07823 mM to 0.02347mM.

Table III-4-12: *absorbance of 1-ferrocenylethanol standard solutions*

Solutions	V_1(mL)	V_2(mL)	Concentration (mM)	Absorption (at $\lambda_{246\text{ nm}}$)
S_1	5	0	0.07823	0.065
S_2	4	1	0.06258	0.060
S_3	2.5	2.5	0.03911	0.037
S_4	1.5	3.5	0.02347	0.025

The ultraviolet absorption spectrum of ferrocenylethanol solved in water were examined in λ_{max} (246 nm) using UV-1800, Shimadzu. Each standard solution is introduced into the UV-vis spectrophotometer cell and the absorbance is recorded. Figure III-4-33 shows the calibration curve obtained by plotting different concentrations of ferrocenylethanol derivatives versus the absorbance.

The equation obtained from the linear calibration graph in the studied concentration range for ferrocene standard solutions is, $y = 0.00776x + 0.00711$ with a correlation coefficient of R^2 = 0.971.

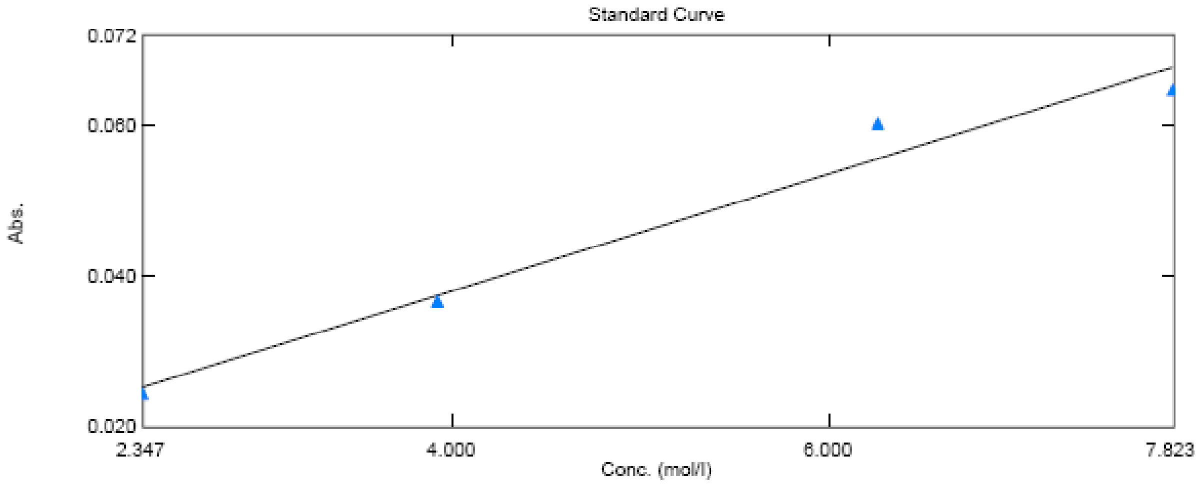


Figure III-4-33: *Calibration curve obtained from UV-visible1800 for different 1-ferrocenylethanol concentrations in aqueous at* λ_{246nm} *wavelength.*

- **Preparation of the real sample of 1-ferrocenylethanol**

the same real sample of 1-ferrocenylethanol, was used in this method , was prepared previously, after the water layer was separated, 3 mL of this layer was then introduced into the into the UV-vis spectrophotometer cell, the absorbance and the concentration of the real sample of 1-ferrocenylethanol were recorded.

- **LogP determination**

The concentration of 1-ferrocenylethanol in water phase was obtained by replacing the absorbance of ferrocene sample 0.019 obtained from UV-vis spectrophotometer, in the equation $y = 0.00776 + 0.00771$ obtained from the linear calibration graph of figure III-4-33, this gives,

$$x = 0.01469\ mM$$

Therefore the concentration of 1-ferrocenylethanol in the aqueous phase is,

$$C_{aq} = 0.01469\ mM$$

The value of concentration measured with maximum precision may be found in the following way:

Obtaining the relative error is gives as,

$$\frac{\Delta A}{A} = \frac{\Delta C_{aq}}{C_{aq}}$$

Thus gives,

$$\Delta C_{aq} = \frac{\Delta A . C_{aq}}{A}$$

$$\Delta C_{aq} = \frac{0.002 \times 1.469 \ \times 10^{-5}}{0.019} = 0.00156463 mM$$

Then the concentration of 1-ferrocenylethanol in the aqueous phase is

$$\Delta C_{aq} + C_{aq} = 0.01469 - 0.00156463 = 0.013126 \, mM$$

The concentration of 1-ferrocenylethanol in the octanol phase C_{oct} can be calculated based on a mass balance using equation (III-4-1)

$$V_{oct} C_{initial} = V_{oct} C_{oct} + V_{aq} C_{aq} \quad \text{with} \quad V_{oct} = V_{aq}$$

Thus,

$$C_{oct} = 1.901409 \ - 0.013126 \ = 1.8882833 \, mM$$

The partition coefficient is calculated using the equation (I-1)

This gives

$$P = \frac{2.681755}{0.005839} = 143.86, \quad and \quad logP = 2.16$$

Or using the obtained value by electrochemical method of concentration of the 1-ferrocenylethanol in the octanol phase,

$$P = \frac{1.888957}{0.013126} = 143.91, \quad and \quad logP = 2.16$$

III-4-4-Resultats and discussion

Square wave voltammetry which is one of the electrochemical methods was successfully used for the first time, to determinate the partition coefficient of ferrocene derivatives. The measurements are carried out in optimized medium has as electrochemical activity obtained by mixing solvents with octanol, and choice a supporting electrolyte appropriate to each ferrocene derivatives according to its function. The values of logP for ferrocene and 1-ferrocenylethanol that were obtained by this technique are not different than those obtained by UV-vis spectrophotometer as shawn in the table III-4-13, thus results confirm the validation of our method.

Table III-4-13: *logP values of ferrocene and 1-ferrocenylethanol*

Compound	logP$_{exp.}$	logP$_{exp2.}$ *	**$\Delta logP_{ex.}$
Ferrocene	2.66	2.66	0
1-Ferrocenylethanol	2.18	2.16	0.02

* logP values of ferrocene and 1-ferrocenylethanol were measured by UV–vis Spectrophotometer.

**$\Delta logP_{ex.} = \left|logP_{\text{exp.}} - logP_{\text{exp2.}}\right|$

The Comparison between theoretical logP and experimental values of ferrocene derivatives were illustrated in table III-4-14.

Table III-4-14: *Comparison between theoretical logP and experimental values*

Compound	RekkerlogP	XlogP	AlogP	$logP_{exp.}$	AE_1	AE_2	AE_3
1	2.66	2.83	2.90	2.64	0.02	0.19	0.26
2	4.58	4.57	4.18	4.59	0.01	0.02	0.41
3	4.12	4.09	4.26	4.10	0.02	0.01	0.16
4	5.17	5.27	5.73	5.04	0.13	0.23	0.69
5	4.66	5.17	5.41	4.68	0.02	0.49	0.73
6	5.18	5.12	5.38	5.23	0.05	0.11	0.15
7	5.70	5.22	5.70	5.62	0.08	0.40	0.08
8	4.45	4.25	4.28	4.42	0.03	0.17	0.14
9	4.48	4.49	4.78	4.44	0.04	0.05	0.34
10	5.11	5.20	5.19	5.08	0.03	0.12	0.11
11	6.42	6.58	6.55	6.47	0.05	0.11	0.08
12	4.75	4.86	3.83	4.63	0.12	0.23	0.80
13	5.08	5.01	3.84	5.01	0.07	00	1.17
14	4.93	5.20	5.53	5.10	0.17	0.10	0.43
15	4.96	4.92	5.88	4.89	0.07	0.03	0.99
16	5.48	5.33	6.23	5.89	0.41	0.56	0.34
17	6.00	5.78	6.76	6.33	0.33	0.55	0.43
18	6.52	6.23	7.21	6.70	0.18	0.47	0.51
19	6.52	6.05	7.08	6.60	0.08	0.55	0.48
20	5.33	5.76	3.81	5.79	0.46	0.03	1.98
21	3.61	4.82	3.21	4.00	0.39	0.82	0.79
22	6.25	7.47	5.05	6.49	0.24	0.98	1.44
23	5.24	5.67	5.38	4.90	0.34	0.77	0.48
24	6.85	7.43	7.03	6.43	0.42	1.00	0.60
25	6.29	7.05	6.76	6.17	0.12	0.88	0.59
26	5.74	6.68	6.28	5.75	0.01	0.93	0.53
27	5.81	6.76	6.15	5.92	0.11	0.84	0.23
28	6.19	7.60	7.28	6.13	0.06	1.47	1.15
29	6.49	7.15	6.91	6.37	0.12	0.78	0.54
30	4.78	4.61	4.64	4.77	0.01	0.16	0.13
31	5.30	4.97	5.09	5.27	0.03	0.30	0.18
32	2.05	2.53	2.00	2.18	0.13	0.35	0.18
33	4.06	3.86	3.57	3.95	0.11	0.09	0.38
34	4.58	4.27	4.24	4.38	0.20	0.11	0.14
35	4.11	4.44	4.07	3.88	0.23	0.56	0.19
36	4.33	4.44	4.07	3.99	0.34	0.45	0.08
37	4.02	3.76	3.93	3.51	0.51	0.25	0.42
38	3.58	3.76	3.93	3.64	0.06	0.12	0.29
39	3.94	4.04	4.05	3.82	0.12	0.22	0.23
40	4.32	5.19	4.74	4.19	0.13	1	0.55

$\mathrm{AE}_1 = \left|RekkerlogP - logP_{exp.}\right|$,$\mathrm{AE}_2 = \left|XlogP - logP_{exp.}\right|$,$\mathrm{AE}_3 = \left|AlogP - logP_{exp.}\right|$

III-4-5-Conclusion

We successfully measured the octanol-water partition coefficients of ten ferrocene derivatives, logP values of experimental and calculated LogP for a series of ten ferrocene derivatives are in good agreement. The results confirm the utility of use of square wave voltammetry techniques for measuring octanol-water partition coefficients of ferrocene derivatives.

Our method nicely provides a solution for measuring the partition coefficient of ferrocene derivatives and potentially all analogous organometallic compounds.

General conclusion

General conclusion

LogP values for 40 ferrocene derivatives with widely varying structure, size and function, were predicted for the first time, the calculation were based upon on the adaptation of some existing methods such as Rekker, XlogP, AlogP approaches used for organic molecules. Values of experimental and calculated logP for substituted ferrocene are in good agreement, this approves the process of adaptation. The calculated values of logP of ferrocene derivatives obtained by the different modified proposed methods were compared, all are very close to each other, however the modified Rekker method remains the most accurate for the calculation of octanol-water partition coefficient of ferrocene derivatives.

New specific correction factor rule for ferrocenyl ring connected to hydroxyl via carbon were proposed and were proved for the calculation of logP according to adapted Rekker method.

Partition coefficient of 10 ferrocene derivatives were determined successfully using for the first time square wave voltammetry which is one of the electrochemical methods, the measurements were carried out in optimized medium, this technique were validated using UV-vis spectrophotometer method.

In the light of the successfully results obtained for logP this indicates the reliability of our models and experimental method, enable us to consider that the process is a solution for calculating partition coefficient for ferrocene derivatives and generalizing it to include all analogous complexes. In the future we look to create a specific model for ferrocene and metallocene.

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Abstract:

Octanol–water partition coefficient, P, is a key physicochemical property for many filed of sciences such as pharmaceutical drugs, analytical chemistry, environmental science in the assessment of environmental fate, transport of organic chemicals and agrochemicals. This work describes new methods for determining logP values for a large number of ferrocene derivatives with widely varying structure, size and function using theoretical calculation and prediction from literature. Calculations are based on the adaptation of some existing methods such as Rekker, XLogP and ALogP.

In order to validate our proposed theoretical method partition coefficients of a numerous ferrocene derivatives were also successfully determined, using for the first time square wave voltammetry techniques.Values of experimental and calculated logP of substituted ferrocene are in good agreement.

Key words: Partition coefficient, logP, lipophilicity, ferrocene derivatives, liquid-liquid extraction, hydrophilicity.

الملخص :

يعتبر معامل التوزيع P في نظام أوكتانول – ماء ، من أهم الخصائص الفيزيو- كيميائية في العديد من العلوم ، كالصيدلة, الكيمياء الزراعية, الكيمياء التحليلية و البيئة . يصف هذا العمل طرق نظرية جديدة لتحديد قيم LogP للعديد من مشتقات الفيروسان والتنبؤ بها حسابيا . نعتمد في الحساب على تكييف الطرق النظرية XLogP , Rekker و ALogP من أجل التاكد من نجاعة التنبؤ ات بالطرق النظرية قمنا بقياسlogP لعدد من مشتقات الفيروسان مخبريا باستعمال تقنية فولطامتري الموجة المربعة. قيم LogP لمشتقات الفيروسان المتحصل عليها حسابيا بمختلف هذه الطرق متقاربة في ما بينها ومتوافقة مع القيم التجريبية.

الكلمات الدالة :معامل التوزيع ,logP , محب للدهون, مشتقات الفيروسان، استخلاص سائل- سائل, محب للماء

Résumé :

Le coefficient de partage dans le système octanol-eau, exprimée par P, est une propriété physico-chimique principale, basées sur laquelle plusieurs domaines scientifique telles que Pharmacologie et chimie agricole. Ce travail décrit une nouvelle et simple méthode pour déterminer des valeurs de LogP pour un grand nombre de dérivés de ferrocène en utilisant le calcul théorique et la prévision de la littérature. Les calculs sont basés sur l'adaptation de certaines méthodes existantes telles que Rekker, XLogP, AFC, et ALogP. Pour valider les méthodes de calcul proposées, logP d'un nombre des drivées ferrocéniques ont été mesurés en utilisant la voltammetrie à onde carrée. Toutes les valeurs de logP des dérivés de ferrocène obtenues par les différentes méthodes proposées sont très proches l'une de l'autre et en bon accord avec les valeurs expérimentales.

Mots clés : Coefficient de partage, logP, lipophilicité, dérivés de ferrocène, l'extraction liquide - liquide, hydrophilicité.